Introduction

The management of type 2 diabetes (T2DM) advanced significantly over the past few years. One of the newest oral antidiabetic therapies are sodium-glucose cotransporter 2 also known as SGLT2i This class works in a new mechanism of action that targets the kidneys by inhibiting the reabsorption of filtered glucose at the level of the nephron. In addition to glucose lowering this class has a lot of other effects that are beneficial for the diabetic patients including weight loss, blood pressure reduction, cardiovascular and renal protection. This class is being prescribed and utilized in more patients due to the growing evidence on the benefits they provide to the diabetic patients. However, the benefits and the risks of SGLT2i should always be considered to have an individualized treatment that maximizes the positive outcomes and reduces any risks.

Mechanism of action

There are 2 types of Sodium-glucose cotransporter (SGLT) proteins: SGLT 1 and SGLT 2.

SGLT1 are high affinity, low capacity transporter proteins, they are mainly expressed in the small intestines and the renal proximal tubule (S3). SGLT2 on the other hand are low affinity high capacity transporters expressed in the proximal convoluted tubules of the kidneys and are responsible of almost 90% of the filtered glucose reabsorption.

SGLT2 inhibitors work in a unique way compared to other glucose lowering agents as they do not interfere with endogenous insulin or incretin pathways. Their action is blocking the SGLT2 transporter in the kidneys. Consequently, it will result in glycosuria and natriuresis, lowering as such the plasma glucose levels.

Available drugs in class

There are 4 different SGLT2 inhibitors available on the market and in different formulations:

- Empagliflozin 10mg and 25mg
- Dapagliflozin 5mg and 10mg
- Ertugliflozin 5mg and 15mg
- Canagliflozin 100mg and 300mg

Common/general benefits of the class

Patients with diabetes are at higher risk of developing cardiovascular disease and have more than 2 times chances of developing heart failure compared to healthy population. In recent cardiovascular outcome trials, SGLT2-i were shown to decrease the risk of hospitalization for heart failure by 30-35%.

In addition to improving glycemic control, SGLT2 inhibitors cause diuresis, weight reduction and decrease in blood pressure. Recently, additional benefits are being explored like improved cardiomyocyte calcium handling, enhanced myocardial energetics, induced autophagy and reduced epicardial fat.

Cardioprotective effect mechanisms

Different mechanisms of SCGLT2 inhibitors' activity contribute to the cardiovascular protection effect. One factor which is primary due to reducing sodium and glucose uptake in the kidneys causing decrease in preload and afterload through diuresis. Another proposed mechanism is the improvement of composition of pro-inflammatory and anti-inflammatory cytokines in the body along with the reduction of cardiac fibrosis found in studies in patients on SGLT2i. An addition an increase in diuresis can cause elevation in red blood cell concentration due to the diurectic effect of these medications. Renal fibroblasts may increase the erythropoietin when glucose level are reduces in the blood (less hyperglycemia and decreased reabsorption in the nephron). Finally, the Thrifty substrate hypothesis suggests an increase in the production alternative energy sources for the heart under condition of consistent mild hyperketonima like beta hydroxybutyrate that is freely taken up by the heart and oxidized in preference to fatty acids. This source of fuel has been associated with increased cardiac metabolic efficiency

Cardiovascular benefits

As per the FDA requirement, a cardiovascular outcome study for every oral antidiabetic medication should be conducted. The efficacy and safety of SGLT2i was tested in different landmark cardiovascular outcome studies.

EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) was the first one published. It was a double blind randomized controlled trial evaluating the effect if empagliflozin on MACE (major adverse cardiovascular events): cardiac death, non-fatal MI and nonfatal stroke. Empagliflozin 10 and 25 mg were compared to placebo in diabetic patients with established cardiovascular disease. The study duration was around 2.6 years and the primary outcome was much lower in the patients on empagliflozin arm driven by a lower rate of cardiovascular death compared to placebo (10.5 versus 12.1%, hazard ratio 0.86, 95% confidence interval (CI) 0.74–0.99, $P <$ 1.1 for noninferiority and $P = 0.04$ for superiority). In addition, hospitalization for heart failure was significantly decreased and the difference with the placebo group was statistically significant. (hazard ratio 0.65, 95% CI 0.50–0.85, $P = 0.002$)

CANVAS (Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes) trial is a double-blind, randomized controlled trial comparing daily canagliflozin (100 mg or optional increase to 300 mg) and placebo on 3 point MACE in patients with symptomatic atherosclerotic CVD (65%) or without known history if CVD but with increased risk factors (35%). Patients on canagliflozin had a lower primary outcome compared to placebo (hazard ratio 0.86, 95% CI 0.75–0.97, $P < 0.001$ for non-inferiority; $P =$ 1.2 for superiority) These results were mainly driven by HHF, there were no major differences in all cause mortality and cardiovascular death compared to placebo.

The DECLARE-TIMI (Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes) Is a double blind randomized controlled trial comparing dapagliflozin to placebo in patients with established CVD (40%) and patients with 2 or more cardiovascular risk factors (60%). The study duration was 4.2 years. No significant difference observed in 3 point (cardiovascular death), MI, or stroke MACE between the

dapagliflozin arm and placebo arm (8.8 and 9.4%, hazard ratio 0.93, 95% CI 0.84–1.03, *P* = 0.17). The cardiovascular death and HHF was however lower in the dapagliflozin group. This difference was mainly driven by the significant decrease in HHF (hazard ratio 0.73, 95% CI 0.61–0.88)

The VERTIS CV is a multicentre, randomized, double-blind, placebo-controlled, event-driven study to assess CV outcomes following treatment with ertugliflozin in patients with type 2 diabetes mellitus (T2DM) and established CV disease. The trial included more than 8,000 patients. The results of this trial indicate that ertugliflozin is non-inferior to placebo for reducing CV events in patients with T2DM and established CVD (hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.85-1.11, p < 0.001 for non-inferiority). Trends were noted for beneficial effect on renal outcomes. Subgroup analysis suggested a benefit for HHF and HHF/CV death with ertugliflozin vs. placebo among patients with higher risk (presence of albuminuria, higher KDIGO class).

SGLT2i side effects

Sglt2i is generally a well-tolerated class. Generally, studies have shown a significant increase in genital mycotic infections related to their mechanism of action. Some other side effects were associated with the use of canagliflozin. CANVAS study has found an increase in amputations and bone fractures in patients taking canagliflozin compared to placebo. Although these side effects were not seen in any of the other safety studies, there was a concern on the effect of SGLT2i on bone mineral density. CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) study on the other side found no increased risk for fracture or amputation with the use canagliflozin in diabetic patients with kidney disease.

Place of SGLT2- inhibitors in management guidelines for type 2 diabetes

Most recently published diabetes management guidelines recognize the widening scope of choices that is provided by use of SGLT2-inhibitors. The decision to include SGL2-inhibitors is based on the principle of individualized patient care.

While the guidelines recommend most often metformin as the initial monotherapy, the use of SGLT2 inhibitors as the initial mono-therapy is an option in patients who are intolerant to metformin.

The most common use is dual combination therapy in which SGLT2 inhibitors are added to metformin. Such a combination is particularly favored in an obese type 2 diabetic in whom weight loss is desired. The same is true in the hypertensive type 2 diabetic in whom a drop in blood pressure, albeit modest results in better cardiovascular outcomes.

For the same above reasons, SGLT2-inhibitors are often included as part of triple therapy which usually include metformin and another oral hypoglycemic. Since the effect of SGLT2-inhibitors is insulin independent, it is also possible to have combination triple therapy which includes insulin

RECOMMENDED REFRENCES

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