The Effect of Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitors on Cardiometabolic Profile; Beyond the Hypoglycaemic Action

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Abstract

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Type 2 diabetes mellitus (T2DM) has growing prevalence worldwide and major clinical implications, chiefly cardiovascular (CV) and renal disease burden. Sodium-glucose co-transporter (SGLT)2 inhibitors are a new drug class in the management of T2DM with a mechanism of action independent of insulin. In addition to their hypoglycaemic effect, SGLT2 inhibitors appear to have haemodynamic and nephroprotective effects. Studies have consistently showed a modest but significant blood pressure (BP) reduction. Metabolic benefits are also attributed to SGLT2 inhibitors with a modest but consistent body weight decrease recorded along with improvements in lipid profile and uric acid levels. Remarkable findings of significant cardioprotective effects came from the recent EMPA-REG study with a particular focus on heart failure. In the kidney, SGLT2 inhibitors reduce hyperfiltration, a precipitant of diabetic nephropathy.

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Keywords

Sodium-glucose co-transporter-2
Inhibitor
Diabetes
Kidney
Cardiovascular
Heart

Abbreviations

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ABPM	Ambulatory blood pressure monitoring
ACR	Albumin to creatinine ratio
BP	Blood pressure
CKD	Chronic kidney disease
CV	Cardiovascular
DBP	Diastolic blood pressure

GFR	Glomerular filtration rate
HCZT	Hydrochlorothiazide
HDL	High density lipoprotein
HR	Hazard ratio
LDL	Low density lipoprotein
OD	Once daily
RAAS	Renin-aldosterone-angiotensin system
SGLT	Sodium-glucose co-transporter
SBP	Systolic blood pressure
TG	Triglycerides
TGF	Tubuloglomerular feedback
VLDL	Very low density lipoprotein

Introduction

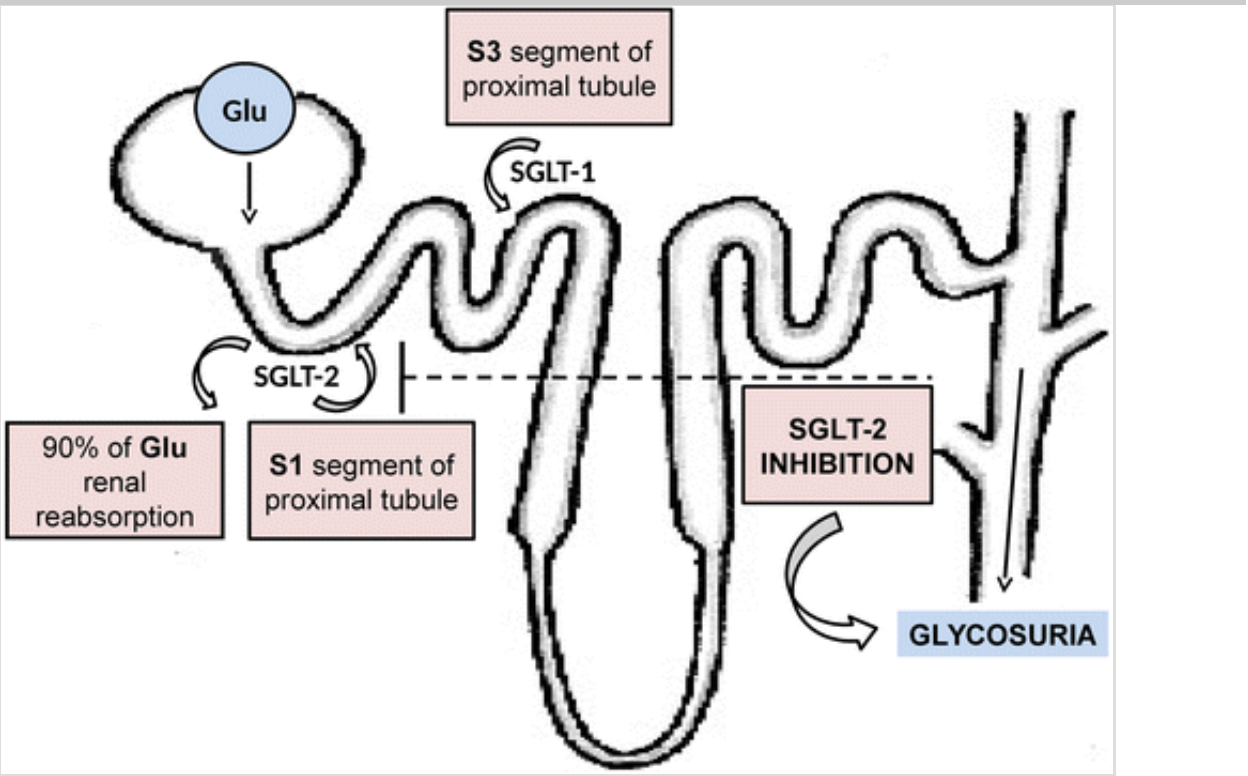
Sodium-glucose co-transporter (SGLT)2 inhibitors constitute a newly employed drug class in the management of type 2 diabetes mellitus (T2DM). Their mechanism of action differs from all other hypoglycaemic agents as they do not rely upon insulin secretion or sensitivity for glucose regulation**,** but instead promote urinary glucose excretion.

SGLT2 is a low-affinity, high-capacity, Na^+/glucose co-transporter expressed on the luminal surface of proximal tubular cells in S1 and S2 segments, which mediates the reabsorption of 80–90% of filtered glucose (Fig. 1) [1]. SGLT1 is also expressed to a far smaller degree in S3 segment of proximal tubule, but contributes less than 10% of tubular glucose reabsorption [2]. In addition to the SGLT2 transport system in the kidney, SGLT1 in the intestine also acts to increase glucose reabsorption. Most SGLT2 inhibitors have no significant effect on SGLT1, but canagliflozin does affect SGLT1. For this reason, data of the performance of SGLT2 inhibitors have been presented in this review at a drug level, rather than class level.

Fig. 1

Schematic representation of SGLT2 inhibitors action in the kidney. SGLT2 are expressed in the S1 segment of the proximal tubule. More than 90% of

filtered glucose is reabsorbed there. SGLT2 inhibitors block glucose reabsorption with resultant glucosuria



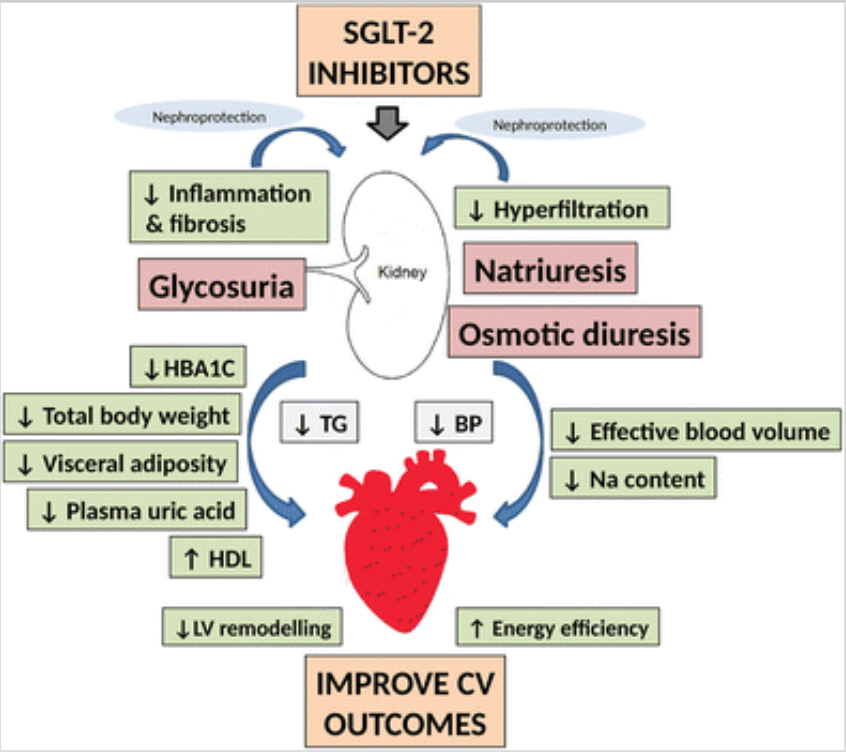
Evidence suggests that SGLT2 inhibitors are potent antihyperglycaemic agents with a low risk of hypoglycaemia, comparable to that of metformin and sitagliptin [3]. A recent meta-analysis suggested a small benefit of high-dose canagliflozin monotherapy in glucose lowering over other SGLT2 inhibitors [4]; whether this is related to canagliflozin dual mechanism of action on both SGLT1 and SGLT2 remains unclear. As previously mentioned, the striking difference to other antidiabetic medications is that their mechanism of action is insulin-independent. However, a mode of action that is reliant upon glomerular filtration means that efficacy is diminished in patients with renal impairment. Therefore, current SGLT2 inhibitors: canagliflozin, dapagliflozin and empagliflozin, are licensed for the management of diabetes in patients if estimated glomerular filtration rate (eGFR) is greater than 45 mls/min. As SGLT2 inhibitors promote glycosuria, intuitively, there will be attendant fluid shifts through osmotic drag. It is therefore unsurprising that SGLT2 inhibitors have effects on the cardio-renal system independent of that of glucose lowering.

This review will highlight recent data derived from randomized, double-blind, placebo-controlled, phase III trials, with a focus on their non-

hypoglycaemic effect on the cardiometabolic profile (Fig. 2). Possible underlying mechanisms will also be discussed.

Fig. 2

Overview of the actions of SGLT2 inhibitors and secondary effects leading to improved cardiovascular outcomes. SGLT2 inhibitors act in the proximal renal tubule causing glycosuria, natriuresis and osmotic diuresis. Thereafter, a series of hemodynamic, metabolic and nephroprotective effects are induced, leading eventually to improved cardiovascular outcomes



Blood Pressure Effects

One of the most prominent, non-hypoglycaemic effect of SGLT2 inhibitors is their blood pressure (BP) lowering action, which has been broadly recorded in large and smaller trials (Tables 1 and 2) [5, 6, 7, 9, 10, 12, 13, 17, 18, 19, 20, 21].

Table 1

Summary of randomised placebo-controlled trials comparing SGLT2 inhibitor monot placebo

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Studies	Intervention	Population	Number	Follow up (weeks)	Effects*	*p*

Stenlof et al. [5]	Canagliflozin 100 or 300 mg OD	T2DM not controlled on diet and exercise/other AHA	587	26	•↓TBW • ↓SBP • ↑HDL	*p* < for
Ferrannini et al. [6]	Dapagliflozin 2.5, 5 or 10 OD	T2DM not controlled on diet and exercise	587	24	• ↓TBW • ↓BP	*p* N bot
Seino et al. [7]	Luseogliflozin 2.5 mg OD	T2DM not controlled on diet and exercise	158	24	• ↓TBW • ↓ WC	*p* < for
Bode et al. [8]	Canagliflozin 100 or 300 mg OD	Older (55–80 years) with T2DM not controlled on other AHA	716	26	• ↓TBW • ↓SBP • ↑HDL • ↑LDL	*p* < for
Kaku et al. [9]	Dapagliflozin 5 or 10 mg OD	T2DM not controlled on diet and exercise	261	24	• ↓TBW • ↓ BP	*p* = to *p* N
Inagaki [10]	Canagliflozin 100 or 200 mg OD	T2DM inadequately controlled on diet and exercise	272	24	• ↓TBW • ↓ BP	*p* < *p* <
Inagaki et al. [11]	Canagliflozin 100 mg OD	T2DM not controlled on insulin, diet and exercise	146	16	• ↓TBW • ↓ SBP • ↑HDL	*p* < *p* = *p* =

Summary of main characteristics and non-hypoglycaemic effects of randomised pl controlled trials comparing SGLT2 inhibitor monotherapy to placebo

AHA anti-hypoglycaemic agent, *T2DM* type 2 diabetes mellitus, *TBW* total body w *TC* waist circumference, *FM* fat mass, *BP* blood pressure, *HDL* high density lipop

*Only findings provided by direct comparisons of drug effects with placebo have included

Table 2

Summary of randomised placebo-controlled trials comparing SGLT2 inhibitor c metformin to placebo

Investigators	Intervention	Population	Number	Follow up (weeks)	Effects*

Bailey et al. [12]	Dapagliflozin 2.5, 5 or 10 mg	T2DM not controlled on metformin (≥1500 mg/day)	534	24	• ↓TBW
Haring et al. [13]	Empagliflozin 10 or 25 mg	T2DM not controlled on metformin (≥1500 mg/day)	637	24	• ↓TBW • ↓BP
Lavalle-Gonzalez et al. [14]	Canagliflozin 100 or 300 mg	T2DM not controlled on metformin (≥1500 mg/day)	1284	26 ~~wks~~	• ↓TBW • ↓SBP
Bolinder et al. [15]	Dapagliflozin 10 mg	T2DM not controlled on metformin (≥1500 mg/day))	182	24	• ↓TBW • ↓ WC • ↓ FM ↓ BP
Kashiwagi et al. [16]	Ipragliflozin 50 mg	T2DM not controlled on metformin (≥1500 mg/day)	168	24	• ↓TBW • ↓ WC • ↑HDL
Summary of main characteristics and non-hypoglycaemic effects of randomised pl controlled trials comparing SGLT2 inhibitor combined with metformin to placebo					
*Only findings provided by direct comparisons of drug effects with placebo have l included					
T2DM type 2 diabetes mellitus, *TBW* total body weight, *TC* waist circumference, *I BP* blood pressure, *HDL* high density lipoprotein					

A recent meta-analysis of 13 trials by Shyangdan et al. [4] indicated that all SGLT2 inhibitors given as monotherapy or combined with other antidiabetic agents—usually metformin—led to a reduction in systolic BP (SBP) compared with placebo; reductions from baseline ranged from 2.6 mmHg with empagliflozin (10 mg once daily (OD)) to 6 mmHg with canagliflozin (300 mg OD). The authors also suggested that dapagliflozin 10 mg might be superior in reducing SBP compared to canagliflozin, empagliflozin and ipragliflozin. Similarly, a previous meta-analysis had shown that SGLT2 inhibitors are significantly more effective compared to both placebo and other antihyperglycaemic agents in reducing SBP (mean difference, −3.77 and −4.45 mmHg, respectively) and diastolic BP (DBP) (mean difference −1.75 and 2.01, respectively) [22]. These came to confirm earlier findings of Baker et al. [23], who also noted that BP-lowering action of SGLT2 inhibitors was not dependent on baseline BP

levels and reductions were not associated with any changes in heart rate or body weight. Baker et al. also highlighted a dose-related SBP lowering effect of canagliflozin.

In patients with T2DM and poorly controlled hypertension on antihypertensive agents, at baseline BP, changes have been assessed with 24-h ambulatory BP monitoring (ABPM). Canagliflozin, 300 mg, led to an early (6 weeks) and significantly greater reduction in mean 24-h SBP and DBP compared to placebo ($p = 0.006$ for both) [21]. Similar findings were noted with empagliflozin 10 or 25 mg with greater reductions in mean 24-h SBP and DBP ($p < 0.001$ vs placebo for both doses) at week 12 [18]. The differences were more pronounced for patients who had a 24-h mean ABPM >130/80 mmHg at baseline. In both studies, the effect, though present, was less prominent on night-time BP suggesting an agreement to circadian BP rhythm. Importantly, the reductions in BP were not accompanied by increases in heart rate.

In a similar population, dapagliflozin led to more pronounced reductions in mean seated and 24-h SBP compared to placebo [24]. A post hoc analysis showed that the mean change in seated SBP related to dapagliflozin was greater in patient groups on beta-blockers or calcium channel inhibitors than those on thiazides, but meaningful reductions were noted in all groups.

The underlying physiology of SGLT2 inhibitor effects on BP is thought to involve more than one mechanism; osmotic diuresis and urinary sodium excretion have been considered the principal mechanisms. Though data are limited, it appears that plasma volume decreases with dapagliflozin treatment when compared with placebo or, more interestingly, with hydrochlorothiazide (HCTZ) [25]. In another study, the addition of canagliflozin to HCTZ in healthy individuals did not confer further change in urine volume, Na excretion, or BP [26]. This discrepancy of SGLT2 inhibition effect on volume between diabetic and non-diabetic individuals most likely reflects the significance of sodium excretion and reduction of total body sodium content over a mere diuretic effect. Patients with diabetes have an increased total exchangeable sodium content compared to non-diabetic individuals [27]. Moreover, the absence of changes in heart rate accompanying BP reductions is suggestive of euvolaemia rather than volume depletion, highlighting the importance of total body sodium

content as a principal pathophysiologic mechanism in diabetic hypertension.

The result of SGLT2 inhibition highly depends on serum glucose levels with the expression of SGLT2 in the proximal tubule to increase under conditions of hyperglycaemia [28]. In this context, it might prove useful to assess whether BP-lowering efficacy of SGLT2 inhibitors varies according to levels of HbA1C. The fact that dapagliflozin showed a more pronounced SBP reduction when added to beta-blockers or calcium channel blockers, compared to thiazides [24], does not come as a surprise, indicating the role of volume contraction in SGLT2 inhibitor antihypertensive effect. The aforementioned mechanisms supposedly mediating BP-lowering effect are physiologically related to eGFR; therefore the magnitude of SGLT2 inhibitor antihypertensive effect should vary according to GFR; subgroup analyses in trials can shed more light.

Less direct effects, associated with SGLT2 inhibitor-induced weight loss (discussed below) may contribute. Even modest weight reductions are associated with a beneficial effect on BP [29]. However, given that the effect on BP is evident early in treatment period, body weight reduction cannot primarily account for this effect. Modification of arterial stiffness has been considered as another mechanism implicated in SGLT2 inhibitors antihypertensive effect, based on findings of reduced arterial stiffness associated with SGLT2 inhibition in young type-1 diabetic patients [30]. Given the complex causal relationship between hypertension and arterial stiffness [31], it is unclear to what extent the BP-lowering effect of SGLT2 inhibitors may follow or actually precede an improvement in vascular properties ~~(Table 3)~~.

Table 3

Main advantages and disadvantages of SGLT2 inhibitors

Advantages	Disadvantages
Glucose lowering independent of insulin	Risk of acute kidney injury
Reduction of body weight and visceral adiposity	Risk of urinary and genital infections
Reduction of blood pressure	Indicated only for eGFR $\geq$ 45 ml/min/1.73 m^2
	Risk of euglycaemic ketoacidosis

Improvement of lipid profile	(rare)
Nephroprotection	
Improved cardiovascular outcomes	

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Metabolic Effects

SGLT2 inhibition is associated with a series of interrelated metabolic effects, primarily represented by amelioration of adverse lipid profile and body weight reductions. Effects on visceral adiposity and hepatic liver content have also been reported (Tables 1 and 2).

Lipid Effects

The majority of individuals with T2DM have underlying insulin resistance and the metabolic syndrome. This is associated with a dyslipidaemic pattern of hypertriglyceridaemia, low high density lipoprotein (HDL) and a predominance of small, dense (pro-atherogenic) low density lipoprotein (LDL). The mechanism underlying this is thought to be due to overproduction of very low density lipoprotein (VLDL) by the liver, leading to an increased plasma concentration of triglycerides (TG) [32, 33] which, via an exchange process mediated by cholesterol-ester transfer protein (CETP), results in a low concentration of HDL-cholesterol as well as the generation of small, dense, cholesterol-ester-depleted LDL. It has been shown that moderate restriction of carbohydrate leads to benefits in weight loss and improvement in the lipid profile of the metabolic syndrome [34].

As would be predicted from dietary studies of carbohydrate restriction, the SGLT2 inhibitors also lead to reduction of TG and an increase in HDL [5, 9, 12, 16, 17, 20, 35]. It has been proposed that the changes in TG and HDL-cholesterol with SGLT2 inhibition are purely a consequence of weight reduction [36]. However, it may be that a reduction in carbohydrate (due to renal losses of glucose) will also reduce plasma TG by reducing hepatic VLDL production.

SGLT2 inhibitors have been consistently associated with an increase in LDL-cholesterol, by up to 10%, which appears to be a class-effect of these

agents [12, 35, 37]. Although meta-analyses of pre-clinical data have shown, no adverse cardiovascular (CV) effects [38], in light of the experience relating to CV disease and rosiglitazone [39], it is imperative that we fully understand the effect on CV disease risk of novel treatments for dysglycaemia. Specifically in this case, how SGLT2 inhibitors influence structural properties of LDL-cholesterol that relate to its atherogenic potential.

Body Weight and Fat Tissue

Obesity, and more particularly central adiposity, is strongly associated with impaired glucose metabolism and an adverse metabolic profile. SGLT2 inhibitors reportedly reduce body weight with preferential effect on adipose tissue.

Several SGLT inhibitors such as canagliflozin, dapagliflozin, luseogliflozin, or tofogliflozin, either as monotherapy or combined with metformin, achieved statistically significant reductions in body weight compared to placebo in RCTs with a consistent dose-related effect and mean difference from placebo ranging from 1.61 kg at lower doses to 2.66 at maximum doses [8, 9, 10, 11, 14, 15, 17, 20, 40], frequently followed by a reduction in waist circumference [7, 15, 16, 40]. This favourable effect has also been recorded in a study of 638 patients randomised to receive empagliflozin (10 or 25 mg OD) or placebo as an add-on to metformin (1500 mg/day) [13].

Visceral adiposity, which is known to be related with an adverse metabolic profile, is likely principally affected. In an RCT which compared dapagliflozin vs placebo as an add-on to metformin, dapagliflozin caused greater reduction in waist circumference at 24 weeks which increased further after 2 years of treatment [15, 40]. The overall weight loss recorded was mainly attributed to adipose tissue loss rather than lean mass as suggested by dual-energy x-ray absorptiometry.

There is much interest in the observation in longer-term clinical trials, whether weight loss observed can be fully explained by glycosuria. For instance, canagliflozin led to a dose-related effect on body weight with mean reductions by 2.2% (1.9 kg) and 3.3% (2.9 kg) after 6 months of treatment at 100 and 300 mg, respectively [5]. The change in body weight was more pronounced over the first 6 weeks of treatment. This may

suggest that patients ‘compensate’ in the long term by increasing calorie intake. However, it may be that standard models to predict weight loss are inadequate. In addition, the metabolic effect of energy restriction is dependent upon baseline weight and adiposity. Individuals with a higher baseline weight and adiposity tend to partition a greater proportion of net energy imbalance towards loss of fat. The energy contents of fat and skeletal muscle are very different with five times more energy required to mobilise 1 kg of fat than lean tissue. Furthermore, lean tissue contributes more than fat tissue to total energy expenditure and when it is lost over fat mass, energy expenditure decreases to a greater extent, making further weight loss become more difficult. In this way, weight loss against time may be thought of as curvilinear rather than linear.

The degree of weight loss reported with SGLT2 inhibitor treatment may be considered as insignificant in an obese individual. However, dietary studies have shown that visceral adipose tissue is lost preferentially in the setting of modest weight loss [41]. Reduction of 5% in body mass index has been shown to decrease liver fat content, measured by magnetic resonance spectroscopy (MRS), by 25.5% [42, 21]. Moreover, reduction of hepatic fat content can lead to favourable changes in the lipoprotein profile [43], which have been associated with SGLT2 inhibitors as previously mentioned.

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Evidence from pre-clinical studies supports a role for SGLT2 inhibition and particularly ipragliflozin, in reduction of hepatic fat content and protection from or even reversal of fibrosis [44, 45]. Activation of AMP kinase with canagliflozin has been proposed as one of the hepatic lipid content lowering mechanism [46]. Furthermore, ipragliflozin improved liver biochemistry [serum alanine aminotransferase (ALT) and gamma-glutamyltransferase (gGT) levels] in T2DM patients (n = 55), 40% of whom had known hepatic steatosis on liver ultrasound scan at baseline, with the effect being independent of body weight change [47]. Whether this is an agent- rather than class-related effect is unclear. Reductions in visceral adiposity as dictated by negative energy balance with SGLT2 inhibition are likely the main contributors. However, improved glucose metabolism in the form of increased insulin sensitivity (discussed below) observed with these agents, may well further prevent hepatic lipid build-up.

Uric Acid Levels

Reductions in serum uric acid levels have been recorded with the use of SGLT2 inhibitors [12, 48, 49, 50]. These are usually small around 10 to 13% but the effect becomes more pronounced among patient with hyperuricaemia at baseline. In a post hoc analysis of pooled data from four RCTs of canagliflozin, a significantly higher percentage of patients with hyperuricaemia at baseline reached reductions to normal serum uric acid levels at 26 weeks of treatment [50]. Serum uric acid lowering action of SGLT2 inhibitors is believed to be mediated by glucosuria through modification of uric acid transport system in the renal tubule [51, 52], i.e. solute carrier family 2, facilitated glucose transporter member 9 (SLC2A9), also known as GLUT9 which secretes urate back into the urine in exchange for glucose [53, 54].

Glucose Metabolism

Beyond reducing blood glucose levels via enhanced urinary excretion, SGLT2 inhibitors affect glucose metabolism by several other ways. In diabetic obese rats, dagliflozin appeared to improve the insulin sensitivity index (measured using a hyperglycaemic clamp) and β cell function as assessed by disposition index, which reached the level of lean control rats [55]. Islet morphology was also significantly improved by dapagliflozin.

In another experimental model, canagliflozin suppressed obesity-associated inflammation in the nervous system and skeletal muscle of obese and diabetic mice [56].

Similarly, empagliflozin reduced insulin resistance and levels of pro-inflammatory cytokines TNF-α, IL-6 and monocyte chemoattractant protein-1 (MCP-1); these changes were accompanied by correspondent changes in atherosclerotic plaque size in ApoE−/− mice fed with a western diet [57].

Furthermore, SGLT2 inhibitors are emerging as an attractive treatment option for patients with diabetes resistant to insulin therapy due to the presence of antibodies. Though this is a not-so-common problem in routine clinical practice, when encountered, management is particularly challenging. There are reports of significant improvement of glucose metabolism with the use of SGLT2 inhibitors in such cases [58, 59].

Among all the above, benefits in body weight and visceral adiposity have been broadly reported with most SGLT2 inhibitors and merit particular consideration given the high-risk metabolic profile of patients with T2DM. Most likely, the series of these agents' actions, discussed above, are at least partly mediated by these two effects. Nevertheless, the clinical significance of SGLT2 inhibitors 'pleiotropic' actions is yet to be established in RCTs. Identifying diabetic subpopulations who might receive maximal treatment benefit would be particularly important.

Renal Effect—'Nephroprotective Effect'

Diabetic nephropathy complicates T2DM in as many as one third of cases [60]. These patients are characterised by increased CV morbidity and mortality [61]. SGLT2 inhibitors have been considered to have a nephroprotective effect, which in some cases has been shown to be independent of their hypoglycaemic action. Data suggest this effect is evident on several aspects of kidney function and resultant from a complex interplay of physiological mechanisms.

Proteinuria and particularly albuminuria is a hallmark of diabetic nephropathy. Furthermore, it appears to hold a causative role in the pathophysiology and progression of renal injury [62]. Animal studies have shown an ameliorating effect of dapagliflozin and empagliflozin on the progression of albuminuria principally linked to their hypoglycaemic action [63, 64]. Consistent findings have been noted in human trials, which, however, have suggested that these effects cannot be fully explained by reductions in serum glucose levels and amelioration of other metabolic parameters. On pooled data analysis, it was shown that within 24 weeks of treatment with empagliflozin, albumin to creatinine ratio (ACR) levels were significantly reduced from baseline compared with placebo in diabetic patients with either microalbuminuria or macroalbuminuria (treatment difference −32%; $p < 0.001$ and −41%; $p < 0.01$) The regression analysis models suggested that this effect cannot be solely attributed to changes in HbA1c, body weight or BP as these appeared to only modestly contribute [65].

Another mechanism that may account for these agents nephroprotective effect is a reduction in glomerular hyperfiltration. The most important evidence comes from Cherney et al. who included 40 subjects with T1DM

in their study. Inulin and paraaminohippurate clearances were measured to estimate GFR and effective renal plasma flow, respectively, and study population was divided in hyperfiltration and normal filtration groups. After 8 weeks of treatment, empagliflozin 25 mg OD was associated with reduced GFR in the hyperfiltration patient group under both euglycaemic and hyperglycaemic conditions. The same patient group showed an increase in angiotensin II and aldosterone levels as well as reductions in plasma nitric oxide (NO) and effective renal plasma flow with an increase in renal vascular resistance both under euglycaemia and clamped hyperglycaemia [66]. No relevant changes were detected in the group of patients with T1DM but normal levels of GFR at baseline. The treatment effect on glycaemic control and body weight was similar between the two groups.

Based on the tubular hypothesis (tubuloglomerular feedback (TGF)), chronic hyperglycaemia in diabetic patients results to increased glucose delivery in the proximal tubule, hence, enhanced glucose reabsorption along with sodium via the SGLT2. The juxtaglomerular apparatus perceives this as a low-effective circulating volume condition leading to an afferent renal vasodilatory response and, therefore, hyperfiltration [67]. NO is one of the principal mediators. It is believed that hyperfiltration leads to glomerular injury and then, a compensatory further increase in filtration rates in the remaining glomeruli, which will eventually result in further glomerular loss and decline in eGFR [68]. SGLT2 inhibitors appear to alter the TGF response by increasing sodium chloride content in the macula densa. Given the prognostic role of hyperfiltration for progression to chronic kidney disease (CKD) in diabetes [69], this effect of SGLT2 inhibitors emerges as one of particular importance.

Cherney et al. emphasised in their study that the blunting effect on hyperfiltration was most likely the result of decreased plasma NO and effective renal plasma flow along with an increase in renal vascular resistance as result of increased sodium chloride delivery to the distal tubule [66].

Furthermore, the observed increase in reninaldosterone-angiotensin system (RAAS) mediators with empaglifozin in the hyperfiltration group represents the decrease in effective circulating volume via SGLT2 inhibitors' mild diuretic effect. It should be noted though that plasma renin

activity was not increased. It would be interesting to know whether there are variations in aldosterone and angiotensin II levels related with time of ingestion of SGLT2 inhibitor and whether these increments are clinically meaningful.

The above observation draws attention to potential meaningful clinical implications with combined use of RAAS and SGLT2 inhibitors resulting in an enhanced nephroprotective effect. In a diabetic animal model, lusegliflozin and lisinopril treatment had maximal nephroprotective effect when compared with each monotherapy [70]. Lusegliflozin reduced the extent of renal injury in the form of glomerular injury, fibrosis and the presence of urinary protein casts and preserved GFR. Insulin treatment with similar hypoglycaemic effect did not yield the same renoprotective result. Gnudi et al. have suggested that this might be the result of the activation of the non-classical RAAS pathway leading to the production of angiotensin (1–7) which has a vasodilatory effect [71]. Angiotensin II increases intraglomerular pressure through preferred vasoconstriction of the efferent vs the afferent arteriole and hence increased filtration. RAAS inhibition reverts this phenomenon; therefore, the combined effect of RAAS with SGLT2 inhibitors on the kidney would be of particular interest.

The clinical implications of the above remain to be established. Whether this might affect progression of diabetic renal disease and effectively reduce relevant morbidity and mortality in the long term needs to be assessed in randomised controlled trials. Furthermore, the mechanisms involved warrant further clarification. However, overall, it appears that the main nephroprotective mechanism of SGLT2 inhibition is reduction in glomerular hyperfiltration, which appears independent of glucose lowering. Further effects appear to be the result of improved diabetes control. The reduction on albuminuria is most likely a combination of these two.

Beneficial Effect on Cardiovascular Outcomes

The EMPA-REG OUTCOME trial has led to a reappraisal of the management of type 2 diabetes with hypoglycaemic medication [48]. This was a randomized controlled trial examining the effect of empagliflozin 10 or 25 mg vs placebo on CV outcomes in a type 2 diabetic population with established CV disease (n = 7020, >99% with established CV disease) after

a median treatment duration of 2.6 years and a median observation period of 3.1 years. The primary composite outcome (death from any CV causes, non-fatal myocardial infarction and non-fatal stroke) was more frequent in the placebo compared to empagliflozin group [12.1 vs 10.5%; hazard ratio (HR) 0.86, 95% CI 0.74–0.99; $p = 0.04$]. Empagliflozin was associated with a relative risk (RR) reduction of 38% in CV mortality (HR 0.62; 95% CI 0.49–0.77; $p < 0.001$), 32% in all-cause mortality (HR 0.68; 95% CI 0.57–0.82, $p < 0.001$), and 35% in hospitalization for heart failure (HR 0.65; 95% CI 0.50 to 0.85; $p = 0.002$). The incidence of myocardial infarction and stroke did not differ between groups. It appeared that the beneficial effect on CV mortality was evident earlier than the effect on primary composite end-point (i.e. CV mortality along with non-fatal myocardial infarction and non-fatal stroke). A subsequent analysis suggested that the composite outcome of heart failure hospitalization and CV death was more frequent in the placebo group compared to the empagliflozin group (8.5 vs 5.7%; HR 0.66, 95% CI 0.55–0.79; $p < 0.001$) with the effect being independent of drug dose or baseline characteristics such as age, race, eGFR and other medications. Consistently, empagliflozin was associated with a lower frequency of hospitalization for heart failure (2.7 vs 4.1%) as well as reduced risk for the composite outcome of hospitalization for or death from heart failure compared with placebo (2.8 vs. 4.5%; HR 0.61, 95% CI 0.47–0.79; $p < 0.001$) The benefit of empagliflozin was observed in the whole study population, irrespective of the presence of heart failure at baseline. Of note, pre-existing heart failure at baseline was defined upon recorded medical history and appeared as low as 10.1%. It may be the case that undiagnosed heart failure (particularly diastolic dysfunction) was present in the study population.

In support of EMPA-REG study findings, the encouraging results from a recent meta-analysis which included data from six regulatory submissions ($n = 37,525$) and 57 trials ($n = 33,385$) regarding a total of seven agents were published [72]. A protective CV effect associated with SGLT2 inhibition was suggested by significant reductions in the risk for major CV events (RR 0.84, 95% CI 0.75–0.95; $p = 0.006$); CV death (RR 0.63, 95% CI 0.51–0.77; $p < 0.0001$) and heart failure (RR 0.65, 95% CI 0.50 to 0.85; $p = 0.002$). All-cause mortality was also decreased in diabetics treated with SGLT2 inhibitors (RR 0.71 95% CI 0.61 to 0.83; $p < 0{\cdot}0001$). However, an increased risk of non-fatal stroke was noted in these patients (RR 1.30, 95% CI 1.00 to 1.68; $p = 0.049$). No difference was noted among different

agents with regards to their effect on CV outcomes.

Given the lack of abundance of RCTs to support an established CV benefit from SGLT2 inhibition, these results should still be interpreted with caution. However, a beneficial effect on CV outcomes distinguishes SGLT2 inhibitors from other oral hypoglycaemic agents such as thiazolidinediones and saxagliptin, which have been associated with adverse outcomes in heart failure [73, 74]. Given the strong link between diabetes and heart failure [75, 76, 77] which is empowered by inherent to T2DM mechanisms further to an adverse cardiometabolic profile [78, 79]. What mechanisms underlie the CV benefit with SGLT2 inhibitors, warrants further consideration. Improvements in classic CV risk factors such as body weight, BP reduction, lipid profile and an overall benefit in adverse metabolic profile common to people with T2DM may be responsible. However, the CV benefit was evident early on during treatment at approximately 12 weeks [80]. This suggests that more acute effects are principally involved with haemodynamic alterations playing possibly a key role, especially with respect to heart failure outcomes. The most direct effect of SGLT2 inhibition is the enhanced urinary glucose and sodium excretion; natriuresis and osmotic diuresis lead to reduction of intravascular volume and, hence reduced pre-load. Furthermore, BP lowering improves afterload with a further benefit from reduced arterial stiffness associated with SGLT2 inhibition. The diuretic effect of SGLT2 inhibitors, particularly in the presence of unrecognized diastolic dysfunction, in combination with a negative net effect on total body sodium content, may improve CV outcome. A novel hypothesis has been recently postulated, suggesting that SGLT2 inhibitors enhance energy efficiency at mitochondrial level in myocardium with the utilization of β-hydroxybutyrate as substrate [81, 82].

Whether SGLT2 inhibition affects left ventricle (LV) remodelling and structural changes associated with heart failure, has been put forward. Data from an experimental study reported empagliflozin treatment in diabetic and hypertensive rats, resulted in reductions in adverse LV remodelling, as suggested by changes in LV mass, and LV dilatation, while increased cardiac contractility [83]. The REFORM trial a, phase IV, RCT, aims to shed further by examining the effect of dapagliflozin on LV parameters in patients with known heart failure [84]. In the meantime, the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE) study is examining the

effect of SGLT2 inhibition on CV events in patients without pre-existing macrovascular disease (i.e. primary prevention) and is due to report in 2019.

Safety Concerns

Relevant to their impact on the metabolic profile, concerns have been raised with regards to several reports of ketoacidosis associated with SGLT2 inhibitor use. This appears to be related to increased glucose excretion especially in the presence of low carbohydrate diet resulting in enhanced ketogenesis [85]. Patients with type 1 diabetes appear more prone [86]. However, pooled data analysis of empagliflozin showed similar rates to placebo [87]. Similarly, despite that this class of drugs may induce a degree of volume depletion, their use has not been associated with significantly increased rates of acute kidney injury [48, 88].

Conclusions

Remarkable findings of significant metabolic and cardioprotective effects of SGLT2 inhibitors have emerged with a particular focus on heart failure but the clinical significance of the above needs to be further assessed(Table 3). In the kidney, SGLT2 inhibitors reduce hyperfiltration, a precipitant of diabetic nephropathy. Given reported ameliorating effects on blood pressure, central obesity and adverse lipid profile, one could suggest that patients with the metabolic syndrome (i.e., a constellation of the above) on top of T2DM might get maximal benefit from treatment with SGLT2 inhibition. Prospective studies should examine whether SGLT2 inhibitors might prevent or retard the development or improve outcomes in kidney disease. The results of their combination with RAAS inhibitors may be of particular interest.

Compliance with Ethical Standards

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Conflict of Interest Dr. Eirini Lioudaki declares that she has no conflict of interest. Dr. Emmanouil Androulakis declares that he has no conflict of interest. Dr. Martin Whyte declares that he has no conflict of interest. Dr. Konstantinos Stylianou declares that he has no conflict of interest. Professor Eugenios Daphnis declares that he has no conflict of interest.

Professor Emmanouil Ganotakis declares that he has no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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