https://doi.org/10.33591/sfp.46.6.u2

Unit No. 2

SGLT2-INHIBITOR AND ITS PLACE IN CONTEMPORARY DIABETES MANAGEMENT

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ABSTRACT

The therapeutic approach for patients with type 2 diabetes is evolving rapidly. The recent published cardiovascular outcomes trials (EMPA-Reg, Canvas and DECLARE-TIMI 58), and DAPA-HF and CREDENCE studies demonstrated the benefits of Sodium-glucose transporter 2 inhibitors (SGLT2i) in improving the outcomes of diabetic patients with cardiovascular disease, heart failure and diabetic nephropathy. The cardiorenal benefits are seen beyond the glycaemic control. The treatment algorithm recommends early use of SGLT2i, especially among those with existing cardiovascular disease, heart failure or kidney disease. The side effects of SGLT2i are related to its underlying mechanisms of action, i.e. a higher incidence of genital yeast infections and urinary tract infections. SGLT2i can also cause euglycaemic ketoacidosis and is not currently indicated for use in patients with type 1 diabetes.

Keywords: SGLT2 inhibitor, cardiorenal, CVOTs

Sodium-glucose transporter 2 inhibitors (SGLT2i) are the newest class of oral glucose-lowering drug. In normal glucose tolerance individual with healthy kidneys, almost all (~90 percent) the filtered glucose in the glomerulus is reabsorbed via SGLT2 in the proximal tubule and returned to the circulation. In hyperglycaemia, when the glomerular filtered glucose exceeds the capacity of glucose reabsorption, glucose is excreted and can be detected in the urine (glycosuria). SGLT2i inhibits the SGLT2 at the proximal renal tubule that is responsible for renal glucose reabsorption. This induces non-physiological glycosuria. The glycosuric effect of SGLT2i is seen in people with or without diabetes mellitus.

Being an oral glucose-lowering drug, SGLT2 inhibitors are efficacious as monotherapy, and as a combination therapy (dual and triple oral therapy or with insulin) with an estimated improvement in the glycosylated haemoglobin (HbA1c) up to 0.9 percent in patients with type 2 diabetes (T2D). Several studies have shown that SGLT2 inhibitors therapy is associated with an improved insulin secretion and decreased insulin resistance. Besides glucose lowering, SGLT2i also lead to a mean three kilograms of body weight loss and a reduction of four mmHg in systolic blood pressure. More recently, SGLT2i have been shown to induce metabolic effects mimicking a fasting state and is associated with an increase in endogenous ketones production. The SGLT2 inhibitors are generally safe and tolerable. Since SGLT2 inhibitors action is independent of insulin, the risk of hypoglycaemia is low. They are contraindicated in patients with a hypersensitivity reaction to this class of drug. Genital yeast infections in men and women and urinary tract infection are the most common side effects. The SGLT2 inhibitors carry a precautionary or serious warning on euglycaemic diabetic ketoacidosis and recently rare cases of Fournier's gangrene. At this juncture, SGLT2 inhibitors are not recommended to be used in patients with type 1 diabetes.

There are currently three registered SGLT2 inhibitors in Singapore; canagliflozin (Invokana), dapagliflozin (Forxiga) and empagliflozin (Jardiance).

THE EXCITING ERA OF DIABETES THERAPEUTICS

The findings of rosiglitazone with an increased risk of myocardial infarction and cardiovascular mortality dampens the enthusiasm that a diabetes drug that targets primarily at insulin resistance would alter the natural history of T2D and reduce cardiovascular events or death.[1] This saga sets the United States (U.S.) Food and Drug Administration (FDA) to impose an unprecedented standard to all pharmaceutical industry to conduct cardiovascular outcomes trials (CVOT) to secure approval of new glucose-lowering agents. Each of these trials must demonstrate non-inferiority of their respective drugs to placebo in terms of major adverse cardiac events (MACE) as the primary composite endpoint.

The dipeptidyl-peptidase inhibitor (DPP) IV inhibitors (sitagliptin, alogliptin, saxagliptin and linagliptin) have demonstrated non-inferiority in 3-point MACE (CV death, non-fatal MI, and non-fatal stroke) compared to placebo. [2,3]

Glucagon-like peptide-1 agonists (GLP-1) are injectable incretin-based therapies, and they improve glycaemia by augmenting insulin secretion and suppressing glucagon release in a glucose-dependent manner. They are potent glucose-lowering agents and can reduce the HbA1c up to 1.5 percent. In addition, GLP-1 agonists reduce body weight by reducing appetite and increasing satiety. In the CVOTs, subcutaneous administration of liraglutide (LEADER, once daily), semaglutide (SUSTAIN-6, once weekly) or dulaglutide (REWIND, once weekly) significantly reduced the 3-point MACE in high-risk patients with cardiovascular disease. A recent systemic review and meta-analysis of the CVOTs of GLP-1 agonists showed beneficial effects of GLP-1 agonists therapy on cardiovascular mortality, and kidney outcomes in patients with T2D.[4] The gastrointestinal side effects (nausea, vomiting, diarrhoea) and the prohibitively high cost of GLP-1

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agonists therapy are the current barriers from wide adoption.

The results of the CVOTs of SGLT2 inhibitors are touted as the game-changer in the management approach of patients with T2D. The review of the CVOTs of SGLT2 inhibitors has been covered extensively elsewhere.[5] Briefly, the EMPA-REG (empagliflozin), DECLARE-TIMI 58 (forxiga) and CANVAS (canagliflozin) trials showed unequivocal benefits in cardiovascular and renal outcomes in people with diabetes mellitus with multiple cardiovascular risk factors and/or those with established cardiovascular disease, with the greatest magnitude of benefit seen in the risk of hospitalisation for heart failure and progression of kidney disease. In a recent meta-analysis, SGLT2 inhibitors reduced 3-point MACE by 11 percent, with the benefit mainly observed in patients with established cardiovascular disease. SGLT2 inhibitors also reduced the risk of cardiovascular death or hospitalisation for heart failure by 23 percent and the progression of kidney disease by 45 percent.[6] The benefits seen in the clinical studies parallel those seen the real-world studies.[7] Notably, these above-mentioned cardiorenal benefits of SGLT2 inhibitors are independent of the reduction in the glycaemia level.

The recent Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial assessed the effects of canagliflozin primarily on kidney outcomes in participants with T2D and albuminuric chronic kidney disease.[5,8] The CREDENCE demonstrated canagliflozin treatment was associated with a 30 percent reduction in the risk of primary outcomes (composite of end-stage kidney disease, doubling of serum creatinine or death from renal or cardiovascular causes) and 34 percent reduction in kidney-specific outcomes (end-stage kidney disease, double of creatinine, or kidney-related death). More recently, the Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) trial showed that dapagliflozin was superior to placebo at preventing cardiovascular deaths and heart failure events among patients with heart failure with reduced ejection fraction, with or without T2D.[9] The underlying reasons for the cardiorenal benefits of SGLT2 inhibitors are likely to be multifactorial, and interested readers are encouraged to read the review on this topic.[5,10] Broadly, SGLT2 inhibitors improve metabolic control (reduction in glycaemia, body weight, blood pressure), improve bioenergetics and metabolism, reduce oxidative stress, inflammation, and fibrosis, and the pre- and post-load on the heart and kidneys.

SGLT2 INHIBITORS IN T2D MANAGEMENT

SGLT2 inhibitors are no longer the new kids on the block in the armamentarium to treat T2D. They change the way we treat T2D, the way we look at the relationship between the patient, diabetes therapy and cardiorenal outcomes. SGLT2 inhibitors are taken orally, and its once-daily administration would improve drug compliance. SGLT2 inhibitors are currently rather affordable, and their overall "beneficial value" is greater than its prescriptive cost, has made SLGT2 inhibitors widely accessible and gained wide adoption. As a glucose-lowering drug, SGLT2 inhibitors could be used as monotherapy or combination therapy (including insulin). The glucose-lowering efficacy of SGLT2 inhibitors depends on the kidney function, with current evidence suggests that the effect on glycaemia level is minimal to modest in patients with eGFR < 45 mL/min/1.73 m^2.

The treatment consideration in patients with newly diagnosed T2D aims to 1) improve glycaemic control and 2) to prevent the incidence or progression of diabetes-related complications. Studies have shown that early intensive treatment aim at HbA1c seven percent or lower will lower the risk of microvascular and macrovascular complications. In patients with long-standing T2D, a multifactorial approach (STENO-2) targeting at 3Hs (hyperglycaemia, hypertension and hyperlipidaemia) has been shown to reduce cardiovascular events, mortality and progression of microvascular complications.

In the recent past, the choice of glucose-lowering drug aims at lowering glycaemia level. In this aspect, in asymptomatic, newly diagnosed T2D patients, lifestyle intervention with monotherapy metformin or combination therapy with metformin could be initiated. The recent CVOTs of SGLT2 inhibitors change the treatment paradigm that the choice of the glucose-lowering agent now aims at improving cardiorenal outcomes, beyond glycaemia control.

The mounting evidence of SGLT2 inhibitors in cardiorenal protection strongly suggests that this class of glucose-lowering drug can alter the natural history of T2D and its cardiorenal complications. Several international and regional guidelines have already placed SGLT2 inhibitors as the first-line choice in the treatment approach of patients with T2D. The 2019 European Society of Cardiology guidelines in collaboration with the European Association for the Study of Diabetes, recommend SGLT2 inhibitors as the first-line treatment option for T2D patients, either drug naïve or on metformin, with atherosclerotic cardiovascular disease or high cardiovascular risk, those are at high risk of heart failure and at those with diabetic kidney disease.[11] The American Diabetes Association/ European Association for the Study of Diabetes consensus report recommends a patient-centred approach in choosing the appropriate pharmacologic treatment of blood glucose.[12] This includes consideration of the efficacy of the glucose-lowering drug and key patient factors: 1) important comorbidities such as atherosclerotic cardiovascular disease and indicators of high ASCVD risk, chronic kidney disease, and heart failure 2) hypoglycaemia risk, 3) effects on body weight, 4) side effects, 5) cost, and 6) patient preferences. Metformin is recommended as the first choice unless there are contraindications. The report emphasises that initial combination therapy would be required in patients presenting with HbA1c levels 1.5–2.0 percent above target since the absolute effectiveness of most oral medications rarely exceeds one percent. In patients with atherosclerotic cardiovascular disease and indicators of high ASCVD risk, chronic kidney disease, or heart failure (with reduced ejection fraction), a SGLT-2 inhibitor or GLP-1 RA is recommended as part of the glucose-lowering regimen independent of the HbA1c level.

In Singapore, the most updated guidance on oral glucose-lowering drugs in T2D was published by the Agency for Care Effectiveness (ACG, Ministry of Health) in 2017. SGLT2 inhibitors are recommended as a second-line agent, especially in patients who are at risk of hypoglycaemia, overweight or with cardiovascular disease, and in those who are not able to tolerate sulphonylureas.[13] With the overwhelming evidence of SGLT2 inhibitors in cardiorenal endpoints, it is time, perhaps, for the next review of the ACG guidance.

CONCLUSION

SGLT2 inhibitors are now used very widely, by diabetologists, primary care physicians, cardiologists and nephrologists. Every prescriber needs to understand the prescription nuances of this class of drug. While the international and local guidelines provide the clinicians with the best available evidence, clinicians and patients need to work together to find and choose the best course of action. The shared decision-making must incorporate what matters most to the patients (values and preferences). The shared decision-making must include the discussion on common (urogenital infection) and rare, but serious (euglycaemic ketoacidosis) adverse effects of SGLT inhibitor.

Does this mean glycaemic control is less important? A meta-analysis of 12 CVOTs found a significant effect of glycaemia lowering on the MACE risk. A lowering of HbA1c of 0.5 percent has been shown to confer a significant risk reduction of 20 percent for MACE, in particular for non-fatal stroke.[14] Achieving optimal glycaemic control is still relevant, especially we have glucose-lowering drugs that have a lower risk of hypoglycaemia.

Lastly, in symptomatic (catabolic) patient or severe hyperglycaemia as defined as a fasting plasma glucose >250 mg/dL (13.9 mmol/L), random glucose consistently >300 mg/dL (16.7 mmol/L), or HbA1c >10 percent, insulin therapy is the choice of therapy. We need to exercise caution and should withhold SLGT2 inhibitor in the acute stress setting, e.g. after a cardiac event, acute heart failure or acute infection, and two to three days prior to surgery. Euglycaemic ketoacidosis has been reported in people given SGLT2 inhibitor during severe acute illness, while on a carbohydrate-restricted diet, extreme physical activity (e.g. running a marathon), during a peri-operative period or excessive alcohol intake.[15]

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LEARNING POINTS

- **The SGLT2 inhibitors exhibit cardio-renal benefits independent of the effect on glycaemia level.**
- **Current therapeutic guidelines for diabetes mellitus recommend early use of SGLT2 inhibitors, especially among those with pre-existing cardiovascular disease, heart failure or kidney disease.**
- **Early diagnosis and intensive treatment, multifactorial intervention on CV risk factors and use of SGLT2 inhibitor or GLP-1 agonist improve cardiorenal outcomes in patients with type 2 diabetes.**
- **The common side effects of SGLT2 inhibitor are genital yeast and urinary tract infections.**
- **Clinicians must observe that in certain situations (e.g. in acute illness), the use of SGLT2 inhibitor could predispose to euglycaemic ketoacidosis.**