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SOdium-glucose CO-transporter inhibition in patients with newly detected Glucose Abnormalities and a recent Myocardial Infarction (SOCOGAMI)

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ABSTRACT

Aims/hypothesis: Established dysglycaemia (impaired glucose tolerance [IGT] or type 2 diabetes [T2DM]) is a risk factor for further cardiovascular events in patients with coronary artery disease. Sodium-glucose cotransporter 2 inhibitors reduce this risk. The aim of the present investigation was to test the hypothesis that empagliflozin exerts beneficial effects on myocardial function in patients with a recent acute coronary syndrome and newly detected dysglycaemia.

Methods: Forty-two patients (mean age 67.5 years, 81 % male) with recent myocardial infarction (n = 36) or unstable angina (n = 6) and newly detected IGT (n = 27) or T2DM (n = 15) were randomised to 25 mg of empagliflozin daily (n = 20) or placebo (n = 22) on top of ongoing therapy. They were investigated with oral glucose tolerance tests, stress-perfusion cardiac magnetic resonance imaging (CMR) and echocardiography at three occasions: before randomisation, after seven months on study drug and three months following cessation of such drug. Primary outcome was a change in left ventricular (LV) end-diastolic volume (LVEDV) and secondary outcomes were a change in a) systolic and diastolic LV function; b) coronary flow reserve; c) myocardial extracellular volume (ECV) in non-infarcted myocardium; d) aortic pulse wave velocity.

Results: Empagliflozin induced a significant decrease in fasting and post load glucose ($p < 0.05$) and body weight ($p < 0.01$). Empagliflozin did not influence LVEDV, LV systolic or mass indexes, coronary flow reserve, ECV or aortic pulse wave velocity. Echocardiographic indices of LV diastolic function (E/e' and mitral E/A ratio) were not influenced. No safety concerns were identified.

Conclusions/interpretation: Empagliflozin had predicted effects on the dysglycaemia but did not influence variables expressing LV function, coronary flow reserve and ECV. An explanation may be that the LV function of the patients was within the normal range.

1. Introduction

Patients with acute myocardial infarction (AMI) often have previously undetected dysglycaemia [1,2]. Contemporary management guidelines [3] recommend screening for dysglycaemia, defined as impaired glucose tolerance (IGT) or type 2 diabetes (T2DM), in all patients with coronary artery disease without known diabetes, since it is an independent risk for future cardiovascular mortality and morbidity [4,5]. This underlines the importance of an early diagnosis and intervention in such patients with the intention to reduce future cardiovascular events.

Targets for life-style modification, platelet stabilization and management of blood lipids and blood pressure are well defined. What remains to be established is the optimal target and best tool for the initial

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management of newly detected dysglycaemia [3]. Among oral agents, pioglitazone or metformin may be considered. These drugs prevent or retard the onset of T2DM among patients with IGT but have not been shown to lower new events in patients with established cardiovascular disease [6]. There are, however, concerns about the possible association with oedema, heart failure and gastrointestinal side effects [3]. Early initiation of insulin did not prove superior to conventional glucose-lowering treatment in the ORIGIN trial [7]. Dipeptidyl peptidase-4 inhibitors are an alternative, however, not yet with proven superiority as regards reduction of cardiovascular events and for one agent, saxagliptin, a potential of heart failure induction [8]. Some Sodium Glucose Transporter-2 inhibitors (SGLT-2 inhibitor) and Glucagon Like Peptide-1 Receptor Agonists (GLP-1 RA) have been shown to reduce major cardiovascular events in T2DM with established or at high risk for cardiovascular disease respectively [9]. However, there are no data on cardiovascular preventive effects in patients with newly detected dysglycemia.

This study tests the hypotheses that 1) the SGLT-2 inhibitor empagliflozin will exert beneficial effects on myocardial structure and function concomitant with improved glucose control and 2) can be safely instituted in patients with recent AMI or unstable angina pectoris and newly detected dysglycaemia.

2. Materials and methods

2.1. Patients

SOdium-glucose CO-transporter inhibition in patients with newly detected Glucose Abnormalities and a recent Myocardial Infarction (SOCOGAMI) was a randomized, double blind, placebo-controlled, investigator-initiated trial. It was designed and executed independently of the funder and conducted at the Cardiology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden. Patients aged $>$ 18 years, who during the previous six months suffered AMI or unstable angina pectoris according to joint European and American recommendations [10] were recruited if they, according to the World Health Organization (WHO) criteria, had newly detected IGT or T2DM confirmed by two screening oral glucose tolerance tests (OGTT). Exclusion criteria were known diabetes (type 1 or 2); contraindications to cardiac magnetic resonance (CMR) imaging; eGFR $<$ 30 ml/min/1.73 m^2; intolerance or contraindications to intravenous adenosine; severe concomitant disease (e.g. malignancy, hepatic failure); planned coronary artery bypass grafting or percutaneous coronary intervention; congestive heart failure NYHA class III-IV; women of childbearing potential.

2.2. Study protocol

During a baseline visit the patients were subjected to a careful investigation including their medical history, concomitant therapies, smoking status, working status, body mass index (BMI), waist circumference, blood pressure and heart rate. Venous blood was collected after 12 h fasting for analyses of fasting plasma glucose, glycated haemoglobin A1c (HbA1c), plasma cholesterol (total, low-density lipoprotein - LDL and high-density lipoprotein - HDL), triglycerides, high sensitivity C-reactive protein (hsCRP), creatinine, NTproBNP and an OGTT was performed. Serum and plasma were stored in −70 °C for subsequent analyses including insulin, proinsulin, C-peptide, and inflammatory biomarkers. Following the OGTT the investigations continued with an echocardiogram and a CMR.

After the completion of all investigations the patients were randomized to either 25 mg of empagliflozin once daily or corresponding placebo. They received a patient diary, equipment for and instruction on self-monitoring of glucose levels and were seen at the outpatient clinic one and three months later. Seven months after randomization all investigations performed during the baseline visit were repeated. Thereafter the study drug was discharged. Ten months after randomization the patient returned for a final visit, during which all investigations were repeated once more.

2.3. Methods

OGTT: was performed via oral administration of 75 g of Glucose in 200 ml water administered on the morning following an overnight fast of 12 h. A plasma glucose curve was obtained for two hours (just before and 30 and 120 min after the glucose intake). Plasma glucose was measured by means of the HemoCue® Glucose 201 RT (HC201RT) equipment [11].

Echocardiography: Comprehensive transthoracic echocardiography was performed by a single, credentialled echocardiographer (AV) in keeping with current recommendations [12] employing a dedicated ultrasound system (Vivid E9, GE Ultrasound, Horten, Norway) 2D gray-scale images were acquired at 50–80 frames/*sec* and Doppler tracings were recorded using a sweep speed of 10 0 mm/*sec*. Digital loops were subsequently exported and analyzed offline (EchoPAC PC, version 11.0.0.0 GE Ultrasound, Waukesha, Wisconsin). Left ventricular (LV) volumes were measured employing apical views and ejection fraction was calculated using the Simpsons biplane method. LV global longitudinal strain (LV GLS) was assessed using two-dimensional speckle tracking echocardiography employing three standard apical views. Mitral inflow interrogation was performed using pulsed-wave (PW) Doppler in the apical four-chamber view, placing the sample volume at the mitral leaflet tips. Mitral E/A ratio was computed using transmitral early (E) and late diastolic velocities (A). Doppler tissue imaging was utilized to measure early mitral annular velocities (e') at both septal and lateral walls and subsequently averaged to calculate E/e'. Left atrial (LA) volume was obtained from apical 4- and 2-chamber views and indexed for body surface area. Right ventricular (RV) dimension was obtained in the RV-focused apical 4-chamber view, and RV systolic function expressed as tricuspid annular plane systolic excursion (TAPSE).

CMR: Patients underwent CMR at 1.5 T (Siemens Aera, Siemens Healthineers, Erlangen, Germany). During the scan, patients received an adenosine infusion of 140 microg/min/kg body weight (Adenosine, Life Medical AB, Stockholm, Sweden). During adenosine stress, first pass perfusion imaging was performed in three short-axis slices (apical, midventricular and basal) by using an intravenous contrast agent (Gadobutrol, Gadovist, Bayer AB, Solna, Sweden) 0.05 mmol/kg body weight administered in a separate cannula. Perfusion imaging was subsequently repeated during the scan in resting conditions using a second dose of Gadobutrol (0.05 mmol/kg body weight). A final dose of Gadobutrol was then administered for a total dose of 0.2 mmol/kg body weight. Myocardial perfusion maps were created on the scanner using the Gadgetron perfusion mapping software [13]. T_1 mapping using the modified Look-Locker inversion recovery (MOLLI) sequence [14] (Siemens WIP 1041) was performed before contrast with a 5 s(3 s)3s sampling scheme [15], and after the final contrast dose with a 4 s(1 s)3s (1 s)2s scheme. Extracellular volume (ECV) maps were created on the scanner from the pre- and post-contrast T_1 maps [16]. The protocol also included cine, steady-state free precession (SSFP) imaging to establish LV volumes, systolic function, stroke volume, and mass. Flow measurements in the ascending aorta and in the abdominal aorta were used for measuring pulse wave velocity. Myocardial infarction was identified visually on LGE images, and all other CMR analyses were performed using Segment CMR. LV volumes and mass were analyzed in accordance with guidelines [17] using the fully automated method based on machine learning algorithms [18]. Pulse wave velocity was calculated using another algorithm in Segment CMR [19] from the flow in the ascending and abdominal aorta and the length in between these two points, see supplementary Fig. 1.

On the perfusion maps, the endocardial and epicardial borders were outlined, excluding regions with artefacts. Artefacts affecting less than

two out of six segments were excluded from the region of interest (ROI). Examinations with images with larger artefacts were excluded. ROIs were placed with a 10 % margin from the borders to avoid partial volume effects. A total of sixteen ROIs were drawn in the three short-axis slices, corresponding to the American Heart Association (AHA) model [20] excluding the apical cap. The global perfusion was calculated as the average perfusion of all the imaged myocardium, and the perfusion reserve (pathologic < 2.0, normal > 2.5) was calculated as the global stress perfusion divided by the global rest perfusion [19–21]. In the midventricular short-axis T_1 maps, one large ROI was placed with a 10 % margin from the endocardial and epicardial borders. The ROI from the T_1 map was copied to the ECV map of the same exam, with small adjustments in size and position to match the ECV map.

2.4. Outcomes

The primary study outcome was the change in the LV end-diastolic volume from baseline to seven months measured by CMR. Secondary outcomes included changes in a) systolic and diastolic LV function; b) coronary flow reserve; c) myocardial extracellular volume (ECV) in non-infarcted (remote) myocardium measured by CMR and echocardiography as appropriate; d) changes in arterial stiffness was studied as aortic flow velocity by means of CMR. Further outcome measures were changes in glucose tolerance studied by means of the OGTT from baseline to seven months.

These outcomes were also investigated ten months after randomization i.e. three months following the cessation of study drug.

A safety evaluation during the time on study drug was conducted on all patients.

2.5. Ethics

All patients signed consent to study participation following written and oral information. The trial was carried out in compliance with principles in the Declaration of Helsinki, 1996 version, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP) and in accordance with applicable regulatory requirements. The protocol was approved by the Regional Ethics committee in Stockholm (Dnr 2015:4/11).

2.6. Statistics

Power calculation: A sample of 60 patients was required to detect an assumed difference in LV end-diastolic volume of 15 % with a significance level of 5 %, and a coefficient of variation of at most 80 % and a power of 80 %. An interim analysis, blinded for the investigators, was performed after the recruitment of 40 patients, who had passed the visit after seven months. This revealed that further patient inclusions would not be meaningful, which was the reason for stopping further inclusions.

All analyses were performed according to the intention to treat principle. Categorical data are reported as frequencies and percentages while continuous variables are reported as mean and standard deviation or median and interquartile range for those non-normally distributed. The primary analysis was a superiority comparison of LV end-diastolic volume index from baseline to the visit after seven months. Comparisons from baseline to seven months for the outcomes were also based on an analysis of variances, ANOVA, adjusted for baseline values.

All statistical analyses were performed using SAS (SAS Institute). Two-sided testing was performed at a significance level of 0.05.

3. Results

As outlined in Fig. 1 a total of 55 patients were screened, of whom 42 (IGT n = 27; T2DM n = 15) fulfilled the inclusion and were free from exclusion criteria. Thirty-six of these patients had suffered an AMI and six unstable angina pectoris within the previous six months. They were randomized to either empagliflozin 25 mg (n = 20) or placebo (n = 22). Relevant clinical characteristics at baseline are presented in Table 1. The average age of the patients was 67 ± 8 years and 81 % were males. The proportion with IGT was 60 % and T2DM 40 % in the empagliflozin group. The corresponding proportions in the placebo group were 68 % and 32 %. As shown in Table 1 the two groups were well balanced as regards baseline characteristics.

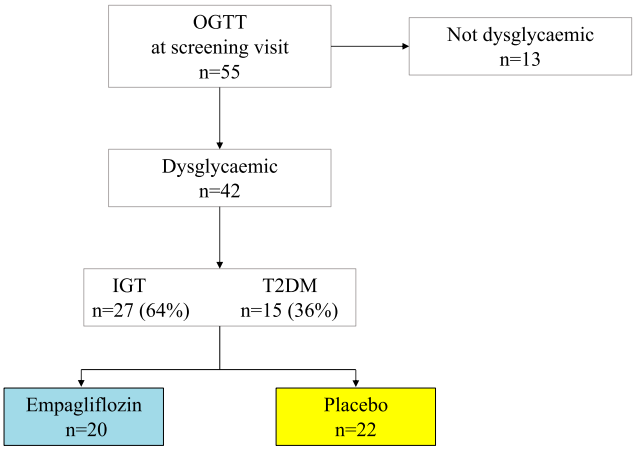

Fig. 1. Patient flow chart. OGTT = oral glucose tolerance test; IGT = impaired glucose tolerance; T2DM = type 2 diabetes mellitus.

Table 1
Clinical characteristics and pharmacological treatment at baseline. Data presented are numbers (%) or mean ± standard deviation if not otherwise stated.

Variable	Empagliflozin n = 20	Placebo n = 22
Men/women	16/4	18/4
Age (years)	67 ± 8	68 ± 8
Body mass index (kg/m^2)	27 ± 4	27 ± 4
Smoking (yes/no)	19/1	19/3
Index event (MI/UA)	17/3	19/3
Medical history		
Peripheral artery disease	1	0
Stroke/TIA	2	0
Heart failure	1	0
Blood pressure (mmHg)		
Systolic	130 ± 16	131 ± 16
Diastolic	79 ± 10	80 ± 10
Heart rate (beats/minute)	62 ± 7	68 ± 8
Laboratory findings		
Haemoglobin (g/L)	142 ± 19	140 ± 10
LDL-cholesterol (mmol/L)	1.4 ± 0.3	1.4 ± 0.6
Triglycerides (mmol/L)	1.3 ± 0.6	3.3 ± 9.3
Creatinine (μmol/L)	86 ± 16	81 ± 18
eGFR (ml/min/1.73 m^2)	68 ± 13	73 ± 14
Troponin (ng/L)	15 ± 14	16 ± 12
hsCRP (mg/L)	1.2 ± 0.8	1.7 ± 2.4
NT-pro-BNP (ng/L)	361 ± 406	249 ± 305
Fasting plasma glucose (mmol/L)	6.5 ± 0.9	6.5 ± 1.1
2-hour post load glucose (mmol/L)	10.9 ± 2.9	10.6 ± 2.9
HbA1c (mmol/mol)	42 ± 6	43 ± 9
Pharmacological treatment		
ACE-inhibitors/ARBs	17 (75)	18 (82)
Beta-blockers	17 (85)	21 (95)
Calcium channel blockers	5 (25)	4 18)
Diuretics	7 (35)	3 (14)
Statins	20 (100)	21 (96)
Antiaggregants	19 (95)	16 (73)
Anticoagulants	0	2 (9)

MI = myocardial infarction; UA = unstable angina; TIA = transitory ischaemic attack; LDL = low-density lipoprotein; eGFR = estimated glomerular filtration rate; hsCRP = high-sensitivity C-reactive protein; BNP = brain natriuretic peptide; HbA1c = glycated haemoglobin A1c; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid.

Changes in clinical and laboratory variables from baseline to the investigation after seven months on study drug are presented in Table 2. Body weight decreased in the empagliflozin and increased in the placebo group (-1.6 vs + 1 kg; p = 0.01). Likewise, there was a significant decrease in both fasting and 2-hour post load glucose in the empagliflozin compared to the placebo group. Otherwise, there were no significant differences between the two groups as regards changes in the laboratory variables including hsCRP.

No unforeseen safety concerns were identified as reported in Supplementary Table 1.

3.1. Cardiac magnetic resonance

The primary outcome, the change in the LV end-diastolic volume index from baseline to seven months measured by CMR, is reported in Fig. 2, which also includes the following secondary outcome variables: LV end-systolic volume, LV stroke volume and LV mass indexes. There were no statistically significant changes in these variables over time i.e. no difference between empagliflozin and placebo. At baseline the mean [SD] LV end-diastolic volume was 146 [33] ml in the empagliflozin and 141 [39] ml in the placebo groups respectively. The corresponding volumes were 145 [41] and 143 [39] by the end of the active treatment period [n.s.] and 148 [47] and 144 [36] by the end of the study. The coronary flow reserve, ECV and aortic pulse wave velocity at baseline, after seven months of treatment and three months after cessation of randomized treatment is presented in Table 3. None of these variables were influenced by empagliflozin.

3.2. Echocardiography

Selected echocardiographic variables that reflect ventricular systolic and diastolic function, supplementing the information gained by CMR are presented in Table 4. LV sub-clinical systolic function as expressed by LV GLS, indices of LV diastolic function represented by E/e' and mitral E/A ratio, RV size and TAPSE were not significantly influenced by empagliflozin.

4. Discussion

In this investigation of patients diagnosed with dysglycaemia detected after an acute coronary syndrome within the previous six months, empagliflozin did not influence various CMR or echocardiographic measures of LV function and dimensions or an expression of aortic wall elasticity. Measures of glycaemic state and body weight were, as expected, reduced by the initiation of empagliflozin, which could be delivered without any unforeseen complications.

Table 2
Changes in clinical and laboratory variables from baseline to seven months on study treatment.

Variable	Empagliflozin n = 20	Placebo n = 22	p-value
Bodyweight (kg)	−1.6 ± 2.4	1.0 ± 3.4	0.007
BMI (kg/m^2)	−0.5 ± 0.8	0.3 ± 1.1	0.006
Blood pressure			
Systolic	1.3 ± 14.1	6.5 ± 11.8	0.193
Diastolic	1.0 ± 6.6	3.0 ± 7.8	0.365
Heart rate (beats/minute)	0.4 ± 8.1	2.4 ± 8.3	0.444
Haematocrit (%)	2.8 ± 9.9	0.6 ± 10.6	0.505
eGFR (ml/min/1.73 m^2)	0.0 ± 5.3	−1.5 ± 5.6	0.381
LDL-cholesterol (mmol/L)	0.1 ± 0.3	0.0 ± 0.6	0.485
hsCRP	0.0 ± 1.2	−0.2 ± 1,6	0.718
Interleukin 6	0.7 ± 2.7	0.5 ± 3.1	0.798
NT-proBNP	−156 ± 295	−26 ± 263	0.145
Fasting plasma glucose (mmol/L)	−0.8 ± 0.9	−0.2 ± 0.8	0.025
2-hour post load glucose (mmol/L)	−1.3 ± 3.0	0.3 ± 1.9	0.045
HbA1c (mmol/mol)	0.8 ± 5.6	0.7 ± 4.2	0.944

BMI = body mass index; eGFR = estimated glomerular filtration rate; hsCRP = high-sensitivity C-reactive protein; BNP = brain natriuretic peptide; HbA1c = glycated haemoglobin A1c.

That SGLT-2 inhibitors have a beneficial impact on cardiovascular events in patients with diabetes and cardiovascular disease is well known from major clinical trials as e.g. reviewed by Ferrannini et al [21]. Even if not known in all details, the reasons for this favorable impact are probably several. A major contributor is a reduction of heart failure-related events, apparent already within a few weeks after the initiation. Induced osmotic diuresis, increased sodium excretion, reduction of interstitial edema and improved myocardial energetics are possible factors that may explain cardiovascular benefits [22]. Moreover, SGLT-2 inhibition improves glycaemic control in an insulin-independent manner. Weight loss and blood pressure reduction are other effects that may contribute by time. Subsequent trials comprising both patients with and without diabetes [21] and with reduced as well as preserved LV ejection fraction [23,24] confirmed the original findings in patients with T2DM.

A concern with the large clinical trials of SGLT-2 inhibitors is that they all addressed patient populations with established cardiovascular disease, in some also overt heart failure, and with at least a substantial part having T2DM since many years. Another problem is that they usually are unable to incorporate time-consuming or complex techniques such as echocardiography and CMR, which may shed light on the impact of LV dimension and function, thereby contributing to improved understanding of mechanisms of action. Thus, there is a need for smaller trials offering an opportunity for more detailed investigations. CMR is a method with high reproducibility permitting investigations on relatively limited patient samples [25]. SOCOGAMI was planned to study the hypothesis that early institution of a SGLT-2 inhibitor, empagliflozin, in patients with newly detected glucose perturbations after an acute coronary event may have a beneficial impact on myocardial dimension, structure and function. However, as described, this was not the case.

The first trial providing detailed information on the impact of a SGLT-2 inhibition on myocardial structure and function was, to the best of our knowledge, presented by Cohen et al [26]. These authors conducted a matched cohort study of patients with T2DM treated with empagliflozin on top of standard therapy versus standard therapy alone. Only about 25 % of their patient population had a history of cardiovascular disease. The participants underwent CMR imaging at baseline and after six months. In contrast with the present results, empagliflozin caused a reduction in LV end-diastolic volume from 155 ml at baseline to 145 ml after six months (p < 0.01) compared with the control group (153 to 158 ml; n.s.). However, in accordance with the present results, empagliflozin did not impact measures of left ventricular mass or ejection fraction or markers of cardiac fibrosis. Verma et al [27], who randomized 97 patients with established T2DM and cardiovascular disease to either empagliflozin or placebo in addition to standard treatment reported on an adjusted regression of the mean CMR estimated LV mass index by 3.35 g/m^2 (p = 0.01) in the empagliflozin compared with placebo group over six months. In accordance with the present data empagliflozin did neither influence the indexed LV volumes nor the LV ejection fraction. Early effects of the SGLT-2 inhibitor dapagliflozin on myocardial function and metabolism in patients with T2DM without heart failure was explored in a study by Oldgren et al [28]. Metformin-treated patients with T2DM were randomized to six weeks of dapagliflozin 10 mg daily (n = 25) or placebo (n = 24). Cardiac function and structure were studied by means of CMR and cardiac oxygen consumption, perfusion and efficiency with positron emission tomography. Dapagliflozin did not influence myocardial efficiency, but peak global radial strain decreased while peak global longitudinal and circumferential strains were unchanged compared with placebo. In contrast, a recent randomized study by Santos-Gallego et al [29] on 84 heart failure patients with reduced LV ejection fraction but free from T2DM found that empagliflozin decreased LV end-diastolic volume and LV end-systolic volume significantly and was associated with a reduction of LV mass. Moreover, empagliflozin significantly improved interstitial

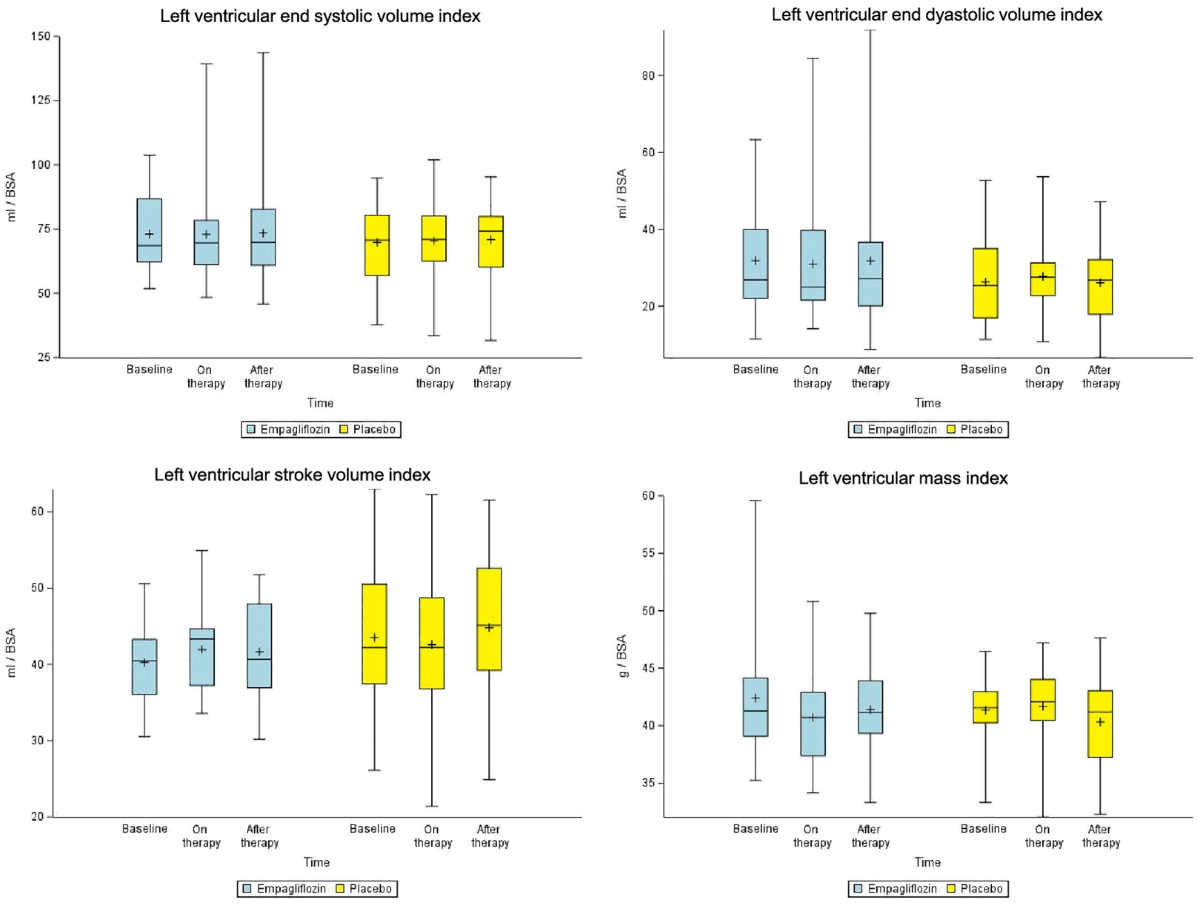

Fig. 2. Box plots of Cardiac Magnetic Resonance Imaging (CMR) measures of left ventricular end-diastolic volume index, left ventricular end-systolic volume index, left ventricular stroke volume index and left ventricular mass index from baseline to seven months on randomized treatment and following cessation of this therapy. Blue bars = empagliflozin group; Yellow bars = placebo group. Data shown are highest and lowest values (whiskers); median value (line in box); highest and lowest quartiles (Q1 and Q3; box limits); and the mean value (+). BSA = body Surface Area.

Table 3
Cardiac magnetic resonance imaging variables at the three studied time points: baseline, after seven months of treatment and three months following cessation of randomized therapy. Data shown are mean ± SD.

Variable	Empagliflozin n = 20	Placebo n = 22	p-value
Coronary flow reserve (ml/min/g tissue)			
Baseline	2.7 ± 0.9	2.9 ± 0.7	0.463
Seven months	3.0 ± 0.9	2.8 ± 0.6	0.387
After cessation	2.7 ± 0.7	2.8 ± 0.9	0.667
Extracellular volume (%)			
Baseline	33 ± 8	30 ± 5	0.098
Seven months	33 ± 6	30 ± 4	0.080
After cessation	32 ± 5	30 ± 4	0.341
Pulse wave velocity (m/*sec*)			
Baseline	6.1 ± 1.8	6.2 ± 1.8	0.965
Seven months	6.5 ± 1.7	6.4 ± 1.5	0.909
After cessation	6.6 ± 2.1	6.0 ± 1.5	0.396

Table 4
Echocardiographic variables at the three studied time points: baseline, after seven months of treatment and three months following cessation of randomized therapy. Data shown are mean ± SD.

Variable	Empagliflozin n = 20	Placebo n = 22	p-value
Left ventricular global longitudinal strain (%)			
Baseline	18 ± 4	19 ± 3	0.430
Seven months	19 ± 3	20 ± 3	0.598
After cessation	18 ± 4	20 ± 3	0.559
E/e' ratio			
Baseline	13 ± 4	11 ± 3	0.043
Seven months	12 ± 5	10 ± 2	0.105
After cessation	13 ± 5	11 ± 3	0.146
Mitral E/A ratio			
Baseline	1.1 ± 0.3	1.2 ± 0.4	0.662
Seven months	1.1 ± 0.6	1.2 ± 0.3	0.611
After cessation	1.2 ± 0.6	1.4 ± 0.4	0.073
Right ventricular end-diastolic diameter (mm)			
Baseline	35 ± 4	35 ± 5	0.882
Seven months	32 ± 8	35 ± 5	0.230
After cessation	33 ± 4	35 ± 4	0.131
Tricuspid Annular Plane Systolic Excursion (mm)			
Baseline	22 ± 3	21 ± 4	0.862
Seven months	23 ± 3	23 ± 4	0.947
After cessation	23 ± 3	23 ± 4	0.640

myocardial fibrosis and aortic stiffness in these patients with heart failure and reduced LV ejection fraction as well as improved their quality of life [30,31].

The discrepant results in the reported investigations are reasonably explained by differences in the patient populations in particular the presence or absence of a compromised left ventricular function. Another factor may be the presence or absence of established, not only newly discovered dysglycaemia. The present patient population had newly discovered IGT or T2DM, while the other studies, apart from the investigation by Santos-Gallego et al [29], recruited people with established T2DM. Moreover, heart failure was an inclusion criterion in the latter study but did not exist in the other studies. As an example, the

present patients had a normal left ventricular function despite their recent history of MI or unstable angina pectoris. The experiences from previous mechanistic investigations [26–29] and in the light of major clinical trials [21,23,24] may be interpreted as if SGLT-2 inhibition exerts a beneficial impact in patients with failing hearts or with impending heart failure, with and without compromised LV ejection fractions and irrespective of the presence of T2DM. However, such treatment does not seem to exert consistent benefits in people with normal cardiac dimensions and function even after an acute coronary syndrome. Another possibility is that the cardiac effects of SGLT-2 inhibition is less efficient in patients with newly discovered dysglycaemia, as in the present population, mainly with IGT and not overt T2DM. This assumption is, however, contradicted by the fact that SGLT-2 inhibition is as efficient in heart failure patients with and without T2DM.

The present study has some strengths and weaknesses. The methods used are the presently most accurate when examining left ventricular dimension and function. The parallel use of CMR and echocardiography with similar outcomes strengthens the results. The length of follow up and that the investigations were repeated after the cessation of study drug further underlines the stability of the observations. A weakness may be the limited number of patients, but it is unlikely that the inclusion of further study participants of the same kind would have changed the results. It should, however, be underlined that the present findings are representative for patients without compromised left ventricular function and should not be inferred for those with impending or overt compromised LV function. Finally, it may be that, in the light of observations made after the initiation of the present study [27], it would have been better to choose LV mass as the primary endpoint rather than LV end-diastolic volume, which may be a more accurate endpoint in patients with reduced LV ejection fraction. Still, and as demonstrated in Fig. 2, there were only small changes in LV mass, making it unlikely that the inclusion of more patients would have changed the outcome in any clinically meaningful way.

In conclusion the SGLT-2 inhibitor empagliflozin reduced glycaemic levels and body weight in patients with newly detected dysglycaemia and a recent acute coronary event but did not influence CMR and echocardiographic variables expressing LV function, coronary flow reserve and ECV. An explanation may be that the LV function of the patients was within the normal range. Further studies in populations with varying extent of LV dysfunction are warranted to confirm this speculation.

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Author contribution

LR drafted the protocol, which was approved by all co-authors. LR and SS led the study. ML and PS conducted and interpreted the CMR and AV the echocardiographic investigations. PN performed the statistical calculations based on plans made by LR, who drafted the first manuscript. All authors critically revised and approved the final version of the manuscript.

Data availability

The database is available by request to the corresponding author.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.110141.

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