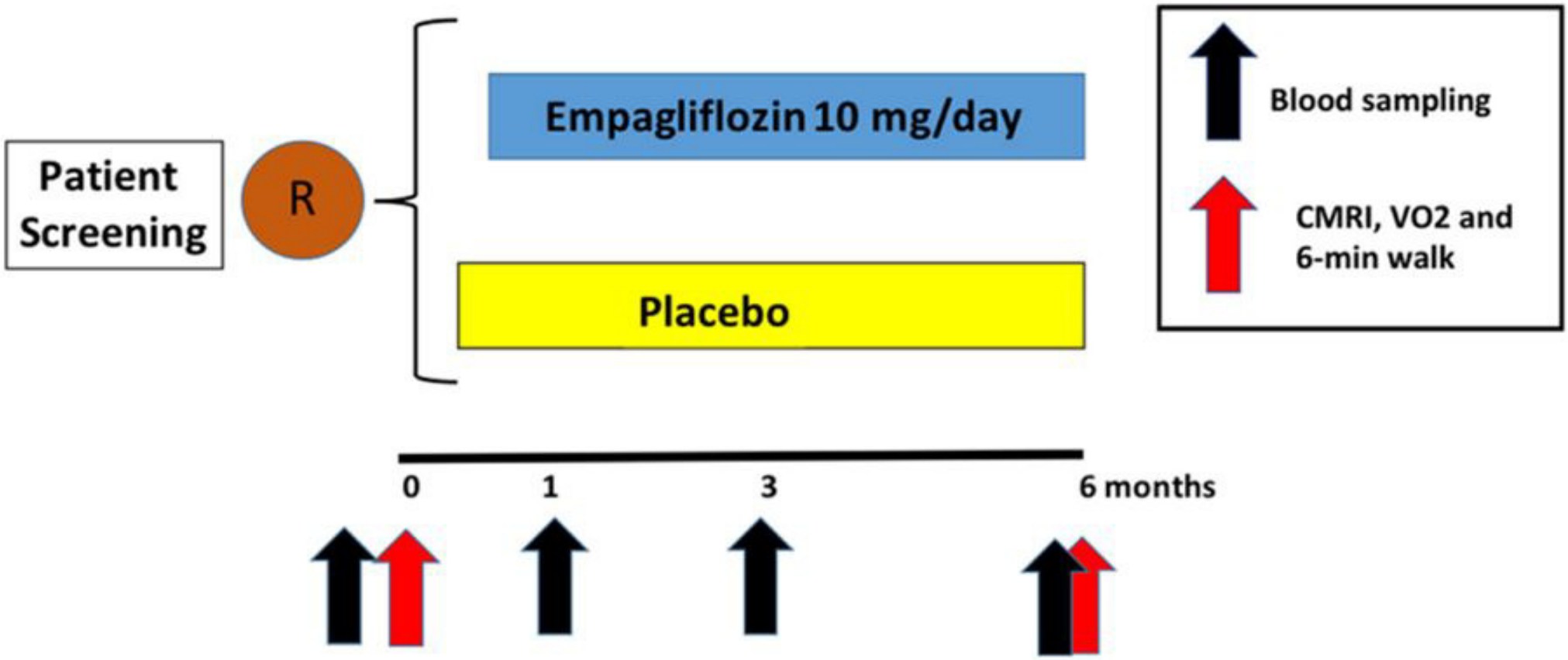
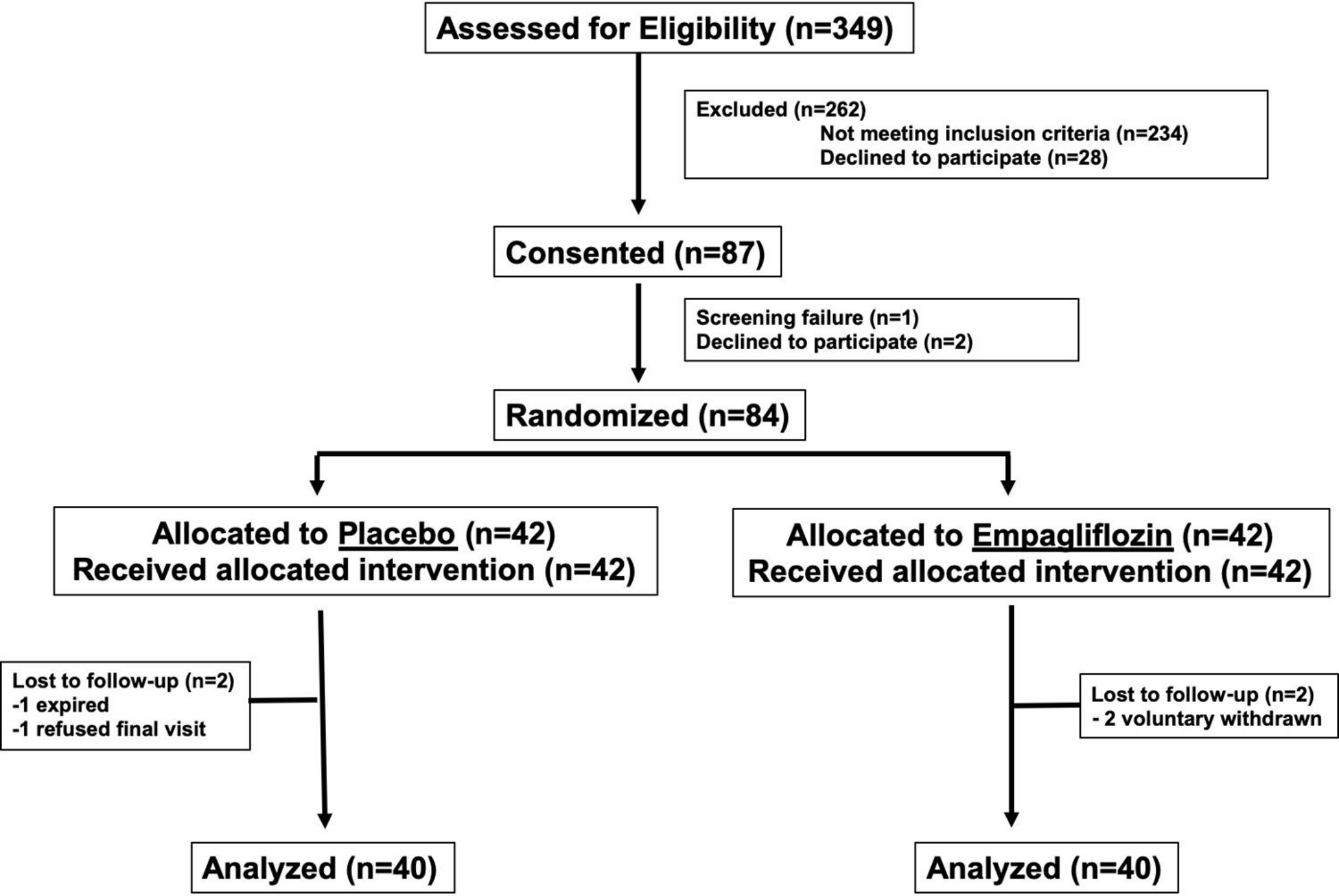
Study Design




Assessed for Eligibility (n=349)
Excluded (n=262)
Not meeting inclusion criteria (n=234)
Declined to participate (n=28)
Consented (n=87)
Screening failure (n=1)
Declined to participate (n=2)
Randomized (n=84)
Allocated to Placebo (n=42)
Received allocated intervention (n=42)
Allocated to Empagliflozin (n=42)
Received allocated intervention (n=42)
Lost to follow-up (n=2)
-1 expired
-1 refused final visit
Lost to follow-up (n=2)
- 2 voluntary withdrawn
Analyzed (n=40)
Analyzed (n=40)

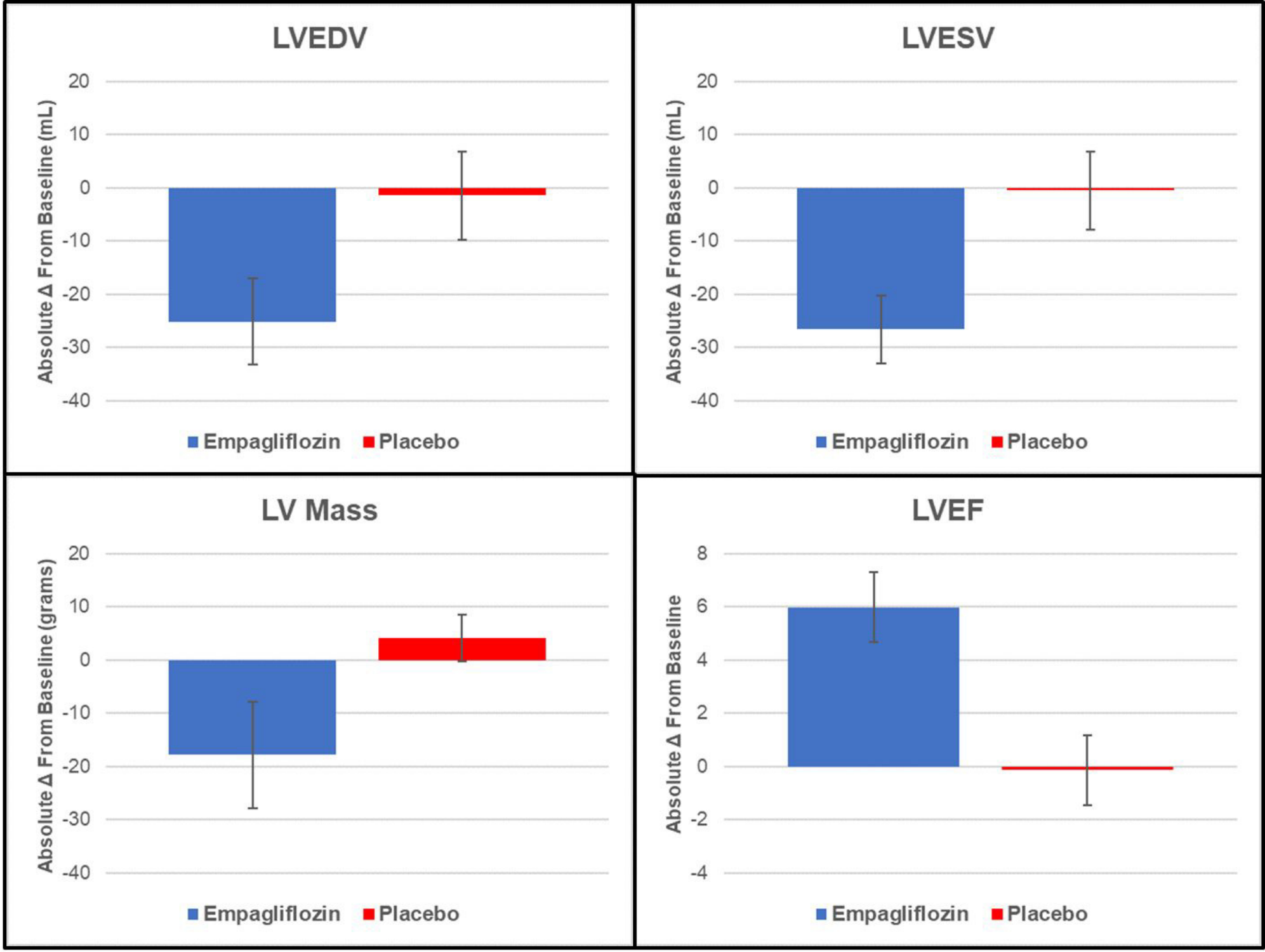

LVEDV
Absolute Δ From Baseline (mL)
20
10
0
-10
-20
-30
-40
Empagliflozin
Placebo
LVESV
Absolute Δ From Baseline (mL)
20
10
0
-10
-20
-30
-40
Empagliflozin
Placebo
LV Mass
Absolute Δ From Baseline (grams)
20
10
0
-10
-20
-30
-40
Empagliflozin
Placebo
LVEF
Absolute Δ From Baseline
8
6
4
2
0
-2
-4
Empagliflozin
Placebo

Figure 3

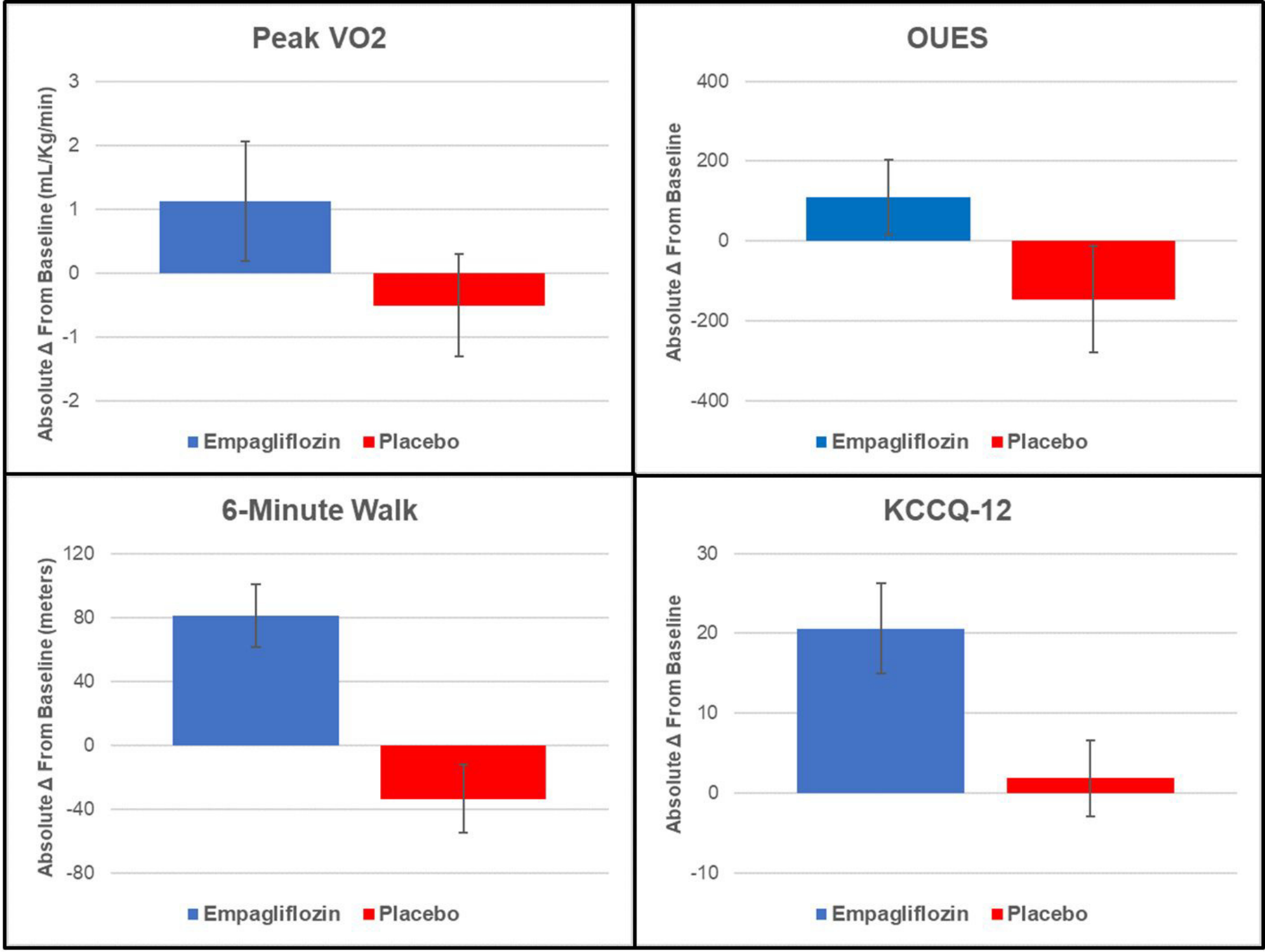
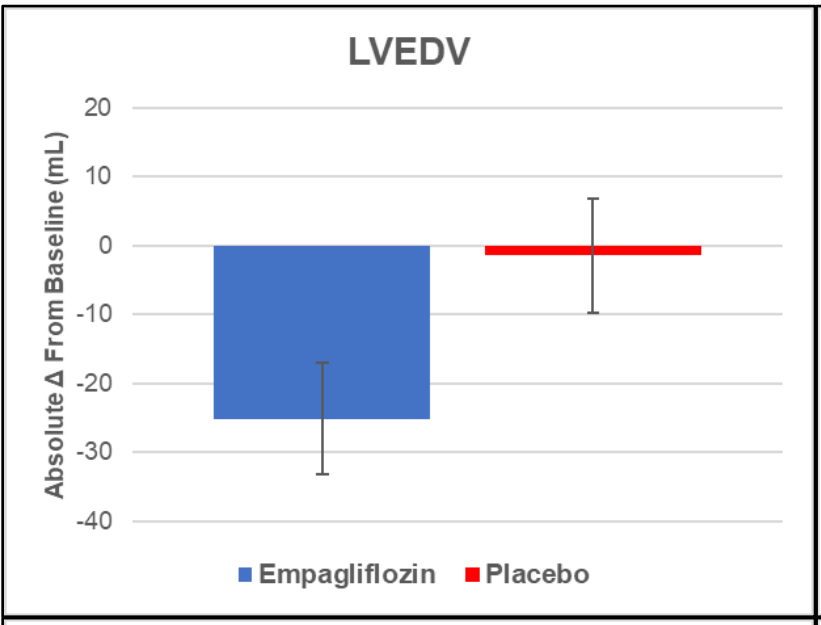
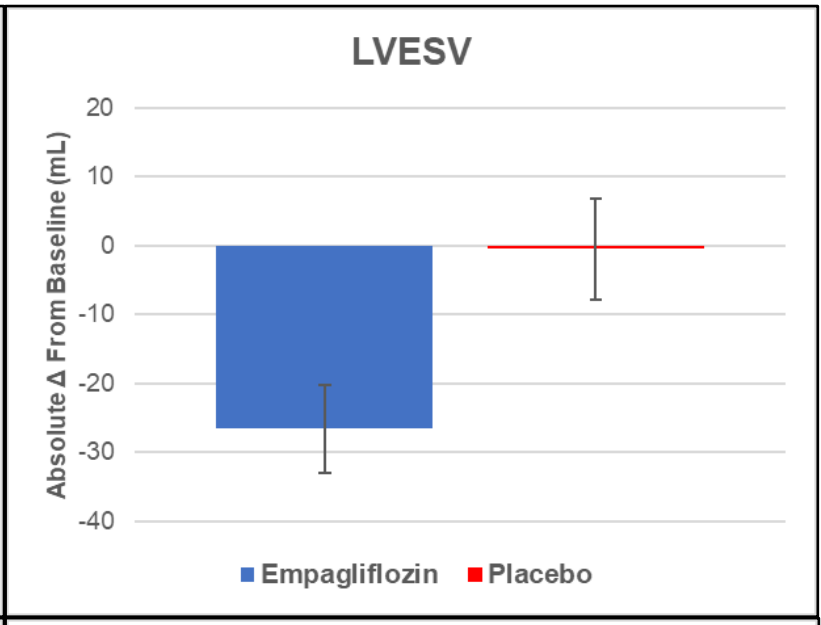
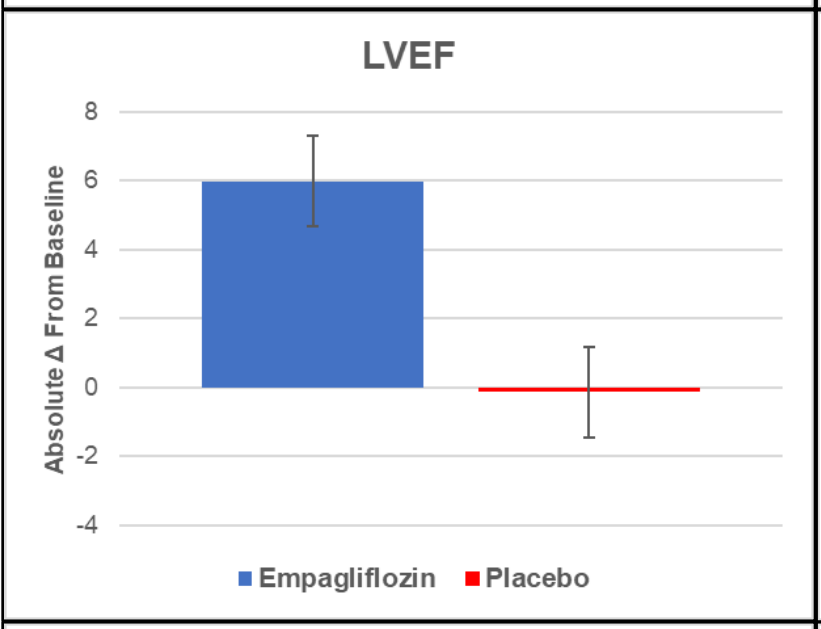
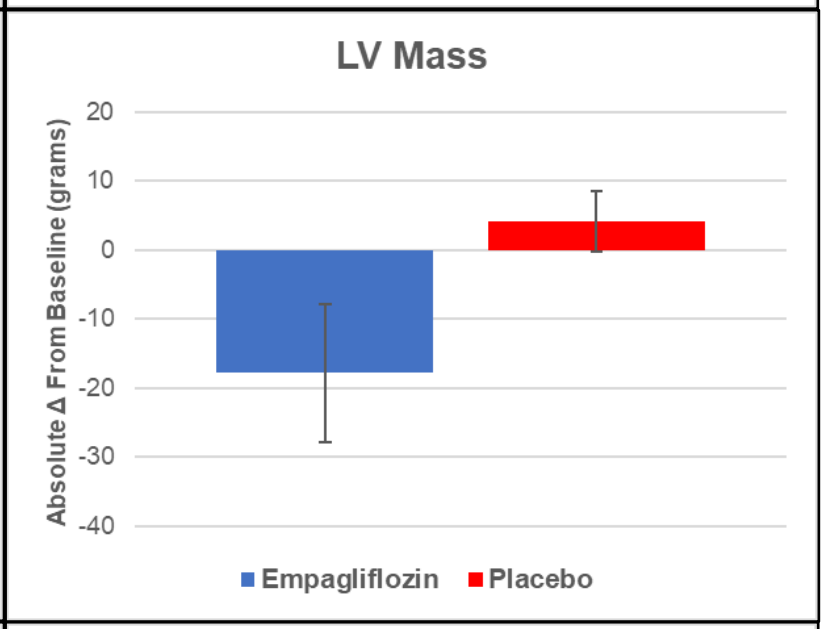

Peak VO2
Absolute Δ From Baseline (mL/Kg/min)
3
2
1
0
-1
-2
Empagliflozin
Placebo
OUES
Absolute Δ From Baseline
400
200
0
-200
-400
Empagliflozin
Placebo
6-Minute Walk
Absolute Δ From Baseline (meters)
120
80
40
0
-40
-80
Empagliflozin
Placebo
KCCQ-12
Absolute Δ From Baseline
30
20
10
0
-10
Empagliflozin
Placebo

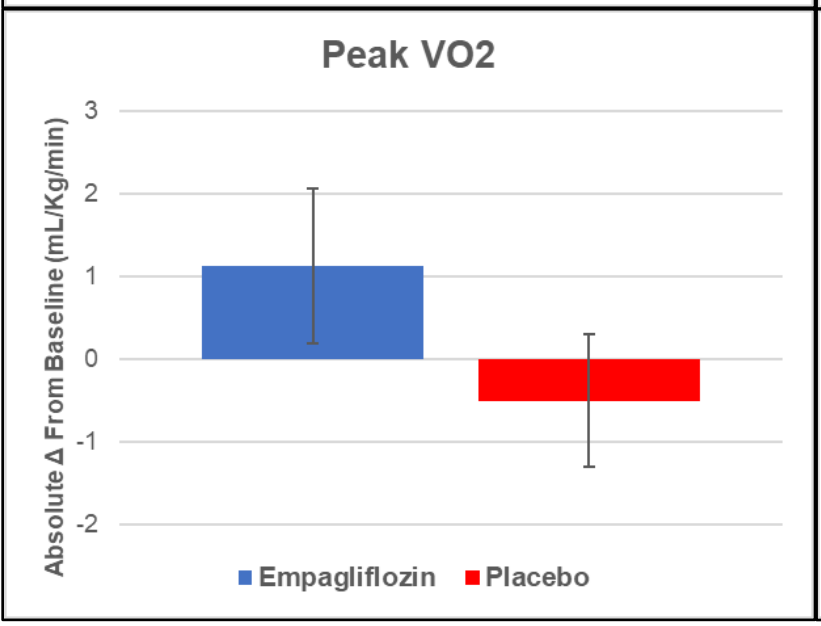
Figure 4

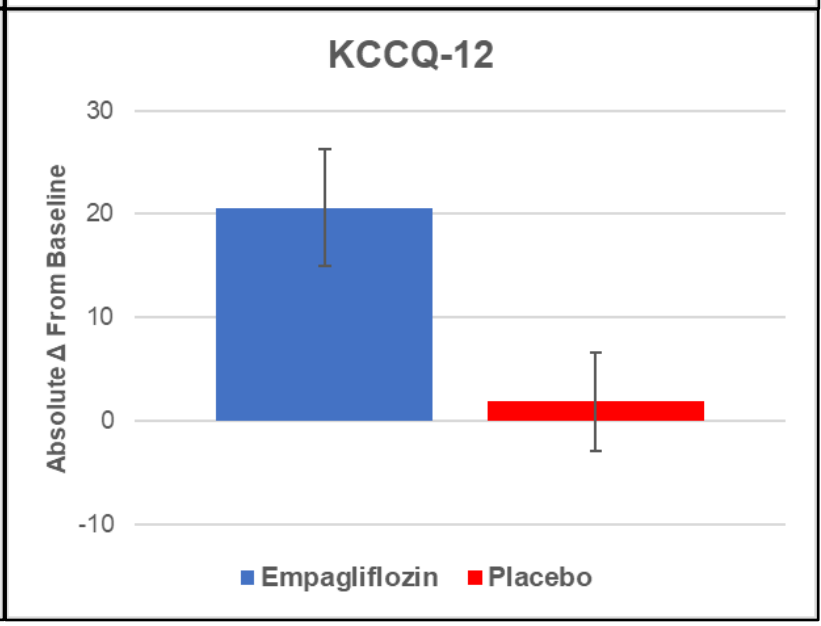

LVEDV
Absolute Δ From Baseline (mL)
20
10
0
-10
-20
-30
-40
Empagliflozin
Placebo


LVESV
Absolute Δ From Baseline (mL)
20
10
0
-10
-20
-30
-40
Empagliflozin
Placebo


LVEF
Absolute Δ From Baseline
8
6
4
2
0
-2
-4
Empagliflozin
Placebo


LV Mass
Absolute Δ From Baseline (grams)
20
10
0
-10
-20
-30
-40
Empagliflozin
Placebo


Peak VO2
Absolute Δ From Baseline (mL/Kg/min)
3
2
1
0
-1
-2
Empagliflozin
Placebo


KCCQ-12
Absolute Δ From Baseline
30
20
10
0
-10
Empagliflozin
Placebo

Empagliflozin in Non-Diabetic Heart Failure Patients with Reduced Ejection Fraction: EMPATROPISM (ATRU-4) Randomized Clinical Trial

Carlos G Santos-Gallego MD*[1,2] Ariana P Vargas-Delgado MD*[1,2] Juan Antonio Requena MD[1,2] Alvaro Garcia-Ropero MD[1,2] Donna Mancini MD[1] Sean Pinney MD[1] Frank Macaluso BS[1] Samantha Sartori PhD[1] Merce Roque MD[1,2] Fernando Sabatel-Perez MD[2] Anderly Rodriguez Cordero MD[1,2] M. Urooj Zafar MD[1,2] Icilma Fergus MD[1] Farah Atallah-Lajam MD[1] Johanna P Contreras MD[1,] Cathleen Varley RN[1,] Pedro R Moreno MD[1] Vivian M Abascal MD[1] Anuradha Lala MD[1] Ronald Tamler MD[3] Javier Sanz MD[1] Valentin Fuster MD, PhD[1] Juan J Badimon PhD[1,2]
On behalf of the EMPA-TROPISM (ATRU-4) investigators

[1] Mount Sinai Heart
[2] Atherothrombosis Research Unit
[3] Division of Endocrinology
Icahn School of Medicine at Mount Sinai
New York City, NY

Short title: Santos-Gallego et al. Empagliflozin in non-diabetic HFrEF

Total word count: 5000

Funding: This research was supported by an independent grant from Boehringer Ingelheim, who provided both drug and financial support for the study

Disclosures: Sean Pinney reports receiving consulting fees from Abbott, Medtronic Inc, and Procryrion Inc; and to receive both consulting and speaking fees from Care Dx. The rest of the authors reported no disclosures.

Twitter handle: @SantosGallegoMD

Corresponding author:

Juan J Badimon, PhD
AtheroThrombosis Research Unit
Mount Sinai Heart
Icahn School of Medicine at Mount Sinai School of Medicine
One Gustave L. Levy Pl.
New York, NY 10029-0310
United States
Telephone: (212) 241-8484
Fax: (212) 426-6962
E-mail: juan.badimon@mssm.edu

ABSTRACT

BACKGROUND

Large clinical trials established the benefits of SGLT2 inhibitors in patients with diabetes and with heart failure with reduced ejection fraction (HFrEF). The early and significant improvement in clinical outcomes is likely explained by effects beyond a reduction in hyperglycemia

OBJECTIVES

To investigate the safety and efficacy of empagliflozin versus placebo on top of optimal medical therapy in non-diabetic HFrEF patients

METHODS

In this double-blind, placebo-controlled trial, non-diabetic HFrEF patients (n=84) were randomized to empagliflozin or placebo for six months. The primary endpoint was change in left ventricle end-diastolic volume (LVEDV) and left ventricle end-systolic volume (LVESV) assessed by cardiac magnetic resonance. Secondary endpoints included changes in LV mass, LVEF, peak oxygen consumption in the cardiopulmonary exercise test, 6-minute walk test, and quality of life

RESULTS

Empagliflozin was associated with a significant reduction of LVEDV (-25.1±26.0 vs -1.5±25.4mL for empagliflozin vs placebo, respectively, $p<0.001$) and LVESV (-26.6±20.5 vs -0.5±21.9 mL for empagliflozin vs placebo, $p<0.001$). Empagliflozin was associated with

reductions in LV mass (-17.8±31.9 vs 4.1±13.4 g, for empagliflozin vs placebo, respectively, p<0.001) and improvements in LVEF (6±4.2 vs -0.1±3.9 p<0.001). Patients who received empagliflozin had significant improvements in peak O2 consumption (1.1±2.6 vs -0.5±1.9mL/min/kg for empagliflozin vs placebo, respectively, p=0.017), oxygen uptake efficiency slope (111±267 vs -146±318, p<0.001), as well as in 6-minute walk test (81±64 vs -35±68 meters, p<0.001) and quality of life (KCCQ-12: 21±18 vs 2±15, p<0.001).

CONCLUSIONS

Empagliflozin administration to non-diabetic HFrEF patients significantly improves LV volumes, LV mass, LV systolic function, functional capacity, and quality of life when compared with placebo. Our observations strongly support a role for SGLT2 inhibitors in the treatment of HFrEF patients independently of their glycemic status.

(www.clinicaltrials.gov NCT 03485222)

CONDENSED ABSTRACT

In this double-blind, placebo-controlled, randomized EMPATROPISM clinical trial, empagliflozin administration to non-diabetic HFrEF patients on top of optimal medical treatment ameliorated cardiac remodeling, reduced LV volumes, decreased LV mass, increased LV systolic function, enhanced functional capacity (both peak oxygen consumption and 6-minute walk test), and improved quality of life when compared with placebo. The results of the EMPATROPISM trial support the use of SGLT2 inhibitors in the treatment of HFrEF patients independently of their diabetic status.

TWEET

The SGLT2i Empagliflozin in HFrEF patients without diabetes significantly improves LV volumes, LV mass, LVEF, peak oxygen consumption, 6-minute walk test, and quality of life when compared with placebo

COMPETENCY IN MEDICAL KNOWLEDGE:

In the double-blind, placebo-controlled EMPATROPISM trial, non-diabetic HFrEF patients were randomized to empagliflozin (10mg/day) or placebo for 6-months. Empagliflozin administration resulted in consistent and significant improvements in cardiac volumes, hypertrophy, LVEF, exercise capacity, functional capacity, and quality of life when compared with placebo. Our data endorse SGLT2 inhibitors as attractive candidates in the treatment of non-diabetic HFrEF patients.

TRANSLATIONAL OUTLOOK:

Previous RCT have demonstrated the benefits of SGLT-2 inhibitors on T2DM patients. Our mechanistic observation and data from the DAPA-HF strongly suggest the benefits of SGLT2 inhibition in heart failure patients independent of their diabetic status.

ABBREVIATIONS USED WITHIN THE TEXT

CMR Cardiac Magnetic Resonance

CPET Cardiopulmonary Exercise Test

HFrEF Heart failure with reduced Ejection Fraction

KCCQ-12 Kansas City Cardiomyopathy Questionnaire

LV Left Ventricle

LV Left Ventricle LVEDV Left Ventricle end diastolic volume

LVESV Left Ventricle end systolic volume

LVEF Left Ventricle Ejection Fraction

OUES Oxygen Uptake Efficiency Slope

RCT Randomized Clinical Trial

SGLT2i Inhibitors of the Sodium-glucose cotransporter-2

VO_2 Oxygen Consumption

6MWT 6-minute walk test

INTRODUCTION

In patients with type-2 diabetes, sodium-glucose co-transporter 2 inhibitors (SGLT2i) reduce the risk of hospitalization for heart failure by 30-35% and improve cardiac outcomes(1-3). The recent clinical trials DAPA-HF(4) and EMPEROR-Reduced(5) have expanded these heart failure benefits of SGLT2i to the realm of patients with heart failure with reduced ejection fraction (HFrEF). Of the utmost importance, these benefits in outcomes occur both in diabetic and non-diabetic patients(6).

These benefits of SGLT2i cannot be explained exclusively by their glucose-lowering effects because the modest hypoglycemic activity of SGLT2i is comparable to other glucose-lowering drugs which do not show improvements in heart failure; the differences in diabetic control were (by design) minimal (equipoise); the benefits would have taken years (while event curves separate in the first month); it would have also reduced atherothrombotic events; and glycemic control has previously failed to reduce heart failure(7).

Based on these observations, we hypothesized that SGLT2i would mitigate adverse left ventricular (LV) remodeling independently of diabetic status, which could explain their benefits in heart failure. This hypothesis was initially approached in our non-diabetic porcine model of heart failure. Empagliflozin significantly ameliorated adverse LV remodeling, decreased LV volumes and LV hypertrophy, reduced neurohormonal activation, and improved cardiac systolic function compared with the control group(8). Moreover, empagliflozin also improved diastolic function in this HFrEF model(9). Based on these experimental results, we designed the EMPATROPISM-trial to translate these preclinical data to human patients(10). This is a randomized, double-blind, placebo-controlled trial to assess the effect of empagliflozin on LV

function and volumes, functional capacity and quality of life (QoL) in non-diabetic HFrEF patients.

METHODS

Trial Design

The EMPATROPISM (NCT 03485222) is a single-site, double-blind, randomized placebo-controlled trial to determine whether empagliflozin improves cardiac function, exercise performance and QoL in non-diabetic HFrEF. The study design and protocol have been approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai. All participants signed an informed consent form prior study entry. Study design is presented in Figure 1.

A more detailed protocol has been previously reported(10). Briefly, all participants met the following inclusion criteria: 1) age>18 years; 2) diagnosis of heart failure (NYHA II-III); 3) LVEF<50%; 4) stable symptoms and medical therapy within the last 3 months.

Major exclusion criteria were: 1) History of diabetes by medical history or any of the established criteria by the American Diabetes Association (including history of diabetes in remission); 2) acute coronary syndrome or cardiac surgery within the last 3 months; 3) Glomerular Filtration Rate<30ml/Kg/min; 4) use of continuous parental inotropic agents; 5) systolic blood pressure<90mmHg; 6) non-MRI compatible cardiac devices; 7) pregnant or lactating women; and 8) any other medical condition considered unappropriated by a study physician.

Clinical visits and randomization

The study included 5 visits over a 6-month period. At baseline (pre-treatment) visit, all participants underwent clinical assessment, anthropometric measurements, 6-minute walk test (6MWT) and the Kansas City Cardiomyopathy Questionnaire (KCCQ-12). Cardiac function was

assessed by cardiac magnetic resonance (CMR); maximal exercise capacity was measured by cardiopulmonary exercise testing (CPET). Thereafter, patients were randomized to receive either empagliflozin or matching placebo for a period of 6-months. Randomization was performed with a secure web-based system stratified with block sizes of 4. Two additional visits at 1- and 3-months post-randomization involved interview, drug dispensation, blood and urine collection for safety and tolerability. At the final visit, the procedures performed at baseline were repeated.

End points

The primary end-point was between-groups change in LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) from baseline to 6-months as compared to placebo. LV volumes are the strongest predictor of adverse cardiovascular outcomes even after adjusting for LVEF and extent of myocardial infarction (11-14). CMR is the gold standard for quantifying cardiac volume and function; the reproducibility of CMR allows for a smaller sample size as compared with echocardiography(12)

Secondary endpoints include the between-groups changes in peak VO_2. CPET with incremental workload and symptoms limited exercise is the gold standard for studying cardiac and pulmonary adaptations to exercise in heart failure patients(15). Other end-points also analyzed included changes in LV Mass, LV ejection fraction (LVEF), LV sphericity index, oxygen uptake efficiency slope (OUES), $VE/VCO_{2,,}$ distance in the 6MWT, and QoL (KCCQ-12).

Safety and Adverse Events

Safety and tolerability issues (eg. hypoglycemia, urinary infections, medication changes, etc.) were monitored. Adverse events were monitored by a data safety monitoring board who adjudicated events.

Procedures involved in the study

Cardiac Magnetic Resonance Imaging (CMR) was performed on a 1.5T magnet (Magnetom Avanto FIT, Siemens) using phased-array surface coils as receivers. Retrospectively ECG-gated cine images were acquired with a steady-state free precession sequence (typical parameters TR 2.8 ms, TE 1.2 ms, 12-15 lines per segment, flip angle 45 degrees, typical voxel size 1.5x1.5x6 mm, 4-mm gap, number of averages 1, bandwidth 930 Hz). Short-axis cine images covering both ventricles from base to apex were obtained during end-expiratory breath-holds. LV volumes, LV mass, and LVEF were quantified as previously reported(8,16) using dedicated analysis software (CMR42, version 5.6.3, Circle Cardiovascular Imaging, Calgary, Canada). Epicardial and endocardial contours were traced in each SSFP cine image to obtain LVEDV, LVESV, LVEF and LV mass; per protocol, the papillary muscles were included in the LV cavity. Sphericity Index was calculated by dividing CMR-calculated LVEDV by the volume of a sphere whose diameter was derived from the major end-diastolic LV long axis, as previously described(17). The LV long-axis was obtained from the CMR dataset as the longest distance between the center of the mitral annulus and the endocardial apex. All CMR assessments were performed in a blind and randomized fashion at the end of the study. The observers were completely blinded to the order of the study, to allocation group, and to any clinical data.

Cardiopulmonary exercise test (CPET).- Patients in fasting state underwent upright incremental bicycle exercise on a cycle ergometer (Lode, Netherlands) with respiratory gas

analysis (Med Graphics Ultima O_2). The patient was connected to the metabolic cart using a disposable mouthpiece and with the nares occluded. Exercise began with unloaded exercise and increased by 25 Watts every 3 minutes. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), minute ventilation (VE), perceived level of exertion (Borg Scale 6-20), pulse oximetry, heart rate and blood pressure measurements were recorded during exercise. Patients were encouraged to exercise until the respiratory exchange ratio was at least 1.1 or the level of perceived exertion was at least 15. The reason the patient stopped exercise was recorded. One investigator (DM) supervised and analyzed the exercise tests. Peak VO_2 was defined as the highest 30sec average of oxygen consumption. The ventilatory threshold was identified as the point at which the ventilatory equivalent for O_2 (VE/VO_2) is minimal, followed by a progressive increase. Ventilation was assessed by correlation of VE and VCO_2 throughout exercise. OUES was determined using the following equation: $VO_2 = a \log_{10} VE + B$. VO_2 in ml/min was plotted on the *y* axis and minute ventilation in L/min was plotted on the semilog transformed *x* axis. The slope of this linear relationship, "a", represents the OUES(18,19).

6 minute walk test (6MWT) was performed according to the guidelines from the American Thoracic Society(20). Patients were instructed to walk as fast and perform as many laps as possible between the distance markers over a 6-minutes period. An un-encouraged test was performed. To minimize variability it is critical to conduct the test at the same time each visit and supervised by the same personnel. The total walked distance was recorded.

Kansas City Cardiac Questionnaire-12 (KCCQ-12) was administered and evaluated according to the questionnaire's instructions(19). The KCCQ-12 was completed by the patients, without assistance by study staff, at randomization and the end of the trial. The KCCQ-12 is a valid, reproducible, responsive tool for assessing disease-specific health status among HF patients. It

quantifies symptoms (frequency, severity, and recent change), physical function, QoL, and social function over the previous 2 weeks. Scores are transformed to a range of 0 to 100 in which higher scores reflect better health status(21).

Statistical Analysis

Our primary endpoint is the between-groups change in LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) from baseline to 6-months. The difference in change is computed between the empagliflozin and placebo arms. It is generally accepted that a 10mL change in LVEDV is clinically significant(22). An internal CMR study at our hospital showed a variation of 12mL for the mean difference of LVEDV. Thus, in order to detect a 10mL difference in LVEDV between the arms with a power of 0.9 and a type-I error of 0.05, a minimum of 72 patients (36/arm) would be required. We estimated a 15% of losses during follow-up or incomplete examinations. Therefore, the final sample size was 84 HFrEF patients without diabetes.

Categorical data are reported as frequencies and percentages; continuous variables are summarized as mean and standard deviation. Data were analyzed on an intention-to-treat basis. No data imputation was performed. Pre/post changes were compared between study groups using a linear mixed model with the group covariate, the binary (pre and post) time covariate, and the group x time interaction term. Differences were considered statistically significant when the p-value of the log-likelihood ratio test on the significance of the interaction term is >0.05. All statistical calculations have been performed with Stata 16.1.

RESULTS

Demographic of study participants

A total of 84 patients provided informed consent form and were randomized 1:1 to empagliflozin or placebo. Table 1 presents demographic characteristics, co-morbidities and medications for all the participants. A high percentage of minorities was enrolled (50% Latinos and 19% African-American). The patients are representative of the typical HFrEF phenotype, with reduced LVEF (36±8%) and dilated LV (Table 2), and were receiving optimal medical treatment. There were no major differences at baseline between both groups. During follow-up, the empagliflolzin group showed reduction in body weight and increase in hematocrit as compared with placebo. During the trial, six patients in the empagliflozin group had their diuretic dose decreased or completely removed by their physicians. Conversely, three patients in the placebo group had their diuretic dosage increased and only one reduced (Table 3).

Safety

During the trial, four patients (two from each group) were lost to follow up (Figure 2), hence eighty patients completed the study (forty patients per arm). In the placebo group, one patient died from ventricular arrhythmia and another did not report to the final visit. In the empagliflozin group no patient died, but 2 patients voluntarily withdrew from the study. Two patients from the placebo group were hospitalized for heart failure worsening compared to none in the treated group. There were no reports of hypoglycemia, ketoacidosis, urinary/genital infections or amputations in any of the groups (Table 1 supplemental data).

CMR data

There were no significant differences at baseline between the groups. Four patients could not be analyzed due to artifact induced by ICD. From baseline to 6 months, the primary endpoint of LVEDV exhibited greater reduction in the empagliflozin group compared with those assigned to placebo (-25.1±26.0 vs -1.5±25.4mL, for empagliflozin vs placebo, respectively; p<0.001; Table 4, Figure 3 and Central Illustration). Furthermore, from baseline to 6 months, LVESV also exhibited greater reduction in the empagliflozin group compared with the placebo arm (-26.6±20.5 vs -0.5±21.9 mL; for empagliflozin vs placebo, respectively; p<0.001). Importantly, the group assigned to empagliflozin experienced greater reduction in LV mass (-17.8±31.9 vs 4.1±13.4g, for empagliflozin vs placebo, p<0.001) and in LV sphericity (Δsphericity index: -0.1±0.08 vs 0.01±0.08g, for empagliflozin vs placebo, p<0.001). Moreover, the empagliflozin arm was associated with a more pronounced increase in LVEF as compared with placebo (6±4.2 vs -0.1±3.9 for empagliflozin vs placebo, p<0.001).

The reductions in LV volumes determined by CMR were paralleled by changes in the plasma concentrations of NT-proBNP; the empagliflozin group showed a 11.5% decrease vs a 8.5% increase in the placebo group (p=0.01).

CPET Data

There were no significant differences in at baseline between the groups. Fifty three patients performed the maximal level of exercise at CPET, while 27 could not reach maximal effort (due to patient refusal, technical problems or sub-optimal test). At the end of the study, empagliflozin was associated with significant improvements in peak VO_2 (1.1±2.6 vs -0.5±1.9mL/min/kg, for empagliflozin vs placebo, p=0.017; Table 4, Figure 4 and Central Illustration) and oxygen uptake efficiency slope (111±267 vs -145±318, for empagliflozin vs placebo, p<0.01) Furthermore,

there was a trend towards improvement in the VE/VCO_2 in the empagliflozin vs placebo group (-1.2±3.4 vs 0.5±3.9, respectively, p=0.09).

6-Minute walk test

There were no significant differences at baseline between groups. All eighty participants completed the baseline and 6-month 6MWT. At the end of the treatment period, the empagliflozin arm was associated with significant improvements in 6MWT as compared with placebo (81±64meters vs -35±68 meters; for empagliflozin and placebo respectively; $p<0.001$; Table 4 and Figure 4).

Quality of life

There were no significant differences at baseline between groups. All eighty participants completed the baseline and 6-month questionnaires. From baseline to six months, the empagliflozin group exhibited greater improvement in in the overall QoL from baseline as compared with placebo (Table 4 and Figure 4).

DISCUSSION

The main findings of the EMPATROPISM trial are that empagliflozin administration to nondiabetic HFrEF patients is associated with amelioration in adverse LV remodeling, with reduction in LV volume, decrease in LV hypertrophy, improvement in LVEF, and a less spherical left ventricle with less pronounced architectural remodeling, as compared with placebo. Of utmost importance, empagliflozin-treated patients exhibited improvement in functional capacity (using both maximal exercise in CPET and submaximal exercise in 6MWT) and increase in QoL as compared with the placebo arm. Our observations suggest that SGLT2i could become a new therapeutic strategy for the treatment of HFrEF patients independently of their diabetic status.

The prevalence of heart failure is increasing due to rising age and increased cardiovascular risk factors in the overall population, is associated with high morbidity and mortality, and is the leading cause of hospitalization of patients over 65 years of age (23). Heart failure is highly prevalent in T2DM patients; however, approximately half of all heart failure patients do not have diabetes(23). Despite optimal medical treatment, mortality of heart failure is still high(23). SGLT2i initially demonstrated to reduce heart failure hospitalizations in diabetic patients(1-3). These initial benefits have been recently expanded to the field of HFrEF(4,5). However, the effects of SGLT2i on cardiac structure and function as well as in functional capacity remain undetermined.

Adverse LV remodeling in heart failure is characterized by LV dilatation, sphericity and hypertrophy(24), which worsens heart failure and begets a vicious circle. The main finding of EMPATROPISM is that empagliflozin significantly reverses and ameliorates LV remodeling as demonstrated by reduced LV volumes, mitigated LV hypertrophy, less spherical LV, and

increased LVEF. Reversing LV remodeling is an important factor in reducing mortality and morbidity in patients with heart failure(24,25). In fact, short-term benefits on LV remodeling are associated with longer-term outcome improvements(14). Importantly, the ameliorated LV remodeling demonstrated in EMPATROPISM parallels the improvement in outcomes observed with DAPA-HF and EMPEROR-Reduced(4,5).

Change in LV volumes was chosen as major-end point because of its strong prognostic value for adverse CV outcomes even after adjusting for LVEF and infarct size(11-14). We want to highlight that both LVEDV and LVESV were significantly reduced by empagliflozin as compared with placebo. This decrease in LV volumes in the empagliflozin-treated patients is supported by a reduction in the plasma levels of NT-ProBNP in the treatment arm. Empagliflozin treatment resulted in a significant regression of LV hypertrophy and LV mass with empagliflozin; this is important because previous studies have associated LV mass regression with better outcomes in HF patients(13). We want to highlight that empagliflozin treatment significantly increased LVEF while no change was seen in the placebo. The between-group difference of 6 absolute points in LVEF is of considerable clinical relevance; especially since sacubitril-valsartan did not improved in the EVALUATE-HF study(26), although we have to note that treatment duration was shorter (3 months) in EVALUATE(26). During heart failure progression, the LV loses its elongated, bullet-like, geometry and acquires a more spherical, balloon-like, conformation; of note, empagliflozin reduces the sphericity and geometrical remodeling of the LV, which is important given that greater sphericity is associated with worse outcomes(17).

This is the first study demonstrating that empagliflozin ameliorates LV remodeling in non-diabetic HF patients. The EMPA-HEART reported LV mass regression but was restricted to a

diabetic population without HF(27). The DEFINE trial investigated HFrEF but focused exclusively on systemic biomarkers and the majority of the patients were diabetic (28). The REFORM trial did not find any improvement in LV remodeling with dapagliflozin on diabetic heart failure patients(29). The contrasting results between REFORM and EMPATROPISM can be explained by the different patients characteristics; REFORM enrolled less advanced patients (50% were in NYHA I, while EMPATROPISM exclusively enrolled NYHA II-III), with higher LVEF (46% in REFORM vs 36% in EMPATROPISM) and with less dilated LV (LVEDV 180mL in REFORM vs 220mL in EMPATROPISM).

CPET provides information on the functional capacity, treatment efficacy and outcome prediction in heart failure(30). PeakVO_2 is a more sensitive parameter of exercise capacity than 6MWT(19), hence its use to determine cardiac transplantation. Furthermore, peakVO_2 allows to investigate the determinants of exercise intolerance, while 6MWT distance does not(31). Importantly, the peak VO_2 in EMPATROPISM significantly increased in the empagliflozin-patients by 1.1 ml/kg/min versus a 0.5 ml/kg/min decline in the placebo, thus demonstrating improvement in functional capacity with SGLT2i. Furthermore, OUES was significantly improved in the treated arm; this is relevant because a higher OUES value reflects improved adaptation of the cardiopulmonary circuit to deliver oxygen for a given amount of ventilation(19). There was also a trend towards improvement of VE/VCO_2 ratio in the empagliflozin group but did not achieve statistical significance (p=0.09). Finally, the 6MWT showed a consistent improvement in treated patients versus a decline in placebo-controls. Noteworthy, both peak VO2, and submaximal measures of exercise performance (6MWT and OEUS) were all concordant in showing improvements in the treated cohort. These data show improved functional capacity after treatment with SGLT2i in HFrEF.

The KCCQ-12 questionnaire is used to evaluate the health status of heart failure patients, and shows a strong association with outcomes (32). A 5-point change in KCCQ-12 overall summary score is considered to be the minimal noticeable clinical difference experienced by patients(33) and also detected by the treating cardiologist as a small deterioration or improvement in heart failure(34). At the end of the study, empagliflozin administration was associated with an increase in the overall QoL from baseline vs placebo. Using this 5-point cut-off parameter, 30 patients in the empagliflozin group showed QoL improvement; conversely, in the placebo group, only 14 patients showed improvements while 10 experienced QoL worsening. This benefit in QoL is supported by the parallel recovery in QoL observed in DAPA-HF, thus confirming the benefits of SGLT2i in HFrEF.

An important observation is the short follow up needed in EMPATROPISM (6 months) to detect significant improvements associated with SGLT2i. This observation coincides with the early separation of the event curves observed in large trials(1,4,5) and the benefits in our animal model (two months)(8).

Our data on amelioration of adverse LV remodeling, improved LVEF, and enhanced cardiopulmonary capacity confirm our previous findings in an experimental model(8). We demonstrated less LV remodeling, boosted LV systolic function (LVEF, contractile reserve, and LV strains), reduced sympathetic overdrive(8) and better diastolic function(9) in non-diabetic pigs with HFrEF. This improvement in LV remodeling with SGLT2i has been independently confirmed in a similar rat model of HFrEF(35). Both the animal and the human data point towards enhanced LV performance in HFrEF after SGLT2i treatment.

The mechanism(s) of the cardiac benefits of SGLT2i remain incompletely understood. Our porcine study suggested that SGLT2i induce a switch in the myocardial metabolism away from

glucose utilization into consumption of fatty acids, ketone bodies and branched-chain aminoacids, which enhances myocardial energetics. This metabolic shift has also been independently confirmed by other groups (35). This hypothesis is further supported by the fact that infusion of ketones in HFrEF patients improve myocardial contractility(36). Therefore, it seems rational to think that this recovery in myocardial energetics will improve heart failure. However, alternative/ mechanisms to explain the benefits of SGLT2i have also been postulated (37,38). An improvement in ventricular loading conditions secondary to a reduction in preload due to the diuretic and natriuretic effect of SGLT2i might decrease congestion and potentially explain the decrease in LV volumes observed in our study. In fact, a previous mediation analysis of the EMPAREG-Outcome trial(39) concluded that changes in markers of plasma volume were the most important mediators of the improvement in prognosis. This is also supported by the finding of reduced pulmonary artery pressure in patients with SGLT2i (40). Additionally, by lowering arterial stiffness(41), SGLT2i may reduce cardiac afterload, with resultant improvement in ventricular arterial coupling and cardiac efficiency. Other hypotheses include the anti-inflammatory/anti-oxidant effects of SGLT2i(42), the increase in erythropoietin with subsequent enhancement of oxygenation(38), and the inhibition of the Na/H exchanger(43).

Limitations

First, the number of patients enrolled in our study is relatively small; however, the high reproducibility of CMR allows for the utilization of reduced sample sizes(22). A second limitation is the relatively high number of dropouts in the CPET. Third, we have exclusively studied HFrEF patietns; whether patients with heart failure with preserved ejection fraction can benefit from SGLT2i cannot be answered by our study and remains to be determined.

Conclusions

The EMPATROPISM trial Our trial, using different but complementary techniques to assess cardio-pulmonary function and activity as well as patients' quality of life; demonstrates the benefits of empagliflozin when administered to non-diabetic HFrEF patients. Therefore, these data suggest the benefits of SGLT2i in the treatment of HFrEF patients independently of their diabetic status.

FIGURE LEGENDS

Figure 1: Design of the EMPATROPISM trial

Figure 2: Flow of participants in the trial: enrollment and follow up

Figure 3: Changes in LV volumes, LV hypertrophy and LV systolic function in the empagliflozin vs placebo arms as determined by cardiac magnetic resonance. Empagliflozin is associated with greater reduction in both left ventricle end diastolic volume (LVEDV) and left ventricle end systolic volume (LVESV), more intense regression in LV mass, and higher improvement in LV ejection fraction (LVEF) between baseline and 6-month time-point as compared with placebo. Graphs represent mean and 95% confidence interval

Figure 4: Changes on exercise capacity, functional capacity and quality of life in the empagliflozin vs placebo arms. Empagliflozin is associated with larger improvement in peak VO2 and OUES as determined by CPET; more pronounced increase in 6-mimute walk test (6MWT) and more enhancement in quality of life (using KCCQ-12) between baseline and 6-month timepoint as compared with placebo. Graphs represent mean and 95% confidence interval

BIBLIOGRAPHY

1. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015.
2. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017;377:644-657.
3. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2018.
4. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019;381:1995-2008.
5. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 2020;Online ahead of print.
6. Petrie MC, Verma S, Docherty KF, et al. Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes. JAMA 2020;323:1353-68.
7. Flores E, Santos-Gallego CG, Diaz-Mejia N, Badimon JJ. Do the SGLT-2 Inhibitors Offer More than Hypoglycemic Activity? Cardiovasc Drugs Ther 2018;32:213-222.
8. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, et al. Empagliflozin Ameliorates Adverse Left Ventricular Remodeling in Nondiabetic Heart Failure by Enhancing Myocardial Energetics. J Am Coll Cardiol 2019;73:1931-1944.
9. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, et al. Empagliflozin Ameliorates Diastolic Dysfunction and Left Ventricular Fibrosis/Stiffness in Non-Diabetic Heart Failure: a Multimodality Study. JACC Cardiovasc Imaging 2020;in press.
10. Santos-Gallego CG, Garcia-Ropero A, Mancini D, et al. Rationale and Design of the EMPA-TROPISM Trial (ATRU-4): Are the "Cardiac Benefits" of Empagliflozin Independent of its Hypoglycemic Activity? Cardiovasc Drugs Ther 2019;33:87-95.
11. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44-51.
12. Migrino RQ, Young JB, Ellis SG, et al. End-systolic volume index is a strong predictor of early and late mortality. The GUSTO-I Angiographic Investigators. Circulation 1997;96:116-21.
13. Verma A, Meris A, Skali H, et al. Prognostic implications of left ventricular mass and geometry following myocardial infarction: the VALIANT (VALsartan In Acute myocardial iNfarcTion) Echocardiographic Study. JACC Cardiovasc Imaging 2008;1:582-91.
14. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. J Am Coll Cardiol 2010;56:392-406.
15. Guazzi E, Bandera F, Ozemek C, Systrom D, Arena R. Cardiopulmonary Exercise Testing: What Is its Value? J Am Coll Cardiol 2017;70:1618-36.
16. Santos-Gallego CG, Vahl TP, Goliasch G, et al. Sphingosine-1-Phosphate Receptor Agonist Fingolimod Increases Myocardial Salvage and Decreases Adverse Postinfarction Left Ventricular Remodeling in a Porcine Model of Ischemia/Reperfusion. Circulation 2016;133:954-66.

17. Mannaerts HF, van der Heide JA, Kamp O, Stoel MG, Twisk J, Visser CA. Early identification of left ventricular remodelling after myocardial infarction, assessed by transthoracic 3D echocardiography. Eur Heart J 2004;25:680-7.
18. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. J Am Coll Cardiol 2000;36:194-201.
19. Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary Exercise Testing in Heart Failure. JACC Heart Fail 2016;4:607-16.
20. Crapo RO, Casaburi R, Coates AL, Laboratories ACoPSfCPF. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-117.
21. Green CP, Porter CB, Bresnahan DR, Spertus J. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245-55.
22. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2000;2:271-8.
23. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation 2019:CIR0000000000000659.
24. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000;35:569-82.
25. Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. JACC Cardiovasc Imaging 2011;4:98-108.
26. Desai AS, Solomon SD, Shah AM, et al. Effect of Sacubitril-Valsartan vs Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. JAMA 2019:1-10.
27. Verma S, Mazer CD, Yan AT, et al. Effect of Empagliflozin on Left Ventricular Mass in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease: The EMPA-HEART CardioLink-6 Randomized Clinical Trial. Circulation 2019;140:1693-1702.
28. Nassif ME, Windsor SL, Tang F, et al. Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial. Circulation 2019;140:1463-76.
29. Singh JSS, Mordi IR, Vickneson K, et al. Dapagliflozin Versus Placebo on Left Ventricular Remodeling in Patients With Diabetes and Heart Failure: The REFORM Trial. Diabetes Care 2020;43:1356-1359.
30. Corrà U, Piepoli MF, Adamopoulos S, et al. Cardiopulmonary exercise testing in systolic heart failure in 2014: the evolving prognostic role: a position paper from the committee on exercise and training of the heart failure association of the ESC. Eur J Heart Fail 2014 16:929-41.
31. Del Buono MG, Arena R, Carbone S, et al. Exercise Intolerance in Patients With Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol 2019;73:2209-2225.
32. Pokharel Y, Khariton Y, Tang Y, et al. Association of Serial Kansas City Cardiomyopathy Questionnaire Assessments With Death and Hospitalization in Patients

With Heart Failure With Preserved and Reduced Ejection Fraction: A Secondary Analysis of 2 Randomized Clinical Trials. JAMA Cardiol 2017;2:1315-1321.
33. Luo N, O'Connor CM, Cooper LB, et al. Relationship between changing patient-reported outcomes and subsequent clinical events in patients with chronic heart failure. Eur J Heart Fail 2019;21:63-70.
34. Spertus J, Peterson E, Conard MW, et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J 2005;50:707/15.
35. Yurista SR, Sillje HHW, Oberdorf-Maass SU, et al. Sodium-glucose co-transporter 2 inhibition with empagliflozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction. Eur J Heart Fail 2019;21:862-873.
36. Nielsen R, Moller N, Gormsen LC, et al. Cardiovascular Effects of Treatment With the Ketone Body 3-Hydroxybutyrate in Chronic Heart Failure Patients. Circulation 2019;139:2129-2141.
37. Zelniker TA, Braunwald E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75:422-434.
38. Verma S, Lopaschuk G. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. JACC Basic Transl Sci 2020;5:632-44.
39. Inzucchi SE, Zinman B, Fitchett D, et al. How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial. Diabetes Care 2018;41:356-363.
40. Mullens W, Martens P, Forouzan O, et al. Effects of dapagliflozin on congestion assessed by remote pulmonary artery pressure monitoring. ESC Heart Fail 2020;26:2071-2073.
41. Chilton R, Tikkanen I, Cannon CP, et al. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. Diabetes Obes Metab 2015;17:1180-93.
42. Garcia-Ropero A, Santos-Gallego CG, Badimon J. The anti-inflammatory effects of SGLT inhibitors. Aging (Albany NY) 2019;11:5866-5867.
43. Uthman L, Baartscheer A, Bleijlevens B, et al. Class effects of SGLT2 inhibitors in mouse cardiomyocytes and hearts: inhibition of Na(+)/H(+) exchanger, lowering of cytosolic Na(+) and vasodilation. Diabetologia 2018;61:722-726.

TABLE 1: Demographic and clinical characteristics of all participants and of each study group

Parameter	All		Empagliflozin		Placebo	
Gender	**N**	**%**	**N**	**%**	**N**	**%**
All	84	100	42	100	42	100
Female	30	36	15	36	15	35.7
Male	54	64	27	63	27	64
Ethnicity						
Caucasian	23	27	16	38	7	17
Hispanic/Latino	42	50	19	45	23	55
African American	16	19	7	16	9	20
Asian	3	4	0	0	3	7
Age (years)						
Mean ± SD	62 ± 12.1		64.2 ± 10.9		59.9 ± 13.1	
<65	52	61	24	57	28	66
>65	32	38	18	43	14	33
CVRFs						
Hypertension	62	74	34	81	28	67
Hyperlipidemia	62	74	32	76	30	71
Cigarette Smoking (past or present)	30	36	18	43	12	29
Diabetes	0	0	0	0	0	0
Atrial Fibrillation	18	21	10	24	8	19
Cause of HF						
Ischemic	42	50	23	55	19	45

Non-Ischemic	41	49	19	45	22	51
Devices (ICD/CRT/Pacemaker)						
	17	20	9	21	8	19
Medications						
Statin	63	75	33	79	30	71
ACEi/ARB (Alone)	35	42	16	38	19	45
ARNi	36	43	21	50	15	36
B-Blockers	74	88	36	86	38	90
Loop Diuretics	46	55	22	52	24	57
Thiazide Diuretics	5	6	3	7	2	5
Mineralocorticoid antagonists	28	33	13	31	15	36
Ca-Blockers	10	12	5	12	5	12
Antiplatelet	55	65	29	69	26	62
Anticoagulants	19	23	10	24	9	21

TABLE 2: Patient characteristics at baseline and at study end. Data expressed as Mean ± SD

	Empagliflozin			Placebo			Δ p value
Patient Characteristics	**Baseline**	**6-month**	**Δ from Bas**	**Baseline**	**6-month**	**Δ from Bas**	
Body Weight (Kg)	84.1 ± 20	82.8 ± 19.9	-1.3 ± 3.3	84.1 ± 21.6	85.6 ± 22.6	1.5 ± 5	<0.01
BMI (Kg/m2)	29.3 ± 6	28.8 ± 5.9	-0.5 ± 1.2	30 ± 6	31 ± 6	0.5 ± 1.9	<0.01
HR (bpm)	74 ± 17	68 ± 11	-6 ± 13	78 ± 15	79 ± 10	1 ± 13	<0.05
Total-Cho (mg/dL)	179 ± 61	175 ± 54	1 ± 27	163 ± 42	166 ± 44	3 ± 29	n.s.
LDL-Cho (mg/dL)	105 ± 53	101 ± 45	0 ± 21	94 ± 39	96 ± 41	2 ± 24	n.s.
HDL-Cho (mg/dL)	53 ± 18	51 ± 18	-1 ± 6	48 ± 11	49 ± 15	1 ± 10	n.s.
TGL (mg/dL)	107 ± 51	110 ± 60	7 ± 43	104 ± 50	102 ± 48	-2 ± 32	n.s.
eGFR (mL/min/1.73m2)	80 ± 21	76 ± 19	-4 ± 10	83 ± 23	86 ± 22	3 ± 9	<0.01
Creatinine (mg/dL)	0.97 ± 0.3	1.01 ± 0.32	0.04 ± 0.14	0.95 ± 0.28	0.91 ± 0.29	-0.04 ± 0.12	<0.01
Glucose (mg/dL)	95 ± 12	93 ± 11	-3 ± 13	100 ± 15	96 ± 15	-4 ± 14	n.s.
HbA1c (%)	5.8 ± 0.3	5.9 ± 0.4	0.1 ± 0.3	5.8 ± 0.5	5.9 ± 0.5	0.1 ± 0.4	n.s.
Haemoglobin (g/dL)	13.2 ± 1.6	13.7 ± 1.8	0.4 ± 1.1	13.4 ± 1.6	13.5 ± 1.7	0.1 ± 0.9	n.s.
Haematocrit (%)	40 ± 4.6	42 ± 5.4	2 ± 3.4	41 ± 5	41 ± 5	0 ± 2.9	<0.05

TABLE 3: Evolution of the number of patients on diuretics and also of the diuretic doses both at baseline and study end.

	Empagliflozin			Placebo		
	Baseline	6 Months		Baseline	6 Months	
Diuretics (Any)	**26**	**24**		**27**	**28**	
		Increase dose	**Decrease dose**		**Increase dose**	**Decrease dose**
Loop Diuretics	21	0	5	23	0	0
Thiazide Diuretics	3	0	1	2	0	1
Mineralocorticoid Antagonists	11	0	1	14	3	0

TABLE 4: Changes in parameters of CMR, CPET, 6MWT and Quality of Life from baseline to study-end for both arms. LVEDV.- Left ventricle end diastolic volume, LVESV.- Left ventricle end systolic volume, LVEF.- Left ventricle Ejection Fraction , LV Mass.- Left Ventricle Mass , OUES.- Oxygen Uptake Efficiency Slope. Data expressed as Mean ± SD.

	Empagliflozin			Placebo			
	Baseline	6-month	Δ from Bas	Baseline	6-month	Δ from Bas	Δ p value
CMR							
LVEDV (mL)	219.8 ± 75.8	194.7 ± 69.7	-25.1 ± 26	210.4 ± 68.9	208.9 ± 72.8	-1.5 ± 25.4	<0.001
LVESV (mL)	143.6 ± 66.3	117.0 ± 60	-26.6 ± 20.5	135.1 ± 54.8	134.5 ± 58.9	-0.5 ± 21.9	<0.001
LVEF (%)	36.2 ± 8.2	42.2 ± 9.2	6.0 ± 4.2	36.5 ± 8	36.3 ± 8.5	-0.1 ± 3.9	<0.001
LVMass (g)	135.2 ± 45.2	117.4 ± 41.7	-17.8 ± 31.9	131.8 ± 54.4	135.8 ± 61	4.1 ± 13.4	<0.001
Sphericity Index	0.62 ± 0.16	0.52 ± 0.11	-0.10 ± 0.08	0.58 ± 0.12	0.59 ± 0.13	0.01 ± 0.08	<0.001
CPET							
Peak VO2 (mL/min/kg)	15.3 ± 4.3	16.4 ± 4.4	1.1 ± 2.6	14.5 ± 3.9	14.0 ± 4.2	-0.5 ± 1.9	0.017
VE/VCO2	29.5 ± 4.6	28.6 ± 4.8	-1.2 ± 3.4	27.4 ± 5.4	28.0 ± 6.7	0.5 ± 3.9	0.09
OUES	1522 ± 425	1633 ± 510	111 ± 267	1630 ± 506	1485 ± 570	-145 ± 318	<0.001
6-Minute Walk (meters)							
	420 ± 93.4	501 ± 100	81 ± 64	452 ± 101	417 ± 113	-35 ± 68	<0.001
KCCQ-12							
	67.7 ± 25.4	88.3 ± 13.3	21 ± 18	71.8 ± 22	73.6 ± 23.3	1.9 ± 15	<0.001

Empagliflozin in Non-Diabetic Heart Failure Patients with Reduced Ejection Fraction: EMPATROPISM (ATRU-4) Randomized Clinical Trial

Carlos G Santos-Gallego MD*[1,2] Ariana P Vargas-Delgado MD*[1,2] Juan Antonio Requena MD[1,2] Alvaro Garcia-Ropero MD[1,2] Donna Mancini MD[1] Sean Pinney MD[1] Frank Macaluso BS[1] Samantha Sartori PhD[1] Merce Roque MD[1,2] Fernando Sabatel-Perez MD[2] Anderly Rodriguez Cordero MD[1,2] M. Urooj Zafar MD[1,2] Icilma Fergus MD[1] Farah Atallah-Lajam MD[1] Johanna P Contreras MD[1,] Cathleen Varley RN[1,] Pedro R Moreno MD[1] Vivian M Abascal MD[1] Anuradha Lala MD[1] Ronald Tamler MD[3] Javier Sanz MD[1] Valentin Fuster MD, PhD[1] Juan J Badimon PhD[1,2]
On behalf of the EMPA-TROPISM (ATRU-4) investigators

[1] Mount Sinai Heart
[2] Atherothrombosis Research Unit
[3] Division of Endocrinology
Icahn School of Medicine at Mount Sinai
New York City, NY

Short title: Santos-Gallego et al. Empagliflozin in non-diabetic HFrEF

Total word count: 5000~~4997~~

Formatted: Font: Not Bold

Funding: This research was supported by an independent grant from Boehringer Ingelheim, who provided both drug and financial support for the study

Disclosures: Sean Pinney reports receiving consulting fees from Abbott, Medtronic Inc, and Procryrion Inc; and to receive both consulting and speaking fees from Care Dx. The rest of the authors reported no disclosures.

Twitter handle: @SantosGallegoMD

Formatted: Underline

Corresponding author:

Juan J Badimon, PhD
AtheroThrombosis Research Unit
Mount Sinai Heart
Icahn School of Medicine at Mount Sinai School of Medicine
~~1~~ One Gustave L. Levy Pl.
New York, NY 10029-0310
United States
Telephone: (212) 241-8484
Fax: (212) 426-6962
E-mail: juan.badimon@mssm.edu

ABSTRACT

BACKGROUND

Large clinical trials established the benefits of SGLT2 inhibitors in patients with diabetes and with heart failure with reduced ejection fraction (HFrEF). The early and significant improvement in clinical outcomes is likely explained by effects beyond a reduction in hyperglycemia

OBJECTIVES

To investigate the safety and efficacy of empagliflozin versus placebo on top of optimal medical therapy in non-diabetic HFrEF patients

METHODS

In this double-blind, placebo-controlled trial, non-diabetic HFrEF patients (n=84) were randomized to empagliflozin or placebo for six months. The primary endpoint was change in left ventricle end-diastolic volume (LVEDV) and left ventricle end-systolic volume (LVESV) assessed by cardiac magnetic resonance. Secondary endpoints included changes in LV mass, LVEF, peak oxygen consumption in the cardiopulmonary exercise test, 6-minute walk test, and quality of life

RESULTS

Empagliflozin was associated with a significant reduction of LVEDV (-25.1±26.0 vs -1.5±25.4mL for empagliflozin vs placebo, respectively, $p<0.001$) and LVESV (-26.6±20.5 vs -0.5±21.9 mL for empagliflozin vs placebo, $p<0.001$). Empagliflozin was associated with

reductions in LV mass (-17.8±31.9 vs 4.1±13.4 g, for empagliflozin vs placebo, respectively, p<0.001) and improvements in LVEF (6±4.2 vs -0.1±3.9 p<0.001). Patients who received empagliflozin had significant improvements in peak O2 consumption (1.1±2.6 vs -0.5±1.9mL/min/kg for empagliflozin vs placebo, respectively, p=0.017), oxygen uptake efficiency slope (111±267 vs -146±318, p<0.001), as well as in 6-minute walk test (81±64 vs -35±68 meters, p<0.001) and quality of life (KCCQ-12: 21±18 vs 2±15, p<0.001).

CONCLUSIONS

Empagliflozin administration to non-diabetic HFrEF patients significantly improves LV volumes, LV mass, LV systolic function, functional capacity, and quality of life when compared with placebo. Our observations strongly support a role for SGLT2 inhibitors in the treatment of HFrEF patients independently of their glycemic status.

(www.clinicaltrials.gov NCT 03485222)

CONDENSED ABSTRACT

In this double-blind, placebo-controlled, randomized EMPATROPISM clinical trial, empagliflozin administration to non-diabetic HFrEF patients on top of optimal medical treatment ameliorated cardiac remodeling, reduced LV volumes, decreased LV mass, increased LV systolic function, enhanced functional capacity (both peak oxygen consumption and 6-minute walk test), and improved quality of life when compared with placebo. The results of the EMPATROPISM trial support the use of SGLT2 inhibitors in the treatment of HFrEF patients independently of their diabetic status.

TWEET

The SGLT2i Empagliflozin in HFrEF patients without diabetes significantly improves LV volumes, LV mass, LVEF, peak oxygen consumption, 6-minute walk test, and quality of life when compared with placebo

COMPETENCY IN MEDICAL KNOWLEDGE:

In the double-blind, placebo-controlled EMPATROPISM trial, non-diabetic HFrEF patients were randomized to empagliflozin (10mg/day) or placebo for 6-months. Empagliflozin administration resulted in consistent and significant improvements in cardiac volumes, hypertrophy, LVEF, exercise capacity, functional capacity, and quality of life when compared with placebo. Our data endorse SGLT2 inhibitors as attractive candidates in the treatment of non-diabetic HFrEF patients.

TRANSLATIONAL OUTLOOK:

Previous RCT have demonstrated the benefits of SGLT-2 inhibitors on T2DM patients. Our mechanistic observation and data from the DAPA-HF strongly suggest the benefits of SGLT2 inhibition in heart failure patients independent of their diabetic status.

ABBREVIATIONS USED WITHIN THE TEXT

CMR Cardiac Magnetic Resonance

CPET Cardiopulmonary Exercise Test

HFrEF Heart failure with reduced Ejection Fraction

KCCQ-12 Kansas City Cardiomyopathy Questionnaire

LV Left Ventricle

LV Left Ventricle LVEDV Left Ventricle end diastolic volume

LVESV Left Ventricle end systolic volume

LVEF Left Ventricle Ejection Fraction

OUES Oxygen Uptake Efficiency Slope

RCT Randomized Clinical Trial

SGLT2i Inhibitors of the Sodium-glucose cotransporter-2

VO_2 Oxygen Consumption

6MWT 6-minute walk test

INTRODUCTION

In patients with type-2 diabetes, sodium-glucose co-transporter 2 inhibitors (SGLT2i) reduce the risk of hospitalization for heart failure by 30-35% and improve cardiac outcomes(1-3). The recent clinical trials DAPA-HF(4) and EMPEROR-Reduced(5) have expanded these heart failure benefits of SGLT2i to the realm of patients with heart failure with reduced ejection fraction (HFrEF). Of the utmost importance, these benefits in outcomes occur both in diabetic and non-diabetic patients(6).

These benefits of SGLT2i cannot be explained exclusively by their glucose-lowering effects because the modest hypoglycemic activity of SGLT2i is comparable to other glucose-lowering drugs which do not show improvements in heart failure; the differences in diabetic control were (by design) minimal (equipoise); the benefits would have taken years (while event curves separate in the first month); it would have also reduced atherothrombotic events; and glycemic control has previously failed to reduce heart failure(7).

Based on these observations, we hypothesized that SGLT2i would mitigate adverse left ventricular (LV) remodeling independently of diabetic status, which could expla~~i~~n their benefits in heart failure. This hypothesis was initially approached in our ~~well-characterized,~~ non-diabetic porcine model of heart failure. Empagliflozin ~~administration~~ significantly ameliorated adverse LV remodeling, decreased LV volumes and LV hypertrophy, reduced neurohormonal activation, and improved cardiac systolic function ~~as~~ compared with the control group(8). Moreover, empagliflozin also improved diastolic function in this HFrEF model(9). Based on these experimental results, we designed the EMPATROPISM-trial to translate these preclinical data to human patients(10). This is a randomized, double-blind, placebo-controlled trial to assess the

effect of empagliflozin on LV function and volumes, functional capacity and quality of life (QoL) in non-diabetic HFrEF patients.

METHODS

Trial Design

The EMPATROPISM (NCT 03485222) is a single-site, double-blind, randomized placebo-controlled trial, to determine whether empagliflozin improves cardiac function, exercise performance and quality of life (QoL) in non-diabetic HFrEF. The study design and protocol have been approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai. All participants signed an informed consent form prior study entry. Study design is presented in Figure 1.

A more detailed protocol has been previously reported(10). Briefly, all participants met the following inclusion criteria: 1) age>18 years; 2) diagnosis of heart failure (NYHA II-III); 3) LVEF<50%; 4) stable symptoms and medical therapy within the last 3 months.

Major exclusion criteria were: 1) History of diabetes by medical history or by any of the established criteria by the American Diabetes Association (also including history of diabetes in remission); 2) acute coronary syndrome or cardiac surgery within the last 3 months; 3) Glomerular Filtration Rate <30ml/Kg/min; 4) use of continuous parental inotropic agents; 5) systolic blood pressure< 90mmHg; 6) non-MRI compatible pacemakers or implantable cardiac defibrillatorscardiac devices; 7) pregnant or lactating women; and 8) any other medical or physical condition considered unappropriated by a study physician.

Clinical visits and randomization

The study included 5 visits over a 6-month period. At baseline (pre-treatment) visit, all participants underwent clinical assessment, anthropometric measurements, 6-minute walk test

(6MWT) and the Kansas City Cardiomyopathy Questionnaire (KCCQ-12). Cardiac function was assessed by cardiac magnetic resonance (CMR); maximal exercise capacity was measured by cardiopulmonary exercise testing (CPET). Thereafter, patients were randomized to receive either empagliflozin or matching placebo ~~control~~ for a period of 6-months. Randomization was performed with a secure web-based system stratified with block sizes of 4. Two additional visits at 1- and 3-months post-randomization involved interview, drug dispensation, blood and urine collection for safety and tolerability. At the final visit, the procedures performed at baseline were repeated.

End points~~.~~

The primary end-point was between-groups change in LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) from baseline to 6-months as compared to placebo. LV volumes are the strongest predictor of adverse ~~CV~~ cardiovascular outcomes even after adjusting for LVEF and extent of myocardial infarction (11-14). CMR is ~~considered~~ the gold standard for ~~assessing~~ quantifying ~~changes in~~ cardiac volume and function; the reproducibility of CMR allows for a smaller sample size as compared with echocardiography(12)

Secondary endpoints include the between-groups changes in peak VO_2. CPET with incremental workload and symptoms limited exercise is the gold standard for studying cardiac and pulmonary adaptations to exercise in heart failure patients(15). Other end-points also analyzed included changes in LV Mass, LV ejection fraction (LVEF), LV sphericity index, oxygen uptake efficiency slope (OUES), $VE/VCO_{2,,}$ distance in the 6MWT, and QoL (KCCQ-12).

Safety and Adverse Events

Safety and tolerability issues (eg. hypoglycemia, urinary infections, medication changes, etc.) were monitored. Adverse events were monitored by a data safety monitoring board who adjudicated events.

Procedures involved in the study

Cardiac Magnetic Resonance Imaging (CMR) was performed on a 1.5T magnet (Magnetom Avanto FIT, Siemens) using phased-array surface coils as receivers. Retrospectively ECG-gated cine images were acquired with a steady-state free precession sequence (typical parameters TR 2.8 ms, TE 1.2 ms, 12-15 lines per segment, flip angle 45 degrees, typical voxel size 1.5x1.5x6 mm, 4-mm gap, number of averages 1, bandwidth 930 Hz). Short-axis cine images covering both ventricles from base to apex were obtained during end-expiratory breath-holds. LV volumes, LV mass, and LVEF were quantified as previously reported(8,16) using dedicated analysis software (CMR42, version 5.6.3, Circle Cardiovascular Imaging, Calgary, Canada). Epicardial and endocardial contours were traced in each SSFP cine image to obtain LVEDV, LVESV, LVEF and LV mass; per protocol, the papillary muscles were included in the LV cavity. Sphericity Index was calculated by dividing CMR-calculated LVEDV by the volume of a sphere whose diameter was derived from the major end-diastolic LV long axis, as previously described(17). The LV long-axis was obtained from the CMR dataset as the longest distance between the center of the mitral annulus and the endocardial apex. All CMR assessments were performed in a blind and randomized fashion at the end of the study. The observers were completely blinded to the order of the study, to allocation group, and to any clinical data.

Cardiopulmonary exercise test (CPET).- Patients in fasting state underwent upright incremental bicycle exercise on a cycle ergometer (Lode, Netherlands) with respiratory gas

analysis (Med Graphics Ultima O_2). The patient was connected to the metabolic cart using a disposable mouthpiece and with the nares occluded. Exercise began with unloaded exercise and increased by 25 Watts every 3 minutes. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), minute ventilation (VE), perceived level of exertion (Borg Scale 6-20), pulse oximetry, heart rate and blood pressure measurements were recorded during exercise. Patients were encouraged to exercise until the respiratory exchange ratio was at least 1.1 or the level of perceived exertion was at least 15. The reason the patient stopped exercise was recorded. One investigator (DM) supervised and analyzed the exercise tests. Peak VO_2 was defined as the highest 30sec average of oxygen consumption. The ventilatory threshold was identified as the point at which the ventilatory equivalent for O_2 (VE/VO_2) is minimal, followed by a progressive increase. Ventilation was assessed by correlation of VE and VCO_2 throughout exercise. OUES was determined using the following equation: $VO_2 = a \log_{10} VE + B$. VO_2 in ml/min was plotted on the *y* axis and minute ventilation in L/min was plotted on the semilog transformed *x* axis. The slope of this linear relationship, "a", represents the OUES(18,19).

6 minute walk test (6MWT) was performed according to the guidelines from the American Thoracic Society(20). Patients were instructed to walk as fast and perform as many laps as possible between the distance markers over a 6-minutes period. An un-encouraged test was performed. To minimize variability it is critical to conduct the test at the same time each visit and supervised by the same personnel. The total walked distance was recorded.

Kansas City Cardiac Questionnaire-12 (KCCQ-12) was administered and evaluated according to the questionnaire's instructions(19). The KCCQ-12 was completed by the patients, without assistance by study staff, at randomization and the end of the trial. The KCCQ-12 is a valid, reproducible, responsive tool for assessing disease-specific health status among HF patients. It

quantifies symptoms (frequency, severity, and recent change), physical function, QoL, and social function over the previous 2 weeks. Scores are transformed to a range of 0 to 100 in which higher scores reflect better health status(21).

Statistical Analysis

Our primary endpoint is the between-groups change in LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) from baseline to 6-months. The difference in change is computed between the empagliflozin and placebo arms. It is generally accepted that a 10mL change in LVEDV is clinically significant(22). An internal CMR study at our hospital showed a variation of 12mL for the mean difference of LVEDV. Thus, in order to detect a 10mL difference in LVEDV between the arms with a power of 0.9 and a type-I error of 0.05, a minimum of 72 patients (36/arm) would be required. We estimated a 15% of losses during follow-up or incomplete examinations. Therefore, the final sample size was 84 HFrEF patients without diabetes.

Categorical data are reported as frequencies and percentages; continuous variables are summarized as mean and standard deviation. Data were analyzed on an intention-to-treat basis. No data imputation was performed. Pre/post changes were compared between study groups using a linear mixed model with the group covariate, the binary (pre and post) time covariate, and the group x time interaction term. Differences were considered statistically significant when the p-value of the log-likelihood ratio test on the significance of the interaction term is >0.05. All statistical calculations have been performed with Stata 16.1.

RESULTS

Demographic of study participants

A total of 84 patients provided informed consent form and were randomized 1:1 to empagliflozin or placebo. Table 1 presents demographic characteristics, co-morbidities and medications for all the participants. A high percentage of minorities was enrolled (50% Latinos and 19% African-American). The patients are representative of the typical HFrEF phenotype, with reduced LVEF (36±8%) and dilated LV (Table 2), and were receiving optimal medical treatment. There were no major differences at baseline between both groups. During follow-up, the empagliflolzin group showed reduction in body weight and increase in hematocrit as compared with placebo. During the trial, six patients in the empagliflozin group had their diuretic dose decreased or completely removed by their physicians. Conversely, three patients in the placebo group had their diuretic dosage increased and only one reduced (Table 3).

Safety

During the trial, four patients (two from each group) were lost to follow up (Figure 2), hence eighty patients completed the study (forty patients per arm). In the placebo group, one patient died from ventricular arrhythmia and another did not report to the final visit. In the empagliflozin group no patient died, but 2 patients voluntarily withdrew from the study. Two patients from the placebo group were hospitalized for heart failure worsening compared to none in the treated group. There were no reports of hypoglycemia, ketoacidosis, urinary/genital infections or amputations in any of the groups (Table 1 supplemental data).

CMR data

There were no significant differences ~~in any of the measured parameters~~ at baseline between the groups. Four patients could not be analyzed due to artifact induced by ICD. From baseline to 6 months, the primary endpoint of LVEDV exhibited greater reduction in the empagliflozin group compared with those assigned to placebo (-25.1±26.0 vs -1.5±25.4mL, for empagliflozin vs placebo, respectively; p<0.001; Table 4, Figure 3 and Central Illustration). Furthermore, from baseline to 6 months, LVESV also exhibited greater reduction in the empagliflozin group compared with the placebo arm (-26.6±20.5 vs -0.5±21.9 mL; for empagliflozin vs placebo, respectively; p<0.001). Importantly, the group assigned to empagliflozin experienced greater reduction in LV mass (-17.8±31.9 vs 4.1±13.4g, for empagliflozin vs placebo, p<0.001) and in LV sphericity (Δsphericity index: -0.1±0.08 vs 0.01±0.08g, for empagliflozin vs placebo, p<0.001). Moreover, the empagliflozin arm was associated with a more pronounced increase in LVEF as compared with placebo (6±4.2 vs -0.1±3.9 for empagliflozin vs placebo, p<0.001).

The reductions in LV volumes determined by CMR were paralleled by changes in the plasma concentrations of NT-proBNP; the empagliflozin group showed a 11.5% decrease vs a 8.5% increase in the placebo group (p=0.01).

CPET Data

There were no significant differences in ~~any of the measured parameters~~ at baseline between the groups. Fifty three patients performed the maximal level of exercise at CPET, while 27 could not reach ~~complete~~ maximal effort ~~CPET~~ (due to patient refusal, technical problems or sub-optimal test). At the end of the study, empagliflozin was associated with significant improvements in peak VO_2 (1.1±2.6 vs -0.5±1.9mL/min/kg, for empagliflozin vs placebo, p=0.017; Table 4, Figure 4 and Central Illustration) and oxygen uptake efficiency slope (111±267 vs -145±318, for

empagliflozin vs placebo, p<0.01) Furthermore, there was a trend towards improvement in the VE/VCO_2 in the empagliflozin vs placebo group (-1.2±3.4 vs 0.5±3.9, respectively, p=0.09).

6-Minute walk test

There were no significant differences ~~in the parameters~~ at baseline between groups. All eighty participants completed the baseline and 6-month 6MWT. At the end of the treatment period, the empagliflozin arm was associated with significant improvements in 6MWT as compared with placebo (81±64meters vs -35±68 meters; for empagliflozin and placebo respectively; p<0.001; Table 4 and Figure 4).

Quality of life

There were no significant differences ~~in the parameters~~ at baseline between groups. All eighty participants completed the baseline and 6-month questionnaires. From baseline to six months, the empagliflozin group exhibited greater improvement in in the overall QoL from baseline as compared with placebo (Table 4 and Figure 4).

DISCUSSION

The main findings of the EMPATROPISM trial are that empagliflozin administration to nondiabetic HFrEF patients is associated with amelioration in adverse LV remodeling, with reduction in LV volume, decrease in LV hypertrophy, improvement in LVEF, and a less spherical left ventricle with less pronounced architectural remodeling, as compared with placebo. Of utmost importance, empagliflozin-treated patients exhibited improvement in functional capacity (using both maximal exercise in CPET and submaximal exercise in 6MWT) and increase in QoL as compared with the placebo arm. Our observations suggest that SGLT2i could become a new therapeutic strategy for the treatment of HFrEF patients independently of their diabetic status.

The prevalence of heart failure is increasing due to rising age and increased cardiovascular CV risk factors in the overall population, is associated with high morbidity and mortality, and is the leading cause of hospitalization of patients over 65 years of age (23). Heart failure is highly prevalent in T2DM patients; however, approximately half of all heart failure patients do not have diabetes(23). Despite optimal medical treatment, mortality of heart failure is still high(23). SGLT2i initially demonstrated to reduce heart failure hospitalizations in diabetic patients(1-3). These initial benefits have been recently expanded to the field of HFrEF(4,5). However, the effects of SGLT2i on cardiac structure and function as well as in functional capacity remain undetermined.

Adverse LV remodeling in heart failure is characterized by LV dilatation, sphericity and hypertrophy(24), which worsens heart failure and begets a vicious circle. The main finding of EMPATROPISM is that empagliflozin significantly reverses and ameliorates LV remodeling as demonstrated by reduced LV volumes, mitigated LV hypertrophy, less spherical LV, and

increased LVEF. Reversing LV remodeling is an important factor in reducing mortality and morbidity in patients with heart failure(24,25). In fact, short-term benefits on LV remodeling are associated with longer-term outcome improvements(14). Importantly, the ameliorated LV remodeling demonstrated in EMPATROPISM parallels the improvement in outcomes observed with DAPA-HF and EMPEROR-Reduced(4,5).

Change in LV volumes was chosen as major-end point because of its strong prognostic value for adverse CV outcomes even after adjusting for LVEF and infarct size(11-14). We want to highlight that both LVEDV and LVESV were significantly reduced by empagliflozin as compared with placebo. This decrease in LV volumes in the empagliflozin-treated patients is supported by a reduction in the plasma levels of NT-ProBNP in the treatment arm. Empagliflozin treatment resulted in a significant regression of LV hypertrophy and LV mass with empagliflozin; this is important because previous studies have associated LV mass regression with better outcomes in HF patients(13). We want to highlight that empagliflozin treatment significantly increased LVEF while no change was seen in the placebo. The between-group difference of 6 absolute points in LVEF is of considerable clinical relevance; especially since sacubitril-valsartan did not improved in the EVALUATE-HF study(26), although we have to note that treatment duration was shorter (3 months) in EVALUATE(26). During heart failure progression, the LV loses its elongated, bullet-like, geometry and acquires a more spherical, balloon-like, conformation; of note, empagliflozin reduces the sphericity and geometrical remodeling of the LV, which is important given that greater sphericity is associated with worse outcomes(17).

This is the first study demonstrating that empagliflozin ameliorates LV remodeling in non-diabetic HF patients. The EMPA-HEART reported LV mass regression but was restricted to a

diabetic population without HF(27). The DEFINE trial investigated HFrEF but focused exclusively on systemic biomarkers and the majority of the patients were diabetic (28). The REFORM trial did not find any improvement in LV remodeling with dapagliflozin on diabetic heart failure patients(29). The contrasting results between REFORM and EMPATROPISM can be explained by the different patients characteristics; REFORM enrolled less advanced patients (50% were in NYHA I, while EMPATROPISM exclusively enrolled NYHA II-III), with higher LVEF (46% in REFORM vs 36% in EMPATROPISM) and with less dilated LV (LVEDV 180mL in REFORM vs 220mL in EMPATROPISM).

CPET provides information on the functional capacity, treatment efficacy and outcome prediction in heart failure(30). PeakVO_2 is a more sensitive parameter of exercise capacity than 6-MWT ~~distance~~(19), hence its use to determine cardiac transplantation. Furthermore, peakVO_2 allows to investigate the determinants of exercise intolerance, while 6MWT distance does not(31). Importantly, the peak VO_2 in EMPATROPISM significantly increased in the empagliflozin-patients by 1.1 ml/kg/min versus a 0.5 ml/kg/min decline in the placebo, thus demonstrating improvement in functional capacity with SGLT2i. Furthermore, OUES was significantly improved in the treated arm; this is relevant because a higher OUES value reflects improved adaptation of the cardiopulmonary circuit to deliver oxygen for a given amount of ventilation(19). There was also a trend towards improvement of VE/VCO_2 ratio in the empagliflozin group but did not achieve statistical significance (p=0.09). Finally, the 6MWT showed a consistent– improvement in treated patients versus a decline in placebo-controls. Noteworthy, both peak VO2, and submaximal measures of exercise performance (6MWT and OEUS) were all concordant in showing improvements in the treated cohort. These data show improved functional capacity after treatment with SGLT2i in HFrEF.

The KCCQ-12 questionnaire is used to evaluate the health status of heart failure patients, and shows a strong association with outcomes (32). A 5-point change in KCCQ-12 overall summary score is considered to be the minimal noticeable clinical difference experienced by patients(33) and also detected by the treating cardiologist as a small deterioration or improvement in heart failure(34). At the end of the study, empagliflozin administration was associated with an increase in the overall QoL from baseline vs placebo. Using this 5-point cut-off parameter, 30 patients in the empagliflozin group showed QoL improvement; conversely, in the placebo group, only 14 patients showed improvements while 10 experienced QoL worsening. This benefit in QoL is supported by the parallel recovery in QoL observed in DAPA-HF, thus confirming the benefits of SGLT2i in HFrEF.

An important observation is the short follow up needed in EMPATROPISM (6 months) to detect significant improvements associated with SGLT2i. This observation coincides with the early separation of the event curves observed in large trials(1,4,5) and the benefits in our animal model (two months)(8).

Our data on amelioration of adverse LV remodeling, improved LVEF, and enhanced cardiopulmonary capacity confirm our previous findings in an experimental model(8). We demonstrated less LV remodeling, boosted LV systolic function (LVEF, contractile reserve, and LV strains), reduced sympathetic overdrive(8) and better diastolic function(9) in non-diabetic pigs with HFrEF. This improvement in LV remodeling with SGLT2i has been independently confirmed in a similar rat model of HFrEF(35). Both the animal and the human data point towards enhanced LV performance in HFrEF after SGLT2i treatment.

The mechanism(s) of the cardiac benefits of SGLT2i remain incompletely understood. Our porcine study suggested that SGLT2i induce a switch in the myocardial metabolism away from

glucose utilization into consumption of fatty acids, ketone bodies and branched-chain aminoacids, which enhances myocardial energetics. This metabolic shift has also been independently confirmed by other groups (35). This hypothesis is further supported by the fact that infusion of ketones in HFrEF patients improve myocardial contractility(36). Therefore, it seems rational to think that this recovery in myocardial energetics will improve heart failure. However, alternative/ mechanisms to explain the benefits of SGLT2i have also been postulated (37,38). An improvement in ventricular loading conditions secondary to a reduction in preload due to the diuretic and natriuretic effect of SGLT2i might decrease congestion and potentially explain the decrease in LV volumes observed in our study. In fact, a previous mediation analysis of the EMPAREG-Outcome trial(39) concluded that changes in markers of plasma volume were the most important mediators of the improvement in prognosis. This is also supported by the finding of reduced pulmonary artery pressure in patients with SGLT2i (40). Additionally, by lowering arterial stiffness(41), SGLT2i may reduce cardiac afterload, with resultant improvement in ventricular arterial coupling and cardiac efficiency. Other hypotheses include the anti-inflammatory/anti-oxidant effects ~~t~~of SGLT2i~~.~~(42), the increase in erythropoietin with subsequent enhancement of oxygenation(38), and the inhibition of the Na/H exchanger(43).

Limitations

First, the number of patients enrolled in our study is relatively small; however, the high reproducibility of CMR allows for the utilization of reduced sample sizes(22). A s~~S~~econd limitation is the relatively high number of dropouts in the CPET. Third, we have exclusively studied HFrEF patietns; whether patients with heart failure with preserved ejection fraction can benefit from SGLT2i cannot be answered by our study and remains to be determined.

Conclusions

The EMPATROPISM trial Our trial, using different but complementary techniques to assess cardio-pulmonary function and activity as well as patients' quality of life; demonstrates the benefits of empagliflozin when administered to non-diabetic HFrEF patients. Therefore, these data suggest the benefits of SGLT2i in the treatment of HFrEF patients independently of their diabetic status.

FIGURE LEGENDS

Figure 1: Design of the EMPATROPISM trial

Figure 2: Flow of participants in the trial: enrollment and follow up

~~**Figure 3:** Changes in left ventricle end diastolic volume (LVEDV), left ventricle end systolic volume (LVESV), Left ventricle Ejection Fraction (LVEF) as Left ventricle Mass (LV Mass) between baseline and end of study for the empagliflozin and placebo groups. Note the significant changes associated with the empagliflozin treatment as compared vs placebo.~~

Figure 3: Changes in LV volumes, LV hypertrophy and LV systolic function in the empagliflozin vs placebo arms as determined by cardiac magnetic resonance. ~~Please note that e~~Empagliflozin is associated with ~~a~~ greater reduction in both left ventricle end diastolic volume (LVEDV) and left ventricle end systolic volume (LVESV), ~~with a~~ more intense regression in LV mass, and ~~with~~ higher improvement in LV ~~Left ventricle~~ e~~E~~jection f~~F~~raction (LVEF) between baseline and 6-month time-point as compared with placebo. Graphs represent mean and 95% confidence interval

~~**Figure 4:** Changes in Peak Oxygen Consumption (pO2), Oxygen Uptake Efficiency Slope (OUES), 6 Minute Walk Test (6 MWT) and Quality of Life (KCCQ) between baseline and end of study for the empagliflozin and placebo groups.~~

Formatted: Line spacing: Double

Formatted: Font: Bold

Formatted: Line spacing: Double

Formatted: Font: Bold

Formatted: Line spacing: Double, Don't adjust space between Latin and Asian text, Don't adjust space between Asian text and numbers

Figure 4: Changes on exercise capacity, functional capacity and quality of life in the empagliflozin vs placebo arms. ~~Please note that e~~Empagliflozin is associated with larger improvement in peak VO2 and OUES as determined by CPET; more pronounced increase in 6-mimute walk test (6MWT) and more enhancement in quality of life (using KCCQ-12) between baseline and 6-month timepoint as compared with placebo. Graphs represent mean and 95% confidence interval

Formatted: Line spacing: Double

BIBLIOGRAPHY

1. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015.
2. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017;377:644-657.
3. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2018.
4. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019;381:1995-2008.
5. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 2020;Online ahead of print.
6. Petrie MC, Verma S, Docherty KF, et al. Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes. JAMA 2020;323:1353-68.
7. Flores E, Santos-Gallego CG, Diaz-Mejia N, Badimon JJ. Do the SGLT-2 Inhibitors Offer More than Hypoglycemic Activity? Cardiovasc Drugs Ther 2018;32:213-222.
8. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, et al. Empagliflozin Ameliorates Adverse Left Ventricular Remodeling in Nondiabetic Heart Failure by Enhancing Myocardial Energetics. J Am Coll Cardiol 2019;73:1931-1944.
9. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, et al. Empagliflozin Ameliorates Diastolic Dysfunction and Left Ventricular Fibrosis/Stiffness in Non-Diabetic Heart Failure: a Multimodality Study. JACC Cardiovasc Imaging 2020;in press.
10. Santos-Gallego CG, Garcia-Ropero A, Mancini D, et al. Rationale and Design of the EMPA-TROPISM Trial (ATRU-4): Are the "Cardiac Benefits" of Empagliflozin Independent of its Hypoglycemic Activity? Cardiovasc Drugs Ther 2019;33:87-95.
11. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44-51.
12. Migrino RQ, Young JB, Ellis SG, et al. End-systolic volume index is a strong predictor of early and late mortality. The GUSTO-I Angiographic Investigators. Circulation 1997;96:116-21.
13. Verma A, Meris A, Skali H, et al. Prognostic implications of left ventricular mass and geometry following myocardial infarction: the VALIANT (VALsartan In Acute myocardial iNfarcTion) Echocardiographic Study. JACC Cardiovasc Imaging 2008;1:582-91.
14. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. J Am Coll Cardiol 2010;56:392-406.
15. Guazzi E, Bandera F, Ozemek C, Systrom D, Arena R. Cardiopulmonary Exercise Testing: What Is its Value? J Am Coll Cardiol 2017;70:1618-36.
16. Santos-Gallego CG, Vahl TP, Goliasch G, et al. Sphingosine-1-Phosphate Receptor Agonist Fingolimod Increases Myocardial Salvage and Decreases Adverse Postinfarction Left Ventricular Remodeling in a Porcine Model of Ischemia/Reperfusion. Circulation 2016;133:954-66.

17. Mannaerts HF, van der Heide JA, Kamp O, Stoel MG, Twisk J, Visser CA. Early identification of left ventricular remodelling after myocardial infarction, assessed by transthoracic 3D echocardiography. Eur Heart J 2004;25:680-7.
18. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. J Am Coll Cardiol 2000;36:194-201.
19. Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary Exercise Testing in Heart Failure. JACC Heart Fail 2016;4:607-16.
20. Crapo RO, Casaburi R, Coates AL, Laboratories ACoPSfCPF. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-117.
21. Green CP, Porter CB, Bresnahan DR, Spertus J. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245-55.
22. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2000;2:271-8.
23. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation 2019:CIR0000000000000659.
24. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000;35:569-82.
25. Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. JACC Cardiovasc Imaging 2011;4:98-108.
26. Desai AS, Solomon SD, Shah AM, et al. Effect of Sacubitril-Valsartan vs Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. JAMA 2019:1-10.
27. Verma S, Mazer CD, Yan AT, et al. Effect of Empagliflozin on Left Ventricular Mass in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease: The EMPA-HEART CardioLink-6 Randomized Clinical Trial. Circulation 2019;140:1693-1702.
28. Nassif ME, Windsor SL, Tang F, et al. Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial. Circulation 2019;140:1463-76.
29. Singh JSS, Mordi IR, Vickneson K, et al. Dapagliflozin Versus Placebo on Left Ventricular Remodeling in Patients With Diabetes and Heart Failure: The REFORM Trial. Diabetes Care 2020;43:1356-1359.
30. Corrà U, Piepoli MF, Adamopoulos S, et al. Cardiopulmonary exercise testing in systolic heart failure in 2014: the evolving prognostic role: a position paper from the committee on exercise and training of the heart failure association of the ESC. Eur J Heart Fail 2014 16:929-41.
31. Del Buono MG, Arena R, Carbone S, et al. Exercise Intolerance in Patients With Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol 2019;73:2209-2225.
32. Pokharel Y, Khariton Y, Tang Y, et al. Association of Serial Kansas City Cardiomyopathy Questionnaire Assessments With Death and Hospitalization in Patients

With Heart Failure With Preserved and Reduced Ejection Fraction: A Secondary Analysis of 2 Randomized Clinical Trials. JAMA Cardiol 2017;2:1315-1321.
33. Luo N, O'Connor CM, Cooper LB, et al. Relationship between changing patient-reported outcomes and subsequent clinical events in patients with chronic heart failure. Eur J Heart Fail 2019;21:63-70.
34. Spertus J, Peterson E, Conard MW, et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J 2005;50:707/15.
35. Yurista SR, Sillje HHW, Oberdorf-Maass SU, et al. Sodium-glucose co-transporter 2 inhibition with empagliflozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction. Eur J Heart Fail 2019;21:862-873.
36. Nielsen R, Moller N, Gormsen LC, et al. Cardiovascular Effects of Treatment With the Ketone Body 3-Hydroxybutyrate in Chronic Heart Failure Patients. Circulation 2019;139:2129-2141.
37. Zelniker TA, Braunwald E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75:422-434.
38. Verma S, Lopaschuk G. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. JACC Basic Transl Sci 2020;5:632-44.
39. Inzucchi SE, Zinman B, Fitchett D, et al. How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial. Diabetes Care 2018;41:356-363.
40. Mullens W, Martens P, Forouzan O, et al. Effects of dapagliflozin on congestion assessed by remote pulmonary artery pressure monitoring. ESC Heart Fail 2020;26:2071-2073.
41. Chilton R, Tikkanen I, Cannon CP, et al. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. Diabetes Obes Metab 2015;17:1180-93.
42. Garcia-Ropero A, Santos-Gallego CG, Badimon J. The anti-inflammatory effects of SGLT inhibitors. Aging (Albany NY) 2019;11:5866-5867.
43. Uthman L, Baartscheer A, Bleijlevens B, et al. Class effects of SGLT2 inhibitors in mouse cardiomyocytes and hearts: inhibition of Na(+)/H(+) exchanger, lowering of cytosolic Na(+) and vasodilation. Diabetologia 2018;61:722-726.