

# Comparison Of Efficacy and Safety of Single and Combinational Therapy Of SGLT-2 Inhibitors in Treatment of Diabetes Mellitus

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**Abstract** Diabetes mellitus is a chronic condition which requires firm glycaemic control with the help of medications and life style changes. Sodium glucose co-transporter 2 inhibitors are novel drugs which exhibit immense benefits on diabetic patients. Currently FDA approved three SGLT-2 where the mode of action is directed towards kidney in potentiating glucose excretion and has pleiotropic effects on reducing HbA1c levels, patient body weight, lipid profile to some extent and blood pressure. Their major positive effects are believed to be focused on cardiovascular and renal functions. SGLT-2 inhibitors especially Dapagliflozin was indicated not only in the management of type 2 diabetes mellitus but also approved for type 1 diabetes mellitus thus providing a way to reduce insulin dose. Risk of hypoglycaemia is significantly increased with use of SGLT-2 inhibitors and insulin in type 1 diabetics but there is no risk when used alone. Many clinical trials were performed and few ongoing trials also suggested good efficacy and safety profiles with use of SGLT-2 inhibitors. Although the use of SGLT-2 inhibitors alone known to be efficacious, their use with other anti-diabetic drug classes presented promising effects. However, SGLT-2 inhibitors are also associated with adverse events such as urinary and genital tract infections, diabetic ketoacidosis, fractures, amputation and kidney injury thus requiring special attention to minimise such effects with appropriate diagnosis and management for better patient survival outcomes. Appropriate SGLT-2 inhibitor use with close patient monitoring, considering prior preventive measures and medication adherence are factors that improve quality of life.

**Keywords:** diabetes mellitus, SGLT-2in, hypoglycaemia, adverse events.

## INTRODUCTION

Diabetes mellitus is a serious condition of increased plasma glucose levels in the body. Type 1 diabetes mellitus is insulin dependent due to diminished pancreatic islet beta cells while type 2 diabetes mellitus is insulin independent due to faulty insulin secretion from beta cells<sup>2</sup>. In US, approximately 1.6 million population are suffering with type 1 diabetes and around 1.5 million new cases of diabetes were emerged in 2018 of which 2, 10,000 cases of type 1 diabetes were reported. It was also estimated that one in three Americans are affected with diabetes by 2050<sup>11, 6</sup>. International Diabetes Federation Diabetes Atlas reported that the incidence of diabetes mellitus was 9.3% in 2019 and further the condition progressed to 578 million population by 2030<sup>15</sup>. Metformin is considered and preferred to be first line medication in diabetic treatment. American Diabetes Association and European Association for the study of diabetes initially recommended six categories of drugs to be used in combination with metformin such as sulfonylureas, thiazolidinedione's, dipeptidyl peptidase 4 inhibitors (DPP-4), glucagon like peptide 1 receptor agonists (GLP-1RAs), sodium-glucose co-transporter 2 inhibitors (SGLT-2in) and insulin. Different safety timelines, mode of action, adverse effects are associated with these drug classes which often leaves a state of confusion on which regimen has to begin after metformin monotherapy<sup>5</sup>.

Many studies were conducted and implicated that SGLT-2in has the affinity of reabsorption of glucose in proximal tubule thereby plasma glucose levels are lowered and initiating urinary excretion of glucose<sup>8</sup>. SGLT-2in not only has positive effects on glycaemic control but also shows promising effects on cardiovascular and renal functions<sup>11</sup>. Besides the satisfactory effects of SGLT-2in they also impose few major side effects<sup>5</sup>. Over the last two decades, both developing and developed countries are facing global health conditions in the name of type 2 diabetes mellitus. Due to beta cell function declination overtime, the anti-diabetic drugs slowly lose their efficacy to maintain optimum glycaemic control except in case of GLP-1RAs and thiazolidinedione's. Under such circumstances, patients are required to be maintained on multiple regimes including insulin eventually leading to uncontrolled glycaemic levels, weight gain and hypoglycaemic risk. To further decline the severe diabetic related complications, strict glycaemic control is essential. Therefore, under strenuous situations new anti-diabetic medications are mandatory to maintain optimum glycaemic control<sup>8</sup>.

This review mainly focuses on efficacy, safety, mode of action, combinational therapy of SGLT-2in with other glucose lowering drugs in the management of diabetes mellitus and incidence of adverse events.

## SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS

US FDA approved four oral SGLT-2 inhibitors namely Canagliflozin, Dapagliflozin, Empagliflozin to be used as monotherapy or along with other hypoglycaemic drug classes. It is appraised to be safe and efficacious in type 2 diabetic patients and impaired renal

function. A meta-analysis analysed that SGLT-2in showed HbA1c levels on an average of 0.79% and 0.61% when used as monotherapy and additional therapy respectively with no serious renal problems, reduced hypoglycaemic risk efficacy<sup>5</sup>.

Table-I Different SGLT-2in with available doses<sup>12</sup>

Drugs	Doses Available
Canagliflozin	5mg, 10mg
Dapagliflozin	100mg, 300mg
Empagliflozin	10mg, 25mg

The mode of action of SGLT-2in is insulin independent and it manifests multiple effects, cardiovascular and renal protective effects as well as adverse events. A meta-analysis reported that there is decrease in systolic and diastolic blood pressure by 2mmHg as a result of several mechanisms including osmotic diuresis which causes plasma contraction, weight reduction, higher vascular stiffness, increased glucose levels relating to oxidative stress and decreased sympathetic nervous system activity. Basically a weight loss of 2-3kg was induced by SGLT-2 receptor blockade. It also shows increase in high and low density level cholesterol and decrease in triglycerides levels. Thereby, left ventricular hypertrophy may be induced as a result of natriuresis with increased sodium balance and volume load and decreases vascular stiffness. Unknowingly, it impairs some factors related to non-alcoholic steatohepatitis, increased alanine aminotransferase and fat content.

Clinical trials were conducted using Empagliflozin and Canagliflozin and assessed the cardiovascular outcomes in type 2 diabetic patients. Initially all patients were treated with anti-hypertensive mostly renin angiotensin aldosterone system inhibitors and statins. Therefore, Empagliflozin reported fewer cardiovascular deaths while both Empagliflozin and Canagliflozin showed few days of hospital stay due to heart failure along with risk of nephropathy<sup>5</sup>.

#### MODE OF ACTION

Hyperglycaemic mechanism was explained with various organs which are involved in glucose homeostasis. Co-transport sodium and glucose is responsible in maintaining renal reabsorption of glucose. About 90% of filtered glucose is reabsorbed by SGLT-2 located at initial two convoluted segments of proximal tubule and remaining 10% is reabsorbed by SGLT-1 present beside the straight segment. In case of type 2 diabetics, glycosuria is decreased along with energy loss due to larger reabsorption which in turn causes hyperglycaemia. On the other hand, central nervous system also involved in maintaining food intake and energy balance. They usually receive, regulate and convey peripheral signals such as changes related to nutrients, hormones. In case of type 2 diabetics, excessive food intake is majorly due to impaired satiety which causes alteration in central metabolic balance<sup>5</sup>.

Sodium-glucose co-transporter 1 inhibitors are predominantly situated in small intestine and SGLT-2in are situated in proximal convoluted tubule segments. Renal absorption of glucose is way greater in diabetic patients when compared in normoglycaemic population. Canagliflozin, Dapagliflozin, Empagliflozin are selective SGLT-2in while Phlorizin is dual SGLT-1, 2 inhibitor<sup>6</sup>.

#### EFFICACY AND SAFETY

SGLT-2in alone or in combinational therapy proved to be efficacious in type 1 and 2 diabetic patients. In 2015, a trial was performed in about 351 type 1 diabetic patients which resulted in reduction in HbA1C levels of greater than 0.4% and no weight gain in about 36.9% in patients with insulin and canagliflozin 100mg, 41.4% in patients with insulin and Canagliflozin 300mg and 14.5% in patients with insulin and placebo. Another study was conducted in about 75 patients with Empagliflozin and insulin versus insulin and placebo therefore reported decrease in 0.49% HbA1c levels against placebo group. Double blind placebo trial was performed in type 1 diabetic patients on insulin when treated with Empagliflozin 10mg, 25mg and placebo for about 52 weeks and Empagliflozin 2.5mg, 10mg, 25mg and placebo for about 26 weeks which resulted in weight reduction and lowering HbA1c levels. Another double blind controlled phase III study was conducted in 813 patients for about 52 weeks when treated with , Dapagliflozin 5mg, 10mg and placebo with insulin showed low HbA1c levels with both doses. The optimum glucose levels are maintained for about additional 2hours a day as the glucose time in range is maintained at a higher rate for about 9.02% and 10.70% for , Dapagliflozin 5mg and 10mg respectively.

All these studies prove consistently that SGLT-2in category of drugs have potent efficiency on plasma glucose control as well as reduction in HbA1c levels and weight gain<sup>11</sup>.

American diabetes association and European association for study of diabetes criteria defined hypoglycaemia into level 1 (less than 70mg/dl), level 2 (less than 54mg/dl) and level 3 (seizure attack, unconscious). One trial conducted resulted in level 1 hypoglycaemia by 22% with use of Sotagliflozin 200mg, 400mg thereby level 2 was reduced by 28% and 30% with use of Sotagliflozin 200mg and 400mg respectively. Furthermore, level 3 was reduced by 2.6%, 2.2% and 6.3% with use of Sotagliflozin 200mg, 400mg and placebo respectively<sup>11</sup>. On the other hand, warning of urinary tract infections leading to sepsis, pyelonephritis with use of SGLT-2in was initially recommended by FDA. Later, in June 2016, FDA issued a label warning that subjects reported acute kidney injury with use of Canagliflozin and , Dapagliflozin but no such cases were reported with Empagliflozin. A serious label warning was issued by the FDA on risk of bone fractures with long term Canagliflozin use but no sufficient evidence with use of , Dapagliflozin and empagliflozin<sup>6</sup>.

#### COMBINATIONAL THERAPY

SGLT-2in can be used in combination with other glucose lowering agents to show promising effects.

SGLT-2in with glucagon like peptide-1 receptor agonists: FDA and EMA approved short acting GLP-1RAs such as exenatide, Liraglutide, Lixisenatide and long acting GLP-1RAs such as Semaglutide, Dulaglutide and Albiglutide. Short acting drugs act by extending rate of glucose entry into duodenum and inhibits glucose absorption from meal thus lowering glucose levels whereas long acting drugs have immense effect on HbA1c levels and fasting sugar levels. Common side effects include retinopathy, vomiting and nausea. SGLT-2in in combination with GLP-1RAs ( , Dapagliflozin 10mg and exenatide 2mg) reported reduction in HbA1c levels by 2% when compared with monotherapy. While addition of dulaglutide to SGLT-2in of dose 0.75mg and 1.5mg showed low HbA1c levels by 1.21% and 1.34% respectively whereas Canagliflozin 10mg and 300mg in combination with GLP-1RAs resulted in reduced HbA1c levels by 1% and 1.06% respectively. This combination use involved in manifesting multiple effects

such as around 3.41kg of weight loss, decrease in systolic blood pressure, exhibiting additive effects, imposing wide renal advantages and believed in decreasing cardiovascular risk which requires further investigation. However this combinational therapy sometimes may potentiate hypoglycaemic condition and may also cause side effects associated with individual drug category.

SGLT-2in with dipeptidyl peptidase 4 inhibitors: Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin and linagliptin are five approved drugs and are known to decrease fasting plasma glucose levels by 1.0-1.5 mmol/L, post-prandial plasma glucose levels by 3.0mmol/L and HbA1c levels by 0.77%. Common side effects are mild, pancreatitis risk, warning label for heart failure. SGLT-2in in combination with DPP-4in showed greater reduction in HbA1c levels by 1.2-1.5% when compared to monotherapy. A meta-analysis also showed lower HbA1c levels with combinational therapy. Multiple effects include no significant changes in body weight, blood pressure and lipid profiles but regulates sodium excretion in urine. DPP-4in alone do not induce cardiovascular renal benefits but may potentiate SGLT-2in induced advantages. Thereby, incidence of genital infections are reduced by 26% and heart failure risk by DPP-4in can be overcome with SGLT-2in use.

SGLT-2in with Sulfonylureas: The most widely used second-line therapy for management of diabetes are sulfonylureas due to its low cost and increased efficacy. They initially act by stimulating insulin secretion by beta cell membrane changes thus low HbA1c levels by 1-1.25% while cardiovascular renal benefits are not yet distinguished.

SGLT-2in with Thiazolidinedione's: Rosiglitazone and Pioglitazone are widely accepted thiazolidinedione's. These agents are peroxisome proliferator activated receptor which improves insulin sensitivity and protect beta cell action thus maintaining glucose control. Pioglitazone is widely used agent which reduces 0.8% of HbA1c levels and is associated with weight gain, edema, fractures and heart failure which could be counter acted with SGLT-2in whereas increased risk of myocardial infarction is associated with use of rosiglitazone, hence not widely accepted.

SGLT-2in with Insulin: A meta-analysis resulted in lowering fasting plasma glucose levels by 0.95mmol/L, HbA1c levels by 0.56% and dose of insulin by 8.79 IU. Thus combinational use showed positive effects on cardiovascular functions while urogenital infections increased by 29% as well as diabetic ketoacidosis risk<sup>5</sup>.

#### ADVERSE EFFECTS

SGLT-2in are related with few serious side effects when used abruptly. The predominant issue encompass urogenital infections, diabetic ketoacidosis, bone fractures and amputation. SGLT-2in display enough risk of urogenital infections due to proliferation of micro-organisms in urine. These type of infections are more prone in females than in males. On the other hand, Sotagliflozin and Empagliflozin do not potentiate urinary tract infections but has an upper hand on mycotic genital infections for about 12.8% and 4.3% with administration of 10mg Empagliflozin and placebo respectively<sup>11</sup>.

In May 2015, a label warning was issued by FDA on diabetic ketoacidosis risk as 44 cases were evaluated in type 2 diabetes, 16 cases in type 1 diabetes, 13 cases of unknown origin and 1 case as a result of autoimmune diabetes. The feasible DKA mechanisms include inhibiting renal reabsorption of glucose leading to increased urinary excretion of glucose and low plasma glucose concentration which further inhibits pancreatic beta cell insulin production thus amplifying alpha cell glucagon secretion leading to break down of fatty acids and lipids finally resulting in ketone bodies formation<sup>6</sup>. A masterpiece clinical trial revealed diabetic ketoacidosis risk of 6%, 4.3% and 0% with administration of Canagliflozin 100mg, 300mg and placebo while risk of 2.3% and 0% with administration of Sotagliflozin 200mg and placebo whereas risk of 4.3% and 3.3% with use of Empagliflozin 10mg and 25mg respectively. Thus all studies revealed diabetic ketoacidosis risk with use of SGLT-2in except for 2.5mg Empagliflozin. In order to overcome such adverse effects appropriate treatment and preventive measures need to be taken to show promising results. All the diabetic patients should be counselled about measures to prevent ketoacidosis, immediately report the symptoms experienced, leaflets including emergency points regarding use of SGLT-2in. All the health care professionals should consider ketone targeted control and prognosis in patients imparting diabetic ketoacidosis symptoms. Emergency department should be notified that any patient admitting with symptoms should initially consider ruling out diabetic ketoacidosis condition by undertaking investigations such as blood ketone levels, bicarbonate levels, venous pH in a way to improve quality of life. The vital ketosis management include body hydration, carbohydrate intake and injecting insulin<sup>11</sup>

Canagliflozin and Ertugliflozin exhibits greater risk of lower limb amputation. Furthermore, risk of bone fracture reported with administration of Canagliflozin. Impaired renal function patients have greater risk with , Dapagliflozin rather than normalised patients with kidney function. One hypothesis evaluated that low estradiol levels, weight loss and decreased blood pressure potentiates fracture risk while on the other hand rise in parathyroid hormone levels, low 1,25 dihydroxy-vitamin D eventually leading to greater risk of bone fractures.

Table-II Adverse effects related to SGLT-2in<sup>7</sup>

Drugs	Urinary tract infections	Genital tract infections	Amputation
Canagliflozin 100mg	2.1%	7.8%	3.5%
300mg	0.6%	8.8%	-
Dapagliflozin 5mg	2%	6.9%	-
10mg	0.6%	5.4%	-
Empagliflozin 10mg	1.7%	3.9%	-
25mg	0%	4.9%	-

#### CONCLUSION

It is thus clearly evident that SGLT-2in are approved and widely indicated in the treatment of type 1 and 2 diabetic patients thereby showing advantageous effects on obese and hypertensive patients and are contraindicated in renal impairment patients with decreased glomerular filtration rate. Glycaemic efficacy, safety, cardiovascular-renal effects, method of administration, cost, weight issues are important patient targeted approaches to minimise risk and significantly control plasma glucose levels. DPP-4in, pioglitazone, sulfonylureas are considered in the management of diabetes mellitus while hypoglycaemic risk patients are confined

to SGLT-2in only. Increased diabetic ketoacidosis and urogenital infections risk can be prevented with clinical education to physicians and patients, counselling programs, patient monitoring in a way to improve quality of life. Scientific insights need to be implicated to bring out innovative methods of treating diabetic patients for better survival outcomes.

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