STUDY PROTOCOL

Effect of Luseogliflozin on Myocardial Flow Reserve in Patients with Type 2 Diabetes Mellitus (LUCENT-J Study)

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ABSTRACT

Introduction: In patients with type 2 diabetes (T2D), treatment with sodium–glucose cotransporter-2 (SGLT2) inhibitors has been shown to reduce hospital admission rates for heart failure (HF). However, the multiple mechanisms hypothesized and investigated to explain the cardioprotection of SGLT2 inhibitors are not fully understood.
Objectives: The effect of luseogliflozin on myocardial flow reserve (MFR) in patients with T2D (LUCENT-J) study aims to examine the effects of SGLT2 inhibitors on myocardial perfusion.
Methods: The LUCENT-J study is a prospective, single-center, randomized, two-arm, parallel-group, open-label (i.e., the radiology readers are blinded), active-controlled study. A cohort of 40 patients with T2D with no or stable (with no history of myocardial infarction and with or without previous percutaneous intervention) coronary artery disease will be included. Patients will be randomized in a 1:1 ratio to luseogliflozin or control and treated for 24 weeks. The primary outcome is the change in MFR, as measured by ^{13}N-ammonia positron emission tomography/computed tomography, from baseline to 24 weeks after treatment initiation.
Planned Outcomes: The LUCENT-J study will elucidate the mechanisms of cardioprotection by SGLT2 inhibitors in patients with T2D.
Trial Registration: Japan Registry of Clinical Trials (JRCTs051220016).

Keywords: Luseogliflozin; SGLT2 inhibitor; Myocardial flow reserve; ^{13}N-ammonia positron emission tomography

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Key Summary Points

Heart failure (HF) is highly prevalent in people with type 2 diabetes (T2D) and is an indicator of poor prognosis.

Sodium–glucose cotransporter-2 (SGLT2) inhibitors reduce hospitalization rates for HF.

The mechanisms underlying the cardioprotective effects of SGLT2 inhibitors are insufficiently understood.

This study aimed to elucidate the effects of SGLT2 on cardiac microcirculation and myocardial flow reserve using ^{13}N-ammonia positron emission tomography and to help understand how SGLT2 inhibitors prevent HF.

INTRODUCTION

Sodium–glucose cotransporter-2 (SGLT2) inhibitors act on the proximal renal tubules to reduce glucose, thereby lowering blood glucose. These drugs were initially developed as antihyperglycemic agents. However, the EMPA-REG trial demonstrated for the first time that a glucose-lowering drug, the SGLT2 inhibitor empagliflozin, both rapidly and significantly decreased the risk of hospitalization for HF and cardiovascular death in patients with T2D [1]. Subsequently, the DECLARE-TIMI58 and CANVAS trials demonstrated the cardiovascular disease benefits of the SGLT2 inhibitor in patients with T2D [2, 3]. The multiple mechanisms hypothesized and investigated to explain the beneficial cardiovascular effects of the SGLT2 inhibitor are the subject of continuous investigation. Furthermore, the DAPA-HF and EMPEROR-Reduced trials showed that in patients with and without T2D, dapagliflozin and empagliflozin improved cardiovascular outcomes [4, 5]. The pleiotropic effects of SGLT2 inhibitors have been shown to reduce the incidence and progression of HF and improve the prognosis of HF.

The mechanisms that appear to play a major role in these functions are (1) natriuresis and osmotic diuresis, (2) inhibition of the sympathetic nervous system, (3) improvement in myocardial energy metabolism, and (4) renal protection. Increased natriuresis and osmotic diuresis have been shown to reduce plasma volume, and improved endothelial function, reduced arterial stiffness, and reduced blood pressure may reduce both preload and afterload of the heart [6, 7].

The reduction in blood pressure in the absence of increasing heart rate caused by SGLT2 inhibitors may be indirectly associated with a reduction in sympathetic nervous system activity [8]. SGLT2 inhibitor treatment prevents the development of salt-induced blood pressure elevation and abnormality of the blood pressure circadian rhythm.

The loss of glucose through urine results in increased plasma levels of ketones. The increased use of ketones for energy production improves the energy supply to the "starving" failing heart [9–11]. There are several important interactions between heart disease and kidney disease. These interactions have been referred to as "cardiorenal syndrome" and exacerbation of HF. Several trials have reported renal protection after SGLT2 inhibitor treatment. Treatment with SGLT2 inhibitors was observed to attenuate renal hyperfiltration by affecting tubular–glomerular feedback mechanisms [12].

Diabetes is a risk factor for atherosclerosis, and HF develops from angina pectoris or myocardial infarction due to reduced left ventricular systolic function (HF with reduced ejection fraction). Conversely, patients with diabetes have diastolic dysfunction despite the absence of coronary artery lesions (HF with preserved ejection fraction; HFpEF). Myocardial microcirculatory dysfunction has been implicated in HFpEF [13, 14].

Cardiac microcirculation can be investigated noninvasively by ^{13}N-ammonia positron emission tomography (PET). ^{13}N-ammonia PET examines myocardial flow reserve (MFR), which is the ratio between myocardial blood flow at rest and at stress-induced hyperemic conditions pharmacologically. In addition to organic coronary artery lesions, microcirculatory dysfunction can also be detected. MFR has been

reported to be reduced by dipyridamole loading of ^{13}N-ammonia PET in patients with T2D [15].

The use of coronary flow reserve as a functional indicator of coronary artery stenosis by cardiac catheterization is useful and has been reported, for example, in the FAME study as an indicator for assessing vascular lesions at the conduit vessel site, whereas MFR represents the effect of microcirculation as well as conduit vessels.

Therefore, in addition to the ischemia diagnosis, the MFR of the whole myocardium has been reported to be very useful for predicting prognosis regardless of the underlying HF [16–19]. ^{13}N-ammonia PET studies can be used to assess not only ischemia but also microcirculatory effects.

This may be important for elucidating the mechanisms underlying the effects of SGLT2 inhibitors in HF. In this study, we investigate the effect of luseogliflozin administration on MFR as a cardioprotective mechanism by SGLT2 inhibitors.

Adrenomedullin is a bioactive peptide with potent vasodilatory properties discovered in brown cell tissue, which is elevated in cardiovascular disease and has physiological effects, including cardiovascular protection [20, 21].

In this study, we will measure ^{13}N-ammonia PET and plasma adrenomedullin levels before and after luseogliflozin administration to analyze and investigate the improvement in myocardial microcirculatory dysfunction and to clarify some of the mechanisms of cardioprotection in diabetes. We hypothesize that improving microcirculatory dysfunction is a mechanism of cardioprotection with SGLT2 inhibitors.

METHODS

Study Design

This is a prospective, single-center, randomized, two-arm, parallel-group, open-label (i.e., the radiology readers are blinded), active-controlled study conducted in patients attending the Division of Diabetes and Lipid Metabolism at the National Cerebral and Cardiovascular Center in Japan. The study aimed to evaluate the effect of luseogliflozin on MFR using ^{13}N-ammonia PET in patients with T2D after 24 weeks of treatment (Fig. 1). Qualifying patients will be randomly assigned to receive luseogliflozin or conventional therapy. In the luseogliflozin group, luseogliflozin will be administered orally in addition to the participant's ongoing diabetic treatment. In the control group, participants will only receive non-SGLT2 inhibitors as ongoing treatment (see the "Treatments" section below).

Ethics Compliance

This study will be conducted in compliance with both the articles of the Declaration of Helsinki (revised in October 2013) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labor and Welfare in Japan. The registration period is from April 28, 2022, to August 31, 2023, and the research period is from April 28, 2022, to May 31, 2024. In accordance with the law for clinical research in Japan, the Nara Medical University Certified Review Board approved the study protocol (approval No. nara0050). Written informed consent has been obtained from all participants.
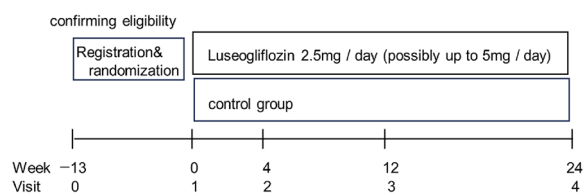

Fig. 1 Study design. A total of 40 patients with type 2 diabetes mellitus (20 patients/group) will participate in this study. After patient eligibility is confirmed by a central managing modality, the enrolled patients will be randomly assigned to the luseogliflozin or control group. In the luseogliflozin group, 2.5 mg luseogliflozin will be administered orally once per day. In the control group, non–sodium–glucose cotransporter-2 (SGLT2) inhibitor treatment will continue. If necessary, the luseogliflozin dose will be increased to up to 5 mg per day

Planned Outcomes

Primary Endpoint

The primary endpoint of the study is the difference between the groups in the amount of MFR change 24 weeks after initiation of administration.

Secondary Endpoints

1. The amount of change in the following items within each group and the difference between the groups at the time of each measurement (4, 12, and 24 weeks) from the start of the study: body weight, body mass index (BMI), systolic blood pressure, diastolic blood pressure, hemoglobin, hematocrit, total protein, albumin, total bilirubin, aspartate aminotransferase (AST), alanine transaminase (ALT), glutamic pyruvic transaminase (ɤ-GTP), serum creatinine, estimated glomerular filtration rate (eGFR), lactate dehydrogenase (LDH), calcium (Ca), sodium (Na), potassium (K), chlorine (Cl), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), uric acid, C-reactive protein (CRP), fasting blood sugar (FBS), immunoreactive insulin (IRI), HbA1c, acetoacetic acid, β-hydroxybutyric acid, and urinary albumin creatinine ratio. The amount of change in the following items within each group and the difference between the groups up to 24 weeks from the initiation of administration: B-type natriuretic peptide (BNP), adrenomedullin, and left ventricular ejection fraction (LVEF) assessed by ^{13}N-ammonia PET.
2. Difference in the amount of change in MFR between the groups with high and low MFR values before administration.

Study Population

The study will include 40 patients with T2D attending the Division of Diabetes and Lipid Metabolism at the National Cerebral and Cardiovascular Center, with HbA1c < 8.5%, under glycemic control by diet, exercise, and with/without pharmacotherapy (except SGLT2 inhibitors) as appropriate. Patients should also be able to provide written informed consent and have stable (no history of myocardial infarction, with or without previous percutaneous coronary intervention) or no coronary artery disease. Table 1 details the inclusion and exclusion criteria.

Randomization

Eligible and consenting participants will be randomized in a 1:1 ratio to luseogliflozin or control using the following assignment factors: sex, age (< 70 or ≥ 70 years), HbA1c (< 8.0 or ≥ 8.0%), MFR (< 1.9 or ≥ 1.9), and whether or not a glucagon-like peptide-1 (GLP-1) receptor agonist will be administered using the web-based minimization dynamic allocation method.

Treatments

In the luseogliflozin group, 2.5 mg of luseogliflozin (Lusefi® tablets 2.5 mg) will be administered orally in addition to the participant's ongoing diabetic treatment. If the effect is insufficient, the dose can be increased to 5 mg (Lusefi® tablets 5 mg) per day. In the control group, treatment with non-SGLT2 inhibitors is continued. Each patient's blood glucose level will be controlled according to the blood glucose control goals established by the Japan Diabetes Society at the discretion of the diabetes specialist.

As far as possible, diabetic and antihypertensive drugs will be continued without modification from the date of informed consent until the date of study initiation. During the treatment period, nitroglycerin, vasodilators, and GLP-1 receptor agonists will not change. However, such events will be recorded if they occur.

MFR ^{13}N Ammonia PET CT

Rest and pharmacological stress PET scanning is conducted using a digital PET/CT system (Discovery MI, GE Healthcare). The procedure is started with a low-dose transmission CT scan

Table 1 Inclusion and exclusion criteria of the LUCENT-J study

Inclusion criteria	Exclusion criteria
1. Patients with type 2 diabetes aged 50 years and older(independent of sex)	1. Type 1 diabetes mellitus
2. Patients with an HbA1c of 8.5% or less (most recent HbA1c within 13 weeks before consent)	2. Patients with heart disease (myocardial infarction, cardiomyopathy, atrial fibrillation, severe valvular disease)
3. Patients who have undergone an ammonia PET examination before the date of consent acquisition and who have an MFR of 3.0 or less (most recent MFR within 13 weeks before consent)	3. Patients with coronary artery disease who are indicated for coronary revascularization or patients with suspected coronary artery disease who are indicated for coronary angiography
4. Patients who have provided written consent	4. Patients with coronary artery disease who are indicated for coronary revascularization or patients with suspected coronary artery disease who are indicated for coronary angiography
	5. Persons with severe renal dysfunction
	6. Patients with severe hepatic dysfunction (ALT or AST five times or greater the standard value)
	7. Patients with malignant tumors currently being treated or during palliative care
	8. Patients participating in or planning to participate in intervention studies using other medicines or medical devices
	9. Smokers
	10. Pregnant or lactating women
	11. Patients with contraindications to luseogliflozin (hypersensitivity, severe ketosis, diabetic coma, severe infections, before or after surgery, serious trauma)
	12. In patients who are young-old ($65 \leq$ age < 75) and latter-stage elderly ($75 \leq$ age), it is patients of the geriatric syndrome or BMI < 18 kg/m^2
	13. Patients who received SGLT-2 inhibitors for 13 weeks before the ammonia PET examination to the date of consent acquisition
	14. Patients who have newly started, changed, or discontinued diabetes treatment drugs, nitroglycerin preparations, vasodilators, or antihypertensive drugs within 13 weeks before obtaining consent (however, temporary drug changes are allowed due to suspected ischemia on ammonia PET scans)
	15. Patients whose participation in this study is deemed inappropriate by the investigator or coinvestigator

PET positron emission tomography, *MFR* myocardial flow reserve, *BMI* body mass index, *SGLT-2* sodium–glucose cotransporter-2

for attenuation correction. A 20-frame (12×10 s, 6×30 s, 2×60 s, and 1×180 s) three-dimensional dynamic emission scan is initiated simultaneously with the intravenous administration of 370 MBq of ^{13}N ammonia over 30 s using an automatic injector. After approximately five half-lives of ^{13}N ammonia had elapsed, pharmacological stress imaging is conducted identically, with a preceding infusion of adenosine (140 µg/kg/min) administered 3 min before 370 MBq of ^{13}N ammonia is intravenously injected automatically over 30 s. The adenosine infusion is continued for 6 min.

The dynamic image dataset is processed using two commercially available pharmacokinetic software packages: syngo myocardial blood flow (MBF) version VB15 (Siemens Medical Solutions) and Corridor 4DM (INVIA Medical Imaging Solutions). MBF is estimated using the time–activity curve (TAC) of the left ventricle input and myocardial uptake in compartment models. MFR is determined as the ratio of adenosine stress hyperemic MBF to resting MBF, with MFR < 2.0 considered abnormal. The MBF and MFR results are expressed in each major coronary artery territory and segment according to the AHA's 17-segment model.

Measurements

Table 2 details the data collection schedule.

Sample Size Calculation

We based the sample size calculation on the published results of a previous trial on the effect of improvement in blood glucose with diabetic drugs on MFR in patients with T2D [22]. Taking into consideration an expected delta of MFR of 0.13 mL/min/g and a standard deviation of 0.16, 16 patients per treatment group are considered a sufficient number to reject the null hypothesis that the population means of the two groups are equal with a power of 85% and an alpha of 0.05. Considering a 20% study dropout rate, the target number of patients was set to 20 per group for 40 patients. Given the small sample size, a high dropout rate was set to account for the large number of dropouts, which would have a considerable impact on the analysis results.

Data Analysis

Analysis Populations

Two analysis groups were defined for the evaluation of effectiveness: a full analysis set (FAS) and a per-protocol set (PPS), with the FAS used for the primary analysis. The safety analysis set will include patients for whom safety assessment data were collected after the start of treatment in the study.

- FAS is defined as the population of participants who provided informed consent and had a measured value for the factors of the primary endpoint at baseline and at least one time point during the treatment period.
- PPS is defined as the population of participants for whom a post-study review did not identify any considerable deviation from the protocol.

Statistical Methods

The primary endpoint will be the difference in the change in MFR from baseline to 24 weeks. The difference in change in MFR from baseline to 24 weeks between the two groups will be tested by analysis of covariance, and summary statistics will be calculated. The covariates will be gender, age, MFR, HbA1c, and GLP-1 receptor agonist. We set the significance level at 0.05 two-sided. We will also perform the same test using BMI added to the covariates as a sensitivity analysis. Summary statistics will also be calculated for uncorrected cases as reference values. As secondary endpoints, we will evaluate the amount of change within each group and the difference in change between groups (those not measured at 4 and 12 weeks only after 24 weeks), and we will calculate the summary statistics quantities for the following items: body weight, BMI, systolic blood pressure, diastolic blood pressure, hemoglobin, hematocrit, HbA1c, FBS, IRI, blood acetoacetic acid, β-hydroxybutyric acid, total protein, albumin, total bilirubin,

Table 2 Schedule of enrollment, interventions, and assessments (SPIRIT flow diagram)

	Enrollment	Allocation	Postallocation			Closeout
			Study Period			
Time point	*-13W*	*0*	*4 W*	*12 W*	*24 W*	
Enrollment						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
Interventions						
Luseogliflozin		←———————————————→				
Assessments						
Participant characteristics*	X					
Vital signs**		X	X	X	X	X
Blood test***	X	X	X	X	X	X
Urine test****		X	X	X	X	X
13N-ammonia PET	X	X			X	
ECG		X			X	
diet/exercise therapy	X	X	X	X	X	X

PET positron emission tomography, ECG electrocardiogram

*Participant characteristics include the following: sex, age, duration of diabetes mellitus, medical history, concomitant medications, and alcohol and smoking habits

**Vital signs include the following: blood pressure, pulse rate, height, body weight, and body mass index

***Blood tests include the following: HbA1c, FBS, IRI, blood acetoacetic acid, β-hydroxybutyric acid, white blood cell count, red blood cell count, hemoglobin content, hematocrit, platelet count, total protein, albumin, total bilirubin, serum creatinine, serum uric acid, eGFR, AST, ALT, ɤ-GTP, LDH, LDL-C, triglyceride, HDL-C, Na, K, Cl, Ca, CRP, BNP and adrenomedullin (only after 24 weeks)

****Urine tests include the following: qualitative test (protein, glucose, urobilinogen, bilirubin, ketone body, occult blood), specific gravity, pH, urine albumin, urine creatinine

serum creatinine, serum uric acid, eGFR, AST, ALT, ɤ-GTP, LDH, LDL-C, TG, HDL-C, Na, K, Cl, Ca, CRP, BNP, adrenomedullin, urinary albumin creatinine ratio, and LVEF. In each group, the change from baseline to 4, 12, and 24 weeks will be tested for each test item. The test will be either paired t test or Wilcoxon signed-rank test. The significance level will be two-sided 0.05. We will compare the change from baseline between the luseogliflozin group and the control groups.

Tests will be Student's *t* test or Wilcoxon rank-sum test. The significance level will be set at 0.05. Subgroup analysis will compare the difference in change in MFR between the luseogliflozin group and the control group in each of the above- and below-median pretreatment MFR data populations. We will test the difference in the change in MFR from baseline to 24 weeks between the two groups by analysis of covariance, and summary statistics will be calculated. The covariates will be gender, age, HbA1c, and use of GLP-1 receptor agonist. The significance level will be set at two-sided 0.05. We will also perform the same test using BMI added to the covariates as a sensitivity analysis.

STRENGTHS AND LIMITATIONS

This is a single-center study with a relatively small number of participants. The main strength of this study is the highly refined gold standard method for assessing MFR by ^{13}N-ammonia PET. Furthermore, the highly selected study population includes patients with T2D with a narrow HbA1c range (HbA1c ≤ 8.5%) who do not require revascularization or who are clinically stable after percutaneous coronary intervention. Therefore, the number of eligible patients is limited by the inclusion criteria, which are time-consuming and costly. However, with the right patients, accurate assessments could be made, and study results could lead to further cardioprotective studies in more patients with diabetes.

CONCLUSIONS

This study will elucidate the effects of SGLT2 on cardiac microcirculation. The results of this study will provide insights into the mechanism by which SGLT2 inhibitors prevent HF.

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Declarations

Conflict of interest. Tamiko Tamanaha, Hisashi Makino, Cheol Son, Ryo Koezuka, Mayu Tochia, Yoko Ohata, Tatsuya Takekawa, Michio Noguchi, Tsutomu Tomita, Kyoko Honda-Kohmo, Miki Matsuo, Emi Tateishi, Tetsuya Fukuda, Yoshihiro Miyamoto, and Kiminori Hosoda have nothing to disclose.

Ethical approval. The study protocol was approved by the Nara Medical University Certified Review Board (approval No. nara0050) and will be conducted in compliance with both the articles of the Declaration of Helsinki (revised

in October 2013) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labour and Welfare in Japan. Written informed consent has been obtained from all participants.

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