Antihypertensive effect of long-term monotherapy with esaxerenone in patients with essential hypertension: relationship between baseline urinary sodium excretion and its antihypertensive effect

Shuichi Ichikawa[a], Junko Tsutsumi[b], Kotaro Sugimoto[b], Satoru Yamakawa[b]

[a]Cardiovascular Hospital of Central Japan, Gunma, Japan; [b]Daiichi Sankyo Co., Ltd., Tokyo, Japan

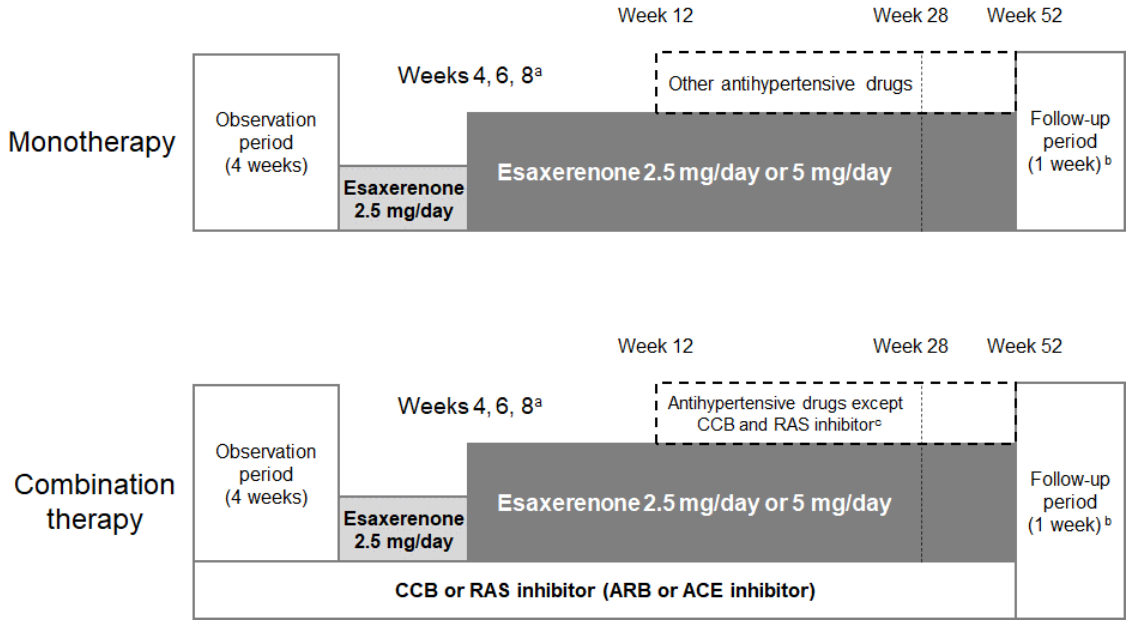
Corresponding author:

Shuichi Ichikawa

Email: ichikawa@ccj.or.jp

Supplementary Material

Fig. S1 Main study design



ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *CCB* calcium channel blocker, *RAS* renin–angiotensin system

[a]The esaxerenone dosage was titrated at weeks 4, 6, and 8 according to the dose escalation criteria.

[b]Follow-up for 1 week after week 28 or 52 with appropriate antihypertensive treatment.

[c]Dose escalation of the baseline CCB or RAS inhibitor, or additional use of only one additional concomitant antihypertensive drug (CCB, thiazide diuretic, or RAS inhibitor) other than a basic antihypertensive drug was permitted at week 12.

15. Rakugi H, Ito S, Itoh H, Okuda Y, Yamakawa S. Long-term phase 3 study of esaxerenone as mono or combination therapy with other antihypertensive drugs in patients with essential hypertension. Hypertens Res. 2019;42:1932–41. https://doi.org/10.1038/s41440-019-0314-7.

Table S1 List of the institutional review boards that approved the research protocols.

Research institute	**Institutional review board**
Matsuda Cardiovascular Clinic	Irahara Clinic
Ono Clinic	Goshozuka Clinic
Shoji Clinic	Irahara Clinic
Hiro Clinic	Goshozuka Clinic
Cardiovascular Hospital of Central Japan (Kitakanto Cardiovascular Hospital)[a]	Cardiovascular Hospital of Central Japan (Kitakanto Cardiovascular Hospital)[a]
Suzuki Clinic	Goshozuka Clinic
Gyoutoku Flower Street Clinic	Goshozuka Clinic
Ebisu Clinic	Yaesu Sakuradori Clinic
Tomo Clinic	Irahara Clinic
Sone Clinic	Goshozuka Clinic
Niwa Family Clinic	Irahara Clinic
Yotsuya Clinic	Goshozuka Clinic
P-One Clinic	P-One Clinic
Yaesu Sakuradori Clinic	Yaesu Sakuradori Clinic
ToCROM Clinic[a]	Osaka Pharmacology Clinical Research Hospital[a]
Kitada Clinic	Yaesu Sakuradori Clinic
Bandou Clinic	Goshozuka Clinic
OCROM Clinic[a]	Osaka Pharmacology Clinical Research Hospital[a]
Oak Clinic, Umeda	Yaesu Sakuradori Clinic
Hiraoka Clinic	Yaesu Sakuradori Clinic

[a]Research institutes and institutional review boards specific to this substudy.

Table S2 Patient composition in this *post-hoc* substudy[a]

	Patients (*n*)
Enrolled in main study as monotherapy group	245
Population who continued to 52-week follow-up period	102
Biomarker data available (pre-specified)	57
Continued monotherapy to the end of study (week 52)	25
Adding antihypertensive drugs after week 12	32

[a]A total of 245 patients received esaxerenone monotherapy in the main study. Only patients in the pre-specified 52-week follow-up population who had biomarker data available (n = 57) and continued monotherapy to the end of study were eligible for inclusion in this *post hoc* analysis (n = 25).

Table S3 Baseline characteristics of patients receiving esaxerenone monotherapy until week 52 in total and patient subgroups based on baseline urinary sodium excretion

Characteristic	Total (*n* = 25)	Baseline urinary sodium excretion	
		Higher (*n* = 13)	Lower (*n* = 12)
Male, *n* (%)	17 (68.0)	12 (92.3)	5 (41.7)
Age, years	57.3 ± 7.5	55.5 ± 7.0	59.2 ± 7.9
Weight, kg	67.5 ± 12.5	71.5 ± 10.6	63.2 ± 13.3
SBP, mmHg	151.6 ± 5.6	153.0 ± 6.6	150.0 ± 4.1
DBP, mmHg	94.9 ± 3.8	96.1 ± 3.8	93.6 ± 3.5
PAC, pg/mL	115.4 ± 31.9	109.2 ± 27.8	122.0 ± 35.9
PRA, ng/mL/h	0.66 ± 0.46	0.69 ± 0.51	0.63 ± 0.42
Urine, mL	1970.0 ± 659.6	2165.4 ± 645.5	1758.3 ± 632.9
Urinary sodium, mEq/L	111.3 ± 40.8	135.6 ± 36.9	84.9 ± 26.1
Urinary sodium excretion, mEq/day	212.8 ± 97.4	283.0 ± 85.5	136.8 ± 24.0
Urinary potassium, mEq/L	32.9 ± 12.0	33.1 ± 11.5	32.7 ± 13.1
Urinary potassium excretion, mEq/day	61.4 ± 23.3	69.1 ± 25.8	53.1 ± 17.6
Urinary Na/K ratio, %	3.7 ± 1.6	4.5 ± 1.8	2.8 ± 1.0
eGFR, mL/min/1.73 m^2	77.8 ± 11.6	77.5 ± 11.7	78.0 ± 11.9
Serum potassium, mEq/L	4.2 ± 0.3	4.3 ± 0.3	4.2 ± 0.3

hANP, pg/mL	22.9 ± 10.1	20.5 ± 9.9	25.4 ± 10.1
NT-proBNP, pg/mL	92.3 ± 95.4	81.0 ± 115.7	104.5 ± 70.3
HbA1c (NGSP), %	5.9 ± 0.7	5.8 ± 0.7	5.9 ± 0.7
LDL cholesterol, mg/dL	137.1 ± 38.1	139.9 ± 45.6	134.0 ± 29.6
Triglycerides, mg/dL	99.7 ± 53.1	106.8 ± 58.6	92.0 ± 47.6
ALT, IU/L	18.8 ± 6.7	18.5 ± 6.7	19.1 ± 7.0

Values are mean ± standard deviation unless otherwise stated.

ALT alanine aminotransferase, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *hANP* human atrial natriuretic peptide, *HbA1c* glycosylated hemoglobin, *K* potassium, *LDL* low-density lipoprotein, *Na* sodium, *NGSP* National Glycohemoglobin Standardization Program, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *PAC* plasma aldosterone concentration, *PRA* plasma renin activity, *SBP* systolic blood pressure

Table S4 Change from baseline of measured parameters in total and patient subgroups based on baseline urinary sodium excretion

Parameters	Total (*n* = 25)			Baseline urinary sodium excretion					
				Higher (*n* = 13)			Lower (*n* = 12)		
	Week 12	Week 28	Week 52	Week 12	Week 28	Week 52	Week 12	Week 28	Week 52
SBP, mmHg	−20.8[a]	−27.6[a]	−23.5[a]	−26.6 [a]	−27.6[a]	−25.0[a]	−14.9[a]	−27.6[a]	−22.1[a]
DBP, mmHg	−10.3[a]	−15.2[a]	−13.1[a]	−13.2 [a]	−14.7[a]	−13.1[b]	−7.3[a]	−15.7[a]	−13.2[a]
PAC, pg/mL	58.2[a]	53.2[a]	70.5[a]	58.3[b]	59.5[b]	62.6[b]	58.1[b]	47.0[b]	78.3[b]
PRA, ng/mL/h	0.68[a]	0.70[b]	0.69[a]	0.75[b]	0.78	0.83[b]	0.61[b]	0.61[b]	0.55[b]
Urine, mL	−444.8[b]	−83.0	−319.0	−727.1[b]	−352.3	−670.5[b]	−162.5	186.4	67.5
Urinary sodium, mEq/L	8.9	−7.7	3.1	8.8	–10.7	4.0	9.0	–4.6	2.2
Urinary sodium excretion, mEq/day	−53.1[b]	−31.9	−44.0[b]	−95.0[b]	−73.3	−87.8[b]	−11.2	9.5	4.3
Urinary potassium, mEq/L	2.7	−0.3	4.1	7.6	6.4	6.5	−2.3	−7.0	1.4

Urinary potassium excretion, mEq/day	−12.2[b]	−4.4	−4.3	−14.2	−3.1	−12.2	−10.3[b]	−5.6	4.4
Urinary Na/K ratio, %	−0.3	−0.1	−0.5	−0.8	−1.0	−0.8	0.2	0.8	−0.2
eGFR, mL/min/1.73 m^2	−4.3[b]	−3.0	−6.3[a]	−3.6	−2.4	−5.5[b]	−5.0[b]	−3.6	−7.1[b]
Serum potassium, mEq/L	−0.04	0.04	0.11	0.01	0.02	0.12	−0.08	0.05	0.10
hANP, pg/mL	−2.1	−5.9[b]	−5.5[b]	−1.5	−5.1	−5.6[b]	−2.6	−6.7[b]	−5.5
NT-proBNP, pg/mL	−32.2	−25.1	−46.8[b]	−43.6	−41.7	−58.4	−20.8	−8.5	−36.2

Values are means.

DBP diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *hANP* human atrial natriuretic peptide, *K* potassium, *Na* sodium, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *PAC* plasma aldosterone concentration, *PRA* plasma renin activity, *SBP* systolic blood pressure.

[a]$p < 0.001$ vs baseline

[b]$p < 0.05$ vs baseline