scientific reports

Check for updates

OPEN

SGLT2 inhibitors reduce the risk of renal failure in CKD stage 5 patients with Type 2 DM

Birdie Huang[1,5], Chieh-Li Yen[2,3,5], Chao-Yi Wu[3], Chung-Ying Tsai[2], Jia-Jin Chen[2,3], Ching-Chung Hsiao[2,3], Yung-Chang Chen[2,3], I-Chang Hsieh[1,5] & Huang-Yu Yang[2,3,4,5]✉

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as a promising therapy for diabetes and CKD patients. However, the pros and cons of SGLT2i in Type2 diabetes patients with CKD stage 5 remained largely unexplored. By using Taiwan's national health insurance research database (NHIRD), this observational cohort study enrolled T2DM patients with newly identified as having CKD5, and the index date defined as the date of CKD5 identification. The enrollees were divided into 2 groups depending on whether SGLT2 inhibitors were used for more than 3 months or not following the index date. A 1:4 propensity score matching was performed to balance characteristics between two groups. The SGLT2-inhibitor group exhibited significantly lower risks of new-onset ESRD (35.9% vs. 58.2%, hazard ratio [HR] 0.59, 95% confidence interval [CI]: 0.59–0.74). For the risks of MACCEs (16.72% vs. 17.66%, HR 0.84, 95% CI: 0.62–1.15), infections related hospitalization (2.4% vs. 2.61%, HR:1.02, 95% CI:0.80–1.31), Infection-associated mortality (3.45% vs. 4.18% HR:0.80, 95% CI:0.41–1.56) and all-cause mortality (13.79% vs. 13.83%, HR:0.95, 95% CI:0.68–1.32), no significant differences were observed between two groups. In conclusion, we provide evidence suggesting that SGLT2 inhibitors may offer renal protection and did not increase infection risks for CKD5 patients with type2 diabetes.

Keywords CKD, Diabetes, ESRD, MACCE, SGLT2 inhibitor

Type 2 diabetes mellitus (T2DM) stands as a leading health concern, impacting populations worldwide as a top-priority disease[1]. T2DM has a global prevalence of approximately 13.5%[2]and its prevalence continues to rise, thereby contributing to the burden of chronic kidney disease (CKD) and other subsequent complications, such as an increased risk of stroke, myocardial infarction (MI), infection, and reduced quality of life[3,4]. Although several medications are presently available to manage blood sugar levels, most oral hypoglycemic agents (OHA) offer limited renal protection and are unable to impede the progression of chronic kidney disease. Recently, Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as a promising therapy for patients with T2DM, offering both cardiovascular and renal protection[5–8]. As an OHA, these medications could inhibit glucose reabsorption in the renal proximal tubules, leading to a reduction in blood glucose levels and aiding in achieving the optimal glycohemoglobin (HbA1c) target. Beyond their blood sugar-lowering effects, SGLT2 inhibitors also exert an additional effect by inhibiting the sodium-glucose co-transporter, which results in a decrease in the reabsorption of sodium in the proximal tubules as well[9]. The increased urinary sodium in the renal tubule, facilitated by the tubular-glomerular feedback mechanism, can effectively mitigate the hyperfiltration of the glomerulus, which has been identified as the primary cause of proteinuria and the decline in renal function[10,11]. Thus, recent guidelines of T2DM treatment have classified SGLT2 inhibitors as the initial option, especially when the primary objective is to prevent chronic kidney disease[12].

In 2020, Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) trial[13], which enrolled patients with an estimated glomerular filtration rate (eGFR) of 25 to 75 ml/min/1.73m2, and proved that the renal protection effect of SGTL2i is consistent irrespective of different baseline eGFR or the presence of T2DM or not. In 2022, Empagliflozin in Patients with CKD (EMPA-KIDNEY) trial additionally extended the baseline eGFR of participants lower to 20 ml/min/1.73m2 and the renal benefits of SGLT2i are still observed[14]. Although these exciting findings hinted that, unlike the reduced glucose-lowering effect along with renal function decline, the renal protection and proteinuria-lowering effect of SGLT2i seem to be less influenced with baseline renal function.

[1]Department of Cardiology, Chang Gung Memorial Hospital, Linkou Branch, Taoyuan, Taiwan. [2]Kidney Research Center, Department of Nephrology, Chang Gung Memorial Hospital, Linkou Branch, No. 5, Fusing St., Gueishan District, Taoyuan 333, Taiwan. [3]College of Medicine, Chang Gung University, Taoyuan, Taiwan. [4]Department of Health Policy and Management, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA. [5]Birdie Huang, Chieh-Li Yen, I-Chang Hsieh and Huang-Yu Yang contributed equally. ✉email: hyyang01@gmail.com

However, as far, there is no direct evidence to prove that SGLT2i could be safely prescribed among patients with CKD stage 5 (eGFR < 15 ml/min/1.73m2) and still had renal or cardiovascular (CV) benefits. For several reasons, the authors believed that this is crucial to evaluate the role of SGLT2i in CKD5 patients. First, main effect of SGLT2i is to decrease hyperfiltration of glomerulus and would result in following reduction of proteinuria and temporary eGFR decline. Although in patients with moderate CKD, the temporary eGFR decline of SGLT2i have been proved safe and renal protective[7,14]. However, the uncertainty remains about whether the reduction of hyperfiltration in patients with extremely low eGFR might result in inadequate uremia clearance, potentially necessitating early initiation of renal replacement therapy. Second, previous studies have demonstrated the cardiovascular protective benefits of SGLT2i, particularly in reducing heart failure-related hospitalizations and mortality. Given the common occurrence of advanced CKD and heart failure simultaneously[15,16], investigating whether the use of SGLT2i could also reduce the risk of heart failure or heart failure-associated complications in CKD5 patients is of great interest. Third, patients with CKD stage 5 are prone to complications such as protein-energy wasting (PEW) and immunodeficiency[17,18], raising the question of whether SGLT2i-induced glucosuria might lead to severe urinary tract infections and exacerbate energy wasting in this population. This aspect is also worthy of investigation for nephrologists.

Since the pros and cons of SGLT2i in patients with CKD stage 5 remained largely unexplored, in this nationwide population-based retrospective cohort study by using Taiwan's national health insurance research database (NHIRD), we aimed to investigate the effectiveness of SGLT2 inhibitors in stage 5 CKD patients with T2DM in the risk of Major Adverse Cardiac and Cerebrovascular Events (MACCE), progression into end stage renal disease (ESRD), infection and infection related mortality.

Methods

Study population

We performed this nationwide population-based retrospective cohort study using Taiwan's NHIRD which was launched in 1995 by National Health Insurance (NHI) program. NHI in Taiwan is a nationwide, single-payer and compulsory health care program which covers 99.8% population (nearly 23.37 million) in Taiwan[19,20]. NHIRD database includes the diagnosis, outpatient clinic visits, hospital admissions, medications prescriptions, and procedures of insured patients. Disease diagnosis are made according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) before 2015 and ICD-10-CM since 2016. The patient's personal identification and information are scrambled before it is used for research. Therefore, this study was approved with a waiver of informed consent from the Institutional Review Board, Chang Gung Medical Foundation's (approval number: 201900840B0). The authors confirmed that all experiments were performed in accordance with relevant guidelines and regulations.

Study design

As illustrated in Fig. 1, we enrolled all patients > 20 years diagnosed with chronic kidney disease stage 5 (eGFR < 15 ml/min/1.73m^2) and type 2 diabetes mellitus between May 1st, 2016 and September 30th, 2020. In previous researches on the basis of Taiwan's NHIRD, patients with stage 5 chronic kidney disease are identified through the diagnosis of CKD accompanied by the prescription of erythropoiesis-stimulating agents (ESAs)[21,22], as the insurance only cover the copayment of the use of ESAs for patients with eGFR < 15 ml/min/1.73m^2 and hematocrit < 28%. Stage 5 chronic kidney disease date was defined as the date patients first prescribed ESAs after at least 3 claims of chronic kidney disease during hospital admission or at outpatient clinics. We defined day 91 after stage 5 chronic kidney disease as the index date for a 90-day observational time for better identification of medications prescribed for these patients.

We excluded patients newly diagnosed with type 2 diabetes mellitus after the index date, those younger than 20 years old, patients who had undergone long-term dialysis therapy or kidney transplantation before the index date, and those with a malignancy diagnosis prior to the index date. A total of 36,184 CKD5 patients with type2 diabetes mellitus were enrolled, of which 248 were continuously prescribed SGLT2 inhibitors.

Study groups and Covariates

All enrolled patients were divided into two groups depending on whether SGLT2 inhibitors were continuously used for 90 days or not between CKD stage 5 date and index date.

The covariates in this study were age, sex, area of residence, occupation, comorbidities, history of hospitalizations, and relevant medications. Comorbidities were identified if they were reported for more than two outpatient visits or one inpatient stay within the year preceding the index date. The history of hospitalization was tracked to three years before the index date. Medications were identified according to the prescriptions between CKD stage 5 date and index date.

End points

The main outcome in this study was Major Adverse Cardiac and Cerebrovascular Events (MACCE), which encompassed percutaneous coronary intervention, coronary artery bypass surgery, thrombolysis therapy, cardiogenic shock, heart failure, malignant dysrhythmia, myocardial infarction, and stroke. Infection, infection-associated mortality, progression to end-stage renal disease and all-cause mortality were considered as secondary outcomes. All-cause mortality was defined as either the withdrawal from the National Health Insurance (NHI) program for more than three months or the patient's appearance in the Taiwan Death Registry. MACCE and infection were identified according to the principal diagnosis during hospitalization or emergency room visits. New-onset ESRD was defined as obtaining a catastrophic illness certificate for permanent dialysis. Disease diagnoses were conducted using ICD-9-CM codes before 2015 or ICD-10-CM codes from 2016 onwards, and most of these codes have been previously validated[23–25].

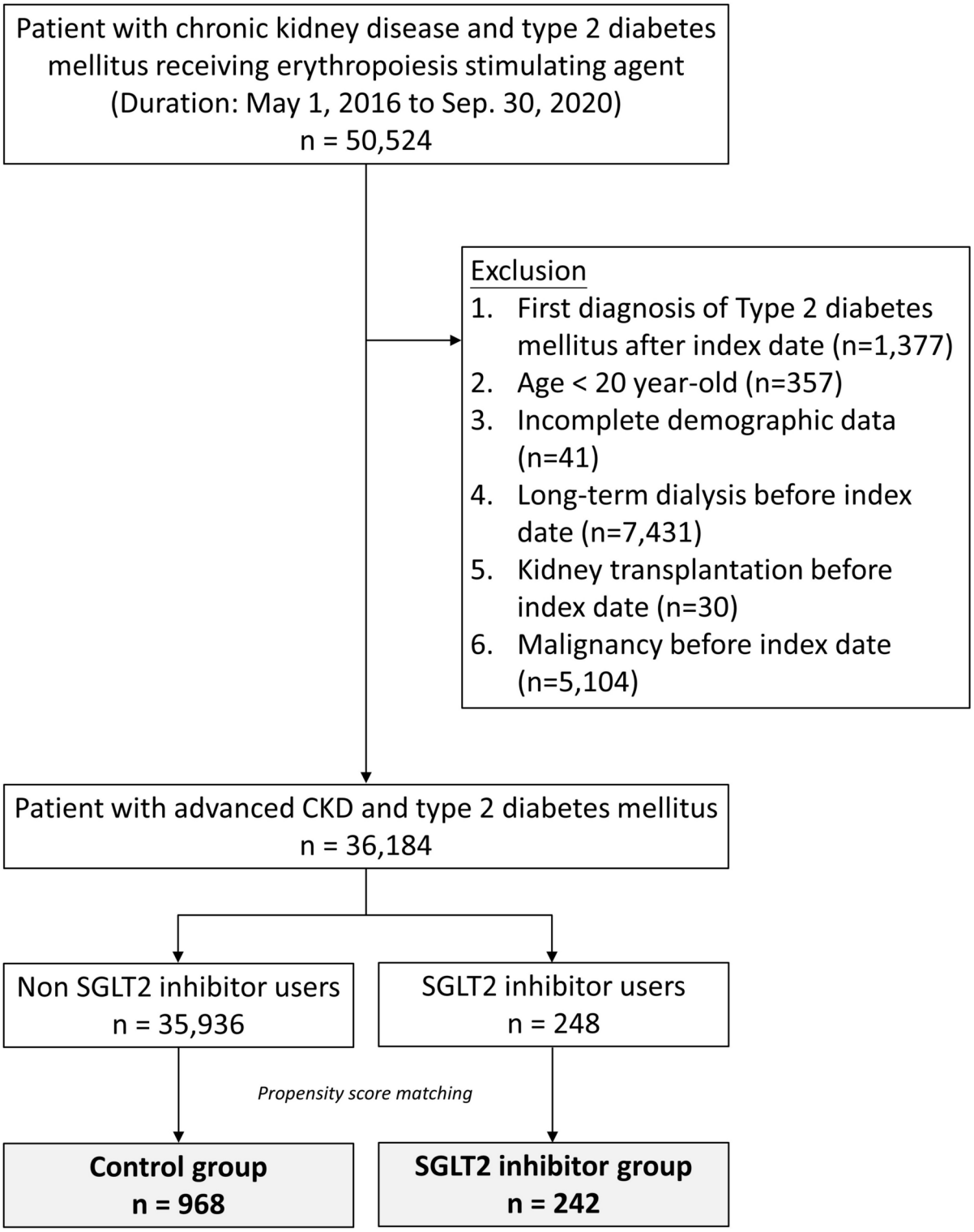

Fig. 1. Flowchart for the inclusion and follow-up of study patients. CKD: chronic kidney disease; SGLT2: sodium-glucose cotransporter 2.

Statistical analysis

To balance the baseline characteristics between the study groups (SGLT2 inhibitor group vs. control group), the propensity score matching was performed, in which each patient in the SGLT2 inhibitor group was matched with four counterparts in the control group. With the covariates being demographics, comorbidities, history of hospitalizations, medications, and index date of CKD stage 5 (variables listed in Table 1), the propensity score was the predicted probability to be in the SGLT2 inhibitor group derived from logistic regression[26]. A greedy

Variable	Propensity Score Matching									
	Before					After				
	SGLT2 inhibitors					SGLT2 inhibitors				
	No		Yes			No		Yes		
	(n = 35,936)		(n = 248)		ASMD	(n = 968)		(n = 242)		ASMD
Age, years (mean, std)	69	13	68	12	0.0699	68	13	68	12	0.0556
Male (n, %)	18,524	51.55	115	46.37	0.1037	436	45.04	112	46.28	0.0249
Area of residence (n, %)					0.0443					0.0684
Urban	19,713	54.86	142	57.26		555	57.33	138	57.02	
Suburban	11,859	33.00	78	31.45		302	31.20	77	31.82	
Rural	4364	12.14	28	11.29		111	11.47	27	11.16	
Occupation (n, %)					0.0766					0.0477
Dependent	15,165	42.2	103	41.53		405	41.84	101	41.74	
Civil servant	349	0.97	3	1.21		10	1.03	3	1.24	
Non-manual worker	2642	7.35	23	9.27		94	9.71	21	8.68	
Manual worker	10,706	29.79	71	28.63		270	27.89	70	28.93	
Other	7074	19.68	48	19.35		189	19.52	47	19.42	
Comorbidity (n, %)										
Hypertension	27,997	77.91	177	71.37	0.1507	688	71.07	175	72.31	0.0275
Hyperlipidemia	15,713	43.72	98	39.52	0.0855	384	39.67	98	40.5	0.0169
Liver cirrhosis	657	1.83	1	0.40	0.1360	3	0.31	1	0.41	0.0167
Systemic lupus erythematosus	99	0.28	1	0.40	0.0220	8	0.83	1	0.41	0.0535
Atrial fibrillation	477	1.33	1	0.40	0.0999	4	0.41	1	0.41	0.0000
Peripheral artery disease	967	2.69	7	2.82	0.0080	22	2.27	7	2.89	0.0391
Connective tissue disease	501	1.39	7	2.82	0.0996	29	3.00	6	2.48	0.0319
Chronic lung disease	3152	8.77	32	12.9	0.1332	106	10.95	31	12.81	0.0575
Renal stone	936	2.60	10	4.03	0.0798	41	4.24	9	3.72	0.0266
Benign prostate hyperplasia	3364	9.36	19	7.66	0.0609	60	6.2	19	7.85	0.0646
Hospitalization history (n, %)										
Heart Failure	8121	22.60	63	25.4	0.0657	221	22.83	60	24.79	0.0460
Myocardial infarction	1913	5.32	16	6.45	0.0479	52	5.37	15	6.2	0.0356
Stroke	2498	6.95	8	3.23	0.1701	31	3.2	8	3.31	0.0062
Infection	13,983	38.91	93	37.5	0.0290	354	36.57	88	36.36	0.0044
Medication (n, %)										
ACEi	2656	7.39	10	4.03	0.1451	46	4.75	10	4.13	0.0301
ARB	21,166	58.9	167	67.34	0.1756	643	66.43	165	68.18	0.0373
Aspirin	11,026	30.68	84	33.87	0.0682	338	34.92	81	33.47	0.0306
Beta-blockers	21,606	60.12	160	64.52	0.0907	613	63.33	157	64.88	0.0323
Calcium channel blockers	16,661	46.36	84	33.87	0.2570	347	35.85	84	34.71	0.0239
Digoxin	721	2.01	5	2.02	0.0007	20	2.07	5	2.07	0.0000
Diuretics	26,694	74.28	174	70.16	0.0921	679	70.14	172	71.07	0.0204
NSAID	12,207	33.97	79	31.85	0.0450	294	30.37	77	31.82	0.0313
Statin	21,148	58.85	177	71.37	0.2650	688	71.07	172	71.07	0.0000
Fibrate	2415	6.72	28	11.29	0.1602	113	11.67	26	10.74	0.0295
Pentoxifylline	15,401	42.86	100	40.32	0.0514	398	41.12	100	41.32	0.0041
Ketosteril	7786	21.67	49	19.76	0.0471	201	20.76	49	20.25	0.0126
Glucose lowering agents										
Sulfonylurea	8844	24.61	105	42.34	0.3825	403	41.63	101	41.74	0.0022
DPP-4i	19,871	55.3	155	62.5	0.1468	612	63.22	151	62.4	0.0170
Thiazolidinedione	2414	6.72	43	17.34	0.3310	140	14.46	40	16.53	0.0572

Continued

Variable	Propensity Score Matching									
	Before					After				
	SGLT2 inhibitors					SGLT2 inhibitors				
	No		Yes			No		Yes		
	(n = 35,936)		(n = 248)		ASMD	(n = 968)		(n = 242)		ASMD
Insulin	17,644	49.1	135	54.44	0.1070	539	55.68	133	54.96	0.0145
GLP-1 Agonist	467	1.3	8	3.23	0.1298	34	3.51	7	2.89	0.0352
Acarbose	2848	7.93	38	15.32	0.2324	147	15.19	37	15.29	0.0028
Meglitinide	7831	21.79	43	17.34	0.1124	165	17.05	42	17.36	0.0082
Follow-up, years (mean, std)	2.00	1.27	1.20	0.95		1.90	1.19	1.20	0.96	

Table 1. Baseline characteristics between SGLT2 inhibitors and control groups. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASMD, absolute standardized mean difference; DPP4i, dipeptidyl peptidase 4 inhibitors; GLP-1, glucagon-like peptide-1; NSAID, non-steroidal anti-inflammatory drug.

nearest neighbor algorithm was adopted with a caliper of 0.2 without replacement[26]. The quality of matching between the groups was confirmed using the absolute standardized mean difference (ASMD), in which a value less than 0.1 indicate a negligible difference between groups.

The comparison of the risk of all-cause mortality between two groups was using a Cox proportional hazard model. The comparison of the risk of other time to event outcomes (i.e., infection death) between two groups was using a subdistribution hazard model that considered death as a competing risk[27]. In both the Cox and subdistribution hazard models, matching pairs were stratified to consider the correlation among patients within the same matching pair[28]. The cumulative incidence rate was plotted using subdistribution cumulative incidence function for time to event outcomes, except for all-cause mortality, whereas Kaplan–Meier survival curves was plotted for all-cause mortality. A 2-tailed p-value of < 0.05 was regarded statistically significant and no adjustment of multiple testing was conducted.

Results

Patient characteristics

Table 1 exhibited the main characteristics of the studied patients. A total of 36,184 adult patients with CKD stage 5 between 2016 and 2020 were eligible. Of them, 248 continuously received SGLT2 inhibitors between CKD5 date and index date (SGLT2 inhibitor group), whereas the other 35,936 patients had not (control group). Before matching, the SGLT2 inhibitor group only exhibited a few differences compared to control group: more common prescriptions for calcium channel blockers, statins, sulfonylurea, thiazolidinedione (TZD), and acarbose. After propensity score matching, all the values of ASMD were less than 0.1, indicating negligible differences between the two groups in these clinical characteristics (Table 1).

Outcome

In the outcome analysis (Table 2), after propensity score matching, the SGLT2i group exhibited a significantly lower risks of new-onset ESRD (36.12% vs. 61.58%, hazard ratio [HR] 0.61, 95% confidence interval [CI]: 0.47–0.77). However, for the risks of MACCE (17.85% vs. 18.58%, HR 0.98, 95% CI: 0.69–1.38), infections related hospitalization (30.36% vs. 29.17%, HR:1.03, 95% CI:0.80–1.33), MACCE-associated mortality (2.19 vs. 2.45, HR:0.89, 95% CI: 0.38–2.07), Infection-associated mortality (3.28% vs. 4.81% HR:0.69, 95% CI:0.34–1.38) and all-cause mortality (13.14% vs. 15.27%, HR:0.86, 95% CI:0.60–1.23), no significant differences were observed between SGLT2i group and control group. The cumulative incidence curves for outcomes were represented in Fig. 2.

Discussion

In this study, we aimed to investigate the relationship between renal and CV outcomes and the use of SGLT2 inhibitors in CKD5 patients with type 2 diabetes mellitus. Though the utilization of SGLT2 inhibitors in CKD5 patients was relatively infrequent as far, limiting the number of SGLT2 inhibitor users in this study. We observed that baseline characteristics between SGLT2 inhibitors group and control group were largely balanced even prior to propensity score matching in this study (Table 1). Therefore, the equilibrium in baseline co-morbidities between the SGLT2 inhibitor group and the control group suggests that we did not recruit a specific population, enhancing the reliability of our results. This study provides insights into the potential benefits of SGLT2 inhibitors in patients with stage 5 CKD, a population was often excluded from clinical trials. The findings suggest that SGLT2 inhibitors may offer renal protection for patients with stage 5 CKD without causing significant adverse cardiovascular effects or increased infection rates. These results indicate that SGLT2 inhibitors might still have a role for slowing down the progression to end-stage renal disease (ESRD) even in patients with late-stage CKD, potentially improving patient outcomes and reducing the burden on healthcare systems. The results of our study align with previous research demonstrating the efficacy of SGLT2 inhibitors in patients with type 2 diabetes mellitus and advanced CKD, including stage 4 CKD[7,8,14]. Our findings extend the evidence base for the use of

	Control group		SGLT2 inhibitors group		SGLT2 inhibitors group vs Control group
	No. of events	Incidence rate* (95%CI)	No. of events	Incidence rate* (95%CI)	Hazard ratio (95%CI)
Before Propensity Score Matching					
MACCE[a]	10,387	17.73(17.39–18.07)	44	16.95(11.94–21.96)	0.86(0.64–1.15)
Infection	15,209	28.13(27.68–28.57)	72	30.26(23.27–37.25)	0.96(0.76–1.21)
New-onset ESRD	22,752	69.29(68.39–70.19)	76	34.47(26.72–42.22)	0.48(0.38–0.60)
MACCE[a] associated mortality	1805	2.51(2.40–2.63)	7	2.34(0.94–4.83)	0.88(0.42–1.86)
Infection associated mortality	4084	5.68(5.51–5.86)	10	3.35(1.27–5.42)	0.55(0.30–1.03)
All-cause mortality	11,466	15.95(15.66–16.24)	40	13.39(9.24–17.54)	0.77(0.57–1.05)
After Propensity Score Matching					
MACCE[a]	166	18.58(15.75–21.4)	42	17.85(12.45–23.25)	0.98(0.69–1.38)
Infection	247	29.17(25.53–32.81)	65	30.36(22.98–37.74)	1.03(0.80–1.33)
New-onset ESRD	377	61.58(55.36–67.79)	71	36.12(27.72–44.53)	0.61(0.47–0.77)
MACCE[a] associated mortality	26	2.45(1.51–3.39)	6	2.19(0.80–4.77)	0.89(0.38–2.07)
Infection associated mortality	51	4.81(3.49–6.13)	9	3.28(1.50–6.24)	0.69(0.34–1.38)
All-cause mortality	162	15.27(12.92–17.63)	36	13.14(8.85–17.43)	0.86(0.60–1.23)

Table 2. Follow-up outcomes before and after propensity score matching. *: per 100 person-years, [a]: MACCE: major advanced cardiovascular events, any coronary artery bypass graft (CABG), myocardial infarction (MI), percutaneous coronary intervention (PCI), cardiogenic shock, new-diagnosis heart failure, coronary revascularization, malignant arrhythmia, or cerebrovascular events; CI: confidence interval; ESRD: End-stage renal disease.

SGLT2 inhibitors in this patient population, highlighting their potential benefit to slow the progression to end-stage renal disease.

According to the current emerging evidence, the protective effect of SGLT2 inhibitors is mainly attributed to the reduction of hyperfiltration of glomerulus[11,29]. However, in CKD5 patients, who have only a fraction of the glomerulus preserved, the major concern for physicians is whether the reduction of glomerular hyperfiltration caused by SGLT2 inhibitors still exerts a renal protective effect or, conversely, leads to inadequate renal toxin clearance and early uremia symptoms. The positive results of this study may partially alleviate these concerns. But it is important to note that most participants in this study initiated the use of SGLT2 inhibitors before reaching CKD stage 5. As a result, this study can only demonstrate that continuing the use of SGLT2 inhibitors after CKD stage 5 can still have a renal protective effect. However, since very few patients have initiated SGLT2 inhibitor treatment after reaching CKD stage 5 in Taiwan so far, this cohort study was underpowered to determine whether newly prescribed SGLT2 inhibitors after CKD stage 5 still provide benefits for renal outcomes. Our research team plans to design a further cohort study to address this question when the prescriptions of SGLT2 inhibitors in CKD stage 5 patients become more prevalent.

Another major concern regarding the prescription of SGLT2 inhibitors is the higher risk of infection[30]. Since SGLT2 inhibitors promote sugar excretion through urine, previous randomized controlled trials (RCTs) involving patients with diabetes mellitus have demonstrated that SGLT2 inhibitors may increase the incidence of skin infections in the vulva and penis regions, particularly fungal infections[31,32]. Some observational studies also indicated that SGLT2 inhibitors may raise the risks of urinary tract infection[33]. On the other hand, advanced CKD patient is a well-known population of frailty, with high risks of protein energy wasting (PEW), immunocompromised, and infection[34,35]. Therefore, the concern of infection may limit the use of SGLT2 inhibitors in patients with advanced CKD, as they are a susceptible population for infections. Additionally, the potential loss of additional sugar and calories after using SGLT2 inhibitors might worsen protein-energy wasting (PEW) among advanced CKD patients, especially in those with inadequate calorie intake, possibly leading to severe infections or even death. Contrary to these speculations, our study demonstrated that the use of SGLT2 inhibitors after reaching CKD stage 5 did not increase the risks of infection and mortality. Particularly, the baseline characteristics, including age, co-morbidities, and history of infection, were very similar between the SGLT2 inhibitors group and the control group even before performing propensity score matching. This suggests that the selection bias between the two groups might be minimal, making our results relatively reliable. We speculate that the lower-than-expected adverse events of SGLT2 inhibitors in advanced CKD patients may be attributed to the reduced daily urine sugar amount coupled with the lower eGFR[36]. As CKD stage 5 patients excrete less sugar and calories in their urine under the influence of SGLT2 inhibitors compared to early CKD patients[37], the subsequent risks of infection or mortality in CKD5 patients may not increase. At last, concerning the risks of CV events, unlike the CV beneficial effects of SGLT2 inhibitors observed in previous studies involving early-stage CKD patients[38,39], this study demonstrates that the use of SGLT2 inhibitors in CKD5 patients neither increases nor decreases the risks of CV events. We have speculated several possible reasons for the neutral effect of SGLT2 inhibitors on CV events in this study. First, as mentioned before, the effect of SGLT2 inhibitors on the excretion of sugar, sodium, and calories diminishes along with eGFR decline and loss of glomerulus function[37].

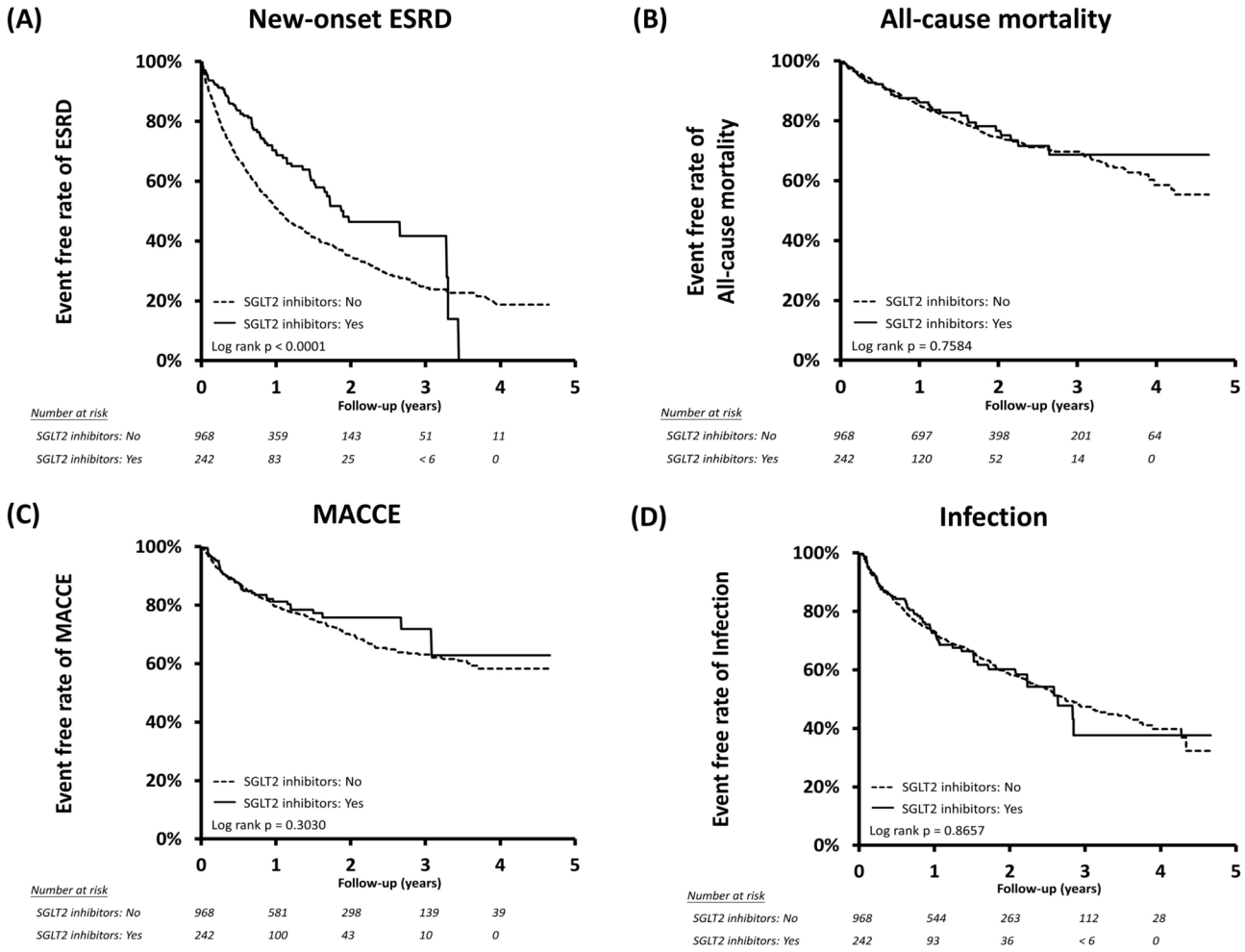

Fig. 2. Event free rate for study outcomes after propensity score matching: (**A**)End-stage renal disease, (**B**) All-cause mortality, (**C**) MACCE, (**D**) Infection. MACCE: major advanced cardiovascular events, any coronary artery bypass graft (CABG), myocardial infarction (MI), percutaneous coronary intervention (PCI), cardiogenic shock, new-diagnosis heart failure, coronary revascularization, malignant arrhythmia, or cerebrovascular events.

Consequently, SGLT2 inhibitors may play a lesser role in weight reduction, sugar control, and hypertension control in CKD5 patients, potentially attenuating their CV benefits. Second, the SGLT2 inhibitors are usually discontinued after initiating dialysis, and the relatively short duration of SGLT2 inhibitor use (mean follow-up of around 1.5 years in this study) may contribute to the observed insignificant CV benefits. Third, it is possible that the CV benefits of SGLT2 inhibitors may exist in certain high CV risk subgroups; however, the small sample size limits our ability to conduct further subgroup analysis. Additional randomized controlled trials or large-scale, high-quality observational studies with sufficient patient numbers could help address this issue.

This year, another study using the NHIRD focused on CKD stage 5 patients was published, demonstrating that the SGLT2 inhibitor group had superior renal outcomes compared to the non-SGLT2i group. The study employed a statistical method known as sequential weekly emulated target trials, treating each week as a new trial. By using this method, CKD5 patients receiving SGLT2 inhibitor treatment were repeatedly enrolled over 10 times, allowing the study to include a significantly larger number of subjects than ours. However, our study exclusively enrolled CKD5 patients who continuously used SGLT2 inhibitors for more than three months to ensure compliance. Additionally, our study evaluated infection-associated outcomes, an important aspect for CKD patients that was not addressed in the prior study.

Some limitations of this study should be acknowledged. First, certain clinical information, such as serum sugar levels, albumin, creatinine, proteinuria, and body mass index, were not available in the NHIRD. This lack of data could potentially influence the assessment of certain outcomes. Second, despite achieving a high degree of similarity in baseline characteristics between the SGLT2 inhibitors group and the control group, an observational study may still entail inherent bias due to its non-randomized nature. Third, the use of SGLT2 inhibitors in advanced CKD patients was still relatively uncommon, resulting in a limited number of enrollees in the SGLT2 inhibitors group. Consequently, the small sample size limited generalizability of this study and made further subgroup analysis infeasible .

Conclusion

In conclusion, our study provides initial evidence suggesting that SGLT2 inhibitors may offer renal protection for patients with stage 5 CKD without increasing cardiovascular risk or infection rates. The positive findings from our study may help alleviate certain concerns about prescribing SGLT2 inhibitors in advanced CKD patients, including the risks of infection or early dialysis. However, it is important to note that one single observational study is insufficient to draw definitive conclusions, and further RCTs are still necessary to establish causality and optimize treatment strategies.

Data availability

All data generated or analysed during the study are included in this published article.

Received: 25 August 2024; Accepted: 2 December 2024
Published online: 18 February 2025

References

1. Cho, N. H. et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res. Clin. Pract.* **138**, 271–281. https://doi.org/10.1016/j.diabres.2018.02.023 (2018).
2. Khan, M. A. B. et al. Epidemiology of type 2 diabetes - global burden of disease and forecasted trends. *J. Epidemiol. Glob. Health* **10**, 107–111. https://doi.org/10.2991/jegh.k.191028.001 (2020).
3. Afkarian, M. et al. Kidney disease and increased mortality risk in type 2 diabetes. *J. Am. Soc. Nephrol.* **24**, 302–308. https://doi.org/10.1681/ASN.2012070718 (2013).
4. Thomas, M. C., Cooper, M. E. & Zimmet, P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. *Nat. Rev. Nephrol.* **12**, 73–81. https://doi.org/10.1038/nrneph.2015.173 (2016).
5. Perkovic, V. et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N. Engl. J. Med.* **380**, 2295–2306. https://doi.org/10.1056/NEJMoa1811744 (2019).
6. Zinman, B. et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N. Engl. J. Med.* **373**, 2117–2128. https://doi.org/10.1056/NEJMoa1504720 (2015).
7. Heerspink, H. J. L. et al. Dapagliflozin in patients with chronic kidney disease. *N. Engl. J. Med.* **383**, 1436–1446. https://doi.org/10.1056/NEJMoa2024816 (2020).
8. Wanner, C. et al. Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. *Circulation* **137**, 119–129. https://doi.org/10.1161/CIRCULATIONAHA.117.028268 (2018).
9. Vallon, V. et al. SGLT2 mediates glucose reabsorption in the early proximal tubule. *J. Am. Soc. Nephrol.* **22**, 104–112. https://doi.org/10.1681/ASN.2010030246 (2011).
10. Thomas, M. C. & Cherney, D. Z. I. The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure. *Diabetologia* **61**, 2098–2107. https://doi.org/10.1007/s00125-018-4669-0 (2018).
11. Ni, L., Yuan, C., Chen, G., Zhang, C. & Wu, X. SGLT2i: beyond the glucose-lowering effect. *Cardiovasc. Diabetol.* **19**, 98. https://doi.org/10.1186/s12933-020-01071-y (2020).
12. Blonde, L. et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. *Endocr. Pract.* **28**, 923–1049. https://doi.org/10.1016/j.eprac.2022.08.002 (2022).
13. Wheeler, D. C. et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol.* **9**, 22–31. https://doi.org/10.1016/S2213-8587(20)30369-7 (2021).
14. Delanaye, P. & Scheen, A. J. EMPA-KIDNEY: empagliflozin in chronic kidney disease. *Rev. Med. Liege.* **78**, 24–28 (2023).
15. House, A. A. Management of heart failure in advancing CKD: Core curriculum 2018. *Am. J. Kidney. Dis.* **72**, 284–295. https://doi.org/10.1053/j.ajkd.2017.12.006 (2018).
16. Chen, J. J., Lee, T. H. & Yang, H. Y. Exploring nontraditional cardiorenal advantages of SGLT-2 inhibitors and GLP-1 receptor agonists. *Kidney Int.* **105**, 442–444. https://doi.org/10.1016/j.kint.2024.01.002 (2024).
17. Oliveira, E. A., Zheng, R., Carter, C. E. & Mak, R. H. Cachexia/Protein energy wasting syndrome in CKD: Causation and treatment. *Semin. Dial.* **32**, 493–499. https://doi.org/10.1111/sdi.12832 (2019).
18. Diaz-Ricart, M. et al. Endothelial damage, inflammation and immunity in chronic kidney disease. *Toxins (Basel)* **12**, 361. https://doi.org/10.3390/toxins12060361 (2020).
19. Lin, L. Y., Warren-Gash, C., Smeeth, L. & Chen, P. C. Data resource profile: the National Health Insurance Research Database (NHIRD). *Epidemiol. Health* **40**, e2018062. https://doi.org/10.4178/epih.e2018062 (2018).
20. Hsieh, C. Y. et al. Taiwan's National Health Insurance Research Database: past and future. *Clin. Epidemiol.* **11**, 349–358. https://doi.org/10.2147/CLEP.S196293 (2019).
21. Hsieh, M. S. et al. Contrast medium exposure during computed tomography and risk of development of end-stage renal disease in patients with chronic kidney disease: A nationwide population-based, propensity score-matched, longitudinal follow-up study. *Med. (Baltim.)* **95**, e3388. https://doi.org/10.1097/MD.0000000000003388 (2016).
22. Lin, C. C. et al. Angiotensin receptor blockers are associated with lower mortality than ACE inhibitors in predialytic stage 5 chronic kidney disease: A nationwide study of therapy with renin-angiotensin system blockade. *PLoS One* **12**, e0189126. https://doi.org/10.1371/journal.pone.0189126 (2017).
23. Hsieh, C. Y., Chen, C. H., Li, C. Y. & Lai, M. L. Validating the diagnosis of acute ischemic stroke in a National Health Insurance claims database. *J. Formos. Med. Assoc.* **114**, 254–259. https://doi.org/10.1016/j.jfma.2013.09.009 (2015).
24. Cheng, C. L., Chien, H. C., Lee, C. H., Lin, S. J. & Yang, Y. H. Validity of in-hospital mortality data among patients with acute myocardial infarction or stroke in National Health Insurance Research Database in Taiwan. *Int. J. Cardiol.* **201**, 96–101. https://doi.org/10.1016/j.ijcard.2015.07.075 (2015).
25. Cheng, C. L. et al. Validation of acute myocardial infarction cases in the national health insurance research database in taiwan. *J. Epidemiol.* **24**, 500–507. https://doi.org/10.2188/jea.je20140076 (2014).
26. Austin, P. C. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm. Stat.* **10**, 150–161. https://doi.org/10.1002/pst.433 (2011).
27. Zhang, X., Zhang, M. J. & Fine, J. A proportional hazards regression model for the subdistribution with right-censored and left-truncated competing risks data. *Stat. Med.* **30**, 1933–1951. https://doi.org/10.1002/sim.4264 (2011).
28. Austin, P. C. Comparing paired vs non-paired statistical methods of analyses when making inferences about absolute risk reductions in propensity-score matched samples. *Stat. Med.* **30**, 1292–1301. https://doi.org/10.1002/sim.4200 (2011).
29. Rabizadeh, S., Nakhjavani, M. & Esteghamati, A. Cardiovascular and renal benefits of SGLT2 Inhibitors: A narrative review. *Int. J. Endocrinol. Metab.* **17**, e84353. https://doi.org/10.5812/ijem.84353 (2019).

30. Gadzhanova, S., Pratt, N. & Roughead, E. Use of SGLT2 inhibitors for diabetes and risk of infection: Analysis using general practice records from the NPS MedicineWise MedicineInsight program. *Diabetes Res. Clin. Pract.* **130**, 180–185. https://doi.org/10.1016/j.diabres.2017.06.018 (2017).
31. Thong, K. Y. et al. Clinical risk factors predicting genital fungal infections with sodium-glucose cotransporter 2 inhibitor treatment: The ABCD nationwide dapagliflozin audit. *Prim. Care Diabetes* **12**, 45–50. https://doi.org/10.1016/j.pcd.2017.06.004 (2018).
32. Nyirjesy, P. et al. Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. *Curr. Med. Res. Opin.* **30**, 1109–1119. https://doi.org/10.1185/03007995.2014.890925 (2014).
33. Uitrakul, S., Aksonnam, K., Srivichai, P., Wicheannarat, S. & Incomenoy, S. The incidence and risk factors of urinary tract infection in patients with type 2 diabetes mellitus using SGLT2 inhibitors: a real-world observational study. *Med. (Basel)* **9**, 59. https://doi.org/10.3390/medicines9120059 (2022).
34. Lorenz, E. C. et al. Frailty in CKD and transplantation. *Kidney Int. Rep.* **6**, 2270–2280. https://doi.org/10.1016/j.ekir.2021.05.025 (2021).
35. Walker, S. R. et al. Association of frailty and physical function in patients with non-dialysis CKD: a systematic review. *BMC Nephrol.* **14**, 228. https://doi.org/10.1186/1471-2369-14-228 (2013).
36. Yau, K., Dharia, A., Alrowiyti, I. & Cherney, D. Z. I. Prescribing SGLT2 inhibitors in patients with CKD: Expanding indications and practical considerations. *Kidney Int. Rep.* **7**, 1463–1476. https://doi.org/10.1016/j.ekir.2022.04.094 (2022).
37. Cherney, D. Z. I. 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.* **93**, 231–244. https://doi.org/10.1016/j.kint.2017.06.017 (2018).
38. Solomon, S. D. et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N. Engl. J. Med.* **387**, 1089–1098. https://doi.org/10.1056/NEJMoa2206286 (2022).
39. Packer, M. et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N. Engl. J. Med.* **383**, 1413–1424. https://doi.org/10.1056/NEJMoa2022190 (2020).

Acknowledgements

The authors thank the statistical assistance and wish to acknowledge the support of the Maintenance Project of the Center for Big Data Analytics and Statistics (Grant CLRPG3N0011) at Chang Gung Memorial Hospital for study design and monitor, data analysis and interpretation. The authors thank Mr. Yu-Tung Huang, and Miss Hui-Tzu Tu, for their assistance in the statistical analysis.

Author contributions

B.H and C.L.Y wrote the main manuscript text. C.L.Y and H.Y.Y proposed the idea of this research. C.Y.W, H.Y.Y, and I.C.H edited the main manuscript. C.Y.T, J.J.C, and C.C.H performed the data curation and analysis. Y.C.C and I.C.H supervised this research. All authors reviewed the manuscript.

Funding

This work was supported by grants from Chang Gung Memorial Hospital, Taiwan, (CORPG3J0301, CMRPG3I0371-2, CORPG3L0451).

Declarations

Competing interests

All authors disclosure there is no financial conflict of interest.

Additional information

Correspondence and requests for materials should be addressed to H.-Y.Y.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.