Malta Medical Journal, 32 (2): Pages (2020)
http://mmsjournals.org/index.php/mmj

MMJ

REVIEW ARTICLE

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

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Type 2 diabetes mellitus is a progressive metabolic disorder. Marked hyperglycaemia leads to serious vascular complications. Hence, addressing this modifiable risk factor is of paramount importance. Sodium-glucose co-transporter 2 (SGLT2) inhibitors represent a relatively new class of antidiabetic agents. They offer an intermediate glucose-lowering effect and through other pleiotropic effects provide cardiac and renal benefits. This review focuses on the mechanism of action, benefits and adverse effects of SGLT2 inhibitors. The authors also delineate the ideal type 2 diabetic candidate to receive SGLT2 inhibitors. This is critical as SGLT2 inhibitors should not be used in a 'one-size-fits-all approach' but their use should be individualized based on certain patient characteristics. This patient-centred approach aims at maximizing the benefits and reduce the risks associated with SGLT2 inhibitors.

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Introduction

Type 2 diabetes mellitus is a complex metabolic disorder in which hyperglycaemia occurs as a result of a number of pathophysiological disturbances. DeFronzo refers to these pathophysiological processes as the ominous octet. These are summarized in Table 1.[1] Marked hyperglycaemia is associated with long term end organ damage due to microvascular and macrovascular complications.[2] Good glycaemic control reduces the risk of onset and progression of such complications.[3] However, achieving optimal glycaemic control remains a challenge. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a relatively new class of oral antidiabetic agents.[4] They offer a new strategy for achieving glycaemic control and have been associated with cardiovascular and renal-outcome benefits.[5] Despite their effectiveness in the treatment of type 2 diabetes, a number of adverse effects have been linked to SGLT2 inhibitors.[6] Hence, SGLT2 inhibitor therapy re-enforces the importance of personalized patient-centred management. The latter approach reduces the risks of adverse effects by the analysis of patient's characteristics prior to the prescription of such agents.[7]

The physiological actions of SGLT2 inhibitors

The kidneys play a pivotal role in glucose handling. In healthy adults, they filter 160-180g of glucose per day.[8] This filtered glucose is then reabsorbed and returned to the systemic circulation via the proximal convoluted tubule. 90% of renal glucose reabsorption is mediated through SGLT2 activity.[9] SGLT2 is a high capacity, low affinity transporter distributed over the luminal surface of the S1 and S2 segment of the proximal convoluted tubule.[10] The residual filtered glucose is reabsorbed by the low capacity, high affinity sodium-glucose co-transporter 1 (SGLT1).[11]

Hyperglycaemia increases the filtered and reabsorbed glucose up to two-fold.[8] Furthermore, in type 2 diabetes, SGLT2 activity seems to be upregulated due to increased expression of the SGLT2 transporter genes. This leads to increased glucose reabsorption with resultant hyperglycaemia.[4, 12]

SGLT2 inhibitors block the reabsorption of the filtered glucose through the SGLT2 in the proximal convoluted tubule, hence inducing glycosuria and osmotic diuresis. This leads to decreased glycated haemoglobin levels, body weight and systolic and diastolic blood pressure.[13-14]

SGLT2 has recently also been discovered on pancreatic α-cells.[15] Inhibition of these transporters by SGLT2 inhibitors, blocks glucose influx into the pancreatic α-cells, leading to increased glucagon secretion.[15] This process blunts the SGLT2 inhibitors' hypoglycaemic effect, as glucagon promotes endogenous glucose production (via glycogenolysis and gluconeogenesis).[16] Another postulated mechanism behind glucagon secretion is the compensatory glucagon release that occurs in response to the acute decline in serum glucose concentration due to the induced glycosuria secondary to SGLT2 inhibition.[17] Overall SGLT2 inhibition results in a reduced insulin: glucagon ratio. This reduced insulin: glucagon ratio meets two of the pathophysiological mechanisms making up the ominous octet leading to hyperglycaemia (Table 1) and hence one would expect SGLT2 inhibitors to increase glucose levels. However, there are two mechanisms by which this ratio may actually

benefit type 2 diabetes patients utilising SGLT2 inhibitors.

Table 1 Pathophysiological Mechanisms making up the Ominous Octet (Adapted from DeFronzo).[1]

1.	Decreased insulin secretion
2.	Decreased incretin effect
3.	Increased lipolysis
4.	Increased renal glucose re-absorption
5.	Decreased glucose uptake
6.	Increased hepatic glucose production
7.	Increased glucagon secretion
8.	Neurotransmitter dysfunction

In fact this reduced insulin: glucagon ratio has been termed as the 'Robin-Hood effect' by one review paper.[18] SGLT2 inhibition lowers insulin secretion, hence preventing unnecessary glucose utilization by peripheral tissues creating a 'pseudo-fasting' state and thus encourages lipolysis to generate free fatty acids.[18] Through β-oxidation and the citric acid cycle, energy is released from fatty acid metabolism. In addition, when the processing capacity of the citric acid cycle is overwhelmed, free fatty acid metabolism leads to the biosynthesis of ketone bodies. Ketone bodies are another alternative energy substrate. Hence, SGLT2 inhibition favours the switch from carbohydrate to lipid metabolism. This also contributes to weight loss in the long term.[18]

Furthermore, the increased glucagon secretion, results in increased endogenous glucose production. Additionally, the reduced insulin secretion prevents unnecessary glucose uptake by peripheral tissues, allowing more glucose to be filtered through the glomerulus. Glucose reabsorption *via* the SGLT2 in the proximal convoluted tubule is however inhibited by SGLT2 inhibitors. The energetic costs of gluconeogenesis and caloric loss of glycosuria promote further weight loss.[19]

As aforementioned, the hyperglycaemia in type 2 diabetes leads to an increase in the concentration of filtered glucose in the proximal convoluted tubules. This results in overactivity of the SGLT2 and SGLT1 transporters with resultant increased glucose and sodium reabsorption. The tubular fluid at the macula densa in the distal convoluted tubule will thus have a reduced sodium concentration. As a response, the tubulo-glomerular feedback system leads to renin-angiotensin-aldosterone system (RAAS) activation and afferent arteriole vasodilatation, with glomerular hyperfiltration being the end result.[20]

The vasodilatory effect on the afferent arteriole is predominantly responsible for the glomerular hyperfiltration observed in diabetes.[12] Glomerular hyperfiltration accompanied by glomerular capillary hypertension is responsible for the initiation and progression of renal disease in diabetes.[12] SGLT2 activity is an important factor in diabetic renal disease pathophysiology, as SGLT2 transporters are upregulated due to enhanced SGLT2 gene expression and due to increased activation of the angiotensin II type 1 receptor generating increased SGLT2 transporters.[12,21] These actions worsen glomerular hyperfiltration and hypertension generating a

vicious cycle that propagates diabetic nephropathy.[12]

By blocking the SGLT2 in the proximal tubule, SGLT2 inhibitors reverse the detrimental mechanisms that lead to glomerular hyperfiltration and hypertension. In fact, treatment with SGLT2 inhibitors is associated with a minimal, reversible decrease in the estimated glomerular filtration rate (eGFR) as a result of afferent arteriole vasoconstriction.[12] This reduction in eGFR with SGLT2 inhibitors mimics that of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB).[12]

Clinical Benefits

SGLT2 inhibitors have a unique mechanism of action independent of insulin secretion and action. In addition, they provide a number of metabolic and haemodynamic effects that reduce the risk of cardiovascular and renal disease.

Glycaemic Control

SGLT2 inhibitors are intermediate glucose-lowering agents, with mean HbA1c reductions of 0.6-1.1% when compared to placebo. A meta-analysis by Monami et al reported a reduction in HbA1c over 24 weeks that was more pronounced in patients who were younger, had a short history of diabetes duration and had a higher body mass index, HbA1c and fasting blood glucose level.[5, 22]

Several studies have demonstrated that SGLT2 inhibitors are non-inferior when compared to other anti-diabetic agents.[4]

In a 78 week double-blind, placebo-controlled trial by Rosenstock et al, type 2 diabetic patients controlled solely on basal insulin who were prescribed empagliflozin required a reduced dose of insulin whereas the placebo group were observed to need an increased insulin dose.[23]

In another 52 week, double-blind trial by Schernthaner et al, type 2 diabetics inadequately controlled on metformin and a sulfonylurea were randomly assigned to canagliflozin or sitagliptin. The HbA1c reduction was significantly greater with canagliflozin (-1.03%, -11.3mmol/mol) when compared to sitagliptin (-0.66%, -7.2mmol/mol). Furthermore, participants on canagliflozin lost weight and had better systolic blood pressure readings when compared to sitagliptin treated patients (p value <0.001). Despite the better glycaemic control, subjects on canagliflozin suffered from increased genital tract infections. However, the overall results of this study have to be reviewed with caution since 38.5% of participants did not complete the study.[24]

Hence, SGLT2 inhibitors provide additional glycaemic control in combination with both oral antidiabetic agents and insulin.

Weight Loss

Glycosuria leads to a negative caloric balance, resulting in a weight loss of circa 2-3kg. This has been demonstrated in 12-week trials of empagliflozin, canagliflozin and dapagliflozin.[25]

This weight loss is usually apparent after 6 weeks from the initiation of SGLT2 inhibitor therapy and the rate of weight loss gradually decreases until it stabilizes between weeks 26-34.[26] Most of the early decline in body weight with SGLT2 inhibition is due to the depletion of hepatic glycogen and the associated water loss. In the long term, mesenteric and subcutaneous adipose tissue loss contributes to further weight loss.[16]

Furthermore, in patients on insulin therapy, SGLT2 inhibitors reduce insulin dose requirements and may mitigate insulin-induced weight gain.

Decrease in Systolic and Diastolic Blood Pressure

Decreases in systolic and diastolic blood pressure by 1.6-6.9mmHg and 0.88-3.5mmHg respectively were demonstrated with SGLT2 inhibitor treatment.[27] SGLT2 inhibitors lead to osmotic diuresis and mild natriuresis. This creates a reduced intravascular volume and an initial reduction in blood pressure readings. In the long term, weight loss and inhibition of the RAAS contributes to decreased blood pressure readings.[27]

Cardiovascular Benefits

Empagliflozin, canagliflozin and dapagliflozin have been associated with reduced cardiovascular morbidity and mortality in type 2 diabetic patients with cardiovascular disease.

The EMPA-REG OUTCOME study showed that empagliflozin reduces the risk of cardiovascular events. Although there were no significant between-group differences in the rates of myocardial infarction or non-fatal stroke, in the empagliflozin group there was a significantly lower death rate from cardiovascular causes (3.7% *vs* 5.9%), hospitalisation for heart failure (2.7% *vs* 4.1%) and death from any cause (5.7% *vs* 8.3%) when compared to the placebo group.[28] Furthermore, the divergence between the empagliflozin and placebo primary outcome curves was evident after only 3 months, suggesting the rapid effect of empagliflozin.[29] On the other hand, in the CANVAS trial it took 1 year for canagliflozin treatment to show separation in the survival curve for major adverse cardiac events (MACE).[29] However one should note that empagliflozin's postulated rapid effect is a matter of debate and further studies are required to ascertain whether pharmacological intra-class effects exist.

The CANVAS trial reported that canagliflozin decreased the rate of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke when compared with placebo occurring in 26.9 *vs.* 31.5 participants per 1000 patient-years respectively with a p value of <0.001 for non-inferiority and a p value of <0.02 for superiority. Like the EMPA-REG OUTCOME study, the reduction in occurrence of the individual components of the composite outcome in those subjects treated with canagliflozin were not statistically significant.[30]

The results of the DECLARE-TIMI 58 trial are similar to the aforementioned studies. Dapagliflozin treatment did not result in a lower rate of MACE (p value of 0.17) but resulted in a lower death rate from cardiovascular causes and hospitalisation rates from heart failure when compared to placebo (p value of 0.005).[31]

These studies demonstrated the significant cardiovascular benefit of empagliflozin, canagliflozin and dapagliflozin in a high risk population with established cardiovascular disease. Further studies are required to assess whether SGLT2 inhibitors will have such a beneficial effect on type 2 diabetics who do not have overt cardiovascular disease.

Heart Failure

As aforementioned, the EMPA-REG outcome and the DECLARE-TIMI 58 trial demonstrated reduced hospitalisation rates for heart failure.[28, 31] In addition, a sub-analysis of the CANVAS trial revealed that canagliflozin

reduced the overall risk of heart failure events in patients with type 2 diabetes mellitus and high cardiovascular risk with no clear difference in effects on heart failure with reduced ejection fraction versus heart failure with preserved ejection fraction.[32]

The natriuretic, glycosuric and metabolic effects of SGLT2 inhibitors benefit patients with heart failure. Furthermore, the above physiological effects have also been demonstrated in patients without diabetes mellitus.[33] In fact, the U.S. Food and Drug Administration (FDA) has approved dapagliflozin as a treatment for heart failure with reduced ejection fraction in patients with or without type 2 diabetes.[34]

Renal Benefits

Empagliflozin and canagliflozin appear to reduce the progression of nephropathy. The secondary analysis of the EMPA-REG outcome revealed that patients on empagliflozin had a reduced risk of incident or worsening nephropathy when compared to the placebo group (12.7% vs 18.8% respectively).[35]

Canagliflozin reduced the progression of albuminuria when compared to placebo in the CANVAS trial (89.4 *vs.* 128.7 participants per 1000 patient years respectively). Additionally, the need for renal replacement therapy and death from renal causes occurred less frequently in the canagliflozin group when compared to placebo (5.5 *vs.* 9 patients per 1000 patient-years).[30]

Risks associated with SGLT2 inhibitors

Genital Tract Infections

The most frequent adverse event of SGLT2 inhibitors are genito-urinary tract infections.[14]

There are several studies that concluded that SGLT2 inhibitor treatment in type 2 diabetics was linked with an increased incidence of urinary tract infections and genital mycotic infections.[36-38]

Nicolle et al, (2015) showed that despite the increased risk of urinary tract infections in type 2 diabetics treated with canagliflozin, there was no risk of serious or upper urinary tract infections.[38]

However, this has been recently challenged and the U.S. FDA has issued warnings about cases of necrotizing fasciitis of the perineum in patients taking SGLT2 inhibitors. The FDA has received 12 reports of Fournier's gangrene between March 2013 and May 2018.[39] Patients with previous genital mycotic infections are at higher risk of developing such infections with dapagliflozin according to Thong et al (2018).[40]

Patients should be informed of the risks of urinary and genital tract infections and advised to seek medical help early on if they develop any symptoms indicative of a urinary tract infection.

Euglycaemic diabetic ketoacidosis

In 2015, the FDA issued a safety warning regarding the risk of diabetic ketoacidosis in people with type 2 diabetes being managed with SGLT2 inhibitors.[41] Fadini et al, (2017) analysed the diabetic ketoacidosis reports from the FDA adverse drug reporting (ADR) system and concluded that SGLT2 inhibitors are associated with diabetic ketoacidosis.[42] They also suggested that this is not limited to any particular demographic or co-morbid population and can occur after any duration of SGLT2 inhibitor use.[42]

One possible pathophysiological event contributing to diabetic ketoacidosis in patients using SGLT2 inhibitors is due to their 'Robin-Hood effect' (kindly refer to section 2.0 The physiological actions of SGLT2 inhibitors).

Despite this, the European Medicines Agency (EMA) states that the benefits of SGLT2 inhibitors continue to outweigh the risks in the treatment of type 2 diabetes.[43] Physicians need to be made aware of the possible risk factors for diabetic ketoacidosis in patients treated with SGLT2 inhibitors. These include:

- Insulin deficiency as in latent auto-immune diabetes of adults[14]
- Type 2 diabetics with evidence of low insulin secretory capability (labile diabetes control, lean body build or episodes of ketosis)[14]
- Sudden reduction in the insulin dose[44]
- Increased insulin requirements such as in post-operative cases and patients with an acute illness[44]
- Alcoholism[44]
- Starvation[44]
- Dehydration

If diabetic ketoacidosis is suspected, blood or urine ketone levels should be checked, even if the patient is normoglycaemic. If diabetic ketoacidosis is confirmed in a patient on SGLT2 inhibitors, these should be stopped immediately. [44]

Lower limb amputations

The FDA and EMA have issued warnings as there was an increased risk of leg and foot amputations with the use of canagliflozin in type 2 diabetics.[6] This cautionary advice is mostly based on the CANVAS trial where 7 cases of lower limb amputations out of 1000 patients resulted in the 100mg canagliflozin group, compared to 3 cases of lower limb amputations out of 1000 patients in the placebo group.[30]

Hence, with such evidence, it might be appropriate to avoid SGLT2 inhibitors in patients with peripheral vascular disease, neuropathy, active foot ulceration or a previous amputation.[14]

Malignancy

The potential carcinogenic effect of any drug cannot be assessed in short term trials.[45] Initial data on dapagliflozin by HW Lin et al, suggested an association with male bladder cancers and female breast cancers.[46] However, Wiviott et al, concluded that dapagliflozin therapy was not associated with increased bladder cancer risk.[31]

A recent meta-analysis by Tang et al, demonstrated that SGLT2 inhibitors were not significantly associated with an overall increased risk of malignancy. However, it was noted that there was an increased risk of bladder cancer with empagliflozin.[45]

Skeletal Fractures

SGLT2 inhibitors may affect bone metabolism.[13] They can lead to increased renal reabsorption of phosphate resulting in an increased serum phosphate concentration. This hyperphosphataemia may promote parathyroid hormone secretion which in turn stimulates bone resorption in order to maintain serum calcium levels.[6] In addition, SGLT2 inhibitors increase the serum concentration of fibroblast growth factor 23 leading to bone disease and decreased 1,25 dihydroxyvitamin D levels. The overall effects are reduced calcium absorption from the gut and impaired bone calcification, hence increasing the overall risk of bone fractures.[6]

There is conflicting evidence on the effect of SGLT2 inhibitors on bone metabolism. A meta-analysis by Tang et al, does not support the harmful effects of SGLT2 inhibitors on bone

fractures.[47] The fracture event rate was 1.59% in the SGLT2 inhibitors group and 1.56% in the control group.[47] Watts et al, reported that the risk of fractures was increased with canagliflozin therapy.[48] A small but statistically significant decrease in total hip bone mineral density was reported with canagliflozin when compared to placebo over a 2 year period (-0.9% and -1.2% reduction in BMD in canagliflozin 100mg and 300mg respectively when compared to placebo).[49] There were no statistically significant changes in BMD at other sites (femoral neck, lumbar spine, distal forearm).[49] Watts et al, concluded that the cause of the increased fracture risk with canagliflozin is unknown and extrinsic factors i.e.: the increased risk of falls due to orthostatic hypotension from the SGTL2 inhibitor induced volume depletion is a more likely explanation.[48] This risk is exacerbated in patients receiving diuretics.[48]

With regards to this issue, further future safety monitoring from randomised controlled trials and studies on SGLT2 inhibitors on bone health and interaction with anti-resorptive therapy are still required.

Table 2 Renal adjusted dosing of canagliflozin, dapagliflozin, empagliflozin and ertugliflozin

	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Starting Dose	100mg daily	5mg daily	10mg daily	5mg daily
Maximum Dose	300mg daily	10mg daily	25mg daily	15mg daily
Renal Adjustment	eGFR >45-60: patients should not be initiated on canagliflozin but if they are already tolerating canagliflozin, use a maximum dose of 100mg daily	eGFR <60: use is not recommended	eGFR >45-60: patients should not be initiated on empagliflozin but if they are already tolerating empagliflozin, use a maximum dose of 10mg daily	eGFR <60: use is not recommended
	eGFR <45: use is contraindicated	eGFR <45: use is contraindicated	eGFR <45: use is contraindicated	eGFR <45: use is contraindicated
	ESRD and Haemodialysis: use is contraindicated	ESRD and Haemodialysis: use is contraindicated	ESRD and Haemodialysis: use is contraindicated	ESRD and Haemodialysis: use is contraindicated

Acute kidney injury

The FDA had issued warnings about the risk of acute kidney injury for canagliflozin and dapagliflozin.[14] However an analysis by Nadkarni et al, revealed that there was no evidence for an increased risk of acute kidney injury (AKI) associated with SGLT2 inhibitor use in patients with type 2 diabetes when compared to non-users over a 1 year follow-up in two large health systems.[50] Nevertheless, renal function should be monitored prior to and during treatment with SGLT2 inhibitors.[51] Table 2 demonstrates the renal adjusted dosing of canagliflozin, dapagliflozin, empagliflozin and ertugliflozin.[52]

Indications for SGLT2 inhibitors

In the past, pharmacological management of diabetes has revolved around improving blood glucose and HbA1c levels. However, nowadays management is shifting towards prescribing antidiabetic agents that also provide cardiovascular benefits and reduce mortality.

The 2019 update to the consensus report "Management of hyperglycaemia in type 2 diabetes" by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends prescribing SGLT2 inhibitors with proven cardiovascular benefit, after initiation of metformin and lifestyle changes in patients with established atherosclerotic cardiovascular disease (ASCVD). Moreover, the consensus report also recommends SGLT2 inhibitor use among type 2 diabetics with ASCVD and heart failure. Another consensus recommendation regarding SGLT2 inhibitors is their use in type 2 diabetics with chronic kidney disease irrespective of cardiovascular disease if the eGFR permits, since they have been shown to provide renal outcome benefits.[7]

Based on the benefits and adverse effects of SGLT2 inhibitors, the ideal type 2 diabetic candidate to receive SGLT2 inhibitor therapy requires the following characteristics:

- young age[22]
- eGFR >45 in empagliflozin and canagliflozin
- eGFR >60 in dapagliflozin and ertugliflozin
- heart failure
- established atherosclerotic cardiovascular disease
- obese/overweight[22]
- hypertensive
- no past/present history of frequent mycotic infections/urosepsis/pyelonephritis and indwelling urinary catheters[14]
- no past history of peripheral vascular disease/neuropathy/active ulceration/gangrene[14]
- no past history of diabetic ketoacidosis or unprovoked ketosis[14]

Dapagliflozin was recently approved for the management of type 1 diabetes mellitus as an add on therapy with insulin, when the latter fails to achieve control in over-weight patients. Despite its significant improvement in glycaemic control and weight loss, there was a higher risk of DKA in patients with type 1 diabetes.[53]

SGLT2 inhibitors and other pharmacological therapies

Before prescribing an SGLT2 inhibitor, physicians should discuss the benefits and adverse events related to these new therapeutic agents. The patient's renal function and overall fluid status must be checked (by assessing blood pressure, jugular

venous pressure, skin turgor, chest auscultation for pulmonary oedema and lower limb oedema). A detailed history should be taken with a focus on any previous urinary tract infections or any features of peripheral vascular disease, while specifically looking for any active ulcerations. A urinalysis is commendable to screen against asymptomatic UTI and ketonuria. Renal function should be monitored pre- and post-treatment initiation.[51] A moderate drop in eGFR is expected when starting an SGLT2 inhibitor.[12] Elderly individuals and other patients who are at risk of falls (e.g.: those suffering from orthostatic hypotension) would benefit from a bone mineral density test prior to SGLT2 inhibitor therapy. Canagliflozin should be avoided in patients with osteoporosis as it was associated with a greater loss of bone mineral density over time.[49]

Current diabetes treatment, anti-hypertensive treatment and diuretic therapy need to be specifically analysed, as treatment adjustment may be necessary.[13]

Diabetic Treatment

In patients receiving a biguanide or an incretin based therapy (DPP4-inhibitors or GLP-1 receptor agonist), an SGLT2 inhibitor can be started without any adjustments. However, these patients should be advised to watch for possible loose stools or vomiting and ensure regular fluid intake. If such gastrointestinal effects occur, the biguanide or incretin based therapy's dose should be lowered and vigorous fluid intake encouraged to reduce the risk of diabetic ketoacidosis. Ideally, treatment with SGLT2 inhibitors should be interrupted or postponed until there is correction of the fluid loss.

In those patients on insulin or insulin secretagogues (sulfonylurea or glinides), treatment adjustment depends on the HbA1c level. If patients have an elevated HbA1c (>8.5%), then no dose adjustment is usually required. Patients with an HbA1c level of <8.5% may need to reduce their insulin/insulin secretagogue dose when initiating an SGLT2 inhibitor.

In all of the above settings, glucose monitoring is essential so that the diabetic treatment is titrated accordingly.[13]

Diuretics

Patients on diuretics may need diuretic dose adjustments. This decision should ideally be taken in conjunction with a cardiologist, especially in cases of chronic heart failure.[13]

Anti-hypertensive Treatment

Patients who are >65 years of age, suffer from atrial fibrillation or frequent syncopal events or orthostatic hypotension or who have a blood pressure <140/80mmHg, may require a lower anti-hypertensive dose if an SGLT2 inhibitor is prescribed. In these patients, blood pressure should be monitored on a weekly basis initially and the dose of anti-hypertensive treatment adjusted as necessary.[13]

In addition, since SGLT2 inhibitors cause a moderate drop in eGFR, patients taking nephrotoxic agents (ACE-i, ARB, NSAIDs, diuretics, digoxin and aminoglycosides) should be closely monitored so as to avoid acute kidney injury.

Conclusion

SGLT2 inhibitors represent a new class of oral antidiabetic medications that not only target glucose homeostasis but through other pleiotropic effects offer cardiac and renal protection. The 2019 update to the consensus report "Management of hyperglycaemia in type 2 diabetes" by the ADA and EASD

recommends SGLT2 inhibitor use with proven cardiovascular benefit, after first line therapy with metformin and lifestyle changes. In addition, SGLT2 inhibitor use is recommended in patients with atherosclerotic cardiovascular disease with co-existent heart failure and in patients with type 2 diabetes and chronic kidney disease (CKD) (irrespective of their cardiovascular disease status) as they reduce CKD progression.[7] Empagliflozin has demonstrated a wide spectrum of beneficial effects ranging from reducing kidney disease progression, hospitalisation for heart failure and cardiovascular and all-cause mortality.[28] Although the trials offer promising data, SGLT2 inhibitor use requires careful patient selection, so that those that will benefit from such therapy will be prescribed these medications. Patients on this treatment need regular monitoring to avoid or pick up adverse effects early on.

Key Points

- SGLT2 inhibitors are a relatively new class of oral antidiabetic agents with a unique mechanism of action, independent of insulin secretion and action.
- SGLT2 inhibitors provide an intermediate glucose-lowering effect by inducing glycosuria and in addition offer cardiac and renal outcome benefits through other pleiotropic effects.
- SGLT2 inhibitors are associated with a number of risks including: genital tract infections, euglycaemic diabetic ketoacidosis, lower limb amputations, skeletal fractures, risk of malignancy and acute kidney injury.
- Empagliflozin has demonstrated a wide spectrum of beneficial effects including the following: a reduction in progression of kidney disease, a decrease in hospital admissions for heart failure and also a reduction in cardiovascular and all-cause mortality.
- When it comes to SGLT2 inhibitors, physicians need to move away from a one-size-fits-all approach towards a more personalized patient-centred management. Despite the multiple benefits SGLT2 inhibitors offer, their prescription requires careful assessment by the prescribing physician to identify those patients who would benefit from such drugs so as to ensure a reduced risk of adverse events.

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