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LETTER TO THE EDITOR

Changes in heart rate in patients with type 2 diabetes mellitus after treatment with luseogliflozin: Subanalysis of placebo-controlled, double-blind clinical trials

In patients with type 2 diabetes mellitus, higher heart rate (HR) is associated with an increased risk of death and cardiovascular complications[1]. Sodium–glucose cotransporter 2 inhibitors were approved as novel antihyperglycemic agents, and are known to decrease blood glucose levels without affecting HR. However, to the best of our knowledge, no detailed analysis has been undertaken in patients stratified by baseline HR. In the present study, we evaluated the changes in HR after treatment with the sodium–glucose cotransporter 2 inhibitor, luseogliflozin, in Japanese patients with type 2 diabetes mellitus.

Three placebo-controlled, double-blind studies of luseogliflozin, including two dose-finding phase 2 studies and a phase 3 randomized study, were merged in this pooled analysis. These studies are registered at the Japan Pharmaceutical Information Center (identifier: JapicCTI-090908, JapicCTI-101191 and JapicCTI-111661)[2–4]. The major inclusion criteria were as follows: Japanese patients with type 2 diabetes mellitus receiving diet and exercise therapy alone, age ≥20 years and with glycated hemoglobin levels ≥6.9% to ≤10.5%. The changes in HR from baseline to 12 weeks after treatment with luseogliflozin were assessed by using a paired *t*-test and an analysis of covariance with baseline as a covariate at a two-sided α level of 0.05. Other clinical parameters were similarly measured using a paired *t*-test. Missing data were not imputed, and all analyses were carried out using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Of 501 patients enrolled in the three studies, 489 were included in this pooled analysis. The patients were divided into three groups as follows: placebo, $n = 183$; luseogliflozin 2.5 mg, $n = 194$; luseogliflozin 5.0 mg, $n = 112$. The mean ± standard deviation age was 58.3 ± 10.0, 58.2 ± 9.6 and 56.8 ± 10.3 years; glycated hemoglobin levels were 7.98 ± 0.74%, 8.09 ± 0.86% and 8.02 ± 0.87%; and number (percentage) of male patients was 132 (72.1), 131 (67.5) and 83 (74.1), respectively.

Table 1 shows the changes in clinical parameters from baseline to 12 weeks when the patients were stratified by baseline HR. Treatment with both luseogliflozin 2.5 mg and 5.0 mg showed significant reductions in HR from baseline in patients with HR >70 b.p.m. Detailed stratification of patients with HR >70 b.p.m. showed that luseogliflozin 2.5 mg significantly decreased the HR in all subgroups compared with the baseline HR, whereas luseogliflozin 5.0 mg significantly decreased the HR only in patients with baseline HR >80 b.p.m. In addition, the decrease with 2.5 mg, but not 5.0 mg, luseogliflozin was also significant compared with the placebo ($P = 0.016$). Although the reason for this result is unknown, it is to be noted that high-density lipoprotein cholesterol and blood urea nitrogen levels were significantly increased from baseline in patients with lower baseline HR (<70 b.p.m.) in the luseogliflozin 2.5 mg group. Additionally, there was no correlation between the change in each parameter from baseline in Table 1 and the change in HR from baseline.

The incidence of adverse events among patients with HR ≥70 b.p.m. and HR <70 b.p.m. at baseline was 40.4% and 42.3%, respectively, in the luseogliflozin 2.5 mg group, and 50.0% and 34.8%, respectively, in the luseogliflozin 5.0 mg group. Although the incidence of adverse events was higher in the 5.0 mg group with higher baseline HR, there were no remarkable adverse events in the higher dose group. Throughout the studies, luseogliflozin was well tolerated. It is suggested that luseogliflozin can effectively decrease the HR in patients with higher baseline HR. Some patients with type 2 diabetes mellitus have elevated central sympathetic activity, which is exacerbated by a malfunction of the negative feedback mechanism as a result of decreased sensitivity of baroreceptor reflexes[5,6]. This results in elevation of peripheral sympathetic activity in the heart, leading to an increase in resting HR. These results suggest that luseogliflozin could calm elevated central sympathetic activity, while having no such effect in patients with normal central sympathetic activity.

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Table 1 | Changes in clinical parameters from baseline to week 12 for all heart rate groups receiving luseogliflozin

Variable (heart rate at baseline)		Placebo		2.5 mg luseogliflozin		5.0 mg luseogliflozin	
		<70 b.p.m.	≥70 b.p.m.	<70 b.p.m.	≥70 b.p.m.	<70 b.p.m.	≥70 b.p.m.
FPG (mg/dL)	*n*	130	53	138	56	66	45
	Changes at week 12	0.4 ± 1.8	0.8 ± 3.4	−19.1 ± 2.0*	−32.1 ± 3.4*	−24.2 ± 3.1*	−22.6 ± 5.1*
	At baseline	(154.8 ± 2.3)	(160.4 ± 4.5)	(152.9 ± 2.1)	(171.2 ± 4.5)	(155.4 ± 3.7)	(156.0 ± 4.6)
HbA1c (%)	*n*	130	53	138	56	66	46
	Changes at week 12	0.09 ± 0.05	0.15 ± 0.08	−0.49 ± 0.05*	−0.68 ± 0.10*	−0.56 ± 0.07*	−0.70 ± 0.08*
	At baseline	(7.97 ± 0.06)	(8.01 ± 0.12)	(7.95 ± 0.06)	(8.44 ± 0.14)	(7.97 ± 0.11)	(8.10 ± 0.13)
Body weight (kg)	*n*	130	53	138	56	66	46
	Changes at week 12	−0.22 ± 0.11*	−0.32 ± 0.21	−1.74 ± 0.11*	−1.95 ± 0.22*	−2.04 ± 0.17*	−2.06 ± 0.23*
	At baseline	(67.15 ± 1.09)	(68.38 ± 1.78)	(66.34 ± 0.93)	(70.96 ± 2.14)	(68.81 ± 1.70)	(70.00 ± 1.96)
BMI (kg/m^2)	*n*	130	53	138	56	66	46
	Changes at week 12	−0.08 ± 0.04	−0.12 ± 0.08	−0.66 ± 0.04*	−0.71 ± 0.07*	−0.77 ± 0.06*	−0.72 ± 0.08*
	At baseline	(25.47 ± 0.35)	(24.90 ± 0.56)	(24.74 ± 0.30)	(26.50 ± 0.74)	(25.69 ± 0.50)	(24.89 ± 0.50)
Uric acid (mg/dL)	*n*	131	52	137	57	66	46
	Changes at week 12	−0.09 ± 0.05	−0.10 ± 0.07	−0.62 ± 0.06*	−0.57 ± 0.12*	−0.56 ± 0.09*	−0.42 ± 0.13*
	At baseline	(5.12 ± 0.10)	(5.22 ± 0.17)	(5.16 ± 0.10)	(5.10 ± 0.20)	(4.90 ± 0.14)	(5.25 ± 0.20)
Triglycerides (mg/dL)	*n*	131	52	137	57	66	46
	Changes at week 12	−8.3 ± 7.7	9.9 ± 12.1	−26.8 ± 6.2*	−35.9 ± 12.5*	−16.1 ± 5.5*	−40.2 ± 17.6*
	At baseline	(154.0 ± 12.5)	(165.6 ± 19.7)	(147.6 ± 7.9)	(167.8 ± 14.3)	(125.7 ± 7.9)	(185.3 ± 25.9)
HDL-C (mg/dL)	*n*	97	34	97	36	33	18
	Changes at week 12	0.8 ± 0.8	−0.6 ± 1.4	4.0 ± 0.8*	1.8 ± 1.1	3.7 ± 1.1*	6.6 ± 1.5*
	At baseline	(57.5 ± 1.5)	(59.6 ± 3.0)	(57.9 ± 1.6)	(51.8 ± 2.1)	(54.0 ± 2.3)	(53.0 ± 3.1)
LDL-C (mg/dL)	*n*	97	34	97	36	33	18
	Changes at week 12	0.8 ± 2.1	−3.3 ± 3.2	0.4 ± 2.1	4.6 ± 3.4	6.2 ± 3.3	10.2 ± 5.3
	At baseline	(124.5 ± 3.3)	(119.1 ± 5.7)	(128.3 ± 2.8)	(133.5 ± 4.7)	(117.8 ± 3.9)	(108.4 ± 7.5)
ALT (IU/L/37°C)	*n*	131	52	137	57	66	46
	Changes at week 12	−1.7 ± 0.8*	−1.5 ± 0.9	−5.0 ± 0.9*	−8.4 ± 1.5*	−4.5 ± 1.4*	−2.6 ± 1.0*
	At baseline	(30.9 ± 1.5)	(26.5 ± 2.0)	(27.9 ± 1.2)	(33.0 ± 2.7)	(26.0 ± 2.0)	(26.5 ± 2.4)
AST (IU/L/37°C)	*n*	131	52	137	57	66	46
	Changes at week 12	−0.5 ± 0.6	−0.9 ± 0.6	−2.6 ± 0.6*	−4.3 ± 1.0*	−1.5 ± 1.1	−0.1 ± 0.8
	At baseline	(27.1 ± 0.9)	(25.2 ± 1.1)	(26.3 ± 0.9)	(27.6 ± 1.6)	(23.9 ± 1.3)	(24.1 ± 1.3)
Hemoglobin (g/dL)	*n*	131	52	137	56	66	46
	Changes at week 12	0.21 ± 0.05*	0.15 ± 0.08	0.71 ± 0.06*	0.63 ± 0.09*	0.88 ± 0.08*	1.00 ± 0.11*
	At baseline	(14.39 ± 0.10)	(14.67 ± 0.18)	(14.48 ± 0.10)	(14.36 ± 0.18)	(14.21 ± 0.15)	(14.67 ± 0.15)
Hematocrit (%)	*n*	131	52	137	56	66	46
	Changes at week 12	0.64 ± 0.16*	0.49 ± 0.24*	2.34 ± 0.18*	2.05 ± 0.29*	2.76 ± 0.26*	2.79 ± 0.34*
	At baseline	(42.24 ± 0.30)	(42.99 ± 0.49)	(42.57 ± 0.30)	(42.16 ± 0.49)	(41.99 ± 0.44)	(43.24 ± 0.45)
BUN (mg/dL)	*n*	131	52	137	57	66	46
	Changes at week 12	0.0 ± 0.2	−0.3 ± 0.3	1.1 ± 0.3*	0.7 ± 0.4	1.5 ± 0.3*	1.4 ± 0.5*
	At baseline	(14.3 ± 0.3)	(13.3 ± 0.4)	(14.7 ± 0.3)	(13.7 ± 0.5)	(13.7 ± 0.4)	(13.9 ± 0.4)

Table 1 (*Continued*)

Variable (heart rate at baseline)		Placebo		2.5 mg luseogliflozin		5.0 mg luseogliflozin	
		<70 b.p.m.	≥70 b.p.m.	<70 b.p.m.	≥70 b.p.m.	<70 b.p.m.	≥70 b.p.m.
Creatinine (mg/dL)	*n*	131	52	137	57	66	46
	Changes at week 12	0.000 ± 0.005	−0.004 ± 0.006	0.002 ± 0.005	0.001 ± 0.008	0.009 ± 0.007	0.018 ± 0.010
	At baseline	(0.692 ± 0.013)	(0.669 ± 0.017)	(0.717 ± 0.013)	(0.652 ± 0.020)	(0.698 ± 0.019)	(0.729 ± 0.018)
SBP (mmHg)	*n*	131	52	137	57	66	46
	Changes at week 12	0.7 ± 1.0	−1.3 ± 1.4	−6.1 ± 1.1*	−6.8 ± 1.4*	−4.2 ± 1.5*	−5.3 ± 2.0*
	At baseline	(127.2 ± 1.1)	(126.6 ± 2.3)	(125.8 ± 1.2)	(128.0 ± 1.7)	(127.4 ± 1.8)	(129.9 ± 2.1)
DBP (mmHg)	*n*	131	52	137	57	66	46
	Changes at week 12	1.3 ± 0.7	−0.9 ± 1.1	−2.0 ± 0.7*	−4.7 ± 1.0*	−2.5 ± 0.9*	−1.9 ± 1.2
	At baseline	(75.1 ± 0.8)	(77.0 ± 1.4)	(74.3 ± 0.8)	(77.7 ± 1.0)	(76.3 ± 1.2)	(77.2 ± 1.6)
Heart rate (b.p.m.)	*n*	130	53	138	56	66	46
	Changes at week 12	0.19 ± 0.51	−2.40 ± 1.06*	0.17 ± 0.55	−5.78 ± 0.95**	0.25 ± 0.67	−3.92 ± 1.23*
	At baseline	(60.71 ± 0.54)	(77.34 ± 0.89)	(60.92 ± 0.48)	(77.32 ± 1.14)	(61.29 ± 0.69)	(78.20 ± 1.19)

Placebo Variable (heart rate at baseline)		<55 b.p.m.	≥55 to <60 b.p.m.	≥60 to <65 b.p.m.	≥65 to <70 b.p.m.	≥70 to <75 b.p.m.	≥75 to <80 b.p.m.	≥80 b.p.m.
Heart rate (b.p.m.)	*n*	28	24	38	40	22	17	14
	Changes at week 12	1.47 ± 0.76	1.70 ± 0.82	−0.54 ± 0.81	−0.92 ± 1.27	−1.33 ± 1.94	−2.55 ± 1.34	−3.91 ± 2.10
	At baseline	(51.59 ± 0.54)	(57.48 ± 0.29)	(62.34 ± 0.22)	(67.50 ± 0.24)	(72.38 ± 0.33)	(76.90 ± 0.35)	(85.66 ± 1.76)

2.5 mg luseogliflozin Variable (heart rate at baseline)		<55 b.p.m.	≥55 to <60 b.p.m.	≥60 to <65 b.p.m.	≥65 to <70 b.p.m.	≥70 to <75 b.p.m.	≥75 to <80 b.p.m.	≥80 b.p.m.
Heart rate (b.p.m.)	*n*	20	34	43	41	26	17	13
	Changes at week 12	1.76 ± 1.16	0.78 ± 1.06	−0.78 ± 0.80	−0.13 ± 1.26	−4.39 ± 1.17*	−5.91 ± 1.61*	−8.40 ± 2.58*
	At baseline	(51.24 ± 0.60)	(57.57 ± 0.24)	(62.12 ± 0.25)	(67.16 ± 0.19)	(71.75 ± 0.27)	(76.82 ± 0.33)	(89.12 ± 2.85)
	P value (vs placebo, ANOVA)	0.885	0.560	0.829	0.585	0.142	0.120	0.278

5.0 mg luseogliflozin Variable (heart rate at baseline)		<55 b.p.m.	≥55 to <60 b.p.m.	≥60 to <65 b.p.m.	≥65 to <70 b.p.m.	≥70 to <75 b.p.m.	≥75 to <80 b.p.m.	≥80 b.p.m.
Heart rate (b.p.m.)	*n*	7	18	22	19	16	19	11
	Changes at week 12	3.23 ± 0.99*	0.19 ± 1.34	1.53 ± 0.97	−2.27 ± 1.39	−2.07 ± 2.12	−3.42 ± 1.81	−7.45 ± 2.62*
	At baseline	(50.56 ± 1.43)	(57.69 ± 0.32)	(62.04 ± 0.31)	(67.79 ± 0.32)	(71.77 ± 0.36)	(77.46 ± 0.37)	(88.84 ± 2.93)
	P-value (vs placebo, ANOVA)	0.281	0.311	0.151	0.534	0.616	0.660	0.434

ALT, alanine aminotransferase; ANOVA, analysis of variance; AST, aspartate aminotransferase; BMI, body mass index; b.p.m., beats per minute; BUN, blood urea nitrogen; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure. Mean ± SE. **P* < 0.05, versus baseline, paired t-test. ***P* = 0.016, versus placebo, ANOVA for heart rate only.

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