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# Review on the use of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 agonists in people with type 2 diabetes *mellitus* and cardiovascular disease

## Revisão sobre o uso de inibidores de cotransportador sódio-glicose 2 e agonistas de peptídeo 1 em pessoas com diabetes *mellitus* tipo 2 e doença cardiovascular

## *Revisión sobre el uso de inhibidores del cotransportador de sodio-glucosa 2 y agonistas de péptido 1 similar al glucagón en personas con diabetes mellitus tipo 2 y enfermedad cardiovascular*

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## ABSTRACT

**Introduction:** Introduction: Type 2 diabetes *mellitus* is an important and growing health problem worldwide. **Objective:** This study aims to evaluate the quality of the evidence available on sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 agonists in people with diabetes *mellitus* and atherosclerotic cardiovascular disease. **Methods:** This integrative review was performed using the following databases: MEDLINE via PubMed, Embase via Cochrane Library, Cochrane Library, LILACS via VHL. The research question was structured as follows: population – people with type 2 diabetes *mellitus* and established cardiovascular disease; intervention – usual treatment, except insulin + sodium-glucose cotransporter 2 inhibitors or usual treatment, except insulin + and glucagon-like peptide 1 agonists; control – usual treatment, except insulin + placebo; outcome – overall mortality, mortality from cardiovascular causes, morbidity, adverse effects. **Results:** Two studies on empagliflozin were selected. This drug associated with the usual treatment was superior to placebo associated with the usual treatment in the primary outcome (hazard ratio — HR 0.86; 95% confidence interval — 95%CI 0.74–0.99; p=0.04), in reducing heart failure hospitalization (HR 0.65; 95%CI 0.50–0.85; p=0.002), in cardiovascular mortality (HR 0.62; 95%CI 0.49–0.77), and in overall mortality (HR 0.68; 95%CI 0.57–0.82; p<0.001). The subgroup of people with diabetes who were not on insulin benefited from using empagliflozin concerning the primary outcome (HR 0.79; 95%CI 0.64–0.97; risk difference — RD 2.5; number needed to treat — NNT 40) and cardiovascular mortality (HR 0.61; 95%CI 0.44–0.85; RD 2; NNT 49). The analysis of the subgroups showed heterogeneity. Participants aged 65 years or older (p=0.01) and those with glycated hemoglobin lower than 8.5 benefited from empagliflozin in the primary outcome. A difference (p=0.05) related to cardiovascular mortality was found, with the use of empagliflozin reducing the risk only in the subgroup with body mass index <30. No significant difference was identified with respect to placebo for fatal and nonfatal stroke nor for the composite outcome of nonfatal disabling stroke and fatal stroke (HR 0.81; 95%CI 0.43–1.50; p=0.50). More people had strokes in the intervention group in which the initial glycated hemoglobin was ≥8.5%, favoring placebo (p=0.01). **Conclusions:** The data found suggest the benefit of the Brazilian public health system using this drug in people with cardiovascular diseases. However, the population groups were heterogeneous, which may help outline strategies for using these medications. Further studies are necessary to assess why isolated cerebrovascular outcomes showed no benefit.

**Keywords:** Diabetes *mellitus,* type 2; Cardiovascular diseases; Sodium-glucose transporter 2 inhibitors; Glucagon-like peptide 1.

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## RESUMO

**Introdução:** Introdução: Diabetes *mellitus* tipo 2 é um importante e crescente problema de saúde para todos os países. **Objetivo:** Este trabalho visa avaliar a qualidade da evidência disponível sobre os fármacos inibidores de sódio-glicose 2 e agonistas de glucagon 1 em pessoas com diabetes *mellitus* e doença cardiovascular aterosclerótica **Métodos:** Realizou-se revisão integrativa utilizando as bases de dados MEDLINE via PubMed, Embase via Cochrane Library, Cochrane Library, LILACS via BVS. A pergunta de pesquisa foi estruturada da seguinte forma: população – pessoas com diabetes *mellitus* tipo 2 e doença cardiovascular estabelecida; intervenção – tratamento usual exceto insulina + inibidores de sódio-glicose 2 ou tratamento usual exceto insulina + agonistas de glucagon 1; controle - tratamento usual exceto insulina + placebo; desfecho – mortalidade geral, mortalidade por causas cardiovasculares, morbidade, efeitos adversos. **Resultados:** Selecionaram-se dois estudos sobre empagliflozina. Esse medicamento associado ao tratamento usual foi superior ao placebo associado ao tratamento usual no desfecho primário (HR 0,86; IC95% 0,74–0,99; p=0,04), na redução de hospitalização por insuficiência cardíaca (HR 0,65; IC95% 0,50–0,85; p=0,002), da mortalidade cardiovascular (HR 0,62; IC95% 0,49–0,77) e da mortalidade geral (HR 0,68; IC95% 0,57–0,82; p<0,001). No subgrupo de pessoas com diabetes que não usavam insulina, houve benefício com empagliflozina em relação ao desfecho primário (HR 0,79; IC95% 0,64–0,97; DR 2,5; NNT 40) e a mortes de causa cardiovascular (HR 0,61; IC95% 0,44–0,85; DR 2; NNT 49). Houve heterogeneidade entre os subgrupos com benefício de empagliflozina no desfecho primário apenas para aqueles com idade ³65 anos (p=0,01) e hemoglobina glicada <8,5 (p=0,01). Em relação às mortes por causas cardiovasculares, houve diferença (p=0,05) com o uso de empagliflozina reduzindo o risco somente no subgrupo com índice de massa corporal <30. Não houve diferença significativa em relação ao placebo para acidente vascular encefálico fatal e não fatal, tampouco no desfecho composto de acidente vascular encefálico debilitante não fatal e acidente vascular encefálico fatal (HR 0,81; IC95% 0,43–1,50; p=0,50). Houve mais pessoas acometidas por acidente vascular encefálico no grupo intervenção em que a hemoglobina glicada inicial era ≥8,5%, favorecendo o placebo (p=0,01). **Conclusões:** Os dados encontrados favorecem o benefício de utilizar esse medicamento no Sistema Único de Saúde em pessoas com doenças cardiovasculares. Entretanto, houve heterogeneidade entre grupos populacionais, o que pode ajudar a delinear estratégias de uso para esses medicamentos. São necessários mais estudos para avaliar qual seria o motivo de não haver benefício em desfechos cerebrovasculares isoladamente.


**Palavras-chave:** Diabetes *mellitus* tipo 2; Doenças cardiovasculares; Inibidores do transportador 2 de sódio-glicose; Peptídeo 1 semelhante ao glucagon.


## RESUMEN

**Introducción:** Diabetes *mellitus* tipo 2 es un importante y creciente problema de salud para todos los países. **Objetivo:** Este trabajo busca evaluar la calidad de la evidencia disponible sobre los fármacos Inhibidores del Cotransportador de Sodio-Glucosa 2 y agonistas de Péptido 1 similar al glucagón en personas con diabetes *mellitus* y enfermedad cardiovascular aterosclerótica. **Métodos:** Se realizó revisión integrativa utilizando las bases de datos MEDLINE vía PubMed, Embase vía Cochrane Library, Cochrane Library, LILACS vía BVS. La pregunta de investigación fue estructurada de la siguiente manera: población – personas con diabetes *mellitus* tipo 2 y enfermedad cardiovascular establecida; intervención – tratamiento usual excepto insulina + inhibidores de sodium-glucose cotransporter-2 o tratamiento usual excepto insulina + agonistas de Péptido 1 similar al glucagón; control – tratamiento habitual excepto insulina + placebo; desenlace – mortalidad general, mortalidad por causas cardiovasculares, morbilidad, efectos adversos. **Resultados:** Se seleccionaron dos estudios sobre empagliflozina. Este medicamento asociado al tratamiento habitual fue superior al placebo asociado al tratamiento usual en el resultado primario (HR 0.86; IC95% 0.74–0.99; p=0,04), en la reducción de hospitalización por insuficiencia cardíaca (HR 0.65; IC95% 0.50–0.85; p=0.002), de la mortalidad cardiovascular (HR 0,62; IC95% 0,49–0,77) y de la mortalidad general (HR 0,68; IC95% 0,57–0,82; p=0,001). En el subgrupo de personas con diabetes que no usaban insulina, hubo beneficio con empagliflozina con relación al desenlace primario (HR 0.79; IC95% 0.64–0.97; DR 2.5; NNT 40) y a muertes de causa cardiovascular (HR 0.61; IC95% 0.44–0.85; DR 2; NNT 49). No hubo diferencia significativa con relación al placebo para accidentes cerebrovasculares fatal y no fatal, tampoco en el resultado compuesto de accidente cerebrovascular debilitante no fatal y fatal (HR 0.81; IC95% 0.43–1.50; p=0.50). Hubo más personas acometidas por accidente cerebrovascular en el grupo intervención en que la hemoglobina glicada inicial era un 8,5%, favoreciendo el placebo (p=0.01). **Conclusión:** Los datos encontrados favorecen el beneficio de utilizar ese medicamento en el Sistema Único de Salud en personas con enfermedad cardiovascular. Entretanto ha habido heterogeneidad entre los grupos de población, lo que puede ayudar a delinear qué estrategias de uso para estos medicamentos. Son necesarios más estudios para evaluar cuál sería el motivo de no haber beneficio en resultados cerebrovasculares aisladamente.


**Palabras-clave:** Diabetes *mellitus* tipo 2; Enfermedades cardiovasculares; Inhibidores del Cotransportador de Sodio-Glucosa 2; Péptido 1 similar al glucagón.

# INTRODUCTION

Type 2 diabetes *mellitus* (DM2) is an important and growing health problem worldwide, regardless of the country's level of development. In 2019, the International Diabetes Federation (IDF) estimated that

9.3% of the world population aged 20 to 79 years (463 million people) lived with diabetes. In Brazil, this figure is approximately 16.8 million. In 2019, around 243,200 deaths of adults aged 20 to 79 years in Central and South America resulted from diabetes or its complications (12.5% of all-cause mortality). More than half (55.6%, 135,200) of the region's diabetes-related deaths occurred in Brazil.[1]

In 2013, the National Health Survey (*Pesquisa Nacional de Saúde* — PNS), carried out by the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* — IBGE) and the Ministry of Health, revealed that 6.2% of the Brazilian population aged 18 years or older reported medical diagnosis of diabetes.[2] In addition to representing an important financial burden for individuals and their families, due to costs with insulin and oral antidiabetic drugs, diabetes also has a relevant economic impact on countries and health systems.[3]

The management of this disease is part of the competencies of family physicians.[4] Pharmacological treatment requires knowledge of medicines, contraindications, and adverse effects. Nevertheless, this knowledge is often restricted to drugs provided by the Brazilian public health system. Among these drugs, the National Relation of Essential Medicines (*Relação Nacional de Medicamentos* — Rename) lists metformin and two sulfonylureas (gliclazide and glibenclamide).[5] However, given the emergence of new antidiabetic drugs, some of which are already included in international guidelines,[6] it is important to ascertain whether the available evidence is enough for the public health system to provide these new medicines.

Metformin remains the first line of pharmacological treatment. Yet, no consensus has been reached on which medication should be used as the second-line drug treatment for DM2.[3,6,7] According to the main DM2 treatment guidelines, the second medicine should be chosen taking into account the patient's characteristics (weight, age, comorbidities, and risk of hypoglycemia), as well as the cost, efficacy, and safety profile of the drug. Those that reduce not only glycemic levels but the risk of microvascular and/or macrovascular complications in the long term should be prioritized.[3]

Since 2008, the Food and Drug Administration requires that new drugs used to control DM2 should prove not to increase cardiovascular risk so as to establish their safety.[8] Safety assessment studies of new hypoglycemic agents began to be published and, in some cases, the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP1) agonists showed apparent benefits in individuals with DM2 and cardiovascular diseases (CVD) or high cardiovascular risk.[9-11] However, most were safety and non-inferiority studies.[12] Nonetheless, DM2 guidelines started to adopt them in their recommendations for patients with atherosclerotic cardiovascular disease.[3,6] For this reason, this study aims to evaluate the quality of the available evidence on SGLT2 inhibitors and GLP1 agonists in people with diabetes *mellitus* and established CVD.

## METHODS

This integrative review[13] searched the following databases: MEDLINE via PubMed, Embase via Cochrane Library, Cochrane Library, LILACS via VHL.

The research question — based on the PICO model (population, intervention, control, income) — was structured as follows:

- P: people with DM2 and established CVD;
- I: usual treatment, except insulin + SGLT2 inhibitors or usual treatment, except insulin + GLP1 agonists;

- C: usual treatment, except insulin + placebo;
- O: overall mortality, mortality from cardiovascular causes, morbidity (retinopathy, neuropathy, nephropathy, cardiovascular events), adverse effects.

The usual treatment includes different oral hypoglycemic agents, in addition to SGLT2 inhibitors or GLP1 agonists. We chose this term because, although metformin is the most commonly used initial treatment, it may not be the case for some studies, depending on where they were performed or on the individual characteristics of the individuals followed.

Inclusion criteria:

- patients with uncontrolled DM2 and established CVD;
- intervention with usual treatment + SGLT2 inhibitors or GLP1 agonists;
- outcome of overall or cardiovascular mortality or DM2 complications or adverse effects;
- systematic reviews, meta-analyses, randomized clinical trials;
- studies conducted in humans.

Exclusion criteria:

- DM2 without CVD;
- type 1 diabetes *mellitus* (DM1) or others;
- interventions other than those defined in PICO;
- different comparators from those defined in PICO;
- other types of study;
- animal studies.

The search strategy used was: (arteriolosclerosis OR atherosclerosis OR stroke OR “cardiovascular diseases” OR “myocardial infarction” OR “angina, unstable” OR “coronary disease” OR “coronary artery disease” OR “acute coronary syndrome” OR “coronary stenosis” OR “coronary occlusion” OR “coronary thrombosis” OR “angioplasty”) (“sodium-glucose transporter 2 inhibitors” OR empagliflozin OR dapagliflozin OR “glucagon-like peptide” OR liraglutide OR semaglutide OR dulaglutide). We used filters for systematic review, meta-analysis, and randomized clinical trials. The search was not restricted by language or year of publication. The drug names used in the search strategy were chosen based on the medications most recommended by guidelines and available in Brazil (verified in the portal of the Brazilian Health Regulatory Agency/*Agência Nacional de Vigilância Sanitária* — ANVISA).[14]

The articles were selected according to the flowchart (Figure 1).

The quality of the selected articles (Table 1) was determined by the Scottish Intercollegiate Guidelines Network (SIGN) tool.[16]

## RESULTS

Of the 704 studies initially identified, 182 were systematic reviews (SRs) and/or meta-analyses, and 522 were randomized clinical trials (RCTs). After removing duplicates, we assessed 595 articles by title and abstract, excluding 521 of them. Among the remaining 74 studies, 1 SR and 2 RCTs did not have their full texts available, 66 RCTs and SRs were excluded for not meeting the inclusion criteria, and 3 RCTs were removed because they did not separately analyze the use or non-use of insulin.

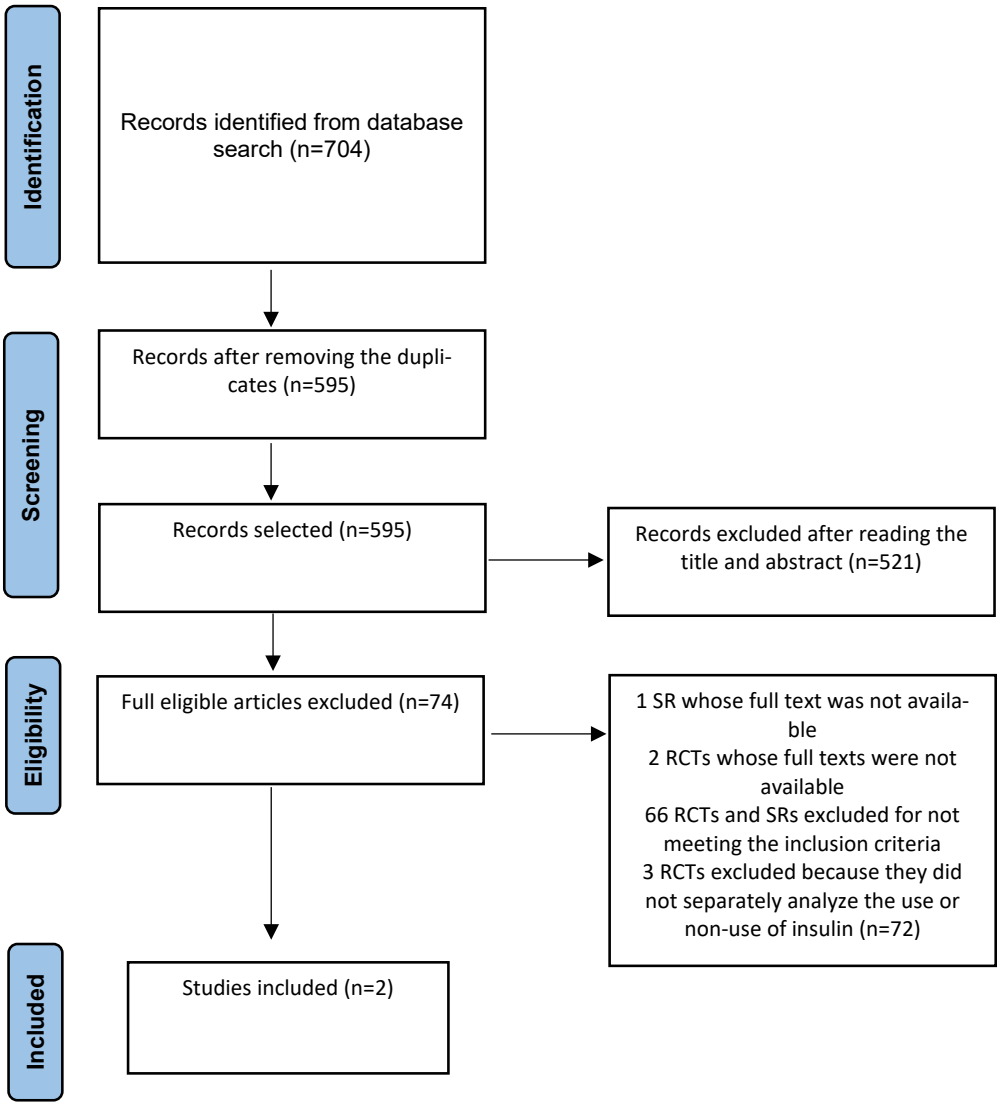


**Figure 1.** Flowchart of article selection.

The mean treatment duration in the studies was 2.5 years for the placebo group and 2.6 years for the empagliflozin group, while the mean observation time was 2.9 years for placebo and 3.0 years for empagliflozin. A total of 99% of the population in the studies had CVD.

In Zinman et al.[17], empagliflozin associated with the usual treatment was superior to placebo associated with the usual treatment in the primary composite outcome (hazard ratio — HR 0.86; 95% confidence interval — 95%CI 0.74–0.99; p=0.04), and no difference was found in the secondary outcome. We emphasize that the benefit in the primary outcome was only verified when considering all people who used empagliflozin, regardless of dose, and that the confidence interval was very close to statistical insignificance (reaching 0.99). When assessed separately, the groups that used 10 or 25 mg of empagliflozin were not superior to the placebo group in the primary outcome. Nor was empagliflozin superior to placebo in isolated outcomes related to acute myocardial infarction (AMI), hospitalization due to stable angina, coronary revascularization, stroke, and transient ischemic attack (TIA). However, it was superior in reducing heart failure hospitalizations (HR 0.65; 95%CI 0.50–0.85; p=0.002), cardiovascular

**Table 1.** Studies selected.

| Author/publication date | Zinman et al.[18] (2017) | Zinman et al.[17] |
|---|---|---|
| **Design** | **Randomized clinical trial** | **Randomized clinical trial** |
| **Study site** | **Multicenter** | **Multicenter** |
| Target population | People with type 2 diabetes *mellitus*, established cardiovascular disease, and glomerular filtration rate >30 mL/min/1.73 $m^2$ who did not receive hypoglycemic agents for at least 12 weeks before randomization and had glycated hemoglobin between 7 and 9% and/or who received hypoglycemic agents for at least 12 weeks before randomization and had hemoglobin glycated between 7 and 10%. | People with type 2 diabetes *mellitus*, established cardiovascular disease, and glomerular filtration rate >30 mL/min/1.73 $m^2$ who did not receive hypoglycemic agents for at least 12 weeks before randomization and had glycated hemoglobin between 7 and 9% and/or who received hypoglycemic agents for at least 12 weeks before randomization and had hemoglobin glycated between 7 and 10%. |
| Interventions evaluated | Empagliflozin 10 and 25 mg | Empagliflozin 10 and 25 mg |
| Main outcomes considered | Time to first fatal or nonfatal stroke, time to first recurrent nonfatal disabling stroke, time to first cardiovascular death, time to first transient ischemic attack. | The primary outcome was a combination of cardiovascular death, nonfatal acute myocardial infarction (excluding silent infarction), or nonfatal stroke. The secondary outcome combined the primary outcome and hospitalization for unstable angina. |
| Number of participants | 7,028 | 7,028 |

mortality (HR 0.62; 95%CI 0.49–0.77), and overall mortality (HR 0.68; 95%CI 0.57–0.82; p<0.001). In absolute numbers, differences in the causes of cardiovascular death between the empagliflozin and placebo groups were higher for sudden death, decompensated heart failure, and other cardiovascular deaths and lower for AMI and stroke. Nevertheless, the authors solely assessed whether there was a difference in cardiovascular mortality among subgroups with only cerebrovascular disease, only coronary artery disease, or only peripheral arterial disease. These subgroups did not show a difference compared to placebo. The heart failure subgroup was not evaluated to determine whether it may have influenced the overall results of cardiovascular mortality reduction. Contrary to heart failure hospitalization, the incidence of AMI and stroke did not decrease, raising doubts over whether the benefits found with empagliflozin would be more related to individuals with diabetes and heart failure than to all people with diabetes and any type of established CVD.

When evaluating the specific study data associated with the objective of the present research, that is, the subgroup of people with diabetes who did not use insulin, we found a benefit of empagliflozin in the primary outcome (HR 0.79; 95%CI 0.64–0.97; risk difference — RD 2.5; number needed to treat — NNT 40) and deaths from cardiovascular causes (HR 0.61; 95%CI 0.44–0.85; RD 2; NNT 49). We highlight that the study also compared subgroups of people using and not using metformin since this drug is cited as first-line treatment in diabetes treatment guidelines. Despite the lack of statistical difference when comparing the primary outcome (p=0.14) among the subgroups that used or did not use metformin, empagliflozin benefitted those who did not take metformin (HR 0.72; 95%CI 0.56–0.94; RD 3.6; NNT 28), contrary to those who used this drug (HR 0.92; 95%CI 0.77–1.10). These subgroups also showed no difference regarding the cardiovascular mortality outcome (p=0.07), but empagliflozin tended to be more beneficial to those who did not use metformin (HR 0.46; 95%CI 0.32–0.68; RD 4.4; NNT 24) compared

to those who did (HR 0.71; 95%CI 0.54–0.94; RD 1.4; NNT 71). These data suggest a greater benefit of empagliflozin among individuals not on metformin. Still, the study did not analyze those who used or did not use metformin in the subgroup that also did not take insulin.

The analysis of the subgroups showed heterogeneity. Participants aged 65 years or older (p=0.01) and those with glycated hemoglobin lower than 8.5 benefited from empagliflozin in the primary outcome. A difference (p=0.05) related to cardiovascular mortality was found, with the use of empagliflozin reducing the risk only in the subgroup with body mass index <30.[17]

As for adverse effects, a higher number of genital infections were reported both by women and men in empagliflozin groups. Urosepsis was identified in 0.4% of people in empagliflozin groups and 0.1% of individuals in the placebo group. Higher doses of empagliflozin seem to have an effect on increased pyelonephritis and urosepsis (10 mg — 0.1 and 0.3%; 25 mg — 0.3 and 0.5%, respectively). However, the authors only compared the total number of people who used empagliflozin with placebo (0.1% of urosepsis and 0.2% of pyelonephritis), thus reducing the overall percentage of these adverse effects and bringing them closer to placebo. This scenario might have contributed to the lack of statistical difference, which might have been present if only the group that received 25 mg of empagliflozin was compared to those on placebo. The proportion of people who had adverse effects, severe adverse effects, and adverse effects that led to treatment discontinuation was similar among the groups.[17]

In Zinman et al.[18], the proportion of fatal and nonfatal stroke was similar in the groups using empagliflozin and placebo (HR 0.72; 95%CI 0.33–1.55; p=0.40). The composite outcome of nonfatal disabling stroke and fatal stroke showed no significant difference (HR 0.81; 95%CI 0.43–1.50; p=0.50). Also, no difference was detected regarding the risk of TIA (HR 0.85; 95%CI 0.51–1.42; p=0.54). However, people in placebo groups presented a significant difference between Europe and North America, with lower rates in Europe (7.8/1,000 versus 15.2/1,000 people/year).[17]

In the subgroup analysis, more people had strokes in the intervention group in which the initial glycated hemoglobin was ≥8.5%, favoring placebo (p=0.01).[18]

Concerning patient follow-up, 97% completed the study observation time, allowing 99.2% of vital data collection. Still, 25.4% discontinued the treatment under evaluation (23.4% in the empagliflozin group and 29.3% in the placebo group) before the end of the study, which may be a source of bias in the result assessment.

## DISCUSSION

Both articles showed high quality according to the SIGN instrument.[16] The fact that the studies allowed the inclusion of other hypoglycemic agents throughout the research to obtain better DM2 control might be considered a source of bias. This situation raises doubts over whether the effects presented depended only on the intervention performed. However, avoiding the use of other medicines that could control DM2 in clinical studies involving individuals with an uncontrolled disease despite the intervention adopted would not be ethical because, given the current scientific knowledge on the subject, this practice could harm them.

The usual treatment varied according to the guidelines of each participating site, but the groups presented a similar number of participants using each hypoglycemic agent.

Considering the objective established in this review, a divergence was noted between the study designs and what has been recommended in recent guidelines,[3,6] as most studies included individuals

on insulin, and the drugs evaluated are suggested as the second line of treatment — after the use of metformin and before the use of insulin — for the mentioned populations. This fact led several studies to be excluded since they did not separately analyze the data of individuals who were not treated with insulin.

Based on the studies examined, we can conclude that the use of empagliflozin in people who are not on insulin therapy had NNT=40 for the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke) and NNT=49 for death from cardiovascular causes.[16] However, the study that evaluated the stroke outcome separately found no significant difference between placebo and control but detected a benefit in favor of placebo in individuals who had initial glycated hemoglobin ≥8.5%.[17]

The data found suggest that the Brazilian public health system could benefit from making this drug available for people with established CVD. Yet, further studies are necessary to assess what would be the best drug combination, whether they should be used with sulfonylureas or other hypoglycemic agents, if they should be continued after the start of insulin therapy, and why isolated cerebrovascular outcomes showed no benefit. In addition, both articles selected are based on the same RCT — EMPA-REG OUTCOME —, which was sponsored by Boehringer Ingelheim and Eli Lily, and their authors are funded by these and other companies.[19]

Limitations of this study include not having explored the gray literature and not performing a manual search for systematic reviews, which may have contributed to the reduced number of selected articles.

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## CONFLICT OF INTERESTS

Nothing to declare.

## AUTHORS' CONTRIBUTIONS

JNG: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. JCO: Conceptualization, Data curation, Formal analysis, Writing – original draft.

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