Anatomía Digital

ISSN: 2697-3391
Vol. 7 No. 3.1, pp. 104 – 127, August 2024

www.anatomiadigital.org

# Empagliflozina y sus beneficios en la protección cardiaca: una revisión actualizada de la literatura

*Empagliflozin and its benefits in cardiac protection: an updated review of the literature*

[1] Samira Delgado Alcivar https://orcid.org/0000-0003-1833-997X
Medical student at the Technical University of Manabí. Ecuador
sdelgado2709@utm.edu.ec

[2] Niurka Moreira Plúa https://orcid.org/0009-0005-7577-462X
Medical student at the Technical University of Manabí. Ecuador.
nmoreira0417@utm.edu.ec

[3] Alisson Mendoza Pincay https://orcid.org/0009-0008-4763-8470
Medical student at the Technical University of Manabí. Ecuador.
amendoza4963@utm.edu.ec

[4] Carmen Bermudez Cedeno https://orcid.org/0009-0006-4682-7072
Medical student at the Technical University of Manabí. Ecuador
cbermudez1804@utm.edu.ec

[5] Gipson Loor Galarza https://orcid.org/0009-0005-3292-8801
Medical student at the Technical University of Manabí. Ecuador
gloor4920@utm.edu.ec

[6] Kevin Bazurto Ponce https://orcid.org/0009-0005-2814-6639
Medical student at the Technical University of Manabí. Ecuador.
kbazurto3954@utm.edu.ec

[7] Kelvin Delgado Alcivar https://orcid.org/0000-0002-3830-016X
Master's Degree in Health Sciences Research Methodology from the International University of La Rioja.
keldelgado98@hotmail.com

[8] John Ponce Alencastro https://orcid.org/0000-0002-3666-7865
Specialist in Diabetology from the Catholic University of Uruguay. Research Professor at the Technical University of Manabí
jhon.ponce@utm.edu.ec

**Scientific and Technological Research Article**
Sent: 06/15/2024
Revised: 12/07/2024
Accepted: 01/08/2024
Published:26/08/2024
DOI: **https://doi.org/10.33262/anatomiadigital.v7i3.1.3151**

Please quote: Delgado Alcívar, S., Moreira Plúa, N., Mendoza Pincay, A., Bermúdez Cedeño, C., Loor Galarza, G., Bazurto Ponce, K., Delgado Alcívar, K., & Ponce Alencastro, J. (2024). Empagliflozin and its benefits in cardiac protection: an updated review of the literature. Digital Anatomy, 7(3.1), 104-127.https://doi.org/10.33262/anatomiadigital.v7i3.1.3151

ISSN: 2697-3391
Vol. 7 No. 3.1, pp. 104 – 127, August 2024

www.anatomiadigital.org

The journal is published by Editorial Ciencia Digital (a prestigious publisher registered with the Ecuadorian Book Chamber with membership number 663).www.celibro.org.ec



**Palabras claves:**
Inhibidores del cotransportador de sodio-glucosa 2; empagliflozina, diabetes mellitus 2, insuficiencia cardiaca.

## Resumen

**Introducción**. La empagliflozina es un inhibidor del cotransportador de sodio-glucosa tipo 2 que fue comercializado por primera vez como hipoglucemiante oral. Con el paso del tiempo, se ha demostrado en diferentes estudios que esta molécula tiene grandes efectos cardioprotectores. **Objetivo.** Describir las propiedades farmacológicas, los beneficios cardiovasculares y mecanismos cardioprotectores de la empagliflozina, aportando información sobre su perfil de seguridad y eficacia a partir de las investigaciones disponibles. **Metodología**. Se realizó una revisión narrativa de la literatura en las bases de datos Medline (Pubmed), Web of Science, ScienceDirect, LILACS, Scielo, EMBASE, Scopus y Latindex, en la cual se describió las propiedades farmacológicas, los beneficios cardiovasculares y mecanismos cardioprotectores de la empagliflozina. **Resultados.** La empagliflozina ha demostrado reducir significativamente el riesgo combinado de hospitalización por insuficiencia cardiaca y muerte cardiovascular en pacientes con insuficiencia cardiaca con fracción de eyección del ventrículo izquierdo reducida, además de una reducción en el riesgo de muerte por todas las causas y muerte cardiovascular en pacientes tratados con inhibidores del SGLT2 como la empagliflozina. **Conclusión**. Esta es una molécula integral con excelentes propiedades hipoglucémicas y cardioprotectoras, además de ser una opción terapéutica efectiva y segura en el manejo de las diferentes formas de insuficiencia cardiaca, proporcionando beneficios significativos en la reducción de hospitalizaciones y mortalidad cardiovascular, tanto en pacientes diabéticos como en no diabéticos. **Área de estudio general:** Medicina. **Área de estudio específica:** Cardiología / Farmacología. **Tipo de estudio:** Artículos originales.

ISSN: 2697-3391
Vol. 7 No. 3.1, pp. 104 – 127, August 2024

www.anatomiadigital.org

**Keywords:**
Sodium-glucose cotransporter 2 inhibitors; empagliflozin, type 2 diabetes mellitus, heart failure.

## Abstract

**Introduction.**Empagliflozin is a sodium-glucose cotransporter type 2 inhibitor that was first marketed as an oral hypoglycemic agent. Over time, numerous studies have demonstrated that this molecule has significant cardioprotective effects. objective. To describe the pharmacological properties, cardiovascular benefits, and cardioprotective mechanisms of empagliflozin, providing information on its safety and efficacy profile based on available research. Methodology. A narrative review of the literature was conducted on the databases Medline (PubMed), Web of Science, ScienceDirect, LILACS, SciELO, EMBASE, Scopus, and Latindex, describing the pharmacological properties, cardiovascular benefits, and cardioprotective mechanisms of empagliflozin. Results. Empagliflozin has been shown to significantly reduce the combined risk of hospitalization for heart failure and cardiovascular death in patients with heart failure with reduced ejection fraction, as well as a reduction in the risk of all-cause mortality and cardiovascular death in patients treated with SGLT2 inhibitors such as empagliflozin. Conclusion. This is a comprehensive molecule with excellent hypoglycemic and cardioprotective properties, as well as an effective and safe therapeutic option in the management of different forms of heart failure, providing significant benefits in reducing hospitalizations and cardiovascular mortality, both in diabetic and non-diabetic patients.

## Introduction

Empagliflozin is a hypoglycemic molecule whose mechanism is the induction of glucosuria by inhibition of the sodium-glucose cotransporter type 2 (SGLT-2). Since its authorization in 2014, it has been used as a complement to metformin in the treatment of type 2 diabetes (T2D) (1). However, in a clinical trial conducted after its commercialization, this drug not only demonstrated that it had an excellent reduction in glycemic levels, but also a significant reduction in hospitalization and major cardiovascular mortality was evident (2).

Anatomía Digital
ISSN: 2697-3391
Vol. 7 No. 3.1, pp. 104 – 127, August 2024
www.anatomiadigital.org

Under this precedent, in order to rule out that the cardiovascular benefits of empagliflozin were a product of chance, the scientific community focused on carrying out new experimental studies with heart patients, regardless of whether they suffered from T2D or not (3, 4), taking into account all the side effects of the active ingredient (hypotension, worsening of kidney function, fungal genital infections, urinary tract infections and increased low-density lipoproteins) (5). The results were excellent, so much so that the United States Food and Drug Administration (FDA) (6) and the European Medicines Agency (EMA) (7) approved its use in 2021 as part of the treatment of symptomatic heart failure.

There are several theories that attempt to explain the mechanisms by which empagliflozin produces cardiovascular benefits, including a reduction in endocardial oxidative stress (8), an improvement in the state of interstitial volume and vascular function, an increase in sodium excretion and/or a reduction in plasma glucose and blood pressure levels (9, 10). However, these processes are still being studied to date, as there is no complete clarity.

In recent years, a clear association between T2DM and heart failure has been demonstrated, with a considerable increase in patients with both morbidities (11). It has been described that diabetic patients have twice the risk of developing heart failure, regardless of the presence or absence of coronary artery disease. In addition, the global prevalence of heart failure in patients with T2DM is around 23% (12).

Given the above, it is essential to consider the objective of describing the pharmacological properties, cardiovascular benefits and cardioprotective mechanisms of empagliflozin, providing information on its safety and efficacy profile based on available research.

## Methodology

A narrative review of the literature was carried out in the following databases: Medline (PubMed), Web of Science, ScienceDirect, LILACS, SciELO, EMBASE, Scopus and Latindex.

The keywords were obtained to carry out a search in documentary language through the permuted and hierarchical terms called DECS (Descriptors in Health Sciences) and MeSH (Medical Subject Headings), these were: “Sodium-Glucose Cotransporter 2 Inhibitors”, “Heart Failure” and “Endocardium”; in addition, the natural term “Empagliflozin” was used to restrict the search. All these descriptors were combined with the Boolean operators AND and OR to proceed with the review in the aforementioned databases. The search strategycan be seen in Figure 1.

Anatomía Digital
ISSN: 2697-3391
Vol. 7 No. 3.1, pp. 104 – 127, August 2024
www.anatomiadigital.org

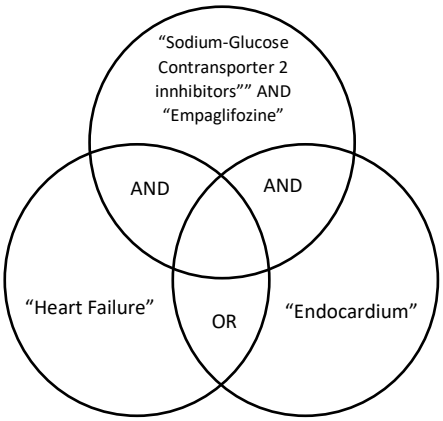


**Figure 1.***Search strategy in databases*

Once the search strategy was carried out, the "snowball" technique was used to select the references that were analyzed in this review. Subsequently, the selection criteria were applied (see Table 1), in order to verify the existence of non-emerging research in the databases.

**Table 1.***Criteria for selecting studies*

| *Inclusion criteria* | *Exclusion criteria* |
|---|---|
| • Studies addressing the cardiovascular benefits of empagliflozin in diabetic and non-diabetic patients.<br>• Studies treating patients with any type of heart failure with empagliflozin.<br>• Original articles, review articles and clinical practice guidelines.<br>• Articles published in Spanish and English in the last 10 years.<br>• References obtained from the search strategy in the indicated databases. | • Studies that include another type of SGLT2 inhibitor other than empagliflozin within their therapeutic approach.<br>• Undergraduate thesis papers, letters to the editor and case reports.<br>• Articles that cannot be retrieved in full electronic format.<br>• References published in another language. |

A total of 115 publications were identified using the "snowball" technique, which were considered relevant after reading their title and abstract. Subsequently, the selection criteria were applied and a total of 40 papers were excluded. The remaining 75 references were evaluated using the methodological validity questionnaires established by the Critical Reading Skills Program in Spanish (CASPe), leaving a total of 46 articles, which met the necessary requirements for this review.

Of the 46 included papers, 16 were original articles with quantitative methodology (1 mixed in vivo analysis with animals/humans, 3 observational articles, and 12 clinical trials), 23 review articles, and seven clinical practice guidelines and pharmacoeconomics

Anatomía Digital
ISSN: 2697-3391
Vol. 7 No. 3.1, pp. 104 – 127, August 2024
www.anatomiadigital.org

guidelines. Taking into account the CASPe questionnaires, the studies were assessed as being of good, average, or poor quality. For all these reasons, if the papers exceeded the criteria established in these questionnaires, they were considered to be a credible source of evidence. Table 2 describes the main original articles included and their results.

## Results

Below are the articles included in the bibliographic and literature review:

**Table 2.***Bibliographic matrix of included studies*

| Authors | Aim | Sample | Methodology | Main results |
|---|---|---|---|---|
| Zinman et al (2) | To examine the effects of empagliflozin, compared with placebo, on cardiovascular morbidity and mortality in patients with T2D and high cardiovascular risk receiving standard care. | 7020 adult patients with T2D and established cardiovascular disease, BMI of 45 or less, and GFR of 30 ml/min/1.73 m2 | Randomized, double-blind, placebo-controlled trial | Patients with T2D and high cardiovascular risk who received empagliflozin had a lower rate of the primary composite cardiovascular outcome and death from any cause compared with placebo. |
| Anker et al. (3) | To analyze the efficacy and safety of empagliflozin in heart failure and renal events according to baseline T2D status and glycated hemoglobin value ranges. | 3730 patients with class II to IV heart failure and LVEF ≤40% | Randomized, double-blind, parallel-group, placebo-controlled, event-driven trial. | Empagliflozin significantly improved cardiovascular and renal outcomes in patients with heart failure and reduced LVEF, regardless of T2D status at baseline and across the glycated hemoglobin spectrum. |
| Packer et al. (4) | To report the effect of empagliflozin in hospitalized and outpatients with heart failure and LVEF >40% | 5988 patients with class II to IV heart failure with an LVEF >40% | Randomized, double-blind, parallel-group, placebo-controlled, event-driven trial | In patients with heart failure with preserved LVEF, empagliflozin produced a significant, early, and sustained reduction in the risk and severity of worsening heart failure events in inpatients and outpatients. |
| Kolijnet al. (8) | To investigate the mechanisms of action of empagliflozin in heart failure with preserved LVEF in humans and mice. | 30 human patients with heart failure and LVEF >40% and obese/diabetic murine rats. | In vivo analysis of human and 17-week-old obese and diabetic mouse rat biopsies. | Empagliflozin reduces inflammatory and oxidative stress in HFpEF and thereby enhances the NO-sGC-cGMP cascade and PKGIα activity through decreased PKGIα oxidation and polymerization, leading to decreased pathological cardiomyocyte stiffness. |

Anatomía Digital
ISSN: 2697-3391
Vol. 7 No. 3.1, pp. 104 – 127, August 2024
www.anatomiadigital.org

**Table 2.***Bibliographic matrix of included studies (continued)*

| Authors | Aim | Sample | Methodology | Main results |
|---|---|---|---|---|
| Sarashina et al. (13) | To investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of empagliflozin at doses ranging from 1 mg to 100 mg in 48 healthy male Japanese subjects. | 48 men aged between 20 and 35 years and BMI of 18-25 with good physical and mental health. | Phase I, randomized, double-blind, placebo-controlled trial. | A dose of 1 mg to 100 mg of empagliflozin had a good safety and tolerability profile in healthy Japanese men. |
| Kanada et al. (14) | To evaluate the pharmacodynamics, pharmacokinetics, safety and tolerability of empagliflozin in Japanese patients with T2D | 100 patients with T2D treated with diet and exercise alone or with an antidiabetic drug other than thiazolidinediones. | Randomized, parallel-group, double-blind, placebo-controlled trial. | In Japanese patients with type 2 diabetes, empagliflozin at doses up to 25 mg once daily for 4 weeks was well tolerated and produced significant improvements in glycemic control compared with placebo. |
| Kovacs et al. (15) | To investigate the efficacy and tolerability of empagliflozin as an add-on to pioglitazone ± metformin in patients with type 2 diabetes (T2D). | 165 patients with T2D aged ≥18 years (and ≤65 years in India) with a body mass index ≤45 kg/m2 and glycated hemoglobin ≥7 and ≤10% | Randomized, double-blind, placebo-controlled, parallel-group, phase 3 study | Empagliflozin 10 mg and 25 mg once daily for 24 weeks as add-on to pioglitazone ± metformin reduced glycated hemoglobin, fasting glucose, and weight and was well tolerated in patients with T2D |
| Hans-Ulrich et al. (16) | To investigate the efficacy and tolerability of empagliflozin as an adjunct to metformin therapy in patients with T2D | 647 adult patients with T2D and glycated hemoglobin ≥7 and ≤10% (≥53 and ≤86 mmol/mol) receiving a dose greater than or equal to 1500 mg/day of metformin. | Randomized, placebo-controlled, double-blind phase III study. | Empagliflozin 10 and 25 mg for 24 weeks as an add-on to metformin treatment significantly improved glycemic control, weight, and blood pressure, and was well tolerated. |

Anatomía Digital
ISSN: 2697-3391
Vol. 7 No. 3.1, pp. 104 – 127, August 2024
www.anatomiadigital.org

**Table 2.***Bibliographic matrix of included studies (continued)*

| Authors | Aim | Sample | Methodology | Main results |
|---|---|---|---|---|
| Hans-Ulrich et al. (17) | To investigate the efficacy and tolerability of empagliflozin as an adjunct to metformin and sulfonylurea in patients with type 2 diabetes | 666 patients with poorly controlled T2D (glycated hemoglobin ≥7 and ≤10%) with metformin and sulfonylurea. | Randomized, placebo-controlled, double-blind phase III study | Empagliflozin 10 and 25 mg for 24 weeks as an add-on to metformin plus sulfonylurea improved glycemic control, weight, and systolic blood pressure and was well tolerated. |
| Fitchett et al. (18) | To assess whether the effects of empagliflozin on cardiovascular outcomes and mortality varied across the countries studied. | 7020 patients with T2D and glycated hemoglobin between 7 and 10%, established cardiovascular disease and GFR ≥30 ml/min/ ·1.73m2 | Randomized, double-blind, parallel-group, placebo-controlled trial | Reductions in key cardiovascular outcomes and mortality with empagliflozin versus placebo were consistent across the range of cardiovascular risk. |
| Biegus et al. (19) | To analyze a spectrum of possible decongestive effects of empagliflozin in acute heart failure compared with placebo and standard medical treatment | 530 patients admitted to hospital with a diagnosis of acute heart failure and treated with a minimum dose of 40 mg of intravenous furosemide or equivalent. | Multinational, multicenter, randomized, double-blind trial, compared with placebo and standard treatment. | Initiation of empagliflozin in patients hospitalized for acute heart failure resulted in early, effective, and sustained decongestion that was associated with clinical benefit at day 90. |
| Laffel et al. (20) | To assess the efficacy and safety of a dosing regimen of empagliflozin versus placebo and linagliptin versus placebo in glycemic control in youth with type 2 diabetes. | 158 adolescent patients (10–17 years) with T2D; glycated hemoglobin 6.5–10.5% [48–91 mmol/mol]) previously treated with metformin or insulin | Randomized, double-blind, placebo-controlled clinical trial. | Empagliflozin provided clinically relevant reductions in glycated hemoglobin, whereas linagliptin did not, and may offer a new treatment option for young people with T2D. |

Anatomía Digital
ISSN: 2697-3391
Vol. 7 No. 3.1, pp. 104 – 127, August 2024
www.anatomiadigital.org

**Table 2.***Bibliographic matrix of included studies (continued)*

| Authors | Aim | Sample | Methodology | Main results |
|---|---|---|---|---|
| Perez-Belmonte et al. (21) | To analyze the clinical efficacy and safety of continued treatment with empagliflozin in very elderly patients with type 2 diabetes hospitalized for acute decompensated heart failure. | 158 patients ≥80 years with T2D and heart failure treated with insulin. | Observational cohort study between September 2015 and June 2021. | In very elderly patients with T2D hospitalized for acute heart failure, continuous administration of empagliflozin before admission reduced NT-proBNP levels and increased diuretic response and urine output compared with a basal-bolus insulin regimen. |
| Okada et al. (22) | To compare the efficacy and safety results of empagliflozin in patients with T2D aged <75 and ≥75 years. | 131 patients with T2D and uncontrolled nocturnal hypertension (44 participants were ≥75 years old and 87 were <75 years old) | Secondary observational subanalysis of data from the SACRA clinical trial (multicenter, double-blind, randomized, parallel study). | Empagliflozin was effective and well tolerated in elderly diabetic patients with uncontrolled nocturnal hypertension when administered for 12 weeks. |
| Böhm et al. (23) | To assess the interaction of age and the effects of empagliflozin in EMPEROR-Preserved (Empagliflozin Outcomes in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trial. | 5988 patients with class II to IV heart failure with an LVEF >40% | Secondary exploratory observational analysis of the EMPEROR-Preserved clinical trial (randomized, double-blind, parallel-group, placebo-controlled, event-driven trial). | Empagliflozin reduced primary outcomes and first and recurrent congestive heart failure and improved symptoms across a broad age spectrum. Older age was not associated with reduced efficacy or significant intolerance. |

*Physiology*

Under normal conditions, all the glucose filtered by the glomerulus is reabsorbed in the renal tubules by means of sodium-glucose cotransporters (SGLT), and therefore, there is no glucosuria (24). SGLT2 are present in the first segment of the proximal convoluted tubule and are responsible for 80-90% of renal glucose reabsorption, while SGLT1 do the same with the remaining 10-20% in the more distal segments; however, these latter cotransporters (SGLT1) are also present in other organs such as the heart and brain (25).

*Mechanism of action: SGLT2 inhibition*

Anatomía Digital
ISSN: 2697-3391
Vol. 7 No. 3.1, pp. 104 – 127, August 2024
www.anatomiadigital.org

Phlorizin is a natural glucoside found mainly in the root bark of apple and other fruit trees (26); it was isolated in the 19th century by Belgian chemists Laurent-Guillaume de Koninck and Jean Servais Stas, serving as the prototype of today's SGLT2 inhibitors (27). Studies conducted in the 1980s with laboratory rats demonstrated that glucose excretion in urine by SGLT2 inhibition was effective in reducing plasma glucose using an insulin-independent mechanism and without risk of hypoglycemia (28). However, phlorizin was discarded as a diabetic treatment for humans in the nineties due to its low oral bioavailability (it had to be used parenterally to be sufficiently active), lack of selectivity (it inhibited SGLT1 and SGLT2) and its multiple adverse effects (diarrhea, dehydration, intestinal malabsorption, interference with glucose uptake in the central nervous system, among others) (27).

Years later, selective molecules to inhibit SGLT2 were developed by American and European pharmaceutical companies, which came onto the market starting in 2014 (in order of appearance: canagliflozin, empagliflozin, dapagliflozin and ertugliflozin) with excellent results in glycemic control (29). For this reason, the American Diabetes Association (ADA) included them in the therapeutic algorithm for T2D in its 2015 clinical practice guideline (1) and in subsequent editions up to the present date (30).

*Pharmacokinetics and pharmacodynamics*

Empagliflozin is a potent selective inhibitor of SGLT2 (2500 times greater than for SGLT1), which prevents renal reabsorption of glucose and induces glucosuria, thereby reducing fasting blood glucose by between 28.08 and 42.66 mg/dL and glycated hemoglobin by 0.5 to 1% (31).

In non-diabetic patients, after oral administration, empagliflozin is rapidly absorbed and reaches its maximum concentration in approximately 1.5 to 2.1 hours. Plasma concentration declines in a biphasic pattern, obtaining a half-life of 13.1 hours. Its clearance in 72 hours is 32.1 to 51.3 mL/min and the cumulative fraction eliminated in urine ranges from 11 to 19% (13). With a dose of 10 mg of empagliflozin, the reabsorption of 40% of filtered glucose is inhibited, and with higher doses, an inhibition of up to 60% is achieved (maximum excretion of 90 g of glucose per day) (13, 31).

In patients with T2D, after multiple doses of empagliflozin (10-100 mg/day for 28 days), its maximum concentration was reached between 1.33 and 3 hours after oral administration; its half-life was 10.3 to 18.8 hours (32). After treatment for four weeks, the total amount of glucose excretion in urine was 64.37 to 78.37 g. (14).

The pharmacokinetic characteristics of empagliflozin have been shown not to be significantly altered in patients with chronic kidney disease (CKD), so that no dose adjustment is necessary (31), however, the amount of glucose excreted decreases

progressively and simultaneously with the glomerular filtration rate (GFR), which is why the latest clinical practice guidelines of "Kidney Disease: Improving Global Outcomes 2024" (KDIGO 2024) recommend its use in patients with GFR > 20 ml / min per 1.73 m2, due to its proven nephroprotective role (33).

In the presence of hepatic impairment, empagliflozin exposure was not more than doubled, therefore no dose adjustment is necessary. In addition, no differences were demonstrated in the amount of glucose excreted in urine (31).

*Adverse effects*

The main adverse effects of empagliflozin are arterial hypotension, genital and urinary tract infections; other less frequent ones include worsening of renal function and increased low-density lipoproteins (5). No interactions of empagliflozin with other drugs have been described (34).

Hypoglycemia. It is defined as a plasma glucose below 70 mg/dL, which may or may not be accompanied by serious symptoms such as: paleness, tremors, diaphoresis, headaches, irritability, seizures, loss of consciousness and even sudden death (30). It has been shown that the risk of hypoglycemia with the use of empagliflozin in monotherapy is very low (almost zero), however, great caution must be taken when used together with insulin or sulfonylureas (35). Urinary tract infections. A post hoc analysis of 3 phase III clinical trials (15 - 17) conducted by Romera et al. (36) determined that urinary tract infections occurred in 9.4% of the placebo group, in 10.2% of the group that used a dose of 10 mg and in 8.3% with 25 mg of empagliflozin.

Genital infections. Genital infections occur because glucosuria, induced by SGLT2 inhibition, creates an environment conducive to bacterial and fungal growth (34). A secondary study found that 4.6% and 3.5% of patients with T2D who used empagliflozin at a dose of 10 and 25 mg respectively had genital infections, compared to 1% incidence with placebo (36). Arterial hypotension. Due to natriuresis, empagliflozin may cause volume depletion with a consequent decrease in blood pressure. According to the Spanish Agency for Medicines and Health Products, between 0.6% and 0.7% of patients treated with empagliflozin reported a hypotensive episode (35).

*First cardiovascular results*

As mentioned above, empagliflozin is a selective SGLT2 inhibitor. Early studies of the molecule reported excellent results in reducing glycated hemoglobin in patients with T2D, as well as zero risk of hypoglycemia (1). Therefore, the FDA and EMA authorized its use in diabetic patients as a complement to metformin (37).

Anatomía Digital
ISSN: 2697-3391
Vol. 7 No. 3.1, pp. 104 – 127, August 2024
www.anatomiadigital.org

An FDA policy established in 2008 required rigorous cardiovascular safety evaluations for new oral antidiabetic drugs (38), which is why the "Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients–removing excess glucose" (EMPA-REG OUTCOME) was developed, which marked a historic milestone by presenting its final results (2, 18). EMPA-REG OUTCOME consisted of a randomized, parallel-group, double-blind, multicenter, international cardiovascular safety trial. It was conducted in 7020 adult patients with T2D, BMI<45, high cardiovascular risk, glycated hemoglobin between 7 and 10%, who were on baseline antidiabetic treatment or diet and exercise regimen. The combined risk of hospitalization for heart failure and cardiovascular death was significantly lower in patients treated with empagliflozin than with placebo [HR: 0.66 (95% CI: 0.55–0.79; $p < 0.001$)], and a significant reduction in heart failure mortality was observed in the empagliflozin group [HR 0.61 (95% CI: 0.47–0.79; $p < 0.001$)] (2, 10, 18). It was concluded that in patients with T2D and high cardiovascular risk, empagliflozin alone or in addition to standard oral therapy showed a reduction in the rate of admissions for heart failure and cardiovascular mortality (18).

*Cardioprotective mechanisms*

With the results of the EMPA-REG OUTCOME clinical trial (18), a new line of research was created in which an attempt was made to explain the mechanisms by which empagliflozin generated cardiovascular benefits. Different hypotheses have been described, including:

Decreased body weight: By generating glucosuria (each gram of glucose excreted is equivalent to a loss of 4 kcal) by inhibiting SGLT2, body weight reduction is promoted. In addition, empagliflozin reduces plasma glucose levels and stimulates lipolysis (39). Reduction of blood pressure: The decrease in blood pressure (between 3-5 mmHg in systolic and 2 mmHg in diastolic) is due to natriuresis and weight loss. The pleiotropic effects of the drug on neurohormonal activity, arterial stiffness and endothelial function may also contribute: they reduce oxidative stress and suppress the renin-angiotensin-aldosterone system (40).

Changes in lipid profile. Empagliflozin increases high-density lipid content in the liver along with a slight decrease in triglycerides, which has a cardioprotective effect (39, 40). In addition, it regulates body composition by decreasing the accumulation of lipids, visceral and subcutaneous fat (39). Changes in vascular stiffness. The decrease in vascular stiffness occurs due to the reduction in body weight, the improvement in arterial distensibility (due to a vasodilatory effect mediated by nitric oxide) and the relaxation of smooth muscle due to a negative sodium balance (41). In turn, empagliflozin leads to improved heart rate variability and a decrease in plasma adrenaline and noradrenaline (39).

Endothelial changes. Empagliflozin increases nitric oxide bioavailability, causing endothelium-dependent vasodilation; it also favorably regulates endothelial cell proliferation, migration, differentiation, survival, and senescence. It also exerts potent antioxidant and anti-inflammatory effects on endothelial cells and inhibits vascular smooth muscle cell contraction (39).

*Benefits in heart failure*

Following the results of the EMPA-REG outcome study (18), the scientific community showed great interest in the effects that empagliflozin may have on patients suffering from heart failure, regardless of whether they are diabetic or not. The main results of this line of research are presented below:

The Empagliflozin outcome trial in patients with chronic heart failure and a reduced ejection fraction (EMPEROR-Reduced) study was a randomized, double-blind, parallel-group, placebo-controlled clinical trial that examined the effect of empagliflozin on chronic heart failure with reduced left ventricular ejection fraction (HFrLVEF) hospitalizations and cardiovascular mortality in patients with chronic heart failure with reduced left ventricular ejection fraction (HFrLVEF). A total of 3,730 patients with LVEF<40% and functional class II, III, and IV (New York Heart Association) participated and had a median follow-up of 16 months (42). The combined risk of hospitalization for heart failure and cardiovascular death was significantly lower in patients treated with empagliflozin than with placebo [HR: 0.75 (95% CI: 0.65–0.86; $p < 0.001$)], with this result being consistent in all patients, regardless of the presence or absence of T2D (3, 42).

A meta-analysis of the results of EMPEROR-Reduced and DAPA-HF (a clinical trial evaluating the efficacy of dapagliflozin in HFrEF) demonstrated that with the use of these SGLT2 inhibitors there was a 13% reduction in all-cause death [pooled HR 0.87 (95% CI: 0.77–0.98; p= 0.018)] and a 14% reduction in cardiovascular death [pooled HR 0.86 (95% CI: 0.76–0.98; p=0.027)]. Furthermore, the combined risk of hospitalization for heart failure and cardiovascular death was significantly lower in patients treated with empagliflozin/dapagliflozin than with placebo [HR: 0.75 (95% CI: 0.68–0.84; $p < 0.001$)] (43).

Years later, the Empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction (EMPEROR-Preserved) study was developed, which was a randomized, double-blind, parallel-group, placebo-controlled clinical trial that analyzed the effect of empagliflozin in 5988 patients with chronic heart failure with preserved LVEF (LVEF>40%), NYHA II, III and IV and elevated levels of NT-proBNP (N-terminal prohormone B-type natriuretic peptide) >300 pg/mL. Empagliflozin reduced the combined risk of hospitalization/emergency or urgency due to heart failure and

cardiovascular death [HR 0.77 (95% CI: 0.67–0.87; p <0.0001)] in a median of 26 months of treatment (4).

For patients with acute heart failure (AHF), the Empagliflozin in patients hospitalized with acute heart failure who have been stabilized (EMPULSE) study was conducted, where symptoms, physical limitations and quality of life were assessed in 530 adults hospitalized for AHF (with NYHA II-III and NT-ProBNP>1600 pg/ml) using the Kansas City Cardiomyopathy Questionnaire (KCCQ). The use of empagliflozin demonstrated a statistically significant net clinical benefit compared to placebo [Win Ratio: 1.36 (p<0.05)], regardless of the degree of symptomatic deterioration at baseline, improving symptoms, physical limitations and quality of life (19).

Based on the results described above, empagliflozin currently has a class IA recommendation in the clinical practice guidelines of the European Society of Cardiology (44) and the American College of Cardiology (45) for use in patients with acute heart failure, chronic heart failure with reduced LVEF, and chronic heart failure with preserved LVEF, regardless of their diabetic status or not.

*Benefits for vulnerable groups*

Children/adolescents: Empagliflozin has not been studied in the pediatric population, so its pharmacokinetics, pharmacodynamics and benefits in this group are still unknown. Recently, its use has been recommended by the FDA (46) and the ADA (30) as part of the hypoglycemic treatment in the adolescent population (10-17 years) suffering from T2D. This is because in phase III of the clinical trial "Diabetes study of linagliptin and empagliflozin in children and adolescents" (DINAMO) it was shown that by inhibiting SGLT2, inducing glucosuria and decreasing body weight, empagliflozin generated a 0.8% reduction in glycated hemoglobin compared to placebo (95% CI: –0.19 to –1.50; p= 0.012), which obtained statistical significance (20). There are no studies on the use of empagliflozin in reducing cardiovascular risk or in the treatment of heart failure in children or adolescents.

Older adults: The mechanisms of action of empagliflozin in older adults are similar to those already described in young adults. Its safety and efficacy in the geriatric population with heart failure was analyzed by some observational studies: Pérez-Belmonte et al. (21) addressed the effects of empagliflozin in patients over 80 years of age with acute heart failure; it was shown that the efficacy and safety of the drug were maintained despite the advanced age of the sample. Okada et al. (22) did not observe significant differences in the incidence of adverse effects generated by empagliflozin between those over 75 years of age versus those younger than that age.

Anatomía Digital
ISSN: 2697-3391
Vol. 7 No. 3.1, pp. 104 – 127, August 2024
www.anatomiadigital.org

A post hoc analysis of the EMPEROR-Preserved trial by Böhm et al. (23) divided the main sample into 4 age categories (<65 years, 65-74 years, 75-79 years and >80 years) and calculated the HR of the primary endpoint (cardiovascular death and hospital admission for heart failure) for each subgroup, with no statistically significant differences between them (p=0.33). Therefore, there are no significant differences in the efficacy and safety of empagliflozin when administered to young and older adults. Regarding older adults with T2D, the criteria for potentially inappropriate prescribing and possible omissions of prescriptions in older people (STOPP/START) indicate that empagliflozin is an inappropriate medication in patients over 65 years of age with symptomatic hypotension (47), therefore, the ADA recommends using them together with metformin only if the patient has established cardiovascular disease and/or high risk of cardiovascular death, being very cautious with the appearance of arterial hypotension (30).

Pregnant women: There are no well-designed studies on the use of empagliflozin in pregnant women, so its use is not recommended during pregnancy (6, 7).

*Social aspect*

Despite the multiple benefits of empagliflozin in the treatment of T2D, cardiovascular risk and heart failure, it has a major limitation: its price. Unlike standard treatment, empagliflozin is twice as expensive on the market, making it difficult for people with a low socioeconomic level to access.

However, at the macroeconomic level in public health, a study carried out in Spain (48) estimated the costs and the number of clinical events in patients with empagliflozin versus other standard treatments in patients with T2D and established cardiovascular disease, predicting life years (LY) and quality-adjusted life years (QALY) over a 10-year horizon. Based on the results of the cost-effectiveness and cost-utility analysis, it was concluded that empagliflozin is a more effective and less expensive therapeutic option in this type of patients. On the other hand, in patients with heart failure, it has been shown that empagliflozin offers a low economic value in state investments when compared to its effect on quality of life and the reduction in hospital admissions (49).

## Conclusions

- In conclusion, empagliflozin is a comprehensive molecule with excellent hypoglycemic and cardioprotective properties, as well as being an effective and safe therapeutic option in the management of different forms of heart failure, providing significant benefits in reducing hospitalizations and cardiovascular mortality, both in diabetic and non-diabetic patients.

## Conflict of interest

The authors declare that they have no conflicts of interest.

**Authors' contribution statement**

Topic selection: All authors participated in the selection and delimitation of the topic.

Abstract development and translation: Samira Delgado-Alcívar and Niurka Moreira-Plúa were appointed to develop the abstract and summary.

Introduction: The section was developed by Samira Delgado-Alcívar, Niurka Moreira-Plúa, Alisson Mendoza-Pincay, Carmen Bermúdez-Cedeño.

Methodology: The methodology was developed by Kelvin Delgado-Alcívar and Jhon Ponce-Alencastro.

Results: All authors participated in the analysis or bibliographic review.

Conclusions: The final section was developed byGipson Loor-Galarza and Kevin Bazurto-Ponce

## *Bibliographic References*

1. American Diabetes Association.Standards of medical care in Diabetes 2015. Diabetes Care [Internet]. 2015 [cited 2024, May 27]; 38(1):1-98. Available in:https://diabetesjournals.org/care/issue/38/Supplement_1

2. Zinman B, Wanner C, Lachin J, Fitchett D, Bluhmki E, Hantel S,Mattheus M, Devins T, Johansen E, Woerle H, Broedl C, Inzucchi. Empa-Reg outcome investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. The New England Journal of Medicine [Internet]. 2015 [cited 2024, May 29]; 373(22): 2117-28. Available at: https://www.doi.org/10.1056/NEJMoa1504720

3. Anker S, Butler J, Fillippatos G, Shahzeb M, Marx N, Lam C,Schnaidt S, Pernille A, Brueckmann M, Jamal W, Bocchi E, Ponikowski P, Perrone S, Januzzi J, Verma S, Böhm M, Ferreira J, Pocock S, Zannad F, Packer M. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status results from the emperor-reduced trial. Circulation [Internet]. 2021 [cited 2024, May 31]; 143(4): 337-49. Available at: https://www.ahajournals.org/doi/epub/10.1161/CIRCULATIONAHA.120.051824

4. Packer M, Butler J, Zannad F, Filippatos G, Ferreira P, Pocock S,Carson P, Anand I, Doehner W, Haass M, Komajda M, Miller A, Pehrson S, Terrlink J, Schnaidt S, Zeller C, Math D, Schnee J, Anker S. Effect of empagliflozin on

worsening heart failure events in patients with heart failure and preserved ejection fraction: emperor-preserved trial. Circulation [Internet]. 2021; [cited 2024, June 1] 144(16): 1284-94. Available at: https://www.ahajournals.org/doi/epub/10.1161/CIRCULATIONAHA.121.056824

5. Ramos C, Tamosiunas G. Empagliflozin, lower CV risk in patients with DM2? Montevideo [Internet]. 2016 [cited 2024, 1 June]; (2). Report No.: 16. Available at: https://www.boletinfarmacologia.hc.edu.uy/images/2016/2016-2/3_empagliflozin.pdf

6. Food and Drug Administration[FDA]. Jardiance [Internet]. 2021 [cited 2024, 3 June]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/204629s033lbl.pdf

7. European Medicines Agency [EMA]. Jardiance [Internet]. 2021 [cited 2024, 5 June]. Available at: https://www.ema.europa.eu/es/documents/overview/jardiance-epar-summary-public_es.pdf

8. Kolijn D, Pabel S, Tian Y, Lódi M, Herwig M, Carrizo A,Zhazykbayeva S, Kovács A, Fülöp G, Falcão I, Reusch P, Van S, Papp Z, Heerebeek, L, Vecchione C, Maier L, Ciccareli M, Tschope C, Mugge A, Bagi Z, Sossalla S, Hamdani N. Empagliflozin improves endothelial and cardiomyocyte function in human heart failure with preserved ejection fraction via reduced pro-inflammatory-oxidative pathways and protein kinase Gα oxidation. Cardiovascular Research [Internet]. 2021 [cited 2024, June 7]; 117(2): 495-507. Available at: https://pubmed.ncbi.nlm.nih.gov/32396609/

9. Marx N, McGuire D. Sodium-glucose cotransporter-2 inhibition for the reduction of cardiovascular events in high-risk patients with diabetes mellitus. European Heart Journal [Internet]. 2016 [cited 2024, 9 June]; 37(1): 3192-3200. Available at: https://pubmed.ncbi.nlm.nih.gov/27153861/

10. Sattar N, McLaren J, Kristensen S, Preiss D, McMurray J. SGLT2inhibition and cardiovascular events: why did EMPA-REG outcomes surprise and what were the likely mechanisms? Diabetology [Internet]. 2016 [cited 2024, June 9]; 59(7): 1333-1339. Available at: https://doi.org/10.1007%2Fs00125-016-3956-x

11. Almero-Ballesteros B, Tarraga-Marcos L, Madrona-Marcos F, Avila JR, Tárraga-López P. Diabetes and heart failure: Are sodium-glucose cotransporter type two inhibitors the future of treatment?Journal of Negative and No Positive

Result [Internet]. 2022 [cited 2024, June 12]; 7(2): 209-34. Available at: https://dx.doi.org/10.19230/jonnpr.4443

12. Palmiero G, Cesaro A, Vetrano E, Pafundi P, Galiero R, Caturano A, Moscarella E, Gragnano F, Salvatore T, Rinaldi L, Calabrio P, Sasso F. Impact of SGLT2 inhibitors on heart failure: from pathophysiology to clinical effects. International Journal of Molecular Sciences [Internet]. 2021 [cited 2024, June 13]; 22(11): 5863. Available at: https://doi.org/10.3390/ijms22115863

13. Sarashina A, Koiwai K, Seman L, Yamamura N, Taniguchi A, Negishi T,Sesoko S, Woere H, Dugi K. Safety, tolerability, pharmacokinetics, and pharmacodynamics of single doses of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in healthy Japanese subjects. Drug Metabolism and Pharmacokinetics [Internet]. 2013 [cited 2024, June 17]; 28(3): 213-9. Available at: https://doi.org/10.2133/dmpk.dmpk-12-rg-082

14. Kanada S, Koiwai K, Taniguchi A, Sarashina A, Seman L, Woerle H. Pharmacokinetics, pharmacodynamics,safety, and tolerability of 4 weeks' treatment with empagliflozin in Japanese patients with type 2 diabetes mellitus. Journal of Diabetes Investigation [Internet]. 2013 [cited 2024, June 18]; 4(6): 613-7. Available at: https://doi.org/10.1111/jdi.12110

15. Kovacs, Seshiah, Swalow, Jone, Rattunde, Woerle. Empagliflozin improvesGlycemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. Diabetes, Obesity and Metabolism [Internet]. 2014 [cited 2024, June 19]; 16(1): 147-158. Available at: https://doi.org/10.1111/dom.12188

16. Hans-Ulrich H, Merker WL, Seewaldt-Becker E, Weimer M, Meinicke T, Broedl U, Woerle H. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care [Internet]. 2014 [cited 2024, June 22]; 37(6): 1650–1659. Available at: https://doi.org/10.2337/dc13-2105

17. Hans-Ulrich H, Merker WL, Seewaldt-Becker E, Weimer M, Meinicke T, Woerle H,Broedl U. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care [Internet]. 2013 [cited 2024, June 23]; 33(11): 3396-404. Available at: https://doi.org/10.2337/dc12-2673

18. Fitchett D, Inzucchi S, Canon C, McGuire D, Scirica B, Johansen E,Sambevski S, Kaspers S, Pfarr E, George J, Zinman B. Empagliflozin reduced mortality and

hospitalization for heart failure across the spectrum of cardiovascular risk in the empa-reg outcome trial. Circulation [Internet]. 2018 [cited 2024, June 24]; 139(11): 1384-1395. Available at: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.118.037778

19. Biegus J, Voors A, Collins S, Kosiborod M, Teerlink J, Angermann C, Tromp J, Ferreira J, Nassif M, Psotka M, Brueckmann M, Salsali A, Blatchford J, Ponikowski P. Impact of empagliflozin on decongestion in acute heart failure: the impulse trial. European Heart Journal [Internet]. 2023 [cited 2024, June 25]; 44(1): 41-50. Available at: https://doi.org/10.1093/eurheartj/ehac530

20. Laffel L, Danne T, Tamborlane W, Klingensmith G, Schroeder C, Neubacher D,Marquard J. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicenter, randomized, double-blind, parallel group, phase 3 trial. Lancet [Internet]. 2023 [cited 2024, June 27]; 11(2): 169-81. Available at: https://doi.org/10.1016/S2213-8587(22)00387-4

21. Pérez-Belmonte L, Sánz-Canovas J, Millans M, Osuna-Sánchez J, López-Sampalo A, Ricci M,Navarro M, López M, Bernal María, Barbancho M, Gómez R. Clinical benefits of empagliflozin in very old patients with type 2 diabetes hospitalized for acute heart failure. Journal of American Geriatrics Society [Internet]. 2022 [cited 2024, July 1]; 70(3): 862-871. Available at: https://doi.org/10.1111/jgs.17585

22. Okada K, Hoshide S, Kato M, Kanegae H, Ishibashi S, Kario K.Safety, and efficacy of empagliflozin in elderly Japanese patients with type 2 diabetes mellitus: a post hoc analysis of data from the SACRA study. The Journal of Clinical Hypertension [Internet]. 2021 [cited 2024, July 2]; 23(4): 860-869. Available at: https://doi.org/10.1111%2Fjch.14131

23. Böhm M, Butler J, Filippatos G, Ferreira J, Pocock S, Abdin A,Mahfoud F, Brueckmann M, Gollop N, Iwata T, Ponikowki P, Wanner C, Zannad F, Packer M, Anker S. Empagliflozin improves outcomes in patients with heart failure and preserved ejection fraction irrespective of age. Journal of the American College of Cardiology [Internet]. 2022 [cited 2024, July 3]; 80(1): 1-18. Available at: https://doi.org/10.1016/j.jacc.2022.04.040

24. Tentolouris A, Vlachakis P, Tzeravini E, Eleftheriadou I, Tentolouris N. SGLT2 Inhibitors:a review of their antidiabetic and cardioprotective effects. International Journal of Environmental Research and Public Health [Internet].

2019 [cited 2024, July 4]; 16(16): 2695. Available at: https://doi.org/10.3390/ijerph16162965

25. Van Baar M, Van Ruliten C, Muskiet M, Van Bloemendaal L, Jzerman R, Van Raalte D. SGLT2 inhibitors in combination therapy: from mechanisms to clinical considerations in type 2 diabetes management. Diabetes Care [Internet]. 2018 [cited 2024, July 6]; 41(8): 1543–1556. Available at: https://doi.org/10.2337/dc18-0588

26. López-Hernández M. Sodium-glucose cotransporter 2 (SGLT2) inhibitors: the kidney as a target for glycemic control in type 2 diabetes mellitus. Internal Medicine of Mexico [Internet]. 2017 [cited 2024, 9 July]; 33(3): 365-371. Available at: https://www.scielo.org.mx/pdf/mim/v33n3/0186-4866-mim-33-03-00363.pdf

27. Valdés-Socin H, Vanoni M. The fabulous history of glyphozins.Journal of the Ecuadorian Society of Nephrology, Dialysis and Transplantation [Internet]. 2023 [cited 2024, 14 July]; 11(2): 91-97. Available at: http://doi.org/10.56867/53

28. Rossetti L, Smith D, Shulman G, Papachristou D, DeFronzo R. Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J.ournal of Clinical Investigation [Internet]. 1987 [cited 2024, July 16]; 79(5): 1510-5. Available at: https://doi.org/10.1172/JCI112981

29. Valdes-Socin H, Scheen A, Jouret F, Grosch S, Delanaye P. From the discovery of phlorizin (a Belgian story) to SGLT2 inhibitors.Revue Médicale de Liège [Internet]. 2022 [cited 2024, July 17]; 77(3): 175-80. Available at: https://rmlg.uliege.be/article/3598?lang=en

30. American Diabetes Association[ADA]. Standards of care in diabetes 2024. Diabetes Care [Internet]. 2024 [cited 2024, 18 July]; 47(1): 1-328. Available at: https://doi.org/10.2337/dc24-SINT

31. Mehta R, Almeda-Valdés P, Juárez-Comboni S, Yamamoto-Cuevas J. Current role of empagliflozin in glycemic control in patients with type 2 diabetes: from preclinical research to phase III studies.Internal Medicine of Mexico [Internet]. 2015 [cited 2024, 19 July]; 31(3): 301-309. Available at: https://www.medigraphic.com/pdfs/medintmex/mim-2015/mim153k.pdf

32. Scheen A. Pharmacokinetic andPharmacodynamic profile of empagliflozin, a sodium glucose co-transporter 2 inhibitor. Clinical Pharmacokinetics [Internet]. 2014 [cited 2024, July 20]; 53(1): 213-225. Available at: https://doi.org/10.1007/s40262-013-0126-x

33. Stevens PE, Ahmed SB, Carrero JJ, Foster B, Francis A, Hall RK, Herrington WG, Hill G, Inker LA, Kazancıoğlu R, Lamb E, Lin P, Madero M, McIntyre N, Morrow K, Roberts G, Sabanayagam D , Schaeffner E, Shlipak M, Levin A. KDIGO 2024 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International [Internet]. 2024 [cited 2024, July 22]; 105(4): S117-S314. https://doi.org/10.1016/j.kint.2023.10.018

34. Nelinson D, Sosa J, Chilton R. SGLT2 inhibitors: a narrative review of efficacy and safety. J.ournal of Osteopathic Medicine [Internet]. 2021 [cited 2024, July 22]; 121(2): 229-39. Available at: https://doi.org/10.1515/jom-2020-0153

35. Spanish Agencyof Medicines and Medical Devices [Internet]. Therapeutic positioning report of empagliflozin (Jardiance®) in type 2 diabetes mellitus. 2017 [cited 2024, 23 July].https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-empagliflozina-jardiance.pdf

36. Romera I, Ampudia-Blasco F, Pérez A, Ariño B, Pfarr E, Giljanovic S,Naderali E. Efficacy and safety of empagliflozin in combination with other oral hypoglycemic agents in patients with type 2 diabetes mellitus. Endocrinology and Nutrition [Internet]. 2016 [cited 2024, 23 July]; 63(10): 519-526. Available at: http://dx.doi.org/10.1016/j.endonu.2016.06.003

37. Inzucchi S, Bergenstal R, Buse J, Diamant M, Ferrannini E, Nauck M,Peters A, Tsapas A, Wender R, Matthews D. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American diabetes association and the European association for the study of diabetes. Diabetes Care [Internet]. 2015 [cited 2024, July 24]; 38(1): 140–149. Available in:https://doi.org/10.2337/dc14-2441

38. US Food and Drug Administration. 73 FR 77724–guidance for industry on diabetes mellitus: evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Federal Register [Internet]. 2008 [cited 2024, 24 July]; 73(1): 77724–77725. Available at: https://www.federalregister.gov/documents/2008/12/19/E8-30086/guidance-for-industry-on-diabetes-mellitus-evaluating-cardiovascular-risk-in-new-antidiabetic

39. Negrete J, Villabona F, Rojas O, Cuellar Y, Torres F, Benegas A,Ortiz D, Bonfante R, Plata J. Cardioprotective effect of sglt2 inhibitors and glp-1 receptor agonists. Ciencia Latina Multidisciplinary Scientific Journal [Internet]. 2022 [cited 2024, 25 July]; 6(4): 2497-2511. Available at: https://doi.org/10.37811/cl_rcm.v6i4.2776

40. Inserra F, Forte E, Elbert A, Waisman G, Castellaro C. Position statement. Effect of SGLT-2 inhibitors on blood pressure, vascular damage, kidney disease and associated cardiovascular risk. Revista of the Argentine Diabetes Society [Internet]. 2023 [cited 2024, 25 July]; 57(3): 140-58. Available at: https://doi.org/10.47196/diab.v57i3.728

41. Nouel A. Cardiovascular effects of sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors): mechanisms of benefit in patients with heart failure. RevChilean Journal of Cardiology [Internet]. 2022 [cited 2024, 25 July]; 41(3): 198-205. Available at: http://dx.doi.org/10.4067/S0718-85602022000300198

42. Packer M, Anker S, Butler J, Filippatos G, Ferreira J, Pocock S,Carson P, Daehner W, Haass M, Komajda M, Miller A, Pehrson S, Teerlink John, Brueckmann M, Jamal W, Zeller C, Schnaidt S, Zannad F. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the emperor-reduced trial. Circulation [Internet]. 2021 [cited 2024, July 26]; 143(4): 326-336. Available at: https://doi.org/10.1161/circulationaha.120.051783

43. Zannad F, Ferreira J, Pocock S, Anker S, Butler J, Fillippatos G,Brueckmann M, Pernille A, Pfarr E, Jamal W, Pacjer M. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the emperor-reduced and DAPA-HF trials. Lancet [Internet]. 2020 [cited 2024, July 26]; 396(10254): 819-29. Available at: https://doi.org/10.1016/S0140-6736(20)31824-9

44. European Society of Cardiology. 2023 update of the 2021 ESC Guidelines on the diagnosis and treatment of acute and chronic heart failure. European Heart Journal [Internet]. 2023 [cited 2024, 26 July]; 44(38): 3720-3826. Available at: https://secardiologia.es/images/2024/Guías/Guía_ESC_2023_Actualización_IC.pdf

45. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM. 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. Journal of American College of Cardiology [Internet]. 2022 [cited 2024, July 27]; 79(17): e263-421. Available at: https://doi.org/10.1016/j.jacc.2021.12.012

46. US Food and Drug Administration.FDA Approves New Class of Drugs to Treat Type 2 Diabetes in Children. [Internet]. Press Releases. 2023 [cited July 3, 2024]. p. 1-3. Available at: https://www.fda.gov/news-events/press-

announcements/fda-approves-new-class-of-drugs-to-treat-type-2-diabetes-in-children

47. Delgado-Silveira E, Molina-Mendoza M, Montero-Errasquin B, Munoz-Garcia M, Rodriguez-Espeso E, Velez-Diaz-Pallares M,Cruz, A. Spanish version of the STOPP/START 3 criteria. Advances in the detection of inappropriate drug prescription in the elderly. Revista Española de Geriatría y Gerontología [Internet]. 2023 [cited 2024, 28 July]; 58(1): 101407. Available at: https://doi.org/10.1016/j.regg.2023.101407

48. Barull C, Massafrets M, Planellas L, Perulero N. Cost-effectiveness analysis of empagliflozin in patients with type 2 diabetes mellitus and established cardiovascular disease in Spain[Boehringer Ingelheim, editor. XXXVII Jornadas de la Salud] [Internet]. 2017 [cited 2024, 28 July]. p. 1 P. Available at: https://www.aes.es/Jornadas2017/pdfs/posters/Aes_2017_23_1.pdf

49. Zheng J, Parizo J, Spertus J, Heidenreich P, Sandhu A. Cost-effectiveness ofempagliflozin in patients with heart failure with preserved ejection fraction. Journal of the American Medical Association [Internet]. 2022 [cited 2024, July 28]; 182(12): 1278-88. Available at: https://www.doi.org/10.1001/jamainternmed.2022.5010

ISSN: 2697-3391
Vol. 7 No. 3.1, pp. 104 – 127, August 2024

www.anatomiadigital.org



Indexaciones