Effects of ipragliflozin on left ventricular diastolic function in patients with type 2 diabetes: A sub-analysis of the PROTECT trial

Brief title: SGLT2i and LV diastolic function

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ABSTRACT

Background: We hypothesized that the beneficial effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors on diastolic function might depend on baseline left ventricular (LV) systolic function.

Methods: To investigate the effects of SGLT2 inhibitors on LV diastolic function in patients with type 2 diabetes mellitus (T2DM), we conducted a post-hoc sub-study of the PROTECT trial, stratifying the data according to LV ejection fraction (LVEF) at baseline. After excluding patients without echocardiographic data at baseline or 24 months into the PROTECT trial, 31 and 38 patients with T2DM from the full analysis dataset of the PROTECT trial who received ipragliflozin or no SGLT2 inhibitor (control), respectively, were included. The primary endpoint was a comparison of the changes in echocardiographic parameters and NT-proBNP from baseline to 24 months between the two groups stratified according to baseline LVEF.

Results: Differences in diastolic functional parameters (e′ and E/e′) were noted between the two groups. Among the subgroups defined according to median LVEF values, those with higher LVEF (≥60%) who received ipragliflozin appeared to have a higher e′ and lower E/e′ than did those who received the standard of care with no SGLT2 inhibitor, indicating longitudinal improvements between baseline and follow-up ($p = 0.001$ and 0.016, respectively).

Conclusions: Ipragliflozin generally improved LV diastolic function in patients with type 2 diabetes, the extent of this improvement might appear to vary with LV systolic function.

Keywords: ipragliflozin, type 2 diabetes mellitus, echocardiography, diastolic function, NT-proBNP.

Introduction

Clinical trials have demonstrated that sodium-glucose cotransporter-2 (SGLT2) inhibitors can improve cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM) by reducing the risk of hospitalization for heart failure (HF) [1-3]. However, these trials have been limited by their lack of a detailed description of the mechanism by which SGLT2 inhibitors are involved in left ventricular (LV) diastolic function [4]. Although the underlying mechanisms by which SGLT2 inhibitors exert their positive effects on LV diastolic function have yet to be fully understood, several hypotheses have been proposed, such as direct modulation of myocardial metabolism, enhancement of endothelial function, and reduction in oxidative stress and inflammation [5-8]. Furthermore, SGLT2 inhibitors may also have a beneficial impact on systemic hemodynamics, body weight, and renal function, which could indirectly contribute to the improvement in LV diastolic function [9, 10]. Despite growing evidence supporting the favorable effects of SGLT2 inhibitors on LV diastolic function [11, 12], further research is required to elucidate the underlying mechanisms and determine the optimal use of these agents in HF patients. A better understanding of the role of SGLT2 inhibitors in LV diastolic function may have important clinical implications by helping clinicians establish effective therapeutic strategies for the management of HF, particularly in patients with preserved ejection fraction for whom a few specific treatment has been fully proven effective [13].

Our randomized trial, PROTECT (prevention of atherosclerosis by SGLT2 inhibitor; multicenter, randomized controlled study), compared the effects of SGLT2 inhibitor treatment with ipragliflozin and non-SGLT2 inhibitor treatment on carotid intima-media thickness in T2DM patients [14]. The PROTECT trial protocol allowed for the collection of several cardiovascular markers, including LV diastolic function and N-terminal pro-brain natriuretic

peptide (NT-proBNP). Based on this data, we hypothesized that ipragliflozin could effectively improve LV diastolic function, which may be dependent on baseline LV systolic function. As a sub-study of the PROTECT trial, the current study aimed to investigate the effects of ipragliflozin on diastolic function and NT-proBNP levels stratified according to baseline LV ejection fraction (EF) to further elucidate the effects of SGLT2 inhibitors in T2DM.

Methods

Study design and population

This study was a post-hoc analysis of the PROTECT trial (UMIN000018440 and jRCT1071220089), a multicenter, prospective, randomized, open-label, and blinded-endpoint investigator-initiated clinical trial conducted in 39 institutions throughout Japan. The detailed rationale and study design of the PROTECT trial have been published elsewhere [14, 15]. The ethics committees of each participating institution approved the study protocol, with written informed consent for participation in the study having been obtained from all subjects. After excluding ineligible patients, a total of 464 patients with T2DM between September 2015 and June 2018 were included and randomly assigned to either add-on ipragliflozin treatment (ipragliflozin group, n = 232) or no SGLT2 inhibitor treatment of standard care (control group, n = 232) at a 1:1 ratio. After excluding patients who had no echocardiographic data at baseline or 24 months into the study, 31 and 38 patients from 12 institutions who received ipragliflozin or no SGLT2 inhibitors, respectively, were included in the present analysis (**Figure 1**). The endpoint of this study was the change in echocardiographic parameters and NT-proBNP 24 months after treatment randomization.

Echocardiographic assessment

Echocardiography was performed at each institution before and 24 months after treatment randomization via standard procedures on a commercially available diagnostic ultrasound machine to measure various hemodynamic parameters. Recordings and measurements were performed according to the guidelines issued by American Society of Echocardiography [16]. LVEF was measured and calculated from apical two- and four-chamber views using bi-plane disk methods. Transmitral flow (TMF) velocity was recorded from the apical long-axis or four-chamber view. The peak early diastolic (E) velocities were measured. The mitral annular motion velocity pattern was recorded from the apical four-chamber view with the sample volume placed at the septal and lateral sides of the mitral annulus measured using pulsed tissue Doppler echocardiography. Early diastolic (e′) peak velocities at the septal and lateral sides were averaged, after which the ratio of E to e′ (E/e′) was calculated. These velocity parameters were used as markers of LV diastolic function. An increase in e' is generally favorable, reflecting improved ventricular relaxation. A higher E/e' ratio indicates elevated left ventricular filling pressures, associated with diastolic dysfunction. Individuals measuring and analyzing the echocardiograms were blinded to the drug assignments.

Laboratory examination

Blood samples were collected at baseline and after 24 months. Serum NT-proBNP levels were measured in a centralized laboratory (SRL Co. Tokyo, Japan) using an electrochemiluminescence immunoassay and nephelometry.

Statistical analysis

Baseline characteristics were summarized using basic descriptive statistics. Chance imbalances among baseline characteristics between the two groups were expressed using standardized difference (std diff). All analyses were conducted according to the intention-to-treat principle. Repeatedly measured HbA1c levels were analyzed using linear mixed models that adjusted for baseline HbA1c and LVEF. The echocardiographic parameters and NT-proBNP at 24 months were analyzed using linear models that adjusted for baseline values and LVEF. NT-proBNP analysis was conducted on the logarithmic scale. For a detailed post-hoc analysis of e′ and E/e′, two types of analyses were performed. First, a subgroup analysis of e′ and E/e′ was performed for the two groups defined using 60% of the baseline LVEF value. A recent review suggests classifying heart function using an LVEF range of 55-60% to create meaningful subgroup of normal EF and non-normal EF [17]. Aligning with this guidance, we chose 60% as our threshold, as it was closer to the median value of our study population. Second, baseline LVEF values were included in the model of e′ or E/e′ using the restricted cubic spline function with 3 knots (located at 10, 50, and 90 percentiles). The estimated changes in the mean value of e′ or E/e′ at 24 months for both treatment groups were plotted against baseline LVEF values. All analyses were performed using R Statistical Software version 4.2.0 (R Core Team 2022), with a *p* value <0.05 indicating statistical significance.

Results

Baseline clinical characteristics

The baseline clinical characteristics of the ipragliflozin and control groups are summarized in **Table 1**. Among the ipragliflozin arm, all patients received the dose of 50 mg daily. Approximately 50% of the patients in the two groups had hypertension, although both

groups had well controlled blood pressure. Some differences in several variables examined were observed between the two groups at baseline. Notably, LVEF was lower in the ipragliflozin group than in the control group (standardized difference = 0.529). Thus, all analyses were performed while adjusting for baseline LVEF values.

Figure 2 shows the changes in HbA1c throughout the study period from baseline to 24 months. Although reductions in HbA1c level were observed in both groups, no significant difference was observed between the two groups [group difference at 24 months (95% CI), −0.051% (−0.315% to 0.214%), p = 0.708]. The final HbA1c levels at 24 months were 7.03% and 6.89% in the ipragliflozin and control groups, respectively.

Effect on laboratory and echocardiographic data

The effects of ipragliflozin on laboratory and echocardiographic data from baseline to 24 months are summarized in **Table 2**. Notably, no significant differences in terms of the changes in LAVi, LVMi, LVEF, TMF-E, and NT-proBNP were observed between the ipragliflozin and control groups (Table 2). However, a difference in diastolic functional parameters (e′ and E/e′) was observed between the groups. Thus, detailed subgroup analyses were performed for these diastolic functional parameters.

Among the subgroups defined according to median baseline LVEF values, those with a higher LVEF (median value: ≥60%) who received ipragliflozin appeared have higher e′ levels than did those who received the standard of care with no SGLT2 inhibitor [group difference: 2.874 (1.155 to 4.593), p = 0.001]. Among those with a lower LVEF (<60%), no clear group difference was observed [group difference: −0.184 (−2.021 to 1.652), p = 0.842] (**Figure 3A**). Differences in the treatment effects on e′ levels were observed between the subgroups defined

according to a baseline LVEF value of 60% (P for interaction: 0.018). This treatment effect heterogeneity was also examined on continuous baseline LVEF values, with our results subsequently showing that the treatment effect appeared to be clearer among those with a baseline LVEF ≥60% than in those with a baseline LVEF <60% (**Figure 3B**).

Among the subgroups defined according to median EF values, those with a higher LVEF (≥60%) who received ipragliflozin also showed lower E/e′ levels than did those who received the standard of care with no SGLT2 inhibitor [group difference: −3.018 (−5.442 to −0.594), p = 0.016]. Among those with a lower LVEF (<60%), no clear group difference was observed [group difference: −0.352 (−2.862 to 2.158), p = 0.780] (**Figure 4A**). The treatment effect heterogeneity on E/e′ levels was also examined on continuous baseline LVEF values, with our results subsequently showing that the treatment effect appeared to be clearer in those with a baseline LVEF of ≥60% than in those with a baseline LVEF <60%, albeit not significantly (P for interaction: 0.133) (**Figure 4B**).

Discussion

The current sub-study of the PROTECT trial aimed to evaluate the impact of ipragliflozin on changes in LV diastolic function and NT-proBNP from baseline to 24 months. As a prospective randomized study, we provided novel insights into the effects of SGLT2 inhibitors on LV diastolic function and NT-proBNP in T2DM. Our findings suggest that ipragliflozin may positively influence LV diastolic function, especially in patients with preserved LVEF (≥60%), and highlight the potential for further research in this area.

Mechanisms by which SGLT2 inhibitors affect LV diastolic function

Several investigators have shown that SGLT2 inhibitors provide beneficial cardiovascular effects as a consequence of changes in several pathways [18, 19]. Various potential mechanisms can account for this phenomenon, including (1) the diuretic effect of SGLT2 inhibitors; (2) hyperketonemia that switches myocardial fuel usage from glucose to ketone bodies and free fatty acids, resulting in more efficient ATP production [8]; and (3) inhibition of cardiac Na^+/H^+ exchanger by SGLT2 inhibitors, thereby reducing intracellular calcium and increasing mitochondrial Ca^{2+}, which restores mitochondrial function and redox state and activates ATP production [20]. These potential mechanisms have been supported by the findings of studies on animal models, such as those that used SGLT2 inhibitors to attenuate myocardial oxidative stress and fibrosis in diabetic mouse hearts or improve coronary microvascular function and cardiac contractility in a pre-diabetic mouse model [9, 10]. More recently, the administration of empagliflozin in a nondiabetic HF porcine model improved diastolic function, mitigated histological and molecular remodeling, and reduced left ventricle and cardiomyocyte stiffness [21]. Based on these favorable cardiovascular effects, SGLT2 inhibitors appear to have promising effects on enhancing diastolic function. Despite the limited number of clinical trials investigating the effects of SGLT2 inhibitors on diastolic function, dapagliflozin has also been shown to promote a significant decrease in estimated LV filling pressure during exercise in patients with T2DM [22]. The effects of SGLT2 inhibitors on diastolic function remains controversial, suggesting the need to identify more valid subtypes.

Impact of SGLT2 inhibitors on NT-proBNP and LV diastolic function

A recent meta-analysis had investigated the impact of SGLT2 inhibitors on NT-proBNP and LV diastolic function. This particular study demonstrated that SGLT2 inhibitor treatment

promoted improvements in NT-proBNP and cardiac function, including LAVi, LVMi, and LVEF, in patients with T2DM [23]. However, no significant decrease in NT-proBNP was observed with SGLT2 inhibitor treatment in our study. Although previous studies have examined the effects of SGLT2 inhibitors on NT-proBNP, their results remain controversial. One possible explanation for this controversy is that the efficacy of SGLT2 inhibitor may depend on the baseline cardiac function given that the efficacy of cardioprotective drugs, including β-blockers and renin–angiotensin–aldosterone system inhibitors, depends on LVEF. HF guidelines have recommended LVEF-guided treatment strategies [24]. Available evidence has strongly suggested the benefits of cardiovascular medications in patients with HF with reduced EF but not in those with preserved EF. The identification of subtypes in which these drugs are useful is therefore an important clinical issue in the field of HF.

In this study, we observed a differential impact of ipragliflozin on LV diastolic function among patients with varying levels of ejection fraction. While the clinical benefits of SGLT2i, such as improved outcomes, are broadly recognized, our findings suggest that these benefits might operate through different mechanisms depending on the EF status. Notably, we found that SGLT2 inhibitors improved the diastolic function in patients with preserved LVEF (i.e., those with an LVEF ≥60%). These changes indicate improved LV relaxation and left atrial pressure, respectively. However, the effects of SGLT2 inhibitors on diastolic function were less clear in patients with reduced LVEF (i.e., those with an LVEF <60%). This insight underscores the importance of considering EF status in tailoring treatments for diabetic patients and highlights the need for further research to elucidate these differential mechanisms.

One possible explanation for this discrepancy is that patients with reduced LVEF may have underlying fundamental structural abnormalities of the left ventricle, such as myocardial

fibrosis or LV hypertrophy, which are comparatively less prevalent in patients with preserved LVEF [25]. These structural abnormalities may limit the ability of SGLT2 inhibitors to improve diastolic function in these patients. Another possible explanation is that the mechanisms by which SGLT2 inhibitors improve diastolic function may differ in patients with reduced LVEF. For instance, in patients with preserved LVEF, SGLT2 inhibitors have been shown to reduce LV mass and improve myocardial energetics, both of which may contribute to improved diastolic function. However, in patients with reduced LVEF, these mechanisms may be less relevant, and other mechanisms, such as reduction in systemic inflammation or improvement in endothelial function, may be more important [26].

Clinical implications

Despite the accumulating evidence regarding the beneficial effects of SGLT2 inhibitor on HF, no study has yet comprehensively evaluated cardiac function to identify patient subgroups that would benefit from SGLT2 inhibitor administration. Our study suggests that the impact of ipragliflozin on LV diastolic function may vary with LVEF status. Although improvements in diastolic function were observed in patients with preserved LVEF, the effects in those with reduced LVEF remain less certain, potentially influenced by structural differences, or varied underlying mechanisms. These findings hint at the need for more targeted investigations into the effects of SGLT2 inhibitors across different HF phenotypes.

Limitations

Given that this study was a sub-analysis of the PROTECT trial, echocardiography was not performed in all subjects. We recognize the inherent limitations of our study, including the

relatively small and specific Japanese patient population, and the study not being originally designed for detailed subgroup analysis. Additionally, we acknowledge that the methods employed, particularly subgroup and cubic spline analysis, can yield varying results based on cut-off values and the number of nodes, especially in smaller samples. This variability has been considered in interpreting our results, which should be viewed as preliminary. These findings provide an impetus for further research in larger and more diverse cohorts, to validate these preliminary insights and understand the underlying mechanisms in a more robust manner. Also, given the exploratory nature of the study, no statistical correction for multiple comparisons was made, and the results should be interpreted as such. Although the participant's background treatment should be, in principle and if possible, unchanged during the trial interval, other medications might have affected NT-proBNP levels and LV diastolic function in the current study. Unfortunately, we could not obtain details regarding medication modifications during the study period. We recognize that the extended duration of 24 months until echocardiographic follow-up, coupled with the relatively small patient population included in these assessments, may introduce potential biases in our study. This limitation could lead to residual confounding factors impacting the interpretation of our findings.

Conclusion

Our study demonstrates a general improvement in LV diastolic function among patients with type 2 diabetes treated with ipragliflozin. Subgroup analysis suggests that this improvement might be more pronounced in patients with preserved ejection fraction. However, these subgroup findings, derived from a limited sample size, should be interpreted with caution. Our research

adds to the growing understanding of SGLT2 inhibitors' effects, indicating the need for more extensive studies to confirm and expand upon these initial observations.

Conflict of interest: TI received lecture fees from JCR Pharmaceuticals and KyowaKirin; and outsourcing fees from Organization for Clinical Medicine Promotion. AT received honoraria from Boehringer Ingelheim Japan and research funding from GlaxoSmithKline, Takeda, Bristol-Myers Squibb and Novo Nordisk. H.T. received honoraria from Abbott Medical Japan, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Kowa, Ono, Mitsubishi Tanabe, and Takeda. M.S. received grants and personal fees from Mitsubishi Tanabe, Takeda, Daiichi Sankyo, Astellas, Pfizer, Novartis, Boehringer Ingelheim, Bayer, MSD, Kowa, and AstraZeneca. N.K. has received honoraria from AstraZeneca, Bayer Yakuhin, Boehringer Ingelheim Japan, Daiichi Sankyo, Eli Lilly Japan, Kowa, Mitsubishi Tanabe Pharma, MSD, Novartis Pharma, Novo Nordisk Pharma, Ono Pharmaceutical, Otsuka, Takeda Pharmaceutical ; Research grant from Asahi Kasei, Astellas, Boehringer Ingelheim Japan, Fuji Yakuhin, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Novartis Pharma, Teijin Pharma; Scholarship from Bayer Yakuhin, Medtronic, Teijin Pharma. All other authors declare no competing interests.

AT and KN are the Editorial Board members of the Cardiovascular Diabetology and were not involved in handling this manuscript during the submission and the review processes.

Funding: This study was funded by Astellas Pharma Inc. Japan, and Prof. Koichi Node received the funding. The funder of the trial had no role in the study design, data collection, data analysis, data interpretation, or writing of the work.

Authors' contributions: All authors conceptualized the trial. KK wrote the draft of the article. TI performed statistical analysis throughout the study. All authors confirmed data collection and study selection criteria, enrolled patients and performed study quality assessment, and approved the final version of the manuscript.

Acknowledgments: The authors thank all the participants, investigators, board members, and medical staff members involved in the PROTECT trial.

Data availability statement: The data are available upon reasonable request from researchers who submit a detailed proposal outlining their intended use of the data and after approval by the principal investigators and the steering committee of the PROTECT study. Inquiries are to be addressed to the corresponding author (or study secretariat: substudy_protect@clin-med.org).

Ethics declarations

Ethics approval and consent to participate: The study was approved by the Ethics Committee Saga University Hospital, following the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant.

Consent for publication: All the authors gave their consent to publication.

Abbreviations: T2DM: Type 2 diabetes, SGLT2: sodium-glucose cotransporter-2, HF: heart failure, NT-proBNP: N-terminal pro-brain natriuretic peptide, LV: left ventricular, EF: ejection fraction.

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Figure legends:

Figure 1. Flow diagram of the patient selection process.

Figure 2. Changes in HbA1c at 4, 12, and 24 months in the two treatment groups.

Abbreviations: HbA1c, Glycated Hemoglobin A1c

Figure 3. Changes in e′ from baseline to 24 months in the two treatment groups. A) All patients and two subgroups defined according to LVEF of 60%. B) Analysis handling the baseline LVEF values as a continuous variable using the restricted cubic spline function. The points at the bottom represent the distribution of the LVEF values.

Abbreviations: LVEF, left ventricle ejection fraction

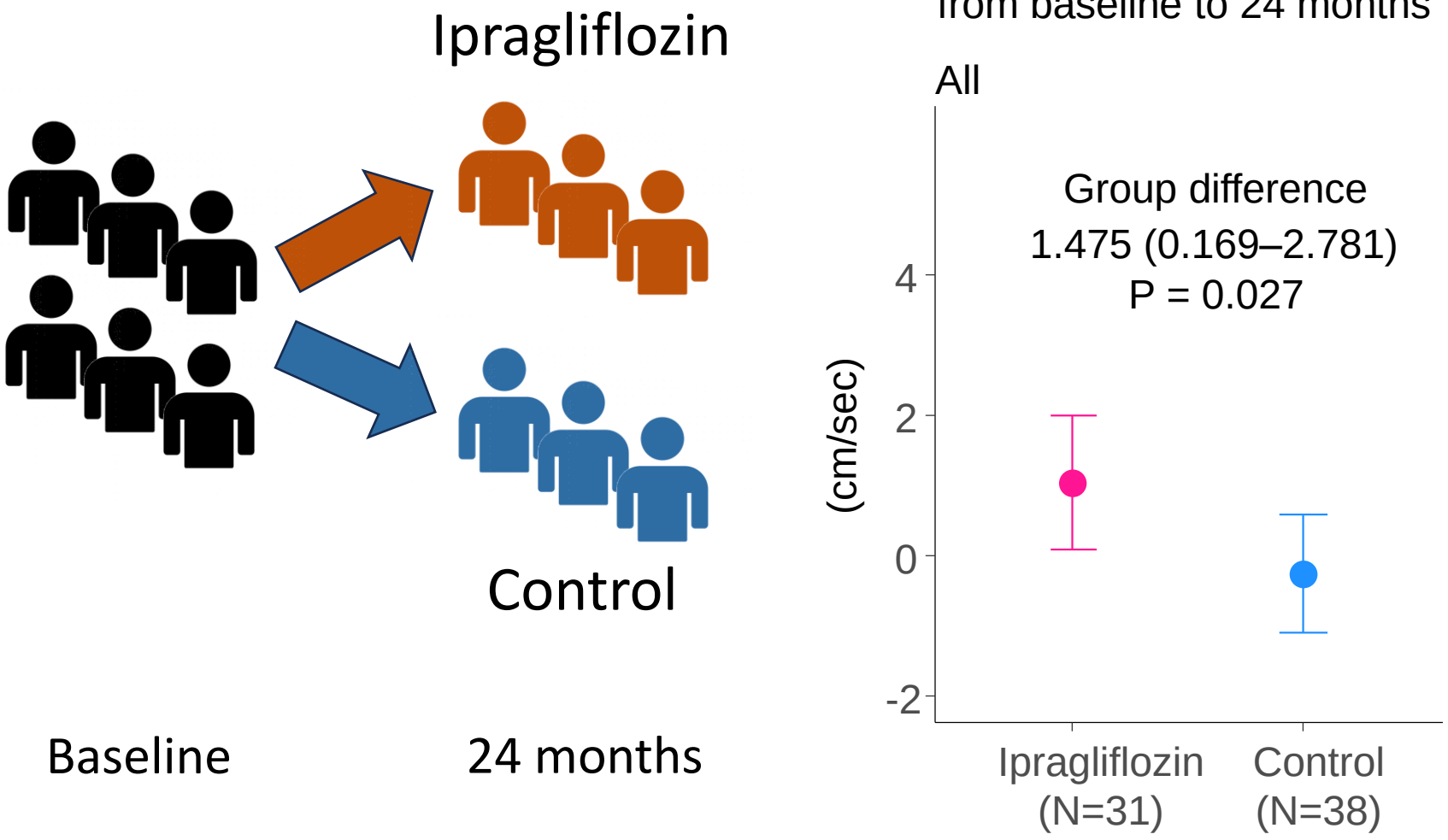
Figure 4. Changes in E/e′ from baseline to 24 months in the two treatment groups. A) All patients and two subgroups defined according to LVEF of 60%. B) Analysis handling the baseline LVEF values as a continuous variable using the restricted cubic spline function. The points at the bottom represent the distribution of the LVEF values.

Abbreviations: LVEF, left ventricle ejection fraction

Highlights

- Study on sodium-glucose cotransporter-2 inhibitors' impact on diastolic function in type 2 diabetes.
- Ipragliflozin improves diastolic function in high left ventricular ejection fraction (LVEF) diabetes patients.
- The effect of ipragliflozin on diastolic function varies with baseline LVEF in diabetes.

Graphical Abstract



Figure

Figure 1

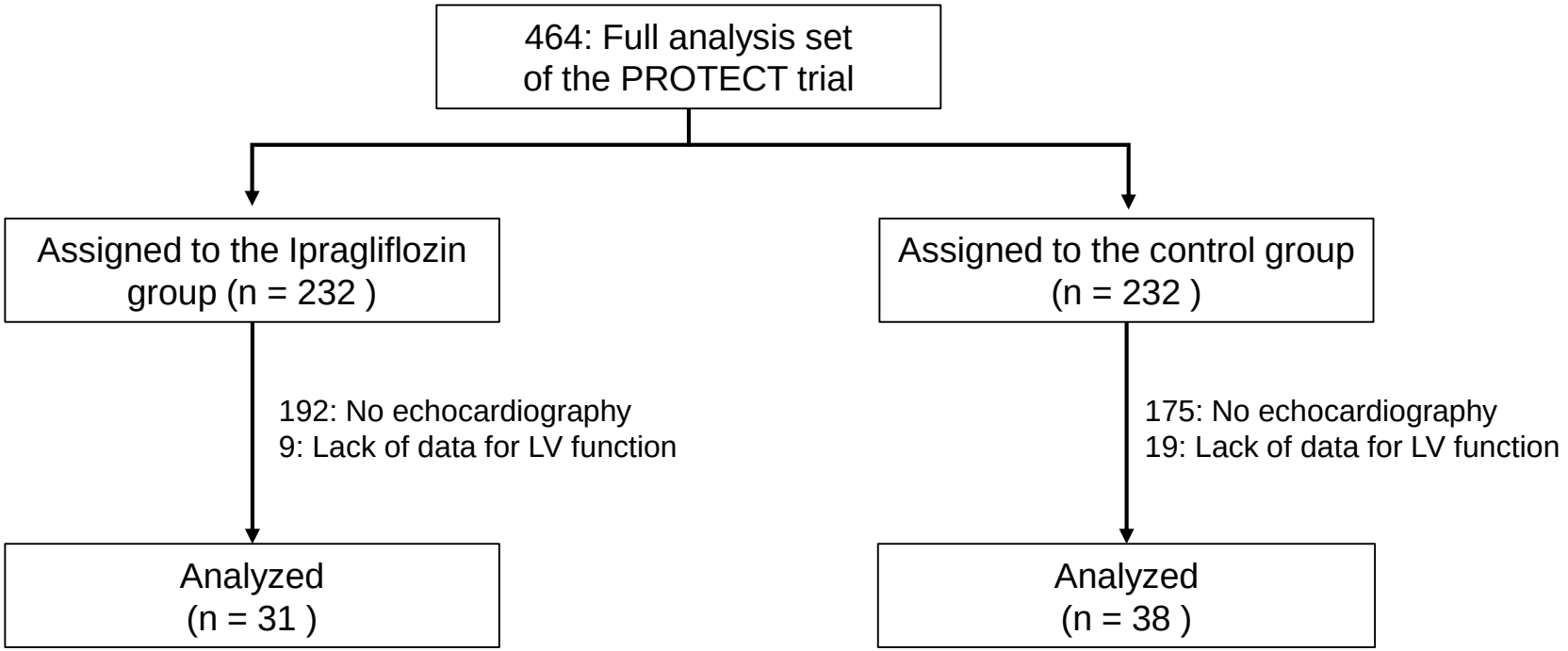


Figure 2

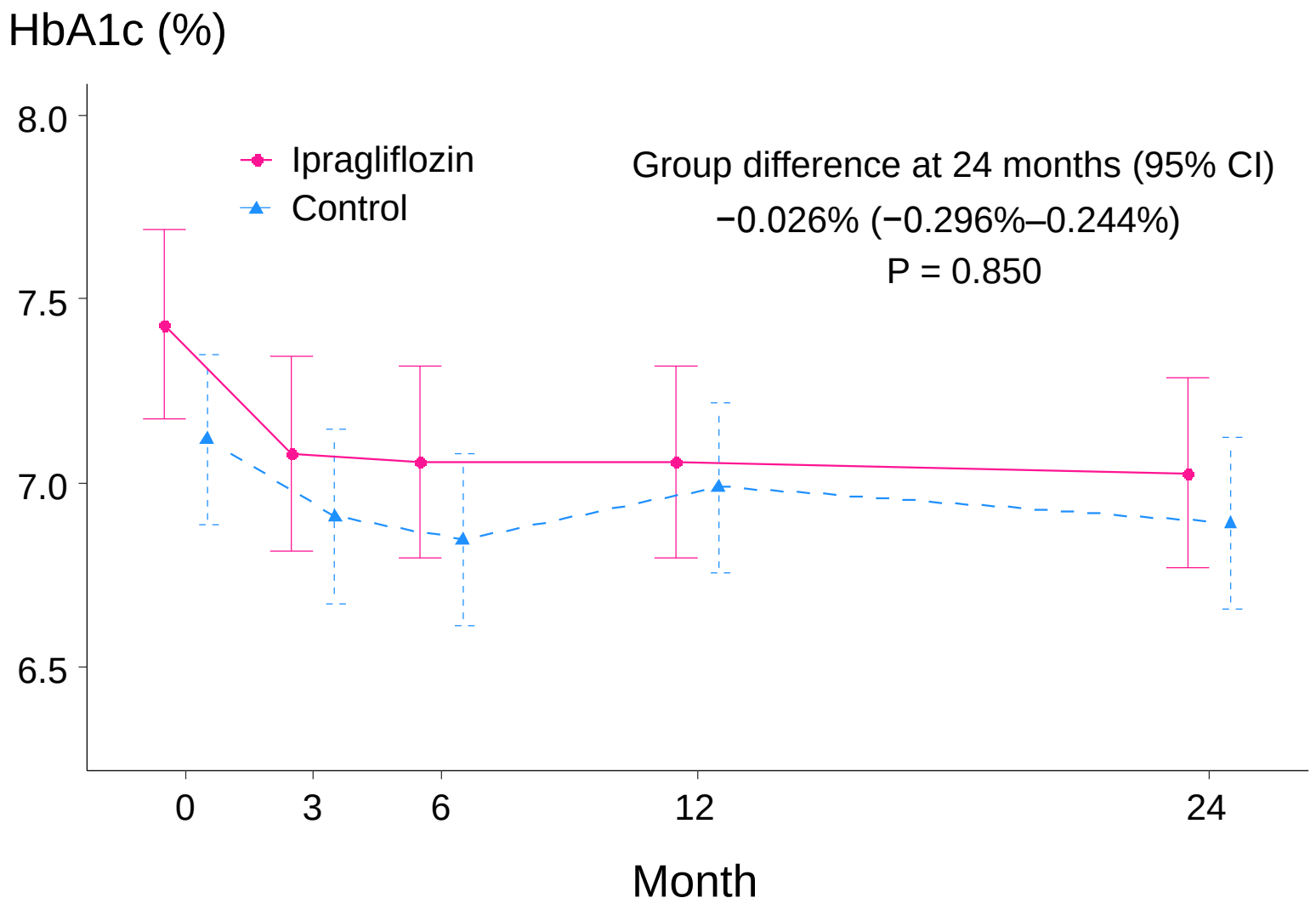

HbA1c (%)
8.0
7.5
7.0
6.5
Ipragliflozin
Control
Group difference at 24 months (95% CI)
−0.026% (−0.296%–0.244%)
P = 0.850
0
3
6
12
24
Month

Figure 3A

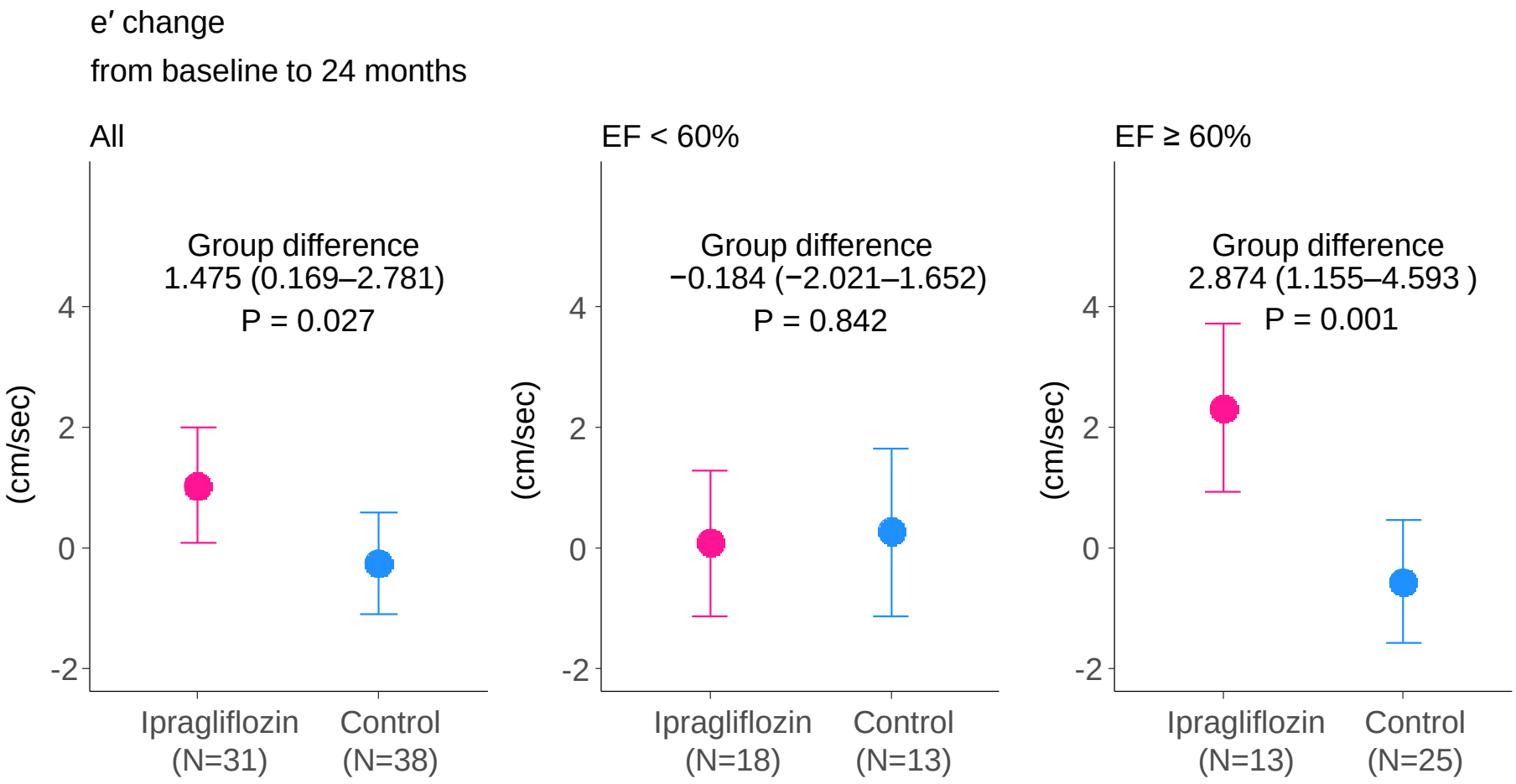

e′ change
from baseline to 24 months
All
Group difference
1.475 (0.169–2.781)
P = 0.027
EF < 60%
Group difference
−0.184 (−2.021–1.652)
P = 0.842
EF ≥ 60%
Group difference
2.874 (1.155–4.593)
P = 0.001
(cm/sec)
4
2
0
-2
Ipragliflozin
(N=31)
Control
(N=38)
Ipragliflozin
(N=18)
Control
(N=13)
Ipragliflozin
(N=13)
Control
(N=25)

Figure 3B

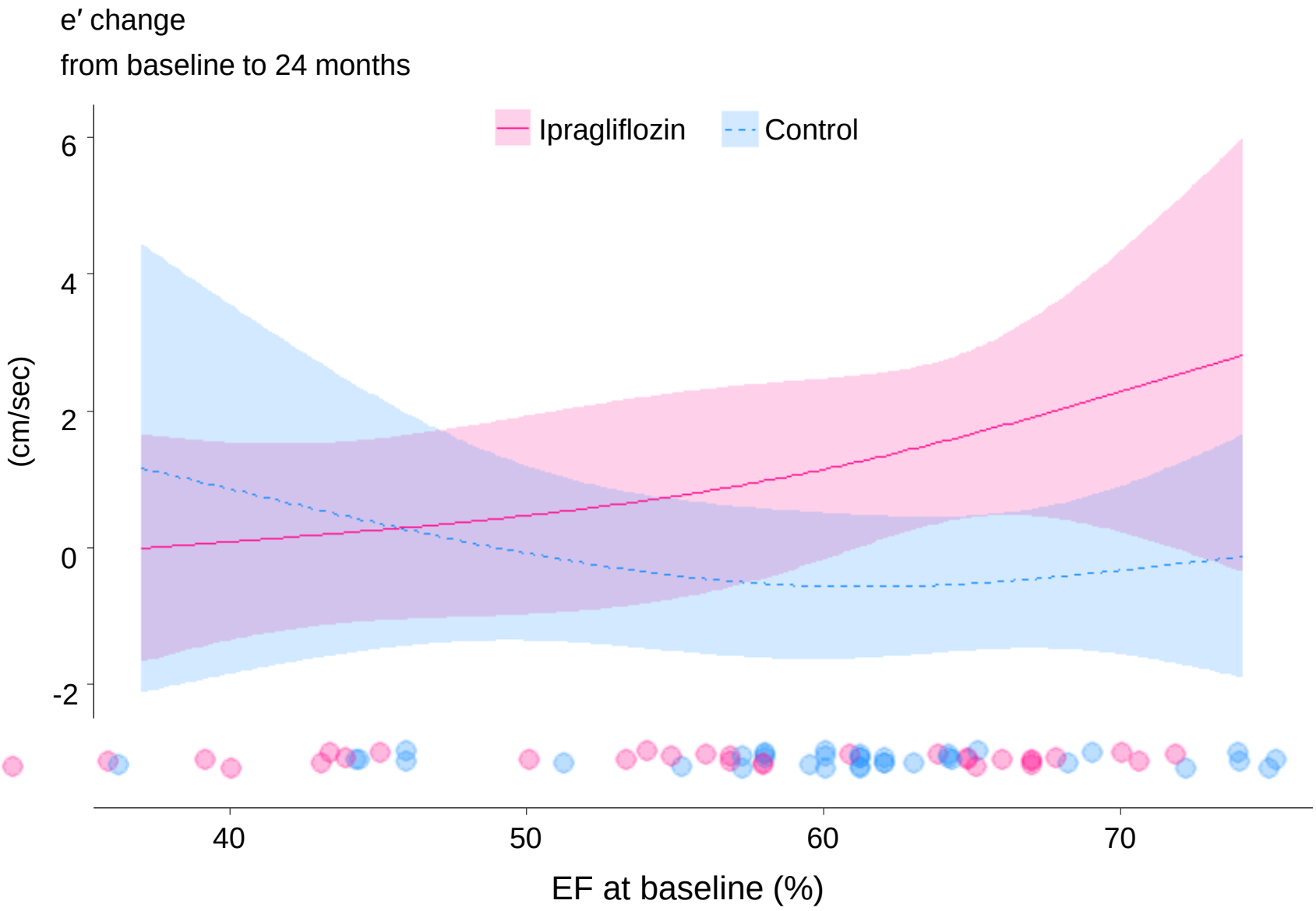

e′ change
from baseline to 24 months
Ipragliflozin
Control
6
4
2
0
-2
(cm/sec)
40
50
60
70
EF at baseline (%)

Figure 4A

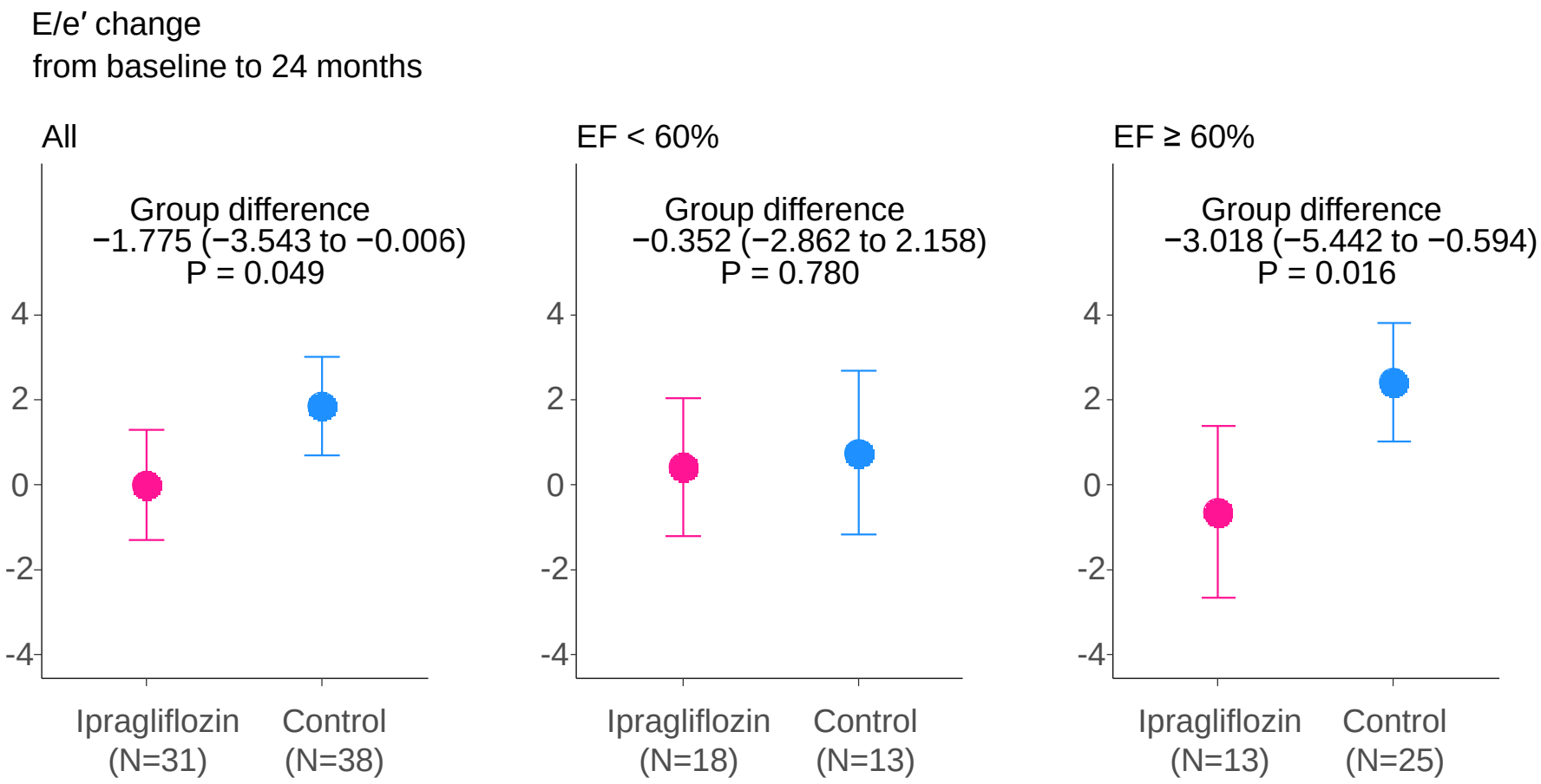

E/e′ change
from baseline to 24 months
All
Group difference
−1.775 (−3.543 to −0.006)
P = 0.049
4
2
0
-2
-4
Ipragliflozin
(N=31)
Control
(N=38)
EF < 60%
Group difference
−0.352 (−2.862 to 2.158)
P = 0.780
4
2
0
-2
-4
Ipragliflozin
(N=18)
Control
(N=13)
EF ≥ 60%
Group difference
−3.018 (−5.442 to −0.594)
P = 0.016
4
2
0
-2
-4
Ipragliflozin
(N=13)
Control
(N=25)

Figure 4B

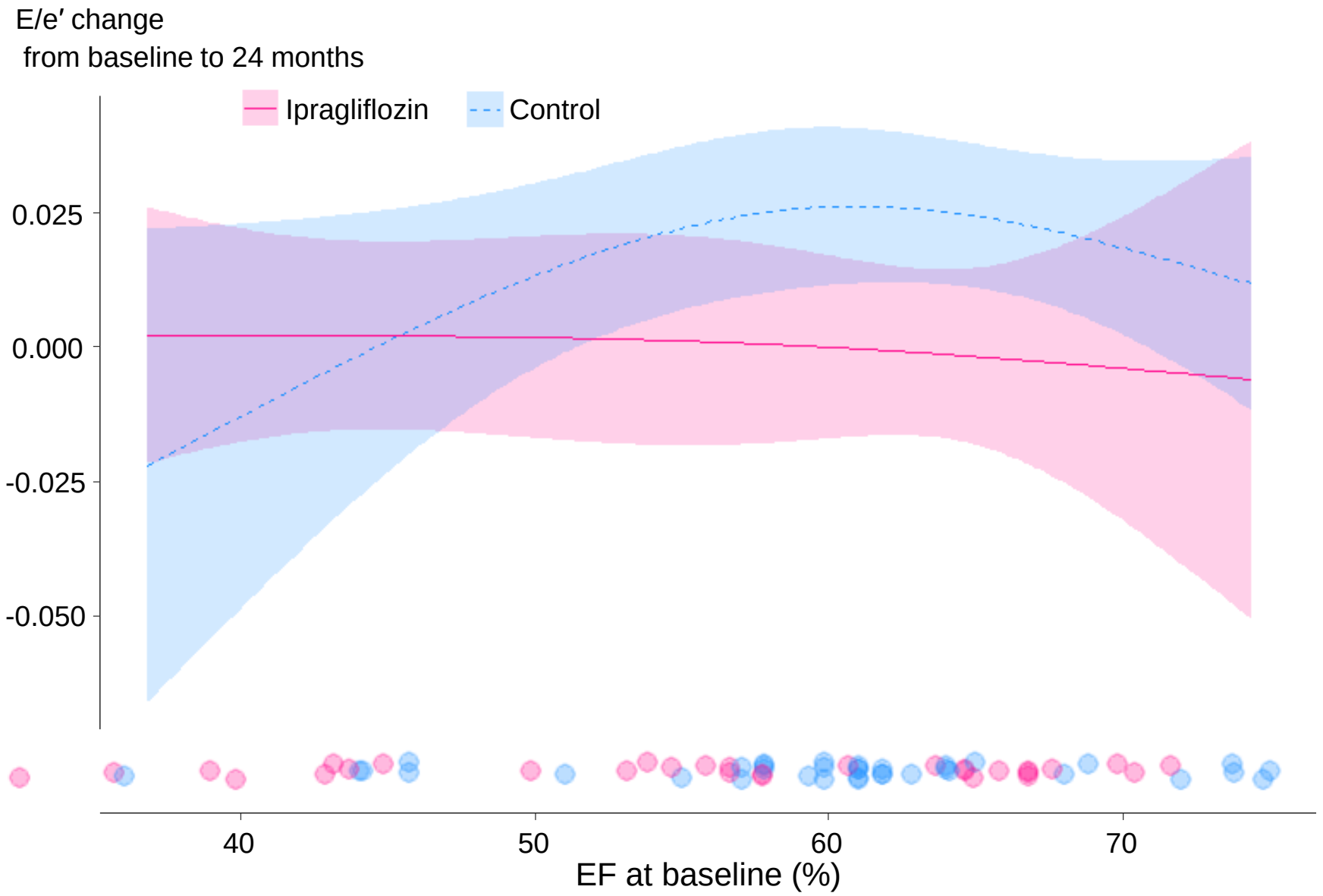

E/e′ change
from baseline to 24 months
Ipragliflozin
Control
0.025
0.000
-0.025
-0.050
40
50
60
70
EF at baseline (%)

Table 1. Clinical characteristics of the patients in the two treatment groups.

	Ipragliflozin	Control	Std diff
Number	31	38	
Clinical background			
Age, yr	66 ± 13	67 ± 10	0.060
Male	22 (71)	21 (55)	0.330
Body mass index, kg/m^2	25.4 ± 4.1	26.1 ± 5.4	0.149
Systolic BP, mmHg	125 ± 18	131 ± 16	0.364
Clinical history			
Hypertension	16 (52)	20 (53)	0.020
Dyslipidemia	16 (52)	18 (47)	0.085
ASCVD	15 (48)	17 (45)	0.073
HF and/or cardiomyopathy	3 (10)	5 (13)	0.110
Medications for non-diabetes			
ACEi/ARB	18 (58)	22 (58)	0.003
Beta blocker	13 (42)	15 (40)	0.050
Statin	22 (71)	23 (61)	0.221
Anti-platelet	13 (42)	16 (42)	0.003
Medication for diabetes			
Insulin	0 (0)	1 (3)	0.003
Sulfonylurea	5 (16)	4 (11)	0.165
DPP-4 inhibitor	20 (65)	16 (42)	0.461
GLP-1RA	0 (0)	0 (0)	-
Thiazolidinedione	0 (0)	0 (0)	-
Laboratory data			
eGFR, mL/min/1.73 m^2	63.6 ± 19.4	73.7 ± 21.1	0.497
HbA1c, %	7.4 ± 0.9	7.1 ± 0.7	0.394
NT-proBNP, pg/mL	268.4 ± 380.5	193.1 ± 330.4	0.211
Echocardiography			
LAVi	33.7 ± 14.7	32.2 ± 9.4	0.118
LVMi	92.5 ± 23.5	95.3 ± 25.2	0.114
LVEF	55.2 ± 12.9	61.2 ± 9.6	0.529
TMF-E	62.2 ± 15.3	67.4 ± 19.6	0.295
e′	7.1 ± 2.7	6.9 ± 1.7	0.072
E/e′	10.1 ± 5.0	10.1 ± 3.0	0.013

Data are expressed as number of patients (percentage) or mean ± SD. A standardized difference (std diff) of <0.2 indicates adequate balance.

Abbreviations: BP, blood pressure; ASCVD, atherosclerotic cardiovascular disease; ACEi/ARB, angiotensin-converting-enzyme inhibitor/angiotensin II receptor blocker; DPP-4, dipeptidyl peptidase 4; GLP-1RA, glucagon-like peptide-1 receptor agonist; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; LAVi, left atrial volume index; LVMi, left ventricular mass index; EF, ejection fraction; TMF-E, early diastolic transmitral flow; e′, early diastolic mitral annular velocity.

Table 2. Change in parameters from baseline to 24 months in each subgroup after adjusting for baseline values of each variable and ejection fraction.

	Estimate (95% CI)			
Outcome	**Ipragliflozin group**	**Control group**	**Group difference (95% CI)**	***P* value**
LAVi change	-1.869 [-5.492 to 1.753]	-0.639 [-3.569 to 2.291]	-1.231 [-5.910 to 3.449]	0.599
LVMi change	-4.007 [-10.482 to 2.467]	0.318 [-5.176 to 5.813]	-4.325 [-12.932 to 4.281]	0.319
EF change	0.526 [-2.094 to 3.147]	2.404 [0.126 to 4.681]	-1.877 [-5.357 to 1.602]	0.285
TMF-E change	7.067 [-0.114 to 14.247]	1.406 [-4.734 to 7.547]	5.660 [-3.828 to 15.148]	0.238
e′ change	1.213 [0.203 to 2.223]	-0.262 [-1.113 to 0.589]	1.475 [0.169 to 2.781]	0.027
E/e′ change	0.069 [-1.287 to 1.426]	1.844 [0.688 to 3.001]	-1.775 [-3.543 to -0.006]	0.049
NT-proBNP proportional change	1.213 [0.992 to 1.483]	1.030 [0.865 to 1.227]	1.177* [0.901 to 1.539]	0.228

* Group ratio of proportional changes in the geometric mean of NT-proBNP.

Abbreviations: LAVi, left atrial volume index; LVMi, left ventricular mass index; EF, ejection fraction; TMF-E, early diastolic transmitral flow; e′, early diastolic mitral annular velocity; NT-proBNP, N-terminal pro-brain natriuretic peptide