

Effect of Canagliflozin on Estimated Fluid Volumes in Patients with Heart Failure and type 2 Diabetes: A Post-hoc Analysis of the CANDLE Trial

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Abstract

Background:

In patients with chronic heart failure (CHF) and type 2 diabetes (T2D), inhibition of the sodium-glucose cotransporter-2 (SGLT2) improves cardiorenal outcomes, but the effects of the SGLT2 inhibitor canagliflozin on body fluid volume and renal function remain to be clarified.

Methods:

This was a post-hoc analysis of 233 patients with CHF and T2D in the CANDLE Trial (UMIN000017669), an investigator-initiated, multi-center, randomized open-label trial that compared the effect of canagliflozin (100 mg, n=113) with glimepiride (starting dose: 0.5 mg, n=120) on changes in N-terminal pro-brain natriuretic peptide. The time courses of estimated plasma volume (ePV, calculated with the Straus formula), estimated extracellular volume (eEV, determined by the body surface area), and estimated glomerular filtration rate (eGFR, calculated with the modified Cockcroft formula) were compared between the canagliflozin and glimepiride groups at weeks 4, 12, and 24.

Results:

Reductions in ePV and eEV were observed only in the canagliflozin group until week 12 (change from baseline at week 12, ePV; -7.63%; 95% confidence interval [CI], -10.71 to -4.55%, $p < 0.001$, eEV; -123.15 mL; 95% CI, -190.38 to -55.92 mL, $p < 0.001$). Whilst ePV stopped falling after week 12, eEV continued to fall until week 24 ([change from baseline at week 24] – [change from baseline at week 12], ePV; 1.01%; 95% CI, -2.30 to 4.32%, $p = 0.549$, eEV; -125.15 mL; 95% CI, -184.35 to -65.95 mL, $p < 0.001$). An initial significant reduction in eGFR was observed in the canagliflozin group (change from baseline at week 4, -4.18 mL/min/1.73 m²; 95% CI, -5.99 to -2.37 mL/min/1.73 m², $p < 0.001$), but after 4 weeks, eGFR stopped falling, and the difference between groups became insignificant (change from baseline at week 24, -1.27 mL/min/1.73 m²; 95% CI, -3.05 to 0.51 mL/min/1.73 m², $p = 0.162$, [change from baseline at week 24] – [change from baseline at week 12], 0.89 mL/min/1.73 m²; 95% CI, -0.74 to 2.51 mL/min/1.73 m², $p = 0.284$).

Conclusions:

Canagliflozin reduced ePV and eEV gradually, whilst glimepiride did not. Maintenance of a modest reduction in ePV by canagliflozin suggests appropriate intravascular volume reduction contributing to cardiorenal benefits in patients with CHF and T2D.

Trial Registration: UMIN000017669

Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of cardiovascular death or hospital admission for heart failure and prevent kidney disease progression in patients with type 2 diabetes (T2D) [1]. Furthermore, in patients with heart failure (HF), regardless of ejection fraction (EF), SGLT2 inhibitors improve mortality and morbidity and renal outcomes irrespective of the presence of T2D [2-5].

The mechanisms underlying these effects remain unknown, and reductions in body fluid volume and tissue decongestion may contribute. Primarily, SGLT2 inhibitors reduce glucose and sodium reabsorption in the proximal convoluted tubules and lead to glucosuria and natriuresis; therefore, they decrease fluid volume but potentially decrease renal function. Indeed, in the Empire HF Renal trial, 12 weeks of treatment with empagliflozin reduced the measured glomerular filtration rate (GFR) compared with placebo in patients with HF, while the estimated circulating plasma volume (ePV) and estimated extracellular fluid volume (eEV) were reduced [6]. Furthermore, we reported previously that empagliflozin, compared with placebo, reduced ePV and eEV at the expense of an initial drop in estimated glomerular filtration rate (eGFR) in patients with miscellaneous cardiovascular disease with T2D [7]. However, glucosuria resulting from treatment with SGLT-2 inhibitors may potentially promote electrolyte-free water clearance and increase plasma osmolarity [8-10], and thereby prevent excess reduction of plasma volume while removing interstitial fluid in the longer term.

We hypothesized that canagliflozin, as well as empagliflozin, can reduce body fluid volume. In the present post-hoc analysis of the CANDLE Trial (UMIN000017669), we aimed to compare the effects of the SGLT-2 inhibitor canagliflozin with those of the sulfonylurea glimepiride on ePV, eEV, and eGFR in the longer term in patients with chronic heart failure (CHF) and T2D.

Methods

Study Design and Participants

The present study was a post-hoc analysis of the CANDLE trial (UMIN000017669), the protocol and main results of which were published previously [11, 12]. Briefly, the CANDLE trial was an investigator-initiated, open-label, randomized, blinded-endpoint trial carried out at 34 centers in Japan. Key inclusion criteria were T2D under poor or suboptimal control, HF with New York Heart Association (NYHA) functional I–III symptoms, stable condition under guideline-directed HF therapy at least 4 weeks before randomization, and an eGFR greater than 45 mL/min per 1.73 m². Key exclusion criteria were HF with NYHA class IV symptoms and history of cardiovascular disease requiring revascularization within 3 months before randomization. Eligible patients were assessed at a screening visit that included medical history, physical examination, and blood tests. At the baseline visit, patients were randomly assigned (1:1) to treatment with canagliflozin or glimepiride. Treatment assignment was carried out with a web-based program with the minimization method, with biased coin assignment balancing for age (<65, ≥65 years), HbA1c level (<6.5%, ≥6.5%), and left ventricular EF (<40%, ≥40%) at the time of screening.

The trial was approved by the institutional review board and independent ethics committees at each site, in compliance with the Declaration of Helsinki and the current legal regulations in Japan.

Estimation of body fluid volume

After randomization, patients initiated canagliflozin 100 mg once daily or glimepiride 0.5 mg once daily for 24 weeks. All patients were treated according to the Japanese treatment guidelines for diabetes that allowed increasing the dose of background therapy for diabetes except for SGLT2 inhibitors and sulfonylureas in both groups. Assessment procedures were repeated at weeks 4, 12 and 24 after the baseline visit. Estimated plasma volume was calculated with the Strauss formula according to the data obtained at each visit [13, 14].

$$\Delta ePV [\%]: 100 \times Hb (\text{base}) / Hb (\text{end}) \times (1 - Ht (\text{end})) / (1 - Ht (\text{base})) - 100$$

Estimated extracellular volume in mL was determined by the body surface area on the basis of the following formula [15], based on the linear correlation between the volume of distribution of ^{51}Cr -EDTA (which is the actual extracellular volume) and the body surface area.

$$eEV [\text{mL}]: (8116.6 \times [0.007184 \times \text{height (cm)}^{0.725} \times \text{weight (kg)}^{0.425}]) - 28.2$$

eGFR was calculated with the modified formula for the Japanese population as follows [16]:

$$eGFR [\text{mL}/\text{min}/1.73 \text{ m}^2]: 94 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739 (\text{if female})$$

Statistical analyses

Baseline characteristics were described by percentages frequencies for categorical variables and by means with standard deviations for continuous variables. All statistical analyses were done by the intention-to-treat principle. For follow-up ePV, eEV and eGFR values, analyses were performed with linear mixed models with adjustment for the baseline value. The mean values with 95% confidence intervals (CI) at weeks 4, 12 and 24 for both groups were plotted and compared with Wald tests. The consistency of treatment effect was examined across subgroups of age, sex, BMI, systolic blood pressure (SBP), HbA1c, eGFR and EF at baseline. All statistical analyses were carried out at the two-sided significance level of 0.05, and no adjustment for multiplicity was considered in this post-hoc sub-analysis. R software version 3.6.3 (R Foundation for Statistical Computing) was used to perform the statistical analyses.

Results

Baseline characteristics

The analysis included 233 patients, of whom 113 received canagliflozin and 120 received glimepiride. Baseline characteristics were well balanced between groups, as shown in [Table 1](#). Across the entire cohort, the mean age was 69 ± 10 years, and 75% were male. The mean LVEF was $56 \pm 14\%$; 67 (28.8%) patients had LVEF $\leq 50\%$, and 166 (71.2%) had LVEF $>50\%$. The median NTproBNP was 252 [96 to 563] pg/mL. NYHA functional class was I or II in 97%, and 42% of patients were receiving a loop diuretic. The mean eGFR was 63.7 ± 15.1 mL/min/1.73 m², and the mean HbA1c was $7.0 \pm 0.9\%$.

Time course of ePV, eEV, eGFR and SBP

Changes in ePV, eEV, eGFR and SBP from baseline to weeks 4, 12 and 24 are shown in [Tables 2 and 3](#) and plotted in [Figure 1](#).

In the canagliflozin group, ePV decreased by -5.71% (95% CI, -7.92 to -3.49%) at week 12, which remained stable at a decrease of -5.26% (95% CI, -7.44 to -3.08%) at week 24. eEV continued to decrease until week 24 by -219.83 mL (95% CI, -267.06 to -172.60 mL) at week 24. eGFR significantly decreased by -4.13 mL/min/1.73 m² (95% CI, -5.45 to -2.82 mL/min/1.73 m²) at week 4 but remained at -3.49 mL/min/1.73 m² (95% CI, -4.77 to -2.20 mL/min/1.73 m²) at week 12, and at -2.92 mL/min/1.73 m² (95% CI -4.26 to -1.65 mL/min/1.73 m²) at week 24. In the glimepiride group, ePV, eEV and eGFR did not change significantly throughout the treatment period. SBP did not change during treatment.

Comparison between canagliflozin and glimepiride effects on body fluid volume

In the canagliflozin group, ePV and eEV decreased gradually until week 12 and stayed lower at week 24 than in the glimepiride group. eGFR became significantly lower at week 4, but the difference became non-significant at 12 weeks. ([Figure 1](#), [Table 3](#)). The effects of canagliflozin versus glimepiride on ePV, eEV and eGFR observed in the overall population were relatively consistent in various patient subgroups. ([Figure 2](#))

Discussion

The results of this analysis demonstrated the effects of canagliflozin treatment compared with glimepiride treatment in patients with CHF and T2D. (1) Reductions in ePV and eEV were observed only in the canagliflozin group and decreased until week 12. (2) In the canagliflozin group, whilst ePV stopped falling after week 12, eEV kept falling until week 24. (3) eGFR in the canagliflozin group became lower than in the glimepiride group at 4 weeks, but the difference became non-significant at 12 weeks.

Effect of canagliflozin treatment on body fluid volume

Diuretic treatment-related weight loss and negative fluid balance are associated with improvements in symptoms [17-20] and recently, for optimal decongestion, discrimination of the interstitial and intravascular compartments has been proposed. Body fluid is divided into intra- and extracellular compartments, and the extracellular compartment is divided into intra- or extravascular volume. A large intravascular volume can cause organ congestion in patients with HF, and a small intravascular volume can cause dehydration, leading to low organ perfusion in CHF. On the other hand, the extravascular volume is mainly interstitial and of unknown significance in organ dysfunction in CHF. Diuretics reduce the fluid volume from the extracellular compartment. Initially, they reduce mainly the intravascular volume rapidly, leading to lower hydrostatic pressure and subsequent fluid removal from the interstitial volume [21, 22]. However, eventually, the response to diuretic treatment predominately reflects fluid loss from the interstitial volume with minimal change in intravascular volume [23]. Recently, it was reported that the degree of interstitial volume reduction was not associated with patient prognosis [23], suggesting that the intravascular volume is more a driver of clinical outcomes than even large changes in the interstitial volume [13, 24].

In this study, canagliflozin treatment of patients with CHF and T2D decreased the eEV as well as the ePV, without a rebound increase over a long period of time. This finding has already been shown with another SGLT2 inhibitor [6, 7]. Consistent results support a class effect of SGLT2 inhibitors on reducing the intravascular volume. Reduction in the intravascular fluid volume, which decreases the ventricular filling pressure and cardiac workload, is a relevant mechanism to explain the reduction in HF risk with SGLT2 inhibitors [25].

Temporal relationship between eGFR and body fluid volume

The mechanisms of the renoprotective effects of SGLT2 inhibitors remain to be elucidated. Lowering intraglomerular hypertension by tubuloglomerular feedback [26-28], reduction of tubular workload [29], anti-inflammation and anti-fibrosis [30, 31] have been reported as major mechanisms. In addition, from our results, we hypothesize that maintenance of optimal intravascular volume results in protection of renal perfusion. In the present study, both ePV and eEV decreased gradually and took more than 4 weeks to become statistically significant; furthermore, ePV decreased until week 12 and stopped decreasing. In contrast, eEV continued to decrease until week 24. The body fluid volume response to canagliflozin is clearly slower than that for loop diuretics, with which strong and rapid diuresis can lead to poor renal perfusion and potential nephrotoxicity [32]. However, this time course of ePV may imply avoidance of excessive decongestion for renal perfusion and maintenance of optimal intravascular volume throughout the 24-week observation period. Moreover, recent studies have identified important differences between SGLT2 inhibitors and loop diuretics. Mathematical model analyses of dapagliflozin and bumetanide have suggested that dapagliflozin produces weaker natriuretic and diuretic effects than bumetanide, and the reduction in blood volume compared with interstitial volume was smaller with dapagliflozin [8]. The ability to provide selective interstitial fluid reduction may be a unique feature of SGLT2 inhibitors, and maintenance of arterial filling may suppress neurohormonal activation [33, 34] and lead to renoprotective

effects. Estimation of the intravascular volume by ePV may reflect renal perfusion and lead to safe clinical management and better understanding of the mechanisms underlying the renoprotective effects of SGLT2 inhibitors in HF treatment.

Limitations

This analysis has several limitations. First, it was conducted post hoc to explore the mechanism underlying the cardiorenal protective effects of canagliflozin. The original study was not specifically designed to examine changes in body fluid distribution, nor did it attempt to balance or stratify patients by different types of HF.

Second, the PV and EV changes were not measured directly, but instead were estimated by widely accepted formulae using Hct, Hb and body weight, because these were validated by comparison with a radiolabeled gold standard method in patients with HF and diabetes [14, 35].

Despite these limitations, the time course of ePV and eEV were theoretically consistent with the change in eGFR, and furthermore with the cardiovascular benefits reported in larger clinical trials. Further study with direct measurement of plasma volume and extracellular volume appears warranted.

Conclusion

Canagliflozin treatment gradually reduced ePV and eEV. Maintenance of a modest reduction in ePV with canagliflozin treatment suggests appropriate intravascular volume contributing to cardiorenal benefits in patients with CHF and T2D.

Abbreviations

BMI, body mass index; CHF, chronic heart failure; CI, confidence interval; EF, ejection fraction; ePV, estimated plasma volume; eEV, estimated extracellular volume; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; Hb, hemoglobin; HbA1c, hemoglobin A1c; HF, heart failure; Ht, hematocrit; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

Declarations

Authors' contributions

All authors contributed to the study conception, design, and procedures. Funding acquisition for the study was carried out by KN, the principal investigator of the CANDLE trial. The data analyses were performed by SF, Takul, AT, and KN. Takul was responsible for the statistical analyses. The first draft of the manuscript was written by SF, and all authors reviewed subsequent drafts of the manuscript. All authors read and approved the final manuscript.

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Competing interests

SF received research funding from Boehringer Ingelheim and research grants from Bayer. Takul received lecture fees from JCR Pharmaceuticals and Kyowa Kirin; and outsourcing fees from Organization for Clinical Medicine Promotion. AT received honoraria from Boehringer Ingelheim and research funding from GlaxoSmithKline and Takeda. MS received honoraria from Astellas, Boehringer Ingelheim, Mitsubishi Tanabe, and AstraZeneca. TM has received honoraria and a research grant from Mitsubishi Tanabe Pharma. Takal received lecture honoraria from Otsuka Pharmaceutical Co. and Daiichi-Sankyo Pharmaceutical. NK has received honoraria from MSD, Astella, AstraZeneca, Novartis Pharma, Ono Pharmaceutical, Daiichi Sankyo, Mitsubishi Tanabe Pharma, Eli Lilly Japan, Boehringer Ingelheim Japan, Takeda Pharmaceutical; research grants from Asahi Kasei, Astellas, Mitsubishi Tanabe Pharma, Teijin Pharma, Terumo, Boehringer Ingelheim Japan, Eli Lilly and Company, Mochida Pharmaceutical, Fuji Yakuhin; and scholarships from Daiichi Sankyo Healthcare, Teijin Pharma, Medtronic, Bayer Yakuhin. All other authors declare no competing interests.

Availability of data and materials

The datasets analyzed during the current study are available from the CANDLE study support office on reasonable request (candle-sub@clin-med.org).

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Ethics approval and consent to participate

The ethics committees of the participating institutions approved the study protocol. Written, informed consent for participation in the study was obtained from all subjects. This trial was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Consent for publication

All authors have read and approved the submission of the manuscript. The manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language. If the manuscript is accepted, we approve it for publication in *Cardiovascular Diabetology*.

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Tables

Table 1

Patient Characteristics

Characteristic	All (N=233)	Canagliflozin group (N=113)	Glimepiride group (N=120)
Age – years	68.58 ± 10.07	68.27 ± 9.77	68.86 ± 10.39
Male, no. (%)	174 (74.7 %)	88 (77.9 %)	86 (71.7 %)
Female, no. (%)	59 (25.3 %)	25 (22.1 %)	34 (28.3 %)
Body mass index – kg/m ²	25.49 ± 3.94	25.30 ± 3.62	25.67 ± 4.23
HbA1c – %	7.00 ± 0.85	6.93 ± 0.74	7.06 ± 0.94
eGFR – mL/min/1.73 m ²	63.68 ± 15.06	64.10 ± 15.27	63.28 ± 14.90
NT-proBNP (median [IQR]) – pg/mL	252.00 [96.00 to 563.00]	245.50 [113.00 to 519.75]	263.00 [82.50 to 651.00]
LVEF – %	56.66 ± 14.41	56.67 ± 14.47	56.64 ± 14.43
LVEF < 50% – no. (%)	67 (28.9 %)	34 (30.4 %)	33 (27.5 %)
NYHA functional classification) — no. (%)			
I	148 (63.5 %)	72 (63.7 %)	76 (63.3 %)
II	79 (33.9 %)	39 (34.5 %)	40 (33.3 %)
III	5 (2.1 %)	2 (1.8 %)	3 (2.5 %)
Unknown	1 (0.4 %)	0 (0.0 %)	1 (0.8 %)
History — no. (%)			
Hypertension	102 (43.8 %)	49 (43.4 %)	53 (44.2 %)
Dyslipidemia	100 (42.9 %)	46 (40.7 %)	54 (45.0 %)
Myocardial infarction	56 (24.0 %)	32 (28.3 %)	24 (20.0 %)
Stroke	16 (6.9 %)	11 (9.7 %)	5 (4.2 %)
Heart failure cause — no. (%)			
Ischemia	100 (42.9 %)	54 (47.8 %)	46 (38.3 %)
Hypertension	62 (26.6 %)	32 (28.3 %)	30 (25.0 %)
Valve	36 (15.5 %)	19 (16.8 %)	17 (14.2 %)
Dilated cardiomyopathy	36 (15.5 %)	17 (15.0 %)	19 (15.8 %)
Medication (Non-diabetic) — no. (%)			
ACE inhibitor or ARB	177 (76.0 %)	89 (78.8 %)	88 (73.3 %)

Beta-blocker	164 (70.4 %)	82 (72.6 %)	82 (68.3 %)
Calcium channel blocker	90 (38.6 %)	46 (40.7 %)	44 (36.7 %)
MRA	86 (36.9 %)	42 (37.2 %)	44 (36.7 %)
Diuretic	99 (42.5 %)	46 (40.7 %)	53 (44.2 %)
Digitalis	20 (8.6 %)	12 (10.6 %)	8 (6.7 %)
Medication (Diabetic) — no. (%)			
Insulin	7 (3.0 %)	4 (3.5 %)	3 (2.5 %)
Metformin	44 (18.9 %)	18 (15.9 %)	26 (21.7 %)
Alpha-glucosidase inhibitor	40 (17.2 %)	16 (14.2 %)	24 (20.0 %)
DPP-4 inhibitor	127 (54.5 %)	64 (56.6 %)	63 (52.5 %)
GLP-1RA	2 (0.9 %)	1 (0.9 %)	1 (0.8 %)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HbA1c, hemoglobin A1c; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide 1 receptor antagonist; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

Table 2

Changes from baseline to weeks 4, 12 and 24 in ePV, eEV, eGFR and SBP

		Canagliflozin group (N=113)		Glimepiride group (N=120)	
		Mean	95% CI	Mean	95% CI
ePV change from baseline	week 4	-2.02	-4.28 to 0.25	0.83	-1.34 to 3.00
	week 12	-5.71	-7.92 to -3.49	1.92	-0.22 to 4.07
	week 24	-5.26	-7.44 to -3.08	1.36	-0.74 to 3.47
eEV change from baseline	week 4	-45.63	-94.77 to 3.50	12.87	-34.10 to 59.84
	week 12	-104.10	-152.28 to -55.91	19.06	-27.83 to 65.94
	week 24	-219.83	-267.06 to -172.60	28.48	-18.13 to 75.08
eGFR change from baseline	week 4	-4.13	-5.45 to -2.82	0.05	-1.20 to 1.30
	week 12	-3.49	-4.77 to -2.20	-1.33	-2.58 to -0.08
	week 24	-2.92	-4.20 to -1.65	-1.66	-2.90 to -0.42
SBP change from baseline	week 4	-2.24	-4.84 to 0.36	-1.96	-4.43 to 0.52
	week 12	-2.81	-5.36 to -0.27	-1.85	-4.34 to 0.64
	week 24	-2.65	-5.18 to -0.13	-0.97	-3.43 to 1.48

ePV, estimated plasma volume; eEV, estimated extracellular volume; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure

Table 3

Changes from baseline in ePV, eEV, eGFR and SBP: Canagliflozin vs Glimepiride

	Difference	95%CI lower	95%CI upper	P value
ePV change from baseline				
Change at week 4	-2.85	-5.98	0.29	0.075
Change at week 12	-7.63	-10.71	-4.55	<0.001
Change at week 24	-6.62	-9.65	-3.59	<0.001
Change at week 12 - Change at week 4	-4.78	-8.17	-1.40	0.006
Change at week 24 - Change at week 4	-3.77	-7.14	-0.40	0.028
Change at week 24 - Change at week 12	1.01	-2.30	4.32	0.549
eEV change from baseline				
Change at week 4	-58.50	-126.48	9.47	0.092
Change at week 12	-123.15	-190.38	-55.92	<0.001
Change at week 24	-248.30	-314.66	-181.95	<0.001
Change at week 12 - Change at week 4	-64.65	-125.02	-4.27	0.036
Change at week 24 - Change at week 4	-189.80	-249.94	-129.66	<0.001
Change at week 24 - Change at week 12	-125.15	-184.35	-65.95	<0.001
eGFR change from baseline				
Change at 4 weeks	-4.18	-5.99	-2.37	<0.001
Change at 12 weeks	-2.16	-3.95	-0.36	0.018
Change at 24 weeks	-1.27	-3.05	0.51	0.162
Change at 12 weeks - Change at 4 weeks	2.03	0.37	3.68	0.016
Change at 24 weeks - Change at 4 weeks	2.91	1.26	4.57	0.001
Change at 24 weeks - Change at 12 weeks	0.89	-0.74	2.51	0.284
SBP change from baseline				
Change at 4 weeks	-0.28	-3.87	3.31	0.877
Change at 12 weeks	-0.96	-4.52	2.59	0.596
Change at 24 weeks	-1.68	-5.20	1.84	0.350
Change at 12 weeks - Change at 4 weeks	-0.68	-4.34	2.98	0.716
Change at 24 weeks - Change at 4 weeks	-1.40	-5.04	2.25	0.453

Change at 24 weeks - Change at 12 weeks -0.72 -4.33 2.90 0.698

ePV, estimated plasma volume; eEV, estimated extracellular volume; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure

Figures

Figure 1

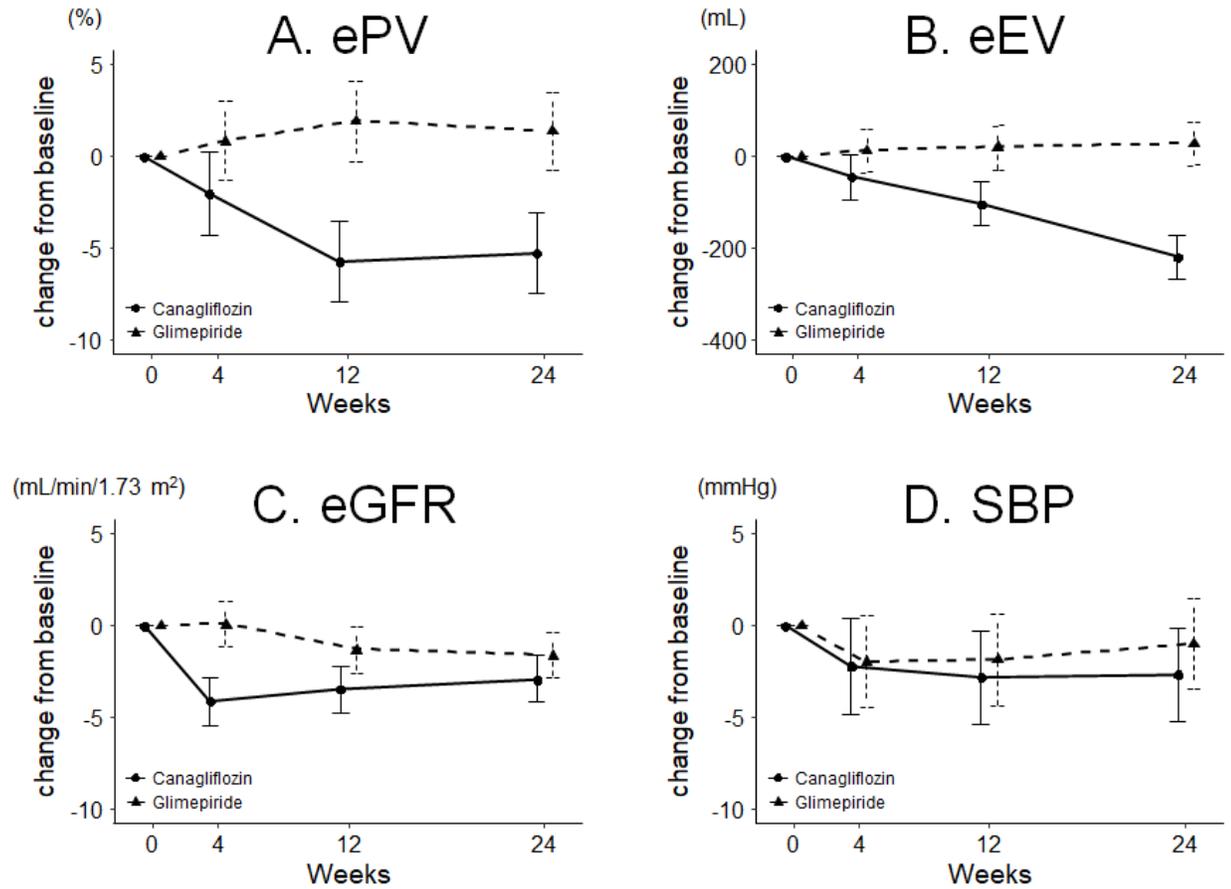


Figure 1

Changes in ePV, eEV, eGFR, and SBP after administration of canagliflozin and glimepiride A. Estimated plasma volume B. Estimated extracellular volume C. Estimated glomerular filtration rate D. Systolic blood pressure Data are expressed as mean (95% confidence interval).

Figure 2-A

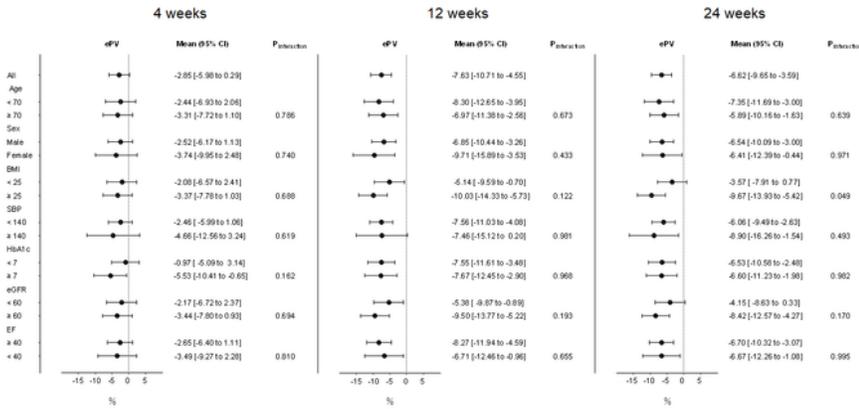


Figure 2-B

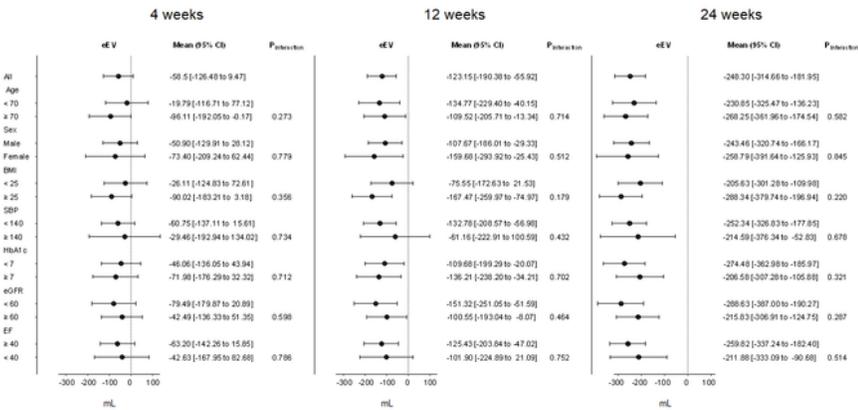


Figure 2-C

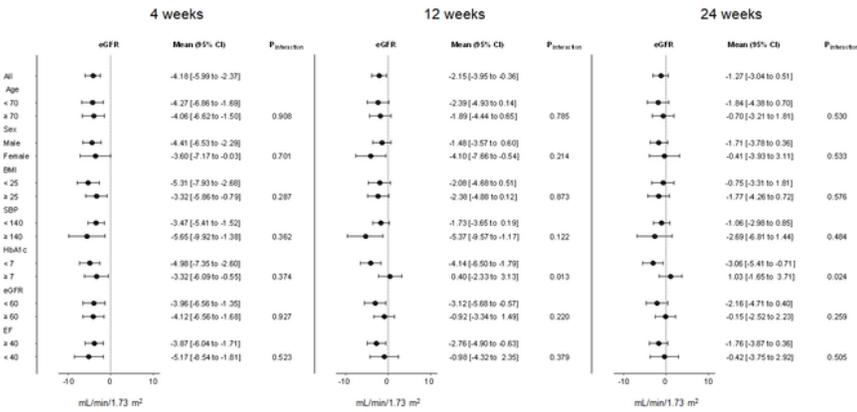


Figure 2

Subgroup analyses of ePV, eEV and eGFR A. Estimated plasma volume B. Estimated extracellular volume C. Estimated glomerular filtration rate BMI, body mass index; SBP, systolic blood pressure; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; pEF, heart failure with preserved ejection fraction; rEF, heart failure with reduced ejection fraction