Effects of luseogliiflozin 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 luseogliiflozin 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 (UMIN00018395), a multicentre, prospective, open-label, randomized controlled trial that assessed the effect of 12 weeks of luseogliiflozin (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. Luseogliiflozin significantly reduced ePV as compared to voglibose at Week 4 \(( r = 0.197, P = 0.015 \)) and at Week 12 \(( r = 0.019, P = 0.015 \)) and left atrial volume index \(( r = 0.283, P = 0.019 \)).

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

Keywords  Estimated plasma volume; Heart failure with preserved ejection fraction; Luseogliiflozin; 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 HFpEF, 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 multi-centre, 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) \(\geq 55\%\), 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: \((1 - \text{haematocrit}) \times (1530 + [41 \times \text{body weight (kg)}])\) in male patients and \((1 - \text{haematocrit}) \times (864 + [47.9 \times \text{body weight (kg)}])\) 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 \times \text{[haemoglobin (at baseline)/haemoglobin (at visit)]} \times [1 - \text{haematocrit (at visit)}/[1 - \text{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 χ² 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 luseogliiflozin 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 m², <60 mL/min/1.73 m²), 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 HFrEF 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 luseogliiflozin 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 luseogliiflozin 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 luseogliiflozin 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, luseogliiflozin 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 m², luseogliiflozin compared with voglibose reduced ePV by −10.83% (95%CI: –15.28 to –6.37%). In patients with eGFR ≥ 60 mL/min/1.73 m², 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, luseogliiflozin 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). Luseogliiflozin 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 luseogliiflozin on the change in ePV at Weeks 4, 12, and
Table 1 Baseline clinical characteristics of this study

| Variables                        | Luseogliozin (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/m²)          |                      |                    |         |
| 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 m²)   | 60.6 ± 19.4           | 56.8 ± 16.5        | 0.185   |
| BNP (pg/mL)                      | 63.7 (46.8–113.8)     | 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/m²)                     | 37.9 ± 16.3           | 38.4 ± 13.5        | 0.84    |
| LVMI (g/m²)                      | 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 luseogliozin 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.
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.

**Figure 2** Changes from baseline in ePV (%) at Week 12 of treatment with luseogliiflozin 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.

| Subgroup                  | Group Difference (95% CI)       | P value for Interaction |
|---------------------------|---------------------------------|-------------------------|
| Overall                   | -8.763 (-12.183 to -5.343)      | 0.486                   |
| Age                       |                                 |                         |
| <65 y                     | -13.13 (-26.629 to 0.368)       |                         |
| ≥65 y                     | -8.394 (-11.991 to -4.797)      |                         |
| Sex                       |                                 |                         |
| Male                      | -11.146 (-15.737 to -6.555)     | 0.062                   |
| Female                    | -4.375 (-9.387 to 0.637)        |                         |
| HgbA1c                    |                                 |                         |
| <8.0 %                    | -8.411 (-11.845 to -4.977)      | 0.541                   |
| ≥8.0 %                    | -11.879 (-32.434 to 8.676)      |                         |
| BNP                       |                                 |                         |
| <100 pg/ml                | -7.978 (-11.805 to -4.152)      | 0.454                   |
| ≥100 pg/ml                | -10.944 (-18.643 to -3.244)     |                         |
| Estimated GFR             |                                 |                         |
| <60 ml/min/1.73 m²        | -10.825(-15.282 to -6.368)      | 0.166                   |
| ≥60 ml/min/1.73 m²        | -6.01(-11.368 to -0.652)        |                         |
| Thiazolidine              |                                 |                         |
| Yes                       | -17.098 (-30.710 to -3.485)     | 0.083                   |
| No                        | -7.682 (-11.174 to -4.189)      |                         |
| Body weight               |                                 |                         |
| <60 kg                    | -6.171 (-11.782 to -0.560)      | 0.232                   |
| ≥60 kg                    | -10.445 (-14.854 to -6.035)     |                         |
| Atrial fibrillation or flutter |                                 |                         |
| Yes                       | -8.777 (-17.131 to -0.422)      | 0.99                    |
| No                        | -8.830 (-12.612 to -5.048)      |                         |
| Prior ASCVD               |                                 |                         |
| Yes                       | -9.420 (14.061 to -4.779)       | 0.54                    |
| No                        | -7.622 (-12.847 to -2.397)      |                         |
| β-blocker                 |                                 |                         |
| Yes                       | -12.874 (-17.346 to -8.403)     | 0.005                   |
| No                        | -2.912 (-8.072 to 2.247)        |                         |
| ACEI/ARB                  |                                 |                         |
| Yes                       | -11.109 (-15.719 to -6.499)     | 0.088                   |
| No                        | -5.062 (-10.116 to -0.007)      |                         |
| Diuretic                  |                                 |                         |
| Yes                       | -12.545 (-18.151 to -6.940)     | 0.093                   |
| No                        | -6.508 (-10.870 to -2.146)      |                         |

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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. Previous studies have reported that SGLT2 inhibitors reduced both the plasma volume measured by labelled human serum albumin and ePV by using laboratory data in patients with T2DM. Other studies have also reported that SGLT2 inhibitors reduced the ePV in patients with T2DM complicated by cardiovascular diseases or HFrEF. In addition, SGLT2 inhibitors reduced pulmonary arterial pressure in patients with heart failure. 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. 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. 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. 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. 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. 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. 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. 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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**References**

1. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; 325: 293–302.

2. Matsumori A. Efficacy and safety of oral candesartan cilexetil in patients with congestive heart failure. *Eur J Heart Fail* 2003; 5: 669–677.

3. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincenzi J, Pocock SJ, Pitt B. EMPHASIS-HF study group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364: 11–21.

4. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. *N Engl J Med* 1999; 341: 709–717.

5. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. carvedilol heart failure study group. *N Engl J Med* 1996; 334: 1349–1355.

6. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. SHIFT Investigators.伊伐布雷定 and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010; 376: 875–885.

7. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. PARADIGM-HF investigators and committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371: 993–1004.

8. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Claussell N, Desai AS, Diáz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM, TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; 370: 1383–1392.

9. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, Manzino L, McMurray JJV, Ruschitzka F, van Veldhuisen DJ, von Lueder TG, Böhm M, Andersson B, Kjekshus J, Packer M, Rigby AS, Rosano G, Wedel H, Hjalmarson Å, Wikstrand J, Kotecha D, Beta-blockers in heart failure collaborative group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J* 2018; 39: 26–35.

10. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006; 27: 2338–2345.

11. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A, I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008; 359: 2456–2467.
12. Zelniker TA, Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. J Am Coll Cardiol 2020; 75: 422–434.

13. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtdo RH, Bhatt DL, Leiter LA, McGuire DK, Wiling JPH, Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcomes trials. Lancet 2019; 393: 31–39.

14. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wiling JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS. DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019; 380: 347–357.

15. McMurray JvJ, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martina FA, Ponikowski P, Sabatine MS, Anand IS, Bélohlávěk J, Böhm M, Chang CE, CPVR, de Boer RA, Desai AS, Diez M, Drozdz J, Dušák A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman Ľ, Merkely B, Nicolau JC, Omran MR, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS. DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in patients with heart failure and reduced ejection fraction. N Engl J Med 2019; 381: 1995–2008.

16. Zelniker TA, Braunwald E. Clinical benefit of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. J Am Coll Cardiol 2020; 75: 435–447.

17. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtdo RH, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wiling JPH, Bonaca MP, Ruff CT, Desai AS, Goto S, Johansson PA, Gause-Nilsson I, Johanson P, Langkilde AM, Raz I, Sabatine MS, Wiviott SD. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation 2019; 139: 2528–2536.

18. Dekkers CJC, Sjöstöm CD, Greasley PJ, Cavin V, Boulton DW, Heerspink HJL. Effects of the sodium-glucose co-transporter-2 inhibitor dapagliflozin on estimated plasma volume in patients with type 2 diabetes. Diabetes Obes Metab 2019; 21: 2667–2673.

19. Matsubayashi Y, Yoshida A, Suganami H, Oe M, Sato T, Yaguchi Y, Fujihara K, Yamada T, Tanaka S, Kaku K, Sone H. Association of estimated plasma volume and weight loss after long-term administration and subsequent discontinuation of the sodium-glucose cotransporter-2 inhibitor tolvagliflozin. Diabetes Obes Metab 2021; 23: 1660–1665.

20. Tanaka A, Shimabukuro M, Teragawa H, Okada Y, Takamura T, Taguchi I, Toyoda S, Tomiyama H, Ueda S, Higashi Y, Node K, EMBLEM Investigators. Reduction of estimated fluid volumes following initiation of empagliflozin in patients with type 2 diabetes and cardiovascular disease: a secondary analysis of the placebo-controlled, randomized EMBLEM trial. Cardiovasc Diabetol 2021; 20: 105.

21. Jensen J, Omar M, Kristorp C, Tunux C, Gustafsson J, Kober L, Gustafsson F, Faber J, Malik ME, Fosbol EL, Bruun NE, Forman JL, Jensen LT, Möller JE, Schou M. Effects of empagliflozin on estimated extracellular volume, estimated plasma volume, and measured glomerular filtration rate in patients with heart failure (Empire HF Renal): a prespecified substudy of a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2021; 9: 106–116.

22. Ejiri K, Miyoshi T, Kihara H, Hata Y, Nagano T, Takashii A, Toda H, Namba S, Nakamura Y, Akagi S, Sakuragi S, Minagawa T, Kawai Y, Nishii N, Fujie K, Yoshikawa M, Nakamura K, Ito H, MUSCAT-HF Study Investigators. Effect of luseogliflozin on heart failure with preserved ejection fraction in patients with diabetes mellitus. J Am Heart Assoc 2020; 19: e015103.

23. Ejiri K, Miyoshi T, Nakamura K, Sakuragi S, Munemasa M, Namba S, Takashii A, Ito H. The effect of luseogliflozin and alpha-glucosidase inhibitor on heart failure with preserved ejection fraction in diabetic patients: rationale and design of the MUSCAT-HF randomised controlled trial. BMJ Open 2019; 9: e026590.

24. Fudim M, Miller WL. Calculated estimates of plasma volume in patients with chronic heart failure-comparison with measured volumes. J Card Fail 2018; 24: 553–557.

25. Stracke MB, Davis RK, Rosenbaum JD, Rosmesil EC. Water diuresis occurred during recumbency by the intravenous infusion of isotonic saline solution. J Clin Invest 1951; 30: 862–868.

26. Nassif ME, Qintar M, Windsor SL, Chouihed T, Chikamori T, Pitt B, Zannad F, Zeiber A, ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2022. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; 33: 1767–1847.

27. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Forjaz C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Pamboukian V, Pieske BM, Popescu BA, Ronn H, Rutten FH, Schaper J, Seferovic P, Steinhäuser J, Trindade PT, Voors AA, Zannad F, Zeiber A, ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; 33: 1767–1847.

28. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Forjaz C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Pamboukian V, Pieske BM, Popescu BA, Ronn H, Rutten FH, Schaper J, Seferovic P, Steinhäuser J, Trindade PT, Voors AA, Zannad F, Zeiber A, ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2022. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2022; 3: 712–720.

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