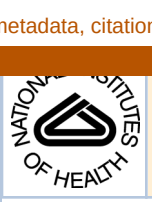

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Nocturnal Non-dipping Of Heart Rate Predicts Cardiovascular Events In Hypertensive Patients

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Abstract

Objective—It is not established whether nocturnal non-dipping of heart rate predicts future cardiovascular disease. We performed this study to test the hypothesis that nocturnal non-dipping of heart rate predicts the risk of incident cardiovascular disease (CVD) independent of nocturnal BP dipping pattern.

Methods—Ambulatory blood pressure monitoring was performed in 457 uncomplicated patients, who were being treated or evaluated for hypertension. They were followed for an average of 72 ± 26 months. Non-dipping heart rate was defined as a night/day heart rate ratio greater than 0.90. We chose two outcomes for this analysis: CVD events (defined as stroke, myocardial infarction, or sudden cardiac death), and all-cause mortality. Cox regression analyses (stepwise method) were used to estimate hazard ratios and their 95%CI, after adjusting for covariates.

Results—In univariate analysis, increased sleep heart rate and non-dipping of heart rate were associated with increased risk of CVD and all-cause mortality, but awake heart rate was not. In multivariable analyses, heart rate non-dipping status significantly predicted an increased risk of CVD events (hazard ratio=2.37, 95%CI=1.22–4.62, P=0.01), but not for all-cause mortality. Increased 24-hour heart rate was significantly associated with increased risk of all cause mortality (hazard ratio=1.67, 95%CI=1.11–2.51, P=0.01).

Conclusions—The risk of future CVD was shown to be 2.4 times as great in those whose heart rate does not exhibit the typical nocturnal decline. The relationship was independent of non-dipping of SBP and did not dependent on diabetes status or BP level.

Keywords

non-dipping of heart rate; cardiovascular disease; ambulatory blood pressure monitoring

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Introduction

Numerous studies have reported that increased heart rate was a risk factor for all-cause mortality [1–7], and cardiovascular disease (CVD) [2–6, 8]. Heart rate is one of the simplest measures of hemodynamics in humans, and could be a marker of general health [5], but it is affected by a variety of conditions such as anemia or physical activity. Regardless of many publications in this theme, the 2006 European Society of Hypertension consensus document recommended further research [9].

Ambulatory blood pressure (ABP) monitoring is regarded as one of the standard methods for the prediction of risk related to blood pressure (BP) because of its good predictability of prognosis [10]. In addition to ABP levels, abnormal circadian rhythms of BP, such as non-dipping or nocturnal rising (inverted dipping), have been reported to be associated with advanced target organ damage and future CVD events [11,12]. In addition, there was a report that a non-dipping pattern of heart rate is associated with increased risk of all cause mortality in epidemiological settings [13–15]. Heart rate evaluated by ABP monitoring indicates both resting and dynamic changes of cardiovascular activity, and should be a better predictor of CVD events than resting heart rate, in the same way as occurs in measures of BP. However, the evidence of ambulatory heart rate on CVD or non-CVD prognosis is not well investigated, and it is still a subject of debate whether ambulatory heart rate is a predictor of future CVD events [13–19]. Therefore we tested the hypothesis that ambulatory heart rate predicts future CVD in patients with hypertension in clinical settings.

Methods

This prospective observational study was performed in a sample of uncomplicated 457 asymptomatic patients with (n=200) or without (n=257) type 2 diabetes who were seen for the evaluation of hypertension in general internal medicine clinics at 3 participating institutes in Japan: 1 clinic and 2 hospitals in the Karatsu-Nishiarita Study [20].

During the period of recruitment, 1996–2002 for the Karatsu-Nishiarita Study, patients were enrolled consecutively while being treated or evaluated for hypertension in the clinic, and agreed to undergo ABP monitoring (ABPM). Hypertension was diagnosed, according to current guidelines [21], when the clinic systolic BP (SBP) was at least 140 and/or diastolic BP (DBP) was at least 90 mmHg on at least two occasions or when the patient had a previous diagnosis of hypertension and was currently using at least one antihypertensive medication. Clinic BP was measured at least twice on two separate occasions after at least 5 minutes of rest in the sitting position and after being fitted with an ABPM. Patients who were taking medications (N=251, 55%) stopped antihypertensive medications for 14 days preceding the ABPM study. Certain patients who were not willing to stop medications long period or considered to be high risk stopped medication for 5 to 7 days [3 (3.0%) in heart rate non-dipper group and 21 patients (5.9%) in heart rate dipper group (P=0.3)]. Type 2 diabetes was diagnosed according to the guidelines of the American Diabetes Association [22] or a previous diagnosis and currently taking anti-diabetic medication. We excluded patients with type 1 or secondary diabetes, renal dysfunction (serum creatinine >1.8 mg/dl), hepatic damage, ischemic heart disease or other cardiac diseases, congestive heart failure, arrhythmias (including atrial fibrillation), stroke (including transient ischemic attacks), or other major concomitant non-cardiovascular diseases. Body mass index (BMI) was calculated as weight /height^2 (kg/m^2). Smoking was defined as current smoking. This study was approved by the Institutional Review Board of each participating hospital or clinic. All the patients studied were ambulatory and gave informed consent for the study.

Ambulatory BP monitoring

Noninvasive ABPM was performed on a weekday with an automatic system (TM2421 or TM2425, A&D, Tokyo) which recorded BP by the oscillometric method and heart rate every 30 minutes for 24 hours. These devices have been previously validated [23]. Awake and sleep time were defined based on patients' diaries recorded during ABPM. Awake, sleep, and 24-hour BP/heart rate were defined as the average of all BP/heart rate in each category. The night-day ratio of BP and heart rate were calculated as sleep/awake ratio of BP and heart rate.

Mean awake and sleep levels of SBP and DBP were computed and the nocturnal BP fall (%) was calculated as (awake SBP–sleep SBP)/awake SBP. Nocturnal BP fall was classified as follows: dipper if the nocturnal BP fall was >10%, non-dipper if it was >0% but <10%, and riser if it was <0% [11, 12, 24].

Follow-up and events

The patients' medical records were reviewed every year after ABPM for the purpose of identifying any new onset of CVD, and all non-CVD events. The 457 participants enrolled in 1996–2002 for the Karatsu-Nishiarita Study were followed from March 2004 to February 2008 for up to 10 years. All patients remained on therapy in the outpatient clinics, and all of them were treated and followed by every 1–2 months. Participants who died from non-cardiovascular causes were also reviewed annually. The average follow-up period was 71.6 ± 25.8 months (range: 9 to 120 months). When patients did not visit the clinics, we interviewed them by telephone. We chose two outcomes for this analysis: CVD events and all-cause mortality. CVD events were defined as either stroke, fatal or non-fatal myocardial infarction (MI), or sudden cardiac death. Soft CVD events such as angina pectoris, congestive heart failure, end-stage renal disease, peripheral artery disease and transient ischemic attack were not included in this study. All-cause mortality included cancer, blood diseases, and infections such as pneumonia, but death from accidents were not included. Stroke or cardiac events were diagnosed by the physician, caring for the patient at the time of the event, and independent neurologists or cardiologists reviewed the cases and confirmed the diagnosis. Stroke was diagnosed on the basis of sudden onset of a neurological deficit that persisted for >24 hours in the absence of any other disease process that could explain the symptoms. Stroke events included ischemic stroke (cerebral infarction and cerebral embolism), hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage), and undefined types of stroke [11]. MI was diagnosed based on the American Heart Association criterion of "definite" MI [25].

Statistical analyses

All statistical analyses were carried out with SPSS/Windows, version 13.0 (SPSS Inc., Chicago, Illinois). The data are expressed as the mean (± SD) or percentage. The chi-square test was used to compare proportions and evaluate the association of categorical variables. Unpaired t -test was performed to test mean differences between groups. Kaplan-Meier survival charts were generated to determine a difference in event rate between patients with heart rate dippers and heart rate non-dippers. The log-rank statistic was used to test the differences between Kaplan-Meier survival curves. Backward stepwise Cox regression models were used to calculate hazard ratios and 95% confidence intervals (CI) of outcome events. The null hypothesis was rejected when two-tailed $P<0.05$.

Results

During the follow-up period, the numbers of events were 37 for CVD events, 29 for all-cause mortality. At baseline, the mean age was 66.9 ± 9.2 years; there were 172 men and

285 women; 44% of patients were type 2 diabetes; 55 % of patients were taking antihypertensive medication. The number of non-dipper was 185 out of 457 (40.5%), which was higher than that of 46/131 (35.1%) by Kario [24], 266/1187 (22.4%) by Verdecchia [26], 526/1542 (34.1%) by Ohkubo[12]; however, the rate of non-dippers was smaller than previous reports of diabetes: 63.9% by Cuspidi [27] and 58% by Brotman [28].

Baseline characteristics are shown in Table 1. The percentage of current smokers was higher in heart rate non-dippers than in heart rate dippers, but the age, sex, BMI, sleep time, antihypertensive medications taken, lipids, and serum creatinine were similar between the groups. The numbers of patients who were taking beta-blockers were similar between the heart rate non-dipper and dipper groups (2.0% vs. 5.0%, P=0.3). The mean duration of diabetes was also similar between the groups (5.1 ± 7.8 yrs in heart rate non-dippers and 4.6 ± 7.3 yrs in dippers). Clinic BP was higher in the heart rate dipper group, but ambulatory BP profiles were similar between the groups. As defined, sleep heart rate and night-day ratio of heart rate were higher in the heart rate non-dipper group, but awake heart rate was higher in the heart rate dipper group than in the counterparts. The correlation between night/day ratio of SBP and night/day ratio of heart rate was significant (r=0.16, P=0.001), but the correlation between heart rate non-dipper and non-dipping of SBP was not significant (P=0.9).

In univariate analysis, non-dipping of heart rate showed a significant relationship with both CVD events and all-cause mortality (Table 2). Increased sleep heart rate was significantly associated with increased risk of CVD events and all-cause mortality, but awake heart rate was not (Table 2). In multivariable analyses, being in the heart rate non-dipper was associated with a 2.4 times increased risk of CVD events (Table 3). On the other hand, the heart rate non-dipper was not associated with all-cause mortality, while increased sleep heart rate was significantly associated with increased risk of all-cause mortality (Table 3). The relationship did not change even after smoking was eliminated from this model.

Discussion

In this observational study, heart rate non-dipping status evaluated by ABPM was significantly associated with increased risk of CVD, even after adjustment for covariates, including BP dipping status. This is in agreement with previous results by showing the positive relationship between heart rate non-dipper and CV events in *clinical settings* [16].

It has been extensively reported that resting or ambulatory heart rate was a predictor of all cause mortality [2,13,15–19], and CV mortality [2] in hypertensive populations. These studies were performed in epidemiological settings using databases consisting of large numbers of patients, and these studies rarely adjusted a degree of anemia or 24-hour heart rate [2,13,15–19]. Regarding the relationship between ambulatory heart rate and prognosis, we are also reporting that a higher heart rate is associated with all-cause mortality. However, in terms of ambulatory heart rate and CV prognosis, few studies have reported a positive finding [14], and some of them reported that heart rate adds little information on the prediction of CVD events [16,17,19]. In a recent report from Japan, heart rate non-dipping was associated with all-cause mortality [15], but not with CVD events. The strength in these studies was that they used CV *mortality* as a robust outcome in their epidemiological database. In practice, CV *morbidity* would be as important as CV mortality. In the present study, although the number of patients was relatively small, we could almost perfectly follow up both CVD and non-CVD events, which could enable us to see practical impacts of heart rate dipping status on the outcomes.

It is not established whether non-dipping of heart rate can be a risk factor for CVD events, in contrast to the established relationship of non-dipping of *blood pressure*. In previous studies, it was discussed that the reduced dipping of sleep heart rate was a risk of all-cause mortality [13–15] and CV mortality [14], because the lack of withdrawal during sleep can represent the status of sympathetic overdrive. Disruption of the circadian variation of autonomic nerve system is the key as we showed the association with advanced cerebrovascular damage [29], and CVD [30]. Higher heart rate caused by sympathetic overdrive could be associated with insulin resistance or direct atherogenetic action on the arteries through increased wall stress [31, 32]. In the present study, although awake heart rate was significantly lower in the heart rate non-dipper group than in the heart rate dipper group, awake heart rate would not be a good marker of sympathetic drive as it is dependent on physical activity and fitness. On the other hand, sleep heart rate was a better marker of mortality than awake or clinic heart rate [13]. Abnormal circadian variation of heart rate would reflect autonomic nerve imbalance which could be associated with adverse prognosis.

In the present study, non-dipping of heart rate was associated with CVD events. There are several possible reasons for the differences in our results from previous studies, which could be the differences of study subjects and design. Our study is clinically based; nearly half of our population had diabetes mellitus; we had detailed follow up of CV events; and ambulatory heart rate was measured without any antihypertensive medications. The adjustment of covariates should be sufficient [9] except for the lack of information about physical activity. The lack of association between non-dipping of SBP and CVD events in our study could be explained by its high prevalence of SBP non-dippers because of the high prevalence of diabetes [30], and the simultaneous inclusion of heart rate dipping and SBP dipping into the models as heart rate non-dipper might outweigh the effect of SBP dipping. As shown in Table 2, non-dipping of SBP has a marginal association with CVD (P=0.08) and a significant association with all-cause mortality (P=0.006), which were lower than those of SBP riser pattern (P=0.01, P=0.003, respectively) in this population. The relationship between SBP dipping pattern and CV events looked like a J-curve, but statistically, it was linear relationship. The relationship between SBP dipping pattern and all-cause mortality was also linear.

With regard to pathophysiologic mechanisms, Ben-Dov et al [13] discussed the possibility that the link between non-dipping heart rate and all-cause mortality could be due to low fitness, and the presence of subclinical CV disease. Palatini et al [17] suggested that the cause of this association was the clustering of several risk factors in subjects with fast heart rate, and sympathetic overactivity. In our population, none of the patients were frail patients, and other risk factors were adjusted satisfactory. But we cannot exclude the influence of subclinical CV disease such as left ventricular hypertrophy, chronic kidney disease, or silent brain infarction, or other conditions such as chronic tiredness or obstructive sleep apnea.

As shown in Table 2, riser pattern was more predictive of CVD events than non-dipping of SBP in this population. When riser pattern (yes or no) was entered in the models of Table 3 in place of non-dipping of SBP, non-dipping of heart rate disappeared for all-cause mortality, but survived for CVD. The higher impact of heart rate non-dipper than SBP non-dipper on the incident CVD might be because heart rate non-dipper might be more closely associated with autonomic neuropathy which is a strong predictor for future CVD events.

There are some limitations in this study. First, the relatively small sample size and small number of events are major limitations of this study. Second, we did not adjust physical activity as a covariate. However, physical activity was rarely adjusted in previous studies. In the present study, because all of the patients were independent in their daily life and came to the clinics regularly, adding it does not seem to change the results. Third, the approach to

stop antihypertensive medications has been commonly used in previous studies of ABPM. Although the clinic BP level was high, the BP level does not always reflect control status of BP. In the present study, clinic BP was measured was in temporally untreated state for treated patients, or untreated state for newly diagnosed hypertensive patients. The patients were treated adequately based on the treatment guidelines of hypertension, and that resulted in relatively fewer numbers of events. The clinic BP level was almost similar to previous reports: 159/98mmHg for dippers and 166/98mmHg for non-dippers by Verdecchia [26]; 172–174/91–98mmHg by Kario [24], conventional BP 173/86mmHg by Staessen [33], clinic BP 160–170/91–93 mmHg in the Dublin Outcome Study [34]. Although clinic heart rate may reflect sympathetic activity, the clinic heart rate was similar between the two groups. Finally, nearly half of this population has diabetes and the results may not be applicable to a non-diabetic population.

In conclusion, the risk of CVD was shown to be 2.4 times as great in those whose heart rate did not exhibit the usual nocturnal decline. The significant relationship was also seen between 24-hour heart rate and all cause of death. Therefore, in addition to ambulatory BP parameters, non-dipping pattern of heart rate and ambulatory heart rate levels should be taken into account as a risk assessment in patients with hypertension in clinical practice.

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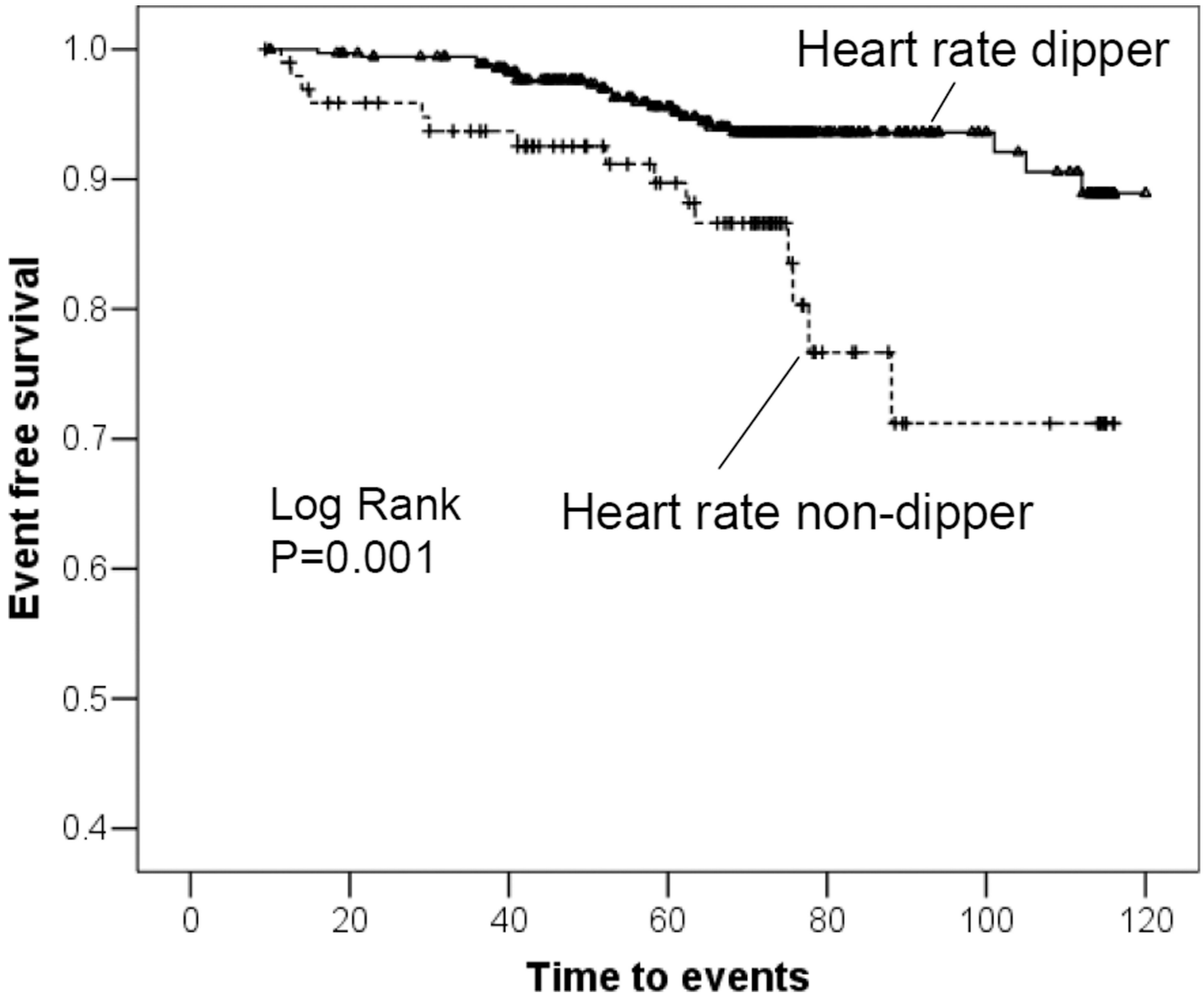

Figure 1.
Event-free survival without a cardiovascular event curves by non-dipping or dipping of heart rate groups. Log-rank statistic between the groups is 11.8 (*P*=0.001).

Table 1

Baseline Characteristics of Subjects

	HR non-dipper (n=99)	HR dipper (n=358)	P
Age (years)	68.2±9.7	66.5±9.0	0.10
Sex (% male)	45.5	35.5	0.08
BMI (kg/m^2)	23.5±3.8	24.0±3.3	0.20
Current smokers (%)	36.4	22.1	0.006
Diabetes (%)	47.5	42.7	0.40
Antihypertensive medication (%)	53.5	55.3	0.82
Sleep time (hrs)	8.4±1.4	8.4±1.4	0.93
Hematocrit (%)	40.5±4.7	40.0±4.0	0.33
Total cholesterol (mg/dL)	201±32	204±35	0.57
Triglycerides (mg/dL)	126±57	123±67	0.66
Serum creatinine (mg/dL)	0.77±0.19	0.77±0.21	0.84
Clinic SBP (mmHg)	150±20	155±20	0.03
Clinic DBP (mmHg)	82±12	85±12	0.01
Clinic HR (bpm)	71±11	73±12	0.13
24-hour SBP (mmHg)	141±17	140±17	0.72
24-hour DBP (mmHg)	79±9	80±10	0.38
24-hour HR (bpm)	69±9	68±8	0.36
Awake SBP (mmHg)	146±17	146±18	0.91
Awake DBP (mmHg)	82±9	83±10	0.29
Awake HR (bpm)	70±10	72±9	0.02
Sleep SBP (mmHg)	131±20	129±18	0.26
Sleep DBP (mmHg)	73±9	73±10	0.90
Sleep HR (bpm)	67±9	59±8	<0.001
Night-day ratio of SBP	0.90	0.89	0.13
Night-day ratio of DBP	0.89	0.88	0.25
Night-day ratio of HR	0.96	0.82	<0.001

Data are shown as means ± SD or percentages.

SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate.

Table 2

Univariate analysis for predicting cardiovascular events and all-cause mortality

Covariates	Cardiovascular disease Hazard ratio (95% CI)	P	All cause mortality Hazard ratio (95% CI)	P
Age (per 5 years)	1.48 (1.21–1.80)	<0.001	1.63 (1.30–2.05)	<0.001
Male sex (%)	1.54 (0.80–2.97)	0.19	3.29 (1.55–7.00)	0.002
Body mass index (kg/m^2)	1.03 (0.94–1.12)	0.55	0.89 (0.79–1.00)	0.05
Diabetes (yes or no)	1.89 (0.96–3.72)	0.064	1.63 (0.77–3.45)	0.2
Current smoking (yes or no)	1.57 (0.77–3.19)	0.21	3.90 (1.87–8.11)	<0.001
Antihypertensive medications	1.83 (0.92–3.64)	0.087	1.07 (0.51–2.22)	0.86
Total cholesterol (per mmol/l)	1.10 (0.76–1.59)	0.61	0.67 (0.44–1.00)	0.052
Creatinine (per μmol/l)	1.02 (1.00–1.04)	0.016	1.02 (1.00–1.04)	0.037
Clinic systolic BP (10mmHg)	1.15 (0.98–1.34)	0.09	1.27 (1.06–1.52)	0.01
24-hr systolic BP (per 10 mmHg)	1.04 (1.02–1.06)	<0.001	1.04 (1.01–1.06)	<0.001
24-hr heart rate (per 10 bpm)	1.10 (0.75–1.63)	0.63	1.60 (1.05–2.46)	0.03
Awake heart rate (per 10 bpm)	0.98 (0.68–1.41)	0.91	1.32 (0.88–1.97)	0.17
Sleep heart rate (per 10 bpm)	1.47 (1.00–2.16)	0.049	2.17 (1.44–3.28)	<0.001
Non-dipping of systolic BP (yes or no)	1.78 (0.93–3.42)	0.082	3.00 (1.37–6.59)	0.006
Riser pattern of SBP (yes or no)	2.46 (1.21–4.99)	0.01	2.58 (1.40–4.77)	0.003
Non-dipping of heart rate (yes or no)	3.00 (1.55–5.80)	0.001	2.38 (1.10–5.13)	0.028

Table 3

Multivariable Cox Regression anlysis for Predicting Cardiovascular Events and All-cause Mortality

Covariates	Cardiovascular disease Hazard ratio (95% CI)	P	All cause mortality Hazard ratio (95% CI)	P
Non-dipping of heart rate (yes or no)	2.37 (1.22–4.62)	0.01	-	
Age (per 5 years)	1.39 (1.12–1.71)	0.002	1.55 (1.23–1.94)	<0.001
sex (male=1, female=0)	-		2.29 (0.92–5.69)	0.075
Diabetes (yes or no)	2.37 (1.18–4.76)	0.02	-	
Current smoking (yes or no)	-		1.94 (0.79–4.77)	0.15
Creatinine (per μmol/l)	1.02 (1.00–1.04)	0.03	-	
24-hr SBP (per 10 mmHg)	1.03 (1.01–1.05)	0.002	1.03 (1.01–1.05)	0.001
Sleep heart rate (per 10 bpm)	-		2.11 (1.37–3.26)	0.001

Backward stepwise Cox regression analysis was used.

Covariates entered in this model was Non-dipping of heart rate, age (per 5years), sex, body mass index, presence of diabetes (yes or no), current smoking (yes or no), antihypertensive meds (yes or no), total cholesterol (mg/dl), serum creatinine (per 0.1mg/dl), 24-hour SBP (per 10mmHg), Sleep heart rate (per 10bpm), non-dipping of SBP (yes or no).