VOLUME - 11, ISSUE - 04, APRIL - 2022 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

General Medicine

EFFECTS OF LINAGLIPTIN ON HEART FAILURE AND RELATED OUTCOME IN TYPE 2 DIABETES PATIENTS WITH HIGH CARDIOVASCULAR AND RENAL RISK IN CREMELINA

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ABSTRACT Cardiovascular disease (CVD) and chronic kidney disease (CKD) are leading causes of morbidity and mortality in patients with type 2 diabetes mellitus. Individuals with type 2 diabetes mellitus are also at increased risk of hospitalization due to heart failure. In addition, the presence of CKD in patients with type 2 diabetes mellitus is associated with an increased risk of both all-cause and CV mortality. Therefore, the CV safety of glucose-lowering therapies has become an important consideration. Dipeptidyl peptidase-4 inhibitors (DPP-4i) are a modern class of glucose-lowering drugs that are considered well-tolerated. CARMELINA (The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin) was designed to evaluate linagliptin's cardiovascular safety and kidney outcomes in people with T2DM at high cardiovascular and renal risk. This paper discusses the outcome of the CARMELINA study regarding heartfailure and other cardiovascular outcomes in type 2 diabetes patients with increased cardiovascular and renal risk.

KEYWORDS :

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is commonly complicated by atherosclerotic cardiovascular disease (ASCVD) and chronic kidney disease. Further, such individuals are at increased risk for heart failure (HF), particularly those with coexisting atherosclerotic cardiovascular disease and kidney disease.[1] Thus, the study of glucose-lowering medications for type 2 diabetes has evolved from prioritizing glycaemic control to assessing the relative cardiovascular (CV) risks and benefits in people with type 2 diabetes mellitus and established CV disease. As a result, there have been important updates to treatment guidelines and recommendations globally. Yet, despite a clear advancement in CV risk management, few studies have assessed the use of glucose-lowering medications in those with type 2 diabetes mellitus who suffer chronic kidney disease (CKD).

However, some dedicated studies have been over the last few years reported. Up to 40% of people with type 2 diabetes mellitus will develop CKD, which is associated with reduced quality of life and lower glycaemic goal attainment. A substantial number of people develop nephrotic-range proteinuria (NRP) or the nephrotic syndrome, and these people are at exceptionally high risk of progression to end-stage kidney disease (ESKD).[2] Moreover, the choice of glucose-lowering therapies is limited in lower ranges of kidney function due to drug accumulation and side effects, as is the data on the safety and efficacy of glucose-lowering therapies in people with type 2 diabetes and NRP, since the majority of recent CV outcome trials in type 2 diabetes do not include people with NRP.[2]

It is well established that the increased risk for HF is exceptionally high in people with coexisting chronic kidney disease or with pre-existing HF.[1] Resultantly, since 2008, the U.S. FDA and regulatory agencies around the world have required that all medications being developed for glucose control in type 2 diabetes undergo a formal clinical trial evaluation to prove CV safety. This resulted in a series of international mega-trials over the past decade with the primary focus of CV assessment of such medications. The large scale clinical trials have been primarily focused on three new classes of diabetes drugs: the dipeptidyl peptidase (DPP) 4 inhibitors (DPP4is); glucagon-like peptide 1 receptor agonists (GLP1-RAs); and sodium-glucose cotransporter 2 inhibitors (SGLT2is).

Clinical Trials With Dipeptidyl Peptidase Inhibitors For Cardiovascular Safety In Type 2 Diabetes Patients

DPP4i are a relatively new class of oral anti-hyperglycaemic drugs to treat type 2 diabetes. Their anti-hyperglycemic effect is achieved through the prevention of degradation of incretin hormones [mainly glucagon-like peptide 1 (GLP1)] by dipeptidyl peptidase-4 (DPP4). GLP1 improves meal stimulated insulin secretion by pancreatic β cells, reducing hyperglycaemia. DPP4i are not associated with weight gain or an excess risk of hypoglycaemia1 and may therefore serve as an alternative to sulfonyl-urea derivatives and may delay insulin use in type 2 diabetes as add-on therapy, especially for people who have contraindications for other glucose-lowering drugs, such as metformin, sodium-glucose reuptake inhibitors (SGLT2i) or GLP1 analogues.[3]

The four DPP4i that have been widely evaluated for the management of type 2 diabetes along with CV risk are sitagliptin, saxagliptin, alogliptin, and linagliptin. Although initial smaller studies suggested that DPP4i may confer cardiovascular protection, the large trials evaluating the DPP4i alogliptin [Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial],[4] sitagliptin [Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trial][5]and saxagliptin [Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) trial][6] showed no obvious benefits with regard to cardiovascular protection compared to the control arm of these studies, and in fact concerns for an elevated risk of heart failure were raised for saxagliptin. These findings

underline the importance of large clinical trials by showing that a weighted sum of smaller trials may sometimes yield a different result than a large multi-centre trial.[7]

Thus, across these trials, there has been heterogeneity with regard to the effects of the 3 DPP-4 inhibitors on the risk of hospitalization HF, ranging from no impact with sitagliptin, the numeric imbalance that was not statistically significant with alogliptin, and statistically significant increased risk with saxagliptin. In a pooled analysis including data from the three pivotal CVOTs with saxagliptin, alogliptin, and sitagliptin, the overall hospitalization HF risk was not significantly different (hazard ratio [HR], 1.14; 95% CI, 0.97–1.34), but because of heterogeneity across the trials, a meta-analytic approach to this matter is of uncertain validity.[1]

The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA)

Linagliptin, an FDA approved DPP-4i for the glycaemic management of type 2 diabetes, does not require dose adjustment in people with CKD as it is 85% eliminated via biliary excretion.[8]

Linagliptin demonstrated glycaemic efficacy and tolerability in people aged ≥70 years in a dedicated phase III randomized clinical trial and a pooled analysis of participants aged ≥65 years from this study and six other phase III trials in individuals aged 18–80 years.[9] CARMELINA was designed to evaluate cardiovascular safety and kidney outcomes.[1]

In this study, CV and kidney safety of Linagliptin were confirmed wherein 6979 individuals with CKD [3000 with estimated glomerular filtration rate (eGFR) 300 mg/g participated in the trial. Linagliptin also reduced albuminuria progression and glycated haemoglobin A1c (HbA1c), regardless of eGFR at baseline (BL), including in those with eGFR< 30 mL/min/1.73m^2.[2] The average glycaemic control improved by 0.36% in the CARMELINA trial, without associated weight gain and no increased risk of hypoglycaemia. CARMELINA, therefore, confirms that DPP4i only achieve modest effects on glucose control compared to usual care, even in the setting of high renal and cardiovascular risk, where clinicians tend to be more careful in achieving a glycaemic target in fear of hypoglycaemia and other adverse events. CARMELINA trial included an analysis of heart failure risk and reassuringly found once more no signal for an increased risk of heart failure associated with Linagliptin use, even among participants with a history of heart failure, CKD and independently of left ventricular ejection fraction. The CARMELINA trial was particularly suitable for this issue, as 26.8% of individuals already had established heart failure at baseline.[3]

In individuals with type 2 diabetes and prevalent atherosclerotic cardiovascular disease (ASCVD) or kidney disease participating in CARMELINA, Linagliptin compared with placebo did not affect the risk for HF or the composite outcomes of HF hospitalization for or cardiovascular death or hospitalization for HF or all-cause death outcomes. There was also no difference between the randomized groups in the risk of hospitalization for HF in subgroups of participants with or without a history of HF at baseline.[1] Further, Linagliptin did not increase the risk for cardiovascular events or hypoglycaemia, and kidney function remained stable in older people (~65-75years of age) with type 2 diabetes and established CVD with albuminuria and kidney disease.[10] The hazard ratio (HR) for 3P-MACE with linagliptin versus placebo was 1.02 [95% confidence interval (CI) 0.89, 1.17] with no significant interaction between age and treatment effect (P = 0.0937). The incidence of adverse events, including hypoglycaemia, increased with age but was similar with Linagliptin and placebo despite glycated haemoglobin A1c reduction with Linagliptin. Furthermore, Linagliptin improved glycaemic control compared with placebo in all age groups without increasing the risk of hypoglycaemia or most other adverse events. Chronic kidney disease is highly prevalent among older people with T2D. CARMELINA studied an enriched study population for kidney disease and was thus able to evaluate kidney outcomes robustly. With no increase in adverse kidney events, Linagliptin exhibited renal safety in all age groups, including older participants who had reduced kidney function (mean eGFR of approximately 45–50 mL/min/1.73 m^2), advancing the evidence base in this more ageing population.[10]

A substantial number of people develop nephrotic-range proteinuria (NRP) or nephrotic syndrome. In CARMELINA, no increase in risk for HF in NRP and type 2 diabetic patients was observed. This differs from a previous trial with another DPP-4i that indicated an increased risk of hospitalization for HF. Linagliptin was well tolerated in this particularly frail population, and its safety profile was comparable to that of placebo.[2] Linagliptin is the only globally available DPP-4i that is not primarily excreted by the kidneys and hence does not require dosage adjustment for patients with kidney disease.[10] These results indicate the probability of heterogeneity across the DPP4i class of anti-diabetic drugs regarding effects on the risk for HF outcomes, with Linagliptin and Sitagliptin having no effects, while Saxagliptin has no effects increasing risk and ongoing uncertainty with regard to the effects of Alogliptin on HF risk.[1]

However, reassuringly, Linagliptin has proven to be a safe drug with low risk for HF in type 2 diabetes patients across all patient groups.

CONCLUSION

CARMELINA results demonstrate that linagliptin did not affect the risk for hospitalization for HF or related HF outcomes, overall or across selected subgroups of interest. This study has opened up a safe therapeutic modality for type 2 diabetes, providing a modest overall reduction of HbA1c without increasing the risk for cardivascular diabetic complications, even in renal complications.

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