

SUPPLEMENTAL MATERIAL

Nighttime Blood Pressure Phenotype And Cardiovascular Prognosis: The Practitioner-Based JAMP Study

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SUPPLEMENTAL METHODS

Study design

The JAMP (Japan Ambulatory Blood Pressure Monitoring Prospective) study was designed to investigate the prognostic impact of ambulatory blood pressure monitoring (ABPM) parameters in general practice. Participants were recruited by general practitioners from 36 prefectures around Japan if they fulfilled the inclusion and exclusion criteria.

ABPM recordings were performed at baseline, and patient demographic and clinical data were collected (including age, sex, body mass index, smoking status, habitual drinking, prevalence of hypertension, diabetes and dyslipidemia, pre-existing coronary artery disease, heart failure or stroke, and use of antihypertensive medication. Patient history data were obtained from medical records.

The next phase was patient follow-up. This was an observational study, and therefore there were no specific recommendations with respect to management of patients, including frequency of visits, type of drug treatment or blood pressure (BP) goal, and no data on BP level or antihypertensive drug use were recorded during follow-up. Practitioners were instructed to carefully report and document all outcome events that occurred during the follow-up and were asked each year about the morbidity and mortality status of the patients. If there was no response to the initial query, practitioners (and then patients) were telephoned by a study physician.

In Japan, there are 47 administrative divisions (prefectures). In 36 of the prefectures, 130 doctors at 116 institutions (72 primary practices, 40 hospital-based outpatient clinics, and 3 specialized university hospitals) agreed with the aims of this study and collected baseline and prospective data from individuals who agreed to participate in this project.

Study inclusion and exclusion criteria

Inclusion criteria:

Patients with at least one of the following cardiovascular risk factors:

- a. Diabetes or glucose tolerance disorder (receiving antidiabetic treatment, or fasting blood sugar ≥ 110 mg/dL, or ≥ 140 mg/dL in a 2-hour 75g oral glucose tolerance test)
- b. Dyslipidemia (receiving lipid-lowering therapy, or total cholesterol > 240 mg/dL)
- c. Hypertension (receiving antihypertensive therapy, or office BP $\geq 140/90$ mmHg or home BP $\geq 135/85$ mmHg)
- d. Current smoker
- e. Renal disease (positive proteinuria or serum creatinine ≥ 1.1 mg/dL)
- f. Atrial fibrillation
- g. Metabolic syndrome
- h. Chronic obstructive pulmonary disease
- i. Sleep apnea syndrome

Exclusion criteria:

Patients with at least one of the following criteria:

- a. Ischemic heart disease, cerebrovascular disease (except for asymptomatic or transient ischemic attack), aortic dissection, chronic arterial obstruction or history of heart failure requiring hospitalization within 6 months
 - b. Requiring hemodialysis
 - c. Any other severe diseases (e.g. cancer, connective tissue disease)
 - d. Inability to provide informed consent (e.g. age < 20 years, cognitive dysfunction)
 - e. Unable to walk unaided (use of cane permitted)
-

Data processing

Each individual used a diary to record information about the times of falling asleep and waking up. After wearing the ABPM device for ≥ 24 hours, participants returned to the clinic where ABPM data were downloaded from the device and electronic data files were sent to the study control center. Data management and statistical analysis were conducted in an independent facility (Jichi Medical University Center of Global Home and Ambulatory BP Analysis [GAP], Jichi Medical University Center of Excellence Community Medicine Cardiovascular Research and Development [JCARD], Shimotsuke, Japan).

Outcome determination

Annual follow-up visits were conducted to determine vital status and the incidence of fatal and nonfatal cardiovascular events. If no clinic follow-up visit was planned, investigators or study secretariat telephoned or sent letters to patients to get the required information.

Cardiovascular disease events were included as follows:

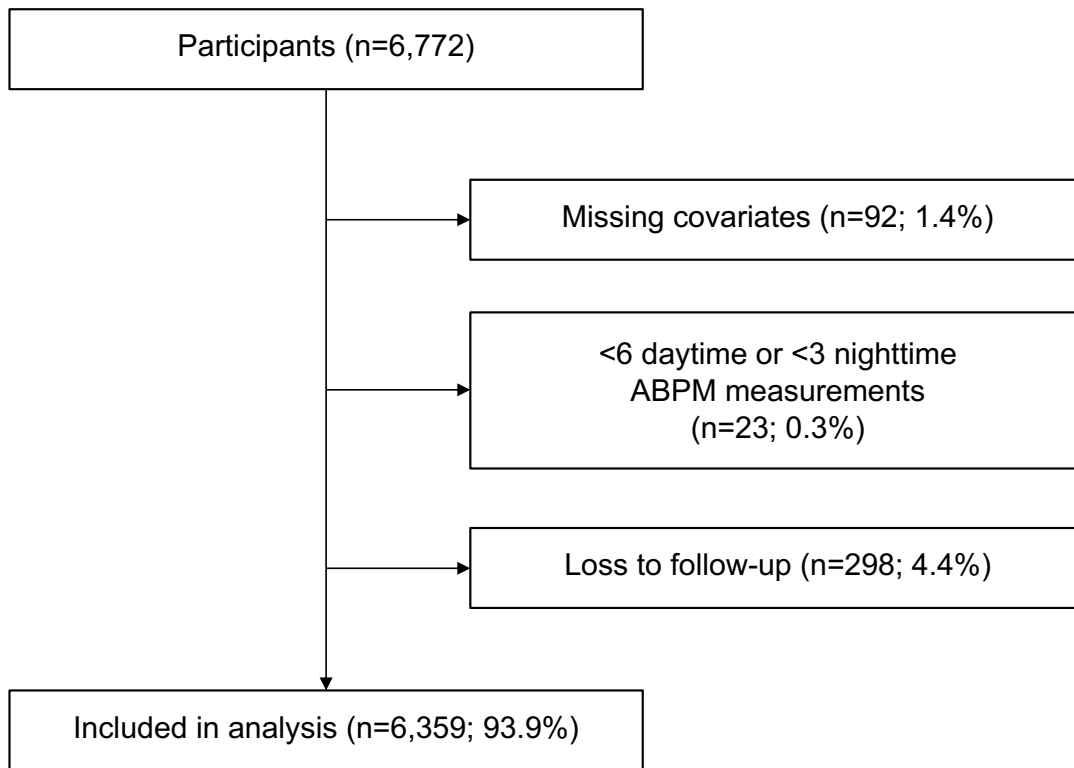
- Atherosclerotic cardiovascular disease (including coronary artery disease and stroke, as defined below)
- Coronary artery disease: acute myocardial infarction, angina pectoris requiring percutaneous coronary intervention, and sudden death within 24 hours of the abrupt onset of symptoms (criteria for myocardial infarction included definite electrocardiographic findings [i.e. ST elevation], typical or atypical symptoms and electrocardiographic findings and abnormal enzymes, or typical symptoms and abnormal cardiac enzymes with or without electrocardiographic findings)
- Stroke (including cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage): sudden onset of neurological deficit persisting for at least 24 hours in the absence of any other disease that could account for the symptoms based on the findings

of brain computed tomography, magnetic resonance imaging or autopsy (transient ischemic attacks, in which the neurological deficit was completely resolved within 24-hr of the onset of symptoms, were not counted as stroke events)

- Heart failure: an event requiring hospital admission due to clinical manifestations of heart failure such as the presence of dyspnea, systemic edema or edema in lower limbs, third heart sound, pulmonary congestion or cardiac dilation on chest X-ray, reduced systolic/diastolic function on echocardiography, and requirement for treatment

SUPPLEMENTAL FIGURES AND FIGURE LEGENDS

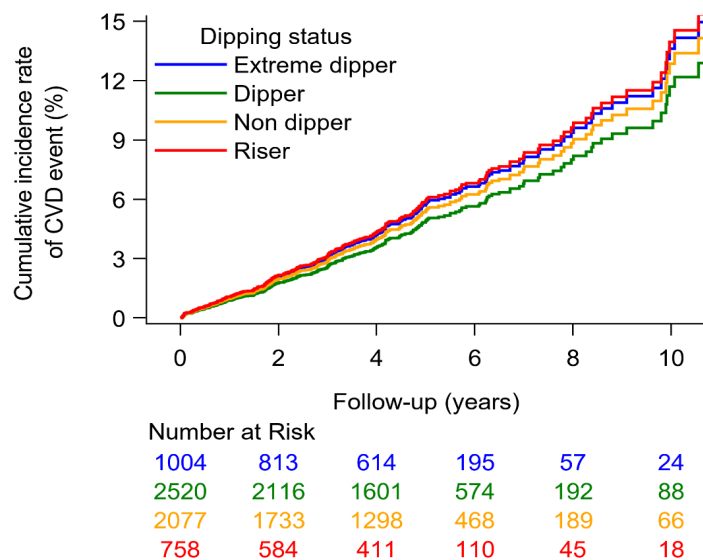
Supplemental Figure I. Flow chart of study participants



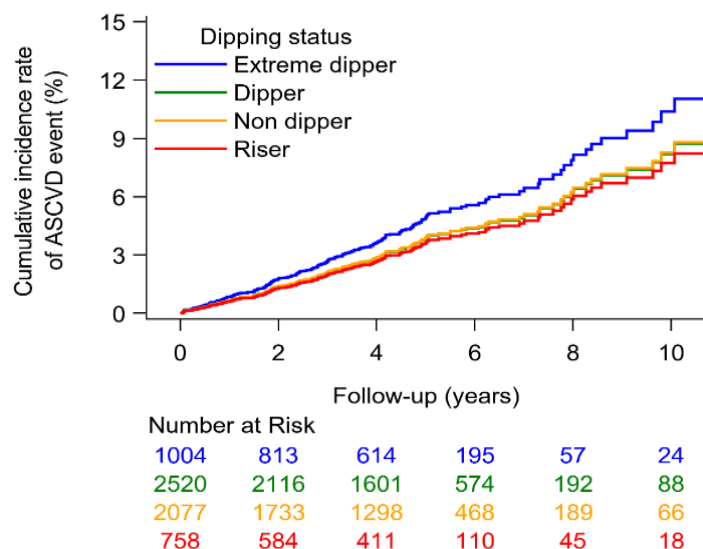
Supplemental Figure II. Cumulative incidence of different cardiovascular disease events by dipping status (adjusted for age, sex, body mass index, smoking, alcohol use, diabetes, dyslipidemia, history of cardiovascular disease, use of antihypertensive drugs, bedtime dosing, office systolic blood pressure, and nighttime systolic blood pressure).

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CVD, cardiovascular disease.

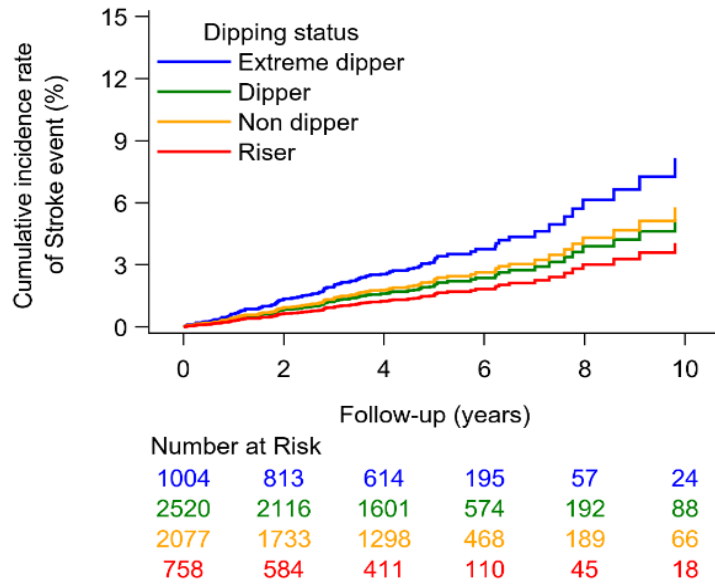
CVD



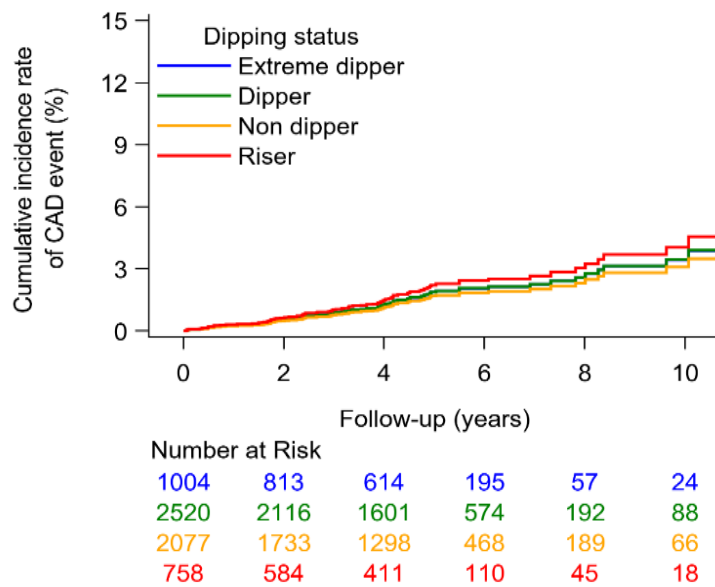
ASCVD



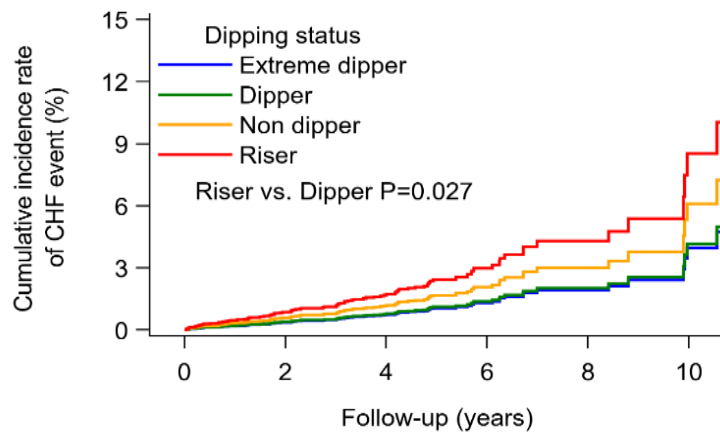
Stroke



CAD



Heart failure



Number at Risk

1004

813

614

195

57

24

2520

2116

1601

574

192

88

2077

1733

1298

468

189

66

758

584

411

110

45

18

SUPPLEMENTAL TABLES

Supplemental Table I. Incidence of cardiovascular disease events by dipping status of nighttime systolic blood pressure

	n	Total CVD (ASCVD + HF)		ASCVD						HF	
				ASCVD (Stroke + CAD)		Stroke		CAD			
		Events	Per 1000 pt-yrs (95% CI)	Events	Per 1000 pt-yrs (95% CI)	Events	Per 1000 pt-yrs (95% CI)	Events	Per 1000 pt-yrs (95% CI)	Events	Per 1000 pt-yrs (95% CI)
Extreme dipper	1,004	38	8.7 (6.3–11.9)	31	7.1 (5.0–10.0)	19	4.3 (2.8–6.8)	12	2.7 (1.6–4.8)	7	1.6 (0.8, –3.3)
Dipper	2,520	97	8.4 (6.9–10.2)	75	6.5 (5.2–8.1)	38	3.3 (2.4–4.5)	37	3.2 (2.3–4.4)	22	1.9 (1.3–2.9)
Non dipper	2,077	114	11.9 (10.0–14.3)	79	8.3 (6.6–10.3)	46	4.8 (3.6–6.4)	33	3.5 (2.5–4.9)	35	3.7 (2.6–5.1)
Riser	758	57	18.4 (14.2–23.8)	33	10.7 (7.6–14.9)	16	5.2 (3.2–8.4)	17	5.5 (3.4–8.8)	24	7.8 (5.2–11.5)

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; pt, patient;; yrs, years.

Supplemental Table II. Improvements in model performance (net reclassification improvement)

	Total CVD		ASCVD				HF			
	(ASCVD + HF)		ASCVD (Stroke + CAD)		Stroke		CAD		NRI (95% CI)	p-value
	NRI (95% CI)	p-value	NRI (95% CI)	p-value	NRI (95% CI)	p-value	NRI (95% CI)	p-value		
Base model	–	–	–	–	–	–	–	–	–	–
Base model + 24-hour SBP*	0.154 (0.048, 0.277)	0.018	0.178 (0.046, 0.312)	0.012	0.163 (–0.039, 0.306)	0.088	0.192 (–0.019, 0.378)	0.071	0.131 (–0.091, 0.397)	0.312
Base model + daytime SBP*	0.080 (–0.048, 0.210)	0.250	0.075 (–0.077, 0.220)	0.330	0.177 (–0.024, 0.348)	0.067	–0.039 (–0.263, 0.175)	0.721	0.049 (–0.169, 0.359)	0.724
Base model + nighttime SBP*	0.150 (0.026, 0.275)	0.011	0.134 (–0.000, 0.271)	0.054	0.170 (–0.034, 0.318)	0.077	0.117 (–0.089, 0.359)	0.243	0.199 (–0.006, 0.443)	0.093
Base model + dipping status*	0.200 (0.059, 0.324)	0.003	0.153 (–0.021, 0.276)	0.056	0.170 (–0.068, 0.353)	0.089	0.162 (–0.042, 0.357)	0.098	0.413 (0.180, 0.625)	<0.001
Base model + 24-hour SBP + dipping status†	0.111 (–0.062, 0.229)	0.107	0.164 (–0.012, 0.284)	0.042	0.170 (–0.068, 0.353)	0.089	0.043 (–0.150, 0.190)	0.642	0.293 (0.082, 0.553)	0.013
Base model + daytime SBP + dipping status†	0.200 (0.022, 0.293)	0.006	0.082 (–0.137, 0.209)	0.335	0.170 (–0.069, 0.352)	0.090	0.104 (–0.061, 0.279)	0.266	0.342 (0.096, 0.585)	0.004

Base model +										
nighttime SBP +	0.072		0.212		0.271		-0.001		0.202	
dipping status [†]	(-0.067, 0.244)	0.358	(0.064, 0.339)	0.004	(0.083, 0.505)	0.023	(-0.190, 0.176)	0.995	(-0.025, 0.470)	0.098

Base model includes age, sex, body mass index, smoking, alcohol use, diabetes, dyslipidemia, history of cardiovascular disease, use of antihypertensive drugs, nighttime prescription, and office systolic blood pressure.

*p-values are differences of base model vs. base model + 24-hour SBP or + daytime SBP or + nighttime SBP or +dipping status.

[†]p-values are differences of base model + ABPM indices vs. base model + ABPM indices + dipping status.

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; NRI, net reclassification improvement; SBP, systolic blood pressure.

Supplemental Table III. Improvements in model performance (integrated discrimination improvement)

	Total CVD		ASCVD				HF			
	(ASCVD + HF)		ASCVD (Stroke + CAD)		Stroke	CAD		IDI (95% CI)	p-value	
	IDI (95% CI)	p-value	IDI (95% CI)	p-value	IDI (95% CI)	p-value	IDI (95% CI)			
Base model	–	–	–	–	–	–	–	–	–	
Base model + 24-hour SBP*	0.0033 (0.0017, 0.0052)	<0.001	0.0024 (0.0015, 0.0033)	<0.001	0.0017 (0.0012, 0.0028)	<0.001	0.0011 (0.0004, 0.0019)	0.003	0.0014 (–0.0005, 0.0037)	0.123
Base model + daytime SBP*	0.0015 (0.0004, 0.0024)	0.003	0.0016 (0.0009, 0.0023)	<0.001	0.0014 (0.0010, 0.0022)	<0.001	0.0006 (0.0001, 0.0011)	0.029	0.0000 (–0.0001, 0.0001)	0.759
Base model + nighttime SBP*	0.0053 (0.0030, 0.0075)	<0.001	0.0025 (0.0016, 0.0035)	<0.001	0.0013 (0.0007, 0.0020)	<0.001	0.0020 (0.0010, 0.0029)	<0.001	0.0062 (0.0013, 0.0125)	0.014
Base model + dipping status*	0.0030 (0.0015, 0.0046)	<0.001	0.0006 (0.0002, 0.0009)	0.001	0.0003 (0.0000, 0.0006)	0.020	0.0014 (0.0006, 0.0022)	0.002	0.0087 (0.0038, 0.0146)	0.004
Base model + 24-hour SBP + dipping status [†]	0.0021 (0.0008, 0.0034)	0.002	0.0003 (0.0000, 0.0006)	0.030	0.0003 (–0.0011, 0.0007)	0.181	0.0011 (0.0005, 0.0019)	0.002	0.0078 (0.0030, 0.0135)	0.004
Base model + daytime SBP + dipping status [†]	0.0035 (0.0015, 0.0054)	<0.001	0.0008 (0.0002, 0.0013)	<0.001	0.0003 (–0.0000, 0.0007)	0.043	0.0016 (0.0007, 0.0024)	<0.001	0.0091 (0.0039, 0.0146)	0.004

Base model +										
nighttime SBP +	0.0005		0.0004		0.0008		0.0005		0.0032	
dipping status [†]	(-0.0000, 0.0010)	0.109	(0.0002, 0.0007)	0.004	(0.0004, 0.0014)	0.001	(0.0000, 0.0010)	0.067	(0.0005, 0.0080)	0.065

Base model includes age, sex, body mass index, smoking, alcohol use, diabetes, dyslipidemia, history of cardiovascular disease, use of antihypertensive drugs, nighttime prescription, and office systolic blood pressure.

*p-values are differences of base model vs. base model + 24-hour SBP or + daytime SBP or + nighttime SBP or +dipping status.

[†]p-values are differences of base model + ABPM indices vs. base model + ABPM indices + dipping status.

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; IDI, integrated discrimination improvement; SBP, systolic blood pressure.