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ORIGINAL ARTICLE

Night–day blood pressure ratio and dipping pattern as predictors of death and cardiovascular events in hypertension

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Our objective was to assess the prognostic significance of the night-time dipping pattern and the night–day blood pressure (BP) ratio for mortality and cardiovascular events in hypertensive patients without major cardiovascular disease at baseline. We performed a meta-analysis on individual data of 3468 patients from four prospective studies performed in Europe. Age of the subjects averaged 61 ± 13 years; 45% were men and 61% were under antihypertensive treatment at the time of ambulatory BP monitoring. The night–day BP ratio and 24-h BP averaged, respectively, 0.907 ± 0.085/0.866 ± 0.095 and 138.1 ± 16.4/82.3 ± 11.0 mm Hg. Total follow-up time amounted to 23 164 patient-years. We used multivariable Cox regression analysis to assess the outcome of reverse dippers, non-dippers and extreme dippers vs dippers, and to assess the hazard ratios associated with 1 standard deviation higher night–day BP ratio. In comparison with dippers, and with adjustment for confounders and 24-h BP, the incidence of cardiovascular events was worse in reverse dippers ($P \leqslant 0.05$), whereas mortality was lower in extreme dippers ($P \leqslant 0.01$); outcome was similar in non-dippers and dippers. The systolic night–day BP ratio independently predicted all-cause mortality and cardiovascular events ($P \leqslant 0.001$), which persisted after additional adjustment for 24-h BP ($P \leqslant 0.05$); appropriate interaction terms indicated that the results were similar in men and women, in younger and older patients and in treated and untreated patients. In conclusion, the dipping pattern and the night–day BP ratio significantly and independently predict mortality and cardiovascular events in hypertensive patients without history of major cardiovascular disease, even after adjustment for 24-h BP.
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Keywords: ambulatory blood pressure; cardiovascular disease; daytime blood pressure; dipping pattern; mortality; night-time blood pressure

Introduction

There is growing evidence that night-time ambulatory blood pressure (ABP) is a better predictor of outcome than daytime ABP in patients with hypertension. When daytime and night-time ABP were included in the same models, night-time ABP was superior to daytime ABP for all-cause,[1,2] cardiovascular (CV), cardiac and stroke mortality.[1] In a recent meta-analysis on individual patient data from four prospective studies performed in Europe and coordinated in Belgium,[3–6] we showed that both daytime and night-time ABP carry prognostic information for mortality and fatal and non-fatal CV disease (CVD) events but that night-time ABP is in general a better predictor of outcome than daytime ABP.[7] Patients with a history of major CVD were excluded from the analysis to avoid reverse causality. However, results on the nocturnal fall of BP or on the night–day BP ratio are not consistent in hypertension. Some individual studies observed a significantly better prognosis in patients with a greater decline in night-time ABP[3,8] but this was not confirmed by others.[5,9] In addition, Kario *et al.*[10] reported in older hypertensives that the relative risk for stroke was greater in extreme dippers than in dippers and non-dippers.

Preliminary data from our meta-analysis[7] indicated that the night–day BP ratio predicts all-cause mortality even over and beyond 24-h ABP in patients with hypertension. In this article, we report categorical analyses in which mortality and the incidence of CVD events of reverse dippers, non-dippers and extreme dippers are compared with dippers, and further explore the prognostic significance of the night–day BP ratio in these patients.

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Materials and methods

We used data from the Belgian Ambulatory Blood Pressure Monitoring database,[7] which contains individual data of hypertensive patients from four studies performed in Europe and coordinated at the Universities of Ghent[5] or Leuven.[3,4,6] Inclusion and exclusion criteria of the individual studies and results on the prognostic significance of various aspects of ABP have been reported previously.[3–6,11–14] The current meta-analysis is based on a total of 3468 hypertensive patients without debilitating illness or major CVD at baseline, such as myocardial infarction, stroke or congestive heart failure (CHF). We included 1108 patients from the Systolic Hypertension in Europe trial,[3] 419 patients from the Ambulatory blood pressure Monitoring and Treatment of Hypertension trial,[4] 1963 patients from the Office BP (OBP) vs ABP study[5] and 222 patients from a study on $\geqslant$60-year-old patients in one primary care practice.[6] The patient selection process has been described in detail.[7]

Blood pressure

OBP was the average of 2[3] or 3[4–6] BPs measured in the sitting position by the auscultatory technique using the fifth Korotkoff sound for diastolic BP, during the baseline visit closest to the ABPM. ABP was monitored during 24 h, by use of validated devices. BP was measured every 15 min[4,6] or at intervals of not more than 30 min[3,5] during daytime and every 30 min[4,6] or at intervals of not more than 60 min[3,5] during the night. In the current analysis daytime ABP was the average BP from 10:00 hours to 20:00 hours and night-time ABP was the average BP from midnight to 06:00 hours, which corresponds well with the actual awake and asleep ABP.[15] We calculated the night–day BP ratio and classified the patients by the systolic night–day BP ratio as follows: reverse dippers if the ratio was >1.0, non-dippers if >0.9 and $\leqslant 1.0$, dippers if >0.8 and $\leqslant 0.9$, and extreme dippers if $\leqslant 0.8$.[10]

Outcomes

Outcome variables were (1) all-cause mortality, (2) non-CV mortality, (3) CV mortality including all fatal CVD events and sudden death, (4) major CVD events, including sudden death, fatal and non-fatal myocardial infarction, stroke and CHF, (5) all CVD events, such as major CVD events plus angina pectoris and transient ischaemic attack (TIA), (6) major coronary heart disease (CHD) including sudden death and fatal and non-fatal myocardial infarction, (7) all CHD, including sudden death, fatal and non-fatal myocardial infarction and angina pectoris, (8) stroke, (9) all cerebrovascular disease (CeVD) events, including stroke and TIA. Sudden death included any death of unknown origin occurring immediately or within 24 h of the onset of acute symptoms, as well as unattended death for which no likely cause could be established. Myocardial infarction was defined as two of the following three disorders: typical chest pain, electrocardiographic changes and increased cardiac enzymes. The diagnosis of angina pectoris required typical symptoms and objective evidence, such as ECG changes at rest or during exercise, coronarographic abnormalities and/or revascularization. CHF included all cases of heart failure, irrespective of hospitalization, and required the presence of three disorders: symptoms such as dyspnoea; clinical signs such as ankle oedema or crepitations; the necessity of treatment. Stroke was defined as a neurological deficit with symptoms continuing for >24 h or leading to death with no apparent cause other than vascular. The diagnosis of TIA required a neurological deficit, which resolved within 24 h. All events that occurred during follow-up were corroborated by the study endpoint committees, using the same diagnostic criteria. One of the authors (RHF) took part in the four committees.

Statistical analysis

Database management and statistical analyses were performed using SAS software, version 8.2 (SAS Institute Inc). Individual patient data from the four studies were pooled for the meta-analysis. Data are reported as mean $\pm$ standard deviation (s.d.) or as percentages. Differences among groups were analysed by analysis of variance and Scheffé's multiple means test. The χ^2-test was used for categorical data. We used Cox proportional hazards regression analysis to assess prognostic significances, after testing the proportional hazards assumption. All analyses were stratified by study. For patients who experienced multiple events, analysis was restricted to the first event under study. We assessed the outcome of reverse dippers, non-dippers and extreme dippers in comparison with dippers, with adjustment for age, gender, smoking, serum total cholesterol, diabetes and antihypertensive treatment at the time of ABPM, and, in addition, for 24-h ABP. Next, we assessed the prognostic significance of the night–day BP ratio and of 24-h ABP. The adjusted hazard ratios (HR) represent the risks associated with a 1 s.d. increment in BP or night–day BP ratio. To assess whether the effect of the night–day BP ratio was independent from 24-h ABP, we included both variables in the same model. Sensitivity analyses were performed for the models which included both 24-h ABP and the night–day BP ratio; analyses were done separately in men and women, in treated and untreated patients and in older and younger patients according to median age of the study population, with tests of heterogeneity by use of appropriate interaction terms. A two-tailed P value $\leqslant 0.05$ was considered significant.

Results

Patient characteristics at baseline

Age of the 3468 included participants averaged 60.8 ± 13.1 years (range: 18–96; median: 62.8); 44.8% were men, 13.7% were current smokers, 8.4% had diabetes and 61.4% were under antihypertensive treatment at the time of ABPM. Body mass index averaged 27.7 ± 4.5 kg/m². OBP averaged 159.0 ± 19.9/91.0 ± 11.7 mm Hg, daytime ABP 143.517.0/87.1 ± 11.7 mm Hg, night-time ABP 129.8 ± 17.6/75.4 ± 12.3 mm Hg, 24-h ABP 138.1 ± 16.4/82.3 ± 11.0 mm Hg, and the night–day BP ratio 0.907 ± 0.085/0.866 ± 0.095.

Table 1 First occurring cardiovascular disease events during follow-up

	Major CVD events	*All CVD events*
Total number	320	473
Fatal CVD events	95	81
Coronary heart disease	52	48
Congestive heart failure	12	10
Stroke	19	13
Others	12	10
Non-fatal CVD events	225	392
Myocardial infarction	68	61
Congestive heart failure	72	60
Stroke	85	75
Angina pectoris	–	155
Transient ischaemic attack	–	41

Abbreviation: CVD, cardiovascular disease.
Data are number of events.

Follow-up

Median follow-up time was 6.57 years (range: 0.08–13.1), and total follow-up time amounted to 23 164 patient-years. Overall, 324 patients died, of whom 145 patients died from a CV cause (CHD: 68 (sudden death: 46); CHF: 29; stroke: 31; others: 17). There were 320 first major CVD events and 473 first CVD events when angina pectoris and TIA were also considered (Table 1).

Baseline characteristics and prognosis according to dipping status

Table 2 summarizes the baseline characteristics of reverse dippers, non-dippers, dippers and extreme dippers, and the number of events which occurred

Table 2 Baseline characteristics of reverse dippers, non-dippers, dippers and extreme dippers, and events during follow-up

	Reverse dippers	*Non-dippers*	*Dippers*	*Extreme dippers*	*Overall* P *value*
Number of patients	421	1407	1295	345	—
Age (year)	62.9 ± 13.2	60.2 ± 13.3*	60.0 ± 13.1*	63.2 ± 11.1†,‡	<0.001
Gender (% men)	41.3	48.1	44.9	35.7 †,‡	<0.001
Body mass index (kg/m²)	28.2 ± 5.0	27.8 ± 4.6	27.6 ± 4.4	27.3 ± 4.4	<0.05
Current smoking (%)	12.4	14.0	13.7	13.9	0.86
Serum cholesterol (mg per 100 ml)	235 ± 42	232 ± 44	236 ± 47	237 ± 43	0.06
Diabetes (%)	11.6	8.2	7.6	7.5	0.07
Antihypertensive treatment (%)	70.1	71.5	54.1*,†	37.4*, †,‡	<0.001
Blood pressure (mm Hg)					
Systolic					
Office	161.0 ± 20.8	157.6 ± 20.6*	158.8 ± 19.0	162.8 ± 18.4†,‡	<0.001
Daytime	138.4 ± 17.6	141.2 ± 16.9*	145.8 ± 16.1*,†	150.2 ± 16.7*,†,‡	<0.001
Night-time	145.7 ± 19.0	133.1 ± 16.3*	125.0 ± 13.9*,†	114.2 ± 13.4*,†,‡	<0.001
24-h	142.2 ± 17.9	137.9 ± 16.7*	137.3 ± 15.5*	137.0 ± 15.6*	<0.001
Night–day ratio	1.054 ± 0.055	0.943 ± 0.028	0.858 ± 0.027	0.760 ± 0.035	—
Diastolic					
Office	90.9 ± 11.8	91.3 ± 11.6	91.2 ± 11.9	89.3 ± 11.4	<0.05
Daytime	84.4 ± 12.5	86.4 ± 11.4*	88.3 ± 11.6*,†	88.9 ± 11.5*,†	<0.001
Night-time	84.2 ± 13.1	77.6 ± 11.4*	72.5 ± 10.8*,†	65.4 ± 10.0*,†,‡	<0.001
24-h	84.6 ± 12.2	82.6 ± 10.9*	81.7 ± 10.8*	80.3 ± 10.2*,†	<0.001
Night–day ratio	1.001 ± 0.090	0.898 ± 0.057	0.822 ± 0.059	0.734 ± 0.069	—
Events (numbers)					
Death	62	111	120	31	—
CV death	28	52	51	14	—
Major CV events	61	115	112	32	—
All CV events	83	174	158	58	—

Abbreviation: CV, cardiovascular.
Values are mean ± s.d., numbers or percentages. Significance of intergroup comparisons.
*$P \leqslant 0.05$ vs reverse dippers.
†$P \leqslant 0.05$ vs non-dippers.
‡$P \leqslant 0.05$ vs dippers.

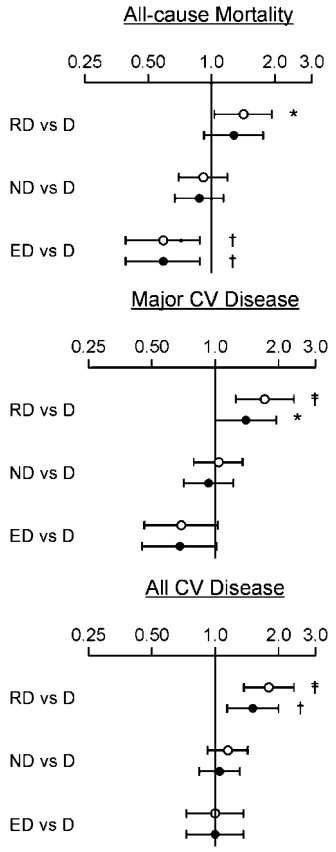

Figure 1 Hazard ratios and 95% confidence limits for all-cause mortality and cardiovascular (CV) disease events of reverse dippers (RV), non-dippers (ND) and extreme dippers (ED) vs dippers (D), with stratification for study and adjustment for age, gender, smoking, total cholesterol, diabetes and antihypertensive treatment, before (open circles) and after (closed circles) adjustment for 24-h blood pressure. *$P \leqslant 0.05$; †$P \leqslant 0.01$; ‡$P \leqslant 0.001$ vs dippers.

in each subgroup. Reverse dippers and extreme dippers were slightly older than non-dippers and dippers, and extreme dippers comprised more women than the other groups. Reverse dippers and non-dippers were more frequently treated with antihypertensive drugs. Daytime ABP increased and night-time ABP decreased progressively across the four BP groups, from reverse dippers to extreme dippers, whereas differences in BP were less marked for 24-h ABP and OBP.

As shown in Figure 1, we assessed the HRs for all-cause mortality and the aggregates of major and all CVD events of reverse dippers, non-dippers and extreme dippers vs dippers, with stratification for study and adjustment for age, gender, smoking, total cholesterol, diabetes and antihypertensive treatment, and, in addition, for 24-h ABP. The HRs for non-dippers vs dippers were never significant. All-cause mortality was lower in extreme dippers than in dippers ($P<0.01$), with similar HRs before and after adjustment for 24-h ABP; the same tendency was observed for major CVD events ($P=0.07$ before and $P=0.06$ after adjustment for 24-h ABP; Figure 1). There were no significant differences for any of the separate CVD components between extreme dippers and dippers.

The HR of reverse dippers vs dippers was significant for major CVD events and all CVD events, both before and after adjustment for 24-h ABP (Figure 1). There was no significant interaction with antihypertensive treatment; for example, the HR for all CVD events, with adjustment for 24-h ABP, amounted to 1.53 (95% confidence interval (CI): 1.04–2.24; $P<0.05$) in untreated patients, and to 1.47 (95% CI: 0.95–2.26; $P=0.08$) in patients under antihypertensive treatment. The worse prognosis in reverse dippers was mainly due to the increased risk for all CHD (HR before adjustment for 24-h ABP: 2.07; 95% CI: 1.44–2.98 ($P<0.001$), and HR after adjustment for 24-h ABP: 1.83; 95% CI: 1.26–2.65 ($P<0.001$), with a similar tendency for CHF (HR before adjustment for 24-h ABP: 2.06; 95% CI: 1.19–3.56 ($P<0.01$) and after adjustment for 24-h ABP: 1.69; 95% CI: 0.95–3.01 ($P=0.07$)), but not for CeVD ($P>0.4$). The HR for all-cause mortality was significant before ($P<0.05$) but not after controlling for 24-h ABP ($P=0.14$; Figure 1).

We also examined the outcome of reverse dippers in comparison with the three other subgroups combined. Reverse dippers were older ($P<0.001$), and diabetes ($P<0.05$) and antihypertensive treatment ($P<0.001$) were more prevalent than in the other patients. After full adjustment, including all covariates and 24-h ABP, the HR of reverse dippers vs all other participants was significant for all-cause mortality, the aggregates of major and all CVD events, all CHD and CHF, but not for all CeVD (Table 3). In addition, these results were similar in treated and untreated patients (data not shown).

Prognostic significance of 24-h blood pressure and night–day blood pressure ratio

Table 4 summarizes the adjusted HRs of the relationships of 24-h ABP and the night–day BP ratio, taken separately, with mortality, and Table 5 summarizes these HRs for fatal and non-fatal CVD events combined. In Figure 2, the results are given for mortality and the aggregates of CVD events, when both 24-h ABP and the night–day ratio were included in the models, together with the other covariates. Systolic 24-h ABP predicted all outcomes; the night–day BP ratio added prognostic precision to 24-h ABP for all-cause mortality, major CVD events and all CVD events. The diastolic night–day BP ratio predicted all-cause and CV mortality, major CVD events and all CVD events, independently from 24-h ABP. The night–day BP ratio did not independently predict the separate CVD components, except for the systolic night–day BP ratio and all CHD (HR: 1.13; 95% CI: 1.01–1.27; $P<0.05$) and the diastolic night–day BP ratio and CHF (HR: 1.20; 95% CI: 1.00–1.44; $P<0.05$).

Figure 3 summarizes the adjusted HRs for all-cause mortality and the aggregates of major

Table 3 Adjusted hazard ratios and 95% confidence interval for mortality and cardiovascular events in reverse dippers vs non-dippers, dippers and extreme dippers combined.

	Death	*Cardiovascular disease*		*All CHD*	*All CeVD*	*CHF*
		Major	*All*			
HR (95% CI)[§]	1.62 (1.22–2.15)[‡]	1.77 (1.33–2.35)[‡]	1.68 (1.32–2.13)[‡]	1.69 (1.24–2.32)[‡]	1.59 (1.06–2.40)*	2.09 (1.29–3.36)[†]
HR (95% CI)[§§]	1.49 (1.12–1.98)[†]	1.53 (1.15–2.04)[†]	1.49 (1.17–1.91)[‡]	1.54 (1.12–2.12)[†]	1.35 (0.89–2.04)	1.83 (1.13–2.97)[†]

Abbreviations: CeVD, cerebrovascular disease; CHD, coronary heart disease; CHF, congestive heart failure; 95% CI, 95% confidence interval; HR, hazard ratio.
Data are hazard ratios and 95% confidence interval, stratified for study and adjusted for [§]age, gender, smoking, total cholesterol, diabetes and antihypertensive treatment and, in addition, [§§] for 24-h blood pressure.
Significance of hazard ratios: *$P \leqslant 0.05$; [†]$P \leqslant 0.01$; [‡]$P \leqslant 0.001$.

Table 4 Adjusted hazard ratios for mortality with 24-h blood pressure and the night–day blood pressure ratio

	Death	*NCV death*	*CV death*	*CHD death*
No. of events	324	179	145	68
Systolic BP				
24-h	1.35 (1.21–1.51)[‡]	1.28 (1.10–1.50)[†]	1.44 (1.22–1.71)[‡]	1.37 (1.07–1.74)[†]
N-D ratio	1.18 (1.07–1.30)[‡]	1.18 (1.03–1.35)*	1.18 (1.03–1.37)*	1.08 (0.86–1.34)
Diastolic BP				
24-h	1.15 (1.01–1.30)*	1.20 (1.01–1.41)*	1.09 (0.90–1.32)	0.99 (0.75–1.32)
N-D ratio	1.15 (1.04–1.28)[†]	1.11 (0.96–1.28)	1.21 (1.04–1.40)[†]	1.13 (0.90–1.43)

Abbreviations: BP, blood pressure; CHD, coronary heart disease; CV, cardiovascular; NCV, non-cardiovascular; N-D ratio, night–day ratio.
Data are hazard ratios (95% confidence intervals) for each 1 s.d. higher BP or night–day BP ratio, stratified for study and adjusted for age, gender, smoking, total cholesterol, diabetes and antihypertensive treatment.
Significance of hazard ratios: *$P \leqslant 0.05$; [†]$P \leqslant 0.01$; [‡]$P \leqslant 0.001$

Table 5 Adjusted hazard ratios for cardiovascular events with 24-h blood pressure and the night–day blood pressure ratio

	Cardiovascular disease		*Coronary heart disease*		*Cerebrovascular disease*		*CHF*
	Major	*All*	*Major*	*All*	*Stroke*	*All*	
No. of events	320	473	129	283	133	155	99
Systolic BP							
24-h	1.52 (1.36–1.69)[‡]	1.45 (1.32–1.59)[‡]	1.44 (1.21–1.71)[‡]	1.39 (1.24–1.57)[‡]	1.73 (1.45–2.06)[‡]	1.60 (1.37–1.87)[‡]	1.45 (1.19–1.78)[‡]
N-D ratio	1.23 (1.11–1.36)[‡]	1.19 (1.09–1.30)[‡]	1.21 (1.03–1.43)*	1.19 (1.06–1.34)[†]	1.21 (1.02–1.43)*	1.15 (1.00–1.35)*	1.22 (1.03–1.45)*
Diastolic BP							
24-h	1.20 (1.06–1.36)[†]	1.19 (1.08–1.32)[‡]	1.14 (0.94–1.39)	1.21 (1.06–1.38)[†]	1.32 (1.08–1.62)[†]	1.23 (1.03–1.47)*	1.04 (0.82–1.32)
N-D ratio	1.16 (1.04–1.29)[†]	1.13 (1.03–1.23)[†]	1.09 (0.91–1.30)	1.10 (0.97–1.24)	1.11 (0.93–1.32)	1.05 (0.90–1.22)	1.21 (1.01–1.45)*

Abbreviations: BP, blood pressure; CHF, congestive heart failure; N-D ratio, night–day ratio.
Data are hazard ratios (95% confidence intervals) for each 1 s.d. higher BP or night–day BP ratio, stratified for study and adjusted for age, gender, smoking, total cholesterol, diabetes and antihypertensive treatment.
Significance of hazard ratios: *$P \leqslant 0.05$; [†]$P \leqslant 0.01$; [‡]$P \leqslant 0.001$.

and all CVD events according to gender, age below or above median age and treatment status, with inclusion of systolic 24-h ABP and the night–day BP ratio in the same models. Although the HR was always significant for 24-h ABP, the night–day BP ratio attained statistical significance in some subgroups, but not in others. However, none of the interaction terms with gender, age and treatment status, respectively, reached statistical significance.

Discussion

The main findings of the current meta-analysis of individual patient data on the prognostic significance of the night-time dipping pattern and the night–day BP ratio in hypertensive patients without major CVD at baseline are as follows: (1) all-cause mortality is lower in extreme dippers than in dippers, and reverse dippers are at higher risk for CVD than dippers, independently from 24-h ABP and other

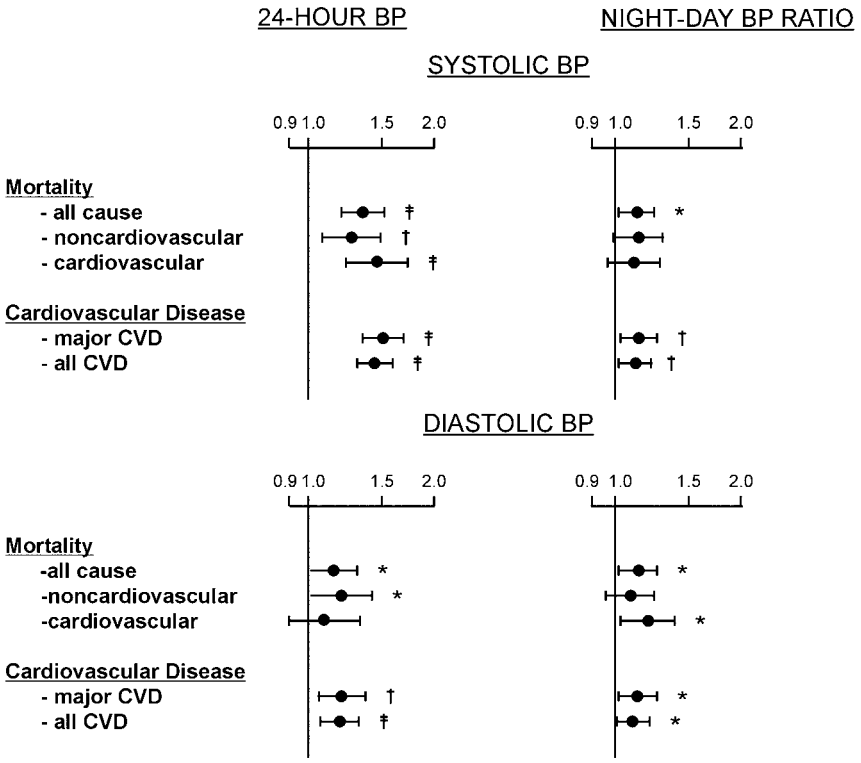

Figure 2 Hazard ratios and 95% confidence limits for mortality and cardiovascular disease (CVD) events with 24-h blood pressure (BP) and the night–day blood pressure ratio, with stratification for study, simultaneous inclusion of 24-h blood pressure and the night–day blood pressure ratio in the models, and adjustment for age, gender, smoking, total cholesterol, diabetes and antihypertensive treatment. *$P \leqslant 0.05$; †$P \leqslant 0.01$; ‡$P \leqslant 0.001$.

confounding factors; (2) the night–day BP ratio significantly predicts all-cause mortality and CVD events, independently from confounders and 24-h ABP, and these results are consistent in subgroups according to age, gender and treatment status.

The current meta-analysis is an extension of a previous analysis in this study population in which we only included hard endpoint and showed that daytime and night-time ABP significantly and independently predict mortality and CVD events; that the predictive power of systolic night-time ABP is superior to that of daytime ABP for mortality, major CHD and stroke; and that the diastolic night-time ABP independently predicts all-cause and CV mortality.[7] In addition, the systolic night–day BP ratio predicted all-cause mortality and the diastolic night–day BP ratio predicted all-cause and CV mortality, independently from 24-h ABP, but not major CHD or stroke.[7]

In this report, we analyse the prognostic significance of the night-time dipping pattern and further explore the prognostic significance of the night–day BP ratio, with inclusion of hard and softer CVD events in the analyses. The softer endpoints, such as angina pectoris, TIA and CHF, were all validated by blinded endpoint committees based on the best available evidence. Strengths of our study are the prospective follow-up, the evaluation of fatal and non-fatal events according to the same criteria by blinded endpoint committees, and the wide and comprehensive spectrum of hypertensive patients with regard to age, gender, type of hypertension, antihypertensive treatment and type of care.

The effect of the nocturnal decline of BP on prognosis had been studied by using the night–day BP ratio as a continuous variable, or by applying dipping categories, such as reverse dippers, non-dippers, dippers and extreme dippers. Our categorical analyses revealed that the association between the night–day BP ratio and all-cause mortality was mainly due to lower mortality in extreme dippers than in dippers, and higher mortality in reverse dippers, which was significant when compared to all other patients and of borderline significance when compared to only dippers. The incidence of CVD events and all CHD was significantly higher in reverse dippers than in dippers, with a tendency for lower incidence of major CVD events in extreme dippers. None of the outcomes differed between non-dippers and dippers. These findings therefore suggest that it is warranted to report the results of the four dipping categories separately in this type of studies, whereas several studies only reported on two categories, that is dippers (including extreme dippers) and non-dippers (including reverse dippers).[8,9,16,17]

A number of other studies reported on the prognostic significance of the night–day BP ratio or the dipping pattern in hypertensive patients or in the population, but data on the four dipping

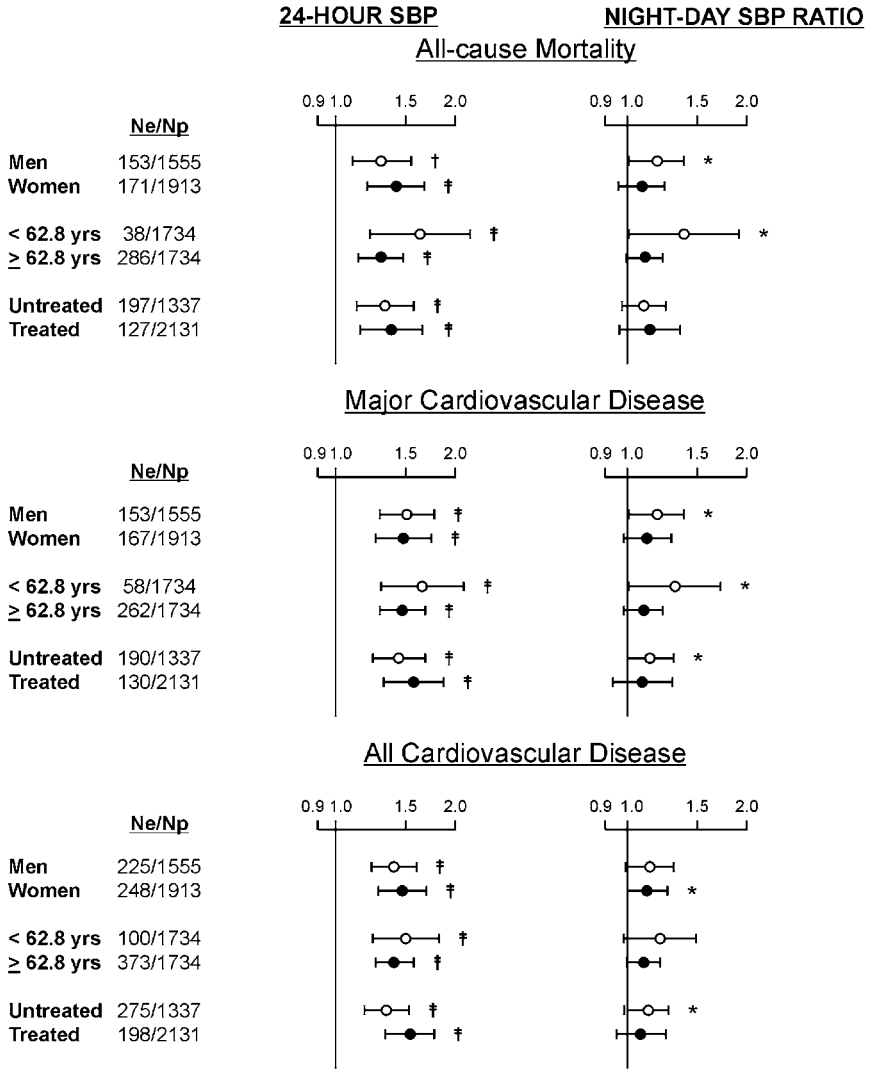

Figure 3 Hazard ratios and 95% confidence limits for all-cause mortality and cardiovascular disease events in subgroups according to gender, median age and treatment status, for 24-h systolic blood pressure (SBP) and the night–day SBP ratio, with stratification for study, simultaneous inclusion of 24-h blood pressures and the night–day blood pressure ratio in the models and adjustment for age, gender, smoking, total cholesterol, diabetes and antihypertensive treatment. $^{*}P \leqslant 0.05$; $^{\dagger}P \leqslant 0.01$; $^{\ddagger}P \leqslant 0.001$. None of the between-subgroup interaction terms was statistically significant. N_e/Np indicates number of events/number of patients.

categories are scarce. Ben-Dov *et al.*[2] reported on patients referred for ABPM and found that all-cause mortality was similar in extreme dippers and dippers in a model controlling for awake ABP and confounders; compared with all dippers, prognosis was significantly and progressively worse in non-dippers and reverse dippers. Kario *et al.*[10] observed a J-shaped relationship between dipping pattern and incidence of stroke in older hypertensives and this relationship remained significant after controlling for 24-h ABP and other covariates. Moreover, the incidence of stroke was significantly higher in extreme dippers than in dippers. We could not confirm this finding in our study population: the night–day BP ratio was not independently predictive of stroke and CeVD and their incidence was not significantly different among the four dipping categories. Ohkubo *et al.*[18] observed in a population-based study, and with adjustment for 24-h ABP and other confounders, that CV mortality was not increased in extreme dippers in comparison with dippers, but became progressively worse in non-dippers and reverse dippers. In a meta-analysis of population-based studies,[19] and with full adjustment including 24-h ABP, reverse dippers were at greater risk than dippers for total mortality, CV mortality and an aggregate of fatal and non-fatal CVD events; non-dippers were at greater risk for total mortality; and risk was not significantly different between extreme dippers and dippers. Incidences of all strokes and of all coronary events did not differ among the four dipping categories.[19] Differences between the meta-analysis by Boggia *et al.*[19] and the current meta-analysis in hypertensive patients are that the majority of subjects were normotensive in the population-based approach and

that the data were from three continents whereas the current meta-analysis was restricted to white European patients with hypertension. Based on our findings and data from the literature, there appears to be little doubt that reverse dipping is associated with a worse prognosis; some studies suggest that prognosis is similar in non-dippers and extreme dippers in comparison with dippers, but other studies suggest a somewhat worse prognosis in non-dippers, or a better or worse prognosis in extreme dippers.

With regard to the night–day BP ratio, we observed that the systolic and diastolic night–day BP ratios were significantly associated with mortality and the aggregates of CVD events, which persisted after adjustment for 24-h ABP for all-cause mortality, aggregates of CVD events and all CHD for systolic ABP, and for all-cause and CV mortality, CVD events and CHF for diastolic BP. In addition, use of appropriate interaction terms and sensitivity analyses indicated that the results were roughly similar in men and women, in younger and older patients, and in treated and untreated patients. It is of note, however, that the prognostic power of 24-h ABP is, in general, stronger than that of the night–day BP ratio. A number of other studies reported on the night–day BP ratio. Khattar *et al.*[9,16] found in patients with essential hypertension that the nocturnal decline in ABP did not carry independent prognostic information for CVD events. By contrast, Hansen *et al.*[17] observed that the night–day BP ratio was significant for CVD events in subjects with elevated daytime ABP, but not in subjects with normal daytime ABP, and these results persisted after adjustment for 24-h ABP. Finally, the night–day BP ratio did not carry any prognostic information in the study by Björklund *et al.*[20] in a population of elderly men.

In general, the predictive power of the night–day BP ratio appears to be largely dependent on the worse prognosis of reverse dippers. Several mechanisms have been invoked to explain the higher night-time ABP and associated worse outcome: nocturnal autonomic dysfunction; disturbed baroreflex sensitivity; sleep apnoea; abnormal sodium handling and nocturnal volume overload.[7,19,21] It has also been shown that there is an inverse relationship between orthostatic systolic BP change and the asleep–awake BP ratio, with more pronounced orthostatic systolic BP reduction in reverse dippers.[22,23] Because of its known association with a worse prognosis,[23,24] orthostatic hypotension may have contributed to the worse outcome of reverse dippers. The fact that these potential mechanisms contributing to the worse prognosis of reverse dippers have not been assessed is a limitation of the current meta-analysis. It has also been suggested that the higher nocturnal ABP might be a marker of disease, leading to lower daytime ABP, or might result from intake of drugs to lower BP during the day. However, we excluded patients with a history of CVD or other coexisting disease at baseline, and sensitivity analyses indicated that the results were similar in treated and untreated patients, so that reverse causality is unlikely to explain the worse prognosis of reverse dippers in our study.

In conclusion, we observed that the night-time dipping pattern and the night–day BP ratio predict mortality and CVD events, over and beyond 24-h ABP, in hypertensive patients without history of CVD. Therefore, it appears to be warranted to perform ABPM over the full 24 h with separate analyses of daytime and night-time ABP.[25] Finally, it is not known if restoring the normal dipping pattern by administering antihypertensive treatment, or part of it, in the evening would improve prognosis in reverse dippers.

What is known about the topic

- There is growing evidence that night-time ambulatory blood pressure is a better predictor of outcome than daytime blood pressure in patients with hypertension.
- Results on the prognostic significance of the night-time dipping pattern and the night–day blood pressure ratio are not consistent, and independence from 24-h blood pressure has not often been studied.

What this study adds

- Among hypertensive patients without major cardiovascular disease, reverse dippers are at higher risk for cardiovascular disease than dippers, and all-cause mortality is lower in extreme dippers than in dippers, independently from 24-h blood pressure and other confounders.
- The night–day blood pressure ratio significantly predicts all-cause mortality and cardiovascular events in these patients, independently from confounding factors and 24-h blood pressure. These results are consistent in subgroups according to gender, age and treatment status.

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