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PROTOCOL PAPER

Rationale and Design of the CANONICAL Study

— Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Canagliflozin for Heart Failure With Preserved Ejection Fraction With Type 2 Diabetes Mellitus —

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Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2-I) have beneficial cardiovascular effects, including reduction in hospitalization for heart failure (HF). The aim of this study is to explore the efficacy and safety of canagliflozin compared with standard diabetes treatment in elderly patients with type 2 diabetes (T2DM) and HF with preserved ejection fraction (HFpEF).

Methods and Results: This is a multicenter, randomized, open-label, parallel-group comparison study designed to evaluate the effects of canagliflozin on fluid retention and cardiac function in T2DM patients with HFpEF. Eligible participants are patients aged ≥65 years with insufficient glycemic control. Qualified patients will be randomly assigned to treatment with 100 mg of canagliflozin or standard diabetic treatment other than SGLT2-I; both groups will be treated for 24 weeks. The primary endpoints are changes in body weight as an indicator of fluid retention and plasma brain natriuretic peptide as an indicator of cardiac function. The secondary endpoints include cardiovascular event rates, changes in the dose of loop diuretics, echocardiographic left ventricular function, and nutritional status.

Conclusions: This study is expected to provide valuable findings regarding the mechanisms of canagliflozin on cardiac function and a potential new therapeutic approach for HFpEF. (UMIN000028668 and jRCTs051180030)

Key Words: Body weight; Brain natriuretic peptide; Canagliflozin; Heart failure with preserved ejection fraction

The number of heart failure (HF) patients worldwide is increasing and is estimated to increase from 979,000 in 2005 to 1.3 million by 2030 in Japan.[1,2] HF with preserved ejection fraction (HFpEF) frequently occurs in elderly people and the prognosis and quality of life are poor.[3] The coexistence of chronic HF and diabetes is known to exacerbate symptoms of HF,[4] and the JASPER registry showed that approximately 40% of HFpEF patients had type 2 diabetes mellitus (T2DM).[5] Thus, treatment of HFpEF complicated with T2DM is an urgent issue in Japan, a country with a super-aging society.

Recent studies have shown that the risk of cardiovascular event and hospitalization for HF (HHF) were reduced by sodium-glucose cotransporter 2 inhibitors (SGLT2-I).[6–8] In the CVD-REAL 2 study, which included Asian subjects, the composite endpoint of all-cause death or HHF decreased by around 50% in patients prescribed SGLT2-I, compared with that in patients prescribed other anti-diabetic drugs.[9] SGLT2-I have a hypoglycemic effect due to the excretion of urinary glucose and also lead to improvement in hemodynamic parameters such as body fluid volume, body weight (BW), and blood pressure. The position statement by the

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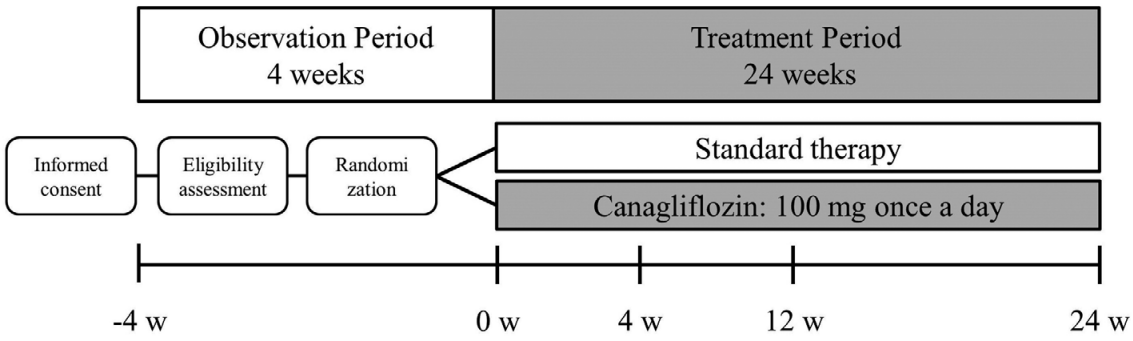

Figure 1. CANONICAL study design.

Table 1. Inclusion and Exclusion Criteria
Inclusion criteria
1. Written informed consent provided prior to participation in the study
2. Age ≥65 years
3. 6.5%≤HbA1c<10.0% in the 8 weeks before consent (patient receiving sulfonylureas or glinides: ≥7.0%)
4. History of heart failure, echocardiographic LVEF ≥50%, and average E/e′ >14 (septal E/e′ >15 or lateral E/e′ >13) or septal e′ <7 cm/s or lateral e′ <10 cm/s, with or without atrial fibrillation
5. Plasma BNP ≥100 pg/mL or plasma NT-proBNP ≥400 pg/mL before consent and plasma BNP ≥40 pg/mL or NT-proBNP ≥125 pg/mL within 8 weeks before consent, with or without atrial fibrillation
6. NYHA cardiac function classification of II–III in the 8 weeks prior to the date of informed consent
7. Unchanged dosage and use of anti-diabetic drugs and drugs for heart failure from at least 8 weeks before the date of informed consent
Exclusion criteria
1. Type 1 diabetes
2. Previous treatment with glucagon-like peptide-1 receptor agonists
3. Need insulin therapy for blood glucose management
4. Severe renal dysfunction or treatment with hemodialysis for end-stage renal disease
5. History of acute coronary syndrome, cerebrovascular disease, myocarditis, contractile pericarditis, or severe valvular disease in the 12 weeks before consent
6. NYHA cardiac function classification of IV
7. BMI <18.5 kg/m^2
8. Pregnancy, breast-feeding, or possible pregnancy
9. Diagnosed or suspected malignant tumors (those who do not have a treatment history of anticancer therapy in the 1 year before consent, and have no plan to do so will not be excluded)
10. Judged by the investigator to be inappropriate for the study

BMI, body mass index; BNP, brain natriuretic peptide; e′, early-diastolic mitral annular velocity; E, peak mitral early filling velocity; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

American Diabetes Association and the European Association for the Study of Diabetes recommends SGLT2-I for the treatment of T2DM patients with established atherosclerotic cardiovascular disease in whom HF coexists or for whom HF is a concern.[10] The mechanism by which SGLT2-I suppressed cardiovascular events and the types of HF for which efficacy can be expected, however, are unknown. Given this background, the CANagliflOziN heart faIlure with preserved ejection fraCtion study for type 2 diAbetes meLlitus (CANONICAL) study aims to examine the effect of canagliflozin on fluid retention and cardiac function compared with standard diabetes treatment for elderly T2DM patients with HFpEF in Japan.

Methods

Design

This is a multicenter, open-label, randomized, parallel-group study comparing the influence of canagliflozin on cardiac function with standard diabetes treatment in elderly patients with T2DM and HFpEF (**Figure 1**). Eligible participants are patients aged ≥65 years with insufficient glycemic control, who are under diet and exercise or receiving an oral hypoglycemic drug other than SGLT2-I. The inclusion/exclusion criteria are listed in **Table 1**. Qualified patients will be randomly assigned to canagliflozin or standard diabetic therapy. In the canagliflozin group, 100 mg canagliflozin (CANAGLU® Tablets 100 mg) will be given orally once per day before or after breakfast in addition to ongoing diabetic treatment for 24 weeks. In the

Table 2. Overview of All Visits and Tests Schedule

	Observation period		Treatment period				Discontinuation
	−4 weeks	−	Baseline	4 weeks	12 weeks	24 weeks	
Permissible range	±2		0	±2	±4	±4	−
Informed consent	X						
Patient characteristics	X						
Registration		X					
Medical examination	X		X	X	X	X	X
Compliance				X	X	X	X
Concomitant therapy	X		X	X	X	X	X
Height/ Body weight	X		X	X	X	X	X
Blood pressure,† heart rate†			X	X	X	X	X
Chest X-ray			X			X	X
Echocardiography	X		X			X	X
Blood test 1‡			X			X	X
Blood test 2‡	X		X	X	X	X	X
Urinalysis§			X	X	X	X	X
Cardiovascular event				X	X	X	X
Electrocardiogram			X	X	X	X	X
Adverse event				X	X	X	X

†Measured at rest in a sitting position. ‡Blood samples are collected under fasting conditions. §First morning void urine sample.

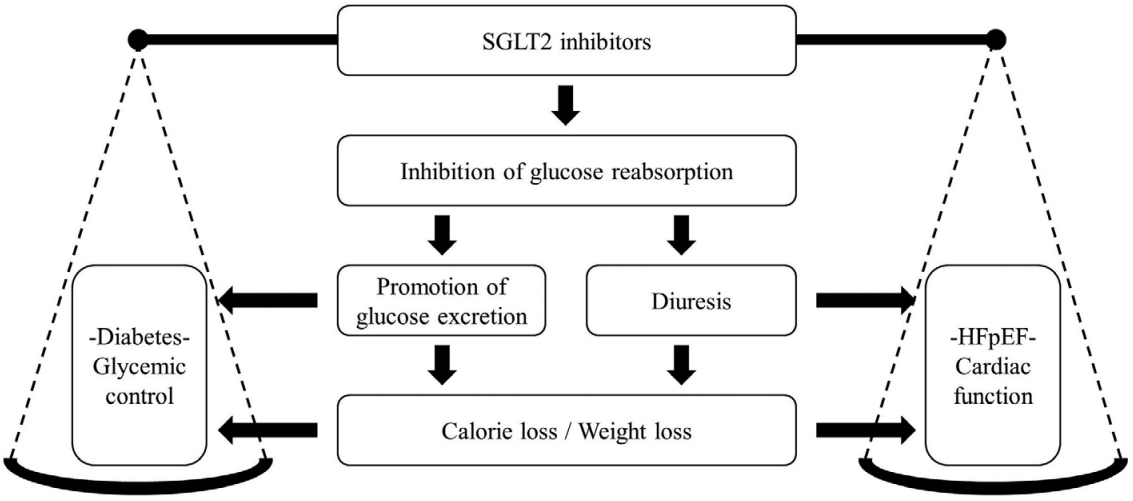

Figure 2. Potential mechanisms of action of sodium-glucose cotransporter-2 (SGLT2) inhibitors on glycemic control and cardiac function. HFpEF, heart failure with preserved ejection fraction.

standard treatment group, anti-hyperglycemic drugs other than SGLT2-I will be used in addition to the ongoing diabetes treatment for 24 weeks. A glycemic (HbA1c) goal will be set for each patient according to the Japanese Diabetes Society guidelines,[11] and the treatment for HF will be carried out in accordance with Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure by the Japanese Circulation Society and Japanese Heart Failure Society.[12]

This study will be carried out in compliance with the articles of the Declaration of Helsinki (revised in October 2013) and according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labor, and Welfare in Japan. The investigator will give a sufficient explanation of the study to each patient and will obtain written informed consent. The independent ethics committees at each institute approved the study protocol. The research period is from 1 October 2017 to 31 March 2021. The study organization is shown in **Supplementary File** (see "**Study Organization**").

Randomization

Registration and allocation of the study participants will be carried out by the central registration modality using an electronic data capturing system. Participants will be dynamically assigned to either the standard treatment group

or the canagliflozin group using the following assignment factors: plasma brain natriuretic peptide (BNP), BW, presence or absence of chronic atrial fibrillation , age, estimated glomerular filtration rate, and sex. The overview of all visits and tests schedule is shown in **Table 2**.

Endpoints

The primary endpoints are the changes from baseline to week 24 in BW and BNP. Secondary endpoints are HHF, cardiovascular death and all-cause deaths, change from baseline in BW at each time point, change in the use of diuretics, HbA1c change from baseline, echocardiography parameters, nutrition status (controlling nutrition status score and geriatric nutritional risk index), and change in thyroid hormone level (FT3, FT4, and thyroid-stimulating hormone). For the safety analysis, adverse events (AE) will be collected. An AE is defined as any unfavorable or unintended sign, symptom, or disease including abnormal laboratory value.

For the efficacy evaluation, the full analysis set (FAS) and the per-protocol set (PPS) will be used. The FAS is defined as the patient population with measured plasma BNP and BW at baseline and for at least 1 time point. The PPS is defined as the patient population that is excluded from the FAS for any of the following: violation of safety-related exclusion criteria, met criteria for study discontinuation, non-compliance with allocated drugs, violation of effectiveness-related inclusion criteria, use of prohibited treatment, study drug compliance rate <70%, or treatment period <16 weeks. The safety analysis set (SAS) will include patients who have any safety evaluation data after the start of study treatment. Other measurements and details of AE are shown **Supplementary File** (see "**Testing Items and Measurements**").

Sample Size

Based on previous reports,[13–16] the difference in BW change from baseline to 24 weeks between the 2 groups should be 2.0±2.0 kg, and the sample size required to detect difference on t-test ($1-\beta=0.98$, $\alpha=0.05$, 2-sided) is estimated to be 34 cases per group. Considering dropout rates, the target number of patients is set at 40 in each group and 80 in total.

Statistical Analysis

For the changes in BW and log-transformed plasma BNP from baseline, the least-squares mean (LS MEAN) difference and the 95% CI will be calculated and amount change in both groups will be compared using an analysis of covariance (ANCOVA) with the baseline value as a covariate. The cumulative survival rates of both groups will be estimated using the Kaplan–Meier method and the rates between the groups will be compared using the log-rank test. The significance level for statistical tests shall be 0.05 on both sides and the confidence coefficient for statistical estimation shall be 95% on both sides. Missing values in the efficacy analysis will be supplemented with the immediately preceding value (last observation carried forward [LOCF]). In addition to the LOCF analysis, an observed case analysis will also be performed.

Discussion

In the present study, the influence of canagliflozin on cardiac function and fluid retention will be evaluated in elderly patients with T2DM and HFpEF. SGLT2-I have been shown to reduce HHF,[6,7] but no obvious reduction in HHF was observed for GLP-1 receptor agonists[17] or DPP-4 inhibitors.[18–20] Thus, there is a possibility that a mechanism other than hypoglycemic action contributes to a reduction in HHF in the patients treated with SGLT2-I. Based on this, we hypothesize that reduction of fluid retention via the diuretic action of SGLT2-I reduces cardiac preload and has a positive effect on cardiac function. This study aims to examine this hypothesis (**Figure 2**).

Some reports on canagliflozin showed an initial increase in urinary sodium excretion and a persistent increase in urinary osmolality due to the urinary glucose excretion.[21,22] This suggests that canagliflozin may reduce fluid load by immediate natriuresis and persistent osmotic diuresis. Hallow et al reported that the diuretic action of dapagliflozin generates a volume of dehydration from the interstitial fluid that is 3-fold greater than that from the blood vessels, and for bumetanide, a loop diuretic, the volume of dehydration from the interstitial fluid and blood vessels is similar.[23] Given that SGLT2-I have a blood pressure-lowering effect without affecting heart rate,[24] there is a possibility that sympathetic nerves are not activated by SGLT2-I. This may also due be to the fact that SGLT2-I generate less hydration from the blood vessels. This suggests that the effect of SGLT2-I on fluid retention is different from that of loop diuretics and may be involved in the reduction in HHF.

Weight gain via an increase in fluid volume due to cardiac congestion has been observed before HHF.[25] The effect of SGLT2-I on weight loss is presumed to be mainly due to a decrease in fluid retention,[26] which may contribute to prevention of worsening HF. Kambara et al reported that an SGLT2-I significantly reduced BW and plasma BNP in elderly patients with T2DM complicated with cardiovascular disease.[27] In their study, patients with decompensated HF accounted for 40% of all patients, but no significant differences in echocardiographic left ventricular ejection fraction were found before or after treatment. The present study will be carried out in a patient population restricted to those with HFpEF, and it will be expected to provide valuable findings regarding the effect of SGLT2-I on cardiac function in elderly patients with T2DM.

This study has the following limitations: a short observation period, a small number of patients, and an open-label modality.

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Disclosures

Potential conflicts of interest of all authors are provided in **Supplementary File** (see "**Potential Conflicts of Interest**").

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Supplementary Files

Please find supplementary file(s);
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