




ORIGINAL ARTICLE

EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Effects of ipragliflozin on left ventricular diastolic function in patients with type 2 diabetes and heart failure with preserved ejection fraction: The EXCEED randomized controlled multicenter study

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Aim: We carried out a randomized controlled trial using ipragliflozin. We analyzed changes in diastolic function using echocardiography in patients with type 2 diabetes and heart failure with preserved ejection fraction.

Methods: We carried out an open-label, multicenter, randomized, two-arm interventional trial. A total of eligible 68 participants were randomly assigned into two groups (ipragliflozin group $n = 36$; conventional treatment group $n = 32$). Primary end-points were the change in E/e' and e' . Secondary end-points were other parameters of echocardiography, plasma NT-proBNP level, New York Heart Association class, hemoglobin A1c and blood pressure.

Results: After 24 weeks of follow up, E/e' decreased in both groups (ipragliflozin: 11.0 vs 10.4; conventional treatment 10.5 vs 10.1; multivariate-adjusted $P = 0.95$). There were no significant differences in the amount of change in E/e' , e' , echocardiography parameters, plasma NT-proBNP level, New York Heart Association class, hemoglobin A1c and blood pressure between the two groups. In the subgroup analysis, ipragliflozin treatment decreased in left ventricular mass index in patients aged ≥ 70 years and also decreased in NT-proBNP levels in patients with baseline NT-proBNP ≥ 400 pg/mL.

Conclusions: In this randomized controlled study carried out in patients with type 2 diabetes and heart failure with preserved ejection fraction, 24-week ipragliflozin treatment did not improve left ventricular diastolic function compared with conventional treatment. As the subgroup, ipragliflozin treatment decreased in left ventricular mass index in participants aged ≥ 70 years. *Geriatr Gerontol Int* 2022; 22: 298–304.

Keywords: heart failure, left ventricular diastolic function, sodium–glucose cotransporter 2 inhibitors.

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Introduction

As the population ages, the prevalence of both heart failure (HF) and diabetes mellitus is increasing.¹ HF is a life-threatening condition that progresses with repeated exacerbations and remissions. HF is also a significant complication of diabetes,^{2,3} and cases of HF associated with diabetes have been shown to have a worse life expectancy than uncomplicated cases.^{4,5} Diabetes itself remains a risk for HF hospitalization.⁶ Research has recently shown that sodium–glucose cotransporter 2 inhibitors (SGLT2i) reduce both cardiovascular disease mortality and hospitalization for HF in patients with type 2 diabetes (T2D).^{7–9} A meta-analysis found SGLT2i reduced major adverse cardiovascular events by 14% and hospitalizations for HF by 24% in patients with cardiovascular disease.¹⁰ Furthermore, it is reported that dapagliflozin reduces the worsening HF and cardiovascular death in patients with and without T2D.¹¹ These results suggest that SGLT2i have the potential to reduce the incidence or worsening of HF.

HF types are HF with reduced left ventricular ejection fraction (HFrEF) and HF with preserved left ventricular ejection fraction (HFpEF). Although there are guideline-recommended therapeutic approaches for HFrEF, effective treatment for HFpEF is currently unclear. The frequency of HFpEF has been increasing every year, and the establishment of a cure is of utmost importance.¹² Recently, empagliflozin has been reported to reduce the risk of HF hospitalization and cardiovascular death in HFpEF.¹³

Therefore, we carried out a multicenter, prospective, open-label, randomized, controlled trial to test the hypothesis that the SGLT2i, ipragliflozin, improves left ventricular diastolic function, left ventricular hypertrophy, and the degree of HF in patients with T2D and HFpEF, named the examination for cardiac function effect by echocardiography in diabetes with chronic heart failure (EXCEED).

Methods

Ethical approval

All procedures involving human participants were carried out in accordance with the ethical standards of the Osaka University Hospital Clinical Research Committee (approval number: 16399), Osaka University Clinical Research Review Committee (N18013), and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all study participants.

Study participants

The study was registered with the University Medical Information Network Clinical Trials Registry (UMIN-CTR; UMIN000027095) and the Japan Registry of Clinical Trials (jRCT; jRCTs051180139). Enrollment and follow-up evaluation took place between 1 August 2017 and 31 December 2019. Outpatients with chronic HF and T2D aged ≥ 20 years were included. The inclusion criteria were as follows: patients with T2D with HFpEF; no SGLT2i use within the past 3 months; and hemoglobin A1c (HbA1c) $\geq 7.0\%$. We defined HFpEF using the following criteria: (i) plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 125 pg/mL¹⁴ and (ii) echocardiographic measured ejection fraction (EF) $\geq 50\%$. However, for patients taking insulin, sulfonylureas, glinides or other agents that might cause severe hypoglycemia, the inclusion criteria were HbA1c $\geq 7.5\%$ for patients aged 65–75 years, and HbA1c $\geq 8.0\%$ for patients aged ≥ 75 years. The exclusion criteria

were patients with any of the following: acute exacerbation of chronic HF, stroke, acute coronary syndrome and percutaneous coronary intervention or coronary artery bypass surgery within 3 months; HF with a New York Heart Association (NYHA) functional classification IV; EF $< 50\%$ or severe valvular disease; chronic atrial fibrillation; severe hepatic dysfunction; estimated glomerular filtration rate < 30 mL/min/1.73m²; concomitant malignancy; and dementia. Patients for whom SGLT2i are contraindicated were also excluded.

Randomization and follow up

At the time of entry, the Research Electronic Data Capture (REDCap) system (<https://www.project-redcap.org/>) was used to record the data and to randomize the patients to either the ipragliflozin group or the conventional treatment group. Randomization was stratified by four criteria: facility, age (≥ 60 years or not), NT-proBNP (≥ 400 pg/mL or not) and HbA1c ($\geq 8.0\%$ or not). The treatment of the conventional treatment group did not change during the study period. Echocardiography, physical examinations, NYHA classification and blood tests were carried out at baseline, 12 weeks and 24 weeks after enrollment.

End-points

The primary end-point was the amount of change in E/e' and e' by echocardiography between baseline and 24 weeks. E indicates the early diastolic transmitral flow velocity, and e' indicates the early diastolic mitral annular velocity. Secondary end-points were the frequency of adverse events and the amount of change in the following parameters: cardiac parameters, as measured by echocardiography, plasma NT-proBNP levels, NYHA classification, HbA1c and blood pressure (BP). Furthermore, we carried out pre-determined exploratory analysis stratified by the cut-off of 70 years-of-age and 400 pg/mL of baseline plasma NT-proBNP level on the secondary outcomes. A plasma NT-proBNP level of 400 pg/mL was according to the statement from the Japanese Heart Failure Society.

Echocardiographic measurements

Echocardiography was carried out in a standard manner at each institution. The standard echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging.¹⁵ Specifically, the early diastolic (E) and atrial wave (A) velocities, and the E -wave deceleration time were measured by pulsed wave Doppler recording from the apical four-chamber view. Spectral pulsed-wave tissue Doppler-derived early diastolic velocity (e') was obtained by averaging the septal and lateral mitral annulus velocity, and the E/e' was calculated to obtain an estimate of left ventricular (LV) filling pressure. LV mass was estimated using the area-length method, and the LV mass index (LVMI) was calculated by dividing LV mass by body surface area.¹⁶ Left atrial (LA) volume was measured using the biplane Simpson's method from the apical two- and four-chamber views. We held a training session for all sonographers involved in this study to ensure that the technique was consistent. The sonographers were blinded to the patients' assignment to treatment, and the review committee for cases reviewed the image data.

Sample size calculation

The sample size for the present study was determined as follows: from the report of Verma *et al.*, we assumed a mean of 8.5 cm/s and 9.7 cm/s at baseline and 24 weeks in lateral *e'*, respectively, and a standard deviation of 1.0 cm/s of change.¹⁷ Further assuming a difference between groups of 0.6 cm/s, it was calculated that at least 44 patients in each group were required to maintain 80% power at the 5% bilateral level of significance; assuming a 10% dropout rate, the target number of cases for the study was determined to be 50 in each group.

Statistical analysis

Data are expressed as the mean ± standard deviation, and frequencies (%) for categorical variables. For the primary endpoint, an analysis of covariance was used, in which the change in *E/e'* or *e'* at 24 weeks was the dependent variable. The linear regression model included the baseline value of *E/e'* or *e'*, the ipragliflozin/control group, the allocation factor HbA1c and age. If the 24-week end-point was missing, it was supplemented with the 12-week value or baseline value using the last observation carried forward method. For the sensitivity analysis, two methods were used to check the effect of the imputation on the estimated values. First, the mixed-effects model adjusted for baseline values of *E/e'* or *e'*, age and HbA1c was used. Second, the Wilcoxon rank-sum test was used. For secondary end-points, the analysis of covariance and the mixed-effects model were used, adjusted for baseline values of age, HbA1c, NT-proBNP level and end-point as covariates. However, generalized estimating equations were used alternatively, because the NYHA classification was an ordinal variable.

R version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria) and sas version 9.4 (SAS Institute, Cary, NC, USA) were used for the statistical analysis, with a two-tailed *P* < 0.05 defined as the significance level.

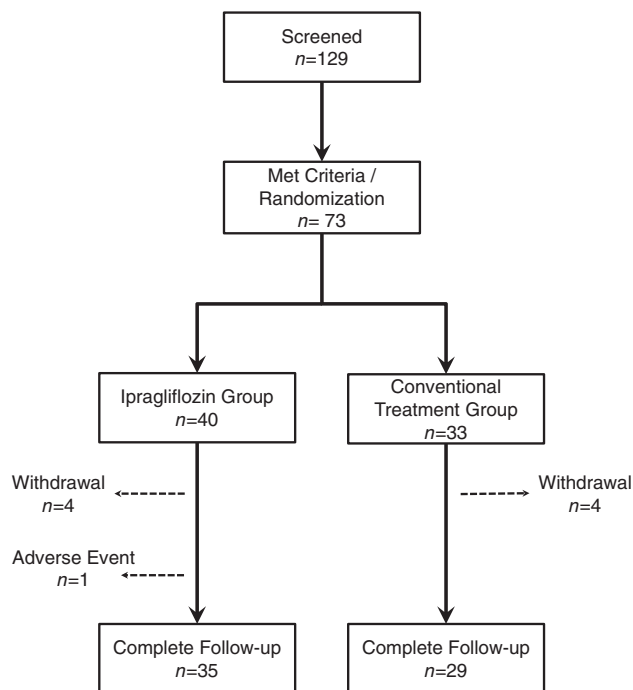


Figure 1 Patient flow.

Results

Of the 129 individuals who consented to participate in the study, 73 were randomized to each group (ipragliflozin, *n* = 40; conventional therapy, *n* = 33; Fig. 1). There was one dropout in both groups before starting the post-assignment treatment phase, bringing the total number of patients evaluated for safety analysis to 71. Including these dropouts, four patients in the ipragliflozin group dropped out of the study during the 24-week follow-up period, and one patient discontinued treatment due to an adverse event (frequent urination). Four patients in the conventional treatment group dropped out of the study. However, we complemented the data at 24 weeks using the last observation carried forward method for one patient in the ipragliflozin group and three patients in the conventional treatment group. A total of 68 patients, 36 in the ipragliflozin group and 32 in the conventional treatment group, were included in the final analysis.

Clinical characteristics of the study participants and the baseline data

The age range of the participants was 51 to 85 years. Table 1 shows the participant characteristics and baseline data. As we stratified facility, age, NT-proBNP and HbA1c at random

Table 1 Baseline characteristics

	Ipragliflozin group (<i>n</i> = 36)	Conventional treatment group (<i>n</i> = 32)	<i>P</i> -value
Sex (male/female)	22/14	19/13	0.88
Age (years)	71.9 ± 8.0	70.3 ± 8.5	0.38
Height (cm)	157.3 ± 10.3	163.7 ± 9.2	0.017
Weight (kg)	63.3 ± 11.2	66.9 ± 15.5	0.38
Systolic BP (mmHg)	136.1 ± 23.0	135.5 ± 22.2	0.90
Diastolic BP (mmHg)	73.1 ± 12.4	70.3 ± 11.6	0.29
Heart rate (b.p.m.)	75.7 ± 9.8	78.3 ± 16.9	0.97
HbA1c (%)	8.1 ± 1.0	7.9 ± 1.1	0.26
Cr (mg/dL)	1.0 ± 0.4	0.9 ± 0.3	0.63
BUN (mg/dL)	18.9 ± 7.0	16.6 ± 6.8	0.17
NT-proBNP (pg/mL)	315.0 ± 260.0	334.4 ± 228.7	0.43
<i>E/e'</i> (cm/s)	11.0 ± 2.8	10.5 ± 4.4	0.36
<i>e'</i> (cm/s)	6.0 ± 1.9	6.6 ± 1.9	0.098
LVMi (g/m ²)	116.9 ± 41.2	125.5 ± 69.6	0.63
LVEF (%)	60.9 ± 7.0	60.4 ± 8.2	0.83
IVC (mm)	11.9 ± 3.1	12.9 ± 3.6	0.33
NYHA class			0.63
I	83.3%	87.5%	
II	16.7%	12.5%	
III	0%	0%	
IV	0%	0%	

BP, blood pressure; BUN, blood urea nitrogen; Cr, creatinine; *E/e'*, ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity; HbA1c, hemoglobin A1c; IVC, inferior vena cava; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

assignment, there were no differences between groups for all laboratory items, except for height.

Primary end-point

In the ipragliflozin group, E/e' was 11.0 ± 2.8 at baseline and 10.4 ± 2.8 at 24 weeks, whereas in the conventional treatment group, E/e' at baseline and 24 weeks was 10.5 ± 4.4 and 10.1 ± 3.6 , respectively. After multivariate adjustment, the difference between the groups was -0.04 (95% confidence interval [CI] -1.3 – 1.2 , $P = 0.95$; Fig. 2a). There was no significant difference between the groups when limiting the participants with E/e'

from eight to 18. In the ipragliflozin group, e' was 6.0 ± 1.9 cm/s at baseline and 5.8 ± 1.7 cm/s at 24 weeks, whereas in the conventional treatment group, e' at baseline and 24 weeks was 6.6 ± 1.9 cm/s and 6.6 ± 1.7 cm/s, respectively. The difference between the groups after multivariate adjustment was -0.3 cm/s (95% CI -0.9 – 0.3 , $P = 0.33$; Fig. 2b).

Secondary end-points

Table 2 shows the changes in echocardiographic parameters at baseline and 24 weeks, and after multivariate adjustment for each group. There was no significant difference between groups at

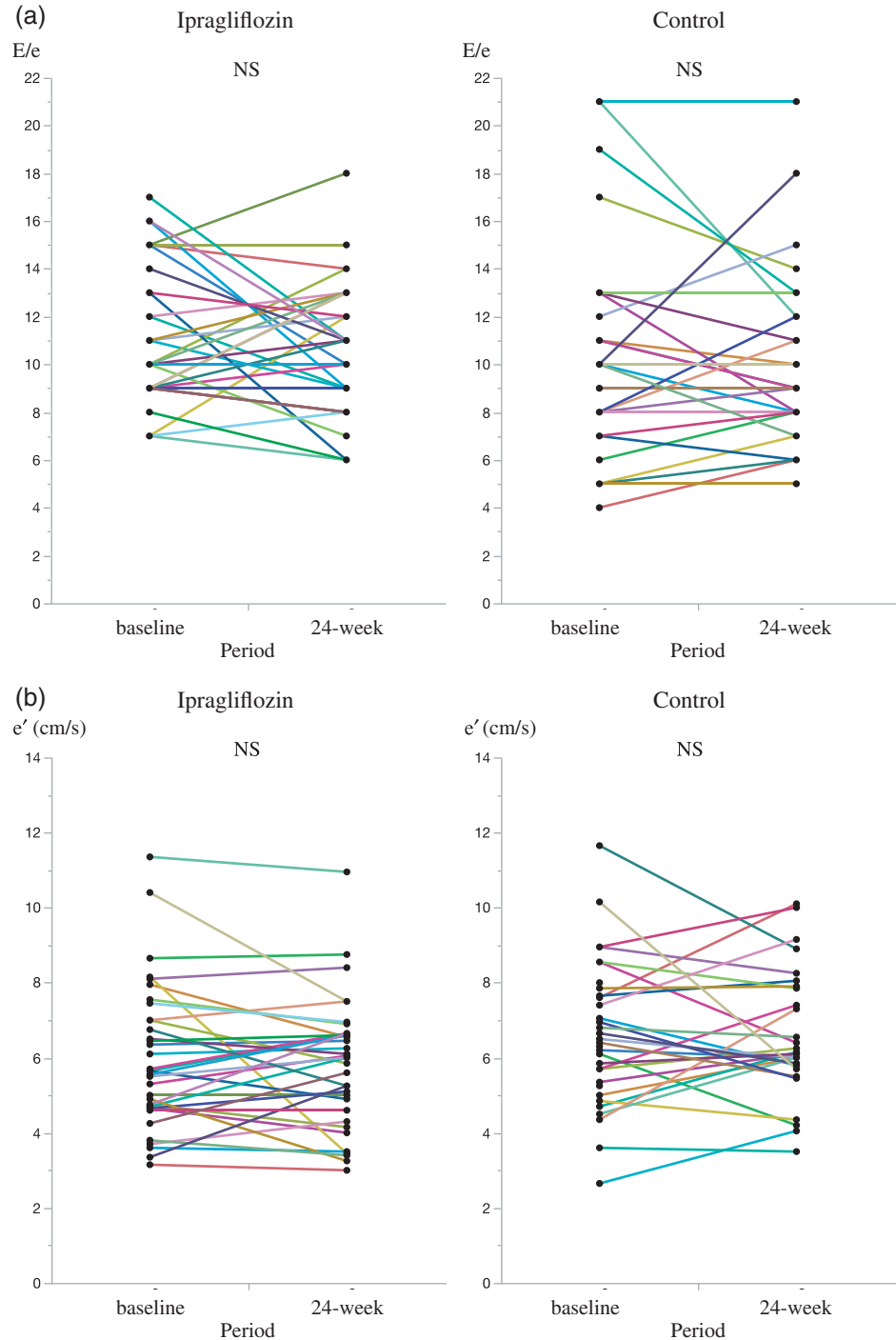


Figure 2 Changes in diastolic function measured by echocardiography between baseline and 24-week treatment. NS, not significant.

Table 2 Changes in echocardiographic parameters in each group

	Ipragliflozin group		Conventional treatment group		Multivariate adjusted difference (95% CI)	P-value
	Baseline	24-weeks	Baseline	24-weeks		
LVMi	116.9 ± 41.2	107.0 ± 39.8	125.5 ± 69.6	126.1 ± 65.5	-10.2 (-28.4, 8.9)	0.27
LAD	36.4 ± 8.1	36.6 ± 5.8	38.2 ± 6.6	37.2 ± 7.5	0.03 (-2.4, 2.4)	0.98
LAV	58.5 ± 21.1	50.9 ± 17.6	56.2 ± 18.4	60.0 ± 22.8	-7.1 (-14.4, 0.2)	0.06
LVEF	60.9 ± 7.0	61.8 ± 6.3	60.4 ± 8.2	59.7 ± 10.2	1.3 (-1.4, 4.0)	0.34
LVEDV	91.0 ± 33.9	91.9 ± 32.1	93.6 ± 46.5	98.6 ± 39.2	-4.9 (-14.9, 5.1)	0.33
LVESV	35.3 ± 15.7	35.6 ± 14.6	41.0 ± 27.9	41.8 ± 23.9	-1.7 (-6.4, 3.1)	0.48
E/A	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.3	0.8 ± 0.3	-0.04 (-0.12, 0.04)	0.28
IVC	11.9 ± 3.1	11.9 ± 3.0	12.9 ± 3.6	11.8 ± 4.3	0.5 (-0.9, 1.9)	0.47
BUN	18.9 ± 7.0	20.6 ± 7.2	16.6 ± 6.8	19.6 ± 8.2	0.6 (-0.7, 1.9)	0.39

BUN, blood urea nitrogen; CI, confidence interval; E/A, ratio of early to late left ventricular inflow velocity; IVC, inferior vena cava; LAD, left atrial diameter; LAV, left atrial volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMi, left ventricular mass index.

24 weeks for any of the items. However, when we carried out subgroup analysis limiting the participants aged ≥70 years (*n* = 38), there was a significant reduction in LVMi in the ipragliflozin group (Supplementary Table S1; Fig. 3). The difference between groups after multivariate adjustment was -19.9 g/m² (95% CI -38.0 to -1.75, *P* = 0.033).

At baseline, the NT-proBNP levels were 315 ± 260.0 pg/mL in the ipragliflozin group and 334.4 ± 228.7 pg/mL in the control group. At 24 weeks, the difference after multivariate adjustment was -118.9 pg/mL (95% CI -278.4-40.6, *P* = 0.14). In a stratified analysis with a cut-off of ≥400 pg/mL at the baseline (*n* = 16), NT-proBNP decreased to a greater extent in the ipragliflozin group (multivariate adjustment difference: -690.2 pg/mL [95% CI -1224.7 to -155.7, *P* = 0.016]).

The change in NYHA functional classification between groups at 24 weeks was 0.311 (95% CI -1.70-2.32, *P* = 0.76) after multivariate adjustment. The HbA1c difference after multivariate adjustment was -0.068% (95% CI -0.40-0.27, *P* = 0.69) at 24 weeks. Also, the change in systolic BP after multivariate

adjustment was 2.5 mmHg (95% CI -5.8-10.8, *P* = 0.55), and the change in diastolic BP was -1.4 mmHg (95% CI -7.2-4.4, *P* = 0.63), showing no difference between groups.

Side-effects and adverse events

Of the safety analysis dataset, two of the 39 patients in the ipragliflozin group experienced side-effects: eczema (*n* = 1) and frequent urination (*n* = 1).

A total of 10 adverse events occurred in eight of the 39 ipragliflozin patients, and 23 adverse events occurred in eight of the 32 conventional treatment patients. The most common adverse event in both groups was acute upper respiratory inflammation: ipragliflozin group, one event (*n* = 1); control group, five events (*n* = 4). Supplementary Table 2 shows the list of serious adverse events. One patient (2 events) experienced serious adverse events in the ipragliflozin group, and five patients (8 events) experienced serious adverse events in the conventional treatment group.

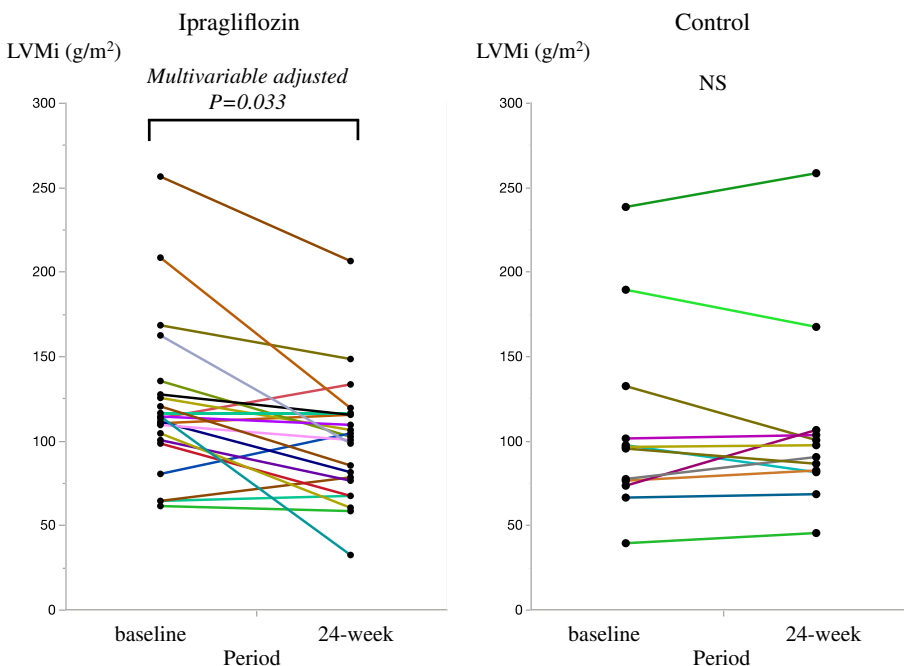


Figure 3 Changes in left ventricle mass index between baseline and 24-week in a subgroup limiting the participants aged ≥70 years.

Discussion

The present study was a randomized controlled, open-label, multicenter trial using ipragliflozin in older T2D patients with HFpEF. As the result, ipragliflozin did not improve the primary end-point of LV diastolic function or the secondary end-points of echocardiographic parameters, plasma NT-proBNP levels, NYHA classification, HbA1c levels and BP compared with conventional treatment. However, in the subgroup analysis, there was a decrease in LVMI in participants aged ≥ 70 years, and a decrease in NT-proBNP levels in participants with baseline NT-proBNP ≥ 400 pg/mL. This shows that ipragliflozin might contribute to a regression of LV hypertrophy or a decrease in NT-proBNP in particular cases.

Cell experiments with empagliflozin have reported that it improved LV diastolic function by promoting phosphorylation of cardiomyocyte myofibers in human and rat myocardium.¹⁸ Verma *et al.* also found that 3 months of empagliflozin treatment was associated with a significant reduction in LVMI.¹⁷ Matsutani *et al.* reported that 3 months of canagliflozin treatment significantly reduced E/e' .¹⁹ Another study of 58 Japanese T2D patients showed that 6 months of dapagliflozin treatment significantly improved the E/e' and LVMI.²⁰ In a placebo-controlled trial, 6 months of empagliflozin treatment in T2D patients with coronary artery disease and EF $>30\%$ significantly reduced LVMI.²¹ Furthermore, canagliflozin significantly reduced NT-proBNP levels at 2 years.²² Although it is difficult to definitively conclude, we can assume that SGLT2i tend to improve LVMI and E/e' .

There are a few possible reasons why we could not achieve a clear improvement in E/e' or e' with ipragliflozin in the present study. The intervention period of 24 weeks was not sufficient. In the HFpEF subanalysis of the DECLARE-TIMI 58 study, the preventive effect of SGLT2i on HF hospitalization was seen after 1 year of treatment.²³ Also, sitagliptin showed a reduction in E/e' with a 2-year follow-up period.²⁴ Therefore, further long-term studies are required to determine the effect on LV diastolic function.

The present study showed a significant reduction in LVMI in the older subgroup. The EMPA-HEART CardioLink-6 Randomized Clinical Trial reports that empagliflozin significantly reduces LVMI in 6-month treatment.²¹ The DAPA-LVH trial reports that dapagliflozin reduces LV mass in 1-year treatment.²⁵ The mechanism of SGLT2i-induced reductions in LV mass might involve a decrease in cardiomyocyte volume, changes in interstitial water content, or both. However, the precise mechanism is not clear. The proposed mechanisms of the preventive effect of SGLT2i on HF hospitalization are as follows: inhibition of kidney hyperfiltration, improvement of chronic inflammation, reduction of serum uric acid level, inhibition of sympathetic nerve activity, weight loss, elevation of hematocrit, elevation of ketone bodies and inhibition of Na^+/H^+ exchanger.^{26,27}

The present study had limitations. First, there might be selection bias on the etiology of HF, because participants with atrial fibrillation and valvular disease were excluded. Second, all participants were Japanese, and therefore these results might not be applicable to people of other ethnicities. Third, we calculated the number of eligible patients to be 50 in each group for sufficient statistical power. However, the number of cases that met the criteria was small. Fourth, we carried out echocardiography at each institution. Fifth, antihypertensive treatment might have affected E/e' . Finally, the intervention period was limited. A more extended period and multiple cardiac function measurements could have clarified the effect of ipragliflozin.

The present randomized controlled trial carried out in patients with T2D mean aged 71 years with HFpEF could not identify

ipragliflozin's superiority on LV diastolic function. However, our study showed that 6 months of ipragliflozin could be safely administered in this population. Furthermore, ipragliflozin treatment decreased in LVMI in participants aged ≥ 70 years, and also decreased in NT-proBNP levels in participants with baseline NT-proBNP ≥ 400 pg/mL. It is well known that the management of HFpEF is challenging.^{28,29} Therefore, further endeavors toward the improved treatment of HFpEF patients is essential, and progress is expected.

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Disclosure statement

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Data Availability Statement

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

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Appendix S1. The EXCEED Study Investigators

Supplementary Table S1 Changes in echocardiographic parameters in each subgroup

Supplementary Table S2 Serious adverse events

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