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EFFECT OF EMPAGLIFLOZIN ON CARDIOVASCULAR OUTCOMES IN PATIENTS WITH HEART FAILURE: A SYSTEMATIC REVIEW

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Abstract:

Empagliflozin is a newer category of anti-diabetic drug. It is a SGLT2 inhibitor and exerts its action by inhibiting the reabsorption of glucose from the tubules in the kidneys that leads to loss of glucose in the urine. There has been great interest in the use of empagliflozin in atherosclerotic cardiovascular diseases, not because of its glucose lowering properties, but due to its improved cardiovascular outcomes. The positive cardiovascular outcomes associated with the use of empagliflozin is independent of its glucose lowering aspect and involves its action on lowering of blood pressure, weight loss and decrease in visceral fat. Several randomized clinical trials have been conducted on the effect of empagliflozin on cardiovascular mortality and they have clearly shown the dominance of empagliflozin as compared to the other glucose lowering therapies. This has revolutionized the use of empagliflozin in patients outside the spectrum of diabetes mellitus and has allowed its entry in the category of drugs which improve cardiovascular mortality. We have conducted this study to further gather clinical evidence regarding the cardiovascular mortality outcomes associated with the use of empaglifozin as compared to other glucose lowering therapies and whether this outcome is also evident in patients without type 2 diabetes mellitus.

Keywords: *Empagliflozin, Heart failure, Diabetes, Cardiovascular outcomes, Lowering blood pressure, Weight loss*

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INTRODUCTION:

Empagliflozin is one of the newer categories of anti-diabetic drug. It is a SGLT2 inhibitor and it performs its action by reducing the absorption of glucose in the kidneys and thus resulting in the loss of glucose from the body via urine. It has shown cardioprotective effects and good results in terms of glycemic control. Unlike other SGLT2 inhibitors, the use of empagliflozin can result in the reduction of risk of heart failure hospitalizations and serious renal outcomes among patients with diabetes[1].

A wide variety of mechanisms have been proposed to explain the cardioprotective role of empagliflozin. These include: 1) lowering blood pressure; 2) increasing diuresis/natriuresis; 3) improving cardiac energy metabolism; 4) preventing inflammation; 5) weight loss; 6) improving glucose control; 7) inhibiting the sympathetic nervous system; 8) preventing adverse cardiac remodeling; 9) preventing ischemia/reperfusion injury; 10) inhibiting the cardiac Na^+/H^+ exchanger; 11) inhibiting SGLT1; 12) reducing hyperuricemia; 13) increasing autophagy and lysosomal degradation; 14) decreasing epicardial fat mass; 15) increasing erythropoietin (EPO) levels; 16) increasing circulating provascular progenitor cells; 17) decreasing oxidative stress; and 18) improving vascular function[2].

The most important aspect in the pathophysiology of heart failure is the dysregulation of salt and water homeostasis[3]. There is maladaptive activation of sodium-conserving pathways despite appropriate or even excess intravascular volume which results in neurohormonal activation[4]. The mainstay of therapy in heart failure is loop diuretics which leads to increased salt excretion from the body but at the expense of neurohormonal activation[5]. SGLT2 inhibitors are glucose lowering drugs that reduce hospitalization in heart failure patients especially in those with reduced ejection fraction. Several mechanisms have been proposed for this action of empagliflozin but the main contributor is the diuretic effect of empagliflozin which leads to decreased total blood volume even in euvoluemic patients[6].

There has been much interest in the cardiovascular benefits of the use of empagliflozin and whether the positive cardiovascular outcomes depend on the glycemic status of patients. Therefore, we present this study to summarize and provide conclusive evidence on the topic of cardiovascular protective aspect of empagliflozin.

METHODS AND MATERIALS:

The PubMed database was searched for publications with the medical subject heading “empagliflozin” and keywords “empagliflozin in heart failure” or “empagliflozin for heart failure in patients without diabetes” Our selection criteria were the English language, the cardio-vascular relevance, full free text article and a time frame of the last ten years (2011-2021).

RESULTS AND DISCUSSION:

The famous “*EMPA-REG OUTCOME”* trial was conducted on patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease (ASCVD) receiving empagliflozin in addition to the other standard of care. The results of the trial showed that the use of empagliflozin resulted in reduction of the risk of 3-point MACE (composite of cardiovascular death, nonfatal MI, or nonfatal stroke) by 14%, cardiovascular death by 38%, all-cause death by 32%, and hospitalization for heart failure (HHF) by 35% in comparison with placebo[7]. The results of the trial showed that treatment with empagliflozin might benefit patients with T2DM and ASCVD irrespective of a history of MI or stroke and across the spectrum of estimated cardiovascular risk.

The CVD-REAL study is a randomized clinical trial to observe the cardiovascular outcomes in the users of SGLT2 inhibitors. The primary outcome was reduction in cardiovascular death and hospitalization for heart failure (HHF)[8]. The results of the trial showed that use of SGLT-2 inhibitors, versus other glucose-lowering drugs, was associated with lower rates of HHF (hazard ratio, 0.61; 95% confidence interval, 0.51-0.73; $P<0.001$); death (hazard ratio, 0.49; 95% confidence interval, 0.41-0.57; $P<0.001$); and HHF or death (hazard ratio, 0.54; 95% confidence interval, 0.48-0.60; $P<0.001$)[9]. The trial showed that the use of empagliflozin has a great extent of positive cardiovascular outcomes as compared to other glucose lowering therapies.

Mikhail Kosiborod et al[9] conducted a randomized clinical trial to observe the effects of use of SGLT2 inhibitors on the cardiovascular outcomes across a study population of 6 countries in the Asia Pacific, the Middle East, and North American regions[9]. The results of the study showed that the use of SGLT2 inhibitors was associated with reduced incidence of death, hospitalization for heart failure and stroke[9]. The results of this trial support the fact that the use of SGLT2 inhibitors has beneficial cardiovascular results

as compared to the use of other glucose lowering therapies. Subodh Verma et al [10] performed a sub-analysis of the *EMPA REG OUTCOME* trial to assess the effect of empagliflozin on cardiovascular outcomes in patients who have undergone coronary artery bypass graft (CABG) surgery[10]. The result of this sub-analysis found that treatment with empagliflozin was associated with profound reductions in cardiovascular and all-cause mortality, hospitalization for heart failure, and incident or worsening nephropathy[10]. This data has profound implications as it indicates that empagliflozin can be used for secondary prevention in patients who have undergone CABG and have type 2 diabetes mellitus.

Anne Zanchi et al[11] performed a double-blind, randomized, placebo-controlled study to observe the effects of empagliflozin on blood pressure and renal oxygenation in non-diabetic and non-hypertensive patients[11]. The primary outcome measures were the acute and chronic effects of empagliflozin on renal tissue oxygenation as measured by BOLD-MRI. The secondary outcomes were the effects of empagliflozin on body weight, office blood pressure and 24-hour blood pressure measurements, renal tubular function, erythropoietin, hematocrit, and ultrasound-assessed renal resistance indexes and length[11]. The results of the trial showed that the use of empagliflozin resulted in the reduction of mean 24-hour blood pressure by 5 mm Hg and also resulted in weight loss as compared to placebo in non-diabetic and non-hypertensive patients[11]. However, there was no alteration of renal tissue oxygenation in the cortex or in the medulla[11]. This trial demonstrates that empagliflozin has beneficial metabolic and blood pressure effects but does not affect renal tissue oxygenation acutely or chronically in non-diabetic subjects with normal renal function. This trial also pointed towards the fact that empagliflozin use can have positive cardiovascular mortality benefit even in patients having no history of diabetes mellitus.

Bernard Zinman et a[12] performed a randomized clinical trial to assess the effect of empagliflozin on cardiovascular outcomes and mortality in patients of type 2 diabetes mellitus[12]. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina[12]. The primary outcome occurred in (10.5%) patients in the pooled empagliflozin group and in (12.1%) patients in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction)[12]. However, there was no statistically significant difference in the secondary outcomes. The results of this trial showed that with the addition of empagliflozin to the standard care there was a lower rate of the primary composite cardiovascular outcome and death from any cause thus showing the positive impact of empagliflozin use.

The EMBLEM trial is a randomized clinical trial that was conducted to observe the effect of empagliflozin on endothelial function in patients having type 2 diabetes mellitus and cardiovascular disease (CVD)[13]. The outcome of this trial shows that empagliflozin use has improved cardiovascular mortality in patients having type 2 diabetes mellitus[13]. The positive cardiovascular outcomes of empagliflozin is not merely limited to its glucose lowering feature but it also extends to lowering of blood pressure, weight loss and loss of visceral fat[13]. The composite effect is improved endothelial function and reduced atherosclerotic activity which eventually results in improved cardiovascular outcomes with empagliflozin use[13]

CONCLUSION:

Type 2 diabetes mellitus forms a major risk factor of cardiovascular disease. Empagliflozin, a SGLT2 inhibitor, is one of the newer anti-diabetic drugs which not only provides good glycemic control but also provides cardiovascular mortality benefit that is independent of its anti-glycemic effect. Empagliflozin use is associated with reduced incidence of death from cardiovascular cause and also reduces the incidence of hospitalization for heart failure. The cardiovascular mortality benefit is also observed in patients without type 2 diabetes mellitus which shows that its underlying mechanism leading to improved cardiovascular outcome is other than its glucose lowering property and it includes lowering of blood pressure, weight loss and improved endothelial function which directly affects the atherosclerotic process. It is clear from this study that empagliflozin is far more superior than the other glucose lowering therapies in terms of its enhanced cardiovascular outcomes and in due time it may become known more for its role in atherosclerotic cardiovascular diseases than in type 2 diabetes, a transition from being an endocrinology drug to being a cardiology drug owing to its better cardiovascular mortality outcome

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