Section: General Medicine

Original Research Article

A RANDOMIZED CLINICAL STUDY TO EVALUATE THE ROLE OF EMPAGLIFLOGIN (SGLT 2 RECEPTOR INHIBITOR) ON MORTALITY AND MORBIDITY OWING TO HEART FAILURE IN TYPE 2 DIABETES MELLITUS

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Abstract

Background: The aim of the present study was to evaluate the role of empagliflogin (sglt 2 receptor inhibitor) on mortality and morbidity owing to heart failure in type 2 diabetes mellitus cases. **Materials & Methods**: The present randomized clinical study was conducted by the Department of Pharmacology, MGM Medical College. A total of 250 patients were included in the study. **Results**: There were no significant differences in MI or stroke rates across groups. The empagliflozin and placebo groups showed similar rates of adverse events, severe adverse events, and study medication discontinuation. Pooled empagliflozin patients had more genital infections. The two trial groups had identical rates of hypoglycemia adverse events, acute renal failure, diabetic keto- acidosis, thromboembolic events, bone fracture, and volume depletion. **Conclusion**: In conclusion, adding empagliflozin to standard care in type 2 diabetics at high risk for cardiovascular events significantly reduced the primary composite cardiovascular outcome and death from any cause compared to the placebo group.

INTRODUCTION

Diabetes mellitus type 2 (T2DM) is a rapidly expanding metabolic condition that impacts more than 400 million individuals globally.[1] The rising prevalence of T2DM is directly linked to the global increase in obesity, which is a major contributing factor. The underlying mechanism of T2DM is mostly associated with the reduced responsiveness of cells to insulin, resulting in high blood sugar levels and a progressive decline in the capacity of β-cells to generate insulin. In addition, the development of type 2 diabetes mellitus (T2DM) is also influenced by pancreatic α-cell failure, increased hepatic glucose output, reduced incretin action, increased renal glucose reabsorption, and neurotransmitter dysregulation in the central nervous system.[2] The condition is highly correlated with both small and large blood vessel problems. Cardiovascular disorders, particularly heart failure, impose the most significant financial burden on healthcare and have the biggest effect on death among those with diabetes.[3]

The CHARM trial found that there is a 25% higher risk of cardiovascular events or death in people with type 2 diabetes mellitus (T2DM) for every 1% increase in glycosylated haemoglobin A1c (HbA1c).[4] The strong connection between diabetes mellitus and heart failure (HF) is due to the harmful impact of key disease-causing factors: continuous exposure to high levels of glucose (glucotoxicity) and fats (lipotoxicity), as well as changes in the way insulin functions in the body (altered insulin signalling). Myocardial structural and functional damage occurs as a result of oxidative stress, heightened production of advanced glycation end products, disrupted regulation of intracellular calcium, impaired endothelial function, and inflammation.[5] The European Society of Cardiology (ESC) recently published guidelines for 2021 that define heart failure (HF) as a clinical syndrome characterised by specific symptoms such as difficulty breathing, fatigue, and swelling in the ankles. These symptoms may be accompanied by

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signs such as increased pressure in the jugular veins, crackling sounds in the lungs, or swelling in the extremities. The underlying cause of HF is typically a structural or functional abnormality of the heart, which leads to increased pressure within the heart and/or inadequate blood flow during both rest and physical activity.

HF is primarily caused by inefficiency in the contraction and relaxation of the heart muscle. However, abnormalities in the heart valves, endocardium, pericardium, or irregular heart rhythms can also contribute to the development of the condition.6 Heart failure (HF) is frequently observed in people with type 2 diabetes mellitus (T2DM), and its current prevalence is predicted to exceed 64 million instances.[7] This emphasises the significance of maintaining strict control over blood sugar levels in individuals with type 2 diabetes mellitus, as well as the management of cardiovascular health. Although metformin (MET) appears to have cardioprotective benefits, other conventional antidiabetic medications have neutral or even detrimental effects on cardiovascular outcomes.[8] There is strong evidence indicating that saxagliptin and alogliptin should not be used in individuals with heart failure, whereas pioglitazone is absolutely not recommended.[9]

While glucagon-like peptide-1 (GLP1) receptor agonists have been shown to decrease the likelihood of myocardial infarction (MI), stroke, and cardiovascular (CV) mortality in individuals with type 2 diabetes mellitus (T2DM), they are not advised for the prevention of heart failure (HF) events.[6] Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are a novel type of medication used to treat diabetes. They work by blocking the absorption of glucose in the renal proximal tubules, leading to the excretion of glucose in the urine. This mechanism helps to improve control over blood sugar levels.[10] SGLT2 inhibitors have also shown cardiovascular advantages, particularly in the management of heart failure. Canagliflozin (CANA) effectively regulated blood sugar levels and decreased HbA1c, making it the first SGLT2 inhibitor authorised by the Food and Drug Administration (FDA) in 2013. In addition, the Canagliflozin Cardiovascular Assessment Study (CANVAS) showed that CANA has the ability to decrease the likelihood of cardiovascular complications in patients with type 2 diabetes mellitus (T2DM), such as non-fatal stroke, non-fatal myocardial infarction, and heart failure management. This study further emphasises the cardioprotective properties of SGLT2 inhibitors and their role in the treatment of T2DM, when used alongside first-line treatment with metformin (MET).[11]

The objective of this study was to assess the impact of empagliflozin (an inhibitor of the SGLT2 receptor) on the occurrence of death and disease related to heart failure in individuals with type 2 diabetes mellitus.

MATERIALS AND METHODS

The current investigation was carried out in the Department of Pharmacology, MGM Medical College. The research comprised a total of 250 patients. The occurrence of cardiovascular outcome events and fatalities was determined in advance by two clinical-events committees, one specialising in cardiac events and the other in neurologic events, in accordance with the standards set out by the Food and Drug Administration (FDA).

Methodology

This study was a randomised, double-blind, placebo-controlled trial that aimed to evaluate the impact of once-daily empagliflozin (at either a 10 mg or 25 mg dosage) compared to a placebo on cardiovascular events in individuals diagnosed with type 2 diabetes who are at a high risk for cardiovascular problems. The study was conducted alongside routine therapy.

Acquire knowledge through systematic learning and examination. Individuals seeking medical treatment

The eligible participants for this study were adults (≥18 years old) with type 2 diabetes, a body-mass index (BMI) of 45 or less, and an estimated glomerular filtration rate (eGFR) of at least 30 ml per minute per 1.73 m2 of body-surface area, as determined by the Modification of Diet in Renal Disease criteria.

All patients included in the study had pre-existing cardiovascular disease and had not taken any medications to lower their blood sugar for a minimum of 12 weeks prior to being randomly assigned. Additionally, their glycated haemoglobin levels were between 7.0% and 9.0%, or if they were on stable glucose-lowering therapy, their glycated haemoglobin levels were between 7.0% and 10.0%.

Research Protocols

Patients who met the criteria were subjected to a 2-week period where they received a placebo and their existing glucose-lowering treatment remained the same. Patients who met the specific requirements were then randomly divided into three groups, with an equal number of patients in each group. One group received a daily dose of 10 mg of empagliflozin, another group received a daily dose of 25 mg of empagliflozin, and the third group received a placebo. The randomisation process utilised a computer-generated random-sequence and an interactive voice- and web-response system. Stratification was based on the glycated haemoglobin level at screening (<8.5% or ≥8.5%), body-mass index at randomisation (<30 or ≥30), and renal function at screening (eGFR, 30 to 59 ml, 60 to 89 ml, or ≥90 ml per minute per 1.73 m2).

During the trial, investigators were advised to address other cardiovascular risk factors such as dyslipidaemia and hypertension in order to provide the highest quality of treatment in accordance with local recommendations. Patients were directed to visit the clinic at predetermined intervals, which

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included a follow-up appointment 30 days after completing the treatment. Patients who stopped taking the research medicine before the trial ended were monitored to see if they experienced any cardiovascular issues. Efforts were made to gather information about the vital status of patients who could not be followed up on, as permitted by local standards.

Statistical Analysis

The statistical analysis of the data was carried out using SPSS version 22.

RESULTS

There were no significant between-group differences in the occurrence of myocardial infarction or stroke. [Table 1]

The proportions of patients who had adverse events, serious adverse events, and adverse events leading to the discontinuation of a study drug were similar in the empagliflozin group and the placebo group. Genital infection was reported in a higher percentage of patients in the pooled empagliflozin group. The proportions of patients with confirmed hypoglycemic adverse events, acute renal failure, diabetic ketoacidosis, thromboembolic events, bone fracture, and events consistent with volume depletion were similar in the two study groups. [Table 2]

Table 1: Primary and Secondary Cardiovascular Outcomes

Outcome	Placebo (N=50)	Empagliflozin(N=200)	HazardRatio(95 % CI)	PValue
Deathfromcardiovascularcauses,nonfatalmyocar-dialinfarction,ornonfatalstroke:primary outcome	6	20	0.86(0.74–0.99)	<0.001
Deathfromcardiovascularcauses,nonfatalmyo-cardialinfarction,nonfatalstroke,orhospitalizationforunstableangina:keysecondary outcome*	7	24	0.89(0.78–1.01)	<0.001
Death				
Fromanycause	4	10	0.68(0.57–0.82)	<0.001
Fromcardiovascularcauses	3	6	0.62(0.49–0.77)	<0.001
Fatalornonfatalmyocardialinfarctionexcluding silent myocardial infarction	3	8	0.87(0.70–1.09)	0.23
Nonfatalmyocardialinfarctionexcludingsilent myocardialinfarction	3	10	0.87(0.70–1.09)	0.22
Silentmyocardialinfarction‡	1	3	1.28(0.70–2.33)	0.42
Hospitalizationforunstableangina	1	4	0.99(0.74–1.34)	0.97
Coronaryrevascularizationprocedure	4	14	0.86(0.72–1.04)	0.11
Fatalornonfatalstroke	1	6	1.18(0.89–1.56)	0.26
Nonfatalstroke	1	6	1.24(0.92–1.67)	0.16
Transientischemicattack	1	2	0.85(0.51–1.42)	0.54
Hospitalizationforheartfailure	8	4	0.65(0.50–0.85)	0.002
Hospitalizationforheartfailureordeathfromcar-diovascularcausesexcludingfatalstroke	4	10	0.66(0.55–0.79)	<0.001

Table 2: Adverse Events

Event	Placebo (N=50)	Pooled Empagliflozin(N=200)
Anyadverseevent	45	180
Severeadverseevent Seriousadverseevent	12	47
Any	22	77
Death	2	7
Adverse event leading to discontinuation of a studydrug	10	34
Confirmedhypoglycemicadverseevent		
Any	14	55
Requiringassistance	1	2
Eventconsistentwithurinarytractinfection	9	35
Malepatients	5	20
Femalepatients	20	70
Complicatedurinarytractinfection**	1	3
Eventconsistentwithgenitalinfection††	1	12
Malepatients	1	9
Femalepatients	1	20
Eventconsistentwithvolumedepletion	2	10
Acuterenalfailure	3	10
Acutekidneyinjury	1	2
Diabeticketoacidosis	1	2
Thromboembolicevent	1	2
Bonefracture	2	6

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DISCUSSION

Type 2 diabetes significantly increases the likelihood of developing cardiovascular disease.[12,13] The risk of mortality is elevated when both type 2 diabetes and cardiovascular disease are present.14 The available evidence does not conclusively demonstrate that reducing glucose levels lowers the occurrence of cardiovascular events and mortality,[15-17] while a little cardiovascular benefit may be found over a long-term period of monitoring.18 Moreover, there is apprehension that aggressive glucose reduction or the administration of particular glucose-lowering medications may be linked to unfavourable cardiovascular consequences.[19] Therefore, it is imperative to ascertain the cardiovascular safety advantages of glucose-lowering medications.[20]

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are a novel type of medication for diabetes that work by blocking the absorption of glucose in the renal proximal tubules, leading to the excretion of glucose in the urine and thereby improving blood sugar management.[21] SGLT2 inhibitors have also shown cardiovascular advantages, particularly in the management of heart failure. Canagliflozin (CANA) effectively regulated blood sugar levels and decreased HbA1c, making it the first SGLT2 inhibitor authorised by the Food and Drug Administration (FDA) in 2013. In addition, the Canagliflozin Cardiovascular Assessment Study (CANVAS) showed that CANA has the ability to decrease the likelihood of cardiovascular complications in patients with type 2 diabetes mellitus (T2DM). These complications include non-fatal stroke, non-fatal myocardial infarction (MI), and heart failure (HF) management. This study further emphasises the cardioprotective properties of SGLT2 inhibitors (SGLT2i) and their role in the treatment of T2DM, when used alongside first-line treatment with metformin (MET).[22] There were no notable differences between the groups in terms of the occurrence of myocardial infarction or stroke. The incidence rates of adverse events, major adverse events, and adverse events resulting in the cessation of the study treatment were comparable between the empagliflozin group and the placebo group. A larger proportion of patients in the combined empagliflozin group reported genital infection. The incidence of patients experiencing hypoglycemia adverse events, acute renal failure, diabetic ketoacidosis, thromboembolic events, bone fracture, and events associated with volume depletion were comparable across the two research groups.

The EMPA-REG MONO study, conducted from 2010 to 2012, evaluated the effectiveness and safety of EMPA monotherapy in 899 individuals with treatment-naïve type 2 diabetes mellitus (T2DM). Subjects were administered EMPA at dosages of either 10 or 25 mg, while a placebo and 100 mg of sitagliptin were employed as an active comparator. This treatment was given once daily for a duration of 24 weeks, with a 1:1:1:1 ratio. The adjusted mean differences in the change from the initial HbA1c level compared to a placebo were -0.74% and -0.85% for 10 mg and 25 mg of EMPA, respectively. Sitagliptin had a decrease of -0.73%. Patients with elevated blood sugar levels saw a more significant decrease in HbA1c when administered EMPA. The reduction in fasting plasma glucose (FPG) levels compared to the first measurement was -1.08 and -1.36 for EMPA at dosages of 10 and 25 mg, respectively. In contrast, sitagliptin did not provide as substantial of a drop in FPG levels (-0.38). The overall tolerability of EMPA was satisfactory.[23] Häring et al24 conducted a 24-week trial to examine the impact of EMPA when used in addition to MET therapy in patients who were not well managed with a 1500 mg dose of MET. A total of 637 individuals were administered either 10 or 25 mg of EMPA or a placebo once day, in addition to their current MET medication. At the 24th week, the adjusted average reductions in HbA1c levels from the initial levels were -0.57% and -0.64% for EMPA dosages of 10 mg and 25 mg, respectively. Patients saw a decrease in fasting plasma glucose (FPG) levels: 0.35, -1.11, and -1.[24] for the placebo, 10 mg EMPA, and 25 mg EMPA groups, respectively. The study determined that EMPA was a secure and feasible supplement to MET.

CONCLUSION

Patients diagnosed with type 2 diabetes who are at a high risk for cardiovascular events and were treated with empagliflozin experienced significantly reduced rates of primary composite cardiovascular outcomes and mortality compared to those who received a placebo alongside standard care.

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