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

Kazuomi Kario,1,a Sadayoshi Ito,2,3 Hiroshi Itoh,4 Hiromi Rakugi,5 Yasuyuki Okuda,6 Motonobu Yoshimura,6 and Satoru Yamakawa6

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.

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
doi:10.1093/ajh/hpaa155

1Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Shimotsuke, Tochigi, Japan; 2Division of Nephrology, Endocrinology and Vascular Medicine, Department of Medicine, Tohoku University School of Medicine, Sendai, Miyagi, Japan; 3Katta General Hospital, Shiroishi, Japan; 4Department of Endocrinology, Metabolism and Nephrology, Keio University School of Medicine, Tokyo, Japan; 5Department of Geriatric and General Medicine, Osaka University Graduate School of Medicine, Suita, Japan; 6Daiichi Sankyo Co., Ltd., Tokyo, Japan.

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).

© The Author(s) 2020. Published by Oxford University Press on behalf of American Journal of Hypertension, Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Correspondence: Kazuomi Kario (kkario@jichi.ac.jp).

Initially submitted June 16, 2020; date of first revision July 27, 2020; accepted for publication October 2, 2020; online publication November 9, 2020.
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.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 m², 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 \(\pm\) SD age of 55.5 \(\pm\) 9.6 years, the majority were male (72.2%), and more than half (51.5%) had received previous antihypertensive therapy (Table 1). 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 \((n = 170)\) | Dipper \((n = 408)\) | Non-dipper \((n = 342)\) | Riser \((n = 78)\) |
|--------------------------|-----------------------------|---------------------|--------------------------|------------------|
| Age, years               | 56.2 \(\pm\) 8.9 n.s.       | 54.7 \(\pm\) 9.6 n.s. | 55.5 \(\pm\) 9.5 n.s.    | 58.0 \(\pm\) 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         |                  |
| \(\geq60\) 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/m²   | 24.7 \(\pm\) 3.3 <0.01      | 25.8 \(\pm\) 4.0 26.2 \(\pm\) 4.4 n.s. | 25.3 \(\pm\) 4.5 n.s.    |                  |
| Office SBP, mm Hg        | 155.0 \(\pm\) 10.0 n.s.     | 154.9 \(\pm\) 9.4 156.0 \(\pm\) 9.9 n.s. | 155.0 \(\pm\) 8.2 n.s.   |                  |
| SBP \(\geq160\) mm Hg, n (%) | 51 (30.0) n.s. 126 (31.4) 149 (34.8) n.s. | 26 (33.3) n.s.     |                  |
| Office DBP, mm Hg        | 97.3 \(\pm\) 5.4 <0.05      | 98.6 \(\pm\) 5.7 98.2 \(\pm\) 5.5 n.s. | 97.2 \(\pm\) 5.9 n.s.    |                  |
| DBP \(\geq100\) mm Hg, n (%) | 57 (33.5) n.s. 170 (41.7) 135 (36.9) n.s. | 28 (35.9) n.s.     |                  |
| Pulse rate, bpm          | 74.8 \(\pm\) 10.1 <0.05      | 72.7 \(\pm\) 9.9 72.2 \(\pm\) 9.9 n.s. | 72.2 \(\pm\) 10.5 n.s.   |                  |
| 24-Hour pulse rate, bpm  | 75.2 \(\pm\) 8.0 <0.001      | 72.3 \(\pm\) 8.8 71.4 \(\pm\) 8.3 n.s. | 71.3 \(\pm\) 8.7 n.s.    |                  |
| 24-Hour SBP, mm Hg       | 161.3 \(\pm\) 14.5 n.s.     | 163.9 \(\pm\) 15.1 167.8 \(\pm\) 15.2 <0.001 | 165.4 \(\pm\) 18.1 n.s.  |                  |
| 24-Hour DBP, mm Hg       | 94.5 \(\pm\) 7.0 <0.001      | 97.3 \(\pm\) 7.8 98.9 \(\pm\) 8.0 <0.01 | 95.9 \(\pm\) 8.3 n.s.    |                  |
| Nighttime SBP, mm Hg     | 130.8 \(\pm\) 14.1 n.s.     | 146.2 \(\pm\) 14.8 159.4 \(\pm\) 15.7 n.s. | 167.3 \(\pm\) 19.9 n.s.  |                  |
| Nighttime DBP, mm Hg     | 76.7 \(\pm\) 7.5 n.s.       | 86.9 \(\pm\) 8.3 92.9 \(\pm\) 9.0 n.s. | 94.7 \(\pm\) 8.9 n.s.    |                  |
| TC, mg/dl                | 208.1 \(\pm\) 35.9 n.s.     | 209.3 \(\pm\) 34.0 209.5 \(\pm\) 33.6 n.s. | 204.1 \(\pm\) 34.2 n.s.  |                  |
| HDL-C, mg/dl             | 62.2 \(\pm\) 19.4 n.s.      | 59.9 \(\pm\) 16.6 59.3 \(\pm\) 16.6 n.s. | 60.9 \(\pm\) 15.0 n.s.   |                  |
| LDL-C, mg/dl             | 120.5 \(\pm\) 32.4 n.s.     | 124.9 \(\pm\) 30.7 127.2 \(\pm\) 29.5 n.s. | 118.2 \(\pm\) 30.4 n.s.  |                  |
| Triglycerides, mg/dl     | 150.6 \(\pm\) 142.5 n.s.    | 140.1 \(\pm\) 115.9 130.4 \(\pm\) 97.6 n.s. | 133.9 \(\pm\) 114.8 n.s. |                  |
| Fasting glucose, mg/dl   | 104.7 \(\pm\) 17.7 n.s.     | 106.9 \(\pm\) 19.7 106.2 \(\pm\) 20.8 n.s. | 104.7 \(\pm\) 16.9 n.s.  |                  |
| HbA1c, %                 | 5.57 \(\pm\) 0.61 n.s.      | 5.66 \(\pm\) 0.62 5.72 \(\pm\) 0.67 n.s. | 5.75 \(\pm\) 0.70 n.s.   |                  |
| Serum creatinine, mg/dl  | 0.77 \(\pm\) 0.13 n.s.      | 0.76 \(\pm\) 0.14 0.77 \(\pm\) 0.14 n.s. | 0.73 \(\pm\) 0.15 n.s.   |                  |
| Serum K⁺, mEq/l          | 4.23 \(\pm\) 0.28 n.s.      | 4.20 \(\pm\) 0.29 4.21 \(\pm\) 0.29 n.s. | 4.19 \(\pm\) 0.29 n.s.   |                  |
| eGFR, ml/minute/1.73 m²  | 79.33 \(\pm\) 12.54 n.s.    | 79.18 \(\pm\) 12.42 77.57 \(\pm\) 11.63 n.s. | 79.06 \(\pm\) 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, glycylated 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,
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).

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

Figure 2a, Table 2, and Supplementary Figure S1A online. 5 mg and eplerenone groups (−5.6 mm Hg [−10.6, −0.6]) in daytime SBP was only found between esaxerenone 5 mg and eplerenone groups (−5.6 mm Hg [−10.6, −0.6]). 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).
The reductions in nighttime BP with esaxerenone may be clinically relevant considering the documented prognostic significance of nocturnal BP. 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). 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. 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). 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. 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. 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. 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. 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. 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. 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 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, 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.

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.

FUNDING
The ESAX-HTN study and this post hoc analysis were funded by Daiichi Sankyo.

ACKNOWLEDGMENTS
The authors thank Nicola Ryan of Edanz Evidence Generation, for providing medical writing services, which were funded by Daiichi Sankyo.

DISCLOSURE
K.K., S.I., H.I., and H.R. have received lecture fees and research funding from Daiichi Sankyo. Y.O., M.Y., and S.Y. are employees of Daiichi Sankyo.

This manuscript was sent to Guest Editor, Charles T. Stier, PhD for editorial handling and final disposition.

REFERENCES
1. Kario K. Nocturnal hypertension: new technology and evidence. Hypertension 2018;71:1009–1010.
2. Kario K, Chen CH, Park S, Park CG, Hoshide S, Cheng HM, Huang QF, Wang JG. Consensus document on improving hypertension management in Asian patients, taking into account Asian characteristics. Hypertension 2018;71:375–382.
3. Li Y, Staessen JA, Lu L, Wang GL, Wang JG. Isolated nocturnal hypertension a novel clinical entity? Findings from a Chinese population study. Hypertension 2007;50:333–339.
4. Li Y, Wang JG. Isolated nocturnal hypertension: a disease masked in the dark. Hypertension 2013;61:278–283.
5. Omboni S, Aristizabal D, De la Sierra A, Li Y, Staessen JA, Hoshide S, Wang GL, Wang JG. Nighttime blood pressure measured by home blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. J Hypertens 2000;18:847–854.
6. Palatini P, Hozawa A, Naga K, Kikuya M, Tsuji I, Ito S, Satoh H, Hisamichi S, Imai Y. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. J Hypertens 2000;21:1250–1283.
7. Kario K, Shin J, Chen CH, Buranakitjaroen P, Chia YC, Divinagracia R, Mancia G, Parati G, ARTEMIS (international Ambulatory blood pressure Registry: TTelemonitoring of hypertension and cardiovascular rISK project) Investigators. Hypertension types defined by clinic and ambulatory blood pressure in 14143 patients referred to hypertension clinics worldwide. Data from the ARTEMIS study. J Hypertens 2016;34:2187–2198.
8. Henskens LH, van Oostenbrugge RJ, Kroon AA, de Leeuw PW, Lodder J. Brain microbleeds are associated with ambulatory blood pressure levels in a hypertensive population. Hypertension 2008;51:62–68.
9. Kario K, Matsuo T, Kobayashi H, Imiya M, Matsuo M, Shimada K. Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Advanced silent cerebrovascular damage in extreme dippers. Hypertension 1996;27:130–135.
10. Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Blunted heart rate dip during sleep and all-cause mortality. Arch Intern Med 2007;167:2116–2121.
11. Boggia J, Li Y, Thijs L, Hansens TW, Kikuya M, Björklund-Bödegård K, Richart T, Ohkubo T, Kuznetsova T, Törp-Pedersen C, Lind L, Ilsen H, Imai Y, Wang J, Sandoya E, O’Brien E, Staessen JA; International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) investigators. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. Lancet 2007;370:1219–1229.
12. Dolan E, Stanton AV, Thom S, Caulfield M, Atkins N, McInnes G, Collier D, Dicker P, O’Brien E; ASCOT Investigators. Ambulatory blood pressure monitoring predicts cardiovascular events in treated hypertensive patients—an Anglo-Scandinavian cardiac outcomes trial substudy. J Hypertens 2009;27:876–885.
13. Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. Hypertension 2011;57:3–10.
14. Ingelsson E, Björklund-Bödegård K, Lind L, Arnlöv J, Sundström J. Diurnal blood pressure pattern and risk of congestive heart failure. JAMA 2006;295:2859–2866.
15. Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. Hypertension 2001;38:852–857.
16. Ohkubo T, Hozawa A, Nagai K, Kikuya M, Tsuji I, Ito S, Satoh H, Hisamichi S, Imai Y. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. J Hypertens 2000;18:847–854.
17. Palatini P, Reboldi G, Beilin LJ, Caigusa E, Eguchi K, Imai Y, Kario K, Ohkubo T, Pierdomenico SD, Schwartz JE, Wing L, Verdecchia P. Added predictive value of night-time blood pressure variability for cardiovascular events and mortality: the Ambulatory Blood Pressure-International Study. Hypertension 2014;64:487–493.
18. Kario K, Kanega H, Tomitan I, Okawara Y, Yano Y, Hoshide S. Nighttime blood pressure measured by home blood pressure monitoring as an independent predictor of cardiovascular events in general practice. Hypertension 2019;73:1240–1248.
19. Drawz PE, Rosenthal N, Babineau DC, Raham M. Nighttime hospital blood pressure—a predictor of death, ESRD, and decline in GFR. Ren Fail 2010;32:1036–1043.
20. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Denison Himmelfarb C, DePalma SM, Gidding S, Janmeros KA, Jones DW, MacLaughlin EL, Muntner P, Oiviabgele B, Smith SC Jr, Wassertheil S, Wexler CC, Stafford RS, Taler SI, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ACP/AMERICAN MEDICAL ASSOCIATION/AGS/APHA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:2199–2269.
21. Williams B, Mancia G, Spering W, Agabiti Rosei E, Azzini M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Rulope L, Zanchetti A, Whitworth A, Kjeldsen SE, Lourenco J, Marti M, Mancia G, Parati G, RAS (international Ambulatory blood pressure Registry: TTelemonitoring of hypertension and cardiovascular rISK project) Investigators. Hypertension types defined by clinic and ambulatory blood pressure in 14143 patients referred to hypertension clinics worldwide. Data from the ARTEMIS study. J Hypertens 2016;34:2187–2198.
22. Kario K, Shin J, Chen CH, Buranakitjaroen P, Chia YC, Divinagracia R, Nailes J, Hoshide S, Siddique S, Sison J, Soenarta AA, Sugunuru GP, Tay J, Teo BW, Turana Y, Zhang Y, Park S, Van Minh H, Wang JG. Expert panel consensus recommendations for ambulatory blood pressure monitoring in Asia: the HOPE Asia network. J Clin Hypertens (Greenwich) 2019;21:1250–1283.
23. Cuspidi C, Measi S, Salerno M, Valerio C, Fusari V, Severgnini B, Lonati L, Magriti F, Zanchetti A. Cardiovascular target organ damage in essential hypertensives with or without reproducible nocturnal fall in blood pressure. J Hypertens 2004;22:273–280.
24. Henskens LH, van Oostenbrugge RJ, Kroon AA, de Leeuw PW, Lodder J. Brain microbleeds are associated with ambulatory blood pressure levels in a hypertensive population. Hypertension 2008;51:62–68.
eperlenone in patients with essential hypertension (ESAX-HTN Study). *Hypertension* 2020; 75:51–58.

24. Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, Murata M, Kuroda T, Schwartz JE, Shimada K. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation* 2003; 107:1401–1406.

25. Kario K, Park S, Chia YC, Sukonthasarn A, Turana Y, Shin J, Chen GH, Buranakitjaroen P, Divinagracia R, Nailes J, Hoshide S, Siddique S, Sison J, Soenarta AA, Sogunuru GP, Tay JC, Teo BW, Zhang YQ, Van Minh H, Tomitani N, Kabutoya T, Verma N, Wang TD, Wang JG. 2020 Consensus summary on the management of hypertension in Asia from the HOPE Asia Network. *J Clin Hypertens (Greenwich)* 2020; 22:351–362.

26. Ruilope L, Nowack C, Bakris GL. Masked and nocturnal hypertension in the ARTS-DN ABPM sub-study with finerenone. *J Am Soc Hypertens* 2016; 10:e7.

27. Kario K. Evidence and perspectives on the 24-hour management of hypertension: hemodynamic biomarker-initiated ‘anticipation medicine’ for zero cardiovascular event. *Prog Cardiovasc Dis* 2016; 59:262–281.

28. Komori T, Eguchi K, Saito T, Hoshide S, Kario K. Riser pattern is a novel predictor of adverse events in heart failure patients with preserved ejection fraction. *Circ J* 2017; 81:220–226.

29. Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohnori K, Michimata M, Matsubara M, Hashimoto J, Hoshi H, Araki T, Satoh H, Hisamichi S, Imai Y. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. *J Hypertens* 2002; 20:2183–2189.

30. Kario K, Shimada K. Differential effects of amlodipine on ambulatory blood pressure in elderly hypertensive patients with different nocturnal reductions in blood pressure. *Am J Hypertens* 1997; 10:261–268.

31. Yano Y, Hoshide S, Tamaki N, Nagata M, Sasaki K, Kanemaru Y, Shimada K, Kario K. Efficacy of eplerenone added to renin-angiotensin blockade in elderly hypertensive patients: the Jichi-Eplerenone Treatment (JET) study. *J Renin Angiotensin Aldosterone Syst* 2011; 12:340–347.

32. Staessen JA, Bieniaszewski L, O’Brien E, Gosse P, Hayashi H, Imai Y, Kawasaki T, Otsuka K, Palatini P, Thijs L, Fagard R. Nocturnal blood pressure fall on ambulatory monitoring in a large international database. The “Ad Hoc” Working Group. *Hypertension* 1997; 29:30–39.

33. Colussi G, Catena G, Sechi LA, Spironolactone, eplerenone and the new aldosterone blockers in endocrine and primary hypertension. *J Hypertens* 2013; 31:3–15.

34. Pelliccia F, Patti G, Rosano G, Greco C, Gaudio C. Efficacy and safety of eplerenone in the management of mild to moderate arterial hypertension: systematic review and meta-analysis. *Int J Cardiol* 2014; 177:219–228.

35. Uzu T, Kimura G. Diuretics shift circadian rhythm of blood pressure from non-dipper to dipper in essential hypertension. *Circulation* 1999; 100:1635–1638.

36. Kario K, Nariyama J, Kido H, Ando S, Takiuchi S, Eguchi K, Niijima Y, Ando T, Noda M. Effect of a novel calcium channel blocker on abnormal nocturnal blood pressure in hypertensive patients. *J Clin Hypertens (Greenwich)* 2013; 15:465–472.

37. Araki K, Homma T, Morikawa Y, Ubuoka N, Tsuruoka H, Aoki K, Ishikawa H, Mizuno M, Sada T. Pharmacological profile of CS-3150, a novel, highly potent and selective non-steroidal mineralocorticoid receptor antagonist. *Eur J Pharmacol* 2015; 761:226–234.

38. Shibata H, Itoh H. Mineralocorticoid receptor-associated hypertension and its organ damage: clinical relevance for resistant hypertension. *Am J Hypertens* 2012; 25:514–523.

39. Calhoun DA. Obstructive sleep apnea and hypertension. *Curr Hypertens Rep* 2010; 12:189–195.

40. Burzynski M, Mekler J, Wachtel N, Ben-Ishay D. Siesta and ambulatory blood pressure monitoring. Comparability of the afternoon nap and night sleep. *Am J Hypertens* 1994; 7:217–221.