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Impact of sodium-glucose cotransporter 2 inhibitors on cardiovascular outcomes in patients with chronic kidney disease: propensity score matched analysis

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Type 2 diabetes mellitus (T2DM) is the most common cause of chronic kidney disease (CKD).[1] Age-adjusted prevalence of CKD in patients with T2DM is approximately 40%, of which majority are mild to moderate.[2] The risk gradient of cardiovascular (CV) mortality in CKD increased linearly with decreased glomerular filtration rate (GFR) but changed little when GFR was greater than 75.[3]

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been shown to lower the risk of adverse CV and renal events in patients with CKD.[4–7] In the DAPA-CKD trial, dapagliflozin reduced the risk of renal or CV death in patients with estimated GFR (eGFR) of 25–75 mL/min/1.73 m^2 regardless of presence or absence of diabetes.[5] More recently, the EMPA-KIDNEY trial that included a wider range of patients with CKD with eGFR at least 20 but less than 90 mL/min/1.73 m^2 also demonstrated lower risk of progression of kidney disease and CV death with empagliflozin.[6] There is paucity of data on the efficacy and safety of SGLT2i in patients with advanced (G4 and G5 stages) CKD. We aimed to compare hospitalization for heart failure (HHF) and CV death between new users of SGLT2i versus non-users across the spectrum of CKD stages.

Patients with CKD and exposure to dapagliflozin or empagliflozin between August 2015 and August 2020 in 16 public hospitals in Hong Kong were analyzed. Initiation of SGLT2i was defined by the earliest prescription date within the study period. The control group had no exposure to SGLT2i throughout the study period. New users of SGLT2i were observed from time of first prescription, whereas non-users were observed from the time of baseline eGFR tested. New users and non-users were followed up until the first occurrence of event of interest (ie, HHF or CV death), all-cause death or the end of study. Subgroup analysis was conducted to detect heterogeneity across stages of CKD.

Of 22 657 patients with CKD, 25.4% (n=5763) were newly prescribed SGLT2i (empagliflozin 16.2% (n=3669), dapagliflozin 9.2% (n=2094)) and 59.1% (n=13 396) were diabetic. The use of SGLT2i decreased with increasing stages of CKD from 23.8% (G1), 45.7% (G2), 19.0% (G3a), 8.6% (G3b), 2.3% (G4) and 0.6% (G5). 7408 patients were included in the final analysis after matching. Matched groups were well balanced at baseline with mean age 64.7±12.8 years and 37.1% female. Median follow-up was 2.8 (IQR: 1.1–5.1) years, contributing to 22 876.5 person-years of observation.

Overall, SGLT2i was associated with reduced risk of HHF (HR 0.12, 95% CI: 0.10 to 0.16) and CV death (HR 0.17, 95% CI: 0.12 to 0.25) compared with non-users. Subgroup analysis revealed benefit of SGLT2i was consistent across all CKD stages for avoidance of HHF (p for interaction=0.12), whereas benefit on CV death was observed in patients with stage G2–5 CKD but not in stage 1 CKD (p for interaction<0.001) (table 1).

The DAPA-CKD trial defined the CV-related outcome as a composition of CV death and HHF, and conducted subgroup analysis for aetiologies of CKD with or without diabetes. However, heterogeneity across the spectrum of CKD was not determined.[5] Moreover, patients with advanced CKD were not included.[5] Similarly, the EMPA-KIDNEY excluded patients with CKD with eGFR less than 20 mL/min/1.73 m^2. The primary outcome was a composite of progression to kidney disease and CV mortality; however, SGLT2i failed to show significant benefit on CV death (HR=0.84 (0.60 to 1.19)). HHF was observed combined with CV death in the EMPA-KIDNEY trial, and

Table 1 CV death among SGLT2i users versus non-users in subgroups stratified by CKD stages

	SGLT2i users			SGLT2i non-users				
CV death	n/N	%	Rate/1000 person-years	n/N	%	Rate/1000 person-years	HR (95% CI)	P for interaction
All patients	34/3704	0.9	4.9	408/3704	11.0	25.6	0.173 (0.121 to 0.248)	
G1: eGFR ≥90	1/583	0.2	0.9	6/270	2.2	4.0	0.320 (0.032 to 3.190)	<0.001
G2: eGFR≥60<90	13/1711	0.8	4.0	53/1315	4.0	7.5	1.151 (0.565 to 2.345)	
G3a: eGFR≥45<60	8/852	0.9	5.3	76/833	9.1	18.9	0.394 (0.183 to 0.846)	
G3b: eGFR≥30<45	5/409	1.2	6.6	108/564	19.1	52.8	0.137 (0.055 to 0.338)	
G4: eGFR≥15<30	7/115	6.1	35.4	93/422	22.0	94.3	0.368 (0.170 to 0.797)	
G5: eGFR <15	0/34	0	0	72/300	24.0	251.8	0.034 (0.002 to 0.462)	

*CKD stages defined by eGFR (mL/min/1.73 m^2).
CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

failed to reach statistical significance (HR=0.84 (0.67 to 1.07)). Subgroup analysis showed risk reduction might be proportionally larger among patients with higher urinary albumin-to-creatinine ratios, indicating that more patients with advanced CKD might benefit most from SGLT2i.[6] Heterogeneity of effect was also observed in our study.

In this real-world study, we demonstrated (1) consistent HHF reduction by utilization of SGLT2i across the spectrum of CKD stages; (2) significant CV benefits of SGLT2i in patients across the spectrum of CKD stages; (3) that the benefit to CV mortality was more marked in patients with G3a and more advanced CKD, but not mild groups. The study involved several limitations. Baseline urinary albumin levels were not routinely measured, which would enhance the CV death risk stratification, especially among G1 and G2 mild CKD. Second, utilization of SGLT2i was restricted by an eGFR above 60 before 2019; therefore, the number of patients with G3, G4 and G5 was small (N=1410). Further studies are warranted to explore the impact of SGLT2i in end-stage CKD.

METHOD

Propensity score was generated to match new users of SGLT2i with non-users (1:1, caliper 0.2). The probability of initiating SGLT2i was estimated using logistic regression model into which baseline eGFR, gender, age, hypertension, diabetes, dyslipidemia, atherosclerotic CV disease and concurrent use of antiplatelet, beta-blocker, statin, ACE inhibitor/angiotensin receptor blocker, oral hypoglycemic agents (ie, acarbose, GLP-1 agonist, sulfonylureas, DPP-4 inhibitors, glitazone, metformin) and insulin were entered. Relative risks of association between users or non-users and occurrence of HHF and CV death were approximated from HRs derived from Cox regression, with subgroup by use of SGLT2i handling as interaction term. Proportional assumption was tested. Statistical procedures were performed using IBM SPSS statistics V.26.

Contributors BPY designed the study, and edited, revised and approved the final manuscript. WS collected, analyzed and interpreted the data, and drafted the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The protocol was approved by our institution's Clinical Research Ethics Committee (CREC) (joint CUHK-NTEC CREC: 2018.304). Written consent was not required for retrospective analysis with non-patient-identifiable data.

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