Cardiovascular Diabetology – Endocrinology Reports

BRIEF REPORT

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Effect of tofogliflozin on cardiac sympathetic nerve activity in type 2 diabetes mellitus patients with heart failure (TARGET-HF): rationale and design of the single-arm intervention trial

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Abstract

Background Cardiac sympathetic nervous dysfunction is linked to poor prognosis in heart failure with reduced ejection fraction (HFrEF), and patients with HFrEF complicated by type 2 diabetes mellitus (T2DM) represent a particularly high risk. Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce heart failure (HF) hospitalizations in patients with T2DM, but the mechanisms underlying these benefits are not fully understood; modulation of cardiac sympathetic activity has been proposed as one contributor. The TARGET-HF trial will investigate whether tofogliflozin improves cardiac sympathetic nerve activity, assessed by I-123 metaiodobenzylguanidine (MIBG) scintigraphy, along with other cardiovascular parameters in patients with HFrEF and T2DM.

Methods This single-arm prospective interventional study will enroll 50 patients with HFrEF (left ventricular ejection fraction < 40%), T2DM (hemoglobin A1c level, 6.5–10.0%), and estimated glomerular filtration rate ≥ 30mL/min/1.73 m^2. Participants will receive oral tofogliflozin (20 mg/day) for 24 weeks. The primary endpoint is the change in the heart-to-mediastinum ratio on delayed I-123 MIBG scintigraphy from baseline to 24 weeks. Secondary endpoints include changes in the early heart-to-mediastinum ratio, washout rate, echocardiographic parameters, and various biomarkers related to HF, inflammation, and metabolism.

Discussion The TARGET-HF trial is the first interventional study to comprehensively evaluate the effects of tofogliflozin on cardiac sympathetic nerve activity using I-123 MIBG scintigraphy in patients with HFrEF and T2DM. By integrating nuclear imaging, echocardiography, and metabolic and biochemical biomarkers, this study aims to

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clarify the mechanisms underlying the cardioprotective effects of SGLT2 inhibitors. Improved understanding of these mechanisms may refine patient selection and guide targeted therapeutic strategies in HF management.

Trial registration Japan Registry of Clinical Trials; approval number: jRCTs041210022 (February 6, 2021).

Keywords Heart failure, Diabetes mellitus, SGLT2 inhibitor, I-123 MIBG scintigraphy

Background

Heart failure (HF) is projected to considerably increase in prevalence in the future, raising global public health concerns [1]. Particularly, the coexistence of type 2 diabetes mellitus (T2DM) and heart failure with reduced ejection fraction (HFrEF) is associated with markedly poor prognosis, highlighting the need for effective treatments targeting both conditions [2, 3]. Recent studies have demonstrated the cardioprotective effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors in patients with HFrEF, showing significant reductions in hospitalizations due to HF and cardiovascular death [4, 5]. Consequently, international HF guidelines now classify SGLT2 inhibitors as Class I drugs with the highest recommendation level for HFrEF [6–8]. While potential mechanisms underlying the cardioprotective effects of SGLT2 inhibitors in HFrEF may involve reduced cardiac preload and afterload, improved myocardial energy metabolism, and enhanced renal function [9], these mechanisms have not been fully elucidated.

Sympathetic nervous system activation is a key pathophysiological feature of HFrEF, contributing to disease progression and adverse outcomes [10]. I-123 metaiodobenzylguanidine (MIBG) scintigraphy is an established method for evaluating cardiac sympathetic activity, and cardiac sympathetic activity parameters, e.g., the heart-to-mediastinum ratio (HMR) or washout rate (WR), in patients with HFrEF are useful for prognostic prediction [11, 12].

To date, no studies have examined the effects of SGLT2 inhibitors on cardiac sympathetic activity in patients with HFrEF and T2DM. Given the high risk of cardiovascular adverse events in these patients, it is important to evaluate the efficacy and safety of SGLT2 inhibitors in this high-risk population. Furthermore, elucidating the mechanism of action in this specific subgroup is essential for optimizing treatment strategies and potentially expanding the clinical applications of SGLT2 inhibitors beyond glycemic control.

The Tofogliflozin mechanism of Action to Retain cardiac function evaluated by I-123 MIBG scintigraphy, Echocardiography and biomarkers in T2DM patients with Heart Failure (TARGET-HF) trial aims to contribute to the optimization of SGLT2 inhibitor therapy in patients with HFrEF and T2DM by focusing on the effects of tofogliflozin on cardiac sympathetic activity while comprehensively evaluating the underlying mechanisms of its cardioprotective actions. We hypothesized that the SGLT2 inhibitor tofogliflozin would improve cardiac sympathetic activity and induce favorable changes in various biomarkers this high-risk population.

Methods

Study design and population

The TARGET-HF trial is a single-arm prospective interventional study designed to investigate the mechanisms of cardioprotection by tofogliflozin in patients with HFrEF and T2DM. This study plans to enroll 50 patients from five domestic institutions. Patients will receive tofogliflozin (20 mg daily) for 24 weeks, with assessment of cardiac sympathetic activity by I-123 MIBG scintigraphy and comprehensive biomarker evaluation at baseline and 24 weeks.

Tofogliflozin was selected as a representative SGLT2 inhibitor commonly used in Japan to enable a prospective mechanistic evaluation of cardiac sympathetic activity with MIBG. The trial is not intended to compare effectiveness across SGLT2 inhibitors; rather, it tests the mechanistic hypothesis within the class while specifically administering tofogliflozin.

Trial structure and oversight

The TARGET-HF trial will be conducted at five university hospitals in Japan. The study will be performed in accordance with the Declaration of Helsinki and the Japanese Clinical Trials Act (Japanese Clinical Trial Registry approval number: jRCTs041210022). The study is funded by Kowa Company, Ltd., but the sponsor will not be involved in the study design, data collection, analysis, or publication of the results. An independent data monitoring committee will monitor trial data, and an event evaluation and safety monitoring committee will periodically evaluate adverse events and safety data.

Study participants

The comprehensive inclusion and exclusion criteria for this trial are shown in Table 1. Eligible participants are adults (≥ 20 years) with T2DM and chronic HF (New York Heart Association [NYHA] class II or III) with reduced left ventricular ejection fraction (LVEF) of < 40%. Additional key inclusion criteria include a stable clinical condition for at least 8 weeks, hemoglobin A1c (HbA1c) level of 6.5–10.0%, an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) level —defined as ≥ 125

Table 1 Inclusion and exclusion criteria

Inclusion criteria		Exclusion criteria	
1	Age ≥ 20 years at the time of informed consent	1	Use of SGLT2 inhibitors within 8 weeks prior to informed consent
2	T2DM with HbA1c level of 6.5–10.0% within 12 weeks prior to informed consent	2	Use of insulin within 8 weeks prior to informed consent
3	Diagnosis of chronic heart failure for at least 8 weeks and NYHA class II or III	3	Change in any medication (including dosage) within 4 weeks prior to informed consent
4	LVEF < 40% within 12 weeks prior to informed consent	4	Symptomatic hypotension or systolic blood pressure <95 mmHg within 12 weeks prior to informed consent
5	NT-proBNP level ≥ 125 pg/mL in sinus rhythm or ≥ 365 pg/mL in atrial fibrillation within 12 weeks prior to informed consent	5	Acute heart failure or hospitalization for heart failure within 4 weeks prior to informed consent
6	eGFR ≥ 30 mL/min/1.73m^2 within 12 weeks prior to informed consent	6	History of myocardial infarction, unstable angina, stroke, or TIA within 12 weeks prior to informed consent
7	Provision of written informed consent	7	History of PCI, CABG, valve repair, or valve replacement within 12 weeks prior to informed consent or planned for these procedures during the study period
		8	Pacemaker implantation within 12 weeks prior to informed consent or planned implantation during the study period
		9	Heart transplantation (history or planned)
		10	Restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic cardiomyopathy, or valvular disease
		11	Symptomatic bradycardia
		12	History of iodine hypersensitivity
		13	Current use of reserpine, tricyclic antidepressants, or labetalol
		14	Parkinson disease
		15	Active malignancy requiring treatment
		16	Hepatic impairment (AST or ALT level ≥3× ULN, or total bilirubin level ≥2× ULN)
		17	Severe renal impairment (eGFR <30 mL/min/1.73 m^2)
		18	Low BMI (<18.5 kg/m^2)
		19	Pregnancy, breastfeeding, or possible pregnancy
		20	Severe ketosis, diabetic coma, or pre-coma
		21	Severe infection, perioperative status, or serious trauma
		22	History of hypersensitivity to components of the study drug
		23	Any other condition deemed inappropriate by the investigator

T2DM, type 2 diabetes mellitus; HbA1c, hemoglobin A1c; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TIA, transient ischemic attack; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal; BMI, body mass index

pg/mL in patients in sinus rhythm or ≥ 365 pg/mL in patients with atrial fibrillation, measured within 12 weeks prior to obtaining informed consent; and preserved renal function (estimated glomerular filtration rate [eGFR] ≥ 30 mL/min/1.73 m^2).

Key exclusion criteria include recent use of SGLT2 inhibitors or insulin, recent changes in medication, symptomatic hypotension, acute decompensated HF, recent cardiovascular events (e.g., myocardial infarction, stroke, or cardiac surgery), and substantial comorbidities, e.g., active malignancy, severe renal or hepatic impairment, or known hypersensitivity to the study drug. Additionally, patients with restrictive, hypertrophic, or inflammatory cardiomyopathies, or those who were pregnant, breastfeeding, or deemed ineligible by the investigator for any other reason were excluded from participation.

Study visits and follow-up

Patients will undergo screening evaluation to determine eligibility. Eligible patients who provide written informed consent will enter a 24-week treatment period, during which they will receive oral tofogliflozin in the morning (Fig. 1). Efficacy and safety assessments are outlined herein. Patients will visit at baseline and 24 weeks for efficacy evaluations including I-123 MIBG scintigraphy, echocardiography, and biomarker assessment. Detailed information on the study schedule and assessments is provided in Table 2.

During the 24-week study, insulin and SGLT2 inhibitors other than the study drug are prohibited. Background HF, antidiabetic, antihypertensive, and lipid-lowering agents must remain unchanged (especially beta-blockers, moxonidine, ACE inhibitors). If a change is clinically unavoidable, it will be documented (agent/dose/date/reason); the participant will remain in the full analysis set (FAS) and

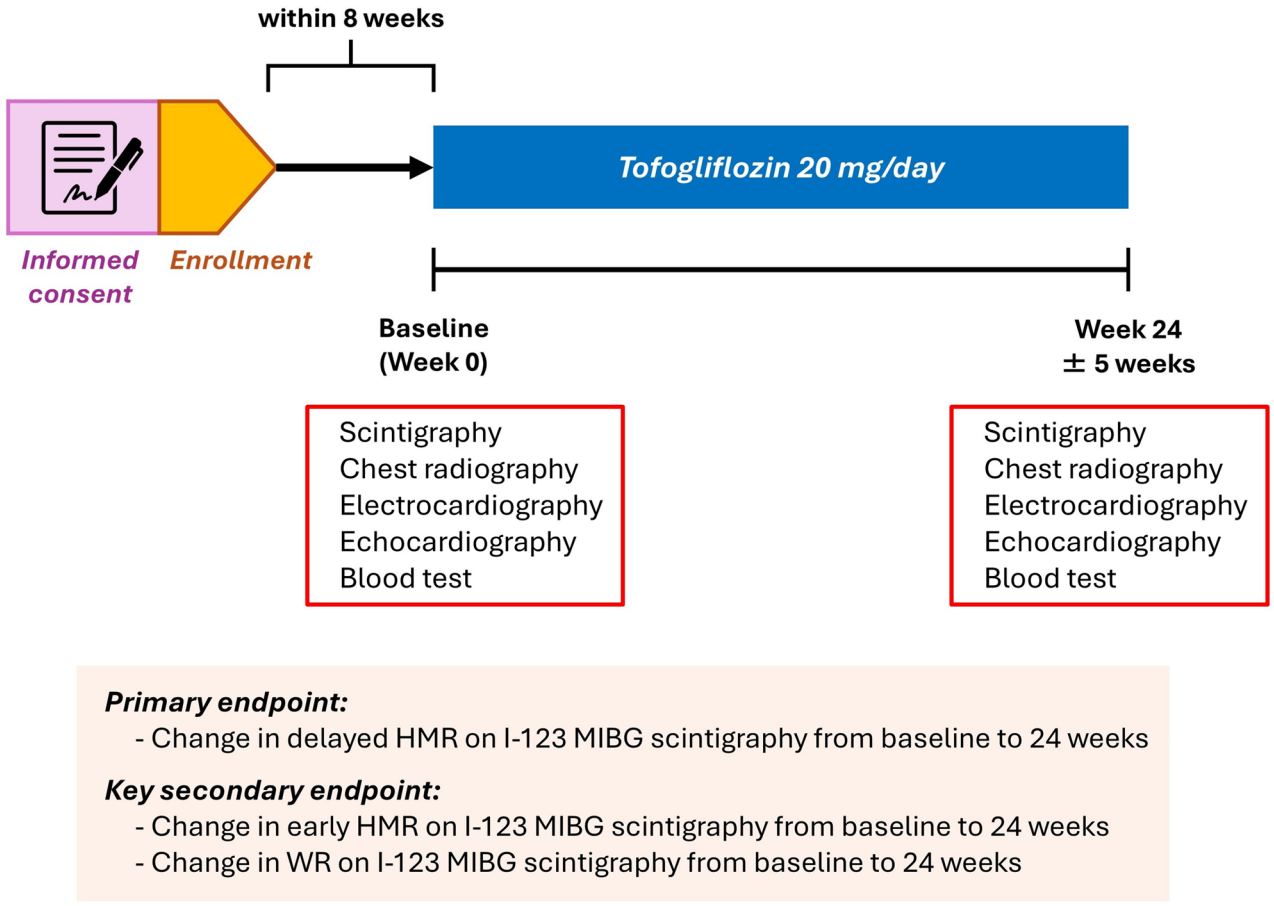


Fig. 1 Study design and schedule of assessments in the TARGET-HF trial. Eligible patients with HFrEF and T2DM will receive tofogliflozin (20 mg/day) for 24 weeks. I-123 MIBG scintigraphy, chest radiography, electrocardiography, echocardiography, and blood tests will be performed at baseline and week 24. The primary endpoint is change in delayed HMR; key secondary endpoints are changes in early HMR and WR. HFrEF, heart failure with reduced ejection fraction; T2DM, type 2 diabetes mellitus; MIBG, metaiodobenzylguanidine; HMR, heart-to-mediastinum ratio; WR, washout rate

safety analysis set (SAS), but will be excluded from the per-protocol set (PPS) for the primary endpoint.

Endpoints

The primary study endpoint is the change in delayed HMR on I-123 MIBG scintigraphy from baseline to 24 weeks. Delayed HMR was selected as the primary endpoint because it is a more stable and reliable indicator for assessing cardiac sympathetic nerve function than early HMR, particularly when accounting for collimator-dependent variations [13–15]. Moreover, delayed HMR has strong prognostic value in patients with HF, and it is the most extensively validated MIBG-derived parameter in clinical studies [16, 17].

Key secondary endpoints include the change in early HMR and the change in WR on I-123 MIBG scintigraphy over the same period. Other secondary endpoints comprise changes in a broad range of cardiovascular, metabolic, and biochemical parameters. These include echocardiographic indices such as LVEF, global longitudinal strain (GLS), left ventricular end-diastolic and end-systolic diameters, left atrial volume, left ventricular volume and mass, deceleration time, E/A ratio, e' velocity, E/e' ratio, E wave and A wave velocities, tricuspid regurgitation pressure gradient, inferior vena cava diameter, and estimated right atrial pressure.

Additionally, changes in glycemic control (HbA1c, fasting glucose, fasting insulin, and homeostasis model assessment-estimated insulin resistance values), hormonal markers (glucagon, active glucagon-like peptide-1, and active gastric inhibitory polypeptide levels), lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, lipoprotein (a), small dense low-density lipoprotein, and apolipoprotein B, AI, and AII levels), hematological markers (white blood cell, red blood cell, platelet count, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, erythropoietin, and troponin T values), renal function (eGFR, serum creatinine, urinary albumin-to-creatinine ratio, uric acid, blood urea nitrogen, and urinary neutrophil gelatinase-associated lipocalin levels),

Table 2 Data collection and follow-up

Assessment	At Enrollment	Baseline (Week 0)	Week 24 (± 5 weeks)	At Discontinuation (± 5 weeks)
Informed consent	✓			
Eligibility confirmation	✓			
Patient background		✓		
Physical examination		✓	✓	✓
Body composition *		△	△	△
Medication record			✓	✓
Nuclear imaging (I-123 MIBG scintigraphy)		✓	✓	✓
Echocardiography		✓	✓	✓
Echocardiography (GLS) *		△	△	△
Electrocardiography		✓	✓	✓
Chest radiography		✓	✓	✓
General blood test		✓	✓	✓
Specialized blood test		✓	✓	✓
General urinalysis		✓	✓	✓
Specialized urinalysis		✓	✓	✓
Adverse events and clinical events			Collected as needed	

✓ = Assessment performed

* Body composition and GLS were optional assessments performed at selected sites

GLS, global longitudinal strain; I-123 MIBG, iodine-123 metaiodobenzylguanidine

liver function (aspartate aminotransferase, alanine transaminase, alkaline phosphatase, and gamma-glutamyl transferase levels), ketone body metabolism (total and fractional ketone body levels), inflammation and oxidative stress markers (high-sensitivity C-reactive protein and urinary 8-hydroxy-2′-deoxyguanosine levels), neurohumoral activity (aldosterone-to-renin activity ratio, dopamine, noradrenaline, adrenaline, and NT-proBNP values), adiponectin, and circulating CD34-positive stem cells will be assessed as secondary outcomes.

Safety assessment

Safety will be continuously monitored throughout the study period. Safety parameters, including adverse events and serious adverse events, e.g., hypoglycemic episodes, genital and urinary tract infections, or hypotension, will be assessed at each study visit or as clinically indicated. All safety-related events will be documented and evaluated according to standard definitions and criteria.

I-123 MIBG scintigraphy

All patients will undergo cardiac I-123 MIBG scintigraphy at baseline and 24 weeks after initiation of treatment (Fig. 2). A standard dose of 111 MBq (3 mCi) of I-123 MIBG will be administered intravenously without weight-based adjustment. Then, imaging will be performed using gamma cameras (Siemens, Munich, Germany) equipped with institution-specific collimators (low energy high resolution [LEHR], low-medium energy general purpose (LMEGP), or medium energy low penetration [MELP]), and the collimator type will be documented. Planar and single photon emission computed tomography (SPECT) images will be acquired at early (15 min post-injection) and late phases (4 h ± 15 min post-injection) [18].

Planar imaging will be performed for 5 min, and SPECT acquisition will be conducted over 13–20 min using a 180° or 360° orbit, depending on the protocol of the institution. Matrix sizes will be set to 128 × 128 or 256 × 256 for planar imaging and 64 × 64 or 128 × 128 for SPECT. An energy window centered at 159 keV with a 20% window width will be used. SPECT images will be reconstructed and submitted in Digital Imaging and Communications in Medicine format.

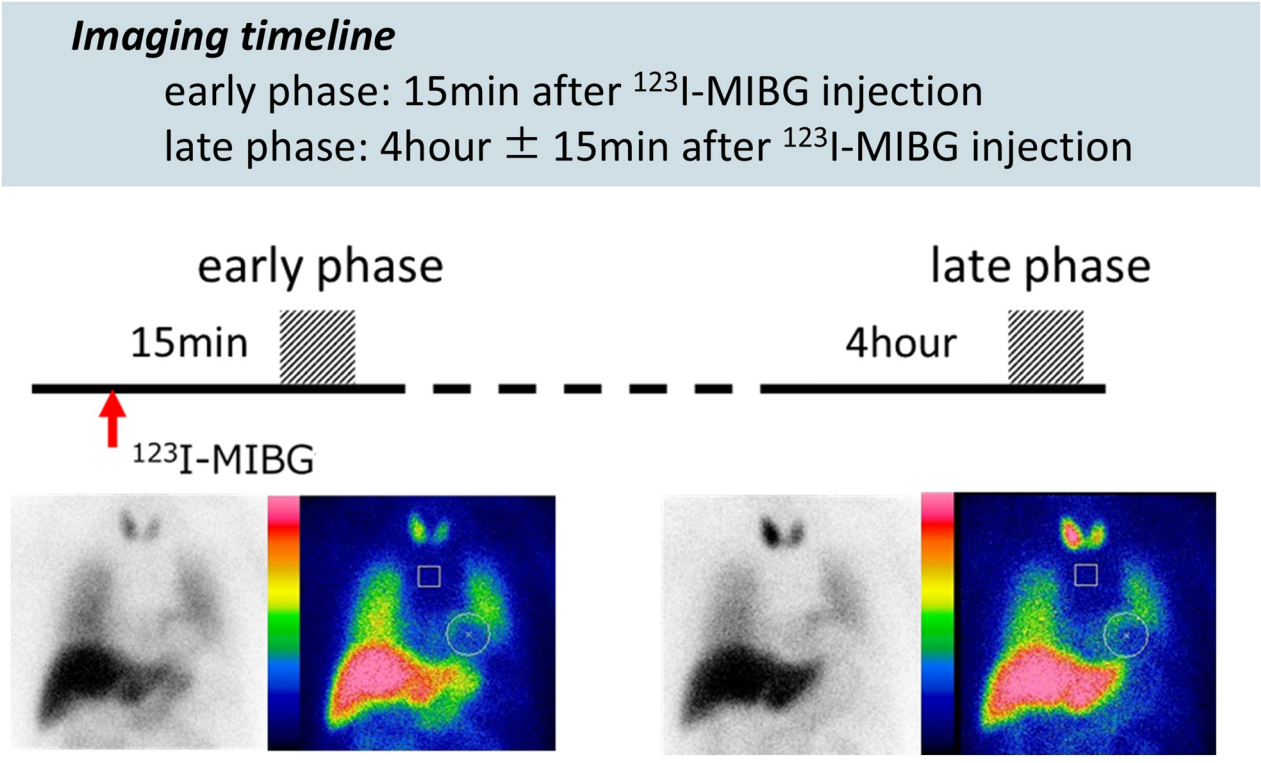
For quantification, early and delayed HMR and WR will be calculated using the smart MIBG software (FUJIFILM RI Pharma Co., Tokyo, Japan) with semi-automated region-of-interest placement. To account for differences in collimator sensitivity, measured HMRs will be converted to standardized values using correction coefficients (LEHR: 0.55, LMEGP: 0.83, MELP: 0.95) and a reference Kstd of 0.88 [19]. All anonymized images will be centrally reviewed at a core laboratory by two independent reviewers. Quality control will be ensured by cross-evaluation of a randomly selected subset of images.

Sample size calculation

The sample size calculation is based on the primary endpoint of change in delayed HMR on I-123 MIBG scintigraphy from baseline to 24 weeks. In the absence of prior interventional data for SGLT2 inhibitors, we assumed an effect size equivalent to that observed with the standard HF therapy ACE inhibitors, as reported in a previous study of patients with dilated cardiomyopathy [11] (mean change 0.12; baseline SD 0.28). Although the reference study used a 12-month treatment period, we adopted these values given the lack of comparable data for a 6-month period. Under these assumptions, 45 patients would provide 80% power with a two-sided alpha of 0.05, and allowing for 10% dropout, the target sample size was set at 50.

Statistical analysis

The FAS will include all enrolled participants who receive at least one dose of study drug and have at least one evaluable assessment of the primary endpoint (at baseline or at 24 weeks). The PPS will include participants who complete both baseline and 24-week assessments without major protocol deviations, including violations



	Planar	SPECT
Imaging time	5 min	13-20 min (15 min)
Matrix size	128×128 or 256×256	64×64 or 128×128
Energy window	159KeV, collect at window 20%	
		180° or 360°

Fig. 2 Imaging protocol for I-123 MIBG scintigraphy. Planar and SPECT images are acquired at 15 min (early phase) and 4 h ± 15 min (late phase) after I-123 MIBG injection. Imaging parameters and regions of interest for calculating heart-to-mediastinum ratio and washout rate are shown. SPECT, single photon emission computed tomography; MIBG, metaiodobenzylguanidine

of prohibited concomitant medications and study-drug adherence < 75% or > 120%. The SAS will include all enrolled participants who receive at least one dose of the study drug (i.e., initiate study treatment), regardless of protocol deviations or availability of efficacy assessments. Participants undergoing any intercurrent intervention will be excluded from the PPS for the primary endpoint and retained in the FAS and SAS.

Efficacy endpoints will be analyzed primarily using the PPS, which includes patients who meet all inclusion and exclusion criteria and adhere to the study protocol. The full analysis set, which includes all enrolled patients, will also be analyzed to support the robustness of the findings. Safety endpoints will be evaluated using the SAS, which comprises all enrolled patients who receive at least one dose of the study drug.

For the primary and key secondary endpoints, descriptive statistics, including the number of observations, mean, standard deviation, minimum, median, and maximum, will be calculated for the delayed HMR, WR, and early HMR at baseline and 24 weeks after tofogliflozin administration. The changes from baseline to 24 weeks will also be summarized, and the two-sided 95% confidence intervals for the mean changes will be estimated. Paired t-tests or Wilcoxon signed-rank tests will be used, as appropriate, to evaluate the significance of changes between baseline and 24 weeks. Additionally, a sensitivity analysis will be performed in patients with available endpoint data at 24 weeks.

Stratified analyses will be performed for the primary, key secondary, and secondary efficacy endpoints, as well as for the incidence of adverse events. Subgroup analyses

will be conducted on the basis of the following baseline characteristics: (1) age (≥ 65 versus [vs.] < 65 years), (2) NYHA functional class (II vs. III), (3) body mass index ([BMI] ≥ 25 vs. <25 kg/m^2), (4) delayed HMR at baseline (above vs. below the median), (5) LVEF at baseline (above vs. below the median), (6) eGFR (≥ 60 vs. <60 mL/min/1.73 m^2), (7) presence or absence of relevant comorbidities and medical history, and (8) presence or absence of concomitant medications.

The differences are considered statistically significant when $P < 0.05$. The same analysis will be performed using PPS to confirm the robustness of the results. An interim analysis is not scheduled during the study.

Discussion

Recent clinical trials have demonstrated significant cardiovascular benefits of SGLT2 inhibitors in patients with T2DM, showing substantial reductions in the risk of HF hospitalization and cardiovascular mortality [4, 20]. However, the exact mechanisms behind these favorable outcomes have not yet been fully elucidated. Accumulated evidence suggests that SGLT2 inhibitors exert cardioprotective effects through multiple pathways beyond glucose reduction [21].

SGLT2 inhibitors are strongly recommended as part of guideline-directed therapy for HFrEF [6–8]; withholding SGLT2 inhibition solely to create a concurrent control group would raise ethical concerns and erode equipoise. Accordingly, TARGET-HF was conceived as a prospective single-arm mechanistic study to interrogate whether and how SGLT2 inhibition modulates cardiac sympathetic activity—quantified by I-123 MIBG imaging—together with echocardiographic and biomarker readouts, rather than to compare effectiveness against alternative HF therapies. Prior observations also suggest potential improvements in MIBG metrics after SGLT2 inhibition, supporting the mechanistic focus of the present design [22–24].

Although tofogliflozin lacks large phase-3 HF outcome trials comparable to dapagliflozin or empagliflozin, the HF benefits of SGLT2 inhibition are considered a class effect [25], and prior clinical data suggest tofogliflozin-associated improvements in cardiac function in T2DM [26]. Moreover, tofogliflozin-specific mechanistic signals—including magnesium-linked autonomic modulation (COMT) and vascular smooth-muscle effects (SERCA2, sGC, Kv7.1)—provide a biologic basis for our mechanistic focus [27]. Given these design considerations, prior studies assessing autonomic/sympathetic function in the context of SGLT2 inhibition provide important context for our mechanistic focus.

Prior reports suggest that SGLT2 inhibition may favorably modulate autonomic/sympathetic function: a case report showed increased I-123 MIBG H/M ratio after therapy [22]; a retrospective study in T2DM with vasovagal syncope indicated improved autonomic balance [23]; and the EMBODY trial assessed empagliflozin using heart-rate variability (e.g., LF/HF) [24]. While informative, these studies used heterogeneous populations and surrogate methods. By contrast, TARGET-HF prospectively evaluates cardiac sympathetic activity with MIBG as a prespecified primary endpoint in high-risk HFrEF with T2DM.

Previously, we demonstrated that cardiac sympathetic dysfunction, as indicated by reduced MIBG uptake in patients with HFrEF due to non-ischemic dilated cardiomyopathy, reflects HF severity and prognosis, and is associated with reverse remodeling after therapeutic interventions [28]. We also reported that the pathophysiological background may involve abnormal expression of the myocardial contraction-related protein SERCA2 [29]. This cardiac sympathetic dysfunction mechanism is a key pathophysiological feature of HFrEF and contributes to disease progression and adverse outcomes [30]. Additionally, excessive sympathetic activity is closely associated with insulin resistance and hyperglycemia in T2DM [31]. Against this background, Matthews et al. previously reported that dapagliflozin, an SGLT2 inhibitor, reduced sympathetic innervation in the kidneys and hearts of high-fat diet-fed mice, and this was accompanied by decreased inflammatory cytokines [32]. These findings suggest that SGLT2 inhibition may lead to reduced sympathetic activity, possibly through anti-inflammatory effects or other mechanisms, such as improvements in hyperglycemia and insulin resistance.

Here, we expect that tofogliflozin administration will significantly improve the delayed HMR on I-123 MIBG scintigraphy, indicating reduced cardiac sympathetic activity. This effect may be mediated by several factors, including decreased insulin and leptin levels, improved insulin sensitivity, reduced blood glucose levels, and attenuated inflammation. Furthermore, the diuretic effect of SGLT2 inhibitors is likely to reduce cardiac preload and afterload, further contributing to decreased sympathetic activity [33].

Another possible mechanism of cardioprotection mediated by SGLT2 inhibitors is the optimization of cardiac energy metabolism. In the failing heart, there is a shift from glucose use to fatty acid oxidation, leading to decreased cardiac efficiency and increased oxidative stress [34]. SGLT2 inhibitors increase the production of ketone bodies, which are more efficient energy substrates for the heart than fatty acids [35]. Additionally, SGLT2 inhibition may stimulate the activity of sirtuin-1, an important regulator of glucose and lipid metabolism that interacts with hypoxia-inducible factor [36]. These metabolic effects may improve cardiac function and inhibit myocardial remodeling in patients with HFrEF.

In addition to the primary endpoint, we plan to assess various secondary endpoints that may provide further insights into the cardioprotective mechanisms of tofogliflozin. These include echocardiographic parameters of systolic and diastolic function, biomarkers reflecting neurohumoral activation, inflammation, oxidative stress, and metabolic status. We anticipate that tofogliflozin administration will lead to improvements in these parameters, consistent with our hypotheses regarding sympathetic activity and cardiac metabolism.

It is important to note that this study will focus on a specific population—patients with HFrEF and T2DM—who are at particularly high risk for adverse cardiovascular outcomes. The coexistence of these conditions is associated with complex pathophysiological interactions involving insulin resistance, chronic inflammation, and oxidative stress [37]. SGLT2 inhibitors may offer unique therapeutic benefits in this patient population by targeting multiple aspects of this network of metabolic abnormalities.

In summary, the TARGET-HF trial is expected to elucidate the multifaceted mechanisms by which tofogliflozin confers cardioprotective benefits in patients with HFrEF and T2DM. By focusing on cardiac sympathetic nerve activity using I-123 MIBG scintigraphy along with an extensive panel of biomarkers, this study aims to clarify the interplay between the metabolic, neurohumoral, and hemodynamic effects of SGLT2 inhibition. The findings will provide new insights into the pathophysiology of HFrEF in the context of T2DM and inform strategies for optimizing SGLT2 inhibitor therapy in this high-risk population.

Appendix

Study organization The study is being managed by the principal investigator (Toyoaki Murohara) and the Steering committee as an investigator-initiated clinical study. The independent data monitoring committee and the event evaluation and safety monitoring committee are organized independently from the study group. A study statistician (Miwa Okada, WDB coco Co., Ltd.) is contributing to ensure statistical accuracy.

Steering committee Toyoaki Murohara (chair, Nagoya University), Toshihisa Anzai (Hokkaido University), Junya Ako (Kitasato University), Yasushi Sakata (Osaka University), and Koichi Node (Saga University).

Independent data monitoring committee Noriyuki Suzuki (WDB coco Co., Ltd.).

Event evaluation and safety monitoring committee Hiroyuki Watada (chair, Juntendo University) and Tatsuaki Matsubara (Aichi Mizuho University).

Medical advisory Masato Odawara (Sanno Hospital).

Research Institute Nagoya University Hospital, Hokkaido University Hospital, Kitasato University Hospital, Osaka University Hospital, and Saga University Hospital.

Abbreviations

FAS	Full analysis set
HF	Heart failure
T2DM	Type 2 diabetes mellitus
HFrEF	Heart failure with reduced ejection fraction
SGLT2	Sodium-glucose cotransporter-2
MIBG	Metaiodobenzylguanidine
HMR	Heart-to-mediastinum ratio
WR	Washout rate
TARGET-HF	Tofogliflozin mechanism of Action to Retain cardiac function evaluated by I-123 MIBG scintigraphy, Echocardiography and biomarkers in T2DM patients with Heart Failure
NYHA	New York Heart Association
LVEF	Left ventricular ejection fraction
HbA1c	Hemoglobin A1c
NT-proBNP	N-terminal pro-B-type natriuretic peptide
eGFR	estimated glomerular filtration rate
GLS	Global longitudinal strain
LEHR	Low energy high resolution
LMEGP	Low-medium energy general purpose
MELP	Medium energy low penetration
SAS	Safety analysis set
SPECT	Single photon emission computed tomography
PPS	Per-protocol set
vs.	Versus
BMI	Body mass index

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Author contributions

TO: Writing–review & editing, Writing–original draft, Investigation, and Conceptualization. YK-B: Writing–review & editing, Supervision, and Conceptualization. SI: Writing–review & editing, Methodology, Data curation, and Investigation. NF: Writing–review & editing, Data curation, and Investigation. Fusako Sera: Writing–review & editing and Investigation. YI: Writing–review & editing and Investigation. AY: Writing–review & editing and Investigation. TN: Writing–review & editing and Investigation. HH: Writing–review & editing, Investigation. RM: Writing–review & editing and Investigation. TA: Writing–review & editing and Supervision. KN: Writing–review & editing and Supervision. JA: Writing–review & editing and Supervision. YS: Writing–review & editing and Supervision. TM: Writing–review & editing, Supervision, and Conceptualization.

Funding

The study is funded by Kowa Company, Ltd., but the sponsor will not be involved in the study design, data collection, analysis, or publication of the results.

Data availability

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

Declarations

Ethics approval and consent to participate

The study will be performed in accordance with the Declaration of Helsinki and the Japanese Clinical Trials Act (Japanese Clinical Trial Registry approval number: jRCTs041210022), and informed consent will be obtained from participants.

Consent for publication
Not applicable.

Competing interests
TO is affiliated with a department sponsored by Medtronic Japan Co., Ltd. TO received research grants from Pfizer Global Supply Japan Inc., Alnylam Japan K.K., and Alexion Pharmaceuticals, Inc., and lecture fees from Pfizer Global Supply Japan Inc., Novartis Pharma Co., Ltd., Astra Zeneca Co. Ltd., and Boehringer Ingelheim Japan Co., Ltd., which were not connected to this work. TN received a research grant from Mitsubishi Tanabe Pharma Corp, Roche Diagnostics K.K. and honoraria from Bayer Yakuhin, Ltd., Kyowa Kirin Co., Ltd., Viatris Pharmaceuticals Japan Inc., Nippon Boehringer Ingelheim Co., Ltd., Bristol-Myers Squibb K.K. TA received honoraria from Daiichi Sankyo Co., Ltd., Boehringer Ingelheim Japan Co., Ltd., Bayer Pharmaceutical Co., Ltd., Astra Zeneca Co. Ltd., Byer and Novartis Pharma Co., Ltd., and clinical research grant from Abott Medical Japan LLC., Otsuka Pharmaceutical Co. Ltd., Japan Lifeline Co., Ltd., Boston Scientific Co. Ltd., Boehringer Ingelheim Japan Co., Ltd., and Daiichi Sankyo Co., Ltd., and scholarship funds from Biotronik Japan Co., Ltd., Medtronic Japan Co., Ltd., Win International Co., Ltd., Medical System Network Co., Ltd., and Hokuyaku Takeyama Holdings, Inc., Terumo Co., Ltd. The other authors declare no conflict of interest.

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