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CANAGLIFLOZIN: A SGLT-2 INHIBITOR FOR THE TREATMENT OF HEART FAILURE IN TYPE-2 DIABETIC PATIENTS

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ABSTRACT

The increased significance of DM as a cardiovascular disease (CVD) risk factor is probably brought on by the fact that DM rates are rising and its relative risk as a CVD risk factor isn't decreasing. As a new class of anti-diabetic medications for the treatment of type 2 diabetes, canagliflozin, a strong and selective sodium glucose co-transporter 2 inhibitor, canagliflozin 300 mg is currenty in trend and has direct or indirect impacts on non-glycemic parameters in addition to regulating blood sugar. Canagliflozin 300 mg, unlike several AHAs, does not cause weight gain; instead, it has a weight-reduction and average systolic and diastolic blood pressure reductions were 4.7 and 1.9 mmHg, respectively. Treatment with canagliflozin resulted in a significant decrease in blood sugar, total cholesterol, LDL cholesterol, and triglyceride levels. Canagliflozin decreased the likelihood of long-term renal function deterioration, decreased albuminuria excretion, and slowed eGFR decline. Patients with type 2 diabetes mellitus and established cardiovascular disease or at high risk of cardiovascular events who were treated with canagliflozin experienced significantly reduced rates of cardiovascular death or hospitalised HF. Canagliflozin is associated with the alleviation of cardiac stress with improvement of diastolic dysfunction and decreased left ventricle mass (LVM). Canagliflozin has demonstrated cardiac and renal protective effects as well as improving oxidative stress, diastolic function, and endothelial function.

KEYWORDS: Diabetes Mellitus, Canagliflozin, Cardiovascular disease, Heart failure.

INTRODUCTION

India is the diabetes epicentre, with 336 million people worldwide currently suffering from Diabetes Mellitus (DM), with that number expected to rise to 439 to 552 million by 2030.[1] 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. The significance of insulin as an anabolic hormone leads to metabolic irregularities in carbohydrates, lipids, and proteins. These metabolic abnormalities are brought on by insufficient insulin levels to produce an adequate response and/or insulin resistance of target tissues, primarily skeletal muscle, adipose tissue, and to a lesser extent, the liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes.[2]

Long-term consequences, such as microvascular illness (such as neuropathy, nephropathy, and retinopathy), as well as macrovascular disease, can increase as a result of the resulting glucotoxicity (such as cardiovascular, cerebral and peripheral vascular diseases).[3] The main risk factors for the emergence of micro- and macrovascular complications of diabetes are chronic hyperglycemia and length of diabetes.[4] The increased significance of DM as a cardiovascular disease (CVD) risk factor is probably brought on by the fact that DM rates are rising and its relative risk as a CVD risk factor isn't decreasing.[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]

SODIUM GLUCOSE TRANSPORTER

SGLTs are multifunctional proteins behaving as Na+/glucose cotransporters, water and urea channels, glucose sensors, and coupled water and urea transporters.[10]

Two isoforms of SGLT function in the proximal convoluted tubule (PCT) to reabsorb substances.[11] In the proximal tubule's luminal membrane, SGLTs are expressed; SGLT2 is found in the S1/S2 segments while SGLT1 is found in the S3 segment. The Na+ electrochemical potential gradient across the luminal membrane drives glucose uptake into the epithelia, while the facilitated glucose transporter GLUT2 diffuses glucose out into the blood across the basolateral membrane.[12]

The transporter in the plasma membrane is depicted as a double-gated protein, with both gates closed in the absence of ligands. External glucose can bind when external sodium binds to the Na2 site, opening the external gate. The inner gate opens to allow Na+ and glucose to leave into the cytoplasm in one step after the external gate closes following glucose binding to trap the sugar in the centre of the protein. The transporter then moves back to its original position. Overall, sodium and glucose are strictly coupled during one transport cycle across the membrane.[13]

SGLT2 and SGLT1 actively transport glucose across the proximal convoluted tubule (PCT) cells of the kidney with variable capacities.[14] A kinetic model for Na+ and glucose transport by SGLT2 is described in that publication. A high-capacity, low-affinity transporter called SGLT2 is mostly present in the PCT's S1 segment.[15] SGLT2 is only expressed in the kidney and is estimated to be responsible for 90% of reabsorbed glucose. The remaining portion of the filtered glucose is reabsorbable by SGLT1, a low capacity, high-affinity transporter that is located in the more distal S2/S3 region of the PCT.[16,17] By coupling sodium transport with the active transport of glucose across the apical (luminal) membrane, SGLT2 catalyses this process.[17,18] The ATP-driven active extrusion of sodium over the anti-luminal surface into the blood maintains the inward sodium gradient across the luminal epithelium.[15,16] Basolateral (anti-luminal) glucose transporter type 2 (GLUT2; also known as SLC2A2) and

GLUT1 facilitative glucose transporters allow intracellular glucose to diffuse passively out of the cell, down a concentration gradient, and across the anti-luminal membrane into the intercellular space, which is in equilibrium with the blood.[19]

SGLT-2 INHIBITORS

As a new family of antidiabetic medications with an insulin-independent action, sodium glucose transporter 2 (SGLT2) inhibitors provide the significant advantages of boosting urine glucose excretion without causing hypoglycemia and promoting weight loss due to a loss of 300–400 kcal/day.[20,21] By inhibiting glucose reabsorption through SGLT blocking, plasma glucose levels would be reduced, thus presenting an unique therapeutic approach without the side effects associated with currently available T2DM medications.[22]

Phlorizin exists in a number of fruits and foods and exhibits many bioactivities. The mechanism of its antidiabetic effect has been known as it can competitively inhibit sodium–glucose symporters (SGLTs).[23]Although studies revealed that phlorizin administered orally to mice blunted the increase in blood glucose levels after ingesting a glucose solution, it was not further developed as a possible anti-diabetes therapy due to poor intestinal absorption and resultant low bioavailability, as well as rapid in vivo β-glucosidase degradation. Another significant disadvantage is that phlorizin also acts on SGLT1, which is mainly expressed in the gastrointestinal tract. SGLT1 gene mutations lead to glucose and galactose malabsorption, dehydration, and diarrhoea.[24]

CANAGLIFLOZIN

For the treatment of type 2 diabetes, canagliflozin, a strong and selective sodium glucose co-transporter 2 inhibitor, has been developed. It decreases plasma glucose by reducing the renal threshold for glucose and raising urine glucose excretion.[21]

Canagliflozin 300 mg has direct or indirect impacts on nonglycemic parameters in addition to regulating blood sugar. Patients with HF, especially those with HFrEF, which is defined as an ejection fraction of less than 40%, were thought to benefit from SGLT2 inhibitors.[25] Patients on canagliflozin had a decreased chance of being admitted to the hospital for heart failure, albuminuria progressing, and significant renal function loss.[26]

EFFECTS OF CANAGLIFLOZIN ON VARIOUS PARAMETERS:

BODYWEIGHT

Canagliflozin (CANTATA) dosages of 100 and 300 mg were examined for body weight reduction in the clinical development programme. Canagliflozin 300 mg, unlike several AHAs, does not cause weight gain; instead, it has a weight-reduction impact that results from a caloric loss of 300–400 kcal per day.[27] Instead of a loss of fluid or lean mass, dual-energy X-ray absorptiometry research showed that this decrease in body weight was mostly caused by the loss of body fat mass.[28] Canagliflozin's ability to reduce weight is a crucial treatment factor for obese or overweight T2DM patients. Interestingly, canagliflozin 300 mg significantly reduced body weight compared with placebo in a 12-week, randomised, double-blinded study of 376 obese and overweight adults without diabetes.[29]

BLOOD PRESSURE

Comparing canagliflozin 100 and 300 mg to placebo, there were statistically significant drops from baseline in systolic blood pressure. In comparison to placebo, both canagliflozin doses also resulted in lower diastolic blood pressure. Compared to placebo, canagliflozin 100 and 300 mg showed little difference in pulse rate (1.6, 0.5, and 1.4 beats per min, respectively).[30] Average systolic and diastolic blood pressure reductions with canagliflozin 300 mg versus placebo were 4.7 and 1.9 mmHg respectively, when measured in a combined placebo-controlled group.[31]

LIPIDS

Compared to a non-diabetic heart, a diabetic heart has an elevated lipid content, or cardiac steatosis, which causes oxidative stress and cardiac failure.[32] Canagliflozin treatmment has demonstrated a decrease of body weight, body fat and the reduction of fat volumes which are possibly related to improvement of LDL, HDL, nonHDL, TG, and blood pressure. With canagliflozin 100 and 300 mg compared with placebo, there were appreciable increases in HDL-C and decreases in triglycerides. Treatment with canagliflozin resulted in a significant decrease in blood sugar, total cholesterol, LDL cholesterol, and triglyceride levels.[33]

RENAL EFFECTS

Canagliflozin decreased the likelihood of long-term renal function deterioration, decreased albuminuria excretion, and slowed eGFR decline. It is likely that SGLT2 inhibitors have a direct renal mechanism for their beneficial effects on the kidneys. Independent of glycemic control, canagliflozin decreases the deterioration in kidney function, according to head-to-

head studies with other glucose-lowering medications. This class of drugs' capacity to improve afferent arteriolar tone by adjusting tubuloglomerular feedback, thereby lowering intraglomerular pressure via mechanisms that parallel and are complementary to those of RAS blockade, is an increasingly cited physiological explanation for their renoprotective properties.[34] The average change in eGFR during the study was -3.9 0.02 mL/min/1.73 m2, compared to -1.08 0.02 mL/min/1.73 m2 in those receiving canagliflozin.[35]

HEART FAILURE

Patients with type 2 diabetes mellitus and established cardiovascular disease or at high risk of cardiovascular events who were treated with canagliflozin experienced significantly reduced rates of cardiovascular death or hospitalized HF.

The normal fuels for the heart are fatty acids or glucose, while lactate, amino acids, and ketones may be used to a lesser extent. The heart can use a variety of energy sources. Increased fatty acid absorption and oxidation combined with decreased glucose oxidation are hallmarks of diabetic cardiomyopathy. These changes in heart mitochondrial energy metabolism result in contractile dysfunction and reduced cardiac efficiency.[36] Ketone bodies function as a "super fuel" in the context of T2DM, with heart failure, where there is limited fuel availability and little energetic reserve, by releasing energy more effectively than fatty acids or glucose.[37] Given that ketone bodies are valuable and effective sources of energy for cardiac tissue, an increase in ketone body uptake in the heart may represent an adaptive and compensating response to the reduced glucose metabolism in the diabetic heart. In DM patients with high cardiovascular risk, administration of a sodium glucose cotransporter 2 (SGLT2) inhibitor is linked to an impressive decrease in cardiovascular and all-cause mortality. This effect is likely due to increased ketone body production and cardiac ketone oxidation as well as hemodynamic effects.[38]

Canagliflozin is associated with alleviation of cardiac stress with improvement of diastolic dysfunction and decreased left ventricle mass (LVM). LVM tends to increase in patients with diabetes and this change is regarded as a risk factor for cardiovascular disorders such as heart failure and sudden death.[39]

NT-proBNP concentrations that are elevated are linked to the diagnosis of heart failure and indicate a higher risk of cardiovascular disease. According to the CANagliflozin Cardio Vascular Assessment Study, canagliflozin therapy is linked to lower levels of NT-proBNP.[40]

The action of canaglifzolin on heart failure has a wide range of potential mediators, many of which are highly plausible given the known causes of heart failure. These mediators include markers of plasma volume. By primarily lowering preload, volume reduction would be expected to mediate the prevention of heart failure.[41] The advantages for HF outcomes may be attributable to an action mechanism that is predominantly influenced by volume and hemodynamic effects. The protection provided may be due to natriuresis-induced decreases in preload and afterload, systemic blood pressure reduction, alteration of the intrarenal renin-angiotensin axis, and decreased arterial stiffness.[42]

ADVERSE EFFECTS

Canagliflozin-related bone fractures have previously been documented.[43] The minor, erratic increases in total hip BMD (but not femoral neck, lumbar spine, or distal forearm BMD) found with canagliflozin are considered the cause of the increased fracture risk with canagliflozin.[44] According to the proposed theory, SGLT-2 inhibitors lower blood sugar and the effective circulation volume, which could increase the risk of fractures and falls.[45]

CONCLUSION

SGLT2 inhibitors have shown promise of being an extremely versatile medication with a brighter tomorrow. Canagliflozin has demonstrated cardiac and renal protective effects as well as improving oxidative stress, diastolic function, and endothelial function. This drug has been effective in patients who had heart failure with preserved ejection fraction and could become first-line therapy for such patients with diabetes. In nations like India, where the prevalence of T2DM and its co-morbid conditions like hypertension and obesity is rising at an alarming rate, the pleiotropic effects of canagliflozin in terms of weight loss, BP reduction and heart failure can be used to their fullest potential. Thus, canagliflozin is an effective antidiabetic agent that may also be useful for the prevention and treatment of heart failure and protection of vital organs.

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