Sodium-glucose cotransporter 2 inhibition: towards an indication to treat diabetic kidney disease

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ABSTRACT

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have clearly demonstrated their beneficial effect in diabetic kidney disease (DKD) on top of the standard of care [blood glucose control, renin–angiotensin system blockade, smoking cessation and blood pressure (BP) control], even in patients with overt DKD. However, the indication of this drug class is still blood glucose lowering in type 2 diabetic patients with estimated glomerular filtration rate >45 mL/min/1.73 m^2. Based on the new evidence, several scientific societies have emphasized the preferential prescription of SGLT2i for patients at risk of heart failure or kidney disease, but still within the limits set by health authorities. A rapid positioning of both the European Medicines Agency and the US Food and Drug Administration will allow patients with overt DKD to benefit from SGLT2i. Clinical experience suggests that SGLT2i safety management may in part mirror renin–angiotensin blockade safety management in patients with overt DKD. This review focuses on the rationale for an indication of SGTL2i in DKD. We further propose clinical steps for maximizing the safety of SGLT2i in DKD patients on other antidiabetic, BP or diuretic medication.

Keywords: chronic renal failure, diabetic kidney disease, ESRD, SGLT2 inhibitors, type 2 diabetes

INTRODUCTION

Diabetic kidney disease (DKD) is the most frequent cause of end-stage kidney disease (ESKD) in developed countries [1–3].

Until 2016, the mainstay of DKD treatment was renin–angiotensin system (RAS) blockade [4]. From 2016, sodium-glucose cotransporter 2 inhibitors (SGLT2i) have clearly demonstrated beneficial effects in DKD on top of the standard of care, namely blood glucose control, RAS blockade, smoking cessation and blood pressure (BP) control [5–9]. Initially, SGLT2i was developed to lower plasma glucose in type 2 diabetes mellitus (T2DM) patients, but large randomized controlled trials (RCTs) have demonstrated both renal and cardiovascular protection in T2DM beyond the benefits derived from improved glycaemic control.

The renoprotective effects of SGLT2i were first observed in three large trials evaluating cardiovascular safety: Empagliflozinn, cardiovascular, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME), Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS Programme), and Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE-TIMI 58). In these studies, SGLT2i reduced albuminuria progression, prevented glomerular filtration rate (GFR) decline and decreased the incidence of renal replacement therapy in T2DM patients without overt DKD [5, 6, 8]. Three further trials address the kidney effects of SGLT2i on patients with overt DKD: Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE), Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (DAPA-CKD), and the Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY). In April 2019, the CREDENCE trial's striking results on kidney and

heart protection were published [7]. In concordance with DAPA-CKD results, some authors suggest the potential use of SGLT2i on top of RAS blockade in the early stages of DKD, when T2DM patients mainly exhibit hyperfiltration and mild albuminuria. With this approach, one expects that the cardiorenal protective effect of this treatment will be offered as prevention and not delayed to the already established DKD [10]. However, further studies in pre-diabetic patients are needed to confirm this hypothesis.

There were initial safety concerns as SGLT2i adverse drug reactions (ADRs) included acute kidney injury (AKI), diabetic ketoacidosis (DKA), amputations, urinary and genital tract infections (UTIs), bladder cancer and bone fractures [11]. However, recent trials have downplayed these risks and the benefit/risk balance remains positive. Interestingly, in a pooled analysis of 11 Phase 3 RCTs, dapagliflozin use in patients with estimated GFR (eGFR) between 12 and 45 mL/min/1.73 m^2 (CKD G3b–4) decreased the urinary albumin creatinine ratio (UACR), BP and body weight without modulating glycated hemoglobin (HbA1c) or increasing major side effects [10]. This observation supports the concept of positive renal and cardiac effects of SGLT2i independent from glycaemic control.

In this review, we describe the molecular mechanism involved in cardiorenal protection in DKD and the current indications for SGLT2i treatment in DKD patients according to the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), as well as suggestions by the scientific community to update the indication to include overt DKD. We also propose clinical practice recommendations for the safe use of SGLT2i in DKD patients on other antidiabetic, hypertension and diuretic treatments.

NEW MOLECULAR MECHANISMS IN CARDIORENAL PROTECTION WITH SGLT2 INHIBITION

SGLT2i have become a promising option to treat T2DM as they decrease glycaemia and improve insulin resistance without producing severe hypoglycaemia [12]. In a meta-analysis published by Yang *et al.* [13], SGLT2i was demonstrated to reduce HbA1c and insulin dosage both in types 1 and 2 diabetic patients. This decrease in insulin doses could reflect an improvement in insulin resistance, which is a key mediator of type 2 diabetes [14]. Furthermore, it might in part explain the weight loss induced by this drug class. SGLT2i additionally reduces cardiovascular complications and slows DKD progression [5, 6, 8, 15–17]. Diverse experimental and clinical studies suggest that the cardiorenal protection exerted by SGLT2i may be explained by mechanisms independent of glycaemia and BP control.

SGLT2 is a glucose/sodium (Na^+) cotransporter located at the apical membrane of proximal tubular cells that drives glucose into cells together with Na^+. It is responsible for the reabsorption of 90% of the filtered glucose load [18–20]. In diabetic patients, the increase in filtered glucose enhances SGLT2 activity, which worsens glycaemic control and promotes Na^+ loading, impairing BP control [21]. Moreover, proximal tubular Na^+ reabsorption results in decreased Na^+ availability at distal tubules and reduces macula densa adenosine signalling to afferent arterioles. The signalling reduction leads to afferent arteriole vasodilation, increases intraglomerular pressure and causes hyperfiltration. Na^+/H^+ exchanger isoform 3 (NHE3) is a proximal tubule Na^+ transporter closely regulated by glucose metabolism and SGLT transporters, which makes it sensitive to SGLT2i [22]. In Otsuka Long-Evans Tokushima Fatty diabetic rats, empagliflozin decreased the tubular expression of NHE3, the Na^+–K^+–2Cl^- cotransporter and the epithelial Na^+ channel as compared with untreated littermates [23]. Therefore, SGLT2i lowers glycaemia and additionally promotes natriuresis by inhibiting both SGLT2 activity and other Na^+ transporters such as NHE3. Thus, the natriuretic effect may contribute to cardiorenal benefits by lowering arterial pressure and re-activating renal tubulo-glomerular feedback signalling from the macula densa that decreases intraglomerular pressure and hyperfiltration. However, prior to SGLT2i use, no other diuretic demonstrated clear cardiorenal protective effects in diabetic patients although they reduced BP or volume overload. For this reason, we believe that the beneficial effects exerted by SGLT2i are the conjunction of diverse molecular mechanisms acting together. More studies on the bench side are needed to elucidate the involved pathways.

Beyond the antidiabetic and natriuretic properties, studies in non-diabetic mice and rats suggest that SGLT2i may exert additional direct kidney- or heart-protective actions [24–28]. Although in some settings SGLT2i did not prevent kidney damage, in most non-diabetic CKD models, they did decrease kidney fibrosis and inflammation [24–28]. The discrepant results may depend on the nature of the different insults tested: SGLT2i did not protect from chronic oxalosis [24] or subtotal nephrectomy [25], while it protected from unilateral ureteral obstruction [26], ischaemia–reperfusion [27] and protein overload [28]. In cultured human tubular cells (HK-2), transforming growth factor beta 1 (TGF-β1) upregulated SGLT2 and type IV collagen expression, and this was prevented by empagliflozin through nuclear factor-κB/Toll-like receptor 4 (NF-κB/TLR4) pathway inhibition, thus linking a key mechanism of DKD and non-DKD CKD progression to SGLT2 [29]. Furthermore, both mice and human glomerular cells also express SGLT2. Indeed, albumin upregulated SGLT2 in mice with protein-overload proteinuria, in albuminuric CKD patients and in cultured human podocytes [28]. Overall, the available evidence of benefit in non-diabetic models supports the existence of glucose-independent nephroprotective effects, and this hypothesis will be addressed in RCTs [26–30].

In search of further molecular targets and downstream mediators of SGLT2i effects, the canagliflozin mechanism of action (MoA) network was explored combining cultured tubular cell transcriptomics profiles and protein expression data from the scientific literature. This identified 44 proteins related to the canagliflozin MoA molecular model that overlapped with proteins in the DKD network model, and 10 of them were involved in DKD progression [31]. Assessment of these in plasma from diabetic patients with UACR > 1.7 mg/mmol included in the efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU trial) identified four candidate factors [tumour necrosis factor receptor 1 (TNFR1), interleukin (IL)-6, matrix metalloproteinase 7 (MMP-7) and

fibronectin 1 (FN1)] that were decreased by canagliflozin, supporting the concept that SGLT2i may modulate inflammatory and fibrosis processes in DKD [31, 32]. In addition, the effects of two SGLT2i (empagliflozin and canagliflozin) and TGF-β1 on gene expression in two human proximal tubular cell lines were studied [33]. All 94 genes, mainly related to extracellular matrix organization, which were upregulated by TGF-β1 and downregulated by the two SGLT2i were identified. Three of these genes [thrombospondin 1 (THBS1), tenascin C (TNC) and platelet-derived growth factor subunit B (PDGF-B)] related to renal fibrosis and CKD progression were then validated on mRNA expression in both cell lines, proving that SGLT2i is able to suppress these genes.

Cardioprotection by SGLT2i has been widely attributed to the improved glycaemia and BP control [34]. However, a direct effect on the heart cannot be disregarded since there is an ongoing controversy on whether SGLT2 is expressed in the heart [35–39]. Recent data support direct effects on the heart since empagliflozin improved high glucose-induced cardiomyocyte dysfunction [40]. Empagliflozin also ameliorated cardiac function in pressure overload-induced heart failure in mice [41] and delayed ischaemic contracture in isolated mouse hearts in an insulin-dependent manner [42]. This last effect may depend on direct inhibition of the Na^+/H^+ transporter NHE1 as empagliflozin interacts with its Na^+-binding domain [42, 43]. NHE1 and NHE3 belong to the same family of Na^+/H^+ transporters. NHE1 is virtually ubiquitously expressed and is responsible for intracellular pH maintenance, while NHE3 expression is restricted to epithelial tissues where it also contributes to transepithelial transport [44]. As mentioned before, in kidney tubules, NHE3 activity depends on SGLT2-mediated glucose transport [22]. It may be speculated that a similar mechanism applies to NHE1 in the heart [22, 40]. Thus, cardioprotection by SGLT2i may also depend on direct inhibition of local SGLT2. Finally, empagliflozin increased glucose transporter-1 (GLUT-1) mediated glucose transport in isolated cardiomyocytes [45], and this could also contribute to SGLT2i cardioprotection.

In summary, there is evidence that SGLT2i exert pleiotropic tissue-protective effects via different mechanisms (Supplementary data, Figure S1): (i) reduction of glycaemia, BP and volume overload; (ii) SGLT2 inhibition in kidney tubules leading to improved metabolic control, natriuresis and decreased hyperfiltration; (iii) local SGLT2 inhibition in other organs, such as the heart [40, 41] or the pancreas [46]; and (iv) SGLT2-independent interference with Na^+/H^+ transporters.

WHEN TO START SGLT2 IN DIABETIC PATIENTS?

As of June 2019, regulatory and scientific society statements and recommendations on the indications and timing of SGLT2i prescriptions differ. This likely reflects the different processing timelines for the wealth of recent information from high cardiovascular risk and DKD RCTs (Table 1) [5–8, 15]. The EMA current indication for SGLT2i is the treatment of insufficiently controlled T2DM as an adjunct to diet and exercise, either as monotherapy when metformin is considered inappropriate due to intolerance or in addition to other medicinal products for the treatment of diabetes, although dapagliflozin may also be used in T1DM (Table 2) [47–51]. Recently, the EMA recognized the positive effect of dapagliflozin on cardiovascular events. However, the US FDA was the first to acknowledge the specific indications in T2DM patients with cardiovascular disease (CVD) to reduce major adverse cardiovascular events (MACEs) for canagliflozin and to reduce cardiovascular death for empagliflozin, based on RCT results (Tables 1 and 2) [47–51]. While the US FDA specifically warns against the use of any SGLT2i in T1DM, the EMA admits the use of dapagliflozin for this indication. Overall, the FDA appears to have moved faster than the EMA in response to cardiovascular safety trial results and clearly distinguishes between specific indications for each drug as per RCT results (Figure 1A). The rapid response is likely related to the FDA request for these trials, and an indication for the treatment of DKD is undergoing priority review. In contrast, the EMA does not state large differences between the three drugs either in indication or in the use according to eGFR data. There are additional differences between major regulatory agencies regarding SGLT2i contraindications for DKD patients with decreased eGFR (Table 3 and Figure 1B).

Since 2016, scientific societies have also suggested the role of SGLT2i in patients with T2DM and specific comorbidities. Table 2 summarizes some of the key position manuscripts. Overall, scientific societies recommend considering SGLT2is as preferential agents to treat T2DM on top of metformin when patients have atherosclerotic CVD, heart failure or DKD. Contrary to the FDA, which provides different regulatory advice for each drug according to specific cardiovascular safety trial results, scientific societies usually use the generic term 'SGLT2i' or 'SGLT2i with evidence of cardiovascular or renal protection'. Additionally, given the striking benefit over heart failure hospitalization, the preferential use of SGLT2i for patients with heart failure is suggested or recommended, although this was not a primary outcome of cardiovascular safety trials. Scientific societies fall short of recommending the use of SGLT2i outside the eGFR limits provided by regulatory authorities (Table 3). It is likely that the range of eGFR at which canagliflozin can be prescribed will expand in the near future, given the renal benefit observed in the CREDENCE trial of canagliflozin versus placebo in patients with overt DKD, in which patients were enrolled with eGFR ≥ 30 mL/min/1.73 m^2, and canagliflozin was not stopped until renal replacement therapy was initiated (Supplementary data, Figure S2A). We believe that this supports an indication of canagliflozin at any eGFR value in non-dialysis patients, always with the caveat that initiation of SGLT2i may decrease the baseline eGFR as it decreases hyperfiltration. In this regard, in T2DM patients with DKD, canagliflozin decreased the relative risk of a composite primary outcome of ESKD (dialysis, transplantation or a sustained estimated GFR of < 15 mL/min/1.73 m^2), doubling of the serum creatinine level or death from renal or cardiovascular causes by 30% versus placebo [hazard ratio (HR) = 0.70; 95% confidence interval (CI) 0.59–0.82; P = 0.00001] [7]. More specifically, a hard component of the composite, the residual risk of ESKD was reduced to 2/100 patient-years of follow-up (Supplementary data, Figure S2B). Taken together with beneficial effects over

Table 1. Key cardiovascular safety and CKD trials of SGLT2i

Drug	Trial	Trial type	CVD (% of patients)	eGFR (mL/min/1.73 m²)	UACR (mg/g)[a]	MACE HR (95% CI)	Stroke/AMI HR (95% CI)	CV death HR (95% CI)	Heart failure hospitalization HR (95% CI)	Renal outcome HR (95% CI)
Canagliflozin	CANVAS [6]	CV safety	65.6	76.5	12.3 (6.65–42.1)	0.86* (0.75–0.97)	Not different	0.87 (0.72–1.06)	0.67 (0.52–0.87)	0.60[b] (0.47–0.77)
	CREDENCE [7]	DKD	50.4	56.2	927 (463–1833)	0.80 (0.55–1.00)	Not different	0.78 (0.55–1.00)	0.61 (0.47–0.80)	0.68[c] (0.54–0.86)
Dapagliflozin	DECLARE-TIMI [8]	CV safety	40.6	85.2	Not available	0.93 (0.84–1.03)	Not different	0.98 (0.82–1.17)	0.73 (0.61–0.88)	0.53[d] (0.43–0.66)
Empagliflozin	EMPA-REG OUTCOME [5, 15]	CV safety	99.1	74	Not available[e]	0.86* (0.74–0.99)	Not different	0.62 (0.49–0.77)	0.65 (0.50–0.85)	0.54[f] (0.40–0.75)

AMI, acute myocardial infarction; MACE, composite of cardiovascular death, myocardial infarction or ischaemic stroke.

[a]Median (interquartile range).

[b]Composite of 40% reduction in eGFR, renal replacement therapy or renal death.

[c]Dialysis for at least 30 days, kidney transplantation or eGFR <15 mL/min/1.73 m² for at least 30 days.

[d]Composite of ≥40% reduction in eGFR to <60 mL/min/1.73 m², end-stage kidney disease or death from renal cause.

[e]UACR ≥ 30 mg/g in 40% of participants.

[f]Doubling of serum creatinine with eGFR ≤45 mL/min/1.73 m², initiation of renal replacement therapy or death from renal disease.

*P < 0.05 for superiority.

pre-specified renal outcomes such as incident or worsening nephropathy (progression to macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy or death from renal disease) and incident albuminuria in patients with milder or no evidence of DKD in cardiovascular safety trials [5, 17], overall data point to a nephroprotective effect at different stages of DKD that warrants preferential use of SGLT2i to treat T2DM patients from very early in the course of DKD, and even before its occurrence to prevent or delay it. The kidney outcomes success of SGLT2i trials for T2DM has set the stage for additional trials enrolling non-T2DM patients [30].

SGLT2 AND DKD: PROS AND CONS

Three large cardiovascular safety trials—EMPA-REG OUTCOME, the CANVAS programme and DECLARE-TIMI 58—demonstrated that SGLT2i reduced albuminuria progression, prevented GFR decline and decreased the incidence of renal replacement therapy [5, 8, 11, 15, 17, 52]. However, these were secondary endpoints and few patients had moderate-to-severe DKD (Table 1), so information on patients with A3 albuminuria or GFR <60 mL/min/1.73 m² was limited. Two ongoing (DAPA-CKD and EMPA-KIDNEY) and one just completed (CREDENCE) RCTs test with different SGLT2i for primary renal endpoints in patients with overt DKD. The CREDENCE trial evaluated the impact of SGLT2 inhibition (canagliflozin 100 mg daily) against placebo in patients with T2DM and DKD defined as UACR >300 mg/g with eGFR from 30 to 90 mL/min/1.73 m² [1, 7]. CREDENCE was stopped prematurely because the pre-specified efficacy criteria for early cessation were reached, thus providing evidence of renal and heart protection in a population partly excluded from prior RCTs [53]. Regarding safety, rates of adverse events were similar between groups, with the exception of DKA (2.2 versus 0.2 events per 1000 patient-years in canagliflozin and placebo patients, respectively) and genital mycotic infection—especially, in male patients—which were more frequent in the canagliflozin group.

Despite the increasing evidence of SGLT2i efficacy in DKD, the use of this drug class is still limited to patients with eGFR >45 mL/min/1.73 m². This restriction may be ascribed to two main reasons: (i) SGLT2i were designed as antidiabetic drugs and their antidiabetic effects depend on the magnitude of glycosuria, which is limited in patients with decreased GFR [54]; and (ii) given the mechanism of action, there was no rationale for their use as antidiabetic agents in patients with an eGFR <45 mL/min/1.73 m². Accordingly, they were not even tested in large numbers of patients with low eGFR, until now. Although exploratory trials had evaluated the efficacy and safety of SGLT2i in established DKD [54], their clinical impact was low, as the sample size was small, the duration short and renal outcomes were not assessed. Interestingly, a meta-analysis of 4000 patients with eGFR from 45 to 60 mL/min/1.73 m² from 11 RCTs demonstrated consistent positive effects of dapagliflozin on BP, body weight, haematocrit, albuminuria, eGFR, bicarbonate, pulse pressure and uric acid. CREDENCE confirmed kidney and cardiovascular benefits for patients starting canagliflozin in overt DKD patients (G3a and G3b, eGFR >30 mL/min/1.73 m²) that maintained therapy up to the

Table 2. Indications (EMA, FDA) or recommendations (ADA-EASD, ESC, EURECA-m and DIABESITY) for the use of SGLT2i

Drug		EMA (as of June 2019) [47]	FDA (as of June 2019) [48]	ADA-EASD 2018 [50]	ESC 2016 [49]	EURECA-m and DIABESITY 2019 [51]	CREDENCE-based likely future suggestions
SGLT2i	Canagliflozin	T2DM control[a]	T2DM control[b] To reduce risk of MACEs in T2DM with established CVD[c]	In T2DM, metformin as first line. SGLT2i as next step when: HbA1C not on target or on target using a second drug that is not an GLP-1RA and athero-sclerotic CVD (on par with GLP-1RA) or heart failure or DKD predominate (not if eGFR under local authorized eGFR)	SGLT2i should be considered early in the course of T2DM patients with CVD (Class II, level B)	Recommendation: add SGLT2i if T2DM and DKD when: HbA1c not on target on metformin; or HbA1c on target and met-formin not tolerated or contraindicated; or HbA1C on target with one agent, consider switch to SGLT2i	Indication to treat T2DM with CKD independently from glycaemia control
	Dapagliflozin	T1DM[d] and T2DM[a] con-trol and to reduce risk of cardiovas-cular effects	T2DM control[b]				?
	Empagliflozin	T2DM[a] control	T2DM control[b] To reduce risk of CV death in T2DM with established CVD[e]				?

CREDENCE based likely future suggestions reflect the authors views regarding potential future guidelines of EMA indications based on the results of the CREDENCE trial. These should be considered hypothetical and may not reflect the eventual decisions by these bodies

[a]Adults with insufficiently controlled T2DM as an adjunct to diet and exercise, either as monotherapy when metformin is considered inappropriate due to intolerance or in addition to other medicinal products for the treatment of diabetes.

[b]As an adjunct to diet and exercise to improve glycaemic control in adults with T2DM.

[c]To reduce the risk of MACE in adult patients with T2DM and established CVD.

[d]Adults with insufficiently controlled T1DM as an adjunct to insulin in patients with body mass index $\geq$27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

[e]To reduce the risk of cardiovascular death in adult patients with T2DM and established CVD.

American Diabetes Association-European Association for the Study of Diabetes (ADA-EASD), European Renal and Cardiovascular Medicine (EURECA-m) and Diabetes and Obesity in Renal Disease (DIABESITY) are European Renal Association (ERA-EDTA) working groups.
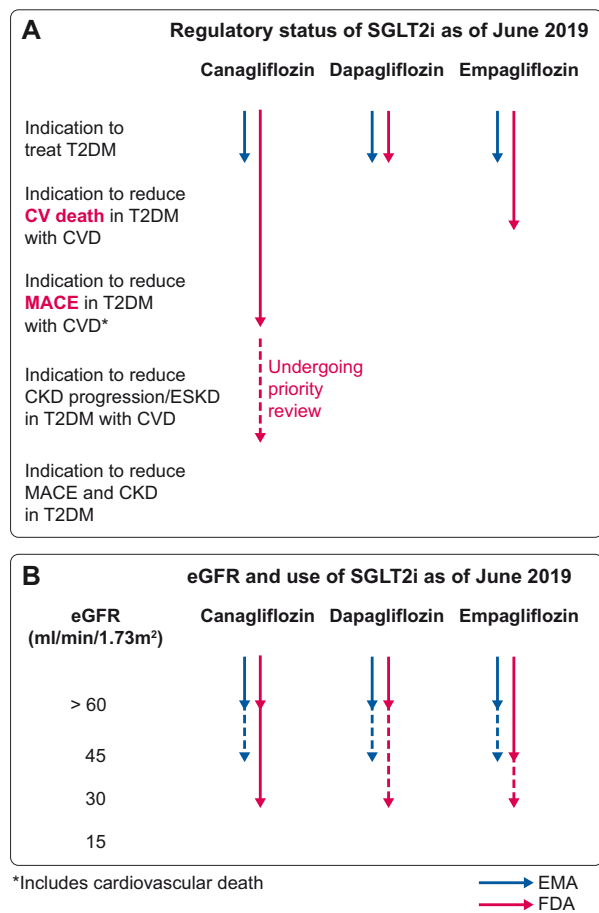
A   Regulatory status of SGLT2i as of June 2019

Canagliflozin   Dapagliflozin   Empagliflozin

Indication to treat T2DM

Indication to reduce **CV death** in T2DM with CVD

Indication to reduce **MACE** in T2DM with CVD*

Undergoing priority review

Indication to reduce CKD progression/ESKD in T2DM with CVD

Indication to reduce MACE and CKD in T2DM

B   eGFR and use of SGLT2i as of June 2019

eGFR (ml/min/1.73m²)   Canagliflozin   Dapagliflozin   Empagliflozin

> 60

45

30

15

*Includes cardiovascular death   → EMA   → FDA

FIGURE 1: (**A**) Regulatory status regarding indications of SGLT2i as of June 2019. The FDA differentiates between the indications of the three SGLT2i according to T2DM patient characteristics, while the EMA does not. In contrast, EMA allows the use of dapagliflozin in T1DM, while the FDA warns against the use of any of these drugs in T1DM. (**B**) Regulatory status regarding use in individuals with decreased eGFR of SGLT2i as of June 2019. Language such as 'contraindicated' or 'should not be used' has been considered equivalent. Discontinuous line represents the situation in which the drug was initiated prior to the deterioration of renal function. Based on the results of the CREDENCE trial [7], we anticipate that at least for canagliflozin, usage will be allowed in the near future up to the initiation of renal replacement therapy.

start of dialysis [7]. This evidence should be sufficient for the approval of the use of this drug class or at least of canagliflozin in patients with eGFR <45 mL/min/1.73 m².

The overall safety record of SGLT2i in patients with moderate-to-severe DKD has been positive [17, 54]. Adverse events were more frequent in patients receiving higher doses of this drug class. However, in CREDENCE, a low canagliflozin dose of 100 mg/day was nephroprotective and safe, suggesting that lower SGLT2i doses achieved renal and heart protection in patients with overt DKD, with eGFR <45 mL/min/1.73 m² (mean eGFR 56 mL/min/1.73 m²) [7].

SAFETY OF SGLT2i: IS THERE A CLASS EFFECT?

Potential ADRs of SGLT2i include AKI [55], DKA [56], foot and toe amputations [17], UTI and genital infections [57],

bladder cancer [58] and bone fractures [59]. The most consistent associations have been with DKA, UTI and genital infections. From 2015 to 2018, the FDA has issued six warnings about ADRs linked to SGLT2i. A review on the safety profile of SGLT2i that selected 27 studies for risk analysis concluded that causality assessment disclosed a correlation between SGLT2i and DKA and UTI [60]. A systematic review and meta-analysis of RCT that included SGLT2i up to May 2018 [61] selected 109 reports on SGLT2i, mainly dapagliflozin, canagliflozin, empagliflozin and ipragliflozin. When compared with placebo, SGLT2i decreased the risk of AKI (RR = 0.59; 95% CI 0.39–0.89; $I^2 = 0.0\%$), while no difference was found for DKA (RR = 0.66; 95% CI 0.30–1.45, $I^2 = 0.0\%$), UTI (RR = 1.02; 95% CI 0.95–1.09, $I^2 = 0.0\%$) or bone fracture (RR = 0.87; 95% CI 0.69–1.09, $I^2 = 1.3\%$). Three studies reported on amputation, with one finding a significantly increased risk. Subgroup analysis did show an increased risk of UTI with dapagliflozin only (RR = 1.21; 95% CI 1.02–1.43, $I^2 = 0.0\%$), but no other analysis supported an increased risk of AKI, DKA, UTI or fracture. The authors concluded that evidence from RCTs did not suggest an increased risk of harm with SGLT2i as a class over placebo or active comparators with respect to AKI, DKA, UTI or fracture. However, wide CIs for many comparisons suggest limited precision, and, therefore, clinically important ADRs could not be ruled out.

In the CANVAS programme, 10 142 T2DM patients were randomly allocated to canagliflozin 100 or 300 mg/day or placebo [18]. Canagliflozin was associated with a significant doubling in the risk for amputations, mainly toe and metatarsal amputations (6.3 versus 3.4 cases per 1000 patient-years, HR = 1.97, 95% CI 1.41–2.75) [62]. The risk was similar for ischaemic and infective aetiologies and for 100 and 300 mg doses. Overall amputation risk was strongly associated with baseline history of prior amputation (major or minor) (HR = 21.31, 95% CI 15.40–29.49) and other established risk factors. No interactions between randomized treatment and participant characteristics explained the effect of canagliflozin on amputation risk. For every clinical subgroup studied, numbers of amputation events projected were smaller than the numbers of MACE averted (HR = 1.97). Additionally, no differences in the incidence of amputations were observed in the CREDENCE RCT in patients with DKD randomized to 100 mg/day canagliflozin. Interestingly, when CREDENCE was started the amputations warning regarding the CANVAS study was already released, and investigators were aware of this ADR. However, no differences regarding baseline peripheral artery disease between the two studies were observed. In the DECLARE study, comparing dapagliflozin versus placebo added to standard care in 17 160 patients followed for a median of 4.2 years, there were no differences in the incidence of amputations, stroke or fractures, with a significant increase of UTI or genital infections and DKA. Moreover, there was a lower risk of hypoglycaemia, AKI and bladder cancer in the dapagliflozin-treated group (Supplementary data, Tables S1 and S2) [8]. To clarify whether the amputation risk could be a class effect of SGLT2i, a thorough collection of prospective data on amputations and other foot-related complications is required in all ongoing and future long-term randomized clinical trials (e.g. DAPA-CKD, Dapagliflozin in Patients with

Drug		EMA (as of May 2019) [47]	FDA (as of May 2019) [44]	ADA-EASD 2018 [50]	ESC 2016 [49]	EURECA-m and DIABESITY 2019 [51]	CREDENCE-based likely future suggestions
SGLT2i	Canagliflozin	Should not be initiated when eGFR <60	Contraindicated if eGFR <30	Authorized eGFR varies with agent and local health authority	No mention	SGLT2i were used in EMPA-REG OUTCOME and CANVAS up to eGFR 30, but current indication is >45 for empagliflozin and canagliflozin and >60 for dapagliflozin'	Use at any GFR not yet on dialysis for kidney and cardiovascular protection
	Dapagliflozin	Should be discontinued at GFR persistently <45	Should not be initiated when eGFR <60 / Contraindicated if eGFR <30				?
	Empagliflozin		Should not be initiated when eGFR <45 / Contraindicated if eGFR <30				?

CREDENCE based likely future suggestions reflect the author's views regarding potential future guidelines of EMA indications based on the results of the CREDENCE trial. These should be considered hypothetical and may not reflect the eventual decisions by these bodies. eGFR in mL/min/1.73 m². EMA, ADA-EASD, ESCEURECA-m and DIABESITY are ERA-EDTA working groups.

Heart Failure and Reduced Ejection Fraction (DAPA-HF) and DECLARE with dapagliflozin; EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved) and EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced); and Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (VERTIS CV) with ertugliflozin).

Recently, the use of SGLT2i has been also associated with Fournier gangrene, a rare urologic emergency characterized by necrotizing infection of the external genitalia, perineum and perianal region. The FDA identified 55 unique cases of Fournier gangrene in patients receiving SGLT2i between 1 March 2013 and 31 January 2019. Age ranged from 33 to 87 years; 39 were men and 16 were women. Time to onset after SGLT2i initiation ranged from 5 days to 49 months. All patients had DKA ($n = 8$), sepsis or septic shock ($n = 9$) and AKI ($n = 4$). Eight patients had faecal diversion surgery, two developed necrotizing fasciitis of a lower extremity that required amputation and one required a lower extremity by-pass procedure because of gangrenous toes. Three patients died. For comparison, the FDA identified 19 Fournier gangrene cases associated with other antidiabetic agents between 1984 and 31 January 2019: metformin ($n = 8$), insulin glargine ($n = 6$), short-acting insulin ($n = 2$), sitagliptin plus metformin ($n = 2$), and dulaglutide ($n = 1$). These patients ranged in age from 42 to 79 years; 12 were men and 7 were women. Two patients died [63]. These findings merit further research.

In conclusion, genital infections are probably the most frequent and documented ADR of the SGLT2i. Other potential ADRs are less consistent and variable data can be found in different RCTs and meta-analysis. Given the similar molecular structure of the available SGLT2i, it is plausible that ADRs observed until now are a class effect. The discrepancies observed in the published RCTs may be ascribed to the differences in patient characteristics as well as in evolving clinical experience with these agents rather than to differences between specific SGLT2i.

CLINICAL RECOMMENDATIONS FOR THE USE OF SGLT2 INHIBITORS IN DKD

A multifactorial intervention is still the best therapeutic approach to T2DM with or without DKD. These include implementing lifestyle interventions, promoting weight loss (healthy diet and exercise) in obese patients, reducing low-density lipoprotein cholesterol levels using statins, treating BP preferentially with RAS blockade and improving glycaemic control [51, 64]. For the latter objective, metformin is still considered the first pharmacological option if tolerated, although safety and prescribed doses should be revised if eGFR is 30–60 mL/min/1.73 m² and the fact sheet recommends stopping the drug when eGFR falls below 30 mL/min/1.73 m² [65], although this is a debated issue. Recent consensus documents have addressed the place of SGLT2i and glucagon-like peptide-1 receptor agonists (GLP-1RAs), in light of cardiovascular and renal outcomes trials [51, 64, 66].
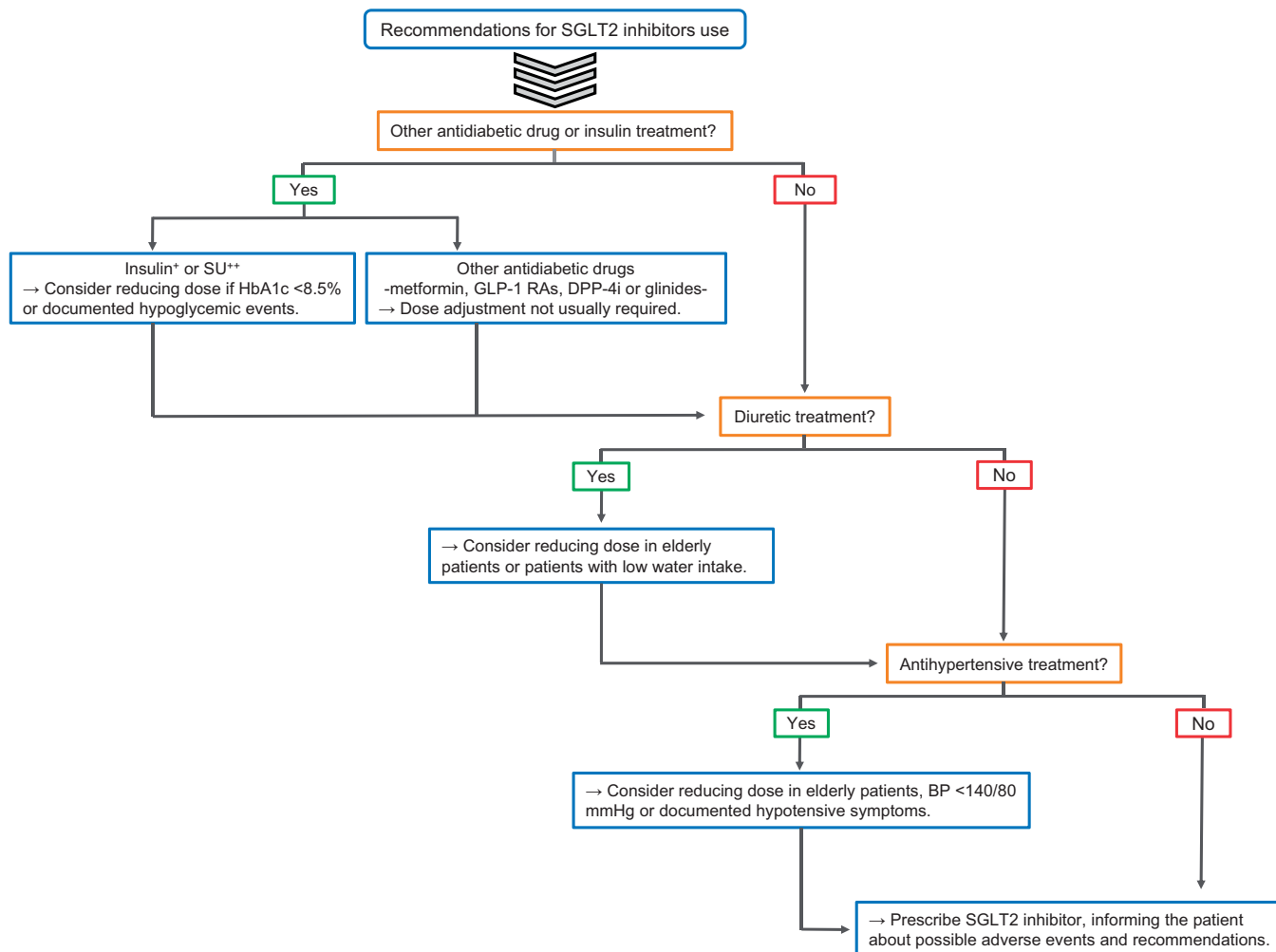
FIGURE 2: Recommendations before starting treatment with SGLT2i. [+]A decrease of 20% of the insulin dose is recommended, especially if there are previously reported hypoglycaemic events or the eGFR is <60 mL/min/1.73 m^2. [++]Sulphonylureas (SU) should be withdrawn if eGFR falls below 45 mL/min/1.73 m^2. DPP-4i, dipeptidyl peptidase 4 inhibitor GLP-1 RAs, glucagon-like peptide-1 receptor agonists. Adapted from reference [68].

These documents consider SGLT2i and GLP-1RAs as second-line therapy in both DKD with unmet glycaemic control (HbA1c >7%) and for controlled DKD patients (HbA1c <7%). Specifically, consensus documents recommend the use of SGLT2i in T2DM patients with established CVD or DKD. These changes shift the focus of this drug prescription from glycaemic control to improved kidney and cardiovascular outcomes.

The mechanistic effect of this drug class, including natriuresis and glycosuria, guides the concomitant use of other drugs and suggests some preventive measures to increase safety when initiating SGLT2i treatment in patients with CKD on other antidiabetic drugs or diuretics. Thus, the lower antidiabetic efficacy of SGLT2i at low eGFR may require a combination with other antidiabetic agents [67]. Severe hypoglycaemia is rarely described with the use of SGLT2i and is usually associated with the add-on therapy to other hypoglycaemic drugs [54, 67]. To prevent hypoglycaemic events in DKD patients, other antidiabetic drugs should be titrated, reduced or withdrawn before starting SGLT2i (Figure 2). This recommendation is particularly important in DKD patients on sulphonylureas (SU) and/or on insulin, which is already associated with an increased risk of hypoglycaemia in CKD [54, 67]. Combination with other antidiabetic drugs, such as GLP-1RAs or metformin, has a much lower risk of hypoglycaemic events [69]. Because of the diuretic effect, doses of other diuretic medications should also be revised and in many cases decreased when starting SGLT2i in DKD patients (Figure 2). In elderly or frail patients, who may have a lower water intake or access, SGLT2i therapy should be carefully initiated and closely monitored.

The routine risk management strategy for SGLT2i is very similar to that for RAS blockers, which is familiar for both patients and physicians. Thus, patients on SGLT2i treatment should be advised to temporarily discontinue the drug if acutely ill, especially in the presence of vomiting, diarrhoea or decreased water intake, to avoid dehydration and volume depletion. Similarly, SGLT2i should be transiently withdrawn during acute infections, fever, surgery and other insulin counter-regulatory states to prevent DKA [67, 70]. DKA is a rare but severe complication of SGLT2i treatment that, unlike classic DKA, is usually associated with mild-to-moderate serum

glucose elevations. DKA may be precipitated by fasting, alcohol intake, excessive reduction of insulin doses, dehydration or acute processes, although some cases remain unexplained [71]. To avoid DKA, SGLT2i should be initiated at the lowest dose possible when blood ketone levels are <0.6 mmol/L [72]. Moreover, it is not advisable to start this drug class in patients with an already known low reservoir of endogenous insulin or low C-peptide. It is recommended that patients self-monitor capillary blood ketones when DKA is suspected, but urine ketones monitoring would be enough. SGLT2i therapy should be discontinued if ketone levels increase. Proper education is important for both the patient and the clinician to be fully aware of factors impacting ketone levels and the protocol to follow if ketone levels increase. In concordance, a nephrologist should suspect euglycaemic DKA when called as consultant in the emergency department for a severe metabolic acidosis with high anion gap in a diabetic patient under SGLT2i therapy. SGLT2i may be not initiated if hypovolaemia or peripheral vascular disease is present or in older frail patients.

CONCLUSIONS

In conclusion, emerging evidence derived from RCTs and meta-analyses point to cardioprotective and nephroprotective effects of SGLT2i that are maintained in patients with full-blown DKD with baseline eGFR up to 30 mL/min/1.73 m^2. The use of at least one of these drugs, canagliflozin at the 100 mg/day dose, was safe and associated with benefits in DKD patients that maintain the drug up to the start of renal replacement therapy. Scientific societies have moved to recommend the preferential use of SGLT2i in patients with DKD. It is expected that regulatory authorities will increase the range of eGFR at which SGLT2i can be used, as well as modify the indications to include nephroprotection. In addition, the development of multidisciplinary teams, including a nephrologist, cardiologist, endocrinologist and primary care doctor for the management of high-risk type 2 diabetic patients (previous history of CVD or DKD), would improve the proper implementation of this class of anti-hyperglycaemic drugs in clinical practice. SGLT2i are generally safe, and some of the initial safety concerns have not been confirmed in more recent RCTs. In any case, both physicians and patients should be well aware of potential ADRs and instructed to discontinue the drug in certain circumstances. Given the protection afforded in patients with low eGFR, where the contribution of improved metabolic control is minimal, it is thought that the molecular mechanisms of cardiovascular and kidney protection expand beyond lowering serum glucose levels. In this regard, RCTs that explore cardiovascular and kidney protection even in patients without T2DM are ongoing.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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CONFLICT OF INTEREST STATEMENT

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