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ORIGINAL ARTICLE

Rationale and Design of the EMPA-TROPISM Trial (ATRU-4): Are the "Cardiac Benefits" of Empagliflozin Independent of its Hypoglycemic Activity?

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Abstract

The SGLT2 inhibitor empagliflozin reduced cardiovascular mortality by 38% and heart failure (HF) hospitalizations by 35% in diabetic patients. We have recently demonstrated the efficacy of empagliflozin in ameliorating HF and improving cardiac function in a *non-diabetic* porcine model of HF mediated via a switch in myocardial metabolism that enhances cardiac energetics. Therefore, we hypothesized that the cardiac benefits of empagliflozin can also be extended to non-diabetic HF patients. The EMPA-TROPISM clinical trial is a randomized, double-blind, parallel group, placebo-controlled, trial comparing the efficacy of and safety of empagliflozin in non-diabetic HF patients. Eighty patients with stable HF for over 3 months, LVEF < 50%, and New York Heart Association functional class II to IV symptoms will be randomized to empagliflozin 10 mg for 6 months or placebo. All patients will undergo cardiac magnetic resonance (CMR), cardiopulmonary exercise test (CPET), 6-min walk test, and quality of life questionnaires. The primary outcome is the change in left ventricular end-diastolic volume measured by CMR. Secondary end-points include change in peak VO2 (CPET); change in LV mass, in LVEF, in myocardial mechanics (strains), in left atrium volumes, in RV function and volumes, in interstitial myocardial fibrosis, and in epicardial adipose tissue (CMR); change in the distance in the 6-min walk test; and changes in quality of life (Kansas Cardiomyopathy questionnaire [KCCQ-12] and the 36-Item Short Form Survey [SF-36]). Safety issues (e.g., hypoglycemia, urinary infections, ketoacidosis,…) will also be monitored. In summary, EMPA-TROPISM clinical trial will determine whether the SGLT2 inhibitor empagliflozin improves cardiac function and heart failure parameters in non-diabetic HF patients (EMPA-TROPISM [ATRU-4]: Are the "cardiac benefits" of Empagliflozin independent of its hypoglycemic activity; NCT 03485222).

Keywords Heart failure · Empagliflozin · SGLT2-inhibitors · Diabetes mellitus · Cardiac magnetic resonance · Cardiopulmonary exercise test · Cardiac remodeling

Introduction

Type 2 diabetes mellitus (T2DM) is a pathological condition characterized by elevated levels of glucose which is associated with high cardiovascular (CV) risk [1–3]. Along with pancreatic β cell dysfunction (that leads to a decrease in insulin secretion) and insulin resistance in skeletal muscle, there are also abnormalities that affect the gastrointestinal tract, pancreatic α cells, liver, adipose tissue, kidneys, and brain [4]. The most recent statistics indicate that there are 422 million diabetic adults worldwide with a projected prevalence of 642 million by 2040 [5]. T2DM patients have a two- to fourfold increased risk of cardiac death and, among those who died over 65 years of age, cardiac-related causes were found in up to 70% of cases [5]. This increasingly pandemic disease represents a high socioeconomic burden with an estimated cost of up to $245 billion in 2012 (i.e., 1 in 5 healthcare dollars) [2, 5]. Although lifestyle changes are key, most

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patients also require pharmacological strategies to control hyperglycemia and ameliorate CV outcomes.

T2DM patients have over twice the risk of incident heart failure (HF) than non-diabetics [6]. Overall, HF is estimated to affect more than 6.5 millions of people in the USA [5], with HF being the underlying cause of more than 1 million hospitalizations every year. These hospitalizations are associated with poor prognosis (50% rate of re-hospitalization within 6 months after discharge and around 33% rate of death within 12 months after discharge). In addition, the prevalence of patient with HF and reduced ejection fraction (HFrEF) is higher and has greater mortality rates than those with preserved ejection fraction (HFpEF) [7]. Therefore, HFrEF represent a therapeutic target to improve survival rates. Between 20 and 40% of all HF patients have T2DM and frequently both conditions cluster with the same CV risk factors such as obesity, hypertension, sleep apnea, dyslipidemia, anemia, chronic kidney disease, and coronary artery disease [6]. It is widely recognized that T2DM is associated with important changes in myocardial structure and function, including a disproportionate left ventricular hypertrophy and increased interstitial myocardial fibrosis [6].

Several drugs have been developed for effective glycemic control in T2DM [4]. Despite the efficacy of these drugs in reducing HbA1c levels, only few of them have showed to hold cardiac benefits. The guidelines recommend a combination of glucose-lowering drugs to achieve HbA1c targets. Selection of combination therapies represents a challenge for physicians, especially for T2DM with concomitant heart disease. Of notice, most of the commonly used antidiabetic drugs are contraindicated in HF patients. Therefore, there is an urgent need for an oral agent capable of improving not only glycemia control but also providing CV benefits. Table 1 shows all the available hypoglycemic interventions and their impact on CV outcomes. To date, clinical trials involving GLP-1 receptor antagonists (exenatide, liraglutide, and semaglutide) and SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) are the only ones that have confirmed cardiac benefits (for a more in-depth review, we refer the reader to other articles [4]). Of interest, the oral administration of SGLT2-i might offer compliance advantage as compared to the parenteral administration of GLP-1RA.

SGLT2 Inhibitors and Cardiovascular Outcomes

The association between poor glycemic control and CV events among T2DM patients is a well-established fact. Long-term glucose control reduces 25% of microvascular events in T2DM but does not affect macrovascular events (myocardial infarction (MI) and stroke). Surprisingly, the recent EMPA-REG OUTCOME trial has offered a major therapeutic breakthrough in the treatment of T2DM patients [8]. Patients with high CV risk (47% with MI history and 25% with stroke history) were randomized to empagliflozin or placebo in addition to standard medical care. The trial was prematurely terminated due to the magnitude of the cardiac benefits. Specifically, empagliflozin significantly reduced by 14% the primary composite end-point of CV mortality, nonfatal MI, and nonfatal stroke (HR 0.86; [0.74–0.99], $p = 0.04$ for superiority). The secondary end points were also significantly reduced in the empagliflozin group (38% relative risk reduction (RRR) for CV death, 32% RRR for death from any cause and 35% RRR for HF-related hospitalizations). The lack of reduction in CV events (MI and stroke) and the fast separation of the event curves within the first 2 months post-treatment initiation led our group to postulate a non-glucose-dependent mechanism responsible for these benefits.

Furthermore, empagliflozin is the first glucose-lowering agent significantly reducing HF hospitalization and slowing renal disease progression among diabetics. In a large randomized trial [9] including over 6000 patients, empagliflozin showed 39% RRR for incident/worsening nephropathy and 44% RRR for doubling serum creatinine level vs. placebo.

Canagliflozin, another SGLT2-i, significantly reduced by 14% the primary composite end-point of CV mortality, nonfatal MI, and nonfatal stroke in the CANVAS program [10]. Of interest, empagliflozin and canagliflozin were similar in preventing HF hospitalization (RRR of 33% with canagliflozin versus 35% with empagliflozin), but canagliflozin did not reduce the secondary end-point of CV mortality (HR 0.87 [0.74–1.01], $p = 0.06$) [10] unlike empagliflozin [8]. Similar to the EMPA-REG OUTCOME, canagliflozin did not affect the rate of MI or stroke.

The recent DECLARE-TIMI58 trial demonstrated that dapagliflozin reduced the co-primary end-point of CV death and HF hospitalization by 17%, which reflected a lower rate of hospitalization for heart failure (HR 0.73; [0.61–0.88]) [11]. This study confirms that the cardiac benefits are probably a class effect of the SGLT2-i pharmacological family.

Importantly, the CANVAS trial showed a significant increase in below-the-knee amputations (6.3 vs. 3.4 participants per 1000 patient-years) [10]. The mechanism behind the increased incidence of amputations has not been clarified yet. This adverse outcome has not been observed in trials involving empagliflozin, and that is why also our group has focused its interest in this drug. However, the recent OBSERVE-4D meta-analysis [12] has concluded that canagliflozin does not increase amputations and has a similar safety profile to others SGLT2-i [12].

Another significant characteristic of this class of drugs is its systemic mechanism of action, which offers a significant safe and well-tolerated profile. Selective inhibition of the SGLT2 receptor in the kidneys increases the urinary excretion of glucose and sodium, and subsequently water excretion following sodium ions. Additionally, they increase lipolysis and fatty acids oxidations, which yield to a weight loss (2–3 kg on

Table 1 Class, generic name, mechanism of action, and effect on CV outcomes of the most common hypogycemic drugs

Class	Generic names	Mechanism of action	CV Outcomes
Sulfonylureas	Gliclazide Glimepiride Glyburide	Stimulate pancreatic insulin secretion	Possible increase in CV death
Biguanides	Metformin Metformin-extended-release	Inhibits hepatic glucose production	Possible CV benefits supported by small trials and number of events
Thiazolidinediones	Pioglitazone Rosiglitazone	Increase insulin sensitivity and reduce hepatic glucose production	Pio—net CV benefits Rosi—increases risk of HF
DPP-4 inhibitors	Linagliptine Saxagliptine Sitagliptine Alogliptine	Intensify the effect of the intestinal incretins	Saxagliptin and alogliptin increase risk for HF Sitagliptine no CV effects
GLP-1 agonists	Exenatide Exenatide extended-release Liraglutide Dulaglutide	Mimics the effect of incretins	Reduces CV death
SGLT-2 receptor inhibitors	Dapagliflozin Empagliflozin Canagliflozin	Inhibit renal glucose reabsorption favoring renal excretion	Decrease CV death and HF hospitalizations

average) [4, 13]. Furthermore, patients treated with SGLT2-i showed a small but consistent drop in systolic blood pressure (3–4 mmHg on average), which is likely related to a direct natriuretic effect. Besides, SGLT2-i have demonstrated to slow progression of microvascular changes affecting T2DM patients and to improve arterial stiffness [13]. Empagliflozin systemic effects are summarized in Fig. 1.

Despite the remarkable cardiac benefits of SGLT2 inhibitors, their underlying mechanism of action remains unclear. Improved glycemic control also seems unlikely given that differences in glycemic control were (by design) minimal, it would also have reduced MI/strokes, the benefits would have taken years, and tight glycemic control has previously failed to reduce either mortality or HF [4]. Empagliflozin hypotensive effect seems unlikely because blood pressure-lowering would also reduce strokes (which remained similar in both groups) and requires years for the curves to separate (while the event curves in EMPA-REG actually separate in 2 months). Empagliflozin diuretic effect also seems unlikely because greater decreases in intravascular volume and net sodium balance are obtained by loop diuretics or thiazides, but these diuretic drugs do not reduce CV death and their effects of HF hospitalizations are much more modest [13]. The NHE inhibition provided by SGLT2-i [14, 15] is an attractive theory as it would reduce cytoplasmic concentrations of sodium and calcium in the cardiomyocyte [14, 15]; however, the NHE1 inhibitor cariporide previously failed to show benefits in human patients [16] so there are probably additional

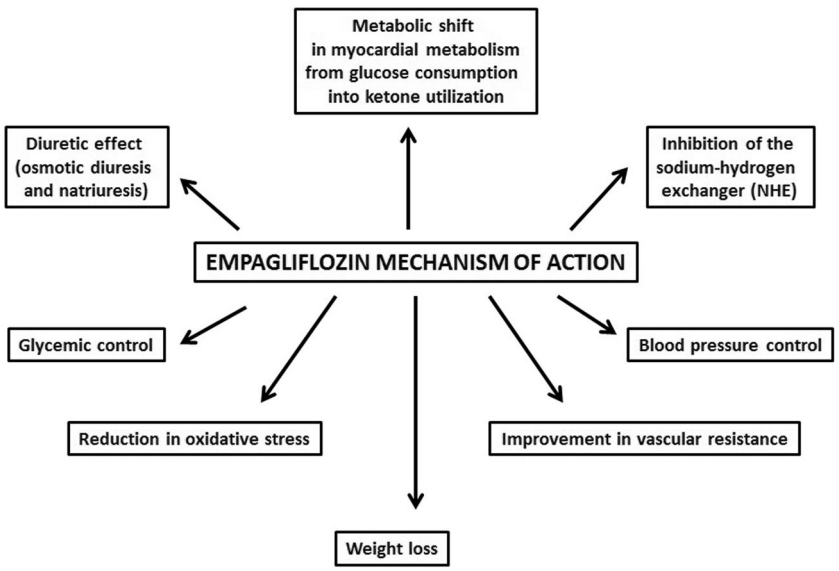

Fig. 1 Empagliflozin systemic effects

mechanisms. We believe that the moderate nature of these effects is not enough to explain neither the magnitude nor the speed of the achieved cardiac benefits.

Therefore, all these findings led to our group to postulate a glucose-independent mechanism of action responsible for the cardiac benefits seen in the mentioned trials. We have approached this hypothesis using a non-diabetic experimental model of ischemia/reperfusion function [17]. This study showed that administration of empagliflozin to non-diabetic pigs with HF during 2 months was associated with significant amelioration of the adverse ventricular remodeling [18], with a reduction in LV volumes and LV mass and an improvement in LV systolic function (both LVEF and strains) [18]. The recent EMPA-HEART study also demonstrated that empagliflozin reduced LV mass, with this effect being more prominent in patients with the highest degree of LV hypertrophy [19]; this study confirms our CMR results [18] and support a mitigation in LV remodeling with empagliflozin. We also demonstrated a switch in myocardial metabolism with fuel utilization moving away from glucose into enhanced consumption of free fatty acid, ketones, and branched-chain aminoacids [18]. Given the normoglycemic nature of our model, our results strongly support the hypothesis of a non-glucose-dependent mechanism responsible for the reduction in CV events in the trials.

Therefore, in order to investigate whether empagliflozin will also ameliorate HF not only in diabetics but also in non-diabetic patients as our preclinical data suggest [18], we have designed the ongoing EMPA-TROPISM clinical trial (NCT03485222). This trial will randomize non-diabetic HFREF patients to receive empagliflozin or placebo on top of optimal medical treatment for HF.

Methods

Overall Study Design

To demonstrate our original hypothesis that the benefits of SGLT2-i observed in T2DM patients will be also attained in non-diabetic patients, as suggested by our preclinical study, we have designed the EMPA-Tropism trial. Trial (ClinicalTrials.gov Unique identifier: NCT03485222). This prospective, randomized, double blinded, placebo-controlled study will randomize non-diabetic patients ($n = 100$) with HFrEF (below 50%) to either empagliflozin or placebo along with their optimal medical treatment for HF. Randomization will be carried out by block randomization in groups of four. The major end points of the study are changes in LV end-diastolic volume (LVEDV) between pre- and post-treatment. We will also evaluate secondary end points including changes in LV mass, LV end-systolic volume (LVESV), and in LV ejection fraction (LVEF) in addition to clinical outcomes such as changes in cardiopulmonary exercise test (CPET), 6-min walk, and quality of life questionnaires. The trial will be conducted at the AtheroThrombosis Research Unit (ATRU), Cardiovascular Institute, Mount Sinai Hospital, New York City, where we have assembled a multidisciplinary team of researchers with expertise in cardiovascular diseases, endocrinology, and cardiac magnetic resonance (CMR). The protocol has been approved by the Mount Sinai Institutional Review Board and received an IND exemption by the FDA. Both treatment and placebo are manufactured and supplied by Boehringer-Ingelheim. The allocated treatment should be taken once a day in addition to their prescribed medication (Fig. 2).

Recruitment

We will use a two-pronged recruitment process. Firstly, candidates will be identified from the Consortium database that includes Mount Sinai Medical Center, Mount Sinai West, Mount Sinai St Luke's, Elmhurst Hospital, and the Bronx VA Medical Center. Database network contains over 10,000 HF patients (including both HFrEF and HFpEF) and considering a high percentage of them with concomitant T2DM, there is still a remaining pool of candidates assuring the feasibility of the trial. We will also consider additional patient recruitment from several CV clinics and medical centers as well as from HF-experienced physicians and from cardiac rehabilitation programs of Mount Sinai Health Network.

The study has received an IND exemption from the FDA and all the procedures are approved by the Institutional Review Board (IRB) of the Icahn School of Medicine at Mount Sinai.

Participant Inclusion and Exclusion Criteria

Participants should meet all the following inclusion criteria and none of the exclusion criteria:

Inclusion Criteria

- Ambulatory patients age > 18 years
- Diagnosis of heart failure (NYHA II to IV)
- LVEF < 50% on echocardiography or CMR within the prior 6 months
- Have stable symptoms and therapy for HF within the last 3 months

Exclusion Criteria

- Diabetes by medical history or any of the established criteria of the American Diabetes Association. Diabetes in remission is also considered as exclusion criteria. Prediabetes (HbA1c 5.7–6.5%) is not an exclusion criteria

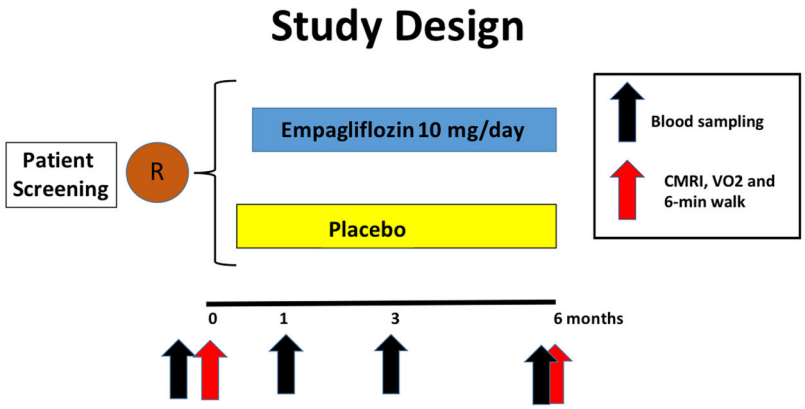

Fig. 2 Design of the study

- Acute coronary syndrome (ACS) or cardiac surgery within the last 3 months.
- Pregnant or lactating women
- Cancer or any other life-threatening condition
- Pancreatitis
- Glomerular filtration rate (GFR) < 30 ml/Kg/min
- Use of continuous parental inotropic agents
- Systolic BP < 90 mmHg
- Psychiatric disease incompatible with being in study
- Any contraindication to CMR procedures
- Any other medical or physical condition considered unappropriated by a study physician

Primary End Point

The primary end point is to determine whether empagliflozin mitigates adverse cardiac remodeling assessed by changes in LVEDV in non-diabetic patients with HFrEF when compared to placebo. LV volumes have shown to be the strongest predictor of adverse CV outcomes even after adjusting for LVEF and MI size [20–22].

Secondary End Points

- To determine changes in LV mass and remodeling index (LV mass/LVEDV) with empagliflozin compared with placebo
- To determine changes in LVESV with empagliflozin compared with placebo
- To determine changes in left atrial volume (an accurate indicator of chronic high LV filling pressures) with empagliflozin compared with placebo
- To determine changes in right ventricular (RV) EDV, RVESV, and RVEF with empagliflozin compared with placebo
- To determine changes in cardiac interstitial fibrosis as assessed by T1 mapping with empagliflozin compared with placebo
- To determine changes in LVEF with empagliflozin compared with placebo
- To determine changes in myocardial strain assessed by CMR tissue tracking with empagliflozin compared with placebo. This parameter has been correlated with CV outcomes in patients with HF, especially global longitudinal strain might have greater prognosis value than LVEF in certain patients such as those with acute HF [23]
- To determine changes in exercise capacity assessed by a cardiopulmonary exercise test (CPET) and oxygen consumption (VO2) with empagliflozin compared with placebo
- To determine changes in visceral and pericardial fat as measured by CMR with empagliflozin compared with placebo
- To determine changes in body composition analysis (BCA) anthropomorphic measurements with empagliflozin compared with placebo
- To determine if there is a change in exercise tolerance by the 6-min walk test (6-MWT) with empagliflozin compared with placebo
- To determine changes in the patient-reported quality of life. Two questionnaires will be used. The Kansas Cardiomyopathy questionnaire (KCCQ-12), which contains 12 questions, scoring patients from 12 (poor quality of life) to 70 (good quality of life). And, the 36-item Short Form Survey (SF-36), in which high score also defines a more favorable health state

Study Flow and Patients Visits

The study involves a total of five visits at Mount Sinai Medical Center in New York City over a period of 6 months.

Upon fulfilling all the inclusion criteria and signing up the informed consent form, patients will undergo a screening visit (visit 1) to assure their eligibility. Thereafter, at visit 2 (baseline/randomization), patients will undergo cardiac magnetic resonance (CMR), cardiopulmonary exercise test (CPET), and 6-min walk test (6MWT); will fill out the QoL questionnaires; and will immediately be randomized to one of the treatment groups. These same procedures will be repeated at visit 5 that will take place 6 months post-randomization. Patients will also be asked to fill out the quality of life questionnaires in both visits 1 and 5.

The intermediate visits (visits 3 and 4) will involve drug dispensation, blood collection for biomarkers as well as safety and tolerability. Participants will be asked about any adverse events and compliance and pill-counting will be documented at each visit. Medications will be dispensed in a double-blind manner at randomization and each one of the subsequent visits. Given the pharmacokinetics of empagliflozin [24], to ensure a dose interval of about 24 h, the medication should be taken at the same time every day. Patients will be monitored for signs of side effects of SGLT2-i such as hypoglycemia, urinary tract infections, bone fractures, and diabetic ketoacidosis [24]. We will also assess clinical outcomes such as HF hospitalization. The effects of the treatment will be assessed by comparing changes in the parameters between the baseline (pre-treatment) visit and 6 months post-treatment initiation (Fig. 3).

Sample Size and Power Calculations

The calculated sample size is 72 HF patients without diabetes (36 patients in each arm); but we are planning to enroll 80 patients to ensure enough participants in the trial and to accomplish the required 36 patients per group at the end of the study.

It is generally accepted that a 10-mL change in LVEDV is clinically significant. An internal CMRI study at our hospital gave a variation of 12 mL for the mean difference of LVEDV. The high reproducibility and sensitivity of CMR as compared with 3D-echo significantly reduces the number of required patients to achieve statistical significance. Thus, in order to detect a difference of 10 mL in LVEDV between the arms, we will require 36 subjects/arm for a total of 72 patients to be able to reject the null hypothesis with a probability (power) of 0.9. The type I error probability associated with this test of this null hypothesis is 0.05. We will enroll additional patients to account for patient loss during follow-up or incomplete examinations.

All data will be presented as mean ± SD. For statistical comparison, data will be initially tested for normality by the Kolmogorov-Smirnov's test. In case the data follow a normal distribution, groups will be compared using the Student's *t* test. If the data do not follow a normal distribution, data will be presented as median ± interquartilic range. Group medians will be compared with the nonparametric Mann-Whitney's *U* (as two groups will be compared); when variances look different (ratio > 2), the Welch *t* test will be used instead. Two-way repeated-measures ANOVA will be used to compare values between two groups at different time-points. All statistical calculations will be performed with SPSS 18.0. Differences were considered statistically significant at values of $P < 0.05$.

Procedures Involved in the Study

Cardiac Magnetic Resonance Imaging (CMR) All the CMR studies will be performed at the Cardiac Imaging Facilities of the Mount Sinai Heart. Images will be acquired with a 3.0-T magnet. Steady-state free precession short axis images (TR 3.6 ms, TE 1.6 ms, flip angle 45, field of view 250 × 250 mm, SENSE factor 3, voxel size 1 × 1 × 5 mm, no gap, number of averages 3, bandwidth 1286 Hz, 12 lines per segment) from the LV apex through the cardiac base (also covering the left atrium) will be used for the quantification of LV volumes, LVEF, LV mass, and left atrium volume, as previously reported [17]. Late gadolinium enhancement (LGE) will be performed 15 min after the administration of gadolinium using an inversion-recovery fast gradient echo sequence (TR 9 ms, TE 5.4 ms, TI optimized to null normal myocardium, gating factor 3, field of view 250 × 250 mm, pixel size 1 × 1 × 5 mm, SENSE factor 3, number of averages 3, bandwidth 232 Hz, TFE factor 16). Look-Locker and MOLLI sequences will be performed before and 10 min after gadolinium administration to evaluate interstitial myocardial fibrosis using the T1 mapping technique. All CMR images will be blindly analyzed using commercially available software (cvi42, Circle Cardiovascular Imaging). Epicardial and endocardial contours will be traced in each SSFP cine image to obtain LVEDV, LVESV, LVEF, and LV mass; by convention, papillary muscles will be included in the LV cavity. LV scar size will be measured by LGE and expressed as a percentage of the LV mass; the absolute LGE size also will be quantified in grams (calculated as volume multiplied by myocardial density [1.05 g/cm3]). LGE will be defined as myocardium with signal intensity was higher than 3 standard deviations of that in remote, normal.

Cardiopulmonary Exercise Test (CPET) CPET will be done prior to randomization and at 6-months on therapy. Patients will report in the fasting state to the Mount Sinai Research Cardiopulmonary Exercise laboratory. Patients will perform a CPET using cycle ergometry with continuous EKG monitoring. Blood pressure will be measured prior to exercise, at the end of each exercise stage, and at peak exercise. Patients will be connected using a mouthpiece to a metabolic cart (Medical Graphics Ultima Cardio 2, St Paul, MN) for continuous breath-by-breath measurement of respiratory oxygen

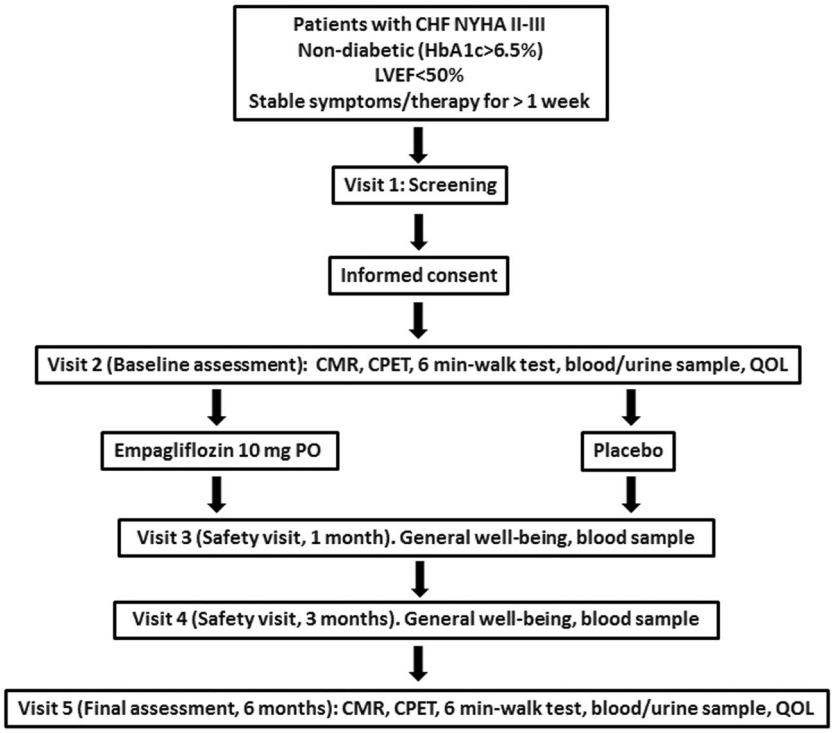

Fig. 3 The flow of the study and patient visits

uptake (VO_2), carbon dioxide production (VCO_2), and minute ventilation. Symptom-limited exercise will be performed. Perceived levels of dyspnea and fatigue will be measured using the Borg scale. Peak VO2, VE/VCO2 ratio, respiratory exchange ratio, and the aerobic threshold will be measured and recorded [25].

6-Min Walk Test (6-MWT) Patients will perform a 6-min walk test prior to and 6 months post-randomization. In a quiet 100-ft. hall, the patients will be instructed to walk as fast and perform as many laps as possible between the distance markers over a period of 6 min. The walk test will be supervised but unencouraged. Blood pressure and heart rate are measured at the start and end of the 6 min. Patients will be allowed to stop and rest if needed. The total distance walk will be recorded.

Discussion

HF and CVD are pathologies frequently associated with T2DM. Most of the commonly used antidiabetic drugs, despite successfully controlling glucose levels, are not very effective in reducing CV risk and outcomes. Indeed, some of them should be considered detrimental in cardiac patients, which makes difficult the management of this population. Recent SGLT2-i trials have significantly improved cardiac outcomes in T2DM patients [8, 10, 11] and seem to show a class effect. The magnitude of these results are changing the way of thinking about glucose-lowering and diabetes management; thus, SGLT2-i inhibitors are becoming a major therapeutic breakthrough in the treatment of T2DM patient at high CV risk.

The major strength and clinical interest of the trial is that, if our hypothesis is confirmed, SGLT2 inhibitors could be used for treating HF patients regardless whether they are diabetic or not. Another advantage is we have selected clinically relevant end-points. The effect of a drug on cardiac remodeling is the best surrogate marker of its efficacy on hard end-points (death/hospitalization). In fact, a consensus paper recommends to new drug treatments for HF to be assessed by their effect on cardiac remodeling [26]; moreover, a recent meta-analysis about HF drugs focusing on 30 mortality trials and 88 remodeling trials showed an excellent correlation between effects on LV remodeling and mortality benefits [22]. This led to the selection of our clinically relevant end-points: LV volumes are the best predictor of outcome in HF even after adjusting for LVEF [20–22]; LV mass is furthermore associated with impaired CV outcomes [27]; myocardial mechanics (especially longitudinal strain) offer superior prognostic information compared LVEF [23], interstitial fibrosis as per T1 mapping also predicts long-term mortality [28], and peak VO2 is the best predictor of survival in advanced HF patients [25]. To improve the safety of the trial, we have also selected empagliflozin instead of canagliflozin due to the lower risk of amputation.

The reduced number of patients and the single site fashion of the trials may represent some limitations; however, the use

of CMR allows the power of the trial to be preserved despite the small sample size. Moreover, one of the goals of the trial is also to contribute to clarify the underlying mechanism of action of SGLT2-i (if it is indeed independent of its glucose-lowering activity) as well as the possibility of correlating the CMR observations with the changes in systemic biomarkers, functional capacity, and quality of life.

Special attention will be provided to the safety evaluation of empagliflozin in non-diabetic patients. We will obviously assess for urinary infections, the most frequent side effect of SGLT2-i [24]. To rule out ketoacidosis, we will measure urinary ketones, plasma pH, and plasma β-hydroxybutyrate levels. However, a recent analysis of 56,325 Korean patients initiated on SGLT2-I that were propensity matched with same number of patients who were started on DPP4-i showed that the risk of hospitalization for DKA was not increased in SGLT2 inhibitor users vs. DPP-4 inhibitor users [29]. We will also actively check for hypoglycemia; however, the risk of hypoglycemia appears low a priori because of two reasons. First, the glucose-lowering effect of SGLT2-I is directly proportional to glycemia; hence, the hypoglycemic risk is very low in normoglycemic patients; in fact, empagliflozin did not significantly reduce glycemias in non-diabetic patients in a previous study [30]. Second, hypoglycemia risk increases if the patients is taking other antidiabetic medications [27], but our patients, being non-diabetic, do not take any other concomitant glucose-lowering medication.

The EMPA-TROPISM trial will provide valuable information on whether the cardiac benefits seen with empagliflozin in T2DM can be extended to non-diabetic HF patients. The large ongoing EMPEROR program will provide data on the benefits of empagliflozin on cardiovascular morbidity and mortality among patients with HFrEF (EMPEROR-Reduced; NCT03057977) and HFpEF (EMPEROR-Preserved; NCT03057951). These trials may ultimately help guide clinical decision-making on the treatment of HF patients with and without T2DM.

Conclusion

The EMPA-TROPISM randomized clinical trial will specifically investigate whether empagliflozin ameliorates HF in non-diabetic patients. We consider empagliflozin as a "cardiac" drug and not merely an antidiabetic agent; thus, we intend to evaluate the safety and efficacy of empagliflozin in HF patients independently of the diabetic status. Together with the event-driven EMPEROR program, the imaging-based EMPA-TROPISM clinical trial will deliver conclusive insights regarding the value of empagliflozin treatment for patients with HF with and without T2DM.

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Compliance with Ethical Standards

Conflicts of Interest Dr. Juan J. Badimon has received an Investigator-Initiated Award from Boehringer-Ingelheim to fund this trial. Dr. Carlos G. Santos-Gallego declares that he has no conflict of interest. Dr. Alvaro Garcia-Ropero declares that he has no conflict of interest. Dr. Donna Mancini has nothing to declare. Dr. Sean P. Pinney declares that he has no conflict of interest. Dr. Johanna P. Contreras declares that she has no conflict of interest. Dr. Icilma Fergus declares that she has no conflict of interest. Dr. Vivian Abascal declares that she has no conflict of interest. Dr. Pedro Moreno declares that he has no conflict of interest. Dr. Farah Atallah-Lajam declares that he has no conflict of interest. Dr. Ronald Tamler declares that he has no conflict of interest. Dr. Anu Lala declares that he has no conflict of interest. Dr. Javier Sanz declares that he has no conflict of interest. Dr. Valentin Fuster declares that he has no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent will be obtained from all individual participants included in the study.

Disclosures This study has been funded by an Investigator-Initiated Grant (1245–0179) provided to Dr. Badimon by Boehringer-Ingelheim.

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