



A Potential Observational Study on Safety, Efficacy and Cardiovascular Risk Assessment of SGLT2 Inhibitors (Canagliflozin and Empagliflozin) in Obese Patients with Type-2 Diabetes Mellitus

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ABSTRACT

Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a class of drugs that work on SGLT2 receptors in the kidneys to decrease glucose reabsorption. Lowering glucose levels mainly aids those with type 2 diabetes (T2DM) and additionally with obesity, also have many other effects on the body by reducing weight and know to help decrease hypertension, acute cardiac failure in the cardiovascular system. Their effects consequently include reductions in HbA1c, blood glucose levels, and blood pressure, but also reductions in body weight and adiposity. The ability to reduce body weight is consistently observed in individuals taking SGLT2 inhibitors, but this weight loss is moderate due to counter-regulatory mechanisms striving to maintain body weight.

Materials and Methods: Data was collect from tertiary care hospital for a period of 6 months to assess the safety and efficacy of SGLT2 inhibitors. Patients with HbA1c level of >7% and obese patients were included in this study. Change from baseline to 6 months follow were recorded for body weight changes, BMI, FBS, PPBS, HbA1c and assessment of Cardiovascular Risk score and safety profile was also assed for all the patients prescribed with SGLT2 inhibitors.

Results: Empagliflozin and Canagliflozin showed significant mean reduction differences in HbA1c, FBS, PPBS, Blood pressure and Body weight and Hip-waist ratio. The statistical analysis was performed by using unpaired t-test for both Treatments and found that FBS, PPBS, HbA1c, Weight, BMI and CV risk score shows no significant difference. DBP in Non hypertension patient's and hypertensive patient's shows no significant difference, but SBP in Non hypertension patient's and hypertensive patient's shows significant difference of >0.05. Empagliflozin and Canagliflozin improved survival with empagliflozin being superior to the other SGLT2i and both drugs showed a similar effect on improving the glycemic parameters and few incidence of adverse events were reported during the study period.

Conclusion: Upon treatment with Empagliflozin and Canagliflozin both drugs are well tolerated and showed a better outcome in all the aspects like safety, efficacy and empagliflozin reduced the cardiovascular effects compared to Canagliflozin. By analyzing all the data these drugs can be given alone or with other conventional OHAs in Obese patients with T2 DM.

Keywords: Diabetes Mellitus, OHAs, Empagliflozin, Canagliflozin, Hypoglycemics, UTIs, Genital mycotic infections.

INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) are closely linked by increasing prevalence worldwide. Obesity is a key modifiable risk factor for the development of diabetes, with 90% of adults with T2DM classified as overweight or obese. There is an estimated threefold increase in the development of diabetes associated with being overweight and a 7-fold increase in those with obesity¹⁻³. In body the accumulation of excessive fat induces a constellation of metabolic abnormalities and many diseases, including insulin resistance, atherogenic dyslipidemia, nonalcoholic fatty liver disease, β -cell dysfunction, prediabetes, and type 2 diabetes. In general, a progressive increase in body mass index (BMI), will progressively increases in the risk of developing type 2 diabetes⁴. Type 2 diabetes is caused by multi-organ insulin resistance, in conjunction with a decline in β -cell insulin secretory function. The worldwide increase in the prevalence of obesity is likely responsible for the increase in the prevalence of type 2 diabetes because obesity influences both insulin action and β -cell function⁵.

Pathophysiology of obesity and T2DM

The mechanisms linking obesity and T2DM are complex and still being understood, but likely involve a combination of:

- Adipose tissue release of excess circulating fatty acids, glycerol, hormones and pro-inflammatory cytokines, impairing cellular insulin signalling and increasing insulin resistance.⁶
- Chronically raised lipid levels leading to impaired islet beta-cell function and lower levels of insulin production.⁷

A range of treatment options are available for people with obesity and T2DM, including low-calorie diets with physical exercise and medications. Obesity should also be considered when choosing medical therapy for T2DM because common diabetes medications may lead to weight gain whereas others (such as glucagon-like peptide-1 agonists and sodium-glucose cotransporter-2 inhibitors) support weight loss in the obese patients mainly when given as add-on therapy or monotherapy⁸.



Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are a new class of oral anti-diabetic drugs (OAD) act by an insulin-independent mechanism, thereby providing a complementary effect when used in combination with other oral AHAs⁹. Canagliflozin and Empagliflozin decreases reabsorption of filtered glucose and reduces renal threshold for glucose, thereby elevating the urinary glucose excretion and reducing raised plasma glucose in patients with T2DM by increasing glucose excretion through urine these drugs are resulting in weight loss of the patients¹⁰.

Canagliflozin (Invokana®) is an SGLT2 inhibitor approved by FDA in 2014 administered as oral tablets with recommended doses of 100 mg & 300 mg. Canagliflozin acts on two types of SGLT receptors: SGLT-1 and SGLT-2. SGLT-2 is expressed in the proximal renal tubules and is responsible for the reabsorption of about 90% of the glucose filtered by the kidneys¹¹.

Canagliflozin when given as first-line monotherapy or add-on therapy to other antihyperglycaemic agents it will improve glycaemic control in adults with T2 DM, including those of older age and/or at high cardiovascular (CV) risk, and also shows a beneficial effect on their bodyweight and blood pressure (BP).¹² Adverse events associated with Canagliflozin are Hypoglycemia genital mycotic infections (GMIs), urinary tract infections (UTIs), osmotic diuresis (thirst or frequent urination), and volume depletion-related events (hypotension, postural dizziness, and orthostatic hypotension)¹³.

Empagliflozin is an antidiabetic agent used in adult patients with type 2 diabetes mellitus works by inhibiting the sodium-glucose co-transporter-2 (SGLT-2) found in the proximal tubules in the kidneys. It was FDA-approved in 2014. Empagliflozin can be used as a single agent or as a combination agent with other antidiabetic products¹⁴.

In 2016, the FDA (United States Food and Drug Administration) approved a new indication for empagliflozin, which was to reduce the risk of cardiovascular death in adult patients with type 2 diabetes and cardiovascular disease. Empagliflozin has been shown to reduce hospitalizations for heart failure and death from cardiovascular causes¹⁵. Patients are at an increased risk of cardiovascular mortality with type 2 diabetes, so prescribers should be made aware of the benefits of empagliflozin. Moreover, empagliflozin is associated with weight loss, with reductions in blood pressure without increasing heart rate¹⁶.

The incidence of adverse effects of Empagliflozin upon treatment, including hypotension, ketoacidosis, acute kidney injury, genital mycotic infections, hypoglycemia when used with insulin, dyslipidemia, Fournier gangrene, and pyelonephritis¹⁷.

MATERIALS AND METHODS

Study Design

The study is planned and conducted as a prospective observational study in two groups by enrolling obese patients with T2 DM patients.

Inclusion Criteria

- Both male and female patients diagnosed with obesity and Type 2 DM with age above 18 years with excess weight, poor diabetic control, Greater BMI (Inclusive of both) and prescribed with SGLT-2 inhibitors as add-on therapy to control Overweight in type 2 diabetes mellitus along with other class of oral Hypoglycemic Agents.
- Patients with HbA1c > 7% are included.
- Obese patients with cardiovascular diseases and patients who are with chronic kidney disease.

Exclusion Criteria

- Patients with the history of type 1 diabetes mellitus.
- History are evidence of gestational diabetes, significant hepatic disease, unstable/rapidly progressing renal disease.
- History or evidence of predispose to ketoacidosis including pancreatic insulin deficiency from any cause, pancreatic surgery and acute febrile illness.
- History or evidence of serious urinary tract infections including urosepsis and pyelonephritis.
- History or evidence of significant systemic diseases, seizures, psychiatric disorders, neurological disorders, metabolic disorders, nutritional disorders and/or allergic rash.
- History of addiction to any steroid use.

Patients who are not willing to participate in the study and patients who lost their follow up are excluded from the study.

Study Procedure:

The study is conducted by randomly selecting the patients from Department of General medicine and Endocrinology having obesity and type 2 DM. Subjects are identified and recruited based on the inclusion and exclusion criteria. Sample size is n=100 patients (50 in each arm) Empagliflozin 10 mg, 25 mg with other OHAs and Canagliflozin with other OHA agents

All the details of Patient's were collected at the time of enrollment and during the every follow up 12 weeks once for a period of 6 months. The parameters assessed in this study are Weight, BMI, diabetic profile includes HbA1c, FBS, PPBS and safety profiles includes adverse reaction and cardiovascular risk assessment was done by using Framingham Risk score.



Statistical Analysis

Statistical Analysis was performed by using ANOVA MODEL (Student's t test) in a SPSS Software latest version 22.0. The results were tabulated as mean \pm standard deviation (SD) and analyzed. The level of significance was determined as its 'p' value with $p > 0.001$ taken as not significant and $p < 0.05$ taken as significant at 1% significance level and $p < 0.001$ taken as highly significant.

RESULTS

A total of 100 patients were enrolled in the study based on the treatment they were received i.e., **Empagliflozin** and **Canagliflozin** in combination with other Oral hypoglycemic agents (OHA'S) and data analysis was performed for all the parameters like weight, BMI, HbA1c, FBS, PPBS, BMI, HWR, Blood Pressure (systolic and diastolic) were documented for 6 months' period. ADR's were also recorded during the study period.

Efficacy Parameters

Total n=100 patients were included in this study for two treatments N=60 was male and N=40 was female. Gender is categorized for two treatments i.e., For Empagliflozin male n=31(62%) and female n=19 (38%), and for Canagliflozin male n=28 (56%) and female n=22 (44%).

For Empagliflozin and Canagliflozin Weight and BMI was measured from baseline to 6 months with two follow-ups. Both Treatments showed significant reduction in weight after 6 months and mean difference for both treatments were mentioned in Table 1 and Figure 1. As P value is <0.001 in both groups it is statistically significant.

Empagliflozin and Canagliflozin showed significant reduction in HbA1c, FBS, PPBS levels after 6 months of treatment and mean difference of HbA1C, FBS & PPBS was given in Table 2 and Figure 2. As P value is <0.001 in both treatments it is statistically significant.

The blood pressure both Systolic (SBP) & Diastolic (DBP) was also assessed for both treatments from baseline to 6 months and Blood Pressure of the patients are categorized in hypertension and non- hypertension patients and their systolic and diastolic blood pressure (SBP and DBP) was assessed. The mean difference was mentioned in Table 3 & Figure 3. DBP in **Non hypertension patient's** and **hypertensive patient's** shows **no significant difference**, but SBP in **Non hypertension patient's** and **hypertensive patient's** shows **significant difference of >0.05** .

By using the Framingham Risk Assessment scale the Cardiovascular Risk was determined for both Empagliflozin and Canagliflozin and both drugs showed a significant mean reduction upon treatment with these drugs for a period of 6 months and the results were mentioned in Table 3 & Figure 3.

When **Empagliflozin** and **Canagliflozin** were compared using unpaired t test, FBS, PPBS, HbA1c, Weight, BMI and CV risk score shows **no significant difference**. Whereas the DBP in **Non hypertension patient's** and **hypertensive patient's** shows **no significant difference**, but SBP in **Non hypertension patient's** and **hypertensive patient's** shows **significant difference of >0.05** .

Table 1: Comparison of Weight and BMI of Empagliflozin and Canagliflozin

Parameters	Empagliflozin (Reduction difference)	Canagliflozin (Reduction difference)	P Value
Weight	3.14	1.47	0.299
BMI	0.64	0.61	0.311

Table 2: Comparison of HbA1c, FBS, PPBS levels in patients who received Empagliflozin and Canagliflozin

Parameters	Empagliflozin (Reduction difference)	Canagliflozin (Reduction difference)	P Value
HbA1c	0.55	0.45	0.378
FBS	17.4	16.04	0.558
PPBS	21.9	17.74	0.461

Table3: Comparison of SBP, DBP in hypertensive and non-hypertensive patients and CV Risk Score of group 2 patients who received Empagliflozin and Canagliflozin

Parameters	Empagliflozin (Reduction difference)	Canagliflozin (Reduction difference)	P Value
Systolic BP in hypertensive patients	4.2	10.77	0.021
Diastolic BP in hypertensive patients	3.61	4.87	0.086
Systolic BP in non- hypertensive patients	1.47	-0.14	0.018
Diastolic BP in non- hypertensive patients	4.63	-4.85	0.214
CV Risk Score	2.17	1.56	0.217



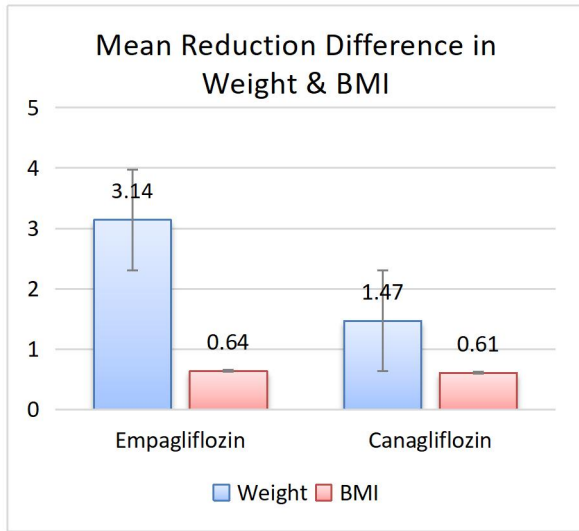


Figure 1: Mean difference in weight and BMI from Baseline to the last follow up.

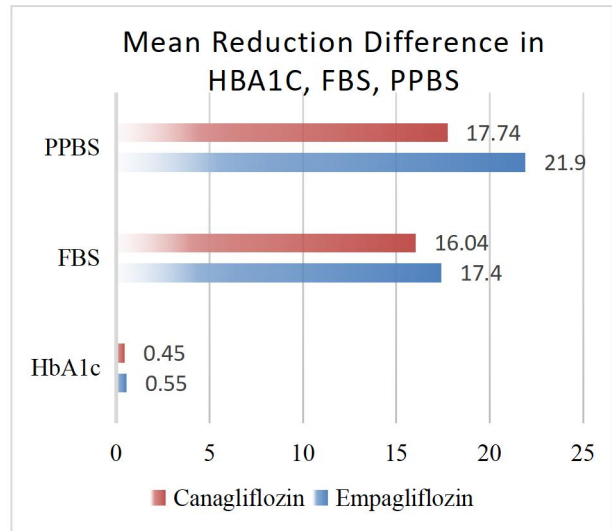


Figure 2: Mean difference in HbA1c, FBS, PPBS from Baseline to the last follow up.

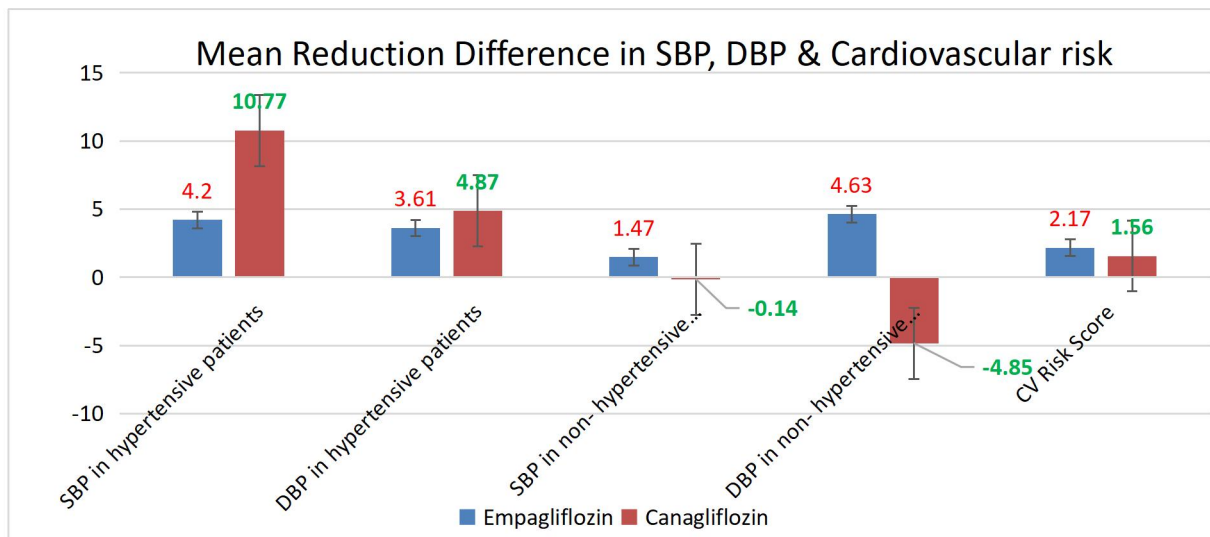


Figure 3: Mean difference in SBP, DBP in both Hypertensive and Non-Hypertensive patients and Cardiovascular risk from Baseline to the last follow up.

Table 4: The incidence of adverse drug reactions were mentioned in below table.

S.NO	Drug Name	Treatment C	Treatment B	P value
1	Hypoglycemic Episodes	14	10	0.870
2	Hypo + Nausea	8	7	0.537
3	Hypo + Weight gain	4	2	0.405
4	Weight Gain	3	4	0.489
5	Vomiting	4	8	0.492
6	Abdominal pain	7	5	0.850
7	UTI	6	9	0.406
8	Genital mycotic infection	7	1	0.980
9	Hypo + UTI	0	3	0.80
10	Hypo + Abdominal pain	1	0	0.320
11	Nausea + Abdominal pain	0	2	0.156
12	postural dizziness	6	0	0.108
13	No ADR'S	4	5	0.594

Safety Profile

The safety parameters were assessed during the study for Empagliflozin and Canagliflozin and both the drugs showed better safety outcomes with fewer incidences of Hypoglycemic Episodes, UTI's, Genital mycotic infections, Postural dizziness and Abdominal pain are more commonly seen in the patients who are treated with SGLT-2 inhibitors (Empagliflozin & Canagliflozin). When statistically comparing the safety profile between two drugs there were no statistically significant difference seen but the Canagliflozin treatment showed more no. of incidence of Adverse Events Compared to Empagliflozin treated groups and incidence of adverse events were mentioned in Table 4.

DISCUSSION

The present study was planned and conducted to determine the efficacy and safety profile of three SGLT2 inhibitors i.e., Dapagliflozin, Empagliflozin and Canagliflozin as an add-on therapy in Obese patients with Type-2 Diabetes mellitus who are overweight and experiencing inadequate glycemic control. In this study the patients are divided based on the Treatment: Empagliflozin with other OHAs and Treatment: Canagliflozin with other OHAs. Although two of the drugs tested in this study demonstrates their beneficial effect to improve blood glucose control in obese patients with Type 2 DM.

In this study all the subject's data were collected during the initial visit (Base line values) and remaining two follow ups (with in a period of every three months once). By analysing the Data, we observed that both the drugs are equally showed a better outcome but in some parameters Empagliflozin was relatively superior to Canagliflozin with respect to decreasing glycemic control, body weight, and Blood pressure from baseline to follow up.

Management of overweight/obese patients with T2 DM poses a challenge in glycemic control and weight reduction. The mechanism of SglT2 inhibitors may help in reduction of weight loss, decrease adiposity, and improve CV outcomes in obese patients who are with Type 2 DM and also for the patients with High Cardiovascular Disease associated hospitalization. As these drugs can be prescribed as an add-on therapy with other OHAs it is bit easy to achieve the efficient control of their glycemic index and weight reduction along with the physical exercise. Due to this these drugs can be used as a monotherapy or combination therapy of either two or even three different class of OHAs.

In our study we found that after treatment with Canagliflozin there was a significant reduction in body weight and glycemic control in the patients with obesity & type2 DM. This finding was similar to the study conducted in Indian population by **Pankaj Aneja, et al**¹⁸ who performed a retrospective study for Canagliflozin to determine the effectiveness and safety of this drug. This signifies that treatment with SGLT-2 inhibitors directly

cause body weight loss via glucose excretion (or) calorie loss in the kidney.

In terms of the glycaemic control with Canagliflozin and Empagliflozin HbA1c, FBS & PPBS levels was reduced and maintained consistently throughout the study. In addition to glucose lowering, these drugs act as osmotic diuretics where almost the glucose was excreted through urine which results in reduction of blood glucose levels T2 DM patients. But when comparing Empagliflozin and Canagliflozin it showed no significance difference.

As the study was conducted for a period of 6 months in this time period both the drugs showed a better glycaemic control and these drugs maintained relatively constant glycaemic control throughout the study period and these results are in consideration with the previously reported meta-analysis study about short term and long term efficacy of SGLT-2 inhibitors as a mono-therapy or additional therapy by **Li, Jian, et al.**¹⁹ In both groups our results about BP are partially inconsistent with those results reported in meta- analysis studies including all randomized clinical trials conducted by **Monami, M., C. Nardini, and E. Mannucci et al.**²⁰

Upon Canagliflozin treatment in both hypertensive and non-hypertensive patients it decreased Blood pressure HbA1c, Fasting and post meal glucose and Body weight where these results are in consideration with the study conducted by **Wei Xiong, et al.**²¹ Reported that patients treated with Canagliflozin showed a significant reduction Diabetic profile, clinical profile and safety profile.

Encouragingly, we observed a decrease in SBP, DBP and cardiovascular risk in T2 DM patient when treated with Empagliflozin and Canagliflozin and the results was similar to the meta-analysis study. In treatment with Empagliflozin the SBP, DBP and cardiovascular risk was reduced and these results are found be similar in the study (**EMPA-REG trials, DECLARE-TIM 58 trial**) which was conducted by **Imprialos, Konstantinos P., Pantelis A. Sarafidis, and Asterios I. Karagiannis.**²² In their study SGLT-2 inhibitors treated group improved cardiovascular morbidity and mortality and found that the use of these drugs was associated with decreased risk of cardiovascular death and cardiovascular hospitalization.

Limitations: The study was planned to determine the Safety, Efficacy and cardiovascular outcome of SglT2 inhibitors ie., Empagliflozin and Canagliflozin with in a time period of 6 months with only two follow ups, due to the less duration of time and sample size we are unable to clearly focus on the detail outcomes on how the cardiovascular Risk was improved by decreasing the cardiovascular mortality and how these class of drugs are significantly reducing the risk of kidney failure in Type 2 DM patients.

CONCLUSION

SGLT-2 inhibitors Empagliflozin and Canagliflozin showed a similar reduction in safety and efficacy parameters in treatment for obese patients with T2 DM, but eventually



when comparing the two Treatments Empagliflozin showed a better outcome in patients with Hypertension which lead to reduced cardiovascular death and hospitalization. Both drugs showed better safety outcomes and well tolerated in Obese Patients with Type-2 Diabetes Mellitus. By considering all the results both drugs can be prescribed to the obese patients with T 2 DM as both the drugs are decreasing the Glycated haemoglobin levels, body weights and other parameters.

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REFERENCES

- Jasleen B, Vishal GK, Sameera M, Fahad M, Deion S, Pemminati S. Sodium-glucose cotransporter 2 (SGLT2) inhibitors: benefits versus risk. *Cureus*. 2023; 15(1):30-36.
- Pereira MJ, Eriksson JW. Emerging role of SGLT-2 inhibitors for the treatment of obesity. *Drugs*. 2019; 79(3):219-30.
- Hossain P, Kavar B, El Nahas M. Obesity and diabetes in the developing world—a growing challenge. *New England journal of medicine*. 2007; 356(3):213-5.
- Klein S, Gastaldelli A, Yki-Järvinen H, Scherer PE. Why does obesity cause diabetes? *Cell metabolism*. 2022 ;34(1):11-20.
- Bogardus C, Tataranni PA. Reduced early insulin secretion in the etiology of type 2 diabetes mellitus in Pima Indians. *Diabetes*. 2002: S262-4.
- Al-Goblan AS, Al-Alfi MA, Khan MZ. Mechanism linking diabetes mellitus and obesity. *Diabetes, metabolic syndrome and obesity: targets and therapy*. 2014:587-91.
- Day C, Bailey CJ. Obesity in the pathogenesis of type 2 diabetes. *The British Journal of Diabetes & Vascular Disease*. 2011 ;11(2):55-61.
- Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, D'Alessio DA, Davies MJ. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes care*. 2020;43(2):487-93.
- Kalra S. Sodium glucose co-transporter-2 (SGLT2) inhibitors: a review of their basic and clinical pharmacology. *Diabetes Therapy*. 2014; 5(2):355-366.
- Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors | FDA [Internet]. [Cited 2022]. Available from: [https://www.fda.gov/drugs/postmarket-drug-safety-](https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/sodium-glucose-cotransporter-2-sgl2-inhibitors)
- information-patients- and providers/sodium-glucose-cotransporter-2-sgl2-inhibitors
- Jakher H, Chang TI, Tan M, Mahaffey KW. Canagliflozin review—safety and efficacy profile in patients with T2DM. *Diabetes, metabolic syndrome and obesity: targets and therapy*. Dovepress, 2019; 209-15.
- Deeks ED, Scheen AJ. Canagliflozin: a review in type 2 diabetes. *Drugs*. 2017;18:1577-92.
- Kumar KP, Ghosh S, Canovatchel W, Garodia N, Rajashekar S. A review of clinical efficacy and safety of canagliflozin 300 mg in the management of patients with type 2 diabetes mellitus. *Indian Journal of Endocrinology and Metabolism*. 2017 ;21(1):196-209.
- Sizar O, Podder V, Talati R. Empagliflozin, 2023.
- Fitchett D, Inzucchi SE, Cannon CP, McGuire DK, Scirica BM, Johansen OE, Sambevski S, Kaspers S, Pfarr E, George JT, Zinman B. Empagliflozin reduced mortality and hospitalization for heart failure across the spectrum of cardiovascular risk in the EMPA-REG OUTCOME trial. *Circulation*. 2019 ;139(11):1384-95.
- Schwaiger E, Burghart L, Signorini L, Ristl R, Kopecky C, Tura A, Pacini G, Wrba T, Antlanger M, Schmaldienst S, Wertzowa J. Empagliflozin in posttransplantation diabetes mellitus: a prospective, interventional pilot study on glucose metabolism, fluid volume, and patient safety. *American Journal of Transplantation*. 2019 ;19(3):907-19.
- Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *New england journal of medicine*. 2015 Nov 26;373(22):2117-28.
- Aneja P, Bhalla G, Parvesh N, Aneja K, Aneja K. Efficacy and safety of canagliflozin 300 mg in overweight and obese type 2 diabetes mellitus patients in a real-world setting: COLOR study. *Indian Journal of Endocrinology and Metabolism*. 2019 May: 307-11.
- Li J, Gong Y, Li C, Lu Y, Liu Y, Shao Y. Long-term efficacy and safety of sodium- glucose cotransporter-2 inhibitors as add-on to metformin treatment in the management of type 2 diabetes mellitus: a meta-analysis. *Medicine*. 2017;27:96-102.
- Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in t pe 2 diabetes: a meta-anal sis of randomized clinical trials *Diabetes, Obesity and Metabolism*. 2014:8(5):457-466.
- Xiong W, Xiao MY, Zhang M, Chang F. Efficacy and safety of canagliflozin in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. *Medicine*. 2016.
- Imprialos KP, Sarafidis PA, Karagiannis AI. Sodium–glucose cotransporter-2 inhibitors and blood pressure decrease: a valuable effect of a novel antidiabetic class? *Journal of hypertension*. 2015; 33 (11):2185-219.

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