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IMPLICATIONS OF THE OUTCOME OF EMPA-REG OUTCOME ON TYPE 2 DIABETES MELLITUS MANAGEMENT

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ABSTRACT

Diabetes has been implicated in micro-and macro-vascular complications. Glycaemic controls have been found to reduce the risk of microvascular complications in type 2 diabetes. However, studies suggest a possible relation between glycaemic control in decreasing macrovascular complications. The traditional approach of aggressive glycaemic management often leads to hypoglycemia. Hypoglycaemia induces a series of physiological effects that increase cardiovascular disease risk (CVD). In fact, most hypoglycaemic agents such as thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors have been approved based on their ability to decrease glycosylated haemoglobin A1c (HbA1c) rather than their ability to prevent CV morbidity and mortality. In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess Glucose (EMPA-REG OUTCOME®) trial, Empagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, have been proven to exert a cardioprotective effect in type 2 diabetes patients. This paper discusses the outcome of EMPA-REG OUTCOME® and its implication in the management of type 2 diabetes patients that are at risk for CVD.

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BACKGROUND

One of the main perils of type 2 diabetes is the risk of developing cardiovascular disease. Further, the presence of these two co-morbid conditions, viz., type 2 diabetes and cardiovascular disease, increases mortality risk.[1] Disrupted glycaemic balance in diabetes is associated with an increased risk

for vascular events and mortality. Furthermore, patients with a chronic disease that exhibit poor renal function and are on a poly-pharmaceutical treatment regimen are at even higher risk for developing vascular complications.[2] Traditionally, the management of diabetes treatment has been to reduce the hyperglycemia seen in diabetes. However, of late, studies in clinical and population settings point out that intensive glucose lowering or the use of specific glucose-lowering drugs may be associated with adverse cardiovascular (CV) outcomes.

Relationship between glycaemic control and vascular complications

The relationship between glycaemic control and microvascular complications has been well established. However, the possibility of a relationship between glycaemic control and macrovascular disease is implicated in the outcome of various epidemiological studies wherein intensive glucose control has often failed to reduce macrovascular events. Intensive glucose control has been found to perpetually increase the risk of hypoglycemia and thereby higher cardiovascular risk.[3]

Hypoglycemia induces a cascade of physiologic events, including oxidative stress, cardiac arrhythmias, ischemic cerebral damage, and even sudden cardiac death.[4] Acute and chronic hypoglycemia increase the risk for cardiovascular diseases (CVD) through several potential mechanisms viz., adrenergic activation, tachycardia, platelet aggregation autonomic dysfunction, bradycardia, and hypokalaemia. These events eventually increase arrhythmogenicity, leading to a pro-thrombotic state, intensifying myocardial ischemia, and having an unfavorable hemodynamic effect.[2] Further, hypoglycemia has also been associated with events of prolonged hospitalization. Thus, hypoglycemia may cause a multitude of consequences that may have a significant impact on societal healthcare costs.[5]

Therefore, it is necessary to establish the cardiovascular safety benefits of glucose-lowering agents.

Hypoglycemia agents and CV risk

Most of the glucose-lowering agents or their combination strategies have shown no significant CV benefit in the risk of death or heart failure. A meta-analysis of the clinical data of rosiglitazone suggests an increased CV risk with its usage. In addition, an unexpected higher risk of hospitalization due to heart failure was observed with the use of glitazones and, more recently, saxagliptin (a dipeptidyl peptidase 4 [DPP-4] inhibitor). These findings have prompted the need for a more stringent assessment of diabetes therapies. As a result, in 2008, the US Food and Drug Administration (FDA) made mandatory requirements for assessing all new diabetes therapies for CV safety and outcomes.

The newest therapeutic class of hypoglycaemic agents-Flozins are sodium-glucose linked transporter 2 (SGLT2) inhibitors. These drugs act by blocking glucose reabsorption from the renal ultrafiltrate, thereby inducing glycosuria. Apart from reducing the HbA1c levels effectively, Flozins result in loss of body weight and a slight reduction in systolic arterial blood pressure. Additionally, Flozins have been implicated in increasing the levels of HDL and LDL cholesterol fractions, as well as adverse effects, such as urinary tract and genitourinary infections.[6–8]

EMPA-REG OUTCOME study and its implications

Empagliflozin is one of the recently introduced Flozin drugs found to be an effective agent for managing diabetes and CV events in clinical trials. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess Glucose (EMPA-REG OUTCOME®) trial evaluated the efficacy and safety of the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin that reduced glycated

haemoglobin (HbA1c); however, it did not increase the frequency of hypoglycaemic adverse events even when used in combination with insulin.[9]

The findings of EMPA-REG OUTCOME® were remarkable, and for the first time, a glucose-lowering agent, empagliflozin, was found to reduce major adverse CV events along with cardiovascular mortality, hospitalization for heart failure, and overall mortality when administered in combination with the standard care in type 2 diabetic patients with high CV risk. Interestingly, the EMPA-REG OUTCOME study was premeditated to assess the CV safety of empagliflozin and not to assess its glucose-lowering effects or how glucose-lowering affects cardiovascular outcomes. Over 7 thousand patients with type 2 diabetes and CV disease took part in the trial. The following were assessed during the trial:

- Primary outcome — death from CV causes, non-fatal myocardial infarction (excluding silent myocardial infarction) or non-fatal stroke;
- Secondary outcome- hospitalization for unstable angina;
- Additional changes in parameters as compared to baseline values: HbA1c levels, weight, WHR, blood pressure, heart rate, LDL and HDL cholesterol levels and uric acid levels

The primary endpoint occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group (10 mg and 25 mg doses) and 282 of 2333 patients (12.1%) in the placebo group, resulting in a 14% relative risk reduction for the primary composite 3-point major adverse cardiovascular events (MACE) of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke in patients receiving empagliflozin compared with those receiving placebo (HR, 0.86; 95.02% CI, 0.74-0.99; P <.001 for noninferiority). With no significant decrease in the relative risk of stroke or myocardial infarction, the MACE risk reduction was primarily driven by a 38% relative risk reduction in cardiovascular death (HR, 0.62; 95% CI, 0.49-0.77; P <.001). In addition, there was a 32% relative risk reduction in all-cause mortality (HR, 0.68; 95% CI, 0.57-0.82; P <.001) and a 35% relative risk reduction in the incidence of hospitalization for heart failure (HR, 0.65; 95% CI, 0.50-0.85; P ¼ .002). An analysis of secondary microvascular outcomes demonstrated that patients on empagliflozin experienced slower progression of kidney disease and a lower risk of progressing to macroalbuminuria than those on placebo.[10] The EMPA-REG outcome study also proved the safety profile of empagliflozin. However, the variance in the primary outcome became evident approximately 3 months after starting empagliflozin, thus making it highly unlikely that empagliflozin's cardioprotective mechanism is related to glucose-lowering or anti-atherosclerotic effects of the drug. Several potential mechanisms of action have been proposed to explain the cardiovascular benefits of empagliflozin since the completion of EMPA-REG OUTCOME, which includes, reductions in HbA1c, body weight, uric acid, and visceral adiposity; hemodynamic effects, such as reductions of blood pressure and intravascular volume, osmotic diuresis, and sympatholytic; hormonal effects, such as increased glucagon, and effects on the renin-angiotensin-aldosterone system; and fuel energetics, such as a shift from glucose or fatty acids to ketone use.[11]

The results of the EMPA-REG outcome implicated that using empagliflozin saves the life of 1 patient per 39 treated (NNT — the number needed to treat). [2]Also, the valuable effect of empagliflozin occurred irrespectively of how well glycemia was controlled. Diabetes management has undergone a paradigm shift after this study.

The pertinent take-away messages from EMPA-REG OUTCOME that are relevant to

practitioners caring for individuals with type 2 diabetes and pre-existing CV disease are-

- It is essential to identify patients with type 2 diabetes at high risk for CV disease. It should be considered the first step in the management of type 2 diabetes.
- Prevention of cardiovascular morbidity and mortality should be one of the critical strategies for the management of type 2 diabetes.
- There is a need for in-depth clinical evaluation of other SGLT2 inhibitors to establishing the beneficial effects are about empagliflozin specifically and not to the whole class of the SGLT2 inhibitors.
- Beneficial effects of empagliflozin have been observed when used in combination with standard therapy.

Since the exact mechanism of empagliflozin's cardioprotective effects is still unknown, detailed investigational studies need to be carried out to understand the CV effects of current diabetic management strategies with or without empagliflozin. To resolve this, an interesting hypothesis was given by Ferrarini et al. that explains the cardioprotective effect of empagliflozin.[12] The hypothesis suggests that under mild and persistent conditions of ketonemia, which occurs during SGLT2 inhibitors treatment, β-hydroxybutyric acid is taken up by various organs, including the heart, which results in oxidation of free fatty acids being displaced. As a result, substrate selection increases the transduction of oxygen consumption into cell metabolism at the mitochondrial level. Besides, SGLT2 inhibitors cause haemoconcentration, resulting in enhanced oxygen release to the tissues, resulting in strong synergy with the metabolic substrate. These cell mechanisms seem to work in conjunction to result in the observed clinical effects viz., increased diuresis and reduced blood pressure; thereby exerting the protective CV effect that was observed during the EMPA-REG OUTCOME trial.[12]

CONCLUSIONS

Poor glycaemic control has contributed tremendously to the burden of diabetic complications and mortality, especially those related to cardiovascular disease. However, aggressive glycaemic management often leads to the complication of hypoglycemia that has been implicated to enhance the risk of cardiovascular disease in type 2 diabetes patients. However, only a few of the available hypoglycaemic agents have shown benefits in reducing cardiovascular risks. When administered with standard therapy, Empagliflozin shows promising results in a reduction in adverse cardiovascular outcomes. The results from the EMPA-REG OUTCOME study have completely rekindled enthusiasm for tackling residual cardiovascular risk in patients with type 2 diabetes. However, detailed investigation to understand the mechanism of the cardioprotective effect of the empagliflozin needs to be done for better and more comprehensive management of type 2 diabetes patients with CV risk. The EMPA-REG OUTCOME study's findings emphasize that the prevention of cardiovascular morbidity and mortality should be one of the primary objectives for the management of type 2 diabetes.

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