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Effects of luseogliflozin on arterial properties in patients with type 2 diabetes mellitus: The multicenter, exploratory LUSCAR study

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Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the occurrence of cardiovascular and renal complications in patients with type 2 diabetes mellitus (T2DM) and represent guideline-recommended therapy in this indication. However, precise mechanisms underlying the beneficial cardiovascular effects of SGLT2 inhibitors are not fully understood. This study investigated the effects of the SGLT2 inhibitor, luseogliflozin, on arterial properties and home blood pressure (BP) in patients with T2DM. This multicenter, single-arm study enrolled adults with T2DM, glycosylated hemoglobin (HbA1c) 6.5%–8.9% in the previous 4 weeks, and an indication for new/additional antidiabetic therapy. Luseogliflozin 2.5 mg/d was given for 12 weeks. Primary outcome was change in cardio-ankle vascular index (CAVI) from baseline to Week 4 and Week 12. Home and office BP, BP variability, and metabolic parameters were secondary endpoints. Forty-seven patients (mean age 63.5 ± 10.7 years) treated with luseogliflozin were included in the full analysis set. CAVI did not change significantly from baseline (mean [95% confidence interval] 8.67 [8.37–8.97]) to Week 12 (8.64 [8.38–8.91]; $P = .750$), but there were significant reductions from baseline in morning home BP, HbA1c, body weight, body mass index, and serum uric acid levels during luseogliflozin therapy. The reduction in morning home systolic BP was ≥ 5 mm Hg and was independent of baseline BP and BP control status. In conclusion, there was no change in arterial stiffness (based on CAVI) during treatment with luseogliflozin, but changes in BP and metabolic parameters were consistent with the known beneficial effects of SGLT2 inhibitors in T2DM.

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1 | INTRODUCTION

A growing body of evidence from randomized clinical trials suggests that treatment with sodium-glucose cotransporter 2 (SGLT2) inhibitors protects against the occurrence of cardiorenal complications in patients with type 2 diabetes mellitus.¹⁻⁴ Based on these data, recent guidelines recommend use of SGLT2 inhibitors as first-line treatment for high cardiovascular risk patients with type 2 diabetes to reduce rates of major adverse cardiovascular events (MACE), hospitalization for heart failure, chronic kidney disease progression, or cardiovascular death, irrespective of baseline glycosylated hemoglobin (HbA1c).⁵

Despite the positive results from clinical trials and evidence-based guideline recommendations for the use of SGLT2 inhibitors, the precise mechanisms underlying the cardiorenal protective effects of these agents remain to be fully elucidated. A number of beneficial cardiovascular effects of SGLT2 inhibitors have been investigated, including reductions in blood pressure (BP),^{6,7} attenuation of the salt sensitivity of BP,⁸ improvements in arterial stiffness,⁹ and sympatholytic effects.⁸ We recently demonstrated that SGLT2 inhibitors significantly reduced out-of-office BP determined using ambulatory or home BP monitoring compared with placebo or control in patients with type 2 diabetes and uncontrolled nocturnal hypertension (a salt-sensitive hypertension phenotype).^{10,11}

Arterial stiffness is gaining increased recognition as an important contributor to the development of hypertension, hypertensive end-organ damage, cardiovascular disease, and all-cause mortality.¹²⁻¹⁶ The results of our recent prospective study in normotensive patients showed that increased arterial stiffness, evaluated using the cardio-ankle vascular index (CAVI), was associated with the future development of hypertension.¹⁷ In addition, arterial stiffness plays a central role in the vicious cycle of hemodynamic stress and vascular disease that triggers organ damage and increases the risk of cardiovascular events, known as the systemic hemodynamic atherosclerotic syndrome (SHATS).¹⁸⁻²¹ Therefore, reducing arterial stiffness has the potential to attenuate this vicious cycle and reduce cardiovascular risk. This is especially the case for patients in the early stage of diabetes, who are at elevated risk of developing vascular complications.²²

The multicenter explorative study of beneficial effect of luseogliflozin on cardiovascular function in Japanese patients with type 2 diabetes mellitus (LUSCAR) investigated the effects of the SGLT2 inhibitor luseogliflozin on arterial properties and home BP in patients with type 2 diabetes.

2 | METHODS

2.1 | Study design

This multicenter ($n = 7$), open-label, single-arm study was conducted in Japan between March 2019 and October 2019. The trial was registered at the Japanese Registry of Clinical Trials (<https://jrct.niph.go.jp/search; jrct031180434>). The study protocol was approved by the Jichi Medical University Clinical Research Ethics Committee

(Tochigi, Japan), and all patients provided written informed consent before study entry. Study procedures were performed in accordance with Clinical Trials Act (Japan) and the principles outlined in the Declaration of Helsinki.

2.2 | Participants

Males or females aged 20-74 years with type 2 diabetes mellitus (treated or untreated), HbA1c 6.5%-8.9% within the 4 weeks prior to enrollment, and an indication for the initiation or addition of new antidiabetic therapy were eligible to participate in the study.

Exclusion criteria included type 1 diabetes mellitus; use of SGLT2 inhibitors, insulin or a glucagon-like peptide-1 (GLP-1) receptor agonist; change in antihypertensive or antihyperglycemic therapy within the previous 12 weeks; history of serious adverse reactions to SGLT2 inhibitors; history of cerebral infarction; severe renal dysfunction (estimated glomerular filtration rate <30 mL/min/1.73 m² or undergoing dialysis); severe liver dysfunction; pituitary dysfunction or adrenal insufficiency; pregnancy, possible pregnancy or breastfeeding; and participation in another clinical study.

2.3 | Intervention

Patients were treated with luseogliflozin (Lusefi[®]) 2.5 mg/d, either as monotherapy (previously untreated patients) or added to existing antidiabetic therapy.

2.4 | Outcomes

The primary outcome was the change in CAVI from baseline to Week 4 and Week 12. Secondary outcomes were changes in the following parameters from baseline to Week 4 and Week 12: ankle-brachial pressure index (ABI); pulse wave velocity (PWV); ECG; BP (average systolic BP [SBP], diastolic BP [DBP], heart rate, and BP variability) based on home and office readings; and metabolic parameters (HbA1c, body weight, body mass index [BMI], lipid levels, and uric acid levels). Changes in the brachial and ankle pulse waveforms were evaluated as exploratory endpoints.

2.5 | Assessments

There was an 8-week observation period at baseline to allow for patient screening, consent, and enrollment. This was followed by a 12-week treatment period; other treatments for diabetes plus nutritional and exercise therapy were continued unchanged throughout the trial. The following assessments were performed at baseline, Week 4, and Week 12: body weight, BMI, ECG, home (morning, evening) and office BP, HbA1c, CAVI, ABI, PWV, and blood and urinary laboratory tests.

BP measurements were performed in accordance with the 2014 Japanese Society of Hypertension guidelines.²³ Office BP was measured after ≥ 5 minutes of rest with the patient seated in a chair with the arm cuff level with the heart. Smoking was prohibited for 30 minutes before the measurement. Several consecutive measurements were taken at intervals of ≥ 1 minute, and the average of two measurements was used to define the office BP. Home BP measurement was performed using a cuff oscillometric device (HEM-7080-IC; Omron Healthcare Co., Ltd., Kyoto, Japan). Patients were instructed to measure their morning home BP (two readings within 1 hour after waking, taken after urination, before taking morning medications and after 1-2 minutes of seated rest) and evening home BP (two readings before bedtime after 1-2 minutes of seated rest) on 5 successive days immediately prior to their scheduled clinic visit at baseline, Week 4, and Week 12.

CAVI was measured using a CAVI device (Vasera VS1500 or VS3000; Fukuda Denshi, Tokyo, Japan). Examinations were performed after a 5-minute rest period. The pressure of all cuffs was kept at 50 mm Hg to minimize the effect of cuff pressure on hemodynamics. BP was then measured. CAVI was determined using the following formula:

$$\text{CAVI} = a \left[(2\rho/\Delta P) \times \ln(P_s/P_d) \text{PWV}^2 \right] + b$$

where a and b are constants, ρ is blood density, ΔP is $P_s - P_d$, P_s is systolic blood pressure, P_d is diastolic blood pressure, and PWV is pulse wave velocity.

PWV was determined by dividing vascular length by the time (T) taken for the pulse wave to travel from the aortic valve to the ankle. However, in practice, T was difficult to obtain because the time the blood left the aortic valve was difficult to identify from the sound of the valve opening. Therefore, because the time between the sound of the aortic valve closing and the notch of the brachial pulse wave is theoretically equal to the time between the sound of the aortic valve opening and the rise of the brachial pulse wave, T was determined by adding the time between the sound of the aortic valve closing and the notch of the brachial pulse wave, and the time between the rise of the brachial pulse wave and the rise of the ankle pulse wave.

The pulse waveforms of the right and left arms and ankles were measured, and digital data were stored in the CAVI device for arterial wave form analysis. The following arterial waveform indices were calculated: percent mean arterial pressure (%MAP) and up-stroke time of ankle pressure waveforms²⁴; and augmentation index and reflection magnitude of the arm pressure waveforms (average of right and left arms).²⁵

2.6 | Statistical analysis

To the best of our knowledge, there is no study to date using CAVI as an outcome measure for evaluating the effect of luseogliflozin on cardiovascular properties. Therefore, it was assumed that the effect of luseogliflozin on cardiovascular properties could be estimated by looking at the change in CAVI at the time during

luseogliflozin treatment when a significant reduction in HbA1c was seen. Therefore, we set the HbA1c difference from baseline at 0.5% and the standard deviation of 1.0%. On this basis, it was calculated that inclusion of 40 patients would provide 80% power at $P = .05$ (2-sided). The target sample size was set at 50 patients to allow for a 20% dropout rate.

Patients who were non-compliant with the Ethical Guidelines for Clinical Research were excluded from all analyses (both efficacy and safety). The full analysis set (FAS) included all enrolled patients who received at least one dose of study medication after enrollment and had at least one set of data during treatment. The safety analysis set (SAS) included all patients who had received at least one dose of study medication after enrollment.

The efficacy analyses were conducted in the FAS. Pearson correlation analysis was used to calculate correlation coefficients for the relationship between changes in two different factors. Mixed-effects model repeated measures (MMRM) analysis was used to evaluate changes in CAVI and other outcomes from baseline to Week 4 or Week 12. MMRM included the time point (baseline, 4, and 12 weeks) as fixed effects, and ages and sex as covariates. Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA) at The Institute of Japanese Union of Scientists & Engineers, Tokyo, Japan. A 2-sided P -value of $< .05$ was considered statistically significant.

3 | RESULTS

3.1 | Patients

A total of 51 patients were enrolled, three withdrew consent prior to treatment and 48 were treated with luseogliflozin. Of these, one additional patient withdrew consent, leaving 47 patients in the FAS (Figure S1). Nearly two-thirds of patients were male, mean age showed an older population (63.5 ± 10.7 years), just over half the population were receiving antidiabetic therapy at baseline, and hypertension and dyslipidemia were the most common comorbidities (Table 1).

3.2 | CAVI

There was no significant change in CAVI during 12 weeks of treatment with luseogliflozin ($P = .750$ vs baseline at Week 12) (Figure 1A, Table 2).

3.3 | Secondary endpoints

Morning home SBP and DBP decreased significantly from baseline after 4 and 12 weeks of treatment with luseogliflozin (Figure 1B), but there was no change in morning heart rate or office BP over time (Table 2). There were also significant reductions in HbA1c (Figure 1C), body weight (Figure 1D), BMI (Table 2), and uric acid

TABLE 1 Patient demographic and clinical characteristics at baseline (full analysis set)

	Patients (n = 47)
Age, y	63.5 ± 10.7
Male, n (%)	30 (63.8)
Weight, kg	72.4 ± 17.7
BMI, kg/m ²	26.8 ± 5.6
Diabetes duration, y	5.7 ± 6.0
Current smoking, n (%)	9 (19.1)
Current alcohol use, n (%)	18 (38.3)
Comorbidities, n (%)	
Peripheral diabetic neuropathy	5 (10.6)
Nephropathy	5 (10.6)
Retinopathy	3 (6.4)
Hypertension	39 (83.0)
Dyslipidemia	25 (53.2)
Cerebrovascular disease	2 (4.3)
Cardiac disease	2 (4.3)
Chronic kidney disease	1 (2.1)
Liver disease	2 (4.3)
Antidiabetic drugs, n (%)	27 (57.4)
Sulfonylureas	0 (0)
α-glucosidase inhibitor	0 (0)
DPP-4 inhibitor	12 (25.5)
Metformin	16 (34.0)
Thiazolidinedione	0 (0)
Glinide	0 (0)
Antihypertensive drugs, n (%)	36 (76.6)
ACE inhibitor	0 (0)
ARB	29 (61.7)
Alpha-/beta-blocker	1 (2.1)
Alpha-blocker	0 (0)
CCB	28 (59.6)
Diuretic	10 (21.3)
CAVI	8.8 ± 1.2
ABI	1.1 ± 0.1
PWV, cm/s	1789.4 ± 308.4
Office SBP, mm Hg	131.8 ± 14.8
Office DBP, mm Hg	75.9 ± 10.4
Office HR, beats/min	72.9 ± 11.3
Morning home SBP, mm Hg	129.6 ± 15.5
Morning home DBP, mm Hg	75.4 ± 10.6
Morning home HR, beats/min	68.8 ± 9.3
Evening home SBP, mm Hg	126.6 ± 15.1
Evening home DBP, mm Hg	71.7 ± 10.2
Evening home HR, beats/min	72.4 ± 9.1
HbA1c, %	7.0 ± 0.5

(Continues)

TABLE 1 (Continued)

	Patients (n = 47)
LDL cholesterol, mg/dL	110.1 ± 25.2
HDL cholesterol, mg/dL	52.6 ± 12.2
Triglycerides, mg/dL	178.3 ± 205.5
Uric acid, mg/dL	6.0 ± 1.2
Estimated glomerular filtration rate, mL/min/1.73 m ²	74.4 ± 19.5

Note: Data are presented as mean ± standard deviation or number of patients (%).

Abbreviations, ABI, ankle-brachial pressure index; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CAVI, cardio-ankle vascular index; CCB, calcium channel blocker; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; PWV, pulse wave velocity; SBP, systolic blood pressure.

(Table 2) during luseogliflozin therapy. Statistically significant and comparable reductions in BP were seen when patients were divided into subgroups based on BP control status at baseline (baseline SBP ≥ 130 mm Hg [uncontrolled] or <130 mm Hg [controlled]) (Figure 2). There were marginally, but not statistically, significant correlations between the 12-week change in morning home SBP and changes in BMI ($r = 0.269$, $P = .089$).

Levels of high-density lipoprotein (HDL) cholesterol were significantly higher than baseline after 12 weeks' luseogliflozin therapy, but there were no significant changes in levels of low-density lipoprotein cholesterol or triglycerides (Table 2).

3.4 | Atrial waveform indices

After 12 weeks' treatment with luseogliflozin, %MAP in the ankle was significantly lower than at baseline (Table 3); other waveform indices did not change significantly during treatment with luseogliflozin.

3.5 | Safety

Luseogliflozin was well tolerated, and no serious adverse events occurred during treatment (Table 4).

4 | DISCUSSION

Although there were significant improvements in BP and other metabolic parameters during treatment with luseogliflozin in patients with type 2 diabetes mellitus, no changes in arterial stiffness measured using CAVI were seen during this single-center, open-label study. However, %MAP, a measure of arterial properties, was significantly improved during luseogliflozin therapy.

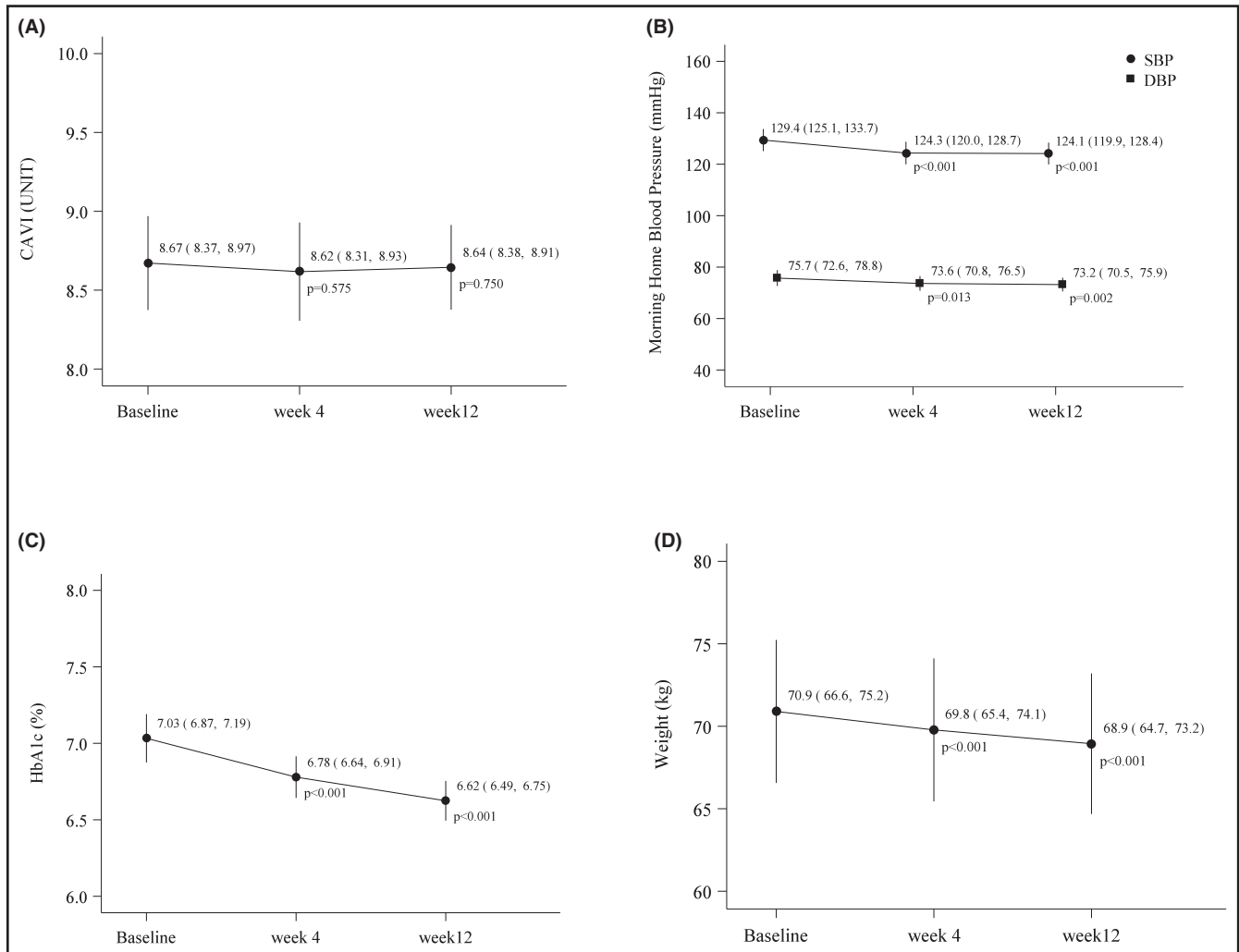


FIGURE 1 Changes in endpoint parameters during treatment with luseogliflozin. A, Cardio-ankle vascular index (CAVI); B, Morning home blood pressure; C, Glycosylated hemoglobin (HbA1c); D, Body weight. DBP, diastolic blood pressure; SBP, systolic blood pressure. Data are adjusted for age and sex, and shown as mean values with 95% confidence intervals

In this study, we used CAVI as a measure of arterial stiffness. This approach is relatively independent of both BP and heart rate and is easy to use and reproducible.^{26,27} CAVI has been shown to be associated with BP variability,^{28,29} and elevated values have been reported in patients with hypertension and diabetes mellitus.³⁰ Preclinical data indicate a potential for SGLT2 inhibitors to improve arterial stiffness.^{31,32} However, we did not see any change in arterial stiffness based on CAVI during treatment with luseogliflozin for 12 weeks in our study. These findings contrast with the results of previous clinical trials that included evaluation of the effects of SGLT2 inhibitors on measures of arterial stiffness. Significant reductions in PWV were seen after 8 weeks' treatment with empagliflozin 25 mg/d in young patients with type 1 diabetes.³³ Post hoc analysis of data from the EMPA-REG BP trial showed a trend toward a reduction in the ambulatory arterial stiffness index ($P = .059$) in patients with type 2 diabetes mellitus treated with empagliflozin for 24 weeks.³⁴ Looking specifically at CAVI, this was significantly reduced 6 months after switching from a dipeptidyl peptidase-4 (DPP-4) inhibitor to the SGLT2 inhibitor

tofogliflozin in patients with type 2 diabetes.³⁵ The latter two trials had a longer duration of action than the current study, and it is possible that treatment with an SGLT2 inhibitor for longer than 12 weeks may be necessary to detect beneficial effects on arterial stiffness in patients with type 2 diabetes mellitus. However, the therapy duration in our study was selected based on data from previous studies, including a large randomized outcome study showing that the beneficial effects of SGLT2 inhibitor therapy on cardiovascular death and hospitalization for heart failure were seen within the first 3 months of therapy.⁴

A number of factors influence both a single CAVI value and evaluation of this parameter over time, including age, sex, body mass index, frailty, serum uric acid levels, lipid levels, smoking status, and vascular tone.³⁶⁻⁴¹ The relative contribution of these factors to our study findings, and the extent to which they influenced the results of earlier studies, cannot be determined.

Although there was no significant change in CAVI and other arterial waveform indices during our study, there was a significant reduction in percent mean arterial pressure (%MAP) in the ankle

TABLE 2 Mixed-effects model repeated measures analysis of changes in endpoint parameters

	Baseline	Week 4			Week 12		
	Estimate	Estimate	Difference vs baseline	P-value	Estimate	Difference vs baseline	P-value
CAVI	8.67 (8.37, 8.97)	8.62 (8.31, 8.93)	-0.05 (-0.25, 0.14)	.575	8.64 (8.38, 8.91)	-0.03 (-0.20, 0.14)	.750
ABI	1.12 (1.10, 1.14)	1.13 (1.11, 1.15)	0.01 (-0.01, 0.04)	.389	1.13 (1.11, 1.15)	0.01 (-0.02, 0.04)	.448
PWV, cm/s ^a	1761.6 (1685.1, 1838.1)	1742.3 (1662.8, 1821.8)	-19.4 (-62.9, 24.2)	.376	1738.4 (1663.4, 1813.5)	-23.2 (-66.0, 19.6)	.281
Office SBP, mm Hg	131.3 (126.7, 135.8)	125.2 (120.3, 130.1)	-6.1 (-9.1, -3.0)	<.001	129.4 (124.7, 134.0)	-1.9 (-5.0, 1.3)	.234
Office DBP, mm Hg	75.9 (72.9, 78.9)	72.5 (69.4, 75.7)	-3.4 (-6.3, -0.5)	.024	76.3 (73.3, 79.3)	0.4 (-2.6, 3.3)	.799
Office HR, beats/min	73.5 (70.1, 76.9)	71.7 (68.7, 74.8)	-1.7 (-3.9, 0.5)	.121	72.3 (69.2, 75.5)	-1.2 (-3.3, 1.0)	.290
Morning home SBP, mm Hg	129.4 (125.1, 133.7)	124.3 (120.0, 128.7)	-5.0 (-7.4, -2.7)	<.001	124.1 (119.9, 128.4)	-5.2 (-7.5, -3.0)	<.001
Morning home DBP, mm Hg	75.7 (72.6, 78.8)	73.6 (70.8, 76.5)	-2.1 (-3.7, -0.5)	.013	73.2 (70.5, 75.9)	-2.5 (-4.1, -0.9)	.002
Morning home HR, beats/min	68.4 (65.8, 70.9)	68.0 (65.4, 70.6)	-0.4 (-1.6, 0.8)	.486	68.3 (65.8, 70.9)	0.0 (-1.3, 1.2)	.970
Evening home SBP, mm Hg	126.5 (122.5, 130.6)	122.4 (118.3, 126.6)	-4.1 (-6.7, -1.5)	.003	121.1 (117.5, 124.7)	-5.5 (-7.4, -3.5)	<.001
Evening home DBP, mm Hg	72.2 (69.7, 74.8)	70.1 (67.7, 72.6)	-2.1 (-3.6, -0.7)	.006	69.4 (67.0, 71.7)	-2.9 (-4.1, -1.6)	<.001
Evening home HR, beats/min	72.4 (70.1, 74.7)	72.6 (70.3, 74.9)	0.2 (-1.4, 1.8)	.807	71.7 (69.5, 74.0)	-0.7 (-2.4, 1.0)	.436
Weight, kg	70.9 (66.6, 75.2)	69.8 (65.4, 74.1)	-1.1 (-1.4, -0.9)	<.001	68.9 (64.7, 73.2)	-2.0 (-2.4, -1.5)	<.001
BMI, kg/m ²	26.8 (25.1, 28.5)	26.4 (24.7, 28.1)	-0.4 (-0.5, -0.3)	<.001	26.1 (24.3, 27.8)	-0.7 (-0.9, -0.6)	<.001
HbA1c, %	7.0 (6.9, 7.2)	6.8 (6.6, 6.9)	-0.3 (-0.3, -0.2)	<.001	6.6 (6.5, 6.8)	-0.4 (-0.5, -0.3)	<.001
LDL cholesterol, mg/dL	110.8 (101.1, 120.5)	111.1 (101.6, 120.7)	0.3 (-4.9, 5.6)	.903	112.2 (102.3, 122.0)	1.4 (-2.9, 5.6)	.511
HDL cholesterol, mg/dL	53.1 (49.0, 57.2)	53.3 (48.7, 57.8)	0.2 (-1.6, 1.9)	.837	56.1 (51.2, 60.9)	3.0 (0.4, 5.6)	.026
Triglycerides, mg/dL	178.6 (112.9, 244.3)	163.0 (90.1, 235.8)	-15.6 (-95.6, 64.4)	.695	134.5 (108.1, 161.0)	-44.0 (-104.8, 16.7)	.151
Uric acid, mg/dL	5.8 (5.5, 6.1)	4.9 (4.6, 5.2)	-0.9 (-1.1, -0.6)	<.001	5.0 (4.7, 5.2)	-0.8 (-1.0, -0.6)	<.001
Estimated glomerular filtration rate, mL/min/1.73 m ²	75.1 (69.4, 80.8)	70.8 (65.3, 76.3)	-4.2 (-7.0, -1.5)	.004	73.9 (68.6, 79.2)	-1.2 (-4.1, 1.7)	.399

Note: Data are adjusted for age and sex, and shown as mean values with 95% confidence intervals.

Abbreviations: ABI, ankle-brachial pressure index; BMI, body mass index; CAVI, cardio-ankle vascular index; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HR, heart rate; LDL; low-density lipoprotein; PWV, pulse wave velocity; SBP, systolic blood pressure.

^aAlso adjusted for systolic blood pressure.

from baseline to Week 12 (Table 3). The %MAP has been shown to be a significant predictor of peripheral arterial disease^{24,42} and might therefore reflect the degree of stiffness in peripheral arteries. It is possible that significant improvements in MAP preceded significant improvements in CAVI, but additional research is needed to determine whether longer duration of therapy with luseogliflozin would be associated with a significant reduction in CAVI.

In this study, patients had relatively well-controlled BP (mean 132/76 mm Hg for office BP and 130/75 mm Hg for morning home BP at baseline, Table 1), but morning home BP was significantly reduced after 12 weeks' treatment with luseogliflozin, reaching 124/73 mm Hg. Although office BP was significantly reduced

versus baseline at Week 4 (125/73 mm Hg), levels at Week 12 were not significantly different from baseline (129/76 mm Hg). The 5 mm Hg reduction seen in morning home SBP during treatment with luseogliflozin is expected to be clinically relevant because this corresponds to a 10 mm Hg reduction in office SBP, which has been shown to be associated with a 22-25% reduction in the rate of coronary heart disease events and a 36%-41% reduction in stroke rate.⁴³

Guideline-recommended target office BP for patients with diabetes is <130/80 mm Hg^{44,45} and for home BP is <125/75 mm Hg.⁴⁴ There is a good rationale for this given that the results of the HONEST study showed that high-risk patients with hypertension, including those with diabetes, obtained the greatest reduction in cardiovascular

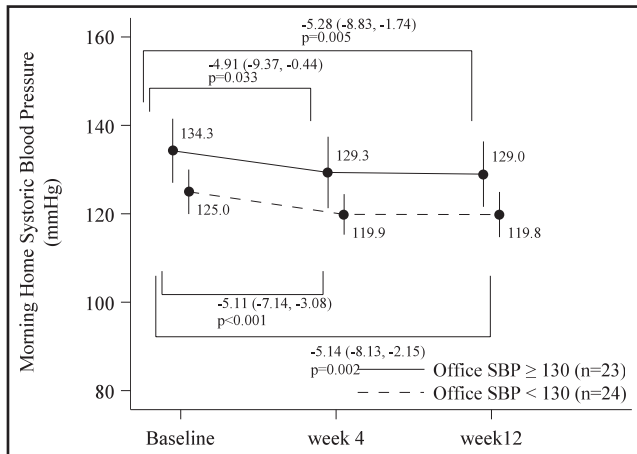


FIGURE 2 Changes in morning home systolic blood pressure (SBP) during treatment with luseogliflozin in patient subgroups based on office SBP control status at baseline. Data are adjusted for age and sex, and shown as mean values with 95% confidence intervals

event risk when morning home SBP was < 125 mm Hg.⁴⁶ The morning home SBP achieved during treatment with luseogliflozin in the current study was below that 125 mm Hg threshold (124 mm Hg at Week 4 and Week 12). In addition, even in diabetic patients with well-controlled BP at baseline (office SBP < 130 mm Hg), treatment with luseogliflozin was associated with a reduction in morning home SBP of approximately 5 mm Hg (from 125.0 to 119.8 mm Hg) (Figure 2), without any increase in morning heart rate (data not shown). Therefore, the significant home BP-lowering effect of luseogliflozin appeared to be independent of BP controls status and did not activate sympathetic tonus.

During treatment with luseogliflozin, there were statistically significant improvements from baseline in a number of important secondary endpoint parameters. Glycemic control improved, as shown by a significant reduction in HbA1c, and body weight and BMI also decreased (Table 2). This reflects an overall improvement in the metabolic profile. Levels of low-density lipoprotein cholesterol and triglycerides remained unchanged throughout the study, but there was a significant increase in HDL cholesterol levels. Levels of HDL have

TABLE 4 Adverse events

	Events (treatment-related events) ^a , n
Inflammation of the upper airway	2
Vulvitis	1 (1)
Decreased estimated glomerular filtration rate	1 (1)
Acute gastritis	1
Lower back pain	1

^aAll adverse events were of non-serious severity.

also been shown to increase during treatment with dapagliflozin.⁴⁷ A significant reduction in uric acid levels was seen during treatment with luseogliflozin, consistent with increased urinary excretion of uric acid secondary to luseogliflozin-induced glycosuria.⁴⁸ Taken together, the findings of the current study are consistent with the documented clinical benefits of luseogliflozin in patients with diabetes.⁴⁹⁻⁵⁴

The most important limitation of our study is the open-label non-comparative design. It is also possible that the lack of statistically significant changes from baseline in CAVI might, in part, be due to small sample size and/or inadequate treatment duration. Furthermore, the external validity of the findings is limited by the single ethnicity nature of the study population.

5 | CONCLUSIONS

This study did not find any significant improvement in CAVI, a relatively BP-independent measure of arterial stiffness parameter, during 12 weeks of treatment with luseogliflozin in patients with type 2 diabetes mellitus. Changes in BP, glucose control, and lipid levels during luseogliflozin therapy in this study were consistent with the documented beneficial effects of SGLT2 inhibitors. The ability to significantly reduce home BP without increasing heart rate in patients with diabetes and well-controlled BP warrants further investigation in clinical trials.

TABLE 3 Mixed-effects model repeated measures analysis of changes in arterial waveform index

	Baseline	Week 4	Difference vs baseline	P-value	Week 12	Difference vs baseline	P-value
	Estimate	Estimate			Estimate		
Ankle %MAP, %	39.6 (38.2, 41.0)	38.8 (37.4, 40.1)	-0.84 (-1.94, 0.27)	.134	37.8 (36.6, 39.0)	-1.79 (-3.02, -0.55)	.005
Ankle upstroke time, msec	148.9 (142.4, 155.5)	150.1 (143.5, 156.6)	1.13 (-5.51, 7.78)	.733	147.6 (140.8, 154.4)	-1.37 (-8.40, 5.67)	.698
Brachial augmentation index, unit	1.23 (1.14, 1.31)	1.20 (1.12, 1.28)	-0.023 (-0.084, 0.037)	.443	1.16 (1.07, 1.25)	-0.069 (-0.143, 0.006)	.069
Brachial reflection magnitude, unit	0.48 (0.45, 0.51)	0.49 (0.46, 0.51)	0.007 (-0.012, 0.027)	.457	0.47 (0.44, 0.50)	-0.007 (-0.030, 0.016)	.548

Note: Data are adjusted for age and sex, and shown as mean values with 95% confidence intervals.

Abbreviation: %MAP, percent mean arterial pressure.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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