



ORIGINAL ARTICLE

A real-world study on SGLT2 inhibitors and diabetic kidney disease progression

Allen Yan Lun Liu ¹, Serena Low², Ester Yeoh³, Eng Kuang Lim¹, Claude Jeffrey Renaud¹, Selene Tse Yen Teoh¹, Grace Feng Ling Tan¹, Chung Cheen Chai¹, Bo Liu¹, Tavintharan Subramaniam³, Chee Fang Sum³ and Su Chi Lim ^{2,3,4}

¹Department of General Medicine, Khoo Teck Puat Hospital, Singapore, ²Clinical Research Unit, Khoo Teck Puat Hospital, Singapore, ³Diabetes Centre, Admiralty Medical Centre, Kampung Admiralty, Singapore and ⁴Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Correspondence to: Allen Yan Lun Liu; E-mail: liu.allen.yl@ktph.com.sg

ABSTRACT

Background. Randomized controlled trials have demonstrated the benefits of sodium–glucose cotransporter 2 inhibitors (SGLT2is) in people with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). However, real-world data on CKD progression and the development of end-stage kidney disease (ESKD) remains scarce. Our aim was to study renal outcomes of people with diabetic kidney disease (DKD) using SGLT2is in a highly prevalent DKD population.

Methods. Between 2016 and 2019 we recruited T2DM patients in the renal and diabetic clinics in a regional hospital in Singapore. Patients prescribed SGLT2is were compared with those on standard anti-diabetic and renoprotective treatment. The outcome measures were CKD progression [$a \geq 25\%$ decrease from baseline and worsening of estimated glomerular filtration rate (eGFR) categories according to the Kidney Disease: Improving Global Outcomes guidelines] and ESKD (eGFR < 15 mL/min/1.73 m²).

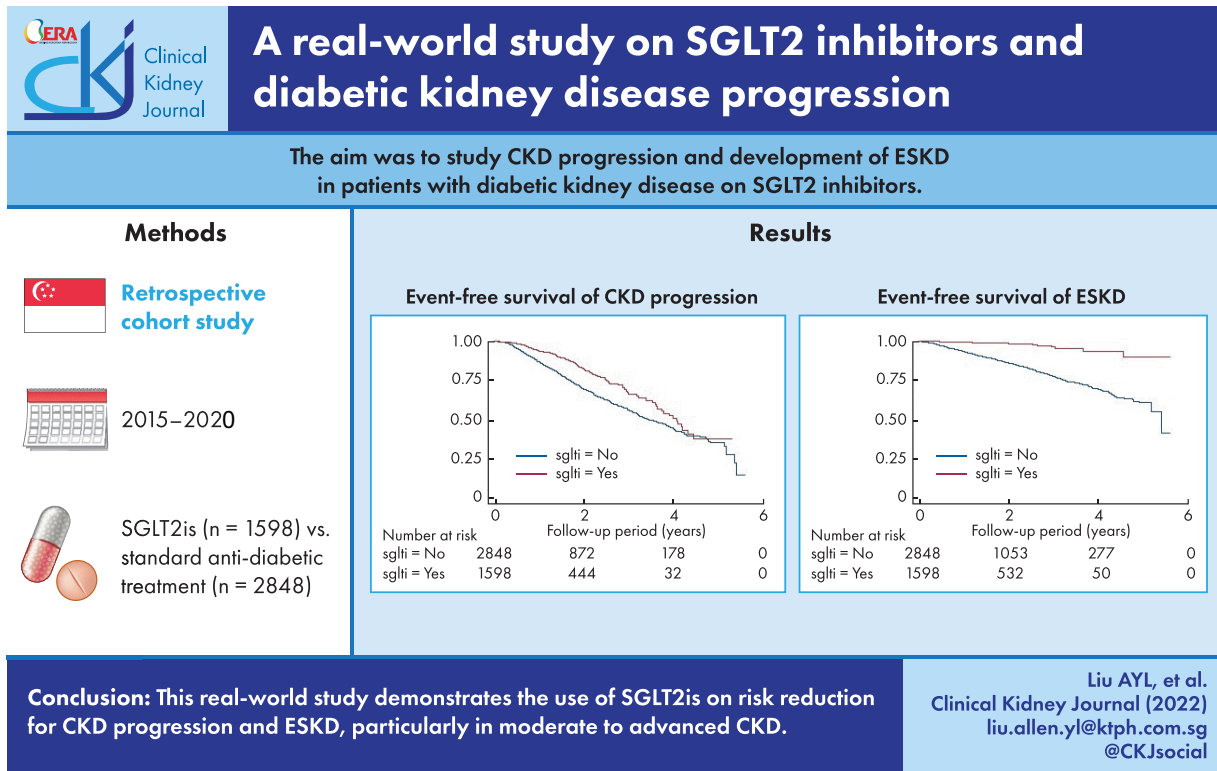
Results. We analysed a total of 4446 subjects; 1598 were on SGLT2is. There was a significant reduction in CKD progression [hazard ratio [HR] 0.60 [95% confidence interval (CI) 0.49–0.74]] with SGLT2is. The HR for eGFR ≥ 45 mL/min/1.73 m² and 15–44 mL/min/1.73 m² was 0.60 (95% CI 0.47–0.76) and 0.43 (95% CI 0.23–0.66), respectively. There was also a reduction in risk for developing ESKD for the entire cohort [HR 0.33 (95% CI 0.17–0.65)] and eGFR 15–44 mL/min/1.73 m² [HR 0.24 (95% CI 0.09–0.66)]. Compared with canagliflozin and dapagliflozin, empagliflozin showed a sustained risk reduction of renal outcomes across CKD stages 1–4.

Conclusions. This real-world study demonstrates the benefits of SGLT2is on CKD progression and ESKD. The effect is more pronounced in moderate to advanced CKD patients.

Received: 7.9.2021; Editorial decision: 24.1.2022

© The Author(s) 2022. Published by Oxford University Press on behalf of the ERA. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

GRAPHICAL ABSTRACT



Keywords: CKD progression, diabetic kidney disease, diabetes mellitus, ESKD, real-world study, SGLT2is

INTRODUCTION

There is an increasing prevalence of diabetic kidney disease (DKD) worldwide. DKD vastly accelerates the prevalence of end-stage kidney disease (ESKD) [1]. According to a local study from Singapore, 53% of people with type 2 diabetes mellitus (T2DM) have concomitant chronic kidney disease (CKD) and 66% of incident ESKD patients have pre-existing DKD [2]. Despite optimal diabetic and blood pressure control with the administration of renin-angiotensin system (RAS) blockers, the heightened risks of kidney disease progression, cardiovascular morbidity and mortality persist. The publication of the clinical benefit of using the sodium-glucose cotransporter 2 inhibitor (SGLT2i), empagliflozin to improve renal and cardiovascular outcomes in DKD provided a supplemental approach and possibly an additive benefit to RAS blockade [3]. The haemodynamic and natriuresis-related pharmacodynamic response to SGLT2is reduces intra glomerular pressure, exerting antihypertensive and anti-albuminuric properties [4]. With their renal function-dependent glycosuric and anti-hyperglycaemic effect, SGLT2is have been consistently demonstrated to have renoprotective effects in major cardiovascular outcome trials [5–8]. The current recommendations from most of these large randomized controlled trials (RCTs) conferred the benefits of SGLT2 inhibition to DKD with an estimated glomerular filtration (eGFR) ≥ 45 mL/min/1.73 m² [3, 6, 7, 9, 10]. However, its haemodynamic, anti-proteinuric and anti-metabolic effects may still be carried on despite reducing eGFR [11]. Given the pleiotropic effects (anti-inflammatory, anti-oxidative and anti-fibrotic) on the heart

[12] and liver [13], in addition to the kidneys [14, 15], the benefits of SGLT2is may extend to more advanced CKD. For example, in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, patients with an eGFR decrease to < 30 mL/min/1.73 m² were allowed to continue canagliflozin until dialysis or transplantation [16]. Therefore the benefit was generally believed to persist even to stage 4 CKD [17]. Renal outcome trials such as the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) [18] and the Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) [19] included patients with an eGFR of 25 and 20 mL/min/1.73 m², respectively, providing further insights that the renoprotective effects of SGLT2is can be extended to patients with advanced CKD.

Nevertheless, the intriguing results from RCTs in which participants are recruited with specific inclusion criteria and monitored with a predefined protocol may not be generalizable in real-world clinical settings [20]. Moreover, most RCTs do not include participants from the Southeast Asian region, where the incidence and prevalence of ESKD due to DKD are among the highest in the world [21]. Currently, there remains a deficiency in knowledge on whether the initiation of SGLT2 inhibition in patients with moderate to advanced CKD in real-world clinical practice could protect DKD patients from CKD progression. Barriers that prohibit the prescription of SGLT2is include perceived ineffective glucose-lowering action with diminished eGFR and concern over a decrease in eGFR in the initial phase of treatment. With a solid impetus for controlling DKD progression despite the lack of standard guidelines

on managing moderate to advanced CKD, clinicians worldwide have been actively pursuing an extension of current prescription criteria by treating DKD patients with SGLT2is with advanced CKD status (eGFR 15–44 mL/min/1.73 m²). Since early 2017 we have been prescribing SGLT2is for DKD patients with an eGFR >20 mL/min/1.73 m² for reno protection and glycaemic control. This study aims to evaluate the renal outcomes of DKD patients with or without SGLT2is in a multi-ethnic Asian population. We hypothesized that SGLT2i use would improve renal outcomes despite initiation of treatment at advanced CKD status.

MATERIALS AND METHODS

This was a retrospective cohort study. The observational period was between January 2015 and December 2020. We recruited patients with T2DM [identified by the International Classification of Diseases, Tenth Revision or haemoglobin A1c (HbA1c) ≥6.5%], age ≥21 years with active follow-up in the Khoo Teck Puat Hospital (KTPH; a 600-bed acute care hospital with secondary- and tertiary-level care) specialist renal clinic and Admiralty Medical Centre (AdMC) Diabetes Mellitus centre and DKD clinic. Patients with known ESKD status were excluded. Referral sources for the KTPH renal clinic were primary care clinicians in both private and public sectors in the northern territory of Singapore. Criteria for referral of DKD patients to the renal clinic were changes in eGFR >10 mL/min/1.73 m², measurements of urine albumin:creatinine ratio (uACR) >100 mg/mmol on two separate occasions and stage 3–4 CKD [i.e. eGFR 15–59 mL/min/1.73 m² according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guidelines for the evaluation of CKD] [22]. The inclusion criteria for referral to the DKD clinic were diabetes mellitus (DM) with persistent macro-albuminuria (uACR >50 mg/mmol) with preserved eGFR (≥60 mL/min) or stage 3–4 CKD. Exclusion criteria for referral to the DKD clinic were comorbidities that preclude renal retardation, such as terminal malignancies; severely limited life expectancy due to advanced organ failure; inability to intensify risk factor control due to psychosocial issues or resource constraints, cognitive impairment or psychiatric illness and stage 5 CKD, where the patient is already on renal replacement therapy (RRT) [23]. Patients followed up in the AdMC DM clinic were DM patients that require standard care for complications related to DM, with or without CKD. The treatment group in our study was T2DM patients who were prescribed one of the following SGLT2is for at least 3 months: canagliflozin (Invokana, Johnson and Johnson Pte, Singapore), empagliflozin (Jardiance, Boehringer Ingelheim Pte, Singapore) and dapagliflozin (Forxiga, AstraZeneca Pte, Singapore). Principal physicians decided on the choice and dosage of SGLT2is based on clinical indications and contraindications. In general, patients with eGFR <45 mL/min/1.73 m² are given a lower dose of SGLT2is (~25–50% less than the recommended dose). The date of treatment initiation was defined by the first filing or an SGLT2i prescription in iPharm (the KTPH outpatient pharmacy system). For patients not taking SGLT2is during the study period, the date of treatment initiation was defined by the first filing of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) prescription or the date of referral, whichever was available. The outcomes of this study were ≥25% decrease from baseline and worsening of eGFR categories according to the KDIGO guidelines [24] and ESKD (sustained eGFR <15 mL/min/1.73 m² for 4 weeks).

De-identified data on demographics and medications were obtained from electronic medical records (Sunrise Enterprise and iPharm with assistance from Integrated Health Information Systems). Spot urine for ACR and blood samples for serum creatinine and HbA1c were collected and measured at the hospital laboratory accredited by the College of American Pathologists. Serum creatinine was quantitated using an enzymatic colourimeter test (Cobas c501; Roche Diagnostics, Mannheim, Germany). HbA1c was determined using a Tina-quant Haemoglobin A1c Gen.3 (Roche Diagnostics). Urinary albumin was determined using an immunoturbidimetric assay (Roche Diagnostics). The Chronic Kidney Disease Epidemiology Collaboration equation was used to estimate eGFR [25].

For analytic purposes, the following additional exclusion criteria were applied to both groups: fewer than two eGFR readings and <3 months follow-up.

Previous studies revealed a composite outcome of a sustained 40% reduction in the decline of the eGFR, the need for RRT or death from renal causes [7]. The incidence over a 2-year follow-up period for renal-related composite outcomes was 1.89% versus 4.14%. To achieve a power of 80% and an α of 0.05, we needed 611 patients on SGLT2is (case) and 1833 patients in all stages of CKD without SGLT2is (control). Overall, we recruited 1598 DKD patients for whom SGLT2is were initiated and 2848 patients as controls (Figure 1).

Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board (DSRB) and the study was conducted according to the Declaration of Helsinki. The DSRB waived written informed consent.

Statistical analysis

Categorical variables were expressed as frequency (percentages) and continuous variables as mean ± standard deviation (SD) or median [interquartile range (IQR)]. Comparison of the baseline characteristics using SGLT2is was performed using the chi-squared test for categorical variables and the Student's t-test or Wilcoxon rank sum test for continuous variables, where appropriate. The Kaplan–Meier method was used to assess the time to event. Multivariate Cox proportional hazards models were constructed to establish the associations with CKD progression and ESKD, adjusting for age, gender and ethnicity in model 1 and age, gender, ethnicity, HbA1c, baseline eGFR, natural log-transformed ACR and use of RAS antagonists in model 2. Covariates with $P < .1$ during univariate analyses or those with established risk factors for CKD progression and ESKD were selected for adjustment to multivariate Cox proportional hazards models [26]. Statistical analysis was performed using Stata version 14.0 (StataCorp, College Station, TX, USA). All statistical tests were two-sided. The results were considered statistically significant for $P < .05$.

Sensitivity analysis

We reran the statistical models using the same outcome measures by defining CKD as a uACR ≥3 mg/mmol or eGFR <60 mL/min/1.73 m². We also incorporated the analysis by categorizing albuminuria according to the KDIGO guidelines (uACR <3 mg/mmol, 3–30 mg/mmol and >30 mg/mmol). Further, we analysed the effects of SGLT2is on patients with or without RAS blockers.

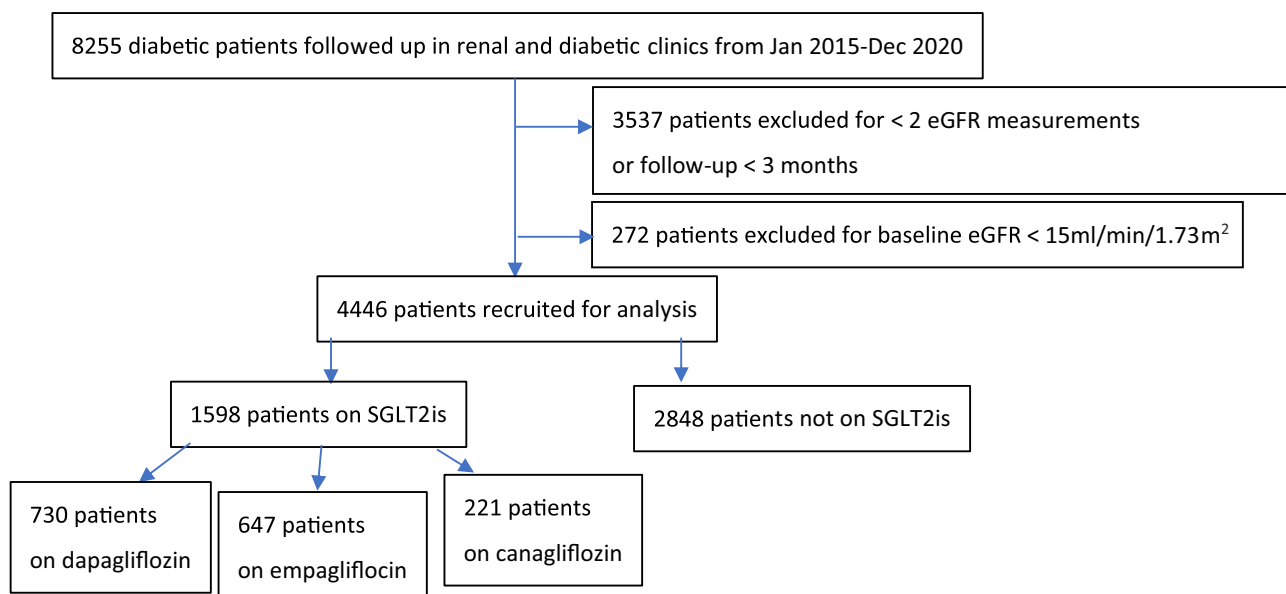


FIGURE 1: Patient selection.

Table 1. Baseline characteristics of patients with and without SGLT2is

Characteristics	Total	SGLT2is	No SGLT2is	P-value
Patients, n (%)	4446 (100)	1598 (35.9)	2848 (64.1)	
Age (years), mean \pm SD	60.6 \pm 13.5	56.0 \pm 12.0	63.1 \pm 13.5	<.0001
Gender (male), n (%)	2328 (52.4)	884 (55.3)	1445 (50.7)	.056
Race, n (%)				<.0001
Chinese	2565 (57.7)	884 (55.3)	1681 (59.0)	
Malay	865 (19.5)	341 (21.3)	523 (18.4)	
Indian	638 (14.4)	259 (16.2)	379 (13.3)	
Other	378 (8.5)	113 (7.1)	265 (9.3)	
ACEi, n (%)	1066 (24)	516 (32.3)	1082 (38.0)	<.0001
ARB, n (%)	1788 (40.2)	814 (50.9)	784 (27.5)	<.0001
Diuretics, n (%)	1143 (25.7)	235 (14.7)	908 (31.9)	<.0001
eGFR at baseline (mL/min/1.73 m ²), mean \pm SD	69.9 \pm 31.7	83.9 \pm 26.4	62.0 \pm 31.8	<.0001
uACR at baseline (mg/mmol), median (IQR)	6.8 (1.5–43.5)	7.2 (1.4–51.5)	5.9 (1.5–37.2)	.281
HbA1c at baseline (%), mean \pm SD	8.3 \pm 1.7	8.8 \pm 1.5	8.1 \pm 1.7	<.0001
CKD stages, n (%)				<.0001
eGFR \geq 45 mL/min/1.73 m ²	3220 (724)	1458 (91.2)	1762 (61.9)	
eGFR 15–44 mL/min/1.73 m ²	1226 (27.6)	140 (8.8)	1086 (38.1)	

ACEi, angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

RESULTS

The duration of follow-up was up to 5.8 years [median 1.4 (IQR 0.8–2.1)]. There were 1461 (32.9%), 1175 (26.4%), 584 (13.1%), 642 (14.4%) and 584 (13.1%) patients with a baseline eGFR >90 , 60–90, 45–<60, 30–<45 and <30 mL/min/1.73 m², respectively, in our cohort. Among patients who received SGLT2is, 764 (47.8%), 479 (30%), 215 (13.4%), 120 (7.5%) and 20 (1.3%) initiated treatment at a baseline eGFR >90 , 60–90, 45–<60, 30–<45 and <30 mL/min/1.73 m², respectively. Baseline char-

acteristics of individuals with and without SGLT2is are shown in Table 1. Supplementary data, Tables S1 and S2 further present the baseline characteristics with an eGFR \geq 45 mL/min/1.73 m² and 15–44 mL/min/1.73 m², respectively. Both groups had comparable uACRs, while patients with SGLT2is tended to be younger, more likely to receive RAS blockers and diuretics and have higher baseline eGFR and HbA1c.

Dapagliflozin, empagliflozin and canagliflozin were prescribed in 730, 647 and 221 patients, respectively (Figure 1). The

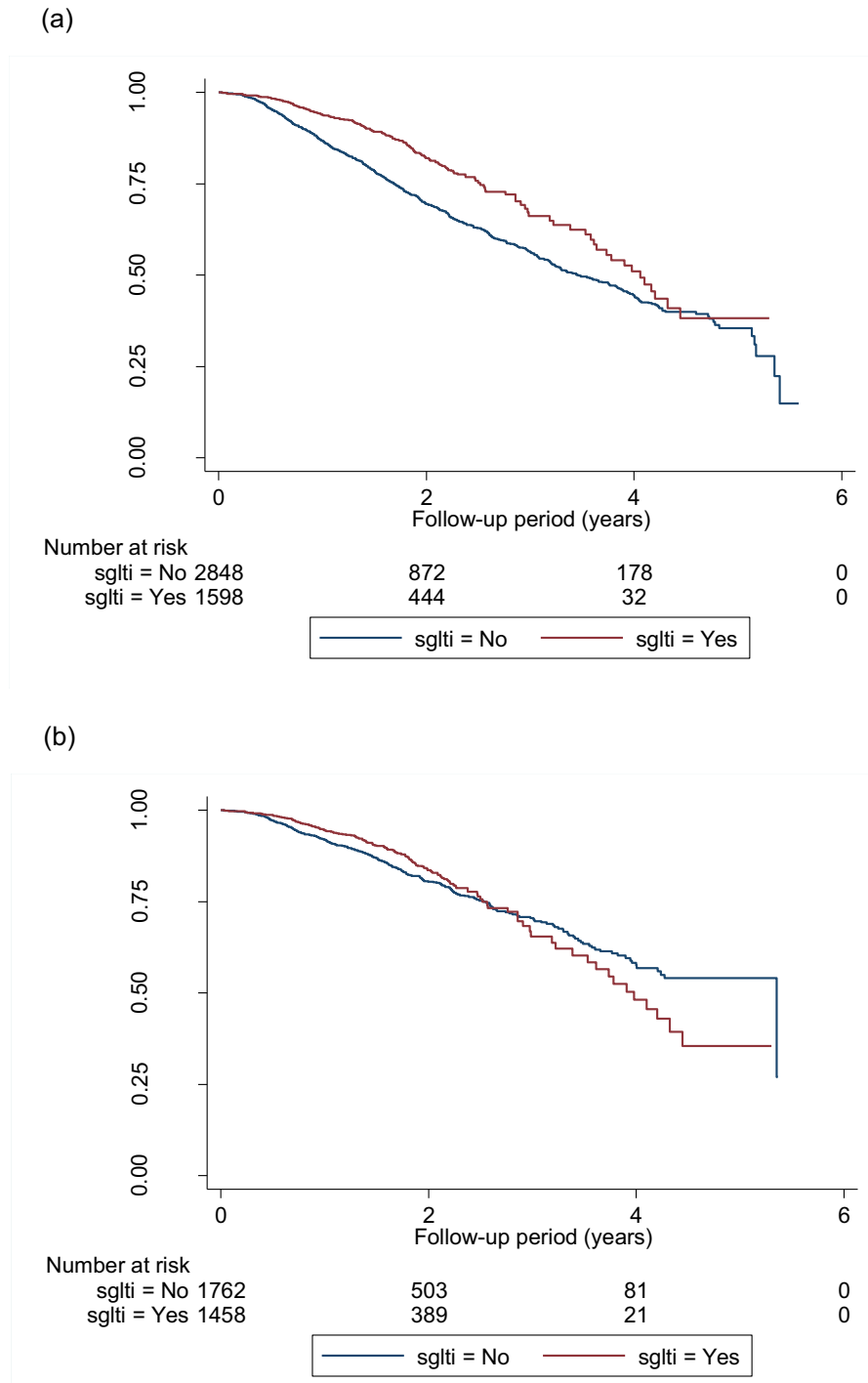


FIGURE 2: Kaplan-Meier survival curves for the event-free survival of CKD progression (defined by $\alpha \geq 25\%$ decrease in eGFR from baseline and worsening of eGFR categories according to KDIGO guidelines) in (a) the whole cohort, (b) patients with eGFR ≥ 45 mL/min/1.73 m² and (c) patients with eGFR 15–44 mL/min/1.73 m². (a) Log-rank test statistics = 58.64, $P < .001$; (b) log-rank test statistics = 1.59, $P = .207$; (c) log-rank test statistics = 12.59, $P < .001$.

average daily dose was 6.1 mg for dapagliflozin (10 mg recommended dose), 17.8 mg for empagliflozin (25 mg recommended dose) and 225 mg for canagliflozin (300 mg recommended dose). More patients with an eGFR of 15–44 mL/min/1.73 m² were prescribed empagliflozin (15%) than dapagliflozin (2.8%) and canagliflozin (10%) (see Supplementary data, Table S3 for baseline characteristics by different SGLT2is).

Effect on SGLT2is on CKD progression

A total of 1058 (23.8%) patients had CKD progression and worsening of eGFR categories according to KDIGO guidelines. Figure 2a–c shows the Kaplan-Meier survival curves for CKD progression for all eGFR categories, eGFR ≥ 45 mL/min/1.73 m² and eGFR 15–44 mL/min/1.73 m² in both groups. Figure 3 shows the funnel

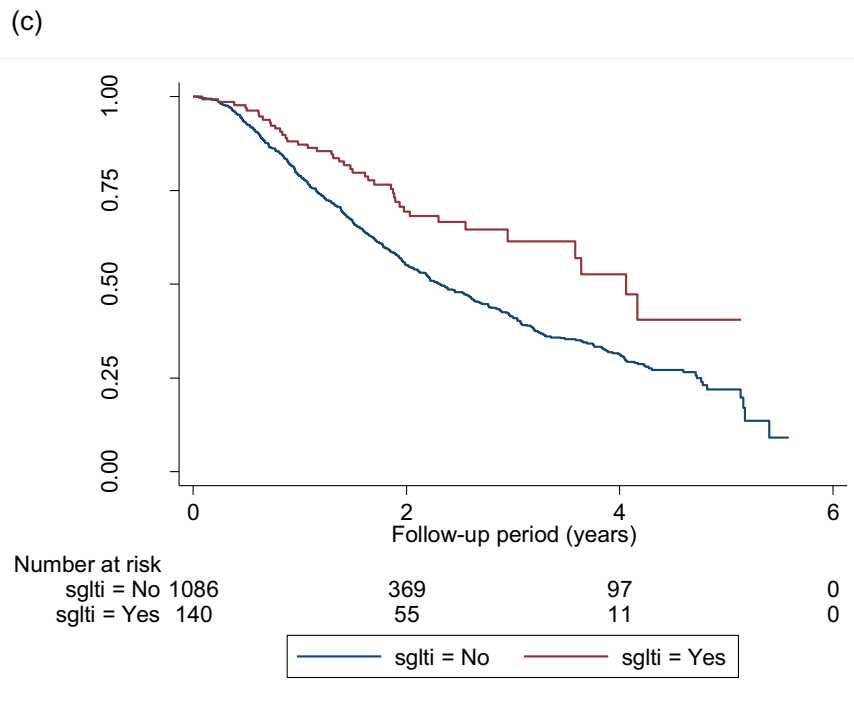


FIGURE 2: Continued.

plot for the hazard ratio (HR) of different models after the adjustment of variables. In model 2 (the fully adjusted model), Cox regression revealed a significant reduction in CKD progression [HR 0.60 [95% confidence interval (CI) 0.49–0.74]; $P < .001$] in the SGLT2i group. The HR for an eGFR ≥ 45 mL/min/1.73 m² and eGFR 15–44 mL/min/1.73 m² was 0.60 (95% CI 0.47–0.76; $P < .001$) and 0.43 (95% CI 0.23–0.66; $P < .001$), respectively.

Our sensitivity analyses revealed a significant reduction in CKD regression with worsening albuminuria (uACR >3 mg/mmol) was incorporated into the CKD definition (Supplementary data, Table S4 for baseline characteristics). The HR for patients with and without CKD was 0.58 (95% CI 0.46–0.72; $P < .001$) and 0.60 (95% CI 0.38–0.96; $P = .033$), respectively (Supplementary data, Figures S1 and S9). The reduction in CKD progression was also shown in our cohort by categorizing albuminuria according to the KDIGO guidelines (Supplementary data, Table S5 for baseline characteristics). The HR for a uACR <3 mg/mmol, 3–30 mg/mmol and >30 mg/mmol was 0.56 (95% CI 0.39–0.81; $P = .002$), 0.62 (95% CI 0.46–0.84; $P = .002$) and 0.55 (95% CI 0.36–0.85; $P = .008$), respectively (Supplementary data, Figures S2 and S10). We further analysed the use of RAS blockers together with SGLT2is and the effects on CKD progression (Supplementary data, Table S6 for baseline characteristics). The HR for patients with and without the use of RAS blockers was 0.59 (95% CI 0.47–0.74; $P < .001$) and 0.59 (95% CI 0.37–0.93; $P = .024$), respectively (Supplementary data, Figures S3 and S11). Supplementary data, Figure S4a–c shows the event-free survival curve for CKD progression for all CKD stages, eGFR ≥ 45 mL/min/1.73 m² and eGFR 15–44 mL/min/1.73 m² for patients on different SGLT2is, respectively. In the fully adjusted model, all three SGLT2is significantly reduced the risk of CKD progression across all eGFR categories [dapagliflozin: HR 0.56 (95% CI 0.42–0.75), $P < .001$; empagliflozin: HR 0.70 (95% CI 0.55–0.89), $P = .003$; canagliflozin: HR 0.44 (95%

CI 0.28–0.68), $P < .001$] (Supplementary data, Figure S12) and in eGFR ≥ 45 mL/min/1.73 m² [dapagliflozin: HR 0.57 (95% CI 0.42–0.78), $P < .001$; empagliflozin: HR 0.69 (95% CI 0.51–0.91), $P = .011$; canagliflozin: HR 0.43 (95% CI 0.25–0.73), $P = .002$]. Only empagliflozin and canagliflozin showed a reduction in risk of CKD progression for patients with eGFR 15–44 mL/min/1.73 m² [empagliflozin: HR 0.49 (95% CI 0.29–0.81), $P = .006$; canagliflozin: HR 0.34 (95% CI 0.15–0.75), $P = .008$] in this subgroup analysis.

Effect on SGLT2is on development of ESKD

A total of 440 (9.9%) patients reached ESKD (sustained eGFR <15 mL/min/1.73 m²) during the study period, 20 (4.6%) of which received SGLT2i treatment. Figure 4a–c shows the Kaplan-Meier survival curves of ESKD. Figure 5 shows the funnel plot of the HR of different models after adjusting variables. In the fully adjusted model, the use of SGLT2i was associated with a lower hazard of ESKD in the entire cohort [HR 0.33 (95% CI 0.17–0.65), $P = .001$], with eGFR ≥ 45 mL/min/1.73 m² [HR 0.50 (95% CI 0.17–1.42), $P = .193$] and with eGFR 15–44 mL/min/1.73 m² [HR 0.24 (95% CI 0.09–0.66), $P = .006$].

Supplementary data, Figure S5 shows the Kaplan-Meier curves for event-free survival of ESKD and CKD status. In the fully adjusted model (Supplementary data, Figure S9) there was a significant reduction in the risk of ESKD in patients with CKD [HR 0.32 (95% CI 0.16–0.65), $P = .002$] but not in patients without [HR 2.59 (95% CI 0.11–63.36), $P = .56$]. When stratified by uACR status, patients receiving SGLT2is with a uACR 3–30 mg/mmol were associated with a significant reduction in the risk of ESKD [HR 0.27 (95% CI 0.10–0.77), $P = .014$] (Supplementary data, Figures S6 and S10). In the model adjusted for age, gender and ethnicity, the HR was 0.36 (95% CI 0.18–0.71, $P = .003$) and 0.10 (95% CI

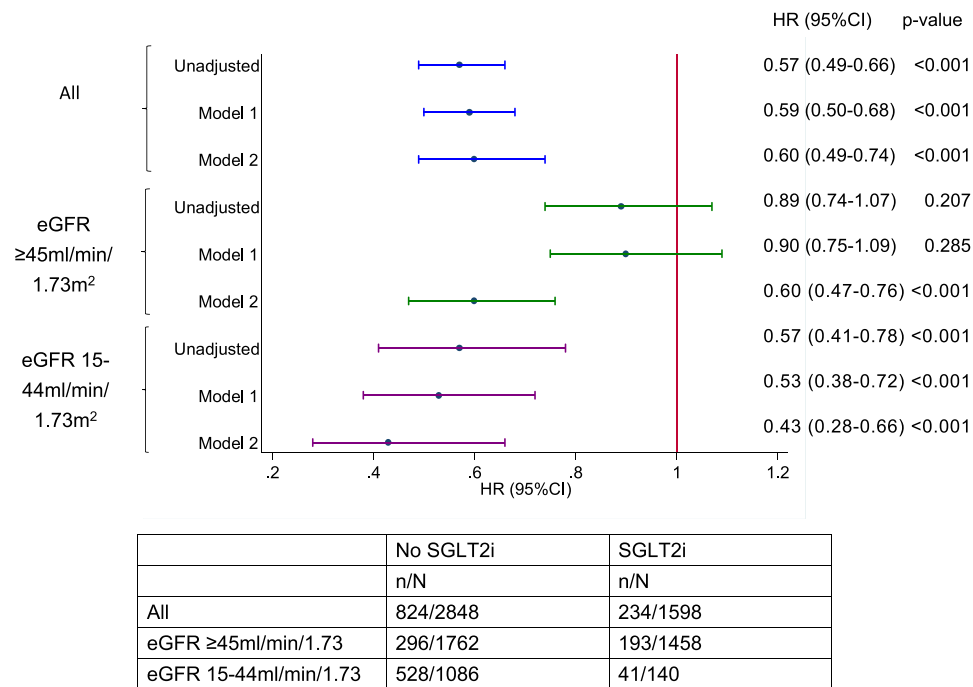


FIGURE 3: Funnel plot of the HR for CKD progression based on eGFR categories with different adjustment models. Model 1 adjusted for age, gender and ethnicity. Model 2 adjusted for age, gender, ethnicity, HbA1c, baseline eGFR, natural log-transformed uACR and use of RAS antagonists.

0.02–0.39, $P = .001$) for RAS blocker users and non-users, respectively (Supplementary data, Figures S7 and S11).

In the fully adjusted model, only empagliflozin was shown to reduce the risk of ESKD in all eGFR categories [HR 0.12 (95% CI 0.03–0.49), $P = .003$] (see Supplementary data, Figure S12) and eGFR 15–44 mL/min/1.73 m² [HR 0.10 (95% CI 0.02–0.71), $P = .021$]. Supplementary data, Figure S8a–c shows the Kaplan–Meier curve for event-free survival of ESKD for all eGFR categories, eGFR ≥ 45 mL/min/1.73 m² and eGFR 15–44 mL/min/1.73 m² for patients on different SGLT2is.

DISCUSSION

Summary of findings

This study demonstrated sustained benefits to DKD patients on composite renal outcomes in patients receiving SGLT2is. Patients with advanced CKD (eGFR 15–44 mL/min/1.73 m²) with SGLT2is significantly reduced the risk of CKD progression and the development of ESKD. Moreover, SGLT2is attenuated the decline of eGFR over time for patients with an eGFR of 15–44 mL/min/1.73 m². Compared with moderate to advanced CKD, the effects of SGLT2is in early CKD (eGFR ≥ 45 mL/min/1.73 m²) were less pronounced. Although all three SGLT2is reduced the risk of CKD progression, empagliflozin was more likely to exert sustained renoprotection from early to advanced CKD. Empagliflozin was also shown to minimize the risk of developing ESKD in our cohort, while there was inadequate power to conclude if other SGLT2is exerted similar effects. Note that the number of patients on empagliflozin among those with low eGFR in our cohort was >4-fold higher than the other two SGLT2is.

Our results from real-world practice revealed comparable risk reduction on CKD progression in RCTs with renal compos-

ite outcomes as primary [3, 16, 18] and secondary endpoints [9, 27, 28]. On the other hand, we found that empagliflozin had a lower risk of developing ESKD, contrary to the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG). Post hoc analysis did not show a significant risk reduction of ESKD as the renal composite outcome [HR 0.60 (95% CI 0.18–1.98)].

SGLT2is, CKD progression and ESKD

Meta-analyses demonstrated benefits on renal composite outcomes across different levels of eGFRs, although the proportional effects on renal protection might be attenuated with declining kidney function [29, 30]. However, there was a more significant reduction in the risk of CKD progression and ESKD in our patients with advanced CKD than in those at an earlier stage. We could argue that our study's number of hard events (ESKD) was small. However, the number of participants who developed ESKD in the EMPA-REG and the Canagliflozin Cardiovascular Assessment Study (CANVAS) were of comparable sizes (27 events in EMPA-REG and 21 in CANVAS). Our cohort is from a region with one of the highest incidences of ESKD secondary to DKD. In this study, 9.9% of patients developed ESKD, compared with 0.37% in EMPA-REG and 0.2% in CANVAS. Therefore, the benefits of SGLT2is on renoprotection may be more profound in real-world practice when prescribed in a highly prevalent DKD population.

The consistency of results was found across other RCTs designed for renal composite outcomes as primary or secondary endpoints. In the CREDENCE trial, 30% of the cohort had an eGFR of 30–45 mL/min/1.73 m². Canagliflozin reduced the renal-specific composite endpoints {ESKD, doubling of serum creatinine, or renal death [HR 0.71

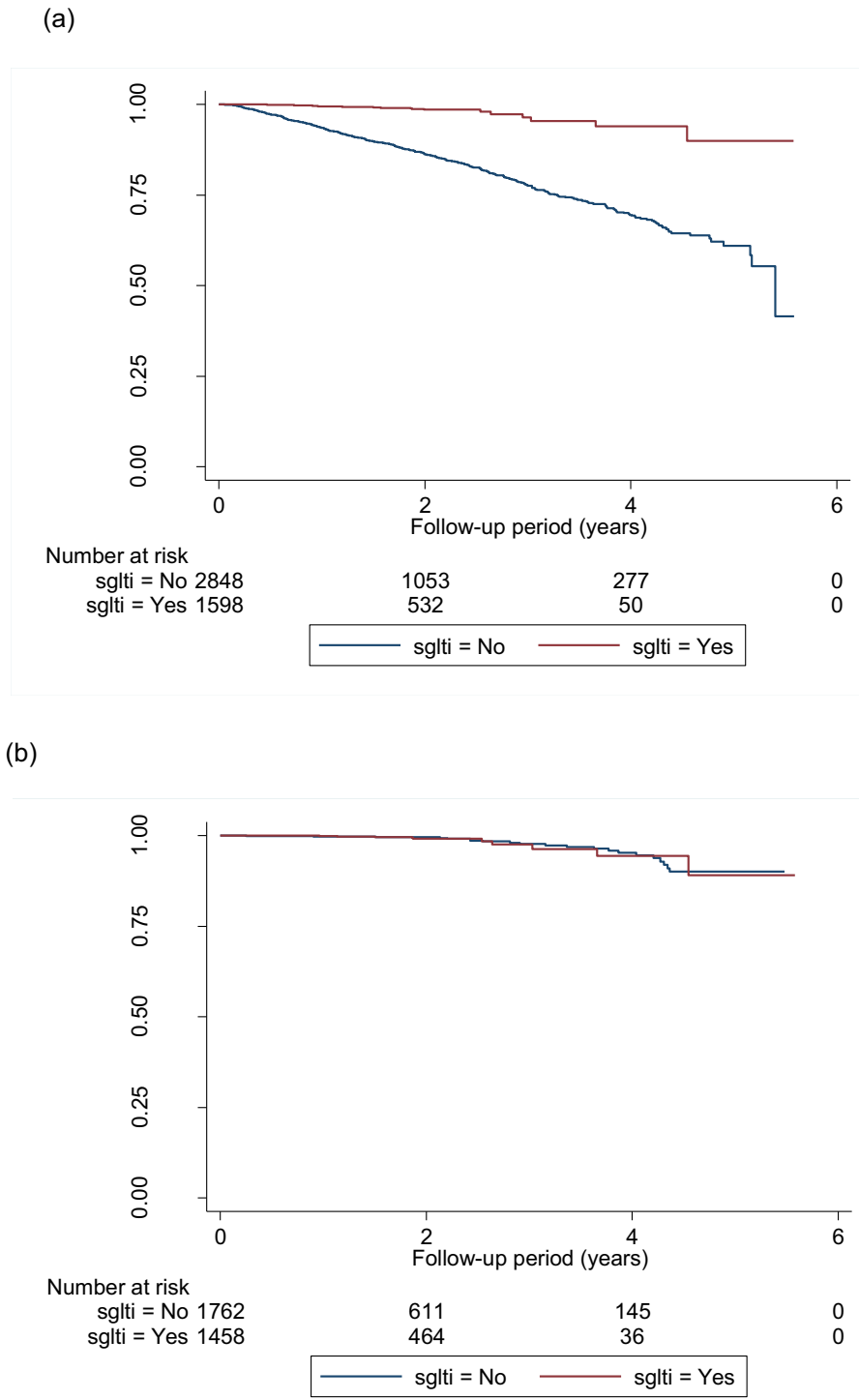


FIGURE 4: Kaplan-Meier survival curves for the event-free survival of ESKD in (a) the whole cohort, (b) patients with an eGFR ≥ 45 mL/min/1.73 m² and (c) patients with an eGFR of 15–44 mL/min/1.73 m². (a) Log-rank test statistics = 150.95, $P < .001$; (b) log-rank test statistics = 0.02, $P = .881$; (c) log-rank test statistics = 36.46, $P < .001$.

(95% CI 0.53–0.94)] but not ESKD alone [HR 0.76 (95% CI 0.56–1.01)] [16]. In the DAPA-CKD trial, 59.1% of participants in the dapagliflozin arm had an eGFR of 15–44 mL/min/1.73 m². The HR for composite primary outcomes (a sustained decline in the eGFR of $\geq 50\%$, ESKD, or death from renal or cardiovascular causes) for this group was 0.49 (95% CI 0.34–0.69) [18]. Further

analysis on CKD stage 4 for the DAPA-CKD cohort, although not adequately powered, showed a statistically non-significant reduction in renal composite outcomes ($\geq 50\%$ sustained decline in eGFR, ESKD or death from kidney disease [HR 0.71 (95% CI 0.49–1.02)]) [31]. A recent meta-analysis including 98 284 patients showed 25 and 38 fewer per 1000 patients in 5 years

(c)

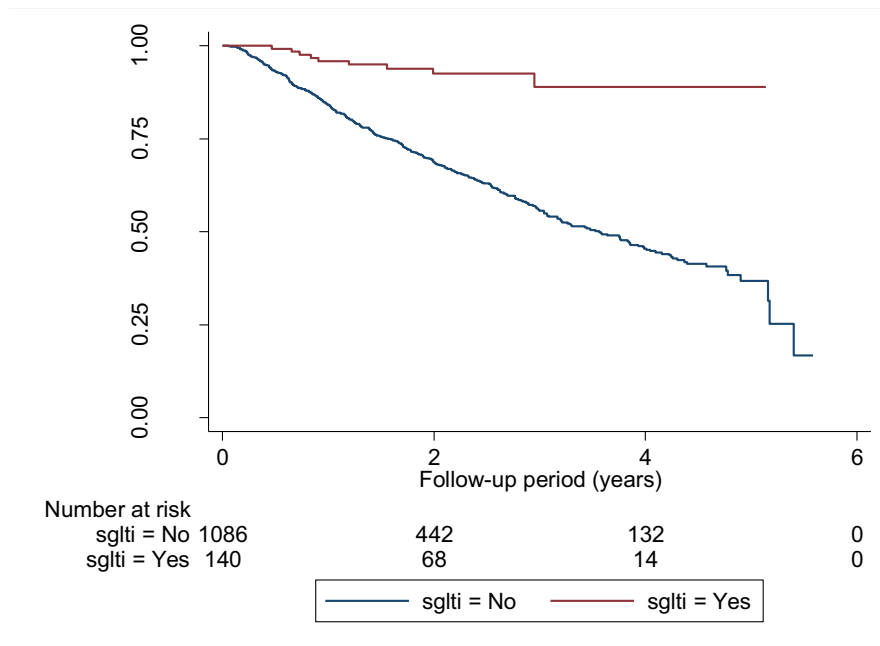


FIGURE 4: Continued.

for high (with CKD) and very high risk (with CKD and cardiovascular disease) groups in the development of ESKD [32]. In response to the findings from the CREDENCE and DAPA-CKD trials, canagliflozin and dapagliflozin were approved for prescription to CKD patients with an eGFR ≥ 30 mL/min/1.73 m². With the upcoming completion of the EMPA-KIDNEY study in 2022–23, there will be a paradigm shift in treatment strategy for advanced CKD and DKD management. There will also be a foreseeable increase in prescription rates across different clinical care settings in the coming decade.

Prescribing SGLT2is in CKD patients

In our cohort, 35.9% of patients across all eGFR categories were prescribed SGLT2is. We had 140 (8.0%) patients who initiated SGLT2is at an eGFR of 15–44 mL/min/1.73 m². There has been a general increasing trend of prescribing SGLT2is since they were approved by the US Food and Drug Administration in the mid-2010s. In one study on the prescription of anti-diabetic drugs in Austria between 2012 and 2018, SGLT2i use increased from 3.7 to 11.7% [33]. However, prescriptions for moderate to advanced CKD remained limited. Only 0.2% of patients with an eGFR ≤ 45 mL/min/1.73 m² in the primary care settings of the UK were given SGLT inhibitors [34]. Early reports on the use of SGLT2is in advanced CKD raised concerns of safety issues, mainly when patients are dehydrated [35, 36]. With its renal function-dependent anti-hyperglycaemic effect, more focus was on weight reduction and blood pressure control and the glucose-lowering effect lessened with lower eGFR [11, 37]. We did not present safety and adverse events data, as only information from outpatient clinics was collected. The DAPA-CKD revealed a similar safety profile between treatment and control groups [18]. Therefore, further

pursuing the use of SGLT2is in patients with moderate to advanced CKD is necessary, with benefits outweighing the risks.

Evidence of real-world studies on renal outcomes

The first real-world study on SGLT2is using renal composite endpoints as the outcome was published in 2019 [38]. Kidney outcomes associated with using SGLT2is in real-world clinical practice (CVD-REAL 3) was studied in a multinational study with outcome measures defined by the rate of eGFR decline, 50% eGFR decline or ESKD. With 35 561 episodes of treatment with SGLT2is (57% of which used dapagliflozin), there was an eGFR decrease per year of 1.53 mL/min/1.73 m² (95% CI 1.34–1.72) and an HR of 0.49 (95% CI 0.35–0.67) for a 50% eGFR decrease or ESKD. The mean eGFR of patients in this observational study was 90.7 mL/min/1.73 m². Another study used the Scandinavian registry (2013–18) to compare SGLT2is versus dipeptidyl peptidase-4 inhibitors on serious renal events (RRT, death from renal causes and hospital admission for renal events) [39]. There was a reduction in these events with patients using SGLT2is [2.6 events per 1000 person-years versus 6.2 events per 1000 person-years; HR 0.42 (95% CI 0.34–0.53)]. Notably, the baseline eGFR was not mentioned in this study. Both studies used retrospective data until 2018, before the results of the CREDENCE and DAPA-CKD trials were published, so patients with advanced CKD were unlikely to be recruited in their cohort. Therefore our real-world study is the first to include patients with moderate to advanced CKD to evaluate the risk of CKD progression and the development of ESKD in a highly prevalent DKD population. Moreover, this study provides a more comprehensive view of how SGLT2is could alleviate the renal disease burden in the community. It also offers crucial information to policymakers

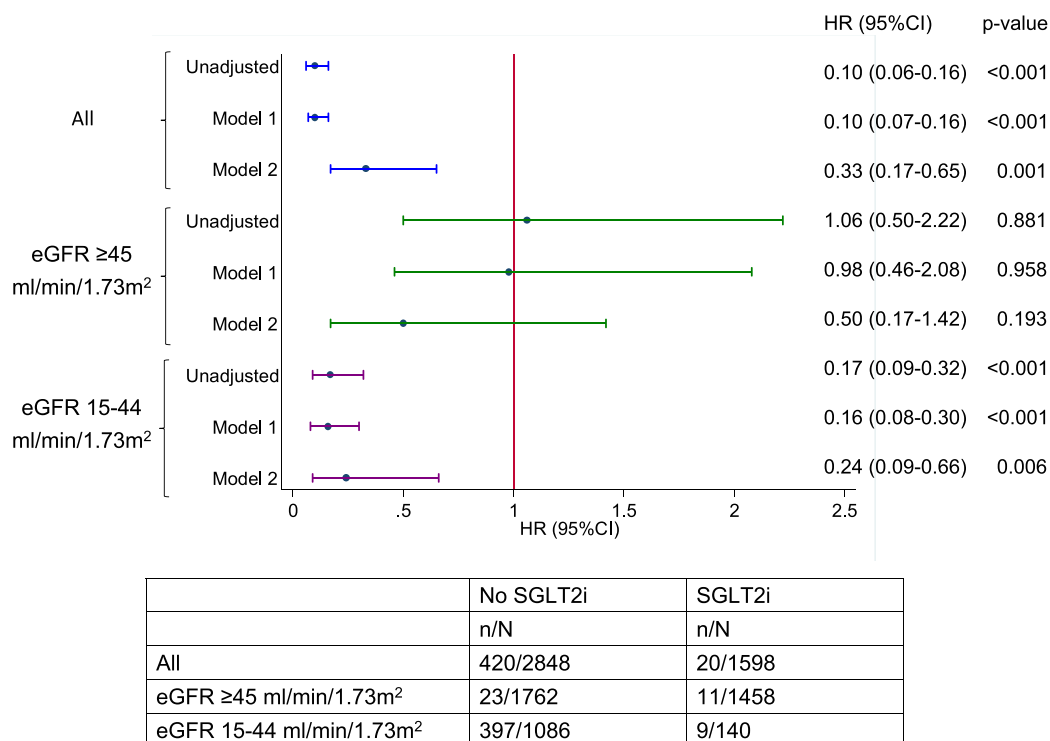


FIGURE 5: Funnel plot of the HR for ESKD based on CKD categories with different adjustment models. Model 1 adjusted for age, gender and ethnicity. Model 2 adjusted for age, gender, ethnicity, HbA1c, baseline eGFR, natural log-transformed uACR and use of RAS antagonists.

on implementing public health measures and reimbursements on using SGLT2is from tertiary to primary care.

Limitations and caveats

This study has several limitations. First, this was a single-centre study on a multi-ethnic Asian T2DM population. We should interpret the results with caution, particularly their generalizability to other ethnic groups. Second, the doses of SGLT2is prescribed to patients varied across the nephrology and endocrinology teams. In general, for patients with lower eGFR, the doses prescribed were 25–50% lower than the recommended dose from RCTs, primarily due to concerns with adverse events. Despite reducing doses, the benefits accrued from using SGLT2is remained strong. Third, we could not avoid indication and time-related biases where those patients prescribed SGLT2is tend to have better predefined outcomes [40, 41]. The systematic differences in baseline characteristics between treatment-exposed and unexposed groups departed from what we usually observed in RCTs. We do not know if patients adhered to the assigned treatment or received medications from other healthcare institutions, leading to misclassification of drug exposure [42]. Essentially we commenced the prescription of SGLT2is in early 2016. This study cohort thus encompasses all patients followed up in our clinics, minimizing selection bias. Fourth, we could not completely rule out unmeasured or unknown confounding factors with the intrinsic fallacy of design in observational studies. Fifth, information on adverse events relating to SGLT2i use in this cohort was not collected. Nonetheless, routine practice of the clinics prescribing SGLT2is is to review patients within 2–4 weeks of SGLT2i

initiation to detect any adverse events and determine continuation or discontinuation of treatment.

CONCLUSIONS

This real-world study demonstrates the benefits of SGLT2is on CKD progression and ESKD in a population with a high prevalence of DKD. The findings of risk reduction on these renal composite outcomes from RCTs are shown in this study to be extrapolated into clinical practice, particularly in moderate to advanced CKD.

SUPPLEMENTARY DATA

Supplementary data are available at [ckj](#) online.

ACKNOWLEDGEMENTS

The first and corresponding author is supported by the Singapore Ministry of Health's National Medical Research Council under its Clinician Investigator Salary Support Program.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

REFERENCES

1. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a

- systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020; 395: 709–733
2. Low SK, Sum CF, Yeoh LY et al. Prevalence of chronic kidney disease in adults with type 2 diabetes mellitus. *Ann Acad Med Singap* 2015; 44: 164–171
 3. Wanner C, Inzucchi SE, Lachin JM et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016; 375: 323–334
 4. Giorgino F, Vora J, Fenici P et al. Renoprotection with SGLT2 inhibitors in type 2 diabetes over a spectrum of cardiovascular and renal risk. *Cardiovasc Diabetol* 2020; 19: 196
 5. Zinman B, Wanner C, Lachin JM et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128
 6. Wiviott SD, Raz I, Bonaca MP et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; 380: 347–357
 7. Neal B, Perkovic V, Mahaffey KW et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 644–657
 8. Cannon CP, Pratley R, Dagogo-Jack S et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020; 383: 1425–1435
 9. Kadowaki T, Nangaku M, Hantel S et al. Empagliflozin and kidney outcomes in Asian patients with type 2 diabetes and established cardiovascular disease: results from the EMPAREG OUTCOME® trial. *J Diabetes Investig* 2019; 10: 760–770
 10. Larmour K, Levin A. Slowing progression in CKD: DAPA CKD and beyond. *Clin J Am Soc Nephrol* 2021; 16: 1117–1119
 11. Park HS, Jung YJ, Lee DY et al. Use of dapagliflozin in patients with advanced diabetic kidney disease. *Kidney Res Clin Pract* 2018; 37: 292–297
 12. Grubić Rotkvić P, Cigrovski Berković M, Bulj N et al. Sodium-glucose co-transporter 2 inhibitors' mechanisms of action in heart failure. *World J Diabetes* 2020; 11: 269–279
 13. Stefan N, Häring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. *Lancet Diabetes Endocrinol* 2019; 7: 313–324
 14. Yaribeygi H, Butler AE, Atkin SL et al. Sodium-glucose co-transporter 2 inhibitors and inflammation in chronic kidney disease: possible molecular pathways. *J Cell Physiol* 2018; 234: 223–230
 15. Chewcharat A, Takkavatakarn K, Isaranuwatthai S et al. Pleiotropic effects of anti-diabetic agents on renal and cardiovascular outcomes: a meta-analysis of randomised controlled trials. *Int Urol Nephrol* 2020; 52: 1733–1745
 16. Perkovic V, Jardine MJ, Neal B et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380: 2295–2306
 17. Tonneijck L, Muskiet MHA, Smits MM et al. Glomerular hyperfiltration in diabetes: mechanisms, clinical significance, and treatment. *J Am Soc Nephrol* 2017; 28: 1023–1039
 18. Heerspink HJL, Stefánsson BV, Correa-Rotter R et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; 383: 1436–1446
 19. Herrington WG, Preiss D, Haynes R et al. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. *Clin Kidney J* 2018; 11: 749–761
 20. Shao SC, Lin YH, Chang KC et al. Sodium glucose co-transporter 2 inhibitors and cardiovascular event protections: how applicable are clinical trials and observational studies to real-world patients? *BMJ Open Diabetes Res Care* 2019; 7: e000742
 21. Khoo CM, Deerochanawong C, Chan SP et al. Use of sodium-glucose co-transporter-2 inhibitors in Asian patients with type 2 diabetes and kidney disease: an Asian perspective and expert recommendations. *Diabetes Obes Metab* 2021; 23: 299–317
 22. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013; 158: 825–830
 23. Low S, Lim SC, Wang J et al. Long-term outcomes of patients with type 2 diabetes attending a multidisciplinary diabetes kidney disease clinic. *J Diabetes* 2018; 10: 572–580
 24. Chapter 2: Definition, identification, and prediction of CKD progression. *Kidney Int Suppl* 2013; 3: 63–72
 25. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612
 26. Low S, Lim SC, Zhang X et al. Development and validation of a predictive model for chronic kidney disease progression in type 2 diabetes mellitus based on a 13-year study in Singapore. *Diabetes Res Clin Pract* 2017; 123: 49–54
 27. Jardine MJ, Zhou Z, Mahaffey KW et al. Renal, cardiovascular, and safety outcomes of canagliflozin by baseline kidney function: a secondary analysis of the CREDENCE randomized trial. *J Am Soc Nephrol* 2020; 31: 1128–1139
 28. Mosenzon O, Wiviott SD, Cahn A et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol* 2019; 7: 606–617
 29. Neuen BL, Young T, Heerspink HJL et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2019; 7: 845–854
 30. Zheng C, Lin M, Chen Y et al. Effects of sodium-glucose co-transporter type 2 inhibitors on cardiovascular, renal, and safety outcomes in patients with cardiovascular disease: a meta-analysis of randomised controlled trials. *Cardiovasc Diabetol* 2021; 20: 83
 31. Chertow G, Vart P, Jongs N et al. Effects of dapagliflozin in stage 4 chronic kidney disease. *J Am Soc Nephrol* 2021; 32: 2352–2361
 32. Palmer SC, Tendal B, Mustafa RA et al. Sodium-glucose co-transporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ* 2021; 372: m4573
 33. Engler C, Leo M, Pfeifer B et al. Long-term trends in the prescription of anti-diabetic drugs: real-world evidence from the Diabetes Registry Tyrol 2012–2018. *BMJ Open Diabetes Res Care* 2020; 8: e001279
 34. Hinton W, Feher MD, Munro N et al. Prescribing sodium-glucose co-transporter-2 inhibitors for type 2 diabetes in primary care: influence of renal function and heart failure diagnosis. *Cardiovasc Diabetol* 2021; 20: 130
 35. Heerspink HJ, Perkins BA, Fitchett DH et al. Sodium glucose cotransporter 2 inhibitor in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation* 2016; 134: 752–772
 36. Yale JF, Bakris G, Cariou B et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and

- chronic kidney disease. *Diabetes Obes Metab* 2013; 15: 463–473
37. Kohan DE, Fioretto P, Tang W et al. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney Int* 2014; 85: 962–971
 38. Heerspink HJL, Karasik A, Thuresson M et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. *Lancet Diabetes Endocrinol* 2020; 8: 27–35
 39. Pasternak B, Wintzell V, Melbye M et al. Use of sodium-glucose co-transporter 2 inhibitors and risk of serious renal events: Scandinavian cohort study. *BMJ* 2020; 369: m1186
 40. Suissa S. Lower risk of death with SGLT2 inhibitors in observational studies: real or bias? *Diabetes Care* 2018; 41: 6–10
 41. Krogh J, Hjorthøj C, Kristensen SL et al. The effect of sodium-glucose transport protein 2 inhibitors on mortality and heart failure in randomised trials versus observational studies. *Diabet Med* 2021; 38: e14600
 42. Hempenius M, Groenwold RHH, de Boer A et al. Drug exposure misclassification in pharmacoepidemiology: sources and relative impact. *Pharmacoepidemiol Drug Saf* 2021; 30: 1703–1715