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To cite this article: André J Scheen & Pierre Delanaye (2021): Understanding the protective effects of SGLT2 inhibitors in type 2 diabetes patients with chronic kidney disease, Expert Review of Endocrinology & Metabolism, DOI: [10.1080/17446651.2022.2014322](https://doi.org/10.1080/17446651.2022.2014322)

To link to this article: <https://doi.org/10.1080/17446651.2022.2014322>



Published online: 15 Dec 2021.



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REVIEW



Understanding the protective effects of SGLT2 inhibitors in type 2 diabetes patients with chronic kidney disease

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ABSTRACT

Introduction: Sodium-glucose co-transporter type 2 inhibitors (SGLT2is) were developed as glucose-lowering agents for the management of type 2 diabetes (T2D). Unexpectedly, they showed a significant reduction in hospitalization for heart failure and hard renal outcomes in patients with and without T2D. Underlying mechanisms remain a matter of debate.

Areas covered: We summarize the protective renal effects of SGLT2is in patients with cardiovascular disease, chronic kidney disease (CKD, especially with albuminuria) or heart failure; a description of the safety of SGLT2is, with a special focus on the risk/benefit balance in people with stage 3 CKD; a comprehensive discussion of mechanisms that could explain nephro-protection; a reappraisal of the positioning of SGLT2is in recent international guidelines.

Expert opinion: Several mechanisms could contribute to improved renal prognosis with SGLT2is, among which a reduction in intraglomerular pressure by restoring the tubuloglomerular feedback, a diuretic effect that contributes to lower albuminuria and renal decongestion, especially if fluid overload is present, a reduction in renal oxygen consumption, an improvement of heart failure status with less cardiorenal syndrome and a lower risk of acute renal injury. All these effects may be mutually not exclusive, and their respective contribution may differ according to patient characteristics.

ARTICLE HISTORY

Received 20 September 2021
Accepted 30 November 2021

KEYWORDS

Acute kidney injury; Albuminuria; Chronic kidney disease; Gliflozin; Heart failure; Nephroprotection; Mechanism; Renal outcome; SGLT2 inhibitor

1. Introduction

Chronic kidney disease (CKD) is a prevalent complication of diabetes mellitus, both in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D) [1,2]. Inhibitors of the renin-angiotensin-aldosterone system (RAAS) have proven their efficacy to improve renal prognosis in patients with diabetes, especially when albuminuria is present [3].

In addition, patients with diabetes and CKD are exposed to a higher risk of cardiovascular disease (CVD) and mortality [4]. Therefore, the main objectives of the management of patients with diabetes and CKD are the lowering of the progression to end-stage renal disease (ESRD) and the reduction of the incidence of major CVD events, including heart failure and mortality [1]. Besides the well-known cardiorenal protective effects of RAAS inhibitors (especially, angiotensin receptor antagonists), finerenone recently was shown to reduce the risks of CKD progression and cardiovascular (CV) events compared to placebo in patients with T2D and CKD [5,6].

Sodium-glucose co-transporter type 2 inhibitors (SGLT2is) emerged in the last few years as effective antidiabetic agents that are associated with both CV and renal protection in patients with T2D at high risk [7]. These effects occur independently of the improvement of glucose control and were

recently confirmed in patients without diabetes either with heart failure [8–10] or with albuminuric CKD [11,12].

The main goals of this comprehensive review are (i) to summarize the protective effects of SGLT2is, mainly on hard renal outcomes, in patients with cardiovascular disease, in patients with CKD and albuminuria and in patients with heart failure; (ii) to describe the safety of SGLT2is, with a special focus on the risk/benefit balance in people with an estimated glomerular filtration rate (eGFR) below 45 ml/min/1.73 m²; (iii) to discuss the proposed mechanisms that could explain protective effects, especially regarding renal issues; and (iv) to briefly reassess the positioning of SGLT2is in recent international guidelines, more particularly in patients with T2D and CKD.

2. Nephroprotective effects of SGLT2is

2.1. Post-hoc renal analyses of cardiovascular outcome trials

Four placebo-controlled randomized clinical trials (RCTs) analyzed the effects of different SGLT2is on a composite CV outcome (major CV events or MACE-3 points: CV mortality, first nonfatal myocardial infarction, first nonfatal stroke) as primary endpoint in patients with T2D and high CV risk: EMPA-REG

Article highlights

- Chronic kidney disease, which may progress to end-stage renal disease, is a common and feared complication among patients with type 2 diabetes
- SGLT2 inhibitors are recent glucose-lowering agents that proved cardiovascular and renal protection in at risk individuals, with or without type 2 diabetes
- Besides a major reduction in hospitalization for heart failure, a reduction in renal composite outcome was consistently demonstrated in large prospective trials in patients with (or at risk of) atheromatous cardiovascular disease, renal disease with albuminuria, and heart failure.
- The potential impact of baseline albuminuria and/or glomerular filtration rate has been investigated showing a positive effect across different categories, yet further studies and analyses are still required.
- Underlying mechanisms that could explain renal protection are multiple: intra-renal hemodynamic changes due to restoration of tubuloglomerular feedback, diuretic effects that may contribute to reduce albuminuria and renal congestion (especially in case of heart failure: cardiorenal syndrome), improved renal oxygenation, combination of positive effects
- SGLT2 inhibitors occupy a privileged place in recent international guidelines published not only by diabetes associations but also by nephrology and cardiology scientific societies.

OUTCOME (for 'EMPAgliflozin cardiovascular OUTCOME events in type 2 diabetes mellitus patients') [13], CANVAS program that combined CANVAS (for 'The Canagliflozin Cardiovascular Assessment') and CANVAS-R (R for 'Renal') [14], DECLARE-TIMI 58 (for 'The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58') [15], and VERTIS CV (for 'Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial') [16]. Patients had a history of established CV disease [13–16] and/or several CV risk factors [14,15]. An SGLT2i was added to standard therapy (among which a RAAS inhibitor in ~80% of patients) and compared with a placebo, with a median follow-up of 2.6 to 4.2 years [13–16]. Baseline eGFR was >30 mL/min/1.73 m² [13,14,16] or >60 mL/min/1.73 m² [15], with mean values ranging between 74.2 and 85.4 mL/min/1.73 m². Albuminuria categorization was more or less similar in the four trials with most patients (around two-thirds) without albuminuria and a minority (around 10%) with macroproteinuria (Table 1). Renal outcomes were secondary endpoints in these trials, yet dedicated prespecified analyses for renal endpoints were published for each of the four trials [17–20]. CV outcomes will not be discussed in detail in this paper as the present review is devoted to patients with T2D and renal outcomes. Of note, only a minority of patients had CKD in these CV outcome trials. To summarize the main CV results, significant reductions in MACE 3-points were observed in two trials (EMPA-REG OUTCOME and CANVAS) [13,14], in CV death or all-cause mortality in one trial (EMPA-REG OUTCOME) [13], in hospitalization for heart failure in all four trials [13–16] and in CV death plus hospitalization for heart failure composite outcome in three trials (EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58) [13–15]. Further extensive analyses of CV outcome results may be found in dedicated meta-analyses [21,22]. (Table 1)

Main renal results are summarized in Table 1. The prespecified composite renal outcome (sustained doubling of serum creatinine and/or $\geq 40\%$ decline in eGFR/end-stage renal

disease/renal death) was significantly reduced in all RCTs, except in VERTIS CV. The difference in VERTIS CV cannot be explained by differences in cohort sizes as shown in Table 1. However, when the renal data from VERTIS-CV were analyzed by using the pre-specified exploratory composite outcome that included sustained 40% decrease from baseline eGFR instead of doubling of serum creatinine, the reduction in composite renal outcomes became significant [20] and fitted in with the results of other trials [23].

A meta-analysis investigated the effects of renal disease (based on three categories of baseline eGFR levels: <60 , 60 – <90 , ≥ 90 mL/min/1.73 m², respectively) on renal outcomes in the first three RCTs, EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 53 [21]. The magnitude of benefit of SGLT2i varied with baseline renal function, with lesser reductions in progression of renal disease in patients with more severe kidney disease at baseline (p for interaction = 0.0258) (Table 2). Another meta-analysis of EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58, plus CREDENCE (for 'Canagliflozin and Renal Events in Diabetes with Established Nephropathy'), confirmed that SGLT2is reduce the risk of dialysis, transplantation, or death due to kidney disease in individuals with T2D and provide protection against acute kidney injury (AKI) [24]. However, the trend for a lower relative nephroprotective effect across baseline GFR categories, from ≥ 90 mL/min/1.73 m² to <45 mL/min/1.73 m², did not reach statistical significance (Table 2).

2.2. Results in RCTs that recruited patients with renal disease

Three placebo-controlled RCTs recruited patients with renal disease at baseline, yet their characteristics were largely different. Two studies analyzed the effects of SGLT2is on a composite renal endpoint plus cardiovascular death as primary outcome in patients with renal disease characterized by reduced eGFR and severe macroproteinuria, CREDENCE [11] (eGFR 30 – < 90 mL/min/1.73 m², urinary albumin-to-creatinine ratio (UACR) > 300 – 5000 mg/g creatinine) and DAPA-CKD (for 'Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease') [12] (eGFR 25 – 75 mL/min/1.73 m², UACR) > 200 – 5000 mg/g creatinine). A notable difference between these two trials is that CREDENCE enrolled only patients with T2D while DAPA-CKD recruited CKD patients with and without T2D. The third trial, SCORED (for 'Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk') [25], recruited exclusively patients with T2D at risk for CV disease and renal disease (eGFR 25 – 60 mL/min/1.73 m²); the primary outcome was a composite CV endpoint including hospitalization for heart failure, with less focus on renal outcomes.

The main renal results are summarized in Table 3. Both canagliflozin 100 mg in CREDENCE and dapagliflozin 10 mg in DAPA-CKD significantly improved renal outcomes in patients with CKD and macroproteinuria. In contrast to the initial observation by Zelniker et al. [21] and in agreement with the meta-analysis by Neuen et al. [24], which included the results from CREDENCE, the relative reduction in the composite renal outcome only tended to be lower in patients with eGFR < 45 mL/min/1.73 m² compared to

Table 1. Renal endpoints in cardiovascular outcome trials with SGLT2is versus placebo.

Clinical trials	SGLT2i	N patients SGLT2i vs placebo	eGFR mean (\pm SD) ml/min/1.73 m ²	% patients with albuminuria <30/30-300/ > 300 mg/g creatinine	Renal composite outcome *	Doubling of serum creatinine	End-stage renal disease	Acute renal injury
EMPA-REG OUTCOME [17]	Empagliflozin 10–25 mg	4687 vs 2333	74.2 \pm 21.6	59.5/28.5/10.9	0.61 (0.53–0.70) p < 0.001	0.56 (0.39–0.79) p < 0.001	0.45 (0.21–0.97) p = 0.04	0.61 (0.39–0.93) NA
CANVAS [18]	Canagliflozin 100–330 mg	5795 vs 4347	76.5 \pm 20.5	69.8/22.6/7.6	0.66 (0.53–0.81) p < 0.001	0.60 (0.48–0.76) p < 0.001	0.68 (0.54–0.86) p = 0.002	0.72 (0.38–1.39) p = NS
DECLARE-TIMI 58 [19]	Dapagliflozin 10 mg	8582 vs 8578	85.4 \pm 15.8	69.1/14.0/6.9	0.53 (0.43–0.66) p < 0.0001	0.54 (0.43–0.67) p < 0.0001	0.31 (0.13–0.79) p = 0.013	NA
VERTIS CV [20]	Ertugliflozin 5–15 mg	5499 vs 2747	76.1 \pm 20.9	59.6/31.0/9.4	0.81(0.63–1.04) p = 0.08 **	0.79 (0.62–1.01) *** p = 0.06	0.96 (0.50–1.83) p = 0.90	0.87 (0.70–1.07) p = 0.19

Notes: Results expressed as « hazard ratio » (with 95% confidence interval and p value). eGFR: estimated glomerular filtration rate. NA: not available. NS: not significant. * Definition may slightly differ across the studies. ** HR = 0.66 (0.50–0.88) if reduction > 40% of eGFR rather than doubling of serum creatinine. *** HR = 0.65 (0.49–0.87) if reduction > 40% of eGFR rather than doubling of serum creatinine.

patients with eGFR \geq 45 ml/min/1.73 m² in both CREDENCE [26] and DAPA-CKD [12] (Table 2). In contrast, no significant improvement could be detected with sotagliflozin in SCORED. While baseline eGFR levels were almost similar in the three studies (around 45 ml/min/1.73 m²), SCORED diverged from the two other studies by the levels of albuminuria [25], which were far lower than those reported in CREDENCE [11] and DAPA-CKD [12] (Table 4). Furthermore, SCORED recruited patients at much lower risk as evidenced by the low number of renal events in the placebo group (on average 6 times lower than in CREDENCE and DAPA-CKD) [25]. We recently analyzed the effects of SGLT2is on hard renal outcomes according to baseline albuminuria [27]. The conclusion was that overall baseline albuminuria levels do not significantly influence the nephroprotection by SGLT2is, with a significant reduction in renal events also present in patients with near normal or mild albuminuria. Nevertheless, in CREDENCE, a greater reduction in the absolute number of events of renal composite outcome was noticed in patients with high (>1000 to <3000 mg/g creatinine) or very high (\geq 3000 mg/g creatinine) UACR compared with patients with an UACR \leq 1000 mg/g creatinine (p for interaction 0.001) [28]. These data were confirmed in a further analysis that investigated the overall incidence rate of kidney-related adverse events that was reduced in patients with UACR > 3000 mg/g creatinine (HR 0.49, 95% CI 0.35–0.67) compared with no protection in patients with UACR \leq 300 mg/g creatinine (HR 1.38, 95% CI 0.76–2.50, p for interaction = 0.008) [29]. These interesting findings deserve confirmation, for instance, in further post-hoc analyses from DAPA-CKD [12].

2.3. Results in RCTs that recruited patients with heart failure

Three placebo-controlled RCTs recruited patients with heart failure at baseline, including patients with and without T2D: DAPA-HF (for 'Dapagliflozin in heart failure') with dapagliflozin 10 mg [8], EMPEROR-Reduced [9] and EMPEROR-Preserved [10], both with empagliflozin 10 mg. In each of them, a composite renal endpoint of \geq 50% (DAPA-HF) or \geq 40% (EMPEROR) sustained decline in eGFR, ESRD or renal death was used as a secondary outcome measure. No differences were noticed between patients with and without T2D concerning the reduction in the primary CV outcome (hospitalization for heart failure and CV mortality) as well as the prespecified secondary composite renal outcome. Regarding renal outcomes, heterogeneous results were reported when comparing patients treated with an SGLT2i versus those on placebo, with a strong trend for reduction (yet not significant) in DAPA-HF [8], a pronounced remarkable reduction by half in EMPEROR-Reduced [9], contrasting with almost no reduction in EMPEROR-Preserved [10] (Table 5). This divergence between the two EMPEROR trials has been emphasized in a recent correspondence to the New England Journal of Medicine. These findings are indeed surprising considering that the baseline eGFR levels and the observed reductions in hospitalization for heart failure in the empagliflozin arm versus the placebo arm were comparable in both studies with reduced versus preserved left ventricular ejection fraction [30]. These data suggest that no improvement of hard renal outcomes

Table 2. Protective effects of SGLT2is on composite renal outcomes according to baseline eGFR.

Baseline eGFR ml/min/1.73 m ²	Reference	≥ 90	60- < 90	< 60	P of interaction	
Meta-analysis of EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58	Zelniker et al 2019 [21]	0.44 (0.32–0.69)	0.56 (0.46–0.70)	0.67 (0.51–0.89)	p = 0.0258	
Baseline eGFR ml/min/1.73 m ²		≥ 90	60- < 90	45- < 60	< 45	p of trend
Same meta-analysis, but including CREDESCENCE	Neuen et al 2019 [24]	0.37 (0.21–0.63)	0.60 (0.48–0.74)	0.55 (0.39–0.76)	0.70 (0.54–0.91)	p = 0.073
Baseline eGFR ml/min/1.73 m ²			60- < 90	45- < 60	< 45	p heterogeneity
CREDESCENCE	Jardine et al 2020 [26]		0.81 (0.52–1.26)	0.47 (0.31–0.72)	0.71 (0.53–0.94)	p = 0.11
Baseline eGFR ml/min/1.73 m ²			≥ 45		< 45	
DAPA-CKD	Heerspink et al 2020 [12]		0.49 (0.34–0.69)		0.63 (0.51–0.78)	NA

Notes: Results are expressed as hazard ratio with 95% confidence interval. eGFR: estimated glomerular filtration rate. NA: not available.

could be observed in patients with diastolic dysfunction and preserved left ventricular ejection fraction, a finding without obvious explanation yet. No information regarding the levels of baseline albuminuria was available in the original publications of these three studies devoted to patients with heart failure.

3. Safety of SGLT2is in patients with CKD

The glucose-lowering efficacy of SGLT2is is decreasing when eGFR is declining so that the use of these agents as antidiabetic medications was initially restricted to patients with T2D and eGFR > 60 ml/min/1.73 m², with a further recommendation to stop the drug when eGFR falls < 45 ml/min/1.73 m² [31]. However, the overall safety profile of SGLT2is in patients with CKD has been shown to be roughly similar to that in patients with normal renal function [31,32]. Furthermore, a reduction in both CV and renal outcomes were reported in patients with eGFR ≥ 25–30 to < 45 ml/min/1.73 m² [12,29,33–

35]. Even among patients with stage 4 CKD (eGFR < 30 ml/min/1.73 m²) and albuminuria from CREDESCENCE [36] and DAPA-CKD [37], the positive effects on renal and CV were consistent, with no evidence of increased risks.

One possible concern when starting a therapy with an SGLT2i may be an initial decrease in eGFR ('dip'). This effect results from a reduction in intraglomerular pressure and likely reflects the protective mechanism of action that will slow down the further sustained decline in eGFR observed with placebo, as discussed later on. Thus, this initial, functional, and reversible, drop in eGFR should not lead to any safety concern [38].

However, some case reports of AKI were submitted to the American Food and Drug Administration (FDA) adverse event report system (FAERS) database [39] and a warning was published by the FDA in 2016, with caution recommended in the presence of diuretics, RAAS inhibitors, and non-steroid anti-inflammatory drugs [40]. Potential mechanisms have been hypothesized to explain such adverse events [41]. However,

Table 3. Effects of SGLT2is on renal outcomes in patients with renal disease with either high or low albuminuria.

Endpoints	CREDESCENCE [11]	DAPA-CKD [12]	SCORED [25]
SGLT2i	Canagliflozin 100 mg	Dapagliflozin 10 mg	Sotagliflozin 200–400 mg
Median follow up (years)	2.62	2.40	1.33
N SGLT2i vs placebo	2202 vs 2199	2152 vs 2152	5292 vs 5292
% of patients with T2D	100%	67.5%	100%
Baseline eGFR ml/min /1.73 m ²	56.2 ± 18.2 (mean ± SD)	43.2 ± 12.3 (mean ± SD)	44.4 (37.1–51.3) (median, IQR)
Baseline albuminuria	927 (463–1833)	965 (472–1903)	74 (18–486)
Median (25–75 percentiles) mg/g creatinine			
% patients with albuminuria <30/30-300/ > 300 mg/g creatinine	All > 300 (> 1000: 46.2%)	All > 200 (> 1000: 48.7%)	35.2/33.4/31.3
40% or 50% loss of eGFR or doubling of creatinine, ESRD or renal death	0.66 (0.53–0.81) p < 0.001	0.56 (0.45–0.68) p < 0.001	0.71 (0.46–1.08) NA
ESRD	0.68 (0.54–0.86) p = 0.002	0.64 (0.50–0.82) p = 0.004	NA
ESRD or renal death	0.72 (0.54–0.97) p = NA	0.66 (0.49–0.90) p = 0.0072	NA
Acute kidney injury	0.85 (0.64–1.13) p = NS	NA	NA
All-cause mortality	0.83 (0.68–1.02) p = NS	0.69 (0.53–0.88) p = 0.004	0.99 (0.83–1.18) NA
Primary outcome (renal composite + cardiovascular mortality)	0.72 (0.59–0.82) p < 0.001	0.61 (0.51–0.72) p < 0.001	NA

Notes: Results are expressed as hazard ratios (with 95% confidence intervals and p values when available).

eGFR: estimated glomerular filtration rate. ESRD: end-stage renal disease. NA: not available. NS: not significant. IQR: interquartile range.

Table 4. Effects of SGLT2is on renal outcomes in patients with heart failure.

Endpoints	Dapa-HF [8]	EMPEROR-Reduced [9]	EMPEROR-Preserved [10]
SGLT2i	Dapagliflozin 10 mg	Empagliflozin 10 mg	Empagliflozin 10 mg
Median follow up (months)	18.2 months	16 months	26.2 months
N SGLT2i vs placebo	2373 vs 2371	1863 vs 1867	2997 vs 2991
% of patients with T2D	42%	49.8%	48.9%
Left ventricular ejection fraction %	31.2 ± 6.7	27.7 ± 6.0	54.3 ± 8.8
Baseline eGFR ml/min /1.73 m ² *	66.0 ± 19.6	61.8 ± 21.7	60.6 ± 19.8
Primary outcome **	0.74 (0.65–0.85) p < 0.001	0.75 (0.65–0.86) p < 0.001	0.79 (0.69–0.90) p < 0.001
Worsening of renal function ***	0.71 (0.44–1.16) p = NA	0.50 (0.32–0.77) p = NA	0.95 (0.73–1.24) p = NA

Notes: Results are expressed as hazard ratios (with 95% confidence intervals and p values when available). eGFR: estimated glomerular filtration rate. ESRD: end-stage renal disease. NA: not available. NS: not significant. * No data on baseline albuminuria mentioned in all three studies. ** Primary outcome: a composite of worsening heart failure and cardiovascular mortality. *** Sustained ≥ 50% (DAPA-HF) or 40% (EMPEROR) loss of eGFR, progression to end-stage renal disease or renal death.

despite FAERS concern, subsequent dedicated examinations of a variety of findings were reassuring. These data were collected in prospective placebo-controlled RCTs, summarized in several meta-analyses of cardio-renal outcome trials [24]. Reassuring findings were also obtained in a larger set of clinical studies [42], large observational studies that used propensity score-matched analyses from electronic medical records [43] and real-world data that compared therapy with SGLT2is versus DPP-4is [44], even in older adult patients with T2D [45,46]. Indeed, all these analyses showed that, if anything, the risk of AKI is reduced rather than increased in SGLT2i users compared to non-users, leading to the conclusion of a recent editorial that 'we can finally stop worrying about SGLT2is and AKI' [47]. Thus, overall, the benefit/risk balance of prescribing an SGLT2i in patients with T2D and an eGFR < 45 ml/min/1.73 m² remains largely positive.(Figure 1)

4. Mechanistic explanations [48]

4.1. The hemodynamic effect: decreasing intraglomerular pressure

Hyperfiltration is the first step of the pathological process leading to CKD in patients with diabetes. This phenomenon has been especially well studied in people with T1D and is less easy to demonstrate in patients with T2D because of some confounding factors such as hypertension and obesity [49]. It is caused by different complex mechanisms. Briefly, various cytokines and growth factors are secreted in response to hyperglycemia, leading to hypertrophy of nephrons (and

particularly of proximal tubules) and increase of filtration surface area that can contribute to hyperfiltration. Moreover, the 'vascular theory' suggests an imbalance in factors that control either the reduction of the afferent arteriolar resistance (like insulin) or the increase in efferent arteriolar resistance (like angiotensin) [49]. The last mechanism leading to hyperfiltration is complementary of the previous ones and called the 'tubular theory.' Hyperglycemia is associated with an increased amount of glucose filtered and thus reabsorbed by the proximal tubules. This increase in glucose reabsorption is accompanied by an increased reabsorption of sodium. This reabsorption at the proximal tubular level is reducing the delivery of sodium to the *macula densa* within the juxtaglomerular apparatus, an effect that is interpreted as a reflection of low effective blood volume. This phenomenon will impair tubuloglomerular feedback, by decreasing the production of adenosine, which normally is acting by increasing afferent arteriolar resistance and decreasing efferent resistance. As a consequence of this afferent vasodilatation and efferent vasoconstriction, intraglomerular pressure is increasing and hyperfiltration occurs as reflected by elevated GFR [49,50].

Hyperfiltration and pathological processes sustaining hyperfiltration are thus associated with an increase in intraglomerular pressure, increased filtration fraction, and vascular changes that could lead to the development of albuminuria, glomerulosclerosis, and progression to CKD [51]. Large CV, and still more renal-dedicated, RCTs have shown an impressive decrease in albuminuria levels with SGLT2is [11–14,27,28]. As previously discussed [3], a parallelism can be made with the efficacy of inhibitors

Table 5. Cardiovascular and renal protection by SGLT2is in patients with T2D and estimated glomerular filtration rate <45 ml/min/m². P values correspond to P for interaction (all not significant) versus other subgroups of renal function (eGFR 45–<60 et 60–<90 ml/min/1.73 m²).

Clinical trials *	MACE 3-points	Hospitalization for heart failure	Renal composite outcome **	Risk of AKI
EMPA-REG OUTCOME [34]	0.79 (0.51–1.22) P interaction = 0.31	0.55 (0.29–1.05) P interaction = 0.91	NA	NA
CANVAS [35]	0.65 (0.41–1.03) P interaction = 0.33	0.45 (0.23–0.88) P interaction = 0.62	0.65 (0.29–1.48) P interaction = 0.59	1.05 (0.30–3.73) P interaction = 0.74
CREDESCENCE [29,33]	0.77 (0.57–1.03) P interaction = 0.74	0.70 (0.46–1.06) P interaction = 0.27	0.73 (0.58–0.91) P interaction = 0.30	0.91 (0.58–1.41) P interaction = 0.90
DAPA-CKD [12]	NA	NA	0.61 (0.53–0.78) *** P interaction = NS	NA

Notes Results are expressed as hazard ratios (with 95% confidence intervals and p values when available). MACE 3-points: major cardiovascular events: cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke. AKI: acute renal injury). * No data for DECLARE-TIMI 58 (only < 60 ml/min/1.73 m²: HR 0.60, 0.35–1.02; p = 0.059) and VERTIS CV. ** Definition slightly different across studies. *** Including cardiovascular mortality
NA = not available. NS: not significant.

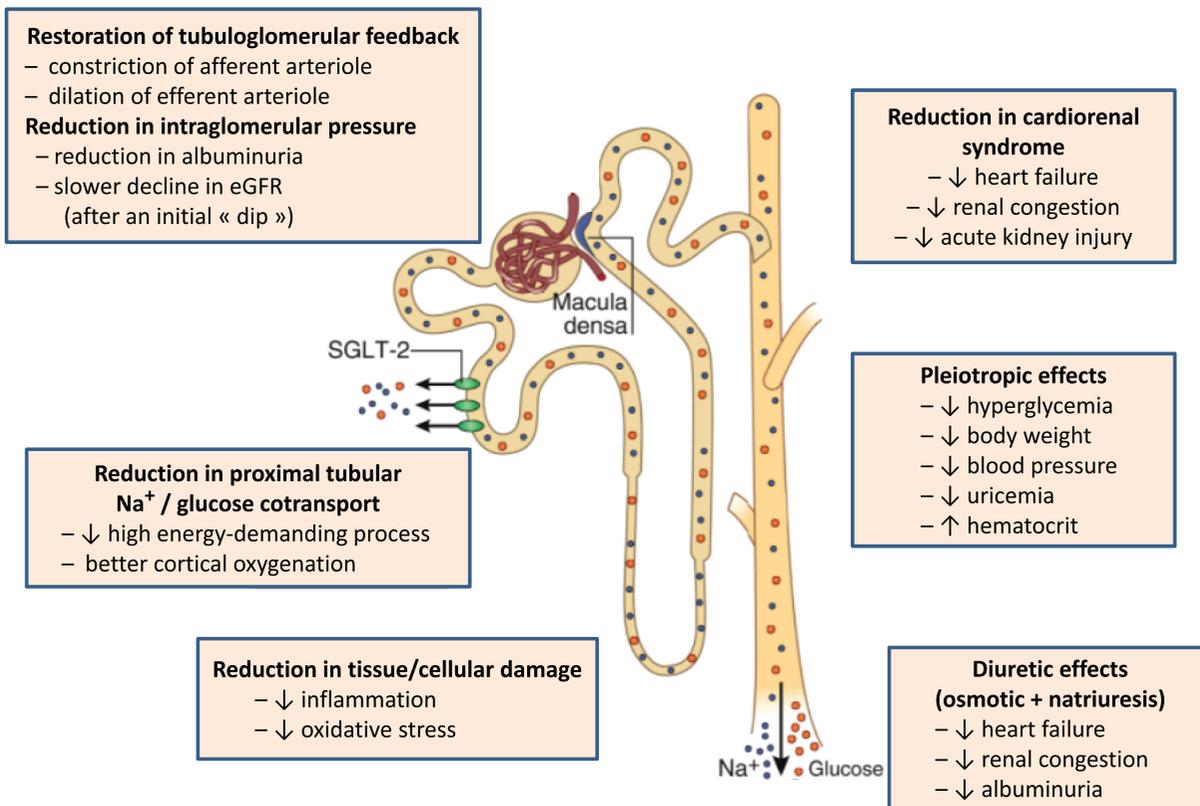


Figure 1. Main mechanisms associated with SGLT2 inhibition that could contribute to nephroprotection. eGFR: estimated glomerular filtration rate. Adapted from *Kidney International* 2018;94: 26–39, Heerspink HJL, Kosiborod M, Inzucchi SE, Cherney DZI. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors [48], Copyright 2018, with permission from Elsevier.

of the RAAS on renal outcomes, demonstrated in several large prospective placebo-controlled RCTs [52]. These drugs diminish the efferent arteriolar resistance by decreasing the vasoconstrictive effect of angiotensin II, interfering in the balance between efferent and afferent arterioles ('vascular theory') [49,53]. This effect explains an initial, and reversible, decrease ('GFR dip') in GFR at the initialization of the therapy with RAAS inhibitors. However, by decreasing intraglomerular pressure, this early effect is associated with a long-term benefit on eGFR decline slope, albuminuria, and hard renal outcomes [52]. The action of SGLT2is is basically a bit different from that of RAAS inhibitors, and more related to the 'tubular theory': intrarenal hemodynamic changes related to an increased production of adenosine secondary to the restoration of the tubuloglomerular feedback with SGLT2is instead of a direct effect due to the inhibition of angiotensin 2 with RAAS blockers [3]. These different effects on the same pathophysiological pathway are probably explaining a potential, yet still debated [54], synergistic effect of these two classes of drugs that showed a nephroprotective effect [3,55]. The final effect on intraglomerular pressure, i.e., a significant reduction, will be comparable with both RAAS inhibitors and SGLT2is. SGLT2is block both glucose and sodium reabsorption, which leads to more delivery of sodium to the *macula densa*, restoration of the tubuloglomerular feedback, and eventually, an increase in afferent arteriolar resistance (and a decrease in efferent resistance) [49,50]. These hemodynamic effects also explain a reversible 'GFR dip' in patients starting therapy

with SGLT2is (similar to that reported with RAAS inhibitors), and, once again by decreasing intraglomerular pressure, the large benefits observed in trials in terms of albuminuria and renal outcomes [11,12,14,15,17,24,27,33].

These hemodynamic effects of SGLT2is have been well investigated in three human studies. In the first one, GFR (inulin clearance) and renal plasma flow (paraaminohippurate clearance) were measured in T1D patients (n = 27 with hyperfiltration and n = 13 with normal GFR) at baseline and after 8 weeks of empagliflozin 25 mg (patients not treated by RAAS inhibitors). A significant decrease in GFR and effective renal blood flow, associated with an increase in renal vascular resistance, was observed. These results are consistent with the 'tubular theory' and the vasoconstrictive effect of SGLT2is on the afferent arteriole [56]. In a second study, GFR (inulin or iohexol clearance) and renal plasma flow (paraaminohippurate clearance) were measured in 24 T2D patients (all treated with metformin) at baseline and 12 weeks after dapagliflozin 10 mg. Contrary to the first mechanistic study, 73% of patients included were treated by stable doses of RAAS inhibitors for at least 3 months. Compared to the control group treated by gliclazide (a sulfonylurea that provided similar glucose control), dapagliflozin decreased GFR from baseline (mean level around 70 mL/min) and effective renal blood flow, but without significant effect on renal vascular resistance (with no difference in patients treated or not by RAAS inhibitors). The investigators estimated intraglomerular pressure, afferent and efferent arteriolar resistance, and suggested that dapagliflozin decreases intraglomerular pressure, especially by a reduction

in arteriolar efferent resistance [54]. In a third recent study in patients with T2D and preserved renal function (almost half of them without RAAS inhibitors) that analyzed intraglomerular hemodynamics, empagliflozin 10 mg (combined with linagliptin) did not change resistance of afferent arterioles, but diminished resistance of efferent arterioles, the final result being preserved renal perfusion and reduced vascular resistance [57]. Refined hemodynamic mechanisms could thus be different in T1D and T2D patients and/or in patients treated or not by RAAS inhibitors. Nevertheless, both SGLT2is and RAAS inhibitors could act synergistically both on afferent and efferent arterioles, and result in the same final protection, i.e., a decrease in intraglomerular pressure [50].

The analysis of results from large RCTs according to baseline albuminuria levels suggests that SGLT2is are efficient also in patients with low, or even normal UACR [27,28], a difference with the results of studies with RAAS inhibitors [58,59]. Of interest, in a *post hoc* analysis of the CANVAS trial, the impact of 18 biomarkers indicative of disease was studied on the renal outcomes. After a complex statistical analysis, the authors concluded that the mechanisms of renal protection could be different according to baseline UACR: UACR mediated 42% and 7% of the effect on the composite renal outcome in those with baseline UACR ≥ 30 mg/g and < 30 mg/g, respectively [60]. A secondary analysis from EMPA-REG OUTCOME indicated that empagliflozin may assist in preventing CKD progression in T2D patients with CVD, irrespective of RAAS inhibitors, and without increasing the risk of AKI. Of interest, for the endpoint 'progression to macroalbuminuria,' analysis indicated that the combination of RAAS blockers and SGLT2is was superior to SGLT2i therapy alone [55].

4.2. Diuretic effect

Because of the unique mechanism of action of SGLT2is, increased glucosuria is associated with osmotic diuresis and some natriuresis, yet the latter seems mostly transient [61]. The potential role of the diuretic effect in the cardiovascular protection by SGLT2is remains a matter of debate [62], yet its effect on the reduction in hospitalization for heart failure may be easily understood [63]. Besides, the potential role of the diuretic effect of SGLT2is on renal outcomes is still unclear [61] even if some mechanistic explanations may be proposed.

4.2.1. Reduction in albuminuria

The presence of albuminuria within the glomerulus is toxic and elicits a sclerotic response that results in mesangial proliferation and glomerulosclerosis [64]. In a meta-analysis of 41 eligible studies, each 30% decrease in albuminuria reduced the risk of ESRD by 27% over a median follow-up of 3.4 years [65]. Albuminuria is one of the major surrogate markers for kidney disease progression and resolution or improvement in albuminuria is one of the best surrogate markers for nephroprotection as previously reported in dedicated studies with RAAS inhibitors [3,66].

Classical diuretics (especially thiazides with their natriuretic effects) seem useful to decrease albuminuria in CKD patients, with a synergistic effect with RAAS inhibitors [67,68]. The

antiproteinuric effect of mineralocorticoid receptor antagonists has been clearly established [67]. The efficacy of loop diuretics has been less explored, yet different investigations suggest that they might share similar antiproteinuric properties [69]. Of note, strong data on classical diuretics showing benefits on hard renal outcomes are lacking except for the mineralocorticoid receptor antagonist finerenone that recently showed a significant reduction in the risk of CKD progression in patients with T2D [5,6].

Thus, the reduction in albuminuria consistently reported with SGLT2is [70,71] may result not only from the reduction in intraglomerular pressure as already discussed but also from a diuretic effect. What so ever, it could contribute to their nephroprotective effects [69] and has been proposed as a marker for improved renal outcomes both in people with and without T2D treated with SGLT2is [72]. In favor of such assumption, recent subanalyses of large prospective RCTs have shown that the early antiproteinuric effect induced by SGLT2i predicts long-term preservation of kidney function [73,74]. Nevertheless, a detailed analysis of available data suggests that the nephroprotection by SGLT2is is observed independently of the albuminuria level at baseline [27], even if a more marked effect may be observed in patients with very high albuminuria [28].

4.2.2. Renal decongestion

Expansion of extracellular fluid volume is central to the pathophysiology of heart failure. Diuretic-induced decongestion in patients with heart failure can improve eGFR by reducing renal venous pressure [75]. SGLT2i therapy could protect diabetic kidney disease from failing by improving latent renal congestion even without symptomatic heart failure [76]. Robust clinical trial evidence to guide the use of diuretics in patients with heart failure is sparse [77] while SGLT2is appear increasingly attractive [78].

Acute heart failure is frequently associated with AKI episodes, known as the cardio-renal syndrome [79,80]. SGLT2is by decreasing the episodes of acute heart failure would contribute to prevent AKI events. It is known that these episodes are associated with a cumulative risk for developing advanced CKD in diabetes mellitus, independent of other major risk factors of progression [81]. Thus, improving cardiac function would potentially have a positive impact on renal 'chronic' outcomes. This observation could be especially relevant to explain the persistent positive effect of SGLT2is in patients with near-to-normal eGFR and near normal level of albuminuria [27].

Thus, the diuretic effect would be particularly interesting in patients with (or at high risk of) heart failure. A post-hoc analysis investigated the relationship between heart failure diagnosis, use of loop diuretics, and outcomes in patients with T2D enrolled in the EMPA-REG OUTCOME trial. Rates of adverse events related to renal function were greater in patients (with or without heart failure) receiving a loop diuretic compared to the other patients. Of note, however, these increases were observed in both groups treated with placebo and empagliflozin, yet with a numerically lower incidence in patients receiving empagliflozin compared with placebo [82].

However, as already pointed out, the type of heart failure might impact the influence of SGLT2is on the development of hard renal outcomes [30]. Despite almost similar effects on the reduction of hospitalization for heart failure in patients with either reduced [9] or preserved [10] left ventricular ejection fraction, an impressive 50% reduction in the composite renal outcome was observed in EMPEROR-Reduced, which contrasted with a trivial 5% reduction in EMPEROR-Preserved [30]. The interpretation of this finding is still unclear.

4.3. Renal oxygen consumption

The reabsorption of glucose and sodium by the proximal tubule is an energy-demanding process, which requires high-level oxygen transport. Indeed, this reabsorption is dependent on the electrochemical gradient of sodium established by the Na^+/K^+ co-transporter, consuming adenosine triphosphate generated by oxidation [83]. In patients with diabetes and increased activity of SGLT2, this oxygen demand is still increased. A chronic renal hypoxia could favor the inflammation and fibrosis (notably by the stimulation of hypoxemia-inducible factors signaling) and thus the progression of CKD [83–88]. Data from animal models have suggested that inhibition of this transport by SGLT2is could improve renal oxygenation by 30% [89]. A cross-over, placebo-controlled study including 13 patients (placebo $n = 6$) with T1D and mild albuminuria showed that a supraphysiologic dose (50 mg) of dapagliflozin was associated with a significant better oxygenation of the cortex assessed by magnetic resonance imaging (MRI) after 6 hours, without any effect on renal perfusion and oxygenation of the medulla [90]. A prospective, randomized and drug-controlled trial was designed to determine the nephroprotective effect exerted by canagliflozin in newly diagnosed T2D patients with normal renal function using blood oxygen level-dependent MRI and arterial spin labeling MRI. The conclusion was that canagliflozin 100 mg also improved the levels of renal oxygenation independent of changes in renal blood perfusion [91].

A decrease in oxygen consumption is thus suggested to have benefits on the progression of CKD, [29]. The term ‘beta-blockers for the kidney’ has been proposed to illustrate this renal effect of SGLT2is [92].

4.4. A combination of different clinical effects

SGLT2i therapy exerts pleiotropic effects that could improve renal outcomes, among which improvement of blood glucose control, weight loss, reduction in arterial blood pressure, decrease of serum uric acid, and increase of hematocrit [7]. Previous detailed analyses suggested that a modest reduction in arterial blood pressure as reported with SGLT2is in patients with T2D and with already well-treated hypertension cannot explain the reduction in renal outcomes [93]. If each single effect could not explain the better renal outcome, yet a contribution of a combination of all of them together could not be excluded [61]. Beyond these combined pleiotropic effects, the favorable effect on intraglomerular pressure, the potential diuretic effect, or the better oxygenation, the clinical impact on cardiovascular events, especially heart

failure, and the lower incidence of adverse events, notably AKI [81] could also explain the remarkable results in terms of nephroprotection observed with SGLT2is [11–15]. SGLT2is by decreasing the episodes of acute heart failure would not only prevent AKI episodes but also would potentially have a positive impact on renal ‘chronic’ outcomes (like serum creatinine doubling or need for dialysis). This observation could be especially relevant to explain the persistent positive effect of SGLT2is in patients with near-to-normal GFR and normal level of albuminuria, whereas the diuretic effect would be particularly interesting in patients with (or at high risk) of heart failure (at least in those with reduced left ventricular ejection fraction) [9,30], and the effect on the intraglomerular pressure would be more relevant in patients with hyperfiltration, CKD and/or high albuminuria levels [27,28,60,94–97]. Reasons of the renal benefits of SGLT2is are thus probably multiple, and mutually not exclusive. Other biochemical mechanisms have also been proposed such as a reduction in low-grade inflammation and oxidative stress, which could lead to a reduction in tissue-cellular damages (Figure 1) [2,26,64].

5. SGLT2 inhibitors in international guidelines

The unique nephroprotective role of SGLT2is has been emphasized in many international guidelines, not only in the diabetes field [98,99], but also among cardiologists [100] and nephrologists [1,101]. As a consequence, patients with renal disease should benefit from an SGLT2i, a pharmacological class that should be preferred to dipeptidyl peptidase-4 inhibitors or glucagon-like peptide-1 receptor agonists. The critical threshold of eGFR for the initiation of an SGLT2i that was initially 60 ml/min/1.73 m² has been now decreased to 30 (or even 25 for dapagliflozin) ml/min/1.73 m², considering the positive benefit/risk balance in this population with stage 3 CKD. Thus, it is obvious that the use of SGLT2is will markedly increase in coming years, not only to prevent CV events, but also to provide renal protection, in combination with RAAS inhibitors.

6. Conclusion

SGLT2is have consistently and remarkably demonstrated a renal protection with not only a significant reduction in albuminuria but also a reduction in a composite renal outcome that combined a sustained loss in eGFR, a progression to ESRD and renal death. Such positive effects on hard renal endpoints appear to be even better than those previously reported with classically recognized nephroprotective drugs as RAAS inhibitors. These positive effects were observed in large prospective placebo-controlled trials among patients already treated with RAAS inhibitors and established atherosclerotic CVD, renal disease, or heart failure. Thereby, SGLT2is have gained a privileged position in the management of patients with or at risk of CKD in all international guidelines, even in patients with stage 3a and 3b CKD where a favorable benefit/risk ratio could also be demonstrated. The renal protection is independent of the improvement of glucose control and is observed also in patients without diabetes. The

underlying mechanisms of the renal benefits of SGLT2is are probably multiple, among which a possible contribution of various pleiotropic effects, a hemodynamic intraglomerular change and a diuretic effect, both contributing to reduced albuminuria, a renal decongestion resulting from the diuretic effect, an increased renal oxygenation, as well as a reduction in cardiorenal syndrome and AKI. All these effects are most probably mutually not exclusive and their respective contribution may differ according to patient characteristics.

7. Expert opinion

Besides the consistent positive effects on the risk of heart failure, a reduction in hard renal outcomes (a composite of sustained loss of eGFR or doubling of creatinine, ESRD, renal death) has been shown in a highly reproducible manner in people with different clinical profiles [21,22,24]. While SGLT2is were developed as glucose-lowering agents for the management of T2D [7], a significant reduction in both CV and renal outcomes has been reported in patients with T2D independently of baseline glycated hemoglobin levels and their SGLT2i-associated reduction during the trials [7]. This cardiorenal protection independent of glucose control has been remarkably confirmed with similar positive results in patients with or without diabetes with either heart failure [8–10] or CKD with albuminuria [12]. These unexpected findings will pave the road for an extension of the use of SGLT2is by both cardiologists [100,102] and nephrologists [1,101], beyond the interest of diabetologists [103]. Despite a huge amount of experimental and clinical studies with SGLT2is in recent years, still several important questions remain open and deserve further investigations; some of them will be briefly discussed in this expert opinion section.

Recent studies have shown that a nephroprotective effect, without increasing the risk of AKI, could be detected even in patients with stage 3b CKD and eGFR as low as 25–30 ml/min/1.73 m². These observations resulted in an extension of the use of SGLT2is in patients with advanced CKD in more recent international guidelines [1,101]. However, one may speculate that SGLT2is would be also useful in patients with stage 4 CKD. Favorable results have been reported in post-hoc analyses in both CREDENCE [36] and DAPA-CKD [37], yet on rather limited subgroups of patients with eGFR < 30 ml/min/1.73 m². Further dedicated studies in patients with more severe CKD are awaited to confirm this hypothesis.

The hemodynamic intraglomerular changes induced by SGLT2is are still a matter of debate. Indeed, whereas a predominant vasoconstriction of the afferent arteriole was considered as the predominant action according to the ‘tubular theory’ (mainly shown in patients with T1D and hyperfiltration) [56], more recent mechanistic studies in patients with T2D showed also a vasodilatory effect on the efferent arteriole (‘vascular theory,’ similar to the mechanism attributed to RAAS inhibitors) [54,57]. What so ever, the final action results in a reduction in the intraglomerular pressure, an effect that explains a biphasic effect on renal function over time: an initial functional and reversible dip in eGFR (associated with an early reduction in albuminuria) and a secondary slowing down of

the eGFR decline slope (still accompanied by a sustained lowering of albuminuria), and an ultimate reduction in hard renal outcomes, including ESRD and renal death [2].

The possible impact of baseline albuminuria in the modulation of the nephroprotective effect of SGLT2is remains not fully resolved. Indeed, a detailed analysis of all available results from RCTs failed to show a significant influence of baseline albuminuria on final renal outcomes over a 3 to 4-year period [27]. Nevertheless, post-hoc analysis of the results from CREDENCE showed a greater reduction in the absolute number of events of renal composite outcome in patients with high (≥ 1000 mg/g creatinine) or very high (≥ 3000 mg/g creatinine) UACR compared with patients with lower levels [28]. Similar analyses from DAPA-CKD are not available yet and would be of potential interest to confirm these findings.

The EMPA-KIDNEY trial (‘Study of heart and kidney protection with empagliflozin’) is currently investigating the effects of empagliflozin, compared with placebo, on CKD progression or CV death in patients with eGFR ≥ 20 to < 45 ml/min/1.73 m² or in patients with eGFR ≥ 45 to < 90 ml/min/1.73 m² with UACR ≥ 200 mg/g on background RAAS inhibitors. Thus, in contrast to CREDENCE [11] and DAPA-CKD [12], EMPA-KIDNEY extends inclusion criteria to patients with low eGFR who have little or no albuminuria [104]. These data will allow to confirm (or not) previous findings reported in SCORED [25], as discussed above.

The role of a diuretic effect of SGLT2is on renal outcomes remains a matter of debate [61]. The precise assessment of a diuretic effect is not so easy because of the interference with some compensatory mechanisms, which could explain different early versus late effects [61]. Of note, the diuretic effect of SGLT2is have specificities with a better safety profile compared with classical diuretics, one of which being a reduction rather than an increase of AKI episodes [61]. Intuitively, a diuretic effect should play a major role in patients with heart failure and contribute to the reduction in hospitalization for heart failure [63]. The demonstration of a significant contribution of a diuretic effect on renal outcomes is more challenging [61]. The relationship between heart and renal functions is well known and designed as the cardio-renal syndrome [79,80]. However, the relationship might be more complex than initially thought [30]. Despite almost similar effects on the reduction of hospitalization for heart failure (and also on the attenuation of eGFR decline during the follow-up) in patients with reduced [9] or preserved [10] left ventricular ejection fraction, an impressive reduction in the composite renal outcome was only observed in EMPEROR-Reduced, which contrasted with almost no reduction in EMPEROR-Preserved [30]. The significance and mechanistic interpretation of these discrepant findings in patients with reduced- versus preserved left ventricular ejection fraction are still unclear, even if differences in the disease pathophysiology and in patient’s characteristics should most probably be involved. Obviously, further investigations are needed to first confirm and then explain these provocative observations.

Finally, one may hypothesize that the contribution of each underlying mechanism to the overall nephroprotection with SGLT2is may vary according to the patient profile. Hence, the restoration of the tubuloglomerular feedback could be the most effective process in patients with CKD and albuminuria,

whereas the diuretic effect could play a predominant role in patients with heart failure and fluid overload. Further well-designed dedicated mechanistic studies are urgently requested to better understand the effects of SGLT2is on renal physiology and clinical outcomes, according to the individual profiles of the patients. Although the inclusion of SGLT2is among diuretics is still a controversial issue, their nephroprotective and cardioprotective properties, confirmed in several landmark trials that included different populations, constitute a true revolution in the treatment of patients with CKD.

Funding

The authors have no funding to report.

Declaration of interest

AJ Scheen has received lecturer/advisor fees from AstraZeneca, Boehringer Ingelheim, Janssen, Merck Sharp & Dohme. He also worked as a clinical investigator in three cardiovascular outcome trials with SGLT2is (EMPA-REG OUTCOME, CANVAS-R, DECLARE-TIMI 58). P Delanaye has received lecturer/advisor fees from AstraZeneca. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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