Nephrol Dial Transplant (2020) 35: i33–i42
doi: 10.1093/ndt/gfz264

ndt
Nephrology Dialysis Transplantation

REVIEW

Sodium-glucose cotransporter 2 inhibitors: extending the indication to non-diabetic kidney disease?

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ABSTRACT

This year the medical community was pleasantly surprised by the results of the first large outcome trial that primarily examined the renal effects of the sodium-glucose cotransporter 2 (SGLT2) inhibitor canagliflozin (CANA) in subjects with diabetes and impaired kidney function. The Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trial showed that CANA, relative to placebo, reduces the risk for end-stage renal disease, doubling of creatinine or renal death by 34% [hazard ratio 0.66 (95% confidence interval 0.53–0.81]. These effects were consistent across baseline estimated glomerular filtration rate (eGFR) and haemoglobin A1c subgroups. In this review we combine the results of the CREDENCE trial with those of several cardiovascular outcome trials with SGLT2 inhibitors and show that, unexpectedly, patients with lower eGFR levels may have greater benefit with respect to cardiovascular outcome than patients with normal kidney function. The cardio- and renoprotective effects of SGLT2 inhibitors seem to be independent of their glucose-lowering effects, as shown in several *post hoc* analyses. In this review we discuss the alleged mechanisms of action that explain the beneficial effects of this novel class of drugs. Moreover, we discuss whether these findings indicate that this class of drugs may also be beneficial in non-diabetic chronic kidney diseases.

Keywords: cardiovascular, CKD, clinical trial, diabetes mellitus, GFR

INTRODUCTION

The proximal tubule in the kidney plays an important role in glucose homoeostasis by reabsorbing glucose from pre-urine back into the blood. Glucose is cotransported together with sodium by sodium-glucose cotransporter 1 (SGLT1), located in the S3 segment of the proximal tubule, and by SGLT2 located in the S1 segment of the renal proximal tubule. The vast majority of filtered glucose is reabsorbed by SGLT2. These SGLTs were discovered in the late 1970s/early 1980s [1]. By blocking SGLT1 and SGLT2 competitively with phlorizin, an old natural drug obtained from the bark of apple trees, urinary glucose excretion increased and plasma glucose normalized in diabetic rats [2, 3]. Yet, phlorizin was not an ideal candidate glucose-lowering drug because of its low oral bioavailability and unselective SGLT1 and SGLT2 inhibition, with intestinal side effects as a result of SGLT1 inhibition, such as diarrhoea and malabsorption [3, 4]. Later on, specific SGLT2 inhibitors were developed as glucose-lowering drugs with fewer intestinal side effects. These drugs had an adequate half-life ($T_{1/2}$)to allow oral once-daily administration [dapagliflozin (DAPA) $T_{1/2}$ 12.2 h, canagliflozin (CANA) $T_{1/2}$ 11–13 h and empagliflozin (EMPA) $T_{1/2}$ 12.4 h] [5]. In 2012, the first SGLT2 inhibitor, DAPA, was given marketing authorization by the European Medicines Agency as a glucose-lowering drug in patients with type 2 diabetes mellitus, followed by approval from the US Food and Drug Administration in 2014 [3]. These regulatory agencies required the industry to conduct large cardiovascular outcome trials to investigate potential harmful cardiovascular side effects. In 2015, the first outcome trial was published with the SGLT2 inhibitor EMPA [6]. This trial, together with the two cardiovascular outcome trials with CANA and DAPA that were published in the years thereafter, showed unexpected cardiovascular and renal beneficial effects of these drugs in patients with type 2 diabetes [6–10]. These patients often received lipid-lowering, antihypertensive and antiproteinuric treatment with renin–angiotensin–aldosterone system (RAAS) blockade, but despite these interventions, the residual risk for progression of diabetic kidney disease remains high [11]. The development of SGLT2 inhibitors provides new perspectives for these patients.

Six to 10 years ago, Phase 2 and 3 studies already showed that SGLT2 inhibitors not only lowered plasma glucose, but also decreased blood pressure, body weight (BW) and proteinuria

Table 1. Summary of outcome trials with SGLT2 inhibitors

Trial and design	Main inclusion criteria	Main cardiovascular outcomes	Main renal outcomes
DECLARE-TIMI 58 DAPA 10 mg or placebo once daily $N = 17\,160$ eGFR = 85.2 mL/min/1.73 m^2 Median follow-up: 4.2 years	Type 2 diabetes HbA1c 6.5–12.0% Established atherosclerotic CVD or multiple risk factors for atherosclerotic CVD Creatinine clearance ≥60 mL/min	17% reduction [HR 0.83 (95% CI 0.73–0.95), P = 0.005] of the composite of cardiovascular death or hospitalization for heart failure. No effect [HR 0.93 (95% CI 0.84–1.03), P = 0.17] on MACEs	47% reduction [HR 0.53 (95% CI 0.43–0.66), P < 0.0001] of renal-specific composite outcome
EMPA-REG OUTCOME EMPA 10 mg, EMPA 25 mg, or placebo once daily $N = 7020$ eGFR = 74.1 mL/min/1.73 m^2 Median follow-up: 3.1 years	Type 2 diabetes HbA1c 7.0–9.0% without glucose-lowering therapy or HbA1c 7.0–10.0% with stable glucose-lowering therapy BMI ≤45 kg/m^2 Established CVD eGFR ≥30 mL/min/1.73 m^2	14% reduction [HR 0.86 (95% CI 0.74–0.99), P = 0.04] of composite of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke	39% reduction [HR 0.61 (95% CI 0.53–0.70), P < 0.001] of renal-specific composite outcome
CANVAS CANA 300 mg, CANA 100 mg or placebo once daily $N = 10\,142$ eGFR = 76.5 mL/min/1.73 m^2 Median follow-up: 2.4 years	Type 2 diabetes HbA1c 7.0–10.5% Established CVD or two or more risk factors for CVD eGFR ≥30 mL/min/1.73 m^2	14% reduction [HR 0.86 (95% CI 0.75–0.97), P = 0.02] of composite of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke	40% reduction [HR 0.60 (95% CI 0.47–0.77)] of renal-specific composite outcome
CREDENCE CANA 100 mg or placebo once daily $N = 4401$ eGFR = 85.2 mL/min/1.73 m^2 Median follow-up: 2.6 years	Type 2 diabetes ≥30 years of age HbA1c 6.5–12.0% Established CKD: eGFR 30–90 mL/min/1.73 m^2 and UACR 300–5000 mg/g	31% reduction [HR 0.69 (95% CI 0.57–0.83), P < 0.001] of composite of cardiovascular death or hospitalization for heart failure	34% reduction [HR 0.66 (95% CI 0.53–0.81), P < 0.001] of renal-specific composite outcome

BMI, body mass index; MACEs, major adverse cardiovascular events.

[12–14]. The recent large cardiovascular outcome trials Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) with EMPA, CANagliflozin cardioVascular Assessment Study (CANVAS) with CANA and Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58 with DAPA reproduced these beneficial effects and also showed that SGLT2 inhibitors lowered the risk for renal events by 34–47%, the risk for cardiovascular events by 7–14% and the risk for hospitalization for heart failure by ∼30% (Table 1). Renal events were defined differently in these three trials as a composite of incidence of kidney replacement therapy/end-stage kidney disease or renal- or cardiovascular death, combined in the EMPA-REG OUTCOME and CANVAS trials with progression to macroalbuminuria and/or doubling of serum creatinine and in the DECLARE-TIMI58 trial with a 40% reduction in estimated glomerular filtration rate (eGFR) (Table 1). The results obtained in these trials were very promising. However, they were not designed to examine changes in renal outcomes, but to test cardiovascular safety in a non-inferiority design compared with placebo. Therefore specific, well-powered renal outcomes trials were launched and small-scale mechanistic studies were initiated to obtain more insight into the underlying renoprotective mechanisms.

This review will focus on the effects and the use of SGLT2 inhibitors in patients with chronic kidney disease (CKD). We will elaborate on the mechanisms underlying the renoprotective effects and question whether, based on these mechanisms, SGLT2 inhibitors might also be indicated for non-diabetic patients with a CKD.

Could SGLT2 inhibitors also be beneficial in patients with reduced kidney function?

SGLT2 inhibitors were officially indicated as an adjunct to diet and exercise to lower blood glucose levels in adults with type 2 diabetes mellitus. The labels do not allow the use of these drugs in subjects with impaired kidney function. Likewise, until recently, regulatory agencies and guidelines advised against prescribing SGLT2 inhibitors to patients with an eGFR <60 mL/min/1.73 m^2 [15–18]. This recommendation was based on studies illustrating that the glucose-lowering effect of SGLT2 inhibitors is less in people with lower kidney functions [6, 9, 12]. A smaller mean haemoglobin A1c (HbA1c) difference was also found in the Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trial, a large outcome trial with CANA that specifically included subjects with lower kidney functions when compared with the CANVAS trial (mean baseline eGFR 56 versus 77 mL/min/1.73 m^2, respectively). The effects on HbA1c throughout the trial were −0.25% [95% confidence interval (CI) −0.20% to −0.31%] and −0.58% (95% CI −0.61% to −0.56%), respectively [10, 19]. This is not surprising since the blood glucose–lowering effect of this class of drugs is dependent on the number of intact nephrons [20]. However, multiple studies have suggested that reductions in blood pressure, BW and proteinuria are independent of glucose control and may persist in people with lower kidney functions [21–24]. For instance, Heerspink *et al.* [24] showed that 2 years of treatment with CANA compared with glimepiride resulted in a smaller annual eGFR decline and a relatively larger urinary

albumin:creatinine ratio (UACR) reduction in subjects with a higher baseline UACR, while the differences in HbA1c between the groups were modest. Adjusting the analysis for these modest differences in HbA1c did not alter the results [24]. Three other groups examined the use of SGLT2 inhibitors in subjects with lower kidney functions and also found attenuated effects on HbA1c but persistent beneficial effects on blood pressure, BW and proteinuria [21–23]. The effects on cardiovascular and renal endpoints might therefore be different from the effects on HbA1c in patients with a reduced kidney function. These findings also suggest that SGLT2 inhibitors may have potential benefits in subjects with CKD, perhaps even in non-diabetic subjects.

Post hoc analyses of the cardiovascular safety trials evaluated whether these short-term beneficial effects can be translated into risk reductions for cardiovascular and renal events in patients with type 2 diabetes mellitus and established CKD [8, 25–27]. The number of subjects with a baseline eGFR <60 mL/min/1.73 m^2 was 1819 (25.9%), 1265 (7.4%) and 2039 (20.1%), in the EMPA-REG OUTCOME, DECLARE-TIMI58 and CANVAS trials, respectively. When looking at the EMPA-REG OUTCOME trial, it was concluded that with EMPA in the subjects with a baseline eGFR <60 mL/min/1.73 m^2, a similar risk reduction for the primary cardiovascular outcome was obtained as in subjects with an eGFR ≥60 mL/min/1.73 m^2 [26]. The relative risk reductions for the primary cardiovascular outcome [3-point major adverse cardiovascular events (MACEs)], cardiovascular death and hospitalization for heart failure were also consistent across baseline eGFR subgroups in the CANVAS programme [25].

In contrast with the cardiovascular outcome trials, the CREDENCE trial was specifically powered to assess cardiorenal outcomes in people with type 2 diabetes and CKD. People with an eGFR between 30 and 90 mL/min/1.73 m^2 and an UACR between 300 and 5000 mg/g were included and randomized to receive treatment with CANA 100 mg/day or placebo. The baseline mean eGFR level was 56 mL/min/1.73 m^2 and the median UACR was 927 mg/g. The trial was stopped early because of overwhelming efficacy. The pre-specified efficacy criteria for early cessation of the trial were achieved at the interim analysis that was conducted after the occurrence of the primary composite renal outcome in 405 patients. Relative to placebo, CANA reduced the risk for end-stage renal disease, doubling of creatinine or renal death by 34% [hazard ratio (HR) 0.66, 95% CI 0.53–0.81]. Also in this trial, the effects were reported to be consistent across baseline eGFR categories [19]. Nearly all patients included in the CREDENCE trial were on a stable dose of RAAS blockade. Adding CANA slowed the progression of eGFR decline by 1.52 mL/min/1.73 m^2/year compared with placebo and did not result in an increase in the risk for acute kidney failure [19]. Other renal outcome trials with EMPA (EMPA-KIDNEY) and DAPA (DAPA-CKD) are ongoing.

Taken together, the data of the outcome trials in patients with type 2 diabetes suggest that SGLT2 inhibitors reduced cardiovascular and renal endpoints regardless of baseline renal function [8, 19, 25, 26]. Surprisingly, a different picture is obtained when data of these trials are combined as shown in Figure 1. This figure shows the primary cardiovascular and renal outcomes of the trials with DAPA, EMPA and CANA per baseline eGFR subgroup (<45, 45–60, 60–90 and ≥90 mL/min/1.73 m^2). Subjects with lower kidney function seem to have greater beneficial effects on cardiovascular outcomes than subjects with better kidney function with respect to relative as well as absolute risk reduction. In line with this, a recent meta-analysis also showed that patients with a lower baseline eGFR have greater reductions of the risk for hospitalization for heart failure than patients with a higher baseline eGFR (P for interaction = 0.007) [28]. These results suggest that from a cardiovascular perspective, especially patients with impaired kidney function benefit from SGLT2 inhibition. Looking at the renal outcomes in Figure 1, one can observe a beneficial effect of SGLT2 inhibitors in all eGFR subgroups. However, the trend seems opposite to the trend for cardiovascular outcomes. The magnitude of the benefit of SGLT2 inhibition appears to be smaller in people with lower eGFR levels. A similar pattern was observed in the meta-analysis of Neuen *et al.* (P_{trend} for eGFR subgroup 0.073) [27]. Yet, when looking at absolute benefit in Figure 1, expressed as the estimated number needed to treat during 5 years to prevent one event, it shows that a still better treatment efficacy is found in the lower eGFR subgroups. For example, the average number needed to treat to prevent a renal event is 21 in the subgroup with eGFR <45 mL/min/1.73 m^2, while it is 30, 62 and 79 in the subgroups of patients with an eGFR 45–60, 60–90 and ≥90 mL/min/1.73 m^2, respectively (Figure 1). These data in Figure 1 suggest that, despite the fact that SGLT2 inhibitors were originally thought to have less efficacy in subjects with lower kidney function, this class of drugs actually has better treatment efficacy in subjects with lower kidney function, especially when looking at cardiovascular events, but possibly also with respect to the absolute number of renal events to be prevented.

Regarding safety, it can be stated that in the cardiovascular outcome trials in patients with type 2 diabetes, the SGLT2 inhibitors were generally well tolerated. Overall, there was no increased risk for hyperkalaemia or acute kidney injury [28]. Only the risk for mycotic genital infections appeared to be increased, which is related to the urinary excretion of glucose [29, 30]. In the CREDENCE trial, no surprising or unknown adverse events were detected. Only the rates of ketoacidosis were higher in the CANA group than the placebo group (2.2 versus 0.2/1000 patients), but the total event rate was low [19]. Subgroup analyses according to baseline kidney function are yet not available.

Based on the new outcome and safety trials, both the American Diabetes Association (ADA) and the European Association for the Study of Diabetes published in 2018 a consensus statement on the management of hyperglycaemia in patients with type 2 diabetes. They now advise considering the use of SGLT2 inhibitors in patients with type 2 diabetes and CKD with or without cardiovascular disease (CVD) (if eGFR is adequate) [17, 31]. The revised ADA guideline also included that DAPA is approved for use in patients with type 2 diabetes and an eGFR ≥45 mL/min/1.73 m^2, instead of ≥60 mL/min/1.73 m^2 [17]. Given the data that are presented in this review,

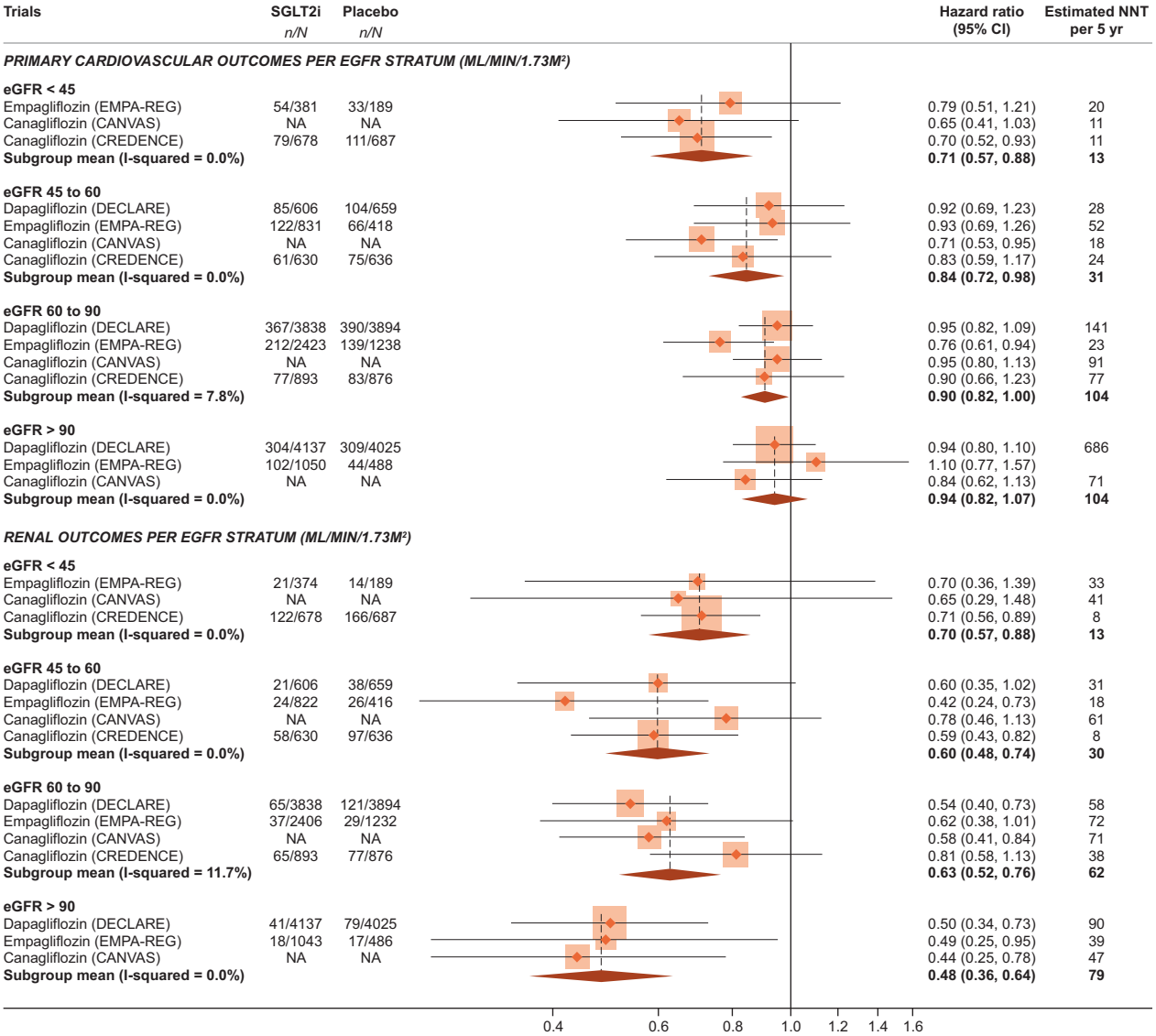

FIGURE 1: The primary cardiovascular and renal outcomes of the SGLT2 inhibitor outcome trials according to baseline eGFR subgroup. Primary cardiovascular outcome was defined as 3-point MACEs. Renal outcomes were defined as sustained 40% decrease of eGFR, renal replacement therapy or end-stage kidney disease, or renal death. Only for the CREDENCE trial, the renal outcome was different, namely, doubling of serum creatinine, end-stage kidney disease or death from renal or cardiovascular causes. The outcomes of subgroup 'eGFR <60 mL/min/1.73 m^{2}' of the DECLARE trial were used in our analysis and were depicted as subgroup 'eGFR 45–60 mL/min/1.73 m^{2}' on the assumption that there were no subjects with a baseline eGFR <45 mL/min/1.73 m^{2}. A detailed description of the methods can be found in the Supplementary data. NNT per 5yr, estimated number needed to treat during 5 years to prevent one event.

we propose that SGLT2 inhibitors can also be used in subjects with CKD and even lower kidney function.

Mechanisms underlying the renoprotective effects of SGLT2 inhibitors

After it became clear that the beneficial renal effects of SGLT2 inhibitors were largely independent of the blood glucose–lowering effect of these drugs, intensive research focused on disclosing what mechanism may underlie their renoprotective effect. Multiple mechanisms have been hypothesized to be responsible [32]. Several recent reviews have addressed the various alleged mechanisms leading to renal protection in detail [33]. Therefore this issue will be only briefly discussed here.

Systemic mechanisms involve a decrease in HbA1c, BW, inflammation and blood pressure that are caused by SGLT2 inhibition, which are known risk factors for the development and progression of CKD [32]. SGLT2 inhibition might also contribute to reverse systemic inflammatory and fibrotic processes, as indicated by the decreases in plasma tumor necrosis factor receptor 1, inerleukin-6 (IL-6), matrix metallopeptidase 7 and fibronectin 1 during CANA therapy [34]. The effects on blood pressure are not restricted to daytime, as nocturnal blood pressure is also decreased, which is a predictor for cardiovascular and renal disease progression [35, 36]. A few articles have also reported that SGLT2 inhibitors reduce aortic stiffness, but others were not able to replicate this [37–39]. Decreases in

blood pressure and arterial stiffness might decrease the cardiac afterload. Furthermore, SGLT2 inhibitors might improve the cardiac preload by lowering plasma volume as a result of osmotic and natriuretic diuresis, secondary to urinary sodium and glucose excretion [40, 41]. These systemic haemodynamic mechanisms can beneficially influence the heart as well as the kidneys.

SGLT2 inhibitors also promote specific intrarenal haemodynamic changes that may protect glomeruli from high-pressure damage. In 2014, Cherney *et al.* [42] showed that EMPA attenuates glomerular hyperfiltration in subjects with type 1 diabetes. Subsequently he and others speculated about a causal mechanism responsible for the attenuation of glomerular hyperfiltration and for the typical 'dip' in GFR that is observed directly after initiation of SGLT2 inhibitors [32]. It was hypothesized that inhibition of SGLT2 decreased the SGLT2-mediated reabsorption of sodium and glucose in the proximal tubule, leading to increased delivery of glucose and sodium chloride to the macula densa. The macula densa interprets this as circulating volume expansion and via tubuloglomerular feedback either dilates the post-glomerular arteriole or constricts the pre-glomerular arteriole. The latter was considered more likely given the absence of changes in vasodilators in the urine. Recently Kidokoro *et al.* [43] explored the glomerular haemodynamic effects of EMPA in a type 1 diabetic mouse model by visualizing the afferent and efferent arteriole with *in vivo* multiphoton microscopy imaging techniques. They also measured the single-nephron glomerular filtration. EMPA significantly constricted the afferent arteriole within 30 min after administration and consequently suppressed glomerular pressure and single-nephron GFR. These effects were abolished by A1 adenosine receptor blockade [43], suggesting that increased adenosine generation following a restored tubuloglomerular feedback mechanism is the key pathway for suppression of hyperfiltration during SGLT2 inhibition.

Inhibition of glucose and sodium reabsorption in the proximal tubule can also lead to other potential beneficial processes in the kidney. For instance, it may improve mitochondrial mechanisms, decrease hypoxic damage to proximal tubular cells and reduce intrarenal inflammation. A recently published *post hoc* analysis of a short-term clinical trial in subjects with type 2 diabetes showed that DAPA, compared with placebo, increased the excretion of urinary ketone bodies and urinary metabolites that are linked to mitochondrial working mechanisms, suggesting a beneficial effect on mitochondria [44]. Plasma metabolites were not changed and there was no correlation with (change in) eGFR, suggesting that the effects were kidney-specific [44]. The authors hypothesized that their results could be explained by the increased availability of alternative fuel sources and/or a reduced workload for proximal tubular cells [44]. SGLT2 inhibition might increase the level of ketone bodies as a result of enhanced lipolysis and reduced insulin levels [45]. SGLT2 inhibition might also stimulate tubular ketone body reabsorption by delivering sodium to the sodium monocarboxylate transporters (SMCT2 and SMCT1) that are dependent on the sodium gradient to reabsorb ketones from the lumen to the proximal tubular cells [45]. Ketone bodies are involved in signalling functions and can act as an alternative energy substrate for tubular cells along with glucose and free fatty acids [45]. Furthermore, SGLT2 inhibition might reduce the workload for proximal tubular cells and decrease hypoxia-induced proximal tubular damage, adenosine triphosphate consumption and mitochondrial fragmentation [44]. The decrease of hypoxic cell damage is illustrated by a reduction in proximal tubular injury marker kidney injury molecule-1 during SGLT2 inhibitor therapy [46]. Some articles also reported reductions in other kidney injury markers such as liver fatty acid–binding protein and N-acetyl β-d-glucosaminidase and of inflammatory markers such as IL-6 [34, 46, 47]. Inflammation is associated with the development and decline of CKD, hence inhibition of inflammatory pathways may also contribute to kidney protection [48].

It is not yet clear whether the above-described mechanisms contribute equally to the favourable kidney outcomes or if certain mechanisms are more important than others. Future experimental studies will have to provide more information and clarification.

Extending to non-diabetic kidney disease

An important question is whether more people can benefit from SGLT2 inhibitors in addition to subjects with diabetes. At this moment it is unknown whether SGLT2 inhibitors affect cardiovascular and renal outcome in non-diabetic subjects since long-term clinical trials that investigate the effects of SGLT2 inhibitors solely in the non-diabetic population are not yet available. An indication may be obtained from studying subgroups of the cardiovascular and renal outcome trials defined by the level of glucose control. When meta-analysed, no large differences are observed between subjects with baseline HbA1c levels greater than or less than 8% (Figure 2) [8]. Recently the DAPA-HF trial was published that examined the effects of DAPA in diabetic and non-diabetic subjects with heart failure and reduced ejection fraction. Fifty-five percent of the subjects in each treatment group were non-diabetic at screening [49]. This trial also found a consistent beneficial effect on the primary composite endpoint, i.e. cardiovascular death, hospitalization for heart failure or urgent heart failure visit, between subjects with and without type 2 diabetes mellitus [HR 0.75 (95% CI 0.63–0.90) and HR 0.73 (95% CI 0.60–0.88), respectively] [49]. There was no significant reduction of the secondary composite renal endpoint, i.e. sustained reduction in eGFR of $\geq$50%, end-stage kidney disease or death from renal causes, but the total event numbers were very low (28 subjects in the DAPA group and 39 subjects in the placebo group), and the number of serious renal events was significantly lower in the DAPA group [49]. Hence it might be that SGLT2 inhibitors also reduces eGFR decline in subjects with well-regulated diabetes mellitus, pre-diabetes or even non-diabetic CKD.

CKD can lead to nephron loss, resulting in an increased single-nephron GFR in the remaining glomeruli. This causes intraglomerular hypertension, which in turn can damage the remaining glomeruli, resulting in proteinuria and glomerulosclerosis. Looking at the renoprotective mechanisms of SGLT2 inhibitors, one can think of several kidney diseases that might

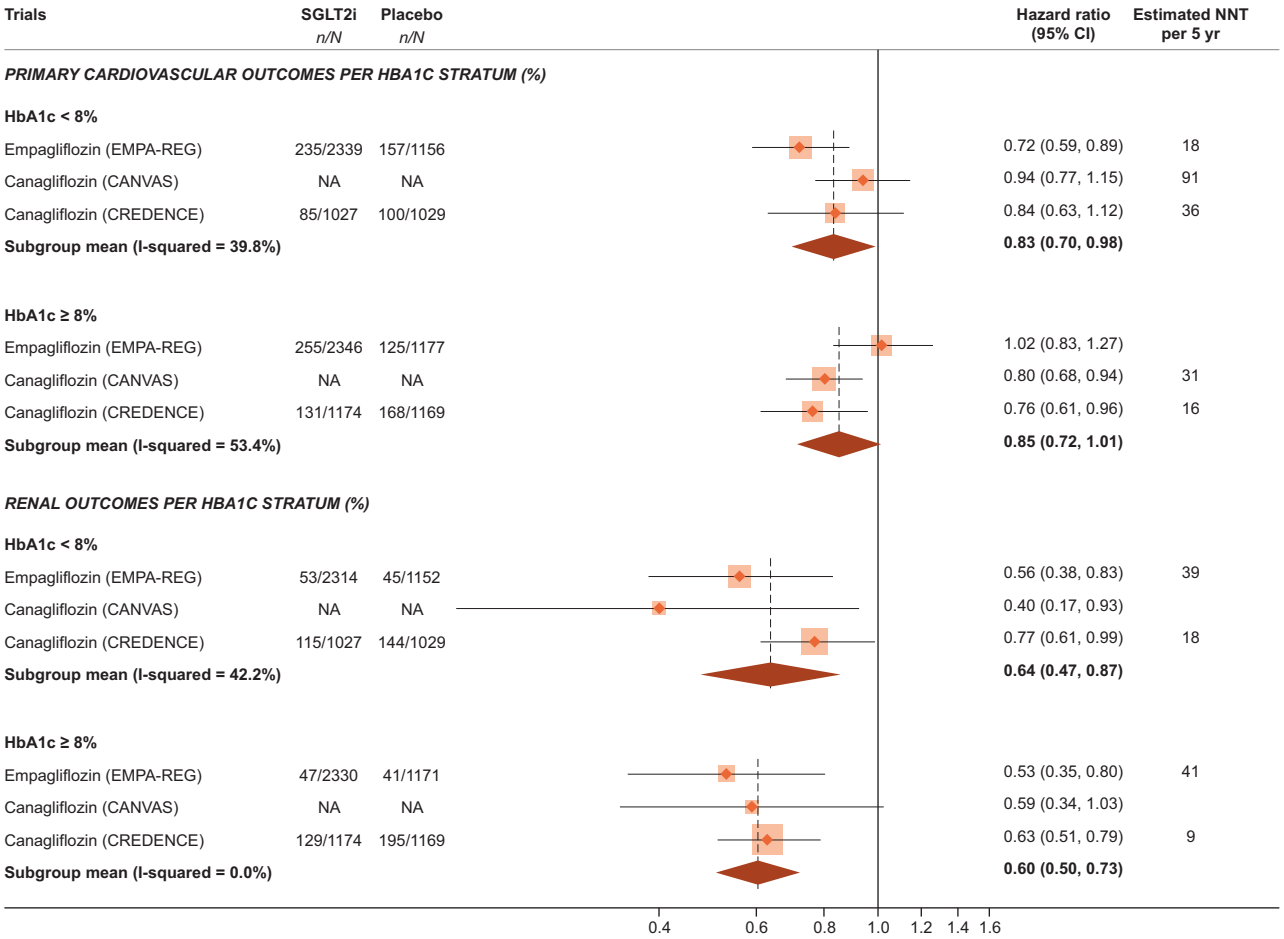

FIGURE 2: The primary cardiovascular and renal outcomes of the SGLT2 inhibitor outcome trials per baseline HbA1c subgroup. The primary cardiovascular outcome was defined as 3-point MACEs. Renal outcomes were defined as a sustained 40% decrease of eGFR, renal replacement therapy or renal death for the EMPA-REG OUTCOME trial; composite of doubling of serum creatinine, end-stage kidney disease or renal death for the CANVAS trial; and a composite of doubling of serum creatinine, end-stage kidney disease and renal or cardiovascular death for the CREDENCE trial. A description of the methods can be found in the Supplementary data.

benefit specifically from SGLT2 inhibitor therapy; for example, obesity-induced CKD, hypertensive nephrosclerosis or focal segmental glomerulosclerosis (FSGS). Obesity-induced CKD is characterized by renal haemodynamic changes resulting in increased renal plasma flow, GFR and filtration fraction, possibly due to afferent arterial vasodilation [50]. SGLT2 inhibitors reduce glomerular hyperfiltration by afferent arterial vasoconstriction and promote BW loss. Both are highly desirable effects in patients with obesity-induced CKD. In patients with hypertensive nephrosclerosis, increased renal plasma flow and glomerular hypertension are a result of arterial stiffening [51]. SGLT2 inhibition can potentially decrease intraglomerular pressure and reduce arterial stiffness in these patients, which could help to slow disease progression. Patients with FSGS or with immunoglobulin A nephropathy might also benefit from SGLT2 inhibition. These glomerular-based diseases often result in proteinuria and hypertension [50]. Most patients respond to RAAS blockade, but not all. Of note, RAAS inhibitors have different mechanisms of action than SGLT2 inhibitors. RAAS inhibitors reduce the intraglomerular pressure by limiting angiotensin II–induced vasoconstriction of the efferent arteriole, while SGLT2 inhibitors activate the tubuloglomerular feedback mechanism, as explained in the previous section. SGLT2 inhibition can therefore be used as an alternative treatment or in addition to RAAS inhibition to further delay the decline of kidney function. However, it is still unclear whether SGLT2 inhibitors are truly effective in non-diabetic kidney diseases.

Currently several preclinical studies have been published that examined the renal effects of SGLT2 inhibitors in non-diabetic animals (Table 2). These studies show contradictory results. Two studies did not find the renoprotective effects of SGLT2 inhibitors. The other studies found a reduction of proteinuria, kidney damage, inflammation and fibrosis after SGLT2 inhibition (Table 2). The heterogeneity of the models that were used makes it difficult to compare the results. Summarizing, Zhang *et al.* [52] used a non-diabetic subtotally nephrectomized rat model representing glomerular hyperfiltration and found no effects on proteinuria, GFR, glomerulosclerosis or tubulointerstitial fibrosis. Ma *et al.* [53] used a mouse model of CKD with tubulointerstitial injury and also did not find beneficial effects on GFR, markers of fibrosis and tubular injury and inflammation. Cassis *et al.* [54] used a proteinuric mouse model of CKD and found that DAPA reduced the number of glomerular lesions, proteinuria and podocyte

Table 2. SGLT2 inhibitors in non-diabetic animals with kidney disease or risk factors for renal function decline

References	Design	Main outcomes	Conclusion
Zhang *et al.* [52]	53 Sprague Dawley rats were assigned to sham surgery + vehicle, sham surgery + DAPA or subtotal nephrectomy (SNx) + vehicle SNx + DAPA Treatment period: 12 weeks	DAPA versus vehicle: no change in SBP, 24-h proteinuria excretion, and GFR; no effect on glomerulosclerosis, tubulointerstitial fibrosis and TGF-β1 mRNA overexpression	No renoprotective effects in a non-diabetic rat model, representing glomerular hyperfiltration
Ma *et al.* [53]	20 C57BL/6N mice were assigned to high oxalate diet + vehicle or high oxalate diet + EMPA Treatment period: 7 or 14 days	EMPA versus vehicle: no effect on calcium oxalate crystal deposition; no effect on GFR decline, plasma creatinine and BUN; no effect on tubular injury, inflammation and fibrosis markers	No renoprotective effects in a non-diabetic mouse model with progressive CKD due to tubulointerstitial disease
Zhang *et al.* [55]	C57BL/6J mice were assigned to Model 1: nephrectomy of the right kidney and 11 days later sham surgery or IR injury left + vehicle or luseogliflozin (LUSEO); Model 2: contralateral kidney was used as a control and sham surgery or IR injury left + vehicle or LUSEO Treatment period: 7 days	LUSEO versus vehicle: no effect on creatinine clearance Week 1 post-IR. Preserved creatinine clearance at Week 4 attenuated TGF-β expression, peritubular capillary congestion and haemorrhage, tissue hypoxia and CD31-positive cell loss at Week 1 and reduced renal interstitial fibrosis at Week 4 increased VEGF-A mRNA expression in Week 1. Inhibition of VEGF by sunitinib inhibited LUSEO-induced renoprotective effects	LUSEO attenuated endothelial rarefaction, renal hypoxia and renal interstitial fibrosis after IR injury in non-diabetic mice, possibly via a VEGF-dependent pathway
Cassis *et al.* [54]	Unilateral nephrectomy was performed and C57BL/6N mice were assigned to control group ($n = 12$), bovine serum albumin (BSA) injections + vehicle ($n = 9$), BSA + DAPA ($n = 8$) or BSA + lisinopril ($n = 8$) Treatment period: 23 days	DAPA and lisinopril reduced SBP. No effects on BW and mGFR decline. DAPA and lisinopril reduced UACR by 63 and 72%, respectively. DAPA attenuated glomerular lesions, macrophage infiltration and podocyte loss. DAPA limited cytoskeletal remodelling *in vitro*	DAPA reduced proteinuria, glomerular lesions and limited podocyte loss in non-diabetic proteinuric mice
Jaikumkao *et al.* [56]	Obese Wistar rats were assigned to control group ($n = 6$), high-fat diet (HFD) ($n = 6$), HFD + metformin ($n = 6$) or HFD + DAPA ($n = 6$) Treatment period: 4 weeks	DAPA reduced renal hyperfiltration, microalbuminuria and expression of antioxidant enzyme superoxide dismutase, increased antioxidant glutathione, suppressed markers of inflammation and fibrosis and suppressed the expression of endoplasmic reticulum stress and renal pro-apoptotic proteins	DAPA decreased renal hyperfiltration, microalbuminuria and markers for renal inflammation, tubulointerstitial fibrosis and apoptosis in a prediabetic rat model

IR, ischaemia-reperfusion; SBP, systolic blood pressure; TGF, transforming growth factor; BUN, blood urea nitrogen; CD31, an endothelial marker.

damage [54]. Another group examined the effects of the SGLT2 inhibitor luseogliflozin (LUSEO) in an acute renal injury model and found that LUSEO attenuated endothelial rarefaction, interstitial fibrosis and renal hypoxia. These effects were observed together with an increase in vascular endothelial growth factor (VEGF), suggesting the influence of a VEGF-dependent pathway [55]. Finally, Jaikumkao *et al.* [56] examined the effects of SGLT2 inhibition in a prediabetic obese rat model and found that DAPA reduces hyperfiltration, microalbuminuria, inflammation and tubulointerstitial fibrosis [56]. All together the preclinical studies show contrary results. This is possibly due to differences in designs and methods, such as differences in group sizes, interspecies differences (mice versus rats), differences in types of experimental kidney diseases, differences in researcher-induced levels of kidney damage or potential differences in baseline eGFR and HbA1c levels.

To our knowledge, only two studies have examined the effects of SGLT2 inhibitors in humans with non-diabetic CKD or risk factors for CKD (Table 3). The first is a pilot study of Rajasekeran *et al.* [57] examining the effects of DAPA on renal haemodynamics and proteinuria in patients with FSGS [57]. Ten subjects with an eGFR $\geq$45 mL/min/1.73 m^2 and urinary protein excretion between 30 mg and 6 g/day were treated with DAPA 10 mg/day for 8 weeks on top of RAAS blocking therapy. DAPA increased 24-h urinary glucose excretion and plasma haematocrit but, remarkably, had no effect on BW, measured GFR, effective renal plasma flow (ERPF) and proteinuria [57]. A *post hoc* sensitivity analysis did show an effect on proteinuria, but only in subjects with a proteinuria level below the median [57]. The second study is a trial from Bays *et al.* [58] examining the effects of CANA in 376 non-diabetic obese subjects. They found a significant loss of BW, a small decrease in eGFR and an increase in haemoglobin, haematocrit and urinary glucose:creatinine ratio [58]. Other mechanistic, small-scale clinical trials in non-diabetic CKD patients are still ongoing. Two of these trials are planned to be published in 2020, DIAMOND (ClinicalTrials.gov,

Table 3. SGLT2 inhibitors in non-diabetic patients with kidney disease or risk factors for renal function decline

References	Design	Main outcomes	Conclusion
Rajasekeran *et al.* [57]	10 participants with biopsy-proven FSGS, eGFR ≥45 mL/min/1.73 m^2, proteinuria of 30 mg–6 g/day and no history of diabetes were treated with DAPA 10 mg/day for 8 weeks as add-on to RAAS blockade therapy	DAPA: increased 24-h urinary glucose excretion and plasma haematocrit; had no effect on BW, aldosterone, renin, 24-h urinary protein, mGFR, ERPF, renal vascular resistance, efferent or afferent resistance, glomerular pressure, renal blood flow or filtration fraction; reduced proteinuria in subjects with urinary proteinuria less than the median (*post hoc* sensitivity analysis). SGLT2 mRNA levels were reduced in FSGS kidney tissue versus healthy controls	DAPA on top of RAAS-blocking treatment had neutral renal haemodynamic and antiproteinuric effects in non-diabetic patients with FSGS
Bays *et al.* [58]	376 non-diabetic obese subjects were randomized to receive placebo, CANA 50 mg/day, CANA 100 mg/day or CANA 300 mg/day Treatment period: 12 weeks	CANA 50, 100 and 300 g/day versus placebo: decreased BW by −0.8, −1.6 and −1.3 kg and BMI by −0.3, −0.6 and −0.5 kg/m^2, respectively; no change in waist circumference and SBP; increased haemoglobin, haematocrit and urinary glucose:creatinine ratio; decreased eGFR by −1.0, −1.8 and 0.3 mL/min/1.73 m^2, respectively	CANA reduced BW but had no beneficial renal effects in non-diabetic obese subjects

mGFR, measured glomerular filtration rate. SBP, systolic blood pressure

NCT03190694) and DAPASALT (NCT03152084). In 2020 and 2022, respectively, the results of large-scale long-term outcome trials DAPA-CKD (NCT03036150) and EMPA-KIDNEY (NCT03594110) are expected. These outcome trials and mechanistic trials will add new information to the existing data of the CREDENCE trial because these trials include patients without diabetes mellitus, patients with an eGFR <30 mL/min/1.73 m^2 and patients with non-proteinuric CKD.

CONCLUSION

The data from recent trials show a pattern that suggests SGLT2 inhibitors are cardiovascular and renoprotective in patients with lower renal functions, in patients with lower HbA1c levels and in patients with non-diabetic kidney disease. However, the available data are limited, especially in the non-diabetic CKD population. Moreover, the current literature in the non-diabetic population sometimes shows inconsistent results. Based on these data, we can only hypothesize, but not yet conclude, that SGLT2 inhibitors have renoprotective effects in non-diabetic patients with CKD. Ongoing and future trials will have to prove whether SGLT2 inhibitors are indeed effective in non-diabetic patients with kidney diseases.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online

CONFLICT OF INTEREST STATEMENT

C.C.J.D. and R.T.G. participate in an investigator-initiated clinical trial with DAPA (DIAMOND, NCT03190694) for which AstraZeneca provided the research medication. Boehringer Ingelheim calculated and provided the numbers of the EMPA-REG OUTCOME trial that were used to make Figures 1 and 2.

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Received: 12.9.2019; Editorial decision: 6.11.2019