ORIGINAL RESEARCH

Factors Associated with the Antihypertensive Effect of Esaxerenone and Serum Potassium Elevation: A Pooled Analysis of Seven Phase III Studies

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ABSTRACT

Introduction: This study investigated factors associated with the antihypertensive effects of esaxerenone and the incidence of serum potassium elevation in patients with hypertension.

Methods: Using pooled data from seven phase III studies, the study analyzed factors associated with changes in office systolic (SBP) and diastolic (DBP) blood pressure from baseline to 12 weeks, and factors associated with incidence of serum potassium levels ≥ 5.5 mEq/L in esaxerenone-treated patients.

Results: Overall, 1466 and 1472 patients were included in the full analysis and safety analysis sets, respectively. Male sex (4.02/2.40 mmHg), weight ≥ 78.4 kg (4.62/2.09 mmHg), hypertension duration ≥ 10 years (2.66/1.71 mmHg), prior antihypertensive treatment (2.38/1.40 mmHg), plasma aldosterone concentration ≥ 120 pg/mL (1.66/1.17 mmHg), urinary albumin-to-creatinine ratio (UACR) ≥ 300 mg/gCr (8.94/4.85 mmHg) or 30–299 mg/gCr (5.17/4.15 mmHg), and smoking (2.62/1.27 mmHg) were associated with mean changes in SBP and DBP. Fasting blood glucose ≥ 126 mg/dL $(-2.73$ mmHg) was associated with the mean change in SBP only, and older age (65–74 years, -2.12 mmHg; and ≥ 75 years, -3.06 mmHg) with mean change in DBP only. Factors significantly associated with incidence of serum potassium levels ≥ 5.5 mEq/L were higher baseline serum potassium (≥ 4.5 mEq/L, odds ratio [OR] 6.702); lower estimated glomerular filtration rate (≥ 90 mL/min/1.73 m^2, OR 0.148; 60–89 mL/min/1.73 m^2, OR 0.331 vs 30–59 mL/min/1.73 m^2, respectively); higher UACR (30–299 mg/gCr, OR 7.317); higher DBP (≥ 100 mmHg, OR 3.248); and grade I hypertension (OR 2.168).

Conclusion: Esaxerenone is effective in patients with a broad range of backgrounds, though some factors may predict increased benefit. Regarding elevated serum potassium, careful therapeutic management is recommended for patients with higher baseline serum potassium and reduced renal function.**Clinical trial registration**: UMIN000047026.

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Key Summary Points
Why carry out this study?
Esaxerenone, an oral, nonsteroidal mineralocorticoid receptor blocker, is well tolerated and effective at managing blood pressure (BP); however, the specific patient groups who would most benefit from esaxerenone treatment are unknown.
This study aimed to identify factors associated with the antihypertensive effect of esaxerenone, and to identify factors associated with an increased incidence of serum potassium elevation.
What was learned from the study?
Several factors including female sex, lower body weight, lower plasma aldosterone concentration, shorter duration of hypertension, no antihypertensive treatment, lower urinary albumin-to-creatinine ratio (UACR), and non-smoking were associated with a stronger reduction in BP under esaxerenone treatment; in addition, factors associated with serum potassium elevation were mainly higher baseline serum potassium, lower estimated glomerular filtration rate (eGFR), and higher UACR.
Esaxerenone is generally effective in all patient groups; however, a stronger BP-lowering effect may be observed in some patients according to their background characteristics.
Higher baseline serum potassium level and reduced renal function including lower eGFR and higher UACR were associated with a higher risk of serum potassium elevation, indicating the need for careful therapeutic management in affected patients.

INTRODUCTION

Hypertension is one of the major risk factors for developing cerebrovascular and cardiovascular diseases [1–3]. Additionally, hypertension often occurs with comorbidities such as diabetes mellitus, dyslipidemia, and chronic kidney disease (CKD), which can further exacerbate the risk of affected patients developing cerebrovascular and cardiovascular diseases [4–6]. Therefore, blood pressure (BP) management in patients with hypertension is important for preventing the development of these diseases.

Mineralocorticoid receptor blockers (MRBs) are one of the options for treating hypertension, and are effective in controlling BP in patients who are unresponsive to conventional antihypertensive therapies when used in combination with first-line antihypertensive agents [7]. However, hyperkalemia may develop in patients who are receiving MRB treatment, particularly in patients with risk factors such as CKD or diabetes mellitus, or if therapies that interfere with potassium homeostasis are used [8]. Nonsteroidal MRBs are third-generation MRBs with both high potency and selectivity against mineralocorticoid receptors [9]. Esaxerenone is an oral, nonsteroidal MRB that has been shown through multiple phase III studies to be generally well tolerated and effective at controlling BP [10–16], with a recent review summarizing the patient background characteristics in which serum potassium levels may be elevated [17].

The efficacy of antihypertensive therapies can differ depending on the background of the patient. For example, renin–angiotensin system (RAS) inhibitors have been shown to be less effective in treating low-renin hypertension, which is a common form of hypertension in elderly patients [18, 19]. A subgroup analysis of the CS3150-A-J301 (ESAX-HTN) study suggested that women and individuals with lower body mass indices had an improved response to esaxerenone treatment [10]; however, the patients in the ESAX-HTN study had similar backgrounds, and therefore additional characteristics associated with different responses to esaxerenone treatment were not identified. In

addition, the results of an exposure–response analysis using population pharmacokinetics analysis suggested that the presence of diabetes mellitus with albuminuria or proteinuria, severe renal dysfunction (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2), and moderate renal dysfunction (eGFR 30 to < 60 mL/min/1.73 m^2) was associated with serum potassium elevation following esaxerenone treatment [20]. However, it is still unknown which specific patient populations will most benefit from the addition of esaxerenone, and whether other patient characteristics affect the antihypertensive effect and incidence of serum potassium elevation with esaxerenone treatment.

We hypothesized that, following treatment with esaxerenone, there will be a group of patients with significantly improved BP control and a group of patients with increased serum potassium. Using the pooled data from the phase III studies of esaxerenone, this study aimed to identify the factors associated with a stronger reduction in BP in hypertensive patients with diverse backgrounds who were receiving esaxerenone treatment. In addition, we examined whether any unknown factors were associated with an increased incidence of serum potassium elevation.

METHODS

Study Design and Patients

This was a post hoc analysis of pooled data from seven previously published Japanese phase III studies of esaxerenone: ESAX-HTN, CS3150-A-J302 (J302), CS3150-A-J305 (J305), CS3150-A-J306 (J306), CS3150-A-J307 (J307), CS3150-B-J308 (ESAX-DN), and CS3150-B-J309 (J309) [10–16]. CS3150-A-J304 was not included in this analysis as the study period was only 8 weeks and not appropriate to include in the pooled analysis [21]. The study designs of each included study and the respective registration identification numbers are shown in Table 1.

Consent was obtained in writing from the participants in each of the previous phase III studies. As this pooled analysis was a secondary

use of data obtained from the seven studies, and in accordance with the Ethical Guidelines for Life Science and Medical Research Involving Human Subjects [22], no new consent was required or obtained from the research participants. The study was conducted in accordance with the principles of the Declaration of Helsinki, the Ethical Guidelines for Human Life Science and Medical Research, and the Act on the Protection of Personal Information. Approval was provided by the ethical review committee at the Kitamachi Clinic (Tokyo, Japan) and the study was registered with the University hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000047026).

Efficacy Endpoint

The efficacy endpoint in this study was the factors associated with a change in office systolic and diastolic BP in a sitting position from baseline to 12 weeks in patients receiving esaxerenone. This time period was chosen to ensure a fixed dosing period of at least 4 weeks of esaxerenone administration, as the majority of the phase III studies were designed to titrate esaxerenone over the first 8 weeks of treatment, and was considered to be a sufficient duration to evaluate the BP-lowering effect. This endpoint was analyzed in the overall population and in a subgroup with both office systolic BP (SBP) ≥ 140 mmHg and diastolic BP (DBP) ≥ 90 mmHg at baseline.

Safety Endpoint

The safety endpoint was the factors associated with incidences of serum potassium elevation in patients, pre-defined as serum potassium levels ≥ 5.5 mEq/L during the treatment period.

Statistical Analyses

For the efficacy endpoints, change in office SBP and DBP from baseline to 12 weeks after esaxerenone treatment was used as the objective variable. Subgroup analyses were performed on data from patients with baseline SBP/DBP

Table 1 Study identifiers and design for each of the clinical studies included in the analysis

(A) Study ID, (B) Study name, (C) Study design, (D) Study dosage, (E) Concomitant antihypertensives	Study patients		Mean change from baseline in SBP/DBP, mmHg		Frequency of serum potassium elevation ≥ 5.5 mEq/L, n (%)
	Enrolled, N	Esaxerenone treatment, n	Week 12	End of study	
(A) **CS3150-A-J301**, NCT02890173, JapicCTI-163348 (B) Comparative study of CS-3150 and eplerenone in patients with essential hypertension (ESAX-HTN) (C) Multicenter, randomized, active-controlled, double-blind, 3-group, parallel-group study (D) Patients received either esaxerenone 2.5 mg/day, 5 mg/day or eplerenone 50 mg/day for 12 weeks (E) None	1001	FAS: 667 SAS: 669	2.5 mg (n = 330): −13.1/−6.4 5 mg (n = 337): −16.5/−8.1	2.5 mg (n = 330): −13.1/−6.4 (12 weeks) 5 mg (n = 337): −16.5/−8.1 (12 weeks)	2.5 mg (n = 331): 15 (4.5) 5 mg (n = 338): 0 (3.0)
(A) **CS3150-A-J302**, NCT02722265, JapicCTI-163176 (B) Long-term administration study of CS-3150, alone or in combination, in patients with essential hypertension (C) Multicenter, open-label, optional titration based on patient response (D) Patients received esaxerenone at 2.5 mg/day, with optional titration up to 5 mg/day, for 28 or 52 weeks (E) See right side	Overall 368	FAS: 368 SAS: 368	−16.1/−7.7	−23.1/−12.5 (52 weeks)	20 (5.4)
	Esaxerenone alone 245	FAS: 245 SAS: 245	−16.3/−7.0	−23.7/−12.3 (52 weeks)	14 (5.7)
	RASi 64	FAS: 64 SAS: 64	−16.8/−9.6	−23.0/−12.6 (52 weeks)	4 (6.3)
	CCB 59	FAS: 59 SAS: 59	−14.8/−8.2	−20.5/−13.1 (52 weeks)	2 (3.4)
(A) **CS3150-A-J305**, NCT02807987, JapicCTI-163288 (B) Studies in hypertensive patients with moderate renal impairment (C) Multicenter, open-label, optional titration based on patient response (D) Patients received esaxerenone 1.25 mg/day, with optional titration up to 2.5 mg/day or 5 mg/day, over 12 weeks (E) RASi	58	FAS: 58 SAS: 58	−17.8/−8.1	−17.8/−8.1 (12 weeks)	7 (12.1)

Table 1 continued

(A) Study ID, (B) Study name, (C) Study design, (D) Study dosage, (E) Concomitant antihypertensives	Study patients		Mean change from baseline in SBP/DBP, mmHg		Frequency of serum potassium elevation
	Enrolled, N	Esaxerenone treatment, n	Week 12	End of study	≥ 5.5 mEq/L, n (%)
(A) **CS3150-A-J306**, NCT02807974, JapicCTI-163293 (B) Study in hypertensive patients with type 2 diabetes mellitus with albuminuria (C) Multicenter, open-label, optional titration based on patient response (D) Patients received esaxerenone 1.25 mg/day, with optional titration up to 2.5 mg/day or 5 mg/day, over 12 weeks (E) RASi	51	FAS: 51 SAS: 51	− 13.7/− 6.2	− 13.7/− 6.2 (12 weeks)	2 (3.9)
(A) **CS3150-A-J307**, NCT02885662, JapicCTI-163349 (B) Studies in patients with primary aldosteronism (C) Multicenter, open-label, optional titration based on patient response (D) Patients received esaxerenone 2.5 mg/day, with optional titration up to 5 mg/day, over 12 weeks (E) CCB, or α-blockers	44	FAS: 44 SAS: 44	− 17.7/− 9.5	− 17.7/− 9.5 (12 weeks)	1 (2.3)
(A) **CS3150-B-J308**, JapicCTI-173695 (B) Placebo-controlled, double-blind, comparative study of CS-3150 in patients with type 2 diabetes mellitus and microalbuminuria (ESAX-DN) (C) Multicenter, randomized, placebo-controlled, double blind, two-group, parallel group study (D) Patients received esaxerenone 1.25 mg/day, titrated to 2.5 mg/day, over 52 weeks (E) RASi	455	FAS: 222 SAS: 226	− 8.9/− 3.7	− 9.9/− 4.5 (52 weeks)	50 (22.1)

Table 1 continued

(A) Study ID, (B) Study name, (C) Study design, (D) Study dosage, (E) Concomitant antihypertensives	Study patients		Mean change from baseline in SBP/DBP, mmHg		Frequency of serum potassium elevation
	Enrolled, N	Esaxerenone treatment, n	Week 12	End of study	≥ 5.5 mEq/L, n (%)
(A) **CS3150-B-J309**, JapicCTI-173696 (B) Safety investigation study of CS-3150 in type 2 diabetes patients with overt albuminuria (C) Multicenter, open-label, dose escalation (D) Patients received esaxerenone 1.25 mg/day, titrated to 2.5 mg/day, over 28 weeks (E) RASi	56	FAS: 56 SAS: 56	− 7.1/− 3.1	− 11.2/− 5.8 (28 weeks)	11 (19.6)

CCB calcium channel blockers, *DBP* diastolic blood pressure, *FAS* full analysis set, *RASi* renin–angiotensin system inhibitors, *SAS* safety analysis set, *SBP* systolic blood pressure

≥ 140/90 mmHg. The effect of each factor on the change in BP, its 95% confidence interval (CI), and *p* value were calculated using univariate and multivariate linear regression models.

In addition, for the occurrence of serum potassium levels ≥ 5.5 mEq/L during the esaxerenone treatment, the effect of each background factor and its 95% CI and *p* value were calculated using univariate and multivariate logistic regression models. All models, including univariate models, had the baseline value and method of administration (starting dose and whether the study design included titration or a set dose of esaxerenone) as covariates.

When missing BP measurements were present after the start of esaxerenone administration, the last observation carried forward method was applied to impute missing values. Missing background factors were categorized as "unknown". Both the ESAX-HTN and J302 studies excluded patients with a urinary albumin-to-creatinine ratio (UACR) of ≥ 30 mg/gCr by study design. Thus, all the patients from these studies were considered to have a UACR < 30 mg/gCr. As esaxerenone is contraindicated in patients with either eGFR < 30 mL/min/1.73 m² or serum potassium levels ≥ 5.0 mEq/L, these patients were excluded from this analysis.

The significance level for hypothesis testing was 5% two-sided, with a two-sided 95% CI. SAS System Release 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

RESULTS

Patients

Patients treated with esaxerenone in the full analysis set (FAS) of each study were included in the efficacy analysis (*N* = 1466). For each study, the number of patients was as follows: ESAX-HTN (*n* = 667), J302 (*n* = 368), J305 (*n* = 58), J306 (*n* = 51), J307 (*n* = 44), ESAX-DN (*n* = 222), and J309 (*n* = 56). The safety analysis set of each study was used for analysis of the safety endpoint (*N* = 1472). For each study, the number of patients treated with esaxerenone in the safety analysis set was as follows: ESAX-HTN (*n* = 669),

J302 (*n* = 368), J305 (*n* = 58), J306 (*n* = 51), J307 (*n* = 44), ESAX-DN (*n* = 226), and J309 (*n* = 56). The subgroup analysis included patients who had both office SBP ≥ 140 mmHg and DBP ≥ 90 mmHg at baseline from the FAS of each study (1192/1466; 81.3%).

Patient characteristics in the overall FAS population and subgroups are shown in Table 2. In the overall FAS population, the mean age ± standard deviation was 58.2 ± 10.5 years; 74.0% were male; body weight was 70.4 ± 13.2 kg; SBP/DBP was 152.8/94.6 ± 11.4/8.6 mmHg; eGFR was 75.5 ± 15.4 mL/min/1.73 m²; serum potassium was 4.2 ± 0.3 mEq/L; complication of diabetes mellitus was 34.7%; prior use of antihypertensives was 68.8%, of which 51.2% used RAS inhibitors, and 47.1% used calcium channel blockers (CCB). There was no prior use of thiazide or loop diuretics.

Efficacy Endpoint

In the overall population, a significant BP reduction was observed in patients treated with esaxerenone. The mean change from baseline at week 12 in SBP and DBP was − 14.4 (95% CI − 15.0, − 13.7) mmHg and − 6.9 (95% CI − 7.3, − 6.5) mmHg, respectively; the change from baseline at week 12 and at the end of study in SBP and DBP for each study is shown in Table 1. The multivariate analysis of factors associated with a change in office SBP/DBP in a sitting position is shown in Table 3, and the univariate analysis of factors is shown in Table S1 in the supplementary material. The estimates (95% CI) indicate the absolute difference in BP change compared to the reference category; negative estimates indicate that BP reduction is larger relative to the reference (i.e., a relatively stronger antihypertensive effect), and positive estimates indicate that the BP reduction is smaller relative to the reference (i.e., a relatively weaker antihypertensive effect). Factors that were significantly associated with a positive estimated change in office SBP in a sitting position from baseline to 12 weeks after esaxerenone treatment relative to the reference (i.e., these factors may be associated with a weaker BP-lowering effect) included male sex

Table 2 Patient characteristics in the full analysis set and subgroup

	Total N = 1466	SBP/DBP ≥ 140/90 mmHg N = 1192
Sex, male	1085 (74.0)	886 (74.3)
Age, years	58.2 ± 10.5	56.2 ± 9.6
Weight, kg	70.4 ± 13.2	70.8 ± 13.0
BMI, kg/m^2	25.8 ± 3.9	25.7 ± 3.9
SBP, mmHg	152.8 ± 11.4	155.2 ± 9.6
DBP, mmHg	94.6 ± 8.6	97.7 ± 5.5
UACR, mg/gCr	138.3 ± 192.0	82.8 ± 170.5
eGFRcreat, mL/min/1.73 m^2	75.5 ± 15.4	77.7 ± 13.9
Serum potassium, mEq/L	4.2 ± 0.3	4.2 ± 0.3
HbA1c, %	6.0 ± 0.8	5.8 ± 0.7
Triglyceride, mg/dL	134.0 ± 101.2	135.1 ± 105.2
PAC, pg/mL	115.5 ± 85.0	121.6 ± 90.5
PRA, ng/mL/h	1.5 ± 2.6	1.1 ± 2.3
Duration of hypertension, years	8.2 ± 7.7	7.5 ± 7.4
Prior treatment for hypertension	1008 (68.8)	736 (61.7)
Other complications	1279 (87.2)	1014 (85.1)
Diabetes mellitus	509 (34.7)	250 (21.0)
Dyslipidemia	753 (51.4)	546 (45.8)
Hyperuricemia	374 (25.5)	283 (23.7)
Prior antihypertensive agents		
RASi	751 (51.2)	485 (40.7)
CCB	690 (47.1)	508 (42.6)

Data are n (%) or mean ± standard deviation

BMI body mass index, *CCB* calcium channel blocker, *Cr* creatinine, *DBP* diastolic blood pressure, *eGFRcreat* estimated glomerular filtration rate based on serum creatinine, *HbA1c* hemoglobin A1c, *PAC* plasma aldosterone concentration, *PRA* plasma renin activity, *RASi* renin–angiotensin system inhibitor, *SBP* systolic blood pressure, *UACR* urinary albumin-to-creatinine ratio

(estimate 4.02 mmHg; $p < 0.001$); higher weight ≥ 78.4 kg (quartile 4) (estimate 4.62 mmHg; $p = 0.002$); duration of hypertension ≥ 10 years (estimate 2.66 mmHg; $p < 0.001$); prior treatment with antihypertensive drugs (estimate 2.38 mmHg; $p = 0.002$); plasma aldosterone concentration (PAC) ≥ 120 pg/mL (estimate 1.66 mmHg; $p = 0.016$); UACR ≥ 300 mg/gCr (estimate 8.94 mmHg; $p < 0.001$) or 30–299 mg/gCr (estimate 5.17 mmHg; $p = 0.020$); and current smoking (estimate 2.62 mmHg; $p = 0.002$). Conversely, fasting blood glucose ≥ 126 mg/dL was associated with a significantly negative estimated change in

Table 3 Multivariate analysis of factors associated with a change from baseline in office sitting systolic and diastolic blood pressure at 12 weeks in the full analysis set

Variables	Class	N	SBP Estimate of the change in BP, mmHg (95% CI)	SBP p value[b]	SBP Overall p value[c]	DBP Estimate of the change in BP, mmHg (95% CI)	DBP p value[b]	DBP Overall p value[c]
Sex	Female[a]	381			< 0.001			< 0.001
	Male	1085	4.02 (2.24, 5.80)	< 0.001		2.40 (1.31, 3.49)	< 0.001	
Age (years)	< 65[a]	1031			0.132			< 0.001
	65–74	347	− 1.30 (− 2.96, 0.37)	0.127		− 2.12 (− 3.16, − 1.09)	< 0.001	
	≥ 75	88	1.03 (− 1.86, 3.92)	0.483		− 3.06 (− 4.89, − 1.23)	0.001	
Weight (kg)	Quartile 1 (< 61.5)[a]	367			0.012			0.119
	Quartile 2 (61.5–69.4)	362	1.14 (− 0.76, 3.04)	0.240		0.55 (− 0.61, 1.71)	0.349	
	Quartile 3 (69.4–78.4)	369	2.14 (− 0.14, 4.42)	0.066		1.21 (− 0.19, 2.60)	0.089	
	Quartile 4 (≥ 78.4)	368	4.62 (1.77, 7.47)	0.002		2.09 (0.34, 3.83)	0.019	
BMI (kg/m²)	< 18.5[a]	12			0.200			0.265
	18.5 to < 24	661	− 3.20 (− 9.86, 3.46)	0.346		− 1.13 (−5.20, 2.94)	0.585	
	25–29	593	− 4.83 (− 11.66, 2.00)	0.166		− 1.84 (− 6.01, 2.33)	0.387	
	≥ 30	200	− 4.30 (− 11.44, 2.84)	0.238		− 0.91 (− 5.27, 3.45)	0.681	
Office SBP (mmHg)	< 160[a]	1073			—			0.009
	≥ 160	393	—	—		1.61 (0.40, 2.81)	0.009	
Office DBP (mmHg)	< 100[a]	1047			0.989			—
	≥ 100	419	− 0.02 (− 2.19, 2.16)	0.989		—	—	
Pulse (bpm)	< 60[a]	134			0.822			0.745
	60–99	1315	− 0.67 (− 2.77, 1.43)	0.531		− 0.42 (− 1.71, 0.87)	0.523	
	≥ 100	17	− 0.55 (− 6.46, 5.36)	0.855		− 1.14 (− 4.76, 2.48)	0.537	

Table 3 continued

Variables	Class	N	SBP			DBP		
			Estimate of the change in BP, mmHg (95% CI)	p value[b]	Overall p value[c]	Estimate of the change in BP, mmHg (95% CI)	p value[b]	Overall p value[c]
Type of hypertension	Normotensive[a]	104			0.848			0.215
	Grade I	737	0.90 (− 2.20, 4.00)	0.569		− 0.24 (− 2.02, 1.54)	0.793	
	Grade II	625	1.15 (− 3.18, 5.49)	0.603		− 1.37 (− 3.72, 0.99)	0.254	
Duration of hypertension (years)	< 5[a]	577			0.002			< 0.001
	5–9	349	1.51 (− 0.07, 3.08)	0.061		1.13 (0.16, 2.09)	0.022	
	≥ 10	496	2.66 (1.17, 4.15)	< 0.001		1.71 (0.80, 2.62)	< 0.001	
	Unknown	44	− 3.37 (− 26.57, 19.84)	0.776		− 3.78 (− 17.98, 10.42)	0.602	
Prior antihypertensive drug treatment	No[a]	458			0.002			0.002
	Yes	1008	2.38 (0.91, 3.86)	0.002		1.40 (0.49, 2.30)	0.002	
PAC (pg/mL)	< 120[a]	929			0.016			0.005
	≥ 120	523	1.66 (0.31, 3.01)	0.016		1.17 (0.35, 1.99)	0.005	
	Unknown	14	1.37 (− 5.06, 7.80)	0.676		0.87 (− 3.06, 4.79)	0.664	
PRA (ng/mL/h)	< 1.0[a]	877			0.066			0.204
	≥ 1.0	575	1.26 (− 0.08, 2.61)	0.066		0.53 (− 0.29, 1.35)	0.204	
	Unknown	14	-	–		–	–	
Serum potassium (mEq/L)	< 4.5[a]	1133			0.272			0.571
	≥ 4.5	333	0.83 (− 0.65, 2.30)	0.272		0.26 (− 0.64, 1.16)	0.571	
eGFRcreat (mL/min/1.73 m^2)	30–59[a]	176			0.770			0.325
	60–89	1071	− 0.97 (− 3.61, 1.67)	0.471		− 1.17 (− 2.78, 0.44)	0.155	
	≥ 90	219	− 0.89 (− 3.90, 2.13)	0.565		− 1.35 (− 3.19, 0.49)	0.150	

Table 3 continued

Variables	Class	N	SBP			DBP		
			Estimate of the change in BP, mmHg (95% CI)	p value[b]	Overall p value[c]	Estimate of the change in BP, mmHg (95% CI)	p value[b]	Overall p value[c]
HbA1c (%)	< 6.9[a]	1202			0.867			0.664
	6.9–7.3	143	0.68 (− 1.82, 3.18)	0.593		0.51 (− 1.02, 2.03)	0.515	
	≥ 7.4	121	0.30 (− 2.40, 3.01)	0.827		− 0.26 (− 1.91, 1.39)	0.758	
Fasting blood glucose (mg/dL)	< 100[a]	530			0.086			0.596
	100–125	578	− 0.54 (− 2.00, 0.90)	0.460		− 0.16 (− 1.04, 0.73)	0.731	
	≥ 126	358	− 2.73 (− 5.19, − 0.29)	0.029		− 0.77 (− 2.27, 0.73)	0.316	
UACR (mg/gCr)	< 30[a]	1079			0.003			0.010
	30–299	273	5.17 (0.81, 9.53)	0.020		4.15 (1.50, 6.80)	0.002	
	≥ 300	69	8.94 (4.16, 13.72)	< 0.001		4.85 (1.94, 7.76)	0.001	
	Unknown	45	3.61 (− 19.30, 26.53)	0.757		3.46 (− 10.57, 17.50)	0.628	
LDL cholesterol (mg/dL)	< 140[a]	1068			0.530			0.452
	140–179	342	0.57 (− 0.89, 2.03)	0.447		0.01 (− 0.88, 0.90)	0.980	
	≥ 180	56	1.57 (− 1.67, 4.80)	0.343		1.26 (− 0.72, 3.23)	0.213	
Triglyceride (mg/dL)	< 150[a]	1062			0.423			0.365
	≥ 150	404	0.58 (− 0.83, 1.98)	0.423		0.40 (− 0.46, 1.26)	0.365	
Complications	No[a]	187			0.289			0.427
	Yes	1279	− 1.07 (− 3.04, 0.91)	0.289		− 0.49 (− 1.69, 0.72)	0.427	
Diabetes mellitus	No[a]	957			0.295			0.493
	Yes	509	1.26 (− 1.09, 3.60)	0.295		− 0.50 (− 1.93, 0.93)	0.493	
Dyslipidemia	No[a]	669			0.346			0.055
	Yes	753	− 0.68 (− 2.09, 0.73)	0.346		− 0.85 (− 1.71, 0.02)	0.055	
	Unknown	44	—	—		—	—	

Table 3 continued

Variables	Class	N	SBP Estimate of the change in BP, mmHg (95% CI)	SBP p value[b]	SBP Overall p value[c]	DBP Estimate of the change in BP, mmHg (95% CI)	DBP p value[b]	DBP Overall p value[c]
Hyperuricemia	No[a]	1048			0.869			0.617
	Yes	374	0.13 (− 1.37, 1.62)	0.869		0.23 (− 0.68, 1.14)	0.617	
	Unknown	44	–	–		–	–	
Smoking status	Never[a]	578			0.008			0.032
	In the past	576	1.25 (− 0.16, 2.65)	0.082		0.85 (− 0.01, 1.71)	0.052	
	Current	312	2.62 (0.96, 4.27)	0.002		1.27 (0.26, 2.28)	0.014	
Alcohol consumption	Never[a]	335			0.812			0.709
	In the past	154	− 0.65 (− 2.90, 1.61)	0.573		0.12 (− 1.25, 1.50)	0.859	
	Current	977	− 0.42 (− 1.94, 1.10)	0.588		0.38 (− 0.55, 1.30)	0.424	

BMI body mass index, *BP* blood pressure, *bpm* beats per minute, *CI* confidence interval, *Cr* creatinine, *DBP* diastolic blood pressure, *eGFRcreat* estimated glomerular filtration rate based on serum creatinine, *HbA1c* hemoglobin A1c, *LDL* low-density lipoprotein, *PAC* plasma aldosterone concentration, *PRA* plasma renin activity, *SBP* systolic blood pressure, *UACR* urinary albumin-to-creatinine ratio

[a]The reference factor for the investigated variable

[b]Relative to the reference measurement

[c]The *p* value indicating statistically significant differences between all classes within the investigated variable

office SBP and a stronger BP-lowering effect of esaxerenone relative to the reference (estimate − 2.73 mmHg; $p = 0.029$).

Similar factors were associated with a change in office DBP, except for age and fasting blood glucose (Table 3). Age ranges of 65–74 years (estimate − 2.12 mmHg; $p < 0.001$) and ≥ 75 years (estimate − 3.06 mmHg; $p = 0.001$) were associated with a negative estimated change in office DBP, indicating a stronger BP-lowering effect of esaxerenone relative to the reference. A fasting blood glucose level of ≥ 126 mg/dL was not associated with changes in office DBP. Additionally, office SBP ≥ 160 mmHg was associated with a positive estimated change in office DBP (estimate 1.61 mmHg; $p = 0.009$), while office DBP ≥ 100 mmHg was not associated with changes in office SBP.

Subgroup Analysis

The results of the subgroup analysis of patients with office SBP ≥ 140 and DBP ≥ 90 mmHg ($n = 1192$) are shown in Table 4 and Table S2 in the supplementary material. Overall, the factors associated with significant differences observed in office SBP in the subgroup were similar to those seen in the overall population, with the exception of patient age, plasma renin activity (PRA), fasting blood glucose, and UACR: an age of 65–74 years was associated with a negative estimated change in office SBP and indicated a stronger BP-lowering effect of esaxerenone (estimate − 2.21 mmHg; $p = 0.022$); and PRA ≥ 1.0 ng/mL/h was associated with a positive estimated change in office SBP and indicated a weaker BP-lowering effect (estimate 2.40 mmHg; $p = 0.001$) in the subgroup analysis. Additionally, higher UACR has a non-significant ($p = 0.074$) but associates with a positive change in office SBP (i.e., a weaker BP-lowering effect of esaxerenone) and fasting blood glucose ≥ 126 mg/dL has a non-significant ($p = 0.073$) but negative estimated change in the subgroup analysis; these factors were significantly associated with changes in office SBP in the overall population.

The following factors were associated with a negative estimated change in office DBP (indicatiing a stronger BP-lowering effect) in the subgroup but not in the overall group: the presence of grade II hypertension compared with grade I hypertension (estimate − 1.95 mmHg; $p = 0.008$), and eGFR of 60–89 and ≥ 90 mL/min/1.73 m^2 compared with 30–59 mL/min/1.73 m^2 (estimate − 3.86 mmHg, $p = 0.013$; and estimate − 3.87 mmHg, $p = 0.018$, respectively). Additionally, as well as in SBP, PRA was identified as a factor associated with a weaker reduction in office DBP for the subgroup, but not in the overall population.

Safety Endpoint

The number of patients in the overall population who experienced serum potassium levels ≥ 5.5 mEq/L during the treatment was 116 out of 1472 patients (7.9%). The incidence of serum potassium levels ≥ 5.5 mEq/L for each study are shown in Table 1, and the factors associated with incidence of serum potassium ≥ 5.5 mEq/L are shown in Table 5 and Table S3 in the supplementary material. For each factor, an odds ratio (OR) greater than 1 (95% CI) indicates higher risk factors and an OR below 1 indicates lower risk factors. The factors associated with an incidence of serum potassium ≥ 5.5 mEq/L were higher baseline serum potassium; lower eGFR; and higher UACR; higher DBP; type of hypertension (grade I vs normotensive) based on the multivariate analysis. Higher baseline serum potassium (≥ 4.5 vs < 4.5 mEq/L, OR 6.702, $p < 0.001$), higher UACR (30–299 vs < 30 mg/gCr, OR 7.317, $p = 0.007$; ≥ 300 vs < 30 mg/gCr, OR 4.360, $p = 0.067$), and higher DBP (≥ 100 vs < 100 mmHg, OR 3.248, $p = 0.020$) were observed to be associated with high-risk for the incidence of serum potassium ≥ 5.5 mEq/L. Additionally, eGFR of 30–59 mL/min/1.73 m^2 was also observed to be associated with high-risk for incidence of serum potassium ≥ 5.5 mEq/L (≥ 90 vs 30–59 mL/min/1.73 m^2, OR 0.148, $p = 0.001$; 60–89 vs 30–59 mL/min/1.73 m^2, OR 0.331, $p = 0.002$).

Table 4 Multivariate analysis for factors associated with a change from baseline in office sitting systolic and diastolic blood pressure at 12 weeks in patients with systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg in the full analysis set

Variables	Class	N	SBP			DBP		
			Estimate of the change in BP, mmHg (95% CI)	p value[b]	Overall p value[c]	Estimate of the change in BP, mmHg (95% CI)	p value[b]	Overall p value[c]
Sex	Female[a]	306			< 0.001			< 0.001
	Male	886	4.08 (2.12, 6.03)	< 0.001		2.13 (0.90, 3.36)	< 0.001	
Age (years)	< 65[a]	939			0.045			< 0.001
	65–74	218	− 2.21 (− 4.10, − 0.32)	0.022		− 2.16 (− 3.35, − 0.97)	< 0.001	
	≥ 75	35	1.00 (− 3.17, 5.17)	0.638		− 2.75 (− 5.37, − 0.13)	0.039	
Weight (kg)	Quartile 1 (< 61.5)[a]	286			0.003			0.015
	Quartile 2 (61.5–69.4)	291	1.48 (− 0.64, 3.59)	0.171		0.78 (− 0.54, 2.11)	0.246	
	Quartile 3 (69.4–78.4)	304	3.38 (0.86, 5.89)	0.009		2.00 (0.42, 3.58)	0.013	
	Quartile 4 (≥ 78.4)	311	5.71 (2.60, 8.83)	< 0.001		3.04 (1.10, 4.99)	0.002	
BMI (kg/m²)	< 18.5[a]	9			0.088			0.161
	18.5–24	551	− 1.08 (− 8.62, 6.47)	0.779		− 0.94 (− 5.67, 3.79)	0.697	
	25–29	469	− 3.25 (− 10.99, 4.50)	0.411		− 2.05 (− 6.91, 2.81)	0.408	
	≥ 30	163	− 1.77 (− 9.84, 6.31)	0.668		− 1.07 (− 6.13, 4.00)	0.679	
Office SBP (mmHg)	< 160[a]	822			—			< 0.001
	≥ 160	370	—	—		2.22 (0.96, 3.47)	< 0.001	
Office DBP (mmHg)	< 100[a]	773			0.379			—
	≥ 100	419	− 1.01 (− 3.25, 1.24)	0.379		—	—	

Table 4 continued

Variables	Class	N	SBP			DBP		
			Estimate of the change in BP, mmHg (95% CI)	p value[b]	Overall p value[c]	Estimate of the change in BP, mmHg (95% CI)	p value[b]	Overall p value[c]
Pulse (bpm)	< 60[a]	104	—		0.875	—		0.630
	60–99	1073	− 0.54 (− 2.89, 1.81)	0.653		− 0.55 (− 2.02, 0.92)	0.464	
	≥ 100	15	0.24 (− 6.04, 6.52)	0.940		− 1.70 (− 5.65, 2.25)	0.399	
Type of hypertension	Normotensive[a]	0			0.508			0.008
	Grade I	590	—	—		—	—	
	Grade II	602	0.84 (− 1.65, 3.34)	0.508		− 1.95 (− 3.38, − 0.52)	0.008	
Duration of hypertension (years)	< 5[a]	511			0.023			0.004
	5–9	277	1.54 (− 0.16, 3.24)	0.076		1.27 (0.20, 2.33)	0.020	
	≥ 10	360	2.22 (0.58, 3.86)	0.008		1.63 (0.60, 2.66)	0.002	
	Unknown	44	− 1.97 (− 25.24, 21.30)	0.868		− 3.36 (− 17.96, 11.25)	0.652	
Prior antihypertensive drug treatment	No[a]	456			< 0.001			0.002
	Yes	736	2.51 (1.04, 3.99)	< 0.001		1.44 (0.51, 2.37)	0.002	
PAC (pg/mL)	< 120[a]	702			0.007			0.016
	≥ 120	487	1.93 (0.53, 3.33)	0.007		1.08 (0.20, 1.96)	0.016	
	Unknown	3	− 5.06 (− 18.59, 8.46)	0.463		− 3.40 (− 11.86, 5.07)	0.431	
PRA (ng/mL/h)	< 1.0[a]	797			0.001			0.011
	≥ 1.0	392	2.40 (0.94, 3.87)	0.001		1.19 (0.27, 2.10)	0.011	
	Unknown	3	—	—		—	—	
Serum potassium (mEq/L)	< 4.5[a]	961			0.764			0.948
	≥ 4.5	231	0.26 (− 1.43, 1.95)	0.764		0.04 (− 1.03, 1.10)	0.948	

Table 4 continued

Variables	Class	N	SBP			DBP		
			Estimate of the change in BP, mmHg (95% CI)	p value[b]	Overall p value[c]	Estimate of the change in BP, mmHg (95% CI)	p value[b]	Overall p value[c]
eGFRcreat (mL/min/1.73 m²)	30–59[a]	63			0.195			0.046
	60–89	935	− 4.49 (− 9.35, 0.38)	0.071		− 3.86 (− 6.91, − 0.81)	0.013	
	≥ 90	194	− 4.44 (− 9.54, 0.65)	0.087		− 3.87 (− 7.07, − 0.68)	0.018	
HbA1c (%)	< 6.9[a]	1083			0.951			0.790
	6.9–7.3	63	0.57 (− 3.02, 4.16)	0.755		0.44 (− 1.81, 2.69)	0.703	
	≥ 7.4	46	0.16 (− 3.94, 4.25)	0.941		− 0.51 (− 3.09, 2.06)	0.695	
Fasting blood glucose (mg/dL)	< 100[a]	508			0.181			0.678
	100–125	512	− 0.23 (− 1.70, 1.25)	0.763		− 0.14 (− 1.06, 0.79)	0.774	
	≥ 126	172	− 2.91 (− 6.10, 0.27)	0.073		− 0.89 (− 2.89, 1.10)	0.380	
UACR (mg/gCr)	< 30[a]	1059			0.358			0.039
	30–299	66	4.12 (− 2.07, 10.31)	0.192		4.96 (1.07, 8.84)	0.012	
	≥ 300	22	6.42 (− 0.63, 13.46)	0.074		6.19 (1.77, 10.62)	0.006	
	Unknown	45	2.39 (− 20.59, 25.38)	0.838		3.00 (− 11.43, 17.43)	0.683	
LDL cholesterol (mg/dL)	< 140[a]	838			0.646			0.470
	140–179	298	0.49 (− 1.08, 2.06)	0.539		0.20 (− 0.78, 1.18)	0.691	
	≥ 180	56	1.33 (− 1.89, 4.55)	0.417		1.26 (− 0.77, 3.28)	0.223	
Triglyceride (mg/dL)	< 150[a]	862			0.169			0.167
	≥ 150	330	1.09 (− 0.46, 2.64)	0.169		0.69 (− 0.29, 1.66)	0.167	
Complications	No[a]	178			0.151			0.345
	Yes	1014	− 1.49 (− 3.53, 0.54)	0.151		− 0.62 (− 1.89, 0.66)	0.345	
Diabetes mellitus	No[a]	942			0.344			0.706
	Yes	250	1.27 (− 1.36, 3.91)	0.344		− 0.32 (− 1.97, 1.33)	0.706	

Table 4 continued

Variables	Class	N	SBP Estimate of the change in BP, mmHg (95% CI)	p value[b]	Overall p value[c]	DBP Estimate of the change in BP, mmHg (95% CI)	p value[b]	Overall p value[c]
Dyslipidemia	No[a]	602			0.632			0.088
	Yes	546	− 0.38 (− 1.93, 1.17)	0.632		− 0.84 (− 1.81, 0.13)	0.088	
	Unknown	44	–	–		–	–	
Hyperuricemia	No[a]	865			0.946			0.866
	Yes	283	− 0.06 (− 1.73, 1.62)	0.946		0.09 (− 0.96, 1.14)	0.866	
	Unknown	44	–	–		–	–	
Smoking status	Never[a]	481			0.017			0.021
	In the past	461	1.63 (0.12, 3.15)	0.035		1.08 (0.13, 2.03)	0.026	
	Current	250	2.44 (0.64, 4.24)	0.008		1.43 (0.30, 2.55)	0.013	
Alcohol consumption	Never[a]	251			0.792			0.643
	In the past	102	0.40 (− 2.28, 3.08)	0.771		0.31 (− 1.37, 1.99)	0.720	
	Current	839	0.59 (− 1.10, 2.28)	0.495		0.51 (− 0.55, 1.57)	0.349	

BMI body mass index, *BP* blood pressure, *bpm* beats per minute, *CI* confidence interval, *Cr* creatinine, *DBP* diastolic blood pressure, *eGFRcreat* estimated glomerular filtration rate based on serum creatinine, *HbA1c* hemoglobin A1c, *LDL* low-density lipoprotein, *PAC* plasma aldosterone concentration, *PRA* plasma renin activity, *SBP* systolic blood pressure, *UACR* urinary albumin-to-creatinine ratio

[a]The reference factor for the investigated variable

[b]Relative to the reference measurement

[c]The p value indicating statistically significant differences between all classes within the investigated variable

Table 5 Multivariate analysis for factors associated with serum potassium levels ≥ 5.5 mEq/L in the safety analysis set

Variables	Class	N	n (%)	OR (95% CI)[b]	p value[c]	Overall p value[d]
Sex	Female[a]	384	23 (6.0)			0.703
	Male	1088	93 (8.5)	0.873 (0.433, 1.758)	0.703	
Age (years)	< 65[a]	1033	54 (5.2)			0.152
	65–74	351	47 (13.4)	1.671 (0.947, 2.947)	0.076	
	≥ 75	88	15 (17.0)	1.938 (0.813, 4.619)	0.136	
Weight (kg)	Quartile 1 (< 61.5)[a]	368	33 (9.0)			0.353
	Quartile 2 (61.5–69.4)	365	30 (8.2)	0.871 (0.448, 1.694)	0.684	
	Quartile 3 (69.4–78.4)	370	38 (10.3)	1.522 (0.694, 3.338)	0.295	
	Quartile 4 (≥ 78.4)	369	15 (4.1)	1.066 (0.354, 3.214)	0.910	
BMI (kg/m^2)	< 18.5[a]	12	1 (8.3)			0.363
	18.5–24	663	63 (9.5)	0.540 (0.054, 5.445)	0.601	
	25–29	597	45 (7.5)	0.399 (0.038, 4.236)	0.446	
	≥ 30	200	7 (3.5)	0.194 (0.015, 2.498)	0.209	
Office SBP (mmHg)	< 160[a]	1076	93 (8.6)			0.136
	≥ 160	396	23 (5.8)	2.063 (0.797, 5.341)	0.136	
Office DBP (mmHg)	< 100[a]	1051	94 (8.9)			0.020
	≥ 100	421	22 (5.2)	3.248 (1.200, 8.786)	0.020	
Pulse (bpm)	< 60[a]	134	9 (6.7)			0.491
	60–99	1321	106 (8.0)	1.648 (0.725, 3.745)	0.233	
	≥ 100	17	1 (5.9)	1.598 (0.162, 15.762)	0.688	
Type of hypertension	Normotensive[a]	105	14 (13.3)			0.016
	Grade I	739	71 (9.6)	2.168 (1.015, 4.631)	0.046	
	Grade II	628	31 (4.9)	0.542 (0.127, 2.316)	0.409	
Duration of hypertension (years)	< 5[a]	580	36 (6.2)			0.712
	5–9	350	32 (9.1)	1.294 (0.720, 2.325)	0.388	
	≥ 10	498	47 (9.4)	0.933 (0.535, 1.629)	0.808	
	Unknown	44	1 (2.3)	0.000 (0.000, Inf)	0.989	
Prior antihypertensive drug treatment	No[a]	459	17 (3.7)			0.852
	Yes	1013	99 (9.8)	1.065 (0.548, 2.072)	0.852	

Table 5 continued

Variables	Class	N	n (%)	OR (95% CI)[b]	p value[c]	Overall p value[d]
PAC (pg/mL)	< 120[a]	933	86 (9.2)			0.543
	≥ 120	525	29 (5.5)	1.353 (0.790, 2.316)	0.271	
	Unknown	14	1 (7.1)	0.914 (0.094, 8.891)	0.939	
PRA (ng/mL/h)	< 1.0[a]	880	49 (5.6)			0.776
	≥ 1.0	578	66 (11.4)	0.928 (0.557, 1.548)	0.776	
	Unknown	14	1 (7.1)	0.928 (0.557, 1.548)	–	
Serum potassium (mEq/L)	< 4.5[a]	1138	41 (3.6)			< 0.001
	≥ 4.5	334	75 (22.5)	6.702 (4.209, 10.671)	< 0.001	
eGFRcreat (mL/min/1.73 m^2)	30–59[a]	178	41 (23.0)			0.001
	60–89	1075	70 (6.5)	0.331 (0.166, 0.659)	0.002	
	≥ 90	219	5 (2.3)	0.148 (0.047, 0.461)	0.001	
HbA1c (%)	< 6.9[a]	1207	74 (6.1)			0.711
	6.9–7.3	144	24 (16.7)	1.355 (0.650, 2.824)	0.417	
	≥ 7.4	121	18 (14.9)	1.223 (0.547, 2.733)	0.624	
Fasting blood glucose (mg/dL)	< 100[a]	532	28 (5.3)			0.884
	100–125	580	36 (6.2)	0.870 (0.469, 1.616)	0.660	
	≥ 126	360	52 (14.4)	0.959 (0.409, 2.247)	0.923	
UACR (mg/gCr)	< 30[a]	1081	48 (4.4)			0.048
	30–299	277	55 (19.9)	7.317 (1.708, 31.342)	0.007	
	≥ 300	69	11 (15.9)	4.360 (0.902, 21.074)	0.067	
	Unknown	45	2 (4.4)	5,874,588 (0.000, Inf)	0.990	
LDL cholesterol (mg/dL)	< 140[a]	1073	85 (7.9)			0.210
	140–179	343	27 (7.9)	1.577 (0.919, 2.706)	0.098	
	≥ 180	56	4 (7.1)	1.787 (0.522, 6.115)	0.355	
Triglyceride (mg/dL)	< 150[a]	1067	86 (8.1)			0.639
	≥ 150	405	30 (7.4)	0.882 (0.523, 1.489)	0.639	
Complications	No[a]	188	11 (5.9)			0.925
	Yes	1284	105 (8.2)	1.039 (0.467, 2.312)	0.925	
Diabetes mellitus	No[a]	959	46 (4.8)			0.768
	Yes	513	70 (13.6)	0.870 (0.346, 2.186)	0.768	

Table 5 continued

Variables	Class	N	n (%)	OR (95% CI)[b]	p value[c]	Overall p value[d]
Dyslipidemia	No[a]	671	46 (6.9)			0.809
	Yes	757	69 (9.1)	0.938 (0.560, 1.572)	0.809	
	Unknown	44	1 (2.3)	0.938 (0.560, 1.572)	—	
Hyperuricemia	No[a]	1053	76 (7.2)			0.802
	Yes	375	39 (10.4)	0.936 (0.555, 1.576)	0.802	
	Unknown	44	1 (2.3)	0.936 (0.555, 1.576)	—	
Smoking status	Never[a]	582	34 (5.8)			0.284
	In the past	578	49 (8.5)	0.972 (0.561, 1.684)	0.919	
	Current	312	33 (10.6)	1.488 (0.813, 2.723)	0.198	
Alcohol consumption	Never[a]	340	21 (6.2)			0.130
	In the past	154	13 (8.4)	1.013 (0.421, 2.433)	0.978	
	Current	978	82 (8.4)	1.707 (0.924, 3.153)	0.088	

BMI body mass index, *bpm* beats per minute, *CI* confidence interval, *Cr* creatinine, *DBP* diastolic blood pressure, *eGFRcreat* estimated glomerular filtration rate based on serum creatinine, *HbA1c* hemoglobin A1c, *Inf* infinity, *LDL* low-density lipoprotein, *OR* odds ratio, *PAC* plasma aldosterone concentration, *PRA* plasma renin activity, *SBP* systolic blood pressure, *UACR* urinary albumin-to-creatinine ratio

[a]The reference factor for the investigated variable

[b]An estimate of the change in serum potassium levels

[c]Relative to the reference measurement

[d]The *p* value indicating statistically significant differences between all classes within the investigated variable

DISCUSSION

This study aimed to identify the factors associated with a weaker or stronger reduction in BP in patients receiving esaxerenone treatment, as well as the factors associated with the high incidence of serum potassium ≥ 5.5 mEq/L, using data derived from seven phase III clinical trials [10–16]. We identified the following factors that may be associated with a stronger antihypertensive effect of esaxerenone both in the overall population and subgroup with SBP/DBP ≥ 140/90 mmHg: female sex, lower weight, shorter duration of hypertension, treatment-naïve patients on antihypertensives, lower PAC, and non-smokers. Moreover, lower UACR may also be associated with a stronger BP-lowering effect

of esaxerenone in the overall population. Patients who are older may also experience a stronger antihypertensive effect of esaxerenone, as evidenced by a greater reduction in DBP. Furthermore, higher eGFR and lower PRA may be associated with a stronger antihypertensive effect of esaxerenone, particularly in the subgroup of patients with high baseline SBP and DBP.

In the 2019 Japanese Society of Hypertension (JSH) guideline, MRB is positioned as the fourth-line antihypertensive drug and currently recommended for treatment-resistant hypertension [23]; however, our findings suggest that treatment-naïve patients who receive esaxerenone as first-line therapy may achieve better antihypertensive efficacy. To date, esaxerenone monotherapy has been shown to have a

comparable antihypertensive effect in combination with a RAS inhibitor and CCB [11]. Future studies are needed to investigate the antihypertensive effect of esaxerenone through comparative studies in the monotherapy, RAS combination, and CCB combination groups.

The finding that the stronger BP reduction in patients with lower PRA levels compared to those with higher levels provides insight into the patients who are best suited to receive esaxerenone treatment. Hypertensive patients who are elderly or have excessive salt intake have lower PRA levels [24, 25]. The present study suggests that a stronger antihypertensive effect is expected in patients aged over 65 years compared with those under 65 years, suggesting that patients with PRA < 1 ng/mL/h may be an optimal patient population for esaxerenone administration.

In the current analysis, the estimated effect on BP was calculated as absolute values to show the change in specific BP values. We believe that presenting the data in this way will be easier for clinicians to understand the clinical effect of each factor on BP, compared to relative measures such as odds ratio. Furthermore, we considered changes in SBP and DBP of 5 mmHg or more to be clinically significant. While not reaching statistical significance in all analyses, patients with UACR < 30 mg/gCr tended to experience a stronger antihypertensive effect that reached our definition of clinical significance, compared with patients with higher UACR. Esaxerenone has previously been reported to improve UACR [12, 13, 15, 16, 26]; this may indicate that the use of esaxerenone during the early stages of diabetes (i.e., in the absence of albuminuria) can provide a stronger antihypertensive effect while simultaneously delaying the transition to microalbuminuria [27]. In addition, this study revealed that the antihypertensive effect of esaxerenone was constant irrespective of the presence or absence of diabetes or the hemoglobin A1c levels, and was partially enhanced at higher fasting glucose levels in office SBP in the overall population. In conjunction with the JSH guidelines recommending RAS inhibitors as treatment for hypertensive patients with diabetes [23], esaxerenone may have a stronger antihypertensive

effect in hypertensive patients with diabetes who have an inadequate response to RAS inhibitors.

Previous analyses of the phase III esaxerenone studies have shown that the presence of diabetes mellitus with albuminuria or proteinuria, moderate renal dysfunction (eGFR $\geq$ 30 to < 60 mL/min/1.73 m^2), elderly patients, patients with higher baseline serum potassium levels, and patients treated with RAS inhibitors were at risk of serum potassium elevation during esaxerenone treatment, resulting in these factors being listed as potential risks on the package insert [17, 20]. These risk factors are generally consistent with those reported in previous studies of other MRBs, such as eplerenone [28, 29], finerenone [30], and spironolactone [29, 31]. In the present analysis, some of these known risk factors for esaxerenone and other MRBs, such as elderly patients and diabetes, were not associated with serum potassium elevation. However, patients with higher baseline serum potassium ($\geq$ 4.5 mEq/L), lower eGFR (30–59 mL/min/1.73 m^2), as well as UACR (30–299 mg/gCr) had significantly higher ORs, and patients with higher UACR ($\geq$ 300 mg/gCr) also had higher OR, although not reaching statistical significance (OR 4.360, p = 0.067). Thus, many of the known risk factors listed on the package insert of esaxerenone were also detected in the present analysis. Patients with lower eGFR and higher UACR have impaired renal function [32, 33], suggesting that these patients may still require careful monitoring and management while receiving esaxerenone treatment.

We acknowledge the limitations of this study. We conducted this study using the data from seven phase III studies with different study designs (e.g., inclusion/exclusion criteria, concomitant medication use, etc.) to include a broad patient population and to retain a larger sample size, although an integrated analysis using only studies with similar designs might more precisely estimate the effect of each factor. Therefore, there are not only differences in patient backgrounds between studies but also potential differences that are not necessarily fully accounted for, which may bias the estimated the effect of the background

factors considered in this study. For example, the phase III protocol for esaxerenone specifies that hypertensive patients with diabetes mellitus should be treated with a RAS inhibitor and that those with essential hypertension should be treated with CCB. Thus, patients categorized with the background factor of "prior antihypertensive drug treatment" would include their unknown medical history as a potential hidden factor. Similarly, the background factor of "diabetes mellitus" may hide the influence of concomitant antihypertensive medications. Conversely, combining studies can increase the statistical power to detect the smaller effect because of the larger data set, even if there are differences in study designs. Regarding the safety endpoint, the total number of incidences of serum potassium levels ≥ 5.5 mEq/L was 116 (7.9%), which might be a somewhat small number of occurrences to detect risk factors. Integration of a larger data set would provide further information and greater precision regarding risk factors associated with serum potassium elevation following esaxerenone treatment.

CONCLUSIONS

This post hoc analysis from seven previously published Japanese phase III studies of esaxerenone investigated the factors that may be associated with the antihypertensive effect of esaxerenone and incidence of serum potassium elevation following esaxerenone treatment. Esaxerenone treatment results in a robust antihypertensive effect in patients with a broad range of backgrounds; however, we found a stronger BP reduction in female patients, patients with lower body weights, with PAC < 120 pg/mL, with a shorter duration of hypertension, who had not received hypertensive treatment before, and with UACR < 30 mg/gCr. Additionally, in the subgroup analysis of patients with baseline SBP/DBP > 140/90 mmHg, patients with PRA < 1 experienced a stronger BP reduction under the esaxerenone treatment. Patients with baseline serum potassium ≥ 4.5 mEq/L, eGFR levels 30–59 mL/min/1.73 m^2, or UACR of 30–299 mg/gCr may be at

higher risk for the incidence of serum potassium elevation via reduced renal function. Careful therapeutic management of patients with reduced renal function is recommended when administering esaxerenone.

ACKNOWLEDGEMENTS

registered with the University hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000047026).

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