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Association of Diurnal Blood Pressure Pattern with Risk for Hospitalization or Death in Men with Heart Failure

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Abstract

Background—An altered diurnal blood pressure (BP) pattern has been linked to risk of developing heart failure (HF). We tested whether an altered diurnal BP pattern is associated with adverse outcomes (hospitalization due to HF exacerbation or death) in HF patients.

Methods and Results—One hundred eighteen HF patients were enrolled from a tertiary care HF clinic and followed for death or heart failure hospitalization for up to 4 years. 24-hour ambulatory BP was monitored. Forty patients (34%) had normal BP dipping pattern (night-day ambulatory BP ratio < 0.9), 44 (37%) had a non-dipping pattern (0.9 ≤ night-day ambulatory BP ratio < 1.0) and 34 (29%) had a reverse dipping BP pattern (night-day ambulatory BP ratio ≥ 1.0). A total of 39 patients had an adverse outcome. Adverse outcome rates were the lowest in dippers and the highest in reverse dippers (Log rank p=0.052). Predictors of adverse outcomes, selected based on log likelihood contrast, were NYHA functional class (Hazard ratio (HR) 1.96, 95% confidence interval (CI) 1.11-3.44), anemia (HR 2.50, 95% CI 1.23-5.08) and dipping status (HR 1.65, 95% CI 1.08-2.50).

Conclusions—In addition to other traditional predictors, blood pressure dipping status may be an important prognostic factor in HF.

Introduction

Blood pressure (BP) varies minute to minute[1] and BP variability may be an important prognostic factor in cardiovascular disease.[2,3] Although conventional office-based BP monitoring is the basis of diagnosis and treatment of hypertension, it does not consider the variations of BP throughout the day. Alternatively, 24-hour ambulatory BP monitoring can capture this variability and provides additional information about the circadian pattern of BP.[2] Numerous studies in hypertension have shown that 24-hour ambulatory BP data are better predictive of adverse cardiovascular outcomes than office-based BP.[4-7] The diurnal BP pattern is also an important piece of data which 24-hour ambulatory BP monitoring can provide. While

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there are considerable data regarding diurnal BP patterns in patients with hypertension, there is much less information on the diurnal BP pattern in patients with heart failure (HF). Recently, the reverse nighttime BP dipping pattern, in which mean nighttime BP is higher than mean daytime BP, was associated with a 2.2-fold higher incidence of HF in 951 Swedish patients.[8] Regarding HF prognosis, only one study has considered 24-hour ambulatory BP data.[9] This study reported that mean 24-hour systolic BP <105 mmHg was significantly associated with increased risk of death in severe HF patients, however only 38 patients were studied and the circadian pattern of BP was not evaluated. Thus, the aim of our study was to examine 24-hour ambulatory BP data in a larger group of patients, and to determine whether diurnal BP patterns are associated with prognosis in patients with symptomatic HF.

Methods

Patients and protocol

The study was a part of a Care Coordination-Home Telehealth program, which started in 2001 at the Malcom Randall Veterans Affairs Medical Center, Gainesville, Florida. Only patients who were enrolled by September 20, 2005 were included for analysis, so that there was a minimum 1 year follow-up on all patients. The study design has been previously published.[10] Briefly, adult veterans with chronic HF were enrolled in the study. Inclusion criteria were symptomatic (New York Heart Association (NYHA) functional class II-IV) HF with documented left ventricular ejection fraction <40%, age greater than 18 years old, active enrollment in the primary care clinic, and new onset (within 6 months) or difficult-to-manage symptoms of HF. Patients were excluded for a documented history of medication noncompliance and for active substance abuse. The protocol was reviewed and approved by the local Institutional Review Board, and all patients gave written informed consent prior to participating in the study.

At baseline, demographic characteristics, weight, height, HF etiology, left ventricular ejection fraction, serum sodium and creatinine levels, blood hemoglobin level, NYHA functional class, and medication profile were recorded. Patients with a documented history of myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft or > 50% diameter stenosis of any of the three major epicardial coronary arteries were classified as having ischemic HF. Other patients were classified as having nonischemic HF. Left ventricular ejection fraction was determined by 2-dimensional echocardiography. Glomerular filtration rate was estimated by a Modification of Diet in Renal Disease equation.[11] Anemia was defined as blood hemoglobin level <13 g/dL in men and <12 g/dL in women.[12]

Ambulatory BP and heart rate were recorded over a 24-hour period during the patient's normal daily activities. The monitors (A&D Medical, Milpitas, CA, model TM-2430EG), which have been validated,[13] were programmed to obtain readings at intervals of not more than 30 minutes between 8 a.m. and 10 p.m. and at intervals of not more than 60 minutes between 10 p.m. and 8 a.m. Criteria for acceptable BP and heart rate recordings included: 1) a minimum of 75% of readings were available for interpretation, and 2) BP and heart rate readings were physiologically reasonable.

Patients were followed in clinic or by telephone for up to 4 years. The primary outcome was time to death or hospitalization due to HF exacerbation, whichever came first. There were two secondary outcomes: 1) time to death and 2) time to hospitalization due to HF. Death was confirmed via medical record and/or population death registry. Hospitalization was confirmed with medical record review or patient interview. Duration of follow-up was defined as the interval from the date of enrollment to the date of the first adverse outcome, the last contact or the study closure.

Statistical analysis

The Statistical Analysis System (SAS, Version 9.1) was used for data analyses. Data are expressed as mean ± standard deviation unless indicated otherwise. Daytime was defined from 9 a.m. to 9 p.m. and nighttime was defined from 1 a.m. to 6 a.m. based on a fixed time method.[14] Mean daytime and nighttime BPs and heart rates were calculated from hourly averages of each parameter during the periods above. The fixed time method, where early morning and late evening periods are excluded for 24-hour ambulatory BP data analysis, is a commonly used analysis approach due to a number of potential advantages. Specifically, this approach results in less BP variation between the old and the young, and essentially eliminates the effects of sleeping patterns, including cultural differences in sleeping patterns, on the diurnal BP pattern.[14] Patients were stratified by diurnal BP pattern: Dippers were defined as patients with night to day mean ambulatory systolic blood pressure (SBP) ratio <0.9, non-dippers were defined as patients with a ratio between 0.9 and 1.0, and reverse dippers were patients with a ratio of ≥ 1.0.

Continuous variables were compared among the strata by analysis of variance and pair-wise t-test using the Bonferroni correction method. Adverse outcome rates were estimated by Kaplan-Meier analysis and were compared among the strata by log rank test. Variables with a *p*-value <0.1 in the univariable proportional hazard analyses were entered into the multivariable proportional hazard models. Models were selected based on log likelihood contrast. Final models were checked by the Cox-Snell residuals method. As exploratory analyses, death and hospital admission due to HF exacerbation were analyzed as secondary outcomes by Kaplan-Meier and proportional hazard analyses.

The fixed time method may introduce biases, by excluding some BP data obtained over the 24-hour period. Thus, as a sensitivity analysis, all the data collected were also analyzed by defining daytime as an interval from 6 a.m. to 11 p.m. and nighttime as an interval from 11 p.m. to 6 a.m. A *p*-value < 0.05 was considered statistically significant.

Results

A total of 118 patients were included for analysis. When they were stratified by nighttime BP dipping pattern, 40 (34%) were dippers, 44 patients (37%) were non-dippers and 34 (29%) were reverse dippers. Table 1 shows baseline characteristics of the study cohort stratified by nighttime BP dipping pattern. Only estimated glomerular filtration rate, percent of patients with diabetes and percent of patients treated with antihyperlipidemics were different among the strata. However, only for the estimated glomerular filtration rate was there an ordered relationship between dipping status and the parameters of interest. Over 90% of the study cohort received pharmacotherapy recommended by the consensus HF management guidelines: 91% of patients received either an angiotensin-converting enzyme inhibitor (ACEI, mostly fosinopril (56%)), an angiotensin receptor blocker (ARB) or both, and 90% of patients received a β-blocker (mostly metoprolol (84%)) at baseline. Importantly, proportions of the patients who received these drug classes were not statistically different among the strata. Also, there were 37% of patients who were prescribed diuretics more often than once a day. However, the frequency of diuretic administration was not associated with dipping status (p=0.4446 by Chi-square test). This suggests that frequency of diuretic administration may not play a role in confounding our data.

There were no differences in clinic SBP and DBP among patients with different diurnal BP patterns (Table 2). However, for data collected by 24-hour ambulatory blood pressure monitoring, all BP categories except for mean daytime DBP were significantly different among the strata. As expected, BPs tended to be lowest in dippers although daytime BPs were similar between non-dippers and reverse dippers. Thus daytime ambulatory data would not allow us

to separate these two groups. There were also no differences in distribution of hypertension as a co-morbidity or in heart rate (Table 1 and Table 2).

There were a total of 39 primary outcome events (deaths or hospitalizations, whichever came first) that occurred over a median 2-year follow-up (Table 3, Primary Outcomes). Kaplan-Meier analysis showed a trend suggesting that dippers had the lowest cumulative primary outcome rate and reverse dippers had the highest rate (Figure 1, log rank p=0.052). Seven variables including nighttime BP dipping status (dipper, non-dipper and reverse dipper) had a p-value <0.1 in univariable proportional hazard regression analyses (Table 4). When contrasted by -2log likelihood values among different multivariable models that included all permutations of the seven variables, a model with 3 variables was the most parsimonious one with all coefficients not statistically zero (Table 5). In this model, NYHA functional class and anemia were significantly associated with increased risk of death or hospitalization with hazard ratios (HRs) of 1.96 (95% confidence interval (CI) 1.11-3.44) and 2.50 (95% CI 1.23-5.08), respectively. In addition, HRs in non-dippers vs. dippers and reverse dippers vs. dippers were 1.65 (95% CI 1.08-2.50) and 2.72 (95% CI 2.29-3.13), respectively. This suggests that nighttime BP dipping status is a significant predictor of the primary outcome. The model appeared to fit the data well when it was verified by the Cox-Snell residuals method. Since BP readings in patients with atrial fibrillation may be inaccurate,[15] and 29% of our patients had atrial fibrillation, a repeat analysis was conducted excluding the patients with atrial fibrillation. Our findings remained valid in this reanalysis, where we noted that NYHA functional class (HR 2.25, 95% CI 1.02-4.94) and dipping status (HR 2.14, 95% CI 1.21-3.77) remained significantly associated with the primary outcomes.

In the secondary analysis, there were 25 deaths and 24 patients with hospitalizations. Ten patients experienced both events, with hospitalization as their first event, followed by death (Table 3; Secondary Outcomes). Secondary outcome analyses showed that the cumulative death rate differed significantly by strata (log rank p=0.04), with the lowest death rate in dippers and the highest in reverse dippers (12.5% in dippers vs. 20.5% in non-dippers vs. 32.3% in reverse dippers). In addition, dipping status was significantly associated with death rate (HR 1.90, 95% CI 1.13-3.20) after adjustment for NYHA functional class (HR 2.15, 95% CI 1.05-4.39) and anemia (HR 2.71, 95% CI 1.13-6.50). However, the cumulative hospitalization rate was not associated with nighttime BP dipping status. Sensitivity analysis showed that when all the ambulatory blood pressure data collected over 24 hours were utilized, dipping status was of borderline statistical significance in death or hospitalization (p=0.06). In this analysis, the HRs of each of the three variables (NYHA functional class, anemia and dipping status) were 2.02 (95% CI 1.16-3.54), 2.42 (95% CI 1.20-4.86) and 1.60 (95% CI 0.98-2.62), respectively, which was consistent with the results from the fixed time method.

Discussion

To our knowledge, this is the largest study to date of diurnal BP patterns in patients with established severe chronic heart failure. Additionally, ours is the first report to identify that the diurnal BP pattern, measured by 24-hour ambulatory BP monitoring, is an independent prognostic factor in symptomatic HF patients. Specifically, non-dippers and reverse dippers had 1.65-fold and 2.72-fold higher risk of death or hospitalization due to HF exacerbation than dippers, after adjustment for several known prognostic factors. The presence of NYHA functional class and anemia in our model as significant prognostic factors supports the validity of the model since NYHA functional class and anemia have been identified as prognostic factors for HF in other studies.[16-18] In addition, since dipping status was not associated with NYHA functional class (Fisher's exact test p=0.5735), dipping status may be a prognostic factor independent of NYHA functional class. Our sensitivity analysis results also support the validity of the model.

Other studies addressing prognostic factors in heart failure have found additional clinical variables that are commonly associated with poor prognosis. However, these prognostic factors are not identical across studies, with left ventricular ejection fraction being an example of a variable that is positively associated with prognosis in some studies[19,20] but not others.[21, 22] This is likely explained by a number of factors, including the population sample size, the severity of HF in the population, and the clinical variables that are considered, among others. Thus, the fact that our analysis did not reveal LVEF or renal function to be significantly associated with prognosis, does not invalidate our model, since significant prognostic factors are often different across studies.

We did not see an association between adverse outcomes and the use of β-blockers or ACE inhibitors in our study, which is likely due to the fact that over 90% of our study cohort received these drug classes at baseline and the drug therapy was maintained throughout the study. In addition, this suggests that diurnal BP pattern may be an important prognostic factor in HF patients even among those treated with appropriate pharmacotherapy as recommended by HF management guidelines.[23] This also implies that HF patients without a nighttime BP dipping pattern may require more diligent monitoring and/or additional therapy.

Although the results of our secondary outcomes should be viewed as exploratory, it is interesting that we saw a significant association of nighttime BP dipping pattern with cumulative death rate while there was no association with cumulative hospitalization rate. This may be explained in part by the intensive monitoring and follow-up that patients receive through the Telehome care program, with benefits including increased patient adherence to treatment, thereby reducing the total number of inpatient hospital days.[10] On the other hand, this intensive monitoring program would not be expected to be able to have the same influence on preventing death as preventing hospitalizations.[24] The physiological basis of our findings is not currently clear. However, the non-dipping BP pattern during the night has been associated with an elevated level of sympathetic activity[25] and this elevated sympathetic activity plays a key role in HF progression.[26] In our study, heart rates were not different for any period (Table 2), nor was the median β-blocker dose at baseline different among the patients with different diurnal BP pattern (median: 50 mg/day of metoprolol equivalent dose in all strata, p=0.32 by the Kruskal-Wallis test). These data suggest that the patients in each stratum had a similar degree of β-blockade with similar β-blocker doses. Therefore, it seems that subtle alterations in the sympathetic nervous system in the non-dippers rather than generalized elevation in sympathetic activity *per se* may have contributed to the outcome differences in our study. In fact, there are data that non-dippers may have higher sensitivity of vascular α_1-adrenergic receptors than dippers, even with similar degrees of β-adrenergic receptor responsiveness.[25] Given that 84% of our population received metoprolol, which has no α_1-adrenergic receptor blocking effects, the dipping status differences may have been larger than would be observed with carvedilol, which blocks α_1-adrenergic receptors.

Abnormal activity of the parasympathetic nervous system has also been noted to be an important prognostic factor in heart failure, reflected by decreased heart rate variability.[27, 28] Since 24 hour ambulatory electrocardiographic data are needed for thorough assessment of heart rate variability, and such data are not available in this study, we cannot exclude that the findings regarding BP dipping status and outcomes are somehow related to heart rate variability.

Perhaps the most likely explanation for our findings is that the differences in nighttime BP are markers for obstructive sleep apnea,[29] which consequently contributed to the adverse outcomes.[30] In our study, 6 patients (5%) had a diagnosis of obstructive sleep apnea at baseline. Because our study population is almost exclusively male, among whom the prevalence of sleep apnea in HF (11 to 37%)[31,32] is higher than our reported range, sleep apnea was probably

under-diagnosed in our study population. Recently, it has been found that mortality is significantly higher in chronic HF patients with sleep apnea compared to patients without sleep apnea.[33] Therefore, further research is needed to evaluate the link between BP dipping patterns in HF, sleep apnea and adverse outcomes.

Our study supports the importance of measuring 24-hour ambulatory BPs (Table 2). Clinic SBP and DBP were not statistically different among the strata. However, almost all BP data by 24-hour ambulatory BP monitoring were statistically different among the strata, and reverse dippers had significantly higher mean nighttime SBP and DBP than dippers and non-dippers. If BP had been taken only in the clinic, these differences could not have been appreciated. Therefore, our data provide evidence that BPs obtained by 24-hour ambulatory BP may be more predictive of adverse cardiovascular outcomes than office-based BP in HF, just as is the case in hypertension.[6,7] In addition, it is important to note that the diurnal BP patterns noted in these HF patients were different from those previously reported in patients with hypertension. Specifically, evidence of a reverse dipper pattern is scant in the hypertension literature. Further, only 34% of HF patients in our study were classified as dippers while numerous studies suggest that 60-70% of hypertension patients are dippers.[3,34,35] What is consistent between the hypertension literature and this study of HF patients is that those with the dipper phenotype have the best outcomes. Further studies are needed to elucidate why the rate of nondipping and reverse dipping is so much higher in HF than in hypertension.

A small sample size is one of the limitations of our study. Because of its nature as a non-experimental study, unmeasured biases might also have been introduced. The fact that our ambulatory BP monitor has not been validated in patients with atrial fibrillation is a limitation of the study. However, some data suggest that 24-hour ambulatory BP monitoring can be successfully used in patients with atrial fibrillation,[36,37] and a reanalysis of the data with exclusion of atrial fibrillation patients supports our primary conclusions. In addition, the patients may have received greater than usual care because they were closely followed by cardiology nurses under the Care Coordination-Home Telehealth program, which might have differentially affected adverse outcomes among the strata. Since our study cohort is almost entirely comprised of males, our data may not be applicable to female HF patients given that women have better survival rates than males with heart failure.[38] Finally, we do not have multiple determinations of the 24-hour ambulatory blood pressure in any of our patients, which may be a limitation of our study.

If our findings could be replicated in a larger cohort, this would suggest that 24-hour ambulatory BP monitoring should be routine in patients with symptomatic systolic HF, in order to identify those at high risk of adverse cardiovascular outcomes. Further, if replicated, our results would suggest that future studies may also need to focus on the high risk group of non-dippers and reverse dippers to identify therapies that might improve their outcomes.

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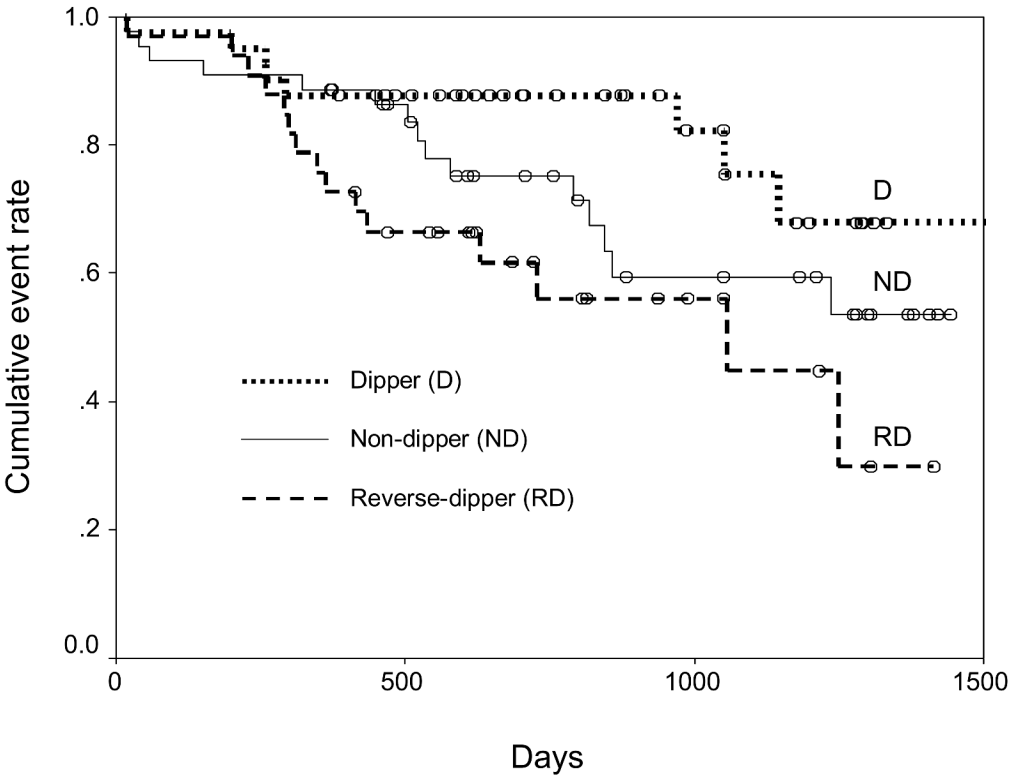

Figure 1.
Cumulative adverse outcome rate among the strata (log rank p=0.052). Dipper = Night to day mean ambulatory systolic blood pressure ratio <0.9, Non-dipper = 0.9 ≤ Night to day mean ambulatory systolic blood pressure ratio <1.0, Reverse dipper = Night to day mean ambulatory systolic blood pressure ratio ≥1.0.

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Table 1

Baseline characteristics by nighttime BP dipping status

Variable	N=118	Dipper (N=40)	Non-dipper (N=44)	Reverse dipper (N=34)
Age (years)	65 ± 12.2	63.5 ± 13.7	66.8 ± 11.1	67.0 ± 11.7
Male	117 (99%)	40 (100%)	43 (98%)	34 (100%)
Caucasians	104 (88%)	36 (90%)	37 (84%)	31 (91%)
Ischemic etiology	87 (74%)	32 (80%)	29 (66%)	26 (76%)
Heart failure duration > 1 year	79 (67%)	25 (63%)	33 (75%)	21 (62%)
NYHA functional class				
II	41 (36%)	14 (37%)	17 (39%)	10 (32%)
III	58 (51%)	17 (45%)	24 (54%)	17 (55%)
IV	14 (13%)	7 (18%)	3 (7%)	4 (13%)
Sodium (mmol/L)	139 ± 3.1	138.7 ± 3.1	139.6 ± 3.4	140.2 ± 2.6
Hemoglobin (g/dL)	13.5 ± 1.9	13.4 ± 2.0	13.7 ± 1.8	13.2 ± 2.0
Anemia	49 (42%)	18 (45%)	16 (36%)	15 (44%)
Ejection fraction	0.25 ± 0.09	0.24 ± 0.10	0.26 ± 0.08	0.26 ± 0.09
Body mass index (kg/m^2)	29.5 ± 5.8	29.1 ± 5.4	29.9 ± 5.6	29.5 ± 6.7
Obesity (%)	46.6	37.5	47.7	55.9
Estimated GFR (ml/min/1.73 m^2)*	65.5 ± 23.5	71.6 ± 25.7	66.2 ± 20.8	57.3 ± 22.6
Past medical history				
Myocardial infarction	70 (59%)	24 (60%)	24 (55%)	22 (65%)
Coronary artery disease	77 (65%)	25 (63%)	29 (66%)	23 (68%)
Implantable cardioverter defibrillator	31 (26%)	7 (18%)	14 (32%)	10 (29%)
Hypertension	72 (61%)	22 (55%)	25 (57%)	25 (74%)
Diabetes mellitus**	48 (41%)	16 (40%)	12 (27%)	20 (59%)
Atrial fibrillation	34 (29%)	12 (30%)	12 (27%)	10 (29%)
Chronic obstructive pulmonary disease	33 (28%)	13 (33%)	9 (20%)	11 (32%)
Medications				
ACEI/ARB	108 (91%)	35 (88%)	42 (95%)	31 (91%)
β-blocker	106 (90%)	34 (85%)	39 (89%)	33 (97%)
Diuretics	104 (88%)	34 (85%)	40 (91%)	30 (88%)
Digoxin	57 (48%)	18 (45%)	22 (50%)	17 (50%)

Variable	N=118	Dipper (N=40)	Non-dipper (N=44)	Reverse dipper (N=34)
Spironolactone	28 (24%)	9 (23%)	11 (25%)	8 (24%)
Antiplatelets	77 (65%)	26 (65%)	30 (68%)	21 (62%)
Warfarin	50 (42%)	19 (48%)	18 (41%)	13 (38%)
Calcium antagonist	15 (13%)	4 (10%)	6 (14%)	5 (15%)
Antihyperlipidemics***	92 (78%)	36 (90%)	28 (64%)	28 (82%)

* p=0.032

** p=0.019

*** p=0.011

NYHA: New York Heart Association, GFR: Glomerular filtration rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker

Dipper: Night to day mean ambulatory systolic blood pressure ratio <0.9

Non-reverse dipper: 0.9 ≤ Night to day mean ambulatory systolic blood pressure ratio <1.0

Reverse dipper: Night to day mean ambulatory systolic blood pressure ratio ≥1.0

Table 2

Blood pressure and heart rate data according to diurnal blood pressure pattern

Variable	Dipper	Non-dipper	Reverse dipper	p-value
Clinic SBP at entry	113.1 ± 18.6	124.3 ± 22.5	120.8 ± 26.3	0.088
Clinic DBP at entry	66.2 ± 8.8	69.1 ± 12.8	67.8 ± 13.8	0.53
Clinic heart rate at entry	78.3 ± 13.9	77.8 ± 15.0	75.4 ± 13.0	0.66
Mean 24-hr SBP	111.3 ± 10.2	125.4 ± 18.1*	128.6 ± 19.3*	<0.0001
Mean daytime SBP	116.9 ± 11.0	127.2 ± 18.6**	124.9 ± 19.0	0.015
Mean night time SBP	97.7 ± 10.5	120.7 ± 17.7*	136.0 ± 20.7*, ***	<0.0001
Mean 24-hr DBP	64.5 ± 6.2	69.7 ± 8.8**	70.9 ± 9.7*	0.002
Mean daytime DBP	67.9 ± 6.7	70.1 ± 8.9	68.9 ± 9.5	0.51
Mean night time DBP	57.0 ± 5.8	67.9 ± 9.4*	76.0 ± 14.0*, ***	<0.0001
Mean 24-hr heart rate	70.3 ± 7.3	71.1 ± 9.6	72.1 ± 12.1	0.74
Mean daytime heart rate	72.7 ± 7.7	73.5 ± 10.0	73.2 ± 12.7	0.93
Mean night time heart rate	66.6 ± 8.2	67.2 ± 10.3	69.7 ± 12.5	0.41

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Unit of BP: mmHg, Unit of heart rate: bpm
Dipper: Night to day mean ambulatory systolic blood pressure ratio <0.9
Non-reverse dipper: 0.9 ≤ Night to day mean ambulatory systolic blood pressure ratio <1.0
Reverse dipper: Night to day mean ambulatory systolic blood pressure ratio ≥1.0

* vs. dipper: p<0.01

** vs. dipper: p=0.015

*** vs. non-dipper: p<0.01

Table 3

Outcomes and follow-up

Outcome	Number	Median time to event (days)
Primary outcomes	39	414
Death	15	630
Hospitalization	24	305
Secondary outcomes		
Death	25	448
Hospitalization	24	305
Overall follow up		761

Table 4

Variables with p-value <0.1 in univariable proportional hazard regression analyses

Variables	HR	95% CI	p-value
Anemia	3.32	1.70 - 6.45	0.0004
NYHA functional class	2.36	1.42 - 3.92	0.0009
Dipping status	1.66	1.09 - 2.53	0.0173
Age	1.04	1.01 - 1.07	0.0205
Estimated GFR	0.98	0.97 - 0.99	0.0209
HF duration	2.13	0.94 - 4.84	0.0706
Etiology	2.14	0.89 - 5.13	0.0889

HR: Hazard ratio, CI: Confidence interval, NYHA: New York Heart Association, GFR: Glomerular filtration rate, HF: Heart failure
Anemia is defined as blood hemoglobin level <13 g/L in men and <12 g/L in women.
Codings were as follows:
Anemia: 0 (non-anemic) and 1 (anemic)
Dipping status: 0 (dipper), 1 (non-dipper) and 2 (reverse dipper)
HF duration: 0 (<1 year) and 1 (≥ 1 year).
Etiology: 0 (non-ischemic) and 1 (ischemic).

Table 5

Multivariable models of proportional hazard regression

Variable	HR	95% CI	p-value
NYHA functional class	1.96	1.11 - 3.44	0.020
Anemia	2.50	1.23 - 5.08	0.011
Dipping status	1.65	1.08 - 2.50	0.020

HR: Hazard ratio, CI: Confidence interval, NYHA: New York Heart Association
Codings were as follows:
Anemia: 0 (non-anemic) and 1 (anemic)
Dipping status: 0 (dipper), 1 (non-dipper) and 2 (reverse dipper)

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