Impact of empagliflozin on left ventricular functions: a single center, phase III, randomized, open-label, active treatment controlled, parallel study in patients with type 2 diabetes and normal left ventricular function" EMPA-HEART Study

Study Number: 1245-128; EUDRACT Code: 2016-0022250-10

FINAL REPORT

Preliminary comments

a) The planned sample size of 30+30 was not achieved due to a higher-than-expected rate of subjects falling into the exclusion criteria (which were particularly stringent) as shown in Suppl. Fig 1 and for the consequence of COVID19 pandemia. We completed 22+22 subjects.

b) In this report we do not report data on body water (D2 H_2O), endothelial function (EndoPAT2000) and on arterial stiffness (CAVI) because the reduction of the sample size caused by COVID19 pandemia, coupled with the limited accuracy of these methods makes the indices unreliable. Nevertheless, if anyone is interested, we will be happy to share the results.

c) 3D echography data acquisition was dropped early in the study due to doubts on their reproducibility; the setting of the cardiopulmonary test (semi recumbent) unfortunately prevents the correct acquisition of the images.

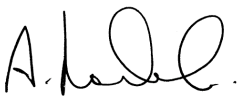
d) We are convinced that, despite the reduced sample size, the acquired data describe a clear and interesting picture: empagliflozin has no direct effect on the myocardium in subjects with perfectly normal contractility, but in those with a subclinical dysfunction the drug has a positive effect, whose size appears clinically relevant. The strength of the observation relies on the particular characteristic of the population (without any heart disease), in whom the diuretic effect and/or on volume regulation of empagliflozin is not expected to play a role, therefore the effect is direct.

e) The report has been prepared in the form of a scientific article, we also include the article published in Cardiovascular Diabetology 2017 in which the study rationale and design was presented and another article in which we evaluated the characteristics of effort intolerance in T2D.

Please find attached at the end of the scientific report two additional documents
a) the communication to AIFA of the end of the study (Synopsis Annex 1)
b) the Safety report (in Italian) and the ADDENDUM Safety report (in english).

Regards

Andrea Natali



Effect of empagliflozin on left ventricular contractility and peak oxygen uptake in subjects with type 2 diabetes without heart disease: results of the EMPA-HEART trial

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ABSTRACT

Background. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are effective in primary prevention of hospitalization for heart failure with uncertain mechanisms.

Methods. The EMPA-HEART trial is a phase III, active-controlled, parallel groups, exploratory study aimed at demonstrating whether the SGLT2i empagliflozin is associated with improved myocardial contractility (left ventricle global longitudinal strain, LV-GLS) and/or cardiopulmonary fitness (VO_{2peak}) in patients with type 2 diabetes (T2D), normal renal and LV systolic functions (2D-Echo EF>50%), and no ischemic or valvular heart disease. Patients were randomized to either empagliflozin 10 mg/die or sitagliptin 100 mg/die for 6 months.

Results. Forty-four patients completed the study, 22 per arm. While glycaemic control similarly improved in both groups, a relative reduction in body weight (-1.6; [-2.7/-0.5] kg, p=0.03) and plasma uric acid (-1.5; [-2.3/-0.6], p=0.002), as well as an increase in haemoglobin (+0.7; [+0.2/+1.1] g/dL, p=0.0003) were evident with empagliflozin. No difference between the treatments was detectable in either LV-GLS after 1 month (empa *vs* sita: +0.44; [-0.10/+0.98] %, p=0.11) and 6 months of therapy (+0.53; [-0.56/+1.62] %), or in VO_{2peak} (+0.43; [-1.4/+2.3] ml/min/kg, p=0.65). With empagliflozin, the subgroup with baseline LV-GLS below the median experienced a significantly greater increase (time*drug p<0.05) in LV-GLS at 1 month (+1.22; [+0.31/+2.13] %) and at 6 months (+2.05; [+1.14/+2.96] %), while sitagliptin only induced a modest improvement in LV-GLS at 6 months (+0.92; [+0.21/+0.62] %).

Conclusions. Empagliflozin has neutral impact on both LV-GLS and exercise tolerance in subjects with T2D and normal LV function. However, in patients with reduced baseline LV-GLS it produces a rapid and persistent amelioration of LV contractility.

Trial registration: EUDRACT Code 2016-0022250-10.

Keywords: empagliflozin, SGLT2, type 2 diabetes, GLS, speckle-tracking, cardiovascular, heart failure, subclinical left ventricular dysfunction

List of abbreviations

AT	anaerobic threshold
BMI	Body Mass Index;
BNP	Brain-derived Natriuretic Peptide;
BP	blood pressure
CO	cardiac output
eGFR	expected Glomerular Filtration Rate;
HbA_{1c}	glycated hemoglobin
HF	Heart Failure;
HFpEF	heart failure with preserved left ventricular ejection fraction
HFrEF	heart failure with reduced left ventricular ejection fraction
HR	heart rate
hsCRP	high-sensitive C-Reactive Protein;
hsTnT	high-sensitivity troponin T
iCPET	imaging cardiopulmonary exercise test
LA	left atrium
LV	Left Ventricle;
LV-GLS	Left Ventricle Global Longitudinal Strain;
LVEF	left ventricular ejection fraction
LVMi	left ventricular mass index
MAP	mean arterial pressure
MPO	myeloperoxidase;
NT-PRO3	N-terminal procollagen 3
NT-proBNP	N-Terminal-proBNP
proADM	pro-adrenomedullin
RER	respiratory exchange ratio
SGLT2i	Sodium-Glucose co Transporter 2 inhibitors;
sPAP	systolic pulmonary artery pressure
SV	stroke volume
SVR	systemic vascular resistance
T2D	Type 2 Diabetes;
TAPSE	tricuspid anulus plane systolic excursion
TNF-α	Tumor Necrosis Factor-alpha;
VCO_2	Cabon dioxide production
VD/VT	dead volume/tidal volume radio
VE	minute ventilation
VE/VCO_2	ventilatory efficiency
VO_2	oxygen uptake
VO_{2peak}	oxygen uptake at peak exercise
$\Delta(a\text{-}v)O_2$	artero-venous difference (peripheral extraction)

1. Introduction

In subjects with type 2 diabetes mellitus (T2D) at high cardiovascular risk, the Sodium-glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin reduces hospitalization for heart failure (HF) by 35% very early (~6 months) after treatment initiation and independently from the presence of established HF at baseline (1). Notably, the drug is effective in preventing HF decompensation in subjects with HF with both reduced (HFrEF) (2) and preserved (HFpEF) left ventricular (LV) ejection fraction (3), irrespective of the presence of T2D, while the effect is less pronounced in T2D patients without overt HF. Nonetheless, despite the recognised impressive prognostic benefits, the mechanistic bases of the slowed clinical progression to overt HF remain ill defined, particularly in those with no clinical or echocardiographic evidence of heart disease.

Across the whole spectrum of HF, SGLT2i have shown positive outcomes on LV systo-diastolic functions and aerobic fitness beyond the amelioration of glycaemic control and the potential benefit on other cardiovascular risk factors, while in T2D without HF data are less straightforward (4). In this latter group, the effect on body fluid volume regulation - considered as a pillar of SGLT2i mechanism of action (5) - is unlikely to play a relevant role. Experimental studies suggested alternative mechanisms of action, such as an improved muscle oxygen/work coupling driven by a larger availability of oxygen (through increased plasma haemoglobin), the use of more efficient metabolic substrates (ketone bodies (6)), and/or a direct effect on myocardial contractility through the inhibition of the Na/H exchanger (7). The difficulty in accruing clinical evidence in support for these hypotheses is possibly due to inadequate experimental methods to concurrently measure each aspect with the necessary precision. In this setting, imaging cardiopulmonary exercise test (iCPET) might have a role since it is a powerful multiparametric technique capable of providing simultaneous measures of metabolic, pulmonary, cardiac, muscular, and vascular variables both at rest and during graded exercise (8).

It is possible to hypothesize that SGLT2i exert their positive effects on primary HF prevention particularly in early and mild forms of myocardial dysfunction, which remain clinically elusive. Indeed, a high prevalence of asymptomatic LV dysfunction has been demonstrated in subjects with T2D, particularly when more sensible techniques are employed, specifically LV global longitudinal strain (LV-GLS) by speckle-tracking echocardiography or mid-wall fractional shortening, with estimates ranging from 50 to 70% (9, 10)(11-13). As a matter of fact, among these nominally asymptomatic subjects, a large proportion (30-45%) shows reduced cardiopulmonary fitness (14) with complex and uncertain pathobiology (15) that is associated with an increased risk of developing symptomatic HF (16).

By using iCPET, this study aimed at verifying whether the treatment with empagliflozin is associated with an improvement in LV contractility (as measured by resting and exercise LV-GLS) and/or in cardiopulmonary fitness (oxygen uptake at peak exercise, VO_{2peak}) in asymptomatic T2D patients without clinical symptoms of heart disease and with normal LV function at echocardiogram. To account for the potential positive effects of improved glycaemic control, we used sitagliptin as an active control, an equally effective glucose lowering agent that has been shown to be neutral on the prevention of HF-related events (17). As pre-specified exploratory analysis, we also verified whether the effect of empagliflozin is more evident in subjects with subtle contractility impairment (reduced LV-GLS) and whether this associates with changes in plasma biomarkers of inflammation, oxidative stress, matrix remodelling, and myocyte strain and injury.

2. Methods

2.1. Rationale, study design, study population, randomization, and study endpoints

The EMPA-HEART trial is a phase III, open label, active-controlled, parallel groups, single centre, exploratory study conducted in Pisa, Italy. This is a proof-of-concept study aiming at

evaluating whether the chronic treatment with the SGLT2i empagliflozin influences myocardial function above and beyond its effect on glycaemic control. The rationale, study design, and the methods of the study have been previously described in detail (18). Briefly, outpatients with T2D of either sex, age 40-80 years, on stable metformin and/or basal insulin without suboptimal glycaemic control (HbA_{1c} 7.0-8.5%) were randomized to either Sitagliptin 100 mg or Empagliflozin 10 mg. Exclusion criteria were a) impaired kidney function (CK-EPI eGFR <45 ml/min/1.76m^2), b) any heart disease defined as presence of clinically relevant cardiovascular symptom, cardiac or vascular disease or valvular defects, history of coronary artery disease or evidence of stress ischemia, reduced (defined as ≤50%) 2D LV ejection fraction (LVEF), cardiac autonomic neuropathy (by Neurotester, Meteda, Rome, Italy), c) any pulmonary, muscular, joint or orthopaedic diseases potentially limiting exercise capacity.

The main objective of the study is to verify whether, in our population of T2D patients with suboptimal glycemic control and without evidence of cardiac disease, the chronic (6 months) treatment with empagliflozin is associated with an improvement in myocardial contractility, as measured by LV-GLS through speckle tracking technology, in comparison to sitagliptin, an equally effective plasma glucose lowering agent presumably neutral on cardiac function. The secondary objective is the comparison of the effects of the 2 treatments on VO_{2peak}. As pre-specified exploratory analysis, we evaluated whether the effect of the treatments on myocardial contractility differs in the subgroup of patients with more pronounced abnormalities at baseline (LV-GLS below the median) and whether there are treatment-related differences in plasma biomarkers. Mechanism-oriented plasma biomarkers were: a) markers of inflammation: tumor necrosis factor-alpha (TNFa) and high-sensitive c-reactive protein (hsCRP); b) oxidative stress: myeloperoxidase (MPO); c) LV parietal stress: natriuretic peptides (BNP and NT-proBNP), pro-adrenomedullin (proADM); d) cardiomyocyte damage: high-sensitive troponin T (hsTnT); e) extracellular matrix remodeling/fibrosis: procollagen (NT-PRO3).

2.2. Cardiopulmonary exercise test protocol

A symptom-limited graded ramp bicycle exercise test was performed in the semi-supine position on a tilting, dedicated, microprocessor-controlled stress echocardiography cycle ergometer (Ergoline ergoselect 2000 GmbH, Germany). A 12-lead electrocardiogram and non-invasive arterial saturation and blood pressure (BP) were monitored continuously. Heart rate (HR) and brachial BP were measured at rest and every minute during exercise using a validated automatic device (Omron M6 Comfort, Kyoto, Japan). The expected VO_{2peak}, estimated on the bases of patient age, height, weight and clinical history (19), was used to adjust the ramp increments (Watt) in order to allow all the patients reaching VO_{2peak} in 8 to 12 min. The protocol included two minutes of unloaded pedalling and four minutes of recovery after peak effort. We excluded from the analysis patients who did not reach a respiratory exchange ratio (RER) >1.0 during the exercise test. Breath-by-breath minute ventilation, carbon dioxide production (VCO_2), and oxygen consumption (VO_2) were measured using a dedicated cardiopulmonary test diagnostic device (Blue Cherry, Geratherm Respiratory GmbH, Germany). We defined VO_{2peak} as the highest median value of the two 30-sec intervals of the last minute of exercise, as previously validated (20-24). The peripheral extraction, that is artero-venous oxygen difference ($\Delta(a\text{-}v)O_2$) was estimated indirectly with a validated and previously used approach by different groups using both our combined iCPET approach (25) and in a different setting with CPET and right heart catheterization (26). Oxygen pulse was calculated as VO_{2peak}/HR and expressed both as absolute values (mL/beat per minute) and in percentage of VO_{2peak}. An automatic procedure was used to detect the anaerobic threshold (AT) based on the V-slope, ventilatory equivalents and end-tidal partial pressure methods; AT was verified visually and, if necessary, recalculated (19). The chronotropic response was calculated as the change in HR from rest to peak exercise, divided by the difference between the age-predicted maximal HR and the resting HR (*i.e.* HR reserve). Chronotropic incompetence was defined as the failure to achieve ≥80% of the HR reserve during exercise (27). In

patients on β-blockers or calcium-channel blockers, chronotropic incompetence was defined as the failure to achieve 62% of HR reserve (27).

2.3. Resting and exercise echocardiography

All patients underwent a comprehensive transthoracic echocardiography examination at rest (GE healthcare vivid e95, Milwaukee, WI, USA) according to the International Recommendations (28). Data collected at each stage, that is at baseline, after 4 minutes, at the AT, and at peak effort, included: left ventricle (LV) and atrial (LA) volumes, stroke volume (SV), peak E-wave and A-wave velocities, tissue Doppler imaging (TDI)-derived S' and e' at the septal and lateral mitral annulus, tricuspid regurgitation velocity and systolic pulmonary artery pressure (sPAP), tricuspid annular plane systolic excursion (TAPSE); LV volumes and LVEF were calculated from the apical two- and four-chamber views using the modified Simpson's rule. LV mass index (LVMi) was calculated according to current guidelines with 2D measures of LV indexed to body surface area. SV was calculated by multiplying the LV outflow tract area at rest by the LV outflow tract velocity-time integral measured by pulsed-wave Doppler during each activity level, as previously validated (14). Cardiac output (CO) was calculated as the multiplication of SV and HR. Systemic vascular resistance (SVR) was calculated as the ratio of the peak mitral regurgitant velocity [m/s] to LV outflow tract time-velocity integral (TVI(LVOT)) [cm]. All measurements were reported as the average of three beats.

We measured global longitudinal strain (GLS) from the apical long-axis view and two- and four-chamber views, ensuring a frame rate >50 Hz (GE healthcare EchoPAC BT 12). We reported the average values from the three apical views at rest and low-load effort, within the first 4 minutes of exercise, GLS was expressed in absolute values, rather negative values as it is usually calculated, to improve readability. We excluded poorly tracked segments and patients were not analysed if more than one segment per view was deemed unacceptable. STE-derived measurements were reported as the average of three beats. Additional 2D echography derived parameters were calculated, and the details are provided in **Suppl. Table 1**.

2.4. Plasma biomarkers assays

TNFa, MPO and hsCRP were measured by ELISA kits (TNF-apha Human, High sensitivity; Myeloperoxidase Human Instant and CRP Human, produced by Invitrogen by Thermo Fisher Scientific, MA, USA). hsTnT, BNP and NT-pro BNP were assayed by ECLIA methodology using commercial kits (Elecsys Troponin T hs, Elecsys BNP, Elecsys proBNP II, respectively) from Roche Diagnostics S.p.A., Milan (Italy) on the COBAS analyser e411. Mid-regional proADM and NT-PRO3 by ELISA kits (Human MR-ProADM and Human Procollagen III N-Terminal Propeptide) produced by MYBIOSOURCE, CA (USA).

2.5. Statistical analysis

Analyses were performed using JMP Pro software version 13.2.1 (SAS Institute, Cary, NC). Values are presented as mean±SD, or as median and interquartile range (IQR), for variables with normal and non-normal distribution, respectively. Comparisons between treatment groups were performed by the Student t-test for unpaired data for continuous variables and by the chi-square test for categorical variables. Variations from baseline to follow-up in the parameters in each of the two groups were presented as mean and [95% CI], the effect of the therapy at each follow-up assessment (1 and 6 months for. LV-GLS; 6 months for the other endpoints and variables) was assessed by *t*-test on the differences from baseline and presented as mean [95% CI] and by ANOVA for repeated measure on the whole data set; considering the *time*drug* interaction effect as the better estimate for testing differences in the response to the two treatments. All tests were conducted at a two-sided (and when of borderline significance also one-sided) α level of 0.05.

3. Results

3.1. Baseline characteristics of the study population

Patient disposition with the Consort 2010 flow diagram is shown in **Suppl. Fig 1.** According to the inclusion and exclusion criteria, 106 consecutive patients were recruited for the study from December 2017 to July 2020; after baseline evaluation, 37 were subsequently excluded because of definitive exclusion criteria (26 for inadequate glycaemic control, 4 for suboptimal ultrasound images during the exercise, 3 for incapacity of performing a maximal iCPET due to discomfort, 2 for ECG signs suggestive of ischemia, 2 for evidence of autonomic neuropathy); 4 declined to participate, 9 did not participate for other reasons (working obligations, logistic problems, discouraged by relatives or by their GPs). The recruitment was interrupted earlier due to lock-down imposed by COVID-19 pandemic. Fifty-six T2D subjects meeting the definitive inclusion/exclusion criteria were randomized to intervention, of which 26 were allocated to treatment with Empagliflozin 10 mg/die, and 29 to Sitagliptin 100 mg/die. During the follow-up, three patients from the Sitagliptin arm abandoned the study for personal reasons, while 1 patient in the Empagliflozin arm abandoned the study because of side effects (genital infections). At follow-up, 8 further patients were excluded because of suboptimal echocardiography images and/or incomplete or unreliable CPET data. The analysis was performed on 44 subjects, 22 in the Empagliflozin arm and 22 in the Sitagliptin arm.

Baseline characteristics of the study population are reported in **Table 1**. The population consisted of adults with T2D, mainly male, with a relatively long duration of T2D, and suboptimal glycaemic control. The two groups had similar age, sex prevalence, BMI, HbA_{1c}, BP values, prevalence of comorbidities, and ongoing treatment for diabetes and/or any cardio-active and lipid lowering therapy. Baseline values of blood tests showed normal values of renal function, as well as an adequately controlled lipid profile, values that were all comparable between the two intervention groups (see **Table 1**). The prevalence of microalbuminuria was low, and no patient had peripheral artery disease (as assessed by ankle-brachial index) or impaired pulmonary function at baseline spirometry (dead volume/tidal volume radio, VD/VT). At baseline 2D-echoDoppler evaluation, all patients showed RV

and LV dimensions, LV mass, RV (tricuspid anulus systolic excursion, TAPSE) and LV systolic (LVEF, mitral anulus Tissue Doppler S') and diastolic function (E/A, E/e', LA volume index, sPAP) within normal range, with no difference between the two groups.

3.2. Changes in clinical and laboratory parameters

At 6 months follow-up, a small reduction in body weight was observed only in the empagliflozin arm, while no change in mean blood pressure or in resting heart rate was evident in either treatment arm (**Table 2**). The two treatments produced a comparable reduction in HbA_{1c} while an increase in plasma haemoglobin concentration - and hematocrit - and a decrease in plasma uric acid were observed after treatment with empagliflozin, but not with sitagliptin. The remaining hematologic parameters (lipids, creatinine, ACR) did not differ from baseline to follow-up in either group (**Table 2**).

3.3. Resting and Exercise echocardiography

Baseline LV-GLS was comparable between the two groups although numerically higher in the empagliflozin group (17.3±2.7 *vs* 15.8±2.2 %, p=0.06). From baseline to 1- and 6-months follow-up, no change in resting LV-GLS was seen in any of the treatment groups (**Figure 1, panel A**); the difference between the treatments was slightly in favour of empagliflozin both at 1 (+0.44 [-0.10/+0.98] %) and 6 months (+0.53 [-0.56/+1.62] %); however, the *time*drug* effect at ANOVA for repeated measures was not statistically significant. The exercise-induced acute increase (from rest to 4 minutes of exercise) in LV-GLS was comparable in the two treatment arms both at baseline (+1.9 [+1.1/+2.6] and +1.9 [+1.2/+2.5] % for empagliflozin and sitagliptin, respectively) and at 6 months follow-up (+1.4 [+0.6/+2.1] *and* +2.0 [+1.2/+2.7] %) (**Table 3**). Likewise, cardiac chamber dimensions and/or geometry were not affected by either treatment, as well as Doppler and tissue-Doppler derived systo-diastolic indices (LA volume index, LVEF, LVMi, E/A ratio, mitral anulus S', e', E/e', TAPSE, sPAP) and SVR (**Table 3 and Suppl. Table 2)**. The neutral effect on cardiac

function was also confirmed by more advanced echocardiographic parameters (left atrial strain, cardiac power output, left and right ventricular-arterial coupling, shown in **Suppl. Table 1**), which did not change in the two intervention arms, neither when measured at rest nor during the three prespecified moments during exercise (4 min, aerobic threshold, peak exercise). SVR were reduced during exercise as expected but were unchanged at follow-up without differences between the treatments.

3.4. Cardiopulmonary exercise test

All patients reached a maximal exercise as required by inclusion criteria, achieving a respiratory exchange ratio (RER) steadily above 1.0 (median: 1.07, IQR: [1.03-1.10]), and the duration of exercise was between 10 and 12 minutes as per protocol. The exercise was well tolerated without discomfort, hypertensive response, or any significant alteration in vital parameters or ECG trace. The achieved VO_{2peak} at baseline in the whole population was 18.9 [15.8-21.3] ml/kg/min, which corresponded to 76±15% of predicted maximal theoretical VO_2 and was similar in the two groups (empagliflozin 18.9±3.8 *vs* sitagliptin 18.8±5.6 ml/min/kg), as was similar the achieved workload 118±25 *vs* 119±22 W). From baseline to 6 months follow-up no change in VO_{2peak} was seen in any of the treatment groups (**Figure 1, panel B**). Also, we could not demonstrate any variation from baseline in each treatment arm or between the arms in the other main parameters derived from iCPET, namely: pulmonary (ventilatory efficiency, oxygen saturation, end-tidal carbon dioxide), skeletal muscle (peripheral oxygen extraction), metabolic (RER, anaerobic threshold), and direct and indirect hemodynamic parameters (HR, CO, oxygen pulse). The results are reported in **Table 3 and Suppl. Table 3)**.

3.5. Mechanism oriented biomarkers

The baseline plasma levels of the biomarkers were within the normal range and no change was observed at 6 months follow-up in either treatment arm or between the treatments **(Suppl. Table 4).**

3.6. Subgroup analysis

As prespecified hypothesis-driven analysis, we divided the 22 subjects enrolled in each arm in two groups of 11 subjects according to the ranking of baseline resting LV-GLS values (median GLS empagliflozin 16.5%, median GLS sitagliptin 16.0%). The subgroups with higher LV-GLS neither on empagliflozin nor on sitagliptin showed changes during the study (**Figure 2**). On the contrary, the subjects with lower baseline LV-GLS experienced an improvement (mean difference [95% CI]) in LV contractility absolute values already at 1 month after therapy with empagliflozin (+1.22 [+0.31/+2.13] %) followed by a further improvement at 6 months (+2.05 [+1.14/+2.96] %). The subjects with lower LV-GLS on sitagliptin showed no change at 1 month (+0.30 [-0.13/+0.73] %) and an improvement at 6 months (+0.92 [+0.21/+0.62] %) (**Figure 2**). The estimated differences between the changes induced by the 2 treatments by paired *t*-test were +0.92 [-0.04/+1.89] % (p=0.05 for 2-side and p=0.03 for one-side superiority of empagliflozin) at 1 month and was maintained at 6 months (+1.08 [+0.01/+2.17] %, p=0.05 for 2-side and p=0.03 for one-side superiority of empagliflozin). The ANOVA for repeated measures detected a significant effect for the interaction term *time*drug* (p=0.04) as well as for the *drug* (p=0.02) and for *time* (p<0.0001) alone.

2. Discussion

The EMPA-HEART is a randomized trial aimed at evaluating whether the treatment with empagliflozin (against sitagliptin as active control, therefore independently of the improvement in metabolic control) is associated with an amelioration of LV contractility and/or cardiopulmonary function in T2D subjects without clinical or echocardiographic evidence of cardiac disease. As compared to sitagliptin, and in line with previous observations (29, 30), the treatment with empagliflozin was associated to a modest reduction in body weight and in serum uric acid, as well as to an increase in hemoglobin and hematocrit. We also observed a trend towards reduced resting mean

blood pressure with empagliflozin (-5 mmHg), which, although not statistically significant, is comparable to what reported by earlier studies (3-4 mmHg) (31).

No significant change in structural parameters were appreciated at resting 2D echocardiography with either treatment. Specifically, no change in LA volume, LV dimensions, LV mass or geometry was seen in either the whole population or in each intervention arm. This is not in contrast with the literature since treatment with sitagliptin was never associated with alterations in cardiac structure, and SGLT2i have been seldom and inconsistently associated with an amelioration of LV structural parameters in T2D subjects without overt HF and/or structural heart disease (4). Specifically, a reduction in LVMi was reported by one trial with echocardiography (4) but not evident in our study, possibly due to the normal baseline values and the very low prevalence of LV hypertrophy, aside from the small sample size and the relatively short duration of follow-up.

Despite a trend towards an improvement, the changes in diastolic function (E wave, E/A ratio, mean e' value, E/e' ratio, LA volume, or sPAP) were not statistically significant in the two intervention groups, either when measured at rest or during exercise. Notably, sitagliptin has been shown to improve E/e' by 20% in a population similar to ours, but only after 24 months (32), and empagliflozin has been reported to ameliorate diastolic function in subject with HFrEF, in whom diastolic dysfunction was moderate to severe (33).

With regard to systolic parameters, the crude indices provided by resting and exercise 2D LVEF did not change significantly at follow-up neither in the whole population nor in the two treatment arms, confirming previous reports of negative effect of SGLT2i on this parameter in T2D subjects without established cardiac disease (4). Even more sensible and less load-dependent parameters such as tissue Doppler S' and speckle-tracking LV-GLS showed no tendency to improve both at 1 and 6 months of follow-up in any of the intervention arms (**Figure 1 and Table 3**). Of note, when considering subgroup analysis, no change was observed in those with higher (*i.e.* normal) LV-GLS

values, whereas the patients with subclinical LV contractile dysfunction (LV-GLS<16.5%) on empagliflozin showed a significant increase in LV-GLS, that was evident at 1 month and further improved at 6 months, while in those on sitagliptin with lower LV-GLS (<16.0%) the increase in contractility was evident only at 6 months and was approximately 50% smaller (**Figure 2**). Still, the similarity between the change in GLS from 1 to 6 months in the two treatment groups suggests that glycaemic control per se might have had a favourable effect on myocardial contractility, as it has been suggested by a recent longitudinal study (34). To place our data in a clinical context, according to a recent paper on chemotherapy-related cardiomyopathy (35), normal values of LV-GLS in adults are defined as >18%, borderline values are 16-18% and abnormal below 16%, which confirms the high prevalence of a subclinical contractility dysfunction of our study group (approx. 50%).

It is known from the literature that SGLT2i are associated with a relatively heterogeneous (2-11 percent over baseline values) amelioration of LV-GLS in subjects with T2D and HF with a gradient that is proportional to the degree of baseline dysfunction, despite no increase in 2D-LVEF (36, 37). However, in T2D subjects without overt HF a 12-months long, randomized, open label clinical trial reported no effect on GLS after treatment with SGLT2i (17±4 *vs* 17±4%) in 40 subject with T2D, normal LVEF and no clinical diagnosis of HF (38). Unfortunately, subgroup analysis according to baseline GLS was not performed in that study. Our results extend the concept that empagliflozin ameliorates systolic function in T2D in proportion to the degree of baseline dysfunction (4) to include also those with early, mild subclinical contractility dysfunction. Since patients with subclinical LV dysfunction represent a substantial fraction (approx. 50%) of the T2D population free from cardiovascular disease and with normal EF at 2D echocardiography, and considering the prognostic value of LV-GLS (16), our finding might represent a solid rationale for verifying through a randomized double blind clinical trial, whether the early use of empagliflozin prevents or delay the development of overt HF in this specific fraction of patients, currently not specifically included in guidelines on the use of SGLT2i in cardiovascular prevention in T2D.

In T2D patients, the condition of reduced VO_{2peak} (14, 39) is associated with adverse cardiovascular outcomes (40); consequently, one may postulate that SGLT2i might exert their cardioprotective effects partly through an increased cardiopulmonary function. In our study, however, cardiopulmonary fitness neither changed significantly in the whole population nor in each study group. All the major parameters influencing VO_{2peak}, i.e. cardiac output, peripheral extraction, and ventilation were unaffected by either treatment, further confirming the neutral effect of either drug on aerobic fitness in this population. In previous pilot studies lacking randomization and active control, VO_{2peak} was increased by 24% after 6 months of therapy with empagliflozin *vs* "usual therapy" in T2D patients with established cardiovascular disease or at high risk (41), and by 10% in HFrEF patients with (42) and without T2D (43) after 1 month of therapy. Conversely, more rigorous studies in T2D and HFrEF failed to substantiate any improvement after SGLT2i either alone (44) or versus an active control (45). Given that the amelioration of glycaemic control is known to ameliorate VO_{2peak} in T2D with established cardiac disease (46, 47), the better glycaemic control achieved after therapy with SGLT2i might justify the positive results of the non-controlled trials that could not be confirmed when active controls were used, as it is in the present study. Interestingly, the subjects with HFrEF and concomitant therapy with loop diuretics showed a greater improvement in cardiorespiratory fitness when taking empagliflozin (44) and this implies a synergism between the two diuretics in volume regulation as elegantly shown by Griffin et al (48). In our population no patient was assuming loop diuretics, and this could partly justify the negative results on VO_{2peak}, which on the other hand confirms that volume regulation is unlikely to be the mechanism through which SGLT2i are effective in primary HF prevention (i.e. in patients with no congestion). Furthermore, our result of unchanged peak workload and peripheral oxygen extraction confirms the lack of clinically relevant effects of SGLT2i on skeletal muscle oxygen/work coupling in all T2D subjects. Also, in the subjects with low LV-GLS, despite a trend in VO_{2peak} in favour of empagliflozin (from 17.7±1.2 to 19.2±1.2 ml/min/kg) *vs* sitagliptin (from 17.8±1.3 to 18.3±0.9 ml/min/kg), the

differences within and between the treatments were not statistically significant. We have recently shown that both effort tolerance (VO_{2peak}) and peripheral oxygen extraction are correlated with LV contractility indices (S' and GLS) in subjects with uncomplicated T2D and normal LV systolic function (14) suggesting the presence of a subclinical myopathy involving both the heart and the skeletal muscle. Likewise, in this study population as a whole, VO_{2peack} showed a trend to be lower in those with LV-GLS below the median (17.5±0.98 *vs* 19.9±0.99 ml/min/kg, p=0.12). Interestingly, the present data support the hypothesis that empagliflozin mainly acts by improving myocardial contractility only in the subjects with mild impairment, while displays no effect on skeletal muscle function. Nevertheless, this hypothesis needs to be confirmed with further evidence.

No significant change in natriuretic peptides was evident from our data, which were in the normal reference values at baseline. This confirms that volume regulation is not relevant in this study population, aligning with the available literature that failed at demonstrating a consistent reduction in natriuretic peptides with SGLT2i, with a trend towards a greater efficacy in patients with HFrEF (49) and higher baseline values (50). Inflammation is a known prognostic and mechanistic determinant of HF pathobiology (51), and SGLT2i might act through their anti-inflammatory effects (52). In our study, markers of myocardial injury, oxidative stress, and inflammation biomarkers did not change at follow-up. We also did not observe significant changes in serum biomarkers of fibrosis, despite one in-vitro evidence of a direct effect of SGT2i on cardiac extracellular matrix (53). Still, the neutral effect on biomarkers of fibrosis agrees with a recent study with cardiac magnetic resonance imaging that could not detect any change in myocardial fibrosis after empagliflozin therapy in T2D subjects with diabetic cardiomyopathy (54).

3. Concluding remarks

In T2D subjects without heart disease empagliflozin is neutral on aerobic fitness and LV systo-diastolic functions, both at rest and during exercise. Nonetheless, it appears to exert an early and sustained amelioration of myocardial contractility in those with subclinical dysfunction as assessed by a mildly reduced resting LV-GLS (<16.5%). These data support the hypothesis that empagliflozin can directly affect the myocardium function in selected patients with subclinical LV systolic dysfunction, possibly justifying its positive effect in HF primary prevention.

4. Limitations

The recruitment was interrupted early due to the COVID-19 pandemics, therefore the power of our study is lower than planned; therefore, we might have missed absolute changes in LV-GLS below 2.5% or 1.7%, which were considered relevant from a clinical and pathophysiology point of view, respectively (18). The data, however, are clear in showing no change in LV-GLS in each group as a whole despite a clinically relevant change (+2.05 [+1.14/+2.96] %) in the subjects with low baseline LV-GLS treated with empagliflozin for 6 months. The reduced sample size also forced us to restrict the secondary endpoints to only one (VO_{2peak}) and the pre-defined exploratory analysis only to sub-group analysis according to baseline LV-GLS and to mechanism-oriented biomarkers. Although LV-GLS is considered an accurate method to evaluate LV contractility, there is evidence that it might be affected by the technology used, age, sex, BMI, and to some extent also by LV loading conditions (55). In our study all these variables remained stable; therefore, while the absolute values might be difficult to interpret, the changes within subjects are robust. This was an open study, but the cardiologist performing the measurements of primary and secondary outcomes was blind to the treatment allocation. We only focused on T2D patients, mainly male of 40-to-80 years old without established cardiovascular disease; therefore, the results should not be applied to different populations. We acknowledge that the technical challenge of acquiring echocardiography images during exercise

may affect SV and CO measurements, despite the technique has been extensively validated and used by different groups. Our imaging protocol was performed in a semi-supine position for a better echocardiographic evaluation; caution is advised to extend our results to other types of exercise (supine or upright).

Legends to the figures:

Figure 1. Box-and-whiskers plots of a) left ventricle global longitudinal strain (GLS) and b) oxygen consumption at peak (VO_{2peak}) at baseline and follow-up visits, expressed in absolute values (%).

Figure 2. Values of left ventricle global longitudinal strain (GLS) at baseline (0), 1 month and 6 months follow-up visits during empagliflozin (red) or sitagliptin (blue) treatment. The population was divided in two subgroups depending on baseline GLS values above (continuous line) or below (dotted lines) median (median for empagliflozin group: GLS 16.4%; median for sitagliptin group: GLS 16.0%). The star indicates a statistically significant *time*treatment effect* at *ANOVA for repeated measures*.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
LN: study design, literature review, screening and recruitment of patients, patient data collection, performance of metabolic and neurovascular tests, clinical measures, randomization, database creation, statistics, figure and table ideation, manuscript preparation and revision
NRP, IF: Echocardiography and cardiopulmonary tests, critical interpretation of data, revision of manuscript
PS: performance of metabolic and neurovascular tests, clinical measures, database creation,
SP: performance of metabolic and neurovascular tests, clinical measures, laboratory tests, blood and urine sample collection and storage, contacts with patients, clinical data storage
DT: recruitment of patients, statistics, figures, critical interpretation of data, manuscript writing
SB: laboratory tests, blood and urine samples preparation and storage
AD: recruitment of patients, critical interpretation of data, revision of manuscript
AN: Study design, recruitment of patients, randomization, statistics, critical interpretation of data, revision of manuscript, tables, and figures.
All authors read and approved the final manuscript.

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Table 1 – Clinical characteristics of the study population

	All patients *(n = 44)*	**Empagliflozin** *(n = 22)*	**Sitagliptin** *(n = 22)*	***p value***
Clinical data				
Male (n, %)	38 (86)	19 (86)	19 (86)	*ns*
Age (years)	61.7 ± 9.7	61.6 ± 9.6	61.8 ± 10.1	*ns*
Duration of DM (years)	9.6 ± 8.0	7.8 ± 6.9	11.1 ± 8.8	*ns*
Weight (kg)	84.6 ± 15.3	83.0 ± 13.6	83.7 ± 12.4	*ns*
BMI (kg/m²)	28.7 ± 5.3	27.8 ± 4.7	29.6 ± 5.7	*ns*
Mean BP (mmHg)	102.6 ± 11.5	102.9 ± 9.9	102.3 ± 13.2	*ns*
Active smokers, (n, %)	10 (23)	6 (27)	4 (18)	*ns*
Hypertension (n, %)	34 (77)	18 (81)	16 (72)	*ns*
Baseline therapy				
Metformin, n (%)	40 (91)	20 (91)	20 (91)	*ns*
Insulin, n (%)	11 (25)	7 (32)	4 (18)	*ns*
Statin, n (%)	32 (73)	18 (81)	14 (63)	*ns*
ACEi/ARBs, n (%)	27 (61)	16 (53)	11 (50)	*ns*
Beta-blockers, n (%)	10 (23)	5 (23)	5 (23)	*ns*
CCB, n (%)	10 (23)	6 (27)	4 (18)	*ns*
ASA, n (%)	16 (36)	4 (41)	7 (32)	*ns*
HCT, n (%)	5 (11)	3 (14)	2 (9)	*ns*
Furosemide, n (%)	1 (2)	0 (0)	1 (5)	*ns*
Blood tests				
HbA_{1c} (mmol/mol)	59.2 ± 6.4	57.8 ± 6.5	60.3 ± 6.2	*ns*
Total Cholesterol (mg/dL)	162 ± 33	159 ± 29	165 ± 38	*ns*
HDL-C (mg/dL)	48 ± 12	49 ± 13	47 ± 11	*ns*
LDL-C (mg/dL)	97 ± 26	95 ± 21	98 ± 30	*ns*
Triglycerides (mg/dL)	131 ± 57	121 ± 59	142 ± 54	*ns*
Haemoglobin (g/dL)	14.2 ± 1.3	14.1 ± 1.1	14.3 ± 1.4	*ns*
Creatinine (mg/dL)	0.89 ± 0.26	0.86 ± 0.31	0.92 ± 0.19	*ns*
eGFR (mL/min/1.73mq)	89.6 ± 17.4	91.5 ± 18.5	87.7 ± 16.5	*ns*
Uric acid (mg/dL)	5.55 ± 1.45	6.01 ± 1.60	5.10 ± 1.10	*ns*
Albumin-creatinin-ratio (mg/g)	5 (0–15)	4 (0-7)	8 (4-36)	*ns*
NT-proBNP (pg/mL)	81 (27-118)	63 (28-121)	33 (16-76)	*ns*
Vascular, and pulmonary assessment				
Ankle-brachial-index	1.16 ± 0.10	1.13 ± 1.1	1.18 ± 1.1	*ns*
VD/VT (%)	16.2 ± 4.9	16.4 ± 3.9	16.1 ± 5.2	*ns*
2D-Echocardiography				
EDVi (mL/m²)	51.5 ± 11.7	52.0 ± 12.2	51.0 ± 11.5	*ns*
LVMi (g/m²)	89.5 ± 17.3	89.9 ± 16.1	89.2 ± 18.9	*ns*
LAVi (mL/m²)	24.9 ± 7.5	24.8 ± 8.4	25.0 ± 6.8	*ns*
LVEF rest (%)	59.3 ± 4.5	60.5 ± 3.6	58.1 ± 5.1	*ns*
E/A ratio	0.90 ± 0.25	0.94 ± 0.26	0.86 ± 0.23	*ns*
E/e' (cm/sec)	8.5 ± 2.5	8.3 ± 2.2	8.7 ± 2.7	*ns*

Table 2 – Mean changes [and 95% CI] from baseline to 6 months follow-up in clinical parameters

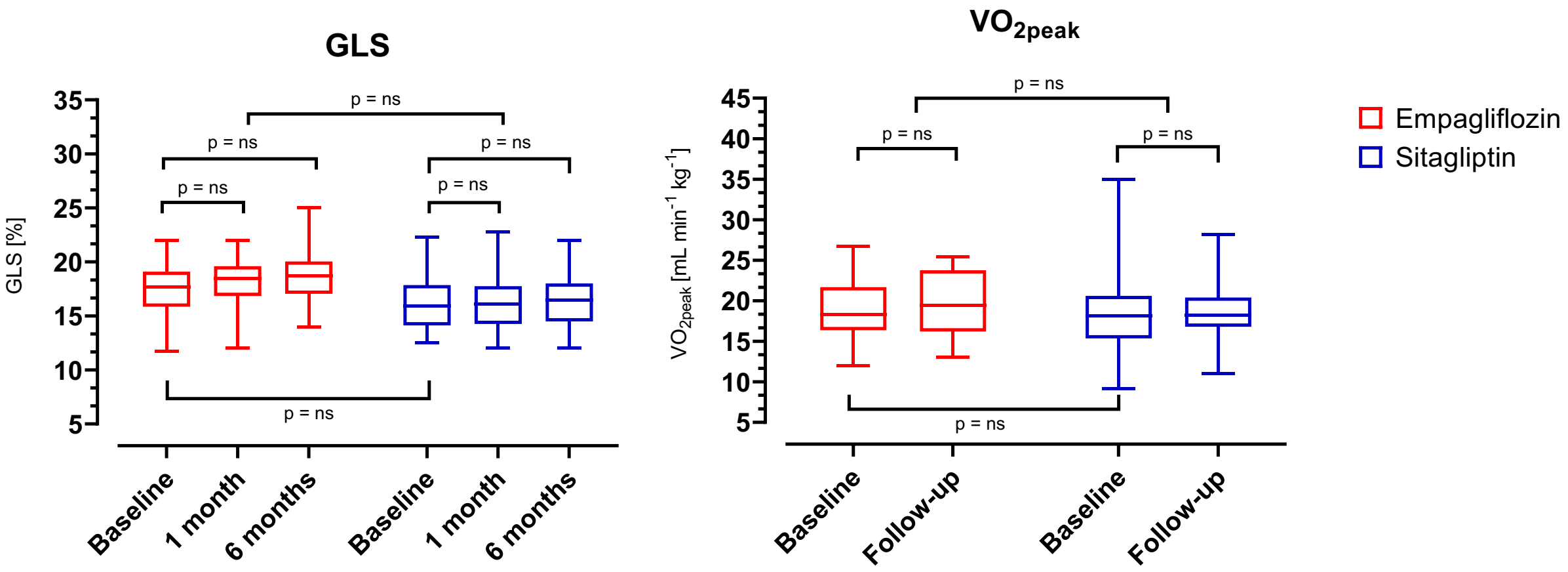
	Empagliflozin *(n = 22)*	**Sitagliptin** *(n = 22)*	p value
Weight (kg)	-1.6 [-2.7/-0.5]*	0.1 [-1.1/1.2]	*0.0315*
HR at rest (beat/min)	0.6 [-1.6/2.8]	-0.4 [-4.5/3.7]	*ns*
MAP rest (mmHg)	-5.4 [-10.7/0.0]	-0.22 [-7.6/7.2]	*ns*
HbA_{1c} (mmol/mol)	-4.6 [-7.4/-1.8]*	-4.9 [-8.8/-0.9]*	*ns*
Total Cholesterol (mg/dL)	-8 [-21/5]	-15 [-30/0]	*ns*
HDL-Cholesterol (mg/dL)	1.3 [-1.4/4.0]	-1.7 [-4.2/0.9]	*ns*
LDL-Cholesterol (mg/dL)	-7 [-19/6]	-7 [-18/3]	*ns*
Triglycerides (mg/dL)	-2 [-28/24]	-14 [-33/6]	*ns*
Hb (g/dL)	0.7 [0.2/1.1]*	-0.5 [-1/-0.1]	*0.0003*
Hct (%)	2.0 [0.7/3.2]*	-1.3 [-2.6/0.0]	*0.0006*
Creatinine (mg/dL)	-0.1 [-0.2/0.1]	-0.0 [-0.1/0.0]	*ns*
eGFR (mL/min/1.73mq)	2.5 [-3.7/8.7]	1.4 [-1.8/4.6]	*ns*
Uric acid (mg/dL)	-1.5 [-2.3/-0.6]*	0.2 [-0.3/0.6]	*0.0023*
ACR (mg/g)	6.1 [-1.9/14.2]	5.0 [-20.6/30.5]	*ns*

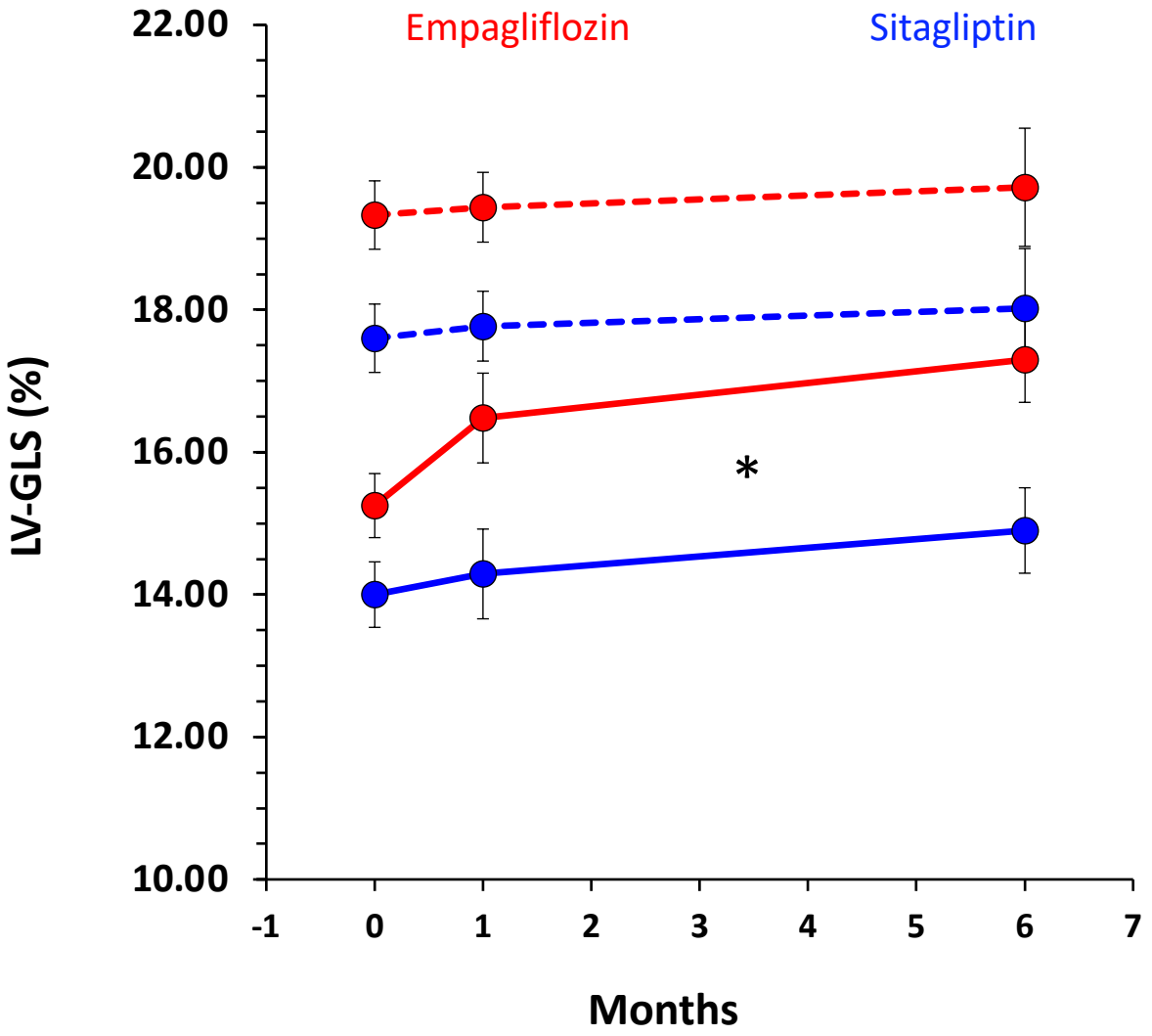
* indicates a statistically significant difference within groups, p value indicates the level of statistical significance of the interaction term *time*treatment* at MANOVA

Table 3 – Mean changes and [95%CI] at *t*-test from baseline to follow-up of echocardiography and respiratory data during the cardiopulmonary exercise test.

	Empagliflozin *(n = 22)*	**Sitagliptin** *(n = 22)*	***p value***
EDVi rest (mL/m²)	2.2 [-0.9/5.2]	3.6 [-1.0/6.3]	*ns*
LVMi rest (g/m²)	4.5 [-1.1/10.2]	1.1 [-2.7/5.0]	*ns*
LAVi rest (mL/m²)	0.5 [-1.3/2.2]	2.0 [-0.4/4.3]	*ns*
CO rest, L/min	0.0 [-0.6/0.6]	0.8 [-0.3/1.4]	*ns*
CO peak, L/min	0.7 [-0.6/1.9]	0.9 [-0.3/2.1]	*ns*
LVEF rest (%)	0.1 [-1.3/1.6]	2.1 [-0.4/3.7]	*ns*
LVEF peak (%)	-0.7 [-2.8/1.5]	2.0 [-0.1/3.9]	*ns*
ΔLVEF	-0.8 [-3.1/1.5]	0.9 [-1.0/2.9]	*ns*
S' mean rest (cm/sec)	0.0 [-0.8/0.9]	-0.1 [-1.0/0.8]	*ns*
S' mean peak (cm/sec)	0.4 [-0.9/1.7]	-0.2 [-1.0/0.6]	*ns*
ΔS' mean	0.4 [-0.8/1.5]	-0.1 [-1.0/0.8]	*ns*
E/e' rest (cm/sec)	-0.5 [-1.3/0.4]	-1.0 [-2.2/0.2]	*ns*
E/e' peak (cm/sec)	-0.3 [-1.5/0.9]	-0.6 [-1.5/0.5]	*ns*
*SVR rest (dyne*sec/cm)*	-143 [-340/-55]	-175 [-290/-60]	*ns*
*SVR peak (dyne*sec/cm)*	-16 [-90/59]	-34 [-126/57]	*ns*
Workload (W)	5 [-1/11]	2 [-5/9]	*ns*
Time of effort (min)	0.0 [-0.9/1.0]	-0.1 [-0.8/0.6]	*ns*
HR at peak (beat/min)	3.0 [-2.1/8.0]	1.3 [-4.4/7.0]	*ns*
HR at peak (%max)	1.9 [-1.3/5.1]	0.8 [-2.8/4.5]	*ns*
Chronotr. Incomp. reverse (n, %)	3 (14)	3 (14)	*ns*
MAP peak (mmHg)	4.6 [-0.7/10.0]	1.7 [-7.1/10.6]	*ns*
RPP peak	1,834 [-478/4,147]	-164 [-2,680/2,353]	*ns*
RER peak	0.00 [-0.03/0.04]	0.01 [-0.02/0.03]	*ns*
VO_2/work slope	0.3 [-0.5/1.1]	0.6 [-0.2/1.4]	*ns*
VO_2 rest (mL/min/kg)	0.5 [-0.1/1.2]	0.6 [-0.1/1.4]	*ns*
VE/VCO2 slope	0.3 [-1.2/1.8]	1.3 [-0.1/2.6]	*ns*
O_2 pulse peak (mL/bpm)	0.1 [-0.7/1.0]	0.5 [-0.2/1.2]	*ns*
O_2 pulse peak (% VO_2peak)	2.8 [-3.0/8.5]	3.0 [-1.1/7.1]	*ns*
AV O_2 diff rest (mL/dL)	0.6 [-0.7/1.8]	0.2 [-1.0/1.4]	*ns*
AV O_2 diff peak (mL/dL)	-0.1 [-0.9/0.7]	-0.2 [-1.3/1.0]	*ns*

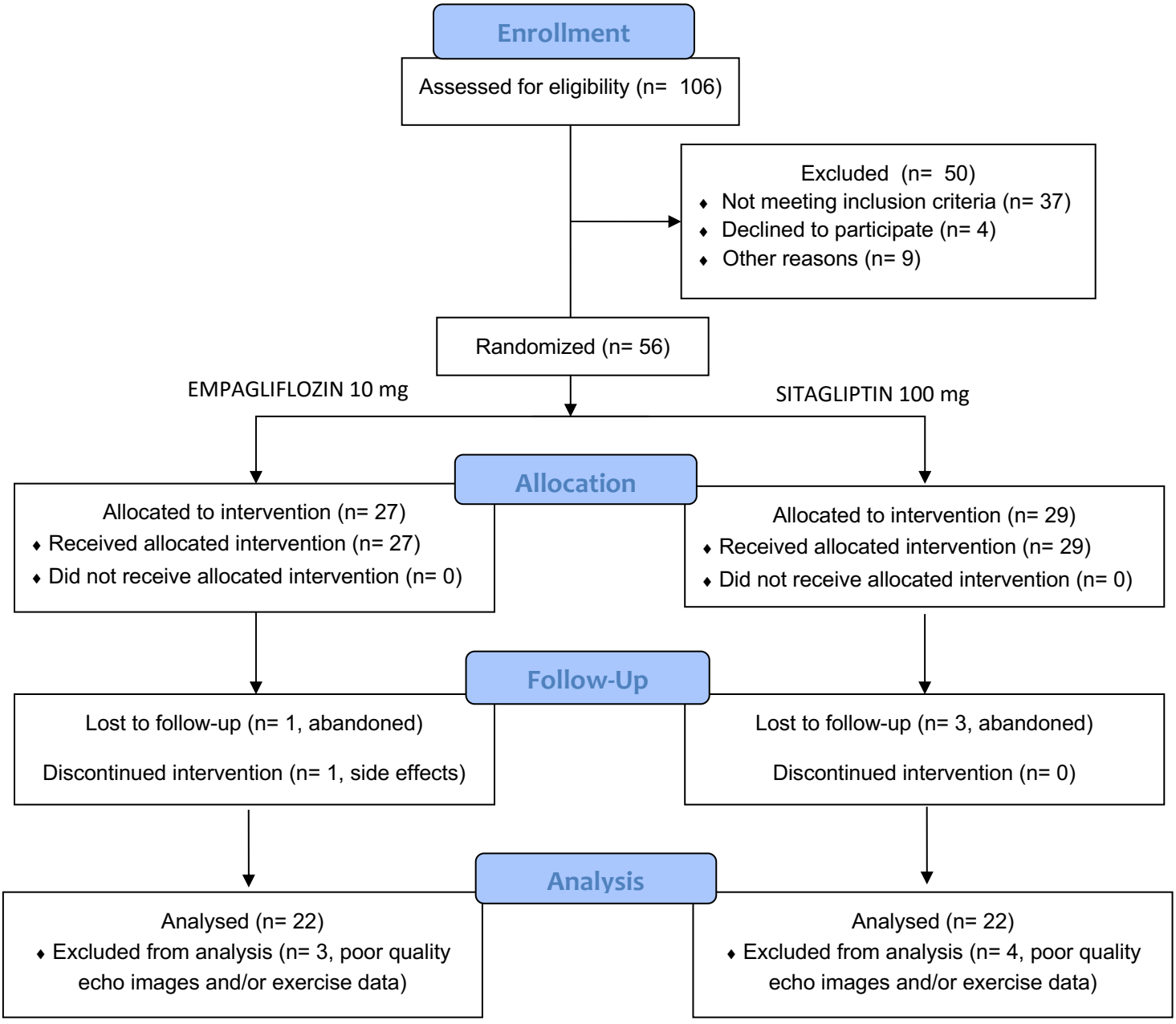
*p value indicates the level of statistical significance of the interaction term time*treatment at ANOVA for repeated measure*


GLS
GLS [%]
35
30
25
20
15
10
5
p = ns
p = ns
p = ns
p = ns
p = ns
p = ns
Baseline
1 month
6 months
Baseline
1 month
6 months
VO2peak
VO2peak [mL min-1 kg-1]
45
40
35
30
25
20
15
10
5
p = ns
p = ns
p = ns
p = ns
Baseline
Follow-up
Baseline
Follow-up
Empagliflozin
Sitagliptin


Empagliflozin
Sitagliptin
22.00
20.00
18.00
16.00
14.00
12.00
10.00
LV-GLS (%)
-1
0
1
2
3
4
5
6
7
Months
*

EMPA-HEART trial

CONSORT 2010 Flow Diagram



Supplemental Table 1 – 2D echography, Doppler, tissue Doppler- and Speckle tracking-derived parameters of systolic and diastolic function at rest and during the cardiopulmonary test.

	Empagliflozin (n = 22)			**Sitagliptin (n = 22)**				
	Baseline	Follow-up	*p value*	Baseline	Follow-up	*p value*	*p value B*	*p value T*
SV rest (mL)	74.8 ± 15.9	73.5 ± 17.0	*ns*	65.7 ± 15.7	74.6 ± 22.3	*ns*	*ns*	*ns*
SV 4 min	94.1 ± 22.2	92.5 ± 22.9	*ns*	81.5 ± 18.2	88.6 ± 23.7	*ns*	*ns*	*ns*
SV AT	100.7 ± 24.1	97.6 ± 20.8	*ns*	93.8 ± 22.0	96.7 ± 25.9	*ns*	*ns*	*ns*
SV peak (mL)	109.1 ± 24.7	106.9 ± 25.2	*ns*	101.6 ± 26.9	104.8 ± 27.8	*ns*	*ns*	*ns*
CO rest, L/min	5.7 ± 1.6	5.7 ± 1.2	*ns*	5.2 ± 1.2	6.0 ± 2.0	*ns*	*ns*	*ns*
CO at 4 min, L/min	8.8 ± 2.1	8.5 ± 1.9	*ns*	8.1 ± 2.2	8.6 ± 2.4	*ns*	*ns*	*ns*
CO at AT, L/min	11.9 ± 3.7	11.3 ± 3.1	*ns*	11.6 ± 3.0	11.6 ± 3.9	*ns*	*ns*	*ns*
CO peak, L/min	14.3 ± 4.2	14.2 ± 3.8	*ns*	13.6 ± 4.3	14.0 ± 4.4	*ns*	*ns*	*ns*
LVEF rest (%)	60.5 ± 3.6	60.6 ± 4.1	*ns*	58.1 ± 5.1	60.7 ± 5.7	*ns*	*ns*	*ns*
LVEF at 4 min (%)	64.2 ± 3.7	63.8 ± 4.1	*ns*	61.0 ± 5.6	64.0 ± 5.6	*ns*	*ns*	*ns*
LVEF at AT (%)	66.9 ± 3.8	66.4 ± 5.2	*ns*	63.8 ± 6.1	67.0 ± 5.7	*ns*	*ns*	*ns*
LVEF peak (%)	69.1 ± 4.7	68.6 ± 5.2	*ns*	66.3 ± 6.9	70.4 ± 5.8	*ns*	*ns*	*ns*
ΔLVEF	8.6 ± 3.1	7.9 ± 4.1	*ns*	8.2 ± 4.0	9.4 ± 2.6	*ns*	*ns*	*ns*
Contractility res (n, %)	15 (52)	14 (48)	*ns*	14 (48)	18 (56)	*ns*	*ns*	*ns*
S' mean rest (cm/sec)	8.8. ± 1.7	9.0 ± 1.9	*ns*	9.8 ± 2.0	9.7 ± 1.7	*ns*	*ns*	*ns*
S' mean 4 min	10.9 ± 1.8	10.9 ± 2.0	*ns*	11.5 ± 2.1	10.7 ± 1.4	*ns*	*ns*	*ns*
S' mean AT	12.7 ± 2.3	13.0 ± 2.6	*ns*	13.4 ± 2.4	12.6 ± 1.5	*ns*	*ns*	*ns*
S' mean peak (cm/sec)	13.9 ± 2.9	14.1 ± 2.9	*ns*	14.5 ± 2.5	14.4 ± 2.2	*ns*	*ns*	*ns*
ΔS' mean	5.2 ± 2.3	5.2 ± 2.2	*ns*	4.7 ± 1.7	4.7 ± 1.4	*ns*	*ns*	*ns*
E/A ratio rest	0.94 ± 0.26	0.92 ± 0.18	*ns*	0.86 ± 0.23	0.84 ± 0.22	*ns*	*ns*	*ns*
E/e' rest (cm/sec)	8.3 ± 2.2	7.7 ± 2.0	*ns*	8.7 ± 2.7	7.8 ± 2.3	*ns*	*ns*	*ns*
E/e' 4 min	9.2 ± 1.9	7.9 ± 2.0	*ns*	9.3 ± 2.2	8.9 ± 2.1	*ns*	*ns*	*ns*
E/e' AT	8.5 ± 1.5	8.2 ± 1.9	*ns*	8.9 ± 1.9	8.6 ± 1.5	*ns*	*ns*	*ns*
E/e' peak (cm/sec)	8.7 ± 1.8	8.2 ± 2.3	*ns*	9.0 ± 2.4	8.6 ± 1.5	*ns*	*ns*	*ns*
Elastance rest	6.2 ± 1.4	5.7 ± 1.6	*ns*	6.0 ± 1.4	6.0 ± 2.0	*ns*	*ns*	*ns*
Elastance peak	12.5 ± 3.7	11.8 ± 3.7	*ns*	12.0 ± 3.6	12.6 ± 4.6	*ns*	*ns*	*ns*
Δ elastance	6.3 ± 2.7	6.1 ± 2.5	*ns*	5.9 ± 2.6	6.6 ± 3.4	*ns*	*ns*	*ns*
TAPSE rest	20.9 ± 2.9	20.6 ± 2.6	*ns*	21.3 ± 2.7	20.1 ± 2.6	*ns*	*ns*	*ns*
TAPSE 4 min	24.5 ± 3.6	24.1 ± 3.0	*ns*	25.8 ± 3.5	22.3 ± 3.2	*ns*	*ns*	*ns*
TAPSE AT	26.7 ± 3.1	26.7 ± 3.3	*ns*	28.0 ± 3.8	24.5 ± 3.5	*ns*	*ns*	*ns*
TAPSE peak	28.5 ± 3.6	28.2 ± 3.2	*ns*	30.1 ± 3.6	27.1 ± 3.8	*ns*	*ns*	*ns*
sPAP rest	24.2 ± 4.3	24.0 ± 3.0	*ns*	23.4 ± 3.9	23.1 ± 2.5	*ns*	*ns*	*ns*
sPAP 4 min	29.2 ± 7.2	27.2 ± 6.2	*ns*	24.5 ± 4.3	25.2 ± 5.6	*ns*	*ns*	*ns*
sPAP AT	34.1 ± 11.9	32.8 ± 8.1	*ns*	30.6 ± 6.2	30.5 ± 8.0	*ns*	*ns*	*ns*
sPAP peak	35.0 ± 12.1	33.8 ± 8.2	*ns*	31.7 ± 7.2	32.0 ± 10.6	*ns*	*ns*	*ns*
CPO rest (W)	1.31 ± 0.39	1.23 ± 0.33	*ns*	1.19 ± 1.36	1.26 ± 0.56	*ns*	*ns*	*ns*
CPO 4 min (W)	2.34 ± 0.73	2.10 ± 0.59	*ns*	2.19 ± 0.71	2.17 ± 0.78	*ns*	*ns*	*ns*
CPO AT (W)	3.71 ± 1.42	3.36 ± 1.13	*ns*	3.66 ± 1.22	3.59 ± 1.67	*ns*	*ns*	*ns*
CPO peak (W)	4.72 ± 1.76	4.80 ± 1.63	*ns*	4.55 ± 1.77	4.71 ± 1.95	*ns*	*ns*	*ns*
CPOM rest (W/100g)	0.77 ± 0.29	0.71 ± 0.26	*ns*	0.68 ± 0.19	0.70 ± 0.27	*ns*	*ns*	*ns*
CPOM 4 min (W/100g)	1.35 ± 0.56	1.19 ± 0.42	*ns*	1.25 ± 0.41	1.22 ± 0.37	*ns*	*ns*	*ns*
CPOM AT (W/100g)	2.11 ± 0.83	1.93 ± 0.76	*ns*	2.08 ± 0.66	2.07 ± 0.89	*ns*	*ns*	*ns*
CPOM peak (W/100g)	2.73 ± 1.03	2.78 ± 1.08	*ns*	2.57 ± 0.89	2.65 ± 1.04	*ns*	*ns*	*ns*
TAPSE/sPAP rest (mm/mmHg)	0.88 ± 0.17	0.86 ± 0.12	*ns*	0.93 ± 0.14	0.88 ± 0.13	*ns*	*ns*	*ns*

TAPSE/sPAP 4 min (mm/mmHg)	0.87 ± 0.17	0.93 ± 0.24	*ns*	1.08 ± 0.22	0.91 ± 0.20	*ns*	*ns*	*ns*
TAPSE/sPAP AT (mm/mmHg)	0.85 ± 0.22	0.86 ± 0.22	*ns*	0.95 ± 0.21	0.84 ± 0.18	*ns*	*ns*	*ns*
TAPSE/sPAP peak (mm/mmHg)	0.88 ± 0.23	0.88 ± 0.25	*ns*	0.99 ± 0.22	0.90 ± 0.20	*ns*	*ns*	*ns*
TAPSE/CO rest (mm/L/min)	3.97 ± 1.37	3.76 ± 0.90	*ns*	4.32 ± 1.19	3.73 ± 1.24	*ns*	*ns*	*ns*
TAPSE/CO 4 min (mm/L/min)	2.96 ± 0.94	2.97 ± 0.77	*ns*	3.42 ± 1.03	2.78 ± 0.86	*ns*	*ns*	*ns*
TAPSE/CO AT (mm/L/min)	2.46 ± 0.85	2.55 ± 0.79	*ns*	2.57 ± 0.70	2.30 ± 0.72	*ns*	*ns*	*ns*
TAPSE/CO peak (mm/L/min)	2.17 ± 0.71	2.13 ± 0.65	*ns*	2.41 ± 0.79	2.10 ± 0.66	*ns*	*ns*	*ns*
LA reservoir strain (%)	36.7 ± 5.0	34.3 ± 38.8	*ns*	38.8 ± 2.6	38.8 ± 2.5	*ns*	*ns*	*ns*
LA reservoir/E/e' (%)	4.60 ± 1.03	4.59 ± 1.45	*ns*	4.97 ± 1.48	5.33 ± 1.52	*ns*	*ns*	*ns*
LA booster strain (%)	16.63 ± 2.81	14.39 ± 4.74	*ns*	17.75 ± 2.29	17.20 ± 0.83	*ns*	*ns*	*ns*
LA conduit strain (%)	20.05 ± 4.03	19.86 ± 6.32	*ns*	21.00 ± 3.48	21.60 ± 2.56	*ns*	*ns*	*ns*
*SVR rest (dyne*cm/sec)*	1,551 ± 442	1,404 ± 258	*ns*	1,640 ± 362	1,475 ± 404	*ns*	*ns*	*ns*
*SVR 4 min (dyne*cm/sec)*	1,105 ± 213	1,075 ± 209	*ns*	1,283 ± 388	1,116 ± 301	*ns*	*ns*	*ns*
*SVR AT (dyne*cm/sec)*	983 ± 249	998 ± 238	*ns*	1,034 ± 306	1,011 ± 275	*ns*	*ns*	*ns*
*SVR peak (dyne*cm/sec)*	873 ± 206	880 ± 185	*ns*	938 ± 273	923 ± 283	*ns*	*ns*	*ns*

Methods.

Data collected at each stage (rest, 4 minutes, anaerobic threshold, peak exercise) included: left ventricle (LV) and atrial (LA) volumes, stroke volume (SV), peak E-wave and A-wave velocities, tissue Doppler imaging (TDI)-derived S' and e' at the septal and lateral mitral annulus, tricuspid regurgitation velocity, tricuspid annular plane systolic excursion (TAPSE) according to latest guidelines [1]. SV was measured by multiplying the LV outflow tract area at rest by the LV outflow tract (LVOT) velocity-time integral measured by pulsed-wave Doppler during each activity level. We used the simplified Bernoulli equation to measure systolic pulmonary artery pressure (PAPs) from the peak tricuspid regurgitation jet, adding the right atrial pressure estimated from imaging of the inferior vena cava at rest. LA reservoir strain was calculated at rest, using the same software, as the average of strain in six segments in the four-chamber and two-chamber. LA strain (booster, conduit) was measured using P wave and QRS as the fiducial point. We excluded poorly tracked segments and patients were not analysed if more than one segment per view was deemed unacceptable. STE-derived measurements were reported as the average of three beats. SV was calculated by multiplying the LV outflow tract area at rest by the LV outflow tract velocity-time integral measured by pulsed-wave Doppler during each activity level, as previously validated [2]. Cardiac output was calculated as the multiplication of SV and heart rate. Images were acquired concurrently with breath-by-breath gas exchange measurements at both baseline and peak of exercise. All measurements were reported as the average of three beats. Cardiac power output (CPO) was measured with the following formula: $CPO = 0.222 * CP\ \left[\frac{L}{min}\right] * mean\ BP\ [mmHg]$, while cardiac power output per mass (CPOM) was calculated as CPO divided by LV mass [g] [3]. TAPSE/sPAP and TAPSE/CO were calculated as ratios between these variables to assess right ventricle ventriculo-arterial coupling.

Abbreviations.

CO, cardiac output; CPO, cardiac power output; CPOM, cardiac power output per mass; e', tissue Doppler-derived early diastolic velocity of the mitral anulus; E/A ratio, early-to-atrial filling wave velocity ratio; EDV, end-diastolic volume; LA, left atrium; LVEF, left ventricular ejection fraction; S', tissue Doppler-derived systolic velocity of the mitral anulus; sPAP, systolic pulmonary artery pressure; SV, stroke volume; SVR, systemic vascular resistance; TAPSE, tricuspid anulus systolic excursion; Δ, rest-to-peak exercise delta.

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Suppl Table – 2D Echocardiograpy, Doppler, Tissue Doppler, and Speckle tracking parameters

	Empagliflozin *(n = 22)*		**Sitagliptin** *(n = 22)*		**p value**
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	
EDVi (mL/m²)	52.0 ± 12.2	54.3 ± 12.4	51.0 ± 11.5	53.9 ± 10.2	ns
LVMi (g/m²)	89.9 ± 16.1	93.9 ± 22.1	89.2 ± 18.9	89.5 ± 17.1	ns
LAVi (mL/m²)	24.8 ± 8.4	25.3 ± 7.6	25.0 ± 6.8	25.6 ± 7.0	ns
CO rest, L/min	5.7 ± 1.6	5.7 ± 1.2	5.2 ± 1.2	5.7 ± 2.0	ns
CO peak, L/min	14.3 ± 4.2	14.2 ± 3.8	13.6 ± 4.3	14.0 ± 4.4	ns
LVEF rest (%)	60.5 ± 3.6	60.6 ± 4.1	58.1 ± 5.1	60.7 ± 5.7	ns
LVEF peak (%)	69.1 ± 4.7	68.6 ± 5.2	66.3 ± 6.9	68.4 ± 5.8	ns
ΔLVEF	8.6 ± 3.1	7.9 ± 4.1	8.2 ± 4.0	9.4 ± 2.6	ns
GLS rest (%)	17.3 ± 2.7	18.7 ± 2.7	15.8 ± 2.3	16.7 ± 2.8	ns
GLS 4 min (%)	19.2 ± 3.2	20.1 ± 2.9	17.7 ± 2.9	18.7 ± 3.1	ns
ΔGLS (%)	1.9 ± 1.8	1.4 ± 1.4	1.9 ± 1.3	2.0 ± 1.9	ns
S' mean rest (cm/sec)	8.8. ± 1.7	9.0 ± 1.9	9.8 ± 2.0	9.7 ± 1.7	ns
S' mean peak (cm/sec)	13.9 ± 2.9	14.1 ± 2.9	14.5 ± 2.5	14.4 ± 2.2	ns
ΔS' mean	5.2 ± 2.3	5.2 ± 2.2	4.7 ± 1.7	4.7 ± 1.4	ns
E/e' rest (cm/sec)	8.3 ± 2.2	7.7 ± 2.0	8.7 ± 2.7	7.8 ± 2.3	ns
E/e' peak (cm/sec)	8.7 ± 1.8	8.2 ± 2.3	9.0 ± 2.4	8.6 ± 1.5	ns
SVR rest (dyne*sec/cm)	1,551 ± 442	1,404 ± 258	1,640 ± 362	1,475 ± 404	ns
SVR peak (dyne*sec/cm)	873 ± 206	880 ± 185	938 ± 273	923 ± 283	ns

Supplementary Table 3 – Main variables measured during cardiopulmonary exercise test expressed as baseline and follow-up values. P value is the result of a two-point ANOVA for repeated measure.

	Empagliflozin *(n = 22)*		**Sitagliptin** *(n = 22)*		**p value**
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	
Workload (W)	118 ± 26	123 ± 31	119 ± 32	121 ± 29	ns
Time of effort (min)	11.3 ± 2.2	11.4 ± 1.7	11.0 ± 2.3	11.0 ± 1.7	ns
HR at rest (beat/min)	76.5 ± 11.6	77.1 ± 11.4	80.2 ± 13.4	79.8 ± 10.8	ns
HR at peak (beat/min)	129.1 ± 15.6	132.1 ± 14.3	133.6 ± 19.6	134.9 ± 18.8	ns
HR at peak (%max)	83.2 ± 9.4	85.1 ± 9.1	86.2 ± 11.9	87.0 ± 11.4	ns
Chronotropic incomp (n, %)	16 (57)	15 (54)	12 (43)	13 (46)	ns
MAP rest (mmHg)	102.9 ± 9.9	97.5 ± 10.2	102.3 ± 13.2	102.1 ± 16.3	ns
MAP peak (mmHg)	145.4 ± 15.7	150.0 ± 17.0	148.1 ± 20.0	149.9 ± 18.8	ns
RPP peak	25,767 ± 7,494	27,601 ± 5,269	28,345 ± 6,641	28,181 ± 6,264	ns
RER peak	1.08 ± 0.07	1.08 ± 0.05	1.08 ± 0.07	1.09 ± 0.06	ns
VO_2/work slope	10.8 ± 1.3	10.0 ± 1.2	10.3 ± 1.4	10.9 ± 1.2	ns
VO_2 rest (mL/min/kg)	4.0 ± 1.3	4.5 ± 1.4	4.1 ± 1.3	4.7 ± 1.4	ns
VO_2 peak (mL/min/kg)	18.9 ± 3.8	19.7 ± 3.7	18.8 ± 5.6	19.2 ± 4.3	ns
VO_2 peak (% VO_{2max})	75.5 ± 16.0	80.5 ± 16.4	77.4 ± 13.1	81.3 ± 10.8	ns
VE/VCO2 slope	27.7 ± 3.6	28.0 ± 3.8	27.5 ± 4.7	28.8 ± 4.51	ns
O_2 pulse peak (mL/bpm)	12.2 ± 2.8	12.4 ± 2.8	11.7 ± 2.8	12.2 ± 2.7	ns
O_2 pulse peak (% VO_2peak)	93.8 ± 19.8	96.6 ± 17.4	92.5 ± 14.6	95.6 ± 14.2	ns
AV O_2 diff peak (mL/dL)	11.5 ± 3.0	11.6 ± 2.5	12.3 ± 3.7	12.5 ± 4.0	ns

Supplementary Table 4 – Mechanism-oriented plasma biomarkers

	Empagliflozin (n = 22)		**Sitagliptin (n = 22)**		
	Baseline	Follow-up	Baseline	Follow-up	p value
hsCRP (mg/dL)	0.114 (0.026-0.216)	0.095 (0.048-0.153)	0.177 (0.090-0.762)	0.156 (0.081-0.405)	ns
BNP (pg/mL)	25 (10-47)	16 (10-46)	12 (10-25)	11 (10-20)	ns
NT-proBNP (pg/mL)	63 (28-131)	54 (26-134)	26 (16-76)	35 (26-53)	ns
TnHS (ng/mL)	9.9 (6.7-16.4)	10.0 (7.6-13.9)	7.8 (5.8-27.0)	8.2 (6.6-15.2)	ns
proADM (nmol/L)	0.080 ± 0.065	0.150 ± 0.120	0.154 ± 0.198	0.119 ± 0.130	na
NT-PRO3 (ng/mL)	5.6 (4.4-6.7)	5.6 (4.0-7.7)	6.7 (5.1-8.9)	6.2 (4.7-7.6)	ns
TNFα (pg/mL)	0.74 (0.46-0.96)	0.79 (0.69-0.96)	0.67 (0.59-0.88)	0.80 (0.66-0.93)	ns

Tumor necrosis factor-alpha (TNFa) and high-sensitive c-reactive protein (hsCRP) myeloperoxidase (MPO), brain natriuretic peptide (BNO) and N-terminal pro-BNO (NT-pro BNP), pro-adrenomedullin (proADM), high-sensitive troponin T (hsTnT), NT procollagen 3 (NT-PRO3) p value indicates the results of the ANOVA for repeated measures results of the time*treatment interaction term

SYNOPSIS

Name of Sponsor/Company: Boehringer Ingelheim	**Individual Study Table Referring to Part Of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*
Name of Finished Product: Jardiance ®		
Name of Active Ingredient: Empagliflozin 10 mg		

Title of Study:

Impact of empagliflozin on left ventricular functions: a single center, phase III, randomized, open-label, active treatment-controlled, parallel study in patients with type 2 diabetes and normal left ventricular function

Study Number: 1245-128. EudraCT Number: 2016-002225-10

Investigators:

Prof. Andrea Natali, dott. Lorenzo Nesti

Study Centre(s):

Pisa, SOD Diabetologia Universitaria, Università di Pisa - Italia

Publication (reference)
NA

Studied period (years): (date of first enrolment: 11/09/2017) (date of last completed: 05/10/2020)	**Phase of development:** Phase III

Objectives:

*Primary endpoint***:** Changes in global longitudinal strain (GLS) from baseline to 1 month and 6 months after treatment initiation.

*Secondary endpoints***:** Changes from baseline at 6 months after treatment initiation in

1. Glycated hemoglobin (HbA_{1c}).
2. ejection fraction, left atrial volume, and E/E', as measured with echocardiography.
3. VO_2 peak, as measured at cardiopulmonary test.
4. myocardial parietal stress plasma biomarker (BNP, NT-proBNP, proadrenomedullin), inflammation/oxidative stress plasma biomarkers (hsCRP, TNF-alpha, mieloperoxidase, uric acid) and cardiac remodeling/cytolysis (type III pro-collagene, troponine);
5. Cardiac autonomic function tests (R-R interval during Valsalva manoeuvre, deep-breathing, lying-to-standing).

Exploratory endpoints: verify the following hypothesis:

1. Whether changes from baseline at 6 months after treatment initiation in plasma markers of cardiomyocyte strain (BNP, NT-proBNP, proadrenomedullin), inflammation/oxidative stress (hsCRP, TNF-α, myeloperoxydase, uric acid), matrix remodeling (procollagen type III) and myocyte injury (Troponin T) help understanding the mechanisms of action through which the treatments exert their effect/s on the heart.
2. Whether the effects of the treatments differ in the subgroup of patients whom at baseline have mild abnormalities in cardiac systolic function or abnormal values of plasma biomarkers or abnormal cardiac autonomic function tests.
3. Whether the changes in cardiac function are dependent on the concomitant changes in blood pressure, body weight and/or the improvement of the metabolic control.

Methodology:

Phase III, open label, active-controlled, parallel group, single center, exploratory clinical trial in patients with type 2 diabetes mellitus with normal 2-D ejection fraction (≥50%) and without inducible myocardial ischemia at cardiopulmonary test, investigating the effects of 24-weeks treatment with empagliflozin in comparison to sitagliptin on left ventricular systolic function, as measured by global longitudinal strain (GLS) through speckle tracking echography.

Patients were randomized to a 24-week treatment with either empagliflozin 10 mg or sitagliptin 100 mg/daily as add-on to the background therapy; the randomization was done with a randomization matrix of 50 numbers calculated using the web-based service at *www.random.org* and assigning pair and even numbers to each of the two treatments.

All patients were randomized after definitive inclusion/exclusion criteria were satisfied. Patients who did not fulfill either entry criteria or safety criteria during the treatment phase were excluded from the study.

A total of seven visits was performed for each study patient as per protocol (namely: screening, baseline, run-in, and randomization, one month, three months, six months, and end-of-study visit). Additional visits have been performed to verify safety criteria at 1, 3 months and at any emergence of clinically relevant signs and/or symptoms.

Number of patients (planned and analyzed):

Fifty (50) patients planned; forty-four (44) patients analyzed

Diagnosis and main criteria for inclusion:

Inclusion criteria:

- Male of female patients affected by type 2 diabetes mellitus
- Subjects aged >40 and <80 years
- HbA_{1c} levels ≥53 and ≤ 69 mmol/mol
- Assuming stable hypoglycemic therapy in the last three months with either:
  - Metformin *or*
  - Metformin + basal insulin
- On stable cardio-active therapies during the last three months at least (anti-hypertensive drugs, diuretics, drugs for asthma, drugs for migraine)
- With preserved kidney function as defined by eGFR ≥45 $ml.min^{-1}.1.73m^2$
- Without signs and symptoms of heart failure and with normal left ventricular systolic unction as defined by NYHA class I - II, and EF≥50%

Test product, dose and mode of administration, batch number:

Empagliflozin 10 mg/daily (experimental drug) as add-on to the background therapy.
Drugs were taken orally, one pill each day, fasting in the morning.

Duration of treatment:

Twenty-four (24) weeks

Reference therapy, dose and mode of administration, batch number:

Sitagliptin 100 mg/daily as add-on to the background therapy.
Drugs were taken orally, one pill each day, fasting in the morning.

Criteria for evaluation

Efficacy:

- Changes in global longitudinal strain (GLS) from baseline to 1 month and 6 months after treatment initiation.
- Changes from baseline at 6 months after treatment initiation in peak VO_2, as measured at cardiopulmonary test.
- Changes from baseline at 6 months after treatment initiation in myocardial parietal stress plasma biomarker (BNP, NT-proBNP, proadrenomedullin), inflammation/oxidative stress plasma biomarkers (hsCRP, TNF-alpha, mieloperoxidase, uric acid) and cardiac remodeling/cytolysis (type III pro-collagene, troponin).
- Subgroup analysis (high *vs* low baseline GLS and/or VO_2).

Safety:

- General adverse events (AEs) and adverse drug reactions (ADRs)
- Changes from baseline of routine laboratory parameters (haematology, blood chemistry and urinalysis) measured after 4 weeks of treatment and at the end of the study.
    - Routine haematology included measurement of red blood cells count, white blood cells count, haemoglobin, haematocrit, differential blood count (neutrophils, lymphocytes, monocytes, eosinophils and basophils), and platelets count.
    - Routine blood chemistry included measurement of: transaminase GOT, GPT, gamma-glutamyltransferase, creatinine, blood-urea-nitrogen, lipid parameters (total cholesterol, low-density-lipoprotein-cholesterol, high-density-lipoprotein-cholesterol, triglycerides), and electrolytes (sodium, chloride, and potassium).
    - Urinalysis included: specific weight, pH, glucose, proteins (albumin/creatinine ratio), blood, ketones.
- Changes from baseline in vital parameters.
- Changes from baseline in ECG trace

Statistical methods:

Analyses were performed using JMP Pro software version 13.2.1 (SAS Institute, Cary, NC). Values are presented as mean±SD, or as median and interquartile range (IQR), for variables with normal and non-normal distribution, respectively. Comparisons between treatment groups were performed by the Student t-test for unpaired data for continuous variables and by the chi-square test for categorical variables. Variations from baseline to follow-up in the parameters in each of the two groups were presented as mean and [95% CI], the effect of the therapy at each follow-up assessment (1 and 6 months for. LV-GLS; 6 months for the other endpoints and variables) was assessed by t-test on the differences from baseline and presented as mean [95% CI] and by ANOVA for repeated measure on the whole data set; considering the time*drug interaction effect as the better estimate for testing differences in the response to the two treatments. All tests were conducted at a two-sided (and when of borderline significance also one-sided) α level of 0.05.

Summary – Conclusions

Efficacy Results

- *Main outcomes*: No difference between the treatments was detectable in either LV-GLS after 1 month (empa vs sita: +0.44; [-0.10/+0.98] %, p=0.11) and 6 months of therapy (+0.53; [-0.56/+1.62] %), or in VO_{2peak} (+0.43; [-1.4/+2.3] ml/min/kg, p=0.65).
- *Secondary outcomes*: While glycaemic control similarly improved in both groups, a relative reduction in body weight (-1.6; [-2.7/-0.5] kg, p=0.03) and plasma uric acid (-1.5; [-2.3/-0.6], p=0.002), as well as an increase in haemoglobin (+0.7; [+0.2/+1.1] g/dL, p=0.0003) were evident with empagliflozin.
- *Exploratory endpoints*: With empagliflozin, the subgroup with baseline LV-GLS below the median experienced a significantly greater increase (time*drug p<0.05) in LV-GLS at 1 month (+1.22; [+0.31/+2.13] %) and at 6 months (+2.05; [+1.14/+2.96] %), while sitagliptin only induced a modest improvement in LV-GLS at 6 months (+0.92; [+0.21/+0.62] %). No change in plasma mechanism-oriented biomarkers was observed.

Safety Results

- No patient developed serious adverse events (SAEs) and/or serious adverse drug reactions (SARs) with either sitagliptin or empagliflozin.
- No patient experienced Unexpected Adverse Reactions (UARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)
- No death was recorded during the study period and during the 30 days following the end of the study period.
- One patient in the empagliflozin arm developed recurrent balanitis (3 episodes) which, despite full recovery with oral anti-micotic agents (fluconazole), discouraged the continuation of the trial.
- One patient in the empagliflozin arm developed mild balanitis (1 episode), which recovered fully with local anti-micotic agents (fluconazole) without any short-term and/or long-term local and/or systemic complications and did not prevent the continuation of the trial.
- No patient developed any other adverse drug reactions (such as: hypoglycemia, dizziness, hypotension, GI symptoms, electrolytes disturbances, creatinine, amylase, or elevation of liver markers).

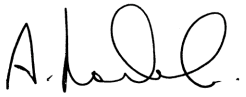
Conclusion

Empagliflozin has neutral impact on both LV-GLS and exercise tolerance in subjects with T2D and normal LV function; however, in patients with reduced baseline LV-GLS it produces a rapid and persistent amelioration of LV contractility.

Date of report

20/12/2021

Prof. Andrea Natali



RELAZIONE SULLA SICUREZZA DELLE PERSONE SOTTOPOSTE A SPERIMENTAZIONE CLINICA

Development Safety Update Reports (DSUR)

Studio Clinico EMPA-HEART

Titolo dello studio: Impact of empagliflozin on left ventricular functions: a single center, phase III, randomized, open-label, active treatment controlled, parallel study in patients with type 2 diabetes and normal left ventricular function.

Numero dello studio: 1245-128.

Codice EUDRACT: 2016-0022250-10.

Promotore:

Prof. Andrea Natali, Dipartimento di Medicina Clinica e Sperimentale, Direttore Sez. Dip. Dietologia, AOUP
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Fax: 050-553235
E-mail: andrea.natali@unipi.it

Relazione sulla sicurezza:

1. **Eventi avversi (*Direttiva 2001/20/CE, art. 2*).**
   - Eventi avversi gravi (SAEs – serious adverse events): nessuno per tutta la durata dello studio. In particolare:
     - Nessun decesso si è verificato durante tutta la durata dello studio né nei 30 giorni dopo il termine del periodo di assunzione della terapia.
     - Nessun evento che mettesse a repentaglio la vita del soggetto.
     - Nessun ricovero ospedaliero o prolungamento di ricovero.
     - Nessuna invalidità o un'incapacità grave o prolungata.
     - Nessuna anomalia o una malformazione congenite o un difetto alla nascita.
     - L'investigatore non è venuto a conoscenza di alcun evento avverso serio verificatosi dopo la fine del trattamento.
   - Eventi avversi non gravi e/o risultati anomali di laboratorio reputati essenziali ai fini della sicurezza (*D.Lvo 211/2003, art.16 (1) CT-3, Sezione 3 (14), Sezione 4 (20-28 -29*)).
     - Un paziente nel braccio empagliflozin (codice paziente LUFR087EX) ha presentato balaniti ricorrenti (3 episodi, trattati con antimicotici topici e sistemici - fluconazolo)

che, nonostante la guarigione completa senza complicanze locali o sistemiche a breve né a lungo termine, ha determinato il ritiro volontario del paziente dallo studio clinico

- Un paziente nel braccio empagliflozin (codice paziente TOMA082EE) ha presentato un unico episodio di balanite lieve (trattato con antimicotici topici e sistemici - fluconazolo) con guarigione completa senza complicanze locali o sistemiche a breve né a lungo termine e che non ha determinato ritiro dallo studio clinico.
- Nessun altro evento avverso né alterazioni significative degli esami di laboratori considerati essenziali ai fini della sicurezza si sono verificati durante tutta la durata dello studio.

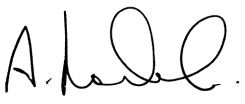
- Eventi avversi di interesse speciale (Adverse events of special interest - AESI) (*RMP, ALLEGATO I Regolamento UE 520/2012; Appendice 4 Accordo sullo Scambio dei Dati sulla Sicurezza - SDEA*):
  - Nessun danno epatico definito da valori AST e / o ALT ≥ 3 volte valore superiore limite (ULN) combinato con un aumento della bilirubina totale ≥ 2 volte ULN misurata nello stesso campione di sangue e/o valori isolati di ALT e / o AST ≥ 5 volte ULN
  - Nessuna riduzione della funzionalità renale definito da un valore di creatinina che mostra un aumento ≥ 2 volte rispetto al basale ed al di sopra dell'ULN.
  - Nessun episodio di Acidosi metabolica, chetoacidosi e/o chetoacidosi diabetica (DKA)
  - Nessun evento che coinvolga l'amputazione degli arti inferiori.
- Gravidanza in soggetti femminili o in partner di soggetti maschili: nessuna per tutta la durata dello studio.

2. Reazioni avverse (*D.Lvo 211/2003, art.2 (p)*)

- Reazioni avverse inaspettate (Unexpected Adverse Reactions - UARs): nessuna per tutta la durata dello studio.
- Sospette reazioni avverse gravi ed inattese (Suspected Unexpected Serious Adverse Reactions - SUSARs) (*Direttiva 2001/20/CE art. 2 definizioni (q)*): nessuna per tutta la durata dello studio.

Pisa, 20/12/2021

Prof. Andrea Natali



Impact of empagliflozin on left ventricular functions: a single center, phase III, randomized, open-label, active treatment controlled, parallel study in patients with type 2 diabetes and normal left ventricular function" EMPA-HEART Study

Study Number: 1245-128; EUDRACT Code: 2016-0022250-10

ADDENDUM to the FINAL REPORT

ADVERSE EFFECTS

MAJOR

No patient has developed serious adverse events with either sitagliptin or Eempagliflozin.

MINOR

One patient in the empagliflozin arm developed recurrent balanitis (3 episodes) which, despite the fully recovered with fluconazole per os, discouraged the continuation of the trial.

One patient in the empagliflozin arm developed balanitis (1 episode), which recovered with local fluconazole and did not prevent the continuation of the trial.

No patient developed hypoglycemia, dizziness, hypotension, GI symptoms, electrolytes disturbances, creatinine, amylase or LT elevations.

Andrea Natali