ORIGINAL ARTICLE

Effect of the Nonsteroidal Mineralocorticoid Receptor Blocker, Esaxerenone, on Nocturnal Hypertension: A *Post Hoc* Analysis of the ESAX-HTN Study

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BACKGROUND

Nocturnal hypertension is an important phenotype of abnormal diurnal blood pressure (BP) variability and a known risk marker for target organ damage and cardiovascular events. This study aimed to assess the differential BP-lowering effects of esaxerenone vs. eplerenone on nocturnal BP in hypertensive patients with different nocturnal dipping patterns.

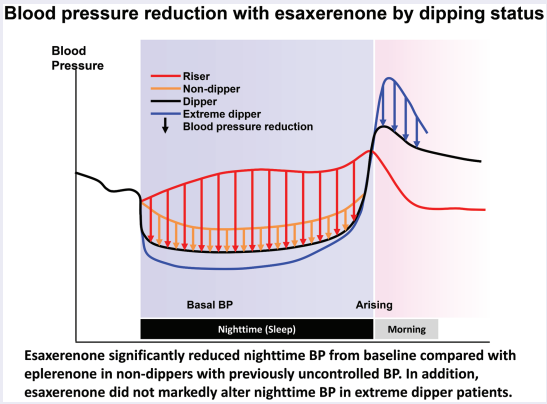
METHODS

This was a *post hoc* analysis of the "Esaxerenone (CS-3150) Compared to Eplerenone in Patients with Essential Hypertension" study (NCT02890173), which was a phase 3, multicenter, randomized, controlled, double-blind, parallel-group clinical study conducted in Japan. Ambulatory BP monitoring data were collected.

RESULTS

Patients (n = 1,001) were randomized to esaxerenone 2.5 mg/day (n = 331) or 5 mg/day (n = 338), or eplerenone 50 mg/day (n = 332). Reductions in nighttime systolic BP (95% confidence interval) were significantly greater with 2.5 and 5 mg/day esaxerenone vs. eplerenone (−2.6 [−5.0, −0.2] and −6.4 mm Hg [−8.8, −4.0], respectively). Esaxerenone significantly reduced nighttime BP from baseline compared with eplerenone in non-dippers with previously uncontrolled BP. In addition, esaxerenone did not markedly alter nighttime BP in extreme dipper patients. In the esaxerenone 5 mg/day group, esaxerenone-induced decreases in nighttime BP were greater than eplerenone-induced decreases in older patients.

GRAPHICAL ABSTRACT



CONCLUSIONS

Esaxerenone may be an effective treatment option for nocturnal hypertension, especially in older patients and those with a non-dipper pattern of nocturnal BP.

Keywords: blood pressure; esaxerenone; essential hypertension; hypertension; Japanese patients; mineralocorticoid receptor blocker; nocturnal blood pressure

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Results of the ESAX-HTN study (NCT02890173) have been published previously (Ito S, Itoh H, Rakugi H, Okuda Y, Yoshimura M, Yamakawa S. Double-blind randomized phase 3 study comparing esaxerenone (CS-3150) and eplerenone in patients with essential hypertension (ESAX-HTN Study). *Hypertension* 2020; 75:51–58).

Blood pressure (BP) shows a diurnal pattern in healthy individuals. BP variability is characterized by 10%–20% lower nighttime BP values than daytime BP values. Nocturnal hypertension (in which nighttime BP values do not decrease [non-dipper pattern], or even increase [riser pattern] vs. daytime BP values) is one important phenotype of abnormal diurnal BP variability. It is a clinical phenotype of salt sensitivity, is particularly common in Asian populations, and is frequently associated with conditions such as diabetes mellitus and chronic kidney disease.[1–6] It is also a known risk marker for target organ damage[7–9] and has been associated with increased risk of cardiovascular and cerebrovascular disease.[10–17] The Japan Morning Surge-Home Blood Pressure (J-HOP) study of 2,545 patients with hypertension, reported that a 10 mm Hg increase in nocturnal home BP was associated with a 23.6% increase in the risk of stroke.[18] Nocturnal hypertension provides a better prediction of cardiovascular risk than clinic/office or daytime BP.[13,19] Nocturnal BP target levels are included in major treatment guidelines.[20–22] Therefore, it is important to understand the effects of novel antihypertensive agents on nocturnal BP.

The novel mineralocorticoid receptor (MR) blocker esaxerenone (MINNEBRO, Daiichi Sankyo) was recently approved in Japan as an antihypertensive agent. Unlike eplerenone and spironolactone, esaxerenone has a nonsteroidal structure, and is a more potent and selective MR blocker (Supplementary Table S1 online). The phase 3, comparative, ESAX-HTN study demonstrated the noninferiority of esaxerenone vs. eplerenone on the BP-lowering effect of office and 24-hour BP evaluated by ambulatory BP monitoring (ABPM).[23] However, there are limited insights into the effects of esaxerenone on nighttime BP compared with eplerenone. This *post hoc* analysis of 24-hour ABPM data from the ESAX-HTN study investigated, for the first time, the differential BP-lowering effects of esaxerenone on nocturnal BP in hypertensive patients with different nocturnal dipping patterns.

METHODS

Study design and population

The ESAX-HTN study was a phase 3, multicenter, randomized, controlled, double-blind, parallel-group clinical trial conducted in Japan.[23] The study protocol was approved by the institutional review board at each study site; all procedures were carried out in accordance with the Declaration of Helsinki. All patients provided written informed consent.

The study was conducted over a 12-week treatment period followed by a 1-week observation period. Patients were randomly assigned in a 1:1:1 ratio using stratified block randomization with a block size of 6 to receive esaxerenone 2.5 mg/day, esaxerenone 5 mg/day, or eplerenone 50 mg/day (all orally before breakfast). Treatments were given in a double-blind, double-dummy manner using over-encapsulated eplerenone. Full details of the study design have been reported previously.[23] In brief, patients with trough systolic BP (SBP) ≥140 and <180 mm Hg, trough diastolic BP (DBP) ≥90 and <110 mm Hg, 24-hour mean BP (ABPM) ≥130/80 mm Hg, estimated glomerular filtration rate ≥60 ml/minute/1.73 m^2, and serum potassium (K^+) 3.5 to <5.1 mEq/l were eligible. To appropriately assess BP diurnal variability, overnight workers were excluded.

Determination and definition of nocturnal hypertension

ABPM was performed at 30-minute intervals over a 25-hour period during week 3 of the washout/observation period and week 12 of the treatment period, as described previously.[23] Average ambulatory BP was determined every 30 minutes. BP was defined based on diary definitions using the following time periods, as described previously[24]: morning BP as the average BP 2 hours after getting up; daytime BP as the average BP from awakening to before bedtime; and nighttime BP as the average BP from bedtime to before getting up. Summaries of ABPM readings of each BP are shown in Supplementary Table S2 online. Dipping patterns were determined for each patient based on the ABPM change in SBP from daytime to nighttime in the observation period, calculated as follows: BP decrease (%) = (1 − nighttime SBP/daytime SBP) × 100. Nighttime SBP dipping (%) was calculated as (1 − average nighttime SBP/average daytime SBP) × 100, and the following 4 nighttime BP dipping patterns were defined: extreme dipper (>20%), dipper (≤20% to >10%), non-dipper (≤10% to >0%), and riser (≤0%).[6,25]

Assessments

The primary objective of this *post hoc* analysis was to compare the change from baseline in nocturnal BP between the esaxerenone and eplerenone groups; other key parameters were also compared.

Nocturnal BP patterns after 12 weeks of treatment were compared with those during the observation period, overall, and by baseline dipping pattern as defined above. ABPM data were used to compare the antihypertensive effects of esaxerenone and eplerenone at different time periods (also as defined above). The following nocturnal BP characteristics were evaluated: maximum nighttime SBP, minimum nighttime SBP, average peak nighttime SBP, pre-awakening nighttime SBP, average nighttime BP surge, and maximum dynamic nighttime BP surge. BP variability for all measurements of 24-hour, daytime, and nighttime SBP was determined using standard deviation (SD), coefficient of variation, and average real variability.

Statistical analysis

An analysis of covariance model was used to compare the changes from baseline in BP, nighttime BP characteristics, and BP variability between esaxerenone and eplerenone treatment groups (BP change from baseline, objective variable; treatment group, explanatory variable; baseline value, covariate). The point estimate (least-squares mean value) and the corresponding 95% confidence interval (CI) were calculated. To evaluate the effects of esaxerenone and eplerenone on nighttime BP in patient subgroups based on age (<60 and ≥60 years), change in BP from baseline within each treatment group was compared between age groups using an analysis of

variance model with age category as the explanatory variable. Statistical analyses were performed using SAS System Release 9.4 (SAS Institute, Cary, NC). The 2-sided significance level was 5%; if the CI for a difference did not include 0, the difference was considered statistically significant.

RESULTS

Patients

The ESAX-HTN study included 1,001 patients randomized to esaxerenone 2.5 mg/day (n = 331), esaxerenone 5 mg/day (n = 338), or eplerenone 50 mg/day (n = 332). Of these, 998 were included in the full analysis set; three patients were excluded due to lack of efficacy data. Patients had a mean ± SD age of 55.5 ± 9.6 years, the majority were male (72.2%), and more than half (51.5%) had received previous antihypertensive therapy (Table 1). Dipper was the most common nocturnal BP pattern (40.9%; 408/998), followed by non-dipper (34.3%; 342/998), extreme dipper (17.0%; 170/998), and riser (7.8%; 78/998). Patient characteristics were similar among dipping pattern groups (Table 1) and are shown at baseline by each treatment group in Supplementary Table S3 online.

Table 1. Patient characteristics at baseline by nocturnal blood pressure pattern

	Extreme dipper (n = 170)	P value (vs. dipper)	Dipper (n = 408)	Non-dipper (n = 342)	P value (vs. dipper)	Riser (n = 78)	P value (vs. dipper)
Age, years	56.2 ± 8.9	n.s.	54.7 ± 9.6	55.5 ± 9.5	n.s.	58.0 ± 10.8	<0.01
<60 years, n (%)	107 (62.9)	n.s.	280 (68.6)	228 (66.7)	n.s.	40 (51.3)	<0.01
≥60 years, n (%)	63 (37.1)	n.s.	128 (31.4)	114 (33.3)	n.s.	38 (48.7)	<0.01
Male, n (%)	136 (80.0)	n.s.	296 (72.5)	241 (70.5)	n.s.	48 (61.5)	n.s.
Body mass index, kg/m^2	24.7 ± 3.3	<0.01	25.8 ± 4.0	26.2 ± 4.4	n.s.	25.3 ± 4.5	n.s.
Office SBP, mm Hg	155.0 ± 10.0	n.s.	154.9 ± 9.4	156.0 ± 9.9	n.s.	155.0 ± 8.2	n.s.
SBP ≥160 mm Hg, n (%)	51 (30.0)	n.s.	126 (30.9)	119 (34.8)	n.s.	26 (33.3)	n.s.
Office DBP, mm Hg	97.3 ± 5.4	<0.05	98.4 ± 5.7	98.2 ± 5.5	n.s.	97.2 ± 5.9	n.s.
DBP ≥100 mm Hg, n (%)	57 (33.5)	n.s.	170 (41.7)	135 (39.5)	n.s.	28 (35.9)	n.s.
Pulse rate, bpm	74.8 ± 10.1	<0.05	72.7 ± 9.9	72.2 ± 9.9	n.s.	72.2 ± 10.5	n.s.
24-Hour pulse rate, bpm	75.2 ± 8.0	<0.001	72.3 ± 8.8	71.4 ± 8.3	n.s.	71.3 ± 8.7	n.s.
24-Hour SBP, mm Hg	161.3 ± 14.5	n.s.	163.9 ± 15.1	167.8 ± 15.2	<0.001	165.4 ± 18.1	n.s.
24-Hour DBP, mm Hg	94.5 ± 7.0	<0.001	97.3 ± 7.8	98.9 ± 8.0	<0.01	95.9 ± 8.3	n.s.
Nighttime SBP, mm Hg	130.8 ± 14.1	n.s.	146.2 ± 14.8	159.4 ± 15.7	n.s.	167.3 ± 19.9	n.s.
Nighttime DBP, mm Hg	76.7 ± 7.5	n.s.	86.9 ± 8.3	92.9 ± 9.0	n.s.	94.7 ± 8.9	n.s.
TC, mg/dl	208.1 ± 35.9	n.s.	209.3 ± 34.0	209.5 ± 33.6	n.s.	204.1 ± 34.2	n.s.
HDL-C, mg/dl	62.2 ± 19.4	n.s.	59.9 ± 16.6	59.3 ± 16.6	n.s.	60.9 ± 15.0	n.s.
LDL-C, mg/dl	120.5 ± 32.4	n.s.	124.9 ± 30.7	127.2 ± 29.5	n.s.	118.2 ± 30.4	n.s.
Triglycerides, mg/dl	150.6 ± 142.5	n.s.	140.1 ± 115.9	130.4 ± 97.6	n.s.	133.9 ± 114.8	n.s.
Fasting glucose, mg/dl	104.7 ± 17.7	n.s.	106.9 ± 19.7	106.2 ± 20.8	n.s.	104.7 ± 16.9	n.s.
HbA1c, %	5.57 ± 0.61	n.s.	5.66 ± 0.62	5.72 ± 0.67	n.s.	5.75 ± 0.70	n.s.
Serum creatinine, mg/dl	0.77 ± 0.13	n.s.	0.76 ± 0.14	0.77 ± 0.14	n.s.	0.73 ± 0.15	n.s.
Serum K^+, mEq/l	4.23 ± 0.28	n.s.	4.20 ± 0.29	4.21 ± 0.29	n.s.	4.19 ± 0.29	n.s.
eGFR, ml/minute/1.73 m^2	79.33 ± 12.54	n.s.	79.18 ± 12.42	77.57 ± 11.63	n.s.	79.06 ± 14.20	n.s.
Hypertension grade, n (%)							
I	87 (51.2)	n.s.	177 (43.4)	154 (45.0)	n.s.	36 (46.2)	n.s.
II	83 (48.8)	n.s.	231 (56.6)	188 (55.0)	n.s.	42 (53.8)	n.s.
Prior antihypertensive treatment, n (%)	86 (50.6)	n.s.	205 (50.2)	182 (53.2)	n.s.	41 (52.6)	n.s.
Comorbid type 2 diabetes, n (%)	21 (12.4)	n.s.	64 (15.7)	56 (16.4)	n.s.	15 (19.2)	n.s.

Abbreviations: bpm, beats/min; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; K^+, potassium; LDL-C, low-density lipoprotein cholesterol; n.s., not significant; SBP, systolic blood pressure; TC, total cholesterol.

Effects of esaxerenone on 24-hour BP trend

Mean BP was reduced in all treatment groups throughout the 24-hour period (Figure 1a), and there were significant reductions from baseline in daytime, nighttime, and morning SBP and DBP in all treatment groups (Figure 1b and Table 2). Reductions in nighttime SBP and morning SBP (95% CI) were significantly greater with esaxerenone 2.5 mg/day compared with eplerenone 50 mg/day (differences of −2.6 mm Hg [−5.0, −0.2] and −3.7 mm Hg [−6.5, −0.8], respectively), and reductions in daytime,

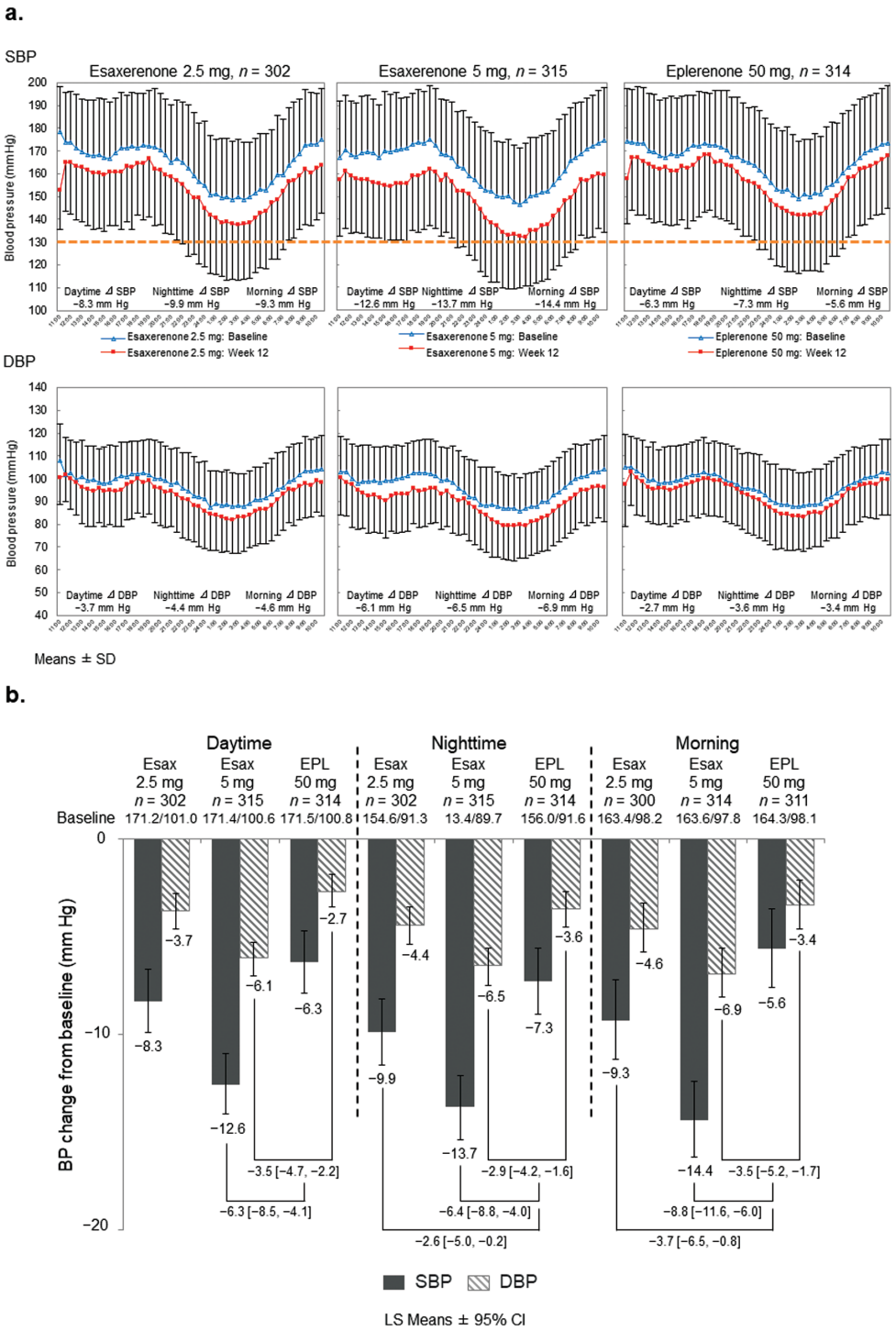

Figure 1. (**a**) Trends in 24-hour blood pressure and (**b**) change from baseline in blood pressure in each time period. Abbreviations: BP, blood pressure; CI, confidence interval; DBP, diastolic BP; EPL, eplerenone; Esax, esaxerenone; LS, least squares; SBP, systolic blood pressure.

Table 2. Change in blood pressure from baseline by dipping status

		Esaxerenone 2.5 mg/day		Esaxerenone 5 mg/day		Eplerenone 50 mg/day	
		Change from baseline (mm Hg)[a]	[95% CI]	Change from baseline (mm Hg)[a]	[95% CI]	Change from baseline (mm Hg)[a]	[95% CI]
ALL							
Daytime	DBP	−3.7	[−4.6, −2.8]	−6.1	[−7.0, −5.3]	−2.7	[−3.5, −1.8]
	SBP	−8.3	[−9.9, −6.7]	−12.6	[−14.1, −11.0]	−6.3	[−7.9, −4.7]
Nighttime	DBP	−4.4	[−5.4, −3.5]	−6.5	[−7.5, −5.6]	−3.6	[−4.5, −2.7]
	SBP	−9.9	[−11.6, −8.2]	−13.7	[−15.4, −12.1]	−7.3	[−9.0, −5.6]
Morning	DBP	−4.6	[−5.8, −3.3]	−6.9	[−8.1, −5.6]	−3.4	[−4.6, −2.1]
	SBP	−9.3	[−11.3, −7.2]	−14.4	[−16.3, −12.4]	−5.6	[−7.6, −3.6]
Extreme dipper							
Daytime	DBP	−4.3	[−6.2, −2.4]	−6.8	[−8.7, −4.9]	−4.3	[−6.2, −2.3]
	SBP	−11.3	[−14.8, −7.8]	−14.4	[−17.8, −10.9]	−8.7	[−12.3, −5.1]
Nighttime	DBP	0.8	[−1.5, 3.0]	0.6	[−1.7, 2.8]	0.8	[−1.5, 3.2]
	SBP	−1.5	[−5.5, 2.5]	0.9	[−3.0, 4.9]	1.2	[−2.9, 5.3]
Morning	DBP	−3.3	[−6.3, −0.3]	−2.9	[−6.0, 0.1]	−2.2	[−5.4, 0.9]
	SBP	−6.8	[−11.5, −2.1]	−7.0	[−11.7, −2.3]	−2.8	[−7.7, 2.1]
Dipper							
Daytime	DBP	−3.9	[−5.3, −2.5]	−7.2	[−8.5, −5.8]	−3.6	[−5.0, −2.2]
	SBP	−9.3	[−11.7, −6.8]	−13.8	[−16.1, −11.4]	−8.3	[−10.7, −5.9]
Nighttime	DBP	−4.0	[−5.4, −2.5]	−6.1	[−7.5, −4.8]	−4.0	[−5.4, −2.7]
	SBP	−8.2	[−10.8, −5.6]	−11.7	[−14.2, −9.2]	−6.5	[−9.0, −4.0]
Morning	DBP	−5.6	[−7.5, −3.6]	−8.7	[−10.6, −6.8]	−4.4	[−6.3, −2.4]
	SBP	−9.1	[−12.1, −6.1]	−16.6	[−19.4, −13.7]	−6.5	[−9.4, −3.6]
Non-dipper							
Daytime	DBP	−3.8	[−5.4, −2.2]	−5.2	[−6.8, −3.6]	−0.8	[−2.3, 0.8]
	SBP	−7.1	[−10.1, −4.1]	−11.0	[−14.0, −8.1]	−3.0	[−5.8, −0.1]
Nighttime	DBP	−7.2	[−8.8, −5.6]	−9.7	[−11.2, −8.1]	−4.2	[−5.7, −2.6]
	SBP	−14.1	[−17.2, −11.1]	−20.5	[−23.5, −17.6]	−9.7	[−12.6, −6.8]
Morning	DBP	−4.8	[−6.9, −2.6]	−6.6	[−8.7, −4.4]	−2.4	[−4.5, −0.2]
	SBP	−10.3	[−14.0, −6.6]	−14.8	[−18.4, −11.1]	−5.2	[−8.8, −1.7]
Riser							
Daytime	DBP	−1.2	[−3.9, 1.6]	−3.0	[−5.8, −0.2]	−2.4	[−5.1, 0.4]
	SBP	−2.0	[−7.5, 3.4]	−8.3	[−13.9, −2.7]	−5.0	[−10.4, 0.5]
Nighttime	DBP	−7.3	[−11.0, −3.7]	−11.0	[−14.8, −7.3]	−9.2	[−12.8, −5.5]
	SBP	−19.3	[−26.5, −12.1]	−29	[−36.4, −21.5]	−21.2	[−28.5, −14.0]
Morning	DBP	−1.5	[−6.0, 3.0]	−7.0	[−11.6, −2.3]	−5.4	[−10.0, −0.9]
	SBP	−11.1	[−19.8, −2.3]	−16.2	[−25.3, −7.1]	−8.8	[−17.7, 0.1]

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]Least-squares means of the change from baseline in blood pressure based on analysis of covariance model.

nighttime, and morning SBP and DBP (95% CI) were significantly greater with esaxerenone 5 mg/day vs. eplerenone 50 mg/day (differences of −6.3 mm Hg [−8.5, −4.1] for daytime SBP; −3.5 mm Hg [−4.7, −2.2] for daytime DBP; −6.4 mm Hg [−8.8, −4.0] for nighttime SBP; −2.9 mm Hg [−4.2, −1.6] for nighttime DBP; −8.8 mm Hg [−11.6, −6.0] for morning SBP; and −3.5 mm Hg [−5.2, −1.7] for morning DBP) (Figure 1b).

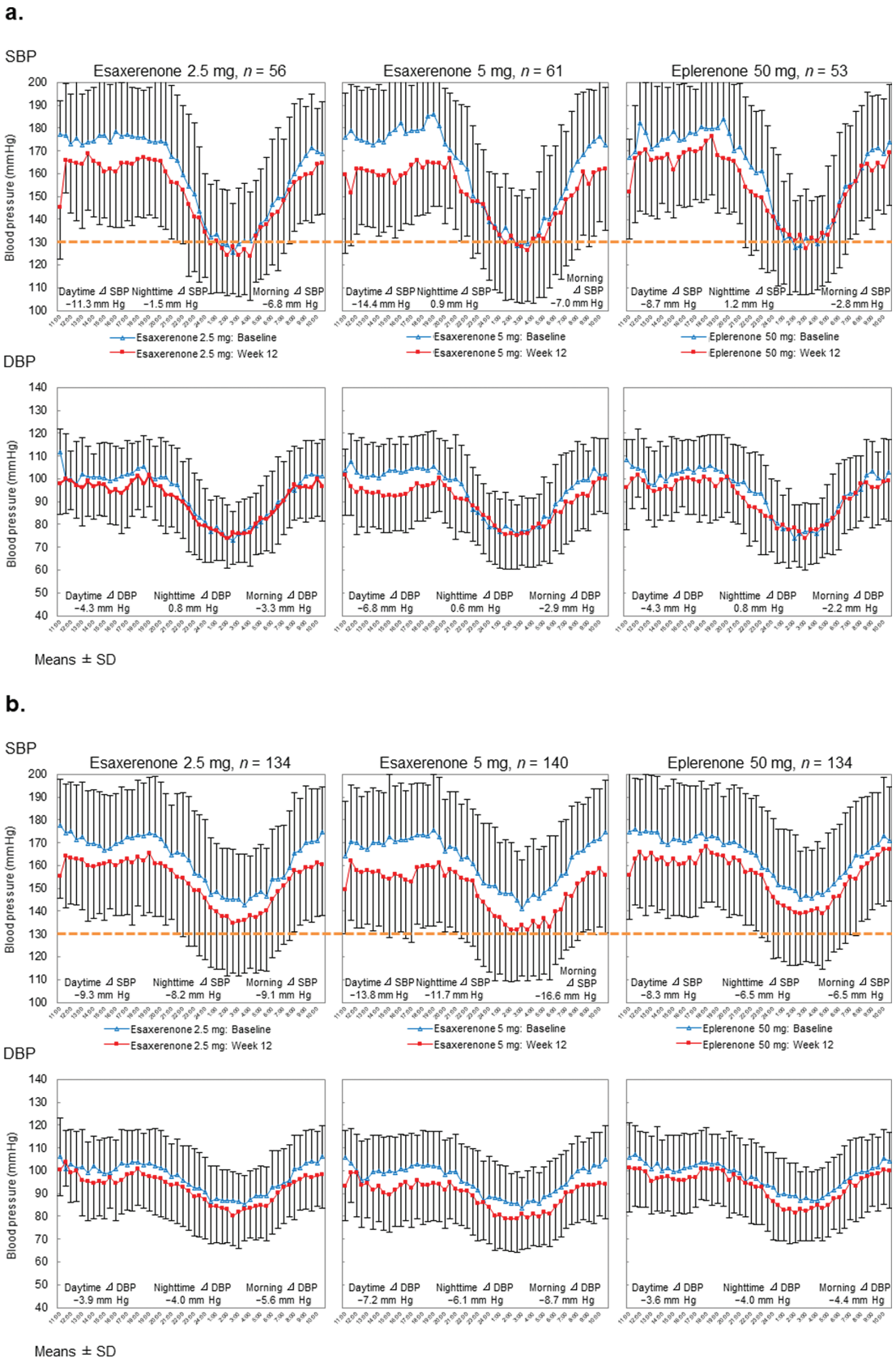

Figure 2. Ambulatory blood pressure monitoring trends by dipping pattern: (**a**) extreme dipper, (**b**) dipper, (**c**) non-dipper, and (**d**) riser. Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

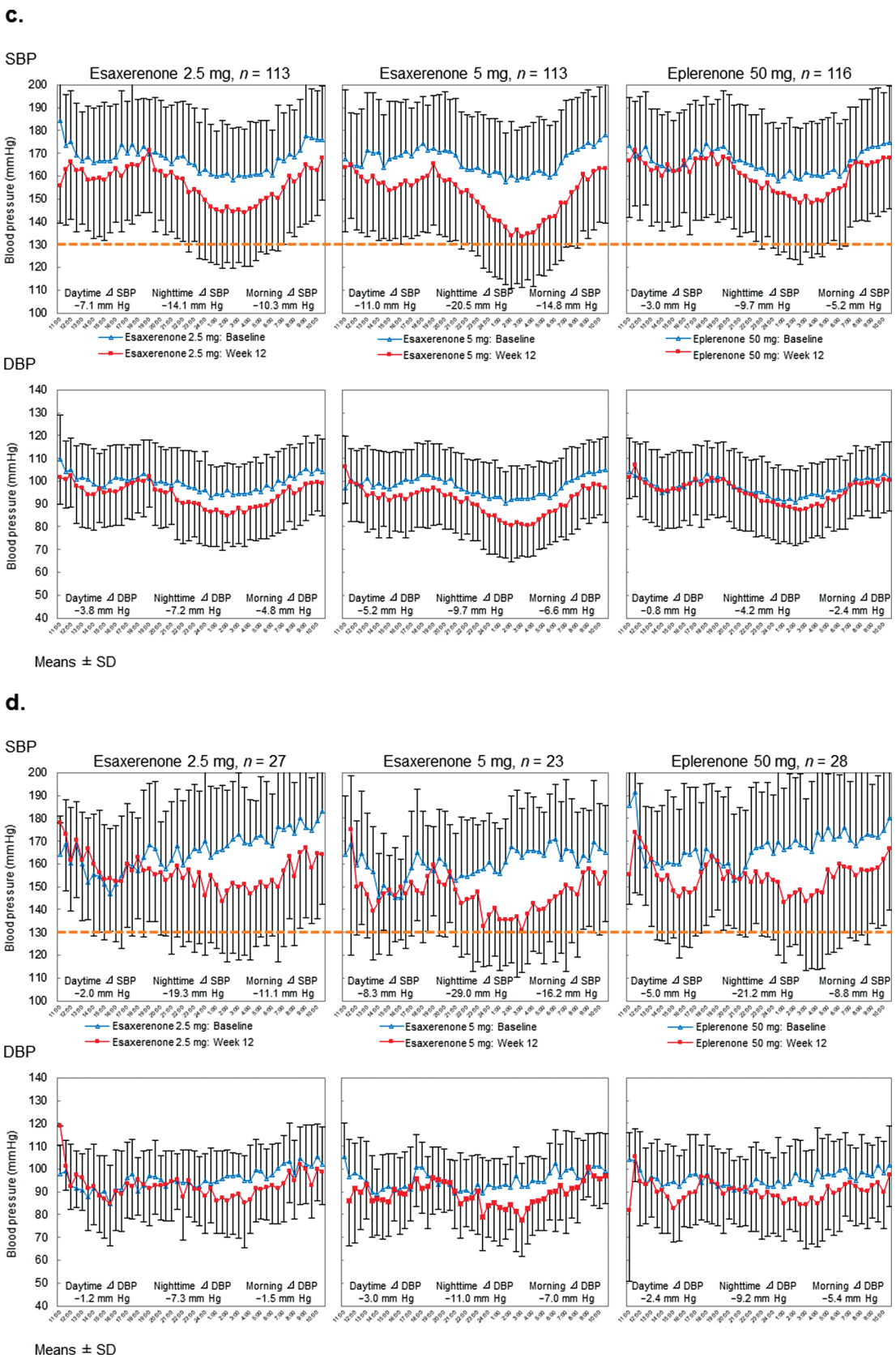

Figure 2. Continued.

BP-lowering effects of esaxerenone by different dipping patterns

In extreme dipper patients, esaxerenone reduced daytime and morning BP values, while nighttime BP remained unchanged (Figure 2a). In this patient subgroup, significant reductions in daytime BP from baseline were found in all treatment groups, while a significant treatment difference in daytime SBP was only found between esaxerenone 5 mg and eplerenone groups (−5.6 mm Hg [−10.6, −0.6]) (Figure 2a, Table 2, and Supplementary Figure S1A online).

Reductions in BP during esaxerenone therapy were consistent across the 24-hour period in dipper patients (Figure 2b). The esaxerenone 5 mg/day group showed significantly greater reductions in BP (95% CI) compared with the eplerenone group (differences of −5.5 mm Hg [−8.8, −2.1] for daytime SBP; −3.6 mm Hg [−5.5, −1.6] for daytime DBP; −5.2 mm Hg [−8.7, −1.7] for nighttime SBP; −2.1 mm Hg [−4.0, −0.1] for nighttime DBP; −10.1 mm Hg [−14.2, −6.0] for morning SBP; and −4.3 mm Hg [−7.0, −1.6] for morning DBP), regardless of the time period (Figure 2b and Supplementary Figure S1B online). The greatest decrease in morning BP (95% CI) was seen in the esaxerenone 5 mg/day group (−16.6/−8.7 mm Hg; differences of −4.3 mm Hg [−7.0, −1.6] for DBP and −10.1 mm Hg [−14.2, −6.0] for SBP) (Table 2 and Supplementary Figure S1B online).

Among non-dipper patients in the esaxerenone 5 mg/day group, the lowest nighttime SBP values were comparable to those of patients with a dipper pattern (130 mm Hg) (Figure 2c). In addition, decreases (95% CI) in daytime SBP/DBP (differences of −8.1 mm Hg [−12.2, −4.0] and −4.4 mm Hg [−6.6, −2.2], respectively), nighttime SBP/DBP (differences of −10.8 mm Hg [−15.0, −6.7] and −5.5 mm Hg [−7.7, −3.3], respectively), and morning SBP/DBP (differences of −9.5 mm Hg [−14.6, −4.5] and −4.2 mm Hg [−7.2, −1.2], respectively) with esaxerenone 5 mg/day in non-dipper patients were significantly greater than those with eplerenone (Figure 2c and Supplementary Figure S1C online). Furthermore, decreases (95% CI) in daytime and nighttime DBP (differences of −3.0 mm Hg [−5.2, −0.8] and −3.1 mm Hg [−5.3, −0.8], respectively) and nighttime SBP (difference of −4.4 mm Hg [−8.6, −0.2]) were significantly greater in the esaxerenone 2.5 mg/day group compared with the eplerenone group (Supplementary Figure S1C online).

Patients with a riser pattern, characterized by increased BP from night to morning, showed significant reductions in nighttime BP from baseline in all treatment groups; however, there were no significant treatment differences, possibly due to the limited sample size (Figure 2d and Supplementary Figure S1D online).

Nocturnal BP characteristics and BP variability

Definitions of nocturnal BP variables are summarized in Supplementary Table S4 online. Both maximum and minimum nighttime SBP values were reduced to a significantly greater extent during treatment with esaxerenone 2.5 and 5 mg/day compared with eplerenone (Supplementary Table S5 online). Esaxerenone 2.5 and 5 mg/day decreased moving lowest nighttime SBP and pre-awakening nighttime SBP to a significantly greater extent than eplerenone. Reduction from baseline in average peak nighttime SBP was significantly greater in the esaxerenone 5 mg/day vs. eplerenone groups. There were no significant differences between groups for change from baseline in average, maximum dynamic, or dynamic nighttime SBP surge. Measures of variability in 24-hour SBP, daytime SBP, and nighttime SBP (SD, coefficient of variation, and average real variability) did not show any variation between the treatment groups (Supplementary Table S6 online).

Nighttime BP in age-based patient subgroups

In both age categories (≥60, <60 years), there were significant differences in nocturnal BP reduction from baseline between the esaxerenone 5 mg/day and eplerenone groups, with the reduction greater in older patients (DBP: −8.0 mm Hg [−9.8, −6.2], SBP: −17.3 mm Hg [−21.0, −13.6]). There was no significant difference between the esaxerenone 2.5 mg/day group and the eplerenone group except for SBP in older patients (Table 3 and Figure 3).

Hyperkalemia

The proportions of patients with elevated serum K^+ (≥5.5 mEq/l) were 4.5%, 3.0%, and 1.8% in the esaxerenone 2.5 mg/day, esaxerenone 5 mg/day, and eplerenone groups, respectively; and hyperkalemia (2 consecutive serum K^+ level readings of ≥5.5 mEq/l or serum K^+ ≥6.0 mEq/l once) in 3 (0.9%), 2 (0.6%), and 0 patients, respectively. All episodes of hyperkalemia were asymptomatic and resolved without additional treatment after discontinuation of study drug. There were no obvious differences between patients aged <60 vs. ≥60 years in the occurrence of elevated serum K^+ or hyperkalemia (Supplementary Table S7 online).

DISCUSSION

This study demonstrated for the first time the differential nocturnal BP-lowering effect of the new MR blocker, esaxerenone, by dipping pattern. Our key finding was the greater reduction of nocturnal BP in the esaxerenone group compared with the eplerenone group, especially in patients with a non-dipper pattern who showed a greater hypotensive effect. Importantly, esaxerenone treatment effects in nighttime BP were observed in patients aged ≥60 years, in whom the non-dipping pattern is common. Reductions from baseline in average peak nighttime SBP with esaxerenone 5 mg/day in this study (−15.0 mm Hg) were slightly higher than eplerenone and were comparable to reductions in nocturnal BP reported with another MR blocker, finerenone, in patients with masked uncontrolled hypertension (−9.5 mm Hg with finerenone 10 mg/day and −12.0 mm Hg with finerenone 20 mg/day).[26]

In the esaxerenone groups, BP reductions were sustained throughout the 24-hour dosing interval, showing long-acting antihypertensive activity. Interestingly, esaxerenone did not reduce BP in patients with an extreme dipper pattern.

Table 3. Comparison of nighttime BP reduction with each treatment by subgroups based on patient age

	Esaxerenone 2.5 mg/day	Esaxerenone 5 mg/day	Eplerenone 50 mg/day
Nighttime ambulatory diastolic BP, mm Hg			
Age <60 years			
Change from baseline (95% CI)[a]	−3.9 (−5.2, −2.6)	−5.5 (−6.8, −4.3)	−3.6 (−4.9, −2.3)
Treatment difference vs. eplerenone (95% CI)[b]	−0.3 (−2.1, 1.6)	−1.9 (−3.7, −0.1)	—
Age ≥60 years			
Change from baseline (95% CI)[a]	−5.8 (−7.4, −4.1)	−8.0 (−9.8, −6.2)	−4.0 (−5.6, −2.4)
Treatment difference vs. eplerenone (95% CI)[b]	−1.8 (−4.1, 0.5)	−4.0 (−6.4, −1.6)	—
Nighttime ambulatory systolic BP, mm Hg			
Age <60 years			
Change from baseline (95% CI)[a]	−7.9 (−10.3, −5.5)	−11.8 (−14.0, −9.6)	−7.7 (−10.0, −5.4)
Treatment difference vs. eplerenone (95% CI)[b]	−0.2 (−3.5, 3.1)	−4.1 (−7.3, −0.9)	—
Age ≥60 years			
Change from baseline (95% CI)[a]	−13.3 (−16.8, −9.9)	−17.3 (−21.0, −13.6)	−7.8 (−11.1, −4.4)
Treatment difference vs. eplerenone (95% CI)[b]	−5.6 (−10.4, −0.8)	−9.6 (−14.6, −4.6)	—

Abbreviations: BP, blood pressure; CI, confidence interval.
[a]Least-squares means of the change from baseline in blood pressure based on an analysis of covariance model.
[b]Least-squares means of the between treatment difference of the change in BP (esaxerenone 2.5 mg/day − eplerenone 50 mg/day; or esaxerenone 5 mg/day − eplerenone 50 mg/day) based on an analysis of covariance model.

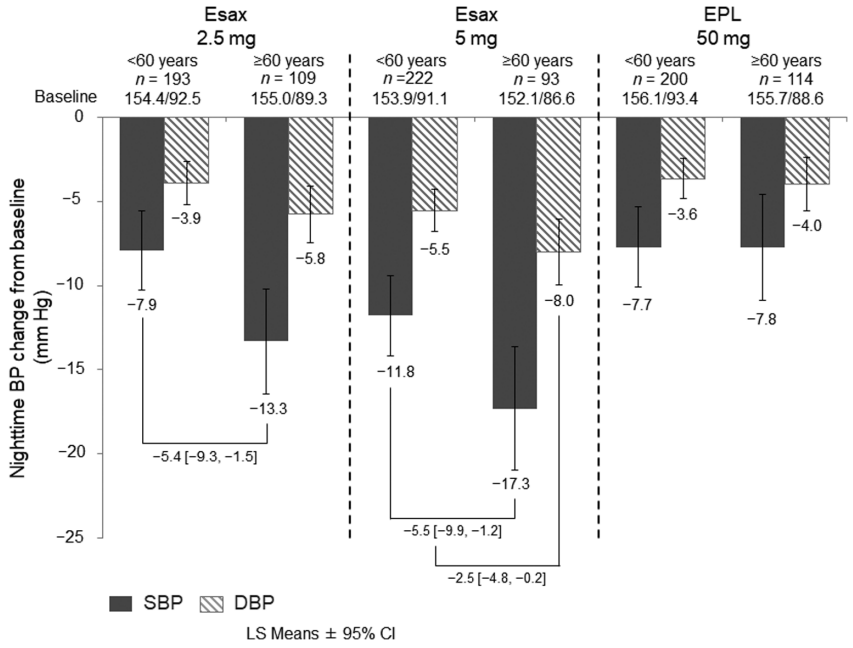

Figure 3. Nighttime blood pressure-lowering effect by age groups. Abbreviations: BP, blood pressure; CI, confidence interval; DBP, diastolic BP; EPL, eplerenone; Esax, esaxerenone; LS, least squares; SBP, systolic blood pressure.

The reductions in nighttime BP with esaxerenone may be clinically relevant considering the documented prognostic significance of nocturnal BP.[27] An analysis of the J-HOP study data showed that a 10-mm Hg increase in nighttime home SBP was associated with a significant increase in cardiovascular risk, independent of office BP, and morning and evening home BP (hazard ratio 1.201; 95% CI 1.046–1.378).[18] Thus, reducing nocturnal BP may contribute to lowering cardiovascular risk in these patients; this needs to be evaluated in larger clinical studies with longer follow-up periods. The riser pattern of nighttime BP has been linked with a particularly poor prognosis in terms of the occurrence of atherosclerotic cardiovascular events, heart failure, and stroke.[14,28,29] The riser pattern was reported as a significant predictor of all-cause mortality and cardiovascular events in patients with heart failure with preserved ejection fraction

(hazard ratio 3.01 vs. other patterns of nocturnal BP; 95% CI 1.54–6.08; $P < 0.01$).[28] Restoration of a dipping pattern of nocturnal hypertension with esaxerenone may therefore contribute to reduced cardiovascular risk during treatment. This may be particularly relevant for Asian patients with hypertension, who have a higher prevalence of nocturnal hypertension compared with non-Asians.[2,6] These suggestions remain speculative until the effects of lowering nocturnal BP on hard clinical endpoints have been evaluated in well-designed and appropriately powered studies. Additional research is also needed to determine the safety of selectively lowering nocturnal BP, especially in older individuals.

Existing antihypertensive treatment options may be less effective in reducing nighttime BP to appropriate levels.[11,30] Eplerenone reduced average 24-hour and nighttime BP in elderly patients with poorly controlled hypertension when added to an angiotensin converting enzyme inhibitor or angiotensin receptor blocker.[31] However, reductions in nocturnal BP with esaxerenone in the current analysis were significantly greater than those of eplerenone 50 mg/day; thus, the esaxerenone results suggest the potential for differential BP-lowering activity based on dipping pattern. This may optimize daily fluctuations in BP and help reduce the risk of cardiovascular events.

The effects of esaxerenone on nighttime BP were significantly greater compared with eplerenone, especially in older (≥60 years) patients, which is of clinical relevance given the aging population demographic. A high proportion of elderly patients are of a non-dipper or riser type, whereby decreasing renal function may contribute to increasing salt sensitivity and elevated nighttime BP.[32] Esaxerenone was well tolerated in older patients, with no notable increases in serum K^+ levels. Increased serum K^+ levels have been reported during MR blocker therapy.[33,34] This is of particular concern in the elderly, in whom renal function may be decreased. However, in this study, rates of elevated serum K^+ with 2.5 mg/day esaxerenone were 4.5% and did not obviously differ between older and younger patients.

To our knowledge, the antihypertensive effects of angiotensin receptor blockers, calcium channel blockers, β-blockers, and diuretics by dipping pattern have not been investigated in the randomized setting, although there are single arm studies.[29,35,36] Several potential mechanisms could explain why esaxerenone might influence nighttime BP differently in patients with different dipping patterns and in older vs. younger patients. Decreased nocturnal BP is associated with circulating blood volume and, therefore, the strong MR inhibitory action of esaxerenone[37] may potentially reduce nocturnal BP by decreasing fluid volume via suppression of sodium reabsorption. However, there are also hypothetical relationships between MR antagonism, aldosterone, resistant hypertension, and sleep apnea,[38,39] which may be relevant to our results, but require further study. Finally, it is also possible that the long half-life of esaxerenone (18.6 hours) compared with eplerenone (5.0 hours) contributes to greater antihypertensive effects. However, as current findings are *post hoc* data, these suggestions are hypothesis generating only and need to be specifically evaluated in future studies.

Our analysis had some limitations. As this was a *post hoc* analysis, no adjustments were made for multiple testing; therefore, it should be considered as hypothesis generating only. Our results may be based on the regression toward the mean phenomenon (observed in both groups). Randomization was not stratified by dipping pattern, meaning the validity of the comparison between treatment groups within each dipping pattern subgroup is not necessarily guaranteed. Only Japanese patients were included, which may limit generalizability. This is particularly relevant given the different cardiovascular risk profiles between Asians and other ethnic groups. The total number of patients in some dipping pattern subgroups was relatively small, potentially limiting statistical power. While patients were instructed to refrain from activities that may affect BP and heart rates during ABPM measurements, daytime napping data were not collected; we cannot deny that daytime napping may have affected the dipping pattern, as has been acknowledged in the literature.[40] The only comparator agent was eplerenone; the nocturnal BP-lowering effects of esaxerenone vs. other antihypertensive agents or placebo remain to be determined. Although the eplerenone dose used in this study was that approved in Japan (50 or 100 mg/day), this may have been lower than needed for some patients; indeed, eplerenone can be given twice daily in other countries. Therefore, the comparison between the pharmacokinetics of esaxerenone and eplerenone and any resultant effect on nighttime BP lowering may be overestimated.

This *post hoc* analysis suggests, for the first time, that esaxerenone effectively treats nocturnal hypertension. These effects were greater in older patients and non-dippers and were significantly greater than those of eplerenone. Reduction in nighttime BP with esaxerenone could contribute to reductions in cardiovascular risk and events, especially in Japanese patients who have a salt-sensitive hypertension phenotype in which elevated nighttime BP is common. This is particularly relevant in older patients, in whom salt sensitivity may be more severe due to declining renal function. These hypothesis-generating results warrant further study.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

Supplementary Table S1. Comparative chemical and pharmacokinetic characteristics of currently available mineralocorticoid receptor (MR) blockers

Supplementary Table S2. Summary of ABPM readings of daytime, nighttime, and morning BP (mm Hg)

Supplementary Table S3. Patient characteristics at baseline by treatment group

Supplementary Table S4. Definition of parameters

Supplementary Table S5. Changes in nocturnal blood pressure parameters

Supplementary Table S6. Blood pressure variability of 24-hour, daytime, and nighttime systolic blood pressure

Supplementary Table S7. Serum potassium (K^+) level increases: overall and in subgroups based on patient age

Supplementary Figure S1. Blood pressure (BP)-lowering effects in each time period by dipping pattern: (A) extreme dipper, (B) dipper, (C) non-dipper, and (D) riser.

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