Effect of Empagliflozin Versus Placebo on Plasma Volume Status in Patients with Acute Myocardial Infarction and Type 2 Diabetes Mellitus

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ABSTRACT

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Introduction: Plasma volume status (PVS), a parameter of the discrepancy between actual plasma volume (PV) and ideal PV, has been recently evaluated as a prognostic marker in patients with heart failure. This subgroup analysis of the EMBODY trial was designed to determine whether a sodium-glucose cotransporter 2 (SGLT2) inhibitor affects the alleviation of heart failure and improvement of PVS in patients after acute myocardial infarction (AMI) with congestive heart failure (CHF).

Methods: The EMBODY trial was a prospective, multicenter, randomized, double-blind, placebo-controlled trial to identify the effect of an SGLT2 inhibitor on cardiac sympathetic hyperactivity in patients with AMI and type 2 diabetes mellitus (T2DM) in Japan. In total, 105 patients were randomized (1:1) to receive 10 mg empagliflozin or a placebo (once daily), 2 weeks after the onset of AMI. In this subanalysis, we investigated the time-course of PVS at baseline and weeks 4, 12, and 24.

Results: Overall, 96 patients were included in the subgroup analysis set (age 64.3 ± 10.9 years, 80.2% men; 46 in the empagliflozin group and 50 in the placebo group). Body weight and PVS decreased in the empagliflozin group compared with the placebo group at 24 weeks (-2.2 vs. $+0.1$ kg, $P < 0.001$, and -5.1 vs. -0.3%, $P < 0.001$, respectively). Decreased PVS, defined as a change in PVS of $< -4.5\%$, was associated with the administration of empagliflozin (odds ratio 2.61, 95% confidence interval 1.11–6.15, $P = 0.028$). N-terminal *pro* b-type natriuretic peptide levels decreased in both the empagliflozin and placebo groups (1028.7–370.3 pg/mL, $P < 0.001$, and 1270.6–673.7 pg/mL, $P < 0.01$, respectively).

Conclusion: Empagliflozin reduced the body weight and PVS. Early SGLT2 inhibitor administration in patients with AMI, CHF, and T2DM

can therefore be effective in reducing the body weight and PVS.

Trial Registration: UMIN 000030158.

Keywords: Acute myocardial infarction; Congestive heart failure; Empagliflozin; Plasma volume status; Sodium-glucose cotransporter 2 (SGLT2) inhibitor

Key Summary Points
Why carry out this study?
Plasma volume status (PVS), an indication of the discrepancy between actual plasma volume (PV) and ideal PV, has been recently evaluated as a prognostic marker in patients with heart failure.
This trial was designed to determine whether a sodium-glucose cotransporter 2 (SGLT2) inhibitor (empagliflozin) affected the improvement of heart failure and PVS in patients after acute myocardial infarction (AMI) with congestive heart failure (CHF).
What was learned from the study?
Empagliflozin reduced not only the body weight but also PVS.
The results suggest that early SGLT2 inhibitor administration in patients with AMI, CHF, and T2DM can be effective in reducing the body weight and PVS.

INTRODUCTION

Plasma volume status (PVS) is a differential marker used in the case of a discrepancy between actual plasma volume (PV) and ideal PV; it has recently been evaluated as a prognostic marker of heart failure [1, 2]. Actual PV has been validated previously [3] and is derived from the values of the hematocrit and the weight of subjects compared with directly measured values of PV, using the curve fitting technique.

$$\text{Actual PV} = (1 - \text{hematocrit}) \times [a + (b \times \text{body weight in kg})] \tag{1}$$

where hematocrit is a fraction, $a = 1530$ in males and 864 in females, and $b = 41$ in males and 47.9 in females.

Using the body weight, the ideal PV is calculated from the following well-established formula [1]:

$$\text{Ideal PV} = c \times \text{body weight (kg)} \tag{2}$$

where $c = 39$ in males and 40 in females.

Subsequently, relative PVS, an index of the degree of deviation in ideal PV, can be calculated using the Kaplan–Hakim formula as follows [1]:

$$\text{PVS} = [(\text{actual PV} - \text{ideal PV})/\text{ideal PV}] \times 100(\%) \tag{3}$$

The EMBODY trial is a prospective, multicenter, randomized, double-blind, and placebo-controlled trial for identifying the effect of empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, on cardiac sympathetic hyperactivity in patients with acute myocardial infarction (AMI) and type 2 diabetes mellitus (T2DM) in Japan [4, 5].

This post hoc analysis of the EMBODY trial was designed to determine whether the SGLT2 inhibitor improves PVS in patients with diabetes with congestive heart failure (CHF) after AMI.

METHODS

In the subgroup analysis of the EMBODY trial, a total of 105 patients with T2DM were randomized (1:1) to receive 10 mg empagliflozin once daily or the placebo, both within 2 weeks of the onset of AMI. Here, we investigated the time-course of changes in PVS at baseline and at weeks 4, 12, and 24. All patients provided informed consent to participate in the trial

between February 2018 and March 2019. The inclusion and exclusion criteria have already been published [3]. Six patients in the empagliflozin group and three patients in the placebo group withdrew their consent and were thus excluded before the medication was initiated.

Ethics

The EMBODY trial was registered at the UMIN in November 2017 (ID: 000030158). Ethics approval was obtained from the local institutional review board of each participating center. The trial was conducted in full compliance with the articles of the Declaration of Helsinki and according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labour, and Welfare and the Ministry of Education, Culture, Sports, Science, and Technology in Japan. After initial screening for eligibility using prior medical records, each patient received an adequate explanation of the trial plan before they provided written informed consent. All participants provided written informed consent prior to study enrolment.

RESULTS

In total, 96 patients were included in the subgroup analysis set (age 64.3 ± 10.9 years, 80.2% men, with 46 and 50 patients in the empagliflozin and placebo groups, respectively). The baseline characteristics were not significantly different between the treatment groups, including left ventricular ejection fraction, and New York Heart Association functional classification (Table 1). During the trial period, no significant differences were observed in terms of the dose and oral administration rate of the optimal medical treatment (including diuretics) between the two groups (Table 2). All patients received both revascularization and heart failure treatments. The empagliflozin group showed significantly decreased body weight and PVS compared with the placebo group at 24 weeks ($- 2.2$ vs. $+ 0.1$ kg, $P < 0.001$, and $- 5.1 \pm 5.8\%$ vs. $- 0.3 \pm 7.2\%$, $P < 0.001$, respectively) (Fig. 1a–c; Table 2). Therefore, an

Table 1 Baseline patient characteristics

Patient characteristics	Empagliflozin group, $n = 46$	Placebo group, $n = 50$	P
Age, year (SD)	63.9 (10.4)	64.6 (11.6)	0.73
Male, n (%)	38 (82.6)	39 (78.0)	0.62
Body weight, kg (SD)	70.1 (13.7)	68.1 (14.4)	0.49
BMI, kg/m^2 (SD)	25.2 (3.7)	25.2 (4.1)	0.99
Systolic blood pressure, mmHg (SD)	129.7 (11.9)	123.1 (15.7)	0.11
Hypertension, n (%)	38 (82.6)	39 (78.0)	0.62
Dyslipidemia, n (%)	34 (73.9)	36 (72.0)	1.00
Smoking, n (%)	24 (52.2)	27 (54.0)	0.92
Transthoracic echocardiography			
Left ventricular ejection fraction, % (SD)	55.1 (14.2)	55.0 (13.7)	0.97
Average E/e′ (SD)	13.47 (7.24)	13.73 (6.26)	0.88
TRPG, mmHg (SD)	17.59 (7.48)	20.71 (11.49)	0.23
Heart failure medication at randomization visit, n (%)			
β-Blocker	41 (89.1)	38 (76.0)	0.11
Diuretic	8 (17.4)	11 (22.0)	0.62
MRA,	11 (23.9)	12 (24.0)	1.00
ACEI	23 (50.0)	28 (56.0)	0.68
ARB	22 (47.8)	19 (38.0)	0.41
Glucose-lowering medication at randomization visit, n (%)			
Biguanide	7 (15.2)	6 (12.0)	0.77
DPP-4 inhibitor	20 (43.5)	23 (46.0)	0.84
NYHA classification, %			
I/II	77.8/7.4	58.1/22.6	0.09
Blood test			
Max CK, IU/L (SD)	2080.7 (2461.6)	2358.7 (2829.1)	0.61

Table 1 continued

Patient characteristics	Empagliflozin group, $n = 46$	Placebo group, $n = 50$	P
HbA1c, % (SD)	6.82 (1.00)	6.89 (0.92)	0.73
LDL-C, mg/dL (SD)	87.5 (29.6)	87.8 (29.1)	0.96
HDL-C, mg/dL (SD)	45.4 (12.7)	46.0 (10.2)	0.78
Triglycerides, mg/dL (SD)	161.7 (119.7)	135.9 (54.4)	0.18
Uric acid, mg/dL (SD)	5.8 (1.4)	5.7 (1.5)	0.94
Creatinine, mg/dL (SD)	0.92 (0.2)	0.92 (1.2)	0.39
eGFR, mL/min/ 1.73 m^2 (SD)	64.6 (15.0)	66.1 (15.7)	0.62
Hematocrit, % (SD)	40.5 (4.6)	40.3 (4.2)	0.86
NT-proBNP, pg/ mL (SD)	1028.7 (1105.6)	1270.6 (1521.0)	0.45

A1c glycated hemoglobin, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin-receptor blocker, *BMI* body mass index, *CK* creatine kinase, *DPP-4* dipeptidyl peptidase-4, *E* peak early diastolic phase mitral inflow velocity, *e'* mitral annular velocity, *eGFR* estimated glomerular filtration rate, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *MRA* mineralocorticoid receptor antagonist, *NT-proBNP* N-terminal *pro* b-type natriuretic peptide, *NYHA* New York Heart Association, *SD* Standard deviation, *TRPG* trans-tricuspid pressure gradient

intergroup difference was observed at 12 and 24 weeks (Fig. 1a, c). On the contrary, the N-terminal *pro* b-type natriuretic peptide (NT-proBNP) level was decreased in both groups (1028.7–370.3 pg/mL, $P < 0.001$, and 1270.6–673.7 pg/mL, $P < 0.01$, respectively), and intergroup differences were not significant ($P = 0.91$) (Fig. 1d; Table 2). Blood test results are presented in Table 2 During the trial period,

no difference was observed between the groups in terms of glycated hemoglobin (HbA1c) levels. Compared to the placebo group, the empagliflozin group exhibited significantly higher hematocrit levels and lower uric acid levels at 24 weeks. The decrease in PVS was defined as a change of $< -4.5\%$, which was the median value calculated using the change in PVS (ΔPVS) of patients from baseline to 24 weeks. Univariate and multivariate logistic regression analyses adjusted for confounding variables (age, NT-proBNP levels, change in body weight, systolic blood pressure, HbA1c levels) indicated that the decrease in PVS was associated with empagliflozin use (odds ratio [OR] 2.61, 95% confidence interval (CI) 1.11–6.15, $P = 0.028$, and OR 3.76, 95% CI 1.11–12.72, $P = 0.033$ for univariate and multivariate models, respectively) (Table 3). Additionally, ΔPVS was not significantly correlated with the change in NT-proBNP (ΔNT-proBNP) in both the empagliflozin ($r = 0.194$, $P = 0.289$) and placebo ($r = 0.254$, $P = 0.109$) groups.

DISCUSSION

A previous study reported that a PVS $> -4\%$ was associated with the worst prognosis [1]. Here, the NT-proBNP levels were significantly decreased in both the empagliflozin and placebo groups. Moreover, ΔPVS had no correlation with ΔNT-proBNP in both groups. In the previous study, canagliflozin, another SGLT2 inhibitor, showed no robust effects on NT-proBNP levels in patients with T2DM and CHF [6]. Moreover, the DEFINE-HF trial showed that in patients with heart failure and reduced ejection fraction with and without T2DM, the use of dapagliflozin over 12 weeks did not affect the mean NT-proBNP level; however an increased proportion of patients on this drug experienced clinically meaningful improvements in the heart failure-related health status, according to the Kansas City Cardiomyopathy Questionnaire overall summary score [7]. We showed that empagliflozin reduced circulating PV independent of NT-proBNP levels. The lack of correlation between ΔPVS and ΔNT-proBNP is similar to that observed upon valsartan administration

Table 2 Blood tests, optimal medical therapy, and plasma volume status in the empagliflozin and placebo groups at baseline and 24 weeks

Blood tests, optimal medical therapy, and PVS	Empagliflozin group ($n = 46$)			Placebo group ($n = 50$)			Intergroup
	Baseline	24 weeks	P	Baseline	24 weeks	P	P
Blood tests							
HbA1c (%)	6.8 ± 1.0	6.6 ± 0.9	0.10	6.9 ± 0.9	6.8 ± 1.0	0.34	0.50
Hematocrit (%)	40.5 ± 4.6	44.2 ± 3.9	< 0.001	40.3 ± 4.2	40.5 ± 4.2	0.81	< 0.0001
Uric acid (mg/dL)	5.8 ± 1.4	4.9 ± 1.4	< 0.001	5.7 ± 1.5	5.8 ± 1.5	0.82	< 0.0001
eGFR (equivalent) (mL/min/1.73 m^2)	64.6 ± 15.0	64.4 ± 16.8	0.84	66.1 ± 15.7	62.8 ± 15.4	0.02	0.10
Serum creatinine (mg/dL)	0.92 ± 0.19	0.94 ± 0.25	0.44	0.89 ± 0.20	0.94 ± 0.21	0.01	0.24
NT-proBNP (pg/mL)	1028.7 ± 1105.6	370.3 ± 530.9	< 0.001	1270.6 ± 1521.0	673.7 ± 1151.1	< 0.01	0.91
LDL-C (mg/dL)	87.5 ± 29.6	79.4 ± 21.3	0.06	87.8 ± 29.1	81.0 ± 25.0	0.09	0.83
HDL-C (mg/dL)	45.4 ± 12.7	49.8 ± 13.0	< 0.001	46.0 ± 10.2	49.2 ± 9.2	0.01	0.52
TG (mg/dL)	161.7 ± 119.7	145.5 ± 75.0	0.25	135.9 ± 54.3	141.0 ± 59.1	0.67	0.30
AST (U/L)	24.7 ± 7.9	23.2 ± 8.5	0.30	24.4 ± 10.3	25.4 ± 14.0	0.47	0.21
ALT (U/L)	26.4 ± 14.8	22.2 ± 13.1	0.04	26.6 ± 16.4	24.2 ± 11.9	0.20	0.54
γ-GTP (U/L)	39.6 ± 29.1	40.0 ± 40.2	0.92	32.4 ± 18.9	39.2 ± 38.1	0.03	0.16
Optimal medical therapy							
β-Blocker, n (%)	41 (89.1)	41 (89.1)	1.00	38 (76)	38 (76)	1.00	0.09
Diuretic, n (%)	8 (17.4)	6 (13.0)	0.57	11 (22)	10 (20)	0.81	0.36
MRA, n (%)	11 (23.9)	11 (23.9)	1.00	12 (24)	12 (24)	1.00	0.99
ACEI, n (%)	23 (50)	20 (43.5)	0.54	28 (56)	22 (44)	0.23	0.96
ARB, n (%)	22 (47.8)	21 (45.7)	0.84	19 (38)	19 (38)	1.00	0.45

Table 2 continued

Blood tests, optimal medical therapy, and PVS	Empagliflozin group (*n* = 46)			Placebo group (*n* = 50)			Intergroup
	Baseline	24 weeks	*P*	Baseline	24 weeks	*P*	*P*
PVS							
PVS (%)	− 4.72 ± 8.95	− 9.79 ± 8.07	< 0.001	− 3.77 ± 9.64	− 4.04 ± 10.12	0.79	< 0.001

ALT Alanine aminotransferase, *AST* aspartate aminotransferase, *PVS* plasma volume status, *TG* triglycerides, *γ-GTP* γ-glutamyl transpeptidase
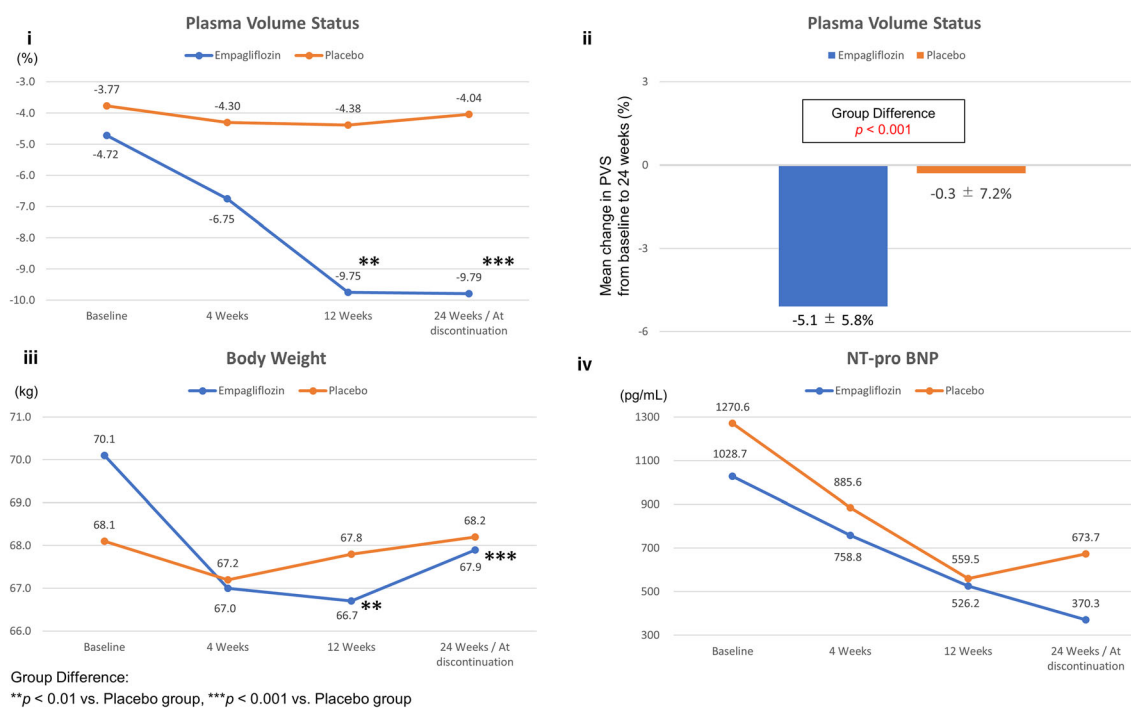
Fig. 1 i Time-course of change in plasma volume status (*PVS*) from baseline to 24 weeks. **ii** Change in PVS between baseline and 24 weeks. **iii** Time-course of change in body weight from baseline to 24 weeks. **iv** Time-course of change in N-terminal *pro* b-type natriuretic peptide (*NT-proBNP*) levels from baseline to 24 weeks

in the Heart Failure Trial [1]. The reason for such a result is unclear, and further research is warranted. The novelty of the current study is that early administration of empagliflozin in patients with AMI and T2DM reduced PVS over a 24-week period. As this study corresponds to a subanalysis, a large-scale, randomized, controlled trial with PVS as the primary endpoint is required in the future to confirm our results.

This study has several limitations. First, the trial period was only 24 weeks; nevertheless, no study has previously examined how PVS changes during 24 weeks after the administration of

Table 3 Odds ratio associated with ΔPVS $< -4.5\%$

Variables	Univariate		Multivariate	
	OR (95% CI)	**P**	OR (95% CI)	**P**
Empagliflozin	2.61 (1.11–6.15)	0.028	3.76 (1.11–12.72)	0.033
Age	1.00 (0.96–1.04)	0.931		
NT-proBNP	1.00 (1.00–1.01)	0.355		
ΔBody weight	0.97 (0.86–1.09)	0.588		
ΔSystolic blood pressure	1.01 (0.98–1.03)	0.697		
ΔHbA1c levels	0.99 (0.58–1.70)	0.977		

CI Confidence interval, *OR* odds ratio, Δ delta

SGLT2 inhibitors. Second, our sample size was small. Third, we excluded patients treated with insulin, glucagon-like peptide 1 analogs, and high doses of sulfonylureas, as well as patients with HbA1c $\geq$ 10%. Therefore, this study did not include patients with poor glycemic control. Finally, although 20% of patients were women, the results were comparable even when the data of female patients were excluded from the analysis.

CONCLUSION

In conclusion, we showed that empagliflozin reduced circulating PV in patients with AMI and T2DM.

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Compliance with Ethics Guidelines. The EMBODY trial was registered at the UMIN in November 2017 (ID: 000030158). Ethics approval was obtained from the local institutional review board of each participating center. The trial was conducted in full compliance with the articles of the Declaration of Helsinki and according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labour, and Welfare and the Ministry of Education, Culture, Sports, Science, and Technology in Japan. After initial screening for eligibility using prior medical records, each patient received an adequate explanation of the trial plan before they provided written informed consent. All participants provided written informed consent prior to study enrolment.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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