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A Review of Empagliflozin Used for the Treatment of Type 2 Diabetes Mellitus



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ABSTRACT

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are the latest class of drugs used for the treatment of type 2 diabetes mellitus (T2DM). Sodium-glucose co-transporter 2 (SGLT2) inhibitors are also called gliflozin. Gliflozin reduce hyperglycemia by increasing urinary glucose excretion and exert favorable effects beyond glucose control with consistent body weight, blood pressure, and serum uric acid reductions. Oral empagliflozin is convenient to adult patients with type 2 diabetes mellitus once daily inhibiting glucose reabsorption from proximal tubules in the kidney through SGLT2 inhibition, empagliflozin provides a novel insulin independent blood glucose reduction mechanism. This is a worthy choice of drug for T2DM patient with CVD. It's also reduces body weight and blood pressure. Mostly reported adverse events were genital mycotic infections and urinary tract infections. This review mainly looks up on the pharmacokinetics, pharmacodynamics, therapeutic efficacy, drug interaction, usage in special population and adverse effect of the novel OHA empagliflozin in the management of T2DM.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex, chronic, and progressive condition associated with a variety of serious microvascular and macrovascular complications. Continuous clinical management and patient self-management are critically important, and a targeted multifactorial treatment strategy is required to reduce the risk of long-term complications¹⁻². Once thought of as just an insulin resistance illness, but now believed that at least eight pathological procedures which led to type 2 diabetes. These include abnormal b-cell insulin secretion, excessive a-cell glucagon production, abnormal incretin effect, insulin resistance at the peripheral tissues, increased hepatic glucose production, increased lipolysis, neurotransmitter dysfunction, and abnormal renal handling of hyperglycemia^{3,4}. Type 2 diabetes mellitus (T2DM) has become a global pandemic. The age-standardized prevalence of diabetes in adults has increased in most countries since 1980 and along with population growth and ageing; this has led to a near quadrupling of the number of adults with diabetes worldwide⁵.

It is now estimated that almost 387 million people have diabetes worldwide. Numbers in developing countries are increasing due to the changes in rates of obesity and inactivity. Diabetes deaths are projected to rise by 50 percent worldwide by 2025. Eighty percent of these deaths will occur in low and middle income countries. Hypertension, which is strongly associated with the presence of albuminuria, is an important predictor of both cardiovascular and renal events in patients with T2DM⁶.

In patients with type 2 diabetes, higher levels of hyperglycemia are associated with increasing risk of vascular events. Each 1% increase in glycosylated hemoglobin (HbA1c) is associated with as much as 38% increased risk of mortality⁷. There is also evidence that more intensive glucose control in newly diagnosed patients may reduce the risk of cardiovascular events such as myocardial infarction⁸. Antihyperglycemic agents are, therefore, a key component of treatment strategies. However, treatment failure is common, partly because of the underlying progressive deterioration of β -cell function and loss of β -cell mass that is characteristic of T2DM⁹⁻¹⁰. Participants newly diagnosed with type 2 diabetes were followed up for 10 years in the UK Prospective Diabetes Study (UKPDS) and intensive control (median A1c, 7.0 percent) was found to lower the overall rate of micro vascular complication by 25 percent compared to conventional treatment (median A1c, 7.9 percent)⁸.

There are currently three SGLT2 inhibitors available in the US. Canagliflozin was approved by the US Food and Drug Administration (FDA) in March 2013 (FDA news release 2013), dapagliflozin in January 2014, and empagliflozin in August 2014¹¹. Empagliflozin (Jardiance) became the third SGLT-2 inhibitor to receive FDA approval for the treatment of type 2 diabetes as an adjunct to diet and exercise. Used as a tablet for oral administration, the recommended dose is 10 mg once daily in the morning, taken with or without food. The dose may be increased to 25 mg in patients tolerating empagliflozin. The FDA approval of empagliflozin was based on a monotherapy study and in a combination study with metformin, sulfonylurea, pioglitazone, and insulin¹²⁻¹³.

Empagliflozin is a selective inhibitor of SGLT2, producing dose dependent urinary glucose excretion increase in healthy volunteers, with up to 90 g of glucose excreted per day. It can be administered orally, and studies of individuals with renal or hepatic impairment suggested that empagliflozin did not require pharmacokinetic based dose adjustment. In Phase II studies in patients with type 2 diabetes, when administered as monotherapy or add-on to metformin, empagliflozin provided improvements in glycosylated hemoglobin (HbA1c) and other glycemic control measures. It also causes reductions in weight and systolic blood pressure. As added to basal insulin, empagliflozin not only improved levels of HbA1c but also reduced doses of insulin. Phase III studies also reported a good safety profile along with significant improvements in HbA1c, weight and blood pressure, without increased risk of hypoglycemia versus placebo. Empagliflozin has demonstrated a strong efficacy and safety profile in clinical trials when administered as monotherapy and as an additional treatment to other glucose-lowering agents¹⁴.

DESCRIPTION OF EMPAGLIFLOZIN

IUPAC name of empagliflozin is (2S,3R,4R,5S,6R)-2-[4-chloro-3-[[4-[(3S)-oxolan-3-yl]oxyphenyl]methyl]phenyl]-6-(hydroxymethyl) oxane-3,4,5-triol.

Synonyms of empagliflozin are-(1S)-1,5-anhydro-1-(4-chloro-3-{4-[(3S)-tetrahydrofuran-3-yloxy]benzyl}phenyl)-D-glucitol;(1S)-1,5-Anhydro-1-C-{4-chloro-3-[[4-[[[(3S)-oxolan-3-yl]oxy]phenyl]methyl]phenyl]-Dglucitol;(1S)-1,5-Anhydro-1-C-[4-chloro-3-[[4-[[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-D-glucitol; D-Glucitol, 1,5-anhydro-1-C-[4-chloro-3-[[4-[[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]M ethyl]phenyl]-, (1S).

Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile; soluble in 50% acetonitrile/water; and practically insoluble in toluene^{15,16}.

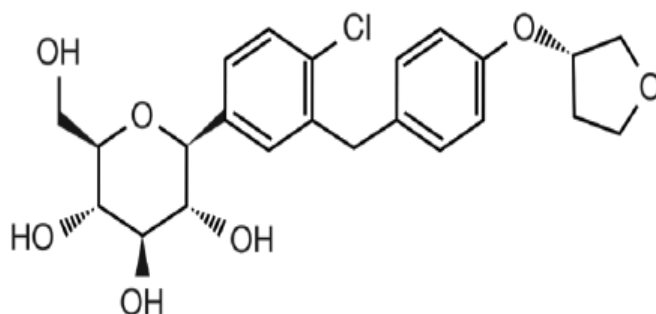


Figure No. 1: Structure of Empagliflozin

MECHANISM OF ACTION

Empagliflozin works by inhibiting the sodium glucose co-transporter-2 (SGLT-2) found in the proximal tubules in the kidneys, through SGLT2 inhibition, empagliflozin reduces renal reabsorption of glucose and increases urinary excretion of glucose. In type 2 diabetes patients, urinary glucose excretion increased by approximately 64 grams per day with 10mg of empagliflozin and 78 grams per day with 25mg. Empagliflozin reduces sodium and volume load causing intravascular contraction through its diuretic and natriuretic properties¹⁷.

Empagliflozin improving glucose control with low risk of hypoglycemia, and results in loss of 240-400 kCal/ day into the urine with associated weight reduction. In addition, a decrease in blood pressure is seen due to osmotic diuresis of glucose and natriuresis of co-transported sodium¹⁸.

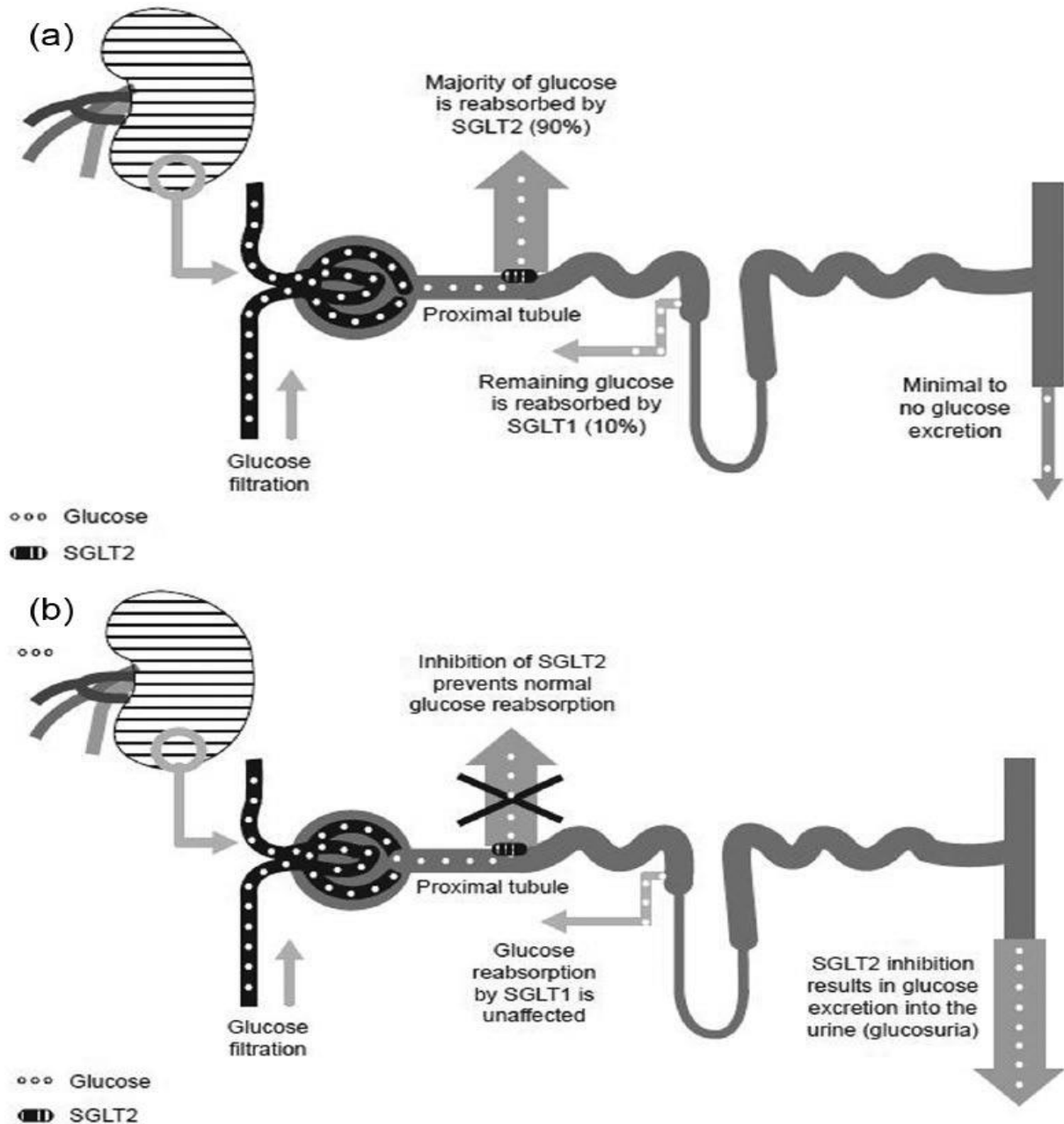


Figure No. 2: normal renal glucose transport (a) and the effect of sodium glucose cotransporter type 2 (SGLT2) inhibition (b). SGLT1, sodium glucose cotransporter type 1¹⁴.

PHARMACODYNAMIC

All doses of empagliflozin had significant pharmacodynamic effects indicated by an increased rate and total amount of urinary glucose excretion (UGE) relative to placebo. In this study, cumulative amounts of glucose excreted in urine over 24 hours after administration of a single dose of empagliflozin ranged from 46 to 90 g/day, similar to the findings of a single rising dose

study in healthy volunteers in which cumulative amounts of glucose excreted in urine within 24 hours of empagliflozin (2.5–100 mg) ranged from 30.6 to 78.6 g/day¹⁹. In a 5-day study, mean 24-h urine volume increase from baseline was 341 mL on Day 1 and 135mL on Day 5 of empagliflozin 25 mg once daily treatment²⁰.

A single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the peak dose), moxifloxacin, and placebo was given to 30 healthy subjects in a randomized, placebo-controlled, active-comparator crossover research. No increase in QTc with either 25 mg or 200 mg empagliflozin was observed. Like other SGLT2 inhibitors, empagliflozin lowers serum uric acid levels, probably through an effect on the urate transporter, solute carrier family 2 (facilitated glucose transporter), member 9 (SLC2A9), which is expressed in the proximal convoluted tubule and is involved in the renal handling of urate²¹.

PHARMACOKINETICS

Pharmacokinetic analyses showed empagliflozin was rapidly absorbed after oral administration, with a median t-max ranging from 1.5 to 2.1 hours across the dose groups. Plasma levels decreased biphasically with a rapid distribution phase and a slower elimination phase. Empagliflozin exposure ranged from 0.5–800 mg to approximately dose-proportional. Half-life of terminal elimination was up to 13.1 hours, with renal clearance ranging from 32.1 mL/min to 51.3 mL/min over 72 hours. The majority of empagliflozin was excreted via the urine in the first 24 hours, with approximately 11–19% of the administered dose excreted unchanged²².

Pharmacokinetic data showed that the oral doses of empagliflozin were rapidly absorbed to steady state on day 5 with moderate accumulation. There was a rapid distribution and a slower phase of elimination, with dose-proportional exposure rises and a half-life of 10–19 h terminal elimination. These results were consistent with those from a single rising dose study conducted in healthy volunteers, which demonstrated approximately dose-proportional increases in exposure and a terminal elimination half-life of 8.6–13 h. These pharmacokinetic features demonstrate the suitability of empagliflozin for once-daily dosing in patients with T2DM²³.

THERAPEUTIC EFFICACY OF EMPAGLIFLOZIN

Effect on Glycemic Control

Empagliflozin, given either as monotherapy or as an add-on therapy to other glucose-lowering agents, has been shown to provide statistically significant and clinically relevant improvements in glycemic control in patients with T2DM *versus* placebo^{24,25,26,27,28}, as measured by the change in the level of glycated hemoglobin (HbA1c). For example, empagliflozin monotherapy (given once daily for 24 weeks) produced a placebo-adjusted mean change from baseline in HbA1c of -0.7% [95% confidence interval (CI) -0.9, -0.6] and -0.9% (95% CI -1.0, -0.7) for the 10 mg and 25 mg doses, respectively ($p < 0.0001$ for each)²⁶. Furthermore, 35–44% of patients receiving empagliflozin achieved HbA1c levels below 7.0% *versus* 12% of those in the placebo group²⁶. Similar changes from baseline in HbA1c levels at week 24 were reported when empagliflozin was given in combination with metformin [adjusted mean difference from placebo + metformin (95% CI) -0.6 (-0.7, -0.4) and -0.6 (-0.8, -0.5) for 10 mg and 25 mg, respectively; $p < 0.001$ for each]²², metformin plus sulfonylurea [adjusted mean difference from placebo + metformin + sulfonylurea (95% CI) -0.6 (-0.8, -0.5) and -0.6 (-0.7, -0.5) for 10 mg and 25 mg, respectively; $p < 0.001$ for each]²⁴, and pioglitazone with/without metformin [adjusted mean difference from placebo + pioglitazone (95% CI) -0.5 (-0.7, -0.3) and -0.6 (-0.8, -0.4) for 10 mg and 25 mg, respectively; $p < 0.001$ for each]²⁹. Although a smaller reduction in HbA1c was observed for empagliflozin (only 25mg dose used) as an add-on to metformin compared with glimepiride (mean dose 2.7 mg/day) plus metformin [week 52, adjusted mean difference from glimepiride (97.5% CI) -0.07 (-0.15, 0.01); $p < 0.0001$ non inferiority], the difference in the observed effect size confirmed empagliflozin was non inferior to glimepiride³⁰.

Effect On Body Weight And Blood Pressure

Empagliflozin compared to placebo significantly reduced body weight, waist circumference (WC) and total and visceral adiposity in 3300 T2DM patients. Whether changes in body composition induced by Empagliflozin will be associated with reduced athero-sclerotic cardiovascular disease (ASCVD) and heart failure risk remains to be determined³¹.

Empagliflozin therapy also produced modest reductions in body weight and blood pressure^{24,25,26,27,28}. For example, empagliflozin given as monotherapy (10 mg and 25 mg given once daily for 24 weeks) reduced body weight by 1.93–2.15 kg (4.25–4.74 lb) *versus* placebo,

and by 2.45–2.67 kg (5.40– 5.89 lb) *versus* sitagliptin comparator, while systolic blood pressure decreased by 2.6–3.4 mmHg and 3.4–4.2 mmHg *versus* placebo and sitagliptin comparator, respectively²⁶.

A 12-week, double-blind, multinational phase III trial (EMPA-REG BP) evaluated the efficacy of empagliflozin 10 or 25 mg once daily in patients with inadequately controlled type 2 diabetes (*i.e.* an HbA1c level of 7–10 %) and hypertension (mean seated office SBP 130–159 mmHg). Once-daily empagliflozin 10 or 25 mg (n = 276/group) for 12 weeks provided significant and clinically relevant improvements in HbA1c levels and 24-h SBP compared with placebo (n = 271). At 12 weeks, adjusted mean changes from baseline in HbA1c in the empagliflozin 10 mg, empagliflozin 25 mg and placebo groups were -0.59, -0.62 and 0.03 %, respectively (both $p < 0.001$ vs. placebo; mean baseline HbA1c 7.9 % in all groups). In the empagliflozin 10 and 25 mg group, adjusted mean reductions in mean 24-h SBP from baseline were 2.95 and 3.68 mmHg compared with an increase of 0.48 mmHg in the placebo group (both $p < 0.001$; mean baseline 24-h SBP 131.2–131.7 mmHg). Empagliflozin recipients also experienced significantly greater improvements from baseline in adjusted mean 24-h DBP and mean seated office SBP and DBP than placebo recipients at study end (all $p < 0.001$ for both empagliflozin groups vs. placebo)²⁸.

Cardioprotective Effect

The effect of empagliflozin on cardiovascular outcomes among patients with type 2 diabetes and prevalent atherosclerotic cardiovascular disease (CVD) was recently evaluated in the EMPA REG OUTCOME trial, a multicenter, randomized, double blind, placebo controlled trial. This study included 7,028 participants with type 2 diabetes and established CVD from 590 centers over 42 countries and tested two doses of empagliflozin (10mg or 25mg) compared with placebo. Over a median follow up of 2.6 years, pooled analyses of the 2 empagliflozin dose groups versus placebo demonstrated a statistically significant 14% reduction in the primary composite outcome of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke (HR 0.86; 95% CI 0.74 to 0.99, $P=0.04$ for superiority). Furthermore, empagliflozin was also associated with significant risk reduction of the individual outcomes of cardiovascular mortality (HR=0.62; 95% CI 0.49 to 0.77), all-cause mortality (HR=0.68; 95% CI 0.57 to 0.82), and hospitalization for heart failure (HR=0.65; 95% CI 0.50 to 0.85). Whether or not these cardiovascular benefits are unique to empagliflozin or represent a class-effect remains to be seen and is the subject of ongoing investigation. Currently, empagliflozin is the only glucose-

lowering agent to have demonstrated CVD risk reduction in a dedicated cardiovascular outcomes trial³².

Consistent with the results of EMPA-REG OUTCOME in patients with T2DM at high CV risk, a meta-analysis of seven glycaemic control trials suggested that empagliflozin was associated with a reduced risk of CV outcomes in patients with T2DM who were considered to be at low/medium CV risk, based on low placebo event rates for 3P-MACE (4.6–28.7 per 1000 patient-years). Suspected CV events were prospectively adjudicated; the HRs for the pooled empagliflozin 10 and 25 mg/day dosage groups ($n = 2770$) versus the placebo group ($n = 1502$) were 0.59 (95% CI 0.36–0.95) and 0.66 (95% CI 0.39–1.12) for 4P-MACE and 3P-MACE (the primary and secondary endpoints, respectively)³³.

Renoprotective Effect

Empagliflozin was associated with slower rates of renal disease and reduced levels of renal occurrences clinically appropriate than placebo when added to standard care. Incident or aggravation of nephropathy happened in 525 of 4124 patients (12.7%) in the empagliflozin group and 388 of 2061 (18.8%) in the placebo group (risk ratio in the empagliflozin group, 0.61 ; 95% confidence interval, 0.53 to 0.70 ; $P < 0.001$). Doubling of the serum creatinine level occurred in 70 of 4645 patients (1.5%) in the empagliflozin group and in 60 of 2323 (2.6%) in the placebo group, a significant relative risk reduction of 44%. Renal-replacement therapy was initiated in 13 of 4687 patients (0.3%) in the empagliflozin group and in 14 of 2333 patients (0.6%) in the placebo group, representing a 55% lower relative risk in the empagliflozin group. There was no significant between-group difference in the rate of incident albuminuria. The adverse-event profile of empagliflozin in patients with impaired kidney function at baseline was similar to that reported in the overall trial population³⁴.

In the analysis of renal outcomes, incident or worsening nephropathy was reduced for empagliflozin (12.7%) compared with placebo (18.8%); HR, 0.61 (95% CI: 0.53, 0.70). Empagliflozin significantly reduced the risk of progression to macroalbuminuria (38%) and doubling of creatinine (44%), as well as the need of starting renal-replacement therapy (55%). The benefits of empagliflozin for the reduction of CV death, all-cause death and hospitalization for HF were observed across a range of baseline subgroups such as HbA1c level and renal function (down to estimated glomerular filtration rate [eGFR] 30 ml/min/1.73 m²)³⁵.

DOSAGE AND ADMINISTRATION

Recommended Dosage

Empagliflozin starts in the morning as 10 mg, and if tolerated, the dose can be boosted to 25 mg. It is suggested that this condition be corrected in patients with volume depletion before starting empagliflozin.

Patients With Renal Impairment

Assessment of renal function is recommended prior to initiation of empagliflozin therapy and periodically thereafter. Empagliflozin should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m². Patients with an eGFR greater than or equal to 45mL/min/1.73 m² do not need to adjust the dose. Empagliflozin should be discontinued if eGFR is less than 45 mL/min/1.73 m².

DRUG INTERACTION

In an open-label, randomized, crossover study of healthy T2DM patients, drug-drug interactions were assessed. Empagliflozin was given with medications commonly used in patients with T2DM. There have been no clinically appropriate interactions between empagliflozin and digoxin, linagliptin, metformin, ramipril, sitagliptin, verapamil, warfarin, or a combination of oral contraceptives (ethinyl estradiol / levonorgestrel). Dose adjustments were not necessary for any drug combinations studied.³⁶

No relevant drug–drug interactions were observed between empagliflozin and the commonly prescribed CV drugs, verapamil, ramipril, and digoxin. Based on standard bioequivalence boundaries, no dose adjustment of digoxin or ramipril is required when coadministered with empagliflozin, and no dose adjustment of empagliflozin is required when coadministered with verapamil or ramipril³⁷.

EMPAGLIFLOZIN IN SPECIAL POPULATION

Pregnancy

Empagliflozin is rated a safety category C in pregnancy. There are currently no controlled human studies of the drug in pregnant women. In animal studies, empagliflozin can cross the placenta and result in impaired kidney development and maturation. However, no evidence of

teratogenicity was found in doses 48-times and 128-times the maximum human clinical dose in rats and rabbits, respectively. It is recommended that the drug be used during pregnancy only if the potential benefit justifies the potential harm to the fetus and no other alternatives are available. Similarly, empagliflozin is considered possibly unsafe for use in lactation, although it is not known if the drug is excreted in human milk. Since there is potential for serious adverse reactions in nursing infants due to the glucose lowering and volume contraction effects of the drug, it is recommended that empagliflozin is discontinued while nursing.

Elderly

The geriatric population represents another special population of interest with regard to treatment with empagliflozin. Because elderly patients often have impaired autonomic function, may be taking diuretics, and are often prescribed multiple medications with significant potential for drug-drug interactions, adverse events related to empagliflozin treatment may be amplified in this group. Furthermore, empagliflozin is expected to have diminished efficacy among elderly patients due to concomitant kidney impairment common in the elderly. Although only 6% of patients included in randomized clinical trials were over age 75, the risk of volume depletion-related adverse reactions and risk for urinary tract infections were increased in this age group compared with younger patients. Therefore, caution is advised when prescribing empagliflozin in the elderly and close monitoring for adverse effects is necessary³².

Chronic Kidney Disease

Chronic kidney disease (CKD) is a well-known complication of T2DM and up to 40% of patients with T2DM have CKD³⁸. Because SGLT2 inhibitors must be filtered at the glomerulus and reach the proximal tubule in the nephron to exert their inhibitory effects, they require a certain degree of glomerular filtration for efficacy³⁹. The efficacy and safety of empagliflozin was evaluated in a study of patients with T2DM and CKD stage 2 (n=290) and stage 3 (n=374) compared with placebo. In general, adverse events were similar between placebo and empagliflozin treated groups. Small decreases in estimated glomerular filtration rate were reported with empagliflozin treatment, with larger changes on average among those with worse baseline renal function, but generally resolved up to 3 weeks after treatment cessation. The glucose lowering benefit of empagliflozin compared with placebo was decreased, and the risks of declining kidney function, volume depletion, and urinary tract infection were increased, with

worsening kidney impairment (CKD stage >3). It is also important to recognize that the efficacy and safety of empagliflozin has not been adequately tested in patients with more severe kidney impairment (CKD stages 4 and 5), or in patients receiving dialysis. In the aforementioned study, a small group (n=30) patients with CKD stage 4 were randomized to receive empagliflozin vs. placebo but empagliflozin treatment did not reduce glycosylated hemoglobin in this group and the incidence of adverse events was higher compared with placebo²⁵. Thus empagliflozin is not likely to be effective in patients with more advanced CKD and its use should be avoided in this patient population, with the product labeling reflecting this contraindication. Furthermore, if a patient treated with empagliflozin goes on to develop CKD stage 4 or higher, empagliflozin should be discontinued and alternative therapies should be considered.

TOLERABILITY

The most frequently occurring adverse events with empagliflozin are urinary tract infections (7.6% with placebo vs 9.3% and 7.6% with empagliflozin 10 and 25 mg, respectively) and genital mycotic infections (in female patients: 1.5% with placebo versus 5.4% and 6.4% with empagliflozin 10 and 25 mg, respectively). Adverse events related to osmotic diuresis and volume contraction have been evaluated from pooled data from Phase I, II, and III studies in >11,000 patients. The general prevalence of volume depletion incidents in that assessment was 1.4% with empagliflozin 10 mg and 1.5% with empagliflozin 25 mg vs. 1.4% with placebo. The incidence of these events was higher in subjects aged ≥ 75 years, those with eGFR <30 mL/min/1.73 m², and those also receiving diuretic therapy. Increased rates of hypoglycemia were not seen in empagliflozin monotherapy or in combination with insulin sensitizers. However, when combined with other medications that have a high risk of hypoglycemia (sulfonylureas or insulin), the empagliflozin arms of these studies had higher rates of hypoglycemia³.

Compared with placebo, empagliflozin doses from 5 to 50 mg the frequency of adverse events was generally similar with empagliflozin (29.6–48.6%), placebo (36.6%) and sitagliptin (35.2%). Hypoglycaemia rates were very low and balanced among groups. Most frequent adverse events with empagliflozin were urinary tract infections (4.0% vs. 2.8% with placebo) and pollakiuria (2.5% vs. 1.4% with placebo). Genital infections were reported only with empagliflozin (4.0%)¹². Common (occurring in 1–10 % of patients) adverse reactions reported in placebo-controlled trials were genital infections (including vaginal moniliasis,

vulvovaginitis, balanitis), urinary tract infections (UTIs), pruritus (generalized) and increased urination⁴⁰.

CONCLUSION

Empagliflozin is a novel drug and valuable treatment option for type 2 diabetes. Empagliflozin has glycemic and nonglycemic benefits. Glycemic advantages are evident with proof based on insulin-independent mechanism reducing HbA1c. Nonglycemic benefits include weight loss and lowering blood pressure.

Empagliflozin was proven superior to placebo for reduction of major adverse cardiovascular risk among patients with T2DM and established CVD. Oral once-daily empagliflozin monotherapy or add-on therapy to other antihyperglycaemics, including insulin, was an effective and well tolerated treatment in adult patients with type 2 diabetes. No dose adjustment of empagliflozin is required when coadministered with ramipril, digoxin, metformin, sitagliptin, verapamil, warfarin, or a combined oral contraceptive (ethinyl estradiol/levonorgestrel). Empagliflozin is contraindicated in renal impaired patients.

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