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ORIGINAL ARTICLE

Effects of luseogliflozin on estimated plasma volume in patients with heart failure with preserved ejection fraction

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Abstract

Aims Sodium glucose co-transporter 2 inhibitors have diuretic effects in both patients with glycosuria and with natriuresis. We sought to assess the effect of luseogliflozin on estimated plasma volume (ePV) in patients with type 2 diabetes and heart failure with preserved ejection fraction (HFpEF).

Methods and results This study was a post-hoc analysis of the MUSCAT-HF trial (UMIN000018395), a multicentre, prospective, open-label, randomized controlled trial that assessed the effect of 12 weeks of luseogliflozin (2.5 mg, once daily, n = 83) as compared with voglibose (0.2 mg, three times daily, n = 82) on the reduction in brain natriuretic peptide (BNP) in patients with type 2 diabetes and HFpEF. The analysis compared the change in ePV calculated by the Straus formula from baseline to Weeks 4, 12, and 24, using a mixed-effects model for repeated measures. We also estimated the association between changes in ePV and changes in other clinical parameters, including BNP levels. Luseogliflozin significantly reduced ePV as compared to voglibose at Week 4 {adjusted mean group-difference −6.43% [95% confidence interval (CI): −9.11 to −3.74]}, at Week 12 [−8.73% (95%CI: −11.40 to −6.05)], and at Week 24 [−11.02% (95%CI: −13.71 to −8.33)]. The effect of luseogliflozin on these parameters was mostly consistent across various patient clinical characteristics. The change in ePV at Week 12 was significantly associated with log-transformed BNP (r = 0.197, P = 0.015) and left atrial volume index (r = 0.283, P = 0.019).

Conclusions Luseogliflozin significantly reduced ePV in patients with type 2 diabetes and HFpEF, as compared with voglibose. The reduction of intravascular volume by luseogliflozin may provide clinical benefits to patients with type 2 diabetes and HFpEF.

Keywords Estimated plasma volume; Heart failure with preserved ejection fraction; Luseogliflozin; Sodium glucose co-transporter 2 inhibitors; Voglibose

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Introduction

There has been a paucity of evidence for treatments that can improve the prognosis of patients with heart failure with preserved ejection fraction (HFpEF), although various medications have resulted in improved prognosis of patients with heart failure with reduced ejection fraction (HFrEF).[1–7] Some clinical trials have evaluated the effectiveness of medical treatments for HFpEF but have not established their benefits.[8–11]

Sodium glucose co-transporter 2 (SGLT2) inhibitors are antidiabetic drugs that promote urinary glucose excretion. SGLT2 inhibitors seem to have some benefits beyond their glucose-lowering effects, promoting natriuresis and osmotic diuresis based on glycosuria.[12] Previous studies have shown that SGLT2 inhibitors reduce the rehospitalization of patients with type 2 diabetes due to heart failure and renal function deterioration.[13,14] In addition, recent studies reported that SGLT2 inhibitors improved the prognosis of patients with HFrEF, regardless of the presence or absence of type 2 diabetes mellitus (T2DM).[15] Moreover, some previous studies have shown that SGLT2 inhibitors reduce hospitalization for heart failure (HF) in patients with HFpEF. [16,17] Recently, SGLT2 inhibitors have been reported to reduce estimated plasma volume (ePV).[18–21] Although these results suggest that SGLT2 inhibitors may be effective in reducing intravascular volume, which may improve heart failure prognosis, there is little evidence of the efficacy of SGLT2 inhibitors on intravascular volume in patients with HFpEF.

In the Management of Diabetic Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction (MUSCAT-HF) trial, brain natriuretic peptide (BNP) concentrations decreased after initiation of either luseogliflozin, an SGLT2 inhibitor, or voglibose, an alpha-glucosidase inhibitor, at Week 12.[22] However, the difference in change in BNP levels was not statistically significant [percent change, −9.0% vs. −1.9%; ratio of change with luseogliflozin vs. voglibose, 0.93; 95% confidence interval (CI), 0.78–1.10; P = 0.26].

In this post-hoc analysis of the MUSCAT-HF trial, we compared the impact of luseogliflozin and of voglibose on the reduction of ePV and evaluated the correlation of change in ePV with BNP level and other clinical parameters in patients with T2DM and HFpEF.

Materials and methods

Study design and participants

This was a post-hoc analysis of the MUSCAT-HF trial, a multicentre, prospective, open-label, randomized controlled trial to assess the effect of luseogliflozin compared with voglibose on left ventricular load in patients with T2DM and HFpEF.[22] Details of the study design and results have been published previously.[22,23] The original study examined the effects of a 12 week treatment of patients with T2DM and HFpEF with luseogliflozin (2.5 mg) once daily vs. voglibose (0.2 mg) three times daily in 165 patients aged $\geq$ 20 years who required additional treatment for T2DM, despite ongoing treatment. HFpEF was defined as a left ventricular ejection fraction (EF) $\geq$ 45%, BNP concentrations $\geq$ 35 pg/mL, and any symptoms. Patients treated with alpha-glucosidase inhibitors, SGLT2 inhibitors, glinides, or high-dose sulfonylurea; renal insufficiency [estimated glomerular filtration rate (eGFR) $<$ 30 mL/min/1.73 m^2); a history of severe ketoacidosis or diabetic coma within 6 months prior to participation; and poorly controlled T2DM [haemoglobin A1c (HgbA1c) $>$ 9.0%) were excluded. Patients were randomly assigned to the two drug arms, and post-randomization follow-up visits were scheduled at Weeks 4, 12, and 24. The primary outcome of the original study was the change in the ratio of BNP concentrations from baseline to 12 weeks of treatment. The investigation conformed to the principles outlined in the Declaration of Helsinki. The study was approved by the Ethics Committee of Okayama University Graduate School of Medicine, Density and Pharmaceutical Sciences. All patients enrolled in this study provided written informed consent. The trial was registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR, UMIN000018395).

Outcomes

The primary outcome of this post-hoc analysis was the between-group differences in the percentage change in ePV from baseline to 12 weeks. Additionally, in the luseogliflozin group, the association between changes in ePV and changes in other clinical parameters was evaluated.

Estimated plasma volume

The ePV at baseline was measured using the Hakim formula as follows: (1 − haematocrit) × (1530 + [41 × body weight (kg)]) in male patients and (1 − haematocrit) × (864 + [47.9 × body weight (kg)]) in female patients.[24] The percentage change in ePV at Weeks 4, 12, and 24 from baseline was calculated using the Strauss formula as follows: 100 × [haemoglobin (at baseline)/haemoglobin (at visit)] × [1 − haematocrit (at visit)]/[1 − haematocrit (at baseline)] − 100.[25] We measured BNP levels in a central laboratory (SRL, Inc. Hachioji, Tokyo, Japan). Haemoglobin, haematocrit, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, serum creatinine, eGFR, and HgbA1c were also evaluated. These parameters were measured in each institution.

Statistical analysis

Categorical variables are presented as numbers (%) and were compared using the χ^2 test. Normally distributed continuous variables are presented as mean ± standard deviation and were compared using Student's *t*-test. Continuous variables that were not normally distributed are presented as medians with interquartile ranges and were compared using the Mann–Whitney *U*-test. The normality of the data distribution was evaluated using the Shapiro–Wilk test. We estimated group differences in the mean percentage change in ePV from baseline to Weeks 4, 12, and 24, and the interaction between follow-up periods and groups using mixed-effect linear regression models. The effects of luseogliflozin vs. voglibose on ePV after 12 weeks were assessed in several subgroups defined by sex, body weight, prior atherosclerotic cardiovascular disease, and factors used at randomization: age (<65 years, ≥65 years), sex, baseline HgbA1c values (<8.0%, ≥8.0%), baseline BNP concentrations (<100 pg/mL, ≥100 pg/mL), baseline renal function (eGFR ≥ 60 mL/min/1.73 m^2, <60 mL/min/1.73 m^2), use of thiazolidine (yes or no), presence or absence of atrial fibrillation or flutter at baseline, presence or absence of prior atherosclerotic cardiovascular disease, use of β-blocker (yes or no), use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (yes or no), and use of diuretic (yes or no). We assessed the associations between changes from baseline to Week 12 in the ePV, BNP levels, and other parameters using Pearson's correlation analyses and linear regression models. Continuous variables that were not normally distributed underwent natural logarithmic transformation prior to use in regression analysis. Statistical significance was defined as $P < 0.05$. These analyses were performed using SPSS statistical software (Version 25; IBM Corp., Armonk, NY, USA).

Patient and public involvement

This research was done without patient and public involvement.

Results

Patient characteristics

This post-hoc analysis included 165 patients with T2DM and HFpEF from 16 hospitals and clinics. The baseline characteristics of the patients are shown in *Table 1*. The baseline variables, including laboratory data and echocardiographic parameters, were similar between the luseogliflozin and voglibose groups, except for the patients' age, aspartate aminotransferase, and alanine aminotransferase.

Comparison of the estimated plasma volume between groups

In the mixed-effect models for repeated measures, there was a statistically significant interaction between the effect of the study drugs and the follow-up periods ($P < 0.001$ for interaction) (*Figure 1*). ePV was reduced more by luseogliflozin than by voglibose from baseline to Week 4 [adjusted mean group-difference, −6.43% (95%CI: −9.11 to −3.74%)], Week 12 [−8.73% (95%CI: −11.40 to −6.05%)], and Week 24 [−11.02% (95%CI: −13.71 to −8.33%)].

The effects of luseogliflozin vs. voglibose on ePV observed in the overall population at Week 12 were similar to those in the various patient subgroups (*Figure 2*). Specifically, compared with voglibose, luseogliflozin reduced ePV by −7.978% (95%CI: −11.81 to −4.14%) in patients with BNP < 100 pg/mL and by −10.94% (95%CI: −18.64 to −3.24%) in patients not using diuretics (*P* value for treatment by subgroup interaction = 0.45). Among patients with an eGFR < 60 mL/min/1.73 m^2, luseogliflozin compared with voglibose reduced ePV by −10.83% (95%CI: −15.28 to −6.37%). In patients with eGFR ≥ 60 mL/min/1.73 m^2, ePV was reduced by −6.01% (95%CI: −11.17 to −4.19%), as compared with voglibose (*P* value for treatment by subgroup interaction = 0.166). Among patients with a body weight < 60 kg, luseogliflozin compared with voglibose reduced ePV by −6.17% (95%CI: −11.78 to −0.56%). In patients with body weight ≥ 60 kg, ePV was reduced by −10.45% (95%CI: −14.85 to −6.04%), as compared with voglibose (*P* value for treatment by subgroup interaction = 0.23). Luseogliflozin decreased ePV by 8.78% in patients with a history of atherosclerotic cardiovascular disease, as well as in patients without atherosclerotic cardiovascular disease (*P* value for treatment by subgroup interaction = 0.54). All *P* values for interaction, except for β-blocker use, were > 0.05.

Association between the estimated plasma volume and clinical parameters

In the Pearson correlation analyses, the change from baseline to Week 12 in log-transformed BNP concentration was positively correlated with the percentage change in ePV (*Figure 3*). There were statistically significant correlations between changes in ePV at Week 12 and concurrent changes in haemoglobin levels and the left atrial volume index (*Table 2*).

Discussion

In this post-hoc analysis of the MUSCAT-HF trial, the impact of luseogliflozin on the change in ePV at Weeks 4, 12, and

Table 1 Baseline clinical characteristics of this study

Variables	Luseogliflozin (n = 83)	Voglibose (n = 82)	P value
Age (years)	71.7 ± 7.7	74.6 ± 7.7	0.017
Male	55 (66)	48 (59)	0.31
Body mass index (kg/m^2)			
Systolic blood pressure (mmHg)	131 ± 17	128 ± 14	0.168
Diastolic blood pressure (mmHg)	71 ± 11	71 ± 10	0.52
Heart rate (beats per minute)	69 ± 13	70 ± 12	0.53
Hypertension	72 (89)	64 (79)	0.087
Dyslipidaemia	65 (80)	61 (75)	0.45
Prior ASCVD	48 (59)	50 (62)	0.75
Atrial fibrillation or flutter	18 (22)	15 (18)	0.59
Medications on admission			
β-blocker	51 (61)	47 (57)	0.39
ACEI/ARB	51 (61)	47 (57)	0.59
MRA	19 (23)	20 (24)	0.97
Loop diuretic	19 (23)	19 (23)	0.97
Thiazide	5 (6.0)	5 (6.1)	0.98
Antidiabetic medication	53 (65)	50 (61)	0.74
Laboratory data			
HgbA1c (%)	7.0 ± 0.7	6.9 ± 0.8	0.52
Haemoglobin (g/dL)	13.5 ± 1.6	13.1 ± 1.6	0.114
Haematocrit (%)	41.4 ± 4.8	40.4 ± 4.2	0.159
AST (IU/L)	27.2 ± 16.8	23.2 ± 7.0	0.048
ALT (IU/L)	25.3 ± 18.5	19.4 ± 9.8	0.010
Blood urea nitrogen (mEq/L)	17.7 ± 5.5	19.1 ± 6.0	0.119
Serum creatinine (mg/dL)	0.94 ± 0.30	0.96 ± 0.29	0.70
Estimated GFR (mL/min/1.73 m^2)	60.6 ± 19.4	56.8 ± 16.5	0.185
BNP (pg/mL)	63.7 (46.8–115.8)	75.1 (42.4–120)	0.87
Echocardiographic data			
LVEF (%)	57 ± 9.4	58 ± 9.4	0.41
E/A	0.77 ± 0.21	0.85 ± 0.29	0.094
e' (cm/s)	5.4 ± 1.5	5.6 ± 1.8	0.66
E/e'	13.0 ± 4.5	13.3 ± 5.6	0.67
LAD (mm)	42.0 ± 7.4	42.5 ± 7.9	0.69
LAVI (mL/m^2)	37.9 ± 16.3	38.4 ± 13.5	0.84
LVMI (g/m^2)	93.0 ± 23.2	91.3 ± 27.5	0.71

ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker, ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; E/A; early/atrial mitral inflow velocity, E/e', Early diastolic filling velocity/early diastolic velocity of the mitral annulus; estimated GFR, estimated glomerular filtration rate; HgbA1c, haemoglobin A1c; LAD; Left atrial dimension, LAVI; left atrial volume index; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.
Data are presented as the number (%), mean ± standard deviation, or median (25th–75th percentile).

Figure 1 Effect of luseogliflozin relative to voglibose on ePV from baseline through Week 24. Adjusted mean changes from baseline in estimated plasma volume (%) and 95% confidence interval are displayed. eGD, estimated group difference; ePV, estimated plasma volume.

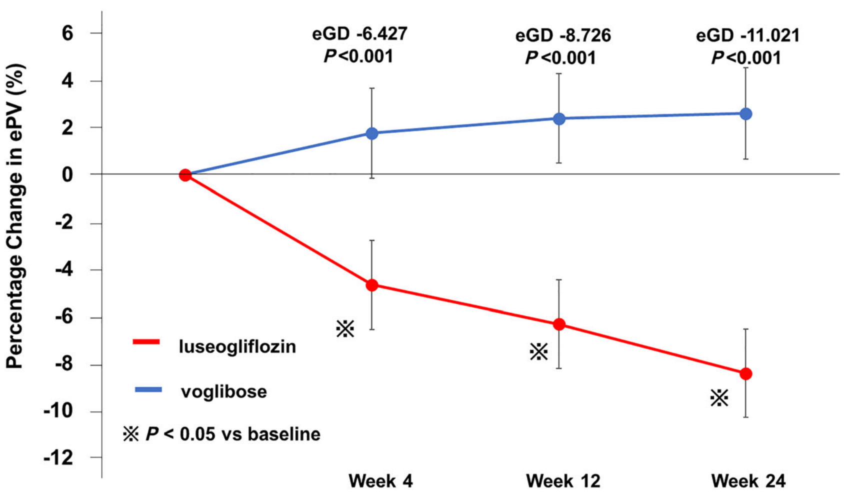

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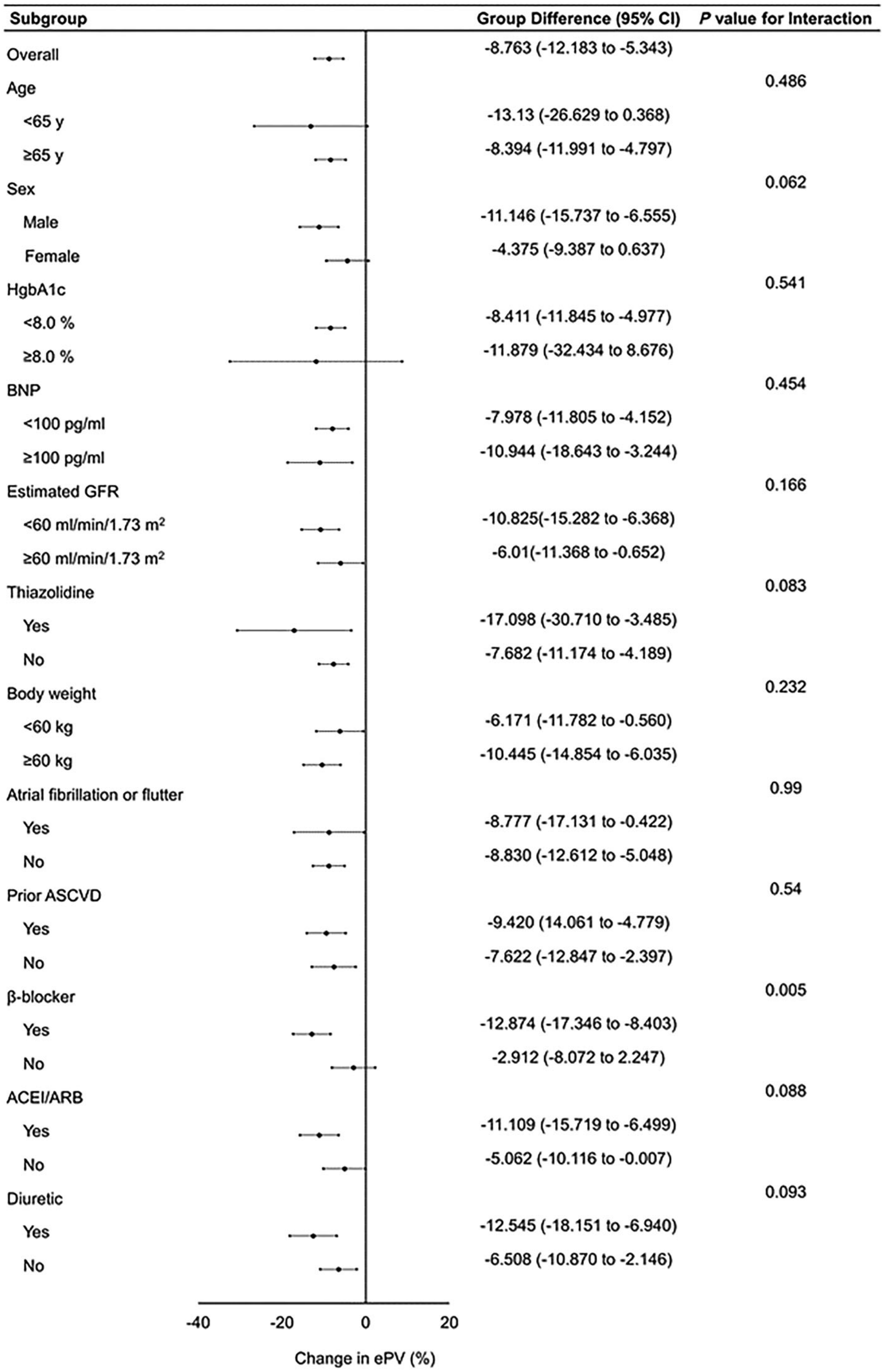
Figure 2 Changes from baseline in ePV (%) at Week 12 of treatment with luseogliflozin relative to treatment with voglibose in various subgroups. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; ASCVD, atherosclerotic cardiovascular disease; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; ePV, estimated plasma volume; HgbA1c, hemoglobinA1c.



24 from baseline was superior to that of voglibose in patients with T2DM and HFpEF. Changes in ePV were significantly associated with changes in BNP and left atrial volume index. To the best of our knowledge, no previous study had demonstrated that SGLT2 inhibitors can reduce fluid volume in patients with T2DM and HFpEF.

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Figure 3 Correlation between changes in ePV and BNP concentration. The mean regression line and 95% confidence intervals are displayed. BNP, B-type natriuretic peptide; ePV, estimated plasma volume.

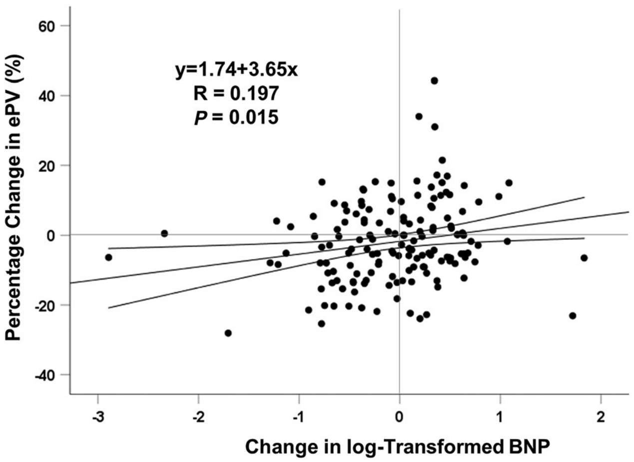

Table 2 Pearson correlations between percentage change from baseline at 12 weeks in e PV and various clinical parameters

	r	*P* value
Body weight	0.026	0.579
Systolic blood pressure	0.055	0.509
Diastolic blood pressure	0.045	0.583
Heart rate	−0.010	0.905
HgbA1c	−0.151	0.061
Haemoglobin	−0.958	<0.001
AST	0.048	0.550
ALT	−0.041	0.609
eGFR	0.139	0.084
LVEF	0.042	0.711
E/e′	−0.088	0.446
LAD	−0.253	0.033
LAVI	0.283	0.019

ALT, alanine aminotransferase; AST, aspartate aminotransferase; E/e′, early diastolic filling velocity/early diastolic velocity of the mitral annulus; estimated GFR, estimated glomerular filtration rate; HgbA1c, haemoglobin A1c; LAD; left atrial dimension; LAVI; left atrial volume index; LVEF, left ventricular ejection fraction.

Efficacy of sodium glucose co-transporter 2 inhibitors for reduction in the estimated plasma volume

Sodium glucose co-transporter 2 inhibitors have some favourable effects on heart failure beyond their glucose-lowering effects.[12] Previous studies have reported that SGLT2 inhibitors reduced both the plasma volume measured by ^{125}I-labelled human serum albumin and ePV by using laboratory data in patients with T2DM.[18,19] Other studies have also reported that SGLT2 inhibitors reduced the ePV in patients with T2DM complicated by cardiovascular diseases or HFrEF.[20,21] In addition, SGLT2 inhibitors reduced pulmonary arterial pressure in patients with heart failure.[26] These results support that SGLT2 inhibitors can reduce intracellular volume by diuretic effects related to both glycosuria and natriuresis, consistent with the results of this study.

Impact of sodium glucose co-transporter 2 inhibitors on heart failure with preserved ejection fraction

It has been reported that SGLT2 inhibitors decreased worsening heart failure in patients with HFrEF, regardless of the presence or absence of diabetes mellitus in a randomized trial.[15] The present study showed that SGLT inhibitors have a favourable effect on ePV reduction in patients with HFpEF. ePV has been reported to be associated with a risk of worse prognosis in patients with heart failure.[27,28] Although the benefit of SGLT2 inhibitors in patients with HFpEF is not yet established, our results showed the possibility that SGLT2 inhibitors could contribute to improving clinical outcomes in patients with HFpEF by reducing plasma volume.

Relationship between estimated plasma volume and cardiac preloads

In the initial investigation of the MUSCAT-HF study, the primary finding was that the SGLT2 inhibitor, luseogliflozin, and the alpha-glucosidase inhibitor did not differ significantly in reducing BNP concentrations after 12 weeks. In contrast, this post-hoc analysis showed a significant reduction in ePV by luseogliflozin, as compared with voglibose, and that the change in ePV was negatively associated with haemoglobin and positively associated with changes in BNP and the left atrial volume index. These results suggest that SGLT inhibitors may reduce intravascular volume and cardiac preload.

Some studies have shown that the level of natriuretic peptides in patients with HFpEF was significantly lower than that in patients with HFrEF, although an increase in natriuretic peptides was associated with a worse clinical outcome in patients with HFpEF.[29,30] Additionally, when heart failure is due to a cause upstream from the left ventricle, pericardial abnormalities, or right-sided heart failure alone, natriuretic peptide concentrations may be initially low, despite severe symptoms, because of the absence of a significant increase in LV wall stress.[31] Changes in BNP may sometimes underestimate the evaluation of the change in intravascular volume in patients with HFpEF because HFpEF has various aetiologies. In this situation, measurement of the change in ePV in addition to that in BNP may add sensitive and valuable information about cardiac preload in patients with HFpEF.

Limitations

This study has several limitations. First, this was a post-hoc analysis of a previous study's results, which included a relatively small number of patients, and had a short follow-up duration. Second, this study targeted the change in ePV from baseline after a period of treatment, but there was no actual measurement of plasma volume, such as by dilution methods using radioisotopes. Actual plasma volume and ePV may differ, because ePV is calculated from laboratory data, which may be influenced by other factors, such as plasma volume and erythropoietic parameters, which may also be influenced by SGLT2 inhibitors.[32] Third, some patients with mild heart failure were included in this study. In this study, patients with a left ventricular EF of ≥45% were enrolled because this study enrolment had started before the latest definition of HFpEF in the ESC Heart Failure Guidelines was changed in 2016.[33,34] In the 2016 ESC Heart Failure Guidelines, heart failure with a left ventricular EF ranging from 40% to 49% were defined as HF with midrange EF. The effect of luseogliflozin on ePV in patients with HFpEF might thus not have been accurately estimated.

Conclusions

In conclusion, ePV in patients with T2DM and HFpEF was significantly reduced by luseogliflozin compared with voglibose. SGLT2 inhibitors may therefore be effective in reducing intravascular volume and cardiac preload in these patients.

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Conflict of interest

Dr Miyoshi received a trust research/joint research fund from Novartis Pharma K. K. Dr Ito received a trust research/joint research fund from Novartis KK. The other authors declare no conflicts of interest.

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