

Comparison of Empagliflozin with other SGLT-2i and the Pharmacological Effects of Empagliflozin

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Abstract. Diabetes mellitus is a pathological illness that is distinguished by compromised metabolic function due to defects in the synthesis and response of insulin, leading to substantial health complications. T2D is now recognized as a pressing global health concern, affecting a large population worldwide. Several studies have demonstrated that Empagliflozin can be categorized as a member of the drug class known as SGLT-2 inhibitors (SGLT-2i). This particular medication has been found to be effective in the treatment of T2D. This article elucidates the pharmacological effects of the substance in question, namely its capacity to reduce blood glucose levels, provide cardioprotection (mitigation of oxidative stress in the myocardium, mitigation of cardiac inflammation, decrease cell death in the cardiac tissue, betterment of Disrupted Electrolyte Homeostasis), influence cardiovascular outcomes, address obesity, impact renal function, and perhaps exhibit anticancer properties. The present study also aims to examine the comparative effects of empagliflozin in relation to other inhibitors across various domains, including cardiovascular events, worsening renal function, metabolic outcomes, and all-cause mortality.

Keywords: Cotransporter-2 inhibitors; empagliflozin; pharmacological effects.

1. Introduction

Diabetes mellitus is a medical condition characterized by impaired metabolic function because of deficiencies in insulin production and responsiveness, resulting in significant health problems [1]. Type 2 diabetes (T2D) has become known as an urgent global health issue, exerting its influence on a vast population around the globe. In 2021, diabetes had a global impact on almost 0.537 billion individuals, with over 90% of them being diagnosed with T2D. It is projected that this figure will rise to 0.783 billion by the year 2045 [2]. This phenomenon results in a significant cost burden on public health. In addition, T2D has been found to be associated with the development of significant comorbidities, including chronic kidney disease (CKD) and cardiovascular disease (CVD). Efforts should be made to address and mitigate the dangers connected with diabetes in order to safeguard the well-being of those who are particularly susceptible to these risks [1].

Numerous classifications of medicines have emerged and been implemented over the course of the previous century with the aim of regulating blood glucose levels and safeguarding the vasculature and critical organs of these individuals [3]. However, individuals diagnosed with diabetes mellitus often experience adverse consequences, including weight gain, hypoglycemia, and hepatorenal harmful effects, as a result of pharmaceutical usage. Hence, the advancement of novel pharmaceutical compounds holds significant significance. Sodium-glucose cotransporter 2 inhibitors (SGLT-2i) represent a novel class of targeted medicines that have emerged for the management of diabetes mellitus, with the potential to also enhance cardiorenal conditions [1]. These exist research that provide evidence indicating that the protein Sodium-glucose cotransporter-2 (SGLT-2) are an innovative sort of drug taken orally for anti-diabetes, which are involved in glucose transport in the kidneys and blocking SGLT-2 has been proved to suppress the intake of glucose by the kidneys, which causes lower blood glucose levels [4,5]. They contain many types of drugs including empagliflozin, sergliflozin, remogliflozin, dapagliflozin, canagliflozin, ipragliflozin, tofogliflozin [4].

Empagliflozin has received approval for the therapeutic management of T2D in adult patients across many regions, including the European Union, United States, and Japan, among other global jurisdictions. The study found that empagliflozin had cardioprotective and renoprotective effects in

patients with T2D and pre-existing CVD, which were primarily unrelated to glycemic management. The cardiovascular (CV) benefits of this medication are evident in the approved labelling for the drug in both the EU and the USA [5]. However, the majority of prior studies were individual studies, and none of them provided a comprehensive systematic overview. This article provides a comprehensive analysis of the pharmacological effects and safety profile of empagliflozin. It also highlights the key differences between empagliflozin and other SGLT-2i.

2. The Pharmacological Effects of Empagliflozin

The administration of empagliflozin can effectively reduce blood glucose levels, safeguard cardiovascular health, enhance cardiac outcomes, promote weight loss, preserve kidney function, and potentially exhibit anti-cancer properties [1,3,6-9].

2.1. Reduces Blood Glucose Concentrations

Empirical evidence has demonstrated that empagliflozin, functioning as a SGLT-2, effectively hinders the functionality of this protein. SGLT-2 is primarily responsible for facilitating glucose absorption from the distal tubule of the renal system. By impeding the activity of SGLT-2, empagliflozin effectively curtails glucose absorption, resulting in a subsequent decrease in the level of glucose in the blood [1,6,7]. Research has demonstrated that after 52 weeks of treatment with empagliflozin in a group of 127 individuals, the level of glycosylated hemoglobin decreased by 0.57% [2]. This also signifies that empagliflozin possesses a hypoglycemic impact.

2.2. Protect the Cardiovascular

The preventive impact of empagliflozin on the CV system of individuals with T2D has been demonstrated through extensive clinical trials. Examples include reducing oxidative stress in the heart muscle, reducing inflammation in the heart, decreasing cell death in the heart tissue, and improving disrupted electrolyte balance [8]. The potential mechanisms are succinctly outlined in the next section.

2.2.1 The mitigation of oxidative stress in the myocardium

The excessive production of reactive oxygen species (ROS) plays a crucial role in the pathogenesis of endothelial dysfunction. Several studies have demonstrated that SGLT-2i not only diminish the level of blood sugar but also possess the capacity to alleviate cardiac oxidative stress and display antioxidant capabilities [7]. The reduction of cardiac oxidative stress by SGLT-2 inhibitors has been found to successfully decrease superoxide levels in cardiac tissue. This reduction in superoxide levels ultimately leads to a decrease in interstitial fibrosis and ventricular hypertrophy [7]. Research findings have indicated that the administration of high dose empagliflozin (30 mg/kg/days) in a murine model of diabetes mellitus exhibits the potential to mitigate myocardial oxidative stress in mice [7]. Clinical trials in humans need to be further explored.

2.2.2 The mitigation of cardiac inflammation

Several studies have indicated that cardiac inflammation is a significant contributor to the development of diabetic cardiomyopathy among those suffering with T2D [7]. However, it has been seen that the administration of empagliflozin can lead to a reduction in cardiac interstitial macrophage infiltration and subsequent alleviation of inflammation in the heart [7]. One potential mechanism involves the reduction of inflammatory cytokine levels and the resulting improvement of the M2/M1 phenotype macrophage ratio by empagliflozin [7]. The M1 phenotype is characterized by its pro-inflammatory tendency, while the M2 phenotype has an anti-inflammatory nature [7]. Another potential method by which empagliflozin may reduce myocardial inflammation is by the reduction of the nucleotide binding oligomerization domain-like receptor 3 (NLRP3) inflammasome [7].

2.2.3 Decreased cell death in the cardiac tissue

These exist research that provide evidence for the pathological state of endoplasmic reticulum stress (ERS), which induces the production of ROS and demonstrates an anti-apoptotic impact [7]. The presence of hyperglycemia and hypoxia can initiate ERS, leading to aberrant protein folding and subsequent cell death in cardiac tissue [7]. Consequently, mitigating ERS can potentially reduce cardiac cell death and alleviate the development of cardiomyopathy. Research has shown that empagliflozin can effectively decrease programmed cell death in heart muscle cells by controlling the ERS pathway [7].

2.2.4 Betterment of disrupted electrolyte homeostasis

Numerous scholarly investigations have examined in patients with diabetic heart failure, there is a dysregulation observed in the Na⁺ and Ca²⁺ exchangers. The dysregulation in question has the potential to contribute to the development of ventricular hypertrophy and subsequent heart failure [7]. Empirical evidence appears to show that empagliflozin possesses the capacity to modulate the activity of Na⁺ and Ca²⁺ exchangers [7]. Furthermore, it is plausible to illustrate that empagliflozin possesses the capacity to alleviate the ventricular hypertrophy and heart failure [7].

2.3. The Cardiovascular Outcomes Associated with the Use of Empagliflozin

The cardiovascular outcomes assessed in one study encompassed cardiovascular death, stroke, heart failure (HF), and all-cause mortality. It conducted revealed a noteworthy decrease of 38% in the frequency of CV mortality and stroke among patients with T2D who were administered empagliflozin. Furthermore, there was a notable decrease of 35% in hospitalization rates among patients experiencing HF, accompanied by a significant reduction of 32% in overall death rates [1]. The aforementioned advantages might be attributed to the mechanism of empagliflozin, whereby they effectively lower sodium levels. This reduction in sodium subsequently leads to a drop in the amount of plasma and pressure in the blood. The decrease in circulation leads to a decrease in both the initial stretching of the heart muscle and the resistance against which the heart pumps., resulting in an enhancement in cardiac blood flow [1, 8].

2.4. The Impact of Obesity

As a result of a clear association between T2D and obesity, a considerable number of patients who are prescribed SGLT-2i make concerted efforts to engage in weight loss strategies in order to improve their prognosis. The mechanism of SGLT-2i involves glucose inhibition absorption within tubules in the kidneys, leading to the excretion of urinary glucose. Consequently, this process leads to caloric depletion, thereby establishing a state of energy deficit. Several articles have reported that patients treated with empagliflozin experience a reduction in energy expenditure of approximately 200 kcal/day. This decrease is attributed to a combination of physiological mechanisms and an increase in beta-oxidation. As a result, patients tend to lose around 3 kg of weight over the course of approximately one year. Additionally, this weight loss is associated with an improvement in insulin sensitivity [1, 3].

2.5. The Impact on Renal Function

The SGLT2 inhibitor (SGLT2i) exerts its effects on the renin-angiotensin-aldosterone system (RAAS) pathway within the renal system by attenuating renin activity by blocking the reintroduction of sodium. The downregulation of this mechanism facilitates renoprotection by impeding hyperfiltration damage. The presence of study findings has been observed. According to reports, the occurrence of severe proteinuria was 45% greater in the group not receiving empagliflozin compared to the group receiving empagliflozin in the EMPA-REG OUTCOME trial [3]. In addition, it should be noted that SGLT2 inhibitors have the ability to reduce the pressure inside the kidney and hyperfiltration of the glomerular system. This mechanism of action is particularly beneficial in the context of renal illness, as it aids in the preservation of the estimated-glomerular filtration rate (eGFR)

in affected individuals. Research indicates that the utilization of Empagliflozin in conjunction with losartan has the potential to enhance the blockade of angiotensin 2 (ANG2), leading to a reduction in glomerular sclerosis. Hence, Empagliflozin exhibits beneficial effects in the backdrop of renal diseases and possesses the capacity to attenuate the course of renal function deterioration [1].

2.6. The Potential Impact of Anticancer Interventions

In addition to its hypoglycemic effects, empirical evidence from multiple researches have demonstrated the anticancer properties of empagliflozin. The potential mechanism can be attributed to the expression of SGLT-2 in many cancer cell lines. So that empagliflozin demonstrates anti-cancer properties in some cancer types, manifesting as the suppression of tumor proliferation of cells, immigration and intrusion, and the initiation of cell death. When empagliflozin is administered alongside specific chemotherapeutic drugs or radiation therapy, it has the potential to enhance therapeutic effectiveness and mitigate the occurrence of associated adverse effects. The potential mechanisms underlying the activities of SGLT-2 inhibitors encompass the suppression of proteins that are connected by β -linkages, activation of the activated protein kinase (AMPK) cellular communication pathway, induction of cycle of cells pause, and suppression of epidermal growth factor receptors (EGFR). Additionally, it was shown that empagliflozin exhibits the ability to activate AMPK, hence triggering apoptosis in cervical cancer cells [9]. The investigation involved the application of empagliflozin at a specified level of dosage (100 $\mu\text{g}/\text{ml}$) to human-derived lung cancer cell Line A549, which led to a cell viability of merely 51%. The experimental findings demonstrated a substantial suppressive impact of empagliflozin on A549 cells [9].

3. The Distinction between Empagliflozin and Other SGLT-2i

The C-glucoside classes of the SGLT-2i pertain to empagliflozin, dapagliflozin, ipragliflozin, canagliflozin, and tofogliflozin and the O-glucosides inhibitors might involve sergliflozin, remogliflozin, and phlorizin [4]. In accordance to the study results, O-glucoside SGLT inhibitors demonstrate a slightly less the capability to inhibit SGLT-2 compared with C-glucoside SGLT inhibitors [4].

The current research is on the talks about the scientific investigation of the effectiveness of a substance when tested in a controlled laboratory environment each of the SGLT-2i, and it also investigates how well they have the ability to discriminate against other belonging to the SGLT clan, among which are SGLT-1, 4, 5, and 6 [4]. SGLT-1 exhibits a strong binding affinity towards glucose and is mostly situated within the S3 section of the tubule at its proximal end. Additionally, SGLT-1 is present in other organs such as the gut, heart, liver, and lung. Its primary role is facilitating the absorption of glucose and galactose within the small intestine. The expression of SGLT-4, 5, and 6 has been seen in the kidney, suggesting their potential involvement in the process of renal monosaccharide and/or salt reabsorption. The expression of SGLT-4 has been demonstrated to be substantially increased within the tiny intestines. The SGLT-5 transporter is specifically localized in the renal cortex. The presence of SGLT-6 has also been identified in both the brain and gut [4].

The research carried out has demonstrated that every one of the inhibitors exhibit an exceptionally high degree of the selectivity for SGLT-4 [4]. Studies in the past was able to show that every one of the inhibitors, except the canagliflozin, showcase selectivity for SGLT-6 [4]. In previously published studies, it was successfully made clear that empagliflozin has a significant level of selectivity in the direction of SGLT-1, SGLT-4, SGLT-5, and SGLT-6. In addition, it has been reported as an excellent inhibitor of SGLT-2, this means which suggests that it might work as an agent of treatment for controlling the symptoms of diabetes [4].

A systematic review and meta-analysis that assessed the clinical results of four SGLT-2i (Empagliflozin/ Dapagliflozin/ Canagliflozin/ Ertugliflozin) in those diagnosed with HF. Table1 summarizes the four inhibitors on comparing results in 5 aspects including comparison of CV outcomes, comparison of deteriorating kidney function, comparison of Metabolic results, sensitivity

analysis on the lower ejection fraction observed in those diagnosed with HF, sensitivity analysis on chronic HF [10]. The analysis of CV outcomes reveals that there is no statistically significant the variance observed with the effectiveness of therapy of four inhibitors [10]. But empagliflozin displayed the most obvious efficacy in lessening the danger rate linked to hospitalization for HF [10]. Canagliflozin demonstrated the greatest effectiveness in dropping the hazard rate due to CV fatalities, a combination of CV deaths and HF hospitalizations, all-cause mortality, and a combination of CV deaths, non-fatal myocardial infarction, and non-fatal stroke [10]. Based on the comparative analysis of deteriorating renal function, it was observed that the three inhibitors exhibited no statistically significant variance in their ability to reduce the hazard rate associated with worsening renal function [10]. The analysis of metabolic outcomes uncovered that there was definitely no statistically significant change in weight per kilogram, HbA1c per millimole per mole, and systolic blood pressure per millimeter of mercury between the two inhibitors [10]. The research of sensitivity analysis on the decrease in ejection fraction observed among individuals who have heart failure uncovered that there was most definitely no choose to major and verifiable distinction in terms of effectiveness therapy between the two inhibitors [10]. The research project on sensitivity analysis carried out with chronic heart failure results showed there was no significant and discernible variance in the therapeutic result, specifically in terms of overall mortality, within the three inhibitors [10].

Table1: Evaluation of the effectiveness of the four inhibitors post-administration

SGLT-2i Compare	Empagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin
Comparison of cardiovascular outcomes	HF hospitalization: sample 11,556 patients EM/CA=0.83, DA/CA=1.41 cardiovascular deaths: sample 10,641 patients DA/CA=1.14, EM/DA=1.08 CV deaths and HF hospitalizations: sample 14,975 patients DA/CA=1.12, EM/CA=1.08, ER/CA=1.25 all-cause mortality: sample 10,666 patients DA/CA=1.07, EM/CA=1.17 CV deaths/non-fatal myocardial infarction/non-fatal stroke: sample 5795 patients DA/CA=1.21, ER/CA=1.26			
Comparison of deteriorating kidney function	sample 11,293 patients DA/CA=1.04, EM/CA=0.83			
Comparison of metabolic outcomes	Mean weight change: sample 8530 patients: EM/DA=0.13 Mean change in HbA1c: sample 8530 patients EM/DA=1.10 Mean change in systolic blood pressure: sample 8530 patients EM/DA=0.59			
Sensitivity analysis on the lower ejection fraction observed in patients with heart failure	sample 8737 patients not have a noticeable and provable distinction			
Sensitivity analysis on chronic heart failure	sample 10,587 patients not have a noticeable and provable distinction			

EM: Empagliflozin; DA: Dapagliflozin; CA: Canagliflozin; ER: Ertugliflozin

A systematic review and network meta-analysis, conducted a comprehensive search on PubMed, www.clinicaltrials.gov, and the Cochrane Central Register of Controlled studies to identify randomized controlled studies that investigated the utilization of canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin in individuals with T2D. The main outcome measure was the occurrence of death from any cause. The secondary outcomes assessed in the study were cardiovascular death and the exacerbation of HF. The evidence was synthesized through the use of network meta-analysis (NMA) [5]. Table 2 presents a comparative analysis of the varying impacts of the four pharmacological treatments across three distinct areas. The data reveals that canagliflozin, dapagliflozin, and empagliflozin showing a significant impact on overall mortality [5]. In addition, empagliflozin exhibits a superior effect compared to both canagliflozin and dapagliflozin [5]. All pharmaceutical substances contain the capacity to significantly decrease the incidence of cardiovascular-related deaths [3, 5]. Furthermore, it has been found that empagliflozin exhibits a higher level of efficacy in decreasing CV mortality in comparison to both canagliflozin and dapagliflozin [5]. All inhibitors, with the exception of Ertugliflozin, demonstrated a reduction in the result of worsening heart failure. However, no additional significant differences were observed among the inhibitors [5].

Table 2: Evaluation of the effectiveness of the four inhibitors post-administration

SGLT-2i Compare	Empagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin
All-cause mortality	Sample 71,719 patients DA/CA=1.08, EM/CA=0.78, ER/CA=1.25			
Cardiovascular mortality	Sample 59,168 patients DA/CA=1.14, EM/CA=0.72, ER/CA=0.58			
Worsening HF	Sample 42,683 patients DA/CA=1.19, EM/CA=1.06			NA

HF: heart failure; NA: not available; EM: Empagliflozin; DA: Dapagliflozin; CA: Canagliflozin; ER: Ertugliflozin

4. Safety

Clinical application of Empagliflozin should pay attention to its safety. The occurrence of genital and urinary tract infections has been commonly documented as adverse effects in relation to the utilization of SGLT-2i. Numerous trials have consistently revealed an elevated risk of genital infections. The elevated presence of glucose in the urinary system is responsible for this risk, as it creates a conducive environment for the proliferation of commensal microbes. The Trial of Empagliflozin CV Outcome Event did not yield statistically significant differences in the occurrence of urinary tract infections events when comparing the active group with the placebo group. The inclusion of a black box warning regarding this danger has been implemented by the FDA [8, 11]. Generally, these infections are non-lethal and typically heal with a brief regimen of antifungal medication [8].

Diabetic ketoacidosis (DKA) is another infrequent although significant adverse event observed among individuals with diabetes who are being treated with SGLT-2i. Hence, it is necessary to assess and address clinical disorders that contribute to an elevated risk [11]. The clinical data indicates that the occurrence rate is roughly 0.2% per 40,000 patients. If any signs of ketoacidosis (such as abdominal pain, nausea, vomiting, trouble breathing, and exhaustion) manifest, the FDA recommends discontinuing the use of the SGLT2 inhibitor [8, 11].

The utilization of SGLT2 inhibitors may lead to hypotension due to volume depletion, which is a significant risk primarily attributed to their diuretic properties. Nevertheless, there were no explicit findings of decreased volume that led to a statistically significant rise in the likelihood of hypotension.

The mitigation of this potential danger can be achieved through the implementation of dose modification in diuretic medication [11].

5. Conclusion

This study provides a concise summary of the medicinal impacts of empagliflozin, which include reducing blood glucose levels, safeguarding cardiovascular health, promoting weight loss, and protecting renal function. Even in a non-diabetic setting, the protective effect of Empagliflozin on cardiomyocytes, kidneys, and faulty ducts remained. These functions offer the possibility of its role in the treatment of other diseases, but more experimental and clinical data are needed to support this. Additionally, it outlines the distinctions between the four inhibitors, particularly focusing on the safety of empagliflozin and various clinical strategies for managing complications. However, there is a scarcity of clinical trials simultaneously assessing the four inhibitors, and further investigation is required to examine the distinctions among them.

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