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The simple trial

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Citation for published version (APA):
Jürgens, M., Schou, M., Hasbak, P., Kjær, A., Wolsk, E., Zerahn, B., Wiberg, M., Brandt-Jacobsen, N. H., Gæde, P., Rossing, P., Faber, J., Inzucchi, S. E., Gustafsson, F., & Kistorp, C. (2021). Effects of empagliflozin on myocardial flow reserve in patients with type 2 diabetes mellitus: The simple trial. *Journal of the American Heart Association*, *10*(15), [e020418]. https://doi.org/10.1161/JAHA.120.020418

Journal of the American Heart Association

Effects of Empagliflozin on Myocardial Flow Reserve in Patients With Type 2 Diabetes Mellitus: The SIMPLE Trial

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BACKGROUND: Sodium–glucose cotransporter 2 inhibitors reduce hospitalizations for heart failure and cardiovascular death, although the underlying mechanisms have not been resolved. The SIMPLE trial (The Effects of Empagliflozin on Myocardial Flow Reserve in Patients With Type 2 Diabetes Mellitus) investigated the effects of empagliflozin on myocardial flow reserve (MFR) reflecting microvascular perfusion, in patients with type 2 diabetes mellitus at high cardiovascular disease risk.

METHODS AND RESULTS: We randomized 90 patients to either empagliflozin 25 mg once daily or placebo for 13 weeks, as add-on to standard therapy. The primary outcome was change in MFR at week 13, quantified by Rubidium-82 positron emission tomography/computed tomography. The secondary key outcomes were changes in resting rate-pressure product adjusted MFR, changes to myocardial flow during rest and stress, and reversible cardiac ischemia. Mean baseline MFR was 2.21 (95% CI, 2.08–2.35). There was no change from baseline in MFR at week 13 in either the empagliflozin: 0.01 (95% CI, −0.18 to 0.21) or placebo groups: 0.06 (95% CI, −0.15 to 0.27), with no treatment effect −0.05 (95% CI, −0.33 to 0.23). No effects on the secondary outcome parameters by Rubidium-82 positron emission tomography/computed tomography was observed. Treatment with empagliflozin reduced hemoglobin A_{1c} by 0.76% (95% CI, 1.0–0.5; $P<0.001$) and increased hematocrit by 1.69% (95% CI, 0.7–2.6; $P<0.001$).

CONCLUSIONS: Empagliflozin did not improve MFR among patients with type 2 diabetes mellitus and high cardiovascular disease risk. The present study does not support that short-term improvement in MFR explains the reduction in cardiovascular events observed in the outcome trials.

REGISTRATION: URL: https://clinicaltrialsregister.eu/; Unique identifier: 2016-003743-10.

Key Words: empagliflozin ■ myocardial perfusion ■ positron emission tomography ■ SGLT2 inhibitor ■ type 2 diabetes mellitus

The landmark EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose) trial[1] demonstrated for the first time that a glucose-lowering drug, the sodium–glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin, rapidly and significantly decreased the risk of hospitalization for heart failure and cardiovascular death in patients with type 2 diabetes mellitus. Subsequent SGLT2i outcome trials, like DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58) and CANVAS (Canagliflozin Cardiovascular Assessment Study), demonstrated cardiovascular disease (CVD) benefits with SGLT2i in patients with type 2 diabetes mellitus with established or high risk of CVD, but the mechanisms underlying

CLINICAL PERSPECTIVE

What Is New?

- This is the first trial examining the effect of empagliflozin on myocardial flow reserve in patients with type 2 diabetes mellitus and cardiovascular risk factors.

What Are the Clinical Implications?

- The treatment had no effect on myocardial flow reserve, suggesting that the cardioprotective effect of empagliflozin is unrelated to the cardiac microcirculation.

Nonstandard Abbreviations and Acronyms

[82]Rb	Rubidium-82 positron emission tomography/computed tomography
CANVAS	Canagliflozin Cardiovascular Assessment Study
DECLARE-TIMI 58	Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58
EMPA-REG OUTCOME	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose
MFR	myocardial flow reserve
SGLT2i	sodium-glucose cotransporter 2 inhibitor

these benefits remain to be elucidated.[2-4] A consistent finding across the SGLT2i trials has been a reduction in admission rate for heart failure, and this result has been the focus of several studies.[5] In patients with type 2 diabetes mellitus, heart failure is the single most frequent and fatal cardiovascular complication, 2 to 4 times more common than myocardial infarction as a first event.[6] Emerging evidence suggests that impaired cardiac microcirculation plays a key role in the inherent high risk of heart failure in type 2 diabetes mellitus, specifically heart failure with preserved ejection fraction.[7] The chronic proinflammatory state of type 2 diabetes mellitus induces dysfunction of the coronary vascular endothelium, as demonstrated by increased expression of cytokines and adhesion molecules.[8,9] Cardiac microcirculation can be investigated noninvasively by positron emission tomography/computed tomography (PET/CT) and a suitable radiotracer such as Rubidium-82 ([82]Rb). Quantitative cardiac [82]Rb-PET/CT allows for measurement of myocardial blood flow at rest and during pharmacologically induced hyperemic conditions ("stress"). The ratio between rest and stress blood flow, known as myocardial flow reserve (MFR), integrates focal coronary arterial stenosis and diffuse atherosclerosis in the large epicardial arteries and the presence of microvascular dysfunction in the myocardium. MFR is a strong marker of the degree of microvascular dysfunction, and it is reduced in patients with type 2 diabetes mellitus.[10] Furthermore, MFR is a predictor of hospitalization for heart failure in patients with heart failure with preserved ejection fraction.[11,12] In animal studies, treatment with empagliflozin improves myocardial microcirculation by enhancing the vasodilatory response and reversing arterial thickening.[13,14] Additionally, canagliflozin has been shown to improve peripheral perfusion in a mouse model.[15] However, MFR was not directly measured in these studies. Recently, treatment with empagliflozin significantly reduced resting myocardial blood flow in a crossover trial of 13 individuals with type 2 diabetes mellitus.[16] MFR increased nonsignificantly; however, the lack of significance may have been attributable to the relatively small sample size. Based on these findings, it seems plausible that treatment with SGLT2i could lead to improved MFR. We hypothesized that part of the beneficial effects of SGLT2i in the prevention of heart failure in type 2 diabetes mellitus could be mediated by improved MFR. The aim of this double-blind, randomized placebo-controlled trial, was to investigate whether treatment with empagliflozin improves MFR, as measured by cardiac [82]Rb-PET/CT in patients with type 2 diabetes mellitus and high risk of CVD.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Trial Design and Participants

The SIMPLE trial (The Effects of Empagliflozin on Myocardial Flow Reserve in Patients With Type 2 Diabetes Mellitus) was a single-center, double-blind, randomized clinical trial assessing the effect of empagliflozin on myocardial flow in high-risk patients with type 2 diabetes mellitus. The design and methods of the SIMPLE trial have been published previously.[17] We enrolled 91 participants with known CVD or high CVD risk between April 4, 2017, and May 11, 2020. Participants

were recruited from the outpatient diabetes mellitus clinics at University Hospital Herlev-Gentofte, Glostrup and Rigshospitalet, Denmark. Patients were considered eligible if they had been diagnosed with type 2 diabetes mellitus at least 3 months before enrollment, had received stable glucose-lowering treatment for 1 month, and their hemoglobin A_{1c} (HbA$_{1c}$) was between 6.5% and 10% (48–86 mmol/mol) if they were receiving glucose-lowering medication, and between 6.5% and 9% (48–75 mmol/mol) if they were drug naive. Participation also required established CVD, defined as a history of myocardial infarction, significant coronary stenosis, unstable angina, ischemic stroke or peripheral artery disease, or the presence of a CVD risk factor defined as albuminuria (urinary albumin–creatinine ratio ≥30 mg/g) or NT-proBNP (N-terminal pro-B-type natriuretic peptide) ≥70 ng/L. Key exclusion criteria were estimated glomerular filtration rate ≤30 mL/min per 1.73 m^2, severe bronchospastic disease (eg, asthma), and treatment with any SGLT2i within 1 month before study enrollment. The study was approved by the Ethics Committee of the Capital Region of Denmark and the Danish Data Protection Agency. The trial was registered on EudraCT (2016-003743-10) and ClinicalTrials.gov (NCT03151343) and carried out in accordance with the Declaration of Helsinki (1993), as well as with the International Conference on Harmonization Guidelines for Good Clinical Practice. The trial was monitored by the Good Clinical Practice unit of Copenhagen, Denmark. The report of the results followed the Consolidated Statement of Reporting Trials guidelines.

Randomization and Masking

Eligible participants were randomly assigned (1:1) to either empagliflozin 25 mg once daily or a matching placebo for 13 weeks. Randomization was carried out by a central pharmacy (Glostrup Pharmacy, Denmark) using block randomization with a block size of 10. Participants and investigators were blinded to the treatment group for the duration of the study.

Myocardial Flow Reserve [82]Rb-PET/CT

Myocardial perfusion was measured using cardiac [82]Rb-PET/CT, which allows for flow quantification in absolute terms. All measurements were performed on a Siemens Biograph mCT/PET 128-slice scanner (Siemens Medical Solutions). Measurements were taken at rest and during adenosine-induced stress. Low-dose noncontrast CT was acquired for attenuation correction. During the scan at rest, approximately 1100 MBq of [82]Rb chloride from a CardioGen-82 Sr-82/Rb-82 generator (Bracco Diagnostics, Inc.) was intravenously infused with a constant flow rate of 50 mL/min. List-mode 3-dimensional data acquisition

was started with the tracer infusion and continued for 7 minutes. Static images were reconstructed with a 2.5-minute delay to allow [82]Rb to clear from the blood pool. Maximal hyperemia was induced with adenosine, infused at 140 µg/kg per minute for 6 minutes. After 2.5 minutes of adenosine infusion, intravenous [82]Rb infusion and list-mode acquisition was performed, using the same protocol as for rest. Myocardial blood perfusion quantification (milliliters per minute per gram) was performed using Cedars-Sinai QGS+QPS 2015.6 software (Cedars-Sinai Medical Center), which is based on a single-compartment model for [82]Rb tracer kinetics.[18]

Rest flow and, by extension, MFR varies according to cardiac work. Adjustment can be made for the cardiac workload by the rate-pressure product[19]: rate-pressure product–adjusted rest flow=(rest flow×10 000)/(heart rate at rest×systolic blood pressure at rest). To assess baseline risk among included patients, the following delineations of MFR were used: MFR values >2.5 were considered normal, values <2.0 were considered impaired MFR, and values between 2.0 and 2.5 were considered intermediate MFR.[20] Additionally, the static images were used to quantify the extent and severity of perfusion abnormalities in the myocardium using Cedars-Sinai QGS+QPS 2015.6 software (Cedars-Sinai Medical Center). The difference between the total perfusion deficit at rest and under stress corresponds to the extent of inducible ischemia in the myocardium, a parameter used for deciding optimal management in patients with known or suspected coronary artery disease.[21]

Study Outcomes

The primary end point was between-group change in MFR from baseline at week 13. Secondary exploratory endpoints included change in resting rate-pressure product–adjusted MFR, rest flow, stress flow, and the extent of reversible ischemia.

Statistical Analysis

The sample size was based on a power calculation of the primary end point, MFR measured by [82]Rb-PET/CT. A change in MFR of 0.5 was considered clinically relevant, and a SD of 0.8 was based on recent studies in the PET/CT department.[22] At a power of 80% and a 2-sided significance level of 5%, 41 participants per group were needed. We aimed to include 92 participants to allow for a dropout rate of 10%. Analyses of the primary end point, change in MFR, and all secondary end points were based on the intention-to-treat population, that is, all patients with baseline measurements that took at least 1 dose of the trial medication. Variables were tested for normality using histograms and qq-plots. Variables with skewed distributions were log-transformed, using the natural logarithm, before

statistical analysis. Transformed data are presented on the log scale. We used a constrained linear mixed model to calculate the change from baseline and between-group difference at week 13 (ie, treatment effect). Baseline adjustment is an inherent feature of the constrained linear mixed model. To account for correlation between repeated measures on the same subject, an unstructured covariance was assumed. Aside from the secondary end points, rate-pressure product–adjusted MFR, rest flow, stress flow, and reversible ischemia, additional exploratory end points were investigated post hoc.

Missing values were deemed missing at random and imputed implicitly by maximum likelihood estimation. When analyzing the per-protocol population, that is, participants with both baseline and follow-up measurements, a constrained linear mixed model was also used. Analysis of change in MFR categories by treatment group was performed using Fisher's exact test. Exploratory analyses were performed to evaluate for potential effect modification across the following predefined subgroups: established versus not established coronary artery disease, history of myocardial infarction, presence of albuminuria at baseline, baseline estimated glomerular filtration rate <90 mL/min per 1.73 m^2, baseline HbA$_{1c}$ >8.5% (69 mmol/mol), duration of diabetes mellitus >10 years, age >65 years, and baseline BMI >30 kg/m^2, and sex. The division of subgroups follows recommendations to improve statistical inference.[23] Descriptive characteristics are reported as mean and corresponding SD. Change from baseline is reported as mean, a 95% CI, and an unadjusted P value, unless stated otherwise. P values <0.05 were considered statistically significant. Statistical analyses and graphical design were carried out using R version 4.0.2 (R Foundation for Statistical Computing).

RESULTS

Of 193 patients screened for eligibility, 91 fulfilled criteria and provided informed consent. Ninety patients received at least 1 dose of the study drug and were included in the intention-to-treat cohort; 45 patients received empagliflozin, and 45 received placebo. Baseline MFR values were obtained for 44 patients in the empagliflozin group and 43 in the placebo group. Of these, 29 had normal MFR, 22 had MFR in the intermediate range, and 36 had impaired MFR. In total, 78 participants, 36 in the placebo group and 42 in the active group, fulfilled per-protocol criteria, since baseline and 13-week ^{82}Rb PET-CT were available (Figure 1). Participants were predominantly men (80%), with mean (SD) HbA$_{1c}$ of 7.6% (±0.9) (59.5±10.3 mmol/mol), and blood pressure of 139 (±14) systolic and 81 (±10) mm Hg diastolic. A total of 51% had a history of coronary disease, defined as either previous myocardial infarction, significant stenosis of a coronary artery, or coronary artery bypass graft. Eight percent of the participants reported having episodes of chest pain. In addition, 16% had a prescription of long- or short-acting nitrates. Mean (SD) left ventricular ejection fraction assessed by echocardiography was 58%±8%. By ^{82}Rb-PET/CT imaging, 10 participants had a reversible ischemia extent of ≥10% at baseline, which was equally distributed within the groups. Diabetes mellitus was well managed, with 32% of the participants receiving 1 glucose-lowering drug, 30% receiving 2, and 33% receiving ≥3. Four percent did not receive any glucose-lowering medication. The prevalence of cardiovascular prevention therapy among the participants was high, with 93% receiving a statin and 79% receiving either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker. The patients were balanced at baseline according to treatment groups (Table 1), except for the use of beta blockers (58% for the empagliflozin group versus 31% for the placebo group; P=0.020).

Myocardial Flow Reserve

At baseline, mean (SD) MFR was 2.21 (95% CI, 2.08–2.35). The intention-to-treat analysis of the primary end point showed no change in MFR at 13 weeks in either group (empagliflozin: 0.01; 95% CI, −0.18 to 0.21; P=0.909 versus placebo: 0.06; 95% CI, −0.15 to 0.27; P=0.559). We did not find any treatment effect (−0.05; 95% CI, −0.33 to 0.23; P=0.716) (Table 2, Figure 2). Analyzing the per-protocol population did not change the main findings of the primary end point (P=0.764 for treatment effect). Two participants in both treatment groups changed MFR category from intermediate to impaired, and 3 participants changed from normal to impaired (P=1.000). There was no effect modification of empagliflozin on MFR by any of the predefined subgroups or beta-blocker use (Figure 3). Further, there was no treatment effect of empagliflozin on the primary end point MFR in patients with baseline intermediate or impaired MFR (P=0.835) or in the subgroup (n=43) of participants without established coronary artery disease (P=0.901).

Secondary Outcomes

We further adjusted the MFR for the rate-pressure product to account for baseline workload. However, the adjusted MFR did not change in either the empagliflozin group (P=0.694) or in the placebo group (P=0.811), and no treatment effect (P=0.653) was observed (Table 2, Figure 2).

Myocardial Blood Flow at Rest and During Stress

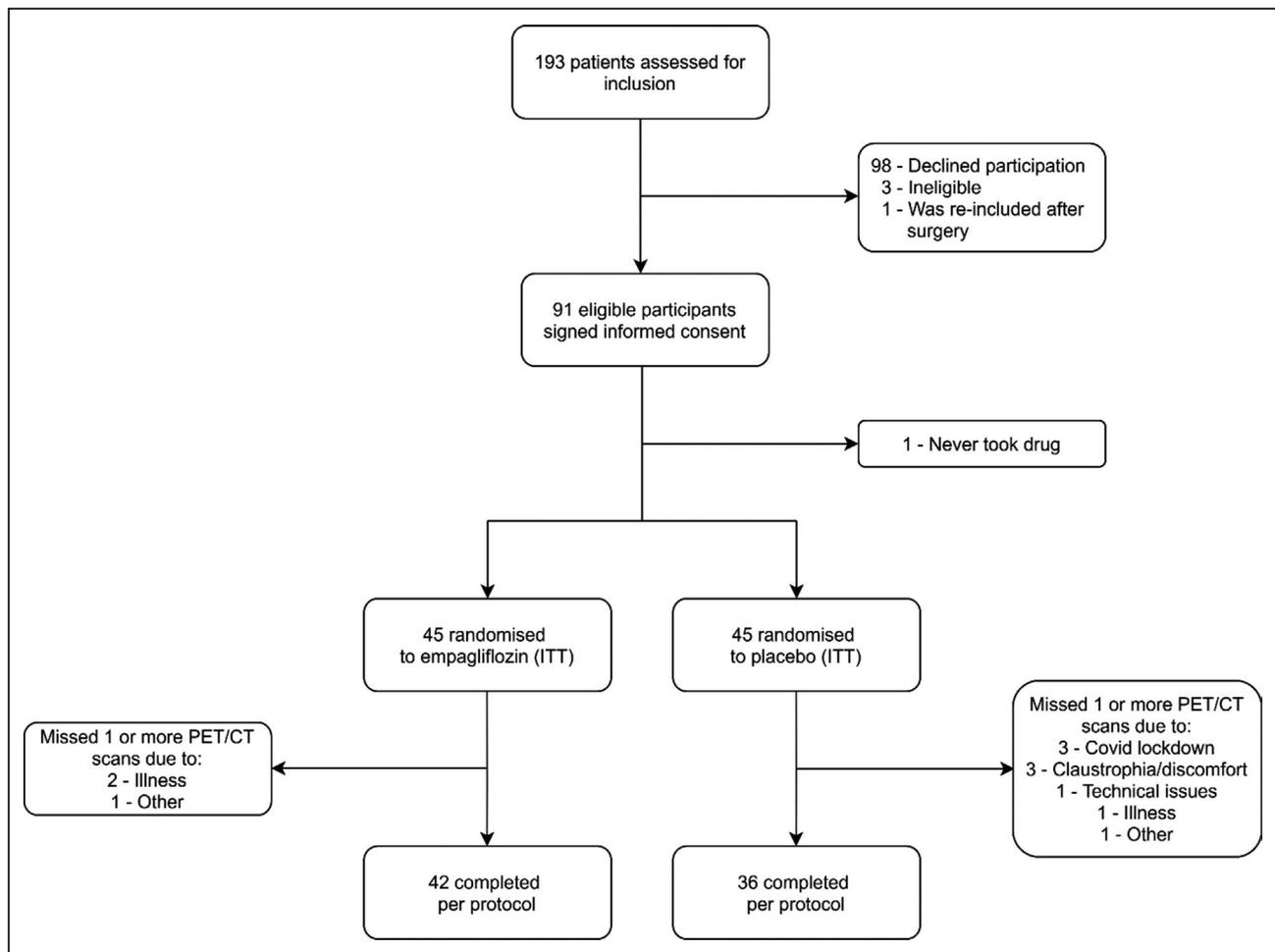In the empagliflozin group, between baseline and week 13, myocardial rest flow decreased by −0.10 mL/min

Figure 1. Consolidated Statement of Reporting Trials flow chart of the inclusion process.
CT indicates computed tomography; ITT, intention to treat; and PET, positron emission tomography.

per g (95% CI, −0.16 to −0.02; P=0.011) and, in the placebo group, the change was −0.15 mL/min per g (95% CI, −0.23 to −0.08; P<0.001). However, there was no difference between groups: +0.06 mL/min per g (95% CI, −0.03 to 0.15; P=0.176). In the per-protocol analysis, there was no treatment effect on rest flow (P=0.188). The analysis of stress flow in the intention-to-treat population showed a reduction between baseline and week 13 in the empagliflozin group of −0.17 mL/min per g (95% CI, −0.34 to −0.01; P=0.044), as well as in the placebo group: −0.20 mL/min per g (95% CI, −0.38 to −0.03; P=0.025). However, at end of study, there was no treatment effect: −0.03 mL/min per g (95% CI, −0.19 to 0.26;, P=0.769). Additionally, no treatment effect on stress flow in the per-protocol analysis (P=0.745) was observed.

Reversible Ischemia

In the intention-to-treat analysis of reversible ischemia, there was no significant change between baseline and week 13 in either group: empagliflozin:

0.74% (95% CI, −0.48 to 1.97; P=0.235), placebo: 0.08% (95% CI, −1.23 to 1.40; P=0.905), as well as no treatment effect 0.66% (95% CI, −1.04 to 0.66; P=0.443). There was also no significant treatment effect on reversible ischemic extent in the per-protocol analysis (P=0.515).

Selected Clinical Parameters

Treatment with empagliflozin decreased HbA$_{1c}$ by 0.76% (95% CI, 1.00–0.51; P<0.001) compared with placebo after 13 weeks (Table 2), and increased hematocrit by 1.69% (95% CI, 0.76–2.62; P<0.001) in comparison with the control group at week 13. In contrast, there was no treatment effect on weight (P=0.512), estimated glomerular filtration rate (P=0.373), heart rate (P=0.972), or systolic blood pressure (P=0.439) between groups at week 13 (Table 2).

Safety

The treatment was generally well tolerated. In total, there were 69 reported adverse events. The most

Table 1. Baseline Characteristics

	Empagliflozin (n=45)	Placebo (n=45)	P Value
Demographic			
Age, y	66±9	67±9	0.675
Male sex, %	76	84	0.492
Known duration of type 2 diabetes mellitus, y	14 (7.5–19)	15 (8–18)	0.500
BMI, kg/m²	31.9±5.5	29.8±5.6	0.072
Systolic blood pressure, mm Hg	139±16	140±13	0.717
Diastolic blood pressure, mm Hg	81±11	81±10	0.909
Biochemistry			
eGFR	79.5±24.0	79.3±21.9	0.966
HbA$_{1c}$, mmol/mol	60.6±10.9	58.4±9.6	0.338
HbA$_{1c}$, %	7.7±1.0	7.5±0.9	0.338
LDL cholesterol, mmol/L	1.7±0.5	1.7±0.5	0,714
HDL cholesterol, mmol/L	1.0±0.2	1.0±0.3	0.561
NT-proBNP, ng/L	119.5 (70.3, 213.8)	103 (46.8, 237.5)	0.813
NT-proBNP >70 ng/L	31 (69)	26 (58)	0.382
UACR, mg/g	17 (9, 42)	25 (11, 82)	0.547
UACR >30 mg/g	14 (31)	16 (36)	0.823
Hematocrit, %	40±4	40±4	0.727
Cardiovascular status n (%)			
History of myocardial infarction	21 (47)	15 (33)	0.282
Coronary stenosis, previous PCI or CABG	27 (60)	20 (44)	0.206
History of stroke	6 (13)	6 (13)	1.000
Peripheral artery disease	3 (7)	3 (7)	1.000
Diabetes mellitus medication			
Metformin	35 (78)	39 (87)	0.408
Insulin	26 (58)	26 (58)	1.000
GLP-1 RA	12 (27)	11 (24)	1.000
DPP-IV inhibitor	6 (13)	12 (27)	0.188
Sulfonylurea	3 (7)	3 (7)	1.000
Antihypertensive medication, n (%)			
ACEi/ARB	38 (84)	33 (73)	0.302
Calcium channel blockers	18 (40)	20 (44)	0.831
Beta-blockers, n (%)	26 (58)	14 (31)	0.020
Lipid lowering medication, n (%)	41 (91)	43 (96)	0.673
⁸²Rb-PET/CT			
MFR	2.17±0.63	2.26±0.67	0.480
RPP-adjusted MFR	1.93±0.64	2.01±0.54	0.511

(Continued)

Table 1. Continued

	Empagliflozin (n=45)	Placebo (n=45)	P Value
Myocardial stress flow, mL/g per min	2.43±0.87	2.47±0.77	0.842
Myocardial rest flow, mL/g per min	1.16±0.36	1.17±0.42	0.835
Baseline reversible extent (TPD, %)	3.81±3.10	5.52±4.88	0.056

Values are presented as means±SD, medians (lower quartile–upper quartile) or percentages, as appropriate. ⁸²Rb-PET/CT indicates Rubidium-82 positron emission tomography/computed tomography; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; DPP-IV, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucose-like peptide-1 receptor agonist; HbA$_{1c}$, hemoglobin A$_{1c}$; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MFR, myocardial flow reserve; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; RPP, rate-pressure product; TPD, total perfusion deficit; and UACR, urinary albumin/creatinine ratio.

common adverse event was polyuria, which was reported by 15 participants, of which 14 belonged to the empagliflozin group. There were 5 serious adverse events in total, 3 in the placebo group and 2 in the empagliflozin group. Only 1 of the serious adverse events in the empagliflozin group, an admission for significant hypotension, was considered related to the treatment. There were no cases of diabetic ketoacidosis. The trial medication was considered an add-on to best practice guidelines and did not replace the participants' glucose-lowering medication. Medication adherence was monitored systematically by adherence queries at scheduled telephone contacts and during a safety visit at the clinic.

DISCUSSION

In the present SIMPLE trial, treatment with the SGLT2i empagliflozin did not change MFR quantified by ⁸²Rb-PET/CT after 13 weeks in patients with type 2 diabetes mellitus and high risk of cardiovascular events. Thus, this clinical trial does not support the hypothesis that the cardioprotective effect of empagliflozin, particularly as it relates to heart failure, is attributable to improved cardiac microcirculatory function. The present trial provides novel data on the actual mechanism underlying the heart failure prevention of the SGLT2i by investigating the effects on MFR by state-of-the-art methods. In the EMPA-REG OUTCOME and DECLARE-TIMI 58 trials, the significant reduction in hospitalization for heart failure occurred within a few weeks.[24] Several mechanisms have been proposed to explain the reduction in heart failure. However, only a few clinical randomized trials have reported on changes in cardiac function and structure with SGLT2i among patients with type 2

Table 2. Primary and Secondary Outcomes

	Baseline (n=90)	Empagliflozin (n=42)	P Value	Placebo (n=36)	P Value	Group difference	P Value
MFR	2.21 (2.08 to 2.35)	0.01 (−0.18 to 0.21)	0.909	0.06 (−0.15 to 0.27)	0.559	−0.05 (−0.33 to 0.23)	0.716
MFR, RPP adjusted	1.97 (1.84 to 2.09)	−0.04 (−0.23 to 0.16)	0.694	0.03 (0.19 to 0.24)	0.811	−0.07 (−0.35 to 0.22)	0.653
Rest flow, mL/g per min	1.16 (1.08 to 1.24)	−0.10 (−0.16 to −0.02)	0.011	−0.15 (−0.23 to −0.08)	>0.001	0.06 (−0.03 to 0.15)	0.176
Stress flow, mL/g per min	2.45 (2.28 to 2.62)	−0.17 (−0.34 to −0.01)	0.044	−0.20 (−0.38 to −0.03)	0.025	−0.03 (−0.19 to 0.26)	0.769
Reversible extent, TPD, %	4.66 (3.77 to 5.55)	0.74 (−0.48 to 1.97)	0.235	0.08 (−1.23 to 1.40)	0.905	0.66 (−1.04 to 0.66)	0.443
HbA$_{1c}$, %	7.63 (7.43 to 7.83)	−0.68 (−0.86 to −0.49)	<0.001	0.08 (−0−11 to 0.27)	0.411	−0.76 (−1.00 to −0.51)	<0.001
HbA$_{1c}$, mmol/mol	59.85 (57.66 to 62.04)	−7.40 (−9.39 to −5.42)		0.86 (−1.21 to 2.95)		−8.27 (−10.94 to −5.60)	
Hematocrit, %	40.43 (39.62 to 41.24)	1.36 (0.67 to 2.04)	<0.001	−0.33 (−1.04 to 0.38)	0.357	1.69 (0.76 to 2.62)	<0.001
eGFR, mL/min per 1.73 m^2	79.39 (74.63 to 84.16)	−0.71 (−3.90 to 2.74)	0.660	1.25 (−1.94 to 4.43)	0.440	−1.96 (−6.29 to 2.37)	0.373
NT-proBNP, log-ng/L	4.83 (4.57 to 5.11)	−0.25 (−0.53 to 0.03)	0.077	−0.12 (−0.40 to 0.16)	0.412	−0.12 (−0.52 to 0.26)	0.506
Weight, kg	95.01 (91.14 to 98.88)	−0.14 (−2.78 to 1.99)	0.893	0.86 (−1.30 to 3.03)	0.432	−1.01 (−4.04 to 2.02)	0.512
HR, bpm	69.16 (66.66 to 71.66)	−0.88 (−3.47 to 1.71)	0.503	−0.94 (−3.45 to 1.56)	0.459	0.06 (−3.47 to 3.60	0.972
Systolic BP, mm Hg	139.55 (136.18 to 142.92)	−5.55 (−10.59 to −0.51)	0.031	−2.93 (−7.57 to 1.71)	0.213	−2.62 (−9.28 to 4.05)	0.439

Values are presented as means (95% CI)). BP indicates blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; MFR, myocardial flow reserve; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RPP, rate-pressure product; and TPD, total perfusion deficit.

diabetes mellitus, and most of these studies of impact of cardiac function by echocardiography did not find any changes after 12 weeks.[23,25,26]

Impaired cardiac microcirculation has been a general finding in patients with type 2 diabetes mellitus, wherein their reduced vasodilator capacity is closely linked with myocardial function and with clinical symptoms of heart failure.[27] MFR is a strong predictor of outcome in patients assessed for coronary heart disease and hypertrophic cardiomyopathy. Indeed, MFR measured by PET/CT provides substantial incremental risk stratification and carries independent prognostic value in patients with type 2 diabetes mellitus.[10] In experimental studies in rodents, treatment with SGLT2i improved coronary microvascular function and improved cardiac contractility in rodents.[28] In patients with type 2 diabetes mellitus, SGLT2i improves endothelial function, which plays a key role for MFR capacity.[29] SGLT2i could thus improve cardiac microcirculation by reducing vascular stiffness and protecting endothelial glycocalyx from sodium overload.[30] The potential functional role of cardiac microcirculation in heart failure[7,27] has been further underlined by the close link between impaired MFR and echocardiographic and hemodynamic important functional parameters of the left

ventricle.[31,32] Therefore, we hypothesized that improvement of cardiac microcirculation could be part of the actual mechanisms behind the rapid decline in hospitalization for heart failure in the SGLT2i outcome trials. We did not, however, find any change with empagliflozin after 13 weeks, and several explanations could be considered. Nonadherence to the study medication may play a role, although it is contradicted by the finding of an expected decrease in HbA$_{1c}$ and increase in hematocrit among participants who received treatment with empagliflozin. The level of change in these 2 parameters was comparable to that which was reported in other SGLT2i trials. It is therefore unlikely that nonadherence was more significant in our study than it was in other SGLT2i trials. Given the relatively short treatment period of the present trial, it cannot be ruled out that more chronic SGLT2i treatment could improve MFR over a longer term. However, the Kaplan-Meier curves for hospitalization for heart failure and for cardiovascular death separated within 13 weeks in the EMPA-REG OUTCOME trial, such that any reasonable contribution from improved microvascular flow should have been detected. Consequently, we do not anticipate that duration of treatment explains the neutral finding regarding MFR in the present trial. The current
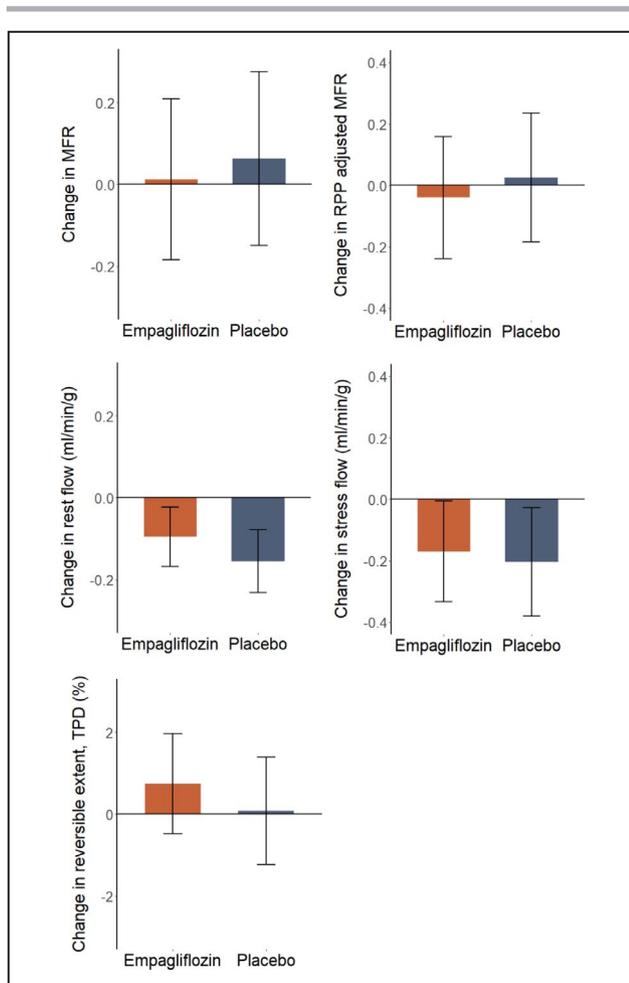
Figure 2. Mean change in 82Rb-PET/CT parameters after 13 weeks of treatment; whiskers indicate the 95% CI.
82Rb-PET/CT indicates Rubidium-82 positron emission tomography/computed tomography; MFR indicates myocardial flow reserve; RPP, rate-pressure product; and TPD, total perfusion deficit.
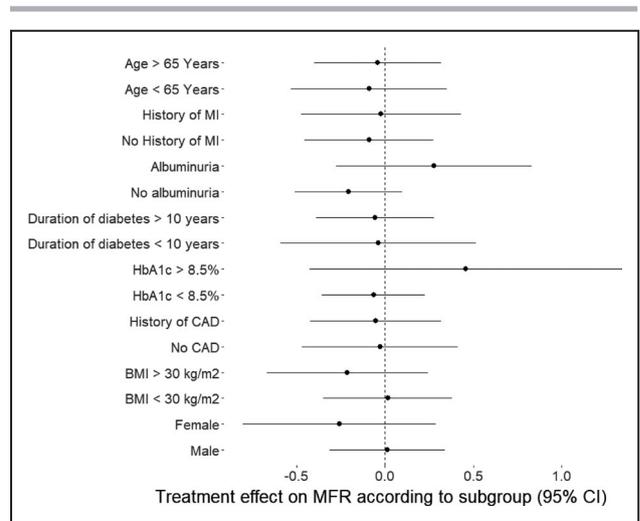

Figure 3. Change in MFR from baseline to 13 weeks according to the pre-defined subgroups. Dots indicate means, bars indicate 95% CI.
CAD indicates coronary artery disease; MFR, myocardial flow reserve; and MI, myocardial infarction.

study population was at high CVD risk and, thus, treated according to guidelines with high prevalence of evidence-based medicine as statins and renin-angiotensin system inhibitors, which are well known to affect endothelial function. It might be speculated that the high prevalence of concomitant treatment somewhat blunted the impact of SGLT2i on MFR. The mean MFR of 2.2 at baseline in the current trial suggests that, even though the patients were enrolled on the basis of known or high risk of CVD, their myocardial blood flow reserve was only moderately reduced as compared with previous type 2 diabetes mellitus study populations, wherein median values as low as 1.6 were reported.[10,33] The percentage of patients with previous myocardial infarction and significant coronary stenosis in the study by Murthy et al[10,33] was comparable to the 51% in our trial, and we did not find any effect modification on the presence of coronary heart disease in this trial. Therefore, the

higher baseline MFR in the current trial and the fact that many participants had MFR in the normal range may, thus, partially explain the lack of treatment response. The secondary end points did not reveal a potential explanation for SGLT2i benefits, since we did not find any change in myocardial blood flow at rest or during stress per se, and no improvements in reversible myocardial ischemia were observed, which may be in contrast with Baker et al,[34] who reported that treatment with canagliflozin improved cardiac stroke volume and work during induced ischemia.

Limitations

This was a single-center study, with a relatively small number of participants. The study was powered to support the primary end point, and secondary end points must, therefore, be considered exploratory. If patients had been enrolled with impaired MFR as an inclusion criterion, this might have increased the power of the primary end point analysis. Furthermore, the study was powered to detect a treatment effect on MFR of 0.8. Based on our findings, the increase in MFR is probably <0.8, and a larger cohort would be required to observe a hypothetical, more modest effect. A higher-than-expected number of the participants did not complete all examinations for other reasons, including a period of the COVID-19 lockdown in laboratory facilities. Dropouts were unbalanced between the groups: 3 from the empagliflozin group and 9 from the placebo group, which should be considered as a limitation. A high proportion of the participants were White men, and the conclusions of this study may, therefore, not necessarily extend

to differently composed populations. In accordance with the study by Lauritsen et al,[16] we found that rest myocardial blood flow decreased in the group that received empagliflozin. However, in contrast, we also found this to be the case for the placebo group. Further, stress flow also decreased in both groups. Stress and rest flow decreased with similar magnitudes, and therefore MFR was unchanged. A possible explanation for the observed decrease in flow could be that the second examination was less stressing for the participants because of familiarity with the procedure.

CONCLUSIONS

Treatment with empagliflozin for 13 weeks did not improve MFR among high-risk patients with type 2 diabetes mellitus. Therefore, the present study does not support that change in MFR explains the immediate reductions in cardiovascular events observed in the SGLT2i outcome trials.

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Acknowledgments

Sources of Funding

Disclosures

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