Effects of Luseogliflozin on Left Ventricular Diastolic Function in Patients with Type 2 Diabetes and Established Cardiovascular Disease.

Yujiro Ina (✉ yujiroiii@yahoo.co.jp)

Saiseikai Fukuoka General Hospital <https://orcid.org/0000-0001-7675-2522>

Takuya Kishi

Kokusai Iryo Fukushi Daigaku

Naotaka Sekiguchi

Saiseikai Fukuoka Sogo Byoin

Original investigation

Keywords: Type 2 Diabetes, Sodium-glucose cotransporter 2 inhibitors, Left ventricular diastolic function, Heart failure with preserved ejection fraction

Posted Date: May 29th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-30054/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background:

This study aimed to evaluate the effect of luseogliflozin, an inhibitor of sodium-glucose cotransporter 2 (SGLT2), on left ventricular (LV) diastolic function in patients with type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).

Methods:

We enrolled 25 patients with T2DM and CVD and performed physical examinations, blood tests, and echocardiography before and 24 weeks after luseogliflozin treatment. The primary endpoint was defined as a change in the septal E/e' ratio as a parameter of LV diastolic function.

Results:

Luseogliflozin administered for 24 weeks significantly reduced HbA1c levels ($8.2 \pm 1.2\%$ to $7.4 \pm 0.6\%$, $p < 0.01$) and systolic blood pressure (125.6 ± 18.1 mmHg to 119.3 ± 16.8 mmHg, $p = 0.04$) compared to baseline. Luseogliflozin significantly reduced left atrial diameter (42.2 ± 5.7 mm to 39.9 ± 6.8 mm, $p = 0.01$) and LV diameter (diastolic, 49.5 ± 6.9 mm to 47.6 ± 7.6 mm, $p = 0.01$; systolic, 35.8 ± 9.1 mm to 33.9 ± 9.8 mm, $p < 0.01$). Early diastolic mitral annular tissue (e') velocity and septal E/e' ratio were significantly improved in the group of e' velocity < 6.0 cm/sec of baseline (e' velocity, 4.8 ± 0.6 cm/sec to 5.8 ± 0.9 cm/sec, $p < 0.01$; septal E/e' ratio, 13.0 ± 4.9 to 10.9 ± 3.4 , $p = 0.03$, respectively).

Conclusions:

These results suggest the possibility that luseogliflozin improves overt LV diastolic function in patients with T2DM and CVD.

Background

Type 2 diabetes mellitus (T2DM) patients have an increased risk of developing heart failure and cardiovascular disease (CVD) [1,2]. Among diabetic patients, the risk of developing chronic heart failure is more than twice as high in men and five times higher in women compared to nondiabetic patients [2]. On the other hand, diabetes is a major complication in patients with heart failure; 25% of patients with chronic heart failure and 42% of patients with acute heart failure have diabetes [3–5]. One of the major complications of heart failure in patients with T2DM is a coronary risk factor, which worsens heart failure with reduced ejection fraction (HFrEF) due to cardiac ischemia. More importantly, diabetes may not only lead to ischemic heart disease but also to left ventricular (LV) diastolic dysfunction and heart failure with

preserved ejection fraction (HFpEF) [6]. LV diastolic dysfunction, which is highly prevalent among patients with diabetes, is an independent and important predictor of adverse outcomes [7,8].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of oral antidiabetic agents that enhance urinary glucose excretion by reducing glucose reabsorption in the renal proximal tubules [9,10]. Large-scale, randomized placebo-controlled trials of SGLT2 inhibitors, such as empagliflozin for the EMPA-REG OUTCOME trial [11], canagliflozin for the CANVAS Program [12], and dapagliflozin for the DECLARE-TIMI 58 [13], found that heart failure-associated hospitalizations in patients with T2DM and CVD were significantly reduced. Additionally, the separation of the placebo and active arms in these studies became apparent within months. Also, these clinical trials have indicated that the cardiovascular benefits of SGLT2 inhibitors were not directly associated with their glucose-lowering effects.

However, it has not been still fully clarified why SGLT2 inhibitors could prevent cardiovascular events [14,15]. Moreover, the benefits of SGLT2 inhibitors in patients with HFpEF have been controversial in clinical trials and animal studies [16,17]. To overcome these backgrounds, we focused on the LV diastolic dysfunction in patients with T2DM and CVD as a major clinical indicator. In this study, we examined the beneficial effects of luseogliflozin, an SGLT2 inhibitor, on LV diastolic dysfunction.

Methods

Patients

A prospective study was performed to investigate the effect of luseogliflozin in patients with T2DM and CVD at a single center. Between July 2015 and October 2016, patients with T2DM and CVD from the outpatient center at Saiseikai Fukuoka General Hospital, Japan, were enrolled. Eligibility criteria were as follows: (1) T2DM with glycated hemoglobin (HbA1c) (NGSP) of $\geq 6.5\%$, $< 10.0\%$; (2) previous history of CVD such as chronic heart failure, ischemic heart disease, arrhythmia, cardiomyopathy, and valvular disease; and (3) experiencing no changes in a treatment regimen for glucose-lowering drugs or any other drugs during the 24 weeks before the start of this study. Exclusion criteria were as follows: (1) already taking an SGLT2 inhibitor, (2) age < 30 years or ≥ 75 years, (3) diagnosis of type 1 diabetes or insulin-dependent diabetes, (4) symptomatic heart failure (NYHA II–IV), (5) severe renal dysfunction (eGFR < 45 mL/min/1.73 m²), (6) severe liver dysfunction (over 3 $\times$ upper limit of normal), (7) diabetic ketoacidosis or diabetic coma, or (8) the presence of malignancy. The protocol was approved by the ethics committee of the Saiseikai Fukuoka General Hospital (approval number: 2019 7 – 3; date: July 7, 2019). This study was conducted according to the principles of the Helsinki Declaration II. The protocol was reviewed and approved by the Institutional Review Board, and all participants provided informed consent before beginning this study. Analysis of all participants was performed anonymously.

Study protocol

Stable heart failure patients who had been taking at least one antidiabetic agent other than an SGLT2 inhibitor were treated with luseogliflozin (2.5 mg/day). After the start of luseogliflozin treatment, the patients had not changed antidiabetic drugs. All participants underwent physical examinations and blood

tests to measure the following: HbA1c, serum creatinine, eGFR, liver function, lipid profile, and N-terminal pro-brain natriuretic peptide (NT-proBNP). In addition, the following clinical data were obtained at baseline and 24 weeks: body weight (BW), body mass index (BMI), and blood pressure.

Echocardiography examination

All patients underwent transthoracic echocardiographic examination using commercially available instruments before and after 24 weeks of luseogliflozin treatment. The left atrial diameter (LAD), left ventricular end-diastolic diameter (LVDd), and end-systolic diameter (LVDs) were measured using two-dimensional guided M-mode. Left ventricular ejection fraction (EF) was assessed using the biplane Simpson's method. Trans-mitral LV inflow velocity was recorded in the apical four-chamber view using pulse-wave Doppler sonography. Peak velocities of the early E-wave (E), atrial-wave (A), E/A deceleration time (DcT) were measured. The e' velocity was obtained, and the E/e' ratio was calculated.

Study outcomes

The primary clinical endpoint was defined as a change in the septal E/e' ratio as a parameter of LV diastolic function between baseline and 24 weeks after the start of luseogliflozin treatment. The secondary endpoints included changes in the following variables at 24 weeks after treatment relative to the baseline: (1) echocardiographic parameters: LAD, LVDs, LVDs, EF, E, A, E/A, DcT, and e' velocity; (2) glycemic control parameters: HbA1c level; (3) lipid parameters: TG, LDL cholesterol, and HDL cholesterol; (4) BW, BMI; and (5) NT-proBNP. Twenty-five patients were enrolled in the present study according to the present inclusion and exclusion criteria.

Statistical analysis

All analyses were performed with commercially available software (Microsoft Excel for Mac version 16.32, USA). Continuous variables are presented as mean $\pm$ standard deviation (SD). Categorical variables are presented as numbers and percentages. Paired t-tests were used to compare variables at baseline and 24 weeks after beginning luseogliflozin treatment.

Multiple regression analyses were performed by increasing and decreasing variables and using the response variables as the change of e' velocity and the change of E/e' ratio (after 24 weeks minus before administration). The explanatory variables were set as almost all parameters (diastolic blood pressure was excluded because some values yielded a deficit). The correlation coefficients between the response variables and the explanatory variables were calculated (all correlation coefficients). The explanatory variables in which the absolute value of the correlation coefficient with the change of e' velocity and the change of E/e' ratio change amount is less than 0.25 were excluded. A *p*-value of < 0.05 was considered statistically significant.

Results

Baseline characteristics of study patients

Table 1 shows the baseline characteristics of the 25 patients. The mean age of patients was 61.4 ± 9.1 years (mean $\pm$ SD), the mean BW was 72.2 ± 11.1 kg, and the mean HbA1c level was $8.2 \pm 1.2\%$. Of the 25 participants, 23 had chronic heart failure, and 19 had ischemic heart disease. Of the patients, 17 were receiving treatment with statins, and 21 patients were undergoing treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).

At 24 weeks after the treatment with luseogliflozin, there was a significant reduction in mean BW, BMI, systolic blood pressure, HbA1c, and liver enzyme levels (AST, ALT, γ -GT) compared to baseline levels. On the other hand, there were no significant differences in serum creatinine, HDL cholesterol, LDL cholesterol, TG, and NT-proBNP levels compared to baseline (Table 2).

Study outcome

There was no significant difference in the septal E/e' ratio at 24 weeks after the treatment with luseogliflozin compared to baseline levels. LAD, diastolic LV dimensions, and systolic LV dimensions were significantly reduced compared with baseline levels (Table 2). In the patients with overt LV diastolic dysfunction, which was determined by an e' velocity of less than 6 cm/sec at baseline (N = 13), the e' velocity and septal E/e' ratio significantly improved from 4.8 to 5.8 cm/sec ($p < 0.01$) and from 13.0 to 10.9 ($p = 0.03$), respectively (Table 3). On the other hand, there was no significant change in e' velocity or E/e' ratio in patients with a baseline e' velocity of 6 cm/sec or more at baseline (N = 12).

Multiple regression analyses were performed with the dependent variables set as the change in e' velocity, referred to as $\Delta e'$, and the change in the E/e' ratio, which is referred to as $\Delta E/e'$. There was a negative correlation between baseline e' velocity and $\Delta e'$. However, this difference was not significant ($p = 0.053$). A significant negative correlation was similarly observed for the E/e' ratio ($p = 0.016$), indicating that patients with a higher E/e' ratio at baseline showed significant improvement with luseogliflozin treatment (Fig. 1).

We found correlations between $\Delta e'$ and dyslipidemia ($r = -0.315$, $p = 0.055$) and the use of biguanides ($r = 0.470$, $p = 0.021$) and calcium channel blockers ($r = -0.428$, $p = 0.060$) at baseline. Similarly, we identified correlations between the E/e' ratio and EF ($r = -0.290$, $p < 0.001$), the use of sulfonylureas ($r = 0.410$, $p < 0.001$), and the use of β -blockers ($r = -0.273$, $p = 0.017$) at baseline (Table 4).

Discussions

This study investigated the effect of luseogliflozin on diastolic function in patients with T2DM and CVD. The results showed that the septal E/e' ratios were not significantly changed among all patients after 24 weeks of luseogliflozin treatment. However, patients with an e' velocity of less than 6 cm/sec at baseline had improved e' velocity and septal E/e' ratios. These results suggest that luseogliflozin may improve LV diastolic function in patients with T2DM and overt LV diastolic dysfunction at baseline. Also, luseogliflozin improved weight loss, glycemic control, and liver function.

Weight loss, lower systolic blood pressure, and decreased HbA1c are common effects of treatment with SGLT2 inhibitors, including luseogliflozin. Previous studies suggested the decrease in BW occurs during the initiation of treatment. This weight loss may be attributed to osmotic diuresis due to increased urinary glucose excretion [18]. The decrease in blood pressure is thought to be caused by a decrease in body fluid volume, and the increased excretion of glucose lowers HbA1c levels. Furthermore, the loss of extra energy likely improved the body's metabolic function which helped improve liver function.

Echocardiographic findings that are used to evaluate LV diastolic function include structural changes, such as an increase in left atrial volume index or LV mass index; functional changes, such as an increased E/e' ratio or reduced e' velocity; and indirect measurements, such as increased tricuspid regurgitant velocity [19]. Among these metrics, e' velocity obtained by tissue Doppler imaging is useful for estimating LV myocardial relaxation activity. Furthermore, decreased e' velocity may indicate the progression of LV diastolic dysfunction [20]. Previous studies have shown that the average E/e' ratio of diabetic patients increases consistently compared to nondiabetic patients [7]. The present study provides us the meaningful clinical implications because this is the first prospective study examining the effects of luseogliflozin on LV diastolic function in patients with T2DM and CVD. While there was no significant change in the septal E/e' ratio after 24 weeks of luseogliflozin treatment, luseogliflozin improved LV diastolic function assessed by e' velocity and E/e' ratio in patients with overt LV diastolic dysfunction at baseline. Recently, several studies have demonstrated the effects of SGLT2 inhibitors on LV diastolic function in patients with diabetes using echocardiography. Verma et al. reported that using empagliflozin for 3 months improved the LV diastolic function based on changes in e' velocity among 10 diabetic patients with CVD [21]. Dapagliflozin [22] and canagliflozin [23,24] significantly reduced the E/e' ratio in T2DM patients, and dapagliflozin was associated with improvement of LV longitudinal myocardial function [25]. This study further confirms the cardioprotective effects of SGLT2 inhibitors.

Cardiovascular prognosis in patients with diabetes is poor because diabetes has been linked to HFrEF and HFpEF [26]. The prevalence of HFpEF has been increasing since 2000 and accounts for more than 50% of hospital admissions for heart failure [27]. ACE inhibitors, ARBs [28], and β -blockers [29] are useful for treating HFrEF, and SGLT2 inhibitors have improved cardiovascular outcomes, including HFrEF, in three large clinical trials: EMPA-REG OUTCOME [11], CANVAS Program [12], and DECLARE-TIMI 58 [13]. On the other hand, few studies are focusing on effective therapeutic agents for treating patients with HFpEF. Considering these clinical studies and our present study, we propose that luseogliflozin may be particularly effective in treating patients with HFpEF.

Some studies showed that SGLT2 inhibitors reduced all-cause mortality [30], and other meta-analyses and systematic reviews suggested that SGLT2 inhibitors protect against CVD and death in diverse subsets of the patients with T2DM regardless of CVD history [31]. Several mechanisms through which SGLT2 inhibitors have improved cardiovascular events have been studied; however, it is unclear which mechanism is most crucial [15]. The potential effects of SGLT2 inhibitors on LV structure and function are multifaceted, and these effects may be due to effects on systemic hemodynamics and metabolism [32]. SGLT2 inhibitors reduce circulating blood volume through osmosis and natriuresis. The diuretic

effect of SGLT2 inhibitors reduces plasma volume, which is a potential factor in reducing hospitalizations due to heart failure [33]. The most commonly used loop diuretics and thiazides also reduce the intravascular volume and pure sodium balance as well as or better than SGLT2 inhibitors. However, in contrast to empagliflozin, these diuretics have not been proven to reduce cardiovascular mortality. This is probably because SGLT2 inhibitors, unlike loop and thiazide diuretics, do not cause reflex activation of the sympathetic nervous system. Such hemodynamic changes in intravascular volume and blood pressure observed during SGLT2 treatment are not accompanied by an increase in heart rate. Therefore, SGLT2 inhibitors may reduce the activation of the reflex sympathetic nervous system or implicate other neurohormonal pathways that affect the heart [34,35]. The significant effects of SGLT2 inhibitors on cardiovascular outcomes may also be attributed to the anti-oxidative, anti-inflammatory, or anti-apoptotic properties of SGLT2 inhibitors as shown in experimental models [15,36,37]. However, whether such effects seen in such preclinical studies affect humans remains to be determined. In the present study, we could not assess the mechanism through which luseogliflozin improved LV diastolic function in patients with T2DM and overt LV diastolic dysfunction at baseline. Further basic experiments are necessary for the future.

In this study, we selected luseogliflozin because it is highly selective for SGLT2 and was previously launched in Japan to treat the patients with T2DM. The structural feature of luseogliflozin is a 5-thioglucose analog that has a sulfur atom in place of oxygen in the glucose ring [38]. Clinical studies have shown that once-daily administration of luseogliflozin, unlike other SGLT2 inhibitors, leads to significant improvement of HbA1c levels at a very low dose of 2.5 mg. Luseogliflozin has the lowest effective dose among all SGLT2 inhibitors prescribed in Japan [18]. Recent inhibition kinetics and binding studies of luseogliflozin have shown that the dissociation of luseogliflozin from SGLT2 appears to be much slower than those of other SGLT2 inhibitors. For instance, the dissociation half-time of luseogliflozin–SGLT2 was approximately 7 h [39]. These characteristics of luseogliflozin might contribute to its long duration of action; however, the exact mechanism of binding is not revealed. Luseogliflozin lowers plasma glucose concentration and BW and has beneficial effects on other clinically relevant parameters, including blood pressure and uric acid, among patients with T2DM [38]. The decreases in HbA1c and BW from baseline to the end of treatment were – 0.63% and – 2.70 kg after 24 weeks of treatment; these results were similar to those produced by other SGLT2 inhibitors [39].

This study contained several limitations that need to be addressed. For instance, it was a single-center study and included a small number of patients without a placebo-controlled group. Further prospective studies with larger populations are needed to confirm our study results. In general, long-term observation is required to investigate the suppression of CV events; since this study was short term, a relationship between CV events could not be confirmed. Furthermore, detail hemodynamic evaluations were not performed using a cardiac catheter examination. Finally, we could not verify whether these effects were specific to luseogliflozin or shared by other SGLT2 inhibitors.

Conclusions

Luseogliflozin improved hemodynamics associated with LV diastolic function in patients with T2DM and CVD. These results demonstrate the potential cardioprotective effects of SGLT2 inhibitors in patients with T2DM with CVD.

Abbreviations

T2DM: type 2 diabetes mellitus; CVD: cardiovascular disease; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; LV: left ventricular; SGLT2: sodium-glucose cotransporter 2; HbA1c: glycated hemoglobin; NT-proBNP: N-terminal pro-brain natriuretic peptide; BW: body weight; BMI: body mass index; LAD: left atrial diameter; LVDd: left ventricular end-diastolic diameter; LVDs: end-systolic diameter; EF: ejection fraction; e': early diastolic mitral annular tissue; E: peak velocities of the early E-wave; A: peak velocities of the atrial-wave; DcT: E/A deceleration time; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker.

Declarations

Ethics approval and consent to participate.

This study was approved by the local ethics committee of Saiseikai Fukuoka General Hospital.

Consent for publication

The consent to publish was obtained from all participants in this study.

Availability of data and materials

The data analyzed during this study are available from the corresponding author of this article upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Taisho Pharmaceutical Co., Ltd. (former Taisho Toyama Pharmaceutical Co., Ltd.) provided funding for analysis and editorial. There is no grant number. They didn't dictate or modify the results of the study.

Authors' contributions

YI wrote the manuscript and research data. TK and NS reviewed/edited the manuscript.

Acknowledgements

We gratefully acknowledge the technical assistance of the physiological laboratory staff of Saiseikai Fukuoka General Hospital.

Authors' information

¹Department of Diabetes, Saiseikai Fukuoka General Hospital, Tenjin 1-3-46, Fukuoka, Chuo-ku, Fukuoka 810-0001 Japan.

²Department of Graduate School of Medicine (Cardiology), International University of Health and Welfare, Enokizu 137-1, Okawa, Fukuoka, 831-8501, Japan.

References

1. Vazquez-Benitez G, Desai JR, Xu S, Goodrich GK, Schroeder EB, Nichols GA, Segal J, Butler MG, Karter AJ, Steiner JF, et al. Preventable Major Cardiovascular Events Associated With Uncontrolled Glucose, Blood Pressure, and Lipids and Active Smoking in Adults With Diabetes With and Without Cardiovascular Disease: A Contemporary Analysis. *Diabetes Care*. 2015;38:905–12.
2. Kannel WB, McGee DL. Diabetes and Cardiovascular Disease: The Framingham Study. *Jama*. 1979;241:2035–8.
3. Stratton I, Adler A, Neil H, Matthews D, Manley S, Cull C, Turner R, Holman R. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *Bmj Clin Res Ed*. 2000;321:405–12.
4. Metra M, Zacà V, Parati G, Agostoni P, Bonadies M, Ciccone M, Cas A, Iacoviello M, Lagioia R, Lombardi C, et al. Cardiovascular and noncardiovascular comorbidities in patients with chronic heart failure. *J Cardiovasc Med*. 2011;12:76–84.
5. MacDonald M, Petrie M, Varyani F, Ostergren J, Michelson E, Young J, Solomon S, Granger C, Swedberg K, Yusuf s, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J*. 2008;29:1377–85.

6. McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. *Lancet Diabetes Endocrinol.* 2014;2:843–51.
7. Bouthoorn S, Valstar GB, Gohar A, Ruijter HM den, Reitsma HB, Hoes AW, Rutten FH. The prevalence of left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in men and women with type 2 diabetes: A systematic review and meta-analysis. *Diabetes Vasc Dis Re.* 2018;15:477-93; DOI:1479164118787415.
8. From AM, Scott CG, Chen HH. The Development of Heart Failure in Patients With Diabetes Mellitus and Pre-Clinical Diastolic Dysfunction. *J Am Coll Cardiol.* 2010;55:300–5.
9. Abdul-Ghani MA, DeFronzo RA, Norton L. Novel Hypothesis to Explain Why SGLT2 Inhibitors Inhibit Only 30–50% of Filtered Glucose Load in Humans. *Diabetes.* 2013;62:3324–8.
10. Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. *Diabetic Med.* 2010;27:136–42.
11. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New Engl J Medicine.* 2015;373:2117–28.
12. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondur N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *New Engl J Medicine.* 2017;377:644–57.
13. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *New Engl J Med.* 2019;380:347-57.
14. Matsumura K, Sugiura T. Effect of sodium glucose cotransporter 2 inhibitors on cardiac function and cardiovascular outcome: a systematic review. *Cardiovasc Ultrasoun.* 2019;17:26.
15. Lan N, Fegan GP, Yeap BB, Dwivedi G. The effects of sodium-glucose cotransporter 2 inhibitors on left ventricular function: current evidence and future directions. *Esc Hear Fail.* 2019;6:927–35.
16. Connelly K, Zhang Y, Visram A, Advani A, Batchu S, Desjardins J, Thai K, Gilbert RE. Empagliflozin Improves Diastolic Function in a Nondiabetic Rodent Model of Heart Failure With Preserved Ejection Fraction. *Jacc Basic Transl Sci.* 2019;4:27–37.
17. Joubert M, Jagu B, Montaigne D, Marechal X, Tesse A, Ayer A, Dollet L, May CL, Toumaniantz G, Manrique A, et al. The Sodium–Glucose Cotransporter 2 Inhibitor Dapagliflozin Prevents Cardiomyopathy in a Diabetic Lipodystrophic Mouse Model. *Diabetes.* 2017;66:1030–40.
18. Seino Y, Sasaki T, Fukatsu A, Ubukata M, Sakai S, Samukawa Y. Efficacy and safety of luseogliflozin as monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, phase 3 study. *Curr Med Res Opin.* 2014;30:1245–55.
19. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure The Task Force for the diagnosis and treatment of acute and chronic heart

- failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–200.
20. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277–314.
 21. Verma S, Garg A, Yan AT, Gupta AK, Al-Omran M, Sabongui A, Teoh H,
 22. Mazer CD, Connelly KA. Effect of Empagliflozin on Left Ventricular Mass and Diastolic Function in Individuals With Diabetes: An Important Clue to the EMPA-REG OUTCOME Trial? *Diabetes Care*. 2016;39:e212–3.
 23. Soga F, Tanaka H, Tatsumi K, Mochizuki Y, Sano H, Toki H, Matsumoto K, Shite J, Takaoka H, Doi T, et al. Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure. *Cardiovasc Diabetol*. 2018;17:132.
 24. Matsutani D, Sakamoto M, Kayama Y, Takeda N, Horiuchi R, Utsunomiya K. Effect of canagliflozin on left ventricular diastolic function in patients with type 2 diabetes. *Cardiovasc Diabetol*. 2018;17:73.
 25. Sezai A, Sekino H, Unosawa S, Taoka M, Osaka S, Tanaka M. Canagliflozin for Japanese patients with chronic heart failure and type II diabetes. *Cardiovasc Diabetol*. 2019;18:76.
 26. Tanaka H, Soga F, Tatsumi K, Mochizuki Y, Sano H, Toki H, Toki H, Matsumoto K, Shite J, Takaoka H, et al. Positive effect of dapagliflozin on left ventricular longitudinal function for type 2 diabetic mellitus patients with chronic heart failure. *Cardiovasc Diabetol*. 2020;19:6.
 27. Varela-Roman A, Shamagian LG, Caballero EB, Ramos PM, Veloso PR, Gonzalez-Juanatey JR. Influence of diabetes on the survival of patients hospitalized with heart failure: A 12-year study. *Eur J Heart Fail*. 2005;7:859–64.
 28. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction. *New Engl J Med*. 2006;355:251–9.
 29. Mancia G, Fagard R, Narkiewicz K, Redán J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, Backer GD, Dominiczak A, et al. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1925–38.
 30. Connelly KA, Gilbert RE, Liu P. Treatment of Diabetes in People With Heart Failure. *Can J Diabetes*. 2018;42:S196–200.
 31. Clegg LE, Heerspink HJL, Penland RC, Tang W, Boulton DW, Bachina S, Fox RD, Fenici P, Thuresson M, Mentz RJ, et al. Reduction of Cardiovascular Risk and Improved Estimated Glomerular Filtration Rate by SGLT2 Inhibitors, Including Dapagliflozin, Is Consistent Across the Class: An Analysis of the Placebo Arm of EXSCEL. *Diabetes Care*. 2018;42:dc181871.
 32. Arnott C, Li Q, Kang A, Neuen BL, Bompont S, Lam CSP, Rodgers A, Mahaffey KW, Cannon CP, Perkovic V, et al. Sodium-Glucose Cotransporter 2 Inhibition for the Prevention of Cardiovascular

- Events in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *J Am Heart Assoc.* 2020;9:e014908.
33. Sattar N, McLaren J, Kristensen SL, Preiss D, McMurray JJ. SGLT2 Inhibition and cardiovascular events: why did EMPA-REG Outcomes surprise and what were the likely mechanisms? *Diabetologia.* 2016;59:1333–1339.
34. Sha S, Polidori D, Heise T, Natarajan J, Farrell K, Wang S-S, Sica D, Rothenberg P, Plum-Mörschel L. Effect of the sodium glucose co-transporter 2 inhibitor canagliflozin on plasma volume in patients with type 2 diabetes mellitus. *Diabetes Obes Metabolism.* 2014;16:1087–95.
35. Chilton R, Tikkanen I, Cannon C, Crowe S, Woerle H, Broedl U, Johansen OE. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. *Diabetes Obes Metabolism.* 2015;17:1180–93.
36. Sano M. A new class of drugs for heart failure: SGLT2 inhibitors reduce sympathetic overactivity. *J Cardiol.* 2018;71:471–6.
37. Kitada K, Nakano D, Ohsaki H, Hitomi H, Minamino T, Yatabe J, Felder RA, Mori H, Masaki T, Kobori H, et al. Hyperglycemia causes cellular senescence via a SGLT2- and p21-dependent pathway in proximal tubules in the early stage of diabetic nephropathy. *J Diabetes Complicat.* 2014;28:604–11.
38. Tahara A, Kurosaki E, Yokono M, Yamajuku D, Kihara R, Hayashizaki Y, Takasu T, Imamura M, Li Q, Tomiyama H, et al. Effects of SGLT2 selective inhibitor ipragliflozin on hyperglycemia, hyperlipidemia, hepatic steatosis, oxidative stress, inflammation, and obesity in type 2 diabetic mice. *Eur J Pharmacol.* 2013;715:246–55.
39. Yabe D, Hamamoto Y, Seino Y, Kuwata H, Kurose T, Seino Y. Sodium glucose co-transporter 2 inhibitor luseogliflozin in the management of type 2 diabetes: a drug safety evaluation. *Expert Opin Drug Saf.* 2017;16:1211–8.
40. Uchida S, Mitani A, Gunji E, Takahashi T, Yamamoto K. In vitro characterization of luseogliflozin, a potent and competitive sodium glucose co-transporter 2 inhibitor: Inhibition kinetics and binding studies. *J Pharmacol Sci.* 2015;128:54–7.
- 41.

Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

Figure 1

Univariate correlates of changes in the e' velocity and E/e' ratio

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.xls](#)
- [Table1.xls](#)
- [Table1.xls](#)
- [Table2.xls](#)
- [Table2.xls](#)
- [Table2.xls](#)
- [Table3.xls](#)
- [Table3.xls](#)
- [Table3.xls](#)
- [Table4.xls](#)
- [Table4.xls](#)
- [Table4.xls](#)