ORIGINAL ARTICLE

Reduction in the magnitude of serum potassium elevation in combination therapy with esaxerenone (CS-3150) and sodium–glucose cotransporter 2 inhibitor in patients with diabetic kidney disease: Subanalysis of two phase III studies

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ABSTRACT

Aims/Introduction: We evaluated the effect of co-administration of esaxerenone and a sodium–glucose cotransporter 2 (SGLT2) inhibitor on the magnitude of serum potassium elevation in Japanese patients with diabetic kidney disease.

Materials and Methods: We carried out a prespecified subanalysis of data from two phase III studies: a multicenter, randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes and microalbuminuria (J308); and a multicenter, single-arm, open-label trial in patients with type 2 diabetes and macroalbuminuria (J309). Changes in serum potassium levels during the studies and other measures were evaluated according to SGLT2 inhibitor use.

Results: In both studies, time-course changes in serum potassium levels, and incidence rates of serum potassium elevation were lower in patients with co-administration of SGLT2 inhibitor in both the placebo and esaxerenone groups than those without the inhibitor. In contrast, time-course changes and mean percentage changes from baseline in urinary albumin-to-creatinine ratio, the proportion of patients with albuminuria remission and time-course changes in blood pressure did not change with or without SGLT2 inhibitor, whereas the albumin-to-creatinine ratio and blood pressure were reduced with esaxerenone. The blood glucose-lowering effect of SGLT2 inhibitor was not affected by esaxerenone.

Conclusions: In Japanese patients with type 2 diabetes and albuminuria treated with esaxerenone, concomitant use of SGLT2 inhibitor reduced the magnitude of serum potassium elevation without any change of its antihypertensive and albuminuria-suppressing effects. Co-administration of esaxerenone and SGLT2 inhibitor might be a beneficial treatment option for patients with diabetic kidney disease.

INTRODUCTION

Diabetic nephropathy is the major cause of end-stage kidney disease requiring chronic dialysis therapy in Japan[1]. Under the therapy, the quality of life and mortality rates of the patients are negatively affected[2–4]. The number of patients with diabetic nephropathy remains large, and the development of therapeutic agents to prevent progression to end-stage kidney disease in these patients is critically needed.

Mineralocorticoid receptor blockers (MRBs) have both anti-hypertensive and organ-protective effects. The non-steroidal MRB, esaxerenone, showed favorable renoprotective effects in an open-label study when administered alongside a renin–angiotensin system (RAS) inhibitor to hypertensive patients with type 2 diabetes and albuminuria[5]. The efficacy and safety of esaxerenone was further evaluated in two phase III studies in patients with diabetic nephropathy[6,7]. Both studies showed favorable albuminuria reduction, albuminuria remission and antihypertensive effects. In addition, the MRB, finerenone, has shown renal event suppression, and was recently (July 2021) approved by the US Food and Drug Administration for the treatment of chronic kidney disease (CKD) associated with type 2 diabetes based on the results of the phase III Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial[8].

MRB-induced hyperkalemia is of clinical concern, especially in renal impairment and diabetes[9], and the dosing range of the MRB eplerenone is limited due to the increased risk of hyperkalemia in patients with diabetes and renal impairment[10]. With proper monitoring coupled with adequate recognition of drug-induced potassium kinetics and risk factors for hyperkalemia, clinical use of MRBs is manageable[9], but further clinical information related to hyperkalemia is still required.

Several studies of sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with type 2 diabetes have shown favorable cardioprotective as well as renoprotective effects[11], and the SGLT2 inhibitor, dapagliflozin, was approved for use in patients with CKD by the US Food and Drug Administration in April 2020. A pooled analysis of 14 randomized, placebo-controlled, double-blind studies showed that use of the SGLT2 inhibitor dapagliflozin was not associated with an increase in serum potassium levels in patients with type 2 diabetes and moderate renal dysfunction receiving RAS inhibitors or concomitant potassium-sparing diuretics[12]. Although the patient population was different, a sub-analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study also reported a decrease in the risk of hyperkalemia when dapagliflozin was administered in combination with an MRB in patients with heart failure and reduced ejection fraction[13].

Considering the expected increase in the clinical use of SGLT2 inhibitors in the future, a better understanding of the effect of combining MRB and SGLT2 inhibitor treatment on renal function is urgently required. We report the results of a prespecified subanalysis of two previously published phase III studies[6,7] that was carried out to evaluate the effect of co-administration of esaxerenone plus an SGLT2 inhibitor on the incidence of serum potassium elevation in Japanese patients with type 2 diabetes and micro- or macroalbuminuria. Other parameters evaluated include urinary albumin-to-creatinine ratio (UACR), blood pressure, estimated glomerular filtration rate (eGFR), blood glucose levels and serum sodium levels.

MATERIALS AND METHODS

Study design and treatment

The study designs of the two phase III studies have been described previously (Figure S1). Briefly, one was a multicenter, randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes and microalbuminuria (the Esaxerenone in Patients with Type 2 Diabetes and Microalbuminuria [ESAX-DN; J308] study)[6], and the second was a multicenter, single-arm, open-label trial in patients with type 2 diabetes and macroalbuminuria (the J309 study)[7]. The current article describes a prespecified subanalysis of data from the two phase III studies, but each post-hoc analysis is noted separately.

In both studies, there was a 4-week run-in period, followed by treatment with oral esaxerenone or placebo. Esaxerenone was initiated at a dose of 1.25 mg/day and gradually increased to 2.5 mg/day based on serum potassium level monitoring. In the ESAX-DN (J308) study, the treatment period was 52 weeks, and in the J309 study, the treatment period was 28 weeks. Both studies also included a 4-week follow-up period. SGLT2 inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors were administered according to the Japanese package inserts, and the dosage and administration of these agents were not changed from 3 months before the start of the study and remained stable throughout the study period.

The two studies were carried out in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocols were approved by the institutional review boards of all participating institutions. Both studies were registered at JapicCTI (J308: JapicCTI-173695; J309: JapicCTI-173696).

Patients

The full lists of inclusion and exclusion criteria have been published[6,7]. Briefly, patients were included if they were aged ≥20 years, had both hypertension and type 2 diabetes mellitus, prior treatment with a RAS inhibitor for at least 12 weeks, UACR 45 to <300 mg/g creatinine (the ESAX-DN [J308] study) or UACR 300 to <1,000 mg/g creatinine (the J309 study) in the first morning urine sample on at least two occasions during the observation period, and eGFR ≥30 mL/min/1.73 m². Exclusion criteria were type 1 diabetes mellitus; glycated hemoglobin ≥8.4%; secondary glucose intolerance; non-diabetic kidney disease; secondary or malignant hypertension; sitting systolic blood pressure ≥160 or <120 mmHg and sitting

diastolic blood pressure ≥100 or <60 mmHg, or serum potassium level <3.5 or ≥5.1 mEq/L (in patients with eGFR ≥45 mL/min/1.73 m^2) or <3.5 or ≥4.8 mEq/L (in patients with eGFR 30 to <45 mL/min/1.73 m^2).

Outcomes
The following outcomes were evaluated in this subanalysis according to both SGLT2 inhibitor and DPP-4 inhibitor use: time-course changes in serum potassium levels during the study periods and changes in serum potassium levels from baseline; incidence rate of serum potassium level ≥5.5 mEq/L and ≥6.0 or ≥5.5 mEq/L on two consecutive occasions (this criteria was defined as a safety end-point for estimating serum potassium elevation); time-course changes in UACR; UACR remission rate; percentage change in UACR from baseline (for both the ESAX-DN [J308] and J309 studies) and the proportion of patients with transition to overt albuminuria (for the ESAX-DN [J308] study only); the proportion of patients with a reduction in UACR of 30, 50 and ≥75% (for the J309 study only); time-course changes from baseline in sitting systolic and diastolic blood pressure; time-course changes in eGFR and change from baseline in eGFR; and time-course change in blood glucose level and serum sodium level. The UACR remission rate was defined as having a UACR <30 mg/g creatinine and ≥30% reduction from baseline on two consecutive occasions in the ESAX-DN (J308) study, and as having a reduction in UACR to <300 mg/g creatinine and ≥30% reduction from baseline on two consecutive occasions in the J309 study at the end of treatment. The definition of the UACR remission rate in the J309 study, and tabulation of serum potassium, blood glucose and serum sodium levels according to SGLT2 or DPP-4 inhibitor use applied for post-hoc analyses.

Statistical analysis
Details of the statistical methods used in the ESAX-DN (J308) and J309 studies have been published previously[6,7]. For patient background characteristics, descriptive statistics were used, with *n* (%) for categorical variables and mean ± standard deviation for continuous variables. Log-transformed values were used to calculate geometric least squares mean percentage changes from baseline in UACR and its 95% confidence interval (CI) at each evaluation time point, and log-transformed baseline values were used as a covariate in the ESAX-DN (J308) study. When calculating the UACR remission rate, patients with missing UACR data at two consecutive time points were considered as not showing remission. The statistical software used for this subanalysis was SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS
Patients
The demographic and clinical characteristics of patients at baseline according to SGLT2 inhibitor use are summarized in Table 1. Within each study, there were no significant differences between the subgroups in terms of UACR, serum sodium and potassium levels, blood pressure or blood glucose at baseline. In both studies, eGFR was lower in the group without SGLT2 use versus the group with co-administration of SGLT2 inhibitors. This is likely because the package inserts for SGLT2 inhibitors recommend cautious administration in patients with moderate renal dysfunction. In both studies, SGLT2 inhibitors were administered at a numerically higher rate in patients with heavier weight and higher body mass index. The patients' demographic and clinical characteristics at baseline according to DPP-4 inhibitor use are summarized in Table S1.

Outcomes
The time-course changes in serum potassium levels during the study periods according to SGLT2 inhibitor use are shown in Figure 1. Serum potassium levels were lower in both the placebo and esaxerenone groups with co-administration of SGLT2 inhibitor versus no SGLT2 inhibitor use in the ESAX-DN (J308) study. Similar results were obtained in the J309 study in patients treated with esaxerenone. In the ESAX-DN (J308) study, serum potassium levels in the esaxerenone plus SGLT2 inhibitor group were not lower than those in the placebo group without SGLT2 inhibitor use. Time-course changes in serum potassium levels during the study periods were not affected by DPP-4 inhibitor use (data not shown).

The incidence rates of serum potassium level ≥5.5 mEq/L and ≥6.0 or ≥5.5 mEq/L on two consecutive occasions were lower with co-administration of SGLT2 inhibitor versus no SGLT2 inhibitor use in the placebo and esaxerenone groups in both studies (Table 2). In the ESAX-DN (J308) study, the incidence rates of serum potassium level ≥5.5 mEq/L among patients who received esaxerenone were 7.8% versus 26.3% with and without co-administration of SGLT2 inhibitor, respectively, and in the J309 study, the incidence rates were 0.0% versus 24.4%, respectively. In the ESAX-DN (J308) study, the incidence rates of serum potassium level ≥6.0 or ≥5.5 mEq/L on two consecutive occasions among patients who received esaxerenone were 0.0% versus 11.4% with and without co-administration of SGLT2 inhibitor, respectively, and in the J309 study, the incidence rates were 0.0% versus 6.7%, respectively.

In the ESAX-DN (J308) study, esaxerenone significantly reduced UACR compared with placebo during the study period, and no effect of adding SGLT2 inhibitor to esaxerenone (both studies) or placebo (the ESAX-DN [J308] study) was seen (Figure 2).

In both studies, the proportion of patients with UACR remission and the mean percentage change in UACR from baseline were similar, regardless of SGLT2 inhibitor use (Figure 3). In the ESAX-DN (J308) study, esaxerenone was associated with a higher UACR remission rate and greater decrease in UACR from baseline compared with placebo, and the

Table 1 | Patient demographic and clinical characteristics at baseline according to sodium–glucose cotransporter 2 (SGLT2) inhibitor use

	ESAX-DN (J308)						J309		
	Placebo			Esaxerenone 1.25–2.5 mg/day			Esaxerenone 1.25–2.5 mg/day		
	Total (*n* = 227)	SGLT2i(−) (*n* = 171)	SGLT2i(+) (*n* = 56)	Total (*n* = 222)	SGLT2i(−) (*n* = 172)	SGLT2i(+) (*n* = 50)	Total (*n* = 56)	SGLT2i(−) (*n* = 45)	SGLT2i(+) (*n* = 11)
Sex (male)	180 (79)	137 (80)	43 (77)	165 (74)	130 (76)	35 (70)	42 (75)	35 (78)	7 (64)
Age (years)	66 ± 9	67 ± 9	61 ± 9	66 ± 10	67 ± 8	60 ± 11	66 ± 10	67 ± 9	58 ± 12
Weight (kg)	70 ± 14	68 ± 13	77 ± 13	70 ± 13	67 ± 12	77 ± 16	72 ± 16	70 ± 14	80 ± 21
Body mass index (kg/m^2)	26 ± 4	25 ± 4	28 ± 4	26 ± 4	25 ± 3	29 ± 5	27 ± 4	26 ± 3	30 ± 6
Sitting systolic BP (mmHg)	140 ± 10	141 ± 10	138 ± 11	140 ± 10	141 ± 10	137 ± 10	143 ± 9	144 ± 10	140 ± 9
Sitting diastolic BP (mmHg)	84 ± 8	83 ± 8	85 ± 8	83 ± 8	83 ± 9	85 ± 7	84 ± 10	83 ± 10	84 ± 12
UACR (mg/g creatinine)	123 ± 59	121 ± 58	129 ± 61	131 ± 63	132 ± 64	127 ± 62	570 ± 174	565 ± 170	587 ± 196
eGFR (mL/min/1.73 m^2)	69 ± 18	67 ± 18	76 ± 19	69 ± 18	67 ± 16	76 ± 23	62 ± 16	60 ± 15	70 ± 21
Serum Na$^+$ (mEq/L)	140 ± 2	140 ± 2	140 ± 2	140 ± 2	141 ± 2	140 ± 2	140 ± 3	140 ± 3	140 ± 2
Serum K$^+$ (mEq/L)	4.3 ± 0.3	4.4 ± 0.3	4.3 ± 0.3	4.4 ± 0.3	4.4 ± 0.3	4.3 ± 0.3	4.3 ± 0.3	4.3 ± 0.3	4.3 ± 0.2
Blood glucose (mmol/L)	7.8 ± 1.7	7.8 ± 1.6	7.7 ± 1.8	7.8 ± 1.5	7.9 ± 1.5	7.5 ± 1.3	7.8 ± 1.5	7.9 ± 1.5	7.4 ± 1.5
HbA1c (%)	7.0 ± 0.6	7.0 ± 0.6	7.2 ± 0.6	7.0 ± 0.6	7.0 ± 0.6	7.2 ± 0.5	7.1 ± 0.7	7.0 ± 0.7	7.2 ± 0.6
LDL cholesterol (mg/dL)	103 ± 28	102 ± 28	106 ± 26	109 ± 26	110 ± 26	108 ± 25	107 ± 26	108 ± 26	103 ± 25
Duration of hypertension (years)	11 ± 8	11 ± 8	11 ± 9	11 ± 8	11 ± 8	11 ± 8	11 ± 10	12 ± 11	7 ± 7
Duration of diabetes (years)	14 ± 9	15 ± 9	13 ± 8	14 ± 8	15 ± 9	12 ± 7	17 ± 9	18 ± 10	14 ± 7
Other complications									
Diabetic retinopathy[†]	107 (47)	79 (46)	28 (50)	102 (46)	76 (44)	26 (52)	35 (63)	28 (62)	7 (64)
Diabetic neuropathy	65 (29)	51 (30)	14 (25)	58 (26)	50 (29)	8 (16)	21 (38)	17 (38)	4 (36)
Hyperlipidemia	175 (77)	134 (78)	41 (73)	170 (77)	130 (76)	40 (80)	41 (73)	34 (76)	7 (64)
Hyperuricemia	68 (30)	55 (32)	13 (23)	78 (35)	64 (37)	14 (28)	18 (32)	16 (36)	2 (18)
Coronary artery disease	17 (7)	14 (8)	3 (5)	19 (9)	15 (9)	4 (8)	7 (13)	6 (13)	1 (9)
Heart failure (≤ NYHA class II)	1 (0.4)	1 (0.6)	0 (0)	2 (0.9)	2 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)
Atrial fibrillation	6 (3)	5 (3)	1 (2)	6 (3)	4 (2)	2 (4)	2 (4)	2 (4)	0 (0)
Other cardiac disorder	7 (3)	5 (3)	2 (4)	6 (3)	5 (3)	1 (2)	2 (4)	2 (4)	0 (0)
Antihypertensive agents									
ARB	214 (94)	160 (94)	54 (96)	209 (94)	161 (94)	48 (96)	51 (91)	42 (93)	9 (82)
ACE inhibitor	13 (6)	11 (6)	2 (4)	13 (6)	11 (6)	2 (4)	5 (9)	3 (7)	2 (18)
Other antihypertensive agents	166 (73)	121 (71)	45 (80)	158 (71)	115 (67)	43 (86)	42 (75)	35 (78)	7 (64)
Calcium channel blocker	155 (68)	111 (65)	44 (79)	148 (67)	109 (63)	39 (78)	42 (75)	35 (78)	7 (64)
Diuretics	26 (11)	23 (13)	3 (5)	16 (7)	13 (8)	3 (6)	8 (14)	8 (18)	0 (0)
Alpha-blocker	15 (7)	11 (6)	4 (7)	16 (7)	12 (7)	4 (8)	3 (5)	3 (7)	0 (0)
Beta-blocker	25 (11)	19 (11)	6 (11)	24 (11)	16 (9)	8 (16)	4 (7)	3 (7)	1 (9)
No. of antihypertensive agents									
Monotherapy	61 (27)	50 (29)	11 (20)	64 (29)	57 (33)	7 (14)	14 (25)	10 (22)	4 (36)
Dual therapy	113 (50)	81 (47)	32 (57)	113 (51)	81 (47)	32 (64)	28 (50)	23 (51)	5 (45)
Triple therapy or more	53 (23)	40 (23)	13 (23)	45 (20)	34 (20)	11 (22)	14 (25)	12 (27)	2 (18)
SGLT2 inhibitor									
Canagliflozin	10 (4)	0 (0)	10 (18)	6 (3)	0 (0)	6 (12)	3 (5)	0 (0)	3 (27)
Dapagliflozin	5 (2)	0 (0)	5 (9)	12 (5)	0 (0)	12 (24)	1 (2)	0 (0)	1 (9)
Empagliflozin	13 (6)	0 (0)	13 (23)	11 (5)	0 (0)	11 (22)	1 (2)	0 (0)	1 (9)
Ipragliflozin	8 (4)	0 (0)	8 (14)	8 (4)	0 (0)	8 (16)	3 (5)	0 (0)	3 (27)
Luseogliflozin	12 (5)	0 (0)	12 (21)	7 (3)	0 (0)	7 (14)	2 (4)	0 (0)	2 (18)
Tofogliflozin	8 (4)	0 (0)	8 (14)	6 (3)	0 (0)	6 (12)	1 (2)	0 (0)	1 (9)

Data are either *n* (%) or mean ± standard deviation. [†]Based on the Davis classification; included patients diagnosed with simple retinopathy, pre-proliferative retinopathy or proliferative retinopathy. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; K$^+$, potassium; LDL, low-density lipoprotein; Na$^+$, sodium; NYHA, New York Heart Association; SGLT2, sodium–glucose cotransporter 2; SGLT2i, SGLT2 inhibitor; UACR, urinary albumin-to-creatinine ratio.
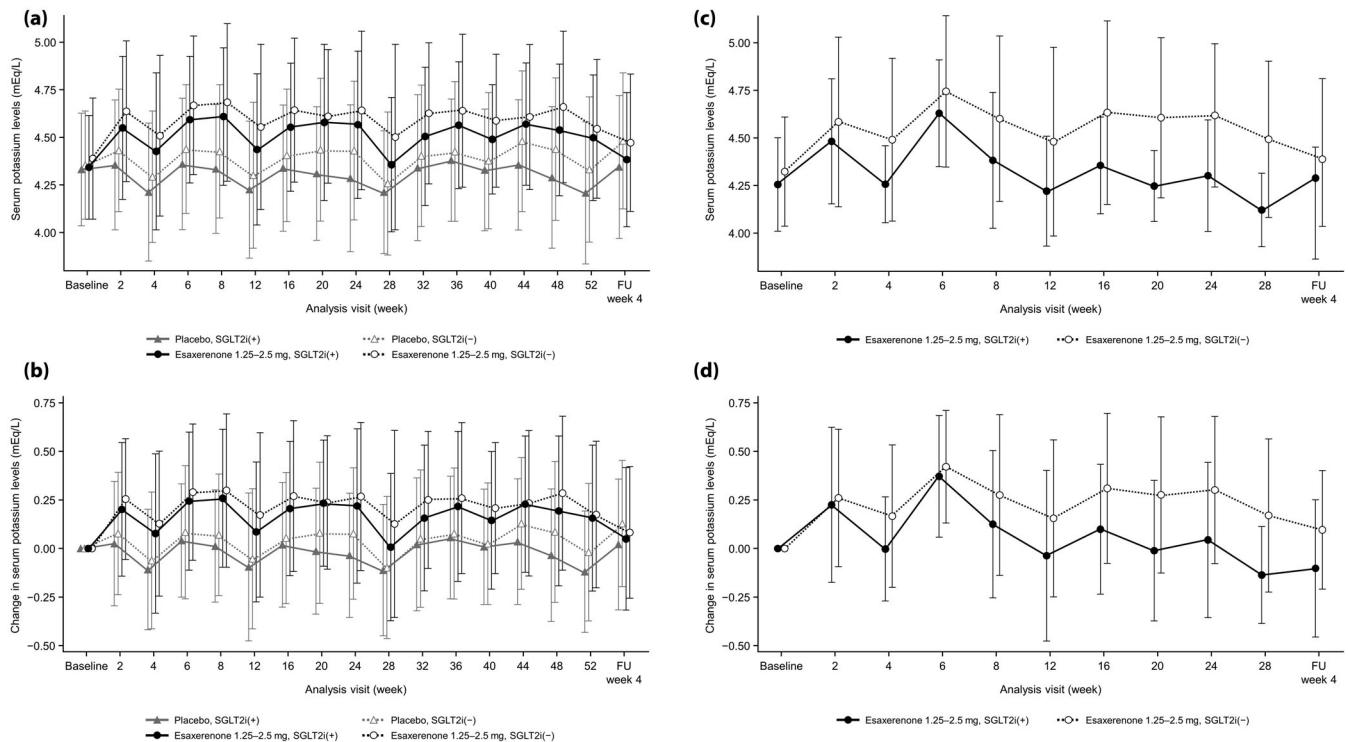
Figure 1 | (a) Time-course of changes (mean ± standard deviation) in serum potassium levels during the study period and (b) changes from baseline in serum potassium levels in the ESAX-DN (J308) study, and (c) changes in serum potassium levels during the study period and (d) changes from baseline in serum potassium levels in the J309 study, according to sodium–glucose cotransporter 2 (SGLT2) inhibitor use. FU, follow up; SD, standard deviation; SGLT2i, SGLT2 inhibitor.

Table 2 | Incidence rate of serum potassium level ≥5.5 mEq/L, and ≥6.0 or ≥5.5 mEq/L on two consecutive occasions according to sodium–glucose cotransporter 2 inhibitor use (post-hoc analysis)

	ESAX-DN (J308)				J309 study	
	Placebo		Esaxerenone 1.25–2.5 mg/day		Esaxerenone 1.25–2.5 mg/day	
	SGLT2i(−) (n = 172)	SGLT2i(+) (n = 57)	SGLT2i(−) (n = 175)	SGLT2i(+) (n = 51)	SGLT2i(−) (n = 45)	SGLT2i(+) (n = 11)
Patients with serum K⁺ ≥5.5 mEq/L	11 (6.4)	3 (5.6)	46 (26.3)	4 (7.8)	11 (24.4)	0 (0.0)
Patients with serum K⁺ ≥6.0 mEq/L or two consecutive measurement of serum K⁺ ≥5.5 mEq/L	5 (2.9)	0 (0.0)	20 (11.4)	0 (0.0)	3 (6.7)	0 (0.0)

K⁺, potassium; SGLT2, sodium–glucose cotransporter 2; SGLT2i, SGLT2 inhibitor.

proportion of patients with a transition from microalbuminuria to overt albuminuria was lower in the esaxerenone group versus the placebo group, with no notable differences according to SGLT2 inhibitor use in either the esaxerenone or placebo groups. In the J309 study, the proportion of patients with UACR reduction of 30, 50 and 75% was similar regardless of SGLT2 inhibitor use.

There were no differences in the antihypertensive effect of esaxerenone (Figure 4) or in the reduction in eGFR with esaxerenone (Figure 5) according to SGLT2 inhibitor use in either study.

Esaxerenone had no effect on the glucose lowering-effect of SGLT2 inhibitor (Figure S2). Serum sodium levels were also not affected by esaxerenone according to SGLT2 inhibitor use (Figure S3).
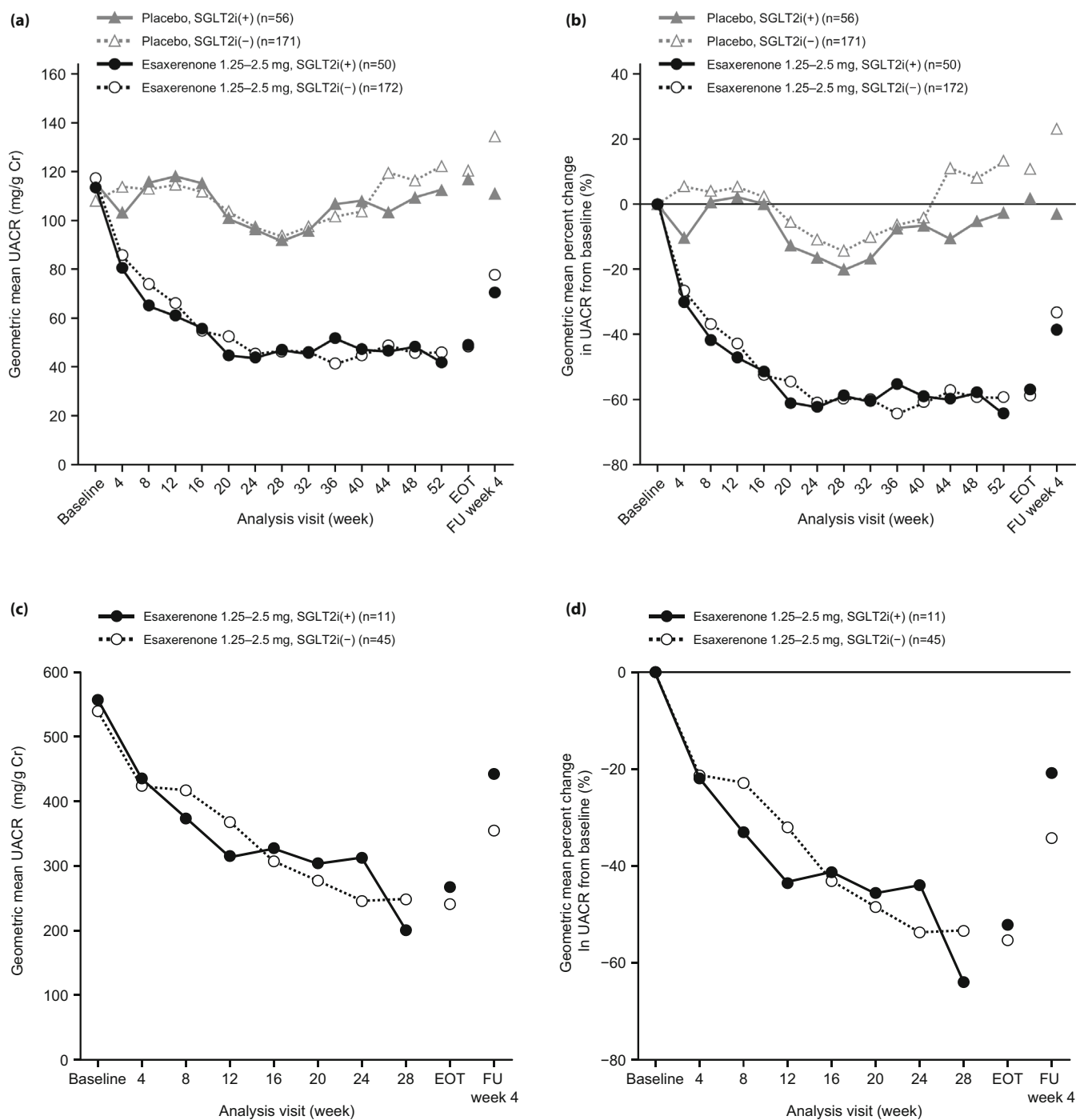
Figure 2 | Time-course of changes in (a) geometric mean urinary albumin-to-creatinine ratio (UACR) and (b) UACR percentage change in the ESAX-DN (J308) study, and changes in (c) geometric mean UACR and (d) UACR percentage change in the J309 study, according to SGLT2 inhibitor use. Cr, creatinine; EOT, end of treatment; FU, follow up; SGLT2, sodium–glucose cotransporter 2; SGLT2i, SGLT2 inhibitor.

The clinical efficacy and safety of esaxerenone, such as changes in UACR, blood pressure and eGFR, in the presence of DPP-4 inhibitors were not different from that in the presence of SGLT2 inhibitors, except for elevated serum potassium, which was not suppressed (Tables S2 and S3).

DISCUSSION

The main findings of the present subanalysis were as follows: in the presence of RAS inhibitors, (i) serum potassium levels and (ii) incidence rates of serum potassium elevation were lower in patients with co-administration with SGLT2 inhibitor
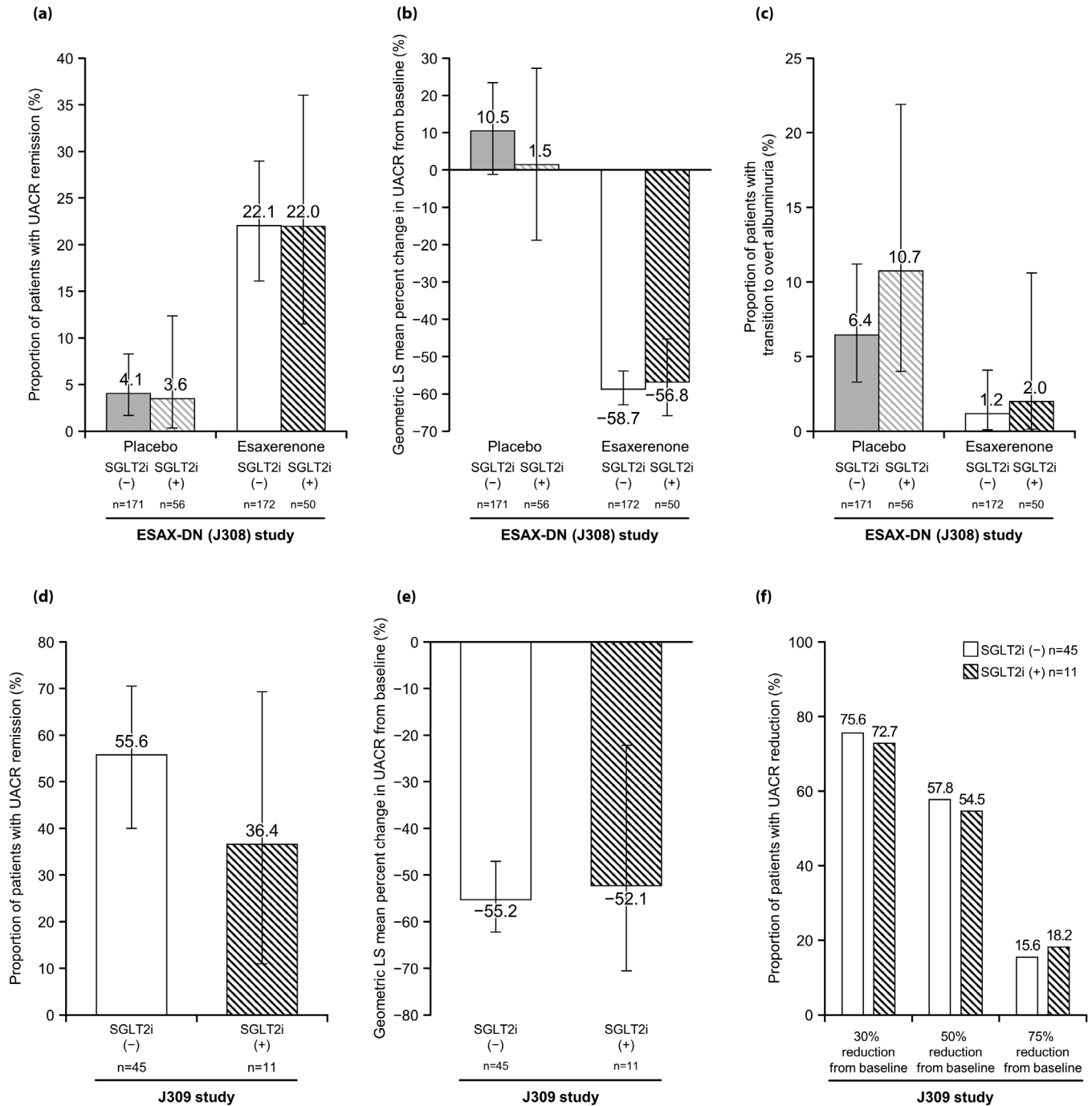
Figure 3 | (a) Urinary albumin-to-creatinine ratio (UACR) remission rate[†], (b) geometric least squares (LS) mean percent change in UACR from baseline and (c) proportion of patients with a transition from microalbuminuria to overt albuminuria in the ESAX-DN (J308) study at the end of treatment, and (d) UACR remission rate[‡], (e) geometric LS mean percentage change in UACR from baseline and (f) proportion of patients with a reduction in UACR of 30%, 50% and 75% in the J309 study at end of treatment, according to sodium–glucose cotransporter 2 (SGLT2) inhibitor use. Error bars show 95% confidence interval. [†]In the ESAX-DN (J308) study, UACR remission was defined as having a UACR <30 mg/g creatinine and ≥30% reduction from baseline on two consecutive occasions at the end of treatment (prespecified analysis). [‡]In the J309 study, UACR remission was defined as having a UACR <300 mg/g creatinine and ≥30% reduction from baseline on two consecutive occasions at the end of treatment (post-hoc analysis). SGLT2i, SGLT2 inhibitor.
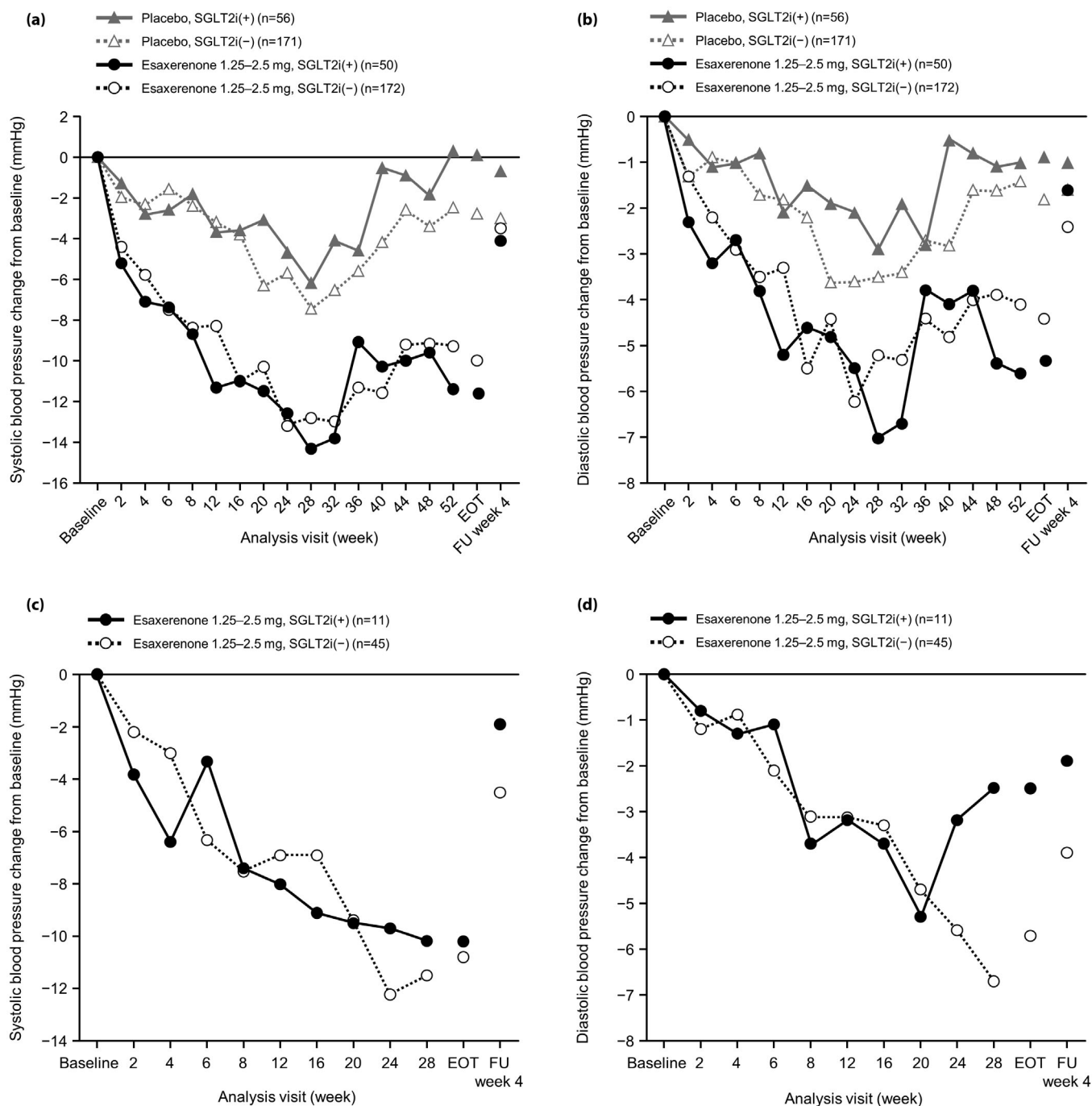
Figure 4 | Time-course of changes from baseline in sitting (a) systolic and (b) diastolic blood pressure in the ESAX-DN (J308) study, and in sitting (c) systolic and (d) diastolic blood pressure in the J309 study, according to sodium–glucose cotransporter 2 (SGLT2) inhibitor use. EOT, end of treatment; FU, follow up; SGLT2i, SGLT2 inhibitor.

than those without the inhibitor in both the placebo and esaxerenone groups; (iii) UACR was significantly reduced with esaxerenone versus placebo, and the changes in UACR were similar regardless of SGLT2 inhibitor use; (iv) reduction in blood pressure and eGFR with esaxerenone were not affected by co-

administration with SGLT2 inhibitor; and (v) DPP-4 inhibitor did not change the increase in serum potassium level, the decrease in UACR, blood pressure and eGFR by esaxerenone.

In previous studies, the effects of individual SGLT2 inhibitors on serum potassium levels have been assessed. In the
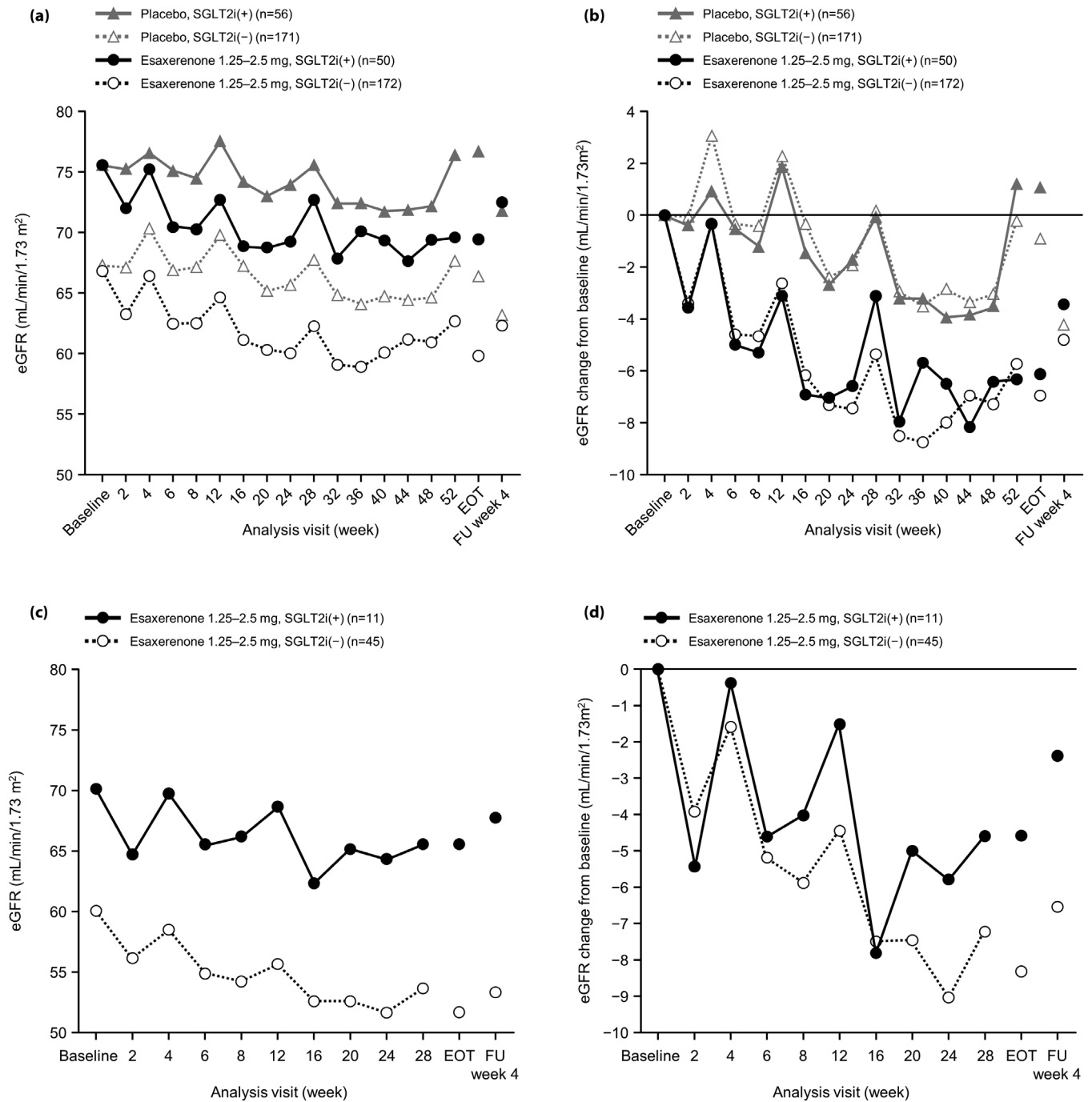
Figure 5 | Time-course of (a) changes in estimated glomerular filtration rate (eGFR) and (b) change from baseline in eGFR in the ESAX-DN (J308) study, and (c) changes in eGFR and (d) change from baseline in eGFR in the J309 study, according to sodium–glucose cotransporter 2 (SGLT2) inhibitor use. EOT, end of treatment; FU, follow up; SGLT2i, SGLT2 inhibitor.

Canagliflozin Cardiovascular Assessment Study (CANVAS) program, there were no meaningful effects of canagliflozin on serum potassium in the overall population or key subgroups[14]. Serum potassium levels did not differ according to canagliflozin dose, and the incidence of hyperkalemia adverse events did not

differ across groups. Similarly, in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE)[15] and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD)[16] trials in patients with CKD, no significant difference was

reported in hyperkalemia adverse events between the SGLT2 inhibitor and placebo groups. Furthermore, in a pooled analysis of 14 randomized clinical trials, dapagliflozin was not found to be associated with an increased risk of hyperkalemia[12]. Finally, the use of empagliflozin in patients with type 2 diabetes and mild CKD (stage 2 and 3) was shown not to be associated with changes in serum potassium levels[17]. Thus, most single drug analyses have reported that SGLT2 inhibitors have no effect on serum potassium levels. However, those data were obtained under clinical trial conditions, and real-world meta-analyses have reported either no effect[18] or a decrease in hyperkalemia (reduction rate 0.84; 95% CI 0.72–0.99)[19]. Conversely, prior data relating to concomitant use of SGLT2 inhibitors and MRBs were consistent with the events identified in this analysis. In a recent subanalysis of the DAPA-HF and FIDELIO-DKD studies, it was reported that co-administration of the SGLT2 inhibitor with MRBs decreased the risk of hyperkalemia[20,21], generating the hypothesis that SGLT2 inhibition might reduce the risk of severe hyperkalemia among MRB users[22]. Based on considerations of the biological function of SGLT2, some reviews have speculated that SGLT2 inhibitors might slightly alter GFR or volume status, or improve insulin resistance, causing serum potassium levels to increase rather than decrease[23,24]. However, taking into consideration the results of these previous clinical trials and our own data, it can be assumed that SGLT2 inhibitors do not increase, but rather decrease serum potassium levels.

The effect on serum potassium elevation differed between SGLT2 and DPP-4 inhibitors; however, there were no differences in the changes in blood pressure, UACR or eGFR with esaxerenone administration. In addition, no differences were observed in patient background or diabetes treatment (blood glucose level). Therefore, using DPP-4 inhibitors as a reference, we consider that the reduction of serum potassium elevation might be attributed to the unique mechanism of action of SGLT2 inhibitors. More research is required to elucidate the detailed mechanisms, but one important point to note is the probable difference in the site of action of SGLT2 inhibitors and MRBs. Although the actual site where SGLT2 inhibitors are involved in the regulation of serum potassium levels is unknown, it is likely to be the proximal tubule where SGLT2 is present, which is clearly different from the distal tubule, the site of action of MRBs[23,25]; thus, the effects of SGLT2 inhibitors and MRBs on serum potassium are likely to occur through different mechanisms. The clinical significance, as well as the inhibitory effect, of SGLT2 inhibitors on serum potassium elevation has not been emphasized, which is thought to be one of the reasons why the mechanism has not been clarified so far, and further research is required.

Data from previous phase III studies in patients with hypertension showed that the side-effect of serum potassium elevation caused by esaxerenone could be managed by drug withdrawal, without the necessity of any additional treatment[9]. The same was true for the two phase III studies in diabetic nephropathy

used for the present subanalysis[6,7]. Although this was a subanalysis of studies in patients with diabetic nephropathy, the results can be applied to hypertensive patients, especially those with moderate renal dysfunction or diabetes mellitus with albuminuria who are at high risk of hyperkalemia. Cautious administration, such as gradually increasing the esaxerenone dosage from 1.25 to 2.5–5 mg/day, is now recommended for hypertensive patients at high risk of serum potassium elevation, including those with both diabetes and albuminuria, and those with moderate renal dysfunction[26]. The results of the present subanalysis, in which co-administration of SGLT2 inhibitor reduced the risk of serum potassium elevation, suggest that more effective antihypertensive treatment with esaxerenone could be provided to these high-risk patients at higher dose and for a longer period of time without withdrawal.

In both studies, SGLT2 and DPP-4 inhibitors were required to have stable dosage and administration from 12 weeks before the start of esaxerenone treatment until the end of the study. SGLT2 inhibitors are known to decrease albuminuria[13,27], blood pressure[28] and eGFR[29] with an initial dip, and all of these effects reach steady state at 12 weeks. Therefore, we consider that one possible reason for the observation that UACR, blood pressure and eGFR remained constant in the placebo group using SGLT2 inhibitors in the ESAX-DN (J308) study might be that these parameters had already undergone their maximum decrease at the start of the study. Furthermore, a series of meta-analyses reported that DPP-4 inhibitors did not alter UACR and blood pressure[30,31], but slightly decreased eGFR (−1.12 mL/min/1.73 m^2)[32]. This small eGFR-lowering effect of DPP-4 inhibitors did not affect eGFR in the placebo group of the ESAX-DN (J308) study. Additionally, in patients taking SGLT2 and DPP-4 inhibitors, blood glucose levels remained constant from the start of esaxerenone administration until the end of the study, which is further evidence that the effects of these agents had reached steady state at the start of esaxerenone administration.

MRBs have been proven to have cardioprotective (eplerenone, spironolactone and finerenone)[33–36] as well as renoprotective (finerenone) effects[36–38] in addition to their antihypertensive effects. The combination of MRBs with SGLT2 inhibitors is expected to overcome the safety limitations of MRBs, and might provide additive cardioprotective and renoprotective effects. A retrospective study of approximately 1.14 million Japanese patients with type 2 diabetes, which investigated trends in the prescription of first-line non-insulin antidiabetic drugs from 2014 to 2017, showed that the use of SGLT2 inhibitors increased from 2.2% in 2014 to 11.4% in 2017[39]. Given that dapagliflozin was approved for CKD patients with or without diabetes in August 2021[40], and empagliflozin and canagliflozin are in development for use in patients with CKD, the prescription rate of SGLT2 inhibitors is expected to increase further in the future. As we are now entering a new era of diabetes treatment with the advent of SGLT2 inhibitors and finerenone, the results of the present subanalysis suggest that the

use of such combination regimens could become a new therapeutic strategy for patients with diabetes, especially for those with hypertension associated with cardiovascular and renal diseases.

The main limitation of the present study was that the study was carried out as a subanalysis. The effect of SGLT2 inhibitors on MRB-induced serum potassium elevation and its pharmacological effects need to be clarified with future randomized controlled trials.

In conclusion, in Japanese patients with type 2 diabetes and micro- or macroalbuminuria treated with esaxerenone, co-administration with SGLT2 inhibitor reduced the magnitude of serum potassium elevation without change of the antihypertensive and albuminuria-suppressing effects in the presence of RAS inhibitor. Co-administration of esaxerenone and SGLT2 inhibitor might be a beneficial treatment option for patients with diabetic kidney disease.

DATA AVAILABILITY STATEMENT

The anonymized data underlying the results presented in this manuscript may be made available to researchers upon submission of a reasonable request to the corresponding author. The decision to disclose the data will be made by the corresponding author and the funder, Daiichi Sankyo Co., Ltd. Data disclosure can be requested for 36 months from article publication.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Study design.

Figure S2 | Mean ± standard deviation change in blood glucose level according to (a,b) sodium–glucose cotransporter 2 (SGLT2) inhibitor or (c,d) dipeptidyl peptidase-4 (DPP-4) inhibitor use in both the ESAX-DN (J308) and J309 studies (post-hoc analysis).

Figure S3 | Mean ± standard deviation change in serum sodium levels according to (a,b) sodium–glucose cotransporter 2 (SGLT2) inhibitor or (c,d) dipeptidyl peptidase-4 (DPP-4) inhibitor use in both the ESAX-DN (J308) and J309 studies (post-hoc analysis).

Table S1 | Patient demographic and clinical characteristics at baseline according to dipeptidyl peptidase-4 inhibitor use.

Table S2 | Incidence rate of serum potassium level ≥5.5 mEq/L and ≥6.0 or ≥5.5 mEq/L on two consecutive occasions according to dipeptidyl peptidase-4 inhibitor use (post-hoc analysis).

Table S3 | Changes in urinary albumin-to-creatinine ratio, urinary albumin-to-creatinine ratio remission rates, transition to overt albuminuria, blood pressure and estimated glomerular filtration rate according to sodium–glucose cotransporter 2 and dipeptidyl peptidase-4 inhibitor use.