

# Gender Differences in Cardiac Function Following Three-Month Administration of Tofogliflozin in Patients With Diabetes Mellitus

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## Abstract

**Background:** Patients with type 2 diabetes mellitus (T2DM) are at increased risk for impairment in heart failure and diastolic relaxation while preserving ejection fraction (EF). Recently, several sodium glucose cotransporter-2 (SGLT2) inhibitors have demonstrated to decrease cardiovascular disease (CVD) events in elderly diabetic patients, although gender difference in the effect of SGLT2 inhibitors is unknown. The objective of the present study was to evaluate gender difference in the effect of tofogliflozin, one of the SGLT2 inhibitors, on CVD function in patients with diabetes mellitus.

**Methods:** This was a retrospective study. Patients received 20 mg of tofogliflozin daily for 3 months. EF, ratio of early filling to atrial filling (E/A), a change in mitral inflow E and mitral e' annular velocities (E/e'), left atrial dimension (LAD) and maximal diameter of inferior vena cava (IVC<sub>max</sub>), including various physiological parameters were measured between baseline, 1 month and 3 months after administration of tofogliflozin. Interaction between gender and time after administration was evaluated using mixed effect model.

**Results:** The results showed significant decrease in E/e' ( $P < 0.01$ ) and significant interaction between time and gender in E/A ( $P < 0.01$ ), following administration of tofogliflozin for 3 months. EF was constantly higher significantly in women ( $P < 0.01$ ).

**Conclusion:** It is concluded that 3-month administration of tofogliflo-

zin decreased E/e' with gender difference in EF and E/A.

**Keywords:** Tofogliflozin; Elderly; Diabetes mellitus; EF; E/A; E/e'

## Introduction

Type 2 diabetes mellitus (T2DM) is one of the most serious causes of cardiovascular disease (CVD), including heart failure (HF) [1, 2]. Sodium glucose cotransporter-2 (SGLT2) inhibitors have been emerged as a new class of antidiabetic drugs that inhibit glucose reabsorption in the renal proximal tubules followed by excretion of glucose into the urine [3]. Six SGLT2 inhibitors (ipragliflozin, dapagliflozin, tofogliflozin, canagliflozin, empagliflozin and luseogliflozin) have been currently available in Japan [4]. Several cardiovascular studies have found that SGLT2 inhibitors significantly reduced major adverse cardiovascular events, death and hospitalizations for HF during the treatment with canagliflozin, empagliflozin and dapagliflozin in T2DM patients with complication of CVD [5-8]. Furthermore, empagliflozin and canagliflozin have been known to decrease cardiovascular risk, including weight loss as well as lowering blood pressure [6, 8-10]. A prospective study has also found that treatment with dapagliflozin improved left ventricular (LV) diastolic functional parameters in T2DM patients with HF [11]. LV diastolic dysfunction has been known to have close correlation with HF [12, 13]. Thus, the use of SGLT2 inhibitors which improves cardiovascular outcomes in patients with T2DM has been attracting attention. Tofogliflozin was found to improve LV dilatation and vascular endothelial function in Japanese patients with T2DM, presumably via elevation of ketone bodies induced by tofogliflozin which might contribute to a protective effect in LV diastolic dysfunction [14, 15]. Recently, our study suggested that there were gender differences in the effect of tofogliflozin in Japanese elderly patients with T2DM using mixed effect model [16]. However, little is known concerning the gender difference of the effect, especially in elderly people. There is a tendency toward dias-

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toxic function aggravating in the elderly. From this view point, it is significant to assess diastolic function after administration of tofogliflozin. Tochiya et al also investigated the effect of tofogliflozin in patients with T2DM but almost all were men and gender difference remains unknown [15]. The objective of this study was to investigate gender differences in the effect of tofogliflozin on the cardiac functions, including LV diastolic function in patients with T2DM.

## Patients and Methods

The present study was a retrospective study to investigate the effect of tofogliflozin, one of the SGLT2 inhibitors, on LV diastolic functional parameters in elderly patients with T2DM. This study included elderly patients with a diagnosis of T2DM who attended clinics at the Kanazawa Medical University Himi Municipal Hospital from April 2017 to March 2019. Elderly was defined as aged  $\geq 65$  years. All patients received a single 20 mg dose of tofogliflozin daily for 3 months. Patients with significant comorbid conditions were excluded. Demographic and baseline characteristics data were collected from patients' medical records. The data for patient characteristics were collected, gender (men/women), age (years), New York Heart Association (NYHA) classification, co-administered drugs, serum glycated hemoglobin (HbA1c), levels of hematocrit, brain natriuretic peptide (BNP), estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), serum electrolyte (i.e. sodium, potassium and chloride) were measured at baseline, 1 month and 3 months.

Echocardiographic examination was performed with commercially available ultrasound systems, Hitachi Ultrasonic Diagnostic Apparatus Hivision Perius. Standard echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging and the Guideline from Japanese Society of Echocardiography [13, 17, 18]. The maximal diameter of the inferior vena cava (IVCmax) was defined by the following procedure. Below the costal arch in parallel with the trunk and in the recumbent position before the inferior vein transitions to the right atrium at end expiration. The largest diameter was measured between 0.5 and 3 cm from the inflow to the right atrium in the IVC long axis cross-section at supine position. Maximum diameter was measured at expiration at the proximal hepatic vein junction. The left atrial dimension (LAD) was also measured. In parallel, ejection fraction (EF) and the ratio of early filling to atrial filling (E/A) were obtained by the early diastolic (E) and atrial wave (A) velocities, and the E-wave deceleration time was measured by means of pulsed-wave Doppler recording from the apical four-chamber view. Spectral pulsed-wave Doppler-derived early diastolic velocity (e') was obtained by averaging the septal and lateral mitral annulus, and the mitral e' annular velocities (E/e') were calculated.

To examine differences in characteristics of the patients between baseline and 3 months after tofogliflozin treatment, paired *t*-test was conducted for each variable, HbA1c, body weight, systolic blood pressure, BNP, eGFR, BUN, serum

**Table 1.** Characteristics of the Patients

Variable	Men (N = 24)	Women (N = 32)
Age (years)	80.2 $\pm$ 6.4	83.1 $\pm$ 6.4
BMI	23.1 $\pm$ 3.3	23.0 $\pm$ 3.5
NYHA I/II (III, IV: none)	22/2	28/2
Co-administered drug		
DPP-4	14	23
BG	7	11
SU	5	3
Insulin	0	0
ARB	6	6
$\beta$ -blocker	5	4
CCB	10	17
Diuretics	4	13

BMI: body mass index; NYHA: New York Heart Association; DPP-4: dipeptidyl peptidase-4; BG: biguanide; SU: sulphonylurea; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker.

electrolytes, blood osmotic pressure, EF, E/A, E/e', LAD and diameter of IVC. In addition, to investigate the source of variation in EF, E/A, E/e', the fixed effect of treatment time period, gender and their interactions (time  $\times$  gender) as well as the random effect of subjects were assessed using analysis of variance with a mixed effect model. All statistical analyses were two-tailed, and  $P < 0.05$  was regarded as statistically significant. The data were analyzed using the freely available EZR (Easy R) software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [19].

## Ethical considerations

The study was conducted in accordance with the guidelines of the Declaration of Helsinki. The study was formally approved by the Clinical Research Ethics Committee of Kanazawa Medical University Himi Municipal Hospital (receipt no. 148).

## Results

The baseline characteristics of 56 elderly patients with T2DM (men: 24, women: 32) are summarized in Table 1. The total number of patients included was 56. Their mean age was 82.0  $\pm$  6.5 (mean  $\pm$  standard deviation (SD)), with range of 67 - 96 years of age. NYHA I/II was 50/4. Co-administered drugs were dipeptidyl peptidase-4 (DPP-4) (n = 37), calcium channel blocker (CCB) (n = 27), biguanide (BG) (n = 18), diuretics (n = 16), etc. During the study period, myocardial infarction, stress cardiomyopathy and exacerbation of HF were not observed. Comparison of patient characteristics at baseline, 1 month and 3 months after administration of tofogliflozin is summarized in Table 2. HbA1c tended to decrease 3 months after administration of tofogliflozin from 7.4% at baseline to 6.7% at 3 months

**Table 2.** Characteristics of Laboratory Test Results

Variable	Baseline	1 month	3 months	P-value*
HbA1c (%)	7.4 ± 1.3	7.0 ± 1.0	6.7 ± 0.8	< 0.01
Body weight (kg)	54.6 ± 10.9	52.5 ± 10.5	51.8 ± 10.1	< 0.01
Systolic blood pressure (mm Hg)	138.4 ± 24.5	125.3 ± 16.9	128.0 ± 20.1	< 0.01
Diastolic blood pressure (mm Hg)	72.0 ± 13.8	70.5 ± 11.5	72.5 ± 12.6	0.81
Hematocrit	37.9 ± 6.9	38.4 ± 5.9	38.4 ± 5.9	0.3
BNP (pg/mL)	222.8 ± 378.5	149.6 ± 240.2	186.8 ± 270.6	0.11
eGFR	60.5 ± 23.2	58.2 ± 24.3	59.3 ± 28.4	0.54
BUN (mg/dL)	19.9 ± 9.9	19.7 ± 7.2	19.5 ± 7.8	0.74
Na <sup>+</sup> (mEq/L)	138.8 ± 3.5	139.5 ± 3.0	140.5 ± 3.3	< 0.01
K <sup>+</sup> (mEq/L)	4.2 ± 0.6	4.2 ± 0.5	4.2 ± 0.5	0.78
Cl <sup>-</sup> (mEq/L)	102.5 ± 12.2	104.4 ± 5.0	106.0 ± 3.3	< 0.05
Blood osmotic pressure (mOsm/L)	292.8 ± 7.2	292.6 ± 7.3	295.1 ± 7.1	< 0.05

\*Paired *t*-test compared to baseline with 3 months after administration. HbA1c: glycated hemoglobin; BNP: brain natriuretic peptide; eGFR: estimated glomerular filtration rate; BUN: blood urea nitrogen.

**Table 3.** Characteristics of Laboratory Test Results

Variable	Baseline	1 month	3 months	P-value*
EF	64.5 ± 8.9	62.3 ± 10.6	63.3 ± 9.3	0.25
E/A	0.69 ± 0.32	0.60 ± 0.18	0.62 ± 0.17	0.31
E/e'	11.7 ± 3.9	9.9 ± 2.9	10.1 ± 3.9	< 0.05
LAD (mm)	38.8 ± 6.8	37.4 ± 6.7	37.6 ± 6.4	0.19
IVCmax (mm)	13.7 ± 3.5	13.5 ± 3.7	13.7 ± 3.6	0.61

\*Paired *t*-test compared to baseline with 3 months after administration. EF: ejection fraction; E/A: early filling/atrial filling; E/e': change in inflow E and mitral e' annular velocities; LAD: left atrial dimension; IVCmax: maximal diameter of inferior vena cava.

( $P < 0.01$ ). Body weight significantly decreased from 54.6 to 51.8 kg ( $P < 0.01$ ). Systolic blood pressures also showed significant decreases from 138.4 to 128.0 mm Hg ( $P < 0.01$ ), while diastolic blood pressure showed no significant changes from 72.0 to 72.5 mm Hg ( $P = 0.81$ ). Serum sodium and chloride significantly increased from 138.8 to 140.5 mEq/L and from 102.5 to 106.0 mEq/L, respectively. Blood osmotic pressure showed significant increase from 292.8 to 295.1. No significant changes were observed on hematocrit, BNP, eGFR, BUN and serum potassium during the treatment with tofogliflozin.

Changes in echocardiographic endpoints are summarized in Table 3. After 3-month administration of tofogliflozin, EF and E/A showed no significant changes from 64.5 to 63.3 and 0.69 to 0.62, respectively. The E/e' showed significant decrease from 11.7 to 10.1 ( $P < 0.05$ ). The LAD and IVCmax showed no significant change from 38.8 to 37.6 mm and from 13.7 to 13.7 mm, respectively. The results of analysis of variance of EF with a mixed effect model are summarized in Table 4, showing that fixed effect (treatment time) was not significant, random effect (subjects) was significant ( $P < 0.01$ ) and gender

**Table 4.** Results of Two-Factor Mixed Effect Model to Evaluate Effects and Interaction of EF

SOV	df	Sum sq.	Mean sq.	F	P-value
Time	2	125.1	62.5	2.4	0.10
Subjects	52	10,305.0	198.2	7.5	< 0.01
Gender	1	1,796.5	1,796.5	9.1	< 0.01
Time × gender	2	81.1	40.5	1.5	0.22
Error	105	2,760.2	26.3		
Total	162	15,067.8			

Analysis of variance table for the mixed effects model. EF: ejection fraction; SOV: source of variance; df: degree of freedom; Sum sq.: sum of squares; Mean sq.: mean squares; F: F statistic.

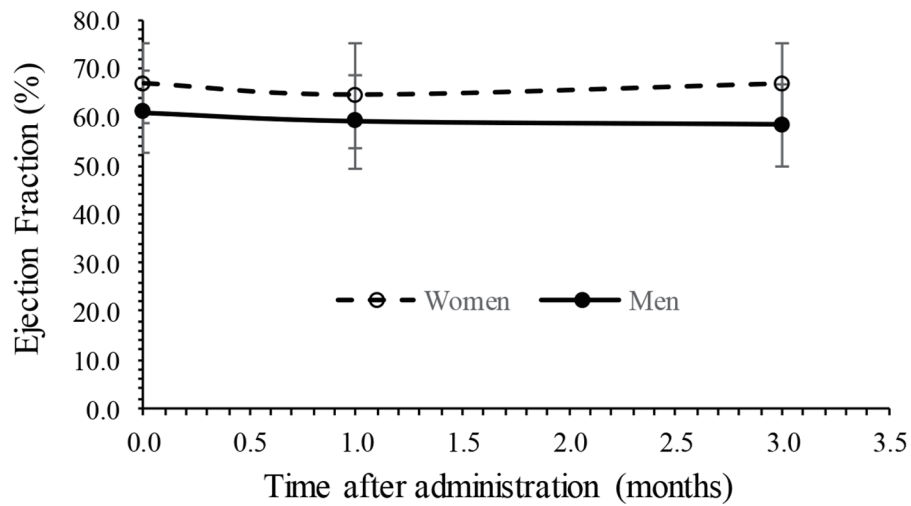


Figure 1. Interaction plot in EF between time and gender. EF: ejection fraction.

Table 5. Results of Two-Factor Mixed Effect Model to Evaluate Effects and Interaction of E/A

SOV	df	Sum sq.	Mean sq.	F	P-value
Time	2	0.04	0.02	2.7	0.07
Subjects	35	2.6	0.1	8.9	< 0.01
Gender	1	0.05	0.05	0.7	0.40
Time × gender	2	0.12	0.06	7.2	< 0.01
Error	105	0.87	0.01		
Total	162	3.7			

Analysis of variance table for the mixed effects model. E/A: early filling/atrial filling; SOV: source of variance; Sum sq.: sum of squares; df: degree of freedom; Mean sq.: mean squares; F: F statistic.

effect was also significant ( $P < 0.01$ ), whereas the interaction (time × gender) was not significant. No interaction can be observed because the time trend of EF was parallel between men and women as shown in Figure 1. The results of analysis of

variance of E/A with a mixed effect model are also summarized in Table 5, showing that fixed effect (treatment time) and gender was not significant, whereas random effect (subjects) and the interaction (time × gender) were significant ( $P < 0.01$ ).

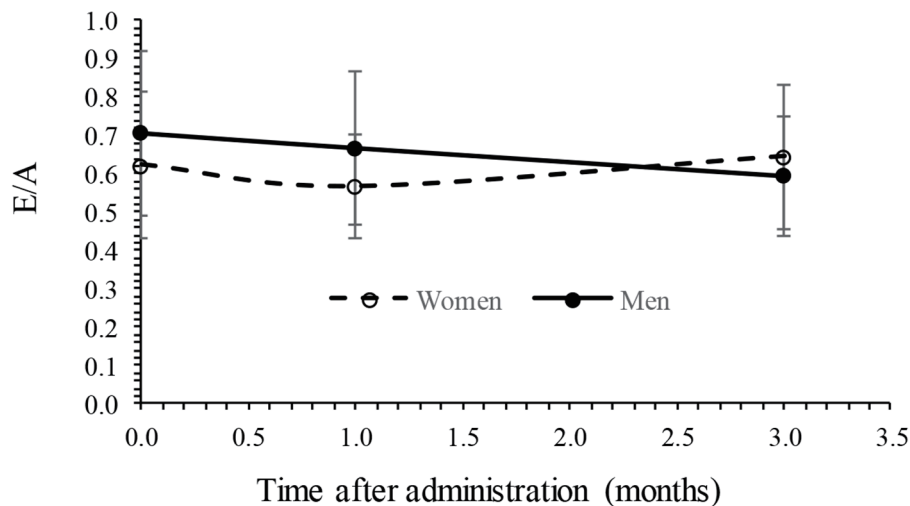


Figure 2. Interaction plot in E/A between time and gender. E/A: early filling/atrial filling.

**Table 6.** Results of two-factor mixed effect model to evaluate effects and interaction of E/e'

SOV	df	Sum sq.	Mean sq.	F	P-value
Time	2	60.9	30.5	11.5	< 0.01
Subjects	52	1012.9	19.5	7.4	< 0.01
Gender	1	36.9	36.9	1.9	0.17
Time × gender	2	11.1	5.6	2.1	0.13
Error	105	277.3	2.6		
Total	162	1,399.1			

Analysis of variance table for the mixed effects model. E/e': change in inflow E and mitral e' annular velocities; SOV: source of variance; Sum sq.: sum of squares; df: degree of freedom; Mean sq.: mean squares; F: F statistic.

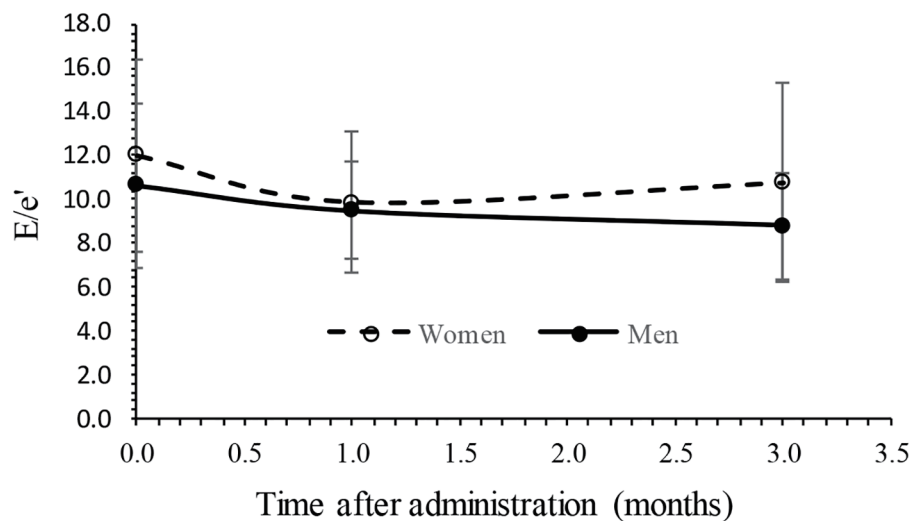
The interaction can be observed because the time trends of E/A were crossed between men and women as shown in Figure 2. The results of analysis of variance of E/e' with a mixed effect model were also summarized in Table 6, showing that fixed effect (treatment time) and random effect (subjects) were significant ( $P < 0.05$ ), whereas gender and the interaction (time × gender) were not significant. Figure 3 shows an interaction plot where women are more likely to decrease than men. The interaction was not significant ( $P = 0.13$ ).

**Discussion**

The present study found that LV diastolic function as measured by E/e' for patients with T2DM had significantly improved 3 months after administration of tofogliflozin in elderly patients with T2DM, consistent with the previous results [14-16]. Other cardiac functional parameters such as diameter of LAD and IVCmax did not change 3 months after administration of tofogliflozin. The results also suggested that body weight and systolic blood pressure significantly decreased, also consistent with the previous results [20]. The results of analysis of variance of cardiac parameters EF, E/A and E/e' with a mixed effect model found that the level of EF was higher in women

than men, interaction (time × gender) was significant in E/A, and time (fixed effect) was significant in E/e'. It has already been known previously that preserved EF tends to be higher in women than men especially in elderly, consistent with the present results [21, 22]. Men are more often contractile disorders in patients with obesity, hypertension, diabetes mellitus, anemia and chronic kidney disease than in women, and in women, estrogen, a women hormone, acts protectively on the myocardium, suggesting the possibility of preserving the LV diastolic function [23, 24].

After menopause, the absence of estrogen causes distension. Hemodynamic effects, such as reductions in blood pressure and intravascular volume, involving osmotic diuresis, may provide a more plausible explanation. Metabolic effects, such as cardiac fuel energetics, and hormonal effects, such as increased glucagon release, may also be included in the mechanism [25]. T2DM is one of the most crucial comorbidities associated with CVD that attributes to end organ damage. T2DM also increases the risk for developing HF [26] and its associated complications, including death [27]. SGLT2 inhibitors have been known to improve glycemia and promote weight loss and body fat mass reduction in humans and animals with diabetes, in part, due to caloric loss by high excretion of urinary glucose and an enhancement of oxidative metabolism from



**Figure 3.** Interaction plot in E/e' between time and gender. E/e': change in inflow E and mitral e' annular velocities.

carbohydrate to fatty acid [28, 29]. The effect of tofogliflozin on cardiac function has been known to increase EF from 48% to 61%, in parallel with increase of ketone bodies (beta-hydroxybutyrate and acetoacetate) levels in a T2DM case [30]. Although we did not measure ketone bodies, the mechanism of the effect may underlie some metabolic shift. Tofogliflozin has been known to be a most selective SGLT2 inhibitor. Compared to SGLT1, the selectivity of tofogliflozin is highest, approximately 3,000-fold [31]. SGLT2 transporter is located mostly in the kidney, whereas SGLT1 is located in various organs, i.e. small intestine, kidney, parotid glands, submandibular glands and in the heart [32]. These results suggest that the effect of SGLT2 inhibitors on cardiac functions commonly observed by both tofogliflozin and canagliflozin may not be mediated via SGLT1. LV diastolic dysfunction is the most frequently observed early LV functional abnormality in patients with T2DM [33]. The LV diastolic dysfunction is thought to be due to the underlying pathophysiological abnormality of cardiac function, and thus its assessment plays an important role for diagnosis of patients with HF. The LV diastolic dysfunction is known to be independently relevant to outcomes in patients with HF [12, 13, 34]. SGLT2 inhibitors have a multimodal effect on cardiac function including improvement in endothelial dysfunction and aortic stiffness [35]. Short-term treatment with empagliflozin is known to reduce LV diastolic function as assessed in terms of  $e'/e'$  [36]. The effects of canagliflozin on LV diastolic function as assessed by  $E/e'$  and left ventricular mass index (LVMI) had significantly improved by 3 months treatment of canagliflozin while maintaining EF [37]. A previous study also showed that 6-month treatment with dapagliflozin improved LV diastolic functional parameters including  $E/e'$ , left atrial volume index (LAVI) and LVMI [11]. Although the precise mechanism of the effect of SGLT2 inhibitors on LV diastolic function remains uncertain, significant correlation was reported between  $E/e'$  and pulmonary capillary wedge pressure [38, 39], indicating that decrease of  $E/e'$  would be beneficial in T2DM patients with HF.

The present study also showed significant decrease in systolic blood pressure during 3-month treatment with tofogliflozin, consistent with the Japanese post-marketing study [20]. Reductions in blood pressure are known to correlate with the amelioration of albuminuria in patients with T2DM [40]. Several clinical trials have also shown that SGLT2 inhibitors exert blood pressure-lowering effects through their diuretic actions, which may partially contribute to the amelioration of albuminuria in diabetic patients [41]. On the other hand, in a rodent study high-dose ipragliflozin reduced the LV chamber size while maintaining stably in blood pressure [42]. The effect of SGLT2 inhibitor on blood pressure still remains controversial, which may be partially caused by the time at which blood pressure was measured. Tofogliflozin has also been known to improve insulin resistance in both animals and humans [43-45].

### Study limitations

The results of our study should be considered in the context of several potential limitations. First, due to the observational

nature of the study, and despite robust statistical techniques, a possibility of residual, unmeasured confounding cannot be excluded. Specifically, certain patient and physician factors may not be adequately captured. Second, the present study evaluated only 3 months of drug treatment period, which could be insufficient to detect change in physiological parameters. Longer-term follow-up will be needed to clarify the effects of tofogliflozin on various physiological parameters. Second, the present study lacks control groups, thus existence of underlying contributors (exercise, diet, restricting smoking and alcohol, etc.) could affect the outcome of this study.

### Conclusion

The present study concluded that 3-month administration of tofogliflozin decreased  $E/e'$  with gender difference in EF and  $E/A$ , under preserving IVC, renal function and electrolyte balance. Tofogliflozin could improve LV diastolic function in elderly patients with T2DM. SGLT2 inhibition may emerge as an effective and safe adjunctive therapy for HF that promotes hemodynamic stability and helps correct volume overload, while avoiding the risks of volume depletion, independent of effects on hyperglycemia. Nevertheless, the mechanisms responsible for the acute cardioprotective effects of SGLT2 inhibition, such as sodium and water homeostasis and plasma volume regulation remain unknown in patients with T2DM and in those with HF. Further studies will be expected to elucidate these mechanisms.

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### Conflict of Interest

None to declare.

### Informed Consent

Informed consents were obtained from all participants.

### Author Contributions

Toshihiro Higashikawa and Tomohiko Ito have made data curation. Toshihiro Higashikawa, Takuro Mizuno, Keiichiro Ishigami, Takuro Mizuno and Kento Takashima designed

the research. Toshihiro Higashikawa conducted data analysis. Toshihiro Higashikawa acquired funding. Toshihiro Higashikawa, Masaru Kohori, Kunihiro Mae and Daisuke Usuda conducted investigation of medical records. Toshihiro Higashikawa, Susumu Takagi, Kento Takeshima, Toshihide Izumida, Shinya Yamada, Kengo Kuroki, Ryusho Sangen and Keito Takashima contributed to methodology. Atsushi Saito, Masaharu Iguchi, Yuji Kasamaki, Akihiro Fukuda, Takeshi Nakahashi, Takashi Nakahashi, Tsugiyasu Kanda and Masashi Okuro supervised this research. Toshihiro Higashikawa wrote original draft of this manuscript. All authors read and approved the final manuscript.

## Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

## Abbreviations

T2DM: type 2 diabetes mellitus; EF: ejection fraction; E/A: early filling/atrial filling; E/e': change in inflow E and mitral e' annular velocities; LAD: left atrial dimension; IVCmax: maximal diameter of inferior vena cava

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