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A POTENTIAL INSTANCE OF ADVERSE DRUG REACTIONS (ADRs) ALLIED WITH SGLT2 INHIBITORS - A NARRATIVE REVIEW

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SIGNIFICANCE OF THIS STUDY :

What is currently known about this subject?

SGLT2 Inhibitors (SGLT2i) play a key role in the treatment of diabetes and cardiovascular diseases which is a growing public health concern around the world now-a-days.

Why is this study being done?

SGLT2 Inhibitors have recently shown beneficial effects in patients with type-2-diabetes and cardio-renal comorbidities, but their Adverse Drug Reactions (ADRs) are less conveyed. Our study focuses on exhibiting these ADRs.

What did the study reveal?

Our study would like to uncover the possible adverse drug reactions associated with SGLT2 Inhibitors in diabetic and non-diabetic patients and to promote the awareness of benefits as well as risks of these agents.

ABSTRACT:

T2DM (Type 2 Diabetes Mellitus) is a significant metabolic condition.The Sodium-Glucose Co-transporter 2 inhibitor (SGLT2i) is an efficient glucose lowering agent in the treatment of type-2-diabetes mellitus (T2DM). They have a potent glucose lowering action, which is insulin independent and shows no glucose energy due to loss of urinary glucose. Sodium-glucose co-transporter-2 drugs restrict glucose reabsorption and allow glucose efflux in the urine via inhibiting SGLT2 in the proximal convoluted tubule (PCT). This study shows the beneficial effects and risks such as genitourinary tract infections, Diabetic ketoacidosis, Postural hypotension, Volume depletion, Dyslipidemia, Lower limb amputation, Skeletal fractures, Acute kidney injury. Patients benefit from sodium glucose co-transporter inhibitors when given as a preventive measure in heart failure or any cardiac complications with diabetes mellitus, patients had optimum glycaemic control when Sodium glucose co-transporter 2 inhibitors (SGLT2i) are

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given as it also has an advantage of weight loss in obese patients, as well as decrease blood pressure. Safety concerns must be said regarding the occurrence of genitourinary tract infections, although they are caused to the mild to moderate level, prefer to recur and lastly lead to discontinuation of the treatment. A caution to the patients who are sodium glucose co-transporter 2 inhibitors along with NSAIDS or RAS inhibitors, they are highly recommended to monitor renal function closely during the course of treatment.

Keywords: Sodium glucose co-transporter 2 inhibitors (SGLT2i), type-2-diabetes mellitus, heart failure,Genito-urinary tract infections, proximal convoluted tubule, RAS inhibitors.

INTRODUCTION:

Diabetes is a growing public health concern around the world [1].T2DM is linked to an increased risk of both macro vascular (atherosclerotic cardiovascular disease and heart failure) and micro vascular complications (chronic kidney disease, as well as eye and nerve damage)[2,3].T2DM is a chronic disease with a high epidemiological and economic burden[4]. Type 2 diabetes mellitus has reached epidemic proportions, with the prevalence expected to double by 2050[5,1].Poor glycemic control, a longer duration of T2DM, insulin treatment leads to the development of heart failure[6,7].Patients with T2DM are more likely to develop cardiovascular disease(CVD) as well as their risk for co-morbidities like obesity, dyslipidemia, hypertension in majority of the population[8,9].

SGLT-2-INHIBITORS:

The Sodium glucose co-transporter 2 inhibitors (SGLT2i) is an efficient glucose lowering agent in the treatment of T2DM, showing significant glycemic control as well as good cardiovascular and renal effects [10].SGLT2i demonstrated the best cardiovascular outcomes, lowering cardiovascular risk[1].The SGLT2i such as canagliflozin, dapagliflozin and empagliflozin have been shown to reduce hyperglycemia in T2DM patients[11]Furthermore, these agents have been shown to have positive effects on non-glycemic variables such as body weight and blood pressure, which may confer additional health benefits [11]. The rationale usage of SGLT2i in the treatment of type 2 diabetes mellitus (T2DM) to decrease renal glucose reabsorption and increase urinary glucose excretion their by reducing hyperglycemia [11].The glucose excreted in the urine as a result of SGLT2i is equivalent to approximately 200-300 calories per day[12].Under normal physiological conditions, both transporters (SGLT1 and SGLT2) reabsorb glucose in the renal proximal tubule (180g/day), but SGLT2i reabsorbs more than 97 percent of the glucose [13,14] Pharmacological inhibition of SGLT2i in the kidney reduces renal glucose reabsorption capacity by 30-50%[15].Surprisingly, SGLT2i not only shown reduction in heart failure admissions and also improvement in major adverse cardiac event (MACE) outcomes in patients with established cardiovascular disease and also slowing the progression of diabetic nephropathy [6].Indeed, large scale trails specifically designed to assess the long-term effects of improved glycaemic control on diabetic complications revealed that the therapy intensification is small, but statistically significant[16].SGLT2i consistently result in weight loss in patients may be due to fluid loss by osmotic diuretic effect, whereas subsequent weight loss is most likely due to caloric loss [17,18].

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Mechanism of action:

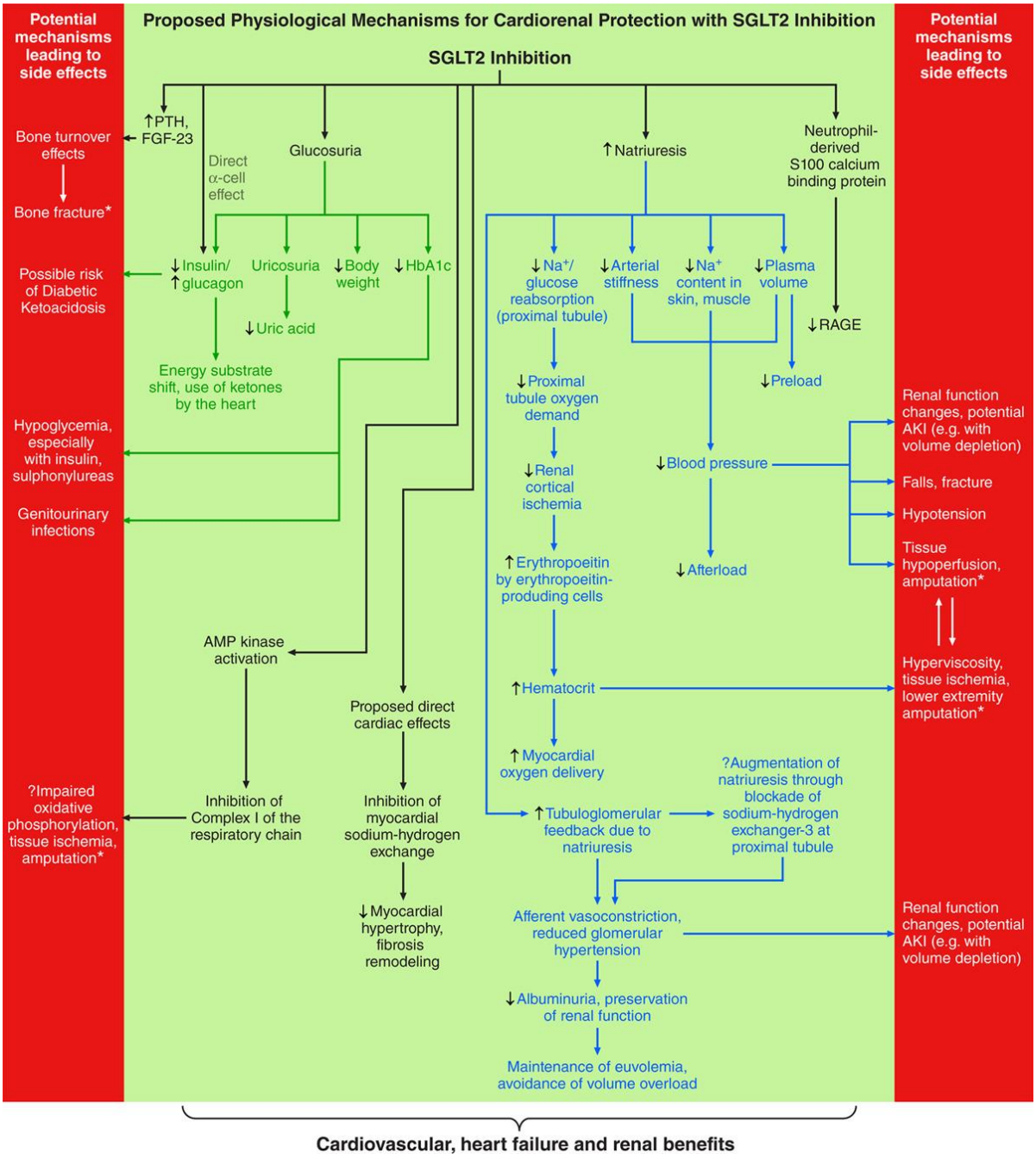


Fig.1 Physiological basis for postulated pathways resulting in cardiorenal advantages and dangers from sodium glucose cotransporter 2 inhibition.

* Only the CANVAS Program was used to report this information. FGF-23 stands for fibroblast growth factor 23; PTH stands for parathyroid hormone; and RAGE stands for receptor for advanced glycation end products [19].

Indications:

Sodium glucose cotransporter-2 inhibitors (SGLT2i) are beneficial in the following conditions:

-Patients who are overweight or hypertensive because of potential weight loss and antihypertensive benefits.
-Patients with cardiovascular disease (e.g., heart failure) not meeting glycaemic goals with other-hypoglycemic agents and lifestyle modifications. (due to potential weight loss and antihypertensive benefits)
-Sodium glucose co-transporter 2 inhibitors (SGLT2i) are being used as a second line agent in patients with concomitant usage of other anti-diabetic agents but still could not achieve their glycemic goals.
-Patients at high risk of hypoglycaemia.
-As a third-line agent in the treatment of inadequate glycaemic control in patients with concomitant use of two or more oral hypoglycemic agents.
-SGLT-2 inhibitors minimize the risk of kidney disease development and cardiovascular disease in individuals with type 2 diabetes who have nephropathy.
Examples of SGLT2i: Dapagliflozin, Canagliflozin, Empagliflozin, Ertugliflozin, Remogliflozin etabonate, Ipragliflozin, tofogliflozin, Sergliflozin etabonate, Luseogliflozin, Etc.,

FIG-2: FDA APPROVED SGLT2 INHIBITORS

Generic agent (brand)	Canagliflozin (Invokana)	Dapagliflozin (Farxiga)	Empagliflozin (Jardiance)
Initial dose (maximum dose)	100 mg/d if eGFR is 45 to <60 and 300 mg/d if eGFR ≥60	5 mg/d (10 mg/d)	10 mg/d (25 mg/d)
Renal dosage adjustments	Discontinue if eGFR is persistently <45 (Contraindicated if eGFR <30)	Do not administer/discontinue with eGFR <60	Do not initiate/discontinue with eGFR persistently <45 (Contraindicated if eGFR <30)
Hepatic dosage adjustments	No adjustment for mild to moderate impairment; not recommended in severe impairment (has not been studied)		None to note
Drug interactions	If receiving concurrent UGT enzyme inducers and eGFR is 45 to <60, consider alternative antihyperglycemic therapy	None to note	
Administration	Administer prior to first meal	Administer in the morning without regard to food	
Common adverse effects	Genital mycotic infections, urinary tract infections, volume-related effects such as dizziness and hypotension		
Available combination products, generic (brand)	canagliflozin + metformin (Invokamet)	dapagliflozin + metformin ER (Xigduo)	empagliflozin + metformin (Synjardy) empagliflozin + linagliptan (Glyxambi)

eGFR, estimated glomerular filtration rate (reported in mL/minute/1.73 m²); UGT, uridine 5'-diphospho-glucuronosyltransferase enzyme inducers (eg, rifampin, phenytoin, phenobarbital, ritonavir).

Source: Federal Practitioner. 2018 Jul;35(7):45.Canagliflozin, dapagliflozin, empagliflozin. Lexicomp, Inc. (Lexi-Drugs®). Accessed October 12, 2015.

ADRs associated with SGLT 2 inhibitors:

Genitourinary tract infections:

The SGLT2 inhibitors dapagliflozin, canagliflozin, and empagliflozin are widely used to treat type 2 diabetes, however they are linked to an increased risk of genitourinary tract infections, aggravating the problem that diabetics are already at a higher risk than the unaffected population[20].
Hence, for patients using SGLT-2i, it is recommended to pay attention to the hygiene of the individual genital area, drink plenty of water, keep the urine flowing, and reduce the incidence of

infection [21]. The UTIs associated with SGLT2 inhibitors were substantially more common in women compared to men [21].

This may be due to the following factors:

1) Women's physiology and anatomy differ from men's because the urogenital tract environment and pH value make UTIs more likely [21].

2) Female urogenital tract blood circulation differs from men, so even when using the same doses, there may be a difference [21].

3)The signs of an early genitourinary infection are mild or nonexistent. Women are frequently overlooked and denied timely treatment [21].

Diabetic Ketoacidosis:

Considering the unexpected link between SGLT2 inhibitors–treated individuals and diabetic ketoacidosis (DKA),Clinicians need realistic information on how to avoid and diagnose this relatively new clinical entity[22].DKA is a medical emergency that affects diabetics and it can occasionally be the first symptom of a new diabetes diagnosis[22]. When compared to other DKA studies, the relatively low fatality rate of DKA cases involving SGLT2 inhibitors is reassuring on this potentially life-threatening illness[22].No specific prescribing guide emerges, but appropriateness remains key to minimize the risk of SGLT2 inhibitors associated with DKA [22].

Case reports of diabetic ketoacidosis in SGLT2 inhibitor-treated patients raise the question of how this group of agents may play a role in the aetiology of ketoacidosis, either directly or indirectly.[23,24]Studies of the exploratory use of SGLT2 inhibitors to treat T1DM patients demonstrate the most clear ketosis-promoting mechanism. Because SGLT2 inhibitors lower glucose levels, the researchers reduced the amount of insulin given to the patients to reduce the risk of hypoglycemia[23,24].The subsequent drop in circulating insulin levels is expected to boost adipose tissue lipolysis and hepatic ketogenesis, raising circulating ketone body levels [23, 24].

Dyslipidemia:

Although SGLT-2 inhibitors have been demonstrated to lower cardiovascular risks, they may also increase the risk of dyslipidemia. In several studies, SGLT2 inhibitors reduced triglyceride levels but elevated LDL and HDL cholesterol levels just marginally [25].In contrast, no substantial alterations in circulating lipoproteins were identified under certain bigger trials[26].These cardiovascular and Reno-protective effects occur despite an increase in LDL-C levels, which has been seen in various clinical publications [27,28].Moreover, this rise in LDL-C occurs alongside other positive alterations in plasma lipoprotein metabolism[29]. The goal of this review is to examine the effects of SGLT2 inhibitors on lipid metabolism in order to better understand how they improve cardiovascular outcomes despite modestly enhancing LDL-C levels[29]. Increases in HDL-C and LDL-C have been linked to the use of SGLT2 inhibitors [30]. The mechanism by which an SGLT2 inhibitor raises LDL-C Levels are uncertain, however a dose-related elevation in LDL-C has been found in SGLT2 inhibitor patients [31]

Postural Hypotension:

The osmotic diuresis caused by SGLT2 inhibitors ultimately result in dehydration, intravascular volume depletion, and postural hypotension[32]. Patients who use diuretics have a greater risk of

postural hypotension and dehydration (2.2–2.7%) than who do not (0.9–1.0%) [33,34]This potential is heightened when thiazides and loop diuretics are combined due to its mode of action, which increases salt and water elimination[32]. Patients above the age of 75 had a 4.4 percent high prevalence of postural hypotension [35-37]. A small increase in clinical symptoms connected with volume deficit, such as postural hypotension and orthostatic hypertension, was reported in clinical studies with canagliflozin at 300 mg, particularly when loop diuretics were taken concurrently[38]. The incidence of volume depletion–related AEs with canagliflozin 100 mg and 300 mg and non canagliflozin was 3.2 percent, 8.8 percent, and 4.7 percent, respectively, among patients on loop diuretics[39]

Lower Limb Amputation:

The FDA as well as EMA have issued a warning concerning an enhanced risk of lower limb amputation, in patients who are on canagliflozin administration [40, 41]. This is a warning based on the continuing initial screening. Canagliflozin Cardiovascular Evaluation Study(CANVAS) clinical study, the frequency were 7, 5, and 3 cases of lower limb amputation, respectively.[42]As it is well known, the vast majority of lower limb amputations in diabetic individuals were performed because of uncontrolled infection and consequent extremity necrosis, this could be linked to other pertinent conditions include diabetes foot(DF) and peripheral arterial disease.[41]Such problems may exist prior to surgery.[41] Techniques that eventually result in amputation Thus far, the peripheral arterial disease (PAD) and DF evaluations are less well defined than amputation in individuals receiving SGLT2i therapy.[41]Individuals with a history of amputation or peripheral vascular disease had the highest absolute risk of amputation (PVD).[41]Lower-limb amputation occurred in 1.9 percent of participants treated with empagliflozin and 1.8 percent of persons treated with placebo, with an incidence rate of 6.5 per 1000 person-years in both groups, according to a post-hoc analysis of the EMPA-REG OUTCOME data.[42]

Skeletal fractures:

Canagliflozin may also raise the likelihood of bone fractures. The rate of all fractures was greater with canagliflozin versus placebo in the CANVAS Program [43].The cause of canagliflozin's increased fracture risk is unknown.Because the transporter SGLT2 is not located in bone, canagliflozin is unlikely to have a direct effect on the skeleton[43]. Other reasons for causing fractures are orthostatic hypotension and postural disorientation and falls [43].May also have a deleterious impact on bone density and bone metabolism [43].

Volume depletion:

SGLT2 inhibitors reduce blood pressure by causing osmotic diuresis. This effect is favourable in people with uncontrolled hypertension, but it can cause postural dizziness, orthostatic hypotension, and dehydration, particularly in elderly people with kidney disease or those on loop diuretics [43].

Adverse events consistent with volume depletion were rare in the EMPA-REG OUTCOME study and occurred at a similar frequency in the empagliflozin and placebo groups [44]. In

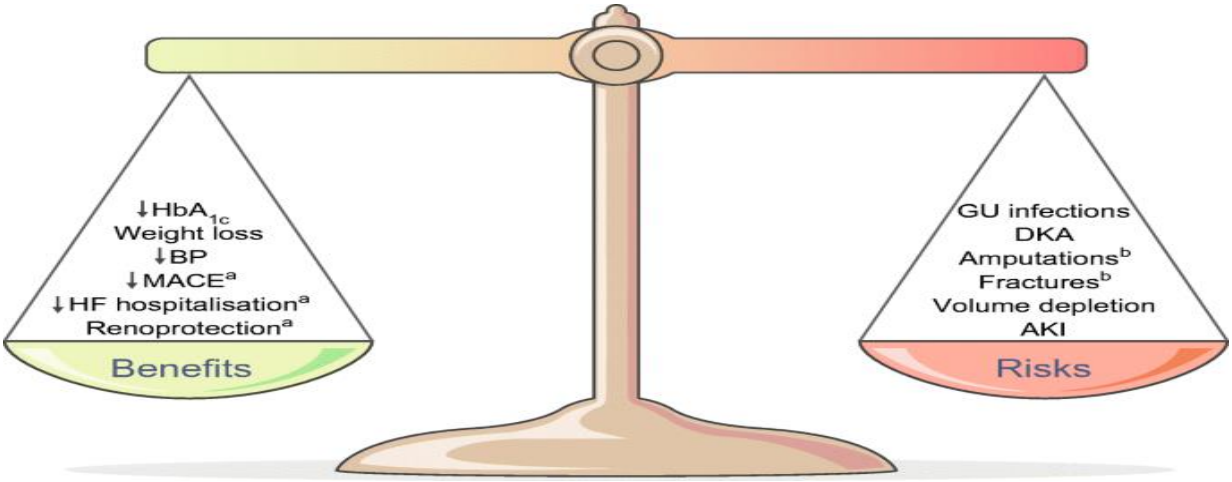
CANVAS, however, volume depletion was more likely in the canagliflozin group compared to the placebo group [45].

Acute kidney injury:

Reports indicating a possible link between SGLT2 inhibitors and severe renal failure prompted the US FDA to publish a warning about the elevated risk of acute kidney injury (AKI) with canagliflozin and dapagliflozin [43].The majority of reported instances happened within one month of initiating medication and improved after withdrawal, while some people required hospitalisation and dialysis. The kidney impairment could have been exacerbated by volume loss, hypotension, or concurrent use of other nephrotoxic drugs[43].An investigation of SGLT2 users and nonusers in two distinct cohorts revealed that SGLT2 inhibitor medication did not raise the risk of AKI [46].Indeed, certain studies support the favourable effect of empagliflozin and canagliflozin on the progression of nephropathy as well as a renal protective effect following an initial minor drop in eGFR[47].

Benefits and Risks Produced by SGLT2 inhibitors:

FIG-3: Risks and Benefits



There are significant risks and benefits associated with SGLT2 inhibitors that have been identified. Only empagliflozin and canagliflozin have been demonstrated to offer cardiovascular and renal benefits, while canagliflozin has been shown to increase the risk of amputations and fractures in large randomised controlled trials. HF stands for heart failure, and GU refers to genitourinary[43].

The activity of the SGLT2 inhibitors is targeted on glucose ejection in the kidneys and is self - reliant of insulin action [48]. Hypoglycemia andweight gain are reduced as a result of such an activity [48].SGLT2 AEs include nausea, tiredness, frequent urination, polydipsia, and xerostomia. SGLT2 inhibitors can cause a variety of other, more serious side effects such as Genito-urinary infections, diabetic ketoacidosis, amputations, fractures, volume depletion, acute kidney injury, dyslipidemia[48].Furthermore, this newer family of anti-hyperglycemic drugs has been shown to have positive results, while there are some side effects[48]. (Fig.4). SGLT-2 inhibitors play a key role depending upon the patient's condition [49]. It has a higher outcome in obese patients,

although it can lead to weight reduction in lean or underweight patients [49].The processes of weight reduction and their impact on cardio-renal consequences appear to be complex and unsolved [50].

Table 1: Clinical Trials of SGLT-2 Inhibitors [19]

Name of Clinical Trial	Drug	Duration	Sample size	Diabetes status	Primary outcomes	Secondary outcomes	NCT	Estimated Reporting
Cardiovascular outcome trials								
EMPA-REG OUTCOME	Empagliflozin 10 mg or 25 mg daily vs placebo	Up to 4.6 years	7020 patients with established cardiovascular complications	All T2DM	14% reduction in 3-point MACE pooled from 10 mg and 25 mg empagliflozin doses	35% reduction in hospitalisation for HF, 39% reduction in the composite renal end point	NCT011 31676	Reported in 2015
CANVAS Program	Canagliflozin 100 mg or 300 mg daily vs placebo	3.6years	10 142 patients with established vascular complications or ≥2 cardiovascular risk factors	All T2DM	14% reduction in 3-point MACE	27% reduction in progression of albuminuria, 70% increase in regression of albuminuria, 40% reduction in the composite renal end point	NCT010 32629	Reported in 2017
CREDENCE	Canagliflozin 100 mg daily vs placebo	4 years	3627 patients with stage 2 or 3 CKD and macroalbuminuria and on ACEi/ARB	All T2DM	ESRD, S-creatinine doubling, renal/CV death	Cardiovascular death, nonfatal MI, nonfatal stroke, hospitalised UAP, hospitalised CHF, composite renal end point	NCT020 65791	Anticipated 2019
DECLARE - TIMI 58	Dapagliflozin 10 mg vs placebo	Upto 6 years	17 276 patients with high risk for cardiovascular events (≥40 y)	All T2DM	Cardiovascular death, nonfatal MI, CV death, hospitalisation because of HF	Renal composite end point ESRD and renal or cardiovascular death, all-cause mortality	NCT017 30534	Anticipated 2019
VERTIS	Ertugliflozin vs placebo	Upto 6.1years	8000 patients with established vascular complications	All T2DM	Cardiovascular death, nonfatal MI, nonfatal stroke	Cardiovascular death, nonfatal MI, nonfatal stroke and hospitalised UAP	NCT019 86881	Anticipated 2019
Large randomised controlled clinical trials in patients with HF								
DEFINE-HF	Dapagliflozin 10 mg daily vs placebo	12 wk	250 patients with HF (≥19 y)	All T2DM	Change in NTproBNP	Change in SBP, weight, HbA1c, BNP, and QoL score by questionnaire	NCT026 53482	TBD

PRESERVED HF	Dapagliflozin 10 mg daily vs placebo	12 wk	320 patients with HF	T2DM or pre-diabetes	Change in NTproBNP	Change in SBP, weight, HbA1c, BNP, and QoL score by questionnaire	NCT030 30235	TBD
DAPA HF	Dapagliflozin 10 mg daily vs placebo	36 months	4500 patients with HFrEF (≥18 y)	Nondiabetic and T2DM (T1DM excluded)	Time to cardiovascular death or hospitalisation for HF or an urgent HF visit.	Time to ≥50% sustained decline in eGFR or ESRD. QoL score by questionnaire. Time to die by any cause.	NCT030 36124	TBD
EMPEROR-Preserved	Empagliflozin 10 mg daily vs placebo	38 months	4126 patients with HFpEF (≥18 y)	Nondiabetic, T1D and T2D eligible	Time to first event of adjudicated cardiovascular death or adjudicated hospitalisation for HF	Change in eGFR. Time to sustain reduction in eGFR. Time to all-cause mortality. Time to DM.	NCT030 57951	TBD
EMPEROR-Reduced	Empagliflozin 10 mg daily vs placebo	38 months	2850 patients with HFrEF (≥18 y)	Non-diabetic, T1D and T2D eligible	Time to first event of adjudicated cardiovascular death or adjudicated hospitalisation for HF	Change in eGFR. Time to sustain reduction in eGFR. Time to all-cause mortality. Time to DM.	NCT030 57977	TBD

Discussion:

Patients benefit from SGLT2 inhibitors when given as a preventive measure in heart failure or any cardiac complications with diabetes mellitus. When SGLT2 inhibitors were given, patients achieved optimal glycemic control, as well as weight loss in obese patients and a reduction in blood pressure.Individuals with a history of genitourinary tract infections should avoid taking this medication because it has an adverse effect of genitourinary tract infection.ADRs can happen to any patient at any time. This medicine did not result in the above-mentioned ADRs in 50% of the patients. This indicates that half of those who used the medicine were completely safe.SGLT-2 inhibitors are advised to be avoided in patients who have very low insulin secretory capacity,prior episodes of ketosis,urinary tract infections and dyslipidemia. According to current SGLT2 inhibitor reviews, data indicate that SGLT2 inhibitors are relatively safe and have beneficial effects in maintaining blood glucose levels and cardiovascular diseases. Data from various research and review articles showed that UTI is the most commonly encountered ADR followed by diabetic ketoacidosis,orthostatic hypotension and dyslipidemia. Many studies show that Empagliflozin had dominant effects preventing the progression from pre and early diabetic nephropathy to diabetic kidney disease as well as further progression of end stage diabetic kidney disease in patients with T2DM who are at high risk of cardiovascular diseases. Moreover, these results were observed in the patients whose blood pressure was given with significant treatment of RAS inhibitors. DKA is of less attention in most of the review and research papers but there is a significant mechanism where SGLT2 inhibitors cause DKA. However, a negligible

number of patients are observed to have this ADR. Regarding the beneficial effects of SGLT-2 inhibitors, it increased supply of Sodium delivering to the macula densa which provides significant benefits in turn activating tubulo-glomerular feedback, resulting in afferent arteriolar vasoconstriction and thereby decrease in glomerular hyperfiltration. A notably increased risk of lower amputation risk for patients with the use of SGLT-2 inhibitors versus patients with the use of GLP-1 agonists was reported in 2 studies. It is obvious that patients taking SGLT-2 inhibitors have a higher risk of hypoglycemia, which is likely owing to the use of other hypoglycemic medications. The use of SGLT-2 inhibitors, either as monotherapy or in combinational anti-hyperglycemic therapy, revealed a larger percentage of clinical safety and positive outcomes than the rate of ADR occurrence, according to the findings of the overall study. Patients should be educated about the hazards associated with the introduction of SGLT2i medication before beginning it. Each person with diabetes should be actively involved in his or her health care team's education, self-management, and treatment planning, including the creation of a specific dietary plan. Apart from SGLT2i administration, patients are advised to follow lifestyle adjustments, including food restrictions and increased physical activity, which is the foundation of underlying management and should be customized to each patient's specific needs. Patients' preferences should also be taken into account before assessing the entire care plan. SGLT2i is effective in patients with diabetes, cardiovascular disease, and obesity because of its diverse therapeutic outcomes.As SGLT2 inhibitors are used in the treatment of DM and cardiovascular diseases, further trials have to be performed to examine the efficacy and safety. However, clinical trials done using SGLT2 inhibitors till date show positive results proving these drugs are safe and effective.Currently available SGLT2 inhibitors Dapagliflozin, empagliflozin, and canagliflozin are still undergoing clinical trials for their safety and efficacy concerns.

Conclusion:

SGLT-2 inhibitors are categorized as unique oral-glucose lowering agents. They have a potent glucose lowering action, which is insulin independent and shows no glucose energy due to loss of urinary glucose. They also have loop-like diuretic effects, associated with reductions in blood pressure and body weight. SGLT2i has shown to have significant benefits in a proportion of patients, including those with diabetes and heart failure, as well as those with uncontrolled diabetes who are using multiple hypoglycemic medications.However, the use of SGLT-2 inhibitors induces effects of Diabetic ketoacidosis, increased risk of genitourinary tract infections and to a lesser extent skin disorders in some patients. Although genitourinary tract infections are usually mild to moderate, they tend to recur and eventually lead to therapy termination.A caution to the patients who are SGLT-2 inhibitors along with NSAIDS or RAS inhibitors, they are highly recommended to monitor renal function closely during the course of treatment.

Conflicts of interest:

The authors have declared no conflicts of interest.

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