RESEARCH ARTICLE

Empagliflozin, Beyond Glucose Reduction. The Unanticipated and Welcomed Cardioprotective Results. Switching the Heart at Four Levels: Energetic, Anatomical, Functional, and Neuro-Hormonal

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Summary
Sodium-glucose cotransporter 2 inhibitors (SGLT2i) like empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin, and sotagliflozin (both a sodium-glucose cotransporter 1 inhibitor [SGLT1i] and SGLT2i), are drugs that inhibit the action of sodium-glucose cotransporters in the proximal renal tubule and/or the intestine. Therefore, causing natriuresis, glucosuria, and reduced intestinal glucose absorption. Besides this mechanism of action, which determines glycemia reduction, there are multiple extra-glycemic mechanisms in extensive research in humans in-vivo, which, beyond in-vitro or experimental studies, is dissecting the mechanisms explaining the initially unanticipated and ultimately incredibly significant and welcomed cardiac and nephroprotective results of these drugs.
This article centers on the cardioprotective effects of empagliflozin, namely, a reduction of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure, among others. These effects were demonstrated in the EMPA-REG and EMPEROR-Reduced clinical outcome trials, which will be initially summarized to later frame them in the results of the mechanistic trials EMPA-HEART, EMPIRE-HF (including sub-studies), EMPA-TROPISM, and "EMPA-PIG." The mechanistic trials showed favorable changes in the left ventricular mass index, left ventricular end-systolic and end-diastolic volumes, extracellular and intravascular volumes, glomerular filtration rate, myocardial remodeling, among others. These were investigator-initiated studies to go beyond in-vitro and experimental evidence. The results and analysis allow us to understand myocardial energy remodeling as an intrinsic myocardial mechanism that underlies anatomical, functional, and neurohormonal myocardial remodeling. Together with other systemic actions, predominantly renal (not discussed in this article), contribute significantly to this drug's clinical benefit.

Introduction

Empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, and sotagliflozin, in the EMPA-REG-Outcome,[1-2] EMPEROR-Reduced,[3] CANVAS,[4] CREDENCE,[5] DECLARE,[6] DAPA-Heart Failure,[7] DAPA-CKD,[8] VERTIS,[9] SCORED,[10] and SOLOIST-WHF trial,[11] respectively, demonstrated heterogeneity in the risk reduction of three Major Adverse Cardiovascular Events (3-point MACE) composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. On the other hand, all showed homogeneity in the reduction of 2-point MACE (cardiovascular death or hospitalization for heart failure), and four Major Adverse Renal Events (4-point MARE) composite of doubling of creatinine/reduction of 50% or more in glomerular filtration rate (GFR), development of end-stage chronic kidney disease (CKD), or renal death or cardiovascular death (Figures 1,2 and 3). As drugs for glycemic control, SGLT1i and SGLT2i, have an intermediate efficacy with a reduction of HbA1c between 0.75 and 1.5%, directly proportional to the baseline level. They are not associated with severe hypoglycemia, although, like other drugs, their co-administration with sulfonylureas and/or insulin can cause it. Its effect on weight loss is intermediate. SGLT2i are administered orally, and currently, they are not recommended with a GFR <30 ml/min/1.73m^2. Volume depletion, hypotension, fungal genital infections, ketoacidosis, Fournier's gangrene, acral amputations, and fractures have been described as the main adverse effects; they are relatively contraindicated in patients at risk of amputations and/or fractures.[12-13]

Regardless of the HbA1c level, the current guidelines recommend SGLT2i as the first-line therapy in patients with type 2 diabetes (T2D) and heart failure with ejection fraction <45% (HFrEF) and/or moderate CKD with GFR between 30 and 60 ml/min/1.73m^2, and an albumin-to-creatinine ratio (ACR) >30 mg/g. In individuals with atherosclerotic cardiovascular disease (ASCVD) without HFrEF and/or CKD, SGLT2i are also considered as an alternative or adjuvant first-line therapy to glucagon-like peptide-1 receptor agonists (GLP1-RA)[12-13].

This article summarizes the results of the cardiovascular outcome trials carried out with empagliflozin,[1-3] and analyzes the EMPA-REG mediation sub-analysis results,[14] EMPA-HEART,[15] and EMPIRE-HF, and substudies.[16-19] Also, "EMPA-PIG"[20] and EMPA-TROPISM,[21] which outline the intrinsic myocardial mechanisms associated with clinical benefit in HFrEF in higher mammals[20] and especially in humans in-vivo.[15-19, 21]

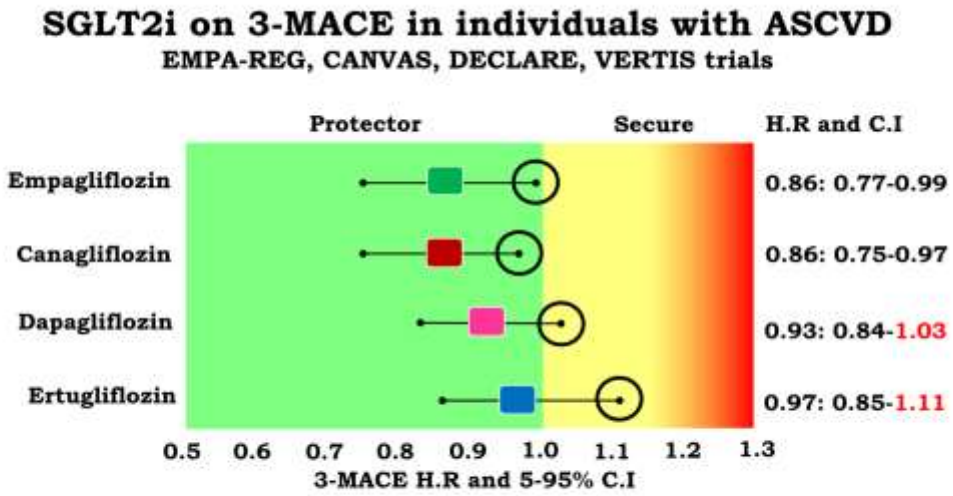

Figure 1: Hazard ratios are illustrated with their lower and upper limits of the confidence interval for the incidence of 3-MACE (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in cardiovascular outcome trials with empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin in a ASCVD population. A protective effect is observed against the 3-MACE with empagliflozin and canagliflozin, not so for dapagliflozin and ertugliflozin, which showed a noninferior or safety result.

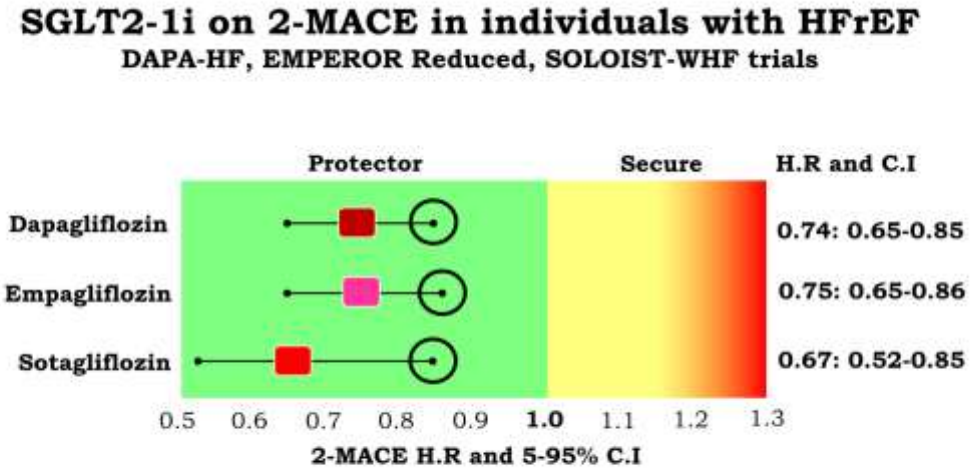

Figure 2: Hazard ratios are illustrated with their lower and upper limits of the confidence interval for the incidence of 2-MACE (cardiovascular death or hospitalization for heart failure) in cardiovascular outcome trials with dapagliflozin, empagliflozin, and sotagliflozin in a HFrEF (with or without T2D) population. A protective effect against 2-MACE with the three referred drugs is observed.

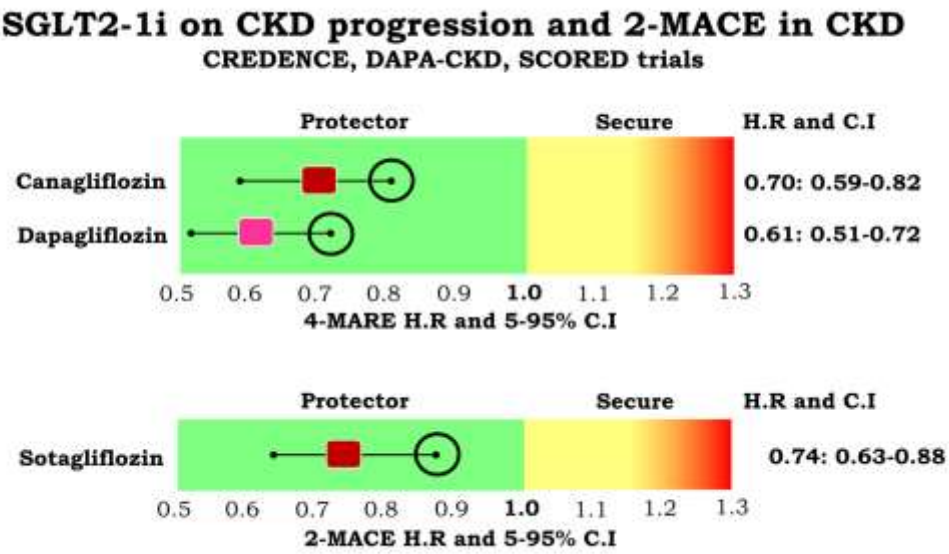

Figure 3: upper panel: Hazard ratios are illustrated with their lower and upper limits of the confidence interval for the incidence of 4-MARE (evolution to end-stage CKD, doubling of creatinine, renal death, or cardiovascular death) in cardiovascular outcome trials with canagliflozin and dapagliflozin in a CKD population (with or without T2D). A protective effect against 4-MARE with the two referred drugs is observed.

Cardiovascular outcome trials with empagliflozin[1, 3]

EMPA-REG OUTCOME trial[1]

This trial evaluated the cardiovascular safety and efficacy of empagliflozin in patients with T2D and ASCVD. It was a multicenter, randomized, double-blind, placebo-controlled study. It included patients ≥18 years with T2D, with HbA1c between 7 and 10% and history of ASCVD (coronary artery disease, cerebrovascular disease, or peripheral arterial disease) with GFR ≥30 ml/min/1.73m^2. They were randomly assigned in a 1:1:1 ratio to empagliflozin 10 or 25 mg/day or placebo. The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction (excluding silent myocardial infarctions), or nonfatal stroke (3-point MACE). The secondary outcome was a composite of some event of 3-point MACE or hospitalization for unstable angina (expanded MACE). The statistical analysis was based on the intention-to-treat principle and to demonstrate noninferiority and, where appropriate, superiority of the pooled doses of empagliflozin versus placebo.

A total of 7,028 patients were randomized, the median observation time was 3.1 years. The average age was 63.1 and 63.2 years, female sex 28.2 and 28.0%, Hispanic 18.1 and 17.9%, body mass index (BMI) 30.6 and 30.7, more than ten years with T2D 57.0 and 57.4%, HbA1c 8.07 and 8.08%, history of coronary artery disease 75.6 and 75.6%, cerebrovascular disease 23.1 and 23.7%, and peripheral artery disease 21.0 and 21.5% in the pooled doses of empagliflozin and placebo, respectively. Adjusted to 3.1 years of follow-up, 3-point MACE occurred in 10.5% (490/4,687) and 12.1% (282/2,333) in the pooled doses of empagliflozin and placebo, respectively (HR: 0.86: 0.74-0.99 with P <0.001 for noninferiority and 0.04 for superiority) (figure 1). The 3-point MACE annualized risk

was 3.38 and 3.90%, respectively. In the analysis of the 3-point MACE components, cardiovascular death occurred in 3.7% (172/4,687) and 5.9% (137/2,333), respectively (HR: 0.62: 0.49- 0.77 with P <0.001); nonfatal myocardial infarction and stroke did not show a significant difference. Adjusted to 3.1 years of follow-up, expanded MACE occurred in 12.8% (599/4,687) and 14.3% (333/2,333) in the pooled doses of empagliflozin and placebo, respectively (HR: 0.89: 0.78-1.01 with P <0.001 for noninferiority and 0.08 for superiority). In the analysis of other secondary outcomes, death from any cause occurred in 5.7% (269/4,687) and 8.3% (194/2,333) respectively (HR: 0.68: 0.57-0.82 with P <0.001), and hospitalization for heart failure (HHF) happened in 2.7% (126/4,687) and 4.1% (95/2,333), respectively (HR: 0.65: 0.50-0.85 with P 0.002).

The authors concluded that both empagliflozin doses (10 and 25 mg/day) were superior to placebo, meaning empagliflozin 10 or 25 mg/day significantly reduced the cardiovascular risk of 3-point MACE and expanded MACE, including the risk of cardiovascular death, death from any cause, and HHF. Empagliflozin was the first antidiabetic drug to demonstrate cardiovascular protection.

EMPEROR-Reduced trial[3]

This trial evaluated the safety and efficacy of empagliflozin in reducing cardiovascular death or HHF in patients with HFrEF with or without T2D. It was a multicenter, randomized, double-blind, placebo-controlled study. It included patients ≥18 years with chronic heart failure (CHF) with standard care, New York Heart Association (NYHA) functional class II, III or IV, left ventricular ejection fraction (LVEF) <40% with GFR ≥20 ml/min/1.73m^2. The study "enhanced" the inclusion criteria with a required level of N-terminal pro-b-type natriuretic peptide (NT-proBNP). In the absence of atrial fibrillation, the required level was >600, >1,000, or >2,500 pg/mL with an LVEF <30, 31-35 or 36-40%, respectively, or LVEF between 30-40% and HHF the year before inclusion. In the presence of atrial fibrillation, the required levels of NT-proBNP were double those already mentioned. They were randomly assigned in a 1:1 ratio to empagliflozin 10 mg/day or placebo. The primary outcome was a composite of cardiovascular death or HHF (2-point MACE). The secondary outcomes were a composite of the first and subsequent episodes of HHF and a reduction of GFR. The statistical analysis was based on the intention-to-treat principle and to demonstrate the superiority of the primary objective and hierarchical order of the secondary objectives of empagliflozin versus placebo.

A total of 3,730 patients were randomized; the median observation time was 16 months (1.3 years). The average age was 67.2 and 66.5 years, female 23.5 and 24.4%, Hispanic 34.4 and 34.5%, BMI 28 and 27.8, T2D 49.8 and 49.8%, LVEF 27.7 and 27.2% (<30% in 71.8 and 74.6%), average NT-proBNP 1,887 and 1,926 pg/mL, average GFR 61.8 and 62.2 ml/min/1.73m^2, unspecified ACR, ischemic etiology 52.8 and 50.7%, non-ischemic etiology 47.2 and 49.3% for empagliflozin and placebo, respectively. Adjusted to 1.3 years of follow-up, 2-point MACE occurred in 19.4% (361/1,863) and 24.7% (462/1,867) (HR: 0.75: 0.65-0.86 with P <0.001) (figure 2), with 15.8 and 21.0 events per 100 individuals/year, for empagliflozin and placebo, respectively. In the analysis of the 2-point MACE components, cardiovascular death occurred in 10.0% (187/1,863) and 10.8% (202/1,867) (HR: 0.92: 0.75-1.12) with 7.6 and 8.1 events per 100 individuals/year and HHF occurred in 13.2% (246/1,863) and 18.3% (342/1,867) (HR 0.69: 0.59-0.81) with 10.7 and 15.5 events per 100 individuals/year, for empagliflozin and placebo, respectively. The benefit was homogeneous among all the prespecified subgroups, including T2D versus nonT2D. However, a greater reduction of 2-point MACE (0.64: 0.45-0.89 versus 0.77: 0.66-0.90) was reported in the subgroup receiving treatment with sacubitril/valsartan (18.3%) versus no sacubitril/valsartan (20.7%).

Adjusted to 1.3 years of follow-up, the total HHF was 388/1,863 and 553/1,867 for empagliflozin and placebo, respectively (HR: 0.70: 0.58-0.85 with P <0.001). Reduction in GFR was -0.55 and -2.28 ml/min/1.73m^2 with a delta of 1.73 ml with intervals between 1.10-2.37 ml/min/1.73m^2 with P <0.001 for empagliflozin and placebo, respectively. Other outcomes not subject to the statistical hierarchy were analyzed in a prespecified manner. Likewise, changes in HbA1c, hematocrit, NT-proBNP, body weight, and systolic blood pressure were analyzed. Both the former and the latter showed variations in favor of empagliflozin versus placebo. In the safety analysis, except for a greater number of genital infections in the empagliflozin group, there were no other relevant differences in the incidence of other adverse events, including fractures or amputations.

The authors concluded that empagliflozin 10 mg/day was superior to placebo in reducing 2-point MACE, especially HHF. Likewise, empagliflozin was superior in reducing the total number of HHF and attenuating the fall in GFR in patients with HFrEF with LVEF <40% and elevation of NT-proBNP with standard care for CHF, regardless of the presence or absence of T2D.

Mechanistic clinical trials with Empagliflozin[14-21]

As mentioned in the introduction, the positive clinical results of the EMPA-REG and EMPEROR-Reduced trials immediately aroused interest in establishing the intrinsic mechanisms of those clinical benefits, initiating a series of research and publications presented and analyzed below.

EMPA-REG OUTCOME trial. Post-hoc mediation analysis

Using a post-hoc mediation analysis of the EMPA-REG OUTCOME trial[1], Inzucchi et al.[14] studied the potential mediation between seven clusters with nineteen variables and the 38% reduction in the relative risk of cardiovascular death observed in that trial. A positively mediated variable is modified by treatment throughout the study, and that said modification has (in the univariate and multivariate analyses) a favorable effect on the outcome analyzed. In this analysis, hematocrit, and hemoglobin, as variables included in the intravascular volumetric status cluster, showed a significant mediation of 51.8 and 48.9%, respectively, with a 38% reduction in the relative risk cardiovascular death. The other variables had an intermediate or absent mediation.

With this result, the authors hypothesized for the first time that reduction in intravascular volume, as reflected in the increase in the red cell mass (probably also favored by an increase in erythropoiesis), could determine the reduction in filling pressures and ventricular workloads as a central mechanism for reducing cardiovascular death risk.

EMPA-HEART trial

Verma et al.[15] conducted the EMPA-HEART trial to hypothesize that the cardiovascular benefit of SGLT2i is associated with a reduction in left ventricular mass. This investigator-initiated clinical trial was a randomized, double-blind, placebo-controlled study. It included patients between 40 and 80 years with T2D in stable treatment for ≥2 months (excluding treatment with SGLT2i, GLP1-RA, and saxagliptin), HbA1c between 6.5 and 10%, coronary artery disease (previous myocardial infarction and/or coronary revascularization), and GFR ≥60 ml/min/1.73m^2. The primary endpoint was the change in the left ventricular mass index (LVMi) measured by cardiac magnetic resonance imaging (MRI) from baseline to six months of treatment with empagliflozin 10 mg/day versus placebo. Secondary endpoints were changes in non-indexed left ventricular end-diastolic and end-systolic volumes, LVEF, and NT-proBNP.

Baseline LVMi was 10.9 and 12.8 g/m^2 for empagliflozin and placebo, respectively. Change in LVMi at the sixth month of treatment was -2.6 and -0.01 g/m^2 for empagliflozin and

placebo, respectively, with an adjusted difference of -3.35 g/m^2 (-5.9 to -0.81 with P 0.01). There were no significant differences in the values of end-diastolic or end-systolic ventricular volumes, LVEF, or NT-proBNP between both groups. There was a significant reduction in favor of empagliflozin in systolic and diastolic blood pressure measured by 24-hour ambulatory monitoring and hematocrit.

The authors concluded that empagliflozin favors the regression of left ventricular mass by a significant reduction in LVMi, without defining whether this was because of a reduction in myocardial mass or intramyocardial interstitial water. The authors did not find a significant correlation between both variables when correlating the changes in systolic and diastolic blood pressure with LVMi. Likewise, there was no correlation between changes in LVMi and changes in hematocrit or NT-proBNP.

EMPIRE-HF trial

In the EMPIRE-HF trial, Jensen et al.[16] Investigated empagliflozin´s effect on NT-proBNP levels in patients with HFrEF with or without T2D (HbA1c 6.5 to 10.0%). This investigator-initiated clinical trial was a randomized, double-blind, placebo-controlled study. It included individuals with or without T2D and HFrEF with LVEF ≤40% with stable treatment for both conditions for at least one month before inclusion. The primary endpoint was the change in NT-proBNP level from baseline to week 12 of treatment with empagliflozin 10 mg/day or placebo. The secondary endpoint was the change in daily physical activity measured with an accelerometer. Likewise, other biochemical, hemodynamic, physical activity parameters (6-minute walk test) and quality of life (KCCQ5) were explored.

A total of 190 patients age 18 years or older were included (18% with T2D and 37% with atrial fibrillation or flutter), mostly (78%) with functional class II-NYHA; average LVEF was 29% and average baseline NT-proBNP was 591 pg/ml. The primary endpoint of the study did not show a significant difference. Empagliflozin had a baseline NT-proBNP of 582 and post-treatment of 478 pg/ml, and the placebo group of 605 and 520 pg/ml, respectively, with an adjusted empagliflozin/placebo difference of 0.98 (0.82-1.11 with P 0.7); there was no significant variation of the result in the sensitivity or subgroup analyses. The secondary endpoint did not show a significant difference between the empagliflozin and placebo groups, nor was there a difference between the two groups in the 6-minute walk test or the quality-of-life assessment (KCCQ5). In other evaluations, there was a significant increase in hematocrit and a significant decrease in systolic blood pressure and body weight in the empagliflozin versus the placebo group, with no change in GFR.

The authors concluded that in patients with or without T2D with HFrEF, mostly in functional class II-NYHA, with an average LVEF of 29% and an average NT-proBNP of 571 pg/ml, empagliflozin 10 mg/day did not show benefit in the primary or secondary endpoints. Hence, in this cohort of mildly symptomatic patients with HFrEF and on standard care, the effect of empagliflozin 10 mg/day on the NT-proBNP level and other surrogate therapeutic endpoints does not reflect the clinical benefit observed in the analyzed clinical outcome trials.[1, 3]

EMPIRE-HF trial. Echocardiographic substudy

In the EMPIRE-HF echocardiographic substudy, Omar et al.[17] investigated the effect of empagliflozin on left atrial and left ventricular volumes and LVEF in patients with HFrEF with or without T2D. This investigator-initiated clinical substudy was a randomized, double-blind, placebo-controlled study. It included patients with or without T2D and HFrEF with LVEF ≤40% in stable treatment for both conditions for at least one month before inclusion. The primary endpoint was the change, measured by biplanar echocardiography, in the left ventricular end-systolic and end-diastolic volume indexes, left atrial volume index, and

LVEF from baseline to week 12 of treatment with empagliflozin 10 mg/day or placebo.
A total of 190 patients were included (18% with T2D and 37% with atrial fibrillation or flutter), mostly (78%) with functional class II-NYHA; average LVEF was 29%, and the average NT-proBNP was 591 pg/ml. The primary endpoint of the substudy demonstrated a significant absolute difference between empagliflozin versus placebo in the left ventricular end-systolic volume index (-4.3: -8.5 to -0.1 ml/m2 with P 0.04) and left ventricular end-diastolic volume index (-5.5: -10.6 to - 0.4 ml/m2 with P 0.03). Likewise, there was a significant reduction in the left atrial volume index. However, there was no significant difference in LVEF. The results did not show heterogeneity between the analyzed subgroups. In other evaluations, the empagliflozin group significantly reduced LVMi (-9.0: -17.2 to -0.9 g/m2 with P 0.03), systolic blood pressure, and hematocrit.
The authors concluded that in patients with or without T2D with HFrEF, mostly in functional class II-NYHA, with an average LVEF of 29% and with an average NT-proBNP of 571 pg/ml, empagliflozin 10 mg/day showed a modest but significant reduction of the left ventricular end-systolic and end-diastolic volumes, probably associated with the reduction of preload, without being able to rule out other potential mechanisms.

EMPIRE-HF trial. Renal substudy
In the EMPIRE-HF renal substudy, Jensen et al.[18] investigated the effect of empagliflozin on extracellular (interstitial) and intravascular (plasma) volumes, and GFR in patients with HFrEF with or without T2D. This investigator-initiated clinical substudy was a randomized, double-blind, placebo-controlled study. It included patients with or without T2D and HFrEF with LVEF ≤40% in stable treatment for both conditions for at least one month before inclusion. The primary endpoint was a change in extracellular and intravascular volumes and GFR from baseline to week 12 of treatment with empagliflozin 10 mg/day or placebo measured by validated methods.
A total of 120 of the 190 patients from the original cohort (12% with T2D) were included. The primary endpoint demonstrated significant absolute differences between empagliflozin versus placebo in the three parameters of the primary endpoint: a) extracellular or interstitial volume (-0.12 L: -0.18 to -0.005 with P 0.00056); b) intravascular or plasma volume (-7.3%: -10.3 to -4.3% with P <0.0001); and c) GFR (-7.5 ml/min/1.73m^2: -11.2 to -3.8 ml/min/1.73m^2 with P 0.00010). The results did not show heterogeneity between the analyzed subgroups. The empagliflozin group showed significant changes in uric acid, hemoglobin, hematocrit, HbA1c, body weight, and systolic blood pressure in other evaluations.
The authors concluded that in patients with or without T2D with HFrEF, empagliflozin 10 mg/day demonstrated a significant reduction in extracellular and intravascular volumes and measured GFR. This result is consistent with the reduction in ventricular volumes shown in the echocardiographic substudy and could explain, at least partially, the hemodynamic-renal clinical benefit observed with SGLT2i.

EMPIRE-HF trial. Hemodynamics substudy
To establish the mechanism by which SGLT2i produces a reduction in the risk of 2-point MACE, Omar et al.[19] designed a clinical substudy to evaluate the effect of empagliflozin on the ratio of pulmonary capillary wedge pressure (PCWP) (from left ventricular filling pressure) to cardiac index (CI) (from myocardial contractile efficiency). This investigator-initiated clinical substudy was randomized, double-blind, placebo-controlled, which explored the effect of empagliflozin on PCWP/CI ratio at rest and peak exercise at baseline and 12 weeks after treatment with empagliflozin 10 mg/day versus placebo. In this substudy, clinically stable individuals with or without T2D with HF, NYHA II-III functional class with EF<40%, with stable treatment for both conditions at least one month before

inclusion. The primary outcome was the change in PCWP/CI ratio at peak exercise measured with right-heart catheterization with a Swan-Ganz catheter at baseline and 12 weeks after treatment with empagliflozin 10 mg/day versus placebo. As a complementary study, transthoracic echocardiography was performed.
A total of 70 of the 190 patients from the original cohort were included, and 66 completed the hemodynamics study; they were randomized into two treatment groups: empagliflozin 10 mg/day versus placebo. The primary outcome of the study demonstrated the following results in the PCWP/CI ratio: empagliflozin at rest -0.86 (-1.71 to -0.02 with P 0.045), placebo at rest -0.37 (-1.21 to +0.47 with P 0.389) with a difference between groups of -0.49 (-1.68 to +0.70 with P 0.418). Empagliflozin at peak exercise -0.42 (1.48 to -0.64 with P 0.437), placebo at peak exercise -0.27 (-1.31 to +0.77 with P 0.609) with a difference between groups of -0.15 (-1.63 to +1.34 with P 0.846). With this result, empagliflozin 10 mg/day did not significantly benefit the change of the PCWP/CI ratio, neither at rest nor at peak exercise. In an exploratory analysis of the PCWP/CI ratio components, empagliflozin significantly reduced PCWP both at rest and peak exercise, with no difference in CI at rest or peak exercise. The authors theorized several reasons to explain their inability to corroborate their hypothesis. They concluded that the isolated reduction in PCWP associated with a reduction in end-diastolic filling pressure measured in echocardiography is the most plausible mechanism associated with empagliflozin's clinical hemodynamic benefit. However, to confirm this, a study with a larger population and greater deterioration of ventricular function would be required.

"EMPA-PIG"

The myocardium in contractile failure can exchange its energy metabolism based on the oxidation of free fatty acids towards another based on the oxidation of glucose and other energy substrates. When inducing glycosuria and reducing glycemia without an increase in insulinemia, SGLT2i increases glucagon and lipogenesis and thus induces ketosis. With this knowledge, Santos-Gallego et al.[20] hypothesized that by inducing ketosis, SGLT2i favor a switch of cardiac metabolism towards one derived from the oxidation of ketone bodies associated with a favorable energetic myocardial remodeling.
To test their hypothesis, they designed an animal study in pigs (females). In a group of 20 animals, myocardial infarction by balloon occlusion of the proximal anterior descending artery was induced. In the subgroup of 14 surviving animals, 3D echocardiography and cardiac MRI were performed 24 hours after infarction. The subgroup of infarcted animals studied at baseline was randomized into two treatment groups, empagliflozin 10 mg/day (7 animals) and placebo (7 animals). After two months of treatment, follow-up 3D echocardiography and cardiac MRI were performed blindly, and cardiac catheterization of the coronary arteries and coronary sinus to measure cardiac metabolites. Finally, the experimental animals were sacrificed to obtain myocardial tissue samples to study cardiac energy and metabolism. The results of both groups were compared with 6 healthy animals studied under the same protocol except myocardial infarction induction.
Weight, blood pressure, blood glucose, and uric acid were lower, and hemoglobin and hematocrit were higher in the group treated with empagliflozin. However, the differences were not statistically significant. Glycosuria and ketonemia were statistically higher in the empagliflozin-treated group. At the 24-hour post-infarction baseline assessment, myocardial infarct size, volumes, and ventricular functions were similar between the control group and the empagliflozin group. After two months of treatment, the results were as follows:

a) The left end-diastolic and end-systolic ventricular volumes, as well as the left ventricular sphericity index, were

significantly lower in the group treated with empagliflozin.

b) LVEF and left ventricular strain were significantly higher and lower, respectively, in the group treated with empagliflozin.
c) The levels of normetanephrine, atrial natriuretic peptide (ANP), and troponin I (TnI) were significantly lower in the group treated with empagliflozin.
d) In the 6 control animals without myocardial infarction, cardiac metabolism predominantly consumed free fatty acids (FFA) over glucose (GL); in the 7 control animals with myocardial infarction, cardiac metabolism predominantly consumed GL via glycolysis (anaerobic metabolism) over FFA; in the 7 animals with myocardial infarction treated with empagliflozin, the cardiac metabolism predominantly consumed ketone bodies (KB) over FFA, branched-chain amino acids (BCAA) and GL. This last energy metabolic switch was associated with higher ATP production, AMP-kinase activity, and myocardial work efficiency in the group treated with empagliflozin.

The authors concluded that in this non-diabetic animal model of ischemia/necrosis-induced heart failure, empagliflozin decreases adverse ventricular remodeling, increases systolic ventricular function, and decreases neuro-hormonal hyperactivation. They also stated that the intrinsic mechanism for this anatomical, functional, and neuro-hormonal remodeling is the energetic switch induced by empagliflozin in the metabolism of the ischemic myocardium, from one dependent on GL to another more efficient dependent (in order of importance) on KB, FFA and BCAA. Thus, postulating that myocardial energy remodeling induced by empagliflozin underlies the anatomical, functional, and neuro-hormonal remodeling.

EMPA-TROPISM

Driven by previously discussed animal trial result,[20] Santos-Gallego et al.[21] designed the EMPA-TROPISM study. It was a randomized, double-blind, placebo-controlled clinical trial, which explored the effect of empagliflozin on left ventricular function and volumes, cardio-respiratory functional capacity, and quality of life in nondiabetic patients with LVEF <50%. The study included nondiabetic patients with HF, functional class II-III NYHA with LVEF <50%, clinically stable, and standard care three months before inclusion.

The primary endpoint was a change in left ventricular end-diastolic and end-systolic volumes assessed by cardiac MRI from baseline and after 6 months of double-blind treatment of empagliflozin 10 mg/day versus placebo. The secondary endpoints included changes from baseline and after 6 months of treatment with empagliflozin 10 mg/day versus placebo in the following parameters: a) maximum O2 consumption assessed by cardiopulmonary exercise test, b) ventricular mass, c) LVEF, d) sphericity index, e) O2 uptake efficiency, f) ventilation/CO2 production ratio, g) 6-min walk test, and h) quality of life (KCCQ-12).

A total of 84 patients were randomized into two treatment groups with similar baseline characteristics. Change in end-diastolic volume was -25.1 ml for empagliflozin versus -1.5 ml in the placebo group with P <0.001. End-systolic volume was -26.6 ml for empagliflozin versus -0.5 ml for placebo with P <0.001. The secondary endpoints that showed significant differences were the following: a) ventricular mass was -17.8 versus 4.1 grams with P <0.001; b) sphericity index -0.1 versus 0.01 with P <0.001; c) LVEF 6 versus -0.1% with P <0.001; d) BNP -11.5 versus -8.5% with P 0.01; e) myocardial O2 consumption 1.1 versus -1.5 ml/min/kg with P 0.017; f) O2 uptake efficiency 111 versus -145 with P <0.01; g) 6-min walk test 64 vs -35 meters; h) quality of life questionnaire with improvement in 30 versus 14 patients, for empagliflozin 10 mg/day versus placebo.

The authors concluded that in a diverse group of individuals with HF-LVEF <50% without T2D, empagliflozin 10 mg/day produces favorable myocardial anatomical remodeling changes, cardiopulmonary physiology, and quality of life.

In their discussion, the authors analyze the similarity of these changes with those reported in their non-diabetic animal model of heart failure[20] and correlate them with the favorable results reported in DAPA-HF[7] and EMPEROR Reduced[3] studies. Finally, they discuss the differences between EMPATROPISM and similar studies with empagliflozin[15-19] and dapagliflozin.[22-23] Without ruling out other hypotheses,[24-28] they highlight myocardial energy remodeling as the potential substrate of reported anatomical, functional, and clinical benefits. This is a highly plausible hypothesis considering the accumulated evidence on this response mechanism to myocardial stress[29]

DISCUSSION

To date, we know that empagliflozin significantly reduces the composite risk of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, mainly on the first component of 3-point MACE (38% relative risk reduction [RRR] for cardiovascular death), in patients with T2D and stable ASCVD (EMPA-REG Outcomes). In patients with or without T2D and HFrEF with an average LVEF of 27%, NT-proBNP close to 2,000 pg/mL and GFR >20 ml/min/1.73m^2 (average 61 ml/min/1.73m2) (EMPEROR-Reduced), empagliflozin significantly reduces the composite risk of cardiovascular death or HHF, mainly on the second component of 2-point MACE (31% RRR for HHF).

From a mechanistic perspective, in patients with T2D, stable ASCVD, and without heart failure, the mediation analysis[14] of the EMPA-REG OUTCOMES study[1] postulated a reduction in intravascular volume, through an increase in hematocrit, as the mediating mechanism of the clinical benefit. However, the EMPA-HEART study[15] in a population similar to that of EMPA-REG Outcomes[1] did not demonstrate a reduction in ventricular end-diastolic or end-systolic volumes, which opens the possibility that the increase in hematocrit is explained by the increase in red cell mass and not by a reduction in intravascular volume per-se. Additionally, this last study presented clear evidence of a significant reduction in LVMi, without being able to differentiate whether this was at the expense of cardiomyocytes, interstitial water, or another component of the myocardial stroma.

With the same mechanistic approach, the EMPIRE-HF study, together with its sub-studies,[16-19] allowed the following analysis of empagliflozin's effect in patients with or without T2D and HFrEF. In patients with HFrEF, functional class II, average LVEF of 27%, and NT-proBNP <600 pg/mL (the anatomical and functional deterioration was less than that of the EMPEROR-Reduced population), the NT-proBNP level did not change significantly. End-diastolic and end-systolic ventricular volumes, and plasma and interstitial volumes, were significantly reduced, and although there was no significant reduction in the PCWP/CI ratio, a nominal reduction in PCWP was documented.

All the above reflects a reduction in plasma and interstitial volumes associated with a reduction in ventricular volumes and end-diastolic ventricular pressure, with no change in inotropism. These data allow us to postulate that in patients with clinically stable and moderate HFrEF, the main benefit of empagliflozin, although not reflected by a reduction in NT-proBNP, is associated with a reduction in both intravascular (preload) and interstitial (edema) volume, most likely linked to improved kidney function (not analyzed in this article).

In this context, we can stand out the complementary evidence of the “EMPA-PIG” and EMPA-TROPISM[20-21] studies in mammals and in-vivo human models without T2D and with HF-LVEF <50% of ischemic etiology, respectively. Beyond findings from in-vitro models and/or lower mammals,[24-29] these two studies contribute substantially to explaining the early clinical benefit of empagliflozin from a cardiocentric approach. Conceptually, the so-called energetic myocardial remodeling, anatomical and functional myocardial remodeling, and neuro-hormonal myocardial remodeling, explained below, stand out.

Myocardial energy remodeling. From the adult energy pattern to the fetal pattern and to SGLT2i pattern

The healthy adult heart can have various energy substrates; the two most important are: a) FFA as palmitic acid with 16 carbons, after 7 steps of β oxidation produce 298 kcal/mol, with an aerobic efficiency of 2.33 mol of ATP per molecule of oxygen used (phosphate/oxygen ratio [P/O ratio] = 2.30); b) GL that produces 224 kcal/mol with an aerobic efficiency of 2.58 mol of ATP per molecule of oxygen used (P/O ratio = 2.58) [20-21, 29].

Under physiological conditions, FFA are incorporated into the cytoplasm, converted to their active cellular form or acyl-CoA (FFA + CoA in the presence of acyl-CoA synthase = Acyl-CoA). Cytoplasmic acyl-CoA, in a first step in the outer mitochondrial membrane, is transformed into acyl-carnitine (acyl-CoA + carnitine in the presence of carnitine acyltransferase I (CPT1) = acyl-carnitine + CoA). This way, acyl-carnitine can be incorporated into the mitochondria and afterward, into the internal mitochondrial membrane by the action of CPT2. Acyl-carnitine is transferred to the mitochondrial matrix, where it exchanges carnitine for CoA and returns to its acyl-CoA structure to join β oxidation in which the final product will be a variable number (directly proportional to the number of carbons of catabolized FFA) of acetyl-CoA molecules (acyl group of acetic acid), which enter the Krebs cycle to produce ATP[, 30].

The healthy adult heart predominantly consumes FFA since its energy production per molecule is higher than GL; although its oxygen consumption is also higher, this fact is irrelevant in a non-ischemic tissue[20-21, 29] **(adult energy pattern)**.

Unlike the healthy adult heart, the ischemic adult heart makes an energy switch, with a predominant GL over FFA consumption **(fetal energy pattern)**. This energy switch tries to compensate for tissue hypoxia with the higher P/O ratio of GL versus FFA (2.5 versus 2.3). However, this compensation mechanism is perennial; eventually, tissue hypoxia limits the GL's aerobic mitochondrial metabolism, thus persisting the cytoplasmic anaerobic metabolism (glycolysis), which has a 16 times lower efficiency (net production of 2 ATP versus 34 ATP per GL molecule). Under this pathophysiological condition, the myocardium can use other energy substrates from the catabolism of GL (lactate) or FFA (ketone bodies) and even BCAA. Among the referred energy substrates, the efficiency of KB stands out, such as D-β-hydroxybutyrate, which produces 244 kcal/mol with an aerobic efficiency of 2.5 mol of ATP per molecule of oxygen used (P/O ratio = 2.50) [29].

Ketosis develops under physiologically extreme conditions such as prolonged and intense exercise; it should not be confused with pathological ketoacidosis. This is due to hormonal counter-regulation with a predominance of glucagon and adrenaline secretion over insulin. The former over activates the hormone-dependent adipocyte lipoprotein lipase (LPL) and thus initiates adipocyte hydrolysis of triglycerides (lipolysis) and the release of long-chain FFA (16 to 18 carbons), which, as previously reviewed, are transformed into acyl-CoA, integrated to β oxidation and finally, converted into acetyl-CoA, are incorporated into the Krebs cycle to produce ATP[29].

Unlike normal insulinemia, in the presence of hypoinsulinemia and hyperglucagonemia, acetyl-CoA production by increased lipolysis cannot be incorporated into other metabolic pathways such as the synthesis of fatty acids or cholesterol (insulin-dependent). Oxalate deficiency limits the entry of acetyl-CoA into the Krebs cycle in the liver. In this metabolic scenario, acetyl-CoA is transformed into KB (acetoacetate, D-β-hydroxybutyrate, and acetone) in the hepatocyte, which are released into the circulation for their elimination or use as energy substrates in other tissues after transformation into acetyl-CoA (a metabolic transformation that only requires 2 instead of 7

metabolic steps and two enzymes, namely β ketoAcyl-CoA and thiolase) [29-30].

As reviewed, it is easy to understand why, in a metabolic environment with a low-efficiency fetal energy pattern, empagliflozin (by inducing glycosuria without hyperinsulinemia) recreates the state of hypoinsulinemia and hyperglucagonemia with increased lipolysis, transforming the fetal energy pattern to one in which, excess FFA and overproduction of KB and its consumption by the failed myocardium are 800% higher than the normal myocardium and 400% higher than the ischemic myocardium. This determines a myocardial metabolic state with greater efficiency to produce ATP (**SGLT2i energy pattern**), which contributes substantially to the anatomical and functional remodeling and eventually to the neurohormonal remodeling discussed below[20-21, 29].

Anatomical and functional myocardial remodeling

Unlike a healthy adult heart with a normal cavitary volume and myocardial mass with an elliptical shape (elliptical pattern), the ischemic heart increases its cavitary volume (dilatation) and its myocardial mass ("compensatory" hypertrophy) proportionally to myocardial damage, at the expense of nonischemic and/or necrotic myocardium, adopting a spherical shape (spherical pattern). In this anatomical remodeling scenario, empagliflozin limits spheroidal remodeling with attenuation of the increase in ventricular volume and myocardial mass to a variable degree. This is associated with functional improvement characterized by an increase in LVEF and reduced ventricular strain or deformation[20-21, 29].

Neuro-hormonal myocardial remodeling

In contrast with the healthy adult heart, the ischemic heart with spherical remodeling and variable deterioration of its function over activates the sympathetic nervous system (SNS) and renin-angiotensin system (RAS) in a "compensatory" way. In the medium and long term, this mechanism is transformed into a harmful cycle to the myocardium and the cardiovascular system. In this environment of neurohormonal hyperarousal, empagliflozin directly (KB effect) [29] or indirectly (remodeling), limits neurohormonal hyperarousal to a variable degree, thus reducing BNP and metanephrine levels[20-21].

CONCLUSION

Accumulated evidence makes it possible to support, as mentioned in the introduction, that energetic myocardial remodeling (switch from a fetal energy pattern to one based on KB "SGLT2i energy pattern") - among other mechanisms - underlies the anatomical, functional, and neuro-hormonal remodeling of the heart with heart failure. This evidence explains one of the most important myocardial mechanisms of the clinical benefit induced by SGLT2i, here reviewed through the solid evidence with empagliflozin (central figure).

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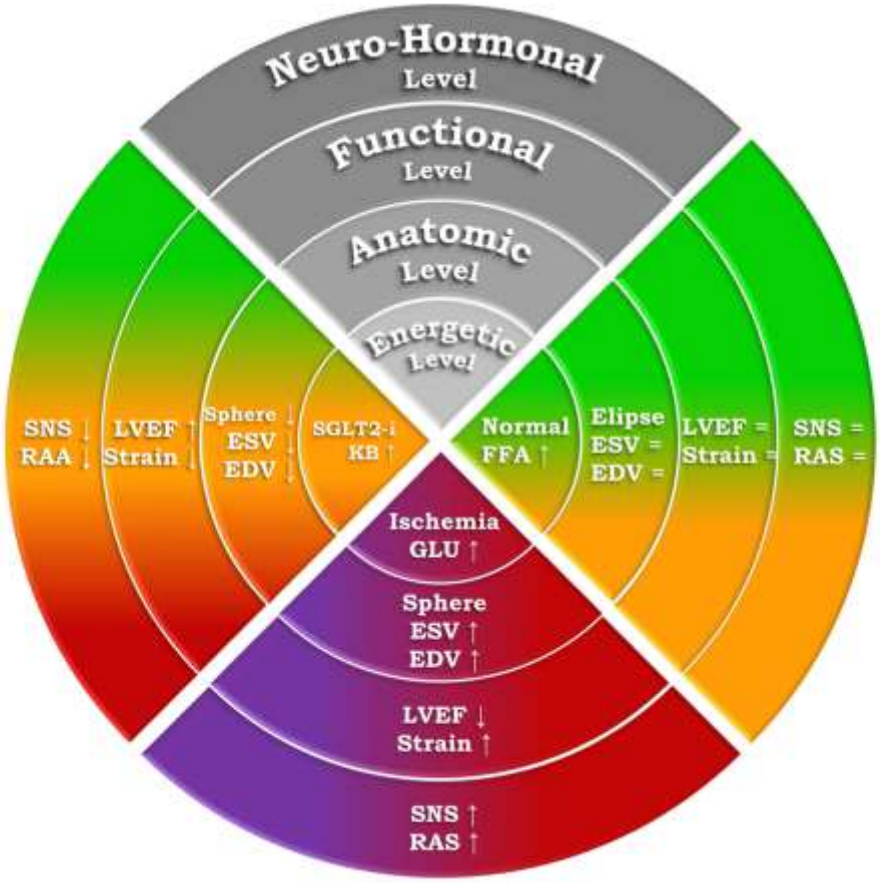

Central figure: The 4 cardiac remodeling levels (energetic, anatomical, functional, and neuro-hormonal) are illustrated with their characteristics in normal conditions, during myocardial ischemia, and under the effect of SGLT2i. In normal condition, the heart consumes FFA, it has an elliptical shape with normal end-systolic/end-diastolic volumes, its ejection fraction is normal without ventricular deformity and without SNS or RAS hyperactivity. The heart with heart failure due to ischemia consumes GL (aerobic and anaerobic) predominantly, adopts a spherical shape with increased end-systolic/end-diastolic volumes, its ejection fraction decreases, and ventricular deformity increases with hyperactivity of the SNS and RAS. The heart with heart failure due to ischemia under the effect of empagliflozin, consumes KB predominantly, reduces its sphericity and end-systolic/end-diastolic volumes, increases its ejection fraction, and reduces ventricular deformity with attenuation of SNS and RAS hyperactivity.

= Normal, ↑ Increased, ↓ Decreased. FFA: Free fatty acids. GLU: Glucose. ESV: Left ventricle end systolic volume. EDV: Left ventricle end diastolic volume. LVEF: Left ventricle ejection fraction. SNS: Sympathetic nervous system. RAS: Renin angiotensin system

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