MMJ

Malta Medical Journal, 2024; 36(1)
http://mmsjournals.org/index.php/mmj/39

REVIEW ARTICLE

Emerging Trends in Diabetes: An Update on the Role of Sodium-Glucose Co-Transporter 2 Inhibitors

Desiree Seguna, Stephen Fava

The incidence of type 2 diabetes mellitus continues to rise world-wide, highlighting the need for better treatment of this condition. The last few decades have seen the emergence of several new anti-diabetic agents. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are novel oral hypoglycaemic agents that have only recently been added to the local government formulary list. We hereby discuss the mechanism of action of this oral class of agents and highlight their role and indications in clinical practice. This review provides a detailed summary of the available cardiovascular outcome trials and how these recommendations have been included in the most recent international guidelines. Finally we highlight the adverse events and contraindications of this class of agents and discuss possible future roles for SGLT-2 inhibitors.

Desiree Seguna
MD, MRCP(UK), MSc
Department of Diabetes & Endocrinology,
Mater Dei Hospital,
Msida, Malta

Stephen Fava
MD, MRCP(UK), FACP, FEFIM, FRCP, MPhil, PhD
Department of Diabetes & Endocrinology,
Mater Dei Hospital,
Msida, Malta

Diabetes poses an ongoing threat to health and economy. According to the International Diabetes Federation (IDF), the estimated prevalence of type 1 (T1D) and type 2 diabetes (T2D) in people aged 20-79 years has risen from 4.6% of the global population in the year 2000 to 9.3% in the year 2019.[1]

The treatment of T2D is challenging, with early diagnosis and access to appropriate care being pivotal to the management of the disease and prevention of secondary complications. T2D is characterised by progressive β-cell failure requiring intensification of treatment. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are novel oral hypoglycaemic agents that block the SGLT2 co-transporter located in the proximal renal tubule. Consequently, these agents lower serum glucose by enhancing its excretion and by blocking its reabsorption from urine. The results are improved glycaemic control and reductions in blood pressure and weight. The glucose-lowering activity of SGLT2 inhibitors is proportional to the ambient glucose levels and the estimated glomerular filtration rate (eGFR). Therefore, greater losses of glucose take place in patients with hyperglycaemia, whereas in patients with euglycaemia the response to treatment is attenuated leading to a lower incidence of hypoglycaemia.

As with any novel treatment, their safety profile remains under rigorous assessment. At present, concerns have arisen around the risk of amputation,

diabetic ketoacidosis (DKA), acute kidney injury (AKI), urinary tract infections (UTIs), bone fractures and cancer. It is hence important that patients are carefully selected based on pre-existing risk factors and foreseeable benefits of treatment.

CLINICAL BENEFITS & INDICATIONS

The sodium glucose co-transporter 2 is expressed in the renal proximal tubule where it reabsorbs ~90% of the filtered glucose load.[2] SGLT2 receptor inhibitors are novel glucose-lowering agents which improve hyperglycaemia by promoting renal excretion of glucose. Their glucose lowering effect is non-insulin mediated and is limited by the filtered load of glucose and the osmotic diuresis that ensues.[2]

Their usefulness in clinical practice can be described in terms of their various outcomes.

Glycaemic Efficacy

SGLT2 inhibitors have modest glucose-lowering effects. Meta-analyses comparing them with placebo found that SGLT2 inhibitors reduced HbA1c by up to an additional 0.7%.[3-6]A systematic review showed that the combination of metformin plus SGLT2 inhibitors lowered HbA1c by a further 0.61% compared with metformin alone.[7]

Weight Loss

The resulting glucosuria results in a net loss of 200–300 kcal/day.[2,8] A reduction in body weight follows the depletion of hepatic glycogen stores, as well as the water loss resulting from the accompanying osmotic diuresis. In the longer term, loss of mesenteric and subcutaneous adipose tissue further contributes to weight loss.[9] A meta-analysis comparing SGLT2 inhibitors with placebo, demonstrated a mean weight reduction of 2.99 kg at two years in the SGLT2 inhibitors group.[6] Compared with metformin monotherapy, the combination of metformin and SGLT2 inhibitors resulted in an additional weight reduction of 2.0 kg.[7]

In insulin-treated patients, the addition of an SGLT2 inhibitor decreased the total daily insulin requirement, mitigating the insulin-associated weight gain.[10] The combination of insulin plus dapagliflozin was associated with a weight reduction of 0.9-1.4 kg, compared to insulin plus placebo, which resulted in weight gain.[11]

The DEPICT-1[10] and DEPICT-2[12] (Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes) trials, evaluated the long-term safety and efficacy of dapagliflozin as an adjunct to insulin in patients with inadequately controlled type 1 diabetes (T1D). Compared with placebo, dapagliflozin led to significant reductions in total daily insulin dose requirements, HbA1c and weight.[10] Dapagliflozin became the first oral medication approved by the National Institute for Health and Clinical Excellence (NICE) as an adjunct to insulin, for the treatment of inadequately controlled T1D in adults with a BMI ≥ 27 kg/m^2.[13] However, in November 2021 NICE withdrew this licence.

Cardiovascular Outcomes

Atherosclerotic Cardiovascular Disease (ASCVD)

Following concerns of a higher risk of myocardial infarction (MI) conferred by rosiglitazone[14], the US Food and Drug Administration (FDA) issued a guidance for industry to perform cardiovascular outcomes trials (CVOTs) for new drugs intended to improve glycaemic control in T2D.[15] In line with this, a number of long-term prospective CVOTs have subsequently been undertaken and published.

The EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcomes and Mortality in Type 2 Diabetes) assessed the effect of empagliflozin vs placebo on cardiovascular outcomes in patients with T2D and established ASCVD. Empagliflozin reduced the risk of major adverse cardiovascular events (MACE) (a composite endpoint of death from cardiovascular causes, non-fatal MI and non-fatal stroke) by 14%, cardiovascular death by 38% and all-cause mortality by 32%. Unlike glucagon-like peptide-1 receptor agonists (GLP-1RA), the reduction in the risk of MACE with empagliflozin was almost exclusively accounted for by the effect on the cardiovascular death component, as empagliflozin did not reduce non-fatal MI or non-fatal stroke.[16]

In the CANVAS Program (Canagliflozin Cardiovascular Assessment Study and Canagliflozin Cardiovascular Assessment Study - Renal), treatment with canagliflozin significantly reduced the risk of MACE (cardiovascular death, non-fatal MI and non-fatal stroke), which was recorded in 26.9 vs 31.5 participants per 1,000 patient-years of the canagliflozin and placebo groups, respectively. Treatment with canagliflozin was, however, associated with an increased risk of amputation (6.3 vs 3.4 participants per 1,000 patient-years).[17] In the CREDENCE (Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation) trial, treatment with canagliflozin was again associated with a lower composite risk of

cardiovascular death, non-fatal MI, or non-fatal stroke.[18]

The DECLARE-TIMI 58 study (Dapagliflozin Effect on Cardiovascular Events Thrombolysis in Myocardial Infarction), assessed the effects of dapagliflozin vs placebo on cardiovascular and renal outcomes in patients with T2D and established ASCVD or multiple risk factors for ASCVD.[19] Dapagliflozin was non-inferior to placebo with regards to MACE (cardiovascular death, non-fatal MI and non-fatal stroke), but reduced a composite of cardiovascular death and hospitalisation for heart failure. This was largely driven by a lower rate of hospitalisation for heart failure as there was no difference in cardiovascular death between the groups. Compared with the EMPA-REG OUTCOME trial[16] and the CANVAS Program[17], the DECLARE-TIMI 58 trial had a lower fraction of participants with established ASCVD and a greater proportion of patients with multiple risk factors for ASCVD, possibly partly explaining the differences in ASCVD outcomes.[19] In a sub-analysis of the primary trial, dapagliflozin decreased cardiovascular outcomes.[20]

The VERTIS CV trial, compared ertugliflozin to placebo in patients with T2D and prevalent CVD disease. Ertugliflozin was associated with a reduction in hospitalisation for heart failure but was non-superior to placebo with regards to death from cardiovascular causes, non-fatal MI, or non-fatal stroke.[21]

Heart Failure

A reduced incidence of heart failure has been reported with the use of empagliflozin,[16,22] canagliflozin[17], dapagliflozin[19]and ertugliflozin.[21]

In EMPA-REG OUTCOME trial, treatment with empagliflozin was accompanied by a 35% reduction in hospitalisation for heart failure when compared with placebo.[16] Similarly, the CANVAS Program[17] and DECLARE-TIMI 58 trial[19]reported reductions in rates of hospitalisation for heart failure of 33% and 27% with canagliflozin and dapagliflozin, respectively. Additional data from the CREDENCE trial with canagliflozin, showed a 39% reduction in hospitalisation for HF.[18]

The majority of patients in all of these study populations did not have HF at baseline (rates of HF 10-14%).[23] However, a subsequent report from the EMPA-REG OUTCOME trial confirmed that empagliflozin consistently improved HF outcomes in patients with and without a previous history of HF.[22]

The DAPA-HF study (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), was conducted in patients with pre-existing heart failure (New York Heart Association [NYHA] class II, III, or IV) and an ejection fraction of <40%. Fifty-eight % of participants did not have a history of T2D. Over a median of 18.2 months, the primary outcome (a composite of worsening HF necessitating hospitalisation or intravenous therapy, or cardiovascular death) occurred in 16.3% vs 21.2% of participants in the dapagliflozin and placebo group, respectively. This effect was consistent, irrespective of the presence or absence of T2D.[24]

The EMPEROR-Reduced trial compared the effects of empagliflozin with placebo in patients with HF and a reduced ejection fraction (HFrEF), with or without diabetes and who were already on standard care for HF. Over 16 months, the primary outcome event (a composite of hospitalisation for worsening HF or cardiovascular death) occurred in 19.4% vs 24.7% of patients in the empagliflozin and placebo group, respectively. This effect was consistent irrespective of the presence or absence of T2D. Compared with placebo, empagliflozin also reduced total HF hospitalisations and adverse renal outcomes.[25]

The DAPA-HF[24] and EMPEROR-reduced[25] trials, extend the benefits of SGLT2 inhibitors in patients with HFrEF but *without* diabetes. The exact mechanisms underlying the reduction in HF hospitalisations with SGLT2 inhibitors remain to be elucidated but cannot only be explained by the modest glucose, weight and blood pressure lowering effects of this class of drugs.

The EMPEROR-preserved trial looked at the effect of empagliflozin on morbidity and mortality, in patients with or without T2D and HF with preserved ejection fraction (HFpEF).[26] Empagliflozin brought about a reduction in cardiovascular death and hospitalisation for heart failure in patients with HFpEF, regardless of the presence or absence of T2D.[26]

In the VERTIS CV trial, rates of hospitalisation for heart failure were lower with ertugliflozin compared to placebo, at 2.5% vs 3.6% respectively.[21]

Renal Outcomes

Initial data on canagliflozin from the CANVAS Program suggested a beneficial effect of canagliflozin compared with placebo on progression of albuminuria and a composite of reduction in eGFR, need for renal replacement therapy or death from renal causes.[17] These findings did not, however, reach statistical significance. Subsequently, the CREDENCE

study was designed to specifically assess the effects of canagliflozin on renal outcomes in patients with T2D and albuminuric stage 3 chronic kidney disease (CKD).[18] Compared with placebo, canagliflozin showed a risk reduction of 30% in a composite renal endpoint of a) end-stage kidney disease (dialysis, transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2), b) doubling of serum creatinine, c) or death from cardiovascular or renal causes. The trial was stopped early due to conclusive evidence of efficacy.

The EMPA-REG OUTCOME trial, showed that compared with placebo, empagliflozin reduced the risk of incident or worsening nephropathy (defined as a composite of urine albumin creatinine ratio (UACR) > 300 mg/g, doubling of serum creatinine, end-stage renal disease [ESRD], or death from ESRD) by 39%.[27]

In the VERTIS CV trial there was no statistically significant reduction in the composite renal endpoint (renal replacement therapy, doubling of serum creatinine, death from renal causes) in the ertugliflozin group. However, the trend was similar to that seen with other SGLT2 inhibitors.[21]

In the DECLARE-TIMI 58 study, the renal outcome (a composite of a sustained decrease of 40% or more in eGFR to <60 mL/min, new ESRD, or death from renal or cardiovascular causes), occurred in 4.3% and 5.6% of patients in the dapagliflozin and placebo group, respectively.[19]

The DAPA-CKD trial investigated the effect of dapagliflozin on renal outcomes in patients with CKD, with or without T2D. The primary outcome (a composite of sustained decline in eGFR of ≥50%, ESRD, or death from renal or cardiovascular causes), occurred in 9.2% vs 14.5% of patients in the dapagliflozin and placebo group, respectively.[28] This trial suggests a role for SGLT2 inhibitors in reducing renal outcomes in patients with, as well as *without* T2D.

ADVERSE EVENTS & CONTRAINDICATIONS

Amputations

The CANVAS Program reported a two-fold risk of lower limb amputations (mainly toe and midfoot) in the canagliflozin group compared with placebo.[17] Those most at risk had a previous history of amputation, peripheral vascular disease, or neuropathy. The CREDENCE trial, however, showed no significant increase in lower limb amputations.[18]Likewise, a *post hoc* analysis of the EMPA-REG OUTCOME trial, showed no increased risk of lower limb amputation.[29]

A pharmacovigilance study using the WHO global database of individual case safety reports (VigiBase), reported an increased risk of toe amputations with canagliflozin, empagliflozin, and dapagliflozin (proportional reporting ratios 7.09, 4.96, and 2.62 respectively).[30] In view of these concerns, SGLT2 inhibitors should be avoided in high-risk patients.

Diabetic Ketoacidosis (DKA)

SGLT2 inhibitors–associated DKA, has been reported in patients with both T1D and T2D.[31] It may be accompanied by euglycaemia, in which case delayed recognition often ensues. Serum or urine ketones should be checked in patients taking SGLT2 inhibitors presenting with nausea, vomiting, malaise or a metabolic acidosis.

In a review of patients with T1D taking SGLT2 inhibitors, 5% developed DKA while 10% developed ketosis.[31] In patients with T2D, DKA rates ranged from 0.16-0.76 events per 1,000 patient-years.[32,33] The CREDENCE trial, reported an increased risk for DKA at 2.2 events per 1,000 patient-years in the canagliflozin group, compared with 0.2 events per 1,000 patient-years with placebo.[18]The risk of DKA is higher amongst patients who have been on SGLT2 inhibitors for >52 weeks and in those aged ≥60 years.[34]

The FDA issued a warning for SGLT2 inhibitors-induced DKA and recommends stopping temporarily before planned surgery.[35] The Scottish Intercollegiate Guidelines Network (SIGN) also recommends temporary withdrawal in high-risk patients including those with low endogenous insulin secretion, states of increased insulin requirement (alcohol misuse, illness or surgery) or dehydration.[8] The European Medicines Authority (EMA) recommended listing DKA as a rare adverse reaction.[36]

Hypoglycaemia

Since the effects of SGLT2 inhibitors are independent of pancreatic β-cell function, this class of agents pose a low risk of hypoglycaemia. However, when combined with hypoglycaemic agents such as insulin or insulin secretagogues, SGLT2 inhibitors may then potentiate the risk of hypoglycaemia.[4] A meta-analysis found no difference in hypoglycaemia risk between metformin and SGLT2 inhibitors monotherapy.[7]

Genitourinary Tract Infections

An increased incidence of genitourinary tract infections has been reported with SGLT2 inhibitors, with odds ratios ranging from 3.21 (95% CI, 2.08-4.93)

for dapagliflozin 2.5 mg to 5.23 (95% CI, 3.86-7.09) for canagliflozin 300 mg.[37] This did not, however, translate into a higher risk of serious or upper urinary tract infections.[38] A previous history of genital fungal infection conferred a higher risk of same with dapagliflozin.[39]

Following 55 reports of Fournier's gangrene, the FDA issued a warning on necrotizing fasciitis of the perineum in patients taking SGLT2 inhibitors.[40]

Hypotension

Studies with SGLT2 inhibitors have reported significant reductions in both systolic and diastolic blood pressures of −4.0 mmHg (95% CI, −4.4 to −3.5) and -1.6 mmHg (0.88-3.5 mmHg) respectively.[41] Initial reductions in BP are likely secondary to the osmotic diuresis and subsequent reduction in intravascular volume.[42] Long-term reductions in BP are likely to result from inhibition of the renin-angiotensin aldosterone system or from the accompanying weight loss.[42] This effect is augmented in older patients and in patients on diuretics, ACEIs or ARBs, resulting in an increased risk of symptomatic hypotension.[43]

Acute Kidney Injury

From March 2013 to October 2015, the FDA received 101 reports of AKI in patients on dapagliflozin and canagliflozin, some of which necessitating hospitalisation and dialysis.[44] Around 50% of cases occurred within one month of commencing treatment and discontinuation led to improvements in eGFR in most cases. It is unknown whether patients had pre-existing CKD. An analysis by Nadkami *et al.* did not report an increased risk of AKI with SGLT2 inhibitors use.[45]

Renal function should be assessed prior to commencement of treatment and should be monitored thereafter. SGLT2 inhibitors should not be used for the treatment of hyperglycaemia in patients with an eGFR <45 mL/minute/1.73 m^2[46] Cautious use is warranted in high-risk patients with HF, liver failure, evidence of hypovolaemia or patients taking diuretics, NSAIDs, ACEI or ARBs.[46]

Bladder Cancer

There is no long-term safety data on the effects of the glucosuria accompanying SGLT2 inhibitors. There was a suggestion that some SGLT2 inhibitors may increase the risk of bladder cancer, particularly empagliflozin. These findings did not, however, reach statistical significance.[48] Initial data on dapagliflozin hinted to a possible increased risk of bladder and breast cancer[48], however, data from the DECLARE-TIMI 58 trial did not support this finding.[19]

Bone Fracture

There is conflicting evidence on the incidence of fractures with SGLT2 inhibitors therapy. In the CANVAS Program, fracture rates were 26% higher with canagliflozin compared with placebo.[17] However, the CREDENCE trial did not show significant differences in rates of fracture between canagliflozin and placebo.[18]A meta-analysis found similar fracture rates with canagliflozin, empagliflozin and dapagliflozin, at around 1.59% vs 1.56% in controls. The events, however, did not reach statistical significance.[47]

Use of canagliflozin has been associated with increased bone turnover markers and decreased total hip bone mineral density.[49,50] Falls resulting from secondary hypotension may contribute to fracture risk.[17]

GUIDELINE RECOMMENDATIONS

In the light of the compelling evidence provided by the CVOTs, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) issued a 2019 update on the "Management of hyperglycaemia in type 2 diabetes".[51] In its statement, the ADA/EASD recommended the use of SGLT2 inhibitors (or GLP-1 receptor analogues) in patients with T2D and established ASCVD.[51] The ADA/EASD further stated that the level of evidence for SGLT-2 inhibitors in T2D was greatest in patients with or without established ASCVD, but with HFrEF (EF <45%) or CKD (eGFR 30 to <60 mL/ min/1.73 m^2 or UACR >30 mg/g (and particularly >300 mg/g).[51]

In patients with T2D and HF (particularly those with HFrEF), SGLT2 inhibitors are recommended in order to reduce HF, MACE, and CV death.[51] In patients with T2D and CKD, SGLT2 inhibitors are recommended to prevent CKD progression, HF, MACE, and CV death.[51] The ADA/EASD recommends initial treatment with lifestyle therapy and metformin, unless contraindicated or not tolerated.[51] This should be followed by the addition of an SGLT2 inhibitors (or GLP-1 receptor analogue) with proven cardiovascular benefit, independent of HbA_{1c}.[51] Use in patients at high risk for amputation or with foot ulcers should only take place following careful, shared decision-making and comprehensive foot care education.[51]

The 2020 consensus statement by the American Association of Clinical Endocrinology (AACE) and the

American College of Endocrinology (ACE), states that in the presence of ASCVD (established or at high risk for), CKD stage 3, or HFrEF, SGLT2 inhibitors (or long acting GLP-1 receptor analogues) with proven efficacy may be preferred over metformin as initial therapy, irrespective of glycaemic control.[52]

According to SIGN, SGLT2 inhibitors with proven cardiovascular benefits can be added to metformin in patients with T2D and established ASCVD.[8]

NICE recommends the use of SGLT2 inhibitors as monotherapy in adults with T2D when metformin is contraindicated or not tolerated and lifestyle interventions fail AND only if a DPP-4 inhibitor would otherwise be prescribed AND a sulfonylurea or pioglitazone is not appropriate.[53]

PRESCRIBING PATTERNS

Following the emergence of compelling evidence from CVOTs, many international bodies have updated their guidelines to clearly define the role of novel agents in the management of T2D.[51,52]

Metformin, alongside lifestyle interventions, remains the preferred initial choice of therapy, unless contraindicated or not tolerated.[8,51-54] Prescribing trends for metformin are hence unlikely to change. On the other hand, prescriptions for sulfonylureas have decreased substantially from 53% in 2010 to 29% in 2017.[55]

In selected high-risk patients, 2020 guidelines recommend SGLT2 inhibitors or long-acting GLP-1 receptor analogues, independent of glycaemic control.[51,52] We hope that this will translate in increased and earlier prescribing of these medications in clinical practice. It is important to note that when combined with insulin or sulfonylureas, SGLT2 inhibitors may potentiate the risk of hypoglycaemia.[4] Therefore, the combination of SGLT2 inhibitors and insulin should be accompanied by a reduction in the total daily dose of insulin prescribed.[10] Given the modest glycaemic effect of SGLT2 inhibitors, it is very unlikely that their use will, however, allow complete cessation of previously established insulin therapy.[7]

LOCAL PERSPECTIVE

SGLT2 inhibitors have recently been added to the Maltese government formulary list for use in T2D patients with an HbA1c between 7% and 10% despite treatment with metformin, sulfonylurea or repaglinide. Patients must have either established ASCVD, HF or CKD (defined as diabetes with micro/macroalbuminuria or an eGFR <60 mL/min/1.73m^2, or both) OR a body mass index (BMI) >30 kg/m^{2}in patients who need to lose weight or in whom weight gain minimisation is necessary.[56]

FUTURE DIRECTIONS

SGLT2 inhibitors have demonstrated a clear benefit in patients with cardiorenal disease, however, they are associated with only modest improvements in glycaemia. They are costly and long-term safety implications of glucosuria are unknown. Monitoring for peripheral vascular disease, urogenital infections, hypovolaemia and decline in renal function, needs to be ongoing.[57]

Evolving data has suggested a role for SGLT2 inhibitors in the treatment of patients with HFrEF[24,25] or CKD[28] but *without* diabetes. The EMPEROR-preserved has furthered our knowledge into the role of SGLT2 inhibitors in patients with or without diabetes and HFpEF.[26] Future studies are needed to understand the role of SGLT2 inhibitors in patients with T2D but *without* established cardiorenal disease.

REFERENCES

1. Williams R, Karuranga S, Malanda B, Saeedi P, Basit A, Besançon S, Bommer C, Esteghamati A, Ogurtsova K, Zhang P, Colagiuri S. Global and regional estimates and projections of diabetes-related health expenditure: Results from the International Diabetes Federation Diabetes Atlas. Diabetes research and clinical practice. 2020 Apr 1;162:108072.
2. Alicic RZ, Neumiller JJ, Johnson EJ, Dieter B, Tuttle KR. Sodium–glucose cotransporter 2 inhibition and diabetic kidney disease. Diabetes. 2019 Feb 1;68:(2)248-57.

3. Musso G, Gambino R, Cassader M, Pagano G. A novel approach to control hyperglycemia in type 2 diabetes: Sodium glucose co-transport (SGLT) inhibitors. Systematic review and meta-analysis of randomized trials. Annals of medicine. 2012 Jun 1;44:(4)375-93.
4. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, Sarigianni M, Matthews DR, Tsapas A. Sodium–glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Annals of internal medicine. 2013 Aug 20;159:(4)262-74.
5. Sun YN, Zhou Y, Chen X, Che WS, Leung SW. The efficacy of dapagliflozin combined with hypoglycaemic drugs in treating type 2 diabetes mellitus: meta-analysis of randomised controlled trials. BMJ open. 2014 Apr 1;4:(4)e004619.
6. Liu XY, Zhang N, Chen R, Zhao JG, Yu P. Efficacy and safety of sodium–glucose cotransporter 2 inhibitors in type 2 diabetes: a meta-analysis of randomized controlled trials for 1 to 2 years. Journal of Diabetes and its Complications. 2015 Nov 1;29:(8)1295-303.
7. Bolen S, Tseng E, Hutfless S, Segal JB, Suarez-Cuervo C, Berger Z, Wilson LM, Chu Y, Iyoha E, Maruthur NM. Diabetes medications for adults with Type 2 diabetes: an update.
8. Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of glycaemic control in people with type 2 diabetes. [Internet] 2017 [cited 2022 April 4]. Available from: https://www.sign.ac.uk/media/1090/signpdf
9. Thomas MC, Cherney DZ. The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure. Diabetologia. 2018 Oct;61:(10)2098-107.
10. Dandona P, Mathieu C, Phillip M, Hansen L, Tschöpe D, Thorén F, Xu J, Langkilde AM. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: the DEPICT-1 52-week study. Diabetes Care. 2018 Dec 1;41:(12)2552-9.
11. Wilding JP, Woo V, Rohwedder K, Sugg J, Parikh S, Dapagliflozin 006 Study Group. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. Diabetes, Obesity and Metabolism. 2014 Feb;16:(2)124-36.
12. Mathieu C, Dandona P, Gillard P, Senior P, Hasslacher C, Araki E, Lind M, Bain SC, Jabbour S, Arya N, Hansen L. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 study): 24-week results from a randomized controlled trial. Diabetes care. 2018 Sep 1;41:(9)1938-46.
13. National Institute of Health and Care Excellence (NICE). Dapagliflozin with insulin for treating type 1 diabetes. [Internet]. 2019 [cited 2022 April 4]. Available from: https://www.nice.org.uk/guidance/ta597
14. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. New England Journal of Medicine. 2007 Jun 14;356:(24)2457-71.
15. Food and Drug Administration (FDA). Guidance for industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. [Internet]. 2008 [cited 2022 April 4]. Available from: https://www.federalregister.gov/documents/2008/12/19/E8-30086/guidance-for-industry-on-diabetes-mellitus-evaluating-cardiovascular-risk-in-new-antidiabetic
16. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015 Nov 26;373:(22)2117-28.
17. Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. New England Journal of Medicine. 2017 Aug 17;377:(7)644-57.
18. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. New England Journal of Medicine. 2019 Jun 13;380:(24)2295-306.

19. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine. 2019 Jan 24;380:(4)347-57.
20. Furtado RH, Bonaca MP, Raz I, Zelniker TA, Mosenzon O, Cahn A, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes mellitus and previous myocardial infarction: subanalysis from the DECLARE-TIMI 58 trial. Circulation. 2019 May 28;139:(22)2516-27.
21. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, Charbonnel B, Frederich R, Gallo S, Cosentino F, Shih WJ. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. New England Journal of Medicine. 2020 Oct 8;383:(15)1425-35.
22. Fitchett D, Butler J, van de Borne P, Zinman B, Lachin JM, Wanner C, Woerle HJ, Hantel S, George JT, Johansen OE, Inzucchi SE. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial. European heart journal. 2018 Feb 1;39:(5)363-70.
23. Vaduganathan M, Januzzi Jr JL. Preventing and treating heart failure with sodium-glucose co-transporter 2 inhibitors. The American Journal of Medicine. 2019 Oct 1;132:(10)S21-9.
24. McMurray JJ, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M. Dapagliflozin in patients with heart failure and reduced ejection fraction. New England Journal of Medicine. 2019 Nov 21;381:(21)1995-2008.
25. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W. Cardiovascular and renal outcomes with empagliflozin in heart failure. New England Journal of Medicine. 2020 Oct 8;383:(15)1413-24.
26. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner–La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, Giannetti N. Empagliflozin in heart failure with a preserved ejection fraction. New England Journal of Medicine. 2021 Oct 14;385:(16)1451-61.
27. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B. Empagliflozin and progression of kidney disease in type 2 diabetes. New England Journal of Medicine. 2016 Jul 28;375:(4)323-34.
28. Heerspink HJ, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JF, McMurray JJ, Lindberg M, Rossing P, Sjöström CD. Dapagliflozin in patients with chronic kidney disease. New England Journal of Medicine. 2020 Oct 8;383:(15)1436-46.
29. Inzucchi SE, Iliev H, Pfarr E, Zinman B. Empagliflozin and assessment of lower-limb amputations in the EMPA-REG OUTCOME trial. Diabetes Care. 2018 Jan 1;41:(1)e4-5.
30. Khouri C, Cracowski JL, Roustit M. SGLT-2 inhibitors and the risk of lower-limb amputation: is this a class effect?. Diabetes, Obesity and Metabolism. 2018 Jun;20:(6)1531-4.
31. Fadini GP, Bonora BM, Avogaro A. SGLT2 inhibitors and diabetic ketoacidosis: data from the FDA Adverse Event Reporting System. Diabetologia. 2017 Aug;60:(8)1385-9.
32. Umpierrez GE. SGLT2 inhibitors and diabetic ketoacidosis—a growing concern. Nature Reviews Endocrinology. 2017 Aug;13:(8)441-2.
33. Erondu N, Desai M, Ways K, Meininger G. Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. Diabetes care. 2015 Sep 1;38:(9)1680-6.
34. Liu J, Li L, Li S, Wang Y, Qin X, Deng K, Liu Y, Zou K, Sun X. Sodium-glucose co-transporter-2 inhibitors and the risk of diabetic ketoacidosis in patients with type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. Diabetes, Obesity and Metabolism. 2020 Sep;22:(9)1619-27.
35. US Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. [Internet]. 2022 [cited 2022 April 4]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about-too-much-acid-blood-and-serious

36. European Medicines Agency, Pharmacovigilance Risk Assessment Committee (EMA)Assessmentreport. ProcedureunderArticle20ofRegulation(EC)No726/2004resultingfrompharmacovigilancedata-SGLT2inhibitors.[Internet].2016[cited2022April4].Availablefrom:https://www.ema.europa.eu/en/documents/referral/sglt2-inhibitors-article-20-procedure-assessment-report_en.pdf

37. LiD,WangT,ShenS,FangZ,DongY,TangH. Urinarytractandgenitalinfectionsinpatientswithtype2diabetestreatedwithsodium-glucoseco-transporter2inhibitors:ameta-analysisofrandomizedcontrolledtrials.Diabetes, ObesityandMetabolism.2017Mar;19:(3)348-55.

38. Nicolle LE, Capuano G, Fung A, Usiskin K. Urinary tract infection in randomized phase III studies of canagliflozin, a sodium glucose co-transporter 2 inhibitor. Postgraduate medicine. 2014 Jan 1;126:(1)7-17.

39. Thong KY, Yadagiri M, Barnes DJ, Morris DS, Chowdhury TA, Chuah LL, Robinson AM, Bain SC, Adamson KA, Ryder RE. Clinical risk factors predicting genital fungal infections with sodium–glucose cotransporter 2 inhibitor treatment: The ABCD nationwide dapagliflozin audit. Primary care diabetes. 2018 Feb 1;12:(1)45-50.

40. Bersoff-Matcha SJ, Chamberlain C, Cao C, Kortepeter C, Chong WH. Fournier gangrene associated with sodium–glucose cotransporter-2 inhibitors: a review of spontaneous postmarketing cases. Annals of Internal Medicine. 2019 Jun 4;170:(11)764-9.

41. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. Journal of the American Society of Hypertension. 2014 Apr 1;8:(4)262-75.

42. Peene B, Benhalima K. Sodium glucose transporter protein 2 inhibitors: focusing on the kidney to treat type 2 diabetes. Therapeutic advances in endocrinology and metabolism. 2014 Oct;5:(5)124-36.

43. Weir MR, Januszewicz A, Gilbert RE, Vijapurkar U, Kline I, Fung A, Meininger G. Effect of canagliflozin on blood pressure and adverse events related to osmotic diuresis and reduced intravascular volume in patients with type 2 diabetes mellitus. The Journal of Clinical Hypertension. 2014 Dec;16:(12)875-82.

44. US Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). [Internet]. 2022 [cited 2022 April 4]. Available from: https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-strengthens-kidney-warnings-diabetes-medicines-canagliflozin-invokana-invokamet-and

45. Nadkarni GN, Ferrandino R, Chang A, Surapaneni A, Chauhan K, Poojary P, Saha A, Ferket B, Grams ME, Coca SG. Acute kidney injury in patients on SGLT2 inhibitors: a propensity-matched analysis. Diabetes Care. 2017 Nov 1;40:(11)1479-85.

46. Dashora U, Gregory R, Winocour P, Dhatariya K, Rowles S, Macklin A, Rayman G, Nagi D, Whitehead K, Beba H, De P. Association of British Clinical Diabetologists (ABCD) and Diabetes UK joint position statement and recommendations for non-diabetes specialists on the use of sodium-glucose co-transporter 2 inhibitors in people with type 2 diabetes (January 2021). Clinical Medicine. 2021 May;21:(3)204.

47. Tang HL, Li DD, Zhang JJ, Hsu YH, Wang TS, Zhai SD, Song YQ. Lack of evidence for a harmful effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors on fracture risk among type 2 diabetes patients: a network and cumulative meta-analysis of randomized controlled trials. Diabetes, Obesity and Metabolism. 2016 Dec;18:(12)1199-206.

48. Lin HW, Tseng CH. A review on the relationship between SGLT2 inhibitors and cancer. International journal of endocrinology. 2014 Oct;2014.

49. Alba M, Xie J, Fung A, Desai M. The effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor, on mineral metabolism and bone in patients with type 2 diabetes mellitus. Current medical research and opinion. 2016 Aug 2;32:(8)1375-85.

50. Bilezikian JP, Watts NB, Usiskin K, Polidori D, Fung A, Sullivan D, Rosenthal N. Evaluation of bone mineral density and bone biomarkers in patients with type 2 diabetes treated with canagliflozin. The Journal of Clinical Endocrinology. 2016 Jan 1;101:(1)44-51.
51. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, D'Alessio DA, Davies MJ. 2019 update to: Management of hyperglycaemia in type 2 diabetes, A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2020 Feb 1;63:(2)221-8.
52. Garber AJ, Handelsman Y, Grunberger G, Einhorn D, Abrahamson MJ, Barzilay JI, Blonde L, Bush MA, DeFronzo RA, Garber JR, Garvey WT. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm–2020 executive summary. Endocrine Practice. 2020 Jan 1;26:(1)107-39.
53. National Institute of Health and Care Excellence (NICE). Canagliflflozin, dapagliflflozin and empagliflflozin as monotherapies for treating type 2 diabetes. [Internet]. 2016 [cited 2022 April 4]. Available from: https://www.nice.org.uk/guidance/ta390
54. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: Management. [Internet]. 2015 [cited 2022 April 4]. Available from: https://www.nice.org.uk/guidance/ng28
55. Dennis JM, Henley WE, McGovern AP, Farmer AJ, Sattar N, Holman RR, Pearson ER, Hattersley AT, Shields BM, Jones AG, MASTERMIND consortium. Time trends in prescribing of type 2 diabetes drugs, glycaemic response and risk factors: a retrospective analysis of primary care data, 2010–Diabetes, Obesity and Metabolism. 2019 Jul;21:(7)1576-84.
56. Outpatients Formulary List. [Internet] 2022 [cited 2022 April 4]. Available from: https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/GFL/outpatients_gfl_mar_pdf
57. Meraz-Muñoz AY, Weinstein J, Wald R. eGFR decline after SGLT2 inhibitor initiation: the tortoise and the hare reimagined. Kidney360. 2021 Jun 24;2:(6)1042-7.