

# Why are SGLT2 inhibitors a good choice in the management of Type 2 Diabetes Mellitus?

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## Abstract

Sodium-glucose co-transporter 2 inhibitors (SGLT2) are the most recent addition to the oral management of type 2 diabetes mellitus. This chronic progressive disease is linked to cardiovascular and renal disease causing millions of deaths each year worldwide. As oral treatment options have expanded over the years, this has made the management of diabetes mellitus more tailored to individuals taking into account their co-existing comorbidities and therefore slightly more challenging.

Several benefits have been reported from SGLT2 including their ability to improve plasma glucose levels, lower blood pressure, weight loss and more importantly their cardiovascular and renal beneficial outcomes making them one of the popular choices for add on to monotherapy in current guidelines.

This article looks at why SGLT are likely to be considered sooner for initiation of the management of diabetes compared to other available medication.

**Key words:**

Sodium-glucose co-transporter 2 inhibitors (SGLT2);  
management Type 2 diabetes

## Introduction

Type 2 diabetes mellitus (T2DM) is a global epidemic affecting millions of people worldwide. In 2017 it was reported to have affected 462 million people ranging from ages 15- 70+ years and was the cause of over 1 million deaths. This chronic condition is expected to increase in prevalence by 2030 carrying a huge economic burden and becoming a significant health concern (1).

Diabetes Mellitus is a metabolic disorder causing hyperglycemia as a result of two main factors. These are the failure of the beta cells in the pancreas's ability to secrete insulin and insulin sensitive tissues to respond to the insulin secreted (2). As a result, hyperglycemia occurs and over a prolonged period, is damaging to several different systems within the human body including the cardiovascular, renal and nervous systems. Other organs affected also include the eyes.

Risk factors for type 2 diabetes mellitus include increasing age, family history, high body mass index and sedentary lifestyle. Obesity and overweight are found to be one of the strongest risk factors for the condition (3). It has been demonstrated by epidemiological studies that managing the modifiable risk factors can therefore help prevent or delay the onset of the diabetes (2).

Although type 2 diabetes mellitus in some cases can be managed initially with modifying risk factors such as diet and weight, many people will require pharmacological management in order to establish glucose hemostasis to prevent associated microvascular and macrovascular complications due to hyperglycemia and its progressive nature (4). This may be with monotherapy initially followed by combination therapy if treatment targets are not successfully reached with one group of anti-hyperglycemic agents (AHA) (4).

Diabetes control is established on how well the glycemic measurements are and include A1c readings as well as self-monitoring of blood glucose or continuous glucose monitoring. Most patients' control is monitored using the Hba1c measurement which reflects the glycemic control over a period of months (5).

Currently there are several groups of medication used for glycemic control and these include biguanides, sulphonylureas, thiazolidinedione, Sodium- glucose co transporter 2 inhibitors and dipeptidyl peptidase 4 inhibitors (DPP4-I) (6). Unfortunately, they are associated with adverse effects which can affect patient compliance. Common side effects include gastrointestinal disturbance, weight gain and hypoglycemic events with older drugs (6).

SGLT2 are a novel group of medications compared to other classes of AHA which have a unique mode of action. They lower glucose levels by reducing glucose reabsorption at the renal tubular level without the assistance of insulin, resulting in glucosuria (7).

There are 3 different SGLT2 which are in use for the management of T2DM, with others undergoing trials. These are Canagliflozin, Empagliflozin and Dapagliflozin.

Their ability to improve glycemic control, cardiovascular benefits as well as causing weight loss and improved blood pressure targets are just some of the reasons why this group of medications is gaining popularity for an early adjunct in the management of diabetes management.

This article will look at the key benefits of SGLT2 in the management of diabetes mellitus and why they may be considered earlier in the pathway than they currently are.

## Benefits

Several benefits have been demonstrated in the control of diabetes mellitus when SGLT2 have been studied individually and compared to other groups of drugs such as DPP4-I and Sulphonylureas. Benefits do appear to be dose dependent and some SGLT2 demonstrate this better than others (8).

### Reduced Hba1c levels

Trials have demonstrated that SGLT2, in particular Canagliflozin, have the ability of causing modest reduction in Hba1c levels up to 1.%. These medications have been studied individually and against other drugs as combination therapy and found that over a prolonged period of time (2 years), SGLT2 are better at maintaining the reduction in Hba1c levels when compared to Sulphonylureas (8,9). Better reduction in Hba1c are dependent on the dose of medication and initial Hba1c levels (8). In addition, they are associated with fewer hypoglycaemic events and can be used with other groups of AHA's.

### Weight loss

This group of medications cause glycosuria which in turn leads to caloric loss and this has been seen with all 3 medications. The weight loss is considered to be 2.5kg at one year (mean weight loss) (10).

### Blood pressure

SGLT2 drugs have been associated with a small reduction in blood pressure due to the resulting osmotic diuresis effect and were found to cause a reduction in systolic blood pressure of 3.4-5.4 mmHg and 1.5-2.2 diastolic value (11).

### Cardiovascular benefits

Empagliflozin and Canagliflozin trials have both demonstrated their ability to reduce Cardiovascular events, hospitalization and heart failure. This is particularly the case for patients with pre-existing cardiovascular disease.

These medications were compared to patients taking a placebo and empagliflozin cardiovascular outcome event trial (EMPA-REG OUTCOME) has shown that a reduced rate of primary major adverse cardiac events (MACE) were seen (8).

This trial showed a risk of death by any cause was reduced by 32% and heart failure hospitalization was reduced by 35% (8).

Canagliflozin similarly demonstrated the reduction of heart failure hospitalization reduction rates in the Canagliflozin Cardiovascular Assessment Study (CANVAS) study (8). It is thought that this cardiovascular benefit is seen amongst the group especially with the current SGLT2 that are in use.

### Nephropathy

Canagliflozin and Empagliflozin have both been shown to reduce nephropathy in diabetic patients. This was demonstrated in the outcomes of the trials named above. Empagliflozin was shown to slow the progression of renal disease whereas canagliflozin was found to reduce progression of albuminuria and renal replacement therapy as well as death secondary to a renal cause (8,9). These outcomes were observed when compared to placebos.

### Adverse Effects

Similarly to most medication, SGLT2 medication do not come without their adverse effects. They are known for causing an increase in genital mycotic infection, diabetic ketoacidosis, volume depletion, amputations (with canagliflozin in patients with pre-existing peripheral vascular disease and previous amputations) and skeletal fractures (8).

### Conclusion

The SGLT2 being the newest addition to the diabetes mellitus oral medication treatment options are currently recommended to be used as second or third line add on agents in the management of type 2 diabetes mellitus. Their beneficial effect such as the ability to reduce Hba1c levels, low hypoglycemic risk when used individually and their ability to reduce primary major adverse cardiac events in particular with empagliflozin make them more appealing to add on to initial monotherapy when treating diabetes mellitus. This is particularly the case for patients with pre-existing cardiovascular and renal disease. More research needs to be done to look into newer SGLT2 medication to see if the benefits are seen across the class of medication and whether they may be recommended for second line agents or monotherapy in the future.

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