

# Use of SGLT-2 inhibitors in the treatment of type 2 diabetes mellitus

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## SUMMARY

**Introduction:** Diabetes mellitus is one of the most common chronic diseases in the world, with high morbidity and mortality rates, resulting in a greatly negative socioeconomic impact. Although there are several classes of oral antidiabetic agents, most of the patients are outside the therapeutic goal range. **Objective:** To review the use of SGLT-2 inhibitors in the treatment of type 2 diabetes mellitus, focusing on their favorable and unfavorable effects, as well as on cardiovascular profile.

**Method:** A literature search on Pubmed database was performed using the following keywords: “SGLT-2 inhibitors,” “dapagliflozin,” “empagliflozin,” “canagliflozin.”

**Results:** SGLT-2 inhibitors are a class of oral antidiabetic drugs directed to the kidney. Their mechanism of action is to reduce blood glucose by inducing glycosuria. Extra-glycemic benefits have been described, such as weight loss, decline in blood pressure and levels of triglycerides and uric acid, and they can slow the progression of kidney disease. Genitourinary infections are the main side effects. There is a low risk of hypotension and hypoglycemia. Diabetic ketoacidosis is a serious adverse effect, although rare. Empagliflozin has already had its cardiovascular benefit demonstrated and studies with other drugs are currently being performed.

**Conclusion:** SGLT-2 inhibitors are a new treatment option for type 2 diabetes mellitus, acting independently of insulin. They have potential benefits other than the reduction of blood glucose, but also carry a risk for adverse effects.

**Keywords:** SGLT-2 inhibitors, type 2 diabetes mellitus, kidney, glycosuria, review.

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## INTRODUCTION

Diabetes mellitus (DM) is currently considered a public health problem, with increasing incidence and prevalence worldwide. The global estimate of DM patients in 2013 was greater than 381 million, projected to increase to approximately 592 million by 2035.<sup>1,2</sup> Type 2 diabetes mellitus (T2DM) is one of the most common metabolic disorders, accounting for 90-95% of adult diabetes.<sup>3</sup>

The pathophysiology of T2DM is complex and multifactorial. Ralph DeFronzo was responsible for the concept of ominous octet – a broader theory, which identified different organs in addition to the pancreas, as well as eight problems, which play a key role in the pathogenesis of T2DM. The main defects include pancreatic beta cell failure and insulin resistance in muscles and liver. Furthermore, incretin deficiency, accelerated lipolysis, hyper-

glucagonemia, insulin resistance in the brain, and increased renal reabsorption of glucose also participate in the development of the disease<sup>4</sup> (Table 1).

**TABLE 1** DeFronzo's ominous octet.

<b>Pancreatic beta cells</b>	Insufficient insulin secretion
<b>Pancreatic alpha cells</b>	Excess glucagon
<b>Fat cells</b>	Increased lipolysis
<b>Muscles</b>	Reduction of peripheral glucose uptake
<b>Liver</b>	Greater hepatic glucose production
<b>Gastrointestinal tract</b>	Decline of incretin activity
<b>Brain</b>	Dysfunction of brain neurotransmitters
<b>Kidneys</b>	Greater renal reabsorption of glucose

The identification of the ominous octet was important, as it provided a paradigm shift in the treatment of DM. DeFronzo proposed the association of drugs to act in all pathophysiological defects of the disease, and not only reduce glycosylated hemoglobin.<sup>4</sup> Although there are several therapeutic options, it is still common to find poorly controlled patients with blood glucose levels outside of the target range. One of the causes that contribute to this is therapeutic inertia of physicians, who end up delaying the association of drugs.<sup>5</sup>

Complementing the therapeutic arsenal currently available for the treatment of T2DM, a new class of drugs called SGLT-2 inhibitors has been approved in recent years by the Brazilian Agency for Sanitary Surveillance (Anvisa, in the Portuguese acronym), with a focus on kidney treatment. They reduce blood glucose by increasing the urinary excretion of excess glucose that would be reabsorbed by the kidneys.<sup>6</sup>

The aim of this article was to review the state of the use of SGLT-2 inhibitors in the treatment of T2DM, focusing on its favorable and unfavorable effects, and its cardiovascular profile.

## METHOD

Bibliographical and transversal search for scientific articles was carried out in the Pubmed (National Center for Biotechnology Information) database. The following keywords were used: "SGLT-2 inhibitors," "dapagliflozin," "empagliflozin," "canagliflozin". The inclusion criteria were: scientific articles in human beings or animals, written in English, Portuguese or Spanish. There was no date restriction for the articles. Scientific articles related to the subject were selected after title and abstract analysis. Articles such as letters to the editor, communications, editorials, comments, articles in other languages and those with partially published data were excluded. The references of the articles selected were also analyzed to identify other articles relevant to the subject.

## THE KIDNEY AS A TREATMENT TARGET

The kidney contributes to glucose homeostasis by filtering plasma glucose through glomeruli and reabsorbing it in the segments 1 (S1) (90%) and 3 (S3) (10%) of the proximal tubule. In healthy subjects, the kidneys filter approximately 180 g of glucose per day. Due to reabsorption, glucose in the urine is either absent or present at very low concentrations (0.03 to 0.30 g/dL).<sup>7,8</sup>

The sodium and glucose linked transporter (SGLT) is a sodium/glucose cotransporter membrane protein. Type 2 (SGLT-2) is present in S1 of the proximal convoluted tubule and is the main glucose transporter, where-

as type 1 is found in S3 of the proximal convoluted tubule and the small intestine.<sup>6,9</sup>

That is why, in recent years, the kidney has become a target organ for the treatment of DM. The class of SGLT-2 inhibitors (SGLTi-2), approved for T2DM, then emerged. SGLT-2 inhibitors, by inhibiting glucose reabsorption in the kidneys, increase urinary glucose excretion, reducing glycemic levels (Figure 1) in an insulin-independent manner, with positive effects on various glycemic parameters, such as glycosylated hemoglobin, fasting and postprandial levels of blood sugar.<sup>10-12</sup> They can then be used at any stage of the disease in both newly diagnosed and long-term diabetes,<sup>13</sup> since they do not depend on insulin secretion or peripheral insulin sensitivity.<sup>14</sup>

Three drugs have been approved in Brazil by the regulatory agency Anvisa: dapagliflozin, empagliflozin and canagliflozin (Table 2). These drugs can be used both as monotherapy or combined with other oral antidiabetic drugs (OAD) or insulin.<sup>12</sup> Dapagliflozin and empagliflozin have a greater sensitivity for SGLT-2, while canagliflozin is the only one that has a significant effect on SGLT-1, but only at high doses (greater than 200 mg). For this reason, it has been suggested that canagliflozin can reduce the levels of blood glucose by double action, both in the kidneys and in the intestine.<sup>15</sup> Nevertheless, more studies are needed to confirm this hypothesis.

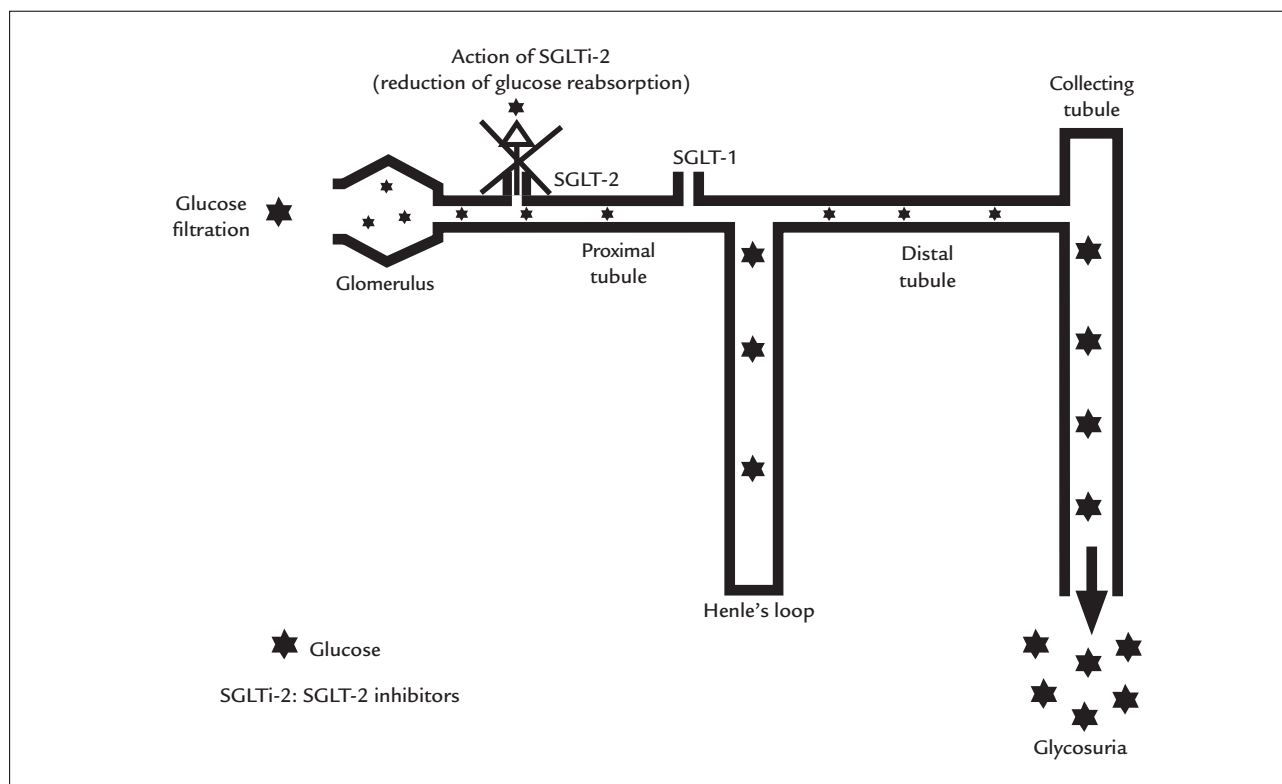
**TABLE 2** SGLT-2 inhibitors.

Active ingredient	Comercial name	Presentation
Canagliflozin	Invokana®	100 and 300 mg
Dapagliflozin	Forxiga®	10 mg
Empagliflozin	Jardiance®	10 and 25 mg

SGLT-2 inhibitors have demonstrated several beneficial extra-glycemic effects in patients with DM. Just like any other drug, they present risks and side effects that should not be overlooked.

## POSITIVE EFFECTS OF SGLT-2

Several studies have already shown that SGLTi-2 can reduce body weight in patients with T2DM, since the elimination of glucose through urine leads to a loss of calories (around 200-300 cal/day), resulting in a negative energy balance.<sup>16-18</sup> A study with dapagliflozin showed a significant reduction in waist circumference, which is consistent with a reduction in fat mass.<sup>19</sup> Studies evaluating body composition suggested that most of the weight loss associated with SGLTi-2 was due to a reduction in visceral or subcutaneous fat.<sup>20,21</sup> This is a beneficial effect for dia-



**FIGURE 1** Action of SGLT-2 inhibitors.

betic patients, since most are overweight and thus present greater insulin resistance. In addition, these drugs differ from other OADs, such as sulfonylurea and insulin, which cause weight gain.<sup>22</sup>

Decreased blood pressure (BP), both systolic (SBP) and diastolic (DBP), was observed with SGLTi-2, without compensatory increase in heart rate. This is because, by causing glycosuria, osmotic diuresis occurs, reducing circulating volume and, consequently, BP levels. Weight reduction and sodium depletion also contribute to this finding.<sup>23,24</sup> In addition, a direct vascular effect, with reduced arterial stiffness, leads to BP change.<sup>25</sup>

The effect of this class on serum lipid levels is mild. Small increase in HDL and LDL levels, but no change in HDL/LDL ratio and a mild reduction in triglyceride levels were found in clinical trials. It is not yet known if these changes are clinically relevant, and further studies are needed on the subject.<sup>19,24</sup>

DM is a major risk factor for cardiovascular disease (CVD) and CVD is the leading cause of morbidity and mortality in diabetics.<sup>26</sup> It is also known that DM is one of the main risk factors responsible for cognitive deficits, such as Alzheimer's disease and vascular dementia.<sup>27</sup>

In a study of obese diabetic rats, administration of empagliflozin was able to significantly improve cardiac fibrosis and inflammation, coronary artery remodeling, vascular dysfunction, and cognitive dysfunction. These benefits were associated with significant attenuation of oxidative stress in cardiovascular and brain tissues.<sup>28</sup>

Uric acid is the end product of purine metabolism. Hyperuricemia, in addition to causing gout, is associated with chronic kidney disease, DM and metabolic syndrome, and is considered a marker of cardiovascular (CV) risk. Reduction of serum uric acid levels has been seen with SGLTi-2 due to increased urinary excretion.<sup>29,30</sup> No increase in kidney uric acid stones was observed with SGLTi-2.<sup>30</sup>

This new class of drugs has already been shown to reduce glycemic levels in animals and humans with type 1 DM (T1DM), in addition to allowing a reduction in insulin dosage.<sup>31-33</sup> These drugs could, thus, be used as an adjuvant therapy in the treatment of DM1, with low risk of hypoglycemia and without weight gain. However, this is not yet an approved therapy for T1DM, and further studies are needed to assess the safety of SGLTi-2 in this group of patients.<sup>33</sup>

Studies in animal and human models have demonstrated that the use of SGLTi-2 has improved markers of renal damage, such as albuminuria, hyperfiltration/hypertrophy, inflammation and expansion of the mesangial matrix, suggesting the possibility of preventing diabetic nephropathy. There can be a slight reduction in glomerular filtration rate at the onset of use, which normalizes after a few weeks.<sup>34,35</sup> A large study with empagliflozin combined with standard treatment in patients at high CV risk showed an improvement in the progression of kidney disease compared to placebo.<sup>36</sup> Since the drug's effect depends on renal function, its benefits will be reduced in patients with this type of dysfunction.<sup>37</sup>

### NEGATIVE EFFECTS OF SGLTi-2

There is a risk of hypoglycemia with SGLTi-2, but at a lower rate. Such a low risk is justified by the fact that these drugs have an insulin-independent mechanism of action. The risk increases when these drugs are associated with insulin or insulin secretagogues.<sup>13</sup>

The main side effects related to the class are urinary and genital infections (vaginal moniliasis, vulvovaginitis, balanitis), attributed to the higher concentration of glucose in the urine. Infections are usually resolved with conventional treatments.<sup>17</sup> In order to avoid such complications, it is recommended to instruct patients about proper hygiene.

Osmotic diuresis caused by SGLTi-2 is responsible for the small rise in hematocrit levels, due to hemoconcentration, but without significant clinical effect verified so far.<sup>13</sup>

The risk of systemic arterial hypotension is low, since the reduction of SBP and DBP is not as marked. SGLTi-2 may increase the effect of thiazide diuretics and loop diuretics, with increased risk of dehydration. Greater attention should be given to the elderly, who are more sensitive to the risk of hypotension, especially those who use diuretics.<sup>23,24</sup>

A more serious and potentially fatal but uncommon adverse effect is the risk of diabetic ketoacidosis (DKA), rare in T2DM but more common in T1DM. These drugs are being used in addition to what has been approved by Anvisa, as an adjunct to insulin treatment in T1DM. There have been reports of atypical presentation, with mild increase in blood glucose and even normoglycemic DKA. This may delay diagnosis and treatment, and thus compromise the patient's prognosis. Some cases were secondary to the occurrence of triggers, such as infection, reduction of water intake or low adherence to insulin therapy. The mechanism involved in this situation is not yet known. If DKA is suspected, the drug must be discontinued immediately, ketone levels should be investigated and appropriate treatment initiated.<sup>38,39</sup>

Canagliflozin was associated with another side effect: bone fracture. A study with this drug demonstrated a significant decline of bone mineral density (BMD) in the hip, raising the hypothesis that it would be secondary to weight loss.<sup>40</sup> Reducing BMD can accelerate the osteoporosis process and increase the risk of fractures.<sup>41</sup> More studies are needed for a more detailed investigation of this risk.

### CARDIOVASCULAR PROFILE

In recent years, for new OADs to be registered and maintain such approval, drug regulatory agencies now require a CV safety study in patients at high risk.<sup>42</sup> The least expected is that it has a neutral effect over placebo.<sup>43,44</sup>

The results of the EMPA-REG OUTCOME study were published in September 2015 at the 51<sup>st</sup> Congress of the European Association for the Study of Diabetes (EASD), which was considered a positive milestone in the history of DM, as the first study to demonstrate cardiovascular superiority with an OAD.<sup>45</sup>

This was a randomized, multicenter, double-blind, placebo-controlled trial that evaluated the effects of standard treatment-associated empagliflozin on the occurrence of CV events. The study included more than 7,000 individuals with T2DM and CVD, either treated or being treated, for a mean period of 3.1 years. There was a significant reduction in the risk of major CV events (CV death, non-fatal acute myocardial infarction [AMI] and non-fatal stroke) by 14%. There was also a significant decrease in CV death rate (38%), in the rate of hospitalization due to heart failure (35%) and death from any cause (32%).<sup>45</sup>

Other effects were found in this study, including reductions in weight and waist circumference, decrease in uric acid levels, decrease in SBP and DBP without any increase in heart rate, and modest increases in LDL and HDL cholesterol.<sup>45</sup> It is not yet known, however, what mechanism provided such benefit. It may have been a multifactorial effect that included an osmotic diuretic factor, a lower rate of hypoglycemia, good cardiac performance (BP decline without tachycardia), change in arterial stiffness, weight loss, and reduction in albuminuria and uricemia.<sup>43,45</sup>

Further studies are underway to show the CV profile of the other SGLTi-2. These are: the Canagliflozin Cardiovascular Assessment (CANVAS) and the Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58). They will clarify whether this CV benefit is a class effect or restricted to empagliflozin, and may contribute by providing more information regarding this new class.<sup>43</sup>

## FINAL REMARKS

Although there are several drugs available to treat DM, glycemic control is still not ideal and leads to a significant increase in morbidity and mortality.

SGLT-2 are the latest oral agents for lowering blood sugar levels, targeting the kidneys, causing glycosuria. They offer the potential to improve glycemic control with a low risk of hypoglycemia, regardless of insulin secretion. These drugs have several favorable effects, such as reductions in weight, BP, uric acid and triglyceride, in addition to reducing the progression of kidney disease, and a proven CV benefit for empagliflozin. Its main adverse effects are: more frequent genitourinary infections, low risk of hypotension, and rare and severe risk of DKA. There is much more to be uncovered about this class of drugs, with promising prospects for the history of diabetes.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## RESUMO

Uso dos inibidores da SGLT-2 no tratamento do *diabetes mellitus* tipo 2

**Introdução:** O *diabetes mellitus* é uma das doenças crônicas mais frequentes no mundo, com altas taxas de morbimortalidade, resultando em um grande impacto negativo socioeconômico. Apesar de existirem diversas classes de antidiabéticos orais, a maioria dos pacientes acometidos está fora da meta terapêutica.

**Objetivo:** Revisar o uso dos inibidores da SGLT-2 no tratamento do *diabetes mellitus* tipo 2, com enfoque nos efeitos favoráveis, desfavoráveis e no perfil cardiovascular.

**Método:** Foi realizada uma pesquisa bibliográfica transversal com artigos científicos obtidos da base de dados Pubmed, utilizando os descritores: “SGLT-2 inhibitors”, “dapagliflozin”, “empagliflozin”, “canagliflozin”.

**Resultados:** Os inibidores da SGLT-2 são uma classe de antidiabéticos orais com atuação no rim. O mecanismo de ação é reduzir a glicemia induzindo glicosúria. Benefícios extraglicêmicos já foram descritos, como redução de peso, pressão arterial, triglicérides e ácido úrico, além de retardar a progressão da doença renal. O principal efeito colateral é a infecção geniturinária, com baixo risco de hipotensão e hipoglicemia. Cetoacidose diabética é um efeito adverso grave, mas infrequente. A empagliflozina já teve seu benefício cardiovascular demonstrado, e estudos com outras drogas estão em andamento.

**Conclusão:** Os inibidores da SGLT-2 são uma nova opção de tratamento do *diabetes mellitus* tipo 2, que atua de forma insulino-independente e com potenciais benefícios adicionais, além da redução da glicemia, mas também com risco de efeitos adversos.

**Palavras-chave:** inibidores da SGLT-2, *diabetes mellitus* tipo 2, rim, glicosúria, revisão.

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