Glyphozines and treatment of cardiac disease.

F.Ferrara, R.La Porta, G.Granata, A.Vitiello

Abstract

Glyphozines also called SGLT2 inhibitors, are a new class of agents that inhibit reabsorption of glucose in the kidney, in proxinal tubules, and therefore lower blood sugar. They act by inhibiting sodium-glucose transport protein 2 (SGLT2). Glyphozines are used in the treatment of type II diabetes mellitus (T2DM). In studies with canagliflozin, a member of this class, the medication was found to enhance blood sugar control as well as reduce body weight and systolic and diastolic blood pressure.[1] In addition to regulate blood glucose, recent studies have shown that glyphozines have important positive cardiovascular benefits, such as weight loss, decreased volaemia and PA, reduced triglycerides, natriuresis and improved endothelial wall dysfunction. Clinical studies have shown reduction in deaths from cardiovascular events among diabetic patients treated with glyphozines. At the moment these drugs are being studied for an extension of the therapeutic indication also for cardiovascular diseases such as heart failure. In this review, we discuss the class of SGLT2 inhibitors in the treatment of diabetes, and studies focused on their possible role in the treatment of cardiac disease.

Introduction

The prevalence of type II diabetes mellitus (T2DM) is on the increase worldwide, tightly linked to the expanding number of individuals who are overweight and obese. T2DM is a metabolic disease commonly characterized by an increase in blood glucose levels and characterized by tissue insulin resistance and insulin reduction production.[2-3-4]. It is important that all forms of diabetes are diagnosed and managed in advance to prevent or slow down its potential complications other organs such as nephropathy, retinopathy, neuropathy, cardiovascular damnages, diabetic foot disease and ulcer. T2DM is also a socio-economic problem considering the high incidence of the disease, therefore, this has contributed to the creation and development of numerous drug treatments. Today, a number of new classes of drugs used to treat T2D have been developed.
T2DM is strongly associated with cardiovascular disease (CVD). Several studies have shown that a significant proportion of diabetic patients are at risk of experiencing acute coronary syndrome and/or heart failure (HF). This is due to abnormal cardiac management of glucose and free fatty acids (FFAs) and the effect of metabolic changes in diabetes on the cardiovascular system (CV). Furthermore, studies have reported that the incidence of HF in diabetic patients is significantly correlated with HbA1c levels. [5,6,7] Hyperglycemia is an independent risk factor for ischemic heart disease (IHD) as several mechanisms lead to vascular damage due to long-term hyperglycemia[8-9]. To clarify the mechanisms responsible for decreased myocardial contractility in the diabetic population, several explanations have been proposed.[10-11] In patients with diabetes, altered metabolism has been associated with increased myocardial oxygen consumption and increased serum free fatty acid (FFA) concentrations. [10] Abnormalities in contractile and regulatory protein expression and cardiomyocyte sensitivity Ca2+ are also found in DM. In diabetes, reduced activity of the sarcoplasmic reticular calcium pump (SR) and the rate of removal of Ca2+ from the cytoplasm in the diastole may be responsible for diastolic dysfunction.[10-11] The main pathogenetic mechanism in HF and DM leading to structural alteration is hyperglycemia. Hyperglycemia leads to the glycation of several macromolecules that result in a decrease in the

elasticity of the vessel walls and in myocardial dysfunction.[10-11]. Hyperglycemia also induces diabetes-specific changes in the microvascular architecture, such as reduced nitric oxide production resulting in endothelial dysfunction. The rennin-angiotensin-aldosterone (RAAS) system is activated at the beginning of T2DM. As HF progresses, the activation of the sympathetic nervous system (SNS) and RAAS increases, leading to a worsening of CV and renal function[10-11-12].

Current therapy

For the treatment of T2DM there are several pharmacological treatment options available. Among the medications used routinely there is insulin replacement therapy. Insulin replacement therapy when used correctly at the appropriate doses and times has shown a significant reduction in mortality in patients with T2DM due to cardiovascular causes, however, some studies show that insulin has not provided benefits for cardiovascular diseases in patients with diabetes that are more severe compared to the standard of care with oral therapies. In this regard, several studies have shown that metformin and glucagon-like peptide 1 agonists (GLP-1) provide greater benefits for cardiovascular disease in diabetic patients. In addition, dipeptidil peptidase-4 inhibitors (DPP4) are associated with increased HF hospitalizations and in 2016 the Food and Drug Administration (FDA) issued an alert for increased HF risk associated with both saxagliptin but not sitagliptin.[13] Therefore, a positive strategy is needed to address the risk of heart failure in diabetes. The first-line drug to manage hyperglycemia in type 2 DM is metformin. The diabetic patient with HF represents a particular challenge in the pharmacological treatment of diabetes. Current management strategies focus on known modifiable risk factors such as glucose, lipids and blood pressure (BP) which produce modest effects. Although these are important risk markers, none of these interventions substantially prevent HF or improve its outcome [14-15].

SGLT-2 inhibitors: An overview

Glyphozines are oral antidiabetic agents that inhibit the SGLT-2 protein in the proximal renal tubules and expel glucose in the urine, thereby lowering blood glucose. Glyphozines are antidiabetic agents because they lower blood glucose independently of insulin. In addition to glycemic control, glyphozines also have several pleiotropic effects, in fact they are the only class of antidiabetic agents that have been shown to decrease the risk of CV events mainly by reducing the development or progression of HF. Infact glyphozines reduces blood pressure, reduces the activity of the sympathetic nervous system, reduces uric acid, reduces glucagon, reduces oxidative stress, and, of course, reduces blood sugar levels. All these factors could theoretically contribute to the blood pressure lowering effect of this class". In addition, glyphozines could improve myocardial energy efficiency through the oxidation of β-hydroxybutyrate and increase hematocrit by improving oxygen transport. Finally, there is a decrease in vascular rigidity and an improvement in endothelial function with the use of glyphozines in diabetes.[16-17-18]. Glyphozines can be used in both monotherapy and polytherapy. [19-20-21-22-23-24-25-26]. The first large-scale study on the safety of CV with SGLT2 inhibitors in patients with T2DM (EMPA-REG OUTCOME) reported beneficial effects on CV events and hospitalization for HF in patients without baseline HF, suggesting that SGLT2I is a only glucose reducing agent and has multiple effects on hemodynamic and metabolic parameters. SGLT2i can be used in selected patients with substantial CV risk, but should be prescribed with great caution in patients taking diuretics.

The EMPA-REG OUTCOME study reported that patients with T2DM and high CV risk who received empagliflozin as an adjunct therapy to standard drugs compared to placebo showed a lower

incidence rate of primary CV outcomes and overall mortality. The study reported a 0.38%-0.85% reduction in HbA1c levels with empagliflozin compared to placebo.[27-28] Another study reported that empagliflozin reduced weight, waist circumference and adiposity indices compared to placebo concluding that empagliflozin significantly reduced weight and adiposity indices with the potential to improve cardiometabolic risk among T2DM patients.

The Canagliflozin Cardiovascular Assessment (CANVAS) study evaluated the efficacy, safety and duration of canagliflozin in more than 10,000 patients with diabetes who had a previous history of CV disease or at least two CV risk factors. The results showed that canagliflozine reduced CV and non-fatal myocardial infarction. The drug also demonstrated potential renal protective effects. Another study with T2DM patients showed that treatment with canagliflozine was associated with clinically significant and dose-dependent reductions in HbA1c, as monotherapy and as part of combination therapy. In addition to reducing HbA1c levels, phase 3 studies on canagliflozine have reported dose-dependent reductions in body weight that are increased by reduction in visceral adiposity, which can reduce CV complications and mortality.[29] A further study reported the effects of canagliflozine on CV biomarkers in elderly DM patients. The study showed that the natriuretic serum N-terminal pro-B serum peptide, high-sensitivity troponin I and soluble ST2 remained unchanged in canagliflozine. These cardiac biomarker data support the beneficial CV effect of SGLT2Is in T2DM patients. When pitted against the two other new HF medication approved in the last 5 years (Ivabrradine and Angiotensin Receptor blocker and Neprilysin inhibitor –ARNI), SGLT-2i have shown comparable benefits although they were not primarily developed for HF patients. [30-31-32-33-34-35-36-37-38-39-40-41-42-43-44-45-46-47]

Conclusion

Glyphozines are agents with an indication for the treatment of diabetes. In addition to antihyperglycemic agents, these drugs also possess various pleiotropic effects, thus providing benefits that go beyond glycemic control. Several studies have shown beneficial effects on CV risk factors by reducing BP, improving endothelial function and arterial stiffness, promoting weight loss, improving the lipid profile. Moreover, this is reinforced by a good safety profile, in fact the incidences of adverse events in clinical trials of glyphozine were similar to those observed with other antidiabetic drugs. The most frequently observed adverse events in subjects with glyphozine are urogenital tract infections, The risk of hypoglycaemia is minimal. These extraordinary characteristics of this class of drugs suggest that glyphozines could add a new dimension to the management of T2DM, on the contrary, a significant reduction in CV deaths and heart failure hospitalizations with these agents has opened a new path for the management of HF with T2DM.

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