Clinical Kidney Journal, 2021, vol. 14, no. 12, 2463–2471

doi: 10.1093/ckj/sfab096
Advance Access Publication Date: 11 June 2021
CKJ Review

CKJ REVIEW

Sodium–glucose cotransporter 2 inhibitors: renal outcomes according to baseline albuminuria

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ABSTRACT

Sodium–glucose co-transporter 2 inhibitors (SGLT2is) reduce albuminuria and hard renal outcomes (decline of renal function, renal replacement therapy and renal death) in patients with/without type 2 diabetes at high cardiovascular or renal risk. The question arises whether baseline albuminuria also influences renal outcomes with SGLT2is as reported with renin–angiotensin–aldosterone system inhibitors. *Post hoc* analyses focusing on albuminuria and renal outcomes of four cardiovascular outcome trials [EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), CANVAS (Canagliflozin Cardiovascular Assessment Study), DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) and VERTIS CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial)] and some renal data from two heart failure trials [Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction)] showed renal protection with SGLT2is without significant interaction ($P > 0.10$) when comparing renal outcomes according to baseline levels (A1, A2 and A3) of urinary albumin:creatinine ratio (UACR), a finding confirmed in a dedicated meta-analysis. Two trials [CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) and DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease)] specifically recruited patients with CKD and UACRs of 200–5000 mg/g. A *post hoc* analysis of CREDENCE that distinguished three subgroups according to UACR (300–1000, 1000–3000 and >3000 mg/g) showed a greater relative reduction in UACR in patients with lower baseline albuminuria levels (P for interaction = 0.03). Patients with a UACR >1000 mg/g showed a significantly greater reduction in absolute (P for interaction < 0.001) and a trend in relative (P for interaction = 0.25) risk of renal events versus those with lower UACR levels. In conclusion, baseline UACR levels do not significantly influence the nephroprotection by SGLT2is, yet the greater protection in patients with very high UACRs in CREDENCE deserves confirmation. The underlying mechanisms of renal protection with SGLT2is might be different in patients with or without (high) UACR.

Keywords: chronic kidney disease, sodium-glucose co-transporter 2 inhibitors, urine albumin-to-creatinine ratio

Received: 24.3.2021; Editorial decision: 26.5.2021

INTRODUCTION

The history of sodium–glucose cotransporter 2 inhibitors (SGLT2is) is amazing. At the beginning, SGLT2is were new antidiabetic drugs acting as glucosuric agents by inhibiting the SGLT2 protein located in the early proximal tubule [1–3]. Because thiazolidinediones have been associated with unexpected adverse cardiovascular outcomes [4, 5], since 2008 the US Food and Drug Administration has required all new glucose-lowering medications to be tested in large randomized controlled trials (RCTs) with endpoints designed to prove cardiovascular safety [6, 7]. To make a long story short, SGLT2is were not only safe, but demonstrated a true added value on primary combined cardiovascular outcomes, with a particularly high benefit in the incidence of hospitalization for heart failure [8–11]. Among secondary outcomes, these drugs were shown to have strong positive effects on several renal outcomes, both intermediate [such as a reduction in urine albumin:creatinine ratio (UACR) and long-term decline in estimated glomerular filtration rate (eGFR)] and hard clinical endpoints (need for chronic dialysis, transplantation, sustained eGFR <15 mL/min/1.73 m^2 and/or death from a renal cause). These positive renal results were confirmed and detailed as either pre-specified or *post hoc* analyses in cardiovascular outcome trials [12–15] and, more recently, in dedicated RCTs including chronic kidney disease (CKD) patients with and without diabetes with renal outcomes as primary efficacy endpoints [16–20]. The safety profile of SGLT2is was excellent, even in CKD patients [21], and in all categories of albuminuria [22, 23]. The proposed main mechanism of such a generic nephroprotection is the following: SGLT2 inhibition at the proximal level increases the amount of sodium delivered at the macula densa, restoring the tubuloglomerular feedback and thereby decreasing the intraglomerular pressure by either vasoconstriction of the afferent arteriole and/or vasodilation of the efferent arteriole [3, 24, 25]. This mechanism also explains an initial haemodynamically driven decrease in GFR ('dipping GFR') with these drugs [26, 27].

Dipping GFR, a significant decline in UACR, and benefits on hard renal endpoints are all reminiscent of another well-known drug story, i.e. inhibitors of the renin–angiotensin–aldosterone system (RAAS) [28]. Of note, the vast majority of patients included in large RCTs with SGLT2is were treated with RAAS inhibitors. It is notable that the beneficial effects of RAAS inhibitors on renal outcomes were largely restricted to patients with either microalbuminuria [Kidney Disease: Improving Global Outcomes (KDIGO) albuminuria category 2 (A2): UACR 30–300 mg/g] or macroalbuminuria [KDIGO albuminuria category 3 (A3): UACR >300 mg/g] but were largely absent in patients without albuminuria [28–30]. Whether the same interaction between albuminuria and the nephroprotective effect is also true for SGLT2is is a question of interest in order to help clinicians select patients most likely to benefit from the therapy. In this narrative review we will mainly discuss the protective effect of SGLT2is on renal outcomes according to baseline UACR levels.

RCTs WITH CARDIOVASCULAR ENDPOINTS

There are four main RCTs published in type 2 diabetic patients whose primary endpoints were composite cardiovascular outcomes: EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) [8], CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-Renal (CANVAS-R) [9], DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) [10] and VERTIS CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial) [11]. Patients included had a history of established cardiovascular disease [8–11] and/or several cardiovascular risk factors [9, 10]. An SGLT2i was added to standard therapy (among which was an RAAS inhibitor in ∼80% of patients and a diuretic in ∼45% of patients) and compared with a placebo, with a median follow-up of 2.6–4.2 years [8–11]. If an eGFR threshold was considered in the inclusion/exclusion criteria (>30 mL/min/1.73 m^2 [8, 9, 11] or >60 mL/min/1.73 m^2 [10]), albuminuria was absent from the inclusion/exclusion criteria in all these trials, except in CANVAS-R, where microalbuminuria (A2) and macroalbuminuria (A3) at baseline were considered among the possible cardiovascular risk factors in patients without previous cardiovascular disease [9]. Nevertheless, albuminuria levels were mentioned in the baseline characteristics in all studies. Albuminuria categorization was quite similar in all these trials (Table 1): 59.6–69.8% of albuminuria category 1 (A1; UACR <30 mg/g), 22.6–31.0% of A2 and 6.9–11.1% of A3. Patients with A3 were thus a minority. As a reminder, renal outcomes were secondary endpoints in these trials, even if dedicated pre-specified analyses for renal outcomes were published for each of the four trials [12–15]. As the present work focuses on renal outcomes, we will not take into consideration results combining both composite renal outcomes and cardiovascular death [10, 12, 13]. The description of renal outcomes in each study and the positive results are detailed in Supplementary data S1 and summarized in Table 1.

Effect on albuminuria

In EMPA-REG OUTCOME, empagliflozin was associated with a lower rate of progression to macroalbuminuria {progression from A1 or A2 to A3; hazard ratio [HR] 0.62 [95% confidence interval (CI) 0.54–0.72]; $P < 0.001$}, but not progression to microalbuminuria [progression from A1 to A2; HR 0.95 (95% CI 0.87–1.04)] [12].

In CANVAS, canagliflozin dampened the progression of albuminuria, defined as an increase of albuminuria of 30% associated with a progression from A1 to A2 [HR 0.80 (95% CI 0.73–0.87)] or A2 to A3 [HR 0.58 (95% CI 0.50–0.68)]. The mean difference in albuminuria (expressed as the geometric mean) between patients treated by canagliflozin and placebo was −9%, −34% and −36% in patients in the A1, A2 and A3 categories, respectively [13]. This relative decrease in albuminuria with canagliflozin was dependent on the baseline albuminuria (a greater reduction in patients with higher baseline albuminuria), with a P-value for interaction of 0.002 [22]. Another *post hoc* analysis suggested that this relative decrease in mean geometric albuminuria was lower in patients with lower GFR categories at baseline (<60 mL/min/1.73 m^2), with a P-value for interaction of 0.01 [31].

To the best of our knowledge, data on the effects of dapagliflozin on UACR from DECLARE-TIMI 58 have not been published in a full-text format.

In a pre-specified analysis of VERTIS CV, progression of albuminuria (progression from A1 or A2 to A3 or from A1 to A2) was lower in patients treated with ertugliflozin [HR 0.79 (95% CI 0.72–0.86)]. Regression of albuminuria (regression from A3 or A2 to A1 or from A3 to A2) was also significantly more frequent in the ertugliflozin-treated group [HR 1.23 (95% CI 1.10–1.36)]. A lower progression and a greater regression were observed in patients with higher baseline albuminuria (P for interaction = 0.02 and 0.04, respectively). At Month 60, the mean difference in

Table 1. Categorization of albuminuria and renal outcomes in the cardiovascular RCTs

Criteria	EMPA-REG OUTCOME ($n = 6953$; Empagliflozin)	CANVAS ($n = 10\,033$; Canagliflozin)	DECLARE-TIMI 58 ($n = 16\,842$; Dapagliflozin)	VERTIS CV ($n = 8246$; Ertugliflozin)
Baseline albuminuria, *n* (%)				
A1 (<30 mg/g)	4171 (60.0)	7007 (69.8)	11 644 (69.1)	4783 (59.6)
A2 (30–300 mg/g)	2013 (29.0)	2266 (22.6)	4029 (23.9)	2492 (31.0)
A3 (>300 mg/g)	769 (11.1)	760 (7.6)	1169 (6.9)	755 (9.4)
Renal outcomes				
HR (95% CI)				
Composite renal outcome	0.54 (0.40–0.75)	0.53 (0.33–0.84)	0.53 (0.43–0.66)	0.81 (0.63–1.04)
creat ×2 or	creat ×2	creat ×2	−40%	creat ×2
−40%	0.56 (0.39–0.79)	0.50 (0.30–0.84)	0.54 (0.43–0.57)	0.64 (0.40–1.01)
		−40%		−40%
		0.60 (0.47–0.78)		0.65 (0.49–0.87)
Need for RRT	0.45 (0.21–0.97)	0.77 (0.30–1.97)	0.31 (0.13–0.79)	0.96 (0.50–1.83)

HR, hazard ratio; CI, confidence interval; RRT, renal replacement therapy.
creat ×2, doubling of the serum creatinine; NA, not available; −40%, decrease ≥40% in eGFR.

albuminuria (expressed as the geometric mean) between patients treated by ertugliflozin and a placebo was −9%, −26% and −34% in patients in the A1, A2 and A3 categories, respectively (greater reduction in patients with higher baseline albuminuria; P-value not available) [15].

Renal outcomes according to baseline albuminuria

Differences in reporting results between trials caused us to consider the renal effect of SGLT2is according to baseline albuminuria categorization separately, with a comparison shown in Table 2. In EMPA-REG OUTCOME, the pre-specified renal endpoint combining progression to macroalbuminuria, doubling of the serum creatinine and eGFR ≤45 mL/min/1.73 m^2, the need for renal replacement therapy (RRT) and death from a renal cause occurred less frequently in empagliflozin-treated patients, whatever the UACR (P for interaction = 0.87). A *post hoc* analysis of this event limited to patients with an eGFR <60 mL/min/1.73 m^2 and/or A3 was also positive for empagliflozin [HR 0.58 (95% CI 0.47–0.71)]. The *post hoc* renal endpoint combining doubling of the creatinine, eGFR ≤45 mL/min/1.73 m^2, the need for RRT and death from a renal cause was analysed according to A1, A2 and A3. The rate of renal events was lower in treated patients in subgroups with A1 and A3 (not A2), but the P-value for interaction was 0.51 (Table 2), suggesting the positive effect of the treatment was not influenced by baseline albuminuria level. A *post hoc* analysis of this combined event limited to patients with eGFR <60 mL/min/1.73 m^2 and/or A3 also showed protection with empagliflozin [HR 0.51 (95% CI 0.31–0.85)] [12].

In CANVAS, the pre-specified composite renal outcome (doubling of creatinine, need for RRT and death from a renal cause) occurred less frequently in patients treated with canagliflozin in the A1 subgroup, but not in the A2/A3 subgroup. However, the P for interaction was not significant (P = 0.09) (Table 2). When the criteria doubling of creatinine was replaced by eGFR reduction >40%, the rate of events was significantly lower for both subgroups (P for interaction = 0.37) [13]. In a *post hoc* analysis, the same renal composite endpoint was considered, but within the three categories of albuminuria. The rate of the event was lower in the canagliflozin-treated A1 and A3 groups, not A2, the P-value for interaction being significant (P = 0.03), mainly driven by a higher beneficial effect in stage A3 [HR 0.48 (95% CI 0.31–0.74)]. Interestingly, the same observation was made when the absolute decrease in events was considered: no difference in A2 [+3 (95% CI −18 to +24)], but significantly fewer events in A1 [−12 (95% CI −19 to −4)] and A3 [–136

Table 2. HR (with 95% CI) for the specific composite renal outcomes in patients treated with SGLT2is versus placebo according to UACR categories in the cardiovascular RCTs

Trials	Treatment	Composite renal outcomes	UACR categories	HR (95%CI)	P for interaction
EMPA-REG OUTCOME	Empagliflozin	Creat ×2	<30 mg/g	NNA but S	0.51
		RRT	from 30 to 300 mg/g	NNA but I	
		Death from renal cause	>300 mg/g	NNA but S	
CANVAS	Canagliflozin	Creat ×2	<30 mg/g	0.22 (0.07–0.69)	0.09
		ESRD	>30 mg/g	0.63 (0.38–1.07)	
		Death from renal cause			
DECLARE-TIMI 58	Dapagliflozin	−40%	<30 mg/g	0.52 (0.37–0.74)	0.30
		ESRD	from 30 to 300 mg/g	0.59 (0.39–0.87)	
		Death from renal cause	>300 mg/g	0.38 (0.25–0.58)	
VERTIS CV	Ertugliflozin	Creat ×2	<30 mg/g	0.92 (0.61–1.39)	0.43
		RRT	from 30 to 300 mg/g	0.80 (0.53–1.21)	
		Death from renal cause	>300 mg/g	0.62 (0.41–0.95)	

UACR, urinary albumin-to-creatinine ratio; creat x 2,doubling of the serum creatinine; ESRD, end-stage renal disease; NNA but S, numbers not available but significant, meaning that the HR is <1 for the treatment and the 95% CI does not cross the zero line; NNA but I, numbers not available but not significant, meaning that the HR is <1 for the treatment and the 95% CI does cross the zero line; RRT, renal replacement therapy. 40%, decrease 40% in eGFR.

(95% CI −227 to −45)], with a highly statistically significant P-value for interaction of 0.004 [22].

In DECLARE-TIMI 58, the composite renal endpoint (decrease ≥40% in eGFR, doubling of serum creatinine, need for RRT and death from a renal cause) occurred less frequently in the three subgroups (A1, A2 and A3) and the P-value for interaction was 0.30 (Table 2) [14].

In VERTIS CV, the composite renal outcome (doubling of creatinine, need for RRT and death from a renal cause) was not different between groups in the whole population (it occurred less frequently in patients treated with ertugliflozin in the A3 subgroup, but the P for interaction according to baseline albuminuria was 0.43) (Table 2). When the criteria doubling of creatinine is replaced by an eGFR reduction >40%, the rate of events was significantly lower in the whole population [HR 0.66 (95% CI 0.50–0.88)] and in the subgroup A1 and A3 (P for interaction = 0.16) [15].

Renal outcomes according to KDIGO risk

The goal of the current review is to focus on the efficacy of SGLT2is according to levels of albuminuria. However, albuminuria is not expected to be fully independent of eGFR levels. Indeed, patients with low GFR levels (<60 mL/min/1.73 m^2) may have higher stages of albuminuria. Even if this classification is not free from criticisms [32], the KDIGO recommendations suggest that mortality and end-stage renal disease (ESRD) risk are enhanced in categories of patients combining both low GFR (<60 mL/min/1.73 m^2) and high albuminuria [33, 34] (G1, eGFR ≥90; G2, eGFR 60–89; G3a eGFR 45–59; G3b, eGFR 30–44; G4, eGFR 15–29; G5, eGFR <15 mL/min/1.73 m^2). Two *post hoc* analyses of EMPA-REG OUTCOME and CANVAS studied the effect of SGLT2is according to the risk defined by the KDIGO [35, 36].

In EMPA-REG OUTCOME, four categories were considered: low risk [*n* = 3332 (47%); G1A1 and G1A2], moderately increased risk [*n* = 2018 (29%); G3aA1, G2A1 and G2A2], high risk [*n* = 2018 (15%); G3bA1, G3aA2, G1A3 and G2A3] and very high risk [*n* = 545 (8%); G3aA3, G3bA2, G3bA3, G4 and G5]. The rate of progression to macroalbuminuria was significantly lower in the empagliflozin-treated groups with a P-value for interaction across the four risk subgroups of 0.16, suggesting a similar positive effect in all categories. The rate of renal endpoint combining doubling of creatinine and eGFR ≤45 mL/min/1.73 m^2, need for RRT and death from a renal cause was also lower in the empagliflozin-treated group, with a P-value for interaction of 0.29 [35].

In the CANVAS trial, the four risk categories were defined slightly differently: low risk [*n* = 5876 (59%); G1A1 and G2A1], moderately increased risk [*n* = 2587 (26%); G3aA1, G1A2 and G2A2], high risk [*n* = 1068 (11%); G3bA1, G3aA2, G1A3 and G2A3] and very high risk [*n* = 500 (5%); G3aA3, G3bA2, G3bA3, G4 and G5]. The incidence rate (expressed in events per 1000 patient-years at risk) of the composite renal outcome (40% of a decrease in eGFR, need for RRT and death from a renal cause) was significantly lower in the canagliflozin-treated group, with a P-value for interaction of 0.6 [36].

In a pre-specified analysis of VERTIS CV, categorization of KDIGO risk was the same as in CANVAS. The incidence rate of the composite renal outcome (40% of a decrease in eGFR, need for RRT and death from a renal cause) was significantly lower in the ertugliflozin-treated group for the low-risk group, but with a P-value for interaction of 0.16 [15].

Additional results from RCTs focusing on heart failure

Following the demonstration of a marked reduction in hospitalization for heart failure with SGLT2is in the four RCTs discussed above, dedicated studies in patients with heart failure have been published [37–39], but UACR data are only available in one of these. In the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) study [38], all patients presented a left ventricular ejection fraction <40%, ∼50% had diabetes and ∼90% were treated with RAAS inhibitors. The renal composite outcome (secondary endpoint) was defined as either a need for dialysis or kidney transplantation or a sustained decrease ≥40% in eGFR or a sustained eGFR <15 mL/min/1.73 m^2 if baseline eGFR was >30 mL/min/1.73 m^2 or a sustained eGFR <10 mL/min/1.73 m^2 if baseline eGFR was <30 mL/min/1.73 m^2. The event rate of renal outcome was lower in patients treated with empagliflozin compared with placebo [HR 0.50 (95% CI 0.32–0.77)] [38]. In EMPEROR-Reduced, UACR was available in 3710 of the 3730 patients included (99.5%). Among them, 396 (11%) were categorized in A3 and 1236 (33%) in A2. The rate of renal outcomes according to albuminuria categorization in a pre-specified analysis showed a significant benefit in patients with A1 [HR 0.25 (95% CI 0.10–0.61)], but not with A2 [HR 0.70 (95% CI 0.37–1.33)] or A3 [HR 0.59 (95% CI 0.24–1.46)]. However, the P-value for interaction was non-significant at 0.16 [40].

RCTs IN CKD PATIENTS

Three large RCTs have been published with inclusion of CKD patients: CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) [16], DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) [18] and SCORED (Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) [20]. Patients included had an eGFR of 30–90 mL/min/1.73 m^2 in CREDENCE [16], 25–75 mL/min/1.73 m^2 in DAPA-CKD [18] and 25–60 mL/min/1.73 m^2 in SCORED [20]. A UACR of 200–5000 mg/g was an inclusion criterion in DAPA-CKD and 300–5000 mg/g in CREDENCE [16, 18]. In SCORED, patients should have one major (if >18 years of age) or two minor (if >55 years of age) cardiovascular risk factors and a UACR >300 mg/g was considered as one major cardiovascular risk factor among others [20]. An important specificity of the DAPA-CKD was the inclusion of non-diabetic patients with CKD [*n* = 1398 (34% of the final cohort)] [20]. Nearly all patients were treated with RAAS inhibitors in CREDENCE and DAPA-CKD [16, 18] and ∼85% in SCORED [20], whereas diuretics at baseline were present in ∼45% of patients in CREDENCE and DAPA-CKD [16, 18] (in SCORED, ∼35% received loop diuretics and ∼30% other diuretics). The median UACR concentration and categorization of UACR are summarized in Table 3. The description of renal outcomes in each study and the positive results are detailed in Supplementary data, Table S2 and summarized in Table 4 for CREDENCE and DAPA-CKD and in Supplementary data, Table S1 for SCORED.

Effect on albuminuria

In CREDENCE, the geometric mean of UACR was lower by 31% on average in the group treated with canagliflozin [16], which corresponded to an absolute reduction of 240 mg/g (95% CI 207–270) [17]. This proportional effect on albuminuria was not different according to baseline eGFR subgroups (−33% if eGFR <45 mL/min/1.73 m^2, −37% if eGFR >45–<60 mL/min/1.73 m^2 and −28% if eGFR >60–< 90 mL/min/1.73 m^2) [17]. The reduction in albuminuria was observed as early as 26 weeks after drug introduction [16]. A *post hoc* analysis showed that the relative decrease in

Table 3. Categorization of albuminuria and median concentrations in three RCTs that recruited patients with CKD

UACR	CREDENCE ($n = 4401$; Canagliflozin)	DAPA-CKD ($n = 4304$; Dapagliflozin)	SCORED ($n = 10\,584$; Sotagliflozin)
Concentration in the placebo group (mg/g), median (IQR)	923 (459–1794)	934 (482–1868)	74 (18–486)
Concentration in the SGLT2i group (mg/g), median (IQR)	931 (473–1868)	965 (472–1903)	75 (17–477)
A1 (<30 mg/g), *n* (%)	31 (0.7)	NA	3709 (35.0)
A2 (30–300 mg/g), *n* (%)	496 (11.3)	NA	3589 (23.9)
A3 (>300 mg/g), *n* (%)	3874 (88.0)	NA	3286 (31.0)
UACR >1000 mg/g, *n* (%)	2053 (46.6)	2079 (48.3)	NA

IQR, interquartile range; UACR, urinary albumin-to-creatinine ratio; NA, not available.

Table 4. Absolute and relative effects on renal outcomes in patients treated with SGLT2i versus placebo in CREDENCE and DAPA-CKD

Outcomes	CREDENCE		CREDENCE, HR (95%CI)	DAPA-CKD		DAPA-CKD, HR (95%CI)
	Participants with an event per 1000 patient-years			Participants with an event per 1000 patient-years		
	Canagliflozin	Placebo		Dapagliflozin	Placebo	
Renal composite outcomes	27.0	40.4	0.66 (0.53–0.81)	33	58	0.56 (0.45–0.68)
Decrease in eGFR ≥50%	NA	NA	NA	26	48	0.53 (0.42–0.67)
Doubling of creatinine	20.7	33.8	0.60 (0.48–0.76)	NA	NA	NA
RRT	20.4	29.4	0.68 (0.54–0.86)	25	38	0.64 (0.50–0.82)
eGFR <15 mL/min/1.73 m^2	13.6	22.2	0.60 (0.45–0.80)	19	28	0.67 (0.51–0.88)
Need for dialysis	13.3	17.7	0.74 (0.55–1.00)	15	22	0.66 (0.48–0.90)

In DAPA-CKD, the number of events was expressed per 100 patient-years (here multiplied by 10 to present the results as in CREDENCE, i.e. per 1000 patient/years). eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; NA, not available.

albuminuria was higher in patients with lower baseline albuminuria: −35% (95% CI −29 to −39) for UACR ≤1000 mg/g, −29% (95% CI −21 to −35) for UACR 1000–3000 mg/g and −14% (95% CI −2 to −28) for UACR ≥3000 mg/g. The P-value for interaction was significant at 0.03. The opposite was observed if an absolute rather than a relative decrease in albuminuria was considered. The absolute decrease was higher in patients with higher baseline albuminuria: −163 mg/g (95% CI −138 to −186) for UACR ≤1000 mg/g, −355 mg/g (95% CI −263 to −439) for UACR 1000–3000 mg/g and −341 mg/g (95% CI −51 to −669) for UACR ≥3000 mg/g (P for interaction not available) [23]. Another *post hoc* analysis of CREDENCE showed that canagliflozin compared with placebo increased the odds of attaining a reduction of albuminuria >30% [odds ratio (OR) 2.69 (95% CI 2.35–3.07); P < 0.001] at Week 26. The regression of albuminuria (defined as progression from A3 to A2 or A1) was more frequently observed with canagliflozin than with placebo [OR 1.85 (95% CI 1.55–2.22); P < 0.001] [41].

The effect of the treatment on albuminuria has still not been detailed for DAPA-CKD and SCORED [18, 20]. In DAPA-CKD, a study that recruited both diabetic and non-diabetic patients with CKD, the median baseline UACR levels were high in both subgroups, yet slightly higher in patients with diabetes [1024.5 mg/g (95% CI 472.5–2111)] than in patients without diabetes [870.5 mg/g (95% CI 472–1533.5)], with more patients with UACR >1000 mg/g (51% versus 44%). Of note, a similar reduction in kidney-specific composite outcome was observed in both subgroups with and without diabetes [HR 0.57 (95% CI 0.45–0.73) versus 0.51 (95% CI 0.34–0.75); P for interaction = 0.57] [19].

Renal outcomes according to baseline albuminuria

In the seminal publication of CREDENCE, the effect of canagliflozin on the composite (specific) renal outcome was reported after stratification for baseline albuminuria (> or <1000 mg/g creatinine). The HR was significantly reduced for patients in the subgroup >1000 mg/g [HR 0.61 (95% CI 0.49–0.76)], but not in the subgroup ≤1000 mg/g [HR 0.90 (95% CI 0.54–1.50)]. Nevertheless, the P-value for interaction was 0.16, suggesting a similar effect whatever the baseline albuminuria [16]. Interestingly, a *post hoc* analysis of the CREDENCE study analysed the association between the early (between baseline and Week 26) decrease in albuminuria (with a threshold defined at −30%) and the renal (specific) composite outcomes. As already described, an early decrease >30% of baseline albuminuria was more frequently observed in patients treated by canagliflozin than in those having received placebo. Each 30% reduction in baseline albuminuria was associated with a lower rate of renal outcomes [HR 0.71 (95% CI 0.67–0.76); P < 0.001]. The analysis according to active treatment or placebo showed that the association between a decrease in albuminuria >30% and renal beneficial outcomes was observed in both groups [canagliflozin: HR 0.64 (95% CI 0.58–0.71); placebo: HR 0.79 (95% CI 0.72–0.86)], but with a P-value for interaction of 0.001, arguing for a stronger risk reduction in renal outcomes with canagliflozin [41].

Another *post hoc* analysis of CREDENCE recently studied the benefits of canagliflozin according to baseline albuminuria [23]. Three subgroups were considered according to UACR: Group 1, ≤1000 mg/g [$n = 2348$ (53%)]; Group 2, >1000–<3000 mg/g [$n = 1547$ (35%)]; Group 3, ≥3000 mg/g [$n = 506$ (12%)]. Higher baseline albuminuria was associated with a higher rate of renal events, as expected. Both relative and absolute risks were considered in this analysis and results are summarized in Table 5. The relative risk for different composite renal events was lower for patients treated with canagliflozin, except in Group 1 (and in Group 2 for some outcomes). However, the P-values for interaction were non-significant, suggesting no difference in the relative risk reduction with canagliflozin between the three

Table 5. Relative and absolute effects of canagliflozin on renal outcomes in three subgroups of patients separated according to baseline UACR in CREDENCE

Outcomes	Participants with an event per 1000 patient-years		Relative effect, HR (95% CI)	P for interaction	Absolute treatment effects (95% CI)*	P for interaction
	Canagliflozin	Placebo				
Reduction in albuminuria	NA	NA				
UACR ≤1000 mg/g	NA	NA	35% (29–39)	0.03	162.9 mg/g (137.9–186)	NA
UACR >1000–<3000 mg/g	NA	NA	29% (21–35)		355.2 mg/g (263.3–438.5)	
UACR ≥3000 mg/g	NA	NA	14% (−2–28)		340.9 mg/g (−51.2–669.0)	
Composite renal outcome						
UACR ≤1000 mg/g	9.2	10.2	0.90 (0.54–1.50)	0.25	−2 (−15–11)	<0.001
UACR >1000–<3000 mg/g	33.6	48.8	0.67 (0.49–0.92)		−37 (−68 to −7)	
UACR ≥3000 mg/g	106.9	172	0.57 (0.41–0.79)		−120 (−200 to −41)	
Dialysis, kidney transplantation, eGFR <15 mL/min/1.73 m^2 or death from a renal cause						
UACR ≤1000 mg/g	6.4	7.2	0.89 (0.48–1.63)	0.36	−2 (−13–9)	0.002
UACR >1000–<3000 mg/g	26.9	34.9	0.75 (0.52–1.07)		−20 (−47–7)	
UACR ≥3000 mg/g	80.8	126.9	0.58 (0.40–0.84)		−91 (−165 to −18)	
Dialysis, kidney transplantation, eGFR <15 mL/min/1.73 m^2						
UACR ≤1000 mg/g	6.0	7.2	0.84 (0.46–1.56)	0.39	−3 (−13–8)	0.002
UACR >1000–<3000 mg/g	26.9	34.9	0.75 (0.52–1.07)		−20 (−47–7)	
UACR ≥3000 mg/g	79.0	125.2	0.57 (0.39–0.83)		−92 (−165 to −19)	
Dialysis, kidney transplantation or death from a renal cause						
UACR ≤1000 mg/g	5.1	4.2	1.19 (0.57–2.48)	0.17	2 (−7–11)	0.003
UACR >1000–<3000 mg/g	17.3	20.9	0.81 (0.52–1.27)		−9 (−31–13)	
UACR ≥3000 mg/g	48.4	81.8	0.54 (0.34–0.86)		−72 (−134 to −10)	
Doubling of serum creatinine						
UACR ≤1000 mg/g	5.4	7.5	0.71 (0.38–1.32)	0.68	−5 (−16–5)	<0.001
UACR >1000–<3000 mg/g	26.5	41.4	0.62 (0.44–0.88)		−37 (−65 to −9)	
UACR ≥3000 mg/g	88.4	146.2	0.56 (0.39–0.80)		−107 (−183 to −32)	

* For event rates the treatment effect is expressed as absolute risk reduction/1000 patients/2.6 years with 95% confidence interval. Reduction in albuminuria: the relative effect is the percentage change in the geometric mean of canagliflozin relative to placebo and the absolute effect is the absolute change in the geometric mean of canagliflozin relative to placebo. eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; HR, hazard ratio; CI, Confidence Interval; NA, not available.

subgroups. However, considering the reduction in the absolute number of outcome events, the number of events was significantly lower in treated patients in Groups 2 and 3 at intermediate and high risk, but not in patients at low risk. In this analysis the P-value for interactions was highly significant at <0.001, suggesting a significantly greater reduction in the absolute number of renal events in patients with higher baseline albuminuria. In Group 3, this decrease corresponded to a low number needed to treat (patients requiring treatment with canagliflozin to avoid one outcome) of 9 (95% CI 5–25) for the composite renal outcome (dialysis, kidney transplantation, eGFR <15 mL/min/1.73 m^2, doubling of creatinine and renal death) [23].

Such detailed analyses are unfortunately still not available from the DAPA-CKD study. To the best of our knowledge, the impact of baseline albuminuria was analysed only on the primary outcome (so, including cardiovascular death). The authors reported a significantly lower rate of events in both subgroups (UACR > and <1000 mg/g) (P for interaction not available) [18].

In SCORED (see Supplementary data, Table S1), a trial that recruited a minority of patients in the A3 category (31%; Table 2), the renal composite outcome was not different in the group treated with sotagliflozin versus placebo, and this absence of significant effect was confirmed in the three subgroups of baseline albuminuria (A1, A2 and A3) (P for interaction not available) [20].

META-ANALYSES

The effects of SGLT2is on renal outcomes in the different large RCTs were globally positive, a finding confirmed in meta-analyses [42–44]. Regarding the specific question discussed in this article, the meta-analysis of EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58 and CREDENCE published by Neuen *et al.* in 2019 is of special interest [45]. The primary renal outcome, i.e. a composite of need for dialysis, renal transplantation and death from a renal cause, was less frequent in patients treated with SGLT2is [HR 0.67 (95% CI 0.52–0.86); P = 0.0019; test of heterogeneity $I^2 = 0\%$]. The same observation was made for other composite renal outcomes. Using data from EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58, the results were analysed according to baseline albuminuria (A1, A2 and A3) and the primary outcome was less frequent in Group A1 [number of events = 208; HR 0.46 (95% CI 0.33–0.63); P < 0.0001; $I^2 = 10.3\%$], at

the limit in Group A2 [number of events = 164; HR 0.69 (95% CI 0.47–1.00); P = 0.051; I^2 = 18.5%] and less frequent in Group A3 [number of events including CREDENCE = 574; HR 0.52 (95% CI 0.38–0.69); P < 0.0001; I^2 = 51%]. Again, the P-value for interaction was not significant at 0.66, suggesting the same nephroprotective effect in the whole UACR range [45].

DISCUSSION

Currently available data leave little room for concerns regarding the efficacy and risk–benefit balance of SGLT2is for renal protection. Both from a clinical and financial healthcare perspective, it remains important to better understand which patients would benefit the most from this new therapy. The question at the beginning of the current article was simple: do SGLT2is have the same renal efficacy in the whole range of albuminuria? As often in medicine, the answer is much more complex than the question. Several explanations can be advanced to argue why such a simple answer is quite difficult. First, large RCTs are not homogeneous in their design, notably in the choice of renal outcomes [46] and/or in the inclusion criteria. Both the DAPA-CKD and CREDENCE trials must be analysed from a different perspective than the cardiovascular outcome trials because, not only eGFR was significantly lower, but more important for our purpose, the levels of albuminuria were much higher compared with those in initial cardiovascular outcomes trials. In EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58 and VERTIS CV, a minority of patients had a UACR >300 mg/g (6.9–11.1%) and few had a UACR >1000 mg/g. In DAPA-CKD and CREDENCE, ∼48% of patients had a UACR >1000 mg/g and the median UACR was 934 and 923 mg/g, respectively. Second, the way results are presented seems important. Indeed, analysing relative or absolute results could lead to different conclusions, at least at first glance. In this context, it remains important to keep in mind that for demonstrating a positive effect on renal event, sufficient renal events should occur during the study period. In other words, and regarding hard renal outcomes like initiation of dialysis, it is obvious that the presence of CKD at baseline, and particularly the presence of high albuminuria (as in CREDENCE or DAPA-CKD), is itself a high risk for future hard renal events [47, 48].

In the cardiovascular studies, SGLT2is had a positive effect on the surrogate marker albuminuria. In EMPA-REG OUTCOME, empagliflozin was associated with a lower rate of progression to macroalbuminuria (progression from A1 or A2 to A3), but not with a lower rate of progression to microalbuminuria (progression from A1 to A2) [12]. In CANVAS and VERTIS CV, the favourable effect on progression of albuminuria was observed for both situations (A1 to A2 or A1/A2 to A3) [13]. However, the relative decrease in albuminuria was dependent on the baseline value: the higher the baseline albuminuria, the greater the benefit [15, 22]. The protective effect of SGLT2is on harder renal outcomes was positive in EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, VERTIS CV and EMPEROR-Reduced, but the analysis according to levels of albuminuria or categorization according to the KDIGO risk score revealed that this positive effect was quite similar for the whole range of albuminuria (or risk), with non-significant P-values for interaction [12–15, 35, 36, 49]. Only one *post hoc* analysis of CANVAS suggested that both the relative and absolute effects on renal events (death from a renal cause, RRT and ≥40% decrease in eGFR) were greater in patients with baseline A3 (compared with A2 and A1) [22].

Analysis of trials including CKD patients with high baseline albuminuria (CREDENCE and DAPA-CKD) also showed strong beneficial effects on renal outcomes [16, 18, 19, 23]. Only *post hoc* analyses of CREDENCE carefully studied the effect and interaction with albuminuria. Patients with higher baseline albuminuria presented a greater reduction in absolute risk (event rates) with canagliflozin [23]. Regarding the effect on 'harder' renal outcomes according to baseline albuminuria, the results were quite different if relative or absolute data were considered. Considering relative changes in renal events, P-values for interactions showed no difference in terms of positive effects on hard renal outcomes if albuminuria > or ≤1000 mg/g was considered in CREDENCE [16]. The same conclusion was made if three groups were considered (<1000, 1000–3000 and >3000 mg/g) [23]. Considering the absolute number of events, a greater reduction was reported when baseline proteinuria was higher [23].

The renal benefit of SGLT2is, as already stated, is obtained by a reduction in intraglomerular pressure, the same 'primary' mechanism as that recognized with RAAS inhibitors [2, 3]. The fact that SGLT2is are particularly efficient in patients with high albuminuria was concordant with this underlying mechanism. Also, the absence of significant renal effects in the SCORED trial, where CKD patients (eGFR <60 mL/min/1.73 m^2) had relatively (compared with CREDENCE) lower baseline albuminuria, encourage pursuing the comparison with RAAS inhibitors, which exert their greater efficacy in patients with high albuminuria. Having said that, caution is required because this conclusion is mainly driven by *post hoc* subgroup analyses of CREDENCE and the results should be considered only as exploratory. Such detailed analyses are still awaited from DAPA-CKD. The ongoing EMPA-KIDNEY trial (ClinicalTrials.gov NCT03594110) will probably give a more definitive answer, as CKD patients with high and low albuminuria have been included.

However, data from the cardiovascular trials suggest a constant benefit effect on renal outcomes in the whole albuminuria range, even if the number of renal events was lower in these trials that recruited patients with lower levels of albuminuria and globally at lower renal risk. Interestingly, Li *et al.* [50] studied in CANVAS the mediating effect of 18 biomarkers (including eGFR) on renal outcome. UACR had a large percentage of mediation in the subgroup of patients with higher baseline UACR. These results suggest that the beneficial renal effect could be mediated differently in patients with high and low baseline albuminuria. One may speculate that the effect on glomerular hypertension would explain the major part of the renal benefit in patients with high albuminuria, whereas other effects might explain renal protection in patients with normal or low albuminuria [50]. In this respect it is interesting to reflect on some differences between RAAS inhibitors and SGLT2is. Both reduce intraglomerular filtration pressure, but the reduction of hard renal outcomes by RAAS inhibitors has only been documented in patients with proteinuria [28–30]. The great majority of patients in the SGLT2is trials received RAAS inhibitors. As SGLT2is induce osmotic diuresis, an increased risk of acute renal failure was anticipated. However, results from RCTs demonstrate the contrary, with a marked and highly significant protective effect on the risk of acute kidney injury with all SGLT2is [45, 51]. The mechanism is unknown [3, 52], but this finding should be considered as a major advantage compared with the safety profile of RAAS inhibitors. Recurring episodes of acute kidney injury have been reported as an important risk factor for the long-term progression of CKD in patients with diabetes [53].

It is beyond the scope of the present article to review all other mechanisms potentially explaining the renal benefit of SGLT2is beyond their effects on albuminuria [2, 3]. In this review we focused on renal outcomes, but we must keep in mind that

SGLT2is have been proven to have strong positive effects on cardiovascular outcomes, and particularly on heart failure events. The bidirectional connection between 'heart' and 'renal' failure is well known as the cardiorenal syndrome [54, 55]. In cardiovascular trials, patients were at high risk of cardiovascular events but a lower risk of renal events. Relatively, patients in CREDENCE and DAPA-CKD were at higher risk of renal events (even if by nature the cardiovascular risk is high in CKD patients). This is well illustrated by the absolute number of renal events in the different studies. The following hypothesis may be proposed: in EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58 and VERTIS CV, the renal benefit effect in patients with normal or near-normal UACR would occur mainly via the positive effect on heart failure: fewer heart failure events and thus fewer (cardio-) renal events. In contrast, in CREDENCE and DAPA-CKD, the renal events occurred more frequently before a 'heart' event, and the renal protection mainly resulted from a direct intrarenal effect of SGLT2is. This hypothesis could be confirmed (or not) by analysing the timing of renal and cardiac events in patients according to baseline albuminuria in the different trials, yet such analyses are not available in the literature.

SGLT2is are considered as real game-changers in the field of nephrology. This class of drug is certainly one of the most efficient since the advent of RAAS inhibitors. As with RAAS inhibitors (and in a complementary action with this class), SGLT2is markedly delay the occurrence of hard renal events like RRT in high-risk renal patients with high baseline albuminuria, most probably via a specific intrarenal mechanism. Moreover, SGLT2is seem to also exert renal benefits in patients with low albuminuria at baseline, possibly via different mechanisms, such as prevention of acute kidney injury or improvement of myocardial performance, especially in patients with or prone to develop heart failure.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

CONFLICT OF INTEREST STATEMENT

A.J.S. has received lecturer/advisor fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi and Servier. He also worked as a clinical investigator in cardiovascular outcome trials with SGLT2is (EMPA-REG OUTCOME, CANVAS-R and DECLARE-TIMI 58). P.D. is a Member of the CKJ Editorial Board and has received lecturer/advisor fees from AstraZeneca. K.M.W. has received lecturer/advisor fees from AstraZeneca.

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