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DOMENICA RUBINO

MD Director, Washington Center for Weight Management and Research

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ORIGINAL ARTICLE

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Effects of 6 weeks of treatment with dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on myocardial function and metabolism in patients with type 2 diabetes: A randomized, placebo-controlled, exploratory study

Jonas Oldgren PhD[1] | Sanna Laurila MD[2,3,4] | Axel Åkerblom PhD[1] | Aino Latva-Rasku MD[3] | Eleni Rebelos MD[3] | Henrik Isackson PhD[1] | Maria Saarenhovi PhD[3] | Olof Eriksson PhD[5] | Kerstin Heurling PhD[5] | Edvin Johansson PhD[5] | Ulrica Wilderäng PhD[6] | Cecilia Karlsson PhD[6] | Russell Esterline PhD[7] | Ele Ferrannini MD[8] | Jan Oscarsson PhD[6] | Pirjo Nuutila PhD[3]

[1]Uppsala Clinical Research Center and Department of Medical Sciences, Uppsala University, Uppsala, Sweden

[2]Heart Center, Turku University Hospital, Turku, Finland

[3]Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland

[4]Satakunta Central Hospital, Pori, Finland

[5]Antaros Medical AB, Mölndal, Sweden

[6]BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

[7]BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, Maryland

[8]Institute of Clinical Physiology, National Research Council, Pisa, Italy

Correspondence
Jonas Oldgren, PhD, Uppsala Clinical Research Center, Dag Hammarskjölds väg 38, Box 6363, SE-751 85 Uppsala, Sweden.
Email: jonas.oldgren@ucr.uu.se

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Abstract

Aim: To explore the early effects of dapagliflozin on myocardial function and metabolism in patients with type 2 diabetes without heart failure.

Materials and Methods: Patients with type 2 diabetes on metformin treatment were randomized to double-blind, 6-week placebo or dapagliflozin 10 mg daily treatment. Investigations included cardiac function and structure with myocardial resonance imaging; cardiac oxygen consumption, perfusion and efficiency with [^{11}C]-acetate positron emission tomography (PET); and cardiac and hepatic fatty acid uptake with [^{18}F]-6-thia-heptadecanoic acid PET, analysed by ANCOVA as least square means with 95% confidence intervals.

Results: Evaluable patients (placebo: n = 24, dapagliflozin: n = 25; 53% males) had a mean age of 64.4 years, a body mass index of 30.2 kg/m^2 and an HbA1c of 6.7%. Body weight and HbA1c were significantly decreased by dapagliflozin versus placebo. Dapagliflozin had no effect on myocardial efficiency, but external left ventricular (LV) work (−0.095 [−0.145, −0.043] J/g/min) and LV oxygen consumption were significantly reduced (−0.30 [−0.49, −0.12] J/g/min) by dapagliflozin, although the changes were not statistically significant versus changes in the placebo group. Change in left atrial maximal volume with dapagliflozin versus placebo was −3.19 (−6.32, −0.07) mL/m^2 (p = .056). Peak global radial strain decreased with dapagliflozin versus placebo (−3.92% [−7.57%, −0.28%]; p = .035), while peak global longitudinal and circumferential strains were unchanged. Hepatic fatty acid uptake

was increased by dapagliflozin versus placebo (0.024 [0.004, 0.044] μmol/g/min; p = .018), while cardiac uptake was unchanged.

Conclusions: This exploratory study indicates reduced heart work but limited effects on myocardial function, efficiency and cardiac fatty acid uptake, while hepatic fatty acid uptake increased, after 6 weeks of treatment with dapagliflozin.

KEYWORDS
dapagliflozin, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes is associated with a heightened risk of cardiovascular (CV) disease and CV mortality.[1] The development of heart failure (HF) in patients with diabetes can occur independently of atherosclerotic CV disease, and the presence of type 2 diabetes is associated with a poorer prognosis in patients with HF.[2] Although improved glycaemic control in patients with type 2 diabetes reduces the risk of microvascular complications, evidence that glucose lowering reduces CV events or hospitalization for HF is sparse.[3,4]

Sodium-glucose co-transporter-2 inhibitors (SGLT2is) are recommended for the treatment of type 2 diabetes; they act on proximal renal tubules to reduce glucose and sodium reabsorption, thereby lowering blood glucose, body weight and blood pressure.[5] CV benefits of SGLT2is in type 2 diabetes have been reported in three large outcome studies investigating the effects of empagliflozin, canagliflozin and dapagliflozin.[6–8] A reduction in hospitalizations because of HF was observed in patients both with and without HF at baseline and was evident within months from the start of treatment, suggesting mechanism(s) with a fast onset. Recently, dapagliflozin has been shown to reduce HF hospitalizations, CV deaths and total mortality in an outcome study of patients with HF and reduced left ventricular (LV) ejection fraction (EF).[9] Importantly, the outcomes were similar in patients with and without type 2 diabetes, yet dapagliflozin had no effect on HbA1c in the HF patients without diabetes.[9] Therefore, the mechanisms responsible for the HF outcome appear to be independent of plasma glucose lowering.

Several different mechanisms responsible for SGLT2i effects on prevention and treatment of HF in type 2 diabetes have been proposed. Increased natriuresis and osmotic diuresis have been shown to reduce plasma volume, and the loss of glucose through the urine results in an enhanced night-time fasting response, including an increased glucagon/insulin ratio and increased plasma levels of ketones.[5,10,11] Further, improved endothelial function, reduced arterial stiffness and reduced blood pressure, together with reduced plasma volume, may reduce both preload and afterload of the heart.[10,12] Increased use of ketones for energy production has been suggested to improve myocardial efficiency, that is, oxygen consumption in relation to mechanical work of the heart.[10,13] Diabetic cardiomyopathy is associated with increased myocardial fatty acid uptake (FAU).[14,15] SGLT2is have been shown to increase plasma free fatty acid (FFA) levels and fasting fatty acid oxidation.[5] Therefore, FAU rates in both the heart and liver were investigated to compare changes in FAU in myocardium with the liver.

The effects of 3–6 months of SGLT2i treatment on cardiac size and function in patients with type 2 diabetes vary,[16–21] but the most consistent findings are reduced LV mass[16–18] and signs of improved diastolic function,[16,17,20] whether patients have a history of CV disease[16–18] or not.[20] There are, to the best of our knowledge, no studies exploring the early effects of SGLT2is in patients with type 2 diabetes investigating both LV function and metabolism.

This exploratory, randomized, placebo-controlled study in patients with type 2 diabetes, but no HF, evaluated the effects of 6 weeks of dapagliflozin treatment on left atrium (LA) and LV function, mass and volumes assessed by magnetic resonance imaging (MRI); myocardial metabolism (oxygen consumption and perfusion) assessed by [^{11}C]-acetate positron emission tomography (PET); and FAU in the myocardium and liver by [^{18}F]-6-thia-heptadecanoic acid ([^{18}F]-FTHA) PET.

2 | METHODS

The Effects of DAPAgliflozin on CARDiac substrate uptake, myocardial efficiency and myocardial contractile work in type 2 diabetes patients (DAPACARD) study[22] was a double-blind, randomized, parallel-group, exploratory, phase IV study to investigate the effects of dapagliflozin on cardiac function and metabolism in patients with type 2 diabetes (NCT03387683). The study was conducted in Turku University Hospital and Turku PET centre, Finland, and in Uppsala University Hospital, Sweden, from 28 February 2018 to 19 March 2019. Data underlying the findings described in this manuscript may be available upon request in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagroup-dt.pharmacm.com/DT/Home.

Patients were randomized in a 1:1 ratio to receive 6 weeks of treatment, either dapagliflozin 10 mg or matched placebo, once daily. The randomization scheme was generated by Parexel International Limited and had a block size of two. No stratification factor was used. Randomization was performed by a central telephone service. Patients were encouraged not to change their lifestyles during the study. Blood samples were taken at baseline and end of treatment in the morning after an overnight fast. Detailed descriptions of analytical methods are provided in the supporting information.

2.1 | Patients

Patients with type 2 diabetes diagnosed at least 6 months prior to the study, aged 40–75 years and with a body mass index (BMI) of 25 kg/m^2 or higher were eligible if they had been treated with a stable dose of metformin for at least 6 weeks before screening, had an HbA1c of 6.0%–9.0% (42–75 mmol/mol), normal LV EF of 50% or higher, and no significant signs or symptoms of coronary artery disease. Exclusion criteria included uncontrolled hypertension, history of stroke, atrial fibrillation, valvular disease, type 1 diabetes, an estimated glomerular filtration rate (eGFR) of less than 45 mL/min/1.73m^2, and use of loop diuretics or other antidiabetic drugs than metformin.

2.2 | Ethics

The study was performed in accordance with the ethical principles originated in the declaration of Helsinki, International Council for Harmonization/Good Clinical Practice, and applicable regulatory requirements. All patients gave informed consent, and the study was approved by the Ethics Committee of the Hospital District of Southwest Finland, Turku, Finland, and by the Regional Ethics Committee in Uppsala, Sweden.

2.3 | Magnetic resonance imaging

The cardiac MRI protocol assessed variables related to the function and structure of the left ventricle and the LA. Functional variables included LV strain, EF and mitral valve flow characteristics, whereas structural variables comprised chamber volumes and LV mass. Details of the methodology and quantification techniques are given in the supporting information.

2.4 | Positron emission tomography

Patients underwent PET studies after overnight fasting. Myocardial oxygen consumption was assessed using intravenous [^{11}C]-acetate injections (dynamic scanning, 32 min) in examinations performed just after the cardiac MRI. LV FAU was measured on a separate day with the palmitate analogue [^{18}F]-FTHA (dynamic scanning of the heart, 27 min). Liver FAU was assessed via a 10-min static scan. LV oxygen consumption (k_{mono}, MVO_2) was estimated with a mono-exponential fitting function from [^{11}C]-acetate LV tissue data,[23] while a one-tissue compartment model was fitted to the LV time-activity curves to estimate myocardial perfusion.[24,25]

The FAU of both the left ventricle and liver was calculated as the product of FFA concentrations and the fractional tracer uptake rate (FUR) of [^{18}F]-FTHA corrected for plasma metabolite radioactivity. PET image analysis was performed using Carimas (v. 2.9).[26] Further details regarding the methods and variable calculations are provided in the supporting information.

2.5 | Power calculation and statistical analysis

This was an exploratory study without formal power calculations for several of the endpoints. Sample size estimation was based on the assumed number of patients needed to identify relevant effects of dapagliflozin versus placebo for two of the endpoints, primarily, peak global longitudinal strain of the left ventricle and, secondarily, myocardial efficiency. For longitudinal LV strain, an effect size of −2.0% and a two-sample *t* test with a two-sided significance level of .05 and power of 0.80 results in a sample size of 17 per group.[27] Assuming a 25% relative effect size of dapagliflozin on myocardial efficiency yielded a sample size of 22 per group.[28,29] With an addition of 15% to safeguard from non-evaluable subjects, a sample size total of 52 was planned. [^{18}F]-FTHA examinations were planned for a minimum total of 40 and a maximum of 44 randomized patients; this was because of ethical reasons and aimed to limit unnecessary exposure to ionizing radiation.

Baseline demographics and characteristics were obtained at either the screening or the randomization visit. Heart rate was assessed during the MRI examination obtained via electrocardiogram leads. Blood pressure was assessed during the PET examination, and was determined as the mean of three measurements.

Treatment effects were analysed using ANCOVA, a linear model with treatment group as the categorical independent variable and the baseline value of the respective endpoint as a covariate. For continuous variables, the normal distribution was checked with histogram plots and, if needed, log-transformed variables were used in the ANCOVA models. We report the results as least square mean (LSM) change from baseline with corresponding 95% confidence intervals for each treatment group as well as for the difference between groups. To evaluate the possible dependence between changes in different endpoints, Pearson correlation was calculated.

3 | RESULTS

3.1 | Study population

The study enrolled 87 patients, and a total of 53 patients, 38 in Finland and 15 in Sweden, were randomized to receive dapagliflozin (n = 27) or placebo (n = 26). None of the patients had a diagnosis of HF or signs or symptoms of coronary artery disease at study entry and all had normal systolic LV function. Four patients were excluded from the evaluable dataset. One patient was withdrawn from the study after randomization, but before first dose of medication because of increased transaminases. Two patients were excluded from the evaluable dataset because of important protocol deviations and one patient was excluded because of a combination of several protocol deviations (Figure S1). Except for the patients excluded from the evaluable dataset, compliance was high in both study groups. No adverse events leading to treatment discontinuation were reported. Thus, the evaluable study population comprised 49 patients, 25 patients randomized to dapagliflozin and 24 to placebo.

Baseline patient characteristics are presented in Table S1. In summary, the mean age was 64.4 years, 53% were males, the mean BMI was 30.2 kg/m^2, and median diabetes duration was 4.5 years. Patients had been on metformin treatment for a median of 3.8 years, the mean HbA1c was 6.7%, and 74% of patients had HbA1c levels of less than 7.0%. Angiotensin-converting enzyme inhibitors were used by 57.7% of patients in the placebo and 68.9% of patients in the dapagliflozin groups, and beta-selective blocking agents by 30.8% of patients on placebo and 15.4% of patients on dapagliflozin. No patients were on loop diuretics, and one patient in each group had treatment with a thiazide. The most commonly reported specific medical history terms were hypertension (76%), dyslipidaemia (61%) and chronic obstructive pulmonary disease (8%). Two patients had prior coronary artery disease and three reported diabetes complications. The groups were generally well balanced, except for a skewed sex distribution, with 68% males in the dapagliflozin group and 38% males in the placebo group.

3.2 | Treatment effects on body weight, blood pressure, haematological and metabolic biomarkers

After 6 weeks of treatment, patients randomized to dapagliflozin, compared with patients randomized to placebo, had significantly reduced body weight (−1.2 vs. +0.2 kg; $p < .001$) (Table 1). There were no changes in systolic or diastolic blood pressure or haemoglobin levels. Haematocrit was significantly increased from baseline in the dapagliflozin group, but the change fell just short of statistical significance from the corresponding change in the placebo group ($p = .07$) (Table 1).

As expected, after 6 weeks of treatment, patients randomized to dapagliflozin had reduced HbA1c (−0.27% vs. −0.01%; $p < .001$) and fasting plasma glucose (−0.39 vs. +0.03 mmol/L; $p = .039$) compared with patients randomized to placebo (Table 1). Changes in plasma levels of FFAs, β-hydroxybutyrate or lactate were not significantly different between the treatment arms, while plasma uric acid levels decreased significantly with dapagliflozin treatment compared with placebo. Dapagliflozin did not change plasma insulin levels, while plasma glucagon levels increased from baseline, but the change was not statistically significant versus placebo. However, the plasma glucagon/insulin ratio was significantly increased in patients treated with dapagliflozin versus placebo. A significant reduction in high-sensitivity C-reactive protein from baseline was observed after 6 weeks in patients on dapagliflozin, but the decrease was not significant versus placebo (−1.05 vs. −0.19 mg/L; $p = .064$). Plasma levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and fibroblast growth factor 21 were not significantly affected by dapagliflozin treatment (Table 1).

3.3 | Heart size, volumes, global strain and strain rates

LV and LA volumes as well as strain and strain rates were determined using MRI (Table 2, Figure 1 and Table S2). No treatment effects were observed on LV mass, end-diastolic, end-systolic or stroke volumes, cardiac output, or LV EF. However, heart rate was significantly reduced by dapagliflozin versus placebo (−3.23 vs. −0.26 min^{-1}; $p = .041$) (Table 2).

Change in left atrial maximal volume with dapagliflozin versus placebo was −3.19 (−6.32, −0.07) mL/m^2 ($p = .046$; Table 2). Changes in left atrial emptying function, early filling/atrial filling or deceleration time were not significantly different between the two treatment groups.

With regard to strain measures, while global longitudinal and circumferential LV strain did not change by dapagliflozin treatment, global radial strain was significantly decreased (−3.10% vs. 0.82%; $p = .035$) in patients randomized to dapagliflozin versus placebo (Figure 1, Table S2). In the dapagliflozin group, the changes in radial LV strain were reciprocally related to the changes in longitudinal strain (rho = −0.47; $p = .02$). A similar relationship was observed in the placebo group concerning the changes in radial versus the changes in longitudinal LV strain (rho = −0.33; $p = .12$). No significant differences in changes between dapagliflozin and placebo in peak systolic or diastolic strain rates were found.

3.4 | Myocardial work and perfusion

There was no significant effect of dapagliflozin treatment on myocardial efficiency, estimated as the ratio between LV mechanical work and oxygen consumption (Figure 2A and Table S3). However, both LV oxygen consumption and external LV work were significantly reduced from baseline after treatment with dapagliflozin (−0.30 [−0.49, −0.12] and −0.095 [−0.145, −0.043] J/g/min, respectively), but the changes did not achieve statistical significance versus placebo (Figure 2B,C and Table S3). [^{11}C]-acetate wash-out (k_{mono}), an estimate of $^{11}CO_2$ production from LV oxidative metabolism, was also significantly reduced from baseline after dapagliflozin treatment (−0.0036 [−0.0061, −0.0011] 1/min), while the change was not statistically significant versus placebo changes (Figure 2D and Table S3). LV perfusion was significantly reduced from baseline to week 6 in both the dapagliflozin (−0.083 [−0.126, −0.039] mL/g/min) and placebo groups (−0.046 [−0.091, −0.002] mL/g/min) (Figure 2E and Table S3).

3.5 | Fatty acid uptake

FAU rates are expressed both as FUR of [^{18}F]-FTHA and as FAU by multiplying the FUR by the corresponding plasma FFA levels at the time of the examination (Figure 3 and Table S4). The changes in myocardial FUR of [^{18}F]-FTHA and FAU were not significantly different between the dapagliflozin and placebo groups. By contrast, liver FAU and FUR of [^{18}F]-FTHA increased significantly by 6 weeks of treatment with dapagliflozin versus placebo ($p = .018$ and $p = .030$, respectively).

TABLE 1 Treatment effects on metabolic and heart biomarkers

	Placebo (n = 24)	Dapagliflozin (n = 25)
Body weight (kg)		
Baseline	83.9 (13.2)	91.0 (12.6)
End-of treatment	84.2 (13.2)	89.8 (12.4)
LSM	0.20 (−0.22, 0.63)	−1.20 (−1.62, −0.78)
LSM for difference, *p*-value	−1.41 (−2.02, −0.79), $p < .001$	
Systolic blood pressure (mmHg)		
Baseline	143.9 (11.9)	142.0 (16.8)
End-of treatment	143.7 (17.0)	139.3 (11.9)
LSM	0.09 (−4.56, 4.74)	−3.09 (−7.64, 1.47)
LSM for difference, *p*-value	−3.18 (−9.69, 3.34), $p = .33$	
Diastolic blood pressure (mmHg)		
Baseline	85.5 (8.0)	85.9 (10.1)
End-of treatment	85.0 (10.0)	83.5 (8.7)
LSM	−0.55 (−3.79, 2.69)	−2.35 (−5.52, 0.82)
LSM for difference, *p*-value	−1.80 (−6.33, 2.74), $p = .43$	
Haemoglobin (g/L)		
Baseline	133.7 (8.8)	138.2 (10.9)
End-of treatment	135.8 (11.1)	140.3 (11.1)
LSM	1.96 (−0.62, 4.55)	2.28 (−0.26, 4.81)
LSM for difference, *p*-value	0.31 (−3.35, 3.98), $p = .86$	
Haematocrit		
Baseline	0.398 (0.028)	0.404 (0.027)
End-of treatment	0.404 (0.030)	0.418 (0.029)
LSM	0.005 (−0.002, 0.012)	0.014 (0.007, 0.021)
LSM for difference, *p*-value	0.009 (−0.0008, 0.018), $p = .07$	
HbA1c (%)		
Baseline	6.67 (0.65)	6.74 (0.58)
End-of treatment	6.66 (0.72)	6.46 (0.41)
LSM	−0.01 (−0.11, 0.09)	−0.27 (−0.37, −0.17)
LSM for difference, *p*-value	−0.26 (−0.40, −0.12), $p < .001$	
Fasting glucose (mmol/L)		
Baseline	7.62 (1.12)	7.66 (1.07)
End-of treatment	7.65 (1.41)	7.32 (0.88)
LSM	0.03 (−0.25, 0.31)	−0.39 (−0.67, −0.11)
LSM for difference, *p*-value	−0.42 (−0.82, −0.02), $p = .039$	
FFAs (mmol/L)		
Baseline	0.78 (0.25)	0.79 (0.21)
End-of treatment	0.79 (0.16)	0.85 (0.25)
LSM	−0.01 (−0.09, 0.08)	0.06 (−0.02, 0.14)
LSM for difference, *p*-value	0.07 (−0.05, 0.18), $p = .27$	
β-hydroxybutyrate (μmol/L)		
Baseline	166 (108)	131 (53)
End-of treatment	132 (80)	142 (56)
LSM	−25.4 (−46.6, −4.3)	3.2 (−17.5, 23.9)
LSM for difference, *p*-value	28.7 (−1.2, 58.6), $p = .060$	

(Continues)

TABLE 1 (Continued)

	Placebo (n = 24)	Dapagliflozin (n = 25)
Lactate (mmol/L)		
Baseline	1.41 (0.46)	1.47 (0.52)
End-of treatment	1.53 (0.46)	1.50 (0.49)
LSM	0.10 (−0.04, 0.24)	0.04 (−0.10, 0.18)
LSM for difference, *p*-value	−0.06 (−0.26, 0.13), *p* = .52	
Uric acid (μmol/L)		
Baseline	356 (66)	362 (78)
End-of treatment	369 (79)	273 (67)
LSM	12.3 (−6.4, 30.9)	−89.2 (−107.5, −70.9)
LSM for difference, *p*-value	−101.5 (−127.6, −75.3), *p* < .001	
Insulin (pmol/L)		
Baseline	66.6 (38.2)	62.4 (29.7)
End-of treatment	67.2 (36.2)	62.6 (38.7)
LSM	0.69 (−7.30, 8.68)	0.12 (−7.70, 7.95)
LSM for difference, *p*-value	−0.57 (−11.76, 10.63), *p* = .92	
Glucagon (pmol/L)		
Baseline	12.3 (6.9)	13.1 (7.7)
End-of treatment	13.1 (6.7)	14.9 (6.8)
LSM	0.73 (−0.80, 2.25)	1.90 (0.41, 3.39)
LSM for difference, *p*-value	1.17 (−0.96, 3.30), *p* = .27	
Glucagon/insulin ratio		
Baseline	0.24 (0.21)	0.24 (0.12)
End-of treatment	0.24 (0.12)	0.31 (0.19)
LSM	−0.01 (−0.05, 0.04)	0.08 (0.03, 0.12)
LSM for difference, *p*-value	0.08 (0.016, 0.15), *p* = .017	
NT-proBNP, ng/L		
Baseline	112.3 (112.9)	69.9 (47.9)
End-of treatment	84.9 (42.8)	73.7 (51.6)
LSM	−11.9 (−29.1, 5.3)	−11.0 (−27.9, 5.8)
LSM for difference, *p*-value	0.9 (−23.6, 25.3), *p* = .94	
FGF21, ng/L		
Baseline	332 (187)	290 (179)
End-of treatment	349 (189)	316 (202)
LSM	20.0 (−27.7, 67.7)	23.6 (−23.1, 70.4)
LSM for difference, *p*-value	3.6 (−63.4, 70.7), *p* = .91	
Hs-CRP, mg/L		
Baseline	2.93 (4.18)	2.69 (3.31)
End-of treatment	2.67 (2.99)	1.70 (2.26)
LSM	−0.19 (−1.06, 0.67)	−1.05 (−1.90, −0.21)
LSM for difference, *p*-value	−0.86 (−2.07, 0.35), *p* = .064	

Abbreviations: FFAs, free fatty acids; FGF21, fibroblast growth factor 21; hs-CRP, high-sensitive C-reactive protein; NT-proBNP, N-terminal-pro-brain natriuretic peptide.

Note: Data are reported as: mean baseline levels (SD) and mean end-of treatment levels (SD); LSM, least square mean (95% CIs) from baseline in the individual groups as well as LSM for difference between the groups, adjusted for baseline.

TABLE 2 Treatment effects on left ventricular (LV) sizes and volumes, atrial volumes and LV compliance (MRI)

	Placebo (n = 24)	Dapagliflozin (n = 25)
LV end-diastolic volume (mL/m^2)		
Baseline	74.2 (14.1)	83.1 (16.7)
End-of treatment	74.5 (12.8)	82.0 (14.2)
LSM	−0.79 (−3.57, 2.00)	−0.02 (−2.80, 2.77)
LSM for difference, *p*-value	0.77 (−3.24, 4.78), *p* = .70	
LV end-systolic volume (mL/m^2)		
Baseline	28.3 (7.7)	32.8 (8.2)
End-of treatment	30.0 (8.0)	33.7 (8.4)
LSM	1.53 (0.17, 2.89)	0.98 (−0.38, 2.34)
LSM for difference, *p*-value	−0.55 (−2.51, 1.41), *p* = .57	
LV stroke volume (mL/m^2)		
Baseline	45.9 (8.3)	50.3 (9.7)
End-of treatment	44.5 (7.3)	48.4 (8.0)
LSM	−2.17 (−4.24, −0.09)	−1.15 (−3.23, 0.92)
LSM for difference, *p*-value	1.01 (−1.97, 3.99), *p* = .50	
Heart rate (min^{-1})		
Baseline	65.0 (9.2)	63.9 (5.6)
End-of treatment	64.5 (9.2)	60.8 (4.7)
LSM	−0.26 (−2.28, 1.76)	−3.23 (−5.21, −1.24)
LSM for difference, *p*-value	−2.97 (−5.80, −0.13), *p* = .041	
Cardiac output (mL/min/m^2)		
Baseline	2965.1 (611.4)	3174.4 (608.7)
End-of treatment	2845.8 (481.4)	2921.6 (509.5)
LSM	−157.6 (−287.5, −27.7)	−214.5 (−334.4, −84.6)
LSM for difference, *p*-value	−56.9 (−242.0, 128.2), *p* = .54	
Ejection fraction (%)		
Baseline	62.1 (5.6)	60.7 (3.8)
End-of treatment	60.1 (6.0)	59.2 (4.8)
LSM	−1.95 (−3.24, −0.66)	−1.57 (−2.86, −0.28)
LSM for difference, *p*-value	0.39 (−1.45, 2.22), *p* = .67	
LV mass (g/m^2)		
Baseline	41.3 (5.7)	44.8 (8.6)
End-of treatment	39.7 (6.3)	43.9 (9.0)
LSM	−1.59 (−2.52, −0.67)	−0.91 (−1.84, 0.02)
LSM for difference, *p*-value	0.69 (−0.64, 2.02), *p* = .30	
Left atrial min volume (mL/m^2)		
Baseline	16.7 (5.0)	16.5 (7.1)
End-of treatment	17.0 (6.7)	16.3 (6.8)
LSM	0.29 (−1.16, 1.74)	−0.24 (−1.66, 1.18)
LSM for difference, *p*-value	−0.53 (−2.56, 1.50), *p* = .60	
Left atrial max volume (mL/m^2)		
Baseline	31.2 (7.7)	33.1 (13.6)
End-of treatment	33.0 (10.7)	31.3 (10.7)
LSM	1.59 (−0.64, 3.82)	−1.60 (−3.79, 0.58)
LSM for difference, *p*-value	−3.19 (−6.32, −0.07), *p* = .056	

(Continues)

TABLE 2 (Continued)

	Placebo (n = 24)	Dapagliflozin (n = 25)
Left atrial emptying function (%)		
Baseline	46.6 (8.6)	49.6 (9.9)
End-of treatment	48.8 (7.3)	48.4 (8.3)
LSM	1.51 (−0.97, 4.00)	−0.58 (−3.01, 1.85)
LSM for difference, *p*-value	−2.10 (−5.59, 1.40), *p* = .23	
E/A (1)		
Baseline	0.91 (0.21)	1.15 (0.34)
End-of treatment	0.89 (0.23)	1.19 (0.40)
LSM	−0.04 (−0.14, 0.06)	0.06 (−0.04, 0.15)
LSM for difference, *p*-value	0.10 (−0.05, 0.25), *p* = .18	
DT (ms)		
Baseline	199.2 (36.1)	186.3 (39.7)
End-of treatment	210.6 (54.8)	190.3 (40.4)
LSM	16.59 (1.76, 31.43)	3.73 (−10.18, 17.64)
LSM for difference, *p*-value	−12.87 (−33.28, 7.55), *p* = .21	

Abbreviations: DT, deceleration time; E/A, early filling/atrial filling.
Data are reported as: mean baseline levels (SD) and mean end-of treatment levels (SD); LSM, least square mean (95% CIs) from baseline in the individual groups as well as LSM for difference between the groups, adjusted for baseline.

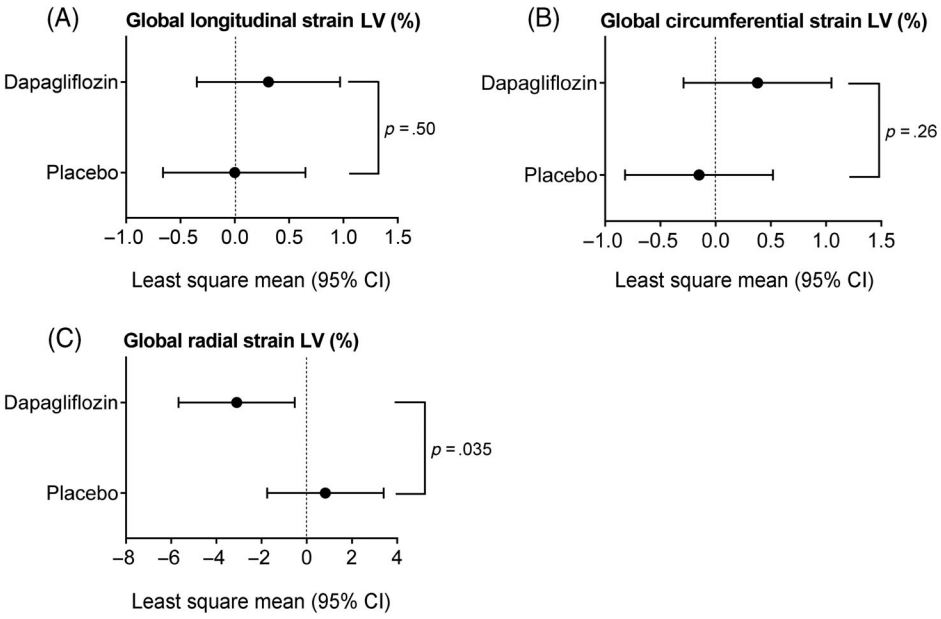

FIGURE 1 Effect of dapagliflozin on global longitudinal (A), circumferential (B) and radial strain (C). Data are least square means of post-treatment to baseline values with 95% CIs. LV, left ventricle

4 | DISCUSSION

This exploratory study is the first investigation of early functional and metabolic cardiac effects of SGLT2is by using both MRI and PET in patients with type 2 diabetes in a double-blinded, placebo-controlled, randomized study design. The 6-week treatment duration was based on previous findings of reductions in hospitalization for HF or CV death in patients with type 2 diabetes already observed within the first months after initiation of SGLT2i treatment in major CV outcome trials.[6–8] The overall effect of 6 weeks of treatment with dapagliflozin indicates reduced LV work and oxygen consumption, which may—at least in part—be attributable to reduced preload. This effect forms a plausible explanation for previous findings of reduced LV mass after 3 or 6 months of SGLT2i treatment.[16–18,20] Moreover, there was a significant increase in hepatic FAU by dapagliflozin treatment but no increase in FAU was observed in the heart.

In line with previous studies in patients with type 2 diabetes, significant reductions in body weight, HbA1c, fasting plasma glucose,

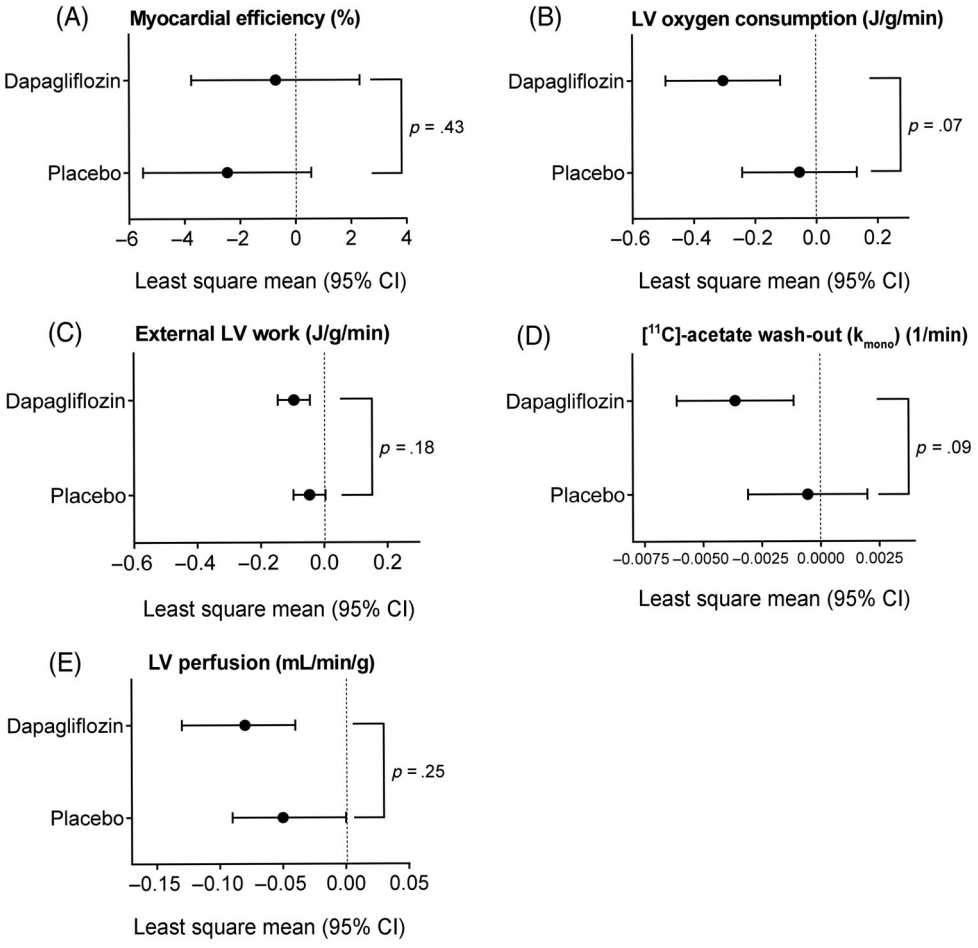

FIGURE 2 Effect of dapagliflozin on myocardial efficiency (A), left ventricular (LV) oxygen consumption (B), external (mechanical) LV work (C), [^{11}C]-acetate wash-out (k_{mono}) (D) and myocardial perfusion (E). Data are least square means of post-treatment to baseline values with 95% CIs

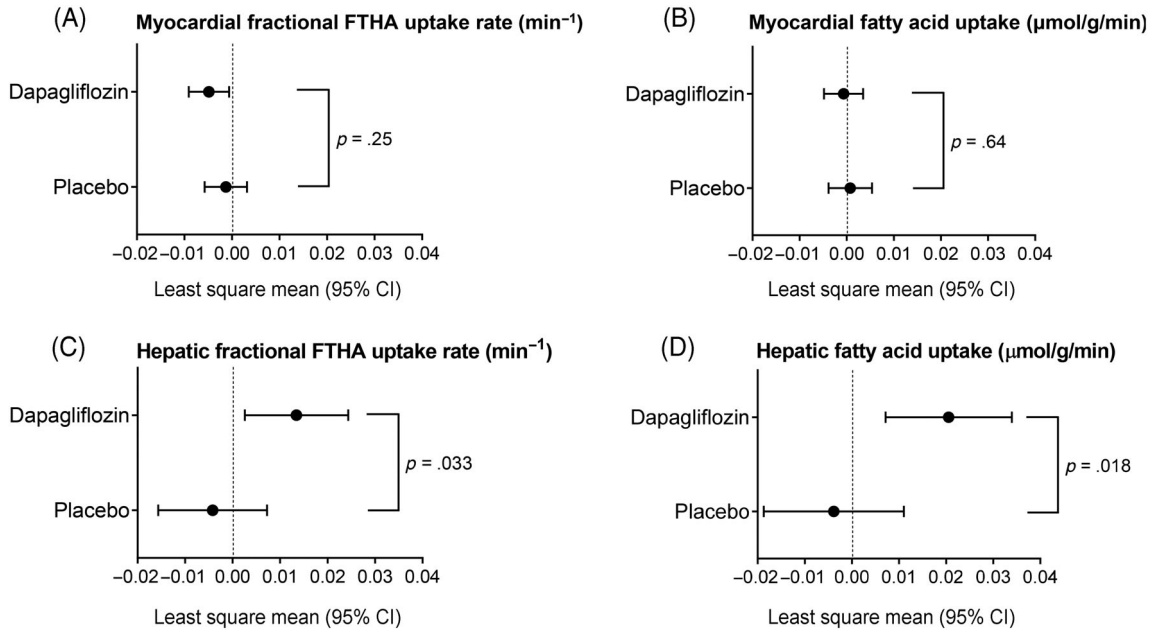

FIGURE 3 Effect of dapagliflozin on fractional [^{18}F]-6-thia-heptadecanoic acid (FTHA) uptake rate and fatty acid uptake in the heart (A, B) and the liver (C, D). Data are least square means of post-treatment to baseline values with 95% CIs

plasma uric acid, as well as increased fasting glucagon/insulin ratio, were observed in the dapagliflozin group.[5,10,12] As was also expected from previous studies,[5,10,12] trends towards increased β-hydroxybutyrate levels and haematocrit by dapagliflozin treatment were observed. In contrast to a prior smaller study in patients with type 2 diabetes without HF,[30] no effects of dapagliflozin on NT-proBNP levels were observed.

4.1 | Heart mass, volumes and strain

Dapagliflozin treatment for 6 weeks had no significant effect on LV mass or volumes, or on cardiac output or LV EF compared with placebo. Previous studies investigating the effects of SGLT2is on LV mass and volumes have been 3 months or longer in duration and have shown reduced LV mass.[16–18,20] Interestingly, heart rate was significantly reduced by dapagliflozin treatment (Table 2). In most studies, SGLT2 inhibition showed no effect on heart rate,[5,10] but a reduction has been observed in patients with a baseline heart rate of less than 70 min^{-1}.[31] Blood pressure was not significantly reduced by dapagliflozin in the current study; however, blood pressure was numerically reduced, as observed in previous studies.[5,10,12] The concomitant lowering of heart rate suggests decreased sympathetic nervous system activity, as found in animal studies[32] and recently observed in patients postmyocardial infarction.[33]

Previous studies have suggested a reduced preload by SGLT2is based on findings of reduced plasma volume.[10,12] In this study, functional indications of reduced preload were observed, including reduced maximal LA volume and global LV radial strain.

The reduction in global LV radial strain by dapagliflozin suggests reduced contraction of the left ventricle. The significant reciprocal association between radial and longitudinal/circumferential strain further support reduced LV contraction, although there were no significant changes in longitudinal or circumferential LV strain. Less negative longitudinal LV strain has previously been shown to be the result of reduced preload induced by lower body negative pressure[34] or tilting.[35] In summary, the changes in atrial volume and LV strains indicate that dapagliflozin treatment reduced cardiac preload and are in line with recent findings of reduced pulmonary capillary wedge pressure after 12 weeks of empagliflozin treatment.[36] Recently, Brown et al. showed improved LV contractility, assessed by global longitudinal LV strain, after 1 year of SGLT2i treatment, suggesting that early reductions in preload may be associated with improved contractility over the long term.[37]

4.2 | Myocardial work and metabolism

It has been shown that myocardial efficiency is reduced in patients with type 2 diabetes compared with healthy controls, and that insulin treatment further decreases efficiency because of increased mechanical heart work.[14] In the current study, myocardial efficiency was not affected by dapagliflozin treatment, but both external LV mechanical work and LV oxygen consumption were reduced from baseline, although these changes were not statistically significant compared with placebo.

In patients with severe HF, the heart uses more ketones for energy production.[38] It has been suggested that the beneficial effect of SGLT2is on HF is at least partly explained by increased availability of ketones for energy production.[5,10,12,39] In an animal model of diabetes (db/db mice), treatment with empagliflozin increased ATP production and heart work, but did not change myocardial efficiency. Addition of β-hydroxybutyrate to perfused db/db hearts did not change glucose or fatty acid oxidation, but further increased ATP production.[40] Short-term infusion of β-hydroxybutyrate in humans with or without HF increased cardiac output, heart rate and myocardial oxygen consumption, without altering myocardial efficiency.[41] In the current study, fasting plasma β-hydroxybutyrate levels tended to have increased (p = .06) after 6 weeks of dapagliflozin compared with placebo (Table 1), in line with numerous previous reports.[5]

In summary, the results indicate reduced heart work after 6 weeks of dapagliflozin treatment, which is in contrast to the acute increase in heart work following infusion of β-hydroxybutyrate. However, it is difficult to ascertain to what extent increased availability of ketones contributed to changes indicating reduced myocardial work after 6 weeks of dapagliflozin treatment.

4.3 | Fatty acid uptake

This study is the first to investigate the effect of SGLT2is on the uptake of fatty acids in the myocardium and the liver in patients with type 2 diabetes. It has previously been shown that plasma FFA levels increase following SGLT2i treatment as a result of the increase in lipolysis triggered by the glucose losses and subsequent lowering of insulin levels.[5] In this study, plasma FFA levels increased numerically in the dapagliflozin group, possibly reflecting the fluctuations in circulating FFAs. Dapagliflozin treatment had no significant effect on FAU or fractional [^{18}F]-FTHA uptake rate in the heart, while it increased in the liver. Myocardial FAU has previously been shown to be higher in patients with diabetes compared with patients without diabetes,[15] and is associated with diastolic dysfunction[42] and reduced myocardial efficiency.[14] Thus, our results are compatible with the interpretation that, despite increased fatty acid availability during treatment with dapagliflozin, the myocardial use of fatty acids is unchanged or even slightly reduced, in line with reduced myocardial work. However, short of measuring net balances of more than one substrate across the heart in vivo, our PET data cannot tell whether dapagliflozin was shifting myocardial substrate utilization away from FFAs and towards glucose or β-hydroxybutyrate for energy production.

The increased FAU in the liver following dapagliflozin treatment is in line with an enhanced fasting response, including the previous observation of increased endogenous glucose production following treatment with an SGLT2i[5,11] and the increased glucagon/insulin ratio. Such an increased hepatic FAU does not appear to result in lipid accumulation (steatosis), as dapagliflozin treatment of patients with type

2 diabetes resulted in reduced liver fat.[30] Instead, the increased uptake must be linked to increased gluconeogenesis. Gluconeogenesis is an ATP-consuming pathway that is fuelled by increased fatty acid oxidation. The finding of increased FAU in the liver therefore strengthens the hypothesis that SGLT2i treatment enhances both gluconeogenesis and fatty acid oxidation in the liver of patients with type 2 diabetes.

4.4 | Limitations

This was an exploratory study investigating the early effects of SGLT2is on myocardial function and metabolism in patients with well-controlled type 2 diabetes without HF, and the results should be considered as hypothesis generating. The low average HbA1c levels at study entry may have affected the results on, for example, FAU in the myocardium; however, the effects of dapagliflozin on CV outcome are not related to glucose control, as observed in the DAPA-HF trial.[9]

The study was performed at two centres, which may have introduced increased variability in the imaging results. To reduce variability, every participant was examined with the same individual scanner both at baseline and at follow-up. Furthermore, each PET scanner was regularly cross-calibrated against an external gamma counter to ensure accurate quantification and comparability.

Despite randomization, there was a skewed sex distribution between the randomized treatment groups. Therefore, all data were reanalysed using sex and treatment as factors in the linear model analysis, but the results did not change. Also, there are data to support that the effects of SGLT2is on HF hospitalization and CV outcome are similar in men and women.[43]

In conclusion, this exploratory study investigated the early effects of treatment with dapagliflozin on heart function and metabolism in patients with type 2 diabetes without HF. Although the effects were limited, there are some key findings: first, the changes in LV global strain variables and LA volume indicate reduced preload and, second, the pattern of reduced myocardial work, oxygen consumption and perfusion of the left ventricle indicate reduced oxygen demand because of reduced preload. The different effects of dapagliflozin on FAU in the heart compared with the liver indicate organ-specific fatty acid fluxes. These findings may add to the understanding of mechanisms leading to the previously observed reduced LV mass, HF hospitalizations and CV death during SGLT2i treatment in type 2 diabetes as well as changes in hepatic fatty acid handling. To corroborate the results of the current study, studies of the early effects of SGLT2is on heart function and metabolism in larger cohorts of patients with type 2 diabetes, and preferably also in patients with HF, are warranted.

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CONFLICT OF INTEREST

JOl reports fees to his institution from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Roche Diagnostics and Sanofi. SL, AL-R, ER, HI and MS have nothing to disclose. AÅ has received speaker´s fees and participated in Advisory Board meetings with AstraZeneca. OE, KH and EJ are employed by Antaros Medical AB and report fees to their institution from AstraZeneca. UW, CK, RE and JOs are employed by AstraZeneca, and JOs, CK and RE hold shares in AstraZeneca. EF reports research grants by AstraZeneca and Janssen, consultancy fees by Sanofi, and speaker fees by AstraZeneca, Boehringer Ingelheim and Lilly&Co. PN reports fees to her institution from AstraZeneca and Glaxo Smith Kline PLC.

AUTHOR CONTRIBUTIONS

JOl, JOs and PN conceived the study design, carried out the analyses and drafted the manuscript. AÅ, OE, KH, EJ, CK, RE and EF conceived the study design. SL, AL-R, ER, HI and MS contributed to data collection. OE, KH, EJ and JOs contributed to data analyses and UW carried out the statistical analyses. All authors reviewed and edited the manuscript.

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DATA AVAILABILITY STATEMENT

Data underlying the findings described in this manuscript may be available upon request in accordance with AstraZeneca's data sharing policy described at https://astrazenecagroup-dt.pharmacm.com/DT/Home.

ORCID

Jonas Oldgren https://orcid.org/0000-0002-9969-3921
Eleni Rebelos https://orcid.org/0000-0003-3050-8692
Ele Ferrannini https://orcid.org/0000-0002-1384-1584
Jan Oscarsson https://orcid.org/0000-0002-4573-517X
Pirjo Nuutila https://orcid.org/0000-0001-9597-338X

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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