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Impact of baseline left ventricular ejection fraction and body mass index on the effect of 24-week Ipragliflozin treatment on left ventricular diastolic function in patients with type 2 diabetes and chronic kidney disease: insights from the PROCEED trial

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Abstract

Background Sodium-glucose co-transporter 2 (SGLT2) inhibitors are important for treating patients with preserved left ventricular (LV) ejection fraction (LVEF). Several studies have assessed the effects of SGLT2 inhibitors on LV diastolic function, with conflicting results. In this sub-analysis of the Program of Ipragliflozin for Endothelial Dysfunction in Chronic Kidney Disease and Type 2 Diabetes (PROCEED) trial—including patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD)—we examined the effect of ipragliflozin compared with non-SGLT2 inhibitor standard therapy (control) on changes in the maximum early diastolic velocity to average early diastolic peak velocity (E/e') ratio (an index of LV diastolic function) via echocardiography.

Methods Of the entire PROCEED trial dataset, 57 participants (ipragliflozin group, n = 28; control group, n = 29) with available echocardiography data at baseline and 24 weeks were included. The primary endpoint was the change in the E/e' ratio from baseline to 24 weeks. The effect of SGLT2 inhibitors on the endpoint was stratified by baseline LVEF, body mass index (BMI), N-terminal pro-brain natriuretic peptide (NT-proBNP) level, estimated glomerular filtration rate (eGFR), and urine albumin-to-creatinine ratio (UACR).

Results No significant difference in the E/e' ratio changes was observed between the ipragliflozin and control groups (group difference: − 0.82 [95% CI: − 2.44 to 0.81]; $P = 0.317$). The E/e' ratio was unaffected by baseline NT-proBNP, eGFR, and UACR levels. However, ipragliflozin significantly reduced the E/e' ratio in patients with LVEF ≥ 60% (n = 21, group difference: − 1.42 [− 2.76 to − 0.08]; $P = 0.038$) or BMI ≥ 25 kg/m^2 (n = 19, group difference: − 1.95 [− 3.56 to − 0.34];

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$P = 0.020$), but not in those with LVEF < 60% (n = 7, group difference: 1.83 [− 4.48 to 8.14]; $P = 0.527$) or BMI < 25 kg/m^2 (n = 9, group difference: 1.34 [− 1.65 to 4.34]; $P = 0.363$). Significant interactions were noted between patients with LVEF ≥ 60% and < 60% ($P_{\text{for interaction}=}0.048$) and BMI ≥ 25 kg/m^2 and < 25 kg/m^2 ($P_{\text{for interaction}=}0.016$).

Conclusions In subgroups with higher LVEF and BMI, ipragliflozin improved diastolic function more than standard treatment. These results may partly support the beneficial effect of SGLT2 inhibitors on LV diastolic performance.

Keywords Chronic kidney disease, Echocardiography, Ipragliflozin, Left ventricular diastolic function, Type 2 diabetes mellitus

Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, a class of medications initially developed for managing type 2 diabetes mellitus (T2DM), have demonstrated cardiovascular benefits beyond their glycaemic control [1]. Recent clinical trials and observational studies suggest that SGLT2 inhibitors may protect against the development or worsening of heart failure [2–6] and reduce rehospitalisation rates in patients with heart failure with preserved ejection fraction (HFpEF) [7, 8]. Consequently, SGLT2 inhibitors are now recommended for use in patients with heart failure, irrespective of left ventricular (LV) ejection fraction (LVEF) values [9].

The mechanisms underlying these effects are multifactorial [10–16]; including metabolic efficiency, reduced cardiac preload and afterload, attenuated myocardial fibrosis, and positive renal effects. SGLT2 inhibitors may also exert pleotropic effects—such as anti-inflammatory actions and inhibition of lipid accumulation [17, 18]—potentially benefiting coronary arteries (e.g., by inhibiting restenosis) [19]. Considering that SGLT2 inhibitors can reduce re-hospitalisation rates among patients with HFpEF [7, 8], their effects on LV diastolic function are also of interest. However, there is still little evidence of SGLT2 expression in cardiomyocytes and its regulatory role in systolic and diastolic function [20]. Moreover, clinical studies regarding the effects of SGLT2 inhibitors on LV diastolic function have yielded mixed results; many have reported a positive effect on LV diastolic function [21–26], whereas others have reported little or no effect [27]. The results may have been influenced by the type of SGLT2 inhibitor, duration of administration, target disease, and method of assessing LV diastolic performance.

Patients with diabetes and chronic kidney disease (CKD) are reported to exhibit frequent LV diastolic dysfunction, and the complications of LV diastolic dysfunction are reported to have an impact on prognosis [28, 29]. We previously conducted the Program of Ipragliflozin for Endothelial Dysfunction in Chronic Kidney Disease and Type 2 Diabetes (PROCEED) trial to evaluate vascular endothelial function in patients with T2DM and CKD treated with ipragliflozin for 24 weeks [30]. In this subanalysis of the PROCEED trial, we sought to investigate the effects of ipragliflozin on LV diastolic function using echocardiography.

Methods

Study design and patients

We conducted a post hoc analysis of the PROCEED trial, a prospective, multicentre, open-label, randomised controlled trial across 11 Japanese sites. This investigator-initiated study was primarily aimed to evaluate the effect of 24-week ipragliflozin treatment on vascular endothelial dysfunction, assessed via reactive hyperaemia index (RHI), in patients with T2DM and CKD. The rationale, design, inclusion and exclusion criteria, and primary results of the trial have been previously outlined [30, 31].

This trial included patients aged ≥ 30 years who had T2DM with glycated haemoglobin levels ranging from 6.0 to 9.0%, established CKD with an estimated glomerular filtration rate (eGFR) of ≥ 30 mL/min/1.73 m^2 but < 60 mL/min/1.73 m^2 and/or urine albumin-to-creatinine ratio (UACR) of ≥ 30 mg/g creatinine, and vascular endothelial dysfunction with an RHI < 2.10. Patients with type 1 diabetes mellitus (DM) and a history of clinically apparent atherosclerotic cardiovascular diseases—including coronary artery disease (CAD), stroke, peripheral artery disease, and symptomatic carotid artery stenosis—were excluded if they had been prescribed SGLT2 inhibitors within 3 months before the eligibility assessment. Patients with malignancies were excluded from the present study. In the PROCEED trial, no restrictions were set on body mass index (BMI) or N-terminal pro-brain natriuretic peptide (NT-proBNP) values.

Between March 2020 and August 2021, 111 eligible patients were randomly assigned to receive either ipragliflozin (ipragliflozin group) or non-SGLT2 inhibitor (control group) treatment at a 1:1 ratio. In total, 108 patients (69 males and 39 females; mean age: 69.0 ± 11.1 years) were included in the final analysis (ipragliflozin group, n = 53; control group, n = 55). In the ipragliflozin group, ipragliflozin treatment was initiated at a daily dose of 50 mg alongside the existing therapy. If the individualised target specified by the Japanese Treatment Recommendations for Diabetes [32] was not met (haemoglobin A1c ≥ 7.0%), the dose was increased to 100 mg once daily. Treatment decisions were at the discretion of

the attending physician. In the control group, patients maintained their background therapy provided their blood glucose levels remained within target for the therapeutic goal.

The PROCEED trial protocol was approved by the Saga University Clinical Research Review Board (Approval No. C20191201), and conducted with strict adherence to the principles of the Declaration of Helsinki and Clinical Trial Act of Japan. All participants provided written informed consent for study participation after receiving complete explanations of the study protocol.

Echocardiographic assessment

Echocardiography was not a mandatory examination in the PROCEED trial, and no specific selection criteria were applied. The trial secretariat encouraged that the test should be carried out when possible; however, the final decision rested with the attending physician at each participating facility. Finally, echocardiographic studies—including LV diastolic function at baseline and 24 weeks—were performed in 57 of 108 enrolled patients (ipragliflozin group: n = 28; control group: n = 29, Fig. 1).

Echocardiography was conducted at each participating institution before and 24 weeks after treatment randomisation. All recordings and measurements were conducted in accordance with the American Society of Echocardiography guidelines, with analysts blinded to study-arm allocation [33]. LVEF and left atrial volume (LAV) were measured and calculated from the apical two- and four-chamber views using the biplane disk method. For the LAV, the LAV index (LAVi) was corrected for body surface area. Trans-mitral flow velocity was measured from either the apical long- or four-chamber perspective and maximum early diastolic velocity (E) was recorded. The velocity pattern of the mitral annular motion was recorded from an apical four-chamber perspective. The specimens were positioned at the septal and lateral aspects of the mitral annulus and quantified using pulsed tissue Doppler echocardiography. The average of the early diastolic (e') peak velocities at the septal and lateral

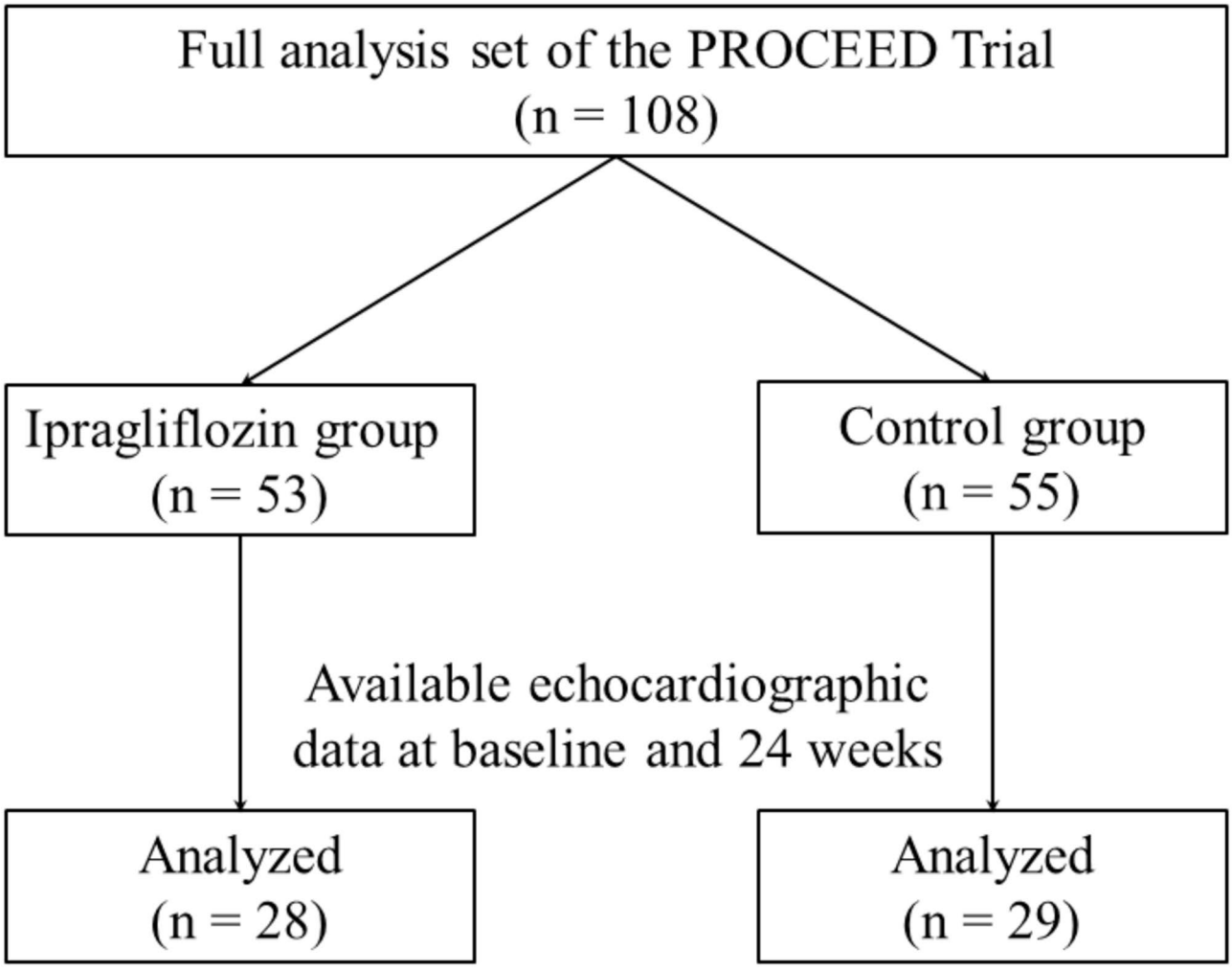

Fig. 1 Study flow chart

sides was computed; thereafter, the maximum early diastolic velocity to average early diastolic peak velocity (E/e') ratio was calculated. Typically, an elevation in e' is beneficial, indicating enhanced ventricular relaxation. A normal E/e' ratio at the lateral or septal sides is considered in the range of < 12 to 15, and a larger E/e' signifies increased LV filling pressures, which are associated with diastolic dysfunction [34].

Laboratory examination

Blood and urine samples were collected at baseline and 24 weeks post-treatment. Among the biomarkers adopted in this sub-analysis, haemoglobin (g/dL), eGFR (mL/min/1.73 m^2), and UACR (mg/g Cre) using spot urine collection were measured at each institution. The NT-proBNP (pg/mL) and procollagen III peptide (P-III-P, ng/mL) levels were recorded as prespecified measures at the central laboratory of SRL Inc. (Tokyo, Japan) [31]. P-III-P is a marker of liver fibrosis; however, it is also a potential marker of myocardial fibrosis [35], and was adopted as such in this study.

Assessments in the present sub-analysis

The changes in echocardiographic parameters—including LAVi, LVEF, E, e', and E/e' ratio—from baseline to 24 weeks were compared in the ipragliflozin and control groups. During echocardiography, the following parameters are generally used to evaluate LV diastolic function: E/A, pressure gradient from tricuspid regurgitation, LAVi, and E/e' ratio [34]. However, the data registered in the PROCEED study included only the LAVi and E/e' ratio [31]. LAVi is an item measured by tracing the left atrium, and there is a possibility of variation in that the measurement is somewhat difficult; conversely, the E/e' ratio is considered to be a simple index with little variation that can be easily obtained [34]. The change in E/e' ratio was the main finding of LV diastolic function assessment and this was assessed according to the parameters at baseline, including LVEF, BMI, NT-proBNP, eGFR, and UACR. Median values were used as cut-off values for NT-proBNP, while a BMI of 25 kg/m^2, eGFR of 60 mL/min/1.73m^2, and UACR of 30 mg/g Cr were the treatment targets used, obtained from the Japanese diabetes guidelines [32]. Regarding LVEF, many patients were comparatively well retained in the present study; an LVEF of 60%, which was used as a clinical index in our previously study [26], was also used in this study. Furthermore, differences in the following markers from baseline to 24 weeks were measured and adopted to assess the potential mechanisms responsible for the changes in LV diastolic function: blood pressure, BMI, biochemical and echocardiographic markers, and RHI. The RHI was the primary endpoint of the PROCEED trial, and its assessment was described in a previous study [31].

Statistical analyses

Continuous variables were summarised as means ± standard deviations or medians (interquartile ranges), depending on the variables' frequency distributions; categorical variables were presented as frequencies and percentages. The baseline characteristics were summarised using descriptive statistics. Chance imbalances in baseline characteristics between the two groups were expressed using the absolute standardised mean difference (ASMD). The baseline-adjusted least-squares mean and their 95% confidence intervals (CIs) were estimated using analysis of covariance to compare treatment effects between the two groups. The baseline E/e' ratio was included as a covariate factor. Analyses using inverse probability weighting based on the propensity scores were also performed to adjust for variables with modest group differences, defined as ASMD > 0.2. Spearman correlation coefficients were calculated to examine correlations between changes in the E/e' ratio from baseline to 24 weeks and several clinical factors. Data were analysed using R 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). All reported probability values were two-sided, and statistical significance was set at $P < 0.05$.

Results

Characteristics of patients in the two groups

Background demographics and clinical characteristics, including laboratory and echocardiographic parameters, are presented in Table 1. Overall, the mean age was 69 years; 61.4% of the cohort were male, 82.5% had hypertension, and 68.4% were taking renin-angiotensin system inhibitors. Regarding diabetes medications, no patients were taking glucagon-like peptide 1 (GLP-1) agonists in this sub-analysis. Modest between-groups differences (ASMD > 0.2) were observed for several clinical parameters including age, male sex, BMI, systolic blood pressure, use of statins/insulin/sulfonylureas/thiazolidinediones, eGFR, UACR, HbA1c, and echocardiographic measures of early diastolic trans-mitral flow; e'; and E/e' ratio.

Changes in echocardiographic parameters

Changes in echocardiographic parameters from baseline to 24 weeks are shown in Table 2. Changes in LAVi and LVEF did not differ between the two groups. For E/e' parameters, changes in the early diastolic trans-mitral flow and e' were not different between the two groups. Thus, the changes in the E/e' ratio were − 0.93 ± 3.15 and 0.21 ± 3.17 in the ipragliflozin and control groups, respectively (group difference: − 0.82 [95% CI: − 2.44 to 0.81]; $P = 0.317$).

Table 1 Clinical characteristics of patients in the two treatment groups

Clinical parameters	Overall	Ipragliflozin	Control	ASMD
Number	57	28	29	
Age (years)	69 ± 12	66 ± 14	71 ± 10	0.43
Male	35 (61.4)	19 (67.9)	16 (55.2)	0.26
Body mass index (kg/m^2)	25.4 ± 4.2	26.3 ± 4.8	24.5 ± 3.5	0.43
Systolic blood pressure (mm Hg)	136 ± 15	134 ± 16	139 ± 15	0.35
Diastolic blood pressure (mm Hg)	77 ± 10	78 ± 8	77 ± 11	0.15
Coronary risk factors				
Current smoker	14 (24.6)	7 (25.0)	7 (24.1)	0.02
Hypertension	47 (82.5)	24 (85.7)	23 (79.3)	0.17
Dyslipidaemia	43 (75.4)	21 (75.0)	22 (75.9)	0.02
Medications (%)				
Non-diabetes				
RAS inhibitors	39 (68.4)	19 (67.9)	20 (69.0)	0.02
Beta blocker	10 (17.5)	6 (21.4)	4 (13.8)	0.20
Statin	29 (50.9)	12 (42.9)	17 (58.6)	0.32
Diabetes				
Insulin	1 (1.8)	1 (3.6)	0 (0.0)	0.27
Sulfonylurea	9 (15.8)	3 (10.7)	6 (20.7)	0.28
DPP-4 inhibitor	36 (63.2)	17 (60.7)	19 (65.5)	0.10
GLP-1 receptor agonist	0 (0.0)	0 (0.0)	0 (0.0)	0.00
Thiazolidinedione	8 (14.0)	5 (17.9)	3 (10.3)	0.22
Laboratory data				
eGFR (mL/min/1.73m^2)	59.4 ± 17.8	57.4 ± 21.0	61.3 ± 14.1	0.22
UACR (mg/g Cr)	253 ± 474	360 ± 634	154 ± 216	0.44
HbA1c (%)	7.2 ± 0.9	7.3 ± 0.9	7.1 ± 0.8	0.22
NT-proBNP (pg/mL)	112 ± 174	129 ± 236	95 ± 79	0.20
Echocardiography				
LAVi (mL/m^2)	29.6 ± 12.2	29.6 ± 14.7	29.5 ± 9.4	0.01
LVEF (%)	64 ± 8	63 ± 8	64 ± 8	0.11
TMF-E (cm/s)	62.3 ± 16.3	65.4 ± 20.3	59.4 ± 10.6	0.37
e' (cm/s)	7.5 ± 2.5	7.2 ± 2.0	7.7 ± 2.8	0.21
E/e' ratio	9.1 ± 3.2	9.6 ± 3.5	8.6 ± 2.9	0.33

Data are expressed as the mean ± standard deviations or frequencies (percentages)

ASMD, absolute standardised mean difference; DPP-4, dipeptidyl peptidase-4; E/e', maximum early diastolic velocity to average early diastolic peak velocity; e', average of the early diastolic mitral annular velocity; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; LAVi, left atrial volume index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; RAS, renin–angiotensin system; TMF-E, early diastolic trans-mitral flow; UACR, urine albumin-to-creatinine ratio

Effect of ipragliflozin on the change in E/e' ratio according to the clinical parameters

The effect of ipragliflozin on the change in the E/e' ratio was examined by classifying patients by baseline LVEF (60%), BMI (25 kg/m^2), NT-proBNP (median 61.00 pg/mL), eGFR (60 mL/min/1.73 m^2), and UACR (30 mg/g Cre; Fig. 2). Ipragliflozin significantly reduced the E/e' ratio in patients with an LVEF ≥ 60% ($P = 0.038$), whereas no significant effect was observed in patients with an LVEF < 60% ($P = 0.527$). Moreover, ipragliflozin significantly reduced the E/e' ratio in patients with a BMI ≥ 25 kg/m^2 ($P = 0.020$), whereas no significant effect was observed in patients with a BMI < 25 kg/m^2 ($P = 0.363$). The baseline values for other clinical parameters, including NT-proBNP, eGFR, and UACR, did not affect changes in the E/e' ratio with or without ipragliflozin.

Table 2 Changes in parameters from baseline to 24 weeks in each sub-group after adjusting for the baseline values of each variable

Outcome	Ipragliflozin group	Control group	Group difference (95% CI)	*P*-value
Change in LAVi (mL/m^2)	0.28 ± 9.03	1.79 ± 9.42	− 1.46 (− 5.31 to 2.40)	0.452
Change in LVEF (%)	1.84 ± 6.18	0.66 ± 7.02	0.83 (− 2.29 to 3.96)	0.595
Change in TMF-E (cm/s)	− 1.63 ± 16.32	0.67 ± 10.24	− 1.26 (− 8.50 to 5.98)	0.728
Change in e' (cm/s)	0.71 ± 1.89	− 0.38 ± 3.56	0.71 (− 0.49 to 1.92)	0.239
Change in E/e' ratio	− 0.93 ± 3.15	0.21 ± 3.17	− 0.82 (− 2.44 to 0.81)	0.317

Data are expressed as the mean ± standard deviation

CI, confidence interval; E/e', maximum early diastolic velocity to average early diastolic peak velocity; e', average of the early diastolic peak velocity; LAVi, left atrial volume index; LVEF, left ventricular ejection fraction; TMF-E, early diastolic trans-mitral flow

Effect of LVEF on changes in the E/e' ratio

Patients in the ipragliflozin and control groups classified by LVEF were as follows: 21 and 24 patients had an LVEF ≥ 60% in the ipragliflozin and control groups, respectively; and seven and five patients had an LVEF < 60% in the ipragliflozin and control groups, respectively. The changes in the E/e' ratio differed between patients with an LVEF ≥ 60% and < 60% ($P = 0.048$; Fig. 2). Post hoc analyses with restricted cubic splines with three knots showed that the association between baseline levels of LVEF and the change in the E/e' ratio was non-linear and significantly different between the treatment groups ($P_{\text{for interaction}} = 0.008$; Fig. 3A). The correlation between changes in the E/e' ratio and clinical parameters stratified by a baseline level LVEF of 60% in the ipragliflozin group is shown in Table 3. The change in the E/e' ratio was associated with systolic and diastolic blood pressure (BP) changes in patients with an LVEF ≥ 60% (n = 21; r = 0.456, $P = 0.038$

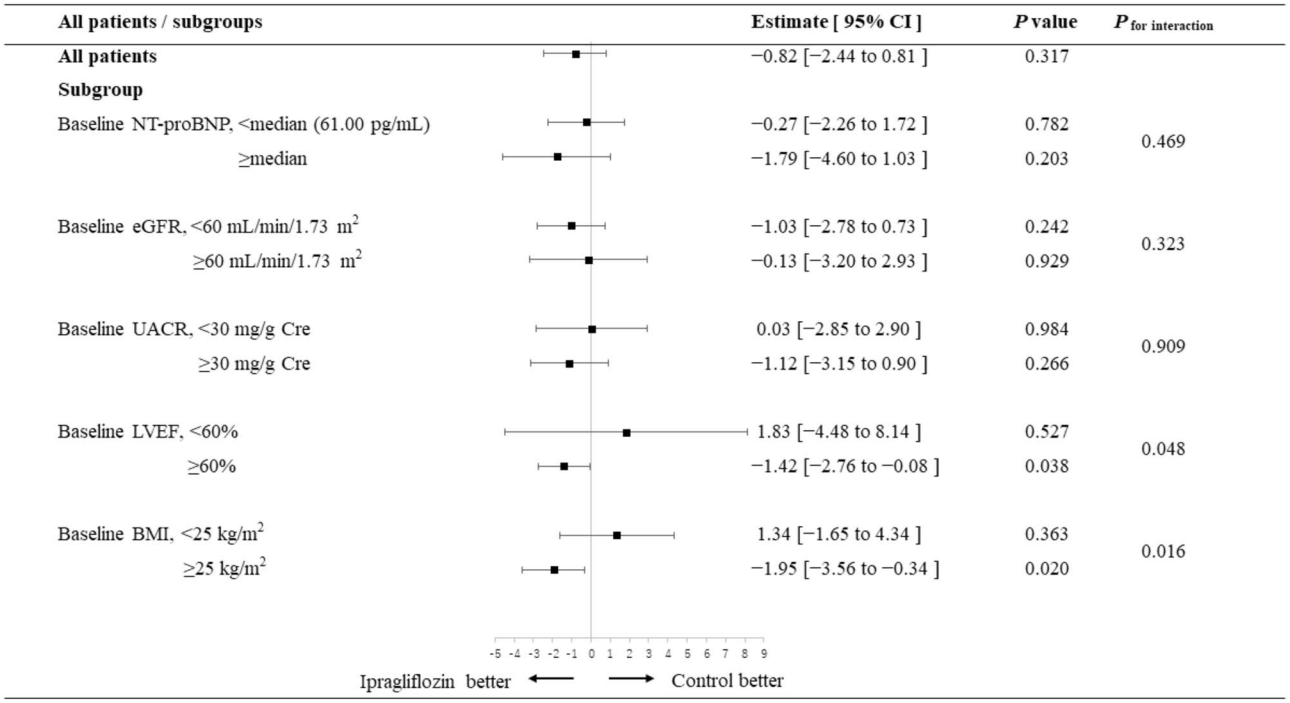

Fig. 2 Sub-group analyses of the difference in the E/e' ratio on echocardiography. Ipragliflozin significantly reduced the E/e' ratio in patients with an LVEF ≥ 60% ($P = 0.038$), whereas no significant effect was observed in patients with an LVEF < 60% ($P = 0.527$). Moreover, ipragliflozin significantly reduced the E/e' ratio in patients with a BMI ≥ 25 kg/m^2 ($P = 0.020$), whereas no significant effect was observed in patients with a BMI < 25 kg/m^2 ($P = 0.363$). Other factors did not influence the change in the E/e' ratio. BMI, body mass index; CI, confidence interval; E/e', maximum early diastolic velocity to average early diastolic peak velocity; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; UACR, urine albumin-to-creatinine ratio

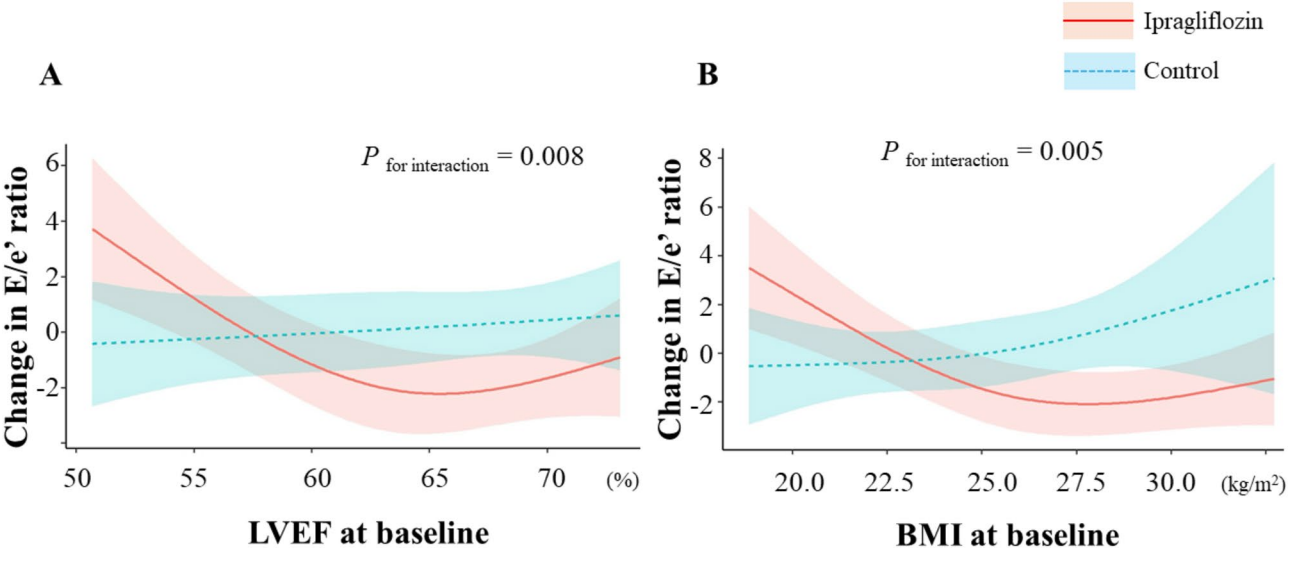

Fig. 3 Differences in the E/e' ratio from baseline to 24 weeks in the two treatment groups based on analysis using the restricted cubic spline function. **A** With baseline LVEF values as continuous variables. **B** With baseline BMI values as continuous variables. Post hoc analyses with restricted cubic splines with three knots showed that the association between baseline LVEF and BMI values and the change in the E/e' ratio was non-linear and significantly different between the treatment groups (A: $P_{\text{for interaction}} = 0.008$; B: $P_{\text{for interaction}} = 0.005$). BMI, body mass index; E/e', maximum early diastolic velocity to average early diastolic peak velocity; LVEF, left ventricular ejection fraction

Table 3 Correlation between changes in the E/e' ratio and each clinical parameter in the ipragliflozin group stratified by baseline LVEF

Factors	Patients with an LVEF < 60% (n = 7)		Patients with an LVEF ≥ 60% (n = 21)	
	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value
Systolic blood pressure (mmHg)	0.464	0.302	0.456	0.038
Diastolic blood pressure (mmHg)	0.500	0.267	0.609	0.003
BMI (kg/m^2)	0.250	0.595	0.055	0.814
Haemoglobin (g/dL)	−0.126	0.788	−0.079	0.733
P-III-P (ng/mL)	−0.214	0.662	−0.057	0.806
UACR (mg/g Cre)	0.600	0.242	0.057	0.806
LAVi (mL/m^2)	−0.786	0.048	0.244	0.287
RHI	0.464	0.302	−0.282	0.216

Data are expressed as the median (interquartile range [IQR]), Spearman's rank correlation coefficient, and *P*-value for testing whether the correlation coefficient is 0

BMI, body mass index; E/e', maximum early diastolic velocity to average early diastolic peak velocity; LAVi, left atrial volume index; LVEF, left ventricular ejection fraction; P-III-P; procollagen III peptide; RHI, reactive hyperaemia index; UACR, urine albumin-to-creatinine ratio

Table 4 Correlation between changes in the E/e' ratio and each clinical parameter in the ipragliflozin group stratified by baseline BMI

Factors	Patients with a BMI < 25 kg/m^2 (n = 9)		Patients with a BMI ≥ 25 kg/m^2 (n = 19)	
	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value
Systolic blood pressure (mmHg)	0.276	0.472	0.357	0.133
Diastolic blood pressure (mmHg)	0.288	0.452	0.507	0.027
BMI (kg/m^2)	0.234	0.544	0.123	0.616
Haemoglobin (g/dL)	0.151	0.699	−0.162	0.506
P-III-P (ng/mL)	−0.300	0.437	−0.030	0.905
UACR (mg/g Cre)	0.524	0.197	0.279	0.247
LAVi (mL/m^2)	−0.033	0.948	0.004	0.986
RHI	−0.283	0.463	−0.292	0.225

Data are expressed as the median (interquartile range [IQR]), Spearman's rank correlation coefficient, and *P*-value for test whether the correlation coefficient is 0

BMI, body mass index; E/e', maximum early diastolic velocity to average early diastolic peak velocity; LAVi, left atrial volume index; P-III-P; procollagen III peptide; RHI, reactive hyperaemia index; UACR, urine albumin-to-creatinine ratio

and r = 0.609, *P* = 0.003, respectively) but not in patients with an LVEF < 60% (n = 7; r = 0.464, *P* = 0.302 and r = 0.500, *P* = 0.267, respectively). Changes in other factors were not associated with changes in the E/e' ratio in sub-groups stratified by LVEF level at baseline.

Effect of BMI on changes in the E/e' ratio

Patients in the ipragliflozin and control groups classified by BMI were as follows: 19 and 12 patients had a BMI ≥ 25 kg/m^2 in the ipragliflozin and control groups, respectively, and nine and 17 patients had a BMI < 25 kg/m^2 in the ipragliflozin and control groups, respectively. The changes in the E/e' ratio differed between patients with a BMI ≥ 25 kg/m^2 and < 25 kg/m^2 (*P* = 0.016; Fig. 2). Post hoc analyses with restricted cubic splines with three knots showed that the association between baseline levels of BMI and the change in the E/e' ratio was non-linear and significantly different between the treatment groups ($P_{\text{for interaction}} = 0.005$; Fig. 3B). The correlation between the changes in E/e' ratio and clinical parameters, based on a baseline BMI of 25 kg/m^2, is shown in Table 4. The change in the E/e' ratio was associated with changes in diastolic BP in patients with a BMI ≥ 25 kg/m^2 (n = 19; r = 0.507, *P* = 0.027) but not in patients with a BMI < 25 kg/m^2 (n = 9; r = 0.288, *P* = 0.452). Changes in other factors were not associated with changes in the E/e' ratio in sub-groups stratified by BMI at baseline.

Effect of ipragliflozin on change in E/e' ratio after adjustments

The results regarding the effects of ipragliflozin on change in E/e' ratio, after adjustments for factors with AMSD > 0.2 using inverse probability weighting based on propensity scores, are shown in Additional File 1. Overall, ipragliflozin reduced E/e' (*P* = 0.015). Significant differences in factors of LVEF (*P* = 0.413) and BMI (*P* = 0.061) between the two groups were not observed; however, the similar trend was observed for LVEF ≥ 60% (*P* = 0.006) and BMI ≥ 25 kg/m^2 (*P* = 0.009).

Discussion

In this sub-analysis of the PROCEED trial, ipragliflozin had no significant effect on changes in the E/e' ratio. However, the effects varied according to LVEF and BMI values at baseline, and spline analyses suggested that the associations between changes in the E/e' ratio and both baseline LVEF and BMI levels were non-linear. For an LVEF < 60%, ipragliflozin had no effect on changes in the E/e' ratio; for an LVEF ≥ 60%, ipragliflozin significantly decreased the change in the E/e' ratio. For a BMI < 25 kg/m^2, ipragliflozin had no effect on changes in the E/e' ratio; for a BMI ≥ 25 kg/m^2, ipragliflozin significantly decreased the change in the E/e' ratio. Furthermore, the changes in the E/e' ratio correlated with changes in systolic and diastolic BP in patients with an LVEF ≥ 60%, and changes in diastolic BP in patients with a BMI ≥ 25 kg/m^2. These results suggest that ipragliflozin may have improved LV diastolic performance, partially due to the reduction in LV afterload, in patients with preserved LVEF or a higher BMI over a 24-week period.

Several studies have investigated the effects of SGLT2 inhibitors on LV diastolic function [21–26]. According to their results [21–26], SGLT2 inhibitors improve LV diastolic function, irrespective of the type of inhibitor, for periods ranging from 3 to 24 months. However, Rai et al. [27] found that empagliflozin did not affect LV diastolic function as assessed by 6 months of cardiac MRI in patients with T2DM and CAD. In their study, approximately 50% of patients underwent coronary artery bypass grafting; thus, it is possible that the changes in the area surrounding the heart after coronary artery bypass grafting also affected subsequent LV diastolic performance. These results highlight the importance of considering comorbidities in target patients when evaluating the effect of SGLT2 inhibitors on LV diastolic performance. Our study included patients with diabetes and CKD but excluded patients with obvious CAD who may have been more susceptible to the effects of SGLT2 inhibitors on LV diastolic performance.

Ipragliflozin was adopted in the PROCEED trial and is one of several SGLT2 inhibitors that demonstrates high selectivity for SGLT2 over other SGLT family members. It persistently binds to SGLT2 [36], and is thus classified as a long-acting SGLT2 inhibitor with rapid onset [37]. We previously evaluated the effects of ipragliflozin, the same drug used in this study, on carotid plaque development for 24 months in patients with T2DM [38]. In a sub-analysis [26], we reported that ipragliflozin only reduced the E/e' ratio in patients with LVEF ≥ 60% at 24 months. Although the present study was conducted in a group of patients with both T2DM and CKD—suggesting that patients with advanced DM were more likely to be included in the present sub-analysis—the results were similar, with ipragliflozin improving LV diastolic performance in patients with LVEF ≥ 60%. Furthermore, ipragliflozin improved LV diastolic function within a relatively short period (24 weeks) when compared with the previous study (24 months) [26]. This effect may also have been more likely as the study included patients with advanced DM; however, it is commonly believed that improvements in LV diastolic function with ipragliflozin are observed relatively early, and that the effects last for 24 months.

The effects of SGLT2 inhibitors on cardiac function were initially reported due to their ability to improve LV systolic function [5, 6, 39]; however, the systems listed here are not the only mechanisms for improving LV diastolic function. To summarise previous reports [10–16], the mechanisms underlying the effect of SGLT2 inhibitors for improving LV diastolic function broadly include the improvement of metabolic efficiency, reduction of cardiac preload and afterload, attenuation of inflammatory or fibrotic processes within the myocardium, and positive effects of SGLT2 inhibitors on renal function. These mechanisms may reduce the left atrial pressure and LV mass index (LVMI), which may contribute to improving LV diastolic function. As a possible mechanism by which SGLT2 inhibitors improve LV diastolic function, there have been reports of improvements in haemoglobin levels [23] or peripheral vascular function [24]. Moreover, several studies have shown that improvements in LV diastolic function are accompanied by a reduction in LVMI [21, 22]. In this present study, ipragliflozin had no overall effect on the E/e' ratio; however, it is noteworthy that the sub-group analysis of several stratified clinical parameters revealed improved LV diastolic performance in patients with an LVEF ≥ 60% or BMI ≥ 25 kg/m^2. Furthermore, in patients with an LVEF ≥ 60%, the decrease in the E/e' ratio correlated with the decrease in systolic and diastolic BPs, suggesting that the decrease in LV afterload may have contributed to the improvement in LV diastolic performance in this patient group.

In patients with a BMI ≥ 25 kg/m^2, the decrease in the E/e' ratio correlated with the decrease in diastolic BP. Diastolic blood BP has been reported to be associated with impaired LV diastolic performance [40, 41], and reductions in BP can improve LV diastolic function in clinical settings [42, 43]. Thus, we hypothesised that the decrease in diastolic BP might have partly contributed to the improvement in LV diastolic performance in this patient group. Recently, it has been reported that the cardiovascular protective effect of SGLT2 inhibitors varies with BMI and may be pronounced in patients with a higher BMI [44, 45]. Patients with obesity may have increased peri-coronary fat, which is reported to be reduced by SGLT2 inhibitors [46]. While this may not directly improve LV diastolic performance, it may have a positive effect in conjunction with the prognostic benefits of SGLT2 inhibitors in patients with obesity. Our results may indirectly support these results; however, confirming these findings requires further investigation. In addition, changes in haemoglobin or endothelial function as assessed by RHI were not associated with changes in the E/e' ratio. Differences in patient characteristics and methodology in assessing endothelial function may contribute to the differences between our study and other studies [23, 24]. Furthermore, inflammatory markers—such as C-reactive protein and LVMI—on echocardiography were not included in the planned measurements in the present study. Thus, the anti-inflammatory effect of ipragliflozin on LV diastolic performance or the accompanying reduction in LVMI by ipragliflozin could not be evaluated, and we cannot rule out the possibility that these factors may have also contributed to our results.

Our study has some limitations. First, the sample size was not set based on a sub-analysis and may have been statistically inadequate due to the small number of cases. Thus, we cannot rule out the possibility that a type II

error occurred in the analysis due to the small number of cases, which did not result in a significant difference. Notably, there was a correlation between changes in BP and changes in E/e' in the subgroup with LVEF ≥ 60% in the ipragliflozin group. However, although there was no significant difference in the subgroup with LVEF < 60%, the correlation coefficient was similar in the two groups (Table 3). We had thought that the mechanism by which ipragliflozin improves LV diastolic function differs between the LVEF ≥ 60% and < 60% groups and that BP reduction was one of the mechanisms; however, this may not be able to fully explain the results. Second, there are statistical limitations. Relatively small differences (ASMD > 0.2) were observed in some baseline clinical parameters; however, no medium differences (ASMD > 0.5) were observed [47]. Results after adjustments by those parameters partly differed from those prior to the adjustments (Additional File 1 and Fig. 2). However, some estimated propensity scores were numerically equal to 0 or 1, indicating that inverse probability weights based on the propensity scores could show statistically inaccurate values. Since this may potentially limit the accuracy and interpretation of the results, we carried out subsequent analyses without adjustment and concluded based on the corresponding results. As this is an exploratory hypothesis-generating study, we also did not adjust for multiple comparisons. Third, while an LVEF ≥ 50% defines HFpEF [48], our sub-analysis included predominantly patients with normal LVEF, with few having LVEF < 60%. In addition, an LVEF of 60% is a relatively commonly used clinical index [26, 49, 50]. An LVEF cutoff of 60% was used in the present analysis; however, our results may have been influenced by this specific threshold choice. We examined the effect of SGLT2 inhibitors on LV diastolic performance; however, our original study did not specifically include patients with HFpEF; thus, it remains unclear whether similar results would be obtained in patients with HFpEF. Fourth, echocardiography data were not centrally analysed due to variations in the echocardiographic equipment used in each facility; instead, locally calculated values were used. Furthermore, differences in examination accessibility between facilities may have influenced patient selection, potentially introducing selection bias. Fifth, while data on LVMI and inflammatory markers was desired, these parameters were not collected in the PROCEED trial. Finally, GLP-1 agonists are commonly used in patients with T2DM at risk of atherosclerosis [51] and have been shown to be clinically effective against HFpEF [52]. Yet, in the present sub-analysis of the PROCEED trial, none of the patients were administered GLP-1 receptor agonists; therefore, the combined effect of ipragliflozin and GLP-1 receptor agonists on LV diastolic performance remains unknown.

Conclusions

In this PROCEED trial sub-analysis of patients with T2DM and CKD, ipragliflozin did not significantly improve LV diastolic function in the overall study cohort. However, it significantly improved LV diastolic function as assessed by the E/e' ratio in participants with preserved LVEF or a higher BMI. Furthermore, it was associated with a reduction in systolic and diastolic BPs in those with preserved LVEF, and diastolic BP in those with a higher BMI. These results suggest that ipragliflozin may have improved LV diastolic performance, partially due to the reduction in LV afterload, potentially providing insights into the mechanism of improvement of LV diastolic function by SGLT2 inhibitor therapy.

Abbreviations

ASMD	Absolute standardised mean difference
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CABG	Coronary aorta-bypass grafting
CI	Confidence interval
CKD	Chronic kidney disease
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase-4
E/e'	Maximum early diastolic velocity to average early diastolic peak velocity
eGFR	Estimated glomerular filtration rate
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated haemoglobin
HFpEF	Heart failure with preserved ejection fraction
IQR	Interquartile range
LVMI	Left ventricular mass index
LAV	Left atrial volume
LAVi	Left atrial volume index
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
NT proBNP	N-terminal pro-brain natriuretic peptide
PROCEED	Program of Ipragliflozin for endothelial dysfunction in chronic kidney disease and type 2 diabetes
P-III-P	Procollagen III peptide
RHI	Reactive hyperaemia index
SGLT2	Sodium-glucose cotransporter 2
T2DM	Type 2 diabetes mellitus
UACR	Urine albumin-to-creatinine ratio

Supplementary Information

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Additional file 1.

Additional file 2.

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Author contributions

All the authors were involved in the planning and execution of the PROCEED trial. HT was responsible for drafting the article and preparing the figures and tables. KT was responsible for the statistical analysis. The other authors critically reviewed the entire manuscript, and all authors read and approved the final version of the manuscript.

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Availability of data and materials
The datasets used and/or analysed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The trial protocol was approved by local certified review boards, and the trial was conducted in compliance with the Declaration of Helsinki and the Clinical Trial Act of Japan. After the patients were initially screened for eligibility based on their prior medical records, they were adequately informed of the trial plan and provided written consent.

Consent for publication
Not applicable.

Competing interests
H.T. has received honoraria from Abbott Medical Japan, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Kowa, Medtronic, and Nihon Medi-Physics. A.T. has received honoraria from Boehringer Ingelheim Japan, Mochida, and Amgen; research funding from Bristol Myers Squibb and Novo Nordisk; A.T. is an Editorial Board member of the journal and not involved in handling this manuscript during the submission and review processes. K.T. has received outsourcing fees from Organization for Clinical Medicine Promotion. N.K. has received honoraria from Sumitomo, Novo Nordisk, Taisho, Eli Lilly Japan, Bayer, Boehringer Ingelheim, Kowa, Daiichi Sankyo, Astellas, MSD, Teijin, Eisai, Novartis, and Mitsubishi Tanabe. M.S. has received honoraria from Astellas Pharma Inc. Y.O. has received honoraria from Astellas, MSD, Mitsubishi Tanabe, Bayer, Novo Nordisk, Kowa and Eli Lilly Japan. K.N. has received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim Japan, Daiichi Sankyo, Eli Lilly Japan, Kowa, Mitsubishi Tanabe, MSD, Novartis, Novo Nordisk, Otsuka; Research grant from Astellas, Bayer, Boehringer Ingelheim Japan, Fuji Yakuhin, Mochida, Novartis; Scholarship from Abbott Medical, Boehringer Ingelheim Japan, Daiichi Sankyo Healthcare, Mitsubishi Tanabe, Teijin. All other authors have nothing to declare.

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