Comparison of the effects of empagliflozin and glimepiride on endothelial function in patients with type 2 diabetes: A randomized controlled study

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Abstract

Background: Among patients with type 2 diabetes and established cardiovascular disease, those receiving empagliflozin have a lower rate of primary composite cardiovascular outcomes and death from any cause. While treatment with sulfonylurea reduces microvascular complications in diabetes, it increases cardiovascular hospitalization or mortality when combined with metformin. In the present study, we assessed the effects of empagliflozin and glimepiride, a commonly prescribed sulfonylurea, on endothelial function using flow-mediated dilation (FMD) to estimate arteriosclerosis and cardiovascular events in patients with type 2 diabetes.

Methods: In this prospective, open-label, randomized, parallel-group study, 58 patients with type 2 diabetes received metformin and glargine before bedtime for 12 weeks. This was followed by additional treatment with either 10 mg empagliflozin or 0.5 mg glimepiride for 12 weeks. The primary outcome was the change in the FMD measurement (DFMDs), measured prior to and after 12 weeks of additional treatment. Secondary outcomes comprised changes in metabolic markers and body composition.

Results: An analysis of the empagliflozin group (n = 30) and glimepiride group (n = 28) showed no significant differences in DFMDs (empagliflozin, −0.19 ± 2.34%; glimepiride, −0.37 ± 2.77%; P = 0.79). Similarly, changes in glycated hemoglobin were similar between the two groups. However, a significant difference in body weight changes was observed between the two groups (empagliflozin, −0.59 ± 2.5 kg; glimepiride, 1.2 ± 3.0 kg; P = 0.02). In addition, an analysis of the body composition revealed that body fluid volume significantly decreased after empagliflozin treatment (baseline, 35.8 ± 6.8 L; after 12 weeks, −0.33 ± 0.72 L; P = 0.03).

Conclusions: Empagliflozin did not improve endothelial function when compared to that with glimepiride for patients with type 2 diabetes but decreased body fluid volumes. This suggested that the coronary-protective effect of empagliflozin is not derived from protection of the endothelial function but rather from a reduction in the risk of heart failure.

Trial Registration: This trial was registered on September 13, 2016; UMIN000024001.

Background

Patients with diabetes are at high risk of cardiovascular events. The assessment of coronary endothelial vasoreactivity has important diagnostic and prognostic implications, particularly for patients with diabetes. Specifically, an estimate of arteriosclerosis and cardiovascular events can be made by measuring endothelial dysfunction [1]. Thus, this parameter might be useful to assess cardiovascular risk in diabetes as well. The flow-mediated dilation (FMD) method evaluates endothelial function in a noninvasive manner, based on the intrinsic ability of blood vessels to respond to blood flow [2]. FMD involves the high frequency ultrasonographic imaging of the brachial artery by reflecting nitric oxide production within the artery. Since FMD can predict cardiovascular events, it has been utilized in numerous investigations of arteriosclerosis [3-5]. However, variables such as age, systolic blood pressure,

body mass index (BMI), sex, the presence of diabetes mellitus, lipid-lowering medication, smoking, and a decrease in visceral adipose tissue mass can impact FMD measurements [6-8].

Blood glucose levels in diabetes can be decreased by preventing proximal tubular glucose reabsorption and increasing urinary glucose excretion using an inhibitor of sodium glucose cotransporter 2 (SGLT2). Notably, such inhibitors can also reduce blood pressure [9] and body weight [9, 10]. The EMPA–REG OUTCOME trial revealed that treatment with empagliflozin, a SGLT2 inhibitor, reduces the risk of cardiovascular outcomes and death from all causes in patients with pre-existing atherosclerotic cardiovascular disease. However, the incidence of myocardial infarction or stroke did not differ significantly between the empagliflozin and placebo groups [11].

Furthermore, a meta-analysis showed that SGLT2 inhibitors improve the composite outcome of myocardial infarction, stroke, or cardiovascular death [12]. However, the effects varied according to the presence or absence of atherosclerotic cardiovascular disease. These inhibitors could reduce composite major adverse cardiovascular events, albeit only in patients with existing atherosclerotic cardiovascular disease. In addition, hospitalization following heart failure was reduced with SGLT2 inhibitor treatment, regardless of the status of atherosclerotic cardiovascular disease or heart failure at baseline. However, the anti-atherosclerotic mechanism of SGLT2 inhibitors remains unclear [12].

In the UK Prospective Diabetes Study (UKPDS) 33 Group, microvascular complications were reduced with sulfonylurea therapy, but no effect on macrovascular disease was seen. Blood glucose control with sulfonylureas decreased the risk of microvascular complications [13]. However, the observation that combined sulfonylurea and metformin therapy increased cardiovascular hospitalization or mortality was concerning [14]. The lack of an effect of sulfonylurea on macrovascular disease could be a result of its inability to affect endothelial function. The effect of reduced microvascular complications was determined to be derived from the strict control of blood glucose and decreased glycated hemoglobin (HbA1c). We thus hypothesized that sulfonylureas might not improve endothelial function. Consequently, in this study we used FMD to compare endothelial function in patients with type 2 diabetes treated with either an SGLT2 inhibitor (empagliflozin) or a sulfonylurea (glimepiride).

Methods

Study design

This study was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000024001) as a prospective, open-label, randomized, parallel–group comparison study. Approval for this study was obtained from the ethics committee of Chigasaki Municipal Hospital (approval No. 2016–04). The study protocol conforms with the provisions of the revised Declaration of Helsinki guidelines. Written, informed consent was obtained from all participating patients.

Inclusion and exclusion criteria

Patients with type 2 diabetes (20–80 years of age) who were hospitalized at the Chigasaki Municipal Hospital for diabetes education and blood glucose control for 1 or 2 weeks were included. They were controlled based on diet and insulin treatments, which changed from previous treatments if they had previously diagnosed diabetes. These patients received metformin and basal insulin therapy prior to discharge after glucotoxicity was ameliorated by insulin treatments and had a BMI ≤ 45 kg/m^2.

Patients were excluded if they showed severe renal (estimated glomerular filtration rate [eGFR] < 45 ml min^{-1} 1.73 m^{-2}) or liver dysfunction, were on steroid therapy, experienced cardiovascular disease and a cerebral infarction within 24 weeks of the study, had cancer, severe infection, or were traumatized, were or could become pregnant, were allergic to empagliflozin, glargine, glimepiride, or metformin, or if the supervising doctor decided that the patient did not qualify for this study.

Treatment and interventions

Patients who were treated with metformin and glargine for 12 weeks after discharge were randomized to receive either 10 mg empagliflozin or 0.5 mg glimepiride daily. According to the Japanese guidelines, a 10-mg dose of empagliflozin is recommended as the initial starting dose. For glimepiride, we selected a dose of 0.5 mg since this dose had similar efficacy in lowering blood glucose to 10 mg empagliflozin. Randomization was stratified by age, HbA1c, and FMD. Blood samples were obtained in a fasting state. Postprandial plasma glucose was measured with a self-monitoring blood glucose system (ONE TOUCH Verio IQ; Johnson and Johnson Co., New Brunswick, NJ, USA). The observation point was two times. Initial measurements of FMD were made prior to additional treatment and randomization. Subsequent measurements were made following additional treatment for 12 weeks. In general, treatment was not changed after randomization. However, if fasting plasma glucose was maintained at under 90 mg/dL, the glargine dose was decreased by one unit, once weekly. Hypoglycemia (i.e. blood glucose < 70 mg/dL) was ascertained using the values recorded by the patients. We instructed the patients to self-monitor blood glucose and hypoglycemia symptoms twice per day.

Flow-mediated dilation

FMD was measured using a UNEX EF38G (UNEXCorporation, Nagoya, Japan) according to the guidelines [2] by clinical technologists at the Chigasaki Municipal Hospital. This machine is an automated edge detection system to measure the brachial artery diameter using high-resolution ultrasound. The pre- and post-artery diameters pressed by the cuff were measured. FMD was calculated based on the following formula: (FMD[%] = [maximum diameter − diameter at rest] × 100 / diameter at rest).

Endpoints and assessments

The primary outcome was the change in FMD and was measured prior to and following 12 weeks of additional treatment (Fig. 1). Secondary outcomes included changes in the levels of metabolic markers in plasma in the fasting state and were measured prior to and following 12 weeks of treatment. Body composition components, such as skeletal muscle and total fat mass, as well as body fluid volume, were

assessed using a multifrequency bioelectrical impedance analyzer (BIA; InBody720; InBody Co., Ltd., Seoul, South Korea).

Sample size and statistical analysis

The effect of SGLT2 inhibitors on endothelial function, as measured by FMD, was unknown at the time this protocol was developed. We estimated that the change in FMD measurement (ΔFMD) with empagliflozin treatment for 12 weeks would be 1.5 ± 2.0% based on the results from a previous study [15]. Based on a two-sided *P*-value of 5% and a power of 80%, a sample size of 58 patients was required to detect a significant difference between the two treatment groups. We used a Student's t-test to compare the ΔFMD averages between the two groups, before and after additional treatment.

Results

Patients

Between June 2016 and 2018, 69 patients with type 2 diabetes agreed to participate in this study. A total of 63 patients were randomized at a one-to-one ratio to either the empagliflozin or glimepiride group. Ultimately, 30 patients in the empagliflozin group and 28 patients in the glimepiride group were analyzed (Fig. 2). The baseline clinical and biochemical characteristics in the two treatment groups were statistically similar (Table 1). Patients received the following drugs in the empagliflozin vs. glimepiride groups prior to enrollment in the study: metformin (23.3% vs. 14.3%), DPP-4 inhibitor (30.0% vs. 28.6%), SGLT2-inhibitor (3.7% vs. 3.6%), sulfonylurea (13.3% vs. 14.3%), α-glucosidase inhibitor (3.3% vs. 7.1%), glinide (0% vs 3.6%), insulin (6.7% vs. 7.1%), and a GLP-1 analogue (0% vs 3.6%).

Table 1 Baseline characteristics of patients

	Empagliflozin group (± SD)	Glimepiride group (± SD)	*P*-value
Age [years]	58.6 ± 8.5	54.3 ± 12.2	0.13
Sex (male/female)	18 / 12	18 / 10	0.74
Estimated duration of diabetes [years]	6.1 ± 7.2	4.9 ± 4.9	0.44
Recently diagnosed diabetes [%]	36.7	39.3	0.84
Current smoker [%]	20.0	39.3	0.11
FMD [%]	5.49 ± 2.05	5.46 ± 2.2	0.96
HbA1c [%]	6.9 ± 1.1	6.6 ± 0.7	1.0
FPG [mg/dL]	136.9 ± 65.2	127.1 ± 52.6	0.37
GA [%]	17.0 ± 3.7	16.3 ± 3.4	0.48
Body weight [kg]	70.0 ± 11.3	69.6 ± 17.1	0.92
BMI [kg/m^2]	26.1 ± 3.7	25.9 ± 5.4	0.9
Cr [mg/dL]	0.76 ± 0.16	0.73 ± 0.16	0.54
eGFR [$mL\ min^{-1}\ 1.73\ m^{-2}$]	74.9 ± 12.9	81.9 ± 19.7	0.11
UA [mg/dL]	5.5 ± 1.2	5.4 ± 1.5	0.96
LDL-C [mg/dL]	94.0 ± 26.7	89.2 ± 28.1	0.51
HDL-C [mg/dL]	54.7 ± 16.0	57.4 ± 16.4	0.52
TG [mg/dL]	197.7 ± 101.1	176.0 ± 131.5	0.2
sBP [mmHg]	129.6 ± 14.9	130.1 ± 20.5	0.9
dBP [mmHg]	80.8±10.0	78.0 ± 9.3	0.28
HR [bpm]	79.4 ± 14.8	77.5 ± 14.3	0.64
Metformin [mg]	883.3 ± 375.6	991.1 ± 473.8	0.34
Glargine [U/kg]	0.14 ± 0.07	0.16 ± 0.11	0.23

Values are shown as the means ± standard deviations (SDs). Paired Student's *t*–tests were used to compare values between different groups.

FMD, flow-mediated dilation; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; GA, glycated albumin; BMI, body mass index; Cr, serum creatinine; eGFR, estimated glomerular filtration rate

Endothelial function

The average baseline FMD values before and after 12-week treatment with empagliflozin and glimepiride are presented in Table 2. No significant difference was observed in the changes in FMD in empagliflozin vs. glimepiride groups.

Table 2 FMD (% ± SD) with treatment

	Empagliflozin	Glimepiride	*P*-value
FMD (0)	5.49 ± 2.05	5.46 ± 2.2	$P = 0.96$
FMD (12)	5.3 ± 2.28	5.09 ± 1.86	$P = 0.71$
	$P = 0.66$	$P = 0.49$	
ΔFMD (12) − (0)	−0.19 ± 2.34	−0.37 ± 2.77	$P = 0.79$

Values are shown as the means ± standard deviations (SDs).

FMD, flow-mediated dilation

FMD (0) means the baseline FMD value at 0 week. FMD (12) means the FMD value at 12 weeks after additional treatment.

Δ indicates the change in the FMD value between 0 and 12 weeks.

P-values in each row refer to a comparison of FMD values at the baseline and at week 12. *P*-values in each line refer to a comparison of changes in FMD values for both groups.

Metabolic markers

The fasting plasma glucose remained unchanged in both groups, with no significant difference evident between the two groups following treatment ($P = 0.69$; Table 3). HbA1c and glycated albumin (GA) levels significantly decreased in both groups ($P \leq 0.05$). However, the changes in these metabolic markers were not significantly different between the two groups (ΔHbA1c, $P = 0.75$ and ΔGA, $P = 0.42$) Uric acid (UA) was significantly decreased in the empagliflozin group ($P < 0.001$) and significantly increased in the glimepiride group ($P = 0.01$). A significant difference between the two groups was also noted in the ΔUA ($P < 0.001$). Systolic ($P = 0.59$) and diastolic ($P = 0.74$) blood pressure along with the heart rate ($P = 0.81$) did not change significantly between the two groups. Empagliflozin treatment significantly increased low-density lipoprotein-C (LDL-C; $P < 0.001$), whereas triglycerides (TGs; $P = 0.31$) and high-density lipoprotein-C (HDL-C; $P = 0.37$) did not change significantly between the two groups. Glimepiride treatment led to a significant increase in body weight ($P < 0.05$) after treatment. In addition, a significant difference was observed in the change in body weight between the two groups ($P = 0.02$). However, in the subgroup of patients for whom a decrease in body weight was observed, ΔFMD was not significantly different between the two groups ($P = 0.62$; Table 4). Glimepiride also led to a significant increase in waist circumference after treatment ($P = 0.004$). Moreover, a significant difference was observed in the change

in waist circumference between the two groups (P = 0.008). With regard to body composition, glimepiride led to a significant increase in total fat mass (P = 0.02). In comparison, empagliflozin significantly decreased body fluid volume (P = 0.03).

Table 3 Changes in metabolic markers

	Empagliflozin	Glimepiride	
Fasting plasma glucose (mg/dL) [mean ± SD]			
Week 12	124.5 ± 52.1	119.9 ± 49.1	
	$P = 0.11$	$P = 0.47$	
ΔFPG	−12.4 ± 44.4	−7.3 ± 52.0	$P = 0.69$
HbA1c (%) [mean ± SD]			
Week 12	6.7 ± 1.1	6.4 ± 0.78	
	$P = 0.001$	$P = 0.01$	
ΔHbA1c	−0.22 ± 0.36	−0.26 ± 0.5	$P = 0.75$
GA (%) [mean ± SD]			
Week 12	16.0 ± 3.2	15.7 ± 3.1	
	$P < 0.001$	$P = 0.05$	
ΔGA	−0.97 ± 1.3	−0.65 ± 1.6	$P = 0.42$
Renal function, Cr (mg/dL) [mean ± SD]			
Week 12	0.79 ± 0.15	0.74 ± 0.16	
	$P = 0.03$	$P = 0.8$	
eGFR (mL min^{-1} 1.73 m^{-2}) [mean ± SD]			
Week 12	72.1 ± 11.7	81.5 ± 20.2	
	$P = 0.02$	$P = 0.8$	
UA (mg/dL) [mean ± SD]			
Week 12	4.8 ± 1.2	5.7 ± 1.4	
	$P < 0.001$	$P = 0.01$	
ΔUA	−0.64 ± 0.9	0.26 ± 0.5	$P < 0.001$
Body weight (kg) [mean ± SD]			
Week 12	69.4 ± 12.0	70.8 ± 18.2	
	$P = 0.22$	$P < 0.05$	
ΔBody weight	−0.59 ± 2.5	1.2 ± 3.0	$P = 0.02$
Waist circumference (cm) [mean ± SD]			
Baseline	91.6 ± 9.2	91.2 ± 15.7	$P = 0.27$

Week 12	90.9 ± 8.9	92.3 ± 15.3	
	$P = 0.07$	$P = 0.004$	
ΔWaist circumference	−0.64 ± 1.8	1.1 ± 2.8	$P = 0.008$
Blood pressure (mmHg) [mean ± SD]			
sBP			
Week 12	130.2 ± 14.2	128.9 ± 19.3	
	$P = 0.79$	$P = 0.62$	
ΔsBP	0.69 ± 13.7	−1.3 ± 13.5	$P = 0.59$
dBP			
Week 12	80.6 ± 7.6	78.6 ± 12.0	
	$P = 0.91$	$P = 0.72$	
ΔdBP	−0.24 ± 10.8	0.64 ± 9.3	$P = 0.74$
Heart rate			
Week 12	80.1 ± 15.4	79.0 ± 12.8	
	$P = 0.76$	$P = 0.55$	
ΔHeart rate	0.68±11.2	1.5±11.6	$P = 0.81$
Lipids (TG, HDL–C, LDL–C) (mg/dL) [mean ± SD]			
LDL-C			
Week 12	107.5 ± 33.0	93.9 ± 29.6	
	$P < 0.001$	$P = 0.33$	
ΔLDL-C	13.5 ± 19.3	4.7 ± 25.2	$P = 0.14$
HDL-C			
Week 12	56.0 ± 12.5	56.4 ± 13.1	
	$P = 0.43$	$P = 0.61$	
ΔHDL-C	1.4 ± 9.4	−1.1 ± 10.9	$P = 0.37$
TG			
Week 12	177.1 ± 86.9	185.7 ± 123.7	
	$P = 0.29$	$P = 0.8$	
ΔTG	−20.6 ± 103.8	9.6 ± 121.5	$P = 0.31$

Body fluid volume (L) [mean ± SD]			
Baseline	35.8 ± 6.8	36.6 ± 8.6	$P = 0.69$
Week 12	35.4 ± 6.9	36.3 ± 8.7	
	$P = 0.03$	$P = 0.32$	
ΔBody fluid volume	−0.33 ± 0.72	−0.35 ± 1.8	$P = 0.94$
Total fat mass (kg) [mean ± SD]			
Baseline	21.1 ± 6.8	20.5 ± 11.0	$P = 0.8$
Week 12	20.6 ± 6.8	21.7 ± 11.6	
	$P = 0.16$	$P = 0.02$	
ΔTotal fat mass	−0.58 ± 2.1	1.2 ± 2.3	$P = 0.006$
Adverse events (%)			
	rash on both arms (3.3%)	hypoglycemia (3.6%)	
Glargine (U) [mean ± SD]			
Baseline	9.4 ± 4.6	11.7 ± 9.0	$P = 0.6$
Week 12	8.4 ± 5.1	9.6 ± 8.9	
	$P = 0.02$	$P < 0.001$	
ΔGlargine	−1.0 ± 2.4	−2.1 ± 3.5	$P = 0.16$

Values are shown as the means ± standard deviations (SDs).
Δ indicates the changes in the FMD values between 0 and 12 weeks.
P-values in each row refers to the comparison of FMD values at the baseline and at week 12. The *P*-value in each line refers to the comparison of changes in FMD values for both the groups.
FMD, flow-mediated dilation; HbA1c, glycated hemoglobin; GA, glycated albumin; Cr, serum creatinine; eGFR, estimated glomerular filtration rate; CysC, cystatin C; eGFRcys, estimated glomerular filtration rate by cystatin C; UA, uric acid; sBP, systolic blood pressure; dBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride

Table 4 Change in FMD (% ± SD) with treatment in the subgroup of patients with decreased body weight during the observation period

	Empagliflozin ($n = 17$)	Glimepiride ($n = 8$)	
ΔFMD (12) − (0)	0.41 ± 2.55	0.94 ± 2.16	$P = 0.62$

FMD, flow-mediated dilation

Δ indicates the change in FMD value between 0 and 12 weeks.
The *P*-value refers to a comparison of changes in FMD values between both the groups.

The fasting C-peptide immunoreactivity (CPR; $P = 0.55$), homeostasis model assessment 2 steady state beta cell (%B) function ($P = 0.2$), homeostasis model assessment 2 insulin sensitivity (%S) ($P = 0.09$), and homeostasis model assessment 2 insulin resistance ($P = 0.22$) were not significantly different between the two groups (Additional file 1, Table A1). In this study, empagliflozin and glimepiride did not affect insulin secretion, insulin sensitivity, pancreatic β-cell function, or insulin resistance. The associations between arterial sclerosis markers and ΔFMD, ΔHbA1c, the change in body weight, ΔHDL-C, and ΔTG were related to ΔFMD. Additionally, the ΔFMD might have been greater if the baseline FMD was lower (Additional file 1, Table A2).

Discussion

Based on the results from this study, we found that although fasting plasma glucose (FPG), HbA1c, and GA were equally improved in both empagliflozin and glimepiride groups, ΔFMD was not significant. A previous study has reported that glimepiride does not result in an improvement in endothelial function [15]. In this study, empagliflozin had no effect on improvements in endothelial function, irrespective of the improvement in glucose levels. To observe the changes in endothelial function induced by drugs that lack the ability to improve glucose levels and exclude the effects of glucotoxicity and temporary endothelial dysfunction associated with high blood glucose, this study was conducted in patients with a steady glucose-controlled state. Although a baseline HbA1c was targeted in this study, severe hypoglycemia did not occur after reducing the glargine dose, as the fasting plasma glucose was maintained under 90 mg/dL. Additionally, GA improved significantly in both the groups. It is possible that glucose variations were improved by both additional treatments. The insulin dose was also decreased significantly in both groups, and this might have resulted in the decrease in body weight. The improvements in ΔHbA1c, body weight, HDL-C, and TG and the reduction in HbA1c in the empagliflozin group did not affect the FMD, although the correlation among the change in the decrease in visceral adipose tissue mass, waist circumference, and ΔFMD has been shown in previous studies [8, 17]. These findings suggest that empagliflozin had no effect on improving FMD although it is effective in improving HbA1c.

Although the long-term administration of empagliflozin has been shown to maintain a stable eGFR [18], we observed that the renal function worsened in the empagliflozin group during the relatively short observation period. It was reported that empagliflozin decreases hyperfiltration mediated by diuresis in the initial term [19]. This might be attributed to the changes in renal dynamics induced by empagliflozin. In a recent study, canagliflozin reduced the risk of kidney failure at a median follow-up time of 2.62 years [20]. Further, losartan resulted in a rapid initial decline in renal function, which led to a slower decrease in long-term renal function [20]. However, it has been reported that an initial rapid decline in renal function leads to kidney failure [21]. Therefore, empagliflozin would be expected to prevent the progression of kidney disease over an extended period.

In Body720, an eight–polar BIA was shown to accurately estimate total and appendicular body composition, independent of age and sex [21]. The body fluid volume was significantly decreased following 12 weeks of empagliflozin treatment. However, it was unclear whether the effect of empagliflozin on the body fluid volume was greater than that of glimepiride. Empagliflozin has been shown to improve hospitalization rates after heart failure [22] and is thought to ameliorate the effects of this disease by decreasing body fluid volume. During the observational period of our study, heart failure was not observed in either treatment group. This suggests that empagliflozin might have a coronary protective effect that is not derived from the impact on endothelial function. This diuretic is known to decrease congestive heart failure, although its effect on reducing cardiovascular event risk is unclear. It was reported that SGLT2 inhibitors result in greater reduction in interstitial fluid volume than blood volume compared to that with loop diuretics [23]. It was hypothesized that improvements in systemic congestion and renal function, derived from decreased hyperfiltration, result in the prevention of cardiovascular events without reducing arterial filling and perfusion.

Based on previous reports, the FMD can be improved when the baseline FMD is low [16] and HbA1c is related to FMD [6]. If baseline HbA1c levels were higher, baseline FMD would be lower and endpoint FMD would improve. However, in both subgroups that showed a lower than median baseline FMD, the ΔFMD did not significantly differ between the two groups (P = 0.83; Table 6). Notably, although SGLT2 inhibitors have a secondary preventive effect on adverse cardiovascular events, they lack a primary preventive effect [12]. However, results from the DECLARE-TIMI 58 study demonstrated that dapagliflozin had both primary, as well as secondary, effects on preventing adverse cardiovascular events. Dapagliflozin was found to decrease cardiovascular death and hospitalization due to heart failure in patients without previous cardiovascular disease [24]. However, in this study, no patients had similar backgrounds, and hence, it was necessary to undertake a secondary intervention.

Table 6 Change in FMD (% ± SD) after additional treatment in subgroups with lower than median baseline FMD

	Empagliflozin ($n = 14$)	Glimepiride ($n = 15$)	
ΔFMD(12) − (0)	0.66 ± 1.96	0.82 ± 1.92	$P = 0.83$

FMD, flow-mediated dilation
Δ indicates the change in the FMD value between 0 and 12 weeks.
The P-value shows the comparison of changes in FMD values for both the groups

The effects of other hyperglycemic agents, like pioglitazone and glucagon-like peptide 1 (GLP-1) analogs, on improving endothelial function have been reported previously [15, 25]. A dipeptidyl peptidase 4 (DPP-4) inhibitor either improved [16], had no effect [26], or worsened [27] endothelial function but did not affect cardiovascular events [28, 29]. In another study, GLP-1 analog treatment enhanced [30, 31] or had no effect on [32] endothelial function. In patients with type 2 diabetes, liraglutide, a GLP-1 analog, was successful in preventing nonfatal myocardial infarction or stroke, along with death from cardiovascular causes [33]. Similar to these findings, results from a meta-analysis showed that significant heterogeneity existed between DPP-4 inhibitors and GLP-1 [34]. Factors such as the size of the study, duration of

intervention, and age or sex of the participants did not affect the mean difference in FMD [34]. Rather, a change in FMD was found to be dependent on the baseline FMD. The low baseline FMD in our study compared to that reported in other studies [16, 25, 35] might have affected the results.

Several limitations were evident in this study. First, as the study participants were outpatients, it was not possible to completely exclude patients who smoked or had a meal before the FMD examination. Moreover, non-compliance of dietary requirements in some patients might have affected the observed change in body weight. Additionally, even though we had included wash-out periods of anti-diabetic therapy for 12 weeks before the study and there were no significant differences between each drug (Additional file 1, Table A3), the long-term effects of anti-diabetic therapy before admission cannot be completely ruled out. Finally, although the number of patients required to detect a significant difference in comparisons of the two groups was adequate, the observation period was relatively short. Although, evidence of the observation period assessed by FMD has not been established yet, a longer study period to monitor any adverse events is required for future studies.

Conclusions

Overall, we found that compared to that with glimepiride, empagliflozin did not improve endothelial function, at least in a 12-week treatment period, for patients with type 2 diabetes without previous cardiovascular disease. However, empagliflozin significantly reduced body fluid volume. Thus, the coronary-protective effect of empagliflozin might not be derived from its ability to prevent endothelial dysfunction, but rather from a reduction in the chances of heart failure.

Abbreviations

ARB/ACE–I, angiotensin type II receptor blocker/angiotensin converting enzyme I; BMI, body mass index; Cr, serum creatinine; CRP, C-reactive protein; CysC, cystatin C; dBP, diastolic blood pressure; DPP, dipeptidyl peptidase; eGFR, estimated glomerular filtration rate; eGFRcys, estimated glomerular filtration rate by cystatin C; F-CPR, fasting C-peptide immunoreactivity; FMD, flow-mediated dilation; FPG, fasting plasma glucose; GA, glycated albumin; GLP, glucagon-like peptide; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA2%B, Homeostasis Model Assessment 2 steady state beta cell (%B) function; HOMA2%S, Homeostasis Model Assessment 2 insulin sensitivity (%S); HOMA2IR, Homeostasis Model Assessment 2 insulin resistance (IR); HR, heart rate; LDL, low-density lipoprotein; L-FABP, liver-type fatty acid binding protein; sBP, systolic blood pressure; TGs, triglycerides; UA, uric acid; U-Alb, urine albumin

Declarations

Ethics approval and consent to participate

Approval for this study was obtained from the ethics committee of Chigasaki Municipal Hospital, approval No. 2016–04. Written, informed consent was obtained from all patients.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YK provided advice on the study design. HT and YK designed the study. HT collected and analyzed the data. HT performed statistical analysis. HT, KI, and MH interpreted the data. HT wrote the manuscript. YK, SS, and YT drafted the manuscript or substantially revised it. All authors read and approved the final manuscript.

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Additional File Legends

File name: Additional file 1

File format: .pdf

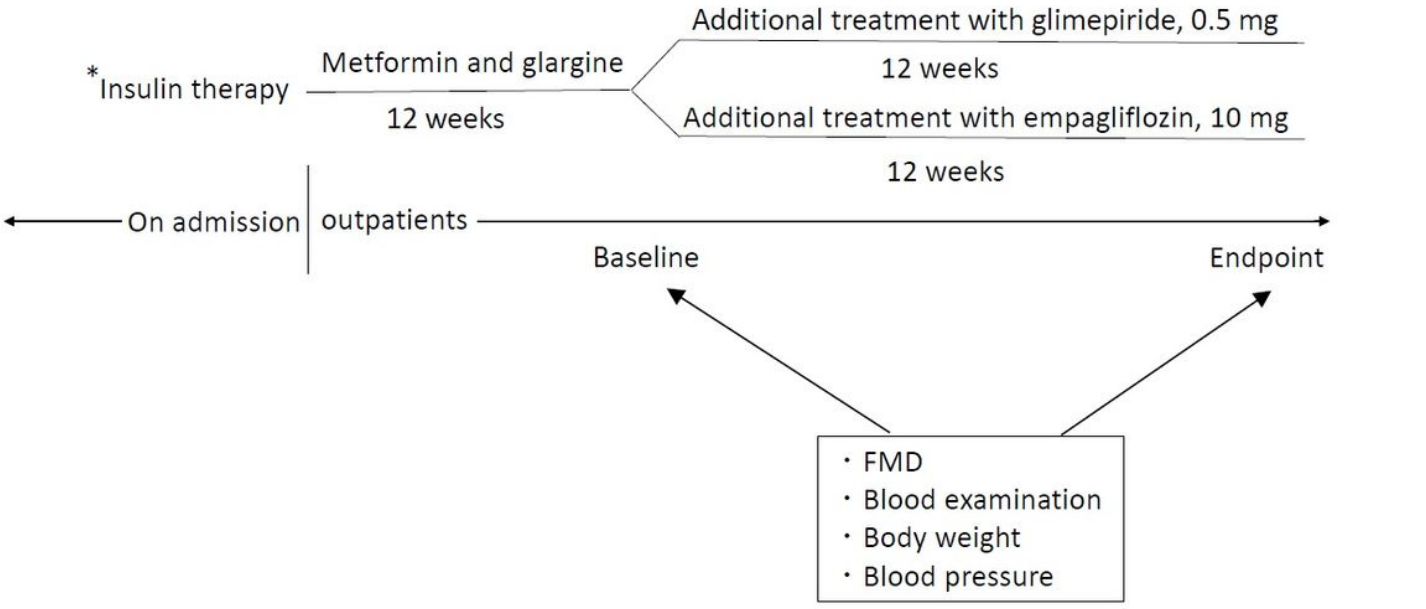
The file comprises three tables as follows:

Table A1. Changes in metabolic markers

Table A2. Associations between arterial sclerosis markers and ΔFMD in all patients (n = 58)

Table A3. Associations between anti-diabetic therapy and ΔFMD in the empagliflozin and glimepiride groups

Figures



*If patients had previously diagnosed diabetes, prior treatments were discontinued and changed to insulin therapy when patients were hospitalized for diabetes education and blood glucose control. Treatments at discharge were metformin and glargine.

Figure 1

Study flow chart. Patients who took metformin and glargine were randomized to empagliflozin or glimepiride groups. Flow-mediated dilation (FMD), blood examination, body weight, and blood pressure were checked at study baseline and endpoints.

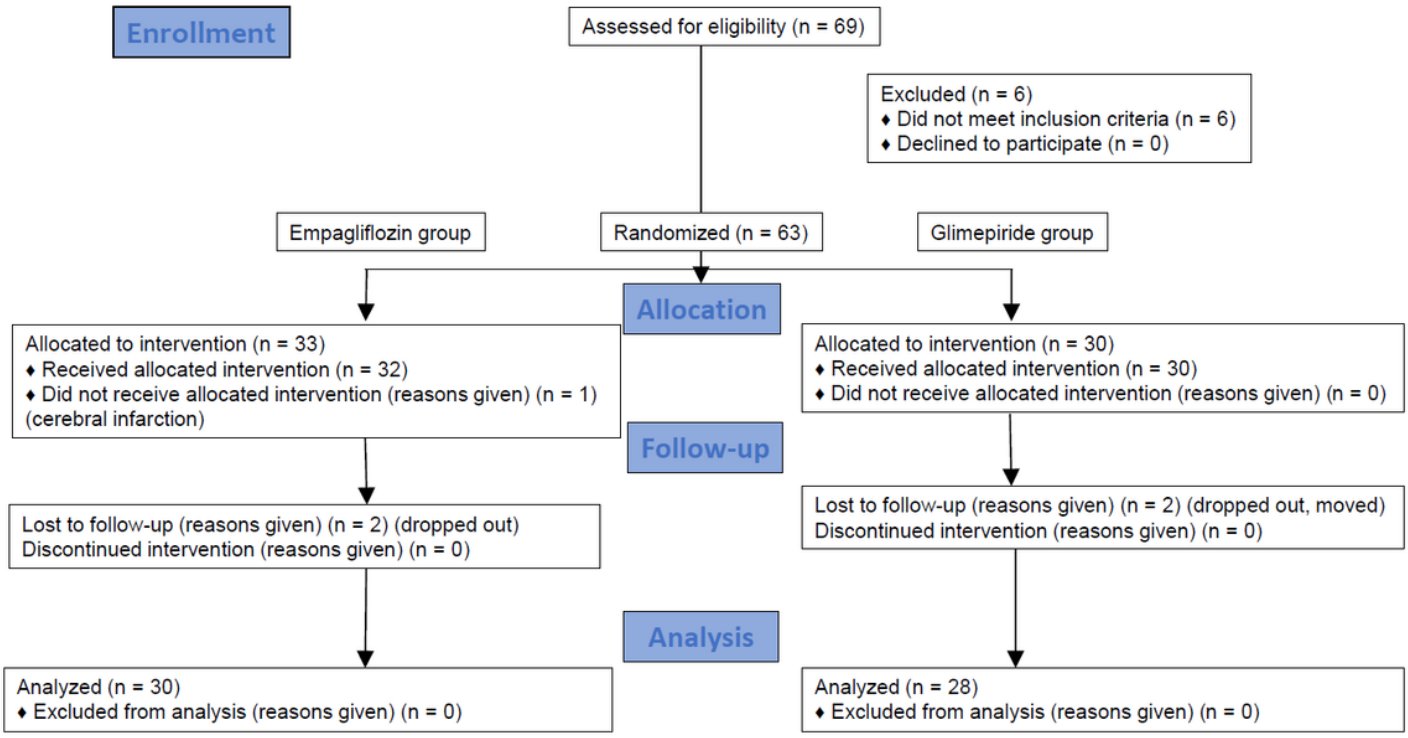


Figure 2

Consort 2010 flow diagram of patient selection. Ultimately, 30 patients in the empagliflozin group and 28 patients in the glimepiride group were analyzed

Supplementary Files

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- AdditionalFile1.pdf