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LINAGLIPTIN: A DPP-4 INHIBITOR FOR THE POTENTIAL TREATMENT OF HEART FAILURE IN TYPE-2 DIABETIC PATIENTS

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ABSTRACT

A series of metabolic illnesses known as diabetes mellitus are characterised by chronic hyperglycemia brought on by deficiencies in insulin secretion, insulin action, or both. DPP-4 inhibitors, known as gliptins, are a class of oral diabetic medications approved by the Food and Drug Administration (FDA) to treat type 2 diabetes mellitus in adults. DPP-4 is a ubiquitous enzyme that acts on incretin hormones, mainly GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory peptide), which maintain glucose homeostasis by increasing insulin secretion and decreasing glucagon secretion. Linagliptin is a DPP-4 inhibitor that was recently approved as a once-daily oral glucose-lowering drug in the USA, Japan, and Europe. Diastolic dysfunction (DD) is one of the early manifestations of CVD in insulin resistant conditions, such as obesity and T2DM and can be identified clinically by echocardiographic findings. Linagliptin-treated rats exhibited significant improvement in impaired LV diastolic function, as well as endothelial function of gastrocnemius feed arteries, and, somewhat surprisingly, this was associated with a reduction in BP. Both pre-clinical and clinical studies have shown beneficial effects of linagliptin on CV dysfunction associated with obesity and diabetes. Blood pressure (BP) responses to DPP-4 inhibitor therapy in humans are either neutral or modestly reduced. There was no heterogeneity of linagliptin effects on baseline estimated glomerular filtration rate or urine albumin-creatinine ratio, or prerandomization left ventricular ejection fraction. Linagliptin has positive benefits on the cardiovascular system beyond those associated with class effects and glycemic management.

KEYWORDS: Linagliptin, DPP-4 Inhibitor, Gliptins, Diabetes, Heart failure.

INTRODUCTION

With 336 million people globally currently suffering from Diabetes Mellitus (DM), with that figure anticipated to climb to 439 to 552 million by 2030, India is the diabetes epicentre.[1] Chronic hyperglycemia, which is a hallmark of a group of metabolic diseases collectively known as diabetes mellitus, is brought on by deficits in insulin secretion, insulin action, or both. The importance of insulin as an anabolic hormone results in abnormalities in the metabolism of proteins, lipids, and carbohydrates. These metabolic disorders are caused by target tissues, principally skeletal muscle, adipose tissue, and to a lesser extent, the liver, developing insulin resistance at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes.[2] The resulting glucotoxicity may have long-term effects, such as a rise in macrovascular disease and microvascular sickness (such as neuropathy, nephropathy, and retinopathy) (such as cardiovascular, cerebral and peripheral vascular diseases).[3] Chronic hyperglycemia and duration of diabetes are the key risk factors for the development of micro- and macrovascular complications of diabetes.[4] The fact that DM rates are increasing and its relative risk as a CVD risk factor isn't declining is likely what has led to the increased significance of DM as a CVD risk factor.[5]

ASSOCIATION OF DIABETES WITH CVD

Artherosclerosis(AS): AS-CVD is a "perfect storm" of cellular and molecular pathophysiologic variables that leads to atherosclerosis. In comparison to persons without diabetes, patients with type 2 diabetes have a higher atherosclerotic plaque burden, a higher atheroma volume, and a smaller coronary artery lumen diameter.[6]

Hyperglycemia: There is a strong epidemiologic link between hyperglycemia and a higher risk of cardiovascular disease. With an estimated 11–16% increase in cardiovascular events for every 1% increase in HbA1c, there is solid evidence suggesting a higher risk for ASCVD with rising dysglycemia.[7]

Insulin resistance: Insulin resistance is highly linked to cardiovascular risk in people according to epidemiologic data. Increased rates of hypertension, dyslipidemia, and reduced glucose tolerance are observed in individuals with insulin resistance.[8]

Diabetes dyslipidaemia: Most type 2 diabetes patients have dyslipidemia, a condition marked by high triglycerides, low HDL-C, and a predominance of tiny, dense LDL

particles.[7] Triglyceride elevation causes free fatty acid elevation, which may result in insulin resistance and dysfunctional cells.[9]

DIPEPTIDYL PEPTIDASE -4 INHIBITORS

Gliptins are a class of oral diabetes drugs that have been given the Food and Drug Administration's (FDA) approval to treat adults with type 2 diabetes mellitus.

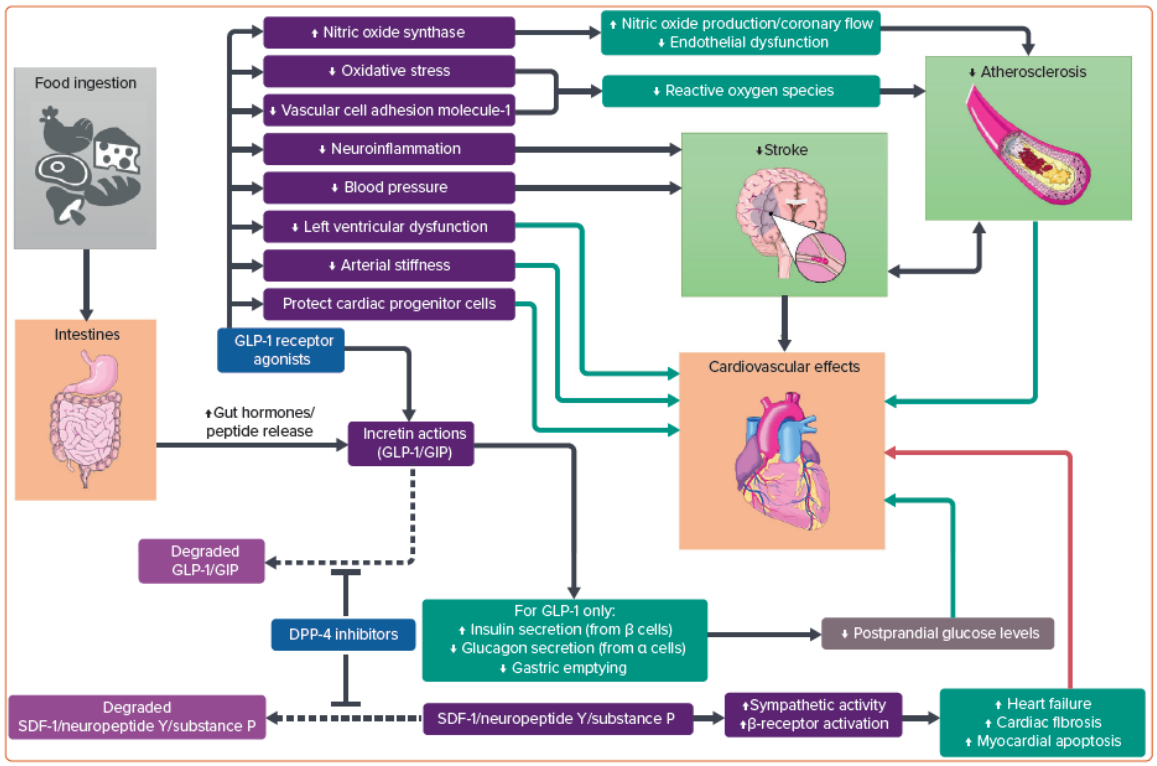
These medications work by activating incretin hormones, which are gut hormones in charge of maintaining glucose homeostasis following oral food ingestion. This class of medications has antihyperglycemic actions in addition to antihypertensive, anti-inflammatory, anti-apoptotic, and immunomodulatory effects on the heart, kidneys, and blood vessels that are not dependent on the incretin pathway.[10]

MECHANISM OF ACTION

The incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory peptide), which increase insulin secretion and decrease glucagon secretion to maintain glucose homeostasis, are primarily affected by the ubiquitous enzyme DPP-4. Based on their structural similarities to the DPP-4 molecule (peptidomimetics, vildagliptin, and saxagliptin), the DPP-4 inhibitors can be separated into those that do and those that do not (non-peptidomimetics, sitagliptin, alogliptin, linagliptin).[12]

Non-peptidomimetics inhibit DPP-4 substrates quickly and effectively by forming non-covalent extracellular contacts with residues in the catalytic region. In contrast, peptidomimetics inhibit the activity of the DPP-4 substrate by creating a reversible covalent enzyme-inhibitor complex. Despite the drug's inactivation, the complex's highly delayed binding to and dissociation from the DPP-4 substrate's catalytic site results in chronic DPP-4 inhibition. This may help to explain why vildagliptin and saxagliptin suppress DPP-4 activity for longer than their relatively short half-lives would predict. It means that the catalytic activity stays inhibited even after the free medication has been removed from the circulation. The particular DPP-4 inhibitors extracellularly inhibit DPP-4. Because the inactivation is extracellular, major intracellular proteins continue to operate, which explains why there hasn't been any immunological malfunction if those proteins had been impacted.[13]

Figure 2: Incretin Physiology and Mechanisms of Action of DPP-4 Inhibitors and GLP-1 Receptor Agonists



Green lines = beneficial mechanisms; red lines = harmful mechanisms; dotted lines= degradation pathways. Dipeptidyl peptidase-4; GIP = gastric inhibitory polypeptide; GLP = glucagon-like peptide; SDF = stromal-cell-derived factor.

Fig 1: Mechanism of action of DPP-4 Inhibitors and GLP-1 Receptor Agonists.

LINAGLIPTIN

Recently, the US, Japan, and Europe approved the DPP-4 inhibitor linagliptin as a once-daily oral glucose-lowering medication. Its molecular structure is different from other DPP-4 inhibitors in that it is xanthine-based. In contrast to other DPP-4 inhibitors, linagliptin is primarily excreted through the bile and the gut, and it has potent and long-lasting DPP-4 inhibition (maximal inhibition of > 90% and inhibition 24 h after dosing of 85% with linagliptin 5 mg at steady state). Linagliptin's pharmacokinetic properties also confer a prolonged terminal half-life (t1/2 > 100 h), and these properties also confer.[14,15,16]

Different DPP-4 inhibitors' CV beneficial effects have recently been studied.[17,18,19]

Notable characteristics include the DPP-4 inhibitor linagliptin's distinctive kinetics, chemical make-up, and strong direct effects on the vasculature. Recent CV outcome studies using DPP-4 inhibitors (CAROLINA AND CARMELINA) offer proof that incretin-based treatments have respectable CV safety profiles for T2DM patients.[20]

CARDIO VASCULAR PROTECTION BY LINAGLIPTIN

Linagliptin has been demonstrated to have positive effects on CV dysfunction linked to diabetes and obesity in both pre-clinical and clinical investigations. These advantages include a reduction in arterial stiffness, endothelial dysfunction, immunological and inflammatory response, diastolic dysfunction, atherosclerosis, coronary artery disease (CAD), myocardial infarction, hypertension, and stroke.[21]

HEART FAILURE AND DIASTOLIC DYSFUNCTION

Diastolic dysfunction (DD), which can be clinically diagnosed by echocardiographic abnormalities, is one of the early CVD presentations in insulin resistant diseases including obesity and T2DM.[22] DD also independently predicts future CV events, the progression to systolic HF, and CV mortality. Additionally, new research suggests that DD can both predate and predict the advancement of T2DM.[23]

Significantly, preclinical research on DPP-4 inhibitors has suggested that they may help both boys and females with DD.[24,25]

Rats given linagliptin significantly improved their LV diastolic dysfunction as well as the endothelial function of their gastrocnemius feed arteries. Surprisingly, this was also accompanied by a decrease in blood pressure.[26]

DYSLIPIDEMIA

Research suggests that GLP-1 may have beneficial effects on dyslipidemia, and recent small studies with DPP-4 inhibitors have shown favourable effects[27, 28] or a neutral effect[29] on postprandial dyslipidemia in patients with T2DM.

HYPERTENSION AND STROKE

Those with T2DM had twice as much hypertension as those without the disease.[30] Human blood pressure (BP) responses to DPP-4 inhibitor treatment are neutral or little decreased.[31] Given that GLP-1 receptors are found in neurons from rats and humans[32] and that native GLP-1 and GLP-1 analogues easily cross the blood brain barrier[33], it is conceivable that incretin enhancer therapy could be neuroprotective. Additionally, there is proof that linagliptin can improve cerebrovascular structure and function that have been damaged.[34,35] Thus, treating T2DM patients at risk of developing cerebrovascular disease or cognopathy may also take into account the cerebro-protective effects of DPP-4 inhibition.

ENDOTHELIAL DYSFUCNTION AND CVD

Endothelial dysfunction in diabetes mellitus is a result of both insulin resistance and hyperglycemia and is linked to the emergence of both macrovascular and microvascular problems of T2DM.[36,37] Endothelial dysfunction, which is frequently demonstrated by decreased bioavailable NO in response to acetylcholine/insulin-mediated vascular relaxation or impaired flow-mediated vasodilation[38,39], is closely linked to insulin resistance and hyperglycemia in diabetes mellitus. Regarding vascular function, linagliptin has strong nitric oxide-enhancing actions.[40,41]

RENOPROTECTION

There was no heterogeneity of linagliptin effects on prerandomization left ventricular ejection fraction, baseline estimated glomerular filtration rate, urine albumin-creatinine ratio, or kidney outcomes in the ongoing Cardiovascular and Renal Microvascular Outcome study with Linagliptin in patients with T2DM (CARMELINA), which is powered to evaluate kidney outcomes and renoprotective effects of this inhibitor.[42]

CONCLUSION

In both preclinical and clinical models, linagliptin protects against the macrovascular and microvascular consequences of diabetes. Linagliptin has positive benefits on the cardiovascular system beyond those associated with class effects and glycemic management. Further proof that linagliptin can be taken safely, without raising the risk of heart failure, in a high-risk cohort of people with T2DM who also have concurrent atherosclerotic cardiovascular disease and/or kidney disease comes from the CARMELINA study.

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