Journal of Advances in Medicine and Medical Research

Volume 36, Issue 7, Page 65-76, 2024; Article no.JAMMR.118046
ISSN: 2456-8899, NLM ID: 101711724
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Adverse Events of the Use of SGLT2 Inhibitors in Patients with Heart Failure: A Systematic Review and Meta-analysis

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Authors' contributions

This work was carried out in collaboration among all authors. 'All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/jammr/2024/v36i75486

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/118046

Systematic Review Article

Received: 09/04/2024
Accepted: 13/06/2024
Published: 18/06/2024

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Cite as: Britto , Mariana Feldner de, Ana Luiza Miranda de Oliveira, Ricardo Simões, Nathalia Sernizon Guimarães, Janaine Cunha Polese, and Alessandra Hubner de Souza. 2024. "Adverse Events of the Use of SGLT2 Inhibitors in Patients With Heart Failure: A Systematic Review and Meta-Analysis". Journal of Advances in Medicine and Medical Research 36 (7):65-76. https://doi.org/10.9734/jammr/2024/v36i75486.

ABSTRACT

Background: Sodium-glucose cotransporter 2 (iSGLT2) inhibitors are a class of medications used in the treatment of Heart Failure (HF) to prevent the development and worsening of the disease. Despite the benefits reported in the literature, it is essential to investigate its adverse effects. **Objective:** To evaluate the occurrence of hypotension, volume depletion and acute kidney injury in patients with HF with reduced (HFrEF) and preserved (HFpEF) ejection fraction using iSGLT2. **Methodology:** Systematic review and meta-analysis previously registered in PROSPERO (CRD42022365684) and carried out in the PubMed, EBSCO and LILACS databases. The risk of bias analysis was performed using the Cochrane risk-of-bias tool for randomized trials. RevMan 3.4.1 was used to perform the data meta-analysis.
Results: Of the 9,474 studies found, ten were included in the review. A risk of hypotension was observed in patients with HF using iSGLT2 (RR: 1.15; 95% CI 1.01 – 1.30; p=0.03; I2= 0%), but there was no risk statistically significant occurrence of volume depletion and acute kidney injury (RR: 1.12; 95% CI 1.95 – 1.33; p=0.17; I2= 0%; RR: 0.85; 95% CI 0 .69 – 1.06; p=0.14; **Conclusion:** In therapy with iSGLT2, an increased risk of adverse events of hypotension was observed, but no increased risk of volume depletion and acute kidney injury was observed. Despite the 15% reduction in relative risk in the outcome of acute kidney injury, the results suggest a renal benefit.

Keywords: Sodium-glucose transporter 2 inhibitors; heart failure; hypotension; systematic review.

1. INTRODUCTION

Heart failure (HF) is a major public health problem associated with death and hospitalization as it affects several systems, especially the kidney [1,2]. This pathology will affect the electrolyte balance, in which there is an imbalance in the glomerular filtration rate, leading to water and sodium retention with refractoriness to diuretics and endogenous natriuretic peptides [3].

Studies have demonstrated benefits of sodium-glucose cotransporter 2 (iSGLT2) inhibitors in reducing mortality, reducing hospitalization and/or worsening HF [4]. Despite the positive effects, there are concerns about iSGLT2 and its adverse effects such as urinary tract infections, dehydration, orthostatic hypotension, postural dizziness, syncope, hypotension, hyperkalemia-induced cardiac arrest, pancreatitis [5], postural hypotension and increased creatinine levels [6,7,8].

Continuous monitoring of volume status in patients with HF may help detect subclinical hemodynamic deterioration, but early detection is challenging [9]. iSGLT2 increase natriuresis and osmotic diuresis, decreasing circulatory volume by almost 7% [10]. In patients with HF, the incidence and impact of acute kidney injury have been reported [11-16]. Donnan et al., [17] evaluated patients with DM and the adverse event of acute kidney injury without proving an increased risk. In contrast, Menne et al., [18], Vukadinovic et al., [19] and Wahinya et al., [20] suggest that iSGLT2 can reduce the occurrence of acute kidney injury with DM.

As it is a relatively new class, there is a need to evaluate these long-term adverse events in patients with HF. Most of these events, such as hypotension, volume depletion and acute kidney injury, are reported by health professionals in clinical practice and cited in studies. Additionally, articles were published including new molecules in the class, such as Bexagliflozin and Licogliflozin. Global guidelines suggest the use of the iSGLT2 class as a priority in patients with HF. Therefore, the objective of this study was to evaluate the occurrence of adverse events in patients with HF using iSGLT2.

2. METHODS

This systematic review and meta-analysis was registered under the code CRD42022365684 on the platform PROSPERO.

2.1 Data Sources and Research

A systematic review and meta-analysis was conducted and described in accordance with the guidelines of the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA). The search for information was carried out in the following databases: PubMed, EBSCO and LILACS [21] in February of 2023, without restrictions on language, location or date. The descriptors were used according to the basis

MeSH and DeCS using the terms *sglt2 inhibitors, heart failure, reduced ejection fraction, preserved ejection fraction, hypotension, volume depletion, acute kidney injury* considering the appropriate booleans for each database. In addition, an active manual search of reference lists and systematic reviews identified as relevant to identify additional studies.

Two independent examiners (MB, AO) carried out the selection by titles using the software Rayyan, and then eligible abstracts were read independently [22]. After grouping the studies selected by both examiners and removing duplicate studies, the full texts of potentially relevant articles were obtained and each examiner independently analyzed the eligibility of the studies. For items that resulted in disagreement, a third examiner (JP) determined the priority of the study to be included. The extracted data was cross-checked. When necessary, the authors of the selected studies were contacted for clarification and to obtain quantitative data or information that was incomplete in the manuscripts. After 15 days without feedback, studies with missing data were excluded.

The articles were included considering the acronym PICOS: (P) population (adult individuals diagnosed with HFrEF or HFpEF); (I) type of intervention (use of iSGLT2); (C) standard therapies; (O) occurrence of hypotension, volume depletion and acute kidney injury and (S) randomized clinical trials. (Chart 1).

2.2 Assessment of study characteristics

2.2.1 Quantitative analysis

Data from the included studies were extracted using a spreadsheet with authors' names, year of publication, type of study, number of participants, name of the study - trial, country, follow-up time, gender, mean sample age, confidence interval, odds ratio, p value, main results (primary and secondary outcome), adverse events (hypotension, volume depletion and acute kidney injury), intervention, and results. After data extraction, studies were excluded if (1) there were any publications of new iSGLT2 studies that did not address the primary or secondary outcome in patients with HF; (2) presented incomplete data; (3) did not receive feedback from the authors.

P: The study with a sample composed of individuals diagnosed with HF was considered those who reported that the participants went through all stages of the algorithm for suspected HF diagnosis, such as: anamnesis, clinical examination, electrocardiogram (ECG) and X-ray of chest. Once the suspicion of HF is confirmed, the doctor may order natriuretic peptide tests and an echocardiogram to evaluate structural function, left ventricular ejection fraction (LVEF) and diastolic function. [23] In addition to these tests, Doppler echocardiography should be used to evaluate the functioning of cardiac anatomical structures and global longitudinal strain to characterize the ventricle, structural abnormalities, contractile performance, reverse remodeling, response to therapy and will probably expand phenotyping beyond EF [24].
I: Any study that used iSGLT2 at any dosage was considered. Different dosages have been exemplified in randomized clinical trials of the class de Isglt2 [25]. In addition, all iSGLT2 molecules will be included: Sotagliflozin, Ertugliflozin, Canagliflozin, Dapagliflozin, Empagliflozin, Luseogliflozin, Ipragliflozin, Tofogliflozin, Bexagliflozin and Licogliflozin.
C: The comparison in this study was standard therapy for the treatment of HF, such as: Renin – Angiotensin System Inhibitors (Angiotensin Converting Enzyme Inhibitors – ACEI; Angiotensin Receptor Blockers – ARB; Angiotensin and Neprilysin Receptor Inhibitors – INRA), Beta-blockers, Mineralocorticoid Receptor Antagonists – MRA, Isosorbide Dinitrate and Hydralazine, Ivabradine, Vericiguat- Soluble guanylate cyclase stimulator, Digoxin and Diuretics [26].
O: Regarding outcomes, studies reporting the occurrence of one or more of the outcomes investigated were included, as a primary or secondary outcome: hypotension, volume depletion and acute kidney injury.
S: Randomized clinical trials will be included.

Chart 1. Inclusion criteria for primary studies according to PICOS

2.3 Quality: Assessment of Risk of Bias

Two evaluators independently analyzed the risk of bias using the RoB 2 (*Cochrane risk-of-bias tool for randomized trials*) to assess the methodological quality of the included studies [27]. Any disagreements were resolved with the assistance of a third evaluator. The domains were classified as low, high or unclear risk of bias and, based on this, the included studies received the general classification for risk of bias: low, when it presented low risk of bias for all domains; high, when one or more domains were scored with a high risk of bias; or unclear, when no domain of the study was scored with a high risk of bias, but was scored with an unclear risk for one or more domains.

2.4 Data Analysis

The meta-analysis was carried out using the Review Manager Software 5.4.1. The Relative Risk (RR) presented by the studies was used for the three outcomes investigated. Random effects were used for all analyses. Heterogeneity between studies was tested using the I^2 test, where scores of 25%, 50% and 75% were considered low, moderate and high heterogeneity, respectivel [28].

3. RESULTS

9474 records were identified in the stipulated databases that met the inclusion criteria, with 974 records being removed due to duplication in the databases. Of the 8500 records, 8436 were excluded by title and abstract evaluation. Four records were entered manually because they were important articles that would contribute to the systematic review. Of the 70 records, 51 were excluded due to full text. Many of these studies relating to AHF were sub analyses of original articles or did not report the population with HF for the adverse event of interest. 19 articles were evaluated for eligibility and searched for retrieval. Of this total, one did not meet the eligibility criteria, five did not return from the authors and three did not have complete data. Of the initial total of records, 10 articles were included in this systematic review and meta-analysis. Fig. 1 contains the PRISMA flowchart with all the search information in databases and records.

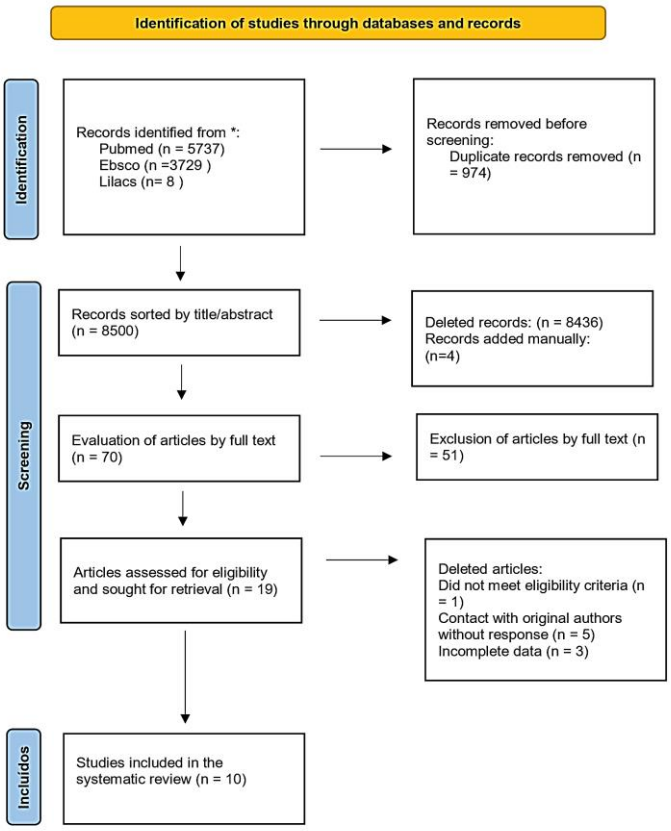

Fig. 1. Flowchart of included studies

Table 1. Characteristics of the included studies (n=10)

Variable	Anker et al., 2021 [29] (n=5988)	Lee et al., 2021 [30] (n=105)	McMurray et al., 2019 [31] (n=4744)	Mordi et al., 2020 [32] (n=23)	Nassif et al., 2019 [33] (n=263)	Nassif et al., 2021 [34] (n=324)	Neal et al., 2017 [35] (n=10142)	Omar et al., 2020 [36] (n=70)	Packer et al., 2020 [37] (n=3730)	Solomon et al., 2022 [38] (n=6263)
Average age - years	71,8	68,7	66,3	69,8	61,3	70,0	63,3	57,5	66,8	71,6
Sex/woman no. (%)	2676 (44,6)	28 (26,7)	1109(23,4)	6 (26,1)	70 (26,6)	184 (56,8)	3633 (35,8)	7 (10,0)	893 (23,9)	2747(43,9)
IMC, kg/m2	29,8	30,7	28,1	33,9	30,6	34,8	32,0	29,5	27,9	29,8
Functional class NYHA II no. (%)	4883 (81,5)	81 (77,1)	3203 (67,5)	NA	173 (65,8)	186 (57,4)	NA	58 (83,0)	2800 (75,0)	4713 (75,2)
FEVE on average (%)	54,3	32,5	31,0	NA	26,4	60,0	NA	26,5	27,4	54,1
Average NT-proBNP-pg/ml	1940	466	2874	2381	2272	675	NA	469	1906	*
Hospitalization for previous HF no. (%)	1369 (22,8)	52 (49,5)	2251 (47,4)	NA	209 (79,4)	181 (55,8)	NA	NA	1151 (30,8)	2539 (40,5)
Atrial fibrillation no. (%)	3057 (51,0)	NA	1818 (38,3)	NA	106 (40,3)	171 (52,7)	NA	18 (26,0)	1369 (36,7)	3552 (56,7)
Hipertension no. (%)	5424 (90,6)	74 (70,5)	NA	NA	NA	NA	9125 (90,0)	NA	2698 (72,3)	5553 (88,6)
Diabetes no. (%)	2938 (49,0)	82 (78,1)	1983 (41,8)	23 (100,0)	166 (63,1)	181 (55,9)	10142 (100,0)	12 (17,0)	1856 (49,8)	2806 (44,8)
TFG estimated – ml/min/1.73 m2	60,6	67,3	65,7	NA	69,0	55,0	76,5	80,5	62,0	61,0

*LVEF – Left ventricular ejection fraction. HF – Heart failure. BMI – Body mass index. NA – Not applicable. NT-ProBNP – N-terminal prohormone of type B natriuretic peptide. NYHA- New York Heart Association GFR – Glomerular filtration rate - *Data mentioned only in the subgroup analysis n= randomized patients*

Table 2. Adverse events of interest extracted from the included studies

Variable	Anker et al., 2021 [29] (n=5988)	Lee et al., 2021 [30] (n=105)	McMurray et al., 2019 [31] (n=4744)	Mordi et al., 2020 [32] (n=23)	Nassif et al., 2019 [33] (n=263)	Nassif et al., 2021 [34] (n=324)	Neal et al., 2017 [35] (n=10142)	Omar et al., 2020 [36] (n=70)	Packer et al., 2020 [37] (n=3730)	Solomon et al., 2022 [38] (n=6263)
Hipotension, n (%)	568 (9,5)	NA	18 (0,4)	1 (4,3)	NA	NA	NA	NA	339 (9,0)	NA
Volume depletion n (%)	NA	NA	NA	NA	19 (7,2)	18 (5,5)	25 (*)	0 (0,0)	381 (10,2)	74 (1,1)
Acute kidney injury n (%)	747 (12,4)	1 (1,9)	69 (1,4)	NA	1 (0,8)	10 (3,1)	3 (*)	0 (0,0)	NA	96 (1,5)
Assessment of outcomes in articles	Sec	Sec	Sec	Sec	Sec	Sec	Sec	Sec	Sec	Sec

NA – Not applicable – (*) – Given non-availability by the author – Sec – secondary

Table 3. Risk of bias in randomized clinical studies

Author	Randomization process	Deviations from intended interventions	Missing outcome data	Outcome measure	Selection of reported result	General bias
Anker et al. 2021 [29]	Low	Low	Low	Low	Low	Low
Lee et al. 2021 [30]	Low	Unclear	High	Low	Low	High
McMurray et al. 2019 [31]	Low	Low	Low	Low	Low	Low
Mordi et al. 2020 [32]	Low	Low	Low	Low	Unclear	Unclear
Nassif et al. 2019 [33]	Unclear	Unclear	Low	Low	Low	Unclear
Nassif et al. 2021 [34]	Low	Low	Low	Low	Low	Low
Neal et al. 2017 [35]	Low	Low	Low	Low	Low	Low
Omar et al. 2020 [36]	Low	Unclear	Low	Low	Low	Unclear
Packer et al. 2020 [37]	Unclear	Unclear	Unclear	Low	Low	Unclear
Solomon et al. 2022 [38]	Low	Low	Low	Low	Low	Low

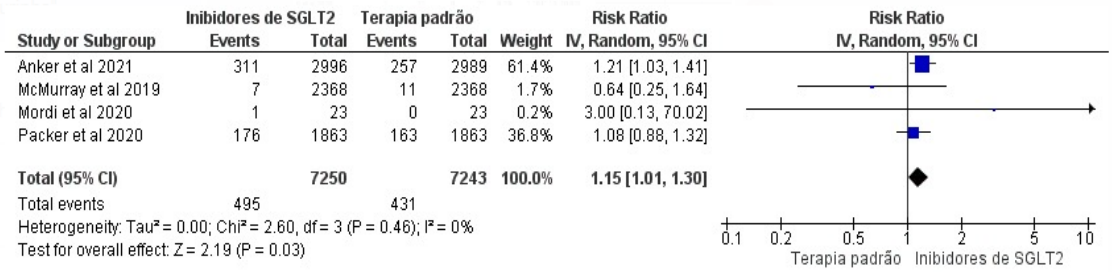

Fig. 2. Forest plot comparing the use of iSGLT2 with standard therapy in relation to the hypotension outcome

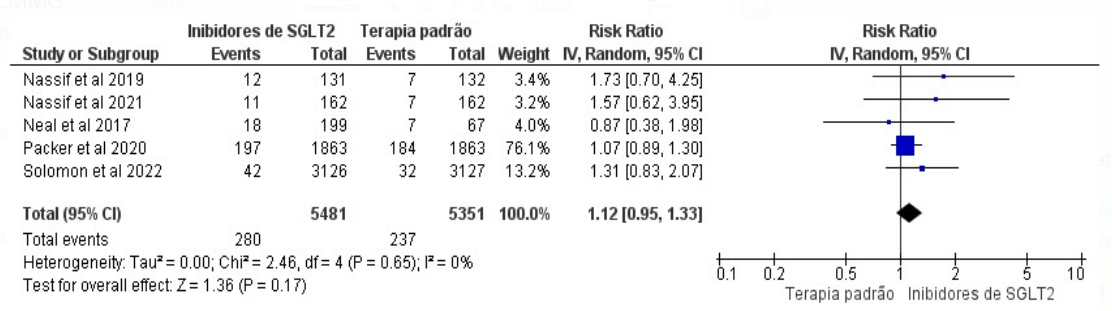

Fig. 3. Forest plot of comparing the use of iSGLT2 with standard therapy in relation to the outcome of volume depletion

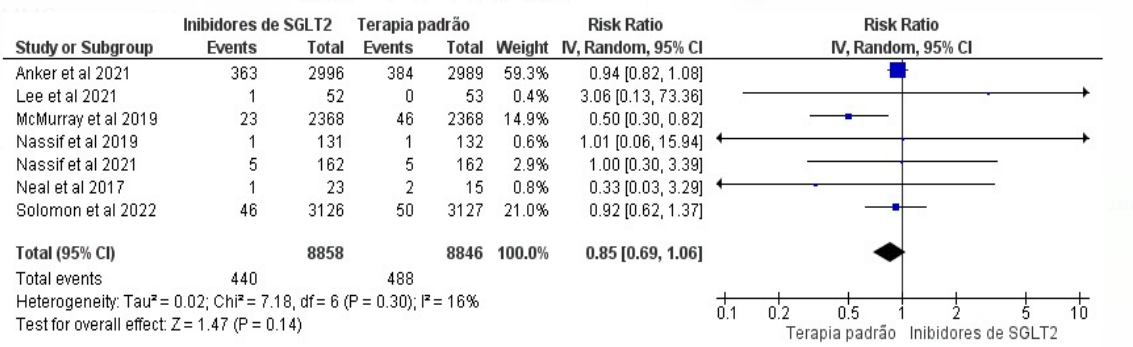

Fig. 4. Forest plot comparing the use of iSGLT2 with standard therapy in relation to the acute kidney injury outcome

Table 1 shows the variables taken from the 10 included studies. Table 2 shows the prevalence of adverse events in each primary study included. Table 3 presents the results of the risk of bias carried out in the 10 randomized clinical studies included.

The Fig. 2 shows the comparison of the use of iSGLT2 with standard therapy in relation to the hypotension outcome in four studies. A statistically significant difference and absence of heterogeneity were observed (RR: 1,15; 95% IC 1,01 – 1,30; P=0,03; I^2= 0%).

Fig. 3 shows the comparison of the use of iSGLT2 with standard therapy in relation to the outcome of volume depletion in five studies. It was observed that there was no statistically significant difference and no heterogeneity (RR: 1,12; 95% IC 0,95 – 1,33; P=0,17; I^2= 0%). The study data Omar et al., [37] were not included in the meta-analysis as both groups had no reported events.

Fig. 4 shows the comparison of the use of iSGLT2 with standard therapy in relation to the acute kidney injury outcome in seven studies. It

was observed that there was no statistically significant difference and low heterogeneity (RR: 0,85; 95% IC 0,69 – 1,06; P=0,14; I^2= 16%). The study data Omar et al., [37] were not included in the meta-analysis as both groups had no reported events.

4. DISCUSSION

The present systematic review and meta-analysis evaluated the outcomes of hypotension, volume depletion and acute kidney injury in patients with HFrEF and HFpEF after the use of iSGLT2. The results demonstrated that iSGLT2 have an increased risk of causing hypotension, but no significant increase in the risk of volume depletion and acute kidney injury associated with medication was observed.

Several articles, systematic reviews and meta-analyses have been published with the aim of evaluating the safety of using iSGLT2 in terms of the occurrence of hypotension, volume depletion and acute kidney injury. Even with so many publications, the literature is controversial about the relationship between the use of class and the outcomes of interest. For years, authors have sought to clarify in more depth the relationship between iSGLT2 and its renal action. Nespoux and Vallon, [39] addressed the drop in GFR induced by the use of the class at the beginning of treatment, as it could increase the risk of acute kidney injury, especially in patients with increased susceptibility (pre-existing low renal function). Despite being a discussion carried out to this day, it was observed, however, that the results of the present systematic review do not support such a theory. Toyama et al., [40] evaluated the efficacy and safety of iSGLT2 in 7363 patients with type 2 diabetes mellitus (T2DM) and CKD. Among the outcomes evaluated and of interest in this systematic review, acute kidney injury was evaluated without increased risk (RR: 0.69; 95% CI: 0.45-1.06). The class also attenuated the drop in estimated GFR and reduced the risk of renal composite outcome (RR: 0,71; 95% IC: 0,53-0,95).

Butler et al., [41] evaluated the safety and efficacy of iSGLT2 in 16,820 patients with HF. Regarding safety events, no increase in the risk of volume depletion was observed (RR: 1,11 0,98–1,25 P = 0,11; I^2 = 0%) and hypotension (RR: 1,05 0,84–1,32; P = 0,65; I^2 = 0%) with iSGLT2 compared to placebo. It has been associated with a decreased risk of acute kidney injury (RR: 0,63 IC 0,45–0,87 P = 0,006; I^2 = 14%). The class did not show an increased risk of serious adverse events. The present systematic review included a difference of three more randomized controlled trials than Butler et al., [41], totaling 22,971 patients evaluated. Another important point is that Butler et al., [41] included patients with AHF and the present analysis was only of patients with CHF. Furthermore, in this review we have studies of patients with HFpEF, subgroup or post hoc analyzes were not used to evaluate adverse events of interest, as in Butler et al., [41]. In the results of both analyses, the outcome of hypotension differs with increased risk in the present review. In the analysis of Butler et al., [41] the event of acute kidney injury presents a significant result, a benefit present in the class of iSGLT2 [42-44].

Rong et al., [16] analyzed the risk of orthostatic hypotension in 12,749 patients with DM2 associated with iSGLT2. 44 cases were reported (29 in the iSGLT2 group and 15 in the control group), with the result being grouped (RR: 1,17; 95% IC: 0,65–2,09). This meta-analysis shows that there was no evidence that iSGLT2 increases the risk of orthostatic hypotension when stratified by age, duration of T2DM and blood pressure. Although the author emphasizes caution when interpreting the data due to the possibility of underestimating the risk of asymptomatic orthostatic hypotension. This analysis presents a difference in the results obtained in the present review in relation to the outcome evaluated. Most of the studies included and evaluated by Rong et al., [16] are not included in the present review, and this could justify the difference in results in the risk of this event caused by iSGLT2.

Deshpande et al., [14] evaluated the safety of iSGLT2 in patients with DM2 and factors related to CVD, with ten articles included in the review. The frequency of acute kidney injury was statistically lower in the iSGLT2 group compared to placebo (2,6% x 3,1%, OR = 0,8; 95% IC 0,74–0,90). As for volume depletion, it was statistically more frequent in the iSGLT2 group compared to placebo 5,7% x 4,6% (OR = 1,2; 95% IC 1.07–1.41). The meta-analysis of the volume depletion outcome was associated with an increase in this event in patients using the class. The author explains that this result was possibly due to osmotic diuresis and glycosuria caused by iSGLT2, with the increase in this incidence being explained by the fact that the studies included in this meta-analysis included

patients with HF with or without CKD. This study differs from the present review as it included patients with AHF. Records of conferences and presentations were also included in the identification process. The outcome of volume depletion and acute kidney injury differs from the present review.

Zheng et al., [13] analyzed the CVD, renal and safety effects of iSGLT2 in 25,108 patients in the iSGLT2 group versus 18,574 in placebo. Safety data showed that the class induces a lower incidence of kidney damage and acute myocardial infarction, but on the other hand increases the risk of infection, amputation, volume depletion (RR: 1,22; 95% IC 1,11–1,33; P<0,0001; I^2=45%) and diabetic ketoacidosis. The present analysis showed divergence in volume depletion results, despite the high heterogeneity presented by Zheng et al., [13].

Menne et al., [18] conducted a review in patients with DM to evaluate the outcome of acute kidney injury through randomized clinical and observational studies. 112 randomized clinical trials and four observational trials with a minimum follow-up of 12 weeks that provided information on at least one renal adverse event (acute kidney injury, combined renal adverse event or related to hypovolemia) were included. In 30 studies, 410 serious adverse events of acute kidney injury were reported. iSGLT2 reduces the risk of acute kidney injury requiring hospitalization by 36% (OR: 0,64; 95% IC: 0,53–0,78 P < 0,001). A total of 1089 acute kidney injury events of any severity were published in 41 studies with reduced risk of acute kidney injury in 25% (OR: 0,75; 95% IC: 0,66–0,84 P < 0,001). Adverse events of hypovolemia were more reported in patients with iSGLT2 (OR: 1,20; 95% IC: 1,10–1,31 P < 0,001) compared to the control group. In observational studies, 777 acute kidney injury events were reported. According to a study, iSGLT2 reduces the chances of acute kidney injury (OR: 0,40; 95% IC: 0,33–0,48 P < 0,001). The review also included patients with type 1 diabetes mellitus (DM1), rarely seen in studies in this class.

Donnan et al., [17] evaluated the post-marketing safety of iSGLT2 identified by health regulatory agencies. The identification of studies in the databases was carried out through randomized clinical trials, with the outcomes studied: acute kidney injury, diabetic ketoacidosis, urinary tract infection, fractures and lower limb amputations, with 109 studies included in the review. When compared to placebo, iSGLT2 had significantly protective results against acute kidney injury (RR: 0,59; 95% IC: 0,39-0,89; I^2 =0,0%), while no difference was found for diabetic ketoacidosis (RR 0,66; 95% IC: 0,30-1,45, I^2 =0,0%), urinary tract infection (RR: 1,02; 95% IC: 0,95-1,09, I^2 =0,0%) or bone fracture (RR: 0,87; 95% IC: 0,69 -1,09, I^2 =1,3%). Evidence from these studies does not suggest an increased risk of the adverse events mentioned due to the use of the class. One limitation seen was that meta-analyses showed very wide confidence intervals for many comparisons suggesting limited precision, therefore clinically important adverse events cannot be ruled out. A point raised by the authors is that the significantly protective result against acute kidney injury was strongly estimated due to the EMPA-REG trial, because although acute kidney injury was reported in 11 studies, meta-analysis was only possible with placebo-controlled clinical trials and not by assets. When the meta-analysis is rerun with a pooled estimate after removing the EMPA-REG study, the result does not become significant. (RR 0,48; 95% IC 0,14 - 1,64; I^2 =0,0%). A difference between this study and the present analysis was that only patients with DM2 were defined, also presenting a statistical difference in the results of acute kidney injury.

Wahinya e Khan, [20] addressed the use of iSGLT2 in primary and secondary outcomes in the prevention of HF in patients with and without DM2, with 13 articles included in the review. Among the various adverse events evaluated by the authors, volume depletion is cited as a potential outcome for the result of hypotension and relates this to the diuretic effect of the class. However, no volume reduction has been reported that resulted in a significant increase in hypotension and this risk can be reduced by adjusting the dose of the diuretic. As for the outcome of acute kidney injury, a renoprotective effect was observed by iSGLT2. A limitation of this study addressed by the authors is that most of the HF prevention and comparator data for patients with and without DM2 came through subgroup analysis data, which may affect the power of the study. The present systematic review used only original randomized clinical studies, and subgroup analyzes were excluded from the research.

Vukadinovic et al., [19] performed a systematic review and meta-analysis with iSGLT2 evaluating the adverse events of hypotension, volume depletion and acute kidney injury in the

population of patients with HFrEF. Five randomized clinical studies were included, totaling a population of 10,050 patients. The outcome of hypotension was reported in 4.5% in the iSGLT2 group and 4.1% in the placebo group (RR 1,09; 95% IC: 0,91–1,31 P = 0,36). Volume depletion occurred in 9.4% in the iSGLT2 group and 8.7% in the placebo group (RR 1.07; 95% CI: 0.95–1.21 P = 0.25). Acute kidney injury was reported in few patients 1.9% in the iSGLT2 group than in the placebo group 2.8% showing low incidence of acute kidney injury (RR 0.69; 95% CI: 0.51–0.93 P = 0 .02). This review showed that iSGLT2 are not associated with a clinically relevant risk of hypotension and volume depletion and that their use reduces the risk of acute kidney injury. Despite the similarities between the present review and Vukadinovic et al., 202219 some points need to be raised. The search criteria reported by them involved the molecules Empagliflozin, Dapagliflozin, Canagliflozin, Ertugliflozin and Sotagliflozin, and in the present study, the molecules involved were Sotagliflozin, Ertugliflozin, Canagliflozin, Dapagliflozin, Empagliflozin, Luseogliflozin, Ipragliflozin, Tofogliflozin, Bexagliflozin and ozina. In the present review, patients with HFpEF and HFrEF were included, and Vukadinovic et al., [19] included only ICFER. In the present review, ten randomized clinical studies were included, totaling a population of 22,971 patients. An important difference between the meta-analyses was the inclusion of the SOLOIST-WHF study because Vukadinovic et al., [19] which presents a profile of a recently hospitalized and acute patient. In the present review, we chose to use only data from chronic patients. The author himself places the inclusion of this study as a limitation because it involves patients with HFpEF and was not an inclusion criterion for PICO. The results presented in the review of Vukadinovic et al., [19] are divergent from those of the present review in relation to the outcomes of hypotension and acute kidney injury.

Although the previous systematic review investigated the effects of the use of iSGLT2 on the adverse events of interest to this dissertation, additional clinical trials were developed in the last year, which could modify the inferences obtained from the meta-analyses. Furthermore, it is necessary to develop systematic reviews based on robust scientific guidelines, in order to provide reliable and bias-free scientific evidence. It is important to highlight that, as it is a relatively recent class of drugs and with the arrival of new studies and molecules on the market, there is still a need to evaluate long-term adverse events.

This review presents strengths and weaknesses. The main points that strengthen this review are the use only of randomized studies for data collection (excluding any post-publication sub analysis of the original study or gray literature), use only of patients with HF, excluding any work with patients with HF, thus avoiding interference in outcomes. Meta-analyses showed zero or low heterogeneity, resulting in uniform data. A weak point, a limitation of the present systematic review, is the assessment of outcomes only in the short term. The literature does not present long-term studies or large records, which are important for evaluating these outcomes. Another limitation is the use of several molecules, dosages and patient profiles within the same analysis, and these studies were performed in different countries with different populations and ethnicities. At last, there is the relationship of patients with HF who are polymedicated and have several comorbidities that could affect the results of the present analysis.

5. CONCLUSION

This systematic review and meta-analysis showed that iSGLT2 therapy leads to an increased risk of hypotensive adverse events. No increased risk of volume depletion and acute kidney injury was observed in association with iSGLT2. Despite the 15% reduction in relative risk (not significant) in the outcome of acute kidney injury, the results suggest a renal benefit. This analysis shows us that despite an increasing number of publications in recent years involving adverse events related to the use of iSGLT2, there is still divergence of results, leading to the need for future work with the class.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

To professor carlos vinícius palhares, from the research and extension sector of the faculty of medical sciences of minas gerais, for reviewing and translating the text into the English version.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Mesquita ET, Jorge AJL, Rabelo LM, Souza Jr. CV. Understanding hospitalization in patients with heart failure. International Journal of Cardiovascular Sciences. 2016.
2. Carlos A, Sousa S, Felice A, Issa C, Ramos Nascimento B, Filho H, et al. Atualização de tópicos emergentes da diretriz brasileira de insuficiência cardíaca 2021. Arq. Bras. Cardiol. 2021;116(6):1174-1212.
3. Alessia Buglioni, Burnett JC. Pathophysiology and the cardiorenal connection in heart failure. Circulating hormones:biomarkers or mediators. Clin Chim Acta; 2015.
4. Zeng Q, Zhou Q, Liu W, Wang Y, Xu X, Xu D. Mechanisms and perspectives of sodium-glucose co-transporter 2 inhibitors in heart failure. Front Cardiovasc Med. 202;8.
5. Jasleen B, Vishal GK, Sameera M, Fahad M, Brendan O, Deion S, et al. Sodium-glucose cotransporter 2 (SGLT2) inhibitors: benefits versus risk. Cureus; 2023.
6. Lai L, Zhang Y, Li X, Zhang Y, Zhang M, zhao. Efficacy and safety of SGLT2 inhibitors in the treatment of heart failure-may raise creatinine levels in patients: a meta-analysis [Internet]. Authorea; 2022.
7. Soloveva A, Fedorova D, Villevalde S, Zvartau N, Mareev Y, Sitnikova M, et al. Addressing orthostatic hypotension in heart failure: pathophysiology, clinical implications and perspectives. J Cardiovasc Transl Res. 2020;13(4):549–69.
8. Cautela J, Tartiere J, Cohen-Solal A, Bellemain-Appaix A, Theron A, Tibi T, et al. Management of low blood pressure in ambulatory heart failure with reduced ejection fraction patients. Eur J Heart Fail. 2020;22(8):1357–65.
9. Min K-D, Asakura M. Evaluation of volume depletion in patients with heart failure using intrathoracic impedance monitoring. Circ J. 2012;76(11):2538–9.
10. Lu H, Meyer P, Hullin R. Use of SGLT2 inhibitors in cardiovascular diseases: why, when and how? Swiss Med Wkly; 2020.
11. Holgado JL, Lopez C, Fernandez A, Sauri I, Uso R, Trillo JL, et al. Acute kidney injury in heart failure: a population study. ESC Heart Fail. 2020;7(2):415–22.
12. Boorsma EM, ter Maaten JM, Voors AA, van Veldhuisen DJ. Renal Compression in Heart Failure. JACC Heart Fail. 2022;10(3):175–83.
13. Zheng C, Lin M, Chen Y, Xu H, Yan L, Dai H. Effects of sodium-glucose cotransporter type 2 inhibitors on cardiovascular, renal, and safety outcomes in patients with cardiovascular disease: a meta-analysis of randomized controlled trials. Cardiovasc Diabetol. 2021;20(1):83.
14. Deshpande R, Patel R, Manjari Regmi, Salih M, Kropp R, Basma Al-bast, et al. Safety outcomes of sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes and other risk factors for cardiovascular disease: a systematic review and meta-analysis. Cardiovasc Endocrinol Metab. 2023;12(2).
15. Butler J, Usman MS, Khan MS, Greene SJ, Friede T, Vaduganathan M, et al. Efficacy and safety of SGLT2 inhibitors in heart failure: systematic review and meta-analysis. ESC Heart Fail. 2020;7(6):3298–309.
16. Rong X, Li X, Gou Q, Liu K, Chen X. Risk of orthostatic hypotension associated with sodium-glucose cotransporter-2 inhibitor treatment: A meta-analysis of randomized controlled trials. Diab Vasc Dis Res. 2020;17(5):147916412095362.
17. Donnan JR, Grandy CA, Chibrikov E, Marra CA, Aubrey-Bassler K, Johnston K, et al. Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis. BMJ Open. 2019;9(1): e022577.
18. Menne J, Dumann E, Haller H, Schmidt BMW. acute kidney injury and adverse renal events in patients receiving sglt2-inhibitors: a systematic review and meta-analysis. Taal MW, editor. PLoS Med. 2019;16(12):e1002983

19. Vukadinović D, Abdin A, Anker SD, Rosano GMC, Mahfoud F, Packer M, et al. Side effects and treatment initiation barriers of sodium-glucose cotransporter 2 inhibitors in heart failure: a systematic review and meta-analysis. Eur J Heart Fail; 2022.
20. Wahinya M, Khan Z. Sodium-Glucose cotransporter-2 (SGLT2) inhibitor therapy for the primary and secondary prevention of heart failure in patients with and without type 2 diabetes mellitus: a systematic review. Cureus; 2023.
21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372(71).
22. Helena A, Luiza A, Carolina Gassen Fritsch, Zouch J, Ferreira PH, Janaine Cunha Polese. Usefulness of machine learning softwares to screen titles of systematic reviews: a methodological study. Syst Rev. 2023;12(1).
23. Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC de, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq. Bras. Cardiol. 2018;111(3).
24. Bozkurt B, Coats A, Tsutsui H. A Report of the Heart Failure Society of America, Heart failure association of the european society of cardiology, japanese heart failure society and writing committee of the universal definition of heart failure consensus conference. Eur J Heart Fail. 2021;23(3).
25. Joshi SS, Singh T, Newby DE, Singh J. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. Heart. 2021;107(13).
26. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. Circulation. 2022;145(18).
27. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
28. Higgins JPT. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557–60.
29. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021; 385(16).
30. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, et al. Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). Circulation; 2020.
31. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21).
32. Mordi NA, Mordi IR, Singh JS, McCrimmon RJ, Struthers AD, Lang CC. Renal and cardiovascular effects of sglt2 inhibition in combination with loop diuretics in patients with type 2 diabetes and chronic heart failure: the recede-chf trial. Circulation; 2020.
33. Nassif ME, Windsor S, Tang F, Khariton Y, Husain M, Inzucchi SE, et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: the define-hf trial. Circulation; 2019.
34. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med. 2021;27:1–7.
35. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes N Engl J Med. 2017;377(7):644–57.
36. Omar M, Jensen J, Frederiksen P, Kistorp C, Lars Videbæk, Mikael Kjær Poulsen, et al. Effect of empagliflozin on hemodynamics in patients with heart failure and reduced ejection fraction. J Am Coll Cardiol. 2020;76(23):2740–51.
37. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15).
38. Solomon SD, McMurray JJV, Claggett B, de Boer RA, De Mets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly

reduced or preserved ejection fraction. N Engl J Med; 2022.

39. Nespoux J, Vallon V. SGLT2 inhibition and kidney protection. Clin Sci (Lond). 2018;132(1):1329–39.
40. Toyama T, Neuen BL, Jun M, Ohkuma T, Neal B, Jardine MJ, et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis. Diabetes Obes Metab. 2019;21(5):1237–50.
41. Butler J, Usman MS, Khan MS, Greene SJ, Friede T, Vaduganathan M, et al. Efficacy and safety of SGLT2 inhibitors in heart failure: systematic review and meta-analysis. ESC Heart Fail. 2020;7(6):3298–309.
42. Elnaggar MR, Zeid AESA, Elhadary GK, Ahmed RM. Predictors and outcome of in-hospital cardiac arrest patients in emergency department suez canal university hospitals. Cardiology and Angiology: An International Journal. 2022;11(4):282–294. Available:https://doi.org/10.9734/ca/2022/v11i4284.
43. Naaim M, Ztati M, Jamili ME, Karimi SE, Hattaoui ME. Heart arrest revealing a killer coronary artery. Asian Journal of Cardiology Research. 2023;6(1):414–419. Available:https://journalajcr.com/index.php/AJCR/article/view/188.
44. Kemp CD, Conte JV. The pathophysiology of heart failure. Cardiovascular Pathology. 2012;21(5):365-71.

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