

**Empagliflozin: an exciting prospect in the treatment of diabetes****Melvin George<sup>1\*</sup>, Karthik Srinivas<sup>2</sup>, Damal Kandadai Sriram<sup>2</sup>**<sup>1</sup>Department of Clinical Research,<sup>2</sup>Department of Diabetology & Endocrinology, Hindu Mission Hospital, West Tambaram, Chennai, Tamil Nadu, India**Received:** 12 November 2017**Accepted:** 04 December 2017**\*Correspondence to:**Dr. Melvin George,  
Email: [melvingeorge2003@gmail.com](mailto:melvingeorge2003@gmail.com)**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.**ABSTRACT**

Type 2 diabetes mellitus (T2DM) continues to be a chronic and disabling disease that is associated with high mortality and morbidity. The epidemic burden of diabetes mellitus has increased in developing countries and Asia is considered as the “diabetic epicentre”. Type 2 diabetes (T2DM), is characterised by reduced secretion of insulin from pancreatic beta cells independently or associated with reduced response of peripheral tissues to circulating insulin. A proper glycaemic control is essential to delay the micro and macrovascular complications of T2DM. Standard anti-diabetic agents including insulin happen to induce minor to major adverse outcomes in certain populations over prolonged period of administration. Hence there has been a compelling need to develop newer and novel approach to treatment of T2DM. Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are a novel category of drugs that happen to reduce glycaemic overload by inducing glycosuria. The safety, efficacy and tolerability profile of these drugs were studied separately under various trials and was approved for use in August 2014 by US-FDA. This review is an attempt to describe the history of SGLT-2 inhibitors, their mechanism of action, safety and efficacy as well as its current status among anti-diabetic agents.

**Keywords:** Complications, Diabetes, Empagliflozin, Efficacy, SGLT2 inhibitors**INTRODUCTION**

Diabetes mellitus type 2 (T2DM) continues to be a chronic and disabling disease, that is associated with high mortality and morbidity. The epidemic burden of diabetes mellitus has increased in developing countries and Asia is considered as the “diabetic epicentre”. A whopping 9% of adults worldwide are affected by T2DM.<sup>1</sup> Even though several pharmacological treatments, such as sulfonylurea metformin, alpha glucosidase inhibitors and incretin analogues are available for the treatment of diabetes. Each of these drugs have a considerable number of limitations making it imperative that we find better attractive alternatives to improve the glycaemic control of these patients and also reduce drug induced maladies.<sup>2</sup> Sodium-

glucose co-transporter 2 (SGLT-2) inhibitors are a novel class of drugs which reduce blood sugar by inducing glycosuria, a mechanism different from the aforementioned anti-diabetic agents.<sup>3</sup> This review is an attempt to describe the history of SGLT-2 inhibitors, their mechanism of action, efficacy and safety as well as its current status

***Mechanism of action***

Kidneys normally filter 180g/day of glucose and hence glycosuria is not typically detected until plasma glucose exceeds 180mg%. The urine thus filtered normally is negative for glucose. Glucose re-absorption in renal tubules is maintained by 2 types of transporters-Glucose

transporters (GLUT's), and Sodium-Glucose co-transporters (SGLT's). SGLT's are large family of membrane proteins that transport glucose in brush border of intestinal epithelium and proximal renal tubules using electrochemical sodium gradient as the source of energy generated by Na<sup>+</sup>-K<sup>+</sup> adenosine triphosphatase.<sup>4-7</sup>

SGLT-2 is a high capacity low affinity Na<sup>+</sup> coupled glucose transporter in apical part of early proximal convoluted tubule, and it is responsible for 90% of glucose reabsorption. In contrast SGLT-1 located in distal PCT reabsorbs the remaining 10% glucose which escaped reabsorption by SGLT-2. SGLT-1 is mainly associated with reabsorption of glucose and galactose in small intestine. Since the mechanism appears to be by inducing glycosuria, SGLT-2 inhibitors are regarded as non-insulin dependent agents of reducing glycaemic overload.<sup>6</sup>

## PHARMACOKINETICS

Empagliflozin is rapidly absorbed in a dose dependent manner, attains peak concentration levels by 1-2 hours and dose dependent increases in urinary glucose excretion was seen up to a dose of 100 mg. The terminal elimination half-life of the drug was 13.1 hours. There are no significant food-drug interactions. Around 11.19% of the drug is excreted unchanged in urine. The maximum plasma concentration of drug was also 20% higher in subjects with mild or severe renal impairment, compared with normal individuals. Renal clearance and fraction of drug excreted in urine was reduced in patients with decreased renal function.<sup>6</sup>

## EFFICACY

Empagliflozin a sodium glucose co-transporter-2 (SGLT2) inhibitor increases the urinary glucose excretion and improves the glycaemic control through the inhibition of renal glucose re-absorption. Empagliflozin has demonstrated excellent pharmacological and safety profile as an anti-diabetic drug. The other benefits of empagliflozin include weight loss, lower risk of hypoglycaemia, and improvements in cardiovascular outcomes, hypertension and renal complications.<sup>8</sup>

### *Efficacy of empagliflozin as an anti-diabetic drug*

In a phase III, (EMPA-REG BP) study, the efficacy, safety, and tolerability of empagliflozin (10mg and 25mg) was evaluated among patients with T2DM and hypertension. At week 12, empagliflozin showed significant and clinical reductions in HbA1c. The adjusted mean difference in the HbA1c levels between placebo, and 25mg of empagliflozin was -0.65% (95% CI -0.75, -0.55) and 10mg of empagliflozin was -0.62% (95% CI -0.72, -0.52) respectively (both P<0.001).<sup>9</sup> The safety, tolerability, pharmacokinetics and pharmacodynamics of 10, 25, 100mg of empagliflozin or placebo was evaluated in T2DM patients for 28 days. The empagliflozin group demonstrated an increase in the urinary glucose excretion

up to 90g/day, and remained consistent over a 4-week study period without change in urine volume. Fasting sugar was reduced by 30-39mg% from baseline by the end of study. Reduction in HbA1c by 0.22-0.36% was seen in empagliflozin group compared with placebo.<sup>10</sup> One of the unexpected findings with SGLT-2 inhibitors was an increase in endogenous glucose modulation in part due to increases in glucagon.<sup>11</sup> Therefore, empagliflozin appears to be an effective anti-diabetic agent.

### *Efficacy of empagliflozin as monotherapy and combination therapy*

Empagliflozin is a well-established drug for the treatment of T2DM patients. In a multi-national 12-week study, 408 patients were randomized to receive 5, 10, 25 mg of empagliflozin or matching placebo or open-label metformin. The empagliflozin group showed significant reductions in the HbA1c levels, fasting plasma glucose (FPG) levels and body weight.<sup>12</sup> In another multicentre, randomised, placebo-controlled, phase 3 trial, T2DM patients were randomized to receive 10 mg, 25 mg of empagliflozin, sitagliptin 100 mg or matching placebo. The empagliflozin (10 and 25 mg) and sitagliptin showed a significant reduction in the levels of HbA1c when compared to placebo.<sup>8</sup> Empagliflozin has also been studied with other single line anti-diabetic drugs such as oral hypoglycemic agents (OHAs) and insulin. The OHAs include metformin, thiazolidinedione,  $\alpha$ -glucosidase inhibitor, DPP4 inhibitor, or meglitinide. The combination therapy of empagliflozin with other existing anti-diabetic drugs has been effective in reducing the glycaemic levels.<sup>13-16</sup> Moreover, the combination therapy has demonstrated no harmful drug interactions. Therefore, monotherapy and combination therapy with empagliflozin is a potential new approach for the treatment of T2DM. However, empagliflozin is yet to be tested against the older molecules such as metformin and sulfonylureas.

### *Efficacy of empagliflozin on cardiovascular outcomes*

Patients with T2DM have 2.5 times greater risk of developing chronic heart failure (CHF) than the normal subjects.<sup>6</sup> In the year 2008, the US Food and Drug Administration (FDA) had issued new guidelines which mandated that robust assessments of cardiovascular outcomes are required for the approval of all anti-diabetic drugs in the future. In the comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors (CVD-REAL) study, SGLT-2 inhibitors were associated with a lower risk of heart failure hospitalization or mortality compared to other glucose lowering drugs.<sup>17</sup>

In the EMPA-REG outcome trial, 7020 patients were randomized to receive 10 or 25mg of empagliflozin or placebo. The study revealed significant differences in the primary composite outcome (cardiovascular mortality, non-fatal myocardial infarction (excluding silent myocardial infarction), or non-fatal stroke between the

empagliflozin [490 of 4687 patients (10.5%)] and placebo group [282 of 2333 patients (12.1%)]. The hazard ratio in the treatment group was (0.86; 95.02% confidence interval [CI], 0.74 to 0.99;  $P < 0.001$  for non-inferiority and  $P = 0.04$  for superiority). There was significant reduction in rates of CV mortality (3.7% vs 5.9%) and shortened hospitalization due to CHF (2.7% vs 4.1%). MI was reported in 4.8% of the empagliflozin group and 5.4% of the placebo. Stroke was seen in 3.5% of the empagliflozin group and 3% of the placebo group. The cardio protective effects of empagliflozin are attributed to changes in arterial stiffness, cardiac function, cardiac oxygen demand, and cardiorenal effects such as reduction in uric acid and albuminuria, and other well-established effects on hyperglycaemia, weight, visceral adiposity, and blood pressure.<sup>11</sup>

### Efficacy of empagliflozin on renal outcomes

Diabetes is one of the leading causes of chronic kidney disease (CKD) worldwide and about 22-40% of the diabetic subjects are prone to the development of CKD or renal impairment. Reduction of interglomerular pressure reduces proximal tubular sodium re-absorption, delivering increased sodium to macula densa which attenuates tubuloglomerular feedback. Other effects include decreased arterial stiffness and vascular resistance, decrease in serum uric acid and renal neurohormonal

mechanism. These may be responsible for improved renal outcomes.<sup>18,19</sup>

In the EMPA-REG outcome trial, the administration of 10 and 25 mg of empagliflozin among patients with estimated glomerular filtration rate (eGFR)  $< 30 \text{ mL/min/1.73 m}^2$  of body surface area improved renal function. The incidence of nephropathy was observed in 12.7% (525 of 4124) of empagliflozin group and 18.8% (388 of 2061) in placebo group. Doubling of serum creatinine was seen in 1.5% (70 of 4645) of empagliflozin group and 2.6% (60 of 2323) of placebo group. The RRT was started in 0.3% (13 of 4687) of empagliflozin and 0.6% (14 of 2333) of placebo group. However, there was no significant difference in the rates of albuminuria.<sup>20</sup> Therefore the administration of empagliflozin may be associated with improvement in long-term renal outcomes. However, further investigations are required to establish the use of empagliflozin in improving long-term renal outcomes.

### SAFETY AND TOLERABILITY

The most commonly reported adverse effects were an increased incidence of hypoglycemia, urinary tract infection (UTI), genital infection and volume depletion. The incidence of volume depletion was increased in older age group patients than the younger age group patients.<sup>21</sup>

**Table 1: Comparison of SGLT2 inhibitors for the treatment of type II diabetes.**<sup>20,27-31</sup>

Name of the drug	Canagliflozin	Empagliflozin	Dapagliflozin
Dosage and frequency	100 mg once daily in patients who have an e-GFR of 45 to less than 60 mL/min/1.73 m <sup>2</sup> 300 mg once daily in patients tolerating 100 mg once daily who have an e-GFR of 60 mL/min/1.73 m <sup>2</sup> or greater and require additional glycaemic control	10 mg once daily, taken in the morning, with or without food Dose may be increased to 25 mg once daily	5 mg once daily, taken in the morning, with or without food Dose can be increased to 10 mg once daily in patients tolerating dapagliflozin who require additional glycaemic control
Names of major trials	CANVAS CANVAS-R CANTATA CANTATA-SU CANTATA-D CANTATA-D2 CANTATA-MSU	EMPA-REG OUTCOME EMPEROR-Preserved EMPEROR-Reduced	DECLARE-TIMI58 DAPHNIS Study DECIDE Study
Cardiovascular outcome benefit	Not proven	Reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease	Evidence from observational studies exist
Renal outcome benefit	Not proven	Studies have shown improvements in renal outcomes	Not proven
Cost of drug (per tablet)	100 mg-Rs. 55/- 300 mg-Rs. 120/-	10 mg-Rs. 43/- 25 mg-Rs. 52/-	5 mg-Rs. 45/- 10 mg-Rs. 50/-

**Table 2: Ongoing Clinical trials with Empagliflozin.<sup>26</sup>**

Study title	Clinical trials.gov identifier	Intervention/comparator	Primary outcome	Current status of trial/phase
Empagliflozin impact on haemodynamics in patients with diabetes and heart failure (EMBRACE-HF)	NCT03030222	Empagliflozin 10mg/ placebo	To compare the change in pulmonary artery diastolic pressure from baseline to end of treatment period between empagliflozin and placebo	Recruiting participants/Phase IV
Effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE)	NCT03200860	Empagliflozin 10mg/ placebo	Change in dyspnoea on VAS analogue scale (AUC), weight change from baseline per 40 mg of Furosemide equivalent, hospital stay of Index admission Change in NTproBNP	Not yet open for participant recruitment /Phase II
Empagliflozin outcome trial in patients with chronic heart failure with reduced ejection fraction (EMPEROR-Reduced)	NCT03057977	Empagliflozin placebo	Composite primary endpoint - Time to first event of adjudicated CV (Cardiovascular) death or adjudicated HHF (Hospitalisation for Heart Failure) in patients with Heart Failure with reduced Ejection Fraction (HFrEF)	Recruiting participants /Phase III
Empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction (EMPEROR-Preserved)	NCT03057951	Empagliflozin placebo	Composite primary endpoint - Time to first event of adjudicated CV (Cardiovascular) death or adjudicated HHF (Hospitalisation for Heart Failure) in patients with Heart Failure with preserved Ejection Fraction (HFpEF)	Recruiting participants /Phase III
Empagliflozin in heart failure: diuretic and cardio-renal effects (EMPA)	NCT03027960	Empagliflozin placebo	Determine if acute SGLT2 inhibition will improve the natriuretic effect of a loop diuretic compared to placebo. Measuring the natriuretic effect of a loop diuretic (placebo v acute SGLT2 inhibition) via urine sodium output	This study is enrolling participants by invitation only/ Phase II
Empagliflozin in heart failure patients with reduced ejection fraction (Empire HF)	NCT03198585	Empagliflozin 10mg placebo	Change in plasma concentrations of NT-proBNP	Recruiting participants /Phase II
Empagliflozin versus placebo on the rate of arrhythmic events in heart failure patients (ERA-HF)	NCT03271879	Empagliflozin 10 mg	PVCs burden is defined as the PVCs percentage of all beats in a pre-specified period captured on ICD or CRTD/P device The change in PVC burden between time on treatment arm versus time on placebo will be calculated and serve as the primary endpoint	This study is not yet open for participant recruitment /Phase IV

Pooled analysis of Phase I-III clinical trials demonstrated favourable benefit-risk profile of empagliflozin in patients with T2DM.<sup>22</sup> Some of the contraindications associated with empagliflozin include any history of serious hypersensitivity reaction, severe renal impairment, end-stage renal disease, or dialysis. Some of the warnings and precautions issued by FDA with respect to empagliflozin

include hypotension, ketoacidosis, acute kidney injury, impairment in renal function, urosepsis and pyelonephritis. The use of empagliflozin is not recommended to geriatric patients, and pregnant and lactating women. It remains to be seen if post marketing surveillance data could throw unwelcome surprises regarding the long-term safety of this molecule.<sup>23</sup>



## CURRENT STATUS

Empagliflozin has been approved for the treatment of T2DM in adults in the USA, Europe and India. The drug was approved by the FDA and EMA in August 2014 and May 2014 respectively. However, the FDA required post marketing studies on the efficacy of the drug molecule in reducing cardiovascular outcomes. The three SGLT2 inhibitors, dapagliflozin, canagliflozin and empagliflozin have been approved for the treatment of T2DM in adults. However, the safety and efficacy of SGLT2 inhibitors for the treatment of type I diabetes is yet to be established and FDA has not approved the drug for the same. There is limited data comparing empagliflozin with other SGLT-2 inhibitors such as dapagliflozin and canagliflozin that are used to treat T2DM. Data from clinical studies have shown similar reductions in HbA1c, body weight, FPG and blood pressure. Compared to dapagliflozin and canagliflozin, empagliflozin has a higher selectivity for SGLT2. A comparison of SGLT2 inhibitors have been shown in Table 1.<sup>23-25</sup> The success of empagliflozin in the EMPA-REG outcomes study has garnered a lot of attention with this molecule and currently as many as 48 trials are listed as ongoing or upcoming in Clinicaltrials.gov (Table 2).<sup>26</sup>

## CONCLUSION

Empagliflozin, a highly selective SGLT-2 inhibitor, is an effective anti-diabetic drug that has been approved in USA, Europe and India for the treatment of T2DM among adults. The drug has been shown to work as mono therapy and also in combination with the existing OHAs and insulin. The results of the recent long-term trials with empagliflozin have yielded gratifying results, with the drug showing a definite advantage in improving both cardiovascular and renal outcomes. With the huge spurt in the number of trials registered with the molecule especially in heart failure and renal disease, it remains to be seen if these additional indications become equally successful. However, the prohibitive cost of the molecule may be a definite dampener in making this a front-line modality of treatment for diabetes in the near future.

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