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Diabetic nephropathy (DN) is the most common cause of end-stage renal disease worldwide. Blood glucose and blood pressure control reduce the risk of developing this complication; however, once DN is established, it is only possible to slow progression. Sodium–glucose cotransporter 2 (SGLT2) inhibitors, the most recent glucose-lowering oral agents, may have the potential to exert nephroprotection not only through improving glycemic control but also through glucose-independent effects, such as blood pressure–lowering and direct renal effects. It is important to consider, however, that in patients with impaired renal function, given their mode of action, SGLT2 inhibitors are less effective in lowering blood glucose. In patients with high cardiovascular risk, the SGLT2 inhibitor empagliflozin lowered the rate of cardiovascular events, especially cardiovascular death, and substantially reduced important renal outcomes. Such benefits on DN could derive from effects beyond glycemia. Glomerular hyperfiltration is a potential risk factor for DN. In addition to the activation of the renin-angiotensin-aldosterone system, renal tubular factors, including SGLT2, contribute to glomerular hyperfiltration in diabetes. SGLT2 inhibitors reduce sodium reabsorption in the proximal tubule, causing, through tubuloglomerular feedback, afferent arteriole vasoconstriction and reduction in hyperfiltration. Experimental studies showed that SGLT2 inhibitors reduced hyperfiltration and decreased inflammatory and fibrotic responses of proximal tubular cells. SGLT2 inhibitors reduced glomerular hyperfiltration in patients with type 1 diabetes, and in patients with type 2 diabetes, they caused transient acute reductions in glomerular filtration rate, followed by a progressive recovery and stabilization of renal function. Interestingly, recent studies consistently demonstrated a reduction in albuminuria. Although these data are promising, only dedicated renal outcome trials will clarify whether SGLT2 inhibitors, in addition to their glycemic and blood pressure benefits, may provide nephroprotective effects.

Diabetes is a worldwide growing public health problem with high risks of severe microvascular and macrovascular complications. Diabetic nephropathy (DN) is a major burden among the chronic complications of diabetes, given that it affects ~30% of patients with diabetes. Indeed, DN is the most common cause of end-stage renal disease in the U.S. (1) and worldwide. Known risk factors for DN include hyperglycemia, hypertension, dyslipidemia, smoking, and obesity as well as ethnic, familial, and genetic predispositions (2). Key clinical trials have demonstrated that early interventions, especially those aimed at primary prevention, are by far more effective and that it is only possible to slow progression once DN is established (2). Thus, large intervention trials on the impact of long-term intensified glucose control on chronic diabetes complications, both in type 1 and type 2 diabetes (2–6), have documented the critical role of glycemic control in preventing the development of early DN as well as in slowing its progression; the recent long-term follow-up

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results of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation Post-Trial Observational Study (ADVANCE-ON) (6) have strengthened the concept that optimal glycemic control is effective in preventing DN and, interestingly, in slowing progression. In contrast, the clinical trials with renin-angiotensin-aldosterone system (RAAS) blockade versus other antihypertensive agents in primary prevention of DN have provided conflicting results and are confounded, when albuminuria (urinary albumin excretion rate) is the primary outcome, by the rapid but reversible decreases in urinary albumin excretion rate and by the differences in blood pressure control. Current conventional therapies to prevent DN and slow its progression, based on blood glucose (2–6) and blood pressure control and RAAS blockade (7–9), are only partially effective, and a substantial residual risk to develop end-stage renal disease still remains (10). Thus, in addition to current therapies, new therapeutic approaches leading to additional risk reduction are needed.

Among the most recent glucose-lowering oral agents, the sodium–glucose cotransporter (SGLT) 2 inhibitors have the potential to exert nephroprotection through improving glycemic control but also through glucose-independent effects, such as blood pressure–lowering and, possibly, some direct renal effects. Interestingly, SGLT2 inhibitors also have renal hemodynamic effects, including reducing glomerular hyperfiltration (11), as well as inhibitory effects on the inflammatory and fibrotic responses of proximal tubular cells to hyperglycemia (12). The SGLT2 is localized to the proximal tubule and is responsible for ~90% of the reabsorption of the glucose filtered by the kidney. In type 2 diabetes, as a consequence of the increased glucose filtered load, there is an increased expression of SGLT2 and an increased reabsorption of glucose; this a maladaptive mechanism contributing to hyperglycemia (13,14). SGLT2 inhibition leads to substantial glycosuria and reduction in fasting and postprandial plasma glucose levels, without stimulating insulin secretion, and therefore without increasing the risk of hypoglycemia. The main nonglycemic effects include blood pressure reduction and weight loss. Given the mode of action, the glucose-lowering efficacy of SGLT2 inhibitors depends on renal function and on plasma glucose levels (15,16).

Several review articles, primarily in nephrological journals (11,12,17–20), have considered the potential nephroprotective effects of SGLT2 inhibitors. The present review will emphasize considerations for the diabetologist, especially in discussion of the use and limitations of SGLT2 inhibitors in improving glucose control in patients with chronic kidney disease (CKD). In addition, this review will summarize the data both in experimental models and in humans on the potential nephroprotective effects of these agents, including important new findings indicating major effects of SGLT2 inhibitors on important renal clinical event rates.

Glucose-Lowering Efficacy of SGLT2 Inhibitors in Patients With CKD

Given their mode of action, which is heavily dependent on the glucose filtered load and therefore on glomerular filtration rate (GFR) (15,16), the efficacy of SGLT2 inhibitors in reducing plasma glucose is expected to be decreased with decreasing renal function. Since glucose-lowering agents for patients with CKD stages 3 and 4 are limited and frequently require dose adjustments, the identification of the cutoff of estimated GFR (eGFR) below which clinically significant reductions in plasma glucose cannot be achieved with SGLT2 inhibitors is crucial. On the basis of the studies performed so far in patients with CKD, these drugs should not be started in patients with eGFR <60 mL/min/1.73 m^2 and should be stopped when eGFR is <45 mL/min/1.73 m^2.

In patients with eGFR 30–60 mL/min/1.73 m^2, dapagliflozin, on top of existing antidiabetes treatments, did not significantly reduce HbA_{1c} from baseline to 24 weeks (placebo −0.32%, dapagliflozin 5 mg −0.41%, and dapagliflozin 10 mg −0.44%) and 104 weeks (21). However, dapagliflozin induced a significant reduction in body weight from baseline (0.21 kg increase with placebo and −1.54 and −1.89 kg for the 5- and 10-mg dose, respectively). Also, systolic and diastolic blood pressure values were significantly decreased in patients receiving dapagliflozin (−6.73 and −2.91 mmHg for dapagliflozin 10 mg at 52 weeks). The reasons for the discrepancy between the effects on blood glucose, blood pressure, and body weight remain unexplained.

In patients with similar eGFR (30–50 mL/min/1.73 m^2), canagliflozin significantly reduced HbA_{1c} from baseline compared with placebo over 52 weeks (0.05% increase for placebo, −0.19% canagliflozin 100 mg, −0.33% canagliflozin 300 mg) (22). The absolute reductions in HbA_{1c} with dapagliflozin and canagliflozin were similar, and the reason for the lack of efficacy in the dapagliflozin study was the substantial reduction in HbA_{1c} in the placebo arm. Canagliflozin also lowered systolic blood pressure (−5.5 mmHg, canagliflozin 100 mg; −6.7 mmHg, canagliflozin 300 mg) and diastolic blood pressure (−2.0 mmHg, canagliflozin 100 mg; −2.4 mmHg, canagliflozin 300 mg) and body weight.

Finally, in patients with eGFR 30–60 mL/min/1.73 m^2, empagliflozin 25 mg also significantly reduced HbA_{1c} compared with placebo over 24 weeks (0.05% increase for placebo, −0.37% empagliflozin 25 mg) (23). Empagliflozin 25 mg decreased body weight (−0.08 kg placebo, −0.98 kg empagliflozin) and both systolic blood pressure (0.4 mmHg placebo, −3.9 mmHg empagliflozin) and diastolic blood pressure (0.2 mmHg placebo, −1.7 mmHg empagliflozin). In this study, empagliflozin was also tested in patients with stage 2 and stage 4 CKD. Not surprisingly, empagliflozin was more efficacious in reducing HbA_{1c} in patients with stage 2 than stage 3 CKD, while it was ineffective in patients with stage 4 CKD. Thus, these studies demonstrate that in patients with eGFR of 30–60 mL/min/1.73 m^2 the efficacy of SGLT2 inhibitors in reducing HbA_{1c} is less than in patients with preserved GFR. Moreover, in patients with eGFR <45 mL/min/1.73 m^2, SGLT2 inhibitors did not lower HbA_{1c} (21–23), and for this reason, discontinuation is recommended when this level of renal insufficiency is reached.

SGLT2 Inhibitors and Glomerular Hyperfiltration

Several decades ago, Brenner (24) performed a series of seminal studies demonstrating that in animal models glomerular hyperfiltration accompanied by glomerular capillary hypertension is a pathophysiological mechanism for initiation and progression of renal disease, regardless of the nature of the initial

renal injury. The hemodynamic hypothesis offered important insights into therapeutic approaches to slow progression of CKD. Observations on glomerular hyperfiltration as a maladaptive compensatory consequence of glomerular injury encouraged the interest in hyperfiltration as a potential mechanism of initiation of DN and therefore as a risk factor. Several studies have analyzed the prognostic role of hyperfiltration in the development of the early manifestations of DN, with conflicting results (25–27). In part, this is due to the significant direct correlation between glycemia and GFR, rendering it difficult to dissect the impact of glycemia and of hyperfiltration on the development of DN. Indeed, while some studies observed that patients with glomerular hyperfiltration have increased risk of fast GFR loss, others did not confirm these findings (25–27).

The two most important pathophysiological mechanisms leading to renal hyperfiltration in diabetes are glomerular hemodynamic abnormalities due to neurohormonal activation and tubular factors. The hemodynamic/neurohormonal hypothesis is based on changes in afferent and efferent arteriolar tone, resulting in glomerular hyperfiltration, mostly due to RAAS activation. The tubular hypothesis is based on the fact that hyperglycemia causes an increase in proximal tubule glucose filtered load in diabetes. This results in overactivity of SGLT2 and SGLT1 and consequent increased tubular reabsorption of glucose and sodium and downstream activation of the tubuloglomerular feedback system (28–31). This increased proximal sodium reabsorption leads to decreased sodium delivery to and transport in the cells of the macula densa, with consequent reduction in ATP breakdown and adenosine production. Adenosine is a strong vasoconstrictor, and its reduction causes vasodilation of the afferent arteriole and thus hyperfiltration (32) (Fig. 1). Abnormalities in the tubuloglomerular feedback system have been described in experimental models of diabetes (28,29,33), and elegant micropuncture studies have demonstrated the mechanisms involved in the tubular hypothesis (33). Increased proximal tubular sodium reabsorption, with consequent reduction in distal delivery, has also been demonstrated in patients with type 1 or type 2 diabetes (30,31).

Studies in animal models have documented that increased glucose reabsorption in the proximal tubule is related to an increased SGLT2 gene expression (13). In human tubular epithelial cells grown from urines of patients with type 2 diabetes (14), there is an increase in the expression and glucose-transport capacity of SGLT2 compared with those from control subjects without diabetes. Thus, SGLT2 inhibition should result in an increased delivery of sodium to the macula densa, a consequent increase in adenosine release, resulting in vasoconstriction of the afferent arteriole leading to a reduction in renal plasma flow and GFR. Accordingly, in SGLT2 knockout mice, the induction of diabetes was associated with less hyperfiltration compared with wild-type diabetic mice (34). Micropuncture studies in rats with streptozotocin-induced diabetes treated with SGLT2 inhibitors demonstrated reductions in proximal sodium reabsorption and in single nephron GFR (35).

On the basis of the encouraging findings in animal models, an interesting study explored the effects of empagliflozin on renal hemodynamics in 40 patients with type 1 diabetes (36) without chronic complications, with normal blood pressure, not on antihypertensive therapy, and with a GFR >60 mL/min/1.73 m^2. At baseline, 27 patients had hyperfiltration (GFR >135 mL/min/1.73 m^2) and 13 had normal GFR. After 8 weeks of empagliflozin treatment (as add-on to insulin) in patients with baseline hyperfiltration, there was a reduction in GFR from 172 ± 23 to 139 ± 25 mL/min/1.73 m^2, while there was no effect in patients with normal baseline GFR (36). In association with this 20% reduction in GFR, there was a parallel reduction in renal plasma flow and increase in renal vascular resistance, likely consequent of afferent

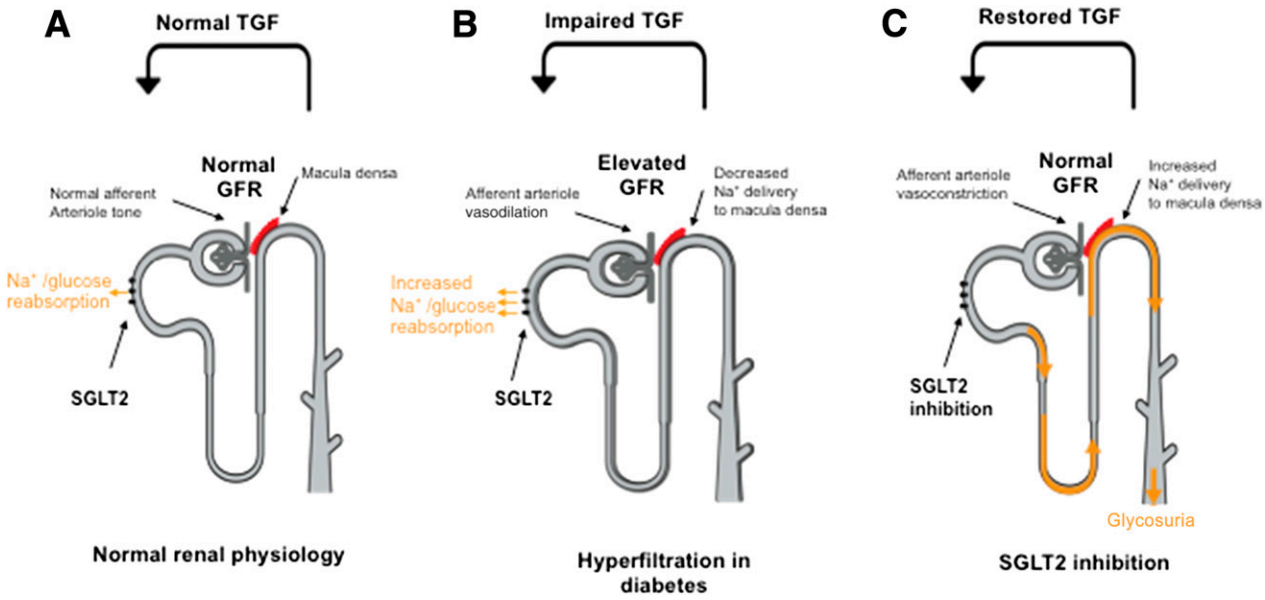

Figure 1—Tubuloglomerular feedback system in normal physiology (*A*), diabetes (*B*), and diabetes after treatment with SGLT2 inhibition (*C*). TGF, tubuloglomerular feedback. Adapted from Cherney et al. (36).

arteriolar vasoconstriction. In a subsequent publication (37), the data were analyzed using the Gomez equation, with estimates of intraglomerular pressure and resistance of afferent and efferent arterioles; the data support the idea that hyperfiltration in diabetes is predominantly due to afferent arteriole vasodilation, with consequent increase in intraglomerular pressure. The afferent arteriole vasodilation was improved with empagliflozin. The reduction in GFR during empagliflozin treatment was not mediated by the RAAS, as there was an increase in both angiotensin II and aldosterone levels as consequence of the diuretic effect (36). This substantial reduction in GFR (−33 mL/min) rivals that of similar patients during ACE inhibition, suggesting that the magnitude of the hemodynamic effects of SGLT2 inhibitors and RAAS blockers is similar. Whether these hemodynamic effects may translate to nephroprotection remains an open question.

SGLT2 Inhibitors: Experimental Data

The most important structural changes in type 1 diabetes occur in the glomeruli, with thickening of the glomerular basement membrane, mesangial expansion, and podocyte injury; in the presence of more advanced DN, however, there are also important changes in the tubules and interstitium with tubular atrophy and interstitial fibrosis and inflammation (38). In contrast, among patients with type 2 diabetes and microalbuminuria or macroalbuminuria and preserved renal function (39), a substantial proportion (~40%) has advanced tubulo-interstitial lesions despite only very mild glomerular lesions. These lesions include thickening and reduplication of tubular basement membrane (especially of the proximal tubules), tubular atrophy, interstitial fibrosis, and chronic inflammation. When proximal tubular cells are grown in high-glucose conditions, there is an increased secretion of inflammatory molecules and profibrotic cytokines (40). In vivo, this leads to activation of inflammatory pathways, recruitment of macrophages, and further tubular damage and interstitial fibrosis. Among the candidate mediators, transforming growth factor-β probably plays a key role, promoting fibrosis and epithelial-to-mesenchymal transformation (41). The increase in glucose trafficking through the proximal tubular cells, consequent of an increased transport of glucose by SGLT2, could promote inflammation and fibrosis. In immortalized human proximal tubular cells, empagliflozin reduced the glucose-induced Toll-like receptor 2 and 4 and nuclear factor-κB expression, both well-known mediators of inflammatory and fibrotic responses in animal models of DN (42). Thus, it is tempting to hypothesize that in patients with type 2 diabetes and tubulointerstitial lesions SGLT2 inhibitors might be particularly useful in reducing tubulointerstitial fibrosis and inflammation.

However, considerable caution is needed in extrapolating findings from experimental models to human diabetes, given that an animal model closely reflecting DN in humans has not yet been developed. Nevertheless, studies performed in animals may provide interesting insights, generating hypotheses to be tested in persons with diabetes. Numerous studies have been performed exploring the effects of SGLT2 inhibitors in animal models of DN. Overall, the effects on renal hyperfiltration are consistent, while the effects on renal enlargement, inflammation, and injury differ, underlying the different susceptibility as well as the confounding effects of different blood glucose levels in the different animal models. In a short-term study, Malatiali et al. (43) observed that the nonspecific SGLT inhibitor phlorizin reduced the increase in kidney size and the glomerular hyperfiltration in streptozotocin-induced diabetic Fisher rats. Different results have been observed in streptozotocin-induced diabetic SGLT2 knockout mice, where there was a reduction in hyperfiltration but not in renal hypertrophy and in markers of inflammation or fibrosis compared with the wild-type diabetic mice (34). As outlined above, data in animal models often differ depending upon the model used. Thus, when streptozotocin-induced diabetic endothelial nitric oxide synthase knockout mice were treated with empagliflozin there was no attenuation of albuminuria (44) or improvement in renal lesions or inflammatory markers (44). In contrast, the beneficial effects of empagliflozin on DN lesions were recently described in normotensive BTBR ob/ob mice, where reductions in glomerular hypertrophy, mesangial matrix expansion, albuminuria, and markers of inflammation were observed (45).

In db/db mice, 12 weeks of treatment with dapagliflozin decreased blood glucose and prevented the increase in albuminuria (46). Interestingly, there was a dose-dependent decrease in mesangial expansion and interstitial fibrosis (46) accompanied by reductions in macrophage infiltration and the gene expression of mediators of inflammation and oxidative stress MCP-1, intracellular adhesion molecule-1, osteopontin, and transforming growth factor-β1.

Taken together, results in animal models suggest that SGLT2 inhibition has hemodynamic effects, attenuating glomerular hyperfiltration and reducing albuminuria. As far as the effects on DN lesions and on mediators of inflammation and fibrosis, the results are conflicting and highly variable depending upon the different experimental models used and the different glucose levels. It is thus difficult from these data to understand whether these beneficial effects are simply related to the reductions in blood glucose and blood pressure or whether there are additional and synergistic direct protective renal effects.

SGLT2 Inhibitors and Renal Function in Clinical Studies

The changes in GFR during SGLT2 inhibition are similar in patients with normal renal function and in those with CKD. The time course of changes in renal function is typically characterized by a rapid decline in GFR during the first weeks of treatment, followed by a progressive recovery that is faster and more evident in patients with normal renal function at baseline. Studies performed in patients with moderate renal impairment (21–23) demonstrated significant renal effects; thus, treatment with dapagliflozin (104 weeks) (21), canagliflozin (26 weeks) (22), and empagliflozin (52 weeks) (23) resulted in an initial decrease in eGFR with a trend toward an increase over time (Figs. 2 and 3). In patients with CKD stage 3, after 1 week of treatment there was a reduction in eGFR (21) with a progressive recovery of GFR during the following weeks (Fig. 2). In a study where patients with eGFR of 30–50 mL/min/1.73 m^2 were randomized to canagliflozin or placebo for 26 weeks (22), a similar eGFR course was observed. Finally, in CKD stage 3, patients treatment with

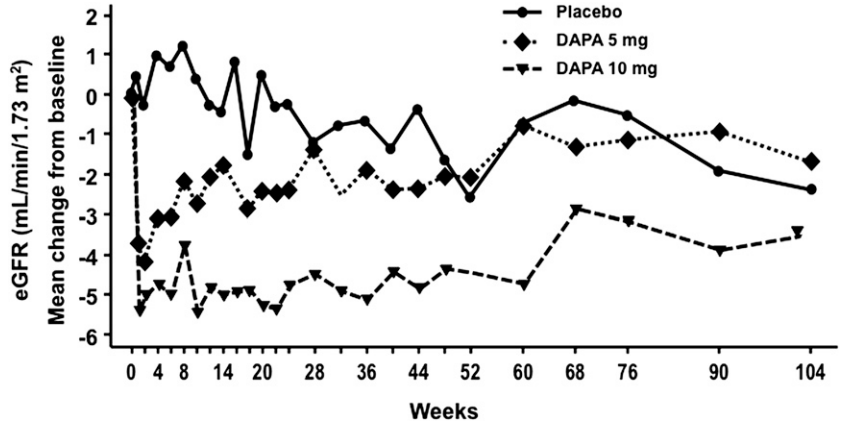

Figure 2—Changes in eGFR over time in subjects with type 2 diabetes with moderate renal impairment treated with placebo and dapagliflozin (DAPA) 5 mg and 10 mg. Adapted from Kohan et al. (21).

empagliflozin 25 mg reduced eGFR by ~4 mL/min at 12 weeks, with a slight recovery at 52 weeks. Interestingly, after drug discontinuation GFR returned to the baseline values, suggesting that the decrease in GFR during treatment is hemodynamic and not consequent of renal injury (23).

In a large study where patients with normal renal function were randomized to canagliflozin or glimepiride on top of metformin for 52 weeks (47), the expected pattern of GFR course was observed, with an initial fall followed by stabilization. In contrast, there was a progressive GFR fall in patients receiving glimepiride (47).

A large pooled analysis of 12 randomized clinical trials of up to 24 (4,545 patients) or 102 (3,036 patients) weeks explored the effects of dapagliflozin on renal function in patients with type 2 diabetes with normal or mildly impaired renal function (48). Mean eGFR showed small transient reductions with dapagliflozin at week 1, which returned to near baseline values thereafter. Mean eGFR changes were not significantly different for dapagliflozin 5 and 10 mg vs. placebo at 102 weeks: −2.52 and −1.38 vs. −1.31 mL/min/1.73 m^2, respectively (48).

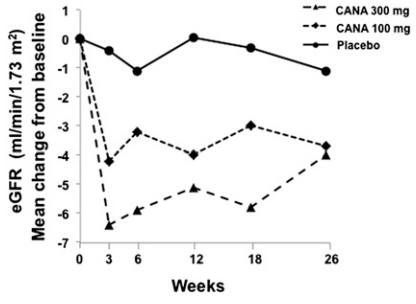

Figure 3—Changes in eGFR over time in subjects with type 2 diabetes with moderate renal impairment treated with placebo and canagliflozin 100 mg and 300 mg. CANA, canagliflozin. Adapted from Yale et al. (22)

In addition to the effects on GFR, SGLT2 inhibitors also influence albuminuria. Table 1 summarizes the results of SGLT2 inhibitors on albuminuria. Additional recent data also support the concept that SGLT2 inhibitors reduce albuminuria. Thus, we observed a reduction in urinary albumin-to-creatinine ratio (UACR) with dapagliflozin in patients with stage 3 CKD (21). In a recent post hoc analysis of this study, we evaluated the effects of dapagliflozin on UACR in patients with microalbuminuria or macroalbuminuria at baseline; we also examined whether changes in UACR were independent of changes in HbA_{1c}, blood pressure, and eGFR (49). A reduction in UACR was evident from the first time point (week 1). At 104 weeks, placebo-corrected reductions of −43.8% and −57.2% in UACR were observed in the dapagliflozin 5 and 10 mg groups, respectively. After adjustment for changes in blood pressure, HbA_{1c}, and eGFR, the UACR reductions were largely maintained, suggesting an independent, direct renal effect (49). By week 104, more patients shifted to a lower UACR category versus a higher UACR category in the dapagliflozin groups.

Similar data have been reported in patients with CKD stage 3 treated with canagliflozin (22): UACR decreased by 30%, 21%, and 7.5% after 52 weeks of treatment with canagliflozin 100 mg, 300 mg, and placebo, respectively. A large pooled analysis in >3,000 subjects, where UACR changes and progression were analyzed as part of a cardiovascular report, described similar findings in patients treated with canagliflozin (50) (Fig. 4). Finally, in a study where patients with CKD stage 3 were treated with empagliflozin 25 mg (23), fewer patients on empagliflozin shifted to a higher category of albumin-to-creatinine ratio (14.2%) compared with placebo (33.6%), and more patients shifted to a lower category (60% with empagliflozin vs. 30% with placebo). A recent post hoc analysis of 458 microalbuminuric patients with type 2 diabetes participating in several clinical trials with empagliflozin confirms a significant reduction in UACR (51). Overall, these studies consistently demonstrate a significant reduction in UACR during SGLT2 inhibition; this reduction occurs early after treatment initiation and lasts, in the longest trial, for up to 2 years. Given that increased UACR is an important manifestation of DN and a predictor of progression, these data support a nephroprotective effect of SGLT2 inhibitors.

The recently published BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial (52) compared the effects of empagliflozin with effects of placebo on cardiovascular outcomes in patients with type 2 diabetes with high cardiovascular risk. In the empagliflozin group, there was a significant reduction in the primary outcome of a composite of cardiovascular events, which included death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke. Specifically, empagliflozin treatment was associated with a reduction in the relative risk for cardiovascular death of 38%, of hospitalization for heart failure of 35%, and of death from any cause of 32% (52).

The EMPA-REG OUTCOME trial analyses of the secondary renal outcomes have recently been presented at the 2015 meeting of the American Society of Nephrology (C. Wanner, personal communication) (53). Compared with those receiving placebo, patients receiving empagliflozin experienced a 39% reduction in the risk of new or worsening nephropathy (defined as a UACR >300 mg/g, doubling of serum creatinine with

Table 1—Effects of SGLT2 inhibitors on albumin excretion rate

					Change in albumin excretion rate		
Study	Subjects	Investigation drug	Comparator	Weeks	Investigation drug	Comparator	Difference
Barnett et al. (2014) (23)	375	Empagliflozin 25 mg	Placebo	52	−155	29	−184
Cefalu et al. (2013) (47)	1,450	Canagliflozin 100/300 mg	Glimepiride	52	−0.1/−0.9	0.7	−0.8/−1.5
Kohan et al. (2014) (21)	252	Dapagliflozin 5/10 mg	Placebo	104	78.0/−11.7	69.7	8.3/−81.4
Yale et al. (2014) (22)	269	Canagliflozin 100/300 mg	Placebo	52	−117.5/−96.2	15.4	−132.9/−111.6

an eGFR of 45 mL/min/1.73 m^2 or less, initiation of renal replacement therapy, or death due to renal disease). When the composite outcome of doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal disease was considered, the relative risk reduction in the empagliflozin group was even more pronounced (46%). These data provide strong support for a nephroprotective effect of SGLT2 inhibitors.

In addition to EMPA-REG OUTCOME trial, there are several ongoing trials with SGLT2 inhibitors with renal end points.

CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation [clinical trial reg. no. NCT02065791]) is evaluating the effects of canagliflozin compared with placebo on the time to the primary composite end point of end-stage renal disease, doubling of serum creatinine, and cardiovascular death in a large number of patients with type 2 diabetes and CKD stages 2 and 3 and proteinuria receiving the maximum dose of ACE inhibitors or angiotensin receptor blocker. CANVAS (CANagliflozin cardioVascular Assessment Study: A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus) (clinical trial reg. no. NCT01032629) (54) is exploring (as secondary end point) the effects of canagliflozin on progression of albuminuria in patients with previous cardiovascular events.

These long-term trials with SGLT2 inhibitors in patients with diabetic kidney disease, using hard renal primary end points, are ongoing and will hopefully further clarify whether these agents confer nephroprotection.

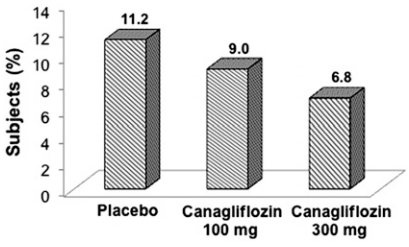

Figure 4—Proportion of participants in canagliflozin cardiovascular safety study of subjects with type 2 diabetes experiencing a ×1-step progression in albuminuria stage. Adapted from ref. 50.

Conclusions

Despite improvements in the management of renal risk factors like hyperglycemia and hypertension, DN remains a major health problem, and new therapeutic options are needed to reduce the burden of renal disease in diabetes. SGLT2 inhibitors are a new class of glucose-lowering agents, with important influences on risk factors for DN: improvement in glycemic control and reduction in both systolic and diastolic blood pressure. SGLT2 inhibition is also associated with weight loss and reduction in uric acid. Both high levels of uric acid and obesity are risk factors for DN and for progression of CKD (47); however, the influences on the kidney of the reductions in body weight and uric acid levels that are obtained with SGLT2 inhibitors are unknown. Preclinical and clinical studies have shown that SGLT2 inhibitors have potentially beneficial renal hemodynamic effects, with reduction of hyperfiltration and intraglomerular pressure. In clinical trials, a positive influence on albuminuria has consistently been documented. It needs to be considered, however, that these "potentially nephroprotective" drugs are less effective in improving glycemic control in patients with impaired renal function. Thus, given the experimental data, the clinical observations on glomerular hyperfiltration and on albuminuria, and the recent secondary renal event analyses of EMPA-REG OUTCOME trial, evidence is increasing that these drugs have substantial nephroprotective effects.

Large long-term ongoing trials, using hard renal end points, will hopefully clarify whether SGLT2 inhibitors, above and beyond their well-known effects of glycemia and blood pressure, also have positive influences on the development and progression of DN.

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References

1. United States Renal Data System. *USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States.* Bethesda, MD, National Institutes of Health, 2012
2. Parving H-H, Mauer M, Fioretto P, Rossing P, Ritz E. Diabetic nephropathy. In *Brenner & Rector's The Kidney.* 9th ed. Brenner BM, Ed. Philadelphia, PA, Saunders Elsevier, 2012, p. 1411–1454
3. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
5. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358:2560–2572
6. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–1406
7. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993;329: 1456–1462
8. Lewis EJ, Hunsicker LG, Clarke WR, et al.; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–860

9. Brenner BM, Cooper ME, de Zeeuw D, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–869
10. Fioretto P, Dodson PM, Ziegler D, Rosenson RS. Residual microvascular risk in diabetes: unmet needs and future directions. Nat Rev Endocrinol 2010;6:19–25
11. Škrtić M, Cherney DZ. Sodium-glucose cotransporter-2 inhibition and the potential for renal protection in diabetic nephropathy. Curr Opin Nephrol Hypertens 2015;24:96–103
12. Komala MG, Panchapakesan U, Pollock C, Mather A. Sodium glucose cotransporter 2 and the diabetic kidney. Curr Opin Nephrol Hypertens 2013;22:113–119
13. Freitas HS, Anhê GF, Melo KF, et al. Na(+)-glucose transporter-2 messenger ribonucleic acid expression in kidney of diabetic rats correlates with glycemic levels: involvement of hepatocyte nuclear factor-1alpha expression and activity. Endocrinology 2008;149:717–724
14. Rahmoune H, Thompson PW, Ward JM, Smith CD, Hong G, Brown J. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. Diabetes 2005;54:3427–3434
15. DeFronzo RA, Hompesch M, Kasichayanula S, et al. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. Diabetes Care 2013;36:3169–3176
16. Ferrannini E, Veltkamp SA, Smulders RA, Kadokura T. Renal glucose handling: impact of chronic kidney disease and sodium-glucose cotransporter 2 inhibition in patients with type 2 diabetes. Diabetes Care 2013;36:1260–1265
17. Gilbert RE. Sodium-glucose linked transporter-2 inhibitors: potential for renoprotection beyond blood glucose lowering? Kidney Int 2014;86:693–700
18. De Nicola L, Gabbai FB, Liberti ME, Sagliocca A, Conte G, Minutolo R. Sodium/glucose cotransporter 2 inhibitors and prevention of diabetic nephropathy: targeting the renal tubule in diabetes. Am J Kidney Dis 2014;64:16–24
19. Schernthaner G, Mogensen CE, Schernthaner GH. The effects of GLP-1 analogues, DPP-4 inhibitors and SGLT2 inhibitors on the renal system. Diab Vasc Dis Res 2014;11:306–323
20. Lovshin JA, Gilbert RE. Are SGLT2 inhibitors reasonable antihypertensive drugs and renoprotective? Curr Hypertens Rep 2015;17:551
21. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int 2014;85:962–971
22. Yale JF, Bakris G, Cariou B, et al.; DIA3004 Study Group. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. Diabetes Obes Metab 2014;16:1016–1027
23. Barnett AH, Mithal A, Manassie J, et al.; EMPA-REG RENAL trial investigators. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2014;2:369–384
24. Brenner BM. Hemodynamically mediated glomerular injury and the progressive nature of kidney disease. Kidney Int 1983;23:647–655
25. Magee GM, Bilous RW, Cardwell CR, et al. Is hyperfiltration associated with the future risk of developing diabetic nephropathy? A meta-analysis. Diabetologia 2009;52:691–697
26. Ruggenenti P, Porrini EL, Gaspari F, et al.; GFR Study Investigators. Glomerular hyperfiltration and renal disease progression in type 2 diabetes. Diabetes Care 2012;35:2061–2068
27. Nelson RG, Bennett PH, Beck GJ, et al.; Diabetic Renal Disease Study Group. Development and progression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. N Engl J Med 1996;335:1636–1642
28. Thomson SC, Vallon V, Blantz RC. Kidney function in early diabetes: the tubular hypothesis of glomerular filtration. Am J Physiol Renal Physiol 2004;286:F8–F15
29. Thomson SC, Blantz RC. Glomerulotubular balance, tubuloglomerular feedback, and salt homeostasis. J Am Soc Nephrol 2008;19:2272–2275
30. Ditzel J, Lervang HH, Brøchner-Mortensen J. Renal sodium metabolism in relation to hypertension in diabetes. Diabete Metab 1989;15:292–295
31. Hannedouche TP, Delgado AG, Gnionsahe DA, Boitard C, Lacour B, Grünfeld JP. Renal hemodynamics and segmental tubular reabsorption in early type 1 diabetes. Kidney Int 1990;37:1126–1133
32. Faulhaber-Walter R, Chen L, Oppermann M, et al. Lack of A1 adenosine receptors augments diabetic hyperfiltration and glomerular injury. J Am Soc Nephrol 2008;19:722–730
33. Vallon V, Richter K, Blantz RC, Thomson S, Osswald H. Glomerular hyperfiltration in experimental diabetes mellitus: potential role of tubular reabsorption. J Am Soc Nephrol 1999;10:2569–2576
34. Vallon V, Rose M, Gerasimova M, et al. Knockout of Na-glucose transporter SGLT2 attenuates hyperglycemia and glomerular hyperfiltration but not kidney growth or injury in diabetes mellitus. Am J Physiol Renal Physiol 2013;304:F156–F167
35. Thomson SC, Rieg T, Miracle C, et al. Acute and chronic effects of SGLT2 blockade on glomerular and tubular function in the early diabetic rat. Am J Physiol Regul Integr Comp Physiol 2012;302:R75–R83
36. Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 2014;129:587–597
37. Skrtić M, Yang GK, Perkins BA, et al. Characterisation of glomerular haemodynamic responses to SGLT2 inhibition in patients with type 1 diabetes and renal hyperfiltration. Diabetologia 2014;57:2599–2602
38. Fioretto P, Mauer M. Histopathology of diabetic nephropathy. Semin Nephrol 2007;27:195–207
39. Fioretto P, Mauer M, Brocco E, et al. Patterns of renal injury in NIDDM patients with microalbuminuria. Diabetologia 1996;39:1569–1576
40. Tang SC, Lai KN. The pathogenic role of the renal proximal tubular cell in diabetic nephropathy. Nephrol Dial Transplant 2012;27:3049–3056
41. Liu Y. New insights into epithelial-mesenchymal transition in kidney fibrosis. J Am Soc Nephrol 2010;21:212–222
42. Panchapakesan U, Pegg K, Gross S, et al. Effects of SGLT2 inhibition in human kidney proximal tubular cells–renoprotection in diabetic nephropathy? PLoS One 2013;8:e54442
43. Malatiali S, Francis I, Barac-Nieto M. Phlorizin prevents glomerular hyperfiltration but not hypertrophy in diabetic rats. Exp Diabetes Res 2008;2008:305403
44. Gangadharan Komala M, Gross S, Mudaliar H, et al. Inhibition of kidney proximal tubular glucose reabsorption does not prevent against diabetic nephropathy in type 1 diabetic eNOS knockout mice. PLoS One 2014;9:e108994
45. Gembardt F, Bartaun C, Jarzebska N, et al. The SGLT2 inhibitor empagliflozin ameliorates early features of diabetic nephropathy in BTBR ob/ob type 2 diabetic mice with and without hypertension. Am J Physiol Renal Physiol 2014;307:F317–F325
46. Terami N, Ogawa D, Tachibana H, et al. Long-term treatment with the sodium glucose cotransporter 2 inhibitor, dapagliflozin, ameliorates glucose homeostasis and diabetic nephropathy in db/db mice. PLoS One 2014;9:e100777
47. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet 2013;382:941–950
48. Kohan DE, Fioretto P, Johnsson K, Parikh S, Ptaszynska A, Ying L. The effect of dapagliflozin on renal function in patients with type 2 diabetes. J Nephrol 2016;29:391–400
49. Fioretto P, Stefansson BV, Johnsson EKA, Cain VA, Sjostrom D. Dapagliflozin reduces albuminuria over 2 years in diabetic patients with renal impairment (Abstract). J Am Soc Nephrol 2015;26:1A
50. U.S. Food and Drug Administration. Canagliflozin: advisory committee meeting [Internet]. Available from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed 18 July 2013
51. Cherney D, von Eynatten M, Lund SS, et al. Sodium glucose cotransporter 2 inhibition with empagliflozin reduces microalbuminuria in patients with type 2 diabetes (Abstract). Diabetologia 2014;57(Suppl. 1):S333
52. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
53. Wanner C, Lachin JM, Fitchett DH, et al. Empagliflozin and clinical outcomes in patients with type 2 diabetes and chronic kidney disease. Late-breaking abstract presented American Society of Nephrology Kidney Week 2015, 3–8 November 2015, San Diego, CA
54. Neal B, Perkovic V, de Zeeuw D, et al. Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)–a randomized placebo-controlled trial. Am Heart J 2013;166:217–223.e11