



ORIGINAL RESEARCH

Effect of Luseogliflozin on Heart Failure With Preserved Ejection Fraction in Patients With Diabetes Mellitus

Kentaro Ejiri , MD, PhD; Toru Miyoshi , MD, PhD; Hajime Kihara, MD, PhD; Yoshiki Hata, MD, PhD; Toshihiko Nagano, MD, PhD; Atsushi Takaishi, MD, PhD; Hironobu Toda, MD, PhD; Seiji Nanba, MD, PhD; Yoichi Nakamura, MD, PhD; Satoshi Akagi, MD, PhD; Satoru Sakuragi, MD, PhD; Taro Minagawa, MD, PhD; Yusuke Kawai, MD, PhD; Nobuhiro Nishii, MD, PhD; Soichiro Fuke, MD, PhD; Masaki Yoshikawa, MD, PhD; Kazufumi Nakamura, MD, PhD; Hiroshi Ito, MD, PhD; for the MUSCAT-HF Study Investigators*

BACKGROUND: Effects of sodium-glucose cotransporter 2 inhibitors on reducing hospitalization for heart failure have been reported in randomized controlled trials, but their effects on patients with heart failure with preserved ejection fraction (HFpEF) are unknown. This study aimed to evaluate the drug efficacy of luseogliflozin, a sodium-glucose cotransporter 2 inhibitor, in patients with type 2 diabetes mellitus and HFpEF.

METHODS AND RESULTS: We performed a multicenter, open-label, randomized, controlled trial for comparing luseogliflozin 2.5 mg once daily with voglibose 0.2 mg 3 times daily in patients with type 2 diabetes mellitus suffering from HFpEF (left ventricular ejection fraction >45% and BNP [B-type natriuretic peptide] concentrations ≥ 35 pg/mL) in a 1:1 randomization fashion. The primary outcome was the difference from baseline in BNP levels after 12 weeks of treatment between the 2 drugs. A total of 173 patients with diabetes mellitus and HFpEF were included. Of these, 83 patients were assigned to receive luseogliflozin and 82 to receive voglibose. There was no significant difference in the reduction in BNP concentrations after 12 weeks from baseline between the 2 groups. The ratio of the mean BNP value at week 12 to the baseline value was 0.79 in the luseogliflozin group and 0.87 in the voglibose group (percent change, -9.0% versus -1.9% ; ratio of change with luseogliflozin versus voglibose, 0.93; 95% CI, 0.78–1.10; $P=0.26$).

CONCLUSION: In patients with type 2 diabetes mellitus and HFpEF, there is no significant difference in the degree of reduction in BNP concentrations after 12 weeks between luseogliflozin and voglibose.

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Key Words: B-type natriuretic peptide ■ diabetes mellitus ■ heart failure ■ sodium-glucose cotransporter 2 inhibitor

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For the past 2 decades, a better prognosis was able to be achieved than was previously possible in patients with heart failure with reduced ejection fraction (EF) because of the advent of guideline-based medicine and device therapy. However, the

effectiveness of these therapeutic agents has not been clarified in heart failure with preserved ejection fraction (HFpEF) in clinical trials.^{1–4} Furthermore, recent guidelines suggest no effective medication for HFpEF.^{5,6}

Correspondence to: Toru Miyoshi, MD, Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan. E-mail: miyoshit@cc.okayama-u.ac.jp
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*A complete list of the MUSCAT-HF Study Investigators can be found in the appendix at the end of the article.

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CLINICAL PERSPECTIVE

What Is New?

- The MUSCAT-HF (Management of Diabetic Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction) study is the first prospective, multicenter, open-label, randomized controlled trial to investigate the drug effect of an sodium-glucose cotransporter 2 inhibitor, luseogliflozin, on BNP (B-type natriuretic peptide) concentrations as the primary outcome compared with an alpha-glucosidase inhibitor, voglibose.
- We found that BNP concentrations decreased after initiation of either luseogliflozin or voglibose; however, there was no significant difference in the degree of reduction in BNP concentrations after 12 weeks for luseogliflozin and voglibose (percent change, -9.0% versus -1.9% ; ratio of change with luseogliflozin versus voglibose, 0.93; 95% CI, 0.78–1.10; $P=0.26$).

What Are the Clinical Implications?

- Our findings support no clear evidence of the effect of sodium-glucose cotransporter 2 inhibitors in reducing BNP concentrations at 12 weeks in patients with type 2 diabetes mellitus with heart failure with preserved ejection fraction and a requirement of further investigations including ongoing larger randomized controlled trials.

Nonstandard Abbreviations and Acronyms

BNP	B-type natriuretic peptide
EF	ejection fraction
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
E/e'	ratio of early mitral inflow velocity to mitral annular early diastolic velocity
HFpEF	heart failure with preserved ejection fraction
MUSCAT-HF	Management of Diabetic Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction
SGLT2	sodium-glucose cotransporter 2

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, which are antidiabetic drugs for promoting urinary glucose excretion, have been suggested to reduce hospitalization for heart failure in patients with type

2 diabetes mellitus in recent randomized controlled trials.^{7–9} Recently, a randomized study showed that dapagliflozin decreased worsening heart failure in patients with heart failure and a reduced EF, regardless of the presence or absence of diabetes mellitus.¹⁰ SGLT2 inhibitors are being studied in large trials for HFpEF, but no detailed data on the effects of SGLT2 inhibitors in HFpEF have been obtained.

To investigate whether an SGLT2 inhibitor has preventative effects on heart failure beyond glucose-lowering effects in patients with HFpEF, we prospectively compared luseogliflozin and alpha-glucosidase in the MUSCAT-HF (Management of Diabetic Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction) trial. We compared the drug efficacy of luseogliflozin (an SGLT2 inhibitor) with voglibose (an alpha-glucosidase inhibitor), which have established safety for cardiovascular events¹¹ as control agents. BNP (B-type natriuretic peptide) was used as the index of the therapeutic effect in patients with type 2 diabetes mellitus and HFpEF. This study aimed to determine the therapeutic effect of this SGLT2 inhibitor on HFpEF in patients with type 2 diabetes mellitus.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

Details of the study design have been published previously¹² (Data S1 through S3). The MUSCAT-HF trial was a multicenter, prospective, open-label, randomized controlled trial for assessing the effect of luseogliflozin (2.5 mg once daily) compared with voglibose (0.2 mg 3 times daily) on left ventricular load in patients with type 2 diabetes mellitus and HFpEF. The change in ratio of BNP concentrations after administration of the study drug from baseline was used as a surrogate biomarker for heart failure (Figure S1 and Table S1). This study was approved by the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and the Okayama University Hospital Ethics Committee, as well as the ethics committee of each participating center. The investigation conforms with the principles outlined in the Declaration of Helsinki. This trial was registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN000018395).

Members of the steering committee also designed the study and are responsible for its conduction. Significant adverse events that occurred within 30 days after final administration of the study drug

or after 30 days with a suspicion of association with the study drug, as well as all pregnancies, were immediately reported to the steering committee and the sponsor by the investigators, in accordance with the guidelines for good clinical practice.

Participants

Patients aged ≥ 20 years with requirement of additional treatment for type 2 diabetes mellitus, despite ongoing treatment, and HFpEF were eligible for participation. HFpEF was defined as a left ventricular EF $\geq 45\%$, BNP concentrations ≥ 35 pg/mL, and any symptoms, such as shortness of breath, orthopnea, and leg edema. The criterion of BNP concentrations was based on the fact that the definition of chronic heart failure according to the European Society of Cardiology guidelines includes BNP concentrations ≥ 35 pg/mL.¹³ Patients with BNP concentrations < 35 pg/mL; treatment with alpha-glucosidase inhibitors, SGLT2 inhibitors, glinides, or high-dose sulfonylurea; renal insufficiency (estimated glomerular filtration rate [eGFR] < 30 mL/min per 1.73 m²); a history of severe ketoacidosis or diabetic coma within 6 months before participation; poorly controlled type 2 diabetes mellitus (hemoglobin A_{1c} $> 9.0\%$); and hypertension were excluded (see full exclusion criteria in Data S1). All participants provided written informed consent before participation. Study candidates were assessed for eligibility within 4 weeks before enrollment.

Interventions and Study Procedures

Patients fulfilling all criteria who provided written informed consent to participate in this study were enrolled and subsequently randomized (1:1) to receive luseogliflozin (2.5 mg once daily) or voglibose (0.2 mg 3 times daily) in addition to their background medication. Luseogliflozin is an SGLT2 inhibitor, which has 1600-fold selectivity of SGLT2 to SGLT1,¹⁴ and is currently approved or marketed in Japan, but not in North America and European countries. Randomization was performed using a computer-generated random sequence web response system. Patients were stratified by age (< 65 years, ≥ 65 years), baseline hemoglobin A_{1c} values ($< 8.0\%$, $\geq 8.0\%$), baseline BNP concentrations (< 100 pg/mL, ≥ 100 pg/mL), baseline renal function (eGFR ≥ 60 mL/min per 1.73 m², < 60 mL/min per 1.73 m²), use of thiazolidine (yes or no), and presence or absence of atrial fibrillation and flutter at screening.

Laboratory data, ECGs, echocardiography, and patients' vital signs, body weight, and waist circumference were evaluated at 4 and 12 weeks after initiation of study treatment. Safety and tolerability were assessed during the treatment period. After 12 weeks, expansion of follow-up for an additional 12 weeks was

continued in patients who agreed. If a patient's glyce-mic control worsened after 4 weeks, the investigator increased the dose of allocated treatment (luseogliflozin 5 mg once daily or voglibose 0.3 mg 3 times daily) and other specific antidiabetic drugs, except for sulfonylureas. Investigators were also encouraged to treat all other cardiovascular risk factors according to the local standard of care. Under the following circumstances, the investigators evaluated the data and patient's vital signs: (1) discontinuation of study treatment; (2) dose increase of specific treatment for heart failure; (3) initiation of new treatment for heart failure; and (4) withdrawal from the study. The permitted medications for treatment of heart failure included angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics, and mineralocorticoid/aldosterone receptor antagonists.

Outcomes

The primary outcome of this study was the change in ratio of BNP concentrations after 12 weeks of treatment from baseline. The main safety outcomes were adverse events, including major adverse cardiovascular events, hypoglycemic adverse events (requiring any intervention), and urinary tract infection. Major adverse cardiovascular events included cardiovascular death, acute coronary syndrome, hospitalization for heart failure, and stroke. Details of the main safety outcomes are shown in Data S3. The main secondary outcomes of this study were the differences in the following parameters between 12 weeks and baseline: the ratio of early mitral inflow velocity to mitral annular early diastolic velocity (E/e'), left ventricular EF, body weight, and hemoglobin A_{1c} values. Further exploratory analysis is listed in Data S1. We also conducted analyses of exploratory clinical outcomes, including changes in systolic blood pressure, heart rate, eGFR, NT-proBNP (N-terminal pro-BNP) concentrations, high-sensitivity C-reactive protein concentrations, the ratio of early to atrial mitral inflow velocity, mitral annular early diastolic velocity, left atrial diameter, left atrial volume index, and left ventricular mass index.

Statistical Analysis

We estimated that the change in ratio of BNP concentrations in the luseogliflozin group would be 30% lower compared with that in the voglibose group according to previous studies of the effect of renin-angiotensin-aldosterone system inhibitors on heart failure.^{15–17} The standard deviation of the natural logarithmic transformation of BNP was estimated as 0.83 on the basis of a previous study.¹⁷ A minimum of 172 patients (86 patients per group) were required to provide 80% power with a 2-sided α level of 0.05 by the Student *t* test between 2 groups. With 10% of patients estimated to

withdraw from participation during the study period, the final enrollment target was set at 190 patients (95 patients per group).

Efficacy analysis was performed according to the treatment to which patients were randomly assigned based on the intention-to-treat analysis. The primary outcome analysis was based on analysis of covariance for the change in ratio of BNP concentrations after 12 weeks from baseline. Adjusted covariates included the assigned treatment (luseogliflozin, voglibose), baseline age (<65 or ≥65 years), baseline hemoglobin A_{1c} values (<8.0% or ≥8.0%), baseline BNP concentrations (<100 or ≥100 pg/mL), baseline renal function (eGFR ≥60 or <60 mL/min per 1.73 m²), use of thiazolidine at baseline, and presence or absence of atrial fibrillation and atrial flutter at baseline as stratified factors of randomization. A similar method was used to analyze the secondary outcomes. Furthermore, the same analysis as that for the primary outcome was performed for the change in ratio of BNP concentrations after 4 and 24 weeks from baseline as sensitivity analyses. For safety analysis, the primary population was all patients who received at least 1 dose of study drug. Analysis of safety outcomes (major adverse cardiovascular events, hypoglycemia, and urinary tract infection) was performed using the Cochran–Mantel–Haenszel test with the same stratification factors as those for the primary outcome. The consistency of drug effects was examined across 6 prespecified subgroups as stratified factors of randomization and the presence or absence of prior atherosclerotic cardiovascular events. All comparisons and analyses were 2-sided with $P < 0.05$ considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 24 (IBM, Armonk, NY) and Stata/SE 15.1 for Mac (StataCorp, College Station, TX).

RESULTS

Study Population

Between December 2015 and September 2018, a total of 173 patients from 16 hospitals and clinics had been screened for this study. A total of 169 patients were enrolled in this study. Of these patients, 86 were assigned to receive luseogliflozin and 83 to receive voglibose. Three (1.8%) patients did not receive any doses of a study drug and were prospectively excluded from all analyses. The safety analyses included a total of 166 patients. A total of 165 patients, with 83 in the luseogliflozin group and 82 in the voglibose group, who had BNP measurements assessed at least once were included in the efficacy analyses (Figure 1). High study drug adherence was observed in each hospital visit

among the study population; the mean administration rate was 96.8% (luseogliflozin: 98.3%, voglibose: 95.2%).

The baseline characteristics of the patients are shown in Table 1. The baseline variables were similar between the luseogliflozin and voglibose groups, except for the patients' age because the majority of patients included in the study were aged ≥65 years. The mean age was significantly younger in patients in the luseogliflozin group than in the voglibose group ($P = 0.017$). The rate of male sex was 66% and 59%, and the rate of patients with prior atherosclerotic cardiovascular disease was 59% and 62% in the luseogliflozin and voglibose groups, respectively. The majority of patients had mild heart failure symptoms at baseline. A total of 160 (97%) patients were classified as New York Heart Association class II, with no significant difference between the 2 groups. There was no significant difference in baseline medications between the 2 groups. More than half of the patients of this study were treated with specific heart failure treatment drugs, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers. Mineralocorticoid receptor antagonists were used in almost 20% of the patients. Antidiabetic medication was administered in 103 (62%) patients.

The mean systolic blood pressure and heart rate were not significantly different between the 2 groups. At baseline, the median BNP concentration was 63.7 (interquartile range, 46.8–115.8) versus 75.1 pg/mL (interquartile range, 42.4–120) and the median NT-proBNP concentration was 203 (interquartile range, 123–389) versus 200 pg/mL (interquartile range, 121–502) between the luseogliflozin and voglibose groups, respectively. No significant differences were observed in any cardiac-related or other biomarker concentrations and echocardiographic parameters between the 2 groups.

Among all patients, the proportions of a left ventricular mass index ≥115 g/m² for men or ≥95 g/m² for women, left atrial volume index >34 mL/m², $e' < 8$ cm/s, and $E/e' \geq 13$ were 21%, 53%, 94%, and 39%, respectively. The baseline echocardiographic parameters were similar between the luseogliflozin and voglibose groups.

Primary Outcome

BNP concentrations decreased over time in the luseogliflozin group. A consistent decrease in BNP concentrations in the luseogliflozin group was observed after 4 and 24 weeks from baseline (Table 2). However, there was no significant difference in the reduction in BNP concentrations after 4 or 12 weeks compared with baseline between the 2 groups. The

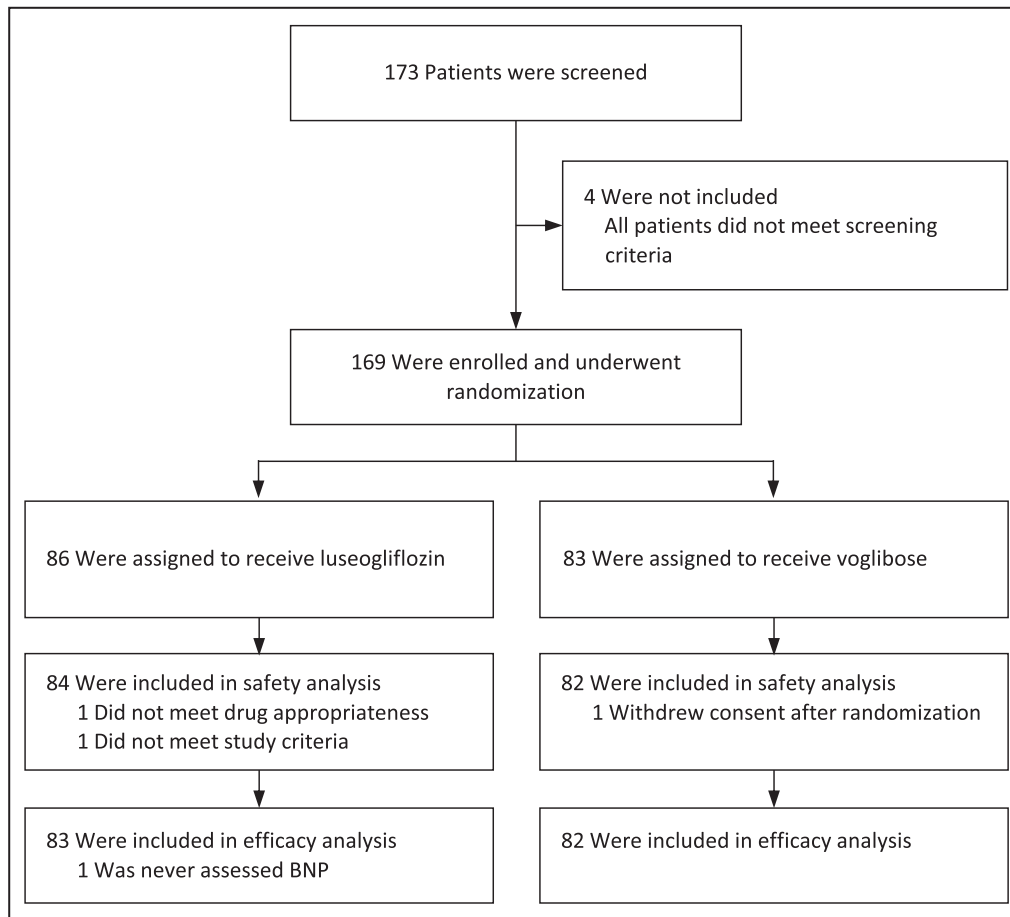


Figure 1. Study flow diagram.
BNP indicates B-type natriuretic peptide.

ratio of the mean BNP value at week 12 to the baseline value was 0.79 in the luseogliflozin group and 0.87 in the voglibose group (percent change, -9.0% versus -1.9% ; ratio of change with luseogliflozin versus voglibose, 0.93; 95% CI, 0.78–1.10; $P=0.26$) (Figure 2).

Secondary and Safety Outcomes

The change in E/e', left ventricular EF, body weight, and hemoglobin A_{1c} levels after 12 weeks in the luseogliflozin group were not significantly different from those in the voglibose group (Table 2). The main safety outcomes, including major adverse cardiovascular events, hypoglycemic adverse events, and urinary tract infection, were not significantly different between the groups (Table 2). No significant difference was observed in other adverse events between the groups. However, the rate of gastrointestinal symptoms in the voglibose group was significantly higher than that in the luseogliflozin group ($P=0.013$). Exploratory hemodynamic and biomarker outcomes are shown in Table 2. No significant differences were observed in the change in heart rate, eGFR, NT-proBNP concentrations,

high-sensitivity C-reactive protein concentrations, E/A, e', left atrial diameter, left atrial volume index, and left ventricular mass index between the groups. However, a significantly greater reduction in systolic blood pressure after 12 weeks compared with baseline was observed in the luseogliflozin group than in the voglibose group ($P=0.036$).

Subgroup Analyses

No statistical significance was observed in the interaction between the effect of study drugs and prespecified patient subgroups (Figure 3).

DISCUSSION

The MUSCAT-HF study is the first prospective, multi-center, open-label, randomized, controlled trial to investigate the drug effect of an SGLT2 inhibitor, luseogliflozin, on BNP concentrations as the primary outcome compared with an alpha-glucosidase inhibitor, voglibose. We found that BNP concentrations decreased after initiation of either luseogliflozin or voglibose. There was no

Table 1. Baseline Characteristics of the Patients

	Luseogliflozin (n=83)	Voglibose (n=82)	P Value
Age, y	71.7±7.7	74.6±7.7	0.017
Median (interquartile range)	72 (67–78)	75 (70–79)	0.027
>60 y, n (%)	77 (93)	80 (98)	0.152
Male, n (%)	55 (66)	48 (59)	0.31
Body weight, kg	64.6±12.7	63.5±13.1	0.57
Body mass index, kg/m ²	25.4±4.3	25.3±4.4	0.85
Waist circumflex, cm	92.6±11.4	91.1±12.1	0.45
NYHA class, n (%)			0.44
I	0	0	
II	79 (96)	81 (99)	
III	3 (4)	1 (1)	
IV	0	0	
Duration of diabetes mellitus, mo	72 (22–130)	72 (36–138)	0.90
Prior diagnoses, n (%)			
Hypertension	72 (89)	64 (79)	0.087
Hyperuricemia	20 (25)	24 (30)	0.48
Cardiovascular disease	48 (59)	50 (62)	0.75
Dyslipidemia	65 (80)	61 (75)	0.45
Chronic kidney disease	29 (36)	27 (33)	0.74
Hepatic disorder	9 (11)	3 (3.7)	0.072
Atrial fibrillation or flutter	18 (22)	15 (18)	0.59
Medications, n (%)			
ACE inhibitor or ARB	51 (61)	47 (57)	0.59
Beta-blocker	53 (64)	47 (57)	0.39
MRA	19 (23)	20 (24)	0.82
Loop diuretic	19 (23)	19 (23)	0.97
Hydralazine	5 (6.0)	5 (6.1)	0.98
Antidiabetic medication	53 (65)	50 (61)	0.74
Hemodynamic parameters			
Systolic blood pressure, mm Hg	131±17	128±14	0.168
Diastolic blood pressure, mm Hg	71±11	71±10	0.52
Heart rate, bpm	69±13	70±12	0.53
Laboratory data			
Hemoglobin A _{1c} , %	7.0±0.7	6.9±0.8	0.52
Hemoglobin, g/dL	13.5±1.6	13.1±1.6	0.114
Hematocrit, %	41.4±4.8	40.4±4.2	0.159
Blood urea nitrogen, mg/dL	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 per 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
NT-proBNP, pg/mL	203 (123–389)	200 (121–502)	0.70
High-sensitivity CRP, mg/L	0.91 (0.41–1.79)	0.73 (0.25–1.66)	0.48

(Continued)

Table 1. Continued

	Luseogliflozin (n=83)	Voglibose (n=82)	P Value
Echocardiographic parameters			
Left ventricular ejection fraction, %	57±9.4	58±9.4	0.41
≥50%	53/73 (73)	52/65 (80)	0.31
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
<8 cm/s	68/71 (96)	61/66 (92)	0.40
E/e'	13.0±4.5	13.3±5.6	0.67
≥13	24/71 (34)	30/66 (46)	0.163
Left atrial diameter, mm	42.0±7.4	42.5±7.9	0.69
Left atrial volume index, mL/m ²	37.9±16.3	38.4±13.5	0.84
>34 mL/m ²	35/68 (52)	32/59 (54)	0.76
Left ventricular mass index, mL/m ²	93.0±23.2	91.3±27.5	0.71
≥115 g/m ² for men or ≥95 g/m ² for women	15/70 (21)	13/63 (21)	0.91

Data are presented as mean±standard deviation, n (%), or median (interquartile range). ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BNP, B-type natriuretic peptide; CRP, C-reactive protein; E/A, ratio of early to atrial mitral inflow velocity; E/e', ratio of early mitral inflow velocity to mitral annular early diastolic velocity; GFR, glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

significant difference in the degree of reduction in BNP concentrations after 12 weeks for luseogliflozin and voglibose. There were no significant differences in the main secondary and safety outcomes, except for gastrointestinal symptoms, between the groups.

Some randomized controlled trials reported that SGLT2 inhibitors robustly reduced cardiovascular adverse events, including hospitalization of heart failure, in patients with diabetes mellitus.^{7–9} In an exploratory analysis from DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58), hospitalization for heart failure in patients with heart failure with reduced EF (<45%) at baseline was significantly reduced, while this reduction in hospitalization for heart failure was not observed in patients with HFpEF.¹⁸ A recent randomized trial showed that dapagliflozin decreased worsening heart failure in patients with heart failure with reduced EF, regardless of the presence or absence of diabetes mellitus.¹⁰ However, the benefit of an SGLT2 inhibitor in patients with HFpEF on hospitalization for heart failure remains unestablished. This study specifically focused on patients with HFpEF using BNP concentrations. Although BNP was a surrogate end point for heart failure, use of the primary outcome of the change in ratio of BNP concentrations after 12 weeks of treatment from baseline was a strength of this study. Additionally, selection of participants to clearly target patients with HFpEF was

Table 2. Outcomes of the Patients in the 2 Groups

	Luseogliflozin (n=83)	Voglibose (n=82)	P Value
Primary outcome, % (95% CI)			
Change in ratio of BNP			
After 4 wk from baseline	-15.48 (-25.32 to -4.33)	-0.13 (-11.56 to 12.78)	0.108
After 12 wk from baseline	-9.0 (-20.0 to 3.4)	-1.94 (-12.3 to 9.6)	0.26
After 24 wk from baseline	-13.99 (-26.65 to 0.85)	0.31 (-12.80 to 15.38)	0.133
Main secondary efficacy outcomes, % (95% CI)			
Change in E/e'	5.20 (-5.83 to 16.24)	1.32 (-5.82 to 8.47)	0.85
Change in left ventricular ejection fraction	2.78 (-2.66 to 8.21)	2.95 (-1.38 to 7.30)	0.62
Change in body weight	-0.84 (-2.54 to 0.85)	-0.57 (-1.98 to 0.85)	0.67
Change in hemoglobin A _{1c}	-1.87 (-3.31 to -0.44)	-1.19 (-3.18 to -0.81)	0.71
Safety outcomes			
	n=84	n=82	
Major adverse cardiovascular outcome	0	0	
Hypoglycemic adverse events	0	1 (1.2)	0.49
Urinary tract infection	0	1 (1.2)	0.49
Any infection	1 (1.2)	1 (1.2)	1.0
Severe hypotension	1 (1.2)	0	1.0
Elevation of blood pressure	2 (2.3)	0	0.50
Gastrointestinal symptoms	0	6 (7.3)	0.013
Bone fracture	0	1 (1.2)	0.49
Fatigue	1 (1.2)	2 (2.4)	0.62
Thirst	1 (1.2)	0	1.0
Exploratory hemodynamic and biomarker outcomes, % (95% CI)			
Change in systolic blood pressure	-3.96 (-6.89 to -1.03)	0.54 (-2.23 to 3.32)	0.036
Change in heart rate	0.49 (-3.48 to 4.45)	2.62 (-1.56 to 6.80)	0.39
Change in estimated GFR	-4.26 (-7.20 to -1.32)	-0.83 (-3.35 to 1.69)	0.061
Change in NT-pro-BNP	-8.43 (-19.84 to 4.60)	-5.50 (-15.17 to 5.27)	0.56
Change in high-sensitivity CRP	22.47 (-1.65 to 52.52)	9.97 (-18.13 to 47.71)	0.55
Change in E/A	3.42 (-2.48 to 9.33)	6.95 (-1.78 to 15.7)	0.57
Change in e'	1.22 (-9.08 to 11.5)	2.46 (-6.26 to 11.2)	0.82
Change in left atrial diameter	2.37 (-1.23 to 5.96)	-1.34 (-5.17 to 2.49)	0.105
Change in left atrial volume index	-4.49 (-14.6 to 5.62)	-0.62 (-11.8 to 10.6)	0.51
Change in left ventricular mass index	-4.23 (-11.9 to 3.41)	2.29 (-3.66 to 8.24)	0.31

Data are presented as 95% CIs or n (%). BNP indicates B-type natriuretic peptide; CRP, C-reactive protein; E/A, ratio of early to atrial mitral inflow velocity; E/e', ratio of early mitral inflow velocity to mitral annular early diastolic velocity; GFR, glomerular filtration rate; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

an advantage of this study. Under this specific study design, this study showed no significant effect on the change in BNP concentrations from baseline with an SGLT2 inhibitor compared with an alpha-glucosidase inhibitor.

We consider that there were various factors that reduced the effect of an SGLT2 inhibitor in this study. First, the majority of patients who were enrolled in our study were at low risk. Almost all patients had New York Heart Association class II symptoms and low BNP levels at baseline. Only 23% of patients were receiving a loop diuretic at baseline, and had relatively lower use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers at baseline.

Additionally, a total of 40% patients did not have prior atherosclerotic cardiovascular disease. Previous reports have shown greater effectiveness of SGLT2 inhibitors in patients with prior myocardial infarction or a high risk of atherosclerotic cardiovascular disease than in those without these conditions.^{19,20} Therefore, patients without these conditions may have had less effectiveness of SGLT2 inhibitors in this study. Second, in our study, luseogliflozin and voglibose reduced BNP levels by 9.0% and 1.9%, respectively, but this difference was not significant. One explanation for this lack of significance is that this study was not sufficiently powered for moderate differences that were actually observed. With a power of 80%

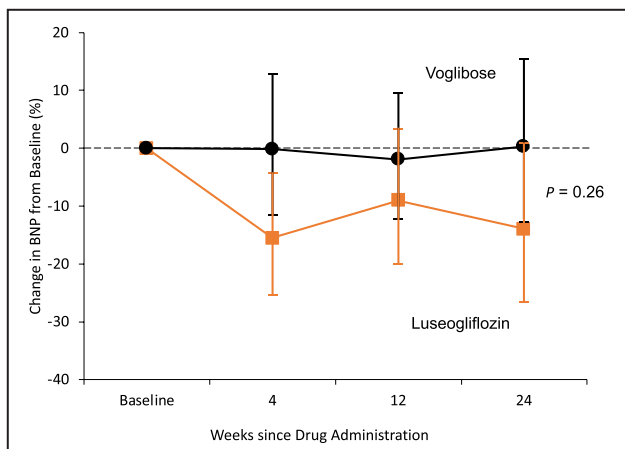


Figure 2. Change in BNP concentrations.

No significant difference was observed in the reduction in BNP concentrations after 12 weeks compared with baseline between the two groups. The ratio of the mean BNP value at week 12 to the baseline value was 0.79 in the luseogliflozin group and 0.87 in the voglibose group (percent change, -9.0% vs -1.9% , ratio of change with luseogliflozin vs voglibose, 0.93; 95% CI, 0.78–1.10; $P=0.26$). BNP indicates B-type natriuretic peptide.

and a sample size of 86 per group, we could statistically detect up to a 30% difference between the 2 groups. Underpowered analysis is susceptible to a type II error. The effect size of a reduction in BNP concentrations in this study was lower than we expected, probably attributable to patients with mild heart failure.

In this study, HFpEF was defined as a left ventricular EF $\geq 45\%$, BNP concentrations ≥ 35 pg/mL, and any symptoms. This definition was modified according to the 2012 European Society of Cardiology (ESC) heart failure guidelines.¹³ The cutoff of the EF for definition of HFpEF in other clinical trials varied from 40% to 50%.^{1,4,21,22} The 2012 ESC heart failure guidelines stated that patients with HF and an EF $\geq 50\%$ are considered as having HFpEF, while patients with an EF ranging from 35% to 50% represent a “gray area.”¹³ The 2013 US guideline stated that HFpEF included an EF $>40\%$.⁵ Based on these documents, we recruited patients with an EF $\geq 45\%$ as HFpEF. With regard to the relevance of structural heart disease, a comprehensive echocardiographic examination was recommended at enrollment in the study. We checked the presence of structural and functional echocardiographic measures as listed in the 2012 ESC heart failure guidelines.¹³ Patients who had at least 1 of these measurements, including left ventricular hypertrophy, left atrial enlargement, and left ventricular diastolic dysfunction, comprised 97% of the study population. Therefore, we consider that almost all of the study population fulfilled the diagnostic criteria of HFpEF in the 2012 ESC heart failure guidelines.¹³

Our study showed a reduction in BNP concentrations in the luseogliflozin group at 4 weeks, which suggested that SGLT2 inhibitors reduce cardiac load immediately after their introduction. Further, luseogliflozin significantly reduced systolic blood pressure compared with voglibose. However, echocardiographic parameters of left ventricular systolic or diastolic function (eg, left ventricular EF and E/e') were similar between the groups. Interestingly, the left atrial volume index and left ventricular mass index appeared to be reduced after luseogliflozin, but this was not significant. Our research group has reported that an SGLT2 inhibitor ameliorated cardiac hypertrophy and fibrosis in hypertensive rats that were fed a high-fat diet.²³ Some studies have also shown that SGLT2 inhibition improves arterial stiffness and achieves lowering of blood pressure in patients with diabetes mellitus.^{24–26} From the results of subgroup analyses, luseogliflozin use tended to be higher in patients with an older age, BNP levels >100 pg/mL at baseline, and atrial arrhythmia (atrial fibrillation or flutter). We consider that these patients' characteristics are representative of heart failure with left ventricular diastolic dysfunction. Therefore, selectively using SGLT2 inhibitors might be beneficial for such patients with severe left ventricular diastolic dysfunction or cardiac afterload, even those with HFpEF. Further detailed studies are required, including ongoing randomized controlled trials.^{27–29}

This study has several limitations. First, this study was not blinded and was an open-label study. Second, the primary outcome of this study was the change in BNP concentrations after 12 weeks of treatment from baseline. This was a surrogate end point, and the follow-up duration was short. Third, the predefined sample size of 190 was not achieved. We started the study, which was designed to be conducted for almost 2 years, for the enrollment period from December 2015. However, the study population did not reach a number required for sufficient statistical power during the pre-specified enrollment period. Therefore, we extended the enrollment period to 3 years until September 2018. Unfortunately, the study included only 169 patients. We could not continue enrollment of new patients because of a shortage of funds. Fourth, there were more patients with mild heart failure in this study than expected. Therefore, differences between study groups might have been diminished. Furthermore, the effect of luseogliflozin on BNP levels in patients with diabetes mellitus and HFpEF might have been overestimated, and the sample size calculation might not have been sufficient for estimating differences between the study groups. Finally, the latest definition of HFpEF in the ESC heart failure guidelines has changed since 2012. In the 2016 ESC heart failure guidelines,⁶ patients with a left ventricular EF ranging from 40% to 49% are

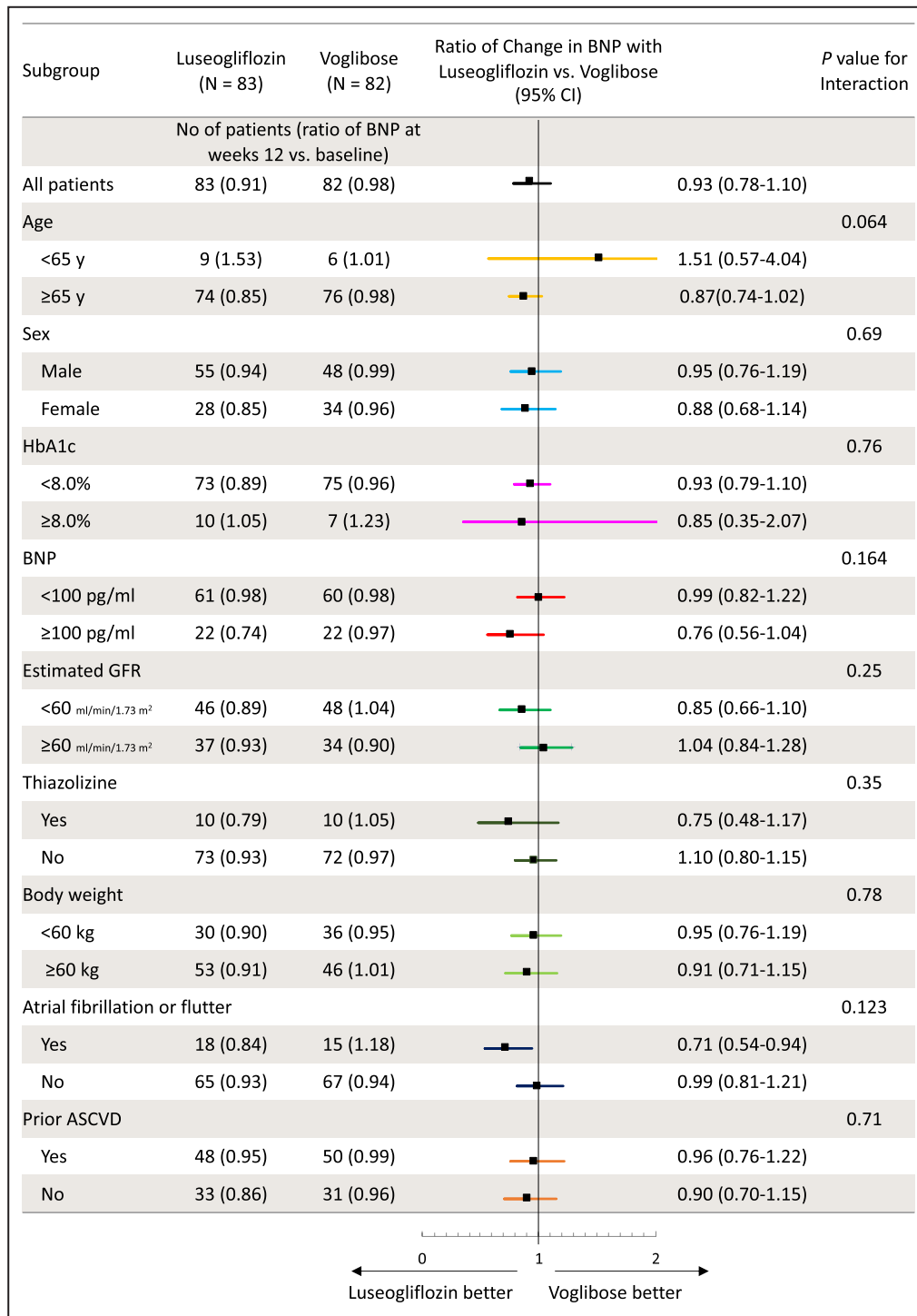


Figure 3. Subgroup analyses of the change in BNP concentrations. Data on the change in ratio of BNP concentrations from baseline to 12 weeks with each treatment according to subgroup are shown. ASCVD indicates atherosclerotic cardiovascular disease; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; and HbA_{1c}, hemoglobin A_{1c}.

newly defined as HF with midrange EF. On the basis of the latest ESC heart failure guidelines,⁶ 24% of patients with a left ventricular EF of <50% in this study did not fulfill the definition of HFpEF.

In conclusion, in patients with type 2 diabetes mellitus and HFpEF, initiation of luseogliflozin does not significantly reduce BNP concentrations over a 12-week follow-up compared with voglibose.

APPENDIX

The MUSCAT-HF Study Investigators

Kentaro Ejiri (Tamano City Hospital and Okayama University Graduate School of Medicine, Density and Pharmaceutical Sciences); Toru Miyoshi, Kazufumi Nakamura, and Hiroshi Ito (Okayama University Graduate School of Medicine, Density and Pharmaceutical Sciences); Hajime Kihara (Kihara Cardiovascular Clinic); Yoshiki Hata (Minamino Cardiovascular Hospital); Toshihiko Nagano (Iwasa Hospital); Atsushi Takaishi (Mitoyo General Hospital); Hironobu Toda (Okayama East Neurosurgery Hospital and Okayama University Graduate School of Medicine, Density and Pharmaceutical Sciences); Seiji Namba (Okayama Rosai Hospital); Yoichi Nakamura (Specified Clinic of Soyokaze Cardiovascular Medicine and Diabetes Care); Satoshi Akagi (Akaiwa Medical Association Hospital and Okayama University Graduate School of Medicine, Density and Pharmaceutical Sciences); Satoru Sakuragi (Iwakuni Clinical Center); Taro Minagawa (Minagawa Cardiovascular Clinic); Yusuke Kawai (Okayama City Hospital); Nobuhiro Nishii (Yoshinaga Hospital and Okayama University Graduate School of Medicine, Density and Pharmaceutical Sciences); Tetsuya Sato and Soichiro Fuke (Japanese Red Cross Okayama Hospital); Masaki Yoshikawa and Hiroyasu Sugiyama (Fukuyama City Hospital); Michio Imai (Imai Heart Clinic); Naoki Gotoh (Gotoh Clinic); Tomonori Segawa (Asahi University Hospital); Toshiyuki Noda (Gifu Prefectural General Medical Center); and Masatoshi Koshiji (Gifu Seiryu Hospital).

ARTICLE INFORMATION

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Affiliations

From the Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Density and Pharmaceutical Sciences, Okayama, Japan (K.E., T. Miyoshi, H.T., S.A., N.N., K.N., H.I.); Department of Internal Medicine, Tamano City Hospital, Okayama, Japan (K.E.); Department of Internal Medicine, Kihara Cardiovascular Clinic, Asahikawa, Japan (H.K.); Department of Cardiology, Minamino Cardiovascular Hospital, Hachioji, Japan (Y.H.); Department of Internal Medicine, Iwasa Hospital, Gifu, Japan (T.N.); Department of Cardiology, Mitoyo General Hospital, Kanonji, Japan (A.T.); Department of Internal Medicine, Okayama East Neurosurgery Hospital, Okayama Japan (H.T.); Department of Cardiology, Okayama Rosai Hospital, Okayama, Japan (S.N.); Department of Cardiovascular Medicine, Specified Clinic of Soyokaze Cardiovascular Medicine and Diabetes Care, Matsuyama, Japan (Y.N.); Department of Internal Medicine, Akaiwa Medical Association Hospital, Okayama, Japan (S.A.); Department of Cardiovascular Medicine, Iwakuni Clinical Center, Iwakuni, Japan (S.S.); Department of Internal Medicine, Minagawa Cardiovascular Clinic, Gifu, Japan (T.Minagawa); Department of Cardiovascular Medicine, Okayama City Hospital, Okayama, Japan (Y.K.); Department of Internal Medicine, Yoshinaga Hospital, Okayama, Japan (N.N.); Department of Cardiovascular Medicine, Japanese Red Cross Okayama Hospital, Okayama, Japan (S.F.); Department of Cardiology, Fukuyama City Hospital, Fukuyama, Japan (M.Y.).

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Disclosures

Dr Miyoshi received a trust research/joint research fund from Novartis Pharma K. K. Dr Nishii is affiliated with the endowment department of Medtronic Japan. Dr Ito received a trust research/joint research fund from Novartis KK. The remaining authors have no disclosures to report.

Supplementary Materials

Data S1–S3

Figure S1

Table S1

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Supplemental Material

Supplemental Methods

Data S1. Study protocol.

Prospective Comparison of Luseogliflozin and Alpha- glucosidase on the Management of Diabetic Patients with Chronic Heart Failure and Preserved Ejection Fraction

I. Summary of study plan

The MUSCAT-HF trial was a multi-center, prospective, open-label, randomized controlled trial to assess the effect of luseogliflozin compared with voglibose on left ventricular load in patients with type 2 diabetes mellitus (T2DM) and heart failure with preserved ejection fraction (HFpEF).

II. Background of study plan

Recent randomized controlled trials showed that sodium glucose cotransporter 2 (SGLT2) inhibitors reduced all-cause mortality, cardiovascular mortality, and hospitalization of heart failure in type 2 diabetes compared with placebo. These results indicated that SGLT2 inhibitors may be effective in lowering glucose levels and reducing cardiovascular events, particularly in patients with heart failure. Given that these trials were not specifically designed to investigate the effect of SGLT2 inhibitors in heart failure patients, no detailed data on their effects in heart failure were obtained.

III. Study plan

1. Purpose

The aim of this study was to evaluate the efficacy of luseogliflozin, an SGLT2 inhibitor, compared with voglibose, an alpha-glucosidase inhibitor, using brain natriuretic peptide (BNP) as the index of therapeutic effect in patients with T2DM and HFpEF. The results of this study will support a novel strategy for the treatment of heart failure using an SGLT2 inhibitor, independent of its glucose-lowering effects.

2. Study population

The planned sample size of this study was 95 patients per group (190 patients in total). The recruitment of study patients was planned to take place from September 2015 to September 2018. Patients aged ≥ 20 years with T2DM (hemoglobin A1c [HbA1C] $\leq 9.0\%$) and HFpEF (left ventricular ejection fraction $\geq 45\%$) needing additional treatment for T2DM despite the ongoing treatment are eligible for participation. The key inclusion and exclusion criteria are detailed in Table 1. Given that the definition of chronic heart failure according to European Society of Cardiology guidelines includes BNP ≥ 35 pg/ml, patients with BNP < 35 pg/ml was

excluded from this study. Study candidates were assessed for eligibility within 4 weeks prior to enrolment.

Inclusion and exclusion criteria

Inclusion criteria
1) Diagnosis of T2DM and left ventricular ejection fraction >45% with current or previous symptoms of heart failure (dyspnea on effort, orthopnea, or leg edema)
2) Inadequately controlled T2DM in patients who have received diet and exercise therapy, a lifestyle modification program, and hypoglycemic medications based on standard guidelines of the Japan Diabetes Society
3) Age >20 years
4) Provision of written informed consent prior to participation
Exclusion criteria
1) BNP <35 pg/ml
2) Use of alpha-glucosidase inhibitors, SGLT2 inhibitors, glinides, or high-dose sulfonylurea
3) Renal insufficiency (eGFR <30 ml/min/1.73m ²)
4) Left ventricular ejection fraction <45%
5) History of severe ketoacidosis or diabetic coma within 6 months prior to participation
6) Serious infection or severe trauma, or perioperative patients
7) Type 1 diabetes mellitus
8) Poorly controlled T2DM (HbA1c >9.0%)
9) Uncontrolled hypertension (systolic blood pressure >160 mmHg)
10) History of stroke, myocardial infarction, or severe cardiovascular disease with hospitalization within 6 months prior to participation
11) Women who are pregnant or breastfeeding
12) Allergy to either investigation product
13) Other medical reason at the investigator's discretion

T2DM, type 2 diabetes mellitus; BNP, brain natriuretic peptide; SGLT2, sodium/glucose cotransporter 2; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1C

3. Consent

- 1) Written informed consent is needed to be received.
- 2) If patients do not have ability of judgment, informed consent cannot be received.

Informed Consent Form

- 1 Purpose
- 2 Efficacy and side effect
- 3 Alternative treatment options
- 4 NO disadvantage by rejection
- 5 Withdrawal rights
- 6 Ethics

4. Interventions

- 1) Voglibose: subjects who receive voglibose (2.5 mg once daily)
- 2) Luseogliflozin: subjects who receive luseogliflozin (2.5 mg once daily)

5. Methods

Patients fulfilling all criteria who provide written informed consent to participate in this study were enrolled and subsequently randomized (1:1) to receive luseogliflozin (2.5 mg once daily) or voglibose (0.2 mg three times daily) in addition to their background medication. Randomization was performed using a computer-generated random sequence web response system. Patients were stratified by age (<65 years, \geq 65 years), baseline HbA1c (<8.0%, \geq 8.0%), baseline BNP (<100 pg/ml, \geq 100 pg/ml), baseline renal function (eGFR \geq 60 ml/min/1.73 m², <60 ml/min/1.73 m²), use of thiazolidine or not, and presence or absence of atrial fibrillation (AF) and flutter (AFL) at screening.

Assessments during the study period are listed in Figure 1. Laboratory data, electrocardiogram, echocardiography and patients' vital signs, body weight, and waist circumference, were evaluated at 4 ± 2 weeks (visit 29 ± 14 days) and 12 weeks (visit 85 ± 28 days) after initiation of study treatment. Safety and tolerability were assessed during the treatment period. The primary outcome of change in BNP compared with baseline was evaluated at 12 weeks (visit 85 ± 28 days) and patients were followed up for an additional 12 weeks (visit 169 ± 28 days) after the end of treatment. If a patient's glycemic control worsens after 4 ± 2 weeks, the investigator could increase the dose of allocated treatment (to luseogliflozin 5 mg once daily or voglibose 0.3 mg three times daily) and other specific T2DM drugs, except for sulfonylureas. Investigators were also encouraged to treat all other cardiovascular risk factors according to local standard of care. Under the following circumstances, the investigator must evaluate the data and patient's vital sign: 1) discontinuation of study treatment; 2) dose increase of specific treatment for heart failure; 3) initiation of new treatment for heart failure; 4) withdrawal from the study. The permitted medications for the treatment of heart failure included angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics, and mineralocorticoid/aldosterone receptor antagonists.

6. End points

Assessments during the study period are listed in Figure 2.

Primary outcome

The primary outcome of this study was the difference in BNP after 12 weeks (visit 85 ± 28 days) of treatment between the luseogliflozin and the voglibose groups, defined as the difference in logarithmic BNP change calculated as follows:

(*) BNP proportional change = BNP (at follow-up)/ BNP (at baseline),

(†) Logarithmic BNP change = logarithmic BNP (at follow-up) – logarithmic BNP (at baseline),

In other words, (*) = exponential (†).

Furthermore, we calculated the ratio of BNP change rate

(‡) The ratio of BNP proportional change (the luseogliflozin group to the voglibose group) = (*) (in the luseogliflozin group)/(*) (in the voglibose group),

(§) The difference of logarithmic BNP change = (†) (in the luseogliflozin group) – (†) (in the voglibose group),

In other words, (‡) = exponential (§)

Secondary outcomes

The key secondary outcomes of this study were the differences in the following parameters between the luseogliflozin and the voglibose groups:

- 1) Ratio of early mitral inflow velocity to mitral annular early diastolic velocity (E/e')
- 2) Left ventricular ejection fraction
- 3) Body weight
- 4) HbA1c

The difference in E/e' and HbA1c between the groups was defined as the difference in logarithmic E/e' and HbA1c using the same calculation as for BNP. The difference in body weight and left ventricular ejection fraction was defined as the difference between those parameters at follow-up and at baseline. Further exploratory analysis is listed in exploratory analysis section.

Safety outcomes: including, but not limited to:

- clinical laboratory tests, vital signs, 12-lead electrocardiogram (ECG), physical examination, and the use of rescue medication

- Adverse events including major adverse cardiovascular events (MACE),

hypoglycemic adverse events (requiring any intervention), and urinary tract infection.

Safety was assessed based on adverse events reported throughout the study, clinical laboratory tests, vital signs, 12-lead electrocardiogram, physical examination, and the use of rescue medication. Prespecified adverse events included MACE, hypoglycemic adverse events (requiring any intervention), and urinary tract infection (details listed in Outcome definitions for adverse events section)

7. Cancellation and withdrawal

Discontinuance criteria

Withdrawal criteria	<ol style="list-style-type: none">1) Inadequate glycemic control after administration of the study drug2) Suspect of adverse side effects of the study drug3) Frequent hypoglycemia4) Onset of adverse cardiovascular event†5) Declaration of withdrawal from the study by the participant6) Turning out of misunderstanding of all criteria for eligibility after enrollment7) Pregnancy after enrollment8) Lower adherence for administration of the study drug (< 70%)9) Assessment of inadequate for the study by the attending doctor
†Cardiovascular event	<ol style="list-style-type: none">1) Addition of heart failure treatment drugs as follows; angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta-blockers, diuretics, and aldosterone antagonists2) Hospitalization of heart failure

8. Study period

Between December 1, 2015 and March 31, 2019

9. Statistics

Sample size and power calculation

The primary hypothesis of this study was that the SGLT2 inhibitor luseogliflozin could reduce cardiac load in patients with T2DM and HFpEF. Therefore, the primary outcome was the difference in change in BNP from baseline to 12 weeks between patients receiving luseogliflozin or voglibose. As of the start of recruitment in September 2015, no interventional study of the effect of SGLT2 inhibitors on heart failure in patients with T2DM had been reported. Therefore, we had estimated that BNP change rate in the luseogliflozin group would be 30% lower as compared with that in the globeose group according to previous studies of the effect of renin-angiotensin-aldosterone system inhibitors on heart failure¹⁵⁻¹⁷. The standard deviation of the natural logarithmic transformation of BNP was estimated at 0.83, in reference to the PARAMOUNT study¹⁷. A minimum of 172 patients (86 patients per group) is required to provide 80% power with a two-sided α level of 0.05 by Student's t-test on the ratio of BNP change rate between the luseogliflozin and voglibose groups. With 10% of patients estimated to withdraw from participation during the study period, the final enrolment target was set at 190 patients (95 patients per group).

Analysis plan

In the efficacy analysis, the primary population comprised the Full Analysis Set (FAS),

defined as all randomized patients who received one dose of study drug and were followed up at least once. Patients with no BNP data and patients who withdrew or discontinued treatment was excluded from the FAS. Missing values at 4, 12, and 24 weeks were replaced by the last observed value for that variable (last observation carried forward). In the primary outcome analysis, baseline observation carried forward analysis was also performed. Efficacy analysis was performed according to the treatment to which patients are randomly assigned, based on the intention-to-treat analysis. The primary outcome analysis was based on an analysis of covariance (ANCOVA) ($\alpha = 0.05$, level of significance) for the ratio of BNP change rate in the FAS. Adjusted covariates included the assigned treatment (luseogliflozin, voglibose), baseline age (<65 or ≥ 65 years), baseline HbA1c (<8.0 or $\geq 8.0\%$), baseline BNP (<100 or ≥ 100 pg/ml), baseline renal function (eGFR ≥ 60 or <60 ml/min/1.73 m²), use of thiazolidine or not at baseline, and presence or absence of AF and AFL at baseline as stratified factors of randomization. Furthermore, BNP change rate, ratio of BNP change rate, and 95% confidence intervals were calculated. The same ANCOVA analysis as for the primary outcome was performed for the ratio of BNP change rate at 4 weeks and 24 weeks between the two groups.

Prespecified subgroup analyses were performed on the primary outcome using ANCOVA (covariates: assigned treatment and BNP at screening) in the following subgroups: baseline age (<65 or ≥ 65 years), baseline HbA1c (<8.0 or $\geq 8.0\%$), baseline BNP (<100 or ≥ 100 pg/ml), baseline renal function (eGFR ≥ 60 or <60 ml/min/1.73 m²), use of thiazolidine or not at baseline, baseline body weight (<60 kg, ≥ 60 kg), and presence or absence of AF and AFL at baseline. Furthermore, exploratory analysis on the primary outcome was performed in subgroups based on blood pressure, heart rate, waist circumference, cardiovascular risk factors (hypertension, T2DM, hyperuricemia, family history, and smoking), alcohol consumption, regular medication, and serum lipid levels (details listed in exploratory analysis section).

The key secondary outcomes, difference in E/e', left ventricular ejection fraction, body weight, and HbA1C at 12 weeks between the luseogliflozin and voglibose groups, were analyzed using the same ANCOVA as for the primary outcome. Subgroup analysis for the key secondary outcomes was performed in the same subgroups as for the primary outcome analysis. The following secondary outcomes was also analyzed using the same analysis plan: E/e', left ventricular ejection fraction, body weight, and HbA1C at 4 and 24 weeks; and exploratory parameters at 4, 12, and 24 weeks.

For the safety analysis, the primary population was the Safety Analysis Set (SAFETY), defined as all patients who receive at least one dose of study drug. Although patients who withdrew without receiving study drug will be excluded from SAFETY, other patients who withdrew for any other reason was included. The safety analysis was performed according to the treatment administered to patients in practice, based on the as-treated

analysis. Analysis of SAEs (MACE, hypoglycemia, and urinary tract infection) was performed using the Cochran–Mantel–Haenszel test with stratification factors of age (<65 or ≥65 years), baseline HbA1c (<8.0 or ≥8.0%), baseline BNP (<100 or ≥100 pg/ml), baseline renal function (eGFR ≥60 or <60 ml/min/1.73 m²), use of thiazolidine or not, and presence or absence of AF and AFL at screening.

All comparisons were planned, and the analyses was two sided With P values <0.05 considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 24 (IBM, Armonk, NY) and Stata/SE 15.1 for Mac (StataCorp, College Station, TX). The statistical analysis plan was developed by the principal investigator and a biostatistician prior to the completion of patient recruitment and database lock.

Exploratory analysis

Further exploratory analysis in this study was planned for such parameters.

- 1) Blood glucose
- 2) Lipid metabolism [total cholesterol, high density lipoprotein, triglyceride, small dense low-density lipoprotein and Malondialdehyde-modified low density lipoprotein]
- 3) Blood pressure
- 4) High sensitive CRP
- 5) Adiponectin, microalbuminuria
- 6) Urinary 8-hydroxy-2'-deoxyguanosine
- 7) Estimated GFR

10. Data management and analysis

Members of the Steering Committee also designed the study and were responsible for its conduction (details listed in Study organization section). Significant adverse events (SAEs) occurring within 30 days after final administration of the study drug or after 30 days with a suspicion of association with the study drug, as well as all pregnancies, was immediately reported to the Steering Committee and the sponsor by the investigator, in accordance with GCP.

11. Ethical consideration

All participants provided written informed consent before enrolling.

This study was conducted according to the principles expressed in the Declaration of Helsinki.

This study was approved by the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and the Okayama University Hospital Ethics Committee, as well as the ethics committee of each participating center. Trial registration: UMIN Clinical Trials Registry (UMIN-CTR), UMIN000018395, <https://upload.umin.ac.jp/cgi-open->

bin/ctr_e/ctr_view.cgi?recptno=R000021301

12. Methods of plan change

When needed, investigators made a discussion and decision of plan change.

Data S2. Laboratory testing

Brain natriuretic peptide, N-terminal brain natriuretic peptide, adiponectin, small dense low-density lipoprotein, malondialdehyde-modified low density lipoprotein, high-sensitive C-reactive protein, microalbuminuria, urinary 8-hydroxy-2'-deoxyguanosine
These parameters were measured in a central laboratory (SRL, Inc. Hachioji, Tokyo, Japan).

White blood cell, red blood cell, platelet, hemoglobin, hematocrit, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, blood urea nitrogen, serum creatinine, uric acid, serum sodium, serum potassium, serum chloride, total cholesterol, high density lipoprotein, triglyceride, total protein, albumin, blood sugar, glycohemoglobin
These parameters were measured in each institution.

Data S3. Outcome definition of adverse events

Major adverse cardiovascular events (MACE) include cardiovascular death, acute coronary syndrome, hospitalization of heart failure, and stroke.

- Cardiovascular death

The cause of death will be determined by the principal condition that caused the death, not the immediate mode of death. Clinical Events Committee (CEC) members will review all available information and use their clinical expertise to adjudicate the cause of death. All deaths not attributed to the categories of cardiovascular (CV) death and not attributed to a non-CV cause are presumed CV deaths and are part of the CV mortality outcome. Death certificates or summaries, if possible, including the date of death and other relevant details, will be provided for all patients who have died. However, if a death certificate is the only information available for review in addition to the patient data in the clinical trial database, the CEC may decide not to use this information as cause of death if another etiology appears more plausible. The following definitions will be used for the adjudication of fatal cases:

Sudden cardiac death. Death that occurs unexpectedly in a previously stable patient and includes the following:

- Witnessed and instantaneous death without new or worsening symptoms
- Witnessed death within 60 minutes of the onset of new or worsening cardiac symptoms
- Witnessed death attributed to an identified arrhythmia (e.g., captured by electrocardiogram or witnessed on a monitor by either a medic or paramedic)
- Subject unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest that dies within 24 hours without identification of a non-cardiac etiology
- Un-witnessed death with no conclusive evidence of another, non-CV, cause of death (i.e. presumed CV death).

Sudden death attributable to acute myocardial infarction (MI) (MI type 3). Sudden death occurring up to 14 days after a documented acute MI (verified either by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombus) where there is no conclusive evidence of another cause of death. If death occurs before the biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

Death attributable to heart failure or cardiogenic shock. Death occurring in the context of clinically worsening symptoms and/or signs of congestive heart failure (CHF) without evidence of another cause of death.

New or worsening signs and/or symptoms of CHF include any of the following:

- New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
- Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration
- Confinement to bed predominantly because of heart failure symptoms
- Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
- Cardiogenic shock not occurring in the context of an acute MI or as the consequence

of an arrhythmia occurring in the absence of worsening heart failure

– Cardiogenic shock is defined as systolic blood pressure (SBP) <90 mmHg for more than 1 hour, lack of response to fluid resuscitation and/or heart rate correction, and judged to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

1. Cool, clammy skin
2. Oliguria (urine output <30 mL/hour)
3. Altered sensorium
4. Cardiac index <2.2 L/min/m²

Cardiogenic shock can also be defined in the presence of SBP ≥90 mmHg or for a time period <1 hour if the blood pressure measurement or time period is influenced by the presence of positive inotropic or vasopressor agents alone and/or with mechanical support <1 hour. The outcome of cardiogenic shock will be based on CEC assessment and must occur after randomization. Episodes of cardiogenic shock occurring before and continuing after randomization will not be part of the study outcome. This category will include sudden death occurring during an admission for worsening heart failure

Death attributable to stroke or cerebrovascular event. Death occurring up to 30 days after a stroke that is either attributable to the stroke or caused by a complication of the stroke.

Death attributable to other CV causes. Death must be caused by a fully documented CV event not included in the above categories (e.g. dysrhythmia, pulmonary embolism, or CV intervention). Death attributable to an MI that occurs as a direct consequence of a CV investigation/procedure/operation will be classified as death due to another CV cause.

Non-CV death

Non-CV death is defined as any death not covered by cardiac death or vascular death. The CEC will be asked to determine the most likely cause of non-CV death. Examples of non-CV death are pulmonary causes, renal causes, gastrointestinal causes, infection (including sepsis), non-infectious causes (e.g., systemic inflammatory response syndrome), malignancy (i.e., new malignancy, worsening of prior malignancy), hemorrhage (not intracranial), accidental/trauma, suicide, non-CV organ failure (e.g., hepatic failure) or non-CV surgery.

- Acute coronary syndrome
ACS includes MI and unstable angina.

MI (non-fatal)

The term MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria (A to C) meets the diagnosis for myocardial infarction.

A. Spontaneous MI (type 1)

To identify a type 1 MI, patients should demonstrate spontaneous symptoms of myocardial ischemia unprovoked by supply/demand inequity, together with ≥1 of the following criteria:

- Cardiac biomarker elevation: Troponin is the preferred marker for adjudicating the presence of acute MI. At least one value should show a rise and/or fall from the lowest cut-point providing 10% imprecision (typically the upper reference limit for the troponin run per standard of clinical care). Creatine kinase-MB is a secondary choice of marker to troponin; a rise in CK-MB above the local upper reference limit would be consistent with myocardial injury.

- ECG changes consistent with new ischemic changes
 - ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]) or ECG manifestations of acute myocardial ischemia (in the absence of left ventricular hypertrophy [LVH] and LBBB):
 - Development of pathological Q waves in the ECG
 1. Any Q-wave in leads V2–V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
 2. Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4–V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4–V6; II, III, and aVF)
 - ST elevation: New ST elevation at the J-point in two contiguous leads with the cut-off points: ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2–V3 and/or ≥ 0.1 mV in other leads
 - ST depression and T-wave changes: New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio > 1
- Imaging evidence of new non-viable myocardium or new wall motion abnormality

B. “Demand”-related (type 2) MI

Patients with type 2 MI should be considered under similar diagnostic criteria as a type 1 MI; however, type 2 MI should be considered present when myocardial ischemia and infarction are consequent to supply/demand inequity, rather than a spontaneous plaque rupture and coronary thrombosis.

C. Percutaneous coronary intervention (PCI)-related MI (type 4a/4b)

For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL within 24 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers $> 3 \times$ 99th percentile URL (troponin or CK-MB $> 3 \times$ 99th percentile URL) are consistent with PCI-related MI. Where the cardiac biomarker is elevated prior to PCI, a $\geq 20\%$ increase in the value of the second cardiac biomarker sample within 24 hours of PCI and documentation that cardiac biomarker values were decreasing (two samples ≥ 6 hours apart) prior to the suspected recurrent MI are consistent with PCI-related MI. Symptoms of cardiac ischemia are not required.

D. Coronary artery bypass grafting (CABG)-related MI (type 5)

For CABG in patients with normal baseline troponin values, elevation of cardiac biomarkers above the 99th percentile URL within 72 hours of the procedure is indicative of peri-procedural myocardial necrosis. By convention, an increase of biomarkers $> 5 \times$ 99th percentile URL (troponin or CK-MB $> 5 \times$ 99th percentile URL) plus at least one of the following is consistent with CABG-related MI:

- New pathological Q waves in at least two contiguous leads on the ECG that persist for 30 days, or new LBBB
- Angiographically documented new graft or native coronary artery occlusion
- Imaging evidence of new loss of viable myocardium

If the cardiac biomarker is elevated prior to CABG, a $\geq 20\%$ increase in the value of the second cardiac biomarker sample within 72 hours of CABG and documentation that cardiac biomarker values were decreasing (two samples ≥ 6 hours apart) prior to the suspected recurrent MI plus new pathological Q-waves in ≥ 2 contiguous leads on the electrocardiogram; or new LBBB, angiographically documented new graft, or native coronary artery occlusion; or imaging evidence of new loss of viable myocardium are

consistent with a periprocedural MI after CABG. Symptoms of cardiac ischemia are not required.

Clinical classification of acute MI. Every MI identified by the CEC will be classified into one of the following categories:

- Type 1: Spontaneous MI related to ischemia arising from a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
- Type 2: MI secondary to ischemia attributable to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension
- Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, with death occurring before blood samples could be obtained or before the appearance of cardiac biomarkers in the blood
- Type 4a: MI associated with PCI
- Type 4b: MI associated with stent thrombosis as documented by angiography or at autopsy
- Type 5: MI associated with CABG

Hospitalization for unstable angina

The date of this event will be the day of hospitalization of the patient including any overnight stay at an emergency room or chest pain unit. Unstable angina requiring hospitalization is defined as all of the following:

- No elevation in cardiac biomarkers (cardiac biomarkers negative for myocardial necrosis) according to conventional assays or contemporary sensitive assays
- Clinical presentation: Cardiac symptoms lasting ≥ 10 minutes and considered to be myocardial ischemia upon final diagnosis with one of the following:
 - Rest angina
 - New-onset (< 2 months) severe angina (Canadian Cardiovascular Society [CCS] Grading Scale, or CCS classification system, classification severity $\geq III$)
 - Increasing angina (in intensity, duration, and/or frequency) with an increase in severity of > 1 CCS class to CCS class $> III$
- Angina requiring an unscheduled visit to a healthcare facility and overnight admission
- At least one of the following:
 - New or worsening ST or T-wave changes by ECG. ECG changes should satisfy the following criteria for acute myocardial ischemia in the absence of LVH and LBBB:
 1. ST elevation: New transient (known to be < 20 minutes) ST elevation at the J-point in two contiguous leads with cut-off points of ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2–V3 and/or ≥ 0.1 mV in other leads
 2. ST depression and T-wave changes: New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio > 1
 - Evidence of ischemia on stress testing with cardiac imaging
 - Evidence of ischemia on stress testing with angiographic evidence of $\geq 70\%$ lesion and/or thrombus in an epicardial coronary artery or initiation/increased dosing of antianginal therapy
 - Angiographic evidence of $\geq 70\%$ lesion and/or thrombus in an epicardial coronary artery

- Heart failure requiring hospitalization

The date of this event will be the day of hospitalization of the patient including any overnight stay at an emergency room or chest pain unit. Heart failure requiring hospitalization is defined as an event that meets all of the following criteria:

- Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12-hour stay (or a date change if the time of admission/discharge is not available)
- Clinical manifestations of heart failure (new or worsening), including at least one of the followings:
 - Dyspnea
 - Orthopnea
 - Paroxysmal nocturnal dyspnea
 - Edema
 - Pulmonary basilar crackles
 - Jugular venous distension
 - Third heart sound or gallop rhythm
 - Radiological evidence of worsening heart failure
- Additional/increased therapy: at least one of the followings:
 - Initiation of oral diuretic, intravenous diuretic, inotrope, or vasodilator therapy
 - Up-titration of oral diuretic or intravenous therapy, if already on therapy
 - Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation, or ventricular pacing to improve cardiac function); or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at the treatment of heart failure

Changes in a biomarker (e.g., brain natriuretic peptide) consistent with CHF will support this diagnosis.

Transient ischemic attack (TIA)

A transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

- Stroke

The rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes will be classified as ischemic, hemorrhagic, or unknown.

Diagnosis of stroke. For the diagnosis of stroke, the following four criteria should be fulfilled:

- Rapid onset of a focal/global neurological deficit with at least one of the following:
 - Change in level of consciousness
 - Hemiplegia
 - Hemiparesis
 - Numbness or sensory loss affecting one side of the body
 - Dysphasia/aphasia
 - Hemianopia (loss of half of the field of vision of one or both eyes)
 - Other new neurological sign(s)/symptom(s) consistent with stroke

Note: If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is no plausible non-stroke cause for the clinical presentation

- Duration of a focal/global neurological deficit ≥ 24 hours OR < 24 hours if attributable to at least one of the following therapeutic interventions:

- Pharmacologic (i.e., thrombolytic drug administration)
- Non-pharmacologic (i.e., neurointerventional procedure such as intracranial angioplasty)

or

- Available brain imaging clearly documents a new hemorrhage or infarct

or

- The neurological deficit results in death
- No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion)

- Confirmation of the diagnosis by at least one of the following:*

- Neurology or neurosurgical specialist
- Brain imaging procedure (at least one of the followings):

- 1 CT scan

- 2 MRI scan

- 3 Cerebral vessel angiography

- Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

If a stroke is reported but evidence of confirmation of the diagnosis by the methods outlined above is absent, the event will be discussed at a full CEC meeting. In such cases, the event may be adjudicated as a stroke on the basis of the clinical presentation alone, but full CEC consensus will be mandatory.

If the acute focal signs represent a worsening of a previous deficit, these signs must have either

- Persisted for more than one week

OR

- Persisted for more than 24 hours and accompanied by an appropriate new CT or MRI finding

Classification of stroke. Strokes are sub-classified as follows:

- Ischemic (non-hemorrhagic): A stroke caused by an arterial obstruction attributable to either a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology. This category includes ischemic stroke with hemorrhagic transformation (i.e. no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan)

- Hemorrhagic: A stroke caused by a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes attributable to primary intracerebral hemorrhage (intraparenchymal or intraventricular), subdural hematoma and primary subarachnoid hemorrhage

- Not assessable: The stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed.

Hypoglycemic adverse events (requiring any intervention)

Hypoglycemic adverse events are defined as the requirement of high-sugar food, drinks, or glucose because of a very low level of blood glucose.

Representative symptoms of hypoglycemia may include:

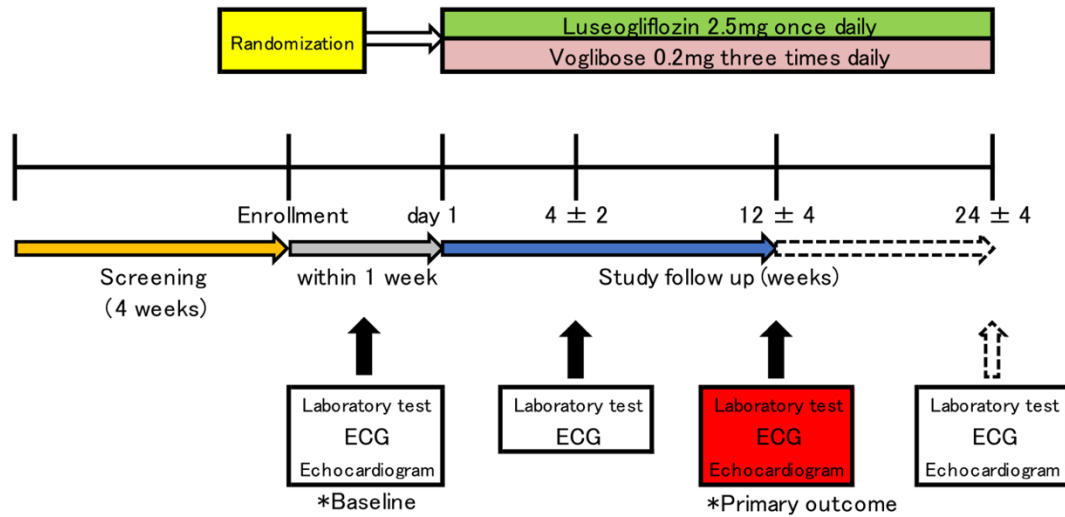
- Irregular heart rhythm

- Fatigue
- Pale skin
- Shakiness
- Anxiety
- Sweating
- Hunger
- Irritability
- Tingling sensation around the mouth
- Crying out during sleep

Urinary tract infection

Urinary tract infection is defined as the requirement of antibiotics because of infectious episodes in any part of the urinary system (kidneys, ureters, bladder, or urethra).

Figure S1. Study design.



Arrows illustrate patients' flow and the timing of follow-up. Patients with type 2 diabetes mellitus are screened whether with heart failure with preserved ejection fraction or without (screening period, yellow arrow). One of the study drugs was administered to patients met inclusion criteria after collection of baseline data within one week after randomization (grey arrow). After administration, mandatory follow-up period is for 12 weeks (study follow-up period, blue arrow). After 12 weeks, expanding follow-up are continued in patients agreed with (Arrow with dotted line). ECG, electrocardiogram.

Table S1. Assessments during the study period.

Assessment	Enrollment	Study follow-up period		Expanding follow-up (if possible)
		4 weeks (visit 29 ± 14 days)	12 weeks (visit 85 ± 28 days)	24 weeks (visit 169 ± 28 days)
Medical examination	X	X	X	X
Written informed consent	X			
Clinical symptoms	X	X	X	X
Adverse events		X	X	X
Treatment discontinuation		X	X	X
Vital signs	X	X	X	X
Body weight	X	X	X	X
Waist circumference	X		X	X
Laboratory tests	X	X	X	X
Electrocardiogram	X	X	X	X
Echocardiography	X		X	X