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Sodium glucose cotransporter (SGLT)-2 inhibitors: do we need them for glucose-lowering, for cardiorenal protection or both?

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Abstract

Sodium glucose cotransporter (SGLT)-2 inhibitors are the newest addition to our treatment armamentarium for the management of hyperglycemia in type 2 diabetes. Glucose-lowering *per se* reduces the risk of microvascular complications, but not the risk of cardiovascular disease, including heart failure and cardiovascular mortality. Also, even when embedded in optimal cardiovascular prevention, a large residual risk remains with respect to progression of diabetic kidney disease.

SGLT-2 inhibitors lower blood glucose levels by inducing glucosuria. Through various proposed mechanisms, among which diuretic and natriuretic effects, SGLT-2 inhibitors decrease heart failure hospitalization, reduce cardiovascular mortality, and mitigate progression of diabetic kidney disease.

In this perspective, we will discuss the glucose-lowering and other protective effects of SGLT-2 inhibitors on the cardiorenal axis, both in primary and secondary prevention. By comparing the glycemic and pleiotropic effects of these agents to other glucose-lowering drugs, we will address questions around whether SGLT-2 inhibitors should be considered primarily as glucose-lowering agents, cardiorenal drugs or both.

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Management of hyperglycemia in patients with type 2 diabetes

In the last few decades we have witnessed a huge increase in the number of pharmacological treatment options for patients with type 2 diabetes (T2D) in order to reduce hyperglycemia and ultimately to attempt to mitigate the risk of long-term cardiovascular (CV) and renal complications (1). While metformin, sulfonylurea and insulin were the only available glucose-lowering agents for several decades, a large number of new drugs have recently been added to our treatment armamentarium. Of these, newer insulin analogues, glucagon-like peptide (GLP)-1 receptor agonists, dipeptidyl-peptidase (DPP)-4 inhibitors and, most recently, sodium glucose cotransporter (SGLT)-1/2 inhibitors have been the subject of intensive investigation in clinical trials. This increase in the availability of treatment options has contributed to improved patient care, but also introduced certain challenges. Each drug class differs in mode of action, efficacy, potential side effects, costs and actions beyond glucose-lowering. Consequently, clinical guidelines have challenged healthcare providers to implement individualized treatment strategies (2, 3). Although this concept of individualized diabetes management (i.e. choosing the right drug for the right patient based on both drug- and patient characteristics) sounds appealing, the vast amount of options and considerations can be a struggle for physicians in clinical practice.

Previous landmark diabetes trials, including the action to control CV risk in diabetes (ACCORD) study, have shed new light on the potential benefits of strict glycemic control to prevent cardiovascular disease (CVD) in T2D patients, thereby reshaping our thoughts on optimal hyperglycemia management (4). In trials that focused on intensive glucose-lowering, microvascular events were diminished, as they showed a reduction or slowed progression of albuminuria but did not largely reduced doubling of serum creatinine or development of end stage renal disease (ESRD). Despite the reduction in microvascular events and non-fatal MI, the impact of strict glycemic control on non-fatal stroke, CV mortality or all-cause mortality of these trials has been limited at best (5, 6), and this strategy may even increase CV risk in T2D patients with longstanding disease (4). In addition to neutral effects of strict glycemic control on CV mortality, glucose-lowering *per se* also does not improve heart failure (HF) (7). Furthermore, besides hyperglycemia other risk factors are operative in the underlying cause of HF in T2D, which may explain the underlying myocardial alterations (8). HF is a disease that is increasingly recognized to cause significant morbidity and mortality in T2D patients, especially in those with established microvascular complications (9). Elucidating the role of intensive control on CV outcomes is even more important now than ever given the striking association between T2D and diastolic HF, or HF with preserved ejection fraction (HFpEF). HFpEF is challenging to diagnose, and is often missed in clinical practice. Because therapies that have shown to impact mortality in patients with HF with reduced ejection fraction (HFrEF), such as beta-blockers or renin-angiotensin-aldosterone system (RAS) inhibitors, have failed to improve outcome in HFpEF, the prognosis of HFpEF is

often poor (10). In addition, multitarget risk factor control of hyperglycemia, blood pressure, LDL-cholesterol, albuminuria and smoking substantially attenuates the risk of myocardial infarction and stroke in T2D patients, but has less benefit on the risk of HF hospitalization (11). It is important to bear in mind that that some glucose-lowering therapies might cause a higher risk of HF or worsening of symptoms in patients with existing HF. For instance, insulin could be harmful via the induced weight gain, fluid retention and SNS activation, especially when HbA1c is not on target (12). In a meta-analysis by Cosmi *et al.* insulin treatment in HF patients was associated with a higher risk of HF hospitalization (13, 14), however this could not be confirmed by dedicated randomized controlled trials (15, 16). Fluid retention might also negatively affect the HF risk with the use of thiazolidinediones (TZD) (17–19). The use of GLP-1 receptor agonist liraglutide has been associated with an unsettling increase in heart rate (20, 21). Last, the implication of the increased HF hospitalization seen with DDP-4 inhibitor saxagliptin in SAVOR-TIMI 53 is still an ongoing debate (22, 23).

As CVD and HF are leading causes of morbidity and mortality in T2D patients (24), especially in context of concomitant DKD, characterized by single-nephron hyperfiltration, increased urinary protein excretion and/or reduced kidney function (25), management of the disease has shifted from the mere focus on glycemic control (“a classic glucose-centric approach”) to prevention or reduction of CV complications. In this regard the so-called pleiotropic effects of newer glucose-lowering agents (effects beyond glucose-lowering *per se*), have become of significant interest. From the reported CV outcome trials (CVOTs) LEADER (liraglutide) (26), SUSTAIN-6 (semaglutide) (27), HARMONY (albiglutide) (28), EMPA-REG OUTCOME (empagliflozin) (29), CANVAS Program (canagliflozin) (30) and DECLARE-TIMI 58 (dapagliflozin) (31), we know that GLP-1 receptor agonists and SGLT-2 inhibitors can improve CV and renal outcomes through mechanisms independent of glycemic control, something that has not been observed with other glucose-lowering drugs.

In this perspective, we will focus on SGLT-2 inhibitors since these agents have shown remarkable effects on the cardiorenal axis. We will argue that these agent do have added value as a cardiorenal drug in T2D patients with HF and/or DKD, and that they should be widely employed in these patients. On the other hand, the added value of SGLT-2 inhibitors in T2D patients without HF and/or DKD, considering other available treatment options, will be questioned. The potential role for SGLT-2 inhibitors in the treatment of HF and chronic kidney disease (CKD) in patients without T2D will also be discussed.

SGLT-2 inhibitors: targeting the kidneys to improve glycemic control

Currently, the four SGLT-2 inhibitors approved for the treatment of T2D by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) are canagliflozin, dapagliflozin, empagliflozin and ertugliflozin. These drugs lower blood glucose levels by inhibiting glucose reuptake in the early proximal tubule. This is achieved by blocking the SGLT-2, which couples sodium to glucose reabsorption in a 1:1 ratio, thereby inducing glucosuria and natriuresis (32). In normoglycemic individuals, approximately 180 grams of glucose is filtered, completely reabsorbed and returned to the circulation each day, an amount that is approximately 30% increased in the context of hyperglycemia (33). This

increased glucose flux could be secondary to proximal tubular growth and upregulated SGLT-2 expression and/or activity, however, SGLT-2 expression does not seem to be enhanced in T2D patients compared to normoglycemic controls, while animal studies reported conflicting results on this topic (34–37).

In a meta-analysis of 45 clinical trials, which included 11,232 T2D patients with baseline HbA1c of 6.9% to 9.2% and excluded patients with severe renal impairment, SGLT-2 inhibition compared to placebo effectively reduced HbA1c by 0.79% when used as monotherapy and by 0.61% when used as add-on (38). Notably, the glucose-lowering efficacy of SGLT-2 inhibitors is directly related to the degree of hyperglycemia and glomerular filtration rate (GFR), therefore reduced efficacy is observed in T2D patients with reduced kidney function (39, 40). Based on these data, SGLT-2 inhibitors are currently only considered for the treatment of T2D after metformin failure in patients with an estimated GFR (eGFR) > 60 ml/min/1.73 m^2 (dapagliflozin), > 45 ml/min/1.73 m^2 (canagliflozin/empagliflozin US) and > 30 ml/min/1.73 m^2 (empagliflozin Canada) (41), which is indicative of the current glucose-centric approach (see Table 1).

Compared to other glucose-lowering agents registered for T2D treatment after failure of lifestyle management and metformin monotherapy, SGLT-2 inhibitors have specific advantages and disadvantages (detailed in Table 2). When evaluated in head-to-head trials against other oral agents such as sulfonylureas and DPP-4 inhibitors, SGLT-2 inhibitors appear to have similar glucose-lowering efficacy, although this may depend on baseline HbA1c and eGFR (42, 43). On the other hand, injectable GLP-1 receptor agonists appear to be more potent with respect to glucose-lowering (44). In the only head-to-head trial that investigated a GLP-1 receptor agonist versus an SGLT-2 inhibitor, the PIONEER-2 study, oral semaglutide reduced HbA1c (−1.3%) to a greater extent than empagliflozin (−0.8%) after 52 weeks of treatment (45).

With respect to weight, SGLT-2 inhibitors induce a modest reduction in bodyweight (~2–3 kg), due to osmotic diuresis and reduction of fat mass, while unintentional weight gain is induced by several other glucose-lowering drugs, such as sulfonylureas, thiazolidinediones, and basal insulin therapy. The achieved weight reduction with SGLT-2 inhibitors is however less impressive than with GLP-1 receptor agonists, in which the delay in gastric emptying, increased satiety feelings and consequent decrease in food intake are supposed to be the underlying mechanism (46–48). In the PIONEER-2 study, oral semaglutide reduced body weight to a greater extent than empagliflozin (−4.7 kg versus −3.8 kg respectively) after 52 weeks of treatment (45).

One of the benefits of SGLT-2 inhibitors is the low risk of hypoglycemia since these agents do not enhance insulin secretion, although it should be noted that the absolute risk of severe hypoglycemic events are relatively low with sulfonylurea use (49). Regarding safety and tolerability, a number of side effects have been reported for SGLT-2 inhibitors which could limit their use. As such, the most frequent complication is the incidence of genital mycotic infections, particularly in women (odds ratio [OR] 3.5, 95% confidence interval [CI] 2.46–2.99) (38). In addition, the use of canagliflozin in particular has been associated with an increase in bone fractures (15.4 versus 11.9 participants per 1000 patient-years; HR 1.26,

95% CI 1.04–1.52)) and lower limb amputations (6.3 versus 3.4 participants per 1000 patient-years; (HR 1.97, 95% CI 1.41–2.75)) (30, 50). Moreover, in patients with low residual insulin secretion capacity or with intact insulin sensitivity (but mostly in type 1 diabetes), increased rates of euglycemic diabetic ketoacidotic events have been noted (30, 31, 51). Finally, episodes of dehydration/hypotension have been reported, especially in the elderly, in CKD patients, and in patients using loop diuretics (52, 53). A final potential hurdle that may prevent the widespread use of SGLT-2 inhibitors relates to pricing and consequently reimbursement. As a novel drug, SGLT-2 inhibitors may be up to 10-times more expensive compared to, for instance, sulfonylurea (depending on the specific country), which has led to restrictions in the prescription and implementation of SGLT-2 inhibitors in many countries, including first-world countries. When the current patents of the SGLT-2 inhibitors expire (mostly between 2025 and 2030) the pricing of these drugs may change, however for now and in the near future we cannot ignore the high costs of SGLT-2 inhibitors compared to agents such as metformin and sulfonylurea.

SGLT-2 inhibitors in type 2 diabetes: cardiovascular outcomes in primary and secondary prevention settings

In 2015, the EMPA-REG OUTCOME trial was the first CVOT that reported the CV effects of an SGLT-2 inhibitor, as required by the 2008 US FDA safety regulations for new glucose-lowering drugs. In EMPA-REG OUTCOME, two doses of empagliflozin (10 and 25 mg daily) were compared to placebo with respect to CV events in 7,020 T2D patients with established CVD and eGFR >30 ml/min/1.73 m^2. After a median follow-up of 3.1 years, empagliflozin (pooled dosages) reduced the primary endpoint 3-point MACE (composed of CV death, nonfatal myocardial infarction or nonfatal stroke) by 14% (HR 0.86, 95% CI 0.74–0.99), which was largely driven by a significant relative risk reduction of 38% in CV death (29). Empagliflozin also reduced the risk of death from any cause (HR 0.68, 95% CI 0.57–0.82) and hospitalization for HF (HR 0.65, 95% CI 0.50–0.85). The results of the EMPA-REG OUTCOME trial led to the recognition of empagliflozin as a CV protective drug for T2D patients by several organizations, including the FDA. Also, empagliflozin-treated patients (pooled doses) had an HR of 0.61 (95% CI 0.53–0.70) for the secondary renal outcome composite of new-onset or worsening of nephropathy (consisting of progression to macroalbuminuria, doubling of serum creatinine accompanied by an eGFR of <45 ml/min per 1.73 m^2, initiation of renal replacement therapy, or renal death) compared with placebo (54). Importantly, established renal endpoints such as doubling of serum creatinine and initiation of renal replacement therapy were individually significantly reduced.

In 2017, the results of the CANVAS Program confirmed that CV benefit is likely to be a class effect of SGLT-2 inhibitors (30). In 10,142 participants with T2D and multiple CV risk factors (as defined in Table 5) or established CVD, canagliflozin (pooled dosages of 100 mg to 300 mg daily) compared to placebo reduced primary endpoint 3-point MACE by 14% (HR 0.86, 95% CI 0.75–0.97) after 2.4 years of follow-up, although the individual components did not reach statistical significance. Furthermore, because reductions in all-cause mortality missed significance (HR 0.87, 95% CI 0.74–1.01), subsequent results in the

prespecified hierarchical sequential testing plan (including favorable effects on hospital admission for HF) were deemed exploratory. The CANVAS Program also supported the renal results of EMPA-REG OUTCOME by showing a 40% relative reduction in the composite renal outcome, although the individual components of this outcome were slightly differently defined than in EMPA-REG OUTCOME (55, 56).

Finally in 2018, DECLARE-TIMI 58 confirmed the cardiorenal protective effect of the drug class, as dapagliflozin (10 mg daily) compared to placebo reduced the primary efficacy endpoint of CV death or hospitalization for HF after 4.2 years by 17% (95% CI 0.73–0.95) in 17,160 T2D patients with multiple CV risk factors (detailed in Table 5) or established CVD, while the renal composite was reduced by 24% (95% CI 0.67–0.87) (31). However, dapagliflozin did not lower its other primary efficacy endpoint, 3-point MACE (HR 0.93, 95% CI 0.83–1.03). The CVOT of ertugliflozin, the fourth registered SGLT-2 inhibitor (VERTIS trial;) is expected to report in 2019 (57).

The recent meta-analysis of all the three CVOTs by Zelniker *et al.* helps to untangle the somewhat puzzling differences in outcomes (58). All CVOTs had different study populations with regard to CV risk. Since almost all of the participants had established CVD at baseline, EMPA-REG OUTCOME is mainly considered as a secondary prevention trial (29). In comparison, CANVAS Program and DECLARE-TIMI studied both secondary and primary prevention, with established CVD in 65.6% and 40.6% of the participants, respectively (30, 31). Separating the group with established CVD from the patients with only multiple risk factors showed that those with established CVD resulted in an improved 3-point MACE HRs (pooled HR 0.86 95% CI 0.80–0.93) with acceptable 5-year numbers-needed-to-treat (NNTs), underpinning the value of SGLT-2 inhibition in this population, as shown in Table 3. However in the group with only multiple risk factors there was no benefit with a pooled HR of 1.00 (95% CI 0.87–1.16) and, calculable only for CANVAS Program, a high NNT (Table 3).

In contrast are the results for HF and CV death (58). Indeed, for the CV death and hospitalization for HF composite, dividing the two groups again results in a strong effect in the established CVD group (pooled HR 0.76, 95% CI 0.69–0.84). However, although a beneficial effect is seen in the multiple risk factor group, this effect is not significant (pooled HR 0.84 95% CI 0.69–1.01). When calculating the NNTs for a 5-year treatment period, primary prevention for HF and CV mortality with an SGLT-2 inhibitor would imply treating 148 to 233 patients for 5 years to prevent one case of CV death or hospitalization for HF. If stratified for HF at baseline, a remarkable NNT of 12 to 25 can be calculated to prevent HF and CV death events in patients with a history of HF. The NNTs for primary HF and CV death prevention vary from 24 to 134 between the CVOTs. In EMPA-REG OUTCOME the results are the most pronounced, which might be due to an underestimation of the prevalence of HF at baseline in a population that only consists of patients with established atherosclerotic CVD (Table 3).

For the renal composite outcomes, the pooled renal benefit depends on kidney function at baseline, as shown in Table 4. The HRs and 5-year NNTs for secondary prevention (eGFR <60 mL/min/1.73m^2) are more or less equal to those of the two composites mentioned

previously, which seems acceptable to justify treatment. On the other hand, renal prevention in patients with eGFR >60 ml/min/1.73m^2 seems less striking. Although the HRs show larger benefit at normal (eGFR ≥90 ml/min/1.73m^2) or mildly impaired (eGFR 60 to <90 ml/min/1.73m^2) renal function, the corresponding NNTs do not follow this trend due to differences in absolute risk reduction between studies. Again, these differences could be due to variances in population. Still, the NNTs of patients with normal kidney function are 48 and 156. Keeping in mind that one year of treatment with an SGLT-2 inhibitor costs around 4,000 to 6,000 US dollar, it may be clear that if these NNT are valid for the general population, primary prevention (treating all T2D patients with CV risk factors or established CVD regardless of baseline renal function) is an expensive approach.

In summary, the pooled data of the 3 CVOTs in our opinion show an important role for SGLT-2 inhibitors as a secondary prevention drug. However, taking into account the high NNTs and current pricing of the agents, we believe the available evidence does not support positive recommendations such as described in the editorial by Verma *et al.* (59) for the use of these agents in a broader population. Primary prevention with an SGLT-2 inhibitor might currently be too expensive to justify implementation in guidelines (31).

SGLT-2 inhibitors and the cardiorenal axis: potential mechanisms of protection

The outcomes of these trials have been met with significant interest in the kidney, endocrine and cardiovascular communities, although the mechanisms underlying the results were and remain incompletely understood. This has led to the development of several hypotheses which aim to explain how SGLT-2 inhibitors may improve cardiorenal outcome and which are currently addressed in several (mechanistic) studies. It is broadly agreed, for a number of reasons, that the glucose-lowering effects of empagliflozin and canagliflozin do not completely explain the observed CV and renal benefit. First, the divergence of the survival and HF curves in EMPA-REG OUTCOME and to a lesser extent in CANVAS Program was observed within 3 months of treatment, making improved glycemic control an unlikely explanation. In the United Kingdom Prospective Diabetes Study (UKPDS), it took 10 years before strict glycemic control was able to modestly reduce CV events (60). Second, as indicated above, trials such as the ACCORD and ADVANCE trial failed to show a reduction in CV mortality despite intensive blood glucose control (61, 62). In addition, despite similar HbA1c reductions in CVOTs with DPP-4 inhibitors and SGLT-2 inhibitors the CV and renal outcomes are very different (neutral with DPP-4 inhibitors versus beneficial with SGLT-2 inhibitors) (63). Furthermore, a reduction in HF hospitalization has not been previously demonstrated by other glucose-lowering drugs in large-scale treat-to-target glycemic trials. Beyond glucose, improvement of other traditional CV risk factors also fails to explain the CV benefit, including modest changes in blood pressure, body weight and uric acid, as reviewed elsewhere (32).

Thus, new ideas have been put forward to explain these cardiorenal benefits. Central in this regard is the crucial notion that, in addition to tubular glucose reuptake, the SGLT-2 transporter is responsible for up to 5% of sodium reabsorption in the proximal tubule.

SGLT-2 inhibition leads to an initial and temporary increase in urinary sodium excretion (64). This results in a reduction in plasma volume, which is reflected by an increase in hematocrit. The contraction in plasma volume would be expected to reduce cardiac preload, while cardiac afterload may be reduced through blood pressure lowering and a decrease in arterial stiffness, which could improve cardiac perfusion (65). Notably, the increase in hematocrit (Ht) was the strongest predictor of CV benefit in EMPA-REG OUTCOME (64). These hemodynamic effects may contribute to reduced cardiac oxygen consumption, while SGLT-2 inhibitors may additionally enhance myocardial oxygenation through increased Ht levels. Cardiac contractility and efficiency could further be improved through increases in glucagon/insulin ratio via SGLT-2 inhibition, thereby stimulate hepatic ketogenesis. Ketone bodies are a useful substrate for the heart and render more ATP per amount of oxygen use (66, 67). Through these actions, SGLT-2 inhibitors may reduce the risk of myocardial ischemia and/or ischemic cardiomyopathy. In addition to these actions, direct cardiac effects have also been suggested as SGLT-2 inhibitors have shown in *in vitro* studies to reduce intramyocellular sodium and calcium concentrations through inhibition of myocardial Na^+/H^+ exchanger activity, while increasing mitochondrial calcium levels (68). Mitochondrial calcium stimulates ATP synthesis and prevents HF in porcine experimental models (69) Finally, SGLT-2 inhibitors may reduce low-grade inflammatory pathways in the CV system, possibly by attenuation of the Nlrp3/ASC inflammasome activation or cardiac fibrosis, thereby preventing HF (70). It is important to stress that the hemodynamic changes of SGLT-2 inhibitors are largely independent of eGFR, since CKD patients have similar CV benefit as the T2D patients with normal kidney function in EMPA-REG OUTCOME and CANVAS Program (71, 72).

The mechanisms by which SGLT-2 inhibitors improve renal outcome are similarly not fully understood. It is speculated that due to reduced tubular sodium reabsorption with subsequent increased sodium (and chloride) delivery to the macula densa, tubuloglomerular feedback is inhibited. This intrarenal autoregulatory response reduces glomerular pressure due to afferent vasoconstriction, as was shown for empagliflozin in patients with type 1 diabetes (73) and reduces albuminuria both in animal models and humans. Clinically, in T2D patients, SGLT-2 inhibition causes an acute dip in eGFR which partially attenuates over time and is reversible after cessation of therapy (74). It is very possible that this reduction in glomerular pressure, which is reminiscent of the effect of RAS blockers, explains the renal benefit of SGLT-2 inhibition. However, modulation of other renal risk factors may also contribute to improve renal outcome, including reductions in hyperglycemia, body weight and blood pressure, and improvements in other systemic hemodynamic parameters and/or endothelial function. In addition, it has been proposed that SGLT-2 inhibitors may reduce hypoxic kidney damage by 1) improving renal oxygenation through increased renal perfusion, capillary rarefaction (75) and erythropoietin production and 2) by reducing renal oxygen consumption due to reduction of tubular workload (76, 77). Finally, SGLT-2 inhibitors may suppress levels of inflammatory mediators and tubular injury markers, which could contribute to improved renal outcome (70). Importantly, similarly as the CV outcomes, renal outcomes are independent of baseline eGFR and albuminuria status (54). Indeed, dapagliflozin-induced reductions in hematocrit, blood pressure, body weight, uric acid, and albuminuria were comparable across groups with varying levels of kidney function (72).

SGLT-2 inhibitors in heart failure and chronic kidney disease patients

A limitation of the CVOT's with respect to assessing the benefit of SGLT-2 inhibition on the cardiorenal axis is that, by design, T2D patients were included with previous CVD or at high-risk of CVD, but not specifically HF patients (either HFpEF or HFrEF) or a CKD population. It is estimated that approximately 10% and 14.4% of the participants in EMPA-REG and the CANVAS Program had HF, while the numbers of CKD patients, defined as eGFR <60 ml/min/1.73 m^2, were 25.9% and 20.1% in EMPA-REG OUTCOME and CANVAS program respectively (54, 56). In addition, the renal outcomes, although prespecified, were secondary outcomes. Thus, in order to truly assess the effects of SGLT-2 inhibition in T2D patients with HF and/or or DKD, new and dedicated trials needed to be designed.

There are five major outcome trials ongoing that focus on the effects of SGLT-2 inhibitors in T2D patients with HF, including DAPA-HF (; HFrEF), DELIVER (; HFpEF), EMPEROR-Preserved (; HFpEF), EMPEROR-Reduced (; HFrEF) and SOLOIST-WHF (). Time to CV death, hospitalization for HF or urgent HF visit will be used as primary outcomes in these chronic HF settings. In addition, the EMPA-RESPONSE trial will examine the effects of empagliflozin on clinical outcome in patients with acute decompensated HF (). Moreover, several, mechanistic studies in T2D-HF patients are ongoing which investigate the effects of SGLT-2 inhibition on systemic hemodynamic function (), left ventricular indices (), sodium excretion (and), tissue sodium content (), physical fitness () and quality of life (and). The reports of these studies will help to conclude whether SGLT-2 inhibitors favorably affect outcomes in T2D patients with HFrEF and HFpEF and which potential pathways are involved.

The renal benefits of SGLT-2 inhibitors in patients with DKD are also being investigated in 3 trials, one of which was recently concluded. Mentioned in a press release, the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE;) trial was stopped prematurely based on the achievement of pre-specified efficacy criteria: doubling of serum creatinine, incident dialysis, renal transplantation, renal or CV death (78) and thus seems to confirm the renal observations done in the SGLT-2 inhibitor CVOTs described above. Other dedicated ongoing renal outcome trials which include DKD patients are DAPA-CKD () and EMPA-KIDNEY ().

Use of SGLT-2 inhibitors beyond diabetes

The glycemic efficacy of SGLT-2 inhibitors is dependent on ambient glucose levels and GFR, which determine the filtered glucose load and consequently the amount of SGLT-2 inhibitor-induced glucosuria. On the other hand, as discussed, the mechanisms of cardiorenal protection appear to be independent of their glucose-lowering effects. This has led to the hypothesis that SGLT-2 inhibitors could also reduce HF and CKD in patients without diabetes.

Therefore, the central question for reduction of HF hospitalization in these patients will be whether or not the natriuretic and or glucosuric effects of SGLT-2 inhibition that result in

volume reduction also occur in patients without hyperglycemia. Also, it is currently uncertain to what extent other factors associated with HF are modulated by SGLT-2 inhibition in normoglycemic individuals, including effects on blood pressure, cardiac substrate metabolism, cardiac oxygen consumption and potential direct cardiac effects. Interestingly, the EMPEROR studies, as well as DAPA-HF and Preserved-HF will also include patients without diabetes, thereby assessing whether reduction of HF hospitalization is also achieved in patients with other causes of heart failure.

The same question holds true with respect to the effects of SGLT-2 inhibition on the progression of non-diabetic kidney diseases. As glomerular hyperfiltration due to ongoing nephron loss is a final common pathway towards end-stage kidney disease, reducing glomerular hypertension should also be protective in other forms of kidney disease, as is evident from studies employing blockers of the RAS. However, a pilot study in 10 normoglycemic patients with focal segmental glomerulosclerosis (FSGS) showed no beneficial renal hemodynamic effects of dapagliflozin, and 24-hour urine protein excretion did not change (79). This raises the contrasting hypothesis that the natriuretic effect of SGLT-2 inhibition underlying inhibition of TGF may be dependent on tubular hyperglycemia. However, given the small sample size and pilot nature of this work, no conclusions can be drawn and this phenomenon requires further investigation. In addition to potential renal hemodynamic benefits, factors such as reduction of blood pressure, body weight, uric acid concentrations and amelioration of renal hypoxia could still be important renal protective mechanisms in the context of nondiabetic CKD. In this light, the results of both small, mechanistic physiology trials such as DIAMOND () and DAPASALT () and large, longer-term renal endpoint trials such as DAPA-CKD () and EMPA-KIDNEY () that include patients with nondiabetic CKD are eagerly awaited.

SGLT-2 inhibitors: glucose-lowering drugs, cardiorenal protectors, or both?

SGLT-2 inhibitors have first been brought to the market as glucose-lowering drugs. Indeed, they lower glucose with similar efficacy as other well-established oral glucose-lowering agents and have the benefit of low risk of hypoglycemia, induce reductions in weight loss and blood pressure, and may have long-term benefit on beta-cell function since they reduce insulin demand (80). However, side effects such as genital infections, euglycemic diabetic ketoacidosis (although scarce), fractures (at least for canagliflozin), amputations (at least for canagliflozin), and high costs have slowed down use of SGLT-2 inhibitors for management of hyperglycemia. In addition, due to reduced glucose-lowering efficacy at lower eGFR ranges, SGLT-2 inhibitors are currently only registered for patients with eGFR >60 ml/min/ $1.73m^2$ in many jurisdictions which indicates a “glucose-centric view” (Table 1).

On the other hand, SGLT-2 inhibitors have shown remarkable cardiorenal protection, not only in T2D patients with established CVD or HF but also those at high risk. Therefore, these agents are being examined in dedicated HF and CKD studies. Based on the positive results that the CVOTs reported and the promising premature halt of the CREDENCE trial, it is critically important to use an individualized medicine approach to address “non-glucose centric” unmet needs in T2D patients with specific cardiorenal morbidities, irrespective of HbA1c level (Table 1) (81). This was recently implemented in the EASD/ADA position

statement (3). The NNTs in T2D patients with established atherosclerotic CVD, HF or impaired kidney function at baseline support using these drugs specifically in secondary prevention setting. However, although more dedicated research in specific populations and more cost-effectiveness analyses are hardly needed, the current NNTs to reduce cardiorenal events in T2D patients without CVD, HF or impaired renal function at baseline, in combination with the current pricing of SGLT-2 inhibitors, do not advocate for the use of these agents for primary prevention (Table 3 and 4).

In conclusion, although SGLT-2 inhibitors were initially developed for glucose-lowering by inducing glucosuria, the indication in T2D patients for these agents in the future will primarily be cardiorenal protection. As such, SGLT-2 inhibitors are likely to fulfill the gap of an enormous unmet medical need in T2D patients: reducing the burden of cardiorenal complications, thereby reducing these morbidities and CV death. Current trials in patients with heart failure (HFpEF and HFrEF) and DKD are ongoing; in several of these trials the potential benefit of SGLT-2 inhibitors beyond diabetes is also being investigated. If these trials support the findings of the recently published studies in T2D, clinicians are likely to embrace SGLT-2 inhibitors as cardiorenal drugs first, and as glucose-lowering agents second.

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Table 1.

Indications for SGLT-2 inhibitors

Where are we now? (41)	**Where are we going? (81)**
Uncontrolled T2D despite metformin and eGFR > 30 – 60 ml/min/1.73 m^2 †	Uncontrolled T2D despite metformin and eGFR > 30–60 ml/min/1.73 m^2 † Controlled T2D and: - CVD - HF (HFpEF or HFrEF) - CKD (eGFR < 60 ml/min/1.73 m^2, hyperfiltration, albuminuria) HF or CKD without T2D

Abbreviations: CKD: chronic kidney disease, CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; T2D: type 2 diabetes mellitus

†if the indication involves glucose-lowering, eGFR threshold depends on SGLT-2 inhibitor and country

Table 2.

The T2D treatment armamentarium

Drug class	HbA1c reduction (%)	Risk of hypoglycemia	Effect on bodyweight	Adverse effects	Cardiovascular effects	Renal effects (progression of DKD)	Average yearly costs ($)[†]
Metformin	1–2	Low	Neutral/decrease due to anorectic effect	Diarrhea, nausea, vit B12 depletion, lactic acidosis	Neutral on HF, potential benefit on CVD[†]	Neutral	1,008–1,296
SU	1–2	Moderate	Increase	Diarrhea/flatulence, URI, UTI	Neutral	Neutral	576–1,116[‡]
SGLT-2 inhibitor	0.5–1	Low	Decrease	Genitourinary infections (all), risk of amputation and bone fractures (canagliflozin)	Benefit (canagliflozin, empagliflozin, dapagliflozin)	Benefit (canagliflozin, empagliflozin, dapagliflozin)	6,144–6.204[§]
GLP-1 receptor agonist	1–1.5	Low	Decrease	Nausea, vomiting, risk of thyroid C-cell tumors (liraglutide, albiglutide, dulaglutide, exenatide extended release)	Neutral (lixisenatide, exenatide extended release) Benefit (liraglutide, semaglutide, albiglutide, dulaglutide)	Benefit (dulaglutide, liraglutide)	7,512–11,616
DPP-4 inhibitor	0.5–0.8	Low	Neutral	May be associated with pancreatitis	Neutral on CVD, potential risk of HF (saxagliptin, alogliptin)	Neutral	5,388–5,724[¶]
TZD	1–1.5	Low	Increase	Fluid retention, risk of bone fractures, bladder cancer (pioglitazone), increase LDL cholesterol (rosiglitazone)	Potential benefit (pioglitazone) Increased risk of HF	Neutral	4,176–4,644
Insulin	1.5–3.5	High	Increase	Hypoglycemia, edema, sodium retention, rash	Neutral	Neutral	1,980–5,112

Symbols:

[†]Based on lowest and highest median Average Wholesale Prices (AWP) in ADA standards of care 2018

[‡]AWP based on glimepiride, glipizide, glyburide

[§]AWP based on canagliflozin, empagliflozin, dapagliflozin

[¶]AWP based on sitagliptin, saxagliptin, linagliptin, alogliptin

Abbreviations: T2D type 2 diabetes, SU sulfonylureas, SGLT-2 sodium glucose cotransporter-2, GLP-1 glucagon like peptide-1, DPP-4 dipeptidyl peptidase-4, TZD thiazolidinedione, URI upper respiratory infection, UTI urinary tract infection, LDL low-density lipoprotein, HF heart failure, CVD cardiovascular disease

Table 3.

Numbers-needed-to-treat of SGLT-2 CVOTs – stratified for CVD and HF

	Patients with MRF	Patients with aCVD		3p MACE		HF and CV death	
				MRF	aCVD	MRF	aCVD
EMPA-REG OUTCOME	0 (0%)	7,020 (100%)	HR	NA	0.86 (0.74–0.99)	NA	0.66 (0.55–0.79)
			ER	NA	37.4 vs 43.9	NA	19.7 vs 30.1
			NNT	NA	38	NA	22
CANVAS Program	3,486 (34.4%)	6,656 (65.6%)	HR	0.98 (0.74–1.30)	0.82 (0.72–0.95)	0.83 (0.58–1.19)	0.77 (0.65–0.92)
			ER	15.8 vs 15.5	34.1 vs 41.3	8.9 vs 9.8	21.0 vs 27.4
			NNT	721	34	233	35
DECLARE-TIMI 58	10,186 (59.4%)	6,974 (40.6%)	HR	1.01 (0.86–1.20)	0.90 (0.79–1.02)	0.84 (0.67–1.04)	0.83 (0.71–0.98)
			ER	13.4 vs 13.3	36.8 vs 41.0	7.0 vs 8.4	19.9 vs 23.9
			NNT	NA	58	148	56
ALL CVOTS	13,672 (39.8%)	20,650 (60.2%)	HR	1.00 (0.87–1.16)	0.86 (0.80–0.93)	0.84 (0.69–1.01)	0.76 (0.69–0.84)

	Patients without HF	Patients with HF		HF and CV death	
				No HF	HF
EMPA-REG OUTCOME	6,314 (89.9%)	706 (10.1%)	HR	0.63 (0.51–0.78)	0.72 (0.50–1.04)
			ER	15.5 vs 24.9	63.6 vs 85.5
			NNT	24	13
CANVAS Program	8,681 (85.6%)	1,461 (14.4%)	HR	0.87 (0.72–1.06)	0.61 (0.46–0.80)
			ER	13.6 vs 15.2	35.4 vs 56.8
			NNT	134	12
DECLARE-TIMI 58	15,436 (90.0%)	1,724 (10.0%)	HR	0.84 (0.72–0.99)	0.79 (0.63–0.99)
			ER	8.9 vs 10.5	45.1 vs 55.5
			NNT	131	25
ALL CVOTS	30,431 (88.7%)	3,891 (11.3%)	HR	0.79 (0.71–0.88)	0.71 (0.61–0.84)

Hazard ratios and event rates are derived from Zelniker et al, 2018 (58). Abbreviations: SGLT-2 sodium glucose cotransporter-2, HF heart failure, 3p MACE 3-point composite of major adverse events, aCVD participants with established atherosclerotic cardiovascular disease, MRF participants with multiple risk factors, HR hazard ratio, ER Events per 1000 patient-years in treatment versus placebo group,

vs versus, NA not available / not applicable. NNT number-needed-to-treat, NNTs are calculated by *1 / (1-EXP(-event rate with SGLT2 inhibition / 1000 [number of patient years] * 5 [time for NNT]) - (1-EXP(-event rate with placebo / 1000 [number of patient years] * 5 [time for NNT])))*

Table 4.

Numbers-needed-to-treat of SGLT-2 CVOTs renal outcome – stratified for eGFR

	eGFR ≥90 mL/min/1.73 m^2	eGFR 60 to <90 mL/min/ 1.73 m^2	eGFR <60 mL/min/1.73 m^2		Renal composite		
					eGFR ≥90 mL/min/ 1.73 m^2	eGFR 60 to <90 mL/min/1.73 m^2	eGFR <60 mL/min/ 1.73 m^2
EMPA-REG OUTCOME	1,529 (21.9%)	3,638 (52.2%)	1,801 (25.8%)	HR	0.21 (0.09–0.53)	0.61 (0.37–1.03)	0.66 (0.41–1.07)
				ER	NA	NA	NA
				NNT	NA	NA	NA
CANVAS Program	2,039 (20.1%)	5,625 (55.5%)	2,476 (24.4%)	HR	0.44 (0.25–0.78)	0.58 (0.41–0.84)	0.74 (0.48–1.15)
				ER	3.8 vs 8.1	4.6 vs 7.4	11.4 vs 15.1
				NNT	48	74	57
DECLARE-TIMI 58	8,162 (47.6%)	7,732 (45.1%)	1,265 (7.4%)	HR	0.50 (0.34–0.73)	0.54 (0.40–0.73)	0.60 (0.35–1.02)
				ER	2.5 vs 4.9	4.2 vs 7.8	8.9 vs 15.2
				NNT	156	57	34
ALL CVOTS	11,730 (34.2%)	16,995 (49.6%)	5,542 (16.2%)	HR	0.44 (0.32–0.59)	0.56 (0.46–0.70)	0.67 (0.51–0.89)

Hazard ratios and event rates derive from Zelniker et al, 2018 (58). Abbreviations: SGLT-2 sodium glucose cotransporter-2, HF heart failure, 3p MACE 3-point composite of major adverse events, eCVD participants with established cardiovascular disease, RF participants with multiple risk factors, HR hazard ratio, ER Events per 1000 patient-years in treatment versus placebo group, vs versus, NA not available / not applicable. NNT number-needed-to-treat. NNTs are calculated by *1 / (1-EXP(-event rate with SGLT2 inhibition / 1000 [number of patient years] * 5 [time for NNT]) - (1-EXP(-event rate with placebo / 1000 [number of patient years] * 5 [time for NNT])))* For EMPA-REG OUTCOME the renal composite is defined as doubling of serum creatinine, initiation of renal replacement therapy, or renal death. In the CANVAS Program, sustained 40% reduction in eGFR (MDRD), the need for renal-replacement therapy, or renal death was used. In DECLARE-TIMI 58, sustained 40% reduction in the eGFR (CKD-EPI), end-stage renal disease, or renal death was used.

Table 5.

Risk factors for CVD in CANVAS Program and DECLARE-TIMI 58

CANVAS Program	DECLARE-TIMI 58
Age ≥ 50 years	Age ≥ 55 years in men and ≥ 60 in women
and 2 of the following:	*and 1 of the following:*
Duration of T2D ≥ 10 years	SBP > 140 mmHg and DBP > 90 mmHg
SBP > 140 mmHg and use of ≥ 1 oral antihypertensive agent	On anti-hypertensive therapy prescribed by a physician
Current daily cigarette smoker	Current tobacco use (5 cigarettes/day or more for at least 1 year at randomization)
Documented microalbuminuria or macroalbuminuria	LDL-C > 3.36 mmol/L (130 mg/dl) within the last 12 months
Documented HDL-C < 1 mmol/L (39 mg/dl)	Lipid lowering therapy prescribed by a physician for documented hypercholesterolemia (see above for criteria)

Abbreviations: T2D type 2 diabetes, SBP systolic blood pressure, DBP diastolic blood pressure, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol