Review Article

The Trajectory of Gliflozins: From Apple Tree Bark to Reduced Overall Mortality in Heart Failure

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Abstract

A small number of drugs have been responsible for major advances in medical practice throughout history, for instance, the discovery of penicillin, insulin, aspirin, and statins. Diabetes treatment began with parenteral insulin, discovered by Banting and Bet approximately a century ago; since then, several classes of oral medications that improve glycemic control have been developed and become available for widespread use. More recently, sodium-glucose cotransporter inhibitors have emerged, with a surprising impact and effect on the treatment of patients with diabetes, heart failure, and renal failure, and they are currently considered one of the greatest therapeutic advances in cardiovascular medicine in the twenty-first century.[1] Initially developed only for glycemic control, their effects on cardiovascular protection have been widely demonstrated in large clinical trials in patients with diabetes, showing a significant reduction in the risk of cardiovascular diseases, prevention of hospitalization due to heart failure by 25% to 35%, and reduction of renal outcomes, regardless of the presence or absence of diabetes and the therapies used to treat these conditions.[2] In this trajectory of discoveries, gliflozins culminated by demonstrating beneficial effects, including reduced cardiovascular mortality and overall mortality in patients with heart failure, regardless of the presence of diabetes mellitus, in all ranges of left ventricular ejection fraction.

Introduction

Phlorizin was isolated from the root bark of apple trees in 1835, and it was initially considered for treatment of malaria due to its bitter taste similar to that of quinine. Phlorizin is a glycoside that is also present in the roots of other fruit trees such as plum, cherry, and pear, with the ability to competitively inhibit sodium-glucose cotransporters (SGLT) present in the kidney and intestine. In 1886, its glucosuric effect was discovered, with a consequent reduction in plasma glucose levels. Studies in insulin-resistant rats after partial pancreatectomy showed that subcutaneous application of phlorizin could normalize glycemic levels; however, due to pharmacological characteristics of low solubility, short half-life, low bioavailability, instability, and gastrointestinal side effects, phlorizin was not considered for pharmacological treatment of diabetes mellitus (DM).[1-3]

In the 1990s, researchers from the University of Kyoto developed a phlorizin analogue with oral absorption capacity, which was the first synthetic SGLT inhibitor with more adequate pharmacological characteristics and proven ability to reduce glycemia in animal models of diabetic rats.[4,5] Subsequently, multiple pharmaceutical companies developed a series of SGLT inhibitors for the treatment of DM.

In 2008, the Food and Drug Administration and the European Medicine Agency expressed concern regarding the increased cardiovascular risk associated with the use of anti-diabetogenic drugs after questioning the cardiovascular safety of rosiglitazone. Accordingly, these regulatory agencies began to require large-scale clinical trials demonstrating safety for the approval of new hypoglycemic medications. Within this context, to comply with regulatory agencies' new rules, SGLT inhibitors were evaluated in a series of large trials designed to demonstrate non-inferiority in relation to major adverse cardiovascular events (MACE), encompassing a diabetic population with cardiovascular disease (CVD) or at high cardiovascular risk. To the great surprise of the scientific community, these studies evaluating cardiovascular safety obtained highly surprising results, observing not only safety, but robust cardiovascular benefit[6] (central Illustration).

Mechanism of action

In healthy adults, the proximal convoluted tubule reabsorbs all the glucose filtered daily, which corresponds to approximately 180 grams, with no glycosuria being observed. Reabsorption is an active process associated with sodium, which occurs through carrier proteins known as SGLT (Figure 1).[7] Two isoforms of cotransporters expressed in the luminal membrane have been described: SGLT1 and SGLT2. SGLT1 have a low capacity to transport glucose, attaching 2 Na^+ ions to each glucose molecule, and they and are responsible for 3% of glucose reabsorbed in the kidney. They are expressed in the most distal portion of the proximal renal tubule (segment 3) and, mainly, in the small intestine. SGLT1 are also found in other tissues, such as the heart and skeletal muscle. SGLT2 have a high glucose transport capacity, coupling 1 Na^+ ion to each glucose molecule. They are present almost exclusively in the initial portion (segment 1) of the proximal convoluted tubule and are responsible for the reabsorption of 97% of glucose and 65% of sodium through the kidneys. In individuals without diabetes, when blood glucose exceeds the renal threshold of 180 mg/dL, the transporters'

Keywords

Heart Failure; Sodium-Glucose Transporter 2 Inhibitors; Mortality.

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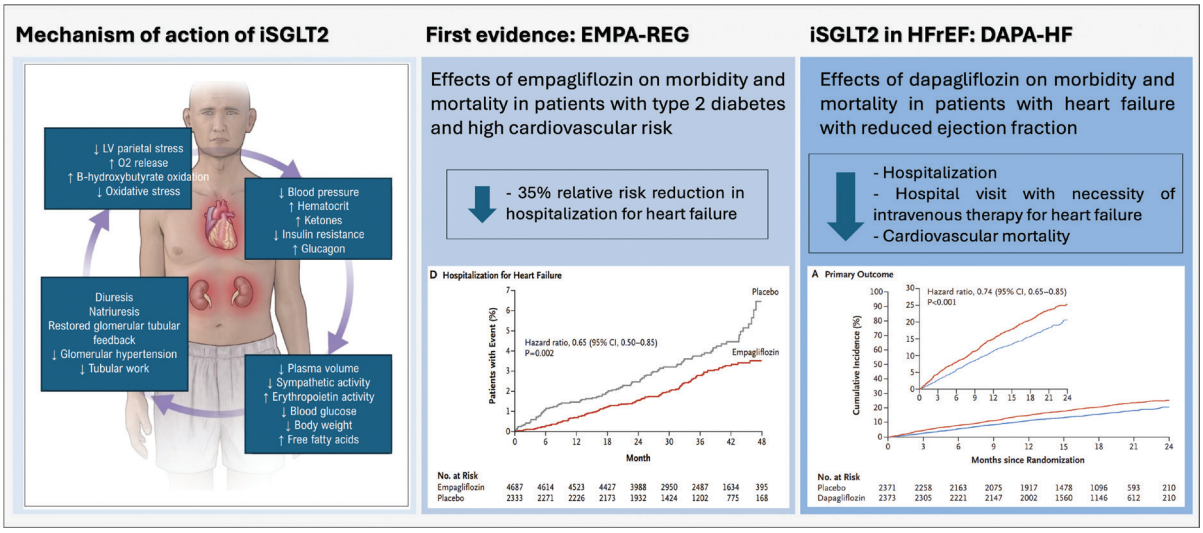
Central Illustration: The Trajectory of Gliflozins: From Apple Tree Bark to Reduced Overall Mortality in Heart Failure



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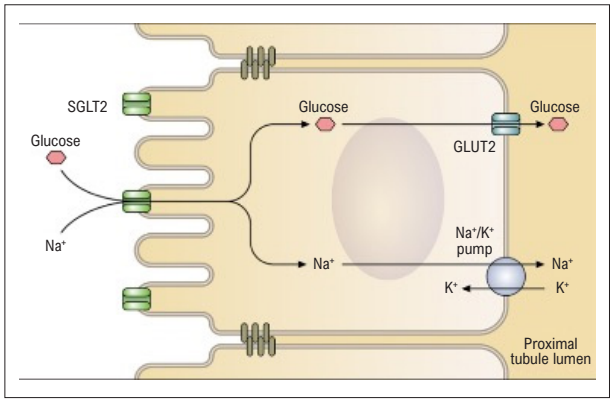

Figure 1 – *Mechanism of action of SGLT2 inhibitors in the proximal tubule. From a study originally published in Kidney International (KI). Bakris GL, et al.[7] GLUT: glucose transporter; SGLT: sodium-glucose cotransporter.*

capacity is saturated, resulting in urinary glucose excretion (Figure 2).[8] However, in the context of diabetes, maximum renal glucose transport is increased due to tubular hypertrophy and, mainly, to increased expression of SGLT1 and SGLT2, raising the glycosuria threshold to values close to 250 mg/dL. This is a maladaptive process that promotes the maintenance of hyperglycemia. The use of SGLT2 inhibitors reduces the renal glucose excretion threshold to values close to 80 to 90 mg/dL. Consequently, glycosuria begins at these values. The use of SGLT inhibitors reduces glucose reabsorption in the proximal tubule, generating glycosuria of around 70 grams per day, in addition to promoting natriuresis and osmotic diuresis. Due to glycosuria, a caloric deficit of approximately 200 kcal per day is established.[9]

Glycemic control

In terms of hypoglycemic potency, this is not a high potency class when compared to other classic anti-diabetogenic medications, such as metformin and sulfonylureas. SGLT2 inhibitors promote a reduction between 0.5% and 1% in glycated hemoglobin. There is a low risk of hypoglycemia, as the effect of SGLT inhibitors does not depend on insulin action. Furthermore, the glucosuric effect is reduced in the state of normoglycemia. In the presence of renal dysfunction with creatinine clearance below 45 ml/kg/min, the glucosuric effect and hypoglycemic potency are attenuated. The risk of hypoglycemia increases when combined with sulfonylureas or insulin. In this case, it is not necessary to suspend SGLT2 inhibitors, but rather to adjust the dose of other medications that pose a greater risk of promoting hypoglycemia.[10]

Benefits of SGLT2 inhibitors beyond glycemic control

Body composition

Data from randomized clinical trials have indicated that gliflozins promote 2 to 3 kg weight loss in the first weeks of use, reaching a plateau within 6 months. The weight reduction effect is attenuated in patients with renal dysfunction. Experimental data suggest that SGLT2 inhibitors trigger a fasting-like state, with increased fatty acid oxidation and ketogenesis, promoting a reduction in adipose tissue and hepatic steatosis.[10] Bioimpedance studies have shown that weight reduction occurs mainly due to the reduction of visceral and subcutaneous adipose tissue, as maintenance of lean mass and a transient reduction in extracellular fluid

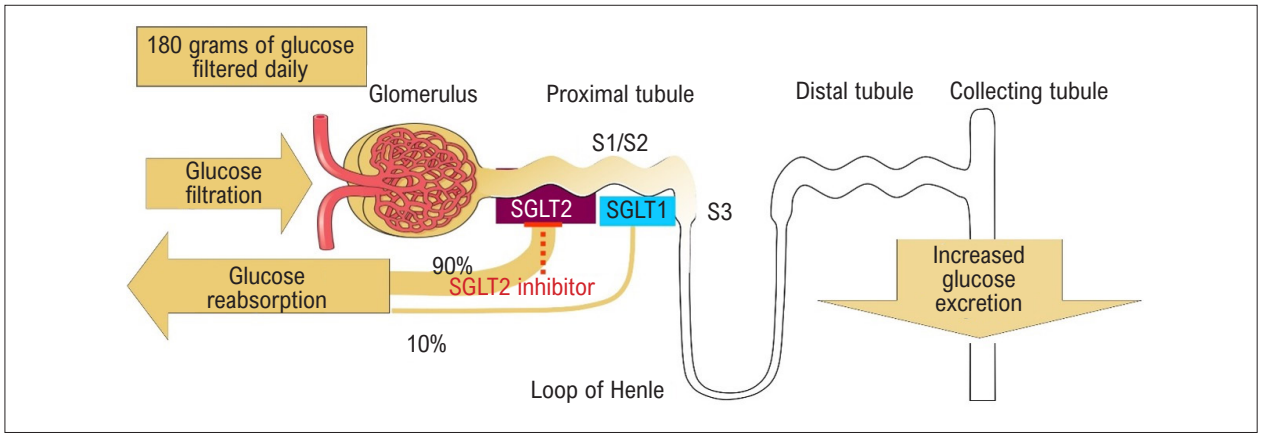

Figure 2 – *Renal physiology and SGLT inhibitors. Adapted from Wright EM.[8] SGLT: sodium-glucose cotransporter.*

occur, with recovery within 6 months. SGLT2 inhibitors also decrease leptin production and reduce perivascular, perivisceral, and pericardial inflammation and adiposity. Epicardial adiposity is metabolically very active in patients with diabetes and is associated with coronary artery disease, atrial fibrillation, and cardiomyopathy.[11]

Increased production of ketone bodies

SGLT2 inhibitors reduce glucose oxidation under baseline conditions and, under insulin stimulation, increase fat oxidation. Furthermore, they modestly, yet significantly increase the production of ketone bodies, resulting in a metabolic condition that resembles prolonged fasting, thus increasing the metabolization of ketones and free fatty acids by the heart, which generates better energy efficiency. A shift toward ketone production and away from glucose oxidation has been proposed as a potential mechanism for the rapid cardiovascular benefit of SGLT2 inhibitor therapy.[10]

Natriuresis

Due to the reabsorption of sodium and glucose in the proximal convoluted tubule, the use of SGLT2 inhibitors is associated with a mild negative balance, with an initial reduction in extravascular fluid and plasma volume. The acute natriuretic effect is due to an increase in urinary volume of around 300 ml per day in the first days using the medication, returning to baseline levels after a few weeks and reestablishing water and saline balance, showing a reduction of approximately 7% in plasma volume within 3 months of treatment.[12]

Blood pressure

Studies have shown that the use of SGLT2 inhibitors is associated with a reduction in systolic blood pressure by 4 to 6 mmHg and a reduction in diastolic blood pressure by 1 to 2 mmHg. The reduction in extracellular volume observed at the beginning of treatment appears to be the main hypotensive mechanism. Over time, other mechanisms contribute to reducing blood pressure, such as weight reduction, reduced adipose tissue, modulation of the renin-angiotensin-aldosterone system, reduced arterial stiffness, and reduced plasma uric acid levels. In patients with chronic kidney disease, there is a reduction in the hypoglycemic effect, but the impact on blood pressure levels remains unchanged. The reduction in blood pressure levels cannot completely explain the rapid reduction in cardiovascular and renal outcomes, since the impact of reduced blood pressure on these outcomes requires long exposure time.[11]

Hematocrit

The use of SGLT2 inhibitors is associated with an increase of approximately 2% in hematocrit, followed by stabilization. The increase in hematocrit and hemoglobin is secondary to hemoconcentration and to an increase in erythropoietin levels with a 7% increase in erythrocyte production. Greater erythropoietin activity may be related to changes in renal blood flow between the cortex and medulla, and it may be an indication of better renal prognosis.[11,13]

Renal effects

In patients with type 2 DM, the increased absorption of sodium and glucose in the proximal tubule due to greater expression of SGLT2 causes vasodilation of the afferent artery and, consequently, glomerular hyperfiltration, which is a fundamental factor in the genesis and progression of diabetic kidney disease. This process promotes glomerular inflammation, fibrosis, and the establishment of diabetic nephropathy. SGLT2 inhibitors, by reducing sodium absorption in the proximal tubule, generate an increase in sodium concentration in the macula densa located in the most distal portion of the nephron adjacent to the glomerulus, increasing glomerular tubular feedback, which, through a cascade of signals mediated by adenosine, causes vasoconstriction of the afferent arteriole. The macula densa also inhibits the production of renin by the cells of the juxtaglomerular apparatus, leading to vasodilation of the efferent arteriole. The combination of afferent vasoconstriction and efferent vasodilation reduces the glomerular filtration rate (GFR), glomerular hypertension,

and albuminuria, leading to nephroprotection (Figure 3).[14] SGLT2 inhibitors also reduce tubular work and oxygen consumption, resulting in reduced kidney injury and increased erythropoietin production.[15]

Glomerular filtration rate and albuminuria

After starting therapy with SGLT2 inhibitors, an acute reduction of approximately 5 ml/kg/min in GFR occurs for several weeks. The mechanism responsible for the acute reduction in GFR is vasoconstriction of the afferent arteriole due to increased glomerular tubular feedback. After an initial drop, levels return to baseline values and remain stable over time, differently than in patients with diabetes not using SGLT2 inhibitors, who tend to experience a progressive decline in GFR. This protective effect on GFR is independent of the history of DM, chronic kidney disease, or CVD.[16,17] Clinical trials and extensive meta-analyses have reported a reduction in albuminuria, prevention of its development, and prevention of progression from microalbuminuria to macroalbuminuria. Furthermore, studies have shown a reduction in the progression of nephropathy and progression to end-stage renal disease. A meta-analysis of 4 large clinical trials (EMPA-REG OUTCOME, CANVAS, CREDENCE, and DECLARE), including more than 38,000 patients with diabetes using SGLT2 inhibitors, showed a 33% reduction in the risk of kidney outcomes consisting of transplantation, death due to kidney disease, or dialysis.[18]

Reduced plasma uric acid levels

The increase in glycosuria promoted by SGLT2 inhibitors leads to uric acid excretion in the proximal convoluted tubule in exchange for glucose reabsorption by the GLUT9 transporter, promoting a 10% to 15% reduction in plasma uric acid levels.[11]

Mechanisms of cardiovascular benefit

Cardiovascular benefits have been extensively studied, and there is apparently no single mechanism responsible; a series of factors are possibly involved, including hemodynamic, anti-inflammatory, and energy substrate factors (Figure 4). The risk reduction of cardiovascular and renal events appears to be independent of the glycemic effect, since the benefits are established quickly after starting therapy with gliflozins, underscoring that glycemic control would require approximately 10 years to generate a measurable cardiovascular impact. Large clinical trials with SGLT2 inhibitors have shown that the cardiovascular and renal benefit is independent of baseline glycated hemoglobin levels or their rate of reduction. Other classes of medications with similar hypoglycemic effects, such as dipeptidyl peptidase 4 inhibitors, did not show a reduction in cardiovascular events in clinical safety studies. In studies with dapagliflozin and empagliflozin, in the context of heart failure (HF), the benefit was observed regardless of the presence of diabetes.

Regarding hemodynamic mechanisms, natriuresis and osmotic diuresis stand out. They reduce extracellular volume and preload, leading to decreased filling pressures, fiber stretching, and arrhythmogenicity. There is also a reduction in left ventricular afterload due to reduced blood pressure levels and improved arterial stiffness. At an energetic level, higher circulating ketone levels are associated with improved mitochondrial function and increased ATP production and contractile performance. In HF, studies in animal models suggest that SGLT2 inhibitors reduce the activity of the Na^+/H^+ exchanger in the myocardium and increase calcium concentration in the mitochondria, which would represent an improvement in excitation-contraction coupling and mitochondrial antioxidant capacity.[11,19]

Side effects

A series of adverse effects are recognized or suspected in the presence of glycosuria and natriuresis. Initially, small studies with SGLT2 inhibitors observed a modest increase in the incidence of urinary tract infections; however, in large-scale studies, no statistical difference was observed between the groups receiving placebo and SGLT2 inhibitors. The most common side effect is genital infection, mainly by Candida species, with a prevalence of 10% in women and 5% in men.

Due to the osmotic diuresis and natriuresis promoted by SGLT2 inhibitors, there is a potential risk of volume depletion and hypotension. This adverse event is uncommon in large clinical trials, and it is more common in the elderly and those using loop diuretics. On the other hand, it is worth highlighting that natriuresis and volume reduction have a positive effect with protective action against the development of clinical symptoms of HF, which could partially explain the rapid reduction in the rate of hospitalization for HF in large clinical trials. The osmotic diuresis promoted by SGLT2 inhibitors is also considered to result in greater free water clearance from the interstitial space than from the intravascular space.[19]

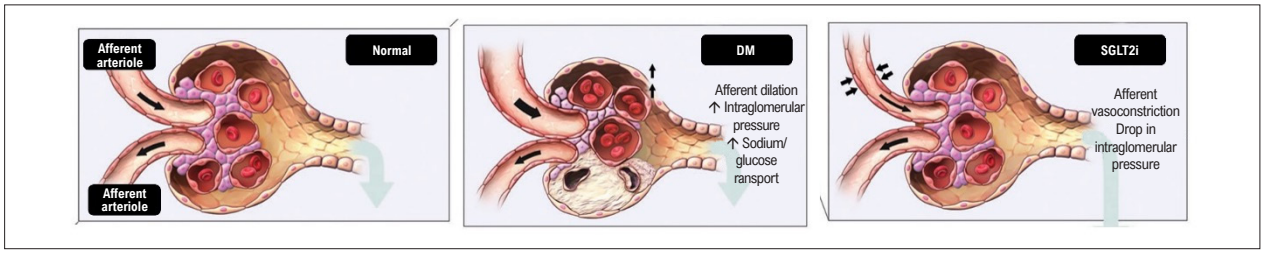

Figure 3 – *Effects of SGLT2i on renal hemodynamics in patients with diabetes mellitus. Adapted from Verma S, et al.[14] DM: diabetes mellitus; SGLT2i: sodium-glucose cotransporter 2 inhibitor.*

Elevation of ketones may occur during use of SGLT2 inhibitors, and this requires attention. Cases of euglycemic diabetic ketoacidosis have been found in patients with type 1 DM in off-label use. Rarely, ketoacidosis has been associated with the use of SGLT2 inhibitors in patients with type 2 DM, and it is more commonly precipitated in insulin users with dose omission or reduction, in the presence of severe acute illness, dehydration, intense exercise, major surgeries, excessive alcohol consumption, or a low carbohydrate diet.[20]

Clinical trials on cardiovascular safety with SGLT2 inhibitors

The first large clinical trial to evaluate the cardiovascular safety of SGLT2 inhibitors in patients with type 2 diabetes was the EMPA-REG OUTCOME Trial, which evaluated 7,020 patients with CVD. The primary outcome was the rate of MACE comprising death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Empagliflozin was not only safe, but, surprisingly, it showed effective cardioprotection. There was a 16% reduction in MACE, a 38% reduction in cardiovascular death, a 35% reduction in hospitalizations due to HF, and a 32% reduction in all-cause mortality. The benefits in reducing HF outcomes were observed as early as 2 to 3 weeks after starting empagliflozin therapy.[16]

Subsequently, the CANVAS PROGRAM, consisting of 2 studies, CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-R (CANVAS-renal), evaluated 10,142 patients with diabetes, and two thirds of the population assessed had a history of CVD. There was a 14% reduction in MACE and a 33% reduction in hospitalizations due to HF.[21,22]

The DECLARE (Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes) trial evaluated the effects of dapagliflozin in 17,160 patients with diabetes, including patients with established atherosclerotic CVD (59% of the sample) and patients without CVD but with multiple risk factors (41% of the sample). In this population with less severity, there was no reduction in MACE, cardiovascular mortality, or all-cause mortality, but the lower rate of hospitalization for HF remained effective, around 27%.[23] Subanalysis of the DECLARE study identified a reduction in cardiovascular death in the group of patients with a history of heart failure with reduced ejection fraction (HFrEF) or infarction.[24] The VERTIS study evaluated ertugliflozin in 8,246 patients with type 2 DM and atherosclerotic CVD; the study did not find a reduction in cardiovascular death, but there was a significant reduction in first hospitalization for HF.[25] More recently, the SCORED Trial, a cardiovascular safety study with sotagliflozin in patients with diabetes and renal dysfunction, showed a reduction in the primary outcome consisting of cardiovascular death, hospitalizations for HF, and emergency room visits for HF.[26]

These 6 large trials evaluated individuals with different spectrums of severity, from patients with CVD to those with multiple risk factors. Together, these trials show a consistent reduction in hospitalization for HF in the population with type 2 DM, even in individuals without prior diagnosis of atherosclerotic CVD or HF, highlighting that the rate of HF diagnosis prior to randomization was 10% to 14% in these clinical trials. The cardiovascular benefits do not appear to be secondary to better glycemic control, highlighting that the difference in glycated hemoglobin between the groups was slight. Meta-analysis of these studies revealed strong evidence of reduced cardiovascular death in patients with CVD and a possible trend towards reduced cardiovascular death in individuals with high CVD risk. Mainly, a robust reduction in the risk of hospitalization for HF was observed in all groups, regardless of history of atherosclerotic CVD or renal function (Figure 5).[27]

Clinical benefits of SGLT2 inhibitors in the treatment of heart failure with reduced ejection fraction

Patients with HFrEF present a very high risk of unfavorable events, such as death and hospitalization due to HF, even when medicated with maximum tolerated doses of neurohormonal blockers; this emphasizes the need to search for new therapies for this condition.[28] In this sense, considering the benefits of SGLT2 inhibitors verified in DM treatment trials addressing safety and monitoring cardiovascular outcomes, investigation began with clinical applicability in the treatment of patients with HF, regardless of the presence of DM.

In 2019, the DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction) study was published, including 4,744 patients with symptomatic HFrEF receiving standard therapy, who were randomized to receive dapagliflozin 10 mg once daily or placebo; only 41.8% of this population had diabetes. After a median follow-up of 18.2 months, the trial showed a 26% reduction in the primary composite endpoint of cardiovascular death or worsening HF (hospitalization or an urgent visit resulting in intravenous

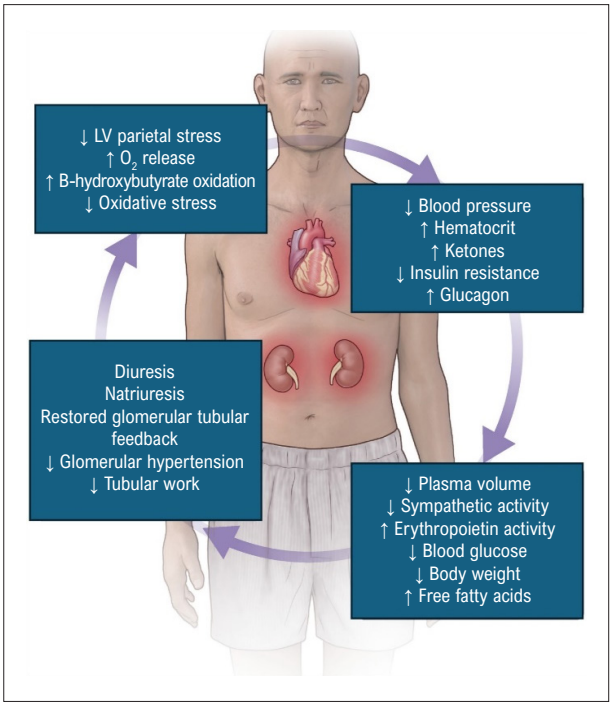

Figure 4 – *Cardiac and renal benefits of sodium-glucose cotransporter 2 inhibitor. Adapted from Braunwald.1 LV: left ventricle.*

therapy for HF). When these outcomes were analyzed alone, there was an 18% reduction in cardiovascular death and a 30% reduction in worsening of HF, regardless of the presence of diabetes. It is important to highlight that there was also a 17% reduction in death from any cause, with a good safety profile, with no significant adverse events (Figure 6).[29]

The following year, the results of the EMPEROR-Reduced (Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure) Trial were published, evaluating the benefit of empagliflozin 10 mg once daily against placebo in 3,730 patients with symptomatic HFrEF and treated with standard therapy. In this study, patients with diabetes accounted for 50.2% of the population. Regarding the primary outcome of cardiovascular death or hospitalization due to worsening HF, a 35% reduction was observed, favoring the empagliflozin group. When analyzed alone, there was a 31% reduction in hospitalization for HF, regardless of the presence of diabetes; however, no benefit was observed in the isolated reduction of cardiovascular death or death from any cause. As with DAPA-HF, there were no relevant adverse events, with a good safety profile.[30]

An analysis of pooled data involving both studies, totaling a population of 8,474 patients, showed a 13% reduction in overall mortality, a 14% reduction in cardiovascular mortality, and a 31% reduction in the risk of hospitalization for HF, establishing a new and important therapeutic pillar for the treatment of HFrEF, which has been approved and recommended by national and international guidelines.[31]

Clinical benefits of SGLT2 inhibitors in the treatment of heart failure with preserved ejection fraction

In recent years, different clinical trials testing the effect of neurohormonal blockers have failed to demonstrate a reduction in cardiovascular events in patients with heart failure with preserved ejection fraction (HFpEF). The publication of cardiovascular safety studies using SGLT2 inhibitors revealed a "light at the end of the tunnel," with the possibility of a treatment that could achieve this objective in this large population of patients.

In 2021, the results of EMPEROR-Preserved (Empagliflozin in Heart Failure with Preserved Ejection Fraction) were published, including 5,988 patients with HF and left ventricular ejection fraction (LVEF) greater than 40%, in New York Heart Association functional class II to IV, who were randomized to empagliflozin 10 mg once daily or placebo. After a median follow-up of 26.2 months, there was a 21% reduction in the primary outcome of cardiovascular death or hospitalization for HF, favoring the use of empagliflozin. Hospitalizations due to HF were reduced by 29%, but without a reduction in the isolated outcome of cardiovascular death and without evidence of benefit in the outcome of reducing death from any cause. The results were consistent in both patients with diabetes and patients without diabetes, and no significant serious adverse events were reported.[32]

The following year, the DELIVER (Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction) trial's results were very similar to those of EMPEROR-Preserved, including 6,263 patients with HF and LVEF greater than 40%, randomized to dapagliflozin 10 mg once daily or placebo. After a median follow-up of 2.3 years, there was an 18% reduction in the primary outcome of worsening HF (consisting of unplanned hospitalization or urgent emergency room visit for HF) or cardiovascular death. However, there was no reduction in cardiovascular death or death from any cause, showing a 23% reduction in hospitalizations due to HF. The results were similar between the different subgroups, including patients with LVEF greater than or equal to 60% and less than 60%, and patients with and without diabetes. Adverse events were similar in both groups, with no significant serious events. It is relevant that 18.4% of participating patients had HF with improved ejection fraction, a population that is generally not included in HF trials.[33]

When evaluating these two clinical trials in association, totaling 12,251 patients, the use of SGLT2 inhibitors

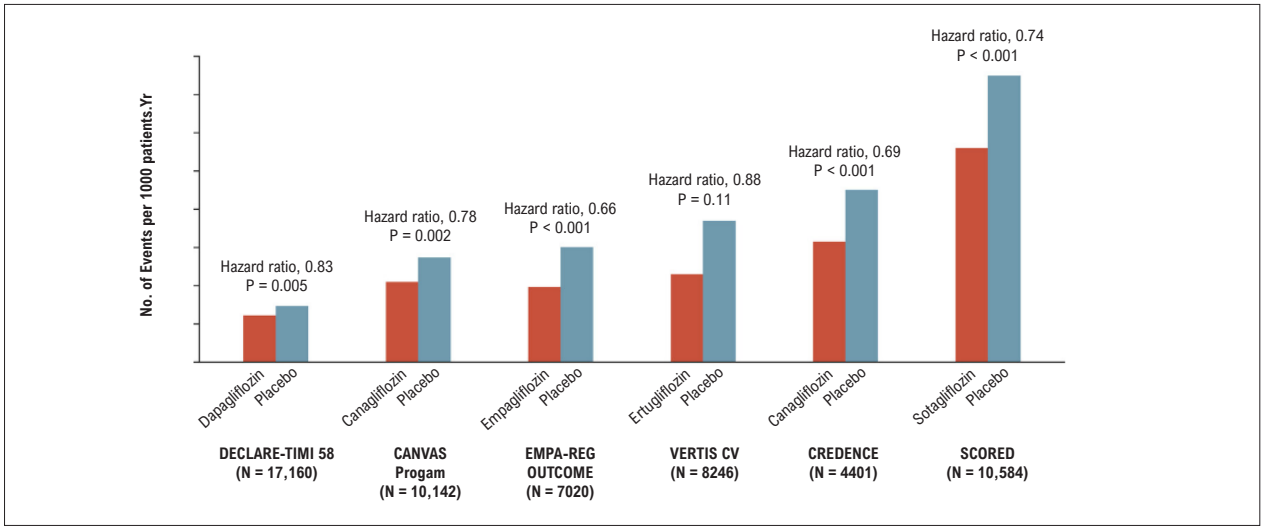

Figure 5 – *Impact on cardiovascular death and hospitalization for heart failure according to 6 large treatment trials on diabetes mellitus with SGLT2 inhibitors. Adapted from Braunwald.[2]*

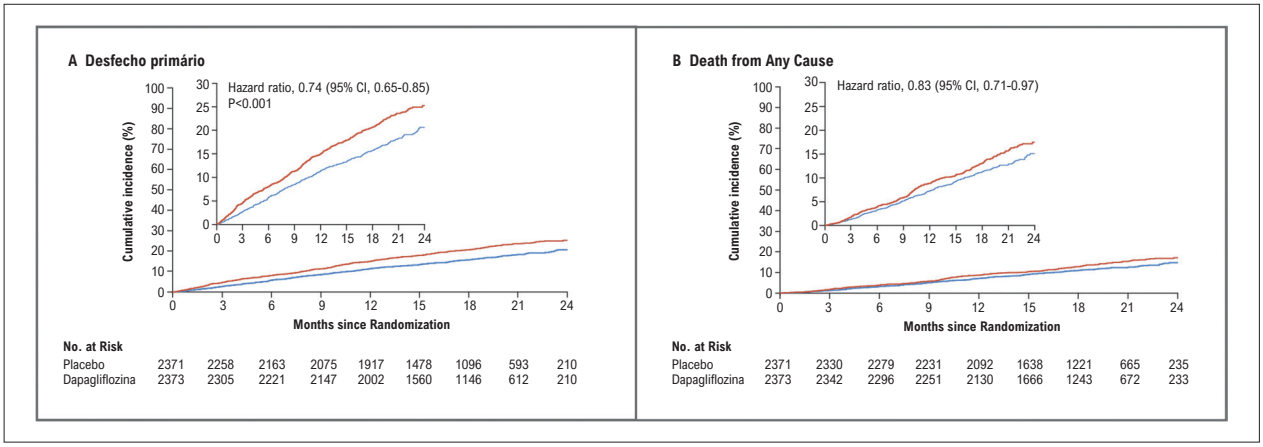

Figure 6 – *Cumulative curves of events observed in the DAPA-HF study. A – Primary outcome (cardiovascular death or heart failure event), with a relative risk reduction of 26%; B – death from any cause, with a relative risk reduction of 17%. From a study originally published in the The New England Journal of Medicine (NEJM). McMurray, et al.*[29]

showed a 20% reduction in cardiovascular death or first hospitalization due to HF. These results were consistent in both components of this outcome, with a 12% reduction in cardiovascular death and a 26% reduction in the first hospitalization for HF, but without an impact on death from any cause.[34]

hus, empagliflozin and dapagliflozin show significant benefits in the treatment of chronic outpatients across the entire LVEF spectrum, being applicable for patients with HFrEF, HFpEF and HF with mildly reduced ejection fraction, including patients with improved LVEF. This is the first class of drugs to demonstrate such a breadth of clinical benefit.

Clinical benefits of SGLT2 inhibitors in the treatment of acute heart failure

Acute HF refers to the rapid or gradual onset of HF signs and symptoms that are severe enough for the patient to seek emergency medical care, leading to unplanned hospitalization or emergency department visit. Acute HF may be the first clinical manifestation of HF, or it may be secondary to acute decompensated chronic HF. This is a crucial time to initiate and/or intensify HF treatment with medications that have an impact on these patients' survival.[35]

Accordingly, EMPA-RESPONSE-AHF (Randomized, double-blind, placebo-controlled, multicenter pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure) randomized 80 patients with acute HF, with or without diabetes, to receive dapagliflozin 10 mg once daily or placebo, with the objective of evaluating variation in dyspnea score by means of a visual scale, response to the diuretic (defined as weight loss for each 40 mg of furosemide), change in NT-proBNP, and length of hospital stay. First decompensation due to HF (*de novo* HF) was present in 47% of these patients. Empagliflozin significantly reduced the combined outcome of worsening in-hospital HF, rehospitalization for HF, or death within 60 days, but there was no impact on the other outcomes evaluated. Urine output up to the fourth day was substantially higher in the empagliflozin group. It was well tolerated, safe, and had no effects on blood pressure or kidney function.[36]

Subsequently, the EMPULSE (Impact of empagliflozin on decongestion in acute heart failure) trial evaluated the effect of empagliflozin 10 mg once daily against placebo on outcomes related to decongestion in 530 patients hospitalized for acute HF. The outcomes evaluated were weight loss, weight loss adjusted for mean daily loop diuretic dose, serum NT-proBNP levels, hemoconcentration, and clinical congestion score 15, 30, and 90 days after the start of treatment. Patients who received empagliflozin demonstrated a significant reduction in decongestion markers at all of time-points assessed. Efficacy was independent of ejection fraction and the presence of diabetes, with a similar rate of adverse events between both groups.[37]

The DICTATE-AHF (Efficacy and Safety of Dapagliflozin in Acute Heart Failure) clinical trial is evaluating the efficacy and safety of initiating dapagliflozin 10 mg once daily within the first 24 hours of hospitalization in patients with type 2 DM with hypervolemic acute HF and estimated GFR of at least 30 mL/min/1.73 m^2. The primary outcome was diuretic response expressed in cumulative weight loss per cumulative dose of loop diuretic equivalent to 40 mg of intravenous furosemide.[38]

The SOLOIST-WHF (Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure) trial with sotagliflozin, an SGLT1 and SGLT2 receptor inhibitor, showed a reduction in events among 1,222 individuals with type 2 DM hospitalized for HF who received this medication during hospitalization or immediately after hospital discharge. Sotagliflozin was associated with a 29% reduction in cardiovascular death or worsening of HF over a mean follow-up of 18 months.[26]

Recommendations for use of SGLT2 inhibitors in clinical practice

In view of this evidence, an analysis of the impact of the association of SGLT2 inhibitors with the treatment of HFrEF using beta-blockers, mineralocorticoid receptor antagonists, and angiotensin receptor-neprilysin inhibitors showed a 62% reduction in cardiovascular death or hospitalization for HF, with a 50% reduction in cardiovascular death, 68% reduction in hospitalization for HF, and 47% reduction in death from any cause, when compared to treatment with beta-blocker and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. Furthermore, these 4 medication classes promoted 2.7 years and 8.3 years free from cardiovascular death or hospitalization for HF and increased survival by 1.4 years and 6.3 years, respectively, for patients aged 80 years and 55 years.[39]

These results have firmly established SGLT2 inhibitors as a new pillar in the treatment of HF, receiving class of recommendation I and level of evidence A for the treatment of HFrEF in the latest updates of European and American guidelines for the treatment of chronic HFrEF, alongside the beta-blocker sacubitril/valsartan and mineralocorticoid receptor antagonists (Figure 7).[40,41]

For the treatment of HFpEF and HF with mildly reduced ejection fraction, the most recent European guidelines recommend the use of dapagliflozin or empagliflozin, also with class of recommendation I and level of evidence A, to reduce the risk of hospitalization for HF or cardiovascular death. Furthermore, the use of these medications also presents the same level of recommendation for prevention of HF in patients with diabetes and chronic kidney disease to reduce the risks of hospitalization for HF or cardiovascular death.[40]

Conclusions

The success story of SGLT2 inhibitors extends from preventing the development of HF in patients with diabetes to reducing overall mortality in patients with HF. This is the first class of drugs to demonstrate a tangible benefit in all ranges of LVEF, in the setting of both chronic outpatient HF and acute HF in hospitalized patients. This trajectory of success has led gliflozins to be recommended medications, with a high level of scientific evidence in international guidelines for the treatment of HF.

Author Contributions

Conception and design of the research and Acquisition of data: Marques F, Valicelli FH, Simões MV; Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for content: Marques F, Valicelli FH, Tanaka DM, Simões MV.

Potential conflict of interest

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

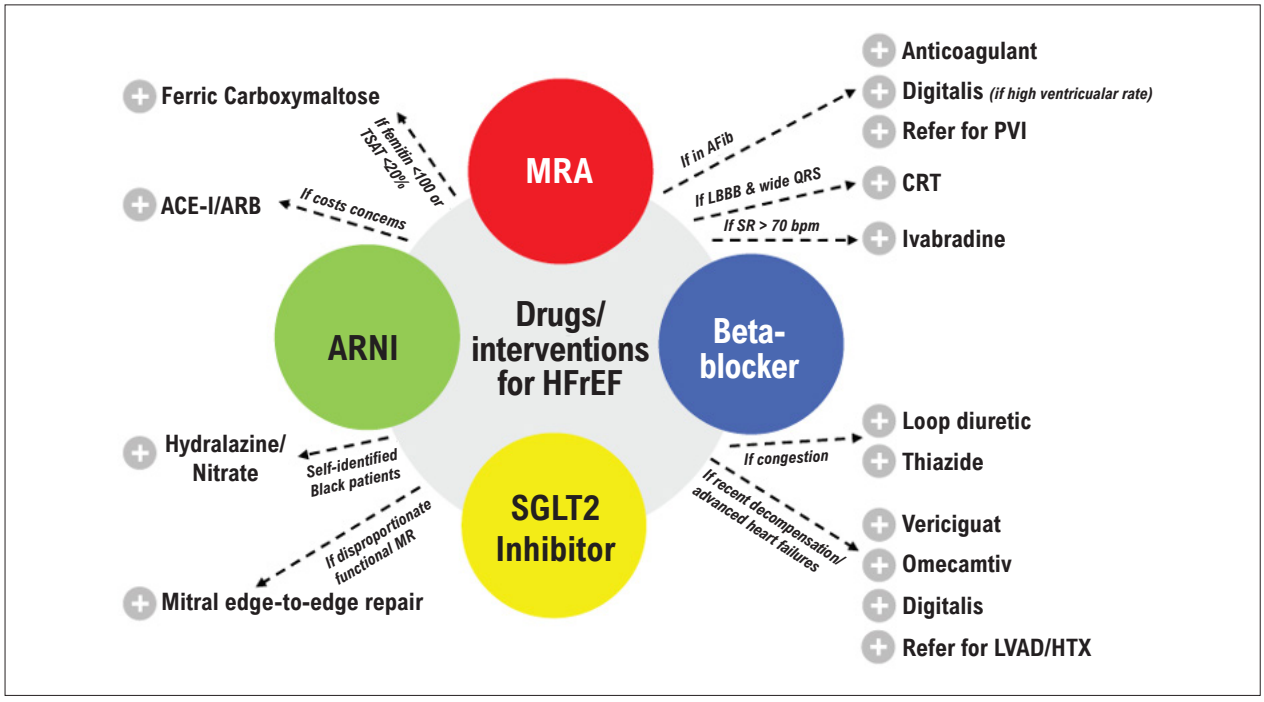

Figure 7 – *Current scenario for the treatment of heart failure with reduced ejection fraction, highlighting the 4 essential drugs aimed at reducing mortality. From a study originally published in the European Heart Journal. Bauersachs J.42 ACE-I: angiotensin-converting enzyme inhibitor; Afib: atrial fibrillation; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor/neprilysin inhibitor; CRT: cardiac resynchronization therapy; HFrEF: heart failure with reduced ejection fraction; HTX: heart transplantation; LBBB: left bundle branch block; LVAD: left ventricular assist device; MR: mitral regurgitation; MRA: mineralocorticoid receptor antagonist; PVI: pulmonary vein isolation; SGLT2: sodium–glucose co-transporter 2; SR: sinus rhythm; TSAT: transferrin saturation.*

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Study association

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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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