SGLT2 INHIBITORS FOR TREATING HEART FAILURE WITH REDUCED EJECTION FRACTION

INIBIDORES SGLT2 NO TRATAMENTO DA INSUFICIÊNCIA CARDÍACA COM FRAÇÃO DE EJEÇÃO REDUZIDA

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Abstract

Introduction: Heart failure (HF) is a syndrome characterized by decreased left ventricular ejection fraction. The use of sodium-glucose transporter 2 inhibitors (ISGLT2) showed efficacy in reducing mortality and hospitalization of patients with HF. **Methodology:** A bibliographic survey was conducted in the main databases to analyze the benefits of ISGLT2 in the main high-impact journals. **Discussion:** EMPA-REG showed lower mortality in the use of empagliflozin than the placebo group (3.7% vs. 5.7%). The canagliflozin study (CANVAS) showed a 14% lower risk of cardiovascular death in patients without cardiovascular disease (CVD) and an 18% lower risk in patients with CVD. DECLARE-TIMI 58 showed that patients with type 2 diabetes mellitus (T2DM) have a lower risk of HF and death from cardiovascular events among patients who used dapagliflozin than patients who received a placebo (4.9% vs. 5.8%). In DAPA HF, the number of deaths from cardiovascular causes was 9.7% vs 11.5% of patients who took placebo. EMPEROR-REDUCED tested empagliflozin and the primary outcome occurred in 361 of 1863 patients (19.4%) in the drug group against 462 of 1867 patients (24.7%) in the placebo group. SOLOIST-WHF analyzed sotagliflozin and observed the occurrence of a primary outcome in 245 patients in the drug group and 355 in the placebo group. **Conclusion:** Patients with HF have gained a new drug class for their treatment, which was mentioned in the most recent guidelines worldwide, but its efficacy in HF with preserved ejected fraction still needs to be tested.

Keywords: Cardiovascular diseases; diabetes mellitus; heart Failure; mortality; renal insufficiency, chronic.

Resumo

Introdução: A insuficiência cardíaca (IC) é uma síndrome clínica caracterizada pela diminuição da fração de ejeção do ventrículo esquerdo. O uso do sodium-glucose linked transporter 2 inhibitors (ISGLT2) em portadores de IC evidenciou eficácia na diminuição de mortalidade e internação. **Metodologia:** Para conduzir a presente pesquisa, realizou-se estudo bibliográfico nas principais bases de dados e analisou-se os benefícios do ISGLT2 nas principais revistas de alto impacto. **Discussão:** O EMPA-REG revelou menor mortalidade no uso de empagliflozina comparado ao placebo (3,7% contra 5,7%). A canaglifozina (estudo CANVAS) evidenciou uma redução de 14% no risco de morte por doença cardiovascular (DCV) em pacientes sem a referida condição cardíaca, contudo, a redução foi de 18% em pacientes com DCV conhecida. O DECLARE-TIMI 58 evidenciou que indivíduos com diabetes mellitus tipo 2 possuem menor risco de IC e falecimento por eventos cardiovasculares entre aqueles que utilizaram a dapagliflozina comparados ao placebo (4,9% contra 5,8%). No Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), o número de mortes por causa cardiovascular foi de 9,7% contra 11,5% dos pacientes que tomaram placebo. No estudo EMPEROR-REDUCED, o desfecho primário ocorreu em 361 dos 1863 pacientes (19,4%) que receberam empagliflozina, em comparação com 462 dos 1867 pacientes (24,7%) no grupo que recebeu placebo. No estudo SOLOIST-WHF, analisando

o efeito da sotagliflozina, observou-se que o desfecho primário ocorreu em 245 pacientes no grupo que recebeu o medicamento comparado com 355 pacientes no grupo que recebeu placebo. **Conclusão:** Os pacientes com IC ganharam uma nova opção para o seu tratamento, a qual é, inclusive, citada nas diretrizes mais recentes de todo o mundo. No entanto, ainda são necessários novos estudos para avaliar sua eficácia e aplicabilidade na IC com fração de ejeção preservada.

Palavras-chave: Diabetes mellitus; insuficiência cardíaca; doenças cardiovasculares; doença renal crônica; mortalidade.

Introduction

Heart failure (HF) is a syndrome characterized by dyspnea or limitation to exertion caused by impaired ventricular filling, blood ejection, or both. HF can be classified according to the ejection fraction: preserved (≥ 50%), intermediate (between 41% and 49%), or reduced (≤ 40%)[1,2].

Studies using the oral antidiabetics sodium-glucose linked transporter 2 inhibitors (ISGLT2) showed its efficacy for reducing hospitalization and mortality due to HF3. ISGLT2 drugs were initially designed for treating type 2 diabetes mellitus (T2DM); however, they seem to be useful for other diseases. Recently, its beneficial effects have been discovered in patients at cardiovascular risk, focusing on HF with reduced ejection fraction (HFREF)[4].

The action mechanism of ISGLT2 in T2DM is the reduction of renal glucose reabsorption by inhibiting the sodium-glucose co-transporter-2 in the proximal tubule of the nephron. The action mechanism of ISGLT2 in HF is not yet known; however, the main studies on the topic (EMPA-REG, CANVAS, DECLARE-TIMI 58, dapagliflozin and Prevention of Adverse Outcomes in Heart Failure [DAPA-HF], dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease [DAPA-CKD], EMPEROR-Reduced, and SOLOIST-WHF) showed a decreased number deaths and hospitalizations due to cardiovascular causes[5-11].

METHODOLOGY

For the selection of the studies, we initially included randomized studies that qualified the ISGLT2 to be incorporated into clinical practice and the most updated guidelines worldwide. Then, complementary readings were chosen, including reviews published in high-impact journals, such as the Lancet, the New England Journal of Medicine, and Circulation.

Studies containing other benefits of ISGLT2 (e.g., renovascular protection) were selected to complement the review, and the literature on the treatment of HF was revisited.

Results and discussion

HFREF is the most important type of HF since it has an elucidated therapeutic basis and established treatments, such as symptom-relieving diuretics, disease-modifying drugs, and device therapies[12,13].

Patients with HFREF should be treated with a β-blocker and an angiotensin-neprilysin receptor inhibitor, except in cases of specific contraindications. The therapy may include the angiotensin-converting enzyme or the angiotensin sensor, and mineralocorticoid receptor antagonists may be added when persistent symptoms occur[14,15].

According to recent studies, ISGLT2 is a class of oral antidiabetics that is beneficial for patients with cardiovascular disease (CVD). The drugs empagliflozin, canagliflozin, dapagliflozin, and sotagliflozin are part of this class, and specific studies have been conducted to evaluate their effects in patients with and without diabetes[16].

One of the first high-impact studies was EMPA-REG, published in 2015, which evaluated 7,020 patients with T2DM and some previous CVD and had a mean follow-up of three years. This study was the first analysis to show the efficacy of ISGLT2 in CVD. The patients with T2DM at high risk of cardiac events receiving empagliflozin added to the standard treatment presented a lower rate of primary composite cardiovascular outcome and death from any cause than the placebo group. The primary outcome was death from cardiovascular causes, which occurred in 490 of 4687 patients (10.5%) from the empagliflozin group and in 282 of 2333 patients (12.1%)

from the placebo group. The hazard ratio in the empagliflozin group was 0.86 (p < 0.001, 95% confidence interval [95%CI]: 0.74 - 0.99)[5,17].

The canagliflozin research (CANVAS), published in 2017, included 10,142 patients with diabetes at high cardiovascular risk and with a mean follow-up of 3.5 years; the primary outcomes (death, acute myocardial infarction, stroke or hospitalization for cardiac causes) were less frequent in the group using canagliflozin than the placebo group (26.9 to 31.5 per 1000 patients per year, p < 0.001, 95%CI: 0.75 - 0.97). However, this study also found that the amputation risk increased by about 56% in patients using canagliflozin[6,18,19].

Dapagliflozin, one of the newest drugs in its class, has two impact studies on its efficacy. In addition, DECLARE-TIMI 58 was published in 2019 and followed 17,160 patients (7,000 with some atherosclerotic disease) for a mean period of 4 years. The study found that cardiovascular death or hospitalization due to HF significantly decreased (p = 0.005, 95%CI: 0.73 - 0.95). Although dapagliflozin does not result in a significant decrease in major cardiac events, it may cause adverse renal outcomes (p = 0.17, 95%CI: 0.84 - 1.03)[7,20].

A study published on dapagliflozin (DAPA HF) in September 2019 included 4,744 patients with HFREF and followed for a mean of 1.5 years; the risk of worsening HF or death from cardiovascular causes was lower in the dapagliflozin group than in the placebo group. Regardless of T2DM, patients (p < 0.001) presented 2.0% fewer deaths (9.6% with dapagliflozin vs. 11.5% in the placebo group; 95% CI 0.69 - 0.98) and 3.7% fewer hospitalizations (9.7% with dapagliflozin vs. 13.4% in the placebo group; 95% CI 0.59 - 0.83) in the primary outcome[7,8,21].

The DAPA-CKD study evaluated the long-term efficacy and safety of dapagliflozin in patients with chronic kidney disease with or without T2DM. Published in September 2020, the study included 4,304 patients, 2,906 (67.5%) with T2DM, and a mean glomerular filtration rate of 43.1 mL/min per 1.73 m2. The study concluded that patients receiving dapagliflozin had a lower risk of primary outcomes than those who received a placebo. In addition, those who received the drug had a lower risk of death from cardiovascular causes or hospitalization due to HF and longer survival than the placebo group (100 [4.6%] vs. 138 [6.4%], respectively, [p = 0.009, 95%CI: 0.55 - 0.92]). Considering those who presented primary outcomes, 112 under dapagliflozin (5.2%, 95%CI: 0.42 - 0.67) had a drop in the glomerular filtration rate estimated at more than 50%[9,22].

The EMPEROR-Reduced, a double-blind study published in 2020, analyzed 3,730 patients with ejection fraction below 40% and presented consistent results in the presence or absence of T2DM. A total of 1,863 received empagliflozin 10 mg once daily for 16 months, and 1,867 patients received a placebo. The primary outcome occurred in 361 of 1,863 (19.4%) in the empagliflozin group and 462 of 1,867 (24.7%) in the placebo group (p < 0.001, 95%CI: 0.65 - 0.86). Patients from the empagliflozin group had a lower risk of cardiovascular death or hospitalization due to HF, regardless of the presence of diabetes. The decreased glomerular function rate was slower, with a lower risk of severe kidney problems in the group receiving the drug; however, uncomplicated genitourinary infections were more often reported[10,23,24].

In November 2020, the SOLOIST-WHF study, published in the New England Journal of Medicine, was the latest study involving an ISGLT2 drug, which sought to evaluate the safety and benefits of sotagliflozin in patients with T2DM and recent hospitalization for decompensated HF. The study included 1,222 patients (608 from the sotagliflozin group and 614 from the placebo group). A total of 600 primary outcomes occurred: 245 in the drug group and 355 in the placebo group (p < 0.001, 95%CI 0.52 - 0.85). Those who received sotagliflozin had reduced cardiovascular mortality and hospitalization due to HF. Although the study was finished early because of the loss of funds from the sponsor, the benefits of this drug in patients with T2DM and HF were evidenced[11,25,26].

COMPLETION

ISGLT2 is very promising for the future treatment of HF, especially for patients with some other pre-existing comorbidity, such as diabetes and chronic kidney disease. However, more

studies must elucidate its real effectiveness and efficacy; in this context, more robust studies are expected for HF with preserved ejection fraction, considering the benefit demonstrated by these medications in patients with reduced ejection fraction. In future international and Brazilian cardiology guidelines, the use of these new drugs for treating CVD may be updated.

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