Original Article

Heart Failure Treatment with SGLT2 Inhibitors: A Systematic Review with Meta-Analysis

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Abstract

Background: **Heart failure (HF) is a clinical diagnosis of a condition that develops secondary to either left ventricular systolic or diastolic functions. Lately, inhibitors of sodium-glucose cotransporter 2 (SGLT2) have been added to the list of drugs used in the management of HF.**

Objectives: **To compare the efficacy of SGLT2 inhibitors to traditional treatment in hospitalization and death for HF.**

Methods: **Relevant databases were searched for articles published until October 2023. Out of 24 nonduplicated screened studies, 11 studies were selected. The primary analysis was for cardiovascular death, and the secondary analysis was for hospitalization for HF.**

Results: **We selected 11 for the systematic review and 8 studies for quantitative analysis, accounting for 54,381 patients from over 800 health centers worldwide. The use of SGLT2 inhibitors significantly reduced cardiovascular death in all patients when compared to placebo (HR 0.85, 95%CI 0.78-0.91) and also reduced hospitalizations for HF (HR 0.71, 95%CI 0.67-0.76).**

Conclusions: **Patients with HF in the use of SGLT2 inhibitors have a better outcome than those with conventional treatment; SGLT2 inhibitors protect 15% from cardiovascular death and 29% from hospitalizations.**

Keywords: **Sodium-Glucose Transporter 2 Inhibitors; Heart Failure; Mortality.**

Introduction

Heart failure (HF) is a clinical diagnosis of a condition that develops secondary to either left ventricular (LV) systolic and diastolic functions.[1] Although there were significant advancements in therapies designed to prevent and/or treat HF once it is established, patients' prognosis after the first hospitalization is still poor.[2] The underlying causes of chronic HF (CFH) are divided into 4 categories: (i) traditional risk factors such as ischemic injury, hypertension, and metabolic syndrome;[3,4] (ii) genetic cardiomyopathies, i.e., hypertrophic cardiomyopathy;[5-7] (iii) valve dysfunction, most commonly aortic stenosis;[3,4] (iv) autoimmune and infectious triggers where the innate and adaptative immune systems are activated to coordinate a primary response.[8,9]

CHF diagnosis requires the presence of symptoms, usually breathlessness, fatigue, paroxysmal nocturnal dyspnea, and/or signs of HF, such as elevated jugular venous pressure, hepatojugular reflux, and third heart sound, and objective evidence of cardiac dysfunction that can be presented by BNP ≥ 35 pg/ml (B-type natriuretic peptide), abnormal electrocardiogram and abnormal findings in echocardiography.[10] After CHF diagnosis, traditional management consists of using an angiotensin-converting enzyme inhibitor or angiotensin receptor-neprilysin inhibitor, beta-blocker, mineralocorticoid receptor antagonist, and loop diuretic for fluid retention.[11-13]

Lately, inhibitors of sodium-glucose cotransporter 2 (SGLT2) have been added to the list of drugs used in the management of HF.[10] Studies have shown that SGLT2 inhibitors reduce the risk of hospitalization for HF,[14-17] and possible mechanisms of actions have been raised such as effects on myocardial metabolism, ion transporters, fibrosis, adipokines, and vascular function that are associated with diuretic and hemodynamic actions and preservation of renal function.[18-22] Therefore, this work aims to compare the efficacy of SGLT2 inhibitors to traditional treatment in hospitalization and death for HF.

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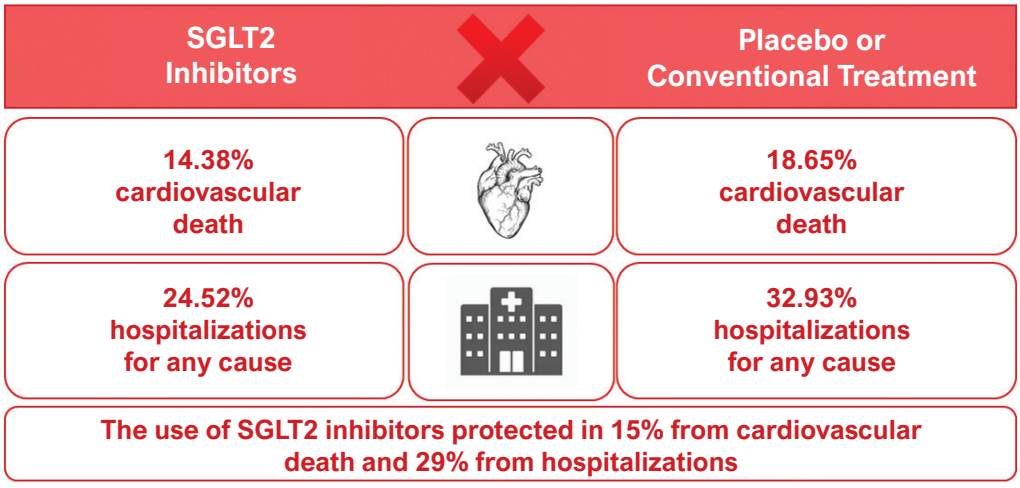
Central Illustration: Heart Failure Treatment with SGLT2 Inhibitors: A Systematic Review with Meta-Analysis



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Cardiovascular death and hospitalizations for any cause in the use of SGLT2 inhibitors and placebo/conventional treatment.

Methods

Search Strategy

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA),[23] Meta-Analysis of Observational Studies in Epidemiology (MOOSE),[24] and Cochrane[25] recommendations, and it was considered exempt from approval by an Institutional Review Board. The guiding question of this review was, "Patients with chronic heart failure using gliflozins have a better outcome than with conventional treatment?". Two electronic databases (MEDLINE/Pubmed and SciELO) were searched for relevant articles using the following terms: "Heart Failure,"/ "Heart Failure with Reduced Ejection Fraction"/ "SGLT2 inhibitor"/ "Cardiovascular Outcome"/ "Dapagliflozin"/ "Empagliflozin"/ "Sotagliflozin"/ "Ertogliflozin"/ "Type 2 Diabetes"/ "Recommended therapy"/ "Outcome"/ "iSGLT2"/ "Insuficiência Cardíaca Crônica"/ "Gliflozina"/ "Empagloflozina"/ "Dapagliflozina"/ "Melhor prognóstico"/ "Tratamento convencional". The search was performed from inception to October 2023 in English, Spanish, and Portuguese languages. Figure 1 displays the PRISMA flow diagram. Two pairs of authors independently screened all titles and abstracts, and relevant records were selected for full review.

Eligibility criteria

We included studies that evaluated cardiovascular death and hospitalization due to CHF with the use of traditional treatment and SGLT2 inhibitors. We excluded studies that had unclear reporting data or outcomes of interest or combined outcomes, making it impossible to analyze the data. For quantitative analysis, we excluded that exclusively evaluated subgroup populations that differed from participants in the review. We selected studies with large samples in prospective studies (randomized clinical trials and cohort studies). Retrospective studies, cross-sectional studies, case reports, abstracts, reviews, editorials, and conference reports were excluded.

Data extraction and risk of bias assessments

Data were gathered by 2 authors using a pre-defined data extraction sheet that included study details, baseline patient demographics, clinical characteristics, and outcomes of interest. Disagreements were resolved by consensus after consulting a senior author. If the baseline patient characteristics were separated by groups, wherever possible, we pooled data attributable to the whole population using mean (SD).[26] The 2 authors also assessed the risk of bias in the included studies, according to the criteria from the Cochrane Handbook for Systematic Reviews of Interventions.[25]

Statistical analysis

All analyses were performed using Review Manager (RevMan) statistical software version 5.4 (Informer Technologies, Inc., Los Angeles, California, USA). Between-study heterogeneity was assessed with I^2 statistic and classified as $<25\%$, indicating low risk of heterogeneity, and $>75\%$ indicated high heterogeneity. The risk of bias analysis was performed using the Risk-of-Bias Tool for Randomized Trials (RoB 2.0),[27] which considers five domains for bias assessment: D1 – bias arising from randomization process;

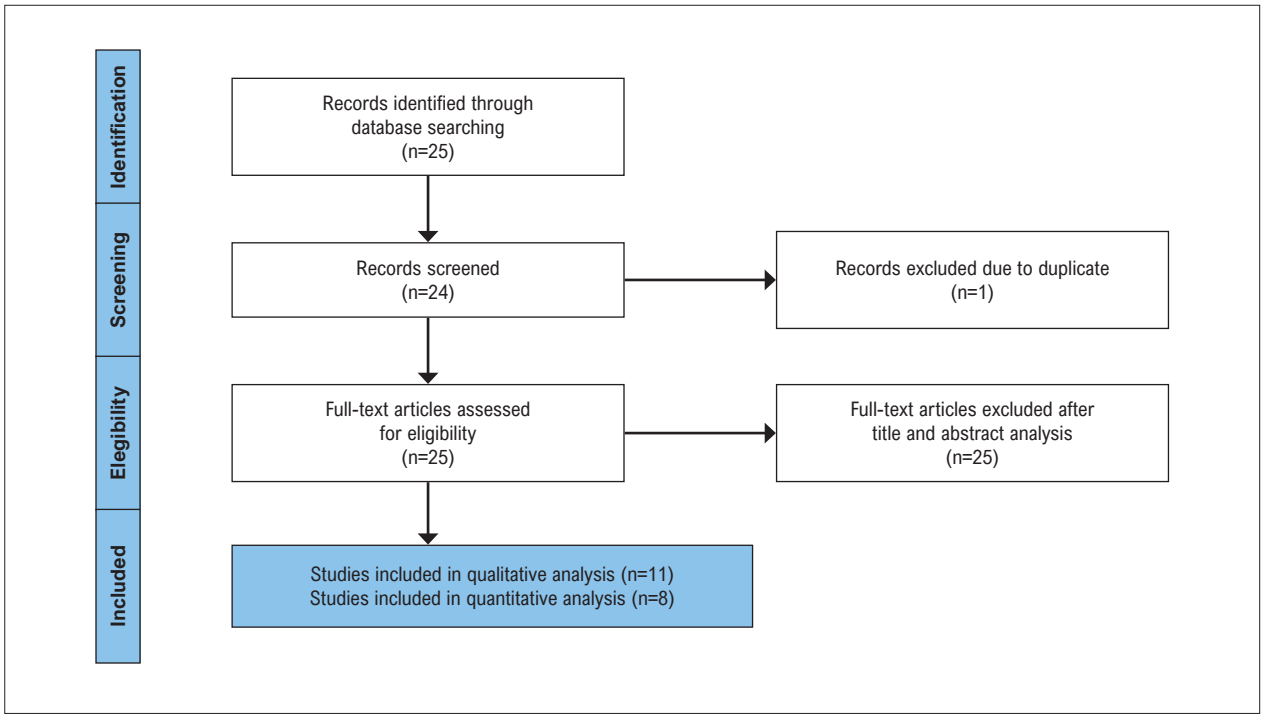

Figure 1 – *PRISMA flowchart. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.*

D2 – bias due to deviations from intended intervention; D3 – bias due to missing outcome data; D4 – bias in the measurement of the primary outcome; D5 – bias in the selection of the reported result. All the domains were classified as low risk, high risk, or unclear risk (or some concerns) for each of the domains.

Results

Study selection

Electronic searches yielded 24 nonduplicated studies. After the title and abstract assessment, 13 studies were excluded, and 11 were selected for full-text evaluation, and they were deemed eligible to be included in our systematic review. For quantitative analyses, 4 studies were excluded from the meta-analysis. A summary of the 11 selected studies for the systematic review is provided in Table 1.

Study population

This meta-analysis accounted for 54,381 patients from over 800 health centers worldwide, and the mean age was 69 years old for the treatment group and 70 years old for the control group. The population characteristics of the studies are summarized in Table 2.

Primary analysis: Cardiovascular death

The analysis of the 8 studies revealed that the use of SGLT2 inhibitors significantly reduced cardiovascular death in all patients when compared to placebo or traditional therapy with low heterogeneity between the studies (HR 0.85, 95%CI 0.78-0.91, $I^2 = 24\%$) (Figure 2).

Secondary analysis: Hospitalization

The analysis of the 8 studies also revealed that the use of SGLT2 inhibitors significantly reduced hospitalization for HF in all patients when compared to placebo or traditional therapy with no heterogeneity between the studies (HR 0.71, 95%CI 0.67-0.76, $I^2 = 0\%$) (Figure 3).

Risk bias assessments

Great companies and statistical centers supervised all studies used for quantitative analyses; they were all randomized and double-blinded. Therefore, the risk of bias was low for almost all evaluated domains (Figure 4).

Discussion

HF is a chronic progressive disease that develops over LV systolic and/or diastolic dysfunction that is the leading cause of hospitalization for individuals older than 65 years old.[37] The most common causes of hospitalization with HF are noncompliance with medications, diet, activity routines, and failure to report worsening symptoms. Since effective treatments have prolonged the survival of patients with myocardial infarction (MI) and acute coronary syndromes, the incidence of people living with HF is growing, and the number of patients at risk of developing HF is projected to rise dramatically.[38]

There are many risk factors for the development of HF, and hypertension may be the most important one. As the blood

Table 1 – Main characteristics and results of the included studies in the systematic review

First author, year (Ref. No.)	No. of participants	Treatment Group	Control Group	Treatment in use	Control in use	Primary Outcome	Results
Solomon, 2022[28]	6,263	3,131	3,132	Dapagliflozin 10mg	Placebo in addition to usual therapy	Cardiovascular death	Primary outcome occurred in 512 of 3,131 patients (16.4%) in the treatment group and in 610 of 3,132 patients (19.5%) in the control group (HR 0.82, 95%CI 0.73-0.92, p < 0.001).
Anker, 2021[29]	5,988	2,997	2,991	Empagliflozin 10mg	Placebo in addition to usual therapy	Cardiovascular death	Primary outcome occurred in 415 of 2,997 patients (13.8%) in the treatment group and in 511 of 2,991 patients (17.1%) in the control group (HR 0.79, 95%CI 0.69-0.90, p < 0.001).
Bhatt, 2021[30]	1,222	608	614	Sotagliflozin 200 ou 400mg	Placebo	HF hospitalization or cardiovascular death	Primary outcome occurred in 245 of 608 patients (40.3%) in the treatment group and in 355 of 614 patients (57.8%) in the control group (HR 0.67, 95%CI 0.52-0.85, p < 0.001).
Lee, 2021[31]	105	52	53	Empagliflozin 10mg	Placebo	Change in LV end-systolic and diastolic volume indexed to body surface area and LV global longitudinal strain	Treatment reduced LV end-systolic volume index by 6.0 mL/m² (p = 0.015) and LV end-diastolic volume index by 8.2 mL/m² (p = 0.0042). There was no significant difference in LV global longitudinal strain.
Santos-Gallego, 2021[32]	84	42	42	Empagliflozin 10mg	Placebo	Change in LV systolic and diastolic volume	Empagliflozin was associated with a significant reduction of LV end-systolic volume (p < 0.001) and LV end-diastolic volume (p < 0.001).
Cannon, 2020[33]	8,246	5,493	2,745	Ertugliflozin 5 ou 15mg	Placebo	MACE	There was no significant difference between both groups in this study.
Jensen, 2020[34]	190	95	95	Empagliflozin 10mg	Placebo	Effects of Empagliflozin on NT-proBNP of HF patients	There was no significant difference between both groups in this study.
Packer, 2020[35]	3,730	1,863	1,867	Empagliflozin 10mg	Placebo in addition to usual therapy	HF hospitalization or cardiovascular death	Primary outcome occurred in 361 of 1,863 patients (19.4%) in the treatment group and in 462 of 1,867 patients (24.7%) in the control group (HR 0.75, 95%CI 0.65-0.86, p < 0.001).
Mc Murray, 2019[36]	4,744	2,373	2,371	Dapagliflozin 10mg	Placebo in addition to usual therapy	Cardiovascular death	Primary outcome occurred in 386 of 2,373 patients (16.3%) in the treatment group and in 502 of 2,371 patients (21.2%) in the control group (HR 0.74, 95%CI 0.65-0.85, p < 0.001).
Wiviott, 2018[16]	17,160	8,574	8,569	Dapagliflozin 10mg	Placebo	MACE or death for HF hospitalization	Dapagliflozin did not result in a significant lower rate of MACE (HR 0.93, 95%CI 0.84-1.03, p = 0.17), but it did result in a significant lower rate of cardiovascular death for HF hospitalization (HR 0.83, 95%CI 0.73-0.95, p = 0.005).
Zinman, 2015[14]	7,020	4,687	2,333	Empagliflozin 10 or 25mg	Placebo	MACE	Primary outcome occurred in 490 of 4,687 patients (10.5%) in the treatment group and in 282 of 2,333 patients (12.1%) in the control group (HR 0.86, 95%CI 0.74-0.99, p = 0.04).

HF: heart failure; HR: hazard ratio; 95%CI: 95% confidence interval; MACE: major cardiovascular events; LV: left ventricle.

pressure rises and as the patient ages, the risk of developing HF also rises. Long-term treatment for hypertension can decrease HF by approximately 50%, approximately.[39] Thus, diabetes mellitus (DM) and metabolic syndrome are also important risk factors for HF since these conditions lead to high blood pressure, high insulin levels, atherosclerosis, coronary artery disease, myocardial ischemia, thrombosis, MI, and other cardiac abnormalities, such as loss of cardiac muscle and ventricular dilation.[40,41]

Gliflozins or sodium-glucose linked transporter 2 (SGLT2) inhibitors are a class of oral drugs used preferentially in the treatment of type 2 DM.[42] Their pharmacodynamics involves the inhibition of SGLT2 channels located in the renal proximal convoluted tubule reducing the renal threshold for glucose excretion from 180 mg/dl for 40 mg/dl.[43] The consequence is lower blood glucose levels, reducing glucotoxicity, and improving β-cell function.[44] Lately, many clinical trials are showing other effects of these drugs on cardiovascular (CV) outcomes, not only preventing CV diseases but reducing CV death and hospitalization for HF.[29-31,36,44]

In this meta-analysis, the use of SGLT2 inhibitors significantly reduced the risk of CV death in 15% (HR 0.85, 95%CI 0.78-091) and the hospitalization for HF in 29% (HR 0.71, 95%CI 0.67-0.76). This result corroborates with Zannad et al.[45] meta-analyses, where they found a 14% reduction in cardiovascular death (HR 0.86, 95%CI 0.76-0.98) and a 25% decrease in hospitalization for HF (0.75, 95%CI 0.68-0.84). These results combine subgroups of patients that have HF + type 2 DM and patients with only HF. The exact mechanisms by which SGLT2 inhibitors can reduce cardiovascular death are not completely established. However, it seems that it can be related to sodium balance, energy homeostasis, and mitigation of cellular stress, and all of these combined can induce cardio- and nephroprotective effects.[46-48]

One mechanism that is considered for the action of SGLT2 inhibitor to be beneficial for patients with HF is that SGLT2 colocalizes and functionally interacts with sodium-hydrogen exchanger (NHE) in the proximal renal tubule. The NHE is primarily responsible for the sodium reuptake after filtration.[49] In HF, NHE activity is increased, and studies have shown that it may be responsible for resistance to diuretics and endogenous natriuretic peptides in these patients.[50,51] However, it has been shown that SGLT2 inhibitors can also interfere with NHE activity, increasing natriuresis that can be potentiated with the use of drugs that block sodium reabsorption in the loop of Henle and distal collecting tubule. This effect largely decreases the intravascular volume, reducing cardiac wall stress and promoting a favorable effect on the development and progression of HF.[52,53]

This mechanism can also be associated with the reduction of hospitalization in HF patients with and without DM since the combined effect of inhibition of SGLT2 and NHE can attenuate cardiomyocyte injury, reducing, by consequence, cardiac hypertrophy, fibrosis, cardiac remodeling, systolic dysfunction,

Table 2 – Population clinical features of the included studies in the meta-analysis

First author, year	No. of participants	No. of Centers	Age (Mean) SGLT2i	Age (Mean) Control	Female SGLT2i (%)	Female Control (%)	Clinical Features SGLT2i (%)	Clinical Features Control
Anker, 2021[29]	5,988	622	71.8	71.9	1,338 (44.6)	1,338 (44.7)	Mean LV ejection fraction 54.4	Mean LV ejection fraction 54.3
Bhatt, 2021[30]	1,222	306	69.0	70.0	198 (32.6)	214 (34.9)	Mean LV ejection fraction 35.0	Mean LV ejection fraction 35.0
Cannon, 2020[33]	8,246	567	64.4	64.4	3,866 (70.3)	1,903 (69.3)	Coronary revascularization 57.8	Coronary revascularization 58.7
McMurray, 2019[36]	4,744	410	66.2	66.5	564 (23.8)	545 (23.0)	Mean LV ejection fraction 31.2	Mean LV ejection fraction 30.9
Packer, 2020[35]	3,730	520	67.2	66.5	437 (23.5)	456 (24.4)	Mean LV ejection fraction 27.7	Mean LV ejection fraction 27.2
Solomon, 2022[28]	6,263	353	71.8	71.5	1,364 (43.6)	1,383 (44.2)	Mean LV ejection fraction 54.0	Mean LV ejection fraction 54.3
Wiviott, 2018[16]	17,160	882	63.9	64.0	3,171 (36.9)	3,251 (37.9)	Atherosclerotic CV disease 40.5	Atherosclerotic CV disease 40.8
Zinman, 2015[14]	7,020	590	63.0	63.2	1,351 (28.8)	623 (28.0)	Atherosclerotic CV disease 75.6	Atherosclerotic CV disease 75.6

SGLT2i: sodium-glucose linked transporter 2 inhibitors; CV: cardiovascular; LV: left ventricle.

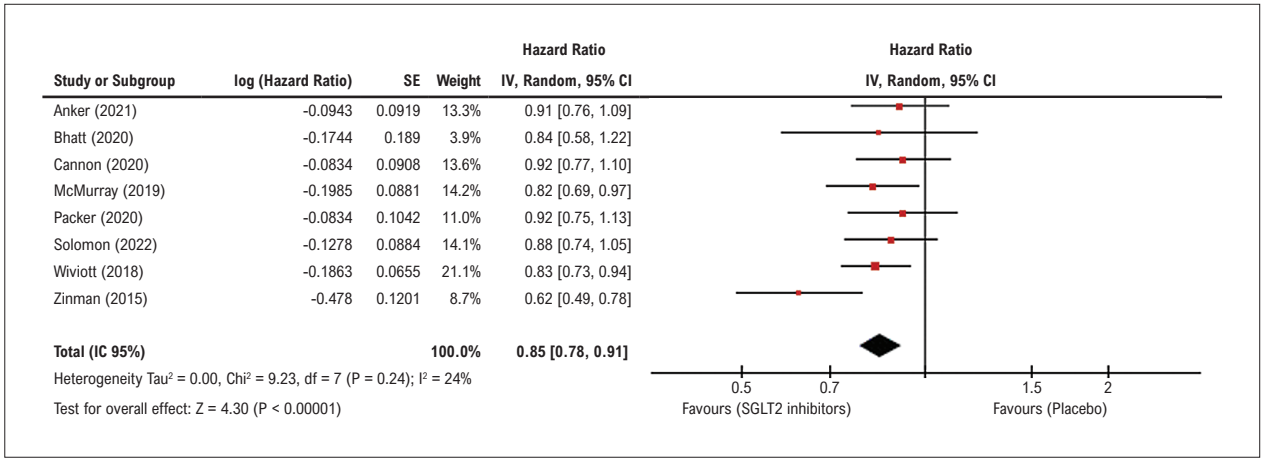

Figure 2 – *Forest plot comparing cardiovascular death between patients in use of SGLT2 inhibitors and placebo or conventional treatment. 95%CI: 95% confidence interval; HR: hazard ratio; SGLT2: sodium-glucose linked transporter 2.*

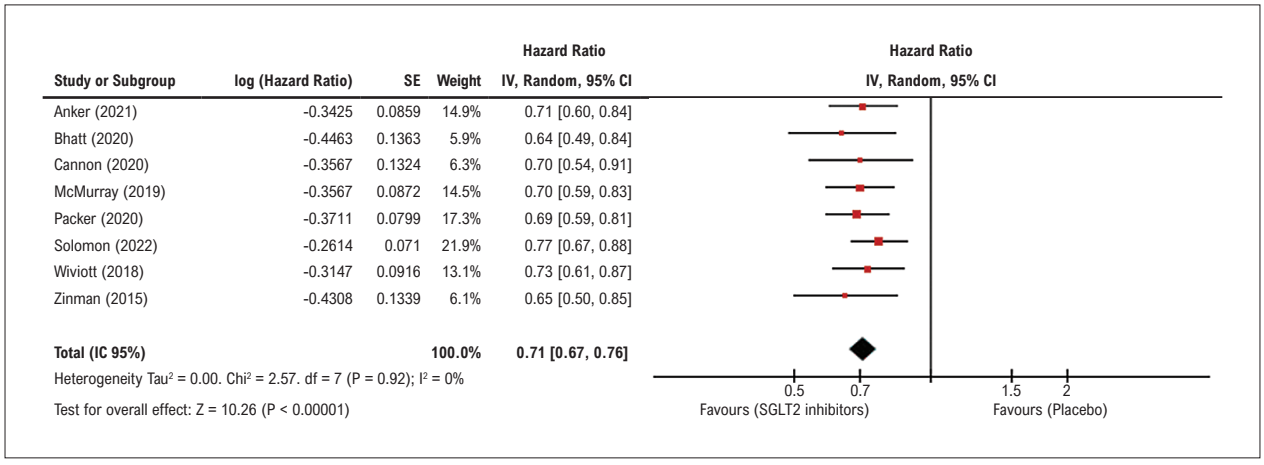

Figure 3 – *Forest plot hospitalization between patients in use of SGLT2 inhibitors and placebo or conventional treatment. 95%CI: 95% confidence interval; HR: hazard ratio; SGLT2: sodium-glucose linked transporter 2.*

and HF. All these reductions have benefits on blood pressure, coronary artery occlusion, α- and β-adrenergic stimulation, and diabetes, reducing the risk for hospitalizations.[54-61]

This study presents limitations that can be highlighted, such as the fact that we only analyzed the endpoints and subgroups that were presented in the publications used in this meta-analysis. Since we did not have access to individual patient data, there was no possibility to perform corrections for the multiplicity of subgroup tests. However, this meta-analysis can complement other meta-analyses of this subject, presenting solid evidence that confirms the important role of SGLT2 inhibitors in the treatment of HF patients with or without type 2 DM to prevent premature cardiovascular death and multiple hospitalizations.

Conclusions

Patients with HF in the use of SGLT2 inhibitors have a better outcome than with conventional treatment, having a lower risk of cardiovascular death and hospitalizations due to HF symptoms. SGLT2 inhibitors protected 15% from cardiovascular death and 29% from hospitalizations.

Author Contributions

Conception and design of the research: Peres-Filho FP, Peres FP, Kerche LE; Acquisition of data: Peres-Filho FP, Silva SU, Peres FP; Analysis and interpretation of the data: Silva SU, Kerche LE; Statistical analysis: Silva SU; Writing of the manuscript: Kerche LE; Critical revision of the manuscript for content: Peres-Filho FP, Silva SU, Peres FP.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

Sources of funding

There were no external funding sources for this study.

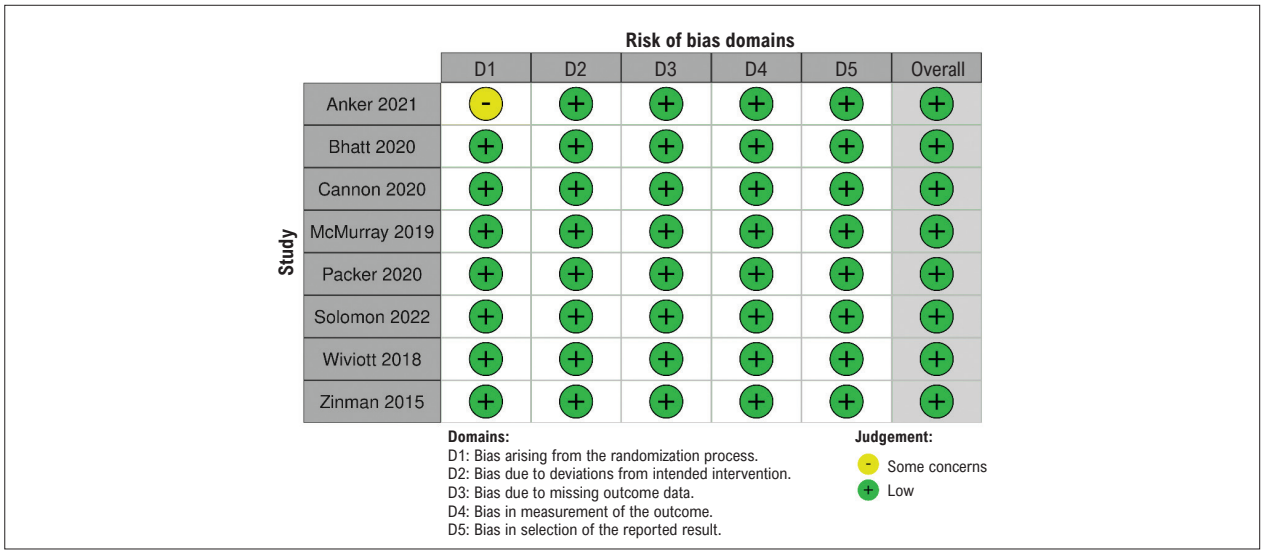

Figure 4 – *raffic light plot of the risk of bias assessment.*

Study association

This article is part of the thesis of master submitted by Fernando Pierin Peres Filho, from Universidade do Oeste Paulista.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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