Review : Sodium-Glucose Co-Transporter (SGLT) 2 Inhibitors - The Answer to Non-Arteriosclerotic Cardiorenal Complications of Diabetes Mellitus

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ABSTRACT

Atherosclerotic vascular disease (ASVD) related complications of type 2 diabetes mellitus (DM) are well known 2 and have been the focus of research in the last two decades. Therapeutic targets in the last two decades have been directed towards achieving tight glycaemic control through insulin dependent and non-insulin dependent mechanisms. The advent of SGLT2 inhibitors marks a paradigm shift in the treatment of type 2 DM, as for the first time targeting renal mechanisms by inhibiting glucose reabsorption has resulted in glycaemic benefit. Although subtle differences in the cardiac outcomes exists in the respective trials of three approved SGLT2 inhibitors-empagliflozin, canagliflozin and dapagliflozin, it is amply clear that risk reduction in heart failure hospitalization and renal death benefits can be attributed to a class effect, which addresses an unmet need in the fight against DM.

In 2016, world health organization reported that 1.6 million deaths globally were directly attributable to diabetes mellitus. [1]Atherosclerotic vascular disease (ASVD) related complications of type 2 diabetes mellitus (DM) are well known[2] and have been the focus of research in the last two decades. However, a critical review of the literature reveals that complications of DM related to heart failure (HF) hospitalizations[3] and microvascular complications leading to diabetic nephropathy (DN)are also important, [4]with HF being the most common first-time presentation of cardiovascular (CV) event (14.1%), even more common than non-fatal myocardial infarction (MI) and cerebrovascular accident.[5] On the other hand, DN, which effects 40% of the patients with DM[6], is the leading cause for death due to end stage renal disease (ESRD) worldwide.[7]

Therapeutic targets in the last two decades have been directed towards achieving tight glycaemic control through insulin dependent and non-insulin dependent mechanisms. Information from the rosiglitazone meta-analysis,-showed an increase in myocardial MI and death,[8,9] ACCORD trial[10] and the ADVANCE study[11] warranted the United States Food and Drug Administration (USFDA) in 2008 to make it mandatory to evaluate the anti-diabetics for CV safety. [12]Subsequently, the trials of the dipeptidyl peptidase (DPP)-4 inhibitors like sitagliptin, saxaglitptin and alogliptin have shown no apparent CV benefit in the TECOS,[13] SAVOR-TIMI-53[14] and EXAMINE studies,[15] while the GLP-1 receptor analogues have shown a reduction in sudden cardiac death leading to an overall Major Adverse Cardiac events (MACE) benefit.[16,17,18] Given the results, it still does not address the unmet need for HF hospitalizations and nephropathy related complications of DM. In this context, a new class of drug, sodium glucose co-transporter (SGLT)-2 inhibitors targets DM by renal mechanisms, shows immense promise.[19] In this report, we review only the cardiac and renal outcomes of the recently published trials on the SGLT2 inhibitors-empagliflozin, canagliflozin and dapagliflozini.e EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; henceforth referred as 'EMPAREG'),[20] CANVAS (Canagliflozin cardiovascular assessment study) - an amalgamation of two trials combined,[21] and DECLARE-TIMI 58 (Dapagliflozin effect on cardiovascular events; hence forth referred as 'DECLARE')[22]

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Chemical structure

SGLT2 inhibitors contain a glucose ring at its core. This ring is liked to two phenol groups though an oxygen molecule by virtue of o-glucoside linkage. This chemical entity has 10 times higher affinity to SGLT2 compared with SGLT1.[23]

Early research on SGLT2 as a therapeutic target

In 1835, while phlorizin, the first SGLT2 inhibitor, was used as an antipyretic, its glucosuric effect via SGLT2 inhibition in the proximal convoluted tubule became established only in the 1970s.[24] Simultaneously, examination and study of familial renal glucosuric (FRG) patients, who have functional mutation in SGLT2 inhibition, revealed that this condition was more of a benign problem due to lack of glucose retention than a full-fledged disease. Collectively, with increased understanding of the early research into SGLT2 inhibition and the benign characteristics of FRG patients, the scientific community started focusing on SGLT2 renal inhibition has a potential target for patients with DM.[25] Eventually, in 2012 dapagliflozin was the first SGLT2 inhibitor approved by the European Medicines agency (EMEA) and USFDA in 2014, followed by canagliflozinand empagliflozin.[25]

Relevant renal physiology and mechanism of action of SGLT2 inhibitors :

Although increased blood glucose level is the main pathological mechanism in DM, glucose renal reabsorption leading to retention is important as glucose is the main source of energy for the human body. This tubular glucose reabsorption mechanism can be visualized in the following way : First step involves activation of Na-K ATPase energy dependent pump on the basolateral membrane, which will result in a net negative Na content inside the proximal tubular cell (PTC), as 3 Na ions are exchanged against 2 K ions from the interstitium. The second step will begin with the driving of the SGLT pump due to the negative electrical gradient created by the deficit of PTC Na ions. As Na is driven in, it results in the movement of glucose against its gradient. Following glucose entry into the tubular cells, the transporter, GLUT-2 activation, will lead to facilitated diffusion of glucose from tubular cells into the interstitium and in this way glucose is retained in the body.[26]

The SGLT2 tubular reabsorption mechanism follows saturable kinetics, with a theoretical limit of 300mg/dl of plasma glucose level. From a pragmatic standpoint, for a healthy individual, this saturation maximum tends to be around 180-200 mg/dl and reports have shown that diabetics tends to have a 20% higher threshold, at around 240 mg/dl. SGLT2 inhibitors decrease this threshold for DM patients by blockage of the SGLT2 transporters in the PTC, inhibiting glucose reabsorption (~40-50%) and inducing glucosuria ***(Figure 1).***[25,27] This leads to decrease in plasma glucose level which is insulin independent and therefore less likely to cause hypoglycaemia resulting in tighter glycaemic control with improved outcomes.

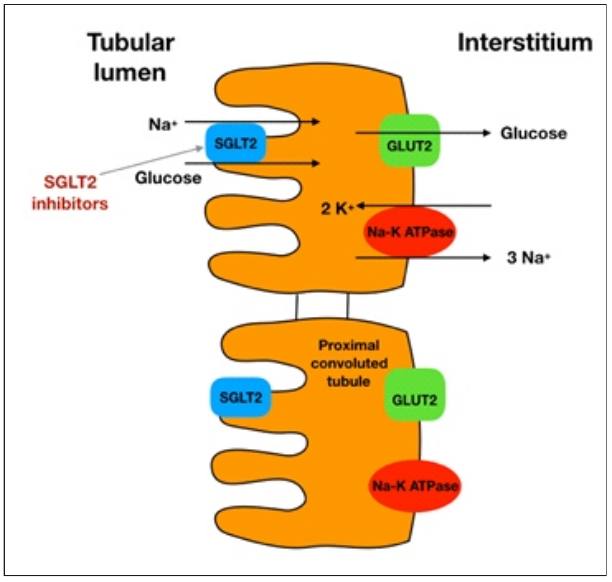

Figure 1 : **Mechanism of SGLT2 inhibitors**

Pharmacokinetics & pharmacodynamic effects :

The three approved SGLT2 inhibitors are available in oral dosage forms. After ingestion, they are rapidly absorbed, reach a tmax in 1-2 hours, have an

oral bioavailability of 60-78%, extensively distributed (74-118 L ~118 L), >85% bound to plasma proteins, $t_{½}$ ranging 11-13 hours and have a low accumulation in the body. SGLT2 inhibitors as a class are metabolized by glucuronide conjugation, have no active metabolites and excreted in urine and faeces, with 1-2% excreted in unchanged form. There is no variability in presence of food or no noteworthy pharmacokinetic interaction that would warrant dosage adjustment. All SGLT2 inhibitors are used as once daily medication. [28,29,30,31]

Pharmacodynamic effects are dose dependent. When fortified with strict diet control and exercise, addition of dapagliflozin to conventional oral hypoglycaemic agents resulted in a weighted mean difference (WMD) of -0.53% (95% confidence interval (CI) -0.58, -0.47; p<0.00001), as shown in a meta-analysis of ten trials.[32] Glycaemic durability was maintained even at the end of three years[20] and SGLT2 inhibitors reduces fasting plasma glucose by 15-35 mg/dl.[33] A unique feature of SGLT2 inhibitorsare beneficial effect on the commonly associated co-morbid conditions- reduction in blood pressure (WMD -1.88 to -4.19 mmHg)[31,32] and weight (WMD -2.81 kg).[31,34] While osmotic diuresis and reduction in plasma volume may explain the blood pressure lowering effects, evidence suggests that decreased in overall fat mass, visceral adipose tissue and subcutaneous fat is responsible for weight lowering effects.[35] Renal clearance of SGLT2 inhibitors in effected by renal function impairment. [31]A similar profile is seen in patients with hepatic impairment- mild to moderate patients of hepatic impairment need no dose adjustment, whereas in severe liver disease, a lower starting dose of 5 mg dapagliflozin is recommended.[36]

Safety :

Because ofglucosuria, urinary tract infections, risk of vulvovaginitis, balanitis and mycotic infections in the genito-urinary tract are the common adverse effects associated with SGLT2 inhibitor use.[37] These infections are, however, mild-moderate in severity and easily manageable. Risk of hypoglycaemia is substantially reduced due to the unique mechanism of action not dependent on stimulation of -cells like sulfonlyureas. Concerns regarding risk of diabetic ketoacidosis, fracture, toe amputation and bladder cancer has to be addressed[38] and will not be the focus of this report.

Cardio-vascular outcomes :

The interpretation for the three land mark trials of SGLT2 inhibitors[20,21,22] is complex because of inconsistent results in the outcomes that were measured. To understand these differences, it is prudent to understand the differences in the design of the different trials in order to make an informed judgement.

Trial entry criteria for established DM was similar with a mean glycosylated haemoglobin (HbA1C) ranging between 8.1% (EMPAREG) and 8.3% (DECLARE); however, 57.4% of the patients had DM for > 10 years in the empagliflozin trial compared to a mean duration of 13.5 ± 7.7years in the canagliflozin trial and a median of 11(inter-quartile range (IQR) 6.0-16.0) in the dapagliflozin trial. Out of the 7020 patients in the EMPAREG trial, 99% of the patients had established CVD, while 66% of the 10,142 patients in the CANVAS study, and only 41% of 17,160 patients the DECLARE study, had established CVD. Additionally, patients on insulin therapy in between the three studies differed i.e 48% vs 50% vs 41% (EMPAREG vs CANVAS vs DECLARE). Another importance difference was in the duration of follow-up: 3.1, 3.6 and 4.2 years for EMPAREG, CANVAS and DECLARE study respectively. More importantly, the renal criteria for trial entry in the EMPAREG and CANVAS was an estimated glomerular filtration rate (eGFR) > 30 mL/min/1.73 m2, computed via Modification of Diet in Renal Disease (MDRD), whereas the DELCARE study used creatinine clearance (CrCl) = 60 mL/min, calculated using Cockcroft-Gault equation, as an entry criteria. Although not an entry criterion, the DECLARE study calculated eGFR using chronic kidney disease Epidemiology collaboration (CKD-EPI) equation. Lastly, more patients in the EMPAREG study had renal impairment, defined by eGFR< 60 mL/min/1.73 m2, as compared to the other two

studies: 74.1% vs 20.1% in CANVAS study vs 7.4% in DECLARE study.

All the trials which assessed the primary variable as a composite outcome-MACE, with CV death, non-fatal MI and non-fatal ischaemic stroke being the individual components, differed in the number of patients achieving the outcome : 772 (EMPAREG) vs 1011 (CANVAS) vs 1559 (DECLARE). In the EMPAREG study and the CANVAS study while there was a statistically significant difference in the hazard ratio (HR) for the primary end point-0.86 (95% CI 0.74-0.99; p = 0.04), 0.86 (95% CI 0.75-0.97; p = 0.08), there was no significant difference in the DECLARE study 0.93 (95% CI 0.84-1.03; p = 0.17). When a composite of CV death along with HF hospitalization (excluding fatal stroke) was assessed, there was a statistically significant difference in all the three studies, predominantly driven by the standalone parameter of HF hospitalization and no significant difference in CV death component compared to the placebo arm ***(Table 1).***

When stroke was evaluated as a standalone measure, the results were somewhat disparate. EMPAREG study showed a slight increase in risk of stroke with a HR of 1.18 (95% CI 0.89-1.56),[20] while the CANVAS study, HR 0.90 (95% CI 0.71-1.15),[21] and the DECLARE study, HR 1.01 (95% CI 0.84-1.21),[22] was almost neutral in comparison to the placebo group.[39] These results emphasize the complexities involved in interpreting the class effect of SGLT2 inhibitors, warranting a bifurcation in the effect attributable to each drug within the same class.

Outcomes in the landmark trials of empagliflozin[20], canagliflozin[21] and dapagliflozin[22]

a Excludes fatal stroke

b Not available

c Some outcomes computed based on review by Kluger[40]

A unique feature of SGLT2 inhibitor trials where assessing its reno-protective effects, a component not addressed by any other anti-diabetic medications. The EMPAREG study used a composite renal outcome measure, defined by a two-fold increase in serum creatinine along with an eGFR of = 45 mL/min/1.73 m2, initiation of renal replacement therapy (RRT) or renal death.[41] Although in the CANVAS study the renal outcome was composite was a composite, the definitions were slightly different. The renal composite comprised of a 40% reduction in eGFR on 2 consecutive occasions instead of a cut-off value for eGFR in the EMPAREG study; want of RRT-defined as eGFR < 15 mL/min/1.73 m2, chronic dialysis or renal transplant; or renal death.[21] Also, in the DECLARE trial a similar composite measure was used, made up of eGFR reduction of = 40% with an upper margin set at < 60 mL/min/1.73 m2; ESRD definition similar to CANVAS study; or renal death along with death due to CV cause.[22] Even though, the definitions varied slightly, the results were, however, consistent, with all the 3 studies showing a significant reduction in HR compared to the placebo group - HR 0.54, 0.60 and 0.53 for empagliflozin, canagliflozin and dapagliflozin. Furthermore in the EMPAREG trial, assessment of eGFR, the measure of renal function, over time showed an initial short-term decrease, followed by a stable steady period and an increase following cessation of the drug.

Discussion :

As EMPAREG and CANVAS study have shown CV outcome benefits (relative risk reduction of ~14%) compared to the placebo group, SGLT2 inhibitors have invoked tremendous interest in the scientific community. They follow other class of drugs like metformin[42] and GLP-1 analogues[16,17] which have shown favourable CV outcomes, previously. The pharmacodynamic effects leading to decreased blood pressure levels by diminishing arterial rigidity, osmotic diuresis resulting in volume loss, favourable weight loss from the central adipose tissue along with increased calorie loss due to glucosuria, reduction in uric acid and oxidative stress, and modulation of metabolic substrates are the proposed mechanism explaining the CV outcome benefit.[18]

On the other hand, the neutral CV outcomes in the DECLARE could be because of the following

reasons. Firstly, the population in the EMPAREG study included only patients with established CVD, and 66% of patients in CANVAS study had a prior CV event. However, the entry criteria for DECLARE study included patients who were at risk for CVD but without established CVD, which constituted 59% of the cases. Considering these factors, the placebo event rate for the EMPAREG, CANVAS and DECLARE study differed : 43.9 vs. 31.5 vs 24.2/1000 patient years of follow-up.[39] Secondly, more patients in the EMPAREG study had renal impairment and a slightly higher number of patients were on insulin therapy, at baseline, both of which are associated with increase in CV events.[7,43]

Apart from MACE, when the HF hospitalization and CV death outcome composite was analyzed in the EMPAREG study, it was clear that reduction in this composite was propelled by a reduction only in HF hospitalization cases, HR 0.66 (95% CI0.55-0.79) and the CV death component remained neutral with a HR of 0.65 (95% CI 0.50-0.85).[20,39] The results were similar across the other two studies,[21,22,40] strongly suggesting that as a class effect, SGLT2 inhibitors on the long run significantly decrease HF complication in diabetes patients. Critically reviewing the literature, it is clear that heart failure hospitalization rate is~4 times higher for diabetic patients compared to patients without DM.44 HF, with a prevalence rate of 14.1% of the overall cases, stands out as the leading cause for first presentation of CV events among diabetic patients.[5] Also, if heart failure develops in a diabetic patient, the 5-year survival outcome is abysmal with a survival rate of only.

Table 1 : **Comparison of different SGLT 2 cardiovascular outcome study results**

	EMPA-REG OUTCOME	CANVAS	DECLARE- TIMI 58
MACE, HR (95% CI; p-value)	0.86 (95% CI 0.74-0.99; p = 0.04)	0.86 (95% CI 0.75-0.97; p = 0.08)	0.93 (95% CI 0.84-1.03; p = 0.17)
MACE event rate: active drug vs placebo (rate per 1000 patient - years vs placebo), (%)	10.5 vs 12.1 (37.4 vs. 43.9)	7.4 vs 9.1 (26.9 vs 31.5)	8.8 vs 9.4 (22.6 vs 24.2)
HF hospitalization + CV death, HR (95% CI; p-value)	0.66 (95% CI 0.55-0.79; p < 0.001)	0.78 (95% CI 0.67-0.91; p = 0.0015)	0.83 (95% CI = 0.73-0.95; p = 0.005)
HF hospitalization + CV death event rate a : active drug vs placebo (rate per 1000 patient -years vs placebo), (%)	5.7 vs 8.7 (19.7 vs. 30.1)	4.1 vs 6.1 (16.3 vs 20.8)	4.9 vs 5.8 (12.2 vs 14.7)
HF hospitalization, HR (95% CI; p-value)	0.65 (95% CI 0.50-0.85; p = 0.002)	0.67 (95% CI 0.52-0.87; p = 0.02)	0.73 (95% CI 0.61-0.88; p = 0.0008)
HF hospitalization event rate : active drug vs placebo (rate per 1000 patient-years vs placebo), (%)	2.7 vs 4.1 (9.4 vs. 14.5)	1.5 vs 2.7 (5.5 vs 8.7)	2.5 vs 3.3 (6.2 vs 8.5)
Composite renal outcome, HR (95% CI; p-value)	0.54 (95% CI 0.40-0.75; p < 0.001).	0.60 (95% CI 0.47-0.77; p < 0.001).	0.53 (95% CI 0.43-0.66; p < 0.001)
Composite renal outcome active drug vs placebo (rate per 1000 patient-years vs placebo), (%)	1.7 vs 3.1 (6.3 vs 11.5)	Na[b] (5.5 vs 9)	1.5 vs 2.8 (3.7 vs 7)

Table 1 : Comparison of different SGLT 2 cardiovascular outcome study results

12%. [45]Although HF following MI due to CHD is common among diabetics,[46] a CHD and hypertension independent mechanism of HF among diabetic patients with no prior MI called 'diabetic cardiomyopathy' is well established.Hupfeld[47] has described this difference in pathophysiological mechanism of HF as disease of the 'pipes' (following MI with prior CHD), and disease of the 'pump' (with no prior CHD). Clinically in the disease of the 'pump', there is a period defined by asymptomatic diastolic dysfunction, followed by overt systolic dysfunction,[48] and the ejection fraction could be reduced or preserved, in contrast to disease of the 'pipes', where it is always preserved.

Molecular mechanisms explaining the beneficial effect of SGLT2 inhibitors on HF revolves around hyper-insulinemia and excess activity of renin-angiotensinogen system.[48,49] SGLT2 inhibitors modulate the insulin levels and cause an increase in -hydroxybutyrate and acetoacetate levels.[50] Along with this, inotropic effect contributed by glucagon [51]secretion from the alpha cells of the pancreas, may contribute to its beneficial effect against HF pathophysiology. Intuitively, mechanism of metabolic substrate switching from high energy consuming 'glucose or fat' to low energy consuming 'ketone' bodies, in highly compromised and energy deficient hypoxic myocardial cells, would provide an advantage and ensure protection from the pathological remodelling of cardiomyocytes in HF patients. This is currently only hypothesized mechanism and would form the basis of hypothesis testing for future research.[52]

Further, a 18% higher numerical increase in the risk of ischaemic stroke in the EMPAREG study was comprehensively analysed in a recently published report.[53] It was argued that volume depletion / hypotensive effect and an increase in hematocrit with SGLT2 inhibitor use would be a likely explanation for an increase in risk of stroke. Both these factors collectively could counteract the blood pressure lowering advantage with SGLT2 inhibitors. While previous meta-analysis had established the casual relationship of hypotensive effect with ischaemic stroke in diabetes,[54] patients in the EMPAREG analysis with the large difference in hypotensive effect did not show any tendency for increased risk of stroke. Similarly, although 41.1% was the mean hematocrit at baseline in the EMPAREG study, patients with wide differences in hematocrit did not show any tendency for increase in stroke. Moreover, attributing an increase in risk of stroke to the entire SGLT2 class would not be prudent as the CANVAS (HR 0.90) and the DECLARE study (HR 1.01) have shown almost neutral results. This was further corroborated in recent meta-analysis which showed the risk of all three SGLT2 inhibitor was comparable to placebo.55However, this increased risk of stroke has to be kept in mind and further explored.

Furthermore, composite pertaining to renal outcome was of particular interest as for the first time an anti-diabetic medication showed a beneficial effect with a relative reduction of 40-47%.[20,21,22] The reduction in renal outcome was consistent across all 3 drugs, suggesting SGLT2 inhibitors as a class shows favourable renal outcomes. This has far reaching consequence as for the first time, the renal complications of DM can be targeted by novel mechanisms other than secondary benefit achieved following glycaemic control. One possible explanation could be- decreased sodium absorption will increase distal sodium delivery to the distal convoluted tubule, where the macula densa activates the tubulo-glomerular feedback mechanism, resulting in modulation of afferent arteriole and decreasing hyperfiltration. [56]Decrease in peripheral vascular resistance, modulation of neuro-hormonal mechanisms and effect on serum uric could be the other mechanism involved in the beneficial renal effects of SGLT2 inhibitors. Moreover, the effect of SGLT2 inhibitors in decreasing intra-glomerular pressure can be explained by blockade of renin angiotensin system.[57,58] This hypothesis is further strengthened as withdrawal of the drug leads to reversing of the changes that were observed.

In spite of the benefit, it is important to discuss the differences in the renal outcome event rate, as EMPAREG study showed a higher rate- 11.5 vs 9 vs

7/1000 patient-years. The observed differences could be because of difference in period of follow-up, duration of patients with diabetes and the differences in the renal entry and the assessment criteria. The national kidney foundation advocates the use of CKD-EPI equation, like in DECLARE study, as the MDRD equation tends to underestimate GFR estimation = 60 mL/min/1.73 m2. [59]Also,in the DECLARE study, CrCl as a measure of GFR using the Cockroft-Gault equation, is usually swayed by body weight.[60]

In totality, because of the differences in the population studied, the 3 drugs within the SGLT2 inhibitor class vary with respect to their approval status. Dapagliflozin is indicated to improve glycaemic control in patients with type 2 DM, in addition to diet and exercise.[61] Empagliflozin is licensed for preventing CV deaths only, [62]while canagliflozin is indicated for preventing CVD,[63] in patients suffering from type 2 DM. With the recently published DERIVE study,[64] all the SGLT2 inhibitors are contraindicated in patients with a eGFR of <45 mL/min/1.73 m2. [65]Future evidence on safety would address the concerns on amputations, diabetic ketoacidosis and bladder malignancies.

Conclusion :

The advent of SGLT2 inhibitors marks a paradigm shift in the treatment of type 2 DM, as for the first time targeting renal mechanisms by inhibiting glucose reabsorption has resulted in glycaemic benefit. Although subtle differences in the cardiac outcomes exists in the respective trials of three approved SGLT2 inhibitors - empagliflozin, canagliflozin and dapagliflozin, it is amply clear that risk reduction in heart failure hospitalization and renal death benefits can be attributed to a class effect, which addresses an unmet need in the fight against DM.

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