



Luseogliflozin, a sodium-glucose cotransporter 2 inhibitor, preserves renal function irrespective of acute changes in the estimated glomerular filtration rate in Japanese patients with type 2 diabetes

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Abstract

Acute decline in estimated glomerular filtration rate (eGFR), a typical finding after initiating sodium-glucose cotransporter 2 (SGLT2) inhibitors, is associated with maintaining renal function in type 2 diabetes. However, the relationship between the magnitude of acute decline in eGFR and the course of eGFR thereafter is not known. A pooled analysis of four 52-week phase III trials of luseogliflozin 2.5 mg daily (or up to 5 mg daily) in Japanese patients with type 2 diabetes was conducted and stratified according to the tertile of magnitude of acute change in eGFR during the 2 weeks after initiation. The mean age, glycated hemoglobin, eGFR, and urinary albumin were 60 years, 7.8%, 79.6 mL/min/1.73 m², and 62.7 mg/g Cr, respectively. Acute change in eGFR varied widely between patients ($N = 941$; mean, -2.3 ; min, -35.5 ; max, 27.6). Patients with greater acute decline in eGFR, characterized by higher baseline eGFR and increased diuretic use, showed rapid recovery and maintenance of eGFR thereafter. Higher eGFR, longer duration of diabetes, and higher body mass index and diuretic use were associated with greater acute decline in eGFR. The course of eGFR from 12 to 52 weeks was maintained regardless of acute changes. Although acute changes in eGFR varied widely among patients with type 2 diabetes, the course of eGFR thereafter was stable regardless of the degree of acute changes.

Keywords Diabetic kidney disease · Sodium-glucose cotransporter 2 inhibitors · Glomerular filtration rate

Introduction

Type 2 diabetes is a leading cause of end-stage renal disease. Type 2 diabetes and diabetic kidney disease impose a considerable burden worldwide, and this burden continues to rise; [1] therefore, their prevention is both challenging

and critical. Selective sodium-glucose cotransporter 2 (SGLT2) inhibitors, a newer class of hypoglycemic drugs, reduce blood pressure, and body weight as well as improve glycemic control [2]. In recent large-scale randomized studies, SGLT2 inhibitors improved renal outcomes by reducing albuminuria and delaying the progression to advanced renal failure in patients with type 2 diabetes [3–6]. Although the precise mechanisms of renal protection are still unclear, restoration of tubuloglomerular feedback has been suggested as one of the primary mechanisms [7].

In patients with diabetes, tubuloglomerular feedback is disrupted because of enhanced sodium reabsorption via SGLT2 [8–11]. In line with this, treatment with SGLT2 inhibitors led to an acute decline in estimated glomerular filtration rate (eGFR) in recent clinical trials in patients with diabetes [3, 4, 12]. Recovery of eGFR after cessation of these drugs during the chronic phase suggested that the acute decline in eGFR results from functional changes rather than structural damage [3, 4]. Such changes in eGFR were also observed in patients with type 2 diabetes treated with a renin-angiotensin system (RAS) inhibitor [13]. In a

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subanalysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, the magnitude of the acute decline in eGFR varied widely [12]. Moreover, patients in whom the acute decline in eGFR was the greatest had slower rates of decline in eGFR over the long term [13].

The results from a recent clinical trial suggest that acute decline in eGFR is a common effect of SGLT2 inhibitors [3, 4]. However, understanding of the distribution of acute changes in eGFR and its impact on the course of eGFR changes thereafter is limited. Thus, we conducted a post hoc analysis of 4 phase III studies of luseogliflozin to determine the distribution of acute changes in eGFR in the first 2 weeks of treatment and its impact on long-term renal protection until 52 weeks after treatment initiation.

Materials and methods

Study design

The pooled analysis consisted of four 52-week, multi-center, phase III studies in Japanese patients with type 2 diabetes who received luseogliflozin 2.5 mg daily (or 5 mg daily after week 24), conducted between May 2011 and October 2012. The studies comprised a combination study with luseogliflozin and glimepiride (TS071-03-1, JapicCTI-111507) [14], a combination study with luseogliflozin and another oral hypoglycemic agent (OHA; e.g., biguanide, dipeptidylpeptidase-4 inhibitor, thiazolidinedione, glinide, or α -glucosidase inhibitor) (TS071-03-2, JapicCTI-111508) [14], a monotherapy study with luseogliflozin (TS071-03-3, JapicCTI-111509) [15], and a study of luseogliflozin in patients with moderate renal impairment (TS071-03-4, JapicCTI-111543). TS071-03-2 and TS071-03-3 were open-label, 52-week studies, whereas TS071-03-1 and TS071-03-4 consisted of two phases: an initial 24-week, placebo-controlled, randomized, double-blind, parallel-group comparative phase, followed by a 28-week open-label phase in which all patients were given luseogliflozin. The pooled analysis excluded all patients in TS071-03-1 and TS071-03-4 who had received placebo in the initial double-blind phase. A summary of the four phase III studies is shown in Supplementary Table 1. All studies were designed in line with the Japanese Guidelines for the Clinical Evaluation of Oral Hypoglycemic Agents and were conducted with the approval of the ethics committee of each participating study site, in accordance with the Declaration of Helsinki, and in compliance with the Good Clinical Practice guidelines and all applicable regulatory requirements.

Patient population

Inclusion criteria for patients with type 2 diabetes in the pooled analysis were age ≥ 20 years, glycosylated hemoglobin (HbA1c) $\geq 6.9\%$ to $\leq 10.5\%$, and >8 weeks of regular dietary therapy before study entry. The diagnosis of type 2 diabetes was based on the Japan Diabetes Society diagnostic criteria. The exclusion criteria were eGFR <45 mL/min/1.73 m² (except TS071-03-4, which included patients with eGFR ≥ 30 to <60 mL/min/1.73 m²), systolic blood pressure/diastolic blood pressure $>170/100$ mmHg, insulin treatment within 8 weeks before study entry, and history of genitourinary infection, dysuria, or clinically apparent hepatic disorder(s).

Interventions

Luseogliflozin was orally administered to all patients at a dosage of 2.5 mg daily before breakfast for 52 weeks. The dose could be increased to 5 mg daily after week 24 in patients with HbA1c $\geq 7.4\%$ at both weeks 16 and 20. All patients were on a controlled diet to ensure consistent caloric intake during the entire study period (weeks -4 to 52). In addition, all patients were prohibited from taking additional insulin preparations, corticosteroids (except for topical use), or OHAs other than those coadministered as specified in each study protocol. The dosage of any coadministered OHA could not be modified during the entire study period. Patients were allowed to remain on any lipid-lowering, antihypertensive, or diuretic agents that they had received before study initiation but were not allowed to change either the drugs or their daily doses during the entire study period.

Statistical analysis

For the pooled analysis, the efficacy and safety analyses included the full analysis set (FAS) and the safety analysis set (SAS) of each study, respectively. The FAS and SAS included all patients who had received at least one dose of the study drug and for whom efficacy and safety variables, respectively, were observed and measured at least once after receiving the study drug. Among these populations, patients who had been randomized to placebo in the FAS and SAS (in TS071-03-1 and TS071-03-4) and those for whom eGFR data were unavailable for baseline, week 2, and week 52 were excluded. The resulting population was defined as the pooled analysis set. Patients were stratified into three groups by the tertile of degree of change in eGFR within 2 weeks (Supplementary Fig. 1): acute decliner (change in eGFR < -5.1 mL/min/1.73 m² within 2 weeks), moderate decliner (change in eGFR ≥ -5.1 to <0 mL/min/1.73 m²

within 2 weeks), and acute elevator (change in $eGFR \geq 0 \text{ mL/min/1.73 m}^2$ within 2 weeks).

$eGFR$ values were calculated using the equations for $eGFR$ developed by the Japanese Society of Nephrology [16] for the Japanese population (male, $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$; female, $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$). All HbA1c values measured in Japan Diabetes Society units were converted to their corresponding National Glycohemoglobin Standardization Program units [17] using a validated equation (HbA1c [National Glycohemoglobin Standardization Program] [%] = $1.02 \times \text{Japan Diabetes Society} [\%] + 0.25\%$) to allow global comparisons. Between-group comparisons of the changes in $eGFR$ and systolic blood pressure, urinary albumin-to-creatinine ratio, and body weight were performed using analysis of variance (ANOVA). The association of baseline values with changes in clinical variables and changes in $eGFR$ was evaluated by regression analysis. The following covariates were used to examine the association between baseline clinical variables and acute change in $eGFR$: age, sex, duration of diabetes, body mass index (BMI), systolic blood pressure, glycated hemoglobin, $eGFR$, log-transformed urinary albumin-to-creatinine ratio, uric acid, and use of calcium channel blockers, RAS inhibitors, diuretics, and β -receptor blockers. The following covariates were included in the adjusted model to examine the association between basal clinical parameters and acute change in $eGFR$: age, sex, and all variables with $P < 0.2$ in the single-regression analysis. In the regression analysis to examine the association between changes in clinical parameters and changes in $eGFR$ from 12 to 52 weeks, the tertiles of acute changes in $eGFR$, changes in systolic blood pressure, urinary albumin-to-creatinine ratio, uric acid, HbA1c, and body weight were used. Age, sex, and changes in clinical variables with $P < 0.2$ in the single regression were included. Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline clinical characteristics

The mean age, HbA1c, $eGFR$, and urinary albumin were 60 years, 7.8%, $79.6 \text{ mL/min/1.73 m}^2$, and 62.7 mg/g Cr , respectively. Most patients had preserved renal function with normal albuminuria or microalbuminuria.

Distribution of acute change in $eGFR$

The degree of acute change in $eGFR$ within the first 2 weeks after initiation of treatment varied widely between patients (Fig. 1). The mean value of acute change in $eGFR$ was

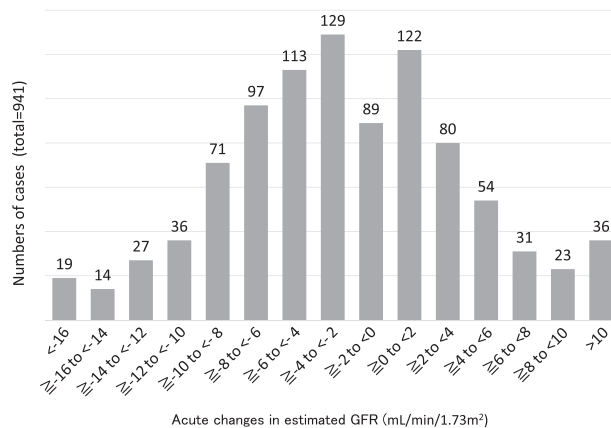


Fig. 1 Distribution of acute changes in $eGFR$. Amount of change in $eGFR$ and the number of cases 2 weeks after luseogliflozin administration. $eGFR$ estimated glomerular filtration rate

$-2.3 \text{ mL/min/1.73 m}^2$. Approximately 63% of the patients showed a decrease in $eGFR$, while ~15% showed an increase in $eGFR$ of more than $4 \text{ mL/min/1.73 m}^2$.

Characteristics according to the degree of acute change in $eGFR$

We divided the patients into three groups according to the tertile of the degree of acute changes in $eGFR$ within 2 weeks. Patients in the first tertile, the acute decliners, were characterized by higher $eGFR$ and lower uric acid (Table 1). On the other hand, patients in the third tertile, the acute elevators, were significantly younger, had a shorter history of diabetes, and had a relatively lower urinary albumin excretion rate, although this was not statistically significant.

Factors associated with the degree of acute change in $eGFR$

Multivariate analysis of the baseline data revealed that age, duration of diabetes, BMI, $eGFR$, and use of diuretics at baseline were inversely correlated with acute changes in $eGFR$ within 2 weeks (Table 2). In the multiple regression analysis using the changes in clinical parameters within the first 2 weeks, reduction in diastolic blood pressure and body weight and elevation of uric acid were significantly associated with an acute decline in $eGFR$ (Supplementary Table 2).

Degree of acute change in $eGFR$ and the course of $eGFR$, urinary albumin, and systolic blood pressure from weeks 2 to 52

Regardless of the acute change, the course of $eGFR$ change from 2 weeks after initiating luseogliflozin tended to

Table 1 Clinical characteristics by tertile of acute changes^a in eGFR

Characteristic	Tertile of acute changes in eGFR			P value		
	Luseogliflozin (N = 941)	Placebo (N = 115)	Acute decliner $\Delta eGFR < -5.1$ (n = 315)		Moderate decliner $-5.1 \leq \Delta eGFR < 0$ (n = 280)	Acute elevator $\Delta eGFR \geq 0$ (n = 346)
Age, years	60.2 ± 10.5	63.7 ± 10.7	60.0 ± 10.8	62.4 ± 10.0	58.5 ± 10.3	<0.001
Male	652 (69.3)	83 (72.2)	204 (64.8)	206 (73.6)	242 (69.9)	0.063
Duration of diabetes mellitus, years	(N = 938)	10.1 ± 8.8 (N = 114)	7.0 ± 6.3 (n = 313)	7.3 ± 6.3	5.6 ± 5.1 (n = 345)	0.001
Body weight, kg	68.6 ± 13.3	65.8 ± 10.7	69.2 ± 14.1	68.1 ± 12.4	68.5 ± 13.2	0.618
BMI, kg/m ²	25.7 ± 4.0	25.0 ± 3.6	26.1 ± 4.5	25.6 ± 3.7	25.6 ± 3.7	0.197
Systolic BP, mmHg	128.4 ± 14.8	129.4 ± 14.7	129.0 ± 14.4	129.4 ± 15.3	127.0 ± 14.6	0.077
Diastolic BP, mmHg	75.7 ± 10	76.0 ± 9.6	76.2 ± 9.8	75.7 ± 10.1	75.4 ± 10.2	0.594
Hemoglobin, g/dL	13.8 ± 1.3	13.6 ± 1.4	13.6 ± 1.4	13.7 ± 1.3	13.9 ± 1.3	0.081
HbA1c, %	7.8 ± 0.8	7.9 ± 0.7	7.9 ± 0.7	7.8 ± 0.8	7.8 ± 0.8	0.520
Serum albumin, g/dL	4.4 ± 0.3	4.4 ± 0.3	4.4 ± 0.3	4.4 ± 0.3	4.5 ± 0.3	0.009
Serum creatinine, mg/dL	0.8 ± 0.2	0.9 ± 0.3	0.7 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	<0.001
eGFR, mL/min/1.73 m ²	79.6 ± 19.1	71.1 ± 21.0	84.0 ± 19.9	73.7 ± 18.1	80.3 ± 17.9	<0.001
Uric acid, mg/dL	5.3 ± 1.3	5.7 ± 1.5	5.2 ± 1.3	5.5 ± 1.3	5.3 ± 1.3	0.009
Total cholesterol, mg/dL	195 ± 32.8	193.7 ± 30.0	195.6 ± 32.0	191.8 ± 31.4	197.0 ± 34.4	0.128
UACR, mg/g Cr	62.7 ± 295.9	137.8 ± 428.1	60.7 ± 291.5	95.1 ± 429.3	38.2 ± 103.9	0.056
<30 mg/g Cr	718 (76.3)	68 (59.1)	239 (75.9)	209 (74.6)	270 (78.0)	–
30 to <300 mg/g Cr	194 (20.6)	38 (33.0)	66 (21.0)	59 (21.1)	69 (19.9)	–
≥300 mg/g Cr	29 (3.1)	9 (7.8)	10 (3.2)	12 (4.3)	7 (2.0)	–
Antihypertensive drugs	489 (52.0)	76 (66.1)	168 (53.3)	167 (59.6)	154 (44.5)	0.001
CCBs	314 (33.4)	49 (42.6)	112 (35.6)	106 (37.9)	96 (27.7)	0.017
RAS inhibitors	402 (42.7)	68 (59.1)	137 (43.5)	143 (51.1)	122 (35.3)	<0.001
ACEIs	41 (4.4)	7 (6.1)	12 (3.8)	18 (6.4)	11 (3.2)	0.119
ARBs	372 (39.5)	64 (55.7)	130 (41.3)	129 (46.1)	113 (32.7)	0.002
DRI	9 (1.0)	0 (0.0)	1 (0.3)	7 (2.5)	1 (0.3)	0.007
Diuretics	104 (11.1)	17 (14.8)	50 (15.9)	34 (12.1)	20 (5.8)	<0.001
Thiazide/thiazide-like diuretics	83 (8.8)	12 (10.4)	39 (12.4)	27 (9.6)	17 (4.9)	0.003
Loop diuretics	8 (0.9)	4 (3.5)	3 (1.0)	4 (1.4)	1 (0.3)	0.295
MR blockers	9 (1.0)	1 (0.9)	5 (1.6)	4 (1.4)	0 (0.0)	0.070
Non-thiazide diuretics	7 (0.7)	1 (0.9)	5 (1.6)	1 (0.4)	1 (0.3)	0.102
Other diuretics	3 (0.3)	1 (0.9)	0 (0.0)	2 (0.7)	1 (0.3)	0.302
α1-receptor blockers	29 (3.1)	3 (2.6)	9 (2.9)	14 (5.0)	6 (1.7)	0.061
β-receptor blockers	64 (6.8)	4 (3.5)	25 (7.9)	26 (9.3)	13 (3.8)	0.015
Others	2 (0.2)	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)	0.555

Data are expressed as n (%) or mean ± standard deviation. Continuous variables were analyzed using ANOVA. Discrete variables were analyzed using the chi-squared test

ACEI angiotensin-converting enzyme inhibitor, ANOVA analysis of variance, ARB angiotensin receptor blocker, BMI body mass index, BP blood pressure, CCB calcium channel blocker, Cr creatinine, DRI direct renin inhibitor, eGFR estimated glomerular filtration rate, $\Delta eGFR$ change in eGFR, HbA1c glycated hemoglobin, MR mineralocorticoid receptor, RAS renin-angiotensin system, UACR urinary albumin-to-creatinine ratio

^aChanges from 0 to 2 weeks after initiation of luseogliflozin

recover or be maintained (Fig. 2). Patients with an acute decline in eGFR showed the greatest degree of recovery in eGFR from week 2 to week 52, although systolic blood pressure was uniformly decreased at week 2 and then increased from week 4 after initiation of luseogliflozin followed by a gradual reduction from week 20 in all groups (Supplementary Fig. 2). The time course of the urinary albumin-to-creatinine ratio was similar to that of systolic blood pressure (Supplementary Fig. 3). Body weight uniformly and constantly decreased during the observational period in all groups except the placebo group (Supplementary Fig. 4).

Factors associated with changes in eGFR from weeks 12 to 52

Since the chronic eGFR slope from 3 months after initiating intervention is considered to be a reliable surrogate marker of long-term renal outcomes such as end-stage kidney disease [18], we additionally examined the impact of acute decline in eGFR within 2 weeks on changes in eGFR from weeks 12 to 52. The tertile of acute changes in eGFR within 2 weeks was not associated with changes in eGFR from weeks 12 to 52 (Table 3). An increase in urinary albumin and a decrease in uric acid were associated with an increase in eGFR from weeks 12 to 52.

Table 2 Association between baseline characteristics and acute changes in eGFR

	Univariate model			Multivariate model		
	β	95% CI	<i>P</i> value	β	95% CI	<i>P</i> value
Age, years	-0.185	-1.131 0.76	0.700	-0.070	-0.124 -0.017	0.010
Sex, male	-0.04	-0.081 0.002	0.062	0.280	-0.708 1.267	0.578
Duration of diabetes mellitus, years	-0.104	-0.177 -0.030	0.006	-0.098	-0.175 -0.021	0.012
BMI, kg/m ²	-0.107	-0.215 0.002	0.053	-0.131	-0.252 -0.009	0.035
Systolic BP, mmHg	-0.031	-0.061 -0.002	0.039	-0.016	-0.048 0.015	0.311
HbA1c, %	-0.628	-1.201 -0.055	0.032	-0.401	-1.005 0.203	0.193
eGFR, mL/min/1.73 m ²	-0.025	-0.048 -0.002	0.031	-0.051	-0.079 -0.023	<0.001
Log UACR	-0.287	-0.654 0.081	0.126	-0.061	-0.448 0.326	0.758
Uric acid, mg/dL	0.245	-0.089 0.578	0.150	0.194	-0.186 0.573	0.317
CCB, yes	-1.141	-2.063 -0.219	0.015	-0.333	-1.439 0.774	0.555
RAS inhibitors, yes	-0.937	-1.817 -0.057	0.037	-0.010	-1.075 1.055	0.985
Diuretics, yes	-2.821	-4.201 -1.442	<0.001	-2.584	-4.087 -1.082	0.001
β -blockers, yes	-1.385	-3.116 0.345	0.116	-0.863	-2.629 0.903	0.338

Multivariate model: adjusted for age, sex, and all clinical variables with *P* value < 0.2 in the univariate model.

BMI body mass index, BP blood pressure, CCB calcium channel blocker, CI confidence interval, eGFR estimated glomerular filtration rate, HbA1c glycated hemoglobin, RAS renin-angiotensin system, UACR urinary albumin-to-creatinine ratio

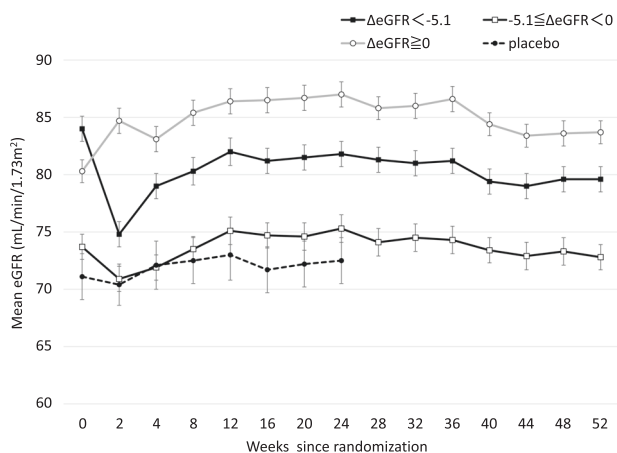


Fig. 2 Mean eGFR over time according to the tertile of acute change in eGFR after initiating luseogliflozin and placebo. The bars indicate standard error. eGFR estimated glomerular filtration rate, Δ eGFR change in estimated glomerular filtration rate

Discussion

In this post hoc pooled analysis of luseogliflozin, acute changes in eGFR varied widely among patients with type 2 diabetes, although systolic blood pressure was uniformly decreased. Older age, higher BMI, longer duration of diabetes mellitus, and higher eGFR and diuretic usage were associated with a greater acute decline in eGFR within 2 weeks. The course of eGFR change from 2 weeks after initiation of luseogliflozin tended to recover or be maintained, regardless of the degree of acute change in eGFR.

In the present study, eGFR initially declined, as shown in previous large-scale randomized controlled studies using SGLT2 inhibitors [3–5]. Although the mean decline in eGFR was -2.3 mL/min/1.73 m², the range and distribution of change in eGFR varied widely. One-third of the patients showed an increase in eGFR during the first 2 weeks after initiating an SGLT2 inhibitor. Thus, acute decline in eGFR may not occur in all patients initiating SGLT2 inhibitors. Similarly, in the RENAAL study, acute change in eGFR during the first 6 months after initiating losartan varied widely among patients with type 2 diabetes [13]. Acute changes associated with both drugs are thought to result from changes in glomerular hemodynamics, since eGFR recovered after discontinuation of these drugs at the end of the studies [3, 4]. A previous study conducted in patients with type 1 diabetes suggested that an acute decline in eGFR may occur specifically in those with glomerular hyperfiltration [19]. Although baseline eGFR was comparable across all tertiles of acute change in eGFR, higher baseline eGFR was significantly associated with an acute decline in eGFR in the present study. A recent animal study showed that empagliflozin was able to restore the tubuloglomerular feedback response [20]. These findings suggest that acute changes in eGFR may be dependent on the basal state of glomerular hemodynamics and that SGLT2 inhibitors improve glomerular hyperfiltration and result in an acute decline in eGFR. In this study, higher BMI and changes in body weight were associated with acute changes in eGFR. In obese patients, enhanced sodium absorption in the proximal tubules may attenuate

Table 3 Association between changes in clinical factors and changes in eGFR from weeks 12 to 52

	β	95% CI	<i>P</i> value
Univariate adjustment			
Tertile of acute changes in eGFR	-0.157	-0.750 0.436	0.604
Changes in systolic BP (week 52–week 12)	0.024	-0.014 0.063	0.215
Changes in urinary albumin creatinine ratio (week 52–week 12)	0.004	0.001 0.006	0.003
Changes in uric acid (week 52–week 12)	-4.119	-4.820 -3.417	<0.001
Changes in systolic HbA1c (week 52–week 12)	0.438	-0.684 1.560	0.444
Changes in body weight (week 52–week 12)	-0.167	-0.423 0.090	0.202
Multivariable adjustment ^a			
Tertile of acute changes in eGFR	-0.200	-0.753 0.352	0.477
Changes in systolic BP (week 52–week 12)	0.021	-0.015 0.057	0.257
Changes in urinary albumin creatinine ratio (week 52–week 12)	0.003	0.001 0.005	0.010
Changes in uric acid (week 52–week 12)	-4.198	-4.907 -3.489	<0.001
Changes in HbA1c (week 52–week 12)	1.651	0.501 2.801	0.005
Changes in body weight (week 52–week 12)	-0.120	-0.383 0.143	0.370

BP blood pressure, CI confidence interval, eGFR estimated glomerular filtration rate, HbA1c glycated hemoglobin, UACR urinary albumin-to-creatinine ratio

^aMultiple regression analysis was performed

tubuloglomerular feedback by decreasing the delivery of sodium and chloride to the macula densa in the distal tubules, eventually causing glomerular hypertension [21]. Moreover, a previous interventional study conducted in patients with proteinuria nephropathies with and without diabetes showed that a reduction in body weight improved proteinuria [22]. Thus, the association between BMI and acute changes in eGFR is suggested to be driven by changes in glomerular hemodynamics. Since a reduction in diastolic blood pressure was associated with acute decline in eGFR, changes in systemic hemodynamics also appear to contribute to acute changes in eGFR by SGLT2 inhibitors. Interestingly, diuretic usage was associated with a greater decline in eGFR. A previous randomized controlled study using ambulatory blood pressure measurement suggested that diuretics may potentiate the blood pressure-lowering effect of SGLT2 inhibitors [23]. Thus, such an interaction between diuretics and SGLT2 inhibitors may affect the acute change in eGFR. In both the acute and chronic phases, changes in uric acid were negatively associated with changes in eGFR. We cannot determine whether the decrease in uric acid causes an increase in eGFR, since the decrease in uric acid might be due to an increase in excretion of uric acid into the urine, accompanied by improved renal function. A recent clinical trial suggested that urate-lowering therapy might be associated with maintaining or improving eGFR in patients with chronic kidney disease without proteinuria [24]. Since SGLT2 inhibitors reduce serum uric acid levels, it is postulated that the urate-lowering effect of SGLT2 inhibitors may assist in retarding the progression of chronic kidney disease [25].

In the present study, one-third of the subjects showed an increase in eGFR. A recent animal study showed that luseogliflozin induced glomerulomegaly [26], a potential morphologic marker of glomerular hyperfiltration [27]. Moreover, this animal study also showed that luseogliflozin induced hypoxia, which is suggested to activate RAS, and increased renin accumulation in juxtaglomerular cells [26]. Such potential stimulation of RAS by SGLT2 inhibitors may be associated with the elevation of eGFR by constriction of the efferent arteriole. Since acute elevators were characterized by a low usage of RAS inhibitors and by a tendency for less albuminuria, which is consistent with the existence of an ischemic condition in the kidney, SGLT2 inhibitors may induce an increase in eGFR in conditions with higher susceptibility to renal ischemia.

Notably, a relatively rapid recovery of eGFR was observed between weeks 2 and 4 among patients with an acute decline in eGFR (tertiles 1 and 2) before the systolic blood pressure began to recover from week 4 after initiating luseogliflozin. A previous study reported that acute diuresis was observed just after initiation of an SGLT2 inhibitor and diminished by week 4 [28]. Therefore, such changes in the diuretic action of SGLT2 inhibitors may be responsible for the rapid changes in eGFR observed within 4 weeks of initiating luseogliflozin. Consistent with this assumption, the concomitant use of diuretics was associated with a greater decline in eGFR, as already described.

Contrary to the findings for RAS inhibitors reported in the RENAAL study, after acute elevation, eGFR was relatively stable from weeks 12 to 52 among the acute elevators. Moreover, acute changes in eGFR during the first 2 weeks were not associated with chronic changes in eGFR

from weeks 12 to 52. Therefore, these findings suggest that SGLT2 inhibitors may have further benefits in addition to improving glomerular hyperfiltration, which is associated with both RAS and SGLT2 inhibitors [29].

Although eGFR substantially recovered after 2 weeks and was maintained over at least 1 year even in patients with an acute decline in eGFR, it is important that acute changes in eGFR are monitored closely when treatment with SGLT2 inhibitors is initiated. Since there is a potential risk of acute kidney injury, especially among patients receiving diuretics, adjusting diuretic dosage, or stopping administration might be necessary for prevention of acute kidney injury, especially during summer, when side effects such as dehydration may occur.

In the present study, data were not available for long-term changes in eGFR, although eGFR was maintained over a period of 1 year after initiating luseogliflozin. Recent studies have shown that eGFR was maintained at stable levels over several years after an acute decline in eGFR, regardless of the basal eGFR levels [4, 30]. More specifically, baseline eGFR in the present study was comparable with that reported in the CANVAS program, and eGFR was maintained during the long term [4]. Moreover, a recent study suggested that chronic changes in eGFR 3 months after initiating intervention might be a reliable surrogate marker of renal outcomes [18]. Thus, it might be expected that many of the patients would have had stable renal function after 52 weeks in the present study.

Several limitations of this study should be noted. First, data were not available for changes in prescriptions, such as RAS inhibitors, during the study period. Thus, the course of eGFR might have been affected by such alterations in prescription, independent of SGLT2 inhibitors. Second, we could not determine whether the changes in eGFR occurred after initiation of the SGLT2 inhibitor or before initiation. Third, seasonal changes in temperature can cause an acute decline in eGFR. Although some factors other than SGLT2 inhibitors might affect the acute changes in eGFR, the present study showed that eGFR after the acute phase recovered or was maintained over 1 year, regardless of the degree of acute change.

In conclusion, acute changes in eGFR may vary widely among patients with type 2 diabetes, even when renal function is preserved. Although the course of eGFR in the chronic phase appeared to be maintained regardless of the degree of acute changes within at least 1 year, further studies are warranted to determine the impact of acute changes in eGFR on the long-term slope of eGFR.

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Compliance with ethical standards

Conflict of interest KK has received speaker's fees from Nippon Boehringer Ingelheim Co., Ltd, Mitsubishi Tanabe Pharma Co., Ltd, Astellas Pharma Inc., MSD K.K., Ono Pharmaceutical Co., Ltd, AstraZeneca K.K., and Taisho Toyama Pharmaceutical Co., Ltd. YO has received speaker's fees from Nippon Boehringer Ingelheim Co., Ltd, Takeda Pharmaceutical Co., Ltd, Daiichi Sankyo Pharmaceutical Co., Ltd. YS has received consulting and/or speaker's fees from MSD K.K., Kao Co., Ltd, Novo Nordisk Pharma Inc., Taisho Pharmaceutical Co., Ltd, Taisho Toyama Pharmaceutical Co., Ltd, Nippon Becton, Dickinson and Company, Nippon Boehringer Ingelheim Co., Ltd, and Takeda Pharmaceutical Co., Ltd. HY and HT are employees of Taisho Pharmaceutical Co., Ltd.

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References

1. Heise T, Seewaldt-Becker E, Macha S, Hantel S, Pinnetti S, Seman L, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics following 4 weeks' treatment with empagliflozin once daily in patients with type 2 diabetes. *Diabetes Obes Metab*. 2013;15:613–21.
2. Katayama S, Hatano M, Issiki M. Clinical features and therapeutic perspectives on hypertension in diabetics. *Hypertens Res*. 2018;41:213–29.
3. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323–34.
4. Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Erondy N, Shaw W, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet Diabetes Endocrinol*. 2018;6:691–704.
5. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347–57.
6. Perkovic V, Jardine MJ, Neal B, Bompont S, Heerspink HJL, Charytan DM, et al. CREDENCE Trial Investigators.

- Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–306.
7. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation*. 2016;134:752–72.
 8. Vallon V, Richter K, Blantz RC, Thomson S, Osswald H. Glomerular hyperfiltration in experimental diabetes mellitus: potential role of tubular reabsorption. *J Am Soc Nephrol*. 1999;10:2569–76.
 9. Thomson SC, Rieg T, Miracle C, Mansoury H, Whaley J, Vallon V, et al. Acute and chronic effects of SGLT2 blockade on glomerular and tubular function in the early diabetic rat. *Am J Physiol Regul Integr Comp Physiol*. 2012;302:R75–83.
 10. Vestri S, Okamoto MM, de Freitas HS, Aparecida Dos Santos R, Nunes MT, Morimatsu M, et al. Changes in sodium or glucose filtration rate modulate expression of glucose transporters in renal proximal tubular cells of rat. *J Membr Biol*. 2001;182:105–12.
 11. Bank N, Aynedjian HS. Progressive increases in luminal glucose stimulate proximal sodium absorption in normal and diabetic rats. *J Clin Invest*. 1990;86:309–16.
 12. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney Int*. 2014;85:962–71.
 13. Holtkamp FA, de Zeeuw D, Thomas MC, Cooper ME, de Graeff PA, Hillege HJ, et al. An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. *Kidney Int*. 2011;80:282–7.
 14. Seino Y, Inagaki N, Haneda M, Kaku K, Sasaki T, Fukatsu A, et al. Efficacy and safety of luseogliflozin added to various oral antidiabetic drugs in Japanese patients with type 2 diabetes mellitus. *J Diabetes Investig*. 2015;6:443–53.
 15. Seino Y, Kaku K, Inagaki N, Haneda M, Sasaki T, Fukatsu A, et al. Fifty-two-week long-term clinical study of luseogliflozin as monotherapy in Japanese patients with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Endocr J*. 2015;62:593–603.
 16. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982–92.
 17. Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, Ito H, et al. Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society. International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. *J Diabetes Investig*. 2012;3:39–40.
 18. Inker LA, Heerspink HJL, Tighiouart H, Levey AS, Coresh J, Gansevoort RT, et al. GFR slope as a surrogate end point for kidney disease progression in clinical trials: a meta-analysis of treatment effects of randomized controlled trials. *J Am Soc Nephrol*. 2019;30:1735–45.
 19. Cherney DZ, Perkins BA, Soleymannou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation*. 2014;129:587–97.
 20. Kidokoro K, Cherney DZL, Bozovic A, Nagasu H, Satoh M, Kanda E, et al. Evaluation of glomerular hemodynamic function by empagliflozin in diabetic mice using in vivo imaging. *Circulation*. 2019;140:303–15.
 21. Zingerman B, Herman-Edelstein M, Erman A, Bar Sheshet Itach S, Ori Y, Rozen-Zvi B, et al. Effect of acetazolamide on obesity-induced glomerular hyperfiltration: a randomized controlled trial. *PLoS ONE*. 2015;10:e0137163.
 22. Morales E, Valero MA, León M, Hernández E, Praga M. Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. *Am J Kidney Dis*. 2003;41:319–27.
 23. Mancia G, Cannon CP, Tikkanen I, Zeller C, Ley L, Woerle HJ, et al. Impact of empagliflozin on blood pressure in patients with type 2 diabetes mellitus and hypertension by background anti-hypertensive medication. *Hypertension*. 2016;68:1355–64.
 24. Kimura K, Hosoya T, Uchida S, Inaba M, Makino H, Maruyama S, et al. Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: a randomized trial. *Am J Kidney Dis*. 2018;72:798–810.
 25. Bailey CJ. Uric acid and the cardio-renal effects of SGLT2 inhibitors. *Diabetes Obes Metab*. 2019;21:1291–8.
 26. Takiyama Y, Sera T, Nakamura M, Ishizeki K, Saijo Y, Yanagimachi T, et al. Impacts of diabetes and an SGLT2 inhibitor on the glomerular number and volume in db/db mice, as estimated by synchrotron radiation micro-CT at SPRING-8. *EBioMedicine*. 2018;36:329–46.
 27. Hill GS, Heudes D, Bariéty J. Morphometric study of arterioles and glomeruli in the aging kidney suggests focal loss of autoregulation. *Kidney Int*. 2003;63:1027–36.
 28. Yasui A, Lee G, Hirase T, Kaneko T, Kaspers S, von Eynatten M, et al. Empagliflozin induces transient diuresis without changing long-term overall fluid balance in Japanese patients with type 2 diabetes. *Diabetes Ther*. 2018;9:863–71.
 29. Perkovic V, Jardine M, Vijapurkar U, Meininger G. Renal effects of canagliflozin in type 2 diabetes mellitus. *Curr Med Res Opin*. 2015;31:2219–31.
 30. Wanner C, Heerspink HJL, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, et al. EMPA-REG OUTCOME Investigators. Empagliflozin and kidney function decline in patients with type 2 diabetes: a slope analysis from the EMPA-REG OUTCOME trial. *J Am Soc Nephrol*. 2018;29:2755–69.