REVIEW ARTICLE

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SGLT2 inhibition in patients with type 2 diabetes and cardiovascular diseases: which are the benefits?

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Abstract: *Two major trials, EMPA-REG OUTCOME trial (with Empagliflozin) and CANVAS trial (with Canagliflozin) have demonstrated the beneficial effects of SGLT2 inhibitors in patients with type 2 diabetes at risk for heart failure. SGLT2 inhibitors possess a unique pharmacological profile and have shown a significant reduction of hospitalization for heart failure in diabetic patients, immediately after treatment commencement. It seems that their effects are beneficial both in heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. SGLT2 inhibitors reduce cardiovascular endpoints in patients with diabetes and high cardiovascular risk, most likely through a reduction of heart failure-related events. Empagliflozin treatment exerts beneficial effects on vascular function and central haemodynamics. Various mechanisms seem to contribute to the beneficial effects of SGLT2 inhibitors in heart failure. Taking into consideration their cardiovascular benefits and the number of ongoing trials with these drugs, there is a possibility to expand their indication to nondiabetic patients with heart failure. This review focuses on the newest insights into the beneficial effects of SGLT2 inhibitors on the cardiovascular system.*

Keywords: *SGLT2 inhibitors, type 2 diabetes, empagliflozin, canagliflozin, heart failure*

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular disease (CVD) and, moreover, their association determines a higher mortality rate [1, 2]. On the other hand, heart failure represents an independent risk factor for developing T2DM [3], and a percentage varying from 20% to 40% of the patients with heart failure have also T2DM [4].

Pharmacological treatment of patients with T2DM is complex and has been continuously improved over the years. The treatment may be with oral antidiabetic agents (OAD) and/or insulin. The main oral antidiabetic agents are:

- Sulfonylureas.
- Alpha-glucosidase inhibitors.
- Thiazolidinediones.
- Glinides.
- Biguanides.
- Dipeptidyl peptidase-4 (DPP-4) inhibitors.
- GLP-1 agonists.

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• Sodium-glucose cotransporter (SGLT2) inhibitors.

ORAL ANTIDIABETIC TREATMENT

The first agent used as OAD in the treatment of T2DM was sulfonylurea that has hypoglycemic effects by stimulating the pancreatic β-cells to secrete insulin, primarily by closing the ATP-sensitive K channels from the β-cells plasma membrane inducing a series of events finalized with insulin release [5].

Alpha-glucosidase inhibitors are a class of OAD which were developed from bacteria. They are inhibiting the action of thealpha-amylase from the intestinal brush border. Their activity is independent of the pancreas and consists of delaying carbohydrate absorption in the gastrointestinal tract, obtaining the control of postprandial hyperglycaemia and, also, cardiovascular benefits [6].

Thiazolidinediones are a class of OAD formed by selective agonists of PPARγ from adipocytes, where they stimulate the fatty acid uptake and adipogenesis, especially in peripheral visceral fat (except the visceral fat). Lowering the concentration of circulating fatty acids and available lipids in the liver and muscle results in improving the patient's sensitivity to insulin. Also, they decrease the concentrations of hormones secreted by adipocytes, particularly adiponectin. Overall, they have mixed effects on circulating lipids and increase total body fat [7].

Glinides are OAD with a rapid effect onset, but short-acting duration [8], which stimulate the pancreatic release of insulin, thus lowering postprandial glycaemia.

Biguanides are OAD, metformin being the most important representative of this class. They are antihyperglycaemic agents, mainly through inhibition of hepatic glucose release and, also, in a lesser extent, through delaying the enteric absorption of glucose and stimulating the uptake of glucose at different levels – skeletal muscle, enterocytes and adipocytes [9].

Recently, new OAD classes, such as DPP-4 inhibitors, GLP-1 agonists or SGLT2 inhibitors, have been developed.

DPP-4 inhibitors act by preventing the inactivation of glucagon-like peptide 1 (GLP-1)[10] and glucose-dependent insulinotropic peptide (GIP) [11], resulting in an increased level of active GLP-1. The overall effect is the lowering of glucose levels through increased insulin secretion and reduced glucagon secretion [10].

GLP-1 agonists are grouped in long-acting and short-acting, after their effect duration. They stimulate insulin secretion and suppress glucagon secretion [12].

SGLT2 inhibitors act on the channels from the proximal convoluted tubules, where they stimulate glucose elimination through urine, by preventing its reabsorption. There is no risk of hypoglycaemia, because they act on blood glucose level and are independent of insulin's action, thus not affecting the pancreatic β-cells. Their limitation is represented by the impairment of the renal function [13].

SGLT2 inhibitors reduce glucose reabsorption in the early proximal tubule, leading to urinary glucose excretion and osmotic diuresis [14]. This class of medication has two main representatives-empagliflozin and canagliflozin, which demonstrated their beneficial effects in patients with T2DM at risk for heart failure in two major trials – EMPA-REG OUTCOME (with Empagliflozin) and CANVAS (with Canagliflozin). SGLT2 inhibitors have hypoglycaemic effects through increasing glycosuria and inhibiting renal glucose reabsorption [15]. They have also several additional beneficial effects, such as improving blood pressure [2, 13, 16–19], intrarenal haemodynamics [2] and albuminuria, reducing body weight [2].

For the management of cardiovascular risk in patients with T2DM, glycaemic control is very important, because it reduces the frequency of diabetic complications – especially microvascular ones [20] and has significant benefits in end-stage renal disease [21, 22]. Weight loss improves cardiovascular risk factors in T2DM on the short-term [23], but not on the long-term [24]. A 10 mm Hg reduction in systolic blood pressure reduces all-cause mortality, macrovascular and microvascular outcomes [25], but even a small blood pressure reduction can diminish cardiovascularrisk [26]. In consequence, it is very important to have a multifactorial approach in the management of T2DM [27].

SGLT2 inhibitors have several potential mechanisms that could explain their cardiovascular benefits, such as decreasing cardiac inflammation [16,28], decreasing cardiac oxidative stress [16,28], decreasing cardiac apoptosis [16,28], attenuating mitochondrial dysfunction [28], improving cardiac calcium and sodium ionic homeostasis [28] and hemodynamic effects, such as reduction in blood pressure [2,16,17] and intravascular volume [16,17] via osmotic diuresis [16] and natriuresis [17].

SGLT2 inhibitors posology is in tablets with rapid oral absorption [29], reaching peak plasma concentrationin 1-2 h [29, 30], and with a half–life of 10.2-13.1 hours [29,30], resulting in only one administration per day. The molecule metabolism is primarily through glucuronidation in the liver, followed by drug excretion through the urinary and faecal route. It is important to emphasize that SGLT2 inhibitors reduce the renal filtration rate (with up to 80 g per day), resulting in the necessity, for patients with an impaired renal function, of a more attentive follow-up and adjustment of doses [30]. The usual doses are canagliflozin – initially 100 mg, with a maximum of 300 mg per day, dapagliflozin – initially 5 mg, with a maximum of 10 mg per day, and empagliflozin – initially 10 mg, with a maximum of 25 mg per day [30].

EMPA-REG OUTCOME was a randomized, double-blind, placebo-controlled trial, which included 7028 patients with T2DM and established cardiovascular disease [1], who received empagliflozin once a day (10 mg or 25 mg dosage) versus placebo, compared to the usual standard of care. The study was multicentric, with 590 sites in 42 countries, and lasted until a minimum of 691 patients developed an adjudicated primary outcome - time to the first occurrence of any of the following adjudicated components of the primary composite endpoint (major adverse cardiovascular events [MACE] – CV death [including fatal stroke and fatal MI], non-fatal MI [excluding silent MI], non-fatal stroke). The trial lasted from September 2010 to April 2013 [1]. More than 99% of the included patients had established cardiovascular disease. The median observation time was 3.1 years, with a mean treatment duration of 2.6 years. As a cardiovascular outcome, a lower percentage of the primary outcome took place in the empagliflozin group (10.5%) than in the placebo group (12.1%) (HR for empagliflozin group, 0.86; 95.02%, CI, 0.74 to 0.99; $p<0.001$ for non inferiority and $p = 0.04$ for superiority); a significantly lower risk of death from cardiovascular causes (HR 0.62; 95% CI, 0.49 to 0.77; $p<0.001$), death from any cause (HR 0.68; 95% CI 0.57 to 0.82, $p<0.001$) and hospitalization for heart failure (HR 0.65; 95% CI 0.50 to 0.85; $p = 0.002$); the occurrence of myocardial infarction or stroke had no significant differences between groups [1]. Glycaemic control, estimated through glycated haemoglobin, was improved by empagliflozin at 12 weeks by −0.54 percentage points (95% CI, −0.58 to −0.49) in the 10 mg group, and by −0.60 percentage points (95% CI: −0.64 to −0.55) in the 25 mg group; at 94 weeks, the differences between empagliflozin group and the placebo group were by −0.42 percentage points (95% CI,−0.48 to −0.36) and by −0.47 percentage points (95% CI, −0.54 to −0.41), respectively; at 206 weeks, the differences between empagliflozin and placebo were by −0.24 percentage points (95% CI, −0.40 to −0.08) and by −0.36 percentage points (95% CI, −0.51 to −0.20), respectively [1]. Cardiovascular risk factors were slightly improved in the empagliflozin group: weight, waist circumference, uric acid level, systolic and diastolic blood pressure, but with small increases in both LDL and HDL cholesterol, with no increase in heart rate [1].

CANVAS consisted of two sister, multicentric, randomized, double-blinded, placebo-controlled trials, which included a total of 10,142 patients with T2DM and high cardiovascular risk [2]. Patients were administered canagliflozin versus placebo in 667 centres from 30 countries until a minimum of 688 cardiovascular events took place. CANVAS trial lasted from 2009 until February 2017 [2]. The inclusion criteria were: patients with T2DM, age ≥ 30 years, with a history of symptomatic atherosclerotic vascular disease, or ≥ 50 years old with 2 or more risk factors for cardiovascular disease. The primary end-point was represented by time to the first occurrence of non-fatal myocardial infarction, non-fatal stroke or cardiovascular-related death. Its results consisted of fewer primary outcome events in the canagliflozin

group versus the placebo group (26.9 vs 31.5 participants, with an event per 1000 patient-years (HR 0.86; 95% CI of 0.75 to 0.97; p<0.001 for noninferiority; p = 0.02 for superiority). The renal outcome was a lesser progression of albuminuria in the canagliflozin group versus placebo group (89.4 vs. 128.7 participants, with an event per 1000 patient-years), with HR 0.73 (95% CI, 0.67 to 0.79); with a regression of albuminuria in canagliflozin group versus placebo group (293.4 vs. 187.5 participants per 1000 patient-years; HR 1.70; 95% CI, 1.51 to 1.91). An important outcome was the composite one -the 40% sustained reduction in eGFR, the need for renal replacement therapy, or death from renal causes, which was observed with a smaller frequency in the canagliflozin group versus the placebogroup (5.5 vs. 9.0 participants per 1000 patient-years HR 0.60; 95% CI, 0.47 to 0.77).

The empagliflozin patients had a mean age of 63 years, with a duration of diabetes of 10 years (57%), a mean HbA1c of 8.1%; cardiovascular risk was present in 99% of them through established cardiovascular disease, 10% of them had a history of heart failure, under treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in 81%, statins in 77% and acetylsalicylic acid in 83% of cases [1].

The canagliflozin patients had a mean age of 63 years, with a duration of diabetes >13.5 years, with a mean HbA1c 8.2%; cardiovascular risk was present, 65% had established cardiovascular disease and 35% multiple risk factors. 14.4% had a history of heart failure and were prescribed treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in 80%, statins in 75% and acetylsalicylic acid in 74% of cases [2].

SGLT2 inhibitors were evaluated through several trials. CANVAS-R, a prospective, randomized, double-blinded, placebo-controlled clinical trial, included patients with T2DM with a history or high risk of cardiovascular events [31]. The primary objective of this trial was limiting kidney disease progression and the results were fewer cases of albuminuria progression 430/2615 cases in the active group versus 581/2615 in the placebo group (HR 0.74), decreased cardiovascular mortality or hospitalized heart failure (61/2906 patients in active group versus 93/2905 patients in placebo group) (HR 0.66) and decreased cardiovascular death (40/2906 patients in the active group versus 60/2905 patients in the placebo group) (HR 0.68)[31]. CREDENCE trial was a randomized, double-blinded, placebo-controlled, parallel-group, multicentre study, with 4,402 participants, in whom the effect of canagliflozin on renal and cardiovascular primary composite endpoint was evaluated: end-stage kidney disease, doubling of serum creatinine, renal or cardiovascular death in subjects with T2DM and diabetic nephropathy [32, 33]. DECLARE-TIMI is a multi-national, randomized, double-blinded, placebo-controlled trial with 17,190 participants with T2DM that aimed to determine whether dapagliflozin versus placebo reduces cardiovascular events, such as cardiovascular death, myocardial infarction or ischaemic stroke [34]. Ertugliflozin CVOT is a randomized, double-blinded, placebo-controlled study, with the primary outcome the first occurrence of MACE after treatment with ertugliflozin in 8,000 patients with T2DM and established cardiovascular disease [35].

20% of diabetes mellitus patients over 65 years-old have heart failure [18]. There are very few OAD for patients with both heart failure and T2DM [18]. SGLT2 inhibitors, in this type of patients, are potentially OAD that can reduce the risk of cardiovascular mortality and heart failure [19]. They reduce all-cause mortality significantly when compared to placebo. Also, they reduce major adverse cardiovascular events when compared to placebo (OR 0.83; 95% CI 0.76–0.92; p<0.001), with the same efficacy for subgroups such as canagliflozin (OR 0.85; 95% CI 0.75–0.97; p=0.02) and empagliflozin (OR 0.82; 95% CI 0.71–0.94; p=0.006)[19]. Significant reductions were observed, when compared to placebo, for non-fatal myocardial infarction (OR 0.85; 95% CI 0.73–0.98; p=0.03) and for heart failure or hospitalisation due to heart failure (OR 0.67; 95% CI 0.59–0.76; p<0.001)(19). Insignificant reductions were observed, when compared with placebo, for non-fatal stroke (OR 1.02; 95% CI 0.85–1.21; p=0.87), atrial fibrillation (OR 0.61; 95% CI 0.31–1.19; p=0.15) and for the occurrence of unstable angina or unstable angina requiring hospitalisation (OR 0.95; 95% CI 0.73–1.25; p=0.73)[19].

CONCLUSIONS

SGLT2 inhibitors, such as empagliflozin, are very important, also, in treating patients with T2DM and heart failure, because they do not only reduce hyperglycaemia [2,13,18,19], but also lead to osmotic diuresis [18], reduce body weight [2,18,19] and blood pressure [2,13,18,19], without increases in heart rate, with favourable effects on markers of arterial stiffness and vascular resistance [18], albuminuria [18,19], and serum uric acid [13,18]. Another benefit of SGLT2 inhibitors is the reduction in the primary composite outcome that consists of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke [18]. Treating heart failure in patients with T2DM is a real challenge, because of the lack of evidence-based guidelines for the management of such patients [18]. Important treatment goals are improving survival rates and preventing hospital admission [18].

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