

The Combination of Non-dipper Heart Rate and High Brain Natriuretic Peptide Predicts Cardiovascular Events: The Japan Morning Surge-Home Blood Pressure (J-HOP) Study

Yukako Ogoyama,¹ Tomoyuki Kabutoya,¹ Satoshi Hoshide,^{1,✉} and Kazuomi Kario^{1,✉}

BACKGROUND

We hypothesized that the association between the dipping heart rate (HR) pattern and cardiovascular (CV) events differs according to the brain natriuretic peptide (BNP) level.

METHODS

We examined a subgroup of 1,369 patients from the Japan Morning Surge Home Blood Pressure study; these were patients who had CV risk factors and had undergone ambulatory blood pressure (BP) monitoring. HR non-dipping status was defined as (awake HR – sleep HR)/awake HR <0.1, and high BNP was defined as ≥ 35 pg/ml. We divided the patients into four groups according to their HR dipper status (dipping or non-dipping) and BNP level (normal or high).

RESULTS

The mean follow-up period was 60 ± 30 months. The primary endpoints were fatal/nonfatal CV events (myocardial infarction, angina pectoris, stroke, hospitalization for heart failure, and aortic dissection). During

the follow-up period, 23 patients (2.8%) in the dipper HR with normal BNP group, 8 patients (4.4%) in the non-dipper HR with normal BNP group, 24 patients (9.5%) in the dipper HR with high-BNP group, and 25 patients (21.0%) in the non-dipper HR with high-BNP group suffered primary endpoints (log rank 78.8, $P < 0.001$). Non-dipper HR was revealed as an independent predictor of CV events (hazard ratio, 2.13; 95% confidence interval, 1.35–3.36; $P = 0.001$) after adjusting for age, gender and smoking, dyslipidemia, diabetes mellitus, chronic kidney disease, BNP, non-dipper BP, 24-h HR, and 24-h systolic blood pressure.

CONCLUSIONS

The combination of non-dipper HR and higher BNP was associated with a higher incidence of CV events.

Keywords: blood pressure; brain natriuretic peptide; cardiovascular event; hypertension; non-dipper heart rate

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Many reports have shown that a blunted nocturnal drop in an individual's blood pressure (BP) (i.e., the non-dipper BP pattern) is related to cardiovascular (CV) events.^{1–4} Like BP, the heart rate (HR) also undergoes diurnal variation in response to changes in sympathetic nerve activity. Specifically, the HR decreases with increases in parasympathetic activity.⁵ Several reports have shown that a decrease in the nocturnal HR decline (i.e., the non-dipper HR pattern) is related to the rates of total death and CV events.^{6–13} Our research has demonstrated that the interaction between the non-dipper HR pattern and the non-dipper BP pattern has a significant synergistic effect

on CV events: i.e., the non-dipper HR pattern is a risk factor for non-dipper BP, and thereby for CV events.⁸ It has also been reported that brain natriuretic peptide (BNP) is associated with CV events,¹⁴ and we showed that the non-dipper HR status was related to a high level of BNP.¹⁵ However, the relationships among the non-dipper HR pattern, BNP levels, and CV prognoses have not been clarified.

In this study, we investigated the association between CV events, non-dipper HR status, and BNP levels in high-risk Japanese outpatients from the Japan Morning Surge-Home Blood Pressure (J-HOP) study.

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

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¹Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan.

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PATIENTS AND METHODS

Patients

This study was performed as part of the J-HOP study. Patients enrolled in the J-HOP study were consecutively recruited from January 2005 to May 2012 by 75 doctors at 71 institutions (45 primary practices, 22 hospital-based outpatient clinics, and 4 specialized university hospitals) throughout Japan. The ethics committee of the internal review board of the Jichi Medical University School of Medicine, Tochigi, Japan approved the protocol. The study protocol was registered on a clinical trials registration site: the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN-CTR): #UMIN00000894. Written informed consent was obtained from all patients enrolled in the study. The details of the J-HOP study have been reported elsewhere.¹⁶ The J-HOP study enrolled 4,310 ambulatory outpatients who had one or more of the following CV risk factors: hypertension, impaired glucose tolerance or diabetes (a fasting glucose level ≥ 126 mg/dl, a glycated hemoglobin level $\geq 6.1\%$, and/or treated diabetes), hyperlipidemia (total cholesterol levels ≥ 240 mg/dl or treated hyperlipidemia), history of cardiovascular disease (coronary artery disease, stroke, aortic dissection, peripheral artery disease, and/or congestive heart failure), current smoking (including the outpatients with chronic obstructive pulmonary disease), chronic renal disease (estimated glomerular filtration rate < 60 ml/min/1.73 m²), atrial fibrillation, metabolic syndrome, and sleep apnea syndrome, and it excluded patients who had malignancy or chronic inflammatory disease. Of these 4,310 participants, we excluded individuals with atrial fibrillation ($n = 161$), and then analyzed a subgroup of 1,369 J-HOP study patients who had undergone ambulatory BP monitoring (ABPM) and whose BNP had been measured.

ABPM and the definition of dipping status

ABPM was performed by a validated machine: ABPM-630 (Nippon Colin, Komaki, Japan), TM-2421, or TM-2425 (A&D, Tokyo). The BP measurements were performed at 30-min intervals for 24 h on a weekday. We determined the periods of waking and sleeping based on the patients' diaries. Nighttime BP was defined as the average of the BP values from the time when the patient went to bed until the time he or she got out of bed. Daytime BP was defined as the average of the BP values recorded during the rest of the day. In the same way, nighttime HR and daytime HR were defined as the average of each of the respective HR values. For purposes of this analysis, we did not define a minimum required number of ambulatory BP readings. The average numbers (SD) of BP readings for the group of all participants were 30.7 (3.5) and 14.3 (3.0) in the daytime and nighttime period, respectively.

Non-dipper BP status was defined as (daytime systolic blood pressure (SBP) – nighttime SBP)/daytime SBP < 0.1 . Non-dipper HR status was defined as (daytime HR – nighttime HR)/daytime HR < 0.1 as described previously.¹² Dipping HR% was defined as (daytime HR – nighttime HR) $\times 100$ /daytime HR. We classified the 1,369 patients into four

groups according to their HR dipper status and BNP levels: those with dipper HR status and normal BNP ($n = 817$); non-dipper HR status and normal BNP ($n = 181$); dipper HR status and high BNP ($n = 252$); and non-dipper HR status and high BNP ($n = 119$).

We also divided patients into the following four groups: dipper HR and normal N-terminal-prohormone BNP (NT-proBNP) ($n = 675$); non-dipper HR and normal NT-proBNP ($n = 148$); dipper HR and high NT-proBNP ($n = 143$); and non-dipper HR and high NT-proBNP ($n = 73$). None of the patients experienced an adverse event due to the ABPM.

Blood examinations

Blood samples were collected in the morning from patients in a fasting state at study enrollment. All assays were performed within 24 h of sample collection at a single laboratory center (SRL Inc., Tokyo). Plasma BNP was measured with a chemiluminescent enzyme assay (MIO2 Shionogi BNP; Shionogi, Osaka, Japan). NT-proBNP was measured with an automated Cobas analyzer using an electrochemiluminescence immunoassay (Roche Diagnostics, Tokyo). We defined the high-BNP group as patients with a BNP level ≥ 35 pg/ml,¹⁷ and the high-NT-proBNP group as patients with a NT-proBNP level ≥ 125 pg/ml.¹⁷

Echocardiographic measurements

Echography was performed by a trained technician at each participating institute. The two-dimensional M-mode or B-mode image was recorded using an ultrasound machine according to the guidelines of the American Society of Echocardiology (ASE) and the European Association of Echocardiography (EAE).¹⁸ Each patient's left atrial diameter and left ventricular mass were obtained. The E/A was measured in the apical left-chamber long-view or four-chamber view by pulsed wave Doppler.

Follow-up and events

We assessed a composite endpoint consisting of fatal and nonfatal events. Fatal and nonfatal coronary artery disease were defined as acute myocardial infarction or angina pectoris requiring percutaneous coronary intervention or leading to sudden death within 24 h of the abrupt onset of symptoms. Fatal and nonfatal stroke were defined as the sudden onset of a neurologic deficit persisting for ≥ 24 h in the absence of any other disease that could account for the symptoms, with the findings of brain computed tomography or magnetic resonance imaging; transient ischemic attack was not included.

Fatal and nonfatal events included congestive heart failure, subarachnoid hemorrhage, and dissecting aorta. These events were ascertained by ongoing reports from a general physician at each institute. If events occurred on ≥ 2 occasions, the first occurrence was included in the analysis. When patients failed to come to the hospital, we interviewed them and/or their families by telephone. A final follow-up survey to reconfirm the clinical outcomes was performed from September 2014 to March 2015.

Statistical analyses

Data are presented as the mean \pm standard deviation or median (25%, 75%) or a percentage. Comparisons between groups were performed using the χ^2 test of independence for categorical variables and analysis of variance for continuous variables. We analyzed the correlations among non-dipping HR, non-dipping BP, 24-h HR, and 24-h SBP. We compared the cumulative incidences

of total clinical CV events among the four groups: i.e., patients exhibiting dipper HR and normal BNP (NT-proBNP); dipper HR and high BNP (NT-proBNP); non-dipper HR and normal BNP (NT-proBNP); and non-dipper HR and high BNP (NT-proBNP). The numbers of patients in each group were plotted in a Kaplan–Meier curve, and the differences in the rate of CV events among the groups were assessed by the log-rank test. We performed an

Table 1. Baseline characteristics according to heart rate-dipping pattern and brain natriuretic peptide level

	Normal BNP		High BNP		P value
	Dipper HR (n = 817)	Non-dipper HR (n = 181)	Dipper HR (n = 252)	Non-dipper HR (n = 119)	
Age, year	61.3 \pm 11.4	63.5 \pm 10.2	71.9 \pm 9.5	71.0 \pm 9.7	<0.001
Male, %	46.8	55.8	41.3	42.9	0.021
Body mass index, kg/m ²	24.7 \pm 3.5	24.8 \pm 3.5	23.9 \pm 3.6	23.7 \pm 3.0	0.001
Current smoker, %	13.6	14.4	8.3	4.2	0.004
Drinker, %	20.4	32.0	13.5	24.4	<0.001
Hypertension, %	94.5	95.0	90.1	89.1	0.016
Dyslipidemia, %	34.9	32.0	35.3	37.8	0.774
Diabetes mellitus, %	26.1	27.6	25.0	31.1	0.627
CKD, %	19.0	18.8	35.7	40.3	<0.001
Previous CVD, %	9.1	13.8	19.8	28.6	<0.001
BNP, pg/ml	12.5 (7.2, 21.0)	12.7 (8.0, 19.4)	60.5 (44.9, 85.8)	66.2 (46.1, 112.0)	<0.001
NT-proBNP, pg/ml (n = 1,039)	37.2 (20.6, 60.2)	40.4 (23.0, 66.1)	151.8 (92.0, 240.7)	186.0 (121.0, 323.7)	<0.001
Number of anti-hypertensive agents, n	1.5 \pm 1.2	1.8 \pm 1.3	1.9 \pm 1.2	2.2 \pm 1.4	<0.001
Calcium-channel blocker, %	50.9	55.8	59.1	54.6	0.120
ACE inhibitor, %	6.4	7.7	6.0	16.0	0.002
Angiotensin II receptor blocker, %	52.0	53.0	60.0	56.3	0.195
β -Blocker, %	8.4	20.8	18.3	42.0	<0.001
Diuretics, %	27.1	26.5	32.9	35.3	0.101
Statin, %	23.0	23.2	26.6	27.7	0.510
Aspirin, %	13.3	18.2	26.2	35.3	<0.001
Clinic SBP, mm Hg	140 \pm 15	139 \pm 15	141 \pm 18	142 \pm 15	0.436
Clinic DBP, mm Hg	83 \pm 11	81 \pm 11	76 \pm 11	75 \pm 10	<0.001
Clinic HR, bpm	73 \pm 11	72 \pm 11	69 \pm 10	66 \pm 12	<0.001
24-h SBP, mm Hg	131 \pm 12	131 \pm 13	130 \pm 15	130 \pm 12	0.761
24-h-DBP, mm Hg	79 \pm 9	78 \pm 9	74 \pm 9	73 \pm 8	<0.001
24-h-HR, bpm	70 \pm 8	70 \pm 9	65 \pm 8	65 \pm 9	<0.001
Daytime SBP, mm Hg	136 \pm 13	136 \pm 13	134 \pm 16	134 \pm 13	0.286
Daytime DBP, mm Hg	82 \pm 10	81 \pm 9	77 \pm 10	76 \pm 9	<0.001
Daytime HR, bpm	74 \pm 9	70 \pm 9	68 \pm 8	65 \pm 9	<0.001
Nighttime SBP, mm Hg	120 \pm 14	119 \pm 15	122 \pm 17	121 \pm 15	0.189
Nighttime DBP, mm Hg	71 \pm 9	71 \pm 9	68 \pm 9	67 \pm 9	<0.001
Nighttime HR, bpm	60 \pm 7	67 \pm 9	56 \pm 7	62 \pm 9	<0.001

Data are the mean \pm SD or median (25%, 75%) or a percentage. Abbreviations: ACE, angiotensin-converting enzyme; BNP, brain natriuretic peptide; BP, blood pressure; bpm, beats/min; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; HR, heart rate; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; SBP, systolic blood pressure.

Table 2. Parameters of cardiac organ damage among four groups defined by dipper status and BNP level

	Normal BNP		P value	High BNP		P value
	Dipper HR	Non-dipper HR		Dipper HR	Non-dipper HR	
LVMI (g/m ²) (n = 1,213)	93.7 ± 21.1	97.5 ± 28.8	0.120	107.9 ± 29.6	108.3 ± 29.9	0.902
LVEF (%) (n = 1,191)	72.3 ± 7.7	69.9 ± 8.9	0.001	70.6 ± 11.0	70.3 ± 9.5	0.797
LAD (mm) (n = 1,207)	36.5 ± 5.2	36.6 ± 4.4	0.757	38.1 ± 6.0	38.1 ± 5.6	0.998
E/A (n = 1,152)	0.87 ± 0.27	0.86 ± 0.27	0.589	0.80 ± 0.27	0.87 ± 0.35	0.051

Abbreviations: BNP, brain natriuretic peptide; HR, heart rate; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

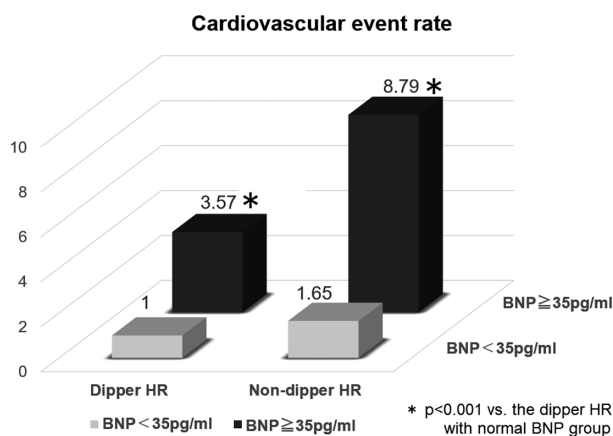


Figure 1. The cardiovascular event rate according to HR and BNP levels. Abbreviations: BNP, brain natriuretic peptide; HR, heart rate.

analysis of variance using the data from the Kaplan–Meier curve. We determined the hazard ratio and 95% confidence interval (CI) of the incidences of total clinical CV events of non-dipper HR and high BNP (models 1–5). We adjusted for age, gender, body mass index (BMI), smoking, drinking, dyslipidemia, diabetes mellitus, and chronic kidney disease (CKD) in model 1; model 2 added BNP to model 1; model 3 added non-dipper BP to model 2; model 4 added 24-h HR to model 3; model 5 added 24-h SBP to model 4. The hazard ratio and 95% CI of the incidences of total clinical CV events in patients with non-dipper HR with high BNP were calculated using Cox regression analyses after adjustments for age, gender, BMI, smoking, drinking, dyslipidemia, diabetes mellitus, CKD, non-dipper BP, 24-h HR, and 24-h SBP (model 6). We also performed a Cox proportional hazard model analysis with log BNP and dipping HR%, with daytime HR and nighttime HR to evaluate the risk of CV events. All statistical analyses were performed with IBM SPSS Statistics ver. 23 software (Chicago, IL), and a probability value <0.05 was considered significant.

RESULTS

Patient characteristics

At baseline, the average age of all patients was 64.4 ± 11.7 years, and the percentage of males was 46%. The non-dipper HR patients (n = 300) were significantly older and were more likely to be using a β-blocker compared with the dipper HR patients (n = 1,069). The BNP level was

significantly higher in the non-dipper HR group compared with the dipper HR group (median BNP 21.6 vs. 17.0 pg/ml, $P < 0.001$). The percentage of patients with the non-dipper BP pattern was not significantly different between the dipper HR and non-dipper HR groups (42.8% vs. 43.0%, $P = 0.938$). We analyzed the correlations among non-dipping HR, non-dipping BP, 24-h HR, and 24-h SBP. Non-dipper HR was not associated with non-dipper BP ($R = 0.002$, $P = 0.94$), 24-h HR ($r = -0.04$, $P = 0.10$), or 24-h SBP ($R = -0.02$, $P = 0.59$).

The characteristics of these four groups established according to HR-dipping pattern and BNP level are summarized in Table 1. The patients with non-dipper HR with high BNP had the highest rate of β-blocker administration, and the highest BNP and NT-proBNP levels. Table 2 shows the numbers of patients with cardiac organ damage in each of the four groups. Among the patients with normal BNP, the left ventricular ejection fraction in those with non-dipper HR was significantly lower than that in those with dipper HR (69.9 ± 8.9% vs. 72.3 ± 7.7%, $P = 0.001$), but there were no significant differences in either left ventricular mass index, left atrial diameter, or E/A according to dipping status. Among the patients with high BNP, the left ventricular ejection fraction in those with the non-dipper HR pattern was not significantly different from that of the patients with dipper HR.

Prognosis

The mean follow-up period was 60 ± 30 months. During the follow-up period, primary endpoints occurred in 23 patients (2.8%) in the dipper HR with normal BNP group, 8 patients (4.4%) in the non-dipper HR with normal BNP group, 24 patients (9.5%) in the dipper HR with high-BNP group, and 25 patients (21.0%) in the non-dipper HR with high-BNP group.

The CV event rates are presented in Figure 1. Among the patients with normal BNP, the dipper HR, and non-dipper HR patterns were not significant factors in CV events. However, in the group of patients with the non-dipper HR pattern and high BNP, the rate of CV events was 8.79 times higher than the rate in the group with the dipper HR pattern and normal BNP. Further, among the patients with high-BNP, those with non-dipper HR showed a high CV event rate that was 2.46 times higher than the CV event rate in patients with a dipper HR pattern.

The Kaplan–Meier curves of the incidence of CV events in the four groups are given in Figure 2. The patients with non-dipper HR and high BNP had a higher incidence

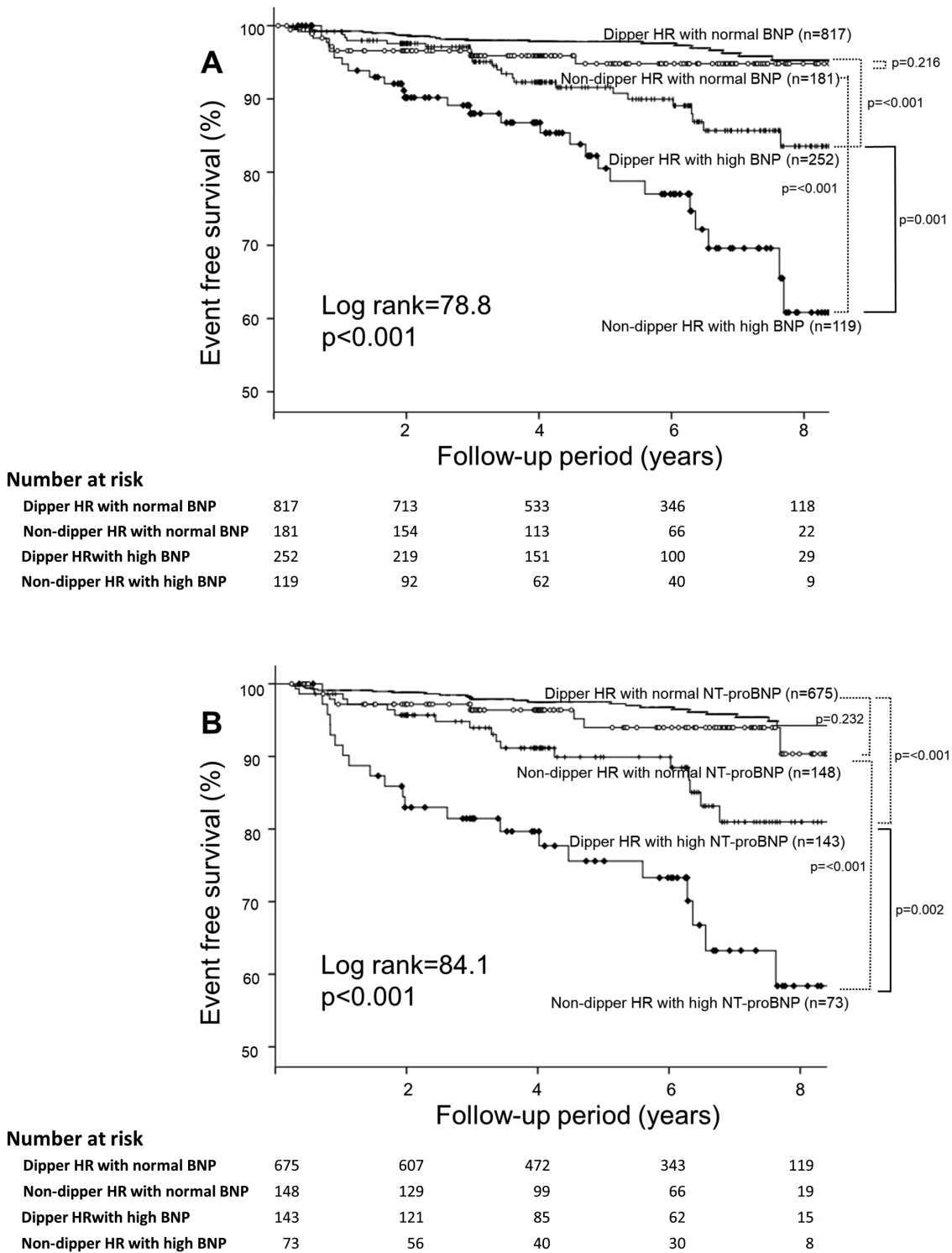


Figure 2. (a) Kaplan–Meier curves for the primary endpoint and different HR and BNP levels (total subjects: $n = 1,369$). (b) Kaplan–Meier curves for the primary endpoint and different HR and NT-proBNP levels (total subjects: $n = 1,039$). Abbreviations: BNP, brain natriuretic peptide; HR, heart rate; NT-proBNP, N-terminal pro-brain-type natriuretic peptide.

of CV events than the patients in the other three groups combined (log rank = 78.8, $P < 0.001$; Figure 2a). The patients with non-dipper HR and high BNP had significantly poorer prognoses compared with the patients

with dipper HR and high BNP ($P = 0.001$). There were no significant differences in the prognoses of the patients with normal-BNP between according to dipper status ($P = 0.216$).

Cox proportional hazard model

We used a Cox proportional hazard model to evaluate the risk of CV events (Table 3). We also performed a Cox proportional hazard model with log BNP and dipping HR% to evaluate the risk of CV events (Supplementary Table S1 online). The hazard ratio of dipping HR% (per -10%) was 1.43 (95% CI 1.07–1.89) and that of log BNP was 3.95 (95% CI 2.36–6.63) after adjusting for age, gender, BMI, smoking, drinking, dyslipidemia, diabetes mellitus, and CKD. Before adjustment, the non-dipper HR status significantly predicted an increased risk of CV events (hazard ratio, 2.72; 95% CI, 1.75–4.25; $P < 0.001$). The non-dipper HR pattern was an independent predictor of the primary endpoint (hazard ratio, 2.13; 95% CI, 1.35–3.36; $P = 0.001$) after adjusting for the parameters of model 5. We performed a Cox proportional hazard model to further analyze the categories derived by non-dipping HR status and BNP status in model 6. Even after adjustment, non-dipper HR with high BNP remained an independent predictor of the primary endpoint (hazard ratio, 6.96; 95% CI, 3.73–13.0; $P < 0.001$). We performed receiver operating characteristic curves and area under curve analyses to assess the discriminative ability of the combination of non-dipping HR and high BNP for the incidental risk of CV events; the area under curve was 0.613. We also performed a Cox proportional hazard model with daytime HR and nighttime HR to evaluate the risk of CV events. The hazard ratio of daytime HR (per 10 bpm) was 0.51 (95% CI 0.34–0.77), and that of nighttime HR (per 10 bpm) was 1.87 (95% CI 1.22–2.85) after adjusting for age, gender, BMI, smoking, drinking, dyslipidemia, diabetes mellitus, and CKD (Supplementary Table S2 online).

Analysis of the association between non-dipper HR, NT-proBNP, and CV events

We also analyzed the primary endpoint among the four groups divided according to HR dipper/non-dipper and NT-proBNP levels. The Kaplan–Meier curves of the incidence of CV events in the four groups are shown in Figure 2b. The patients with non-dipper HR and high NT-proBNP also had a higher incidence of CV events compared with the patients in the other three groups (log rank = 84.1, $P < 0.001$; Figure 2b). In addition, the patients with non-dipper HR and high NT-proBNP had significantly poorer prognoses than the patients with dipper HR and high NT-proBNP ($P = 0.002$).

Analysis for patients without β -blockers

We also analyzed the patients after excluding those taking β -blockers. Even in patients without β -blockers, patients with non-dipper HR and high BNP had a significantly higher incidence of CV events than patients in the other three groups (log rank = 46.0, $P < 0.001$; Figure 3a), and patients with non-dipper HR and high NT-proBNP also had a significantly higher incidence of CV events than patients in the other three groups (log rank = 52.5, $P < 0.001$; Figure 3b).

DISCUSSION

This study is the first to show that general practice outpatients (patients with a history of or risk factors for cardiovascular disease, or both) exhibiting the non-dipper HR pattern and having high BNP have poorer prognoses than those with the dipper HR pattern and high BNP.

Table 3. Cox regression analysis for cardiovascular events (total subjects: $n = 1,369$)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	Hazard ratio (95% CI)	<i>P</i>	Hazard ratio (95% CI)	<i>P</i>	Hazard ratio (95% CI)	<i>P</i>	Hazard ratio (95% CI)	<i>P</i>	Hazard ratio (95% CI)	<i>P</i>	Hazard ratio (95% CI)	<i>P</i>
Non-dipper HR	2.29 (1.46–3.60)	<0.001	2.02 (1.28–3.18)	0.003	2.09 (1.32–3.29)	0.002	2.09 (1.33–3.30)	0.001	2.13 (1.35–3.36)	0.001	—	—
BNP ≥ 35 pg/ml	—	—	3.53 (2.15–5.80)	<0.001	3.36 (2.04–5.53)	<0.001	3.46 (2.07–5.76)	<0.001	3.27 (1.96–5.46)	<0.001	—	—
Non-dipper HR with high BNP	—	—	—	—	—	—	—	—	—	—	6.96 (3.73–13.0)	<0.001
Non-dipper BP	—	—	—	—	1.58 (0.99–2.51)	0.055	1.59 (1.00–2.54)	0.051	1.63 (1.02–2.60)	0.040	1.65 (1.03–2.63)	0.036
24-h HR, 10 bpm	—	—	—	—	—	—	1.07 (0.81–1.41)	0.634	1.03 (0.78–1.36)	0.826	1.04 (0.79–1.37)	0.767
24-h SBP, 10 mm Hg	—	—	—	—	—	—	—	—	1.21 (1.03–1.42)	0.023	1.20 (1.02–1.42)	0.027

In model 1, the hazard ratio and 95% CI were adjusted for age, gender, BMI, smoking, drinking, dyslipidemia, diabetes mellitus, and CKD. In model 2, the hazard ratio and 95% CI were adjusted for age, gender, BMI, smoking, drinking, dyslipidemia, diabetes mellitus, CKD, and BNP. In model 3, the hazard ratio and 95% CI were adjusted for age, gender, BMI, smoking, drinking, dyslipidemia, diabetes mellitus, CKD, BNP, and non-dipper BP. In model 4, the hazard ratio and 95% CI were adjusted for age, gender, BMI, smoking, drinking, dyslipidemia, diabetes mellitus, CKD, BNP, non-dipper BP, and 24-h HR. In model 5, the hazard ratio and 95% CI were adjusted for age, gender, BMI, smoking, drinking, dyslipidemia, diabetes mellitus, CKD, BNP, non-dipper BP, 24-h HR, and 24-h SBP. In model 6, the hazard ratio and 95% CI were adjusted for age, gender, BMI, smoking, drinking, dyslipidemia, diabetes mellitus, CKD, non-dipper BP, 24-h HR, and 24-h SBP. Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; bpm, beats/min; CI, confidence interval; CKD, chronic kidney disease; HR, heart rate; SBP, systolic blood pressure.

In this study, even among patients with a normal BNP level, those with non-dipper HR had lower ejection fraction, while among patients with a high BNP level, those with non-dipper HR had higher CV events. The increase in CV risk factors and CV events among patients with

a non-dipper HR pattern differed between the normal and high-BNP groups. These results demonstrate that a helpful risk classification could be made by investigating the dipping HR pattern, especially in patients with high BNP.

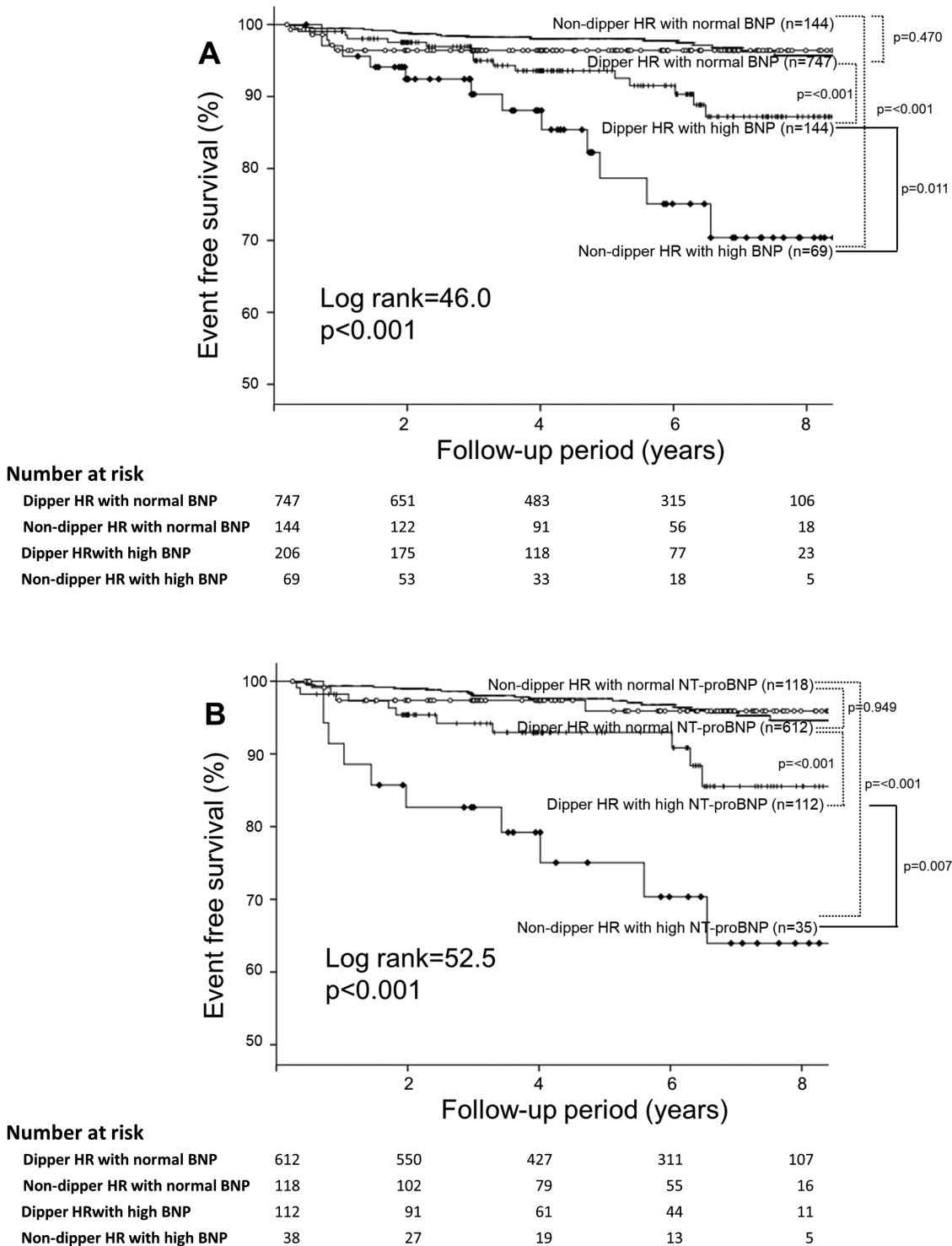


Figure 3. (a) Kaplan–Meier curves for the primary endpoint and different HR and BNP levels (patients without β -blockers: $n = 1,166$). (b) Kaplan–Meier curves for the primary endpoint and different HR and NT-proBNP levels (patients without β -blockers: $n = 877$). Abbreviations: BNP, brain natriuretic peptide; HR, heart rate; NT-proBNP, N-terminal pro-brain-type natriuretic peptide.

Cuspidi *et al.* investigated the HR change between the daytime and nighttime in a general clinical outpatient population; they reported that the lowest-quartile group in nocturnal HR reduction ($\leq 13\%$) had a 1.8-fold greater risk of CV events than the highest-quartile group ($>23\%$).¹⁹ In an analysis of 457 uncomplicated hypertensive patients, Eguchi *et al.* reported that the patients with the non-dipper HR pattern had a 2.37-fold higher risk of CV events compared with the patients with the dipper HR pattern.⁹ Ben-Dov *et al.* reported a 2.67-fold greater incidence of all-cause death in a group of hypertensive patients with blunted nocturnal HR.¹² Verdecchia *et al.* demonstrated that non-dipper HR status was significantly associated with CV events even after the adjustment for traditional risk factors in untreated hypertensive patients, but the significance of the association disappeared after further adjustment for average 24-h SBP.²⁰ In the present study, we observed a 2.72-fold increased risk of CV events in the non-dipper HR group before correction, and a 2.29-fold increased risk remained even after adjustment by age, sex, BMI, smoking, diabetes, dyslipidemia, and CKD. When we added $\text{BNP} \geq 35$ to age, sex, BMI, smoking, diabetes, dyslipidemia, and CKD, the risk was still significantly increased at 2.02-fold.

Moreover, among the patients with high BNP in our study, those exhibiting the non-dipper HR pattern had a 2.46-fold higher CV event rate than those with the dipper HR pattern. BNP is not only a surrogate marker for organ damage but also a predictor of CV events. In the Framingham Heart Study, Wang *et al.* showed that a high-BNP level was an independent predictor of CV events and mortality.¹⁴ Our present findings demonstrated for the first time that the combination of the non-dipper HR pattern and a high-BNP value confers a high risk of CV events in individuals at coronary risk. Oba *et al.* reported a relationship between the non-dipper HR status and BNP in a cross-sectional study.¹⁵ In our study, the non-dipper HR status was still associated with CV events even after adjustment for BNP, left ventricular mass index, and the left atrial diameter. The size of the left atrium is associated with left ventricular pressure and volume overload, and the left atrial diameter has been shown to independently predict CV death, congestive heart failure, atrial fibrillation, and stroke.²¹ Cuspidi *et al.* reported an increase in the left atrial volume before the appearance of left ventricular hypertrophy, and showed this cardiac organ damage was related to the non-dipper HR pattern.¹⁹ However, in our present study there was no significant difference in the left atrial diameter between the dipper HR and non-dipper HR groups. Among patients in the normal BNP group, those with non-dipper HR had lower left ventricular ejection fraction. These results might indicate that both an elevated BNP pattern and a non-dipper HR pattern are in fact biological markers of left ventricular dysfunction or failure, and non-dipper HR may be useful for CV prediction. Nonetheless, this finding is still interesting and may be useful in CV prediction. Our analyses revealed that the non-dipper HR status was independently associated with CV events even after adjustment for cardiac organ damage, including the left atrial diameter.

In this study, the non-dipper HR pattern was associated with a high incidence of CV events, but only among the patients with high-BNP levels. BNP reflects both

volume overload and pressure overload, and is related to abnormal hemodynamics of nighttime BP rise and BP daily fluctuation.²² Venous perfusion is increased by being in a supine position for nighttime sleep, and thus the HR is usually decreased by a feedback mechanism for controlling BP.²³ In our previous study we reported that increased delta HR by body posture (upright HR – supine HR) was positively associated with the BNP and left ventricular mass index, and might indicate potential cardiac overload.²⁴ Moreover, patients with CV risk are known to exhibit an impaired baroreceptor reflex.^{25,26} As a result, the decrease in physiological nocturnal HR is impaired, resulting in a non-dipper HR pattern. A similar physiological mechanism might be at play in patients with high BNP. The non-dipper HR pattern might be caused by enhanced sympathetic activity at night, concomitant with the resulting organ disorder. Our results suggest that a high-BNP level and the non-dipper HR status might be useful for the risk stratification of CV events.

LIMITATIONS

There were several limitations in this study. First, because this was an observational study, the results do not allow us to determine the causal relationship between BNP levels and the non-dipper HR pattern. An interventional study in a different population is needed. Second, the numbers of events were relatively low in the general population. Further studies including a larger number of patients will be needed to assess the association among CV events, BNP levels, and the non-dipper HR pattern. Third, we did not investigate variables such as physical activity, alcohol consumption and quality of sleep, all of which have been shown to influence circadian variations in HR.

SUPPLEMENTARY MATERIAL

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

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