



Review Article

Current status of Sodium-Glucose Co-Transporter Type 2 (SGLT2) inhibitors in treating diabetes mellitus

Ingale Nikita S¹, Turankar Avinash V¹, Wagh Mitali S¹, Motghare Vijay M^{1,*}

¹Dept. of Pharmacology, Government Medical College, Nagpur, Maharashtra, India



ARTICLE INFO

Article history:

Received 14-03-2021

Accepted 22-03-2021

Available online 19-04-2021

Keywords:

Canagliflozin

Dapagliflozin

Empagliflozin

Ertugliflozin

Sodium-glucose cotransporter-2 inhibitors

Shotagliflozin

Type 2 diabetes mellitus

ABSTRACT

Background: Diabetes Mellitus is a spreading pandemic to the countries around the globe, despite of scientific breakthroughs and better healthcare facilities. Sodium-Glucose Co-Transporter Type 2 inhibitors (SGLT2i) are the latest class of oral anti-hyperglycemic agents that have been approved for the treatment of type II diabetes mellitus.

Aim: In this review, we have comprehended the evidence for antidiabetic and extra-glycaemic effects of SGLT2i.

Materials and Methods: The information is collected based on safety trials, randomized controlled trials (RCT), meta-analyses and real-world data.

Results: SGLT2i are rapidly establishing their role in the treatment of diabetes mellitus. The beneficial effects extend beyond glycaemic control, impressive cardio protective and Reno protective effects and included improvement in blood pressure, uric acid concentrations, body weight and oxidative stress.

Conclusion: Especially in patients with type 2 diabetes, SGLT2 inhibitors may be another option in those patients requiring additional glucose lowering and in those with acceptable risk factors. More research on the long term outcomes of SGLT2i is warranted.

© This is an open access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>) which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

1. Introduction

Globally, in past three decades, cases of diabetes mellitus has quadrupled. Diabetes mellitus is the ninth major cause of death.¹ Every one person in 11 adult populations worldwide now have diabetes mellitus. Amongst this, 90% of adult population suffer from type 2 diabetes mellitus (T2DM). Its is not surprising to note that Asia is a major area of the rapidly emerging T2DM global epidemic. China and India are the new top two cynosures for this global epidemic.¹ Global burden of T2DM is expected to increase to 578 million (10.2%) by 2030 and to 700 million (10.9%) by 2045.² Type 2 diabetes (T2D) is an endocrinal metabolic disease commonly presented with obesity, hypertension, dyslipidaemia, non-alcoholic fatty liver disease (NAFLD) and hyperuricemia as defined by the

American Diabetes Association (ADA).³ Development of complications like cardiovascular (CV) and renal disease, are the key determinants of hospitalizations, morbidity, and mortality in T2DM.^{4,5} Cardiovascular disease (CVD) is the leading cause of death in people with T2DM.⁶

Through this review, we aim to endow physicians in making informed decisions for choosing and prescribing Sodium-Glucose Co-Transporter Type 2 (SGLT2) inhibitors (SGLT2i) that best suits their patient which may vary according to duration of existing Diabetes mellitus (DM), presence of any CV history, heart or renal failure, and any other co-morbidity. The information is collected based on safety trials, randomized controlled trials (RCT), meta-analyses and real-world data.

* Corresponding author.

E-mail address: vm.motghare@gmail.com (M. Vijay M).

2. Diabetes Mellitus- Current Comprehensive Approach

Number of conditions like severity of hyperglycaemia, risks of hypoglycaemia, body mass index, hepatic and renal associated functions can affect the selection and application of a glucose lowering therapy. Even patient related factors like, ability to self monitor the blood glucose level, and medication cost also affect the choice of drugs. However, immediate requirement to act with a well defined strategy has to be put forth for this disease with its multiple complications. Achievement of complete glycaemic regulation by assessment of present glycaemic status is the ultimate goal of the underlying platform. Analysis of the associated disorder would help providing the healthcare facilities to the affected people. Known pathogenic disturbances of the disease are targeted either by reducing the deterioration of β -cell function or improving insulin sensitivity. In recent years, treatment strategies have focused on the development of novel therapeutic options that will provide long and good glucose control. This may further even help in blunting of disease progression. Optimal management of type 2 diabetes should include early initiation of therapy using multiple drugs having different mechanisms of action.

ADA 2021 guidelines stat that metformin must be the first drug of choice to be started for every patient with T2DM. Further, ADA demands the selection of the second agent added on metformin, in T2DM with CV disease and if there is presence of Chronic kidney disease (CKD).⁷ Older antidiabetic agents such as metformin, thiazolidinediones, sulfonylureas and meglitinides, dipeptidyl peptidase inhibitors are proved drugs for tight glycemic control. These drugs have evidently shown reductions in microvascular complications. No major effect on macro vascular disease was observed though.⁸ Moreover, pharmacotherapy of T2DM also includes range of deleterious side effects like proliferative retinopathy with insulin,⁹ edema, and heart failure hospitalizations especially with thiazolidinediones and hypoglycaemia especially with sulfonylureas.¹⁰ Therefore, in 2008 United States Food and Drug Administration (FDA) asked for CV outcomes trials for novel antihyperglycaemic medications to provide data on safety of the medications. FDA ensured that new drugs for the treatment of T2DM would not increase the risk for myocardial infarction or CV death.¹¹ Therefore, the idea of a more comprehensive approach to cardiovascular risk management in T2DM has emerged as an interesting approach. The latest 2021 guidelines of ADA recommend a personalized approach with the two latest classes of antidiabetic medications, glucagon peptide-1 receptor agonists (GLP1-RA) and SGLT2i.⁷ The inhibition of SGLT2 was introduced 130 years ago by Belgian and French scientists, hence is not a novel approach.¹² Few of the oral agents are approved for the treatment of

T2DM by the U.S. Food and Drug Administration and the European Medicines Agency: Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin and Sotagliflozin.

3. SGLT2 inhibition- Physiology

Several types of SGLT proteins have been identified as proteins functioning independently of insulin. Inhibition of these proteins resulted in changes that favourably improved carbohydrate metabolism, thus became an attractive topic for the treatment for diabetes mellitus.¹³

Of all the filtered glucose in the kidney tubules and almost all of it gets reabsorbed by SGLT2 proteins expressed in the proximal convoluted tubule of the kidneys. They are located in the early S1 segment of the proximal tubule. They are totally responsible for the reabsorption of 80%–90% of filtered glucose in the kidneys. SGLT1s are also located in the S2/S3 segment of proximal tubule reabsorb and are meant to reabsorb the remaining 10%–20% of filtered glucose. Thus, glucose that escapes SGLT2 is reabsorbed by SGLT1 in more distal tubular segments.¹⁴

SGLT2 and SGLT1 transporters are an ideal target for the treatment of diabetes because they are responsible for roughly all of filtered glucose reabsorption.¹⁵ In patients with type 2 diabetes, threshold for reabsorption of glucose is usually observed to be on a higher side and the expression of the SGLT2 can be up-regulated causing an adaptive response that worsens hyperglycaemia.¹⁶ SGLT2 inhibition can almost reduce this threshold to as low as 40 to 120 mg/dL.¹⁷ The mode of action of SGLT2i is independent of insulin and unlike any other anti-diabetic agents.¹⁸

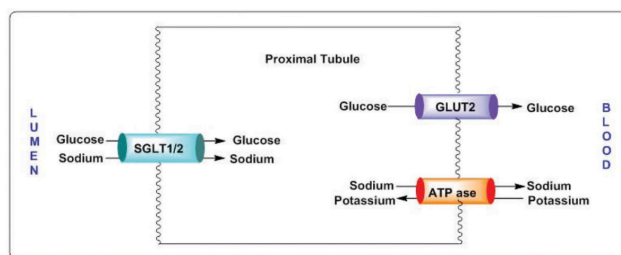


Fig. 1: Cotransport of glucose and sodium by SGLT1 and SGLT2 in the PCT.¹⁹

4. SGLT2 Inhibitors

Very few SGLT2 inhibitors have been approved for the treatment of type 2 diabetes. Few oral agents that are approved for the treatment of T2DM by the U.S. FDA and the European Medicines Agency include Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin and Sotagliflozin. They have been approved for mono, dual, and triple therapy.²⁰ Combination drugs approved by the FDA: Canagliflozin/Metformin,

Dapagliflozin/Metformin, Empagliflozin /Metformin and Empagliflozin /Linagliptin.²¹ There are several other similar compounds in the pipeline that may be approved in this class.

4.1. Dapagliflozin

In a study, after 24 weeks of intervention, the administration of Dapagliflozin 1, 2.5 and 5 mg once daily resulted in a reduction of HbA1c by 0.68%, 0.72%, and 0.82%, respectively.²² Treatment with Dapagliflozin versus placebo resulted in greater reductions in HbA1c (−0.67% with 2.5 mg, −0.70% with 5 mg and −0.84% with 10 mg)²³ Dapagliflozin has been also experimented as add-on therapy with glimepiride 4 mg/day. It was a 24-week, randomized, double-blind, placebo-controlled, parallel-group, international, multicentre trial enrolled patients with uncontrolled T2DM [haemoglobin A1c (HbA1c) 7–10%] receiving sulphonylurea monotherapy. In this trial, at 24 weeks, HbA1c adjusted mean changes from baseline for placebo versus dapagliflozin 2.5/5/10 mg groups were −0.13 versus −0.58, −0.63, −0.82%, respectively (all $p < 0.0001$ vs. placebo). Corresponding fasting plasma glucose values were −0.11, −0.93, −1.18, −1.58 mmol/l, respectively. In placebo versus dapagliflozin groups, serious adverse events were 4.8 versus 6.0–7.1%; events suggestive of genital infection 0.7 versus 3.9–6.6%; hypoglycaemic events 4.8 versus 7.1–7.9%; and events suggestive of urinary tract infection 6.2 versus 3.9–6.9%. No renal infections were reported.²⁴

4.2. Canagliflozin

Efficacy of Canagliflozin was assessed in a meta-analysis of 6 RCTs in subjects who were treated with metformin monotherapy. Administration of Canagliflozin 100 and 300 mg reduced HbA1c by 0.59% and 0.74%, respectively. Similarly, reduction in FPG was by 27 mg/dL and by 32 mg/dL, respectively. Nevertheless, hypoglycaemic events were significantly higher when added on insulin or Sulphonylurea.²⁵

4.3. Empagliflozin

In a multicentric, randomised, placebo-controlled, phase 3 trial, Empagliflozin's effect on glycaemia was observed. Adults (aged ≥ 18 years) who had not received oral or injected anti-diabetes treatment in the previous 12 weeks, with HbA1c concentrations of 7–10% were randomly allocated patients with a computer-generated random sequence into placebo, empagliflozin 10 mg, empagliflozin 25 mg, or sitagliptin 100 mg once daily for 24 weeks. After 24 weeks of intervention, HbA1c was reduced by 0.74% for Empagliflozin 10 mg, by 0.85% for Empagliflozin 25 mg, by 0.73% in Sitagliptin arm.²⁶

4.4. Ertugliflozin

When Ertugliflozin was compared with glimepiride in terms of glycemic control in patients with T2DM inadequately controlled with metformin. The change in HbA1c was −0.6%, −0.6%, and −0.7% in the Ertugliflozin 15 mg, 5 mg, and glimepiride groups, respectively. In addition, the incidence of symptomatic hypoglycaemia was higher with glimepiride. Hence, Ertugliflozin was found non-inferior to glimepiride in reducing HbA1c when added to metformin in patients with T2DM. Extension of this study had confirmed this findings.²⁷

4.5. Sotagliflozin

Sotagliflozin is a dual sodium–glucose co-transporter-2 and 1 (SGLT2/1) inhibitor for the treatment of both type 1 and T2DM. The drug has a dual action. It blunts and delays absorption of glucose from the gastrointestinal tract. Also it hampers the reabsorption of glucose in the proximal tubule of the kidney, respectively.²⁸

The efficacy of sotagliflozin as a treatment for inadequately controlled T1DM has been assessed in the in Tandem clinical trial program. Tandem was a double-blind placebo-controlled phase III clinical trial. More than 3000 patients were recruited. Sotagliflozin 200 and 400 mg/day significantly reduced HbA_{1C} levels [0.36 and 0.41% least squares mean (LSM) reduction vs. placebo, respectively (both $p < 0.001$)] from a mean baseline of 7.57% and improved diabetes treatment satisfaction questionnaire scores in both active treatment groups ($p < 0.001$) at the 24-week endpoint. Net clinical benefit at week 52, were HbA_{1C} $< 7.0\%$. This was without severe hypoglycaemia or diabetic ketoacidosis. Sotagliflozin was recently approved for use as an adjunct to insulin in T1DM, who have failed to achieve adequate glycaemic control despite optimal insulin therapy in the European Union. However, the FDA Endocrinologic and Metabolic Drugs Advisory Committee was divided, citing concerns regarding diabetic ketoacidosis, leading the FDA to issue a safety report for this indication in the USA.²⁹

5. SGLT2 inhibitors- Benefits

5.1. Cardiovascular and renal benefits

In cardiovascular and renal outcomes trials, reduction in major adverse cardiovascular events and hospitalization for heart failure were evidently seen by SGLT2i.^{30,31} All renal parameters like progression of albuminuria, doubling of serum creatinine, initiation of renal replacement therapy or death due to renal disease were found to be reduced, further supporting this finding. Interestingly, these effects appeared were independent of glucose-lowering efficacy. Large observational studies have confirmed all these findings.^{32,33}

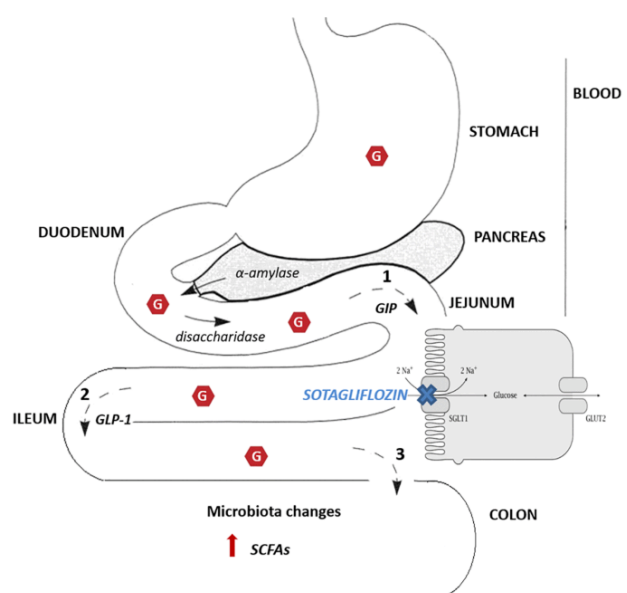


Fig. 2: Intestinal effects of SGLT-1 inhibition by Sotagliflozin²⁹

In view of the robustness of these findings, current ADA 2020 Guidelines, recommend that patients with T2D and CVD or at high renal risk should receive an SGLT2 inhibitor.⁷

The CV safety of Empagliflozin was assessed in Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPAGLIFLOZIN -REG OUTCOME). 7020 patients with T2DM and coronary or cerebrovascular disease were randomized to receive two different doses of Empagliflozin (10, 25 mg) or placebo. The median observation period was 3.1 years. Patients received lipid-lowering medication, antiplatelet and renin-angiotensin-aldosterone system inhibitors. Treatment with Empagliflozin resulted in a 38% reduction of death from CV causes.¹⁸

In CV trial of dapagliflozin, the results of the Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) are evident. A total of 17,160 patients with T2DM and established atherosclerotic CV disease were randomized to receive either Dapagliflozin 10 mg or placebo. Treatment was given for median period of 4.2 years. Treatment with Dapagliflozin resulted in a 17% reduction of the composite outcome of CV death or hospitalization for HF. Also, Dapagliflozin reduced the composite renal outcome by 24% ($\geq 40\%$ decrease in eGFR to < 60 mL/min/1.73 m², new end-stage renal disease, or death from renal or CV causes).³⁰

The CANVAS (Canagliflozin Cardiovascular Assessment Study) Program trial was also conducted to assess the CV safety of Canagliflozin. It was a combination of two sub-studies: the CANVAS and the CANVAS-R study (CANVAS-Renal). With the merge of these two studies, the effect of two different doses of Canagliflozin (100 and

300 mg) versus placebo on CV disease was examined. The mean follow-up was 3.6 years. Significant reduction (by 14%) of the composite 3 Point-MACE (CVD events, admission for HF, cardiac death) primary endpoint in the group receiving Canagliflozin was demonstrated in the study.³¹ Meta-analysis of the EMPAGLIFLOZIN -REG OUTCOME, the CANVAS Program, and the DECLARE-TIMI 58 trials had evidently revealed significant findings about efficacy of these drugs. SGLT2i reduced major cardiac events (MI, stroke, or CV death) significantly by 11%. On the other hand, SGLT2i reduced the risk of CV death or hospitalization for HF by 23%. Regarding all-cause mortality, SGLT2i reduced the risk by 15%.^{34,35}

5.2. Body weight

Data from clinical trials, show that the total weight loss seen by these drugs is 2–3 kg as monotherapy or add-on treatment over 20–23 months.³⁶ Among SGLT2i, a meta-analysis showed that Canagliflozin 300 mg leads to greater weight reduction when compared with Dapagliflozin 5 mg.³⁷

5.3. Other metabolic effects

SGLT2 inhibitors have found significant reductions in Blood Pressure, with greater reductions seen in systolic (1.66 to 6.9mmHg) than diastolic (0.88 to 3.5mmHg) BP in large studies.¹⁷ About Lipid profile, many trials have shown no change in lipid parameters. Few trials have shown a modest but statistically significant increase in both HDL and LDL cholesterol with no effect on triglycerides or the LDL/HDL ratio. Also, while triglyceride and small dense LDL levels tend to decrease modestly.¹⁷ SGLT2i has shown to reduce serum uric acid concentrations, mechanism being increased renal uric acid excretion. This was also proved in a study where, patients with type 1 diabetes (T1D), where uric acid excretion significantly increased after SGLT2i induced glycosuria.³⁸ In animal studies, Empagliflozin was evident in reducing oxidative stress in the streptozotocin-diabetic rat model. Mechanism found was interference with NADPH oxidase activity. Thus, Empagliflozin therapy was observed to be associated with reduced levels of oxidative stress, inflammation in animal model of diabetes.³⁹

6. SGLT2 Inhibitors- Warnings

These drugs are generally considered to be safe with minimal side effects after its administration. SGLT2i has been associated with incidence of lower urinary tract and genital infections on a slight higher side. Genital infections occur frequently with SGLT2i due to increased mycotic growth in high glycosuria. Diabetic ketoacidosis (DKA) typically is defined as the triad of hyperglycaemia (blood glucose > 250 mg/dL), anion gap metabolic acidosis, and the presence of urine or plasma ketones. After reviewing FDA

Adverse Event Reporting System database entries since the approval of Canagliflozin in March 2013, the FDA issued a warning in May 2015 about the risk of DKA associated with SGLT2 inhibitors. SGLT2i when administered in maximum doses, induces a rapid increase in urinary glucose excretion, ranging 50–100 g/day. Because of the rapid decline in glucose, plasma insulin levels also rapidly decrease. This as a compensation, further increases blood glucagon levels. These consequences into inhibition of gluconeogenesis in the liver as well as augmented endogenous glucose production. Thus, in SGLT2-treated type 2 diabetes patients, the lower insulin-to-glucagon ratio stimulates lipolysis augmenting more Free Fatty Acid delivery to the liver. This worsens the condition by mild stimulation of ketogenesis.⁴⁰

In 2016 the FDA issued a warning of an increased risk of acute kidney injury (AKI) with Dapagliflozin and Canagliflozin, based on hundreds of confirmed cases of AKI.⁴¹ Similar findings were observed in meta-analysis too.³⁴

In September 2015, the FDA strengthened the warnings related to the increased risk of bone fractures for Canagliflozin and Canagliflozin/metformin. Therefore, the FDA demanded new information about decreased bone mineral density to the labels for Canagliflozin and Canagliflozin/metformin.⁴² Acute pancreatitis was another rare side effect that has been observed with the use of Canagliflozin. Mechanism remains unknown.⁴³ The FDA had issued Boxed Warning in 2017 for the increased risk of amputations in relation to the potential benefit of Canagliflozin.⁴⁴ In 2020 FDA Drug Safety Communication, from review of data from another three new clinical trials, this Boxed Warning about amputation risk from Canagliflozin has been removed.⁴⁵

7. SGLT2 Inhibitors- Current Outlook and Perspectives

SGLT2i have completely revolutionized the treatment of T2DM. Still, many queries remain unanswered. Surprisingly, whether these effects can be generalized to the general diabetic patients or to be kept with cardiac or renal disease remains unclear. Despite all the data we have due to intensive research, the mechanisms of cardio-renal protection SGLT2i still remains elusive.

Thereby, head-to-head Randomized Controlled Trials as well as real-world data is highly essential. Like many other new drugs, the value of SGLT2 inhibitors has been questioned because of their high price. Finally, according to some studies, SGLT2i have proven such impressive benefits in not only in CV morbidity and mortality, but also in metabolic disorders that often coexists with DM. it has proven to reduce excess body weight and lower blood pressure too. Therefore, SGLT2i surely have promising future, which can be clarified by further clinical trials. Dual

SGLT1i and SGLT2i like Sotagliflozin seems to represent a promising treatment for both type 1 and type 2 diabetes. It can be effective either alone or in combination with metformin in type 2 diabetes or, with an adequate insulin administration, in type 1 diabetes.

8. Source of Funding

None.

9. Conflict of Interest

The authors declare that there is no conflict of interest.

References

- Lahnwong S, Chattipakorn SC, Chattipakorn N. Potential mechanisms responsible for cardioprotective effects of sodium–glucose co-transporter 2 inhibitors. *Cardiovasc Diabetol.* 2018;17(1):101. doi:10.1186/s12933-018-0745-5.
- Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract.* 2019;157:107843. doi:10.1016/j.diabres.2019.107843.
- American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2021. *Diabetes Care.* 2021;44(S-1):15–33.
- Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM. CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med.* 2019;380(24):2295–306.
- Wanner C, Inzucchi SE, Lachin JM, Fitchett D, Eynatten MV, Mattheus M. EMPAGLIFLOZIN -REG OUTCOME Investigators. Empagliflozin gliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med.* 2016;375(4):323–34.
- Leon BM, Maddox TM. Diabetes and cardiovascular disease: epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes.* 2015;6:1246–58.
- Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2021. *Diabetes Care.* 2021;44:111–24.
- Eleftheriadou I, Grigoriopoulou P, Liberopoulos E, Liatis S, Kokkinos A, Tentolouris N. Update on Cardiovascular Effects of Older and Newer Anti-diabetic Medications. *Curr Med Chem.* 2018;25(13):1549–66. doi:10.2174/0929867324666170530075533.
- Penman A, Hancock H, Papavasileiou E, James M, Idowu O, Riche DM. Risk Factors for Proliferative Diabetic Retinopathy in African Americans with Type 2 Diabetes. *Ophthalmol.* 2016;23(2):88–93. doi:10.3109/09286586.2015.1119287.
- Powell WR, Christiansen CL, Miller DR. Meta-Analysis of Sulfonylurea Therapy on Long-Term Risk of Mortality and Cardiovascular Events Compared to Other Oral Glucose-Lowering Treatments. *Diabetes Ther.* 2018;9(4):1431–40. doi:10.1007/s13300-018-0443-z.
- Zannad F, Stough WG, Lipicky RJ, Tamargo J, Bakris GL, Borer JS, et al. Assessment of cardiovascular risk of new drugs for the treatment of diabetes mellitus: risk assessment vs. risk aversion. *Eur Heart J Cardiovasc Pharmacother.* 2016;2(3):200–5.
- Jörgens V. The roots of SGLT inhibition: Laurent-Guillaume de Koninck, Jean Servais Stas and Freiherr Josef von Mering. *Acta Diabetol.* 2019;56(1):29–31.
- Shubrook JH, Bokaie BB, Adkins SE. Empagliflozin in the treatment of type 2 diabetes: evidence to date. *Drug Des Dev Ther.* 2015;9:5793–803.
- van Baar M, van Ruiten C, Muskiet MHA, van Bloemendaal L, IJzerman RG, van Raalte D. SGLT2 Inhibitors in Combination Therapy: From Mechanisms to Clinical Considerations in Type

- 2 Diabetes Management. *Diabetes Care*. 2018;41(8):1543–56. doi:10.2337/dc18-0588.
15. Fioretto P, Giaccari A, Sesti G. Efficacy and safety of dapagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in diabetes mellitus. *Cardiovasc Diabetol*. 2015;14(1):142. doi:10.1186/s12933-015-0297-x.
 16. Moses RG, Colagiuri S, Pollock C. SGLT2 inhibitors: New medicines for addressing unmet therapeutic needs in type 2 diabetes. *Aust Med J*. 2014;7(10):405–20. doi:10.21767/amj.2014.2181.
 17. Desouza CV, Gupta N, Patel A. Cardiometabolic Effects of a New Class of Antidiabetic Agents. *Clin Ther*. 2015;37(6):1178–94. doi:10.1016/j.clinthera.2015.02.016.
 18. Zinman B, Wanner C, Lachin JM. Empagliflozin gliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–28.
 19. Zurek AM, Yendapally R, Urteaga EM. A Review of the Efficacy and Safety of Sodium–Glucose Cotransporter 2 Inhibitors: A Focus on Diabetic Ketoacidosis. American Diabetes Association; 2017. Available from: <https://dx.doi.org/10.2337/ds16-0030>. doi:10.2337/ds16-0030.
 20. Handelsman Y, Bloomgarden ZT, Grunberger G, Umpierrez G, Zimmerman RS, Bailey TS, et al. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. *Endocr Pract*. 2015;21(Suppl 1):1–87.
 21. Watts NB, Bilezikian JP, Usiskin K, Edwards R, Desai M, Law G, et al. Effects of Canagliflozin on Fracture Risk in Patients With Type 2 Diabetes Mellitus. *J Clin Endocrinol Metab*. 2016;101(1):157–66. doi:10.1210/jc.2015-3167.
 22. Bailey CJ, Iqbal N, T'joen C, List JF. Dapagliflozin monotherapy in drug-naïve patients with diabetes: a randomized-controlled trial of low-dose range. *Diabetes Obes Metab*. 2012;14(10):951–9. doi:10.1111/j.1463-1326.2012.01659.x.
 23. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2010;375(9733):2223–33. doi:10.1016/s0140-6736(10)60407-2.
 24. Strojek K, Yoon KH, Hrubá V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2011;13(10):928–38. doi:10.1111/j.1463-1326.2011.01434.x.
 25. Yang T, Lu M, Ma L, Zhou Y, Cui Y. Efficacy and tolerability of canagliflozin as add-on to metformin in the treatment of type 2 diabetes mellitus: A meta-analysis. *Eur J Clin Pharmacol*. 2015;71:1325–32.
 26. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ, et al. Empagliflozin gliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: A randomised, double-blind, placebo-controlled. *Lancet Diabetes Endocrinol*. 2013;1:208–19.
 27. Hollander P, Hill J, Johnson J, Jiang ZW, Golm G, Huyck S, et al. Results of VERTIS SU extension study: safety and efficacy of ertugliflozin treatment over 104 weeks compared to glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Curr Med Res Opin*. 2019;35(8):1335–43. doi:10.1080/03007995.2019.1583450.
 28. Cefalo CMA, Cinti F, Moffa S, Impronta F, Sorice GP, Mezza T, et al. Sotagliflozin, the first dual SGLT inhibitor: current outlook and perspectives. *Cardiovasc Diabetol*. 2019;18(1):1–4. doi:10.1186/s12933-019-0828-y.
 29. Markham A, Keam SJ. Sotagliflozin: First Global Approval. *Drugs*. 2019;79(9):1023–9. doi:10.1007/s40265-019-01146-5.
 30. Wiviott SD, Raz I, Bonaca MP. Dapagliflozin and cardiovascular outcomes in Type 2 diabetes. *N Engl J Med*. 2019;380(4):347–57.
 31. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Eng J Med*. 2017;377(7):644–57. doi:10.1056/nejmoa1611925.
 32. Raschi E, Poluzzi E, Fadini GP, Marchesini G, Ponti FD. Observational research on sodium glucose co-transporter-2 inhibitors: A real breakthrough? *Diabetes Obes Metab*. 2018;20(12):2711–23. doi:10.1111/dom.13468.
 33. Fadini GP, Solini A, Manca ML, Penno G, Gatti A, Anichini R, et al. Effectiveness of dapagliflozin versus comparators on renal endpoints in the real world: A multicentre retrospective study. *Diabetes Obes Metab*. 2019;21(2):252–60. doi:10.1111/dom.13508.
 34. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393(10166):31–9. doi:10.1016/s0140-6736(18)32590-x.
 35. Mearns ES, Sobieraj DM, White CM, Saulsberry WJ. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. *PLoS One*. 2015;10(4):e0125879. doi:10.1371/journal.pone.0125879.
 36. Cefalu WT, Stenlöf K, Leiter LA, Wilding JPH, Blonde L, Polidori D. Effects of canagliflozin on body weight and relationship to HbA1c and blood pressure changes in patients with type 2 diabetes. *Diabetologia*. 2015;58(6):1183–7. doi:10.1007/s00125-015-3547-2.
 37. Mearns ES, Sobieraj DM, White CM, Saulsberry WJ, Kohn CG, Doleh Y, et al. Comparative Efficacy and Safety of Antidiabetic Drug Regimens Added to Metformin Monotherapy in Patients with Type 2 Diabetes: A Network Meta-Analysis. *PLOS ONE*. 2015;10(4):e0125879. doi:10.1371/journal.pone.0125879.
 38. Lytvyn Y, Škrčić M, Yang GK, Yip PM, Perkins BA, Cherney DZI. Glycosuria-mediated urinary uric acid excretion in patients with uncomplicated type 1 diabetes mellitus. *Am J Physiol Renal Physiol*. 2015;308(2):F77–F83. doi:10.1152/ajprenal.00555.2014.
 39. Tahara A, Kurosaki E, Yokono M, Yamajuku D, Kihara R, Hayashizaki Y. Effects of sodium-glucose cotransporter 2 selective inhibitor ipragliflozin on hyperglycaemia, oxidative stress, inflammation and liver injury in streptozotocin-induced type 1 diabetic rats. *J Pharm Pharmacol*. 2014;66(7):975–87. doi:10.1111/jphp.12223.
 40. FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. 2015 [3/1/16]. Available from: <http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm>.
 41. U.S. Food and Drug Administration. [(Accessed on 1 June 2019)]. Available from: <https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-strengthens-kidney-warnings-diabetes-medicines-canagliflozin-invokana-invokamet-and>.
 42. FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. Available from: <http://www.fda.gov/Drugs/DrugSafety/ucm461449.htm>.
 43. Cheungpasitporn W, Srivali N, Thongprayoon C, Ungprasert P. Acute pancreatitis in the use of canagliflozin: A rare side-effect of the novel therapy for type 2 diabetes mellitus. *J Basic Clin Pharm*. 2015;6(3):101. doi:10.4103/0976-0105.160753.
 44. U.S. Food & Drug Administration (2017) FDA Drug Safety Communication: FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). Available from: <https://www.fda.gov/downloads/Drugs/DrugSafety/UCM558427.pdf>.
 45. Administration USFD, editor. FDA removes Boxed Warning about risk of leg and foot amputations for the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR); 2020. Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin>. Accessed 26.

Author biography

Ingale Nikita S, Assistant Professor

Turankar Avinash V, Associate Professor

Wagh Mitali S, Junior Resident 2

Motghare Vijay M, Professor and Head

Cite this article: Nikita S I, Avinash V T, Mitali S W, Vijay M M. Current status of Sodium-Glucose Co-Transporter Type 2 (SGLT2) inhibitors in treating diabetes mellitus. *Indian J Pharm Pharmacol* 2021;8(1):10-16.