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Review Article

A REVIEW ON PHARMACOLOGY AND THERAPEUTIC EFFECTS OF EMPAGLIFLOZIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Empagliflozin, a sodium glucose cotransporter 2 inhibitor, a newer class of antihyperglycemic agent, which offers the convenience of once-daily oral administration and carries a low inherent risk of hypoglycemia as a result of its unique mechanism of action, enabling it to be used as monotherapy and as an adjunct with other antidiabetic drugs. Empagliflozin has a unique mechanism of action by inhibiting glucose and sodium reabsorption in the proximal tubule of the kidney; they induce urinary glucose excretion and natriuresis. In patients with diabetes, empagliflozin results in glucose lowering, blood pressure (BP) reduction and weight loss. Empagliflozin reduced cardiovascular morbidity and mortality in patient with type 2 diabetes mellitus and established cardiovascular disease in the EMPA-REG OUTCOME trial®. The recommended starting dosage of empagliflozin is 10 mg daily. The dosage may be increased to a maximum of 25 mg/day in patients tolerating empagliflozin 10 mg/day. The most common adverse effect observed with empagliflozin (sodium glucose cotransporter 2 inhibitors) is an increment in mycotic genital infections. In this review article, we discussed the pharmacological properties, therapeutic effects, and adverse events that are associated with the administration of empagliflozin in patients with type 2 diabetes mellitus. In conclusion, empagliflozin provides greater therapeutic benefits in the management of type 2 diabetes mellitus and reduce the associated cardiovascular risk factors such as blood pressure (BP) and weight.

Keywords: Empagliflozin, Sodium glucose cotransporter 2 inhibitors, Type 2 diabetes mellitus.

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INTRODUCTION

Empagliflozin is an sodium glucose cotransporter 2 (SGLT2) inhibitor which is sold under the brand name of Jardiance®. It is an anti-hyperglycemic agent which is effective and well tolerated. It was approved on May 2014 by the European medicines agency and august 2014 by the USFDA for the treatment of type 2 diabetes mellitus in USA, EU, Japan, and other parts of world. Jardiance was developed by Boehringer Ingelheim and Eli Lilly Company [1-3].

Empagliflozin offers the convenience of oral administration once daily and carries a low risk of hypoglycemia because of its unique mechanism of action, enabling it to be used as monotherapy and as adjunct with other antidiabetic drugs such as pioglitazone, sulfonylureas, biguanides to better glycemic control in patients with type 2 diabetes mellitus beyond lowering glucose, empagliflozin exerts a beneficial effect on some non-glycemic outcomes, such as reduction in blood pressure (BP) and body weight. In the EMPA-REG outcome study, empagliflozin reveals cardioprotective and renoprotective effects largely independent of glycemic control in patients with type 2 diabetes mellitus and cardiovascular disease; the beneficial outcomes on cardiovascular events in this population are reflected in the approved labeling for the drug in the EU [4] and USA [5].

This review mainly focuses on the mechanism of glucose reabsorption, pharmacology, and therapeutic efficacy of empagliflozin in the management of patients with type 2 diabetes mellitus.

PHARMACOLOGICAL PROPERTIES OF EMPAGLIFLOZIN

Empagliflozin is available orally which is an competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2) with an antihyperglycemic activity. Upon administration of empagliflozin orally, it selectively and potently inhibits SGLT2 in the kidneys, thereby reducing the reabsorption of glucose in the proximal tubule. SGLT2 inhibition leads to increases urinary glucose excretion by the kidneys, which results in reduction of plasma glucose levels in an insulin-independent manner. SGLT2, a transport protein exclusively present in the proximal renal tubules and mediates approximately 90% of renal glucose reabsorption from tubular fluid. The pharmacokinetic and pharmacodynamic properties are mentioned in Table 1.

MECHANISM OF GLUCOSE REABSORPTION

Glucose is a polar compound and cannot permeate through the walls of nephron which are made of lipids therefore glucose is reabsorbed by the nephrons with the help of glucose transporters which utilize ATP and create an ionic gradient that helps in the transport of glucose. These glucose transporters are present in the proximal convoluted tubule (PCT) of the nephron. Two types of Na^+/K^+ cotransporters are present in the apical membrane of PCT: SGLT2 and SGLT1 [19]. Even though the amino acid sequences of SGLT1 and SGLT2 are similar, they have remarkable differences. SGLT2 is a high capacity/low affinity Na^+/K^+ cotransporter whereas SGLT1 is a low capacity/high affinity Na^+/K^+ cotransporter. SGLT2 is responsible for reabsorption of 90% of glucose whereas SGLT1 is responsible for the remaining 10%. The former is found in the early part of the PCT (S1 segment) while the later is found in the later part of PCT (S2 segment) and proximal straight tubule (S3 segment) [20] (Fig. 1).

The active transport of glucose is done by SGLT through Na^+/K^+ ATPase channel which is present in the basolateral membrane of the PCT. The Na^+/K^+ ATPase pump extrudes three Na+ ions from the lumen into the blood and in return brings in two K+ ions. This leads the way to the formation of a downhill Na+ ion gradient. The SGLT proteins utilize the energy generated by this downhill gradient to transport one glucose molecule (against the uphill glucose gradient) and one Na+ ion across the apical membrane of the PCT. This is a secondary active transport [21]. The glucose is then move into the blood with the help of facilitated transport by glucose transporter type 2 and glucose transporter type 1 which are present on the basolateral membrane of PCT [22,23] (Fig. 2).

Table 1: Overview of pharmacological properties of empagliflozin

Pharmacokinetic parameters	
General	Orally administered once daily [4,5]. Absorbed rapidly (tmax reached <2 h post dose) [6]. EMP exposure unaffected by food increases dose proportionally (in the therapeutic dose range) and reveals linear pharmacokinetics with respect to time [4,5]. Vdssof 73.8L, CL/F of 10.6 L/h, and t1/2 of 12.4 h [4,5]. Metabolized majorly by glucuronidation and excreted primarily unchanged in urine and feces [7]
Special population	Pharmacokinetics was unchanged by age, gender, race, or body mass index [4,5]. EMP exposure increased moderately with decreasing renal function and increased less than two-fold with decreasing hepatic function [6]
Potential drug interactions	EMP is not connected with any clinically relevant drug-drug interactions [8]. Coad ministration with known inducers of UDP-glucuronosyltransferase enzymes should be avoided because of the higher risk of decreased efficacy [4]
Pharmacodynamics parameters	
Glycemic effects in patients with type 2 diabetes mellitus	Inhibit glucose reabsorption, and notably increased urine glucose excretion and decreased blood glucose compared to placebo, from day 1 onward [9]. Induced glycosuria in both the fasting and fed and improved β-cell function and insulin sensitivity [10,11]. EMP 10 and 25 mg/day achieved maximal anti-hyperglycemic efficacy [12]
Non glycemic effects	Reduced blood pressure and body weight; effect on body weight and blood pressure from Phase III studies of 10–104 weeks duration. Decreased arterial stiffness and resistance [13,14], adiposity [15,16], cardiac work load [13,14], serum uric acid [17], and preserved renal function (estimated glomerular filtration rates) [18]

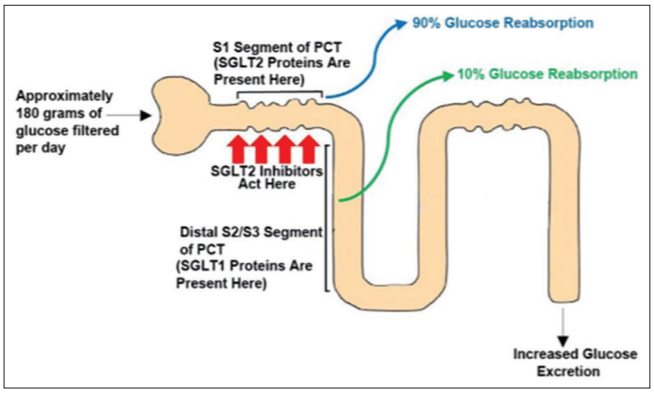

Fig. 1: Mechanism of glucose reabsorption

In this article, we will focus on empagliflozin which is an SGLT2 inhibitor. The drug works by inhibiting the aforementioned process and therefore decreases glucose reabsorption which leads to increased e2cretion of glucose in urine and therefore leads to reduced blood glucose levels. However, SGLT2 inhibitors only inhibit 30–50% of renal glucose reabsorption. One hypothesis describes that SGLT2 inhibitors are particular to SGLT2. SGLT1, which normally reabsorb at submaximal capacity, begin to reabsorb glucose with maximum capacity when complete inhibition of SGLT2 takes place [24].

MECHANISM OF ACTION OF EMPAGLIFLOZIN

Empagliflozin has a unique mechanism of action by inhibiting glucose and sodium reabsorption in the proximal tubule of the kidney, they promote urinary glucose excretion and natriuresis. In diabetes, these effects cause glucose lowering, BP reduction, and weight loss [25-27]. The mechanism of action of other glucose lowering agents usually involves an increase in insulin secretion (i.e., sulfonylureas, and glucagon-like peptide-1 receptor agonists) or decrease in insulin resistance (i.e., metformin, and thiazolidinediones), which develops in either suppression of hepatic glucose production or increased tissue glucose uptake. In contrast, empagliflozin promote urinary glucose and sodium disposal, which represents a well-defined and new metabolic mechanism of action (Fig. 2) [28]. The mechanism of action is unique for empagliflozin and potentially used as an adjunct therapy to lower glucose levels when used with other glucose lowering therapies.

The SGLT-2 inhibitors clinically available differ in their selectivity for SGLT-2 versus SGLT-1 transporters (Table 2). That difference may be relevant for their overall metabolic effects, as the role of SGLT-1 in glucose homeostasis is different from that of SGLT-2. The SGLT-2 blockade achieved by the available inhibitors is of approximately 50% of the filtered glucose load [29], despite *in vitro* studies indicating that 100% inhibition of the SGLT-2 transporter should be achieved at the drug concentrations attained in humans [29,30]. Possible explanations include incomplete inhibition of SGLT-2 and/or compensatory increase in SGLT-1 activity, suggesting an important role of SGLT-1 in renal glucose reabsorption under certain circumstances [31]. In this context, among the available SGLT-2 inhibitors, empagliflozin has the highest SGLT-2/SGLT-1 affinity ratio and canagliflozin the lowest [32,33]. Novel SGLT inhibitors with greater effects on SGLT-1 are currently under development.

DOSAGE AND ADMINISTRATION OF EMPAGLIFLOZIN

In the EU [4] and the USA [5], the recommended starting dosage of empagliflozin is 10 mg daily. The dosage may be increased to a maximum of 25 mg/day in patients tolerating empagliflozin 10 mg/day [4,5], the glycemic efficacy of empagliflozin is reliant on renal function. Empagliflozin should be stopped if estimated glomerular filtration rates (eGFR) <45 ml/min/1.73 m^2 and should not be used in patients with end stage renal disease or those who are on dialysis, as it is not expected to be effective [4,5]. Local prescribing information should be consulted for detailed information concerning with the use of empagliflozin in other special patient populations, as well as contraindications, warnings, and precautions.

THERAPEUTIC EFFECTS OF EMPAGLIFLOZIN

Glucose lowering

The glucose-lowering effect of empagliflozin is modest but comparable to other class of antidiabetic medications. In placebo/active controlled clinical randomized trials, SGLT-2 inhibitors produce a mean reduction in glycated hemoglobin (HbA1c) of ~0.7% (ranging from 0.4% to 1.1%, and depending on the baseline HbA1c) [34-37]. The SGLT-2 inhibitors were used as either monotherapy or in combination with sulfonylureas, pioglitazone, sitagliptin, and/or insulin. In a meta-analysis of randomized controlled trials (RCTs) comparing SGLT-2 with placebo (45 studies, n=11.232), and SGLT-2 induced a mean reduction of 0.66% in HbA1c (95% confidence interval [CI] −0.73% to −0.58%) [38]. This effect was similar in magnitude across the individual studies, where diverse background therapies were used. In addition, when compared with active comparators (such as metformin, sulfonylureas, and sitagliptin) as either monotherapy or add on treatment (13 studies, n=5.175), SGLT-2 inhibitors also had a favorable effect in lowering HbA1c (−0.06% 95% CI −0.18% to −0.05%) [38]. It is important to note that the glucose lowering effect of SGLT-2 inhibitors in individuals with moderate or severe renal impairment is decreased in magnitude, probably related to the diminished glycosuria. In randomized clinical trials with Stage 2 and Stage 3 chronic kidney disease (CKD), the

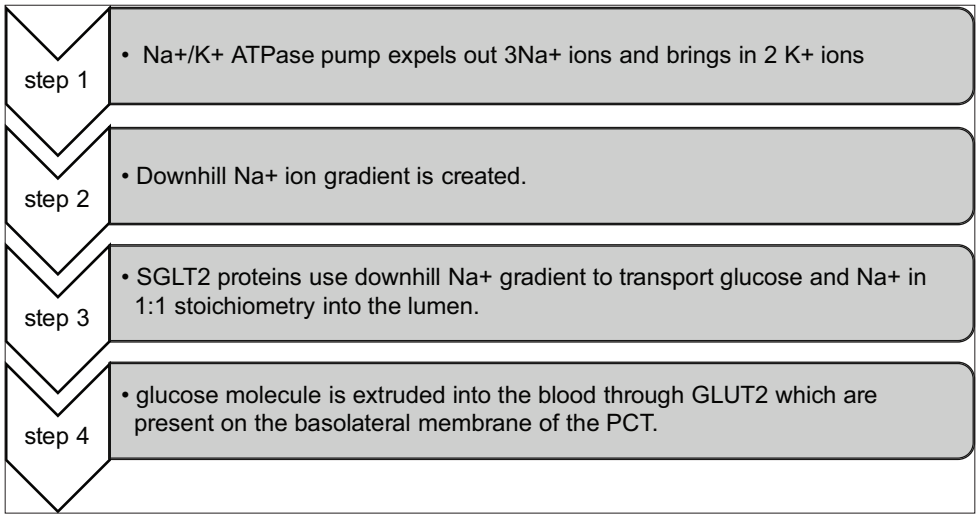

Fig. 2: Steps involved in glucose reabsorption by the proximal convoluted tubule

Table 2: Characteristics of SGLT1 and SGLT2 Cotransporters

Na^+/K^+ cotransporters	SGLT1	SGLT2
Site	Kidney, small intestine	Kidney
Location in kidney	S2 segment (distal part of PCT) and S3 segment of the nephron (late proximal tubule)	S1 segment (early part of PCT)
Capacity for glucose uptake	Low	High
Affinity for glucose	High; Km=0.4 mM	Low; Km=0.2 mM
Amount of glucose reabsorbed in the kidney	10%	90%

PCT: Proximal convoluted tubule, SGLT1: Sodium glucose cotransporter 1, SGLT2: Sodium glucose cotransporter 2

treatment difference in HbA1c versus placebo in subjects treated with empagliflozin 10 mg was −0.52% for Stage 2 CKD as compared to −0.42% in Stage 3CKD [39].

Regarding the anti-hyperglycemic potency of individual SGLT-2 inhibitors, there is a lack of head-to-head RCTs comparing the available SGLT-2 inhibitors. Indirect estimates have been obtained from network meta-analysis [40,41]. Network analysis comparing canagliflozin, dapagliflozin, and empagliflozin found a tendency toward greater glucose-lowering efficacy of higher doses of canagliflozin over empagliflozin and dapagliflozin, respectively. Specifically, canagliflozin 300 mg reduced HbA1c more than other SGLT-2 inhibitors, with the mean difference ranging from 0.20% to 0.64%. However, the significance of these small differences between SGLT-2 inhibitors is likely not relevant.

Weight loss

The persistent glycosuria promoted by SGLT-2 inhibitors translates into whole body energy deficit (~250–450 Kcal/day) leading to weight loss [26,27]. Clinical studies with empagliflozin reported weight loss of 2–3 kg over 12 weeks of treatment [33,42]. Although the weight loss is seemed to be plateau after 6 months of treatment, trails with up to 24 months of follow-up demonstrated that an overall weight loss effect of approximately 2.99 kg is maintained over long-term therapy [43]. It is hypothesized that the chronic glycosuria and consequent chronic energy deficit induced by SGLT-2 inhibition over a long-term may trigger an adaptive increase in energy intake, as evidenced in clinical studies. Otherwise, the weight loss effect of SGLT-2 inhibitors (empagliflozin) would be even greater.

BP lowering

The inhibition of SGLT-2 is associated with osmotic diuresis (due to glycosuria) and enhanced natriuresis [26,27]. The combination of these hemodynamic mechanisms produces clinically significant lowering of BP, with a systolic BP reduction of ~2.5 mmHg and diastolic BP reduction by ~1.5 mmHg reported in a meta-analysis of 43 RCTs (n=22.528) [44]. In addition, SGLT-2 inhibitors were associated with a reduction in 24-h systolic and diastolic BP in RCTs evaluating BP by a 24-h ambulatory BP-monitoring device [45]. The BP lowering effect is unique for an antidiabetic medication and possibly contributes to its observed cardioprotective effect, discussed in above Fig. 3. Interestingly, clinical studies demonstrated that SGLT-2 inhibition is not associated with an increase in heart rate, despite this consistent drop in BP [25]. This may represent an inhibitory effect on the usual baroreflex-mediated increase in sympathetic tone that accompanies a decrease in BP.

Other metabolic effects

In addition to glucose lowering and BP and weight loss, SGLT-2 inhibition has been associated with other metabolic effects. SGLT-2 inhibitors were reported to be associated with reduction in serum uric acid [46] due to elevated urinary uric acid excretion and decreased tubular reabsorption. This effect may be beneficial, as elevated serum uric acid has been associated with cardiovascular disease and the incidence of type 2 diabetes mellitus [47,48]. Another related metabolic consequence of SGLT-2 inhibition is an increment of glucagon secretion, presumably due to reduced inhibition of the alpha-cells by intra-islet insulin [10,49]. The increment in glucagon secretion may partially responsible for an enhanced endogenous glucose production observed with SGLT-2 inhibition [50,51]. This paradoxical increment in endogenous glucose production occurs parallel with a reduction in fasting glucose and HbA1c, as discussed above. This effect could represent a physiological compensatory response to the increased glycosuria induced by SGLT-2 inhibition.

An effect of SGLT-2 inhibition on lipid metabolism was also demonstrated in clinical studies that there is a small increase in both low-density lipoprotein (LDL) cholesterol (ranging from 3 to 6 mg/dl) and high-density lipoprotein cholesterol (ranging from 0.6 to 3.5 mg/dl) [33]. These increases have been hypothesized to result from augmented hepatic fatty acid oxidation triggered by SGLT-2 inhibition [25]. The small increase observed in LDL cholesterol does not appear to impact the overall cardiovascular benefit of SGLT-2 inhibitors demonstrated in clinical trials.

RENAL OUTCOMES

The mechanism of action of SGLT-2 inhibitors (empagliflozin) mainly targets renal system, so these drugs would be expected to impact hemodynamics. Indeed, SGLT-2 inhibitors results in an increase in creatinine, a drop in systolic BP (~4 mmHg), and a 200–400 mL increase in urine output, with the later waning over time [10]. The decrease in eGFR (~5 ml/min/1.73 m^2) induced by SGLT-2 inhibitors is rapid, dose-dependent plateaus for an extended period of time and is reversed within 2 weeks of drug discontinuation [18,39,52]. This initial decline in eGFR is possibly related to afferent arteriolar vasoconstriction secondary to a tubuloglomerular feedback mechanism that reduces intraglomerular hypertension, leading acutely to a reduction in glomerular filtration. Conversely, long-term treatment with SGLT-2 inhibitors resulted in stabilization of eGFR, translating into a renoprotection as compared to placebo in two RCTs (Table 3) [6,18].

In the EMPA-REG OUTCOME trail, empagliflozin was associated with a reduction in incident or worsening nephropathy (defined as progression to macroalbuminuria, doubling of serum creatinine level, initiation of renal replacement therapy, or death from renal disease) as compared to placebo (12.7% vs. 18.8%, respectively; hazard ratio 0.61, 95% CI 0.53–0.70) [18].

EMPAGLIFLOZIN IN THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS

Empagliflozin is an effective and well tolerated, once-daily oral anti-hyperglycemic agent with a low inherent risk of hypoglycemia that can be used as monotherapy or as an add on therapy to other class of antihyperglycemic agents. With complementary modes of action to improve glycemic control in patients with type 2 diabetes mellitus [6]. Both approved dosages (10 mg and 25 mg/day) achieve near maximal antihyperglycemic efficacy. In practice, the choice of dosage will most likely depend on the achievement of metabolic targets and occurrence of adverse events [53].

Beyond lowering glucose, empagliflozin also exerts non glycemic effects such as weight loss, reduction in BP, and volumetric loss [54].

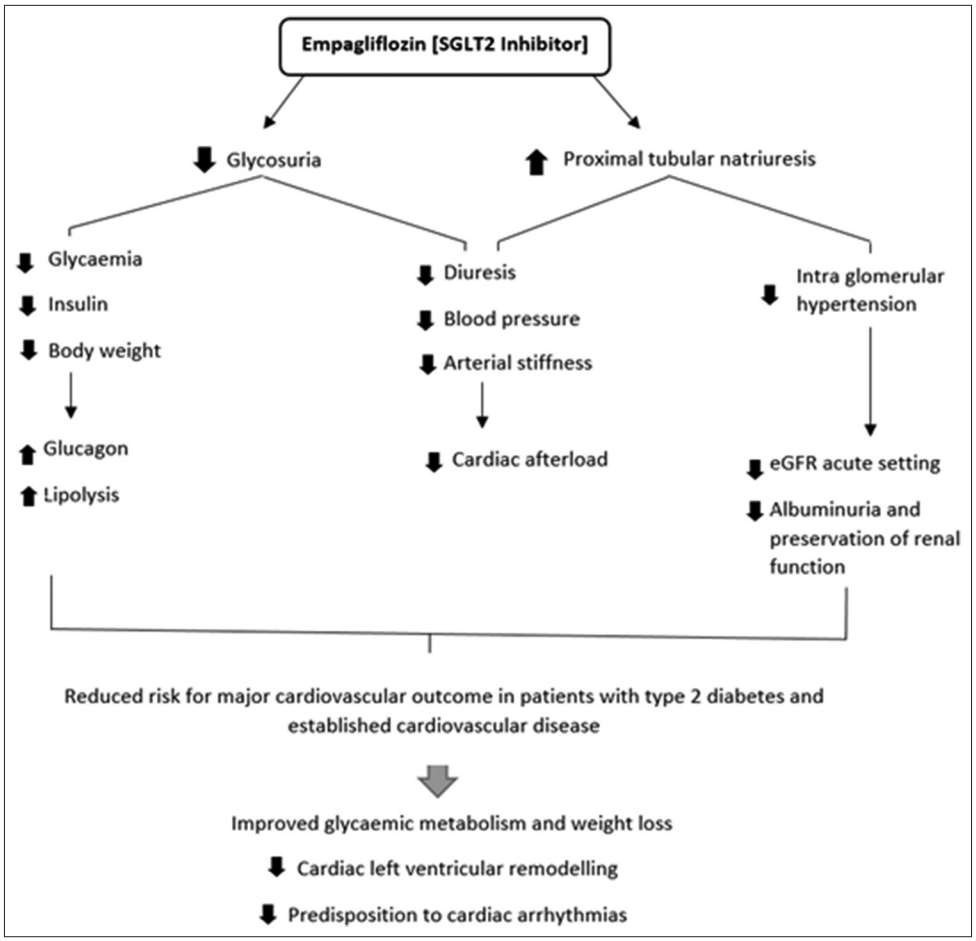

Fig. 3: Mechanism of action of empagliflozin (sodium glucose cotransporter 2 inhibitors) and proposed hypothesis of cardioprotective effects

Table 3: Risk reduction in renal outcomes associated with empagliflozin (sodium glucose cotransporter 2 inhibitor) in patients with type 2 diabetes mellitus

Renal outcome	Risk reduction (%)	Study (reference)
Incident or worsening nephropathy	↓39	EMPA-REG
Progression of macro albuminuria	↓38	EMPA-REG
Doubling of serum creatinine	↓44	EMPA-REG
Initiation of renal replacement therapy	↓55	EMPA-REG
Death from renal disease	↓56	EMPA-REG [18]

These effects of empagliflozin decrease the incidence of cardiovascular diseases [EMPA-REGOUTCOME].

ADVERSE EFFECTS ASSOCIATED WITH EMPAGLIFLOZIN

The most common adverse effect observed with empagliflozin (SGLT2 inhibitors) is an increment in mycotic genital infections, which occurred in 4.5% more participants of empagliflozin than placebo in EMPA-REG OUTCOME trial [53]. The use of empagliflozin was not associated with increased frequency in urinary infections, diabetic ketoacidosis (DKA), or hypoglycemia. As anticipated, increments in hematocrit and osmotic diuresis occurred more frequently with the active treatment of empagliflozin. However, the rates of serious adverse events leading to drug discontinuation, acute renal failure, and acute kidney injury were no increased by empagliflozin [6,53]. It is important to note that although empagliflozin was not associated with increased incidence of DKA in EMPA-REG OUTCOME, other studies have documented an increased risk of diabetic keto acidosis with SGLT2 inhibitors use, particularly off-label use in type 1 diabetes mellitus or insulin deficient type 2 diabetes mellitus.

CONCLUSION

The introduction of SGLT2 inhibitors has provided a greater efficacy in the management of type 2 diabetes mellitus especially in a population with cardiovascular disease. Current guidelines recommend the use of empagliflozin as an adjunct therapy along with other anti-hyperglycemic agents. "A patient centered approach is more important to guide the choice of pharmacologic agent Jasper the American diabetic association. The following considerations should be considered in the management of type 2 diabetes mellitus such as efficacy, history of atherosclerotic cardiovascular disease, hypoglycemia risk, renal function, delivery method (oral/subcutaneous), cost, and patient preferences." However, empagliflozin reduces the incidence of cardiovascular diseases proved from the EMPA-REG OUTCOME studies. In future. empagliflozin provides greater therapeutic benefits in the management of type 2 diabetes mellitus and reduces the associated cardiovascular risk factors such as BP and weight.

AUTHORS' CONTRIBUTIONS

Ajay Chadeve conceptualized all the research data and pharmacological outcomes of empagliflozin by performing literature search and wrote and edited the manuscript.

CONFLICTS OF INTEREST

The authors declare that there are no any conflicts of interest.

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REFERENCES

1. FDA Approves Jardiance (Empagliflozin) Tablets for Adults with Type 2 Diabetes. Eli Lilly and Company; 2014. Available from: https://www.investor.lilly.com/releasedetail.cfm?releaseid=863787. [Last accessed on 2020 Jan 02].
2. FDA Approves Jardiance (Empagliflozin) Tablets for Adults with Type 2 Diabetes. Boehringer Ingelheim; 2014. Available from: http://www.us.boehringeringelheim.com/news_events/press_releases/pressreleasearchive/2014/08-01-14-fda-approves-jardianceempagliflozin-tablets-reduce-blood-sugar-levels-adults-type-2-diabetes.html. [Last accessed on 2020 Jan 10].
3. EPAR Summary for the Public: Jardiance. European Medicines Agency. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Summary_for_the_public/human/002677/WC500168595.pdf. [Last accessed on 2020 Jan 10].
4. European Medicines Agency. Jardiance 10 and 25 mg Film-coated Tablets: Summary of Product Characteristics; 2014. Available from: http://www.ema.europa.eu. [Last accessed on 2020 Jan 04].
5. Boehringer Ingelheim Pharmaceuticals, Inc. Jardiance® (Empagliflozin) Tablets, for Oral Use. US Prescribinginformation; 2016. Available from: http://www.docs.boehringeringelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf. [Last accessed on 2019 Nov 29].
6. Scott LJ. Empagliflozin: A review of its use in patients with Type 2 diabetes mellitus. Drugs 2014;74:1769-84.
7. Chen LZ, Jungnik A, Mao Y, Philip E, Sharp D, Unseld A, *et al*. Biotransformation and mass balance of the SGLT2 inhibitor empagliflozin in healthy volunteers. Xenobiotica. 2015;45:520-9.
8. Scheen AJ. Pharmacodynamics, efficacy and safety of sodiumglucose co-transporter Type 2 (SGLT2) inhibitors for the treatment of Type 2 diabetes mellitus. Drugs 2015;75:33-59.
9. Heise T, Seewaldt-Becker E, Macha S, Hantel S, Pinnetti S, Seman L, *et al*. Safety, tolerability, pharmacokinetics and pharmacodynamics following 4 weeks' treatment with empagliflozin once daily in patients with Type 2 diabetes. Diabetes Obes Metab 2013;15:613-21.
10. Ferrannini E, Muscelli E, Frascerra S, Baldi S, Mari A, Heise T, *et al*. Metabolic response to sodium-glucose cotransporter 2 inhibition in Type 2 diabetic patients. J Clin Invest 2014;124:499-508.
11. Al Jobori H, Daniele G, Adams J, Cersosimo E, Solis-Herrera C, Triplitt C, *et al*. Empagliflozin treatment is associated with improved beta cell function in T2DM. J Clin Endocrinol Metab 2018;103:1402-7.
12. Riggs MM, Seman LJ, Staab A, MacGregor TR, Gillespie W, Gastonguay MR, *et al*. Exposure-response modelling for empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in patients with Type 2 diabetes. Br J Clin Pharmacol 2014;78:1407-18.
13. Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC, *et al*. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with Type 2 diabetes. Diabetes Obes Metab 2015;17:1180-93.
14. Chilton RJ, Gullestad L, Fitchett D. Effects of empagliflozin on cardiac and vascular hemodynamic markers by subgroups of age, sex, and hypertension in patients with T2DM and high CV risk: EMPA-reg outcome. Diabetes 2017;66 Suppl 1:A119.
15. Neeland IJ, McGuire DK, Chilton R, Crowe S, Lund SS, Woerle HJ, *et al*. Empagliflozin reduces body weight and indices of adipose distribution in patients with Type 2 diabetes mellitus. Diab Vasc Dis Res 2016;13:119-26.
16. Neeland IJ, McGuire DK, Fernandez CS. Effect of empagliflozin on anthropometry and indices of visceral and total adiposity in patients with Type 2 diabetes and high cardiovascular risk: EMPA-reg outcome. Diabetologia 2016;59 Suppl 1:S348.
17. Kohler S, Zeller C, Iliev H, Kaspers S. Safety and tolerability of empagliflozin in patients with Type 2 diabetes: Pooled analysis of phase I-III clinical trials. Adv Ther 2017;34:1707-26.
18. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, *et al*. Empagliflozin and progression of kidney disease in Type 2 diabetes. N Engl J Med 2016;375:323-34.
19. Brown GK. Glucose transporters: Structure, function and consequences of deficiency. J Inherit Metabo Diseases 2000;23:237-46.
20. Lee YJ, Lee YJ, Han HJ. Regulatory mechanisms of Na+/glucose cotransporters in renal proximal tubule cells. Kidney Int Suppl 2007;106:S27-35.
21. Rang HP, Ritter JM, Flower RJ, Henderson G. Rang and Dale's Pharmacology. 8th ed. London, United Kingdom: Churchill Livingstone; 2015.
22. Poudel RR. Renal glucose handling in diabetes and sodium glucose cotransporter 2 inhibition. Indian J Endocrinol Metabo 2013;17:588-93.
23. Kaplan JH. Biochemistry of Na, K-ATPase. Annu Rev Biochem 2002;71:511-35.
24. Abdul-Ghani MA, DeFronzo RA, Norton L. Novel hypothesis to explain why SGLT2 inhibitors inhibit only 30-50% of filtered glucose load. Diabetes 2013;62:3324-8.
25. Ferrannini E. Sodium-glucose co-transporters and their inhibition: Clinical physiology. Cell Metab 2017;26:27-38.
26. Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: Rationale and clinical prospects. Nat Rev Endocrinol 2012;8:495-502.
27. Heerspink HJ, Perkins BA, Fitchett DH. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: Cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 2016;134:752-72.
28. Kramer CK, Zinman B. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors in patients with Type 2 diabetes mellitus: The road ahead. Eur Heart J 2016;37:3201-2.
29. Liu JJ, Lee T, DeFronzo RA. Why do SGLT2 inhibitors inhibit only 30-50% of renal glucose reabsorption in humans? Diabetes 2012;61:2199-204.
30. Komoroski B, Vachharajani N, Boulton D. Dapagliflozi, a novel SGLT2 inhibitor, induces dose dependent glucosuria in healthy subjects. Clin

Pharmacol Ther 2009;85:520-6.
31. Grempler R, Thomas L, Eckhardt M, Himmelsbach F, Sauer A, Sharp DE, *et al*. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: Characterisation and comparison with other SGLT-2 inhibitors. Diabetes Obes Metab 2012;14:83-90.
32. Mudaliar S, Polidori D, Zambrowicz B, Henry RR. Sodium-glucose cotransporter inhibitors: Effects on renal and intestinal glucose transport: From bench to bedside. Diabetes Care 2015;38:2344-53.
33. Clar C, Gill JA, Court R, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in Type 2 diabetes. BMJ Open 2012;2:e001007.
34. Musso G, Gambino R, Cassader M, Pagano G. A novel approach to control hyperglycemia in Type 2 diabetes: Sodium glucose co-transport (SGLT) inhibitors: Systematic review and meta-analysis of randomized trials. Ann Med 2012;44:375-93.
35. Stenlof K, Cefalu WT, Kim KA. Efficacy and safety of canagliflozin monotherapy in subjects with Type 2 diabetes mellitus in adequately controlled with diet and exercise. Diabetes Obes Metab 2013;5:372-82.
36. Rosenstock J, Jelaska A, Frappin G, Salsali A, Kim G, Woerle HJ, *et al*. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled Type 2 diabetes. Diabetes Care 2014;37:1815-23.
37. Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC, *et al*. Comparison of empagliflozin and glimepiride as add on to metformin in patients with Type 2 diabetes: A 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol 2014;2:691-700.
38. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, *et al*. Sodium-glucose cotransporter 2 inhibitors for Type 2 diabetes: A systematic review and meta-analysis. Ann Intern Med 2013;159:262-74.
39. Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ, *et al*. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with Type 2 diabetes and chronic kidney disease: A randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2014;2:369-84.
40. Shyangdan DS, Uthman OA, Waugh N. SGLT-2 receptor inhibitors for treating patients with Type 2 diabetes mellitus: A systematic review and network meta-analysis. BMJ Open 2016;6:e00941.
41. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in Type 2 diabetes mellitus: Systematic review and network meta-analysis. Diabetes Obes Metab 2016;18:783-94.
42. Zhang L, Feng Y, List J, Kasichayanula S, Pfister M. Dapagliflozin treatment in patients with different stages of Type 2 diabetes mellitus: Effects on glycemic control and body weight. Diabetes Obes Metab 2010;12:510-16.
43. Liu XY, Zhang N, Chen R. Efficacy and safety of sodium-glucose cotransporter 2 inhibitors in Type 2 diabetes: A meta-analysis of randomized controlled trials for 1 to 2 years. J Diabetes Complications 2015;29:1295-303.
44. Mazidi M, Rezaie P, Gao HK, Kengne AP. Effect of sodium-glucose cotransport-2 inhibitors on blood pressure in people with Type 2 diabetes mellitus: A systematic review and meta-analysis of 43 randomized control trials with 22 528 patients. J Am Heart Assoc 2017;6:e00400.
45. Baker WL, Buckley LF, Kelly MS, Bucheit JD, Parod ED, Brown R, *et al*. Effects of sodium-glucose cotransporter 2 inhibitors on 24 hour ambulatory blood pressure: A systematic review and meta-analysis. J Am Heart Assoc 2017;6:e005686.
46. Zhao Y, Xu L, Tian D, Xia P, Zheng H, Wang L, *et al*. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: A meta-analysis of randomized controlled trials. Diabetes Obes Metab 2018;20:458-62.
47. Kramer CK, von Mühlen D, Jassal SK, Barrett-Connor E. A prospective study of uric acid by glucose tolerance status and survival: The Rancho Bernardo study. J Intern Med 2010;267:561-66.
48. Kramer CK, von Muhlen D, Jassal SK. Serum uric acid levels improve prediction of incident Type 2 diabetes in individuals with impaired fasting glucose: The Rancho Bernardo Study. Diabetes Care 2009;32:1272-73.
49. Bonner C, Kerr-Conte J, Gmyr V, Queniat G, Moerman E, Thévenet J, *et al*. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med 2015;21:512-17.
50. Polidori D, Sha S, Mudaliar S, Ciaraldi TP, Ghosh A, Vaccaro N, *et al*. Canagliflozin lowers postprandial glucose and insulin by delaying intestinal glucose absorption in addition to increasing urinary glucose excretion: Results of a randomized, placebo-controlled study. Diabetes Care 2013;36:2154-61.
51. Merovci A, Solis-Herrera C, Daniele G, Eldor R, Fiorentino TV, Tripathy D, *et al*. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest 2014;124:509-14.
52. Cefalu WT, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, *et al*. Efficacy and safety of canagliflozin versus glimepiride in patients with Type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet 2013;382:941-50.
53. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al*. Empagliflozin, cardiovascular outcomes, and mortality in Type 2 diabetes. N Engl J Med 2015;373:2117-28.
54. de Leeuw AE, de Boer R. Sodium-glucose cotransporter 2 inhibition: Cardioprotection by treating diabetes-a translational viewpoint explaining its potential salutary effects. Eur Heart J Cardiovasc Pharmacother 2016;2:244-55.