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Impact of empagliflozin in patients with diabetes and heart failure

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ABSTRACT

Heart failure (HF) is a common disease with increased risk for mortality and morbidity among patients with type 2 diabetes mellitus (T2DM). Optimal glycemic control in this patient population is challenging as many available therapies can potentially exacerbate symptoms of HF. Empagliflozin is one in a novel class of agents, the sodium glucose co-transporter 2 (SGLT2) inhibitors, that lowers blood glucose by increasing urinary glucose excretion and improves glycemic control and lowers body weight and blood pressure. In the recent EMPA-REG OUTCOME trial, empagliflozin was shown to improve cardiovascular outcomes in patients with T2DM and established cardiovascular risk where it reduced HF hospitalizations and cardiovascular death, with a consistent benefit among patients both with and without baseline HF. Here, we review the empagliflozin data on HF outcomes and discuss potential mechanisms for its benefits in HF with a focus on the potentially significant impact that empagliflozin may have on the care of patients with T2DM and HF in the future.

Key words: Empagliflozin, Heart failure, SGLT2 inhibitor, Type 2 diabetes mellitus

Abbreviations: CKD, chronic kidney disease, HF, heart failure, SGLT2, sodium glucose co-transporter 2, T2DM, type 2 diabetes mellitus.

Introduction

Heart failure (HF) is a common and deadly disease with an estimated prevalence of more than 5.7 million in the United States [1]. HF contributes to 1 in every 9 deaths in the United States and there is an estimated 5-year survival of 50% at the time of diagnosis [1]. HF is a frequent comorbidity among patients with type 2 diabetes mellitus (T2DM), especially among older adults (~22% in patients ≥65 years) [2], and may be an important mediator of left ventricular systolic and diastolic dysfunction leading to HF [3]. Furthermore, a diagnosis of T2DM carries an adverse prognosis among those with

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systolic HF and has been shown to increase risk for all-cause mortality and cardiovascular death in both ischemic and non-ischemic etiologies of HF [4].

The optimal management of T2DM in HF remains a challenge due to multiple factors. Some anti-hyperglycemic therapies such as insulin and thiazolidinediones promote weight gain and fluid retention thereby potentially counteracting the beneficial effects of glycemic control on HF. Therapies such as the thiazolidinediones and saxagliptin, a dipeptidyl-peptidase 4 (DPP-4) inhibitor, have been associated with signals of increased risk of HF compared with standard care, resulting in product-label cautionary language modifications required by the FDA [5,6]. Furthermore, until recently, there have been no anti-hyperglycemic therapies for T2DM shown to modify HF outcomes.

Recently, a novel class of medications, the sodium glucose co-transporter 2 (SGLT2) inhibitors, have been approved for management of glycemic control in T2DM. A medication in particular, empagliflozin, has recently been shown to improve both glycemic control and cardiovascular outcomes, a first for a glucose lowering therapy in the modern area [7]. Here, we review the mechanism of action of empagliflozin, summarize current data focused on HF outcomes, highlight important safety issues pertinent to the HF population, and consider the potential future impact of empagliflozin on the growing population of patients with T2DM and with or at risk for HF.

Mechanism of action

Glucose is freely filtered into the urine at the glomerulus and reabsorbed by both SGLT proteins 1 and 2 located in the proximal tubule of the kidney. SGLT2 transports approximately 90% of filtered glucose back into the systemic circulation by coupling glucose transport to the electrochemical sodium gradient [8], while SGLT1 reabsorbs the remaining 10% under normal physiologic conditions [9]. Empagliflozin, as well as other SGLT2 inhibitors presently in clinical use (canagliflozin and dapagliflozin), selectively inhibits SGLT2, which decreases the renal tubular threshold for glycosuria and increases urinary excretion of glucose, thereby reducing blood glucose independent of insulin. This unique mechanism of action avoids many of the limitations of other anti-hyperglycemic agents such as weight gain and hypoglycemia that occur through augmented insulin secretion.

Since sodium is co-transported with glucose, inhibition of SGLT2 also causes a small natriuresis in addition to the osmotic diuresis resulting from increased urinary glucose excretion. This results in an increase of 107–450 mL of urine output per day [10]. Furthermore, there may also be greater increases in hemoglobin and hematocrit concentrations among empagliflozin treated groups compared with placebo or active controls. These changes appear to be a class effect with all SGLT2 inhibitors, although a recent systematic review found that empagliflozin demonstrated the largest increase in hematocrit [11]. Whether these changes are related to volume contraction leading to hemoconcentration or off-target effects such as erythropoietin stimulation and increased red cell mass remains to be determined.

The pharmacodynamics of empagliflozin were evaluated in a phase I study of healthy adults. This study demonstrated that over the first 24 h, glucose reabsorption was inhibited by 40% on average across doses studied, with a graded association with increasing dose up to 60% inhibition of glucose reabsorption up to a dose of 100 mg, with no further increase at higher doses [12]. In patients with T2DM, this equates to excretion of urinary glucose ranging from 78 to 90 g/day, depending on the dose and on circulating concentrations of glucose [13]. In both patients with T2DM and healthy subjects, empagliflozin has similar pharmacokinetic properties. It is rapidly absorbed orally reaching peak levels in 1.5 h with 78% bioavailability [14]. Once absorbed, it is metabolized in the liver by glucuronidation into 3 conjugates, with each metabolite consisting of less than 10% of the drug in circulation [14]. The half-life of empagliflozin is approximately 12.4 h. The drug is primarily excreted by the kidney and in the feces as mostly unaltered drug. None of the pharmacodynamics or pharmacokinetics properties of empagliflozin have been specifically studied in patients with HF.

Clinical outcomes

There are six phase III, randomized, controlled clinical trials demonstrating the efficacy of empagliflozin at lowering glycosylated hemoglobin (HbA1c) as monotherapy or add-on to existing diabetes therapies [15–20]. None of these trials specifically included or excluded patients with HF; however, only the EMPA-REG PIO [18] trial had a pre-specified data collection and analysis for signs and symptoms of HF and edema. The proportion of participants with HF at baseline was not reported. In this study, patients with HbA1c $\geq$7 and $\leq$10% were randomized to treatment with once daily empagliflozin (10 mg or 25 mg) or placebo as add-on therapy to pioglitazone $\pm$ metformin for 24 weeks. At 6 weeks post-randomization, there was no increase in the frequency of edema or HF in patients receiving empagliflozin and pioglitazone compared with placebo. Peripheral edema was reported in 2 patients receiving placebo and 1 receiving empagliflozin 25 mg; 1 patient receiving empagliflozin 10 mg reported symptoms of HF.

In 2015, the results of the EMPA-REG OUTCOME trial were published in the New England Journal of Medicine demonstrating the beneficial effects of empagliflozin on cardiovascular morbidity and mortality [21]. This multicenter, randomized, double-blind, placebo-controlled trial evaluated 7028 patients with T2DM and established cardiovascular risk randomized to either 1 of 2 doses of empagliflozin (10 mg or 25 mg daily) or placebo. Cardiovascular risk was defined as the presence of at least one of the following: history of myocardial infarction or stroke, coronary artery disease with documented evidence of unstable angina, ischemia by non-invasive testing, or coronary angiography/revascularization, and peripheral arterial disease. Pooled analyses of the 2 empagliflozin dose groups compared with placebo showed a 14% reduction in the primary composite outcome of 3-point major adverse cardiovascular events (MACE): cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke over a median treatment period of 2.6 years and median follow-up