Original Research Paper

Volume - 11 | Issue - 03 | March - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Medical Science

EMPAGLIFLOZIN: EMPOWERING VASCULO-METABOLIC OUTCOME

Dr Bharat Kumar Gupta

Kalyan Health Care, M. R. Complex, Near Bhuteshwar Temple, Bhuteshwar, Mathura - 281004

ABSTRACT Increased risk for the development of cardiac and other vascular events, heart failure (HF), and decline in renal function is common to the majority of the type 2 diabetes mellitus (T2DM) patients. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are the new class of drugs that were introduced for the treatment of T2DM due to their ability to increase urinary glucose excretion thereby reducing hyperglycemia. SGLT2 receptors are majorly located in the proximal convoluted tubule of the nephron and are responsible for almost 90-95% of tubular reabsorption of the glucose in the nephron. T2DM patients have an upregulated SGLT2 receptors which increase the glucose reabsorption in them leading to hyperglycemia. Empagliflozin is one such SGLT2 inhibitor approved by FDA that increases urinary glucose excretion along with sodium excretion. Characteristically, empagliflozin also offers cardioprotective and reno-protective functions. The article discusses the cardioprotective and reno-protective benefits of empagliflozin along with the clinical trials that are being carried out to study the efficacy of empagliflozin.

KEYWORDS :

INTRODUCTION

Type 2 diabetes mellitus (T2DM), a global pandemic, is associated with significantly augmented cardiovascular (CV) risks [1]. Both type 1 and 2 diabetes mellitus (DM) are established foremost risk factors for the induction as well as the advancement of cardiovascular diseases, with elevated risk for morbidity and mortality[2]. It has been found that in a DM patient, there is almost a 2-to-3-fold higher risk of developing cardiovascular complications. This risk is further amplified in the aging population with the co-morbid condition of chronic renal impairment[3]. DM especially, T2DM is a complex, progressive metabolic disease that is associated with multiple pathologies[4] viz.,

- Abnormal β-cell insulin secretion
- Excessive α-cell glucagon production
- Abnormal incretin effect
- Insulin resistance at the peripheral tissues
- Increased hepatic glucose production
- Increased lipolysis
- Neurotransmitter dysfunction
- Abnormal renal handling of hyperglycemia

In T2DM patients, elevated hyperglycemia has been found to be associated with a higher risk of vascular events. In fact, every 1% increase in glycosylated hemoglobin (HbA1c) can result in an almost 38% increased risk of mortality. Elevated HbA1c values have thus been well correlated with microvascular and macrovascular complications and are an important risk predictor tool. Further, the presence of albuminuria is associated with the cardiovascular condition of Hypertension, which is a vital predictor of both cardiovascular as well as renal events in T2DM patients[4]. Thus, there is a close association between diabetes and cardiovascular (CV) disease, especially myocardial infarction (MI), stroke, peripheral arterial disease (PAD), cardiomyopathy, and heart failure (HF).

Multiple factors make the optimal management of T2DM with cardiovascular predisposition a challenge, viz., anti-hyperglycemic therapies like that of insulin and thiazolidinediones leads to retention of fluid and weight gain, thereby potentially nullifying the beneficial effects of glycemic control on cardiovascular complications. On the other hand, anti-diabetic therapies of the thiazolidinediones and saxagliptin (which is a dipeptidyl-peptidase4(DPP-4) inhibitor) have been found to be linked with signs of elevated risk of cardiovascular complications. Thus, confounding the situation of a diabetic patient with cardiovascular complications.

Glucose homeostasis and role of sodium-glucose cotransporters

Normal glucose homeostasis maintenance is a highly complex process that involves multiple organs interactions viz., liver, muscle, adipocytes, pancreas, and neuroendocrine system. Amongst these, kidneys play a central role in glucose homeostasis. Kidneys reabsorb all the filtered glucose, which is essentially an adaptive mechanism that is carried out to ensure the availability of sugar for providing sufficient energy, especially during the fasting state. However, in a diabetic patient, this process becomes maladaptive /malfunctioning. In diabetic patients, hyperglycemia additionally enhances the expression and activity of the sodium-glucose cotransporter (SGLT2) present in the renal proximal tubules. Consequently, glucose reabsorption can be amplified by as much as 20% in diabetic patients especially with poorly controlled diabetes[4]. SGLT2, found in the proximal tubule of the nephron, is a low-affinity, high-capacity glucose transporter that carries out almost 90% of glucose reabsorption. The remaining glucose uptake is carried out by the SGLT1 cotransporters. Thus, inhibition of this glucose transporter in a diabetic patient seems to be a viable therapeutic target that can help to restore the glucose homeostasis in diabetics[5]. Additionally, it has been found that inhibition of SGLT2 is accompanied by sodium loss i.e., diuretic effect along with weight loss and reduction in blood pressure. Thus, SGLT2 inhibitors offer the dual benefit of restoring glucose homeostasis along with enhanced sodium loss, which results in a reduction in blood pressure.

Empagliflozin- A Sodium-glucose cotransporter inhibitor

There are three FDA-approved SGLT2 inhibitors available currently in the market, namely, Canagliflozin, Dapagliflozin, and Empagliflozin. Of the three, Canagliflozin inhibits both SGLT1 as well as SGLT2, while both, Dapagliflozin and Empagliflozin selectively inhibit SGLT2 cotransporters only. Amongst three SGLT2 inhibitors, Empagliflozin exhibits the highest selectivity (~2500 folds) for the SGLT2 cotransporters. Empagliflozin increases excretion of glucose 60-100 g/day, thereby offering better control of glucose homeostasis and improving HbA1c. Additionally, osmotic diuresis of glucose and elimination of co-transported sodium results in the reduction of blood pressure. This is further accompanied by weight loss (~240-400 kCal/day).

Thus, Empagliflozin, an SGLT2-inhibitor, serves the dual function of an antidiabetic drug (which normalizes the blood glucose) as well as a diuretic and hypotensive agent (that resolves salt-sensitive hypertension). Hence, Empagliflozin is an SGLT2-inhibitor, which is essentially an antidiabetic drug that can strongly prevent heart and renal failure[4]. Heart failure is a common comorbidity among T2DM patients, especially in patients $\geq$ 65 years of age.

Empagliflozin is a drug that acts at different pharmacological levels and targets to provide a diabetic-cardiac advantage. By exerting favorable hemodynamic effects on the glomerulus, Empagliflozin inhibitors decrease the albuminuria and uric acid levels. Empagliflozin enhances natriuresis, osmotic diuresis, and weight loss, consequently reducing the systolic blood pressure (SBP). Furthermore, Empagliflozin induces afferent arteriolar constriction that results in the reduction of the single nephron glomerular filtration rate (GFR), thereby reducing intraglomerular pressure.

Mechanistically, elevated levels of intracellular Na^+ and Ca^{2+} and reduced levels of mitochondrial Ca^{2+} results in HF. Empagliflozin has been found to increase the mitochondrial Ca^{2+} thereby providing the additional benefit in diabetic cardiomyopathy. Empagliflozin inhibits the cardiac Na^+/hydrogen exchanger (NHE), which subsequently

results in reduced cytosolic Na^+ and Ca^{2+} concentrations along with elevated mitochondrial Ca^{2+} concentration. This results in a cardioprotective effect as increased cardiac intracellular Na^+ and NHE activity have been associated with the occurrence of arrhythmias, myocardial hypertrophy, and aggravation of HF[6]. Further, empagliflozin has been found to prevent myocardial fibrosis by counteracting the upregulation of profibrotic and prohypertrophic proteins such as epithelial sodium channel (ENaC) and myocardial serum/glucocorticoid regulated kinase 1 (SGK1)[7]. The reduction in myocardial fibrosis is also believed to be associated with a reduction in reducing epicardial fat. The reduction in epicardial fat results in reducing the concentration of noxious stimuli, including leptin and components of the RAAS, that are involved in cardiac and vascular inflammation and fibrosis[8]. Empagliflozin treatment also stimulates rapid hormonal changes in glucose metabolism. After a while with empagliflozin treatment, ketogenesis is induced due to increased free fatty acid oxidation, thereby shifting the substrate to fat. This results in increased β-hydroxybutyrate metabolism by the heart which improved the mitochondrial function and eventually myocardial performance[6].

In diabetic kidney disease, microvascular alterations play an important role that eventually leads to an end-stage renal disease requiring renal replacement therapy. The pathogenesis of diabetic nephropathy, characterized by a reduction in GFR and/or albuminuria, involves amplified intraglomerular pressure, glomerular hyperfiltration, and fibrotic processes. Also, bidirectional cardiac and renal function interactions result in HF and renal dysfunction which are driven by factors viz., systemic hypertension, neurohormonal activation, endothelial dysfunction, hyperglycemia, and systemic inflammation. Thus, diabetes, HA, and chronic renal failure becomes a vicious interdependent cycle. Adjustments and modifications in tubuloglomerular feedback with the usage of empagliflozin are thought to play an important role in neurohormonal activation, maintenance of fluid volume, and extracellular electrolyte homeostasis. A reduction in the concentration of circulating natriuretic peptides is observed on treatment with the empagliflozin. This reduction in natriuretic peptides constricts the afferent tubule arterioles thereby leading to enhanced diuresis and natriuresis. This results in a modest reduction of the GFR initially along with the reductions in hyperfiltration and intraglomerular pressure, thus providing are renal protection and preserving renal function. This reduction of the intraglomerular hydrostatic pressure represents the renoprotective effect of empagliflozin.

However, inhibition of glucose absorption also leads to volume reduction which is believed to be the underlying cause for the possible toe amputation or fractures. Further, increased urinary glucose concentrations provide a conducive environment for bacterial and fungal growth, thus leading to increased incidences/risk for genital and urinary tract infections, which may eventually lead to urosepsis and pyelonephritis. Various benefits and certain side effects offered by empagliflozin are represented in Fig 1.

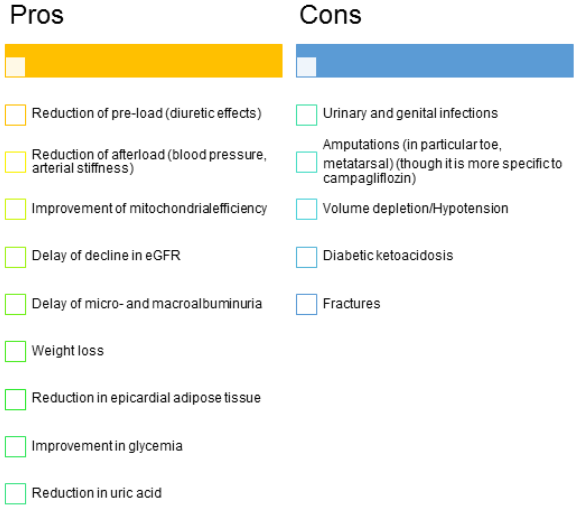

Figure 1: Pros and cons of using Empagliflozin for management of diabetes with cardiac and renal protection

Safety and Efficacy of Empagliflozin- EMPA-REG OUTCOME Trial

A number of clinical trials have confirmed the efficacy and effectiveness of empagliflozin in the management of diabetes along with additional cardioprotection effects. In 2015, a randomized, double-blind, placebo-controlled trial, the EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes), was conducted in 7,020 patients with T2DM. The primary endpoints of the trials, a composite of myocardial infarction, stroke, and cardiovascular death, were found to be significantly reduced (hazard ratio [HR]: 0.86; 95% confidence interval [CI]: 0.74 to 0.99) over a median follow-up of 3.1 years (21). This was primarily due to a 38% reduction of cardiovascular death (HR: 0.62; 95% CI: 0.49 to 0.77). Also, all-cause mortality was reduced (HR: 0.68; 95% CI: 0.57 to 0.82). Additionally, it was observed that a 35% decrease in hospitalization for HF in patients randomized to empagliflozin (HR: 0.65; 95% CI: 0.50 to 0.85). These findings suggest reductions in both cardiovascular and total mortality that were essentially facilitated by favorable hemodynamic effects. It is important to note that in EMPA-REG, a reduction in cases of hospitalizations for HF and cardiovascular death on treatment with empagliflozin was observed both in patients with and without HF at baseline. Post-hoc analysis revealed that a reduction in the incidence of nephropathy or worsening of pre-existing renal disease by 43% in the HF group on treatment with empagliflozin when compared with the placebo group. Furthermore, a 50% reduction in the progression to macroalbuminuria in patients being treated with empagliflozin versus those on placebo was observed[9,10]. The cardioprotective outcome of the EMPA-REG OUTCOME trial prompted FDA to shift the position of Empagliflozin from an adjunctive hyperglycaemic therapeutic agent to CVD risk-reducing agent to be used in DM patients.

Empagliflozin has been found to reduce both systolic (4 to 6 mm Hg) and diastolic (1 to 2 mm Hg) pressures without elevating the heart rate in T2DM patients (21,22). This reduction in blood pressure persistent and is believed to be due to multiple mechanistic reasons that contribute to increasing diuresis viz., remodeling of the nephron, improved endothelial function, reduced arterial stiffness, and loss of body weight due to glycosuria. Reduced arterial stiffness and pressure result in reduced cardiac afterload that results in a persistent reduction in blood pressure[6].

In an exploratory analysis from the EMPA-REG OUTCOME trials, the indicators of plasma volume (e.g., hematocrit and hemoglobin) were identified as a marker of the incidences of cardiovascular death. Further, intrarenal RAAS, as indicated by the urinary angiotensinogen -to-creatinine ratio, was found to be reduced in T2DM patients treated with SGLT2, Empagliflozin. A number of clinical trials on Empagliflozin are underway, enlisted in Table1.

Table 1: Ongoing clinical trials of empagliflozin, along with their objectives[11] (https://clinicaltrials.gov)

S. No.	Trial number	Trial objective
1	NCT03057951	EMPagliflozin outcome trial in patients with chronic heart failure with a preserved ejection fraction
2	NCT03057977	EMPagliflozin outcome trial in patients with chronic heart failure with a reduced ejection fraction
3	NCT03128528	Effect of Empagliflozin on the reduction of tissue sodium content in patients with chronic heart failure
4	NCT03198585	Empagliflozin in heart failure patients with a reduced ejection fraction
5	NCT03200860	Effects of Empagliflozin on clinical outcomes in patients with acute decompensated heart failure
6	NCT03332212	Mechanistic cardiac magnetic resonance study to investigate the effects of empagliflozin treatment on cardiac physiology and metabolism in patients with heart failure
7	NCT03448406	Effect of 12 weeks treatment of once-daily empagliflozin 10 mg compared with placebo on exercise ability and heart failure symptoms, in patients with chronic heart failure with preserved ejection fraction (HFpEF)

8	NCT03448419	Effect of 12 Weeks treatment of once-daily empagliflozin 10 mg compared with placebo on exercise ability and heart failure symptoms, in patients with chronic heart failure with reduced ejection fraction (HFrEF)
9	NCT03485222	Safety and Efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in heart failure patients with reduced ejection fraction without diabetes

The findings of these clinical studies will further help to establish the safety and efficacy of empagliflozin for the management of diabetes along with cardiac and renal morbidity.

Concurrently, trials are also being conducted on other SGLT2 inhibitors, viz., canagliflozin and dapagliflozin, and to study their efficacy in cardiac and renal protection in diabetes patients. Canagliflozin Cardiovascular Assessment Study (CANVAS) trial is being carried out to assess the cardiovascular and renal safety and efficacy of canagliflozin in T2DM patients and high CVD risk in a randomized, multicentric, double-blinded, placebo-controlled trial[12]. While, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) is a multicentric, randomized, double-blinded, placebo-controlled trial. The objective of the DECLARE-TIMI 58 trial is to evaluate cardiovascular safety, as the primary endpoint of MACE and efficacy, as defined by the primary endpoint of MACE and composite of CVD death and HF-related hospitalization, on treatment with dapagliflozin[13,14].

Interestingly, Empagliflozin, canagliflozin, and dapagliflozin are also being evaluated in patients with T1DM.

CONCLUSION

Empagliflozin is an antidiabetic drug that is an SGLT2 inhibitor and provides unique benefits viz., cardioprotection, reduction in the risk of hospitalizations for HF, enhanced diuresis, reduction in blood pressure, and body weight. Additionally, empagliflozin has been found to reduce the incidence of progressive nephropathy and proteinuria in diabetics along with reducing the need for renal replacement therapy, thus offering a reno-protective effect as well. The reduction of HF, renal and cardiovascular outcomes and all-cause mortality offers a startling advantage. The clinical trials so far have proven the potential safety and efficacy of the empagliflozin. It is expected that outcome of a number of ongoing trials will open up novel avenues for the management of diabetes with cardiac and renal complications.

REFERENCES

1. Pancholia AK. Sodium-glucose cotransporter-2 inhibition for the reduction of cardiovascular events in high-risk patients with diabetes mellitus. *Indian Heart Journal*. 2018;70(6):915-921. doi:10.1016/j.ihj.2018.08.022
2. Iborra-Egea O, Santiago-Vacas E, Yurista SR, et al. Unraveling the Molecular Mechanism of Action of Empagliflozin in Heart Failure With Reduced Ejection Fraction With or Without Diabetes. *JACC: Basic to Translational Science*. 2019;4(7):831-840. doi:10.1016/j.jacbts.2019.07.010
3. Marx N, Davies MJ, Grant PJ, et al. Guideline recommendations and the positioning of newer drugs in type 2 diabetes care. *The Lancet Diabetes and Endocrinology*. 2021;9(1):46-52. doi:10.1016/S2213-8587(20)30343-0
4. Chawla G, Chaudhary KK. A complete review of empagliflozin: Most specific and potent SGLT2 inhibitor used for the treatment of type 2 diabetes mellitus. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*. 2019;13(3):2001-2008. doi:10.1016/j.dsx.2019.04.035
5. Sattar N, Petrie MC, Zinman B, Januzzi JL. Novel Diabetes Drugs and the Cardiovascular Specialist. *Journal of the American College of Cardiology*. 2017;69(21):2646-2656. doi:10.1016/j.jacc.2017.04.014
6. Zelniker TA, Braunwald E. Cardiac and Renal Effects of Sodium-Glucose Co-Transporter 2 Inhibitors in Diabetes: JACC State-of-the-Art Review. *Journal of the American College of Cardiology*. 2018;72(15):1845-1855. doi:10.1016/j.jacc.2018.06.040
7. Ghosh RK, Ghosh GC, Gupta M, et al. Sodium-Glucose Co-transporter 2 Inhibitors and Heart Failure. *American Journal of Cardiology*. 2019;124(11):1790-1796. doi:10.1016/j.amjcard.2019.08.038
8. Packer M. Leptin-Aldosterone-Neprilysin Axis. *Circulation*. 2018;137(15):1614-1631. doi:10.1161/CIRCULATIONAHA.117.032474
9. Butler J, Zannad F, Fitchett D, Zinman B, Koitka-Weber A, von Eynatten M, Zwiener I, George J, Brueckmann M, Cheung AK WC. Empagliflozin Improves Kidney Outcomes in Patients With or Without Heart Failure. *Circ Heart Fail*. 2019;12(6):e005875.
10. Fitchett D, Inzucchi SE, Cannon CP, et al. Empagliflozin Reduced Mortality and Hospitalization for Heart Failure Across the Spectrum of Cardiovascular Risk in the EMPA-REG OUTCOME Trial. *Circulation*. 2019;139(11):1384-1395. doi:10.1161/CIRCULATIONAHA.118.037778
11. https://clinicaltrials.gov
12. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M MD. CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(7):644-657.
13. Mosenzon O, Wiviott SD, Cahn A, Rozenberg A, Yanuv I, Goodrich EL et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol*. 2019;7:606-617.
14. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380(4):347-357.