PROSPECTIVE STUDY ON PRESCRIBING PATTERN AND SHORT-TERM OUTCOMES OF SGLT-2 INHIBITORS IN A TERTIARY CARE HOSPITAL

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CERTIFICATE

This is to certify that the dissertation work entitled**"PROSPECTIVE STUDY ON PRESCRIBING PATTERN AND SHORT-TERM OUTCOMES OF SGLT-2 INHIBITORS IN A TERTIARY CARE HOSPITAL"**was carried out by **Reg. no. 261640602.** The work mentioned in the dissertation was carried out at the Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore, Tamilnadu, under the guidance of **Dr. C. Sankar, M.Pharm (Ph.D.)** for the partial fulfilment for the degree of Master of Pharmacy during the academic year 2017-2018 and is forwarded to The Tamilnadu Dr. M.G.R. Medical University, Chennai.

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This is certified that the dissertation work entitled **"PROSPECTIVE STUDY ON PRESCRIBING PATTERN AND SHORT-TERM OUTCOMES OF SGLT-2 INHIBITORS IN A TERTIARY CARE HOSPITAL"** is a bonafide work carried out by **Reg. no. 261640602**. The work mentioned in the dissertation was carried out at the Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore.

DATE: Dr. C. SANKAR, M. PHARM, Ph. D.

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DECLARATION CERTIFICATE

I do hereby declare that the dissertation work entitled **"PROSPECTIVE STUDY ON PRESCRIBING PATTERN AND SHORT-TERM OUTCOMES OF SGLT-2 INHIBITORS IN A TERTIARY CARE HOSPITAL"**was carried out at Diabetology and Endocrinology Department, Kovai Medical Center and Hospital, Coimbatoreand submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment for the Degree of **MASTER OF PHARMACY,**was done under direct supervision and guidance of **Prof.Dr.C. SANKAR.,**during the academic year 2017-2018.

Reg.No: 261640602

EVALUATION CERTIFICATE

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Examination Centre: Department of Pharmacy Practice, Coimbatore

Date:

Internal Examiner: **External Examiner:**

Convener of Examination:

Dedicated

to

GOD ALMIGHTY

"the most compassionate the most merciful"

MYBELOVED FAMILY& FRIENDS

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ABSTRACT

Background: Sodium glucose co-transporter (SGLT-2) inhibitors are new class of anti-diabetic therapy and shown to reduce cardiovascular mortality and heart failure in patients with T2DM with previous CV events or established cardiovascular disease. The aim of the study was to determine the prescribing pattern and short-term outcomes of SGLT-2 inhibitors. The primary outcome was to study the effect of SGLT-2 inhibitor as an add-on to insulin.

Methods: The prospective observational study was conducted which included 315 patients receiving SGLT-2 inhibitors for the management of T2DM mellitus with eGFR ≥40ml/min/1.73m2. The study population was divided into two- SGLT-2 + insulin ± OHA and SGLT-2 + OHA, which were further sub-divided based on duration of diabetes i.e., patients with ≤5 years and >5 years of T2DM respectively. The study was followed-up at 2 months and 4 months. At the time of entry, complete medical history and laboratory evaluation were obtained. Patients demographics were also considered and recorded. The change in HbA1C, FBS, RBS, body weight, BMI, and lipid profile were measured at 2 month and 4 months. The patients were interviewed to assess ADR (if any) and it was confirmed by Naranjo ADR Scale. The adherence of the patients toward the medication was assessed with Morisky patient medication adherence scale.

Result: The study showed that empagliflozin + biguanides + insulin + DPP-4 was the most prescribed combination. The glucose lowering (HbA1c, FBS and RBS) effect was more in empagliflozin + insulin ± OHA treated patients. Body weight, BMI and LDL was found decreased while HDL was slightly increased. Hypoglycemia was the mostly reported ADR and was more in insulin treated patients. Only one case of geno-mycotic infections was reported. Insulin treated patients had lower adherence towards the medication and hypoglycemic events was more in those patients.

Conclusion: In conclusion, SGLT-2 inhibitor (empagliflozin) was found to significantly improve glycemic parameters along with reduction in body weight, BMI, and LDL with good effect on HDL in Indian T2DM patients with mild ADR when prescribed as add-on to insulin or other OHA.

1. INTRODUCTION

Diabetes mellitus was first reported in Egyptian manuscript about 3000 years ago. In 1936, the distinction between type I and type II DM was clearly made. Type II DM was first described as a component of metabolic syndrome in 1988.[1]

Type II diabetes (formerly known as non-insulin dependent DM) is due to insufficient insulin production from beta cells in the setting of insulin resistance.[2] Insulin resistance, which is the inability of cells to respond adequately to normal levels of insulin, occurs primarily within the muscles, liver and fat tissue. In the liver, insulin normally suppresses glucose release.[3]

The prevalence of Type II DM is increasing all over the world, especially in South Asia. India has largest population of diabetic patients. The International Diabetes Federation (IDF) estimates the number of people with diabetes in India will reach 80 million by the year 2025.[4]

DIABETES AND CARDIOVASCULAR DISEASE:

People with type II DM have two-to four-folds increased risk for coronary heart disease compared to those without diabetes,[5] as well as other vascular disorders (consisting of heart failure, cardiac dysrhythmia, sudden death, hypertensive disease, pulmonary embolism, and aortic aneurysm). Heart failure is a particularly common complication of T2DM and is associated with poor outcomes.[6] The risk associated with diabetes is higher at younger ages and lower at higher ages. For instance, at the age of 60 years, a patient with T2DM and cardiovascular disease (CVD) has reduced life expectancy of 12 years compared with the general population, according to a study by the Emerging Risk Factors Collaboration (689,300 participants; 91 European cohorts), [7] and of 2 years at age 67 years in Sweden.[5] There is,

therefore, a need for novel treatment for T2DM that not only improve glycemic control but also reduce the risk of CVD.

MANAGEMENT OF TYPE II DIABETES MELLITUS – "CARDIOVASCULAR CONSIDERATION":

Historically, the aim of glucose-lowering therapy in diabetes is to reduce microvascular complications. Whereas, interventional studies focused on intensive glucose reduction in T2DM have only had a minor or no effect in reducing cardiovascular risk.[8] In 1998, the UK Prospective Diabetes Study (UKPDS) found that a subgroup of obese patients randomized to metformin had a reduction in myocardial infraction.[9]Since then, metformin had become the standard first-line drug treatment for T2DM.[10] In the last two decades, numerous therapeutic options have emerged for T2DM, including dipeptidyl peptidase-4 inhibitor (DPP-4i), glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors.

In 2008, following the withdrawal of rosiglitazone from the market because of its association with increased risk of HF and MI,[11] the US Food and Drug Administration (FDA) mandated CV outcome trials (CVOTs) on glucose-lowering drugs (GLDs).[12] In 2012, the European Medicines Agency (EMA) also published a guideline requiring CVOTs for new GLDs for which specific CV claims are made or that are suspected of having detrimental CV effects.[13] As a result, two drugs – empagliflozin (an SGLT-2 inhibitor) and liraglutide (a GLP-1 receptor agonist) – have a level A recommendation in the American Diabetes Association (ADA) 2018 Standards of Medical Care in Diabetes.[14]

Class	Generic names	Mechanism of action	CV outcomes
Sulfonylureas	GliclazideGlimepirideGlyburide	Stimulate pancreatic insulin secretion	Possible increase in CV death
Biguanides	Metformin	Inhibit hepatic glucose production	Possible CV benefits supported by small trials and number of events
Thiazolidinediones	Pioglitazone Rosiglitazone	Increase insulin sensitivity and reduce hepatic glucose production	Pioglitazone CV benefits. Rosiglitazone increases risk of HF
DPP-4 inhibitors	Linagliptin Saxagliptin Sitagliptin Alogliptin	Intensify the effect of the intestinal incretins	Saxagliptin and alogliptin increases the risk for HF whereas sitagliptin has no CV effect
GLP-1 agonists	Exenatide Liraglutide	Mimics the effect of incretins	Reduce CV death
SGLT-2 receptor inhibitors	Empagliflozin Canagliflozin Dapagliflozin	Inhibit renal glucose reabsorption favouring renal excretion	Decrease CV death and HF hospitalization, rare hypoglycaemia, decrease blood

			pressure and body weight

Table 1: Class, generic name, mechanism of action, and side effect on CV outcomes of most commonly used hypoglycemic drugs.[15]

SODIUM-GLUCOSE CO-TRANSPORTER-2 (SGLT-2) INHIBITORS:

Inhibitors of sodium-glucose cotransporters type-2 (SGLT-2) are new glucose-lowering agents with an original insulin-independent mode of action developed for the treatment of type-II diabetes mellitus.[16] They specifically target the kidney by blocking the reabsorption of filtered glucose. This effect results in increased urinary glucose excretion, especially when hyperglycemia is present and provided that renal function is maintained.[17] This mechanism of action holds promise for patients with T2DM not only in terms of improvements in glycemic control, with a limited risk of hypoglycemia, but also considering the potential benefits of weight loss resulting from increased glucosuria and arterial blood pressure reduction associated with the osmotic/diuretic effect.[18] These agents share a negligible risk of drug–drug interactions, an interesting characteristic in T2DM patients generally exposed to multiple pharmacological agents.[19] However, caution is requested in patients with renal impairment.[20] Numerous randomized controlled trials (RCTs) evaluated SGLT2 inhibitors as monotherapy in diet-treated patients or as add-on therapy to different glucose-lowering agents, including insulin.[21,22] They are now integrated as second or third-line therapy in the algorithm of the 2015 position statement by the American Diabetes Association (ADA) and the European Association for the study of Diabetes (EASD).[23]

FDA APROVED SGLT-2 INHIBITORS:

1. Empagliflozin (Boehringer Ingelheim and Eli Lilly, approved as Jardiance by US FDA in 2014).[24]
2. Dapagliflozin (AstraZeneca, approved as Farxiga by US FDA in 2014).[25]
3. Canagliflozin (Janssen Pharmaceuticals, approved as Invokana by US FDA in 2013).[26]

PHYSIOLOGY OF RENAL GLUCOSE REABSORBTION:

At normal concentrations of plasma glucose, the kidneys actively reabsorb almost all filtered glucose (approximately 180 g/day) with less than 1% excreted in the urine.Glycosuria occurs when plasma glucose concentrations exceed the glucose reabsorbing capacity of the proximal tubules. This renal threshold for glucose is about 11 mmol/L.[27]

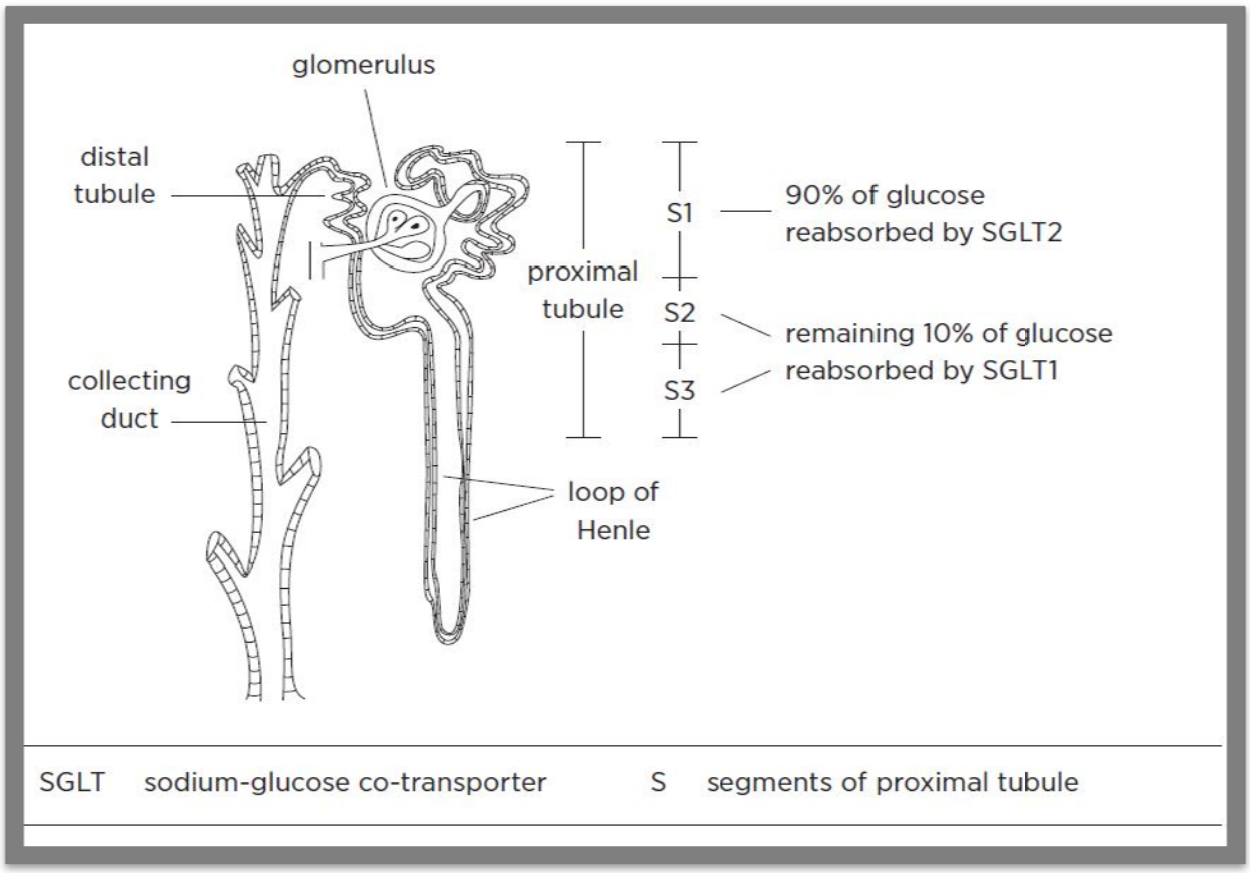
Glucose is a hydrophilic molecule which needs to be transported across cell membranes to enter cells. Glucose transport can either be facilitative or active. Facilitative transport is driven by the concentration gradient across the cell membrane. Active transport is driven by sodium co-transport. Uptake of glucose in the intestine and kidneys is by active transport, mediated by members of the SGLT family. SGLT-1 and SGLT-2 are responsible for glucose reabsorption in the proximal tubules of the kidneys (Fig. 1).[28]

SGLT-2 is a low-affinity, high capacity glucose transporter located in segment 1 of the proximal tubule (in the apical membrane of the tubule cells). Under normal circumstances SGLT-2 reabsorbs about 90% of the filtered glucose (Fig. 2). SGLT-2 is minimally expressed in other tissues.[29]

SGLT-1 is a high-affinity, low capacity glucose transporter predominantly found in enterocytes of the small intestine where it transports glucose and galactose from the gut lumen across the gut wall. In the kidney SGLT-1 is located in segments 2–3 of the proximal tubule.

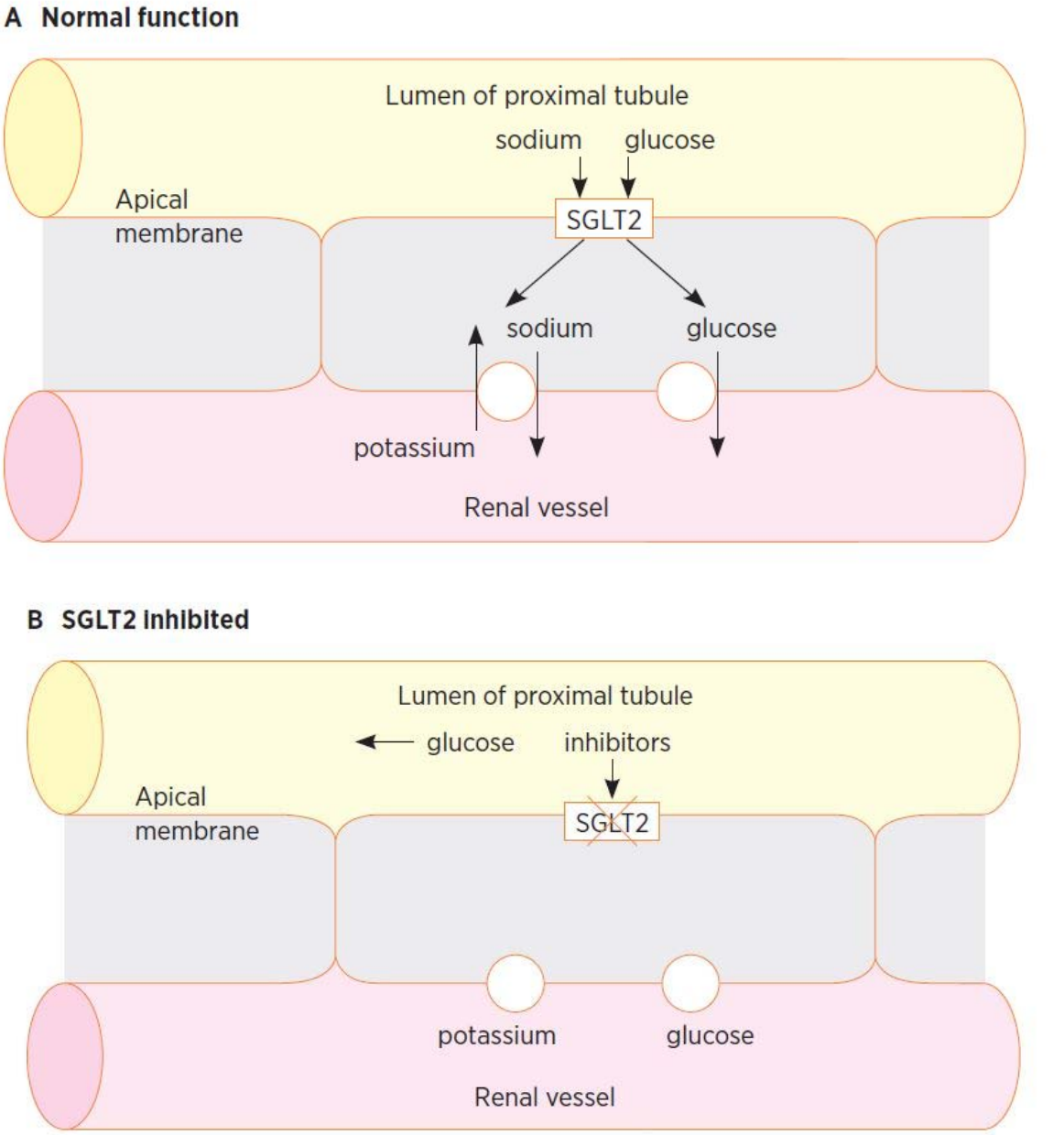
Following glucose reabsorption by SGLT-2 early in the proximal tubule the remaining 10% of filtered glucose is reabsorbed by SGLT-1 later in the proximal tubule.[30]

Figure 1: Location of SGLT1 and SGLT2 in the proximal tubules of the kidney.[30]



SGLT-2 inhibitor mediated inhibition of glucose reabsorption in the proximal tubule leads to the excretion of about 90% of glucose through renal mechanism. Excess diuresis favor blood pressure and calorie loss, but sometimes leads to genital mycotic infections.[30]

Figure 2: Action of SGLT2 in the proximal tubule.[30]



PHARMACOLOGY OF SGLT-2 INHIBITORS:

TheSGLT-2 inhibitors approved by FDAare empagliflozin, dapagliflozin and canagliflozin, have high bioavailability. These drugs can be taken once a day, preferably before the first meal of the day. These drugs are highly protein bound in plasma and are metabolized in the liver via glucuronidation.With these characteristics there is a low propensity for pharmacokinetic drug–drug interactions. However, inducers of glucuronidation can cause a modest increase in the metabolism of SGLT-2 inhibitors. When inducers of glucuronidation (e.g. rifampicin, phenytoin or ritonavir) are prescribed, the product information for canagliflozin recommends a higher dose of 300 mg daily (usual starting dose 100 mg daily) or using an alternative blood glucose-lowering drug. The product information for dapagliflozin and empagliflozin does not recommend a dose increase. Inhibition of metabolism by other glucuronidated drugs, for example mefenamic acid, is possible.[31]The clinical significance of these potential interactions with either drug is likely to be low. Canagliflozin may increase the plasma concentration of digoxin so digoxin concentrations should be monitored when starting or stopping canagliflozin.

Pharmacodynamic drug interactions may occur with thiazides and loop diuretics, increasing diuresis and the risk of dehydration. Changes in renal tubular handling of potassium associated with SGLT-2 inhibition may be significant in patients at higher risk of hyperkalaemia, for example those with baseline renal impairment, taking ACE inhibitors or taking potassium-sparing diuretics.[30]

In patients with mild to moderate liver impairment, no significant increase in drug concentrations was seen with either drug. A lower starting dose of dapagliflozin (5 mg) is recommended in patients with severe liver disease. There are no published data for canagliflozin and empagliflozin in severe liver disease.

According to EMPA-REG[32] and CANVAS[33] trials, the reported adverse events associated with empagliflozin and canagliflozin are genital mycotic infections and diabetic ketoacidosis.

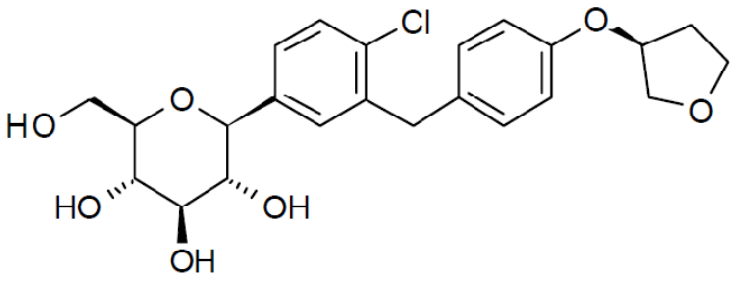
Bladder cancer was reported with canagliflozin which diminish the clinician favor.

EMPAGLIFLOZIN:

Empagliflozin is the latest SGLT-2i approved by US FDA for the treatment of T2DM. In the EMPA-REG OUTCOME[32] trial, empagliflozin added to standard of care reduced the risk of 3-point major adverse cardiovascular (CV) events (3-point MACE: composite of CV death, non-fatal myocardial infarction, or non-fatal stroke) by 14%, CV death by 38%, hospitalization for heart failure by 35%, and all-cause mortality by 32% in patients with type 2 diabetes (T2DM) and established CV disease.

- Empagliflozinis chemically (1S)-1,5-anhydro-1-(4 – chloro-3-{4-[(3S)-tetrahydrofuran-3-yloxy] benzyl} phenyl)-D-glucitol.

Figure 3: Chemical structure of Empagliflozin[34]



- Empagliflozin is available in 10 mg and 25 mg, should be taken once a day.

- It had the elimination half-life of about 12.4 hour.
- After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations (C_{max}) with a median time to reach C_{max} (t_{max}) of 1.5 h post-dose.
- The apparent steady-state volume of distribution was estimated to be 73.8 L plasma protein binding was 86.2%.
- primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.
- The apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis.
- Approximately 54.4% of the drug are excreted through urine.

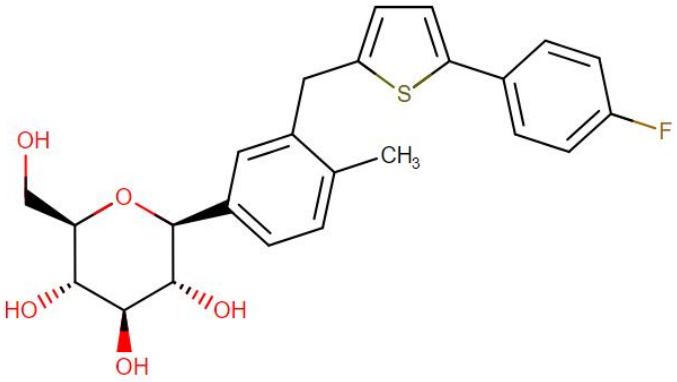
CANAGLIFLOZIN:

CANVAS[33] trial proofs the effect of treatment with canagliflozin on cardiovascular, renal, and safety outcomes. In two trials involving patients with T2DM and an elevated risk of cardiovascular disease, patients treated with canagliflozin had lower risk of cardiovascular events than those who received placebo but greater risk of amputation, primarily at the level of the toe or metatarsal.

- Canagliflozin is available in 100 mg and 300 mg tablets, should be taken once a day.
- Canagliflozin is chemically (2S,3R,4R,5S,6R)-2-[3-[[5-(4-fluorophenyl)thiophen-2-yl]methyl]-4-methylphenyl]-6-(hydroxymethyl)oxane-3,4,5-triol.
- Canagliflozin is rapidly absorbed achieving peak plasma concentration in 1-2 hours and has a bioavailability of 65%.

- It is glucuronidated into two inactive metabolites, M7 and M5 by uridine diphosphate-glucuronosyltransferase (UGT) 1A9 and UGT2B4, respectively.

Figure 4: Chemical structure of Canagliflozin[35]

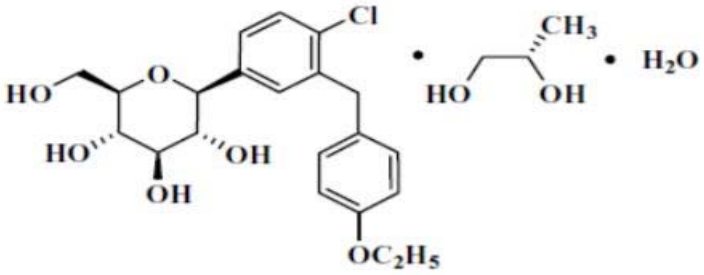


- Reaches steady state in 4 days.
- The half-life of orally administered canagliflozin 100 mg and 300 mg in healthy participants is 10.6 and 13.1 hours, respectively.

DAPAGLIFLIOZIN:

DECLARE-TIMI58[36] trial demonstrate the effect of dapagliflozin on cardiovascular outcomes when added to standard therapy in patients with T2DM with either established cardiovascular disease or cardiovascular risk factors.

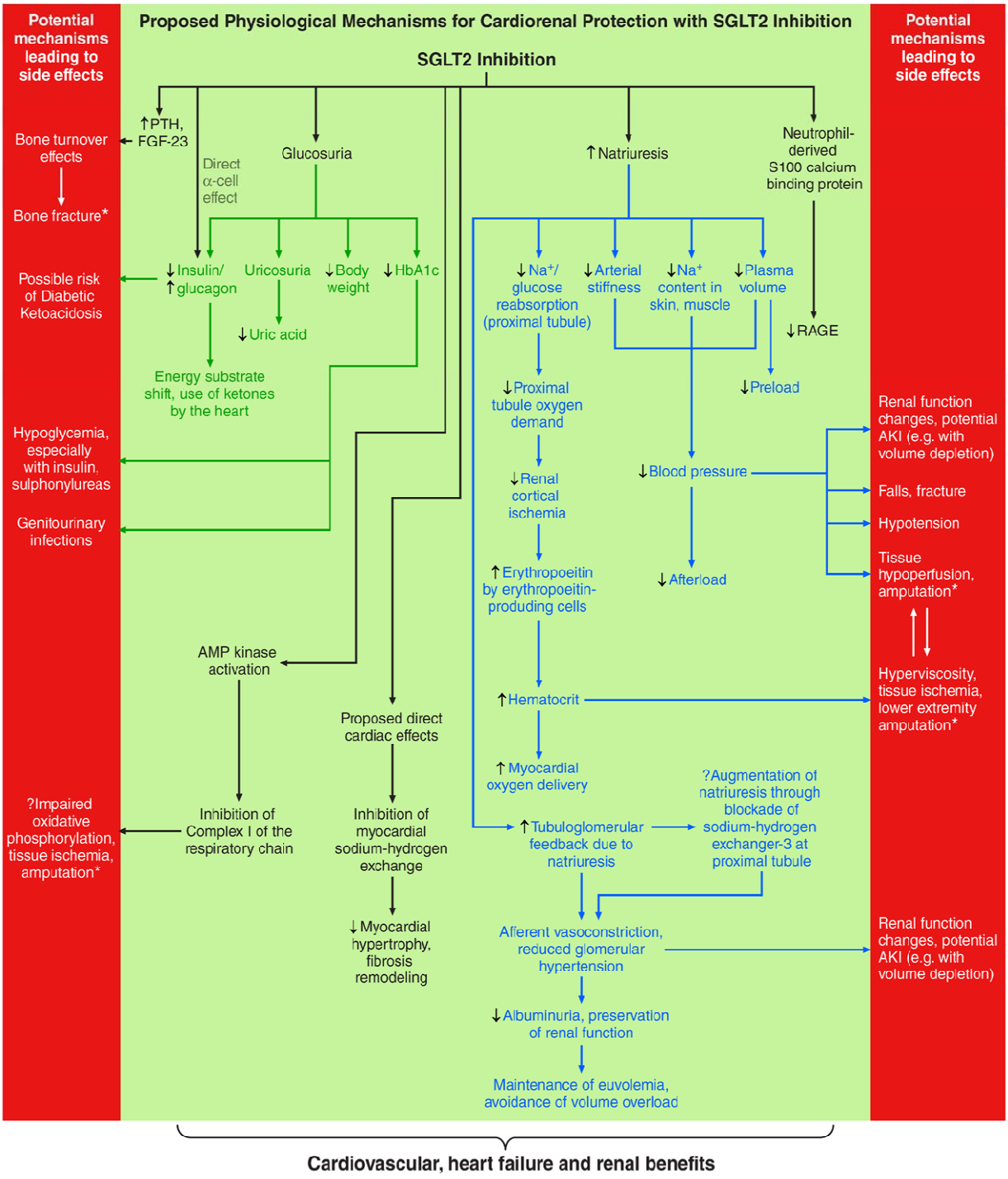
Figure 5: Chemical structure of Dapagliflozin[37]



- Dapagliflozin achieve peak plasma concentration within 2 hours.
- Bioavailability 78%
- Dapagliflozin metabolism occurs predominantly in the liver and kidneys by uridine diphosphate-glucuronosyltransferase-1A9 to the major metabolite dapagliflozin 3-O-glucuronide.
- The half-life for orally administered dapagliflozin 10 mg is 12.9 hours.
- Maximal increases in urinary glucose excretion were seen at doses ≥20 mg/day in patients with T2DM.

CARDIO-RENAL BENEFITS AND RISK ASSOCIATED WITH SGLT-2 INHIBITORS – "PROPOSED MECHANISM":

Figure 6: Integrated physiological basis for proposed mechanisms leading to cardiorenal benefits and risks associated with sodium glucose cotransport-2 inhibition.[38]



MAJOR CLINICAL TRIALS WITH SGLT-2 INHIBITORS:

Table 2: List of major clinical trials conducted for SGLT-2 inhibitor.[38]

Name of Clinical Trial	Type	Treatment Arms	Duration	Sample Size
CARDIOVASCULAR OUTCOME TRIALS				
EMPA-REGOUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients)	Double-blind, placebocontrolled RCT (phase 3)	Empagliflozin10 mg or 25mg daily vs placebo	Up to4.6 years	7020 patients with established cardiovascular complications (≥18 y)
CANVAS Program (Canagliflozin Cardiovascular AssessmentStudy)	Double-blind, placebocontrolled RCT (phase 3)	Canagliflozin 100 mg or 300 mg daily vs placebo	3.6 years	10 142 patients with established vascular complications or ≥2 cardiovascular risk factors (>30 y)
CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in	Double-blind, placebocontrolled RCT (phase 3)	Canagliflozin 100 mg daily vs placebo	4 years	3627 patientswith stage 2 or 3 CKDand macro-albuminuriaand on ACEi/ARB (>30 y)

Participants with Diabetic Nephropathy)				
DECLARE-TIMI 58 (Multi-centre Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events)	Double-blind, placebocontrolled RCT (phase 3)	Dapagliflozin 10 mg vs placebo	Up to 6 years	17,276 patients with high risk for cardiovascular events (≥40 y)
EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction)	Double-blind, placebocontrolled RCT (phase 3)	Empagliflozin 10 mg daily vs placebo	38 months	4126 patients with HFpEF (≥18 y)

SGLT-2 INHIBITORS IN TYPE II DIABETES MELLITUS:

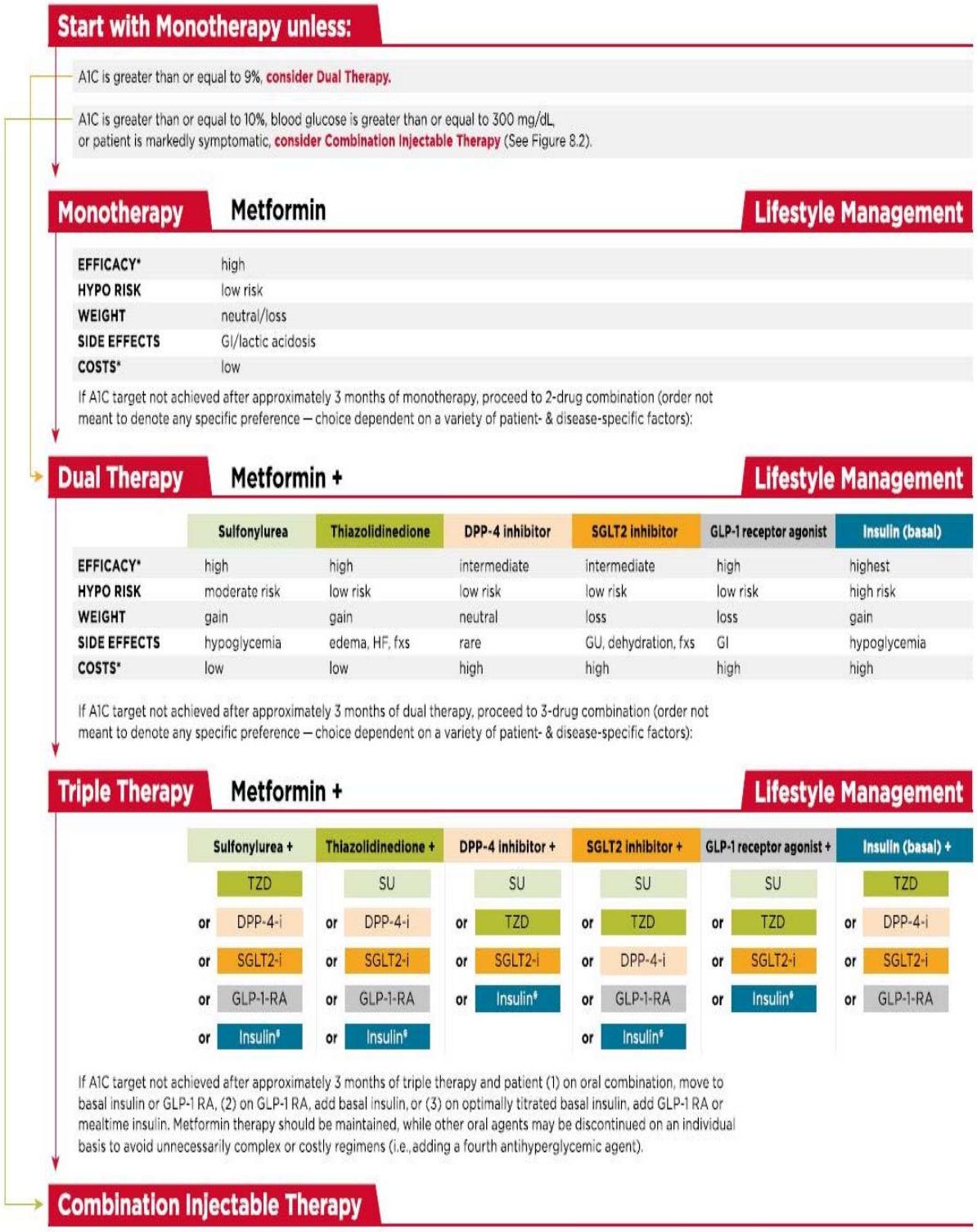
Treatment with an SGLT-2 inhibitor causes dose-dependent urinary net glucose loss of 20–70g per day. This varies with the degree of hyperglycemia. The US Food and Drug Administration analyses of clinical trials found dapagliflozin reduces glycated hemoglobin (HbA_{1C}) in patients with type 2 diabetes by 4–9 mmol/mol (0.4–0.8%), depending on the initial HbA_{1C}[32].Similarly, for canagliflozin there was a dose-dependent HbA_{1C} reduction of 4–11 mmol/mol (0.4–1%),[31]whereas empagliflozin shows 0.6-1% reduction in HbA_{1C}.[36]This is comparable to the effect of dipeptidyl peptidase 4 inhibitors, but less than that of metformin,

sulfonylureas or glucagon-like peptide-1 analogue.[39]The reduction in blood glucose concentrations occurs independently of any increase in insulin concentrations or decrease in peripheral insulin resistance. In addition, the glycosuria causes a caloric loss, which has been associated with an average weight loss of 2–3 kg over 6–12 months in clinical trials.

According to American Diabetes Association, 2017 guidelines[40] for the treatment of type II diabetes mellitus, SGLT-2 inhibitors shall be used as dual-therapy or triple-therapy with other oral hypoglycemic drugs (OHD).

POSITION OF SGLT-2 INHIBITORS IN AMERICAN DIABETES ASSOCIATION GUIDELINES:

Figure 7: Pharmacologic therapy for type II diabetes by ADA,2017[40]



According to American Diabetes Association (ADA), American Association of Clinical endocrinologists (AACE), European Society and NICE (UK) guidelines suggest that SGLT-2 inhibitors should be considered over other oral hypoglycemic therapy especially in patients having established cardiac disease or risk of cardiovascular disease with/or increased incidence of hypoglycemia and/or weight gain. The present study plays an important role in focusing the effect of SGLT-2 inhibitor as an add-on to insulin or other OHA.

2. LITERATURE REVIEW

- **Laffel*et al.*, (2018)**[41] conducted a single dose, open-label, randomized, parallel group study with empagliflozin 5 mg, 10 mg and 25 mg in 39 young people with T2DM aged 10-17 years to assess the pharmacokinetic and pharmacodynamic profile of single dose empagliflozin. The study shows there is a dose-dependent increase in urinary glucose excretion, along with decrease in plasma blood glucose and body weight.
- **Jobori*et al.*, (2018)**[42] included 15 patients with T2DM for an open-label study in which all the patients were treated with 25 mg empagliflozin/day and received a hyperglycaemic clamp before and at 48 hours and 14 days. The study shows, lowering the plasma glucose concentration with empagliflozin cause a rapid increase in β-cell function. The effect of empagliflozin occurs rapidly and last for the entire treatment period (i.e., 14 days).
- **Inzucchi*et al.*, (2018)**[43]conducted an exploratory analysis to identify the mechanism behind 38% reduction in the risk of CV death observed with empagliflozin versus placebo in patients with T2DM and established CVD in EMPA-REG OUTCOME trial which included 7020 patients.The primary analysis of CVD with empagliflozin versus placebo was based on Cox proportional hazard regression model. The study shows, changes in the haematocrit and haemoglobin which play a role in plasma volume appears to be the variables with largest impact on HR and CV death with empagliflozin and placebo group.
- **Xiaoling*et al.*, (2018)**[44]conducted a meta-analysis with 55 placebo control trial to evaluate the weight changes associated with different SGLT-2 inhibitors. The study summaries that there was significant reduction in the body weight

(empagliflozin 10 mg and 25 mg shows -1.84 kg and -1.93 kg respectively) in patients with T2DM who received different doses of SGLT-2 inhibitors.

- **Verma *et al.*, (2018)**[45] conducted a sub-analysis of EMPA-REG OUTCOME trial, in which they randomized patients with self-reported history of coronary artery bypass graft (CABG) in empagliflozin 10 mg, 25 mg and placebo group. The study concludes, there was a profound reduction in the cardiovascular and all-cause mortality, hospitalization for heart failure, and incidences of worsening nephropathy. These data have important implications for secondary prevention of cardiovascular events after CABG in individuals with T2DM.
- **Zinman*et al.*, (2018)**[32] performed a sub-analysis of EMPA-REG OUTCOME trial to determine the relative CV prevention effect of empagliflozin in women versus men in which they compared 2004 women and 5016 men. In conclusion, CV death, HF hospitalization, and incident or worsening nephropathy rate reduction induced by empagliflozin were not different between men and women.
- **Irace*et al.*, (2018)**[46] designed a non-randomized, open, prospective cohort study including 35 T2DM outpatients who received empagliflozin in combination with insulin or metformin to study the effect of empagliflozin on blood viscosity and shear stress in carotid arteries. Blood viscosity, shear stress and carotid wall thickness were measured at 1 and 3 months. This study is the first reported the empagliflozin caused increase in haematocrit, blood viscosity and wall shear stress. IMT was markedly reduced.
- **Refardt*et al.*, (2018)**[47] performed a double-blind placebo-controlled randomised crossover study in 14 healthy volunteers to study the short-term urinary volume output in syndrome of inappropriate antidiuresis (SIADH).

They induced an artificial SIADH model by administration of desmopressin and overhydration. Afterwards, 25 mg empagliflozin or placebo was given. In SIADH model, empagliflozin increased urinary excretion due to osmotic diuresis and due to short-term treatment, serum sodium level remained unchanged. Further, real-life study needed to examine empagliflozin as a new treatment for SIADH.

- **Yasui*et al.*, (2018)**[48] randomized 100 Japanese T2DM patients to receive 1, 5, 10 and 25 mg empagliflozin or placebo once daily. Changes from baseline 24-hour urine volume and fluid intake were assessed at 1, 27 and 28 days after the initiation of empagliflozin. Finally, treatment initiation with empagliflozin was associated with transient diuresis; overall urine volume return towards baseline level within 4 weeks of treatment.
- **Kohler *et al.*, (2018)**[49] assessed the effect of empagliflozin on bone fractures and bone mineral density in patients with T2DM in pooled placebo-controlled trial and head-to-head study versus glimepiride. In the trials, they randomized the patients to receive 10 mg or 25 mg empagliflozin and placebo. The study shows, empagliflozin did not increase the risk of bone fracture compared with placebo in pooled analysis of >12000 patients or compared with glimepiride in 4-year head-to-head study.
- **Hattori *et al.*, (2018)**[50] conducted an open label, single centre, prospective study which included 109 T2DM patients. Empagliflozin 10 mg or placebo was randomly administered once daily for 12 weeks as add-on therapy. The empagliflozin treated group shows, significant reduction in the blood glucose along with remnant-particle cholesterol (RLP-C) which is closely associated

with amelioration of insulin sensitivity in diabetic patients who have insulin resistance.

- **Kuchay*et al.*, (2018)**[51] randomly assigned 50 T2DM patients into either empagliflozin group (10 mg empagliflozin + standard treatment for T2DM) or control group (standard treatment for T2DM without empagliflozin) for 20 weeks. Change in liver fat was measured by MRI-derived proton density fat fraction (MRI-PDFF). As a result, empagliflozin shows a reduction in the liver fat and improves ALT level in patients with T2DM and non-alcoholic fatty liver disease (NAFLD).
- **Muller *et al.*, (2018)**[52] conducted a double-blind, randomized, placebo-controlled study to examine the effect of empagliflozin 10 mg in renal tissue oxygenation in non-diabetic patients, which can be measured by blood oxygenation level-dependent magnetic resonance imaging (BOLD-MRI). They grouped into normal, over-weight and obese non-diabetic patients, each contain 15 subjects. BOLD-MRI was measured before and 180 min after the administration of empagliflozin 10 mg or placebo. The sequence of measurement was repeated after 1 month of empagliflozin or placebo treatment. Finally, they concluded that empagliflozin has a profound effect on renal physiology and inhibition of SGLT-2 with empagliflozin affects the renal tissue oxygenation, determined by BOLD-MRI. This is the first study that reflects inhibition of SGLT-2 with empagliflozin.
- **Nunez *et al.*, (2018)**[53] conducted a pilot study with 19 T2DM patients who has previous history of heart failure and they underwent cardiopulmonary exercise testing before and 30 days after initiation of empagliflozin therapy. In this

study, empagliflozin was associated with 1-month exercise improvement capacity in T2DM patients with symptomatic HF.

- **Kawamori*et al.*, (2018)**[54] conducted a trial by including 433 patients who were previously receiving anti-diabetic drugs for ≥12 weeks. Patients who were previously treated with linagliptin were then randomized to treated with empagliflozin or placebo. The HbA_{1C} level was recorded at 12, 28 and 54 weeks. The study concludes, empagliflozin-linagliptin combination therapy is a good glucose lowering therapeutic option for Japanese T2DM patients.
- **Shiba *et al.*, (2017)**[55]randomized 1403 T2DM patients to receive empagliflozin 10 mg, 25 mg and placebo. Empagliflozin was well tolerated and the HbA_{1C}, fasting plasma glucose and body weight was improved across age and degree of obesity.
- **Tanaka *et al.*, (2017)**[56] performing an ongoing trial to study the effect of empagliflozin on endothelial function (EMBLEM trial). They randomized 110 T2DM patients with known history of CVD to receive empagliflozin 10 mg once daily or placebo. The primacy outcome of the trial is change in reactive hyperemia(RH)-peripheral arterial tonometry-derived RH index at 24 weeks from baseline. The secondary outcomes include, change from baseline for vascular related markers like arterial stiffness, sympathetic nervous activity, and parameters for cardiac and renal functions. EMBLEM is the first trial to assess the effect of empagliflozin on endothelial function in patients with T2DM and established CVD.
- **Kaku *et al.*, (2017)**[57] randomised 1517 Asian race T2DM patients to receive empagliflozin 10 mg, 25 mg or placebo which is 21.6% of EMPA-REG trial population. The study shows reduction in the CV risk and all-cause mortality

with empagliflozin vs. placebo were consistent between Asian population and overall population in EMPA-REG trial.

- **Mordi*et al.*, (2017)**[58] prepared a protocol for RECEBE-CHF which is a randomized controlled, double blind, cross-over trail, where they include 34 patients with T2DM and known CHF. Renal physiology test was performed at two points: 1 and 6 weeks for each group (empagliflozin 25 mg and placebo). The participants were enrolled in the trial for 16 weeks. The primary outcome was to study the effect of empagliflozin vs placebo on urine output. The secondary outcome was to study the effect of empagliflozin on glomerular filtration rate, cystatin C, urine sodium excretion, urine protein/creatinine ratio and urine albumin/creatinine ratio when compared with placebo.
- **Zinman*et al.*, (2017)**[59] randomized 7020 patients to receive empagliflozin 10 mg, 25 mg or placebo with mean observation time for 3.1 years. They concluded that patients who received empagliflozin versus placebo doesn't show either reduction or increase in the risk of cerebrovascular events.
- **Cherney*et al.*, (2017)**[60] randomly assigned 7028 patients aged 18 years and above with T2DM and established CVD to receive empagliflozin 10 mg, 25 mg or placebo until 691patients experienced an arbitrated event included in the primary outcomes. They analysed the urine albumin-to-creatinine ratio (UACR) and concluded that empagliflozin shows significant reduction in the UACR from early as week 12 and was maintained under chronic treatment. In the study the effect of empagliflozin on microalbuminuria and macroalbuminuria seems to be at least equivalent to RAS inhibitors.
- **Wanner*et al.*, (2016)**[61] randomly included 7020 patients with T2DM and an estimated GFR of at least 30ml per minute to receive empagliflozin (10mg or

25mg) or placebo once daily. About 12.7% of the patients in empagliflozin group and 18.8% in placebo group reported worsening or incidence of nephropathy. They concluded that empagliflozin was related to slower progression of kidney disease and lower rate of clinically relevant renal events.

- **Softeland*et al.*, (2016)**[62] conducted a 24-week double blind randomized study where they included patients with previous therapy by linagliptin for 16 weeks. The patients are then randomized to receive empagliflozin 10mg, 25mg or placebo for 24 weeks. They concluded that, empagliflozin was associated with improved glycaemic control and weight versus placebo as an add-on treatment to linagliptin 5mg.
- **Thomas *et al.*, (2016)**[63] conducted a retrospective study to assess adoption rate of anti-obesity pharmacotherapies and SGLT-2i. They extracted the prescribing pattern data from Prescription Audit™ and Xponent™. The study concluded that, the number of prescriptions for antidiabetics was 15 times the number for anti-obesity and mean increase in prescription/month were 25,259 for SGLT-2, 5154 for new anti-obesity therapy.
- **Neeland*et al.*, (2015)**[64]randomized 3300 patients with T2DM to receive empagliflozin 10mg, 25mg or placebo in clinical trial of 12 weeks duration. They assessed the change in body weight, waist circumference, estimated total body fat, index of central obesity and visceral adiposity index. The study concludes a significant reduction in the body weight and adipose indices along with improvement in the cardiometabolic risk among patients with T2DM in the empagliflozin group.
- **Nishimura*et al.*, (2015)**[65]randomized 60 T2DM patients to receive empagliflozin 10mg, 25mg or placebo once daily as monotherapy for 28 days.

The effect of empagliflozin on PPG and 24-hour glycaemic variability in Japanese patients with T2DM were studied. The study shows, empagliflozin was associated with reduction in the PPG from first day and improved daily glucose control in Japanese patients with T2DM.

- **Defronzo*et al.*, (2015)**[66] randomized 686 patients to receive empagliflozin 25mg/linagliptin or empagliflozin 10mg/linagliptin or empagliflozin 25mg or empagliflozin 10mg as add-on to metformin for 52 weeks. The primary endpoint was change from baseline HbA1c at week 24. The conclusion was, empagliflozin/linagliptin as second-line therapy shows a significant reduction in the HbA1c compare to individual components in 52 weeks study.
- **Kovacs *et al.*, (2015)**[67]investigated the safety and efficacy of empagliflozin as an add-on to pioglitazone with or without metformin, for which they randomized 498 T2DM patients to receive empagliflozin 10mg, 25mg or placebo for 24 weeks in EMPA-REG PIO™ study. They assessed the change in glycaemic control, body weight, as primary consideration and concluded that empagliflozin 10mg or 25mg as add-on therapy to pioglitazone with or without metformin was well tolerated and HbA1c and body shows a significant reduction.
- **Pieber*et al.*, (2015)**[68] randomized 75 T1DM patients with HbA1c ≥7.5 to ≤10.5% to receive empagliflozin 2.5mg, 10mg, 25mg or placebo as adjunct to insulin for 28 days. The primary outcome was change in baseline in 24-hour urinary glucose excretion on day 7. In patients with type 1 diabetes, empagliflozin for 28 days as adjunct to insulin increased UGE, improved HbA1c and reduced weight with lower insulin doses compared with placebo and without increasing hypoglycaemia.

- **Zinman*et al.*, (2015)**[69] randomized 7020 T2DM patients with established cardiovascular disease to receive empagliflozin 10mg, 25mg or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal stroke or nonfatal myocardial infraction with the mean observation time of 3.1 years. The study shows 38% reduction in the death due to CV causes, 37% reduction in the hospitalization due to HF and 32% reduction in the death from any cause in the empagliflozin group as compared to placebo.
- **Rosenstock *et al.*, (2015)**[70] randomized 500 inadequately controlled T2DM patients to receive empagliflozin 10mg, 25mg or placebo for 78 weeks. The primary outcome was change in baseline HbA1c at 18 weeks and secondary outcome were change in HbA1c and insulin dose at week 78. They concluded that empagliflozin added to basal insulin improved glycaemic control and reduced weight with similar risk of hypoglycaemia to placebo.
- **Kadowaki*et al.*, (2015)**[71] conducted a randomized, double blind, placebo controlled, dose finding, 52-week, phase IIb trial in Japanese T2DM patients. They randomized the patients to receive empagliflozin 5mg, 10mg, 25mg, 50mg or placebo for 12 weeks followed by extension of 40 weeks for empagliflozin 10mg and 25mg. The study shows, empagliflozin 10mg and 25mg as monotherapy results in the significant reduction in HbA1c, FPG, body weight and blood pressure.
- **Araki *et al.*,(2015)**[72]conducted a study in T2DM patients who were previously received with biguanides, thiazolidinedione, α-glucosidase inhibitor, or DPP4 inhibitor to received empagliflozin 10 or 25mg as add-on for 52 weeks. The change from baseline glucose level at 52 weeks was the endpoint and they

concluded that empagliflozin as add-on to other oral anti-diabetic therapy for 52 weeks were well tolerated and were associated with reduction in HbA_{1C}.

- **Haering*et al.*, (2015)**[73] randomized T2DM patients who where inadequately controlled on metformin or sulfonylurea were randomized to receive empagliflozin 10mg or 25mg or placebo. The primary end point was change from baseline HbA_{1C} and secondary outcome was change in body weight and mean daily glucose at 24 hours. The study shows, empagliflozin as an add-on to metformin or sulfonylurea were associated with reduction in HbA_{1C}, body weight and mean glucose.
- **Halimi*et al.*, (2014)**[74] studied the safety and adverse effects of SGLT-2 inhibitors. The study reports the events of genital mycotic infections and urinary tract infections in female patients, but rarely. The study shows, the beneficial effects on body weight, glucose control, blood pressure and triglycerides. Reported events of hypoglycaemia was lower.
- **Ridderstrale*et al.*, (2014)**[75] conducted a double-blind phase-III trail in which they randomized T2DM patients to receive empagliflozin 25mg once daily or glimepiride 1-4mg once daily as add-on to metformin for 104 weeks. The primary composite outcomes were change in baseline HbA1c level at 52 and 104 weeks. The study shows, empagliflozin is not inferior to glimepiride and well tolerated and effective as second-line treatment for patients with T2DM who have not achieved good glycaemic control on metformin.
- **Kadowaki*et al.*, (2014)**[76] randomized 547 T2DM Japanese patients to receive empagliflozin 5mg, 10mg, 25mg, 50mg or placebo for 12 weeks. The glycaemic control test was done at 12 weeks. The reported adverse events were lesser in empagliflozin group as compared to placebo. The conclusion was,

empagliflozin as monotherapy reduced HbA1c, FPG, body weight, and SBP and was well tolerated.

- **Rosenstock *et al.*, (2014)**[77] randomized T2DM patients who were inadequately comtrolled on insulin + metformin to receive empagliflozin 10 or 25mg or placebo once daily as an add-on to insulin for 52 weeks. The primary endpoint was change from baseline HbA_{1C} at week 18. The secondary outcome was change in insulin dose, HbA_{1C} and body weight at week 52. The study shows a reduction in the HbA_{1C}, body weight and insulin dose after 52 weeks.
- **Roden*et al.*, (2013)**[78] conducted a randomized, double-blind, placebo controlled, phase-III trial. They randomized the patients with previous history of receiving anti-diabetic treatment for 12 weeks to receive empagliflozin 10mg, 25mg, placebo or sitagliptin 100mg once daily for 24 weeks. The change in HbA1c from baseline were recorded. The study show, empagliflozin shows a tolerable and efficacious strategy to reduce HbA1c in patients with T2DM who had previously received anti-diabetic treatment.

3. AIM AND OBJECTIVES

AIM

To study the prescribing pattern and short-term outcomes of SGLT-2 inhibitors in patients with Type II Diabetes mellitus aged 20 years and above in a tertiary care hospital.

OBJECTIVES

- To study the glucose lowering effect of SGLT-2 inhibitors with insulin or OHA in ≤5 years and >5 years of Type II Diabetes mellitus.
- To study the change in body weight and lipid profile in patients receiving SGLT-2 inhibitors.
- To study the ADR associated with add-on therapy of SGLT-2 inhibitors along with patient medication adherence.

4. METHODOLOGY

STUDY SITE:

The study was performed in the Department of Diabetology and Endocrinology, Kovai Medical Center and Hospital (KMCH) at Coimbatore, Tamilnadu, India. The proposed protocol for the study was presented and approved by the Hospital Ethical Committee (Annexure 1).

STUDY DURATION:

The study was carried out from 10th February 2018 to 25th August 2018 (6 months).

STUDY POPULATION:

The study is a hospital based prospective study in which all the patients receiving SGLT-2 inhibitor for the management of T2DM from the Diabetology and Endocrinology department, Cardiology department and General medicine department were considered. The study included describing data collected in terms of their level of measurement and summarizing them in form of tables, graphs and numerical values. Mainly the Paired *'t'* test was used to finalize the study.

SOURCE DATA:

Patient medical record – Patient medical record is observed and the required data such as register no., age, gender, comorbidities, body weight, BMI, FBS, RBS, HbA_{1C}, total cholesterol, triglycerides, HDL, LDL, eGFR, and received therapy was recorded. The social habits, duration of comorbidities, ADR and the patient

medication adherence were noted by using Morisky Patient Medication Adherence Scale was done by direct interviewing the patient.

STUDY CRITERIA:

- **Inclusion criteria:** Any T2DM patient aged 20 years and above receiving SGLT-2 inhibitor with eGFR ≥40ml/min/1.73m^2.
- **Exclusion criteria:** Patient aged less than 20 years, pregnant woman, T1DM and eGFR ≤40ml/min/1.73m^2 were excluded from the study.

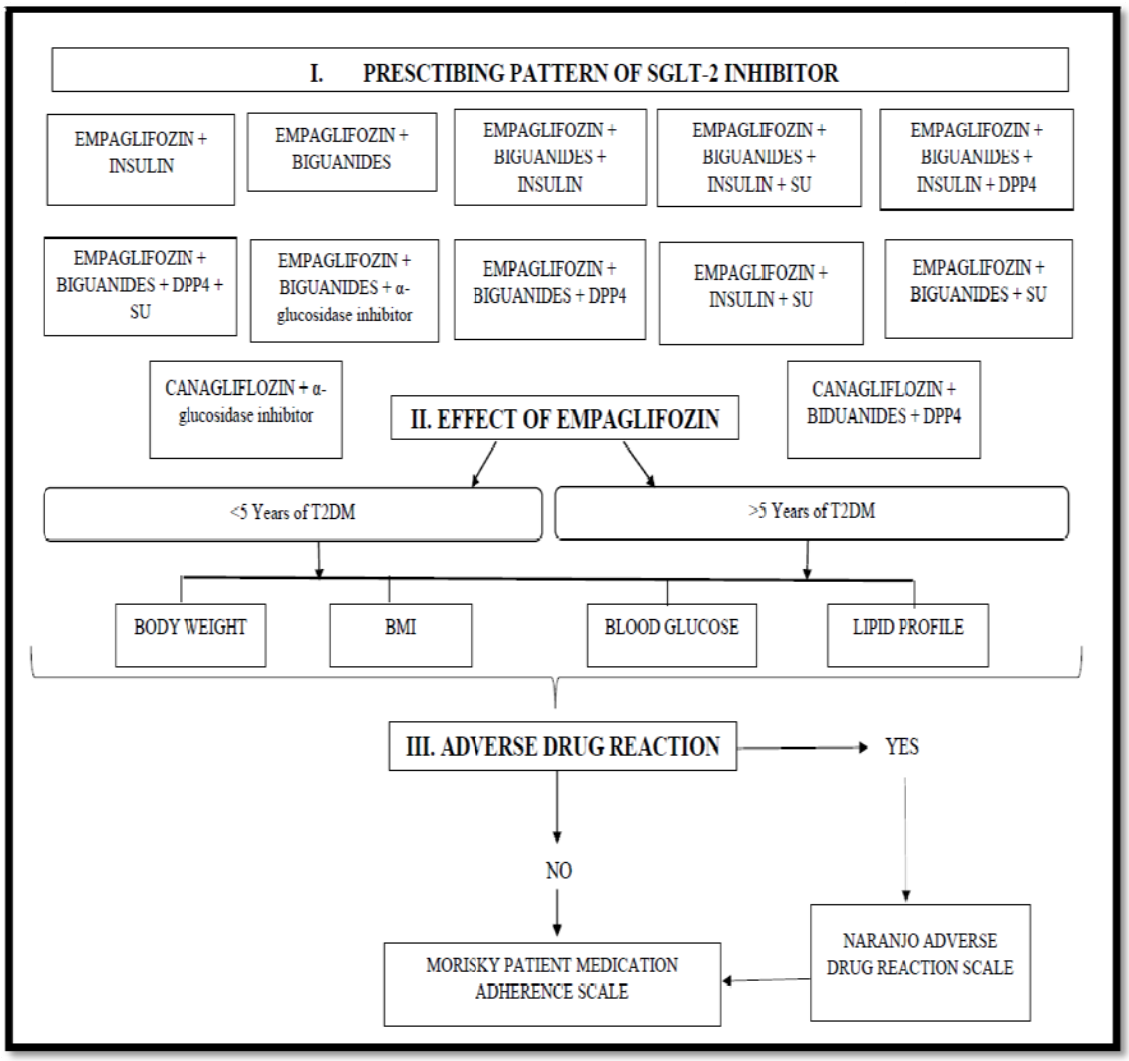
METHOD OF DATA COLLECTION:

- Data collection form.
- Naranjo Adverse Drug Reaction Scale.
- Morisky Patient Medication Adherence Scale.
- Communication with the patients.

STUDY PROTOCOL:

The study was carried out after receiving approval from the Ethical committee of the hospital on 10th February, 2018. The patients receiving SGLT-2 inhibitor for the management of T2DM with eGFR ≥40ml/min/1.73m^2 were included in the study .A total of 315 patients were studied by the time period of 6 months. The essential data such as, patient's demographics information's, past medical history and clinical data such as, body weight, BMI, FBS, RBS, HbA_{1C}, total cholesterol, triglycerides, HDL, LDL, eGFR rate, prescribed drugs were collected using data collection form. The reported ADR was confirmed by Naranjo ADR Scale and adherence questionnaire was used to note the patient's medication adherence. All the data were assessed based on duration of T2DM mellitus.

Figure 8: Patient recruitment and randomization.



5. TABLES AND GRAPHS

Table 3: Distribution of study population based on gender (n=315)

GENDER	POPULATION	PERCENTAGE (%)
MALE	188	59.68
FEMALE	127	40.31

Figure 9: Plot for overall study population based on gender (n=315)

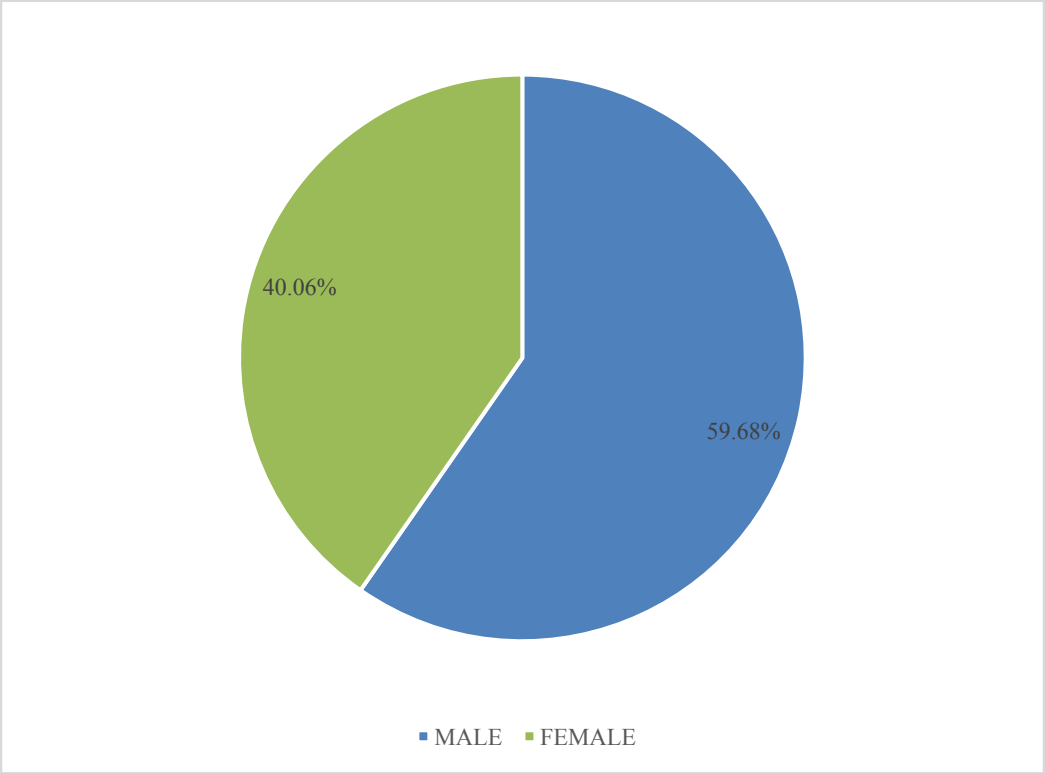


Table 4: Distribution of study population based on age (n=315)

AGE GROUP	POPULATION	PERCENTAGE (%)
21-30	3	1.00
31-40	20	6.34
41-50	68	21.58
51-60	121	38.41
61-70	72	22.85
71-80	29	9.20
81-90	2	0.63

Figure 10: Plot of overall study population based on age (n=315)

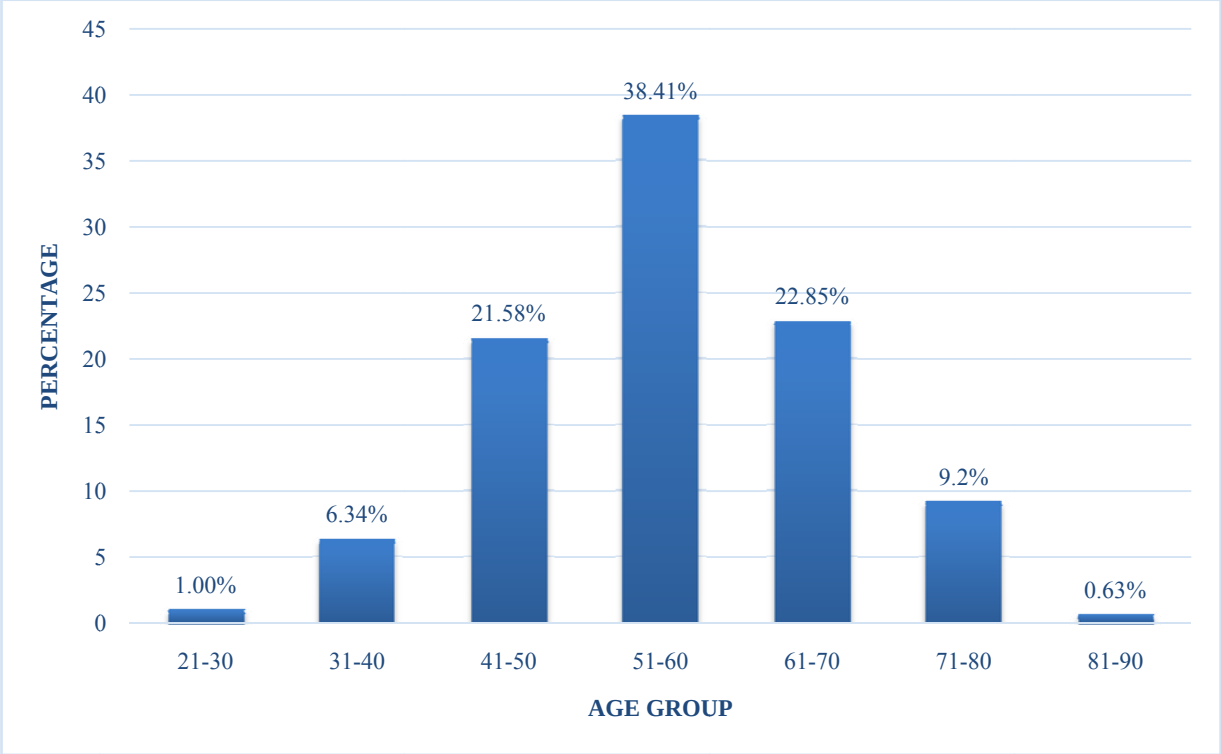


Table 5: Distribution of study population based on comorbidities (n=315)

COMORBIDITIES	POPULATION	PERCENTAGE (%)
Hypertension	135	42.85
Myocardial infraction	26	8.25
Stroke	2	0.63
Angina	19	6.03

Figure 11: Plot of overall study population based on comorbidities (n=315)

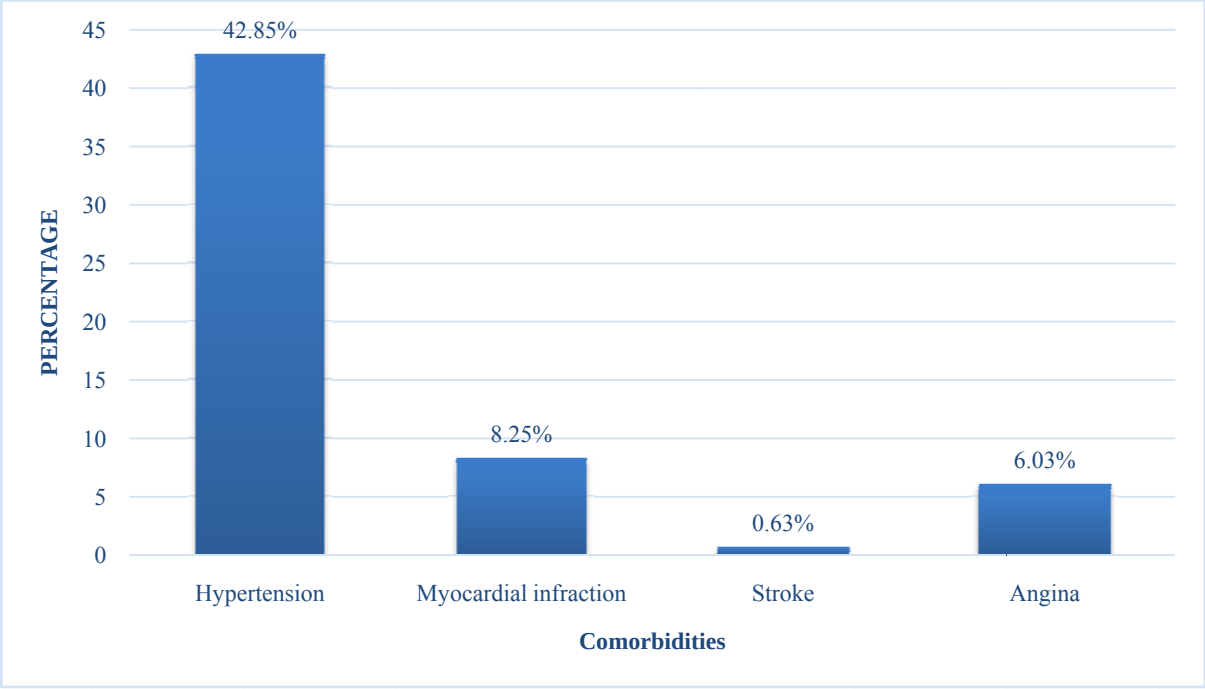


Table 6: Distribution of study population based on BMI (n=315)

CATEGORY	POPULATION	PERCENTAGE (%)
Underweight	0	0
Normal	14	4.44
Over-weight	200	63.49
Obese	102	32.06

Figure 12: Plot of overall study population based on BMI(n=315)

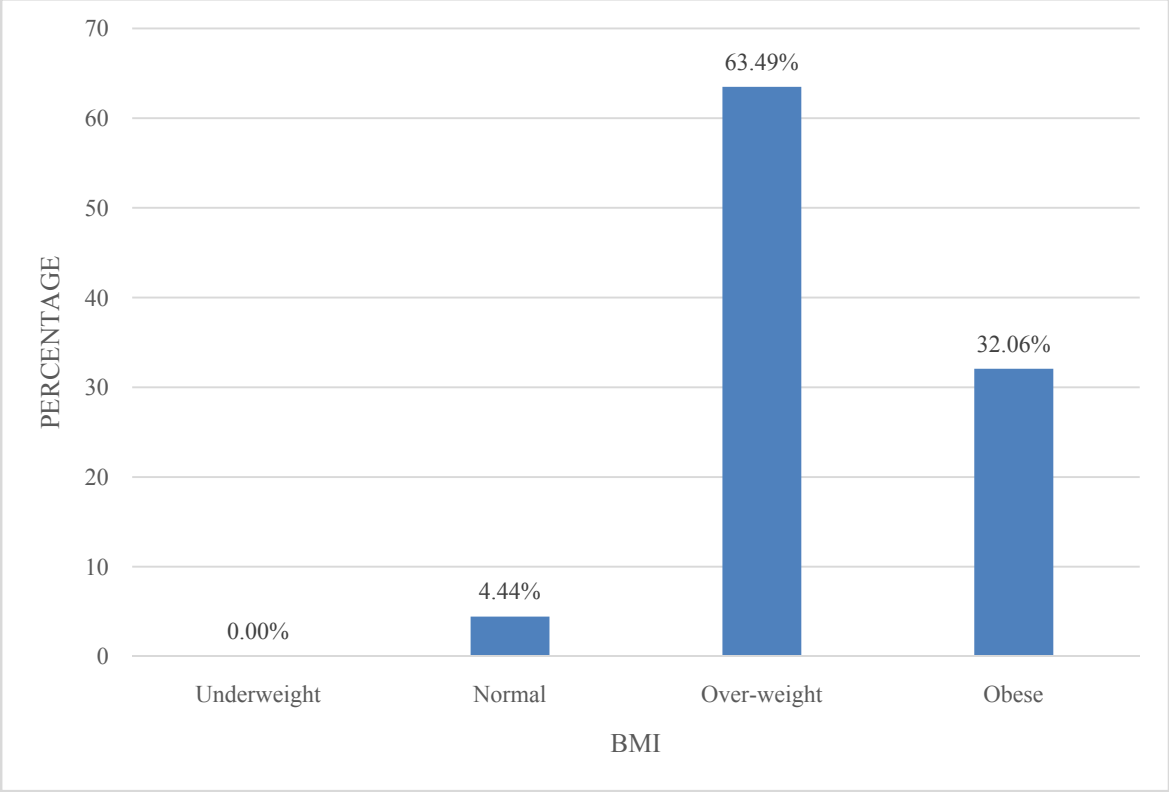


Table 7: Distribution of study population based on duration of T2DM (n=315)

DURATION	POPULATION	PERCENTAGE (%)
1-5 Years	54	17.14
6-10 Years	168	53.33
11-15 Years	48	15.23
16-20 Years	32	10.15
21-25 Years	13	4.12

Figure 13: Plot of overall study population based on duration of T2DM (n=315)

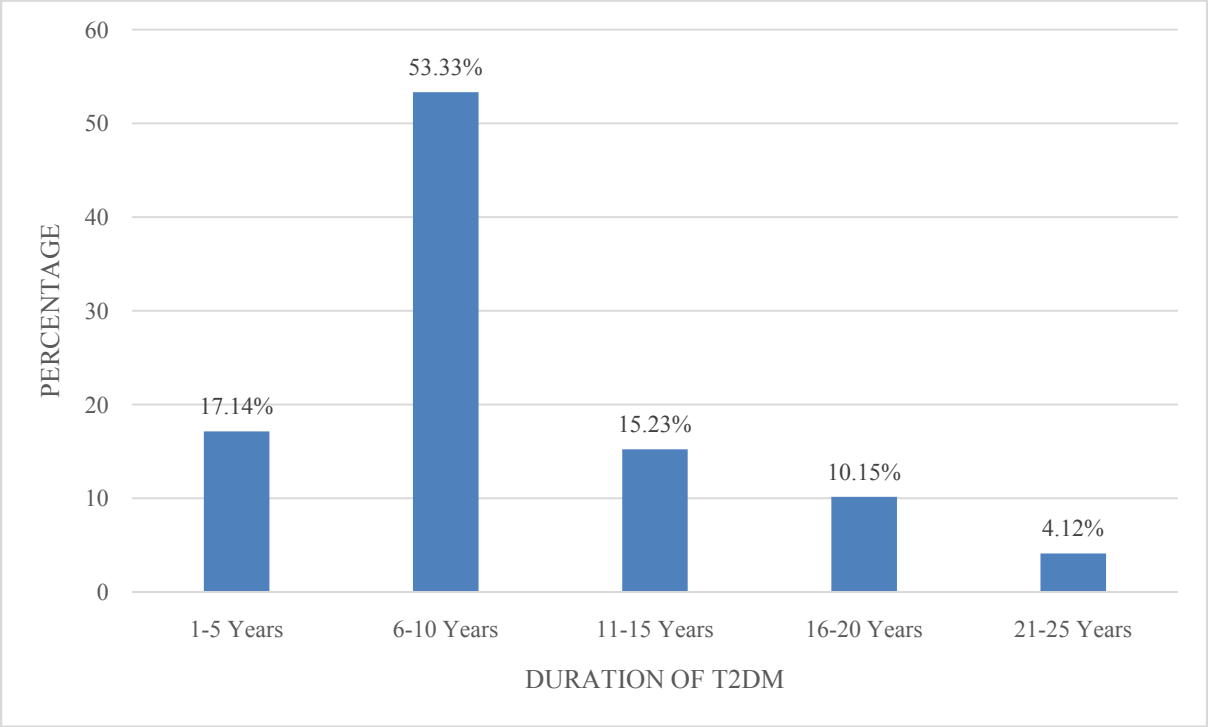


Table 8: Distribution of study population based on prescribing pattern (n=315)

SN	PRESCRIBING PATTERN	POPULATION	PERCENTAGE (%)
1.	EMPAGLIFLOZIN + INSULIN	20	6.34
2.	EMPAGLIFLOZIN + BIGUANIDES	27	8.57
3.	EMPAGLIFLOZIN + BIGUANIDES + INSULIN	43	13.65
4.	EMPAGLIFLOZIN + BIGUANIDES + INSULIN + SU	32	10.15
5.	EMPAGLIFLOZIN + BIGUANIDES + INSULIN + DPP4	51	16.19
6.	EMPAGLIFLOZIN + BIGUANIDES + DPP4 + SU	50	15.87
7.	EMPAGLIFLOZIN + BIGUANIDES + α-glucosidase inhibitors	6	1.90
8.	EMPAGLIFLOZIN + BIGUANIDES + DPP4	28	8.88
9.	EMPAGLIFLOZIN + INSULIN + SU	12	3.80
10.	EMPAGLIFLOZIN + BIGUANIDES + SU	46	14.60

Figure 14: Plot of overall study population based on prescribing pattern (n=315)

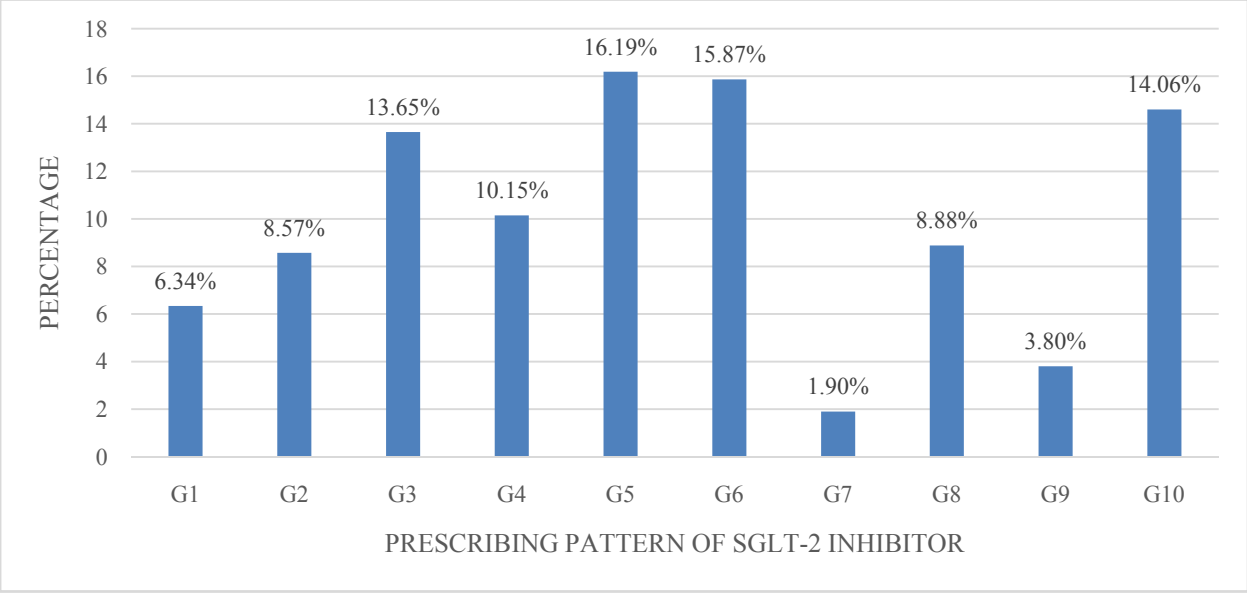


Table 9: Distribution of study population based on duration of T2DM and treatment received (n=315)

TREATMENT	EMPAGLIFLOZIN + INSULIN ± OHA		EMPAGLIFLOZIN + OHA	
DURATION OF T2DM	**Population**	**Percentage (%)**	**Population**	**Percentage (%)**
≤5 Years	11	3.49	43	13.65
>5 Years	122	38.73	139	44.12

Figure 15: Plot of overall study population based on duration of T2DM and treatment received (n=315)

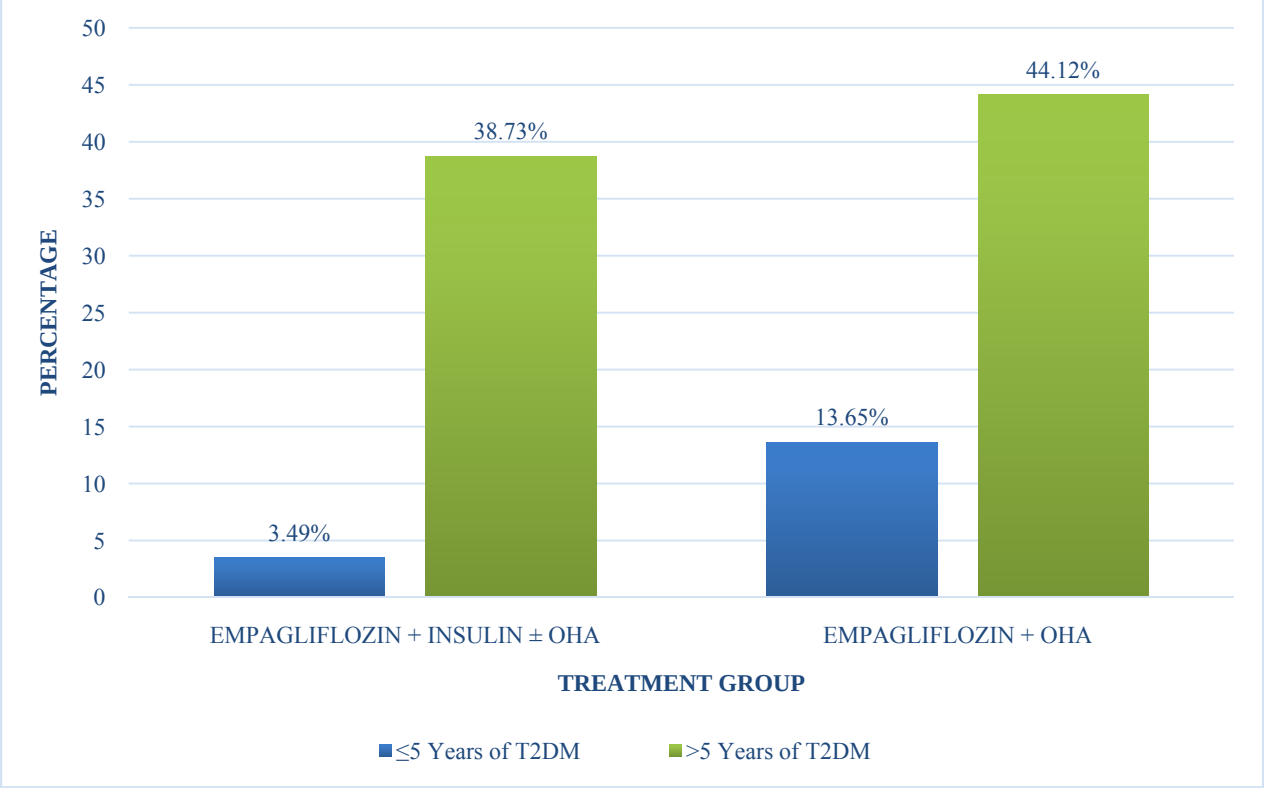


Table 10: Effect of SGLT-2 inhibitor on body weight (n=315)

DURATION OF T2DM	>5 Years			≤5 Years		
TREATMENT	Baseline	After 2 Months	After 4 Months	Baseline	After 2 Months	After 4 Months
Empagliflozin + Insulin ± OHA	79.53±14.32	78.2±13.65 **(*0.001)**	77.27±13.58 **(*0.000)**	81.05±11.21	79.98±10.97 **(*0.000)**	78.97±10.7 **(*0.000)**
Empagliflozin + OHA	86.86±16.09	85.12±14.96 **(*0.000)**	84.12±14.78 **(*0.000)**	78.96±11.38	77.81±11.43 **(*0.000)**	76.85±11.32 **(*0.000)**

***p* value ≤0.001 is considered to be statistically significant

Figure 16: Plot for effect of SGLT-2 inhibitor on body weight (n=315)

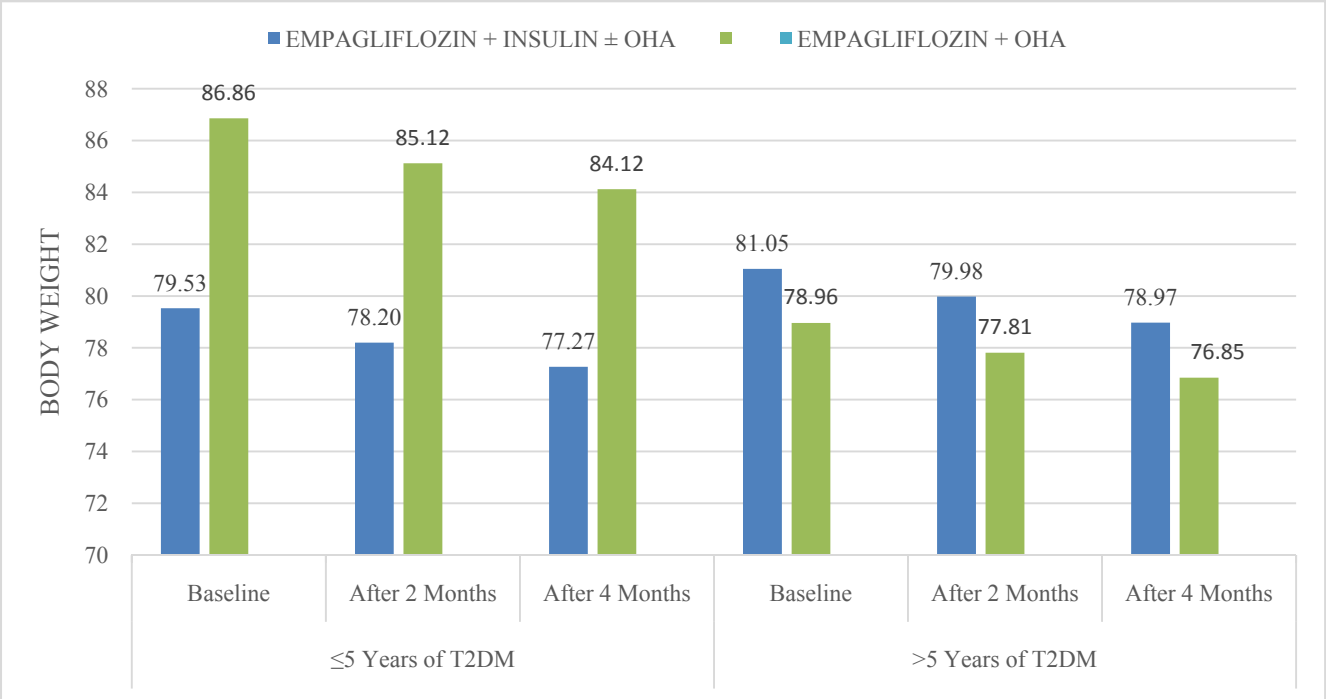


Table 11: Effect of SGLT-2 inhibitor on BMI (n=315)

DURATION OF T2DM	≤5 Years			>5 Years		
TREATMENT	Baseline	After 2 Months	After 4 Months	Baseline	After 2 Months	After 4 Months
Empagliflozin + Insulin ± OHA	29.7±4.5	29.20±4.24 **(*0.082)**	28.87±4.18 **(*0.004)**	29.60±3.30	29.24±3.24 **(*0.000)**	28.89±3.13 **(*0.000)**
Empagliflozin + OHA	31.53±4.93	30.93±4.61 **(*0.000)**	30.44±4.50 **(*0.000)**	28.56±2.54	28.16±2.56 **(*0.000)**	27.93±2.66 **(*0.000)**

***p* value ≤0.001 is considered to be statistically significant

Figure 17: Plot for effect of SGLT-2 inhibitor on BMI (n=315)

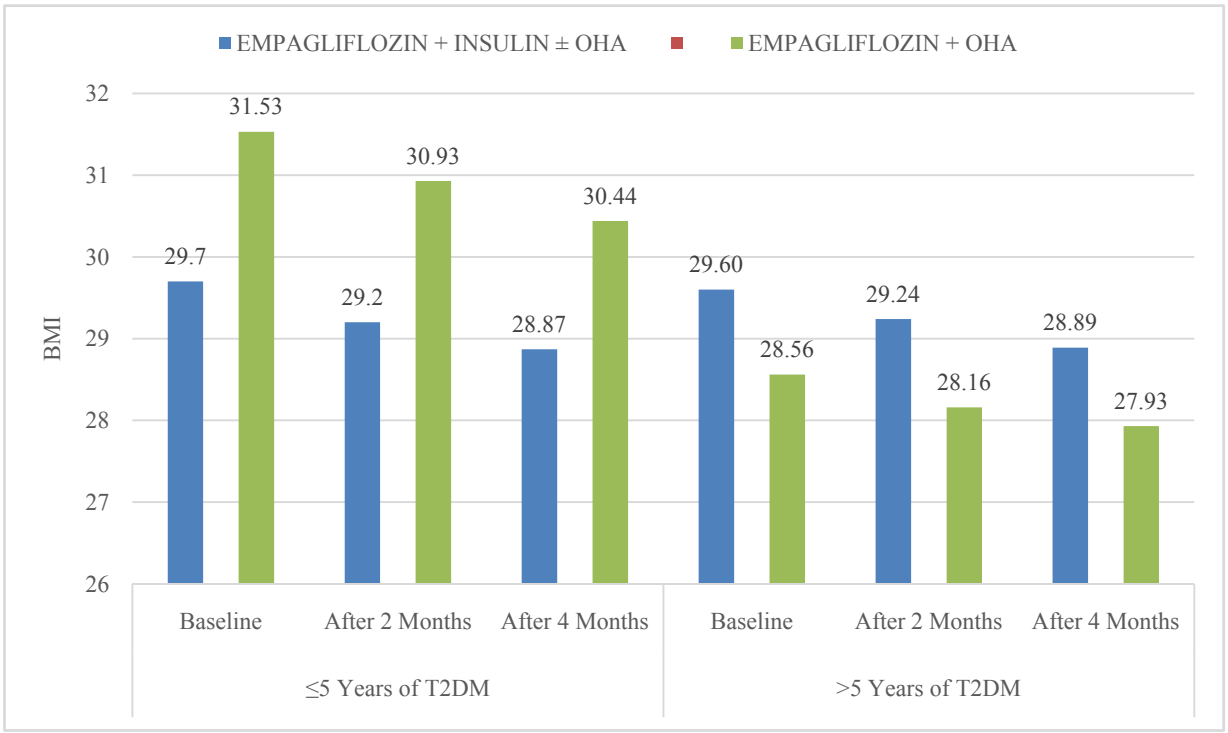


Table 12: Effect of SGLT-2 inhibitor on FBS (n=315)

DURATION OF T2DM	≤5 Years			>5 Years		
TREATMENT	Baseline	After 2 Months	After 4 Months	Baseline	After 2 Months	After 4 Months
Empagliflozin + Insulin ± OHA	246.45±93.30	217.09±110.98 **(*0.265)**	180.81±77.97 **(*0.008)**	228.39±71.06	176.61±54.31 **(*0.000)**	140.22±45.44 **(*0.000)**
Empagliflozin + OHA	184.95±41.97	150.40±34.69 **(*0.000)**	116.65±25.15 **(*0.000)**	205.72±57.32	116.22±46.87 **(*0.000)**	129.53±38.31 **(*0.000)**

***p* value ≤0.001 is considered to be statistically significant

Figure 18: Plot for the effect of SGLT-2 inhibitor on FBS (n=315)

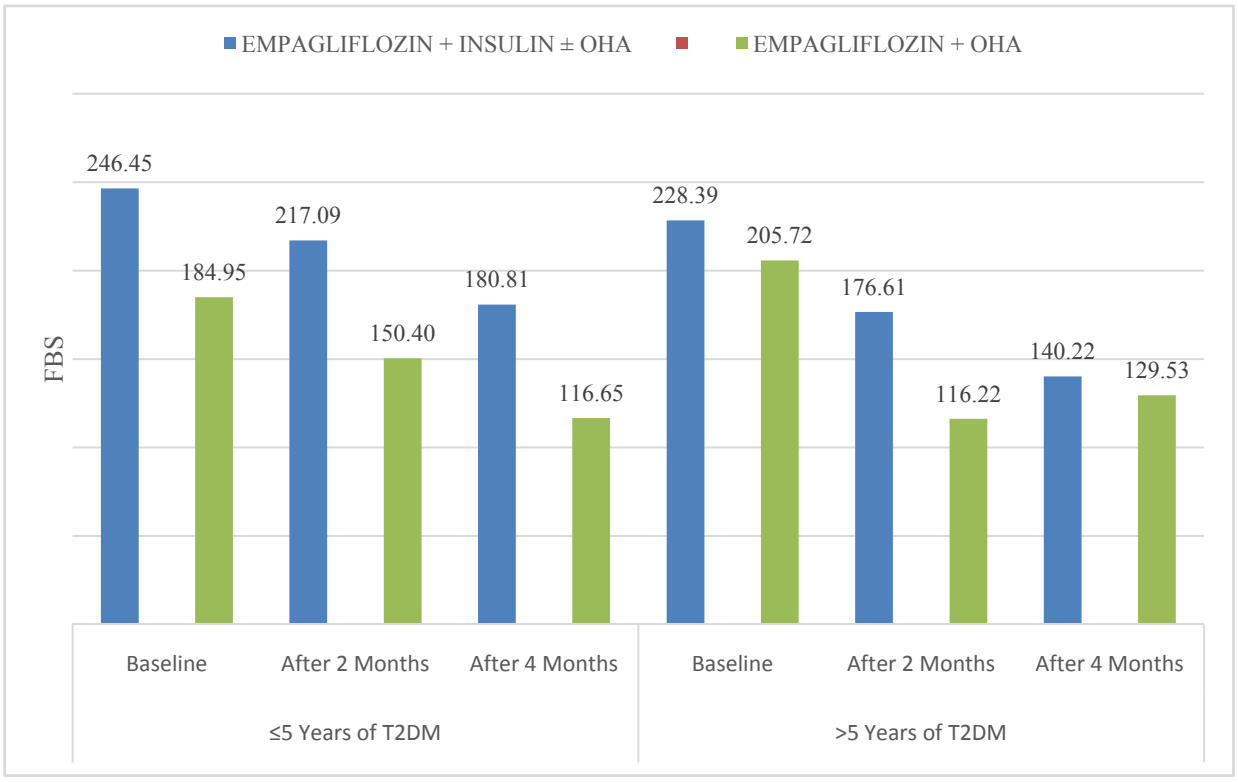


Table 13: Effect of SGLT-2 inhibitor on RBS (n=315)

DURATION OF T2DM	≤5 Years			>5 Years		
TREATMENT	Baseline	After 2 Months	After 4 Months	Baseline	After 2 Months	After 4 Months
Empagliflozin + Insulin ± OHA	333±137.48	245.81±93.97 **(*0.009)**	199.81±71.92 **(*0.001)**	288.21±85.64	234.16±55.02 **(*0.000)**	203.69±41.39 **(*0.000)**
Empagliflozin + OHA	256.91±53.49	217.51±40.38 **(*0.000)**	181±33.54 **(*0.000)**	272.69±55.61	233.46±44.57 **(*0.000)**	191.07±35.73 **(*0.000)**

***p* value ≤0.001 is considered to be statistically significant

Figure 19: Plot for the effect of SGLT-2 inhibitor on RBS (n=315)

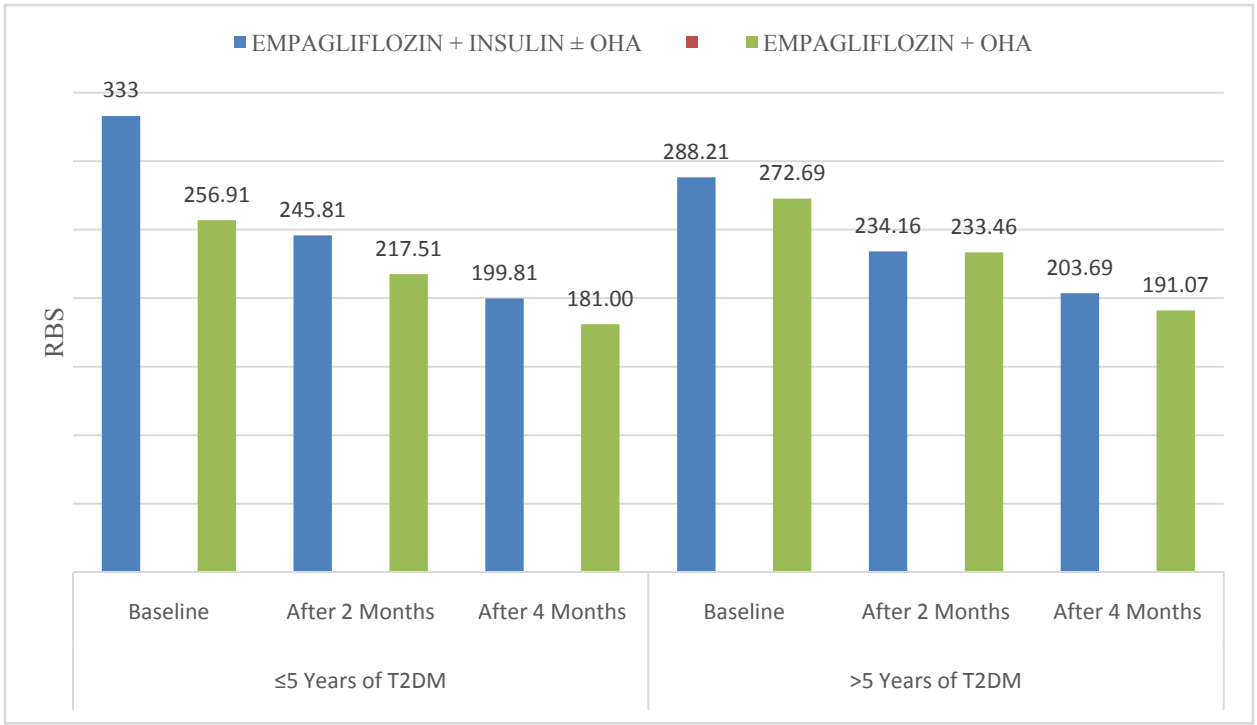


Table 14: Effect of SGLT-2 inhibitor on HbA1c (n=315)

DURATION OF T2DM	≤5 Years			>5 Years		
TREATMENT	Baseline	After 2 Months	After 4 Months	Baseline	After 2 Months	After 4 Months
Empagliflozin + Insulin ± OHA	11.33±1.67	9.4±1.21 **(*0.000)**	8.57±1.03 **(*0.000)**	9.43±1.32	8.45±0.92 **(*0.000)**	7.82±0.85 **(*0.000)**
Empagliflozin + OHA	8.30±0.86	7.72±0.76 **(*0.000)**	7.19±0.58 **(*0.000)**	8.56±1.16	7.90±0.98 **(*0.000)**	7.47±0.84 **(*0.000)**

***p* value ≤0.001 is considered to be statistically significant

Figure 20: Plot for the effect of SGLT-2 inhibitor on HbA1c (n=315)

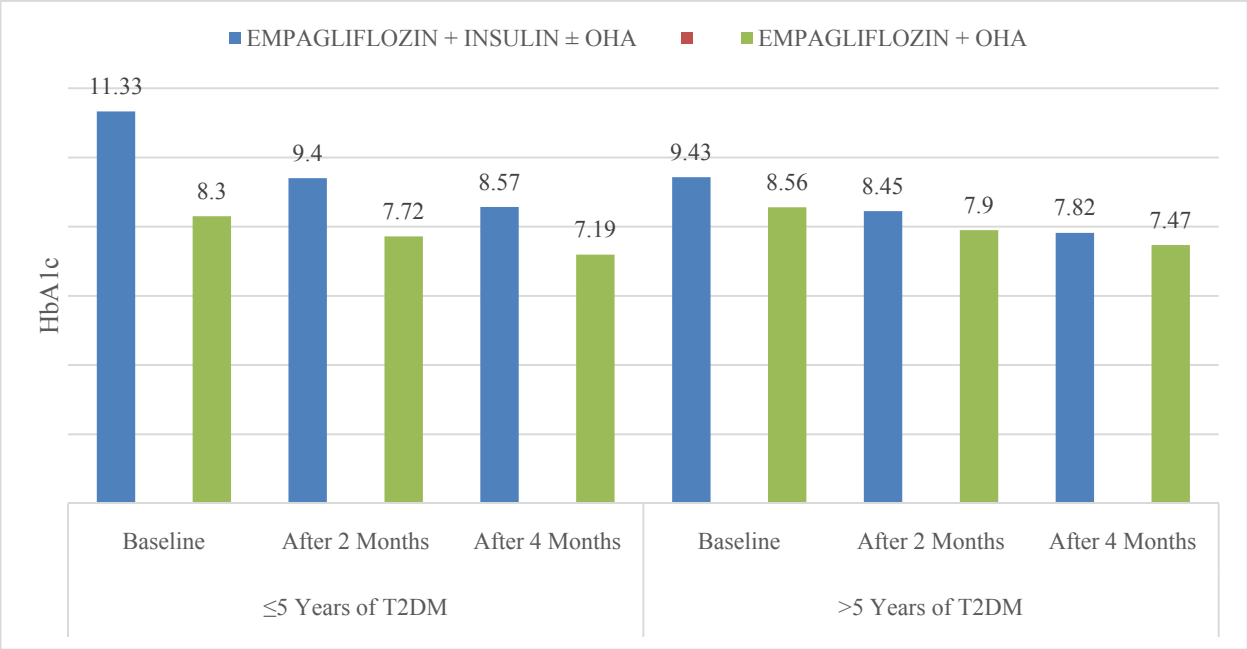


Table 15: Effect of SGLT-2 inhibitor on total cholesterol (n=315)

DURATION OF T2DM	≤5 Years			>5 Years		
TREATMENT	Baseline	After 2 Months	After 4 Months	Baseline	After 2 Months	After 4 Months
Empagliflozin + Insulin ± OHA	200.72±58.50	198.27±48.39 **(*0.616)**	194.63±44.15 **(*0.302)**	225.94±75.09	216.94±65.51 **(*0.008)**	209.84±62.58 **(*0.006)**
Empagliflozin + OHA	221.67±65.37	207.12±59.09 **(*0.006)**	200.63±54.66 **(*0.005)**	241.25±87.77	228.87±79.78 **(*0.006)**	219.50±71.01 **(*0.004)**

***p* value ≤0.001 is considered to be statistically significant

Figure 21: Plot for the effect of SGLT-2 inhibitor on total cholesterol (n=315)

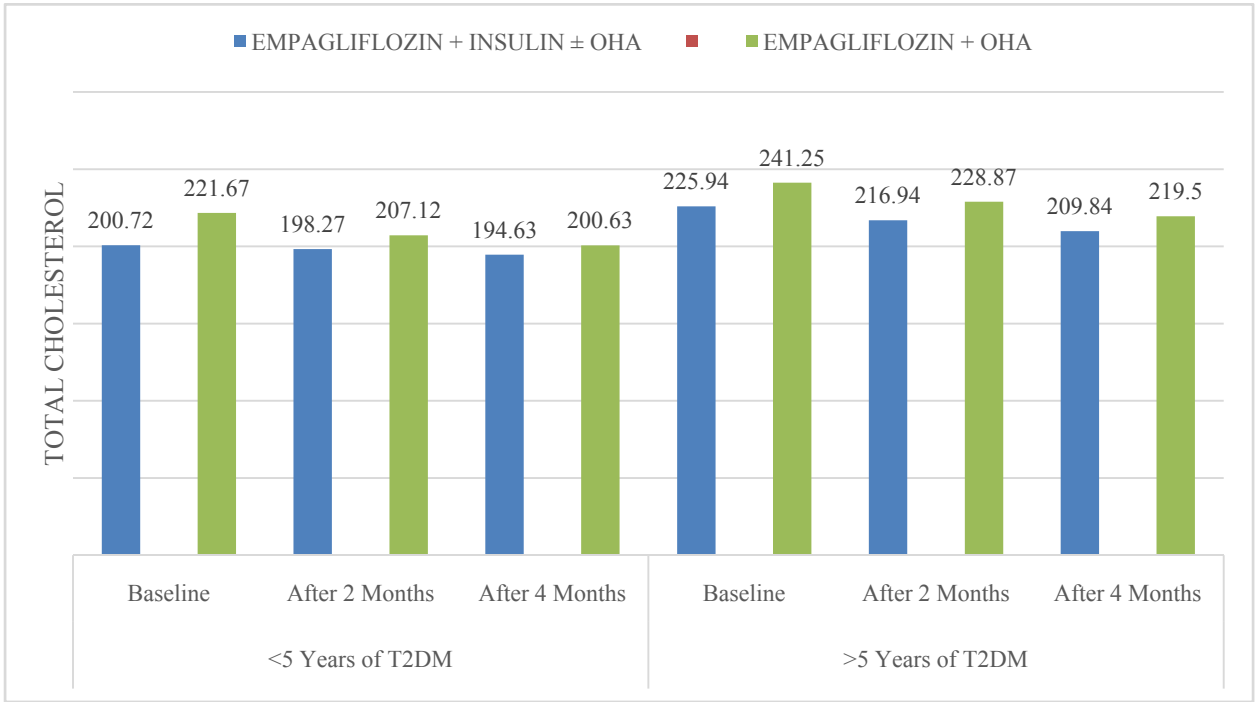


Table 16: Effect of SGLT-2 inhibitor on triglycerides (n=315)

DURATION OF T2DM	≤5 Years			>5 Years		
TREATMENT	Baseline	After 2 Months	After 4 Months	Baseline	After 2 Months	After 4 Months
Empagliflozin + Insulin ± OHA	216±60.57	202.09±56.11 **(*0.008)**	208.09±75.67 **(*0.297)**	238.82±78.48	225.89±72.23 **(*0.241)**	219.22±68.43 **(*0.009)**
Empagliflozin + OHA	223.56±77.77	211.74±66.97 **(*0.007)**	199.74±62.72 **(*0.006)**	256.06±89.14	242.12±83.47 **(*0.041)**	233.25±79.75 **(*0.006)**

***p* value ≤0.001 is considered to be statistically significant

Figure 22: Plot for the effect of SGLT-2 inhibitor on triglycerides (n=315)

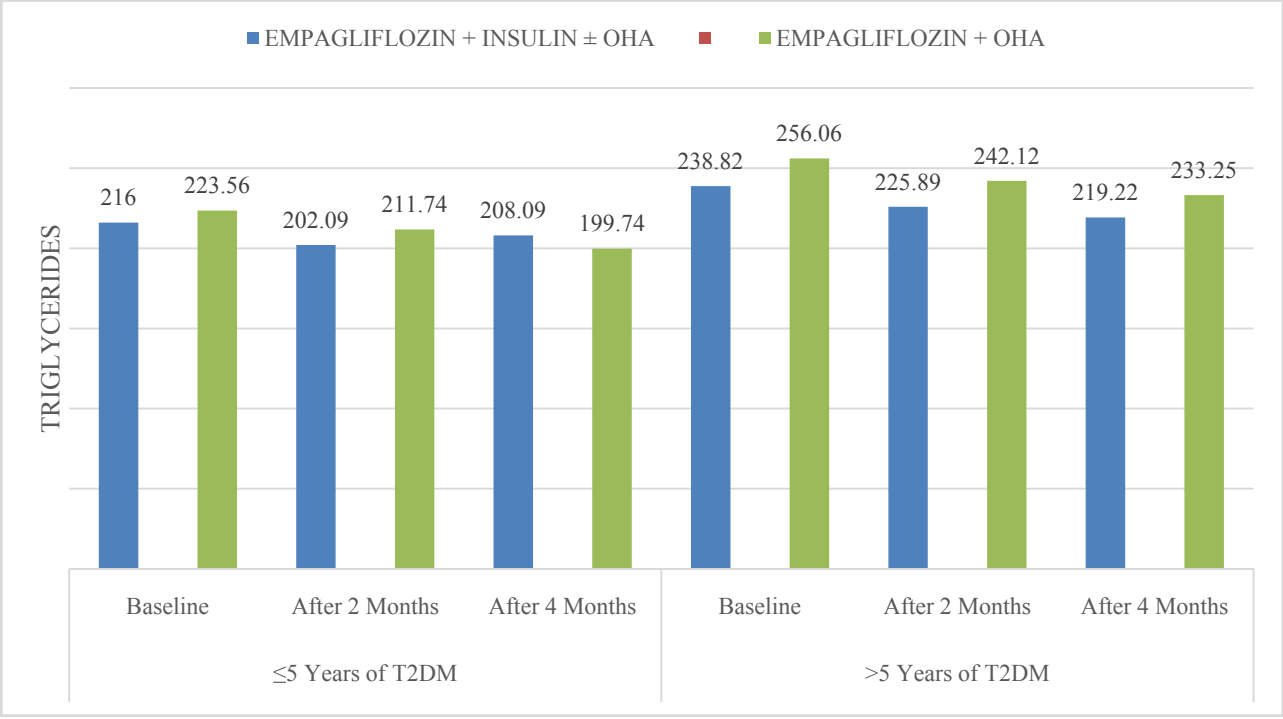


Table 17: Effect of SGLT-2 inhibitor on HDL level (n=315)

DURATION OF T2DM	≤5 Years			>5 Years		
TREATMENT	Baseline	After 2 Months	After 4 Months	Baseline	After 2 Months	After 4 Months
Empagliflozin + Insulin ± OHA	37.45±3.14	37.45±2.84 **(*1.000)**	38.09±3.98 **(*0.111)**	34.30±4.25	34.64±3.96 **(*0.003)**	35.21±3.64 **(*0.000)**
Empagliflozin + OHA	35.67±4.42	35.91±4.30 **(*0.455)**	36.19±4.07 **(*0.053)**	34.96±6.59	35.07±5.99 **(*0.467)**	35.86±5.62 **(*0.000)**

***p* value ≤0.001 is considered to be statistically significant

Figure 23: Plot for the effect of SGLT-2 inhibitor on HDL level (n=315)

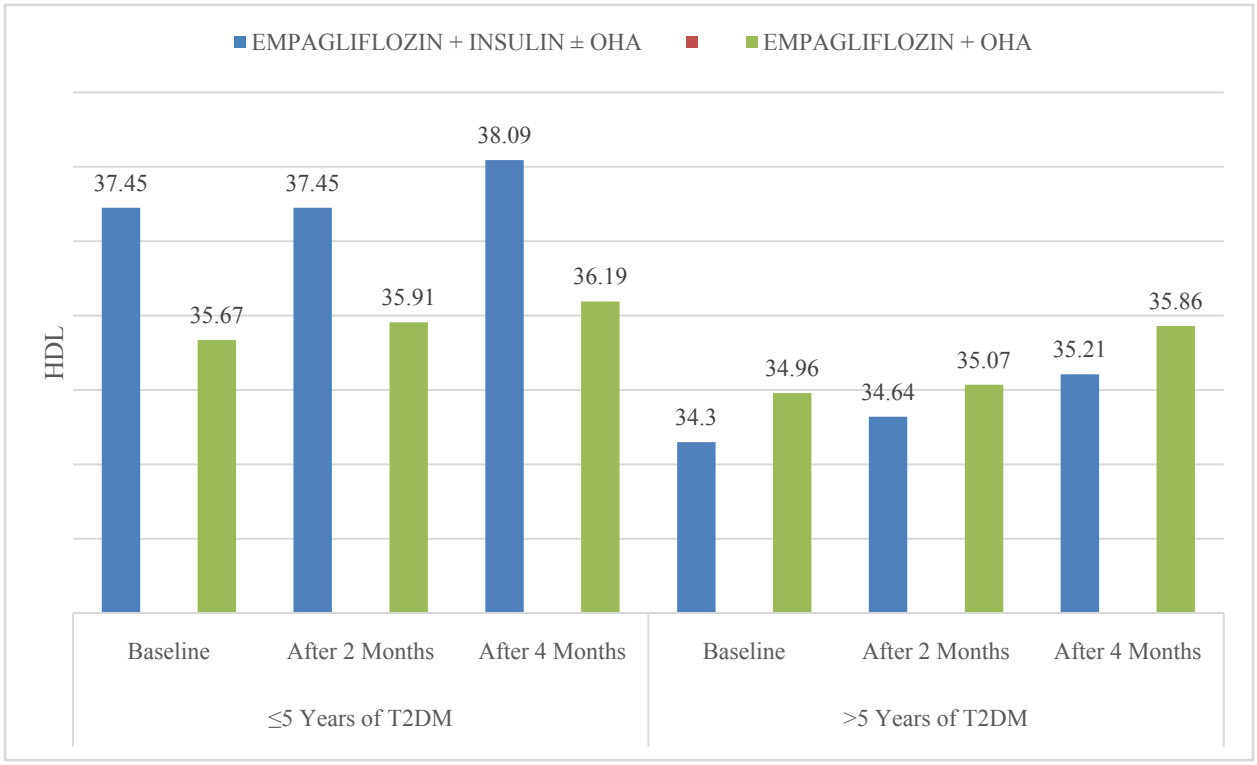


Table 18: Effect of SGLT-2 inhibitor on LDL level (n=315)

DURATION OF T2DM	≤5 Years			>5 Years		
TREATMENT	Baseline	After 2 Months	After 4 Months	Baseline	After 2 Months	After 4 Months
Empagliflozin + Insulin ± OHA	98.45±53.19	96.90±45.49 **(*0.729)**	96.27±46.43 **(*0.646)**	116.61±41.74	107.69±38.10 **(*0.000)**	102.52±36.17 **(*0.000)**
Empagliflozin + OHA	117.77±49.52	112.95±44.97 **(*0.092)**	109.12±41.82 **(*0.003)**	117.21±52.09	112.17±45.32 **(*0.004)**	107.69±42.17 **(*0.000)**

***p* value ≤0.001 is considered to be statistically significant

Figure 24: Plot for the effect of SGLT-2 inhibitor on LDL level (n=315)

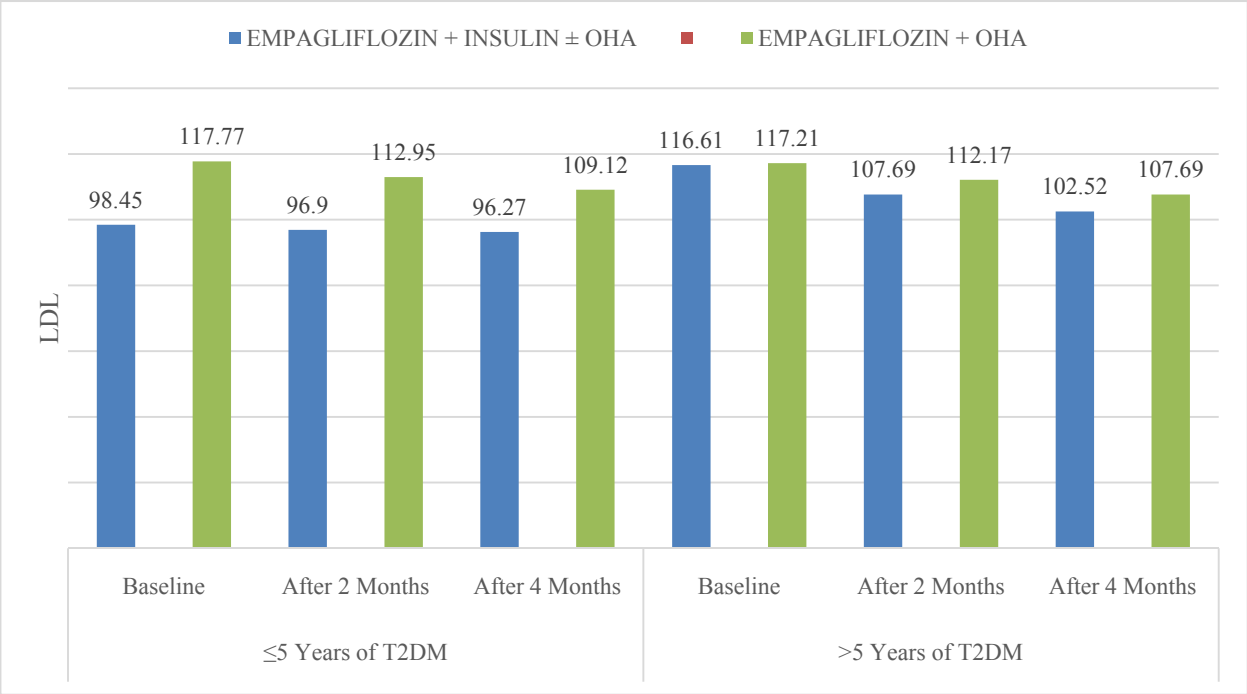


Table 19: Distribution of ADR in the study population (n=315)

TREATMENT	DURATION OF T2DM	≤5 Years		>5 Years	
	ADR	After 2 Months	After 4 Months	After 2 Months	After 4 Months
Empagliflozin + Insulin ± OHA	Hypoglycemia	2	0	26	14
	Geno mycotic infection	0	0	0	0
	Ketoacidosis	0	0	0	0
Empagliflozin + OHA	Hypoglycemia	0	1	5	2
	Geno mycotic infection	0	0	1	1
	Ketoacidosis	0	0	0	0

Figure 25: Plot for the events of hypoglycemia in the study population (n=315)

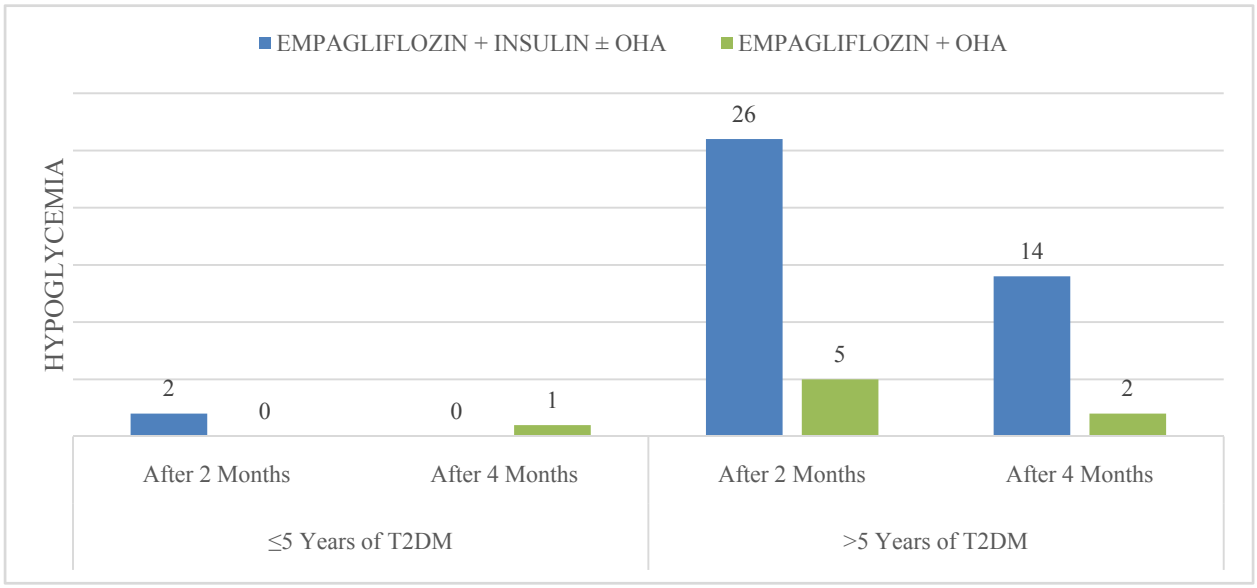


Table 20: Distribution of ADR based on Naranjo ADR Scale in the study population (n=315)

NARANJO SCALE	≤5 Years				>5 Years			
	Empagliflozin + Insulin ± OHA (n=11)		Empagliflozin + OHA (n=43)		Empagliflozin + Insulin ± OHA (n=122)		Empagliflozin + OHA (n=139)	
	After 2 Months	After 4 Months	After 2 Months	After 4 Months	After 2 Months	After 4 Months	After 2 Months	After 4 Months
Definite ADR	0	0	0	0	0	0	0	0
Probable ADR	0	0	0	0	0	0	1	1
Possible ADR	2 (18%)	0	0	0	26 (21.31%)	12 (9.83%)	5 (3.59%)	1 (0.71%)
Doubtful ADR	0	0	0	1 (2.32%)	0	2 (1.63%)	0	1

Table 21: Distribution of study population based on Morisky Patient Medication Adherence Scale (n=315)

MORISKY SCALE	≤5 Years				>5 Years			
	Empagliflozin+ Insulin ± OHA (n=11)		Empagliflozin + OHA (n=43)		Empagliflozin + Insulin ± OHA (n=122)		Empagliflozin + OHA (n=139)	
	After 2 Months	After 4 Months	After 2 Months	After 4 Months	After 2 Months	After 4 Months	After 2 Months	After 4 Months
Low adherence	0	0	0	0	11 (9.01%)	0	1 (1.7%)	0
Medium adherence	2 (18.18%)	0	3 (6.9%)	2 (4.6%)	18 (14.75%)	13 (10.6%)	10 (7.7%)	4 (2.8%)
High adherence	9 (81%)	11 (100%)	40 (93%)	41 (95.3%)	93 (76.22%)	109 (89.3%)	128 (92%)	135 (97.1%)

Table 22: Relationship between hypoglycemic episodes and patient medication adherence in insulin taking group

EMPAGLIFLOZIN + INSULIN ± OHA							
ADR	**Duration of T2DM**	**High adherence**		**Medium adherence**		**Low adherence**	
		After 2 Months	After 4 Months	After 2 Months	After 4 Months	After 2 Months	After 4 Months
Hypoglycemia	≤5 Years	0	0	3	0	0	0
	>5 Years	5 (4.06%)	1 (0.81%)	10 (8.19%)	13 (10.65%)	11 (9.01%)	0 (0%)

Table 23: Student paired t-test for empagliflozin + insulin ± OHA therapy

Parameter	Duration of T2DM	Baseline	R-1	R-2	R-1 t-value	R-2 t-value	R-1 *p*-value	R-2 *p*-value
		Mean ± SD	Mean ± SD	Mean ± SD				
EMPAGLIFLOZIN + INSULIN ± OHA								
BODY WEIGHT	≤5 Years	79.55±14.320	78.18±13.65	77.27±13.58	4.892	5.926	**0.000**	**0.000**
	>5 Years	81.05±11.21	79.98±10.97	78.97±10.7	12.727	15.534	**0.001**	**0.000**
BMI	≤5 Years	29.64±4.5	29.36±4.2	28.91±4.1	1.936	3.730	**0.082**	**0.004**
	>5 Years	29.60±3.3	29.24±3.24	28.89±3.13	7.096	10.920	**0.000**	**0.000**
FBS	≤5 Years	246.45±93.30	217.09±110.98	180.82±77.97	1.180	3.313	0.265	**0.008**
	>5 Years	228.39±71.06	176.61±54.31	140.22±45.44	13.460	18.871	**0.000**	**0.000**
RBS	≤5 Years	333±137.48	245.82±93.97	199.82±71.92	3.222	4.589	**0.009**	**0.001**
	>5 Years	288.21±85.64	234.16±55.02	203.69±41.39	11.798	14.387	**0.000**	**0.000**
HbA1c	≤5 Years	11.27±1.67	9.45±1.21	8.55±1.03	6.901	7.596	**0.000**	**0.000**
	>5 Years	9.43±1.32	8.45±0.92	7.82±0.85	12.038	20.015	**0.000**	**0.000**
Total cholesterol	≤5 Years	200.73±58.50	198.27±48.39	194.64±44.150	0.518	1.087	0.616	0.302
	>5 Years	225.94±75.09	216.94±65.51	209.84±62.58	5.810	8.197	**0.008**	**0.006**
Triglyceride	≤5 Years	216±60.57	202.09±56.11	208.09±75.67	3.330	1.099	0.616	0.302
	>5 Years	238.82±78.48	225.89±72.23	219.22±68.43	7.852	9.212	0.241	**0.009**
HDL	≤5 Years	37.45±3.14	37.45±2.84	38.09±3.98	0.000	1.750	1.000	0.111
	>5 Years	34.3±4.25	34.64±3.96	35.21±3.64	3.067	6.964	**0.003**	**0.000**
LDL	≤5 Years	98.45±53.19	96.91±45.49	96.27±46.43	0.356	0.474	0.729	0.646
	>5 Years	116.61±41.74	107.69±38.10	102.36±36.17	5.195	6.891	**0.000**	**0.000**

****p* value ≤0.001 is considered to be statistically significant

Table 24: Student paired t-test for empagliflozin + OHA therapy

Parameter	Duration of T2DM	Baseline	R-1	R-2	R-1 t-value	R-2 t-value	R-1 *p*-value	R-2 *p*-value
		Mean ± SD	Mean ± SD	Mean ± SD				
EMPAGLIFLOZIN + OHA								
BODY WEIGHT	≤5 Years	86.86±16.09	85.12±14.96	84.12±14.78	5.616	6.967	**0.000**	**0.000**
	>5 Years	78.96±11.21	77.81±11.43	76.85±11.32	9.739	16.454	**0.000**	**0.000**
BMI	≤5 Years	31.53±4.93	30.93±4.61	30.44±4.50	5.013	7.572	**0.000**	**0.000**
	>5 Years	28.56±2.54	28.16±2.56	27.93±2.66	7.057	6.854	**0.000**	**0.000**
FBS	≤5 Years	184.95±41.97	150.40±34.69	116.65±25.15	8.061	10.490	**0.000**	**0.000**
	>5 Years	205.72±57.32	116.22±46.87	129.53±38.31	11.704	19.284	**0.000**	**0.000**
RBS	≤5 Years	256.91±53.49	217.51±40.38	181±33.54	5.897	10.225	**0.000**	**0.000**
	>5 Years	272.69±55.61	233.46±44.57	191.07±35.73	12.462	22.123	**0.000**	**0.000**
HbA1c	≤5 Years	8.3±0.86	7.72±0.76	7.19±0.58	6.998	11.707	**0.000**	**0.000**
	>5 Years	8.56±1.16	7.9±0.98	7.47±0.98	10.251	16.478	**0.000**	**0.000**
Total cholesterol	≤5 Years	221.67±65.37	207.12±59.09	200.63±54.66	4.268	5.268	**0.006**	**0.005**
	>5 Years	241.25±87.77	228.87±79.78	219.5±79.78	5.624	9.526	**0.006**	**0.004**
Triglyceride	≤5 Years	223.56±77.77	211.74±66.97	199.74±62.72	3.837	5.661	**0.007**	**0.006**
	>5 Years	256.06±89.14	242.12±83.47	233.25±79.75	8.655	13.028	0.041	**0.006**
HDL	≤5 Years	35.67±4.42	35.91±4.30	36.19±4.07	0.754	1.995	0.455	0.053
	>5 Years	34.96±6.59	35.07±5.99	35.85±5.62	0.730	6.088	0.467	**0.000**
LDL	≤5 Years	117.77±49.52	112.95±44.97	109.12±41.82	1.725	3.175	0.092	**0.003**
	>5 Years	117.21±52.09	112.17±45.32	107.69±42.17	2.939	6.136	**0.004**	**0.000**

****p* value ≤0.001 is considered to be statistically significant

6. RESULTS

A total of 315 patients receiving SGLT-2 inhibitor as a therapy for T2DM were enrolled in the study. These patients received 10 different combinations of SGLT-2 inhibitors based on the pharmacological classification (Table 8 and Figure 14). The results show that, empagliflozin was the most prescribed SGLT-2 inhibitorwhile canagliflozin and dapagliflozin were the least. The most prescribed combination with empagliflozin was biguanides or insulin along with other combinations such as DPP4, sulfonylurea and α-glucosidase inhibitors. Mostly prescribed combination was empagliflozin + biguanides + insulin + DPP4 (16.19%) followed by empagliflozin + biguanide + DPP4 + SU (15.87%). Empagliflozin + biguanides + SU (14.6%), empagliflozin + biguanide + insulin (13.65%), empagliflozin + biguanide + insulin + SU (10.15%), empagliflozin + biguanides + DPP4 (8.88%), empagliflozin + biguanides (8.57%), empagliflozin + insulin (6.34%) were the major other prescribing pattern whereas empagliflozin + insulin + SU (3.8%) and empagliflozin + α-glucosidase inhibitors (1.9%) are the least prescribed pattern.

GENERAL DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION:

The patients were categorized based on their gender. There were 188 males (59.7%) and 127 females (40.3%) in the study. The result of this study shows higher predominance of male for T2DM. (Table 3 and Figure 9).

Study population was categorized into 7 groups based on the age. It was found that about 38.41% patients were under the age category of 51-60and least were in the age category of 81-90 years. (Table 4 and Figure 10).

About 42.85% of the study population had previous medical history of hypertension and 15% of the patients had established CV disease(Table 5 and Figure 11).

SGLT-2 inhibitors are mostly prescribed to over-weight (63.49%) and obese (32.06%) patients(Table 6 and Figure 12). In the study population 17.14% patients had less than 5 years of established T2DM whereas 82.85% patients had more than 5 years of T2DM (Table 7 and Figure 13).

So,the study population were divided into two groups namely patients with ≤5 years of T2DM and >5 years of T2DM. They are further divided into two sub-groups namely empagliflozin with insulin ± OHA and empagliflozin with OHA. (Table 7 and Figure 7)

All the T2DM patients enrolled in the study was reviewed at 2 months and 4 months. The primary composite outcomes were change in HbA1c, FBS, RBS from baseline as glycemic control and change in body weight, BMI, lipid profile and eGFR as beneficial effect of the drug.

GLYCEMIC CONTROL:

The glycemic efficacy was assessed by analyzing the mean change in the value of Fasting Blood Sugar (FBS), Random Blood Sugar (RBS) and Glycated hemoglobin (HbA1c) from the baseline to 2 months followed by 4 months.

OTHER PARAMETERS:

Change in body weight and lipid profile was also assessed by analyzing the mean value of body weight, BMI, total cholesterol, triglycerides, HDL and LDL.

CLINICAL EFFICACY OF SGLT-2 INHIBITOR:

Based on the study, it was found that, glucose lowering effect were more in patients treated with empagliflozin + insulin ± OHA with marked decrease in HbA1c whereas FBS were more reduced in patients with longer duration of T2DM while RBS shows a significant reduction in patients treated with insulin.

The study demonstrates, more reduction in the HbA1c among the patients treated with empagliflozin + insulin ± OHAwith a mean reduction of 1.93% (9.4±1.21 with *p* value ≤0.001) and 2.76% (8.57±1.03 with *p* value ≤0.001) after 2 months and 4 months respectively among the patients with≤5 years of T2DM. Empagliflozin + insulin ± OHA shows similar reduction of HbA1c in >5 years group by 0.98% (8.45±0.92 with *p* value ≤0.001) and 1.61% (7.82±0.85 with *p* value ≤0.001) after 2 months and 4 months of therapy respectively. Empagliflozin + OHA treated group also showed a significant reduction in the HbA1c by 0.58% (7.72±0.76 with *p* value ≤0.001) and 1.11% (7.19±0.58 with *p* value ≤0.001) in ≤5 years and 0.66% (7.90±0.98 with *p* value ≤0.001) and 1.09% (7.47±0.84 with *p* value ≤0.001) in >5 years after 2 months and 4 months respectively (Table 14 and Figure 20).

More the duration of T2DM more was the decrease in FBS. Empagliflozin + OHA in ≥5 years of T2DM shows a significant mean reduction in the FBS by 89.53mg/dl (116.22±46.87 with *p* value ≤0.001) and 91.22 mg/dl (129.53±38.31 with *p* value ≤0.001) after 2 months and 4 months respectively. Empagliflozin + insulin ± OHA also shows almost similar significant reduction in the FBS by 51.78mg/dl (176.61±54.31 with *p* value ≤0.001) and 88.17mg/dl (140.22±45.44 with *p* value ≤0.001) after 2 and 4 months respectively. FBS lowering effect withempagliflozin + insulin ± OHA and empagliflozin + OHA were almost similar with mean

reduction by 29.36mg/dl (217.09±110.98 with *p* value ≤0.265) and 34.55mg/dl (150.40±34.69 with *p* value ≤0.001) after 2 months respectively and 65.64mg/dl (180.81±77.97 with *p* value ≤0.008) and 68.3mg/dl (116.65±25.15 with *p* value ≤0.001) after 4 months respectively (Table 12 and Figure 18).

The study shows significant reduction in the RBS in all groups. The mean reduction of RBS was more in empagliflozin + insulin ± OHA treated group with mean reduction of 87.19mg/dl (245.81±93.97 with *p* value ≤0.009) and 54.05mg/dl (234.16±55.02 with *p* value ≤0.001) after 2 months in ≤5 years and >5 years of T2DM respectively. The mean reduction was 133.19mg/dl (199.81±71.92 with *p* value ≤0.001) and 54.05mg/dl (234.16±55.02 with *p* value ≤0.001) after 4 months in ≤5years and >5 years respectively. Empagliflozin + OHA also shows a significant reduction in the both ≤5 years and >5 years group. After 2 months of therapy, the mean reduction of 39.4mg/dl (217.51±40.38 with *p* value ≤0.001) and 39.23mg/dl (233.46±44.57 with *p* value ≤0.001) in ≤5 years and >5 years group respectively. After 4 months of therapy, the mean reduction was 75.91mg/dl (181±33.54 with *p* value ≤0.001) and 81.62mg/dl (191.07±35.73 with *p* value ≤0.001) in ≤5 years and >5 years respectively (Table 13 and Figure 19).

Change in body weight were more in patients with ≤5 years of T2DM. There was a mean reduction of 1.74kg (85.12±14.96 with *p* value ≤0.001) and 2.74kg (84.12±14.78 with *p* value ≤0.001) in empagliflozin + OHA with ≤5 years of T2DM after 2 months and 4 months respectively. Also, there was mean reduction of 1.33 kg (78.2±13.65 with *p* value ≤0.001) and 2.26kg (77.27±13.58 with *p* value ≤0.001) after 2 and 4 months respectively in empagliflozin + insulin ± OHA group. Therapy with empagliflozin +OHA in >5 years of T2DM shows a significant mean reduction by 1.15kg (77.81±11.43 with *p* value ≤0.001) and 2.11kg

(76.85±11.32 with *p* value ≤0.001) after 2 and 4 months respectively. About 1.07 kg (79.98±10.97 with *p* value 0.001) and 2.08kg (78.97±10.7 with *p* value ≤0.001) mean reduction of body weight was recorded after 2 months and 4 months respectively in empagliflozin + insulin ± OHA treated patients with >5 years of T2DM (Table 10 and Figure 16).

BMI lowering effect was more in ≤5 years of T2DM patients. Empagliflozin + OHA treated patients with ≤5 years of T2DM was reported mean reduction of 0.6kg/m^2 (30.93±4.61 with *p* value ≤0.001) and 1.09kg/m^2 (30.44±4.50 with *p* value ≤0.001) after 2 months and 4 months respectively. Empagliflozin + insulin ± OHA treated patients also reported significant reduction in BMI by 0.5kg/m^2 (29.20±4.24 with *p* value ≤0.001) and 0.36kg/m^2 (29.24±3.24 with *p* value ≤0.001) after 2 months for ≤5 years and >5 years of T2DM. Mean reduction of BMI in >5 years of T2DM treated with empagliflozin + OHA found to be least but it also shows a significant change in 2 months and 4 months by 0.41kg/m^2 (28.16±2.56 with *p* value ≤0.001) and 0.63kg/m^2 (27.93±2.66 with *p* value ≤0.001) respectively (Table 11 and Figure 17).

The study demonstrates that, the lipid profile was well maintained in all groups (which includes patients with or without statins). The mean total cholesterol for empagliflozin + insulin ± OHA in ≤5 years was 198.27±48.39 and 194.63±44.15 after 2 months and 4 months respectively, while for >5 years it was 216±65.65 and 209±62.58 after 2 months and 4 months respectively. There was a similar effect on empagliflozin + OHA treated group with mean total cholesterol of 207.12±59.09 and 200.63±54.66 after 2 months and 4 months respectively in ≤5 years group while in >5 years mean total cholesterol was 228.87±79.78 and 219.50±71.01 after 2 months and 4 months of therapy respectively (Table 15 Figure 21).

The level of triglycerides was well maintained after the 4-month duration of therapy with or without statin in all the groups. It reflects its beneficial effect towards the patients with hyperlipidemia with T2DM. The mean triglycerides level in empagliflozin + insulin ± OHA treated group was 202.09±56.11 and 208.09±75.67 after 2 and 4 months respectively in <5 years of T2DM while it was 225.89±72.23 and 219.22±68.43 in >5 years after 2 and 4 months respectively. The result was similar in empagliflozin + OHA treated group with mean triglycerides level of 211.74±66.97 and 199.74±62.72 in 2 and 4 months respectively in ≤5 years of T2DM, but it was 242.12±83.47 and 233.25±79.75 in >5 years respectively (Table 16 and Figure 22).

The HDL level was found slightly increased in the study population with or with statin. Empagliflozin + insulin ± OHA in ≤5 years shows mean HDL of 37.45±2.84 and 38.09±3.98 after 2 and 4 months respectively but in >5 years it was 34.64±3.96 and 35.21±3.64 after 2 and 4 months of therapy. While in empagliflozin + OHA treated group mean HDL level was 35.91±4.30 and 36.19±4.07 after 2 and 4 months respectively in ≤5 years while, 35.07±5.99 and 35.86±5.62 after 2 and 4 months respectively in ≥5 years of T2DM patients (Table 17 and Figure 23)

The LDL level after the therapy doesn't show much reduction but well maintained. Empagliflozin + insulin ± OHA in ≤5 years of T2DM shows mean LDL level of 96.90±45.49 and 96.27±46.43 after 2 and 4 months respectively. But, in >5 years of T2DM it was 107.69±38.10 and 102.52±36.17 after 2 and 4 months respectively. In empagliflozin + OHA treated group, LDL level was 112.95±44.97 and 109.12±41.82 in ≤5 years of T2DM after 2 and

4 months respectively while it was 112.17±45.32 and 107.69±42.17 in ≥5 years of T2DM (Table 18 and Figure 24).

The eGFR level was ≥60ml/min/1.73m^2 in all the groups after the 4 months therapy. The eGFR level ≥40ml/mon/1.73m^2 was considered as an inclusion criterion, as explained in the methodology.

SAFETY OF SGLT-2 INHIBITORS:

After 2 months of therapy, hypoglycemia was the major ADR reported and out of which 26 (21%) + 2 (18%) reported hypoglycemia was in empagliflozin + insulin ± OHA treated group in >5 years and ≤5 years respectively. Empagliflozin + OHA in ≤5 years doesn't report any hypoglycemic events after 2 months but >5 years of T2DM reported 5 (3.5%) cases of hypoglycemia (Table 19 and Figure 25).

But the catching point is that, there were only 14 cases (11.47%) of hypoglycemia were reported in the empagliflozin + insulin ± OHA treated patients after 4 months of therapy. Also, only 2 (1.43%) and 1case(2.3%) of hypoglycemia were reported in empagliflozin + OHA treated patients in >5 years and ≤5 years of T2DM respectively.

There were only 1 case of geno-mycotic infection reported in the entire study population, particularly in empagliflozin + OHA treated patients for >5 years of T2DM (Table 19).

No events of diabetic ketoacidosis were reported in the entire study population.

All the reported ADR was confirmed by Naranjo Adverse Drug Reaction Scale and which shows, 21.1% , 18%, and 3.59% of theADR which was reported in empagliflozin + insulin ±

OHA in ≥5 years, empagliflozin + insulin ± OHA in ≤5 years and empagliflozin + OHA in >5 years respectively was confirmed as possible ADR after 2 months of therapy while only 9.83% and 0.71% of reported ADR in empagliflozin + insulin ± OHA in >5 years and empagliflozin + OHA in >5 years of T2DM respectively was confirmed as possible ADR followed by 2.32% and 1.63% of doubtful ADR was reported in empagliflozin + OHA in ≤5 years and empagliflozin + insulin ± OHA in >5 years of T2DM respectively after 4 months of therapy (Table 20).

After 2 months of therapy, the study population were divided into three based on their adherence towards the medication using Morisky Patient Medication Adherence Scale. The result shows, insulin taking group had lower adherence towards the medication. But, after the counselling given to from diabetic clinic (DMTAC), the adherence was improved which was recorded after 4 months (Table 21 and 22).

7. DISCUSSION

The study was designed to identify the prescribing pattern of SGLT-2 inhibitors. The study reveals 10 different prescribing patterns for empagliflozin, 2 for canagliflozin and no dapagliflozin receiving patients were found in this 6-month study. Patients receiving canagliflozin were excluded for the clinical efficacy study because of the limited number of cases. Among the 10 prescribing patterns of empagliflozin, about 16.19% of the study population received empagliflozin + biguanides + insulin + DPP4. There is no previous study conducted on these combinations except that**Rosenstock *et al.*, (2014)**[77] conducted a study on improved glycemic control with empagliflozin + biguanide + insulin. Also, **Scheen*et al.*, (2016)**[79] performed a combination therapy with DPP-4 inhibitors. Both the studies showed a significant reduction in the glycemic control and body weight which was quite similar to the present study. Empagliflozin was mostly prescribed as second-line therapy after metformin. According to **Defronzo*et al.*, (2015)**[66] empagliflozin + gliptin combination was effective on patients with inadequately controlled T2DM with metformin. In our study, 40.95% of the study population received empagliflozin + gliptins ± insulin or other OHAs.

Empagliflozin + insulin ± OAH was received by 50.15% of the study population. According to **Rosenstock *et al.*, (2015)**[70] empagliflozin as an addon to insulin in patients with inadequately controlled T2DM was effective in improving glycemic control and reduced body weight with similar risk of hypoglycemia as that of placebo.

About 44.4% of the study population received different combinations with sulfonylureas. According to **Haering*et al.*, (2015)**[73] empagliflozin as add-on to metformin and sulfonylureas shows a significant reduction in the HbA1c and weight versus placebo.

Empagliflozin + biguanides with α-glucosidase inhibitor was the least prescribed combination in our study.

In the present study, we enrolled 315 patients receiving empagliflozin as a therapy for T2DM. The study was categorized based on gender. There were 188 (59.7%) of male and 127 (40.3%) of female in the entire study population. This result shows higher predominance for T2DM in male than in female.This was similar to the previous study conducted by **Gale *et al.*, (2011)**[80] which showed higher prevalence of T2DM in men than women.

The study population were then categorized based on the age group, where 38.4% of the study population came under the age group of 51-60 years. This was similar to the study conducted by**Basim*et al.*, (2017)**[81] where the mean age was 56.4 years.

Among the study population, hypertension was the major comorbidity reported (42.9%), followed by myocardial infraction (8.3%), stroke (0.6%) and angina (6%). The result was similar to the previous study conducted by **Lastra*et al.*, (2014)**[82] which showed hypertension is present in 50% of patients with T2DM and contribute significantly to macrovascular and microvascular complications in diabetes mellitus.

According to **Muhammad*et al.*, (2016)**[83] myocardial infraction, stroke and angina are the major comorbidities associated with T2DM.

Among the study population, a greater number of patients were over-weight (63.49%) and Obese (32.06%). This revels, over-weight and obese patients are more prone to get T2DM. According to**Torgerson *et al.*, (2004)**[84] risk of affecting T2DM is mostly linked to presence and duration of over-weight and obesity.

The study population was categorized into five groups based on the duration of T2DM. About 53.3% of the study population had 6-10 years of T2DM. Astudy conducted by **Cortez *et al.*, (2014)**[85] which showed 28.2% had diabetes for <5 years, 35.2% had 5-10 years of diabetes while 36.6% of the study population had >10 years of diabetes.

The study population was then divided into two based on the therapy received, namely empagliflozin + insulin ± OHA and empagliflozin ± OHA. Which was further subdivided into two, namely patients with ≤5 years and >5 years of T2DM.

Among the sub-divided group, a greater number of patients had more than 5 years of T2DM i.e., 44.12% in empagliflozin + OHA and 38.73% in empagliflozin + insulin ± OHA treated group.

The glucose lowering efficacy was assessed by analyzing the mean change in the value of HbA1c, Fasting blood sugar (FBS), and Random blood sugar (RBS) from the start of the therapy to the end of 4 months study period in each group with follow-up at the end of 2nd month. The beneficial effect of empagliflozin such as body weight, BMI, total cholesterol, triglycerides, HDL and LDL was assessed at 2 months followed by 4 months.

Empagliflozin has been demonstrated to improve glycemic control when used in combination with insulin or with other OHAs. In this study, the reduction in HbA1c with empagliflozin + insulin was greater than those with empagliflozin + OHA treated group.

In this study, at the end of 4 months of therapy HbA1c, FBS and RBS were significantly (*p* value ≤0.001) reduced by 8.57±1.03, 180.81±77.97 and 199.81±71.92 respectively in ≤5 years and 7.82±0.85, 140.22±45.44 and 203.69±41.39 in >5 years of T2DM in empagliflozin + insulin

± OHA treated patients. The result of this study perfectly complies with the former study conducted by **Rosenstock *et al.*, (2014)**[77]were the empagliflozin add-on to insulin improved glycemic control and body weight with similar risk of hypoglycemia to placebo.

Another study conducted by **Rosenstock *et al.*, (2015)**[70] there was statistically significant improvement in the HbA1c with empagliflozin + insulin treated group. Addition of empagliflozin to insulin improved glycemic control, lower insulin doses and achieved HbA1c level of 7.2% and 7.1% in 10 mg and 25 mg respectively. In the clinical trial conducted in various sites, it has been shown to be safe and effective in T2DM patients when used as an add-on to insulin ± other OHA.

In the study population empagliflozin + OHA treated patients also shows a significant (*p* value ≤0.001) reduction in the HbA1c, FBS and RBS, but, the reduction was more in insulin treated group.A study conducted by **Araki *et al.*, (2015)**[72] also shows Japanese T2DM patients treated with empagliflozin as an add-on to other oral anti-diabetic therapy for 52 weeks were well tolerated and were associated with clinically meaningful reduction in the HbA1c.

Astudy conducted by **Goldman *et al.*, (2018)**[86] concludes, combination therapy with empagliflozin and metformin in T2DM who were inadequately controlled by metformin was effective in glucose lowering.

Another study conducted by **Kawamori*et al.*, (2018)**[54] where the combination therapy with empagliflozin and linagliptin shows significant reduction in the HbA1c in Japanese T2DM patients. This was the phase III trial for fixed dose combination of empagliflozin and linagliptin.

Another study conducted by **Haering*et al.*, (2015)**[73] shows empagliflozin as an add-on to metformin and sulfonylurea for 76 weeks was well tolerated and led to sustained reduction of HbA1c and weight.

In the study population, as the duration T2DM increases, the FBS reduction was also increased with empagliflozin treated group.

Body weight gaining is one of the serious issues associated with the management of T2DM, specially in over-weight or obese patients. In this study, body weight shows a marked decrease in all the empagliflozin treated group with minimum mean reduction of 2.08kg in all group after 4 months of study. Empagliflozin + OHA and empagliflozin + insulin ± OHA shows an almost close reduction in the body i.e., 2.74kg and 2.26kg respectively. So, it is a beneficial factor which should be considered in the management of T2DM. Also, as we described above, we had about 95.52% of study population received empagliflozin was over-weight or obese patients with T2DM. So, according to our study, empagliflozin must be a good choice for the management of T2DM in over-weight and obese.

According to **Haering*et al.*, (2015)**[73] empagliflozin as an add-on to other OHAs shows a significant reduction in the body weight. It was a double-blind trail which included 666 patients with T2DM to receive 10mg, 25mg or placebo once daily.

Another study conducted by **Goldman *et al.*, (2018)**[86] combination therapy with empagliflozin and metformin is very suitable for the patients with T2DM who are inadequately controlled with metformin, in particular, patients with modest reduction in the body weight and blood pressure.

According to **Rosenstock *et al.,*** empagliflozin with insulin show significant reduction in body weight by 2.2±0.5kg and 2.2±0.5kg in 10mg and 25mg empagliflozin respectively as an add-on to insulin. This result compiles with the body weight reduction in insulin treated group in our study.

Zinman*et al.,* (2015)[69] in EMPA-REG OUTCOME trial shows, empagliflozin was associated with reduction in the body weight, waist circumference, uric acid level, systolic and diastolic blood pressure with increase in heart rate and good action on HDL and LDL.

In this study, BMI was considered as an important parameter because, most of the patients were obese and overweight with T2DM and some with other cardiovascular disease. In this study, BMI was found a decrease of about 1.09kg/m^2 in the empagliflozin + OHA treated group. But the result was almost similar with insulin treated group which was 0.83kg/m^2 after 4 months of therapy in patients.

In this study, duration of study was associated with reduction in the BMI. Empagliflozin + insulin ± OHA shows a marked decrease in BMI by 0.71kg/$m^2$and 0.63kg/m^2 in empagliflozin + OHA treated patients after 4 months of therapy.

According to **Neeland*et al.,* (2016)**[87] empagliflozin was associated with the higher urinary excretion of glucose by reducing the renal tubular threshold for glycosuria. This leads to excretion of 60-100g/day of glucose, which results in improving glucose control with lower risk of hypoglycemia and results in loss of 240 to 400kCal/day into urine with associated body weight and BMI reduction.

Neeland*et al.*, (2016)[87]studied beneficial effect of empagliflozin on blood pressure. The study shows decrease in blood pressure was due to osmotic diuresis of glucose and natriuresis of co-transported sodium.

In our study, lipid profiles were well maintained in all the empagliflozin received group.About 55.5% patients in the entire study population received empagliflozin + statins and there were less events of complications reported. All the lipid parameters such as total cholesterol, triglycerides, HDL and LDL level were improved with the therapy.

But according to the resultscripted by**Zinman*et al.*, (2015)**[69] in EMPA-REG OUTCOME trial which included 7020 T2DM patients with established CVD, the empagliflozin was associated with slight increase in both HDL and LDL. This might be because in our study patients with hyperlipidemia received statins along with empagliflozin.

There was not much change found in eGFR level in our study, 99.3% had >90ml/min/1.73m^2.

The treatment with empagliflozin was well tolerated over the 4 months treatment period. Mild hypoglycemia (10.47%) and geno-mycotic infection (0.31%) was the adverse events reported in the entire study population. These adverse events were confirmed by Naranjo ADR Scale. No events of diabetic ketoacidosis were reported among the study population.

Geno-mycotic infection was reported in empagliflozin + OHA treated patients, particularly with empagliflozin + metformin + glimepiride and the drug were discontinued after 4 months of therapy and was treated with topical anti-fungal agents. The result was similar to the study

conducted by **Zinman*et al*., (2015)**[69] where the events of geno-mycotic infection reported were 1.7% of the entire study population (n=7020).

Hypoglycemic events were more in empagliflozin + insulin ± OHA receiving patients i.e., 8.8% of entire study population (n=315). The hypoglycemic events were reported more in patients with more than 5 years of T2DM i.e., 21% (n=122) and 18 % (n=11) in less than five years of T2DM.

Particularly, after 2 months of therapy the events of hypoglycemia were more in patients received only empagliflozin as an add-on to insulin i.e., 40% (n=20) and 27.9% (n=43) with empagliflozin add-on to metformin + insulin. But, after 4 months of therapy the hypoglycemic events were lesser in insulin treated patients i.e., 25% and 11.62% in empagliflozin + insulin and empagliflozin + metformin + insulin respectively.

The result was similar to the study conducted by **Rosenstock *et al*., (2015)**[70] where the reported events of hypoglycemia after 18 weeks of therapy with empagliflozin as an add-on to insulin showed 20% and 28%with 10mg and 25mg empagliflozin respectively. But at the end of their study i.e., after 72 weeks, there were 36% of reported hypoglycemia in both the doses which was similar to placebo.

After 2 months of study, the adherence of the patient towards the medication were recorded using morisky patient medication adherence scale, which shows insulin receiving patients who are reported with hypoglycemia had low (9.01%) or medium adherence (8.19%). So, the patients are counselled at diabetic clinic (DMTAC) and reports of hypoglycemia recorded after 4 months, which shows, 13% of reported hypoglycemic patients were in medium adherence and only 1% in

high adherence. This clearly indicates the relation between patient medication adherence and hypoglycemia in insulin receiving patients.

During the study period, a cost analysis was conducted among the patients received empagliflozin. From the cost analysis study, it was observed that empagliflozin added to standard therapy was found cost-effective as the clinical events associated with it is lesser. The fact is supported by, **Gourzoulidis*et al.*, (2018)**[88] his study shows empagliflozin added to standard of care was estimated to be cost effective.

8. CONCLUSION

Out of the collected data from 315 patients receiving SGLT-2 inhibitors 12 prescribing pattern was studied out of which empagliflozin + biguanide + insulin + DPP-4 was the most prescribed combination followed by empagliflozin +biguanide + DPP-4 + SU. There were very few patients who received canagliflozin and no patients with dapagliflozin. From the study population, the predominance of T2DM is higher in males than females with the age group 51-60 and most of the patients were observed in the duration was 6-10 years. The study shows empagliflozin was mostly prescribed to over-weight or obese patients with/without established cardiovascular complications.

The study provides an evidence of safety and efficacy of empagliflozin as add-on to insulin or in combination with other OHA in patients with T2DM.

The results pointed out that, all the group of patients showed an improvement in their glycaemic parameters such as HbA1c, FBS and RBS during the study period and from the group comparison study it was observed that patients receiving empagliflozin with insulin ± OAH had better glycaemic control than empagliflozin + OHA therapy.

The study demonstrates a significant reduction in the body weight and BMI in all the groups, but slightly more in patients with ≤5 years of T2DM. It had a beneficial effect on HDL and LDL as well.

Hypoglycaemia was the most reported ADR among those prescribed with empagliflozin + insulin ± OHA only. One patient reported with geno-mycotic infection leading to stop of the therapy among empagliflozin + OHA receiving group.

In conclusion, empagliflozin was found tosignificantly improve glycaemic parameters along with reduction in body weight, BMI, HDL and LDL in Indian T2DM patients with mild ADR when prescribed as add-on to insulin or other OHA.

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DATA COLLECTION FORM

Reg. No.: **OP No.:**

Name: **Age:** **Sex: M/F**

Marital status: **Married** ☐ **Single** ☐

Smoking: **Yes** ☐ **No** ☐ **Height:**

Alcohol: **Yes** ☐ **No** ☐

Family history		
Diabetes mellitus:	**Yes** ☐	**No** ☐
Hypertension:	**Yes** ☐	**No** ☐
Chronic Kidney Disease:	**Yes** ☐	**No** ☐

Date of initiation of SGLT-2 inhibitor therapy:

Past medical history	**Yes**	**No**	**Duration**	**After receiving SGLT-2 inhibitor**			
				Ist Review		**IInd Review**	
				Yes	**No**	**Yes**	**No**
Diabetes mellitus:							
Hypertension:							
Myocardial infraction:							
Stroke:							
Angina:							

Parameters considering in the study	**Initial**	**After Ist review**	**After IInd review**
Body weight			
BMI			
Blood pressure 1. Systolic 2. Diastolic			
FBS			
RBS			
HbA_{1C}			
Total cholesterol			
Triglycerides			
HDL			
LDL			
Creatinine			
eGFR			
Albumin			

TREATMENT		
Initial	**Ist Review**	**IInd Review**

ADVERSE DRUG REACTION				
Hypoglycaemic episodes	**Ist Review**		**IInd Review**	
	Yes	**No**	**Yes**	**No**
Genital mycotic infections				
Ketoacidosis				

NARANJO ADVERSE DRUG REACTION PROBABILITY SCALE

QUESTIONS	YES	NO	DO NOT KNOW	SCORE (R-1)	SCORE (R-2)
1. Are there previous conclusive reports on this reaction?	+1	0	0		
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0		
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0		
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0		
5. Are there alternative causes (other than drug) that could on their own have caused the reaction?	+1	+2	0		
6. Was the drug detected in blood (or other fluids) in concentration known to be toxic?	+1	0	0		
7. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0		
8. Did the patient have similar reaction to the same or similar drugs in any previous exposure?	+1	0	0		
9. Was the adverse event confirmed by any objective evidence?	+1	0	0		

10. Did the reaction reappear when a placebo was given?	-1	+1	0		
TOTAL					

SCORING FOR NARANJO ADR MONITORING SCALE:

- 9 = definite ADR
- 5-8 = probable ADR
- 1-4 = possible ADR
- 0 = doubtful ADR

MORISKY MEDICATION ADHERENCE SCALE

QUESTIONS	PATIENT ANSWER (Y/N)	SCORE (R-1)	SCORE (R-2)
1. Do you sometimes forget to take your medicine?			
2. People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine?			
3. Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?			
4. When you travel or leave home, do you sometimes forget to bring along your medicine?			
5. Did you take all your medicines yesterday?			
6. When you feel like your symptoms are under control, do you sometimes stop taking your medicine?			
7. Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?			
8. How often do you have difficulty remembering to take all your medicine? __ A. Never/rarely __ B. Once in a while __ C. Sometimes __ D. Usually __ E. All the time • A=0, B-E= 1			

*Y=1, N=0

Scores: >2 = low adherence
1 or 2 = medium adherence
0 = high adherence