Morning Blood Pressure Surge, Dipping, and Risk of Coronary Events in Elderly Treated Hypertensive Patients

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BACKGROUND
The independent prognostic significance of morning surge (MS) of blood pressure (BP) is not yet clear. We investigated the association between MS of systolic BP and risk of coronary events in elderly treated hypertensive patients.

METHODS
The occurrence of coronary events was evaluated in 1,191 elderly treated hypertensive patients (age range 60–90 years). Subjects were divided according to tertiles of MS of systolic BP of the population as a whole, by dipping status and by group-specific tertiles of MS of systolic BP in dippers and nondippers.

RESULTS
During the follow-up (9.1 ± 4.9 years, range 0.4–20 years), 120 coronary events occurred. In the population as a whole, coronary event risk was not significantly associated with tertiles of MS of systolic BP, whereas nondippers were at higher risk than dippers. When nondippers and dippers were analyzed separately, by group-specific tertiles of MS of systolic BP, coronary event risk was associated with MS of systolic BP in dippers but not in nondippers. After adjustment for various covariates, Cox regression analysis showed that dippers in the third tertile (>23 mm Hg) of MS of systolic BP (hazard ratio 1.912, 95% confidence interval 1.048–3.488, $P = 0.03$) and nondippers (hazard ratio 1.739, 95% confidence interval 1.074–2.815, $P = 0.02$) were at higher coronary event risk than dippers with MS of systolic BP <23 mm Hg .

CONCLUSIONS
In elderly treated hypertensive patients, high MS of systolic BP predicts coronary events in dippers but not in nondippers. Nondippers, however, show higher risk of coronary events independently of MS in systolic BP.

Keywords: ambulatory blood pressure; blood pressure; coronary events; dippers; hypertension; morning surge; nondippers.

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A diurnal variation in the onset of cardiovascular events, with a peak incidence in the morning, has been reported.[1–4] Ambulatory monitoring has shown that blood pressure (BP) tends to display a similar diurnal variation, getting the highest level during the morning. This finding suggested that a high morning surge (MS) of BP might be implicated in the occurrence of cardiovascular events. Some investigators evaluated the association between MS of BP and subsequent cardiovascular complications, both in hypertensive patients[5–11] and in general populations,[12–16] but the results were conflicting.[17,18]

On the other hand, ambulatory BP monitoring has also revealed that nighttime BP pattern may be different in hypertensive patients. Indeed, some patients show a reduction of BP higher than 10% during the night (dippers), whereas others do not (nondippers). In this context, some studies indicated that patients with higher nighttime BP and blunted BP dip from day to night have increased cardiovascular risk.[5,19,20]

It is worth noting that nondippers show lower MS in BP, whereas dippers show higher MS of BP. Thus, nondippers are at increased cardiovascular risk than dippers but show lower MS of BP that could be protecting, whereas dippers are at lower risk than nondippers but show a higher MS of BP that could be harmful. In such a context, it is problematic to reconcile the adverse prognostic significance of nondipping with the statement that a high MS in BP is also a predictor of poor outcome when hypertensive patients are analyzed as a whole. We suggest that dippers and nondippers should be analyzed separately with group-specific cut-off points and we have recently reported that high MS in BP predicts stroke in dippers but not in nondippers or hypertensive patients as a whole.[10]

With respect to coronary events, to the best of our knowledge, a single study has specifically evaluated the influence of MS in BP on this outcome in a general population.[14] The aim of this study was to investigate the relationship between MS of BP and incidence of coronary events in an elderly treated hypertensive population analyzed as a whole and according to dipping status.

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METHODS

Subjects

Since 1992, we built two prospective databases of our initially untreated or initially treated hypertensive patients with the purpose to evaluate the prognostic value of ambulatory BP parameters and other risk markers. This study is one of those carried out with the database of initially treated subjects. We studied 1,191 sequential treated hypertensive patients aged ≥60 years (range 60–90 years) prospectively recruited from December 1992 to December 2012 who were referred to our hospital outpatient clinic for evaluation of hypertension. Sixty-two patients were lost during follow-up. Subjects with secondary hypertension were excluded. All the patients underwent clinical evaluation, electrocardiogram, routine laboratory tests, echocardiographic examination and noninvasive ambulatory BP monitoring. Study population came from the same geographical area (Chieti and Pescara, Abruzzo, Italy). The study was in accordance with the Second Declaration of Helsinki and was approved by the institutional review committee. Subjects gave informed consent.

Office BP measurements

Clinic systolic and diastolic BP recordings were performed by a physician by using a mercury sphygmomanometer and appropriate-sized cuffs. Phase V was used to determine diastolic BP. Measurements were performed in triplicate, 2 minute apart, and the mean value was used as the BP for the visit.

Ambulatory BP monitoring

Ambulatory BP monitoring was performed with a portable noninvasive recorder (SpaceLabs 90207, Redmond, WA) on a day of typical activity, within 1 week from clinic BP measurement. Each time a reading was taken, subjects were instructed to remain motionless and to record their activity on a diary sheet. Technical aspects have been previously reported.[21] Ambulatory BP readings were obtained at 15-minute intervals from 6 am to midnight, and at 30-minute intervals from midnight to 6 am. The following ambulatory BP parameters were evaluated: daytime (awake period), nighttime (asleep period), and 24-hour systolic and diastolic BP, weighted standard deviation (SD) of 24-hour BP as an index of BP variability[22] according to the formula [(daytime SD × awake time in hours) + (nighttime SD × asleep time in hours)]/24, the extent of BP reduction from day to night (those with BP reduction <10% were defined as nondippers and those with BP reduction ≥10% were defined as dippers), and pre-awakening MS of BP defined as the difference between the mean BP during the 2 hours after waking and the mean BP during the 2 hours before waking. Recordings were automatically edited (i.e., excluded) if systolic BP was >260 or <70 mm Hg or if diastolic BP was >150 or <40 mm Hg and pulse pressure was >150 or <20 mm Hg.[21] Subjects had recordings of good technical quality (at least 70% of valid readings).

In the present population, from exploratory analysis, systolic BP was a better predictor of coronary events than diastolic BP. Moreover, it has been reported that systolic BP is superior to diastolic BP in predicting prognosis in older subjects.[14,23] Thus, in this study, we used systolic BP to define various parameters.

First, we divided the whole population according to tertiles of MS of systolic BP (≤7.5 mm Hg; >7.5 and ≤17.4 mm Hg; >17.4 mm Hg) and dipping status (nondippers and dippers). Then, we analyzed nondippers according to group-specific tertiles of MS of systolic BP (≤2.5 mm Hg; >2.5 and ≤11.5 mm Hg; >11.5 mm Hg) and dippers according to group-specific tertiles of MS of systolic BP (≤14.5 mm Hg; >14.5 and ≤23 mm Hg; >23 mm Hg) separately.

Echocardiography

Measurements of interventricular septal thickness, left ventricular (LV) internal diameter, and posterior wall thickness were made according to standardized methods, within 1 month from clinic visit. LV mass was calculated using the formula introduced by Devereux *et al*.[24] Individual values for LV mass were indexed by height$^{2.7}$ and LV hypertrophy was defined as LV mass/height$^{2.7}$ >50 g/m$^{2.7}$ in men and >47 g/m$^{2.7}$ in women.[25]

Follow-up

Subjects were followed-up in our hospital outpatient clinic or by their family doctors. The occurrence of cardiovascular events was recorded during follow-up visits or by telephone interview of the patient followed by a clinical visit. Data were collected by the authors of this study. Those reviewing the endpoints were blinded to MS of systolic BP data. In the present report, we focused on coronary events that included fatal myocardial infarction, sudden death, nonfatal myocardial infarction, and coronary revascularization. Myocardial infarction was defined according to current criteria in various periods.[26–28]

Statistical analysis

Standard descriptive statistics were used. Groups were compared by using one-way analyses of variance and unpaired *t*-test, where appropriate. Bivariate correlation was used when needed. Event rates are expressed as the number of events per 100 patient-years based on the ratio of the observed number of events to the total number of patient-years of exposure up to the terminating event or censor. Survival curves were estimated using the Kaplan–Meier product-limit method and compared by the Mantel (log-rank) test. Cox regression analysis was used to evaluate univariate and multivariate association of factors with outcome. First, univariate association between various variables and coronary events was evaluated. Then, multiple regression analysis was performed reporting in the final model variables that were significantly ($P < 0.05$) associated with outcome in univariate analysis. The forced entry model was used. Statistical significance was defined as $P < 0.05$. Analyses were made with the SPSS 21 software package (SPSS, Chicago, IL).

RESULTS

Characteristics and BP values of the study population as a whole, by tertiles of MS of systolic BP of all the patients and by dipping status, are summarized in Table 1. Low-density lipoprotein cholesterol, clinic and ambulatory BP, except for 24-hour diastolic BP, weighted BP SD and MS of BP (by definition) were significantly different across tertiles of MS of systolic BP. Age, clinic, daytime and nighttime BP, and MS of BP were significantly different between dippers and nondippers.

Characteristics of nondippers and dippers according to group-specific tertiles of MS of systolic BP are reported in Table 2. Gender distribution, clinic and nighttime BP, weighted systolic BP SD and MS of BP (by definition) were different across tertiles in nondippers. Clinic and ambulatory BP, except for nighttime diastolic BP, weighted BP SD and MS of BP were significantly different across tertiles in dippers.

At baseline, 291 (24%), 562 (47%), and 338 (29%) patients received single, double, and triple antihypertensive therapy, respectively. Single and triple therapies were more frequent in the second and first tertile of MS of BP, respectively, in the global population. Double and triple therapies were more frequent in dippers and nondippers, respectively. Single, double, and triple therapies were not different across tertiles of MS of BP in nondippers and dippers analyzed separately. Moreover, 274 (23%) patients received antiplatelet drugs and 138 (12%) received statin therapy. For both drugs, there was no difference across tertiles of MS of systolic BP of the study group as a whole, between dippers and nondippers, and across group-specific tertiles of MS of systolic BP in dippers and nondippers. MS in systolic BP was significantly correlated with the reduction of systolic BP from day to night ($r = 0.64$; $P < 0.01$). Moreover, MS in systolic BP was correlated with weighted systolic BP SD in the population as a whole ($r = 0.11$; $P < 0.01$) and in dippers ($r = 0.26$; $P < 0.01$), but not in nondippers ($r = -0.05$; $P = 0.18$).

At follow-up, 405 (34%) patients received antiplatelet or anticoagulant drugs, 294 (25%) received statin, 266 (22.5%) received single antihypertensive therapy, 458 (38.5%) received double therapy, and 467 (39%) received triple therapy. During the follow-up (9.1 ± 4.9 years, range 0.4–20 years), 120 coronary events occurred. Specifically, there were 35 fatal myocardial infarctions, 54 nonfatal myocardial infarctions, and 31 coronary revascularizations. The event-rate of the population as a whole was 1.11 per 100 patient-years.

Table 1. Characteristics of study population as a whole, by tertiles of morning surge of SBP of all the patients and by dipping status

		Tertiles of morning surge of SBP				Dipping status		
	All (*n* = 1,191)	1-Tertile (*n* = 403)	2-Tertile (*n* = 383)	3-Tertile (*n* = 405)	*P*	Nondippers (*n* = 643)	Dippers (*n* = 548)	*P*
Age, years	69 ± 6	69 ± 6	68 ± 6	69 ± 6	0.10	69 ± 6	68 ± 6	<0.01
Men, *n* (%)	506 (42)	168 (42)	169 (44)	169 (42)	0.73	288 (45)	218 (40)	0.08
Body mass index, kg/m^2	28 ± 4	28 ± 5	28 ± 4	28 ± 4	0.93	28 ± 4	28 ± 4	0.24
Smokers, *n* (%)	141 (12)	44 (11)	48 (12)	49 (12)	0.76	68 (11)	73 (13)	0.14
Previous events, *n* (%)	104 (9)	37 (9)	28 (7)	39 (10)	0.48	64 (10)	40 (7)	0.11
Diabetes, *n* (%)	148 (12.5)	54 (13)	38 (10)	56 (14)	0.19	87 (14)	61 (11)	0.21
eGFR, ml/min/1.73 m^2	64.1 ± 14	64 ± 14	65.2 ± 14	63.3 ± 15	0.20	64.5 ± 15	63.8 ± 14	0.42
LDL cholesterol, mg/dl	128 ± 30	125 ± 29	131 ± 31	127 ± 30	0.04	127 ± 30	129 ± 30	0.12
LV hypertrophy, *n* (%)	369 (31)	127 (31)	110 (29)	132 (33)	0.48	205 (32)	164 (30)	0.47
Clinic SBP, mm Hg	150 ± 18	147 ± 17	148 ± 17	156 ± 19	<0.01	149 ± 17	152 ± 19	<0.01
Daytime SBP, mm Hg	135 ± 14	133 ± 14	133 ± 14	140 ± 15	<0.01	134 ± 15	137 ± 14	<0.01
Nighttime SBP, mm Hg	124 ± 15	129 ± 15	120 ± 14	121 ± 14	<0.01	129 ± 15	116 ± 13	<0.01
24-Hour SBP, mm Hg	132 ± 14	132 ± 14	129 ± 13	134 ± 14	<0.01	133 ± 14	131 ± 13	0.06
Weighted SBP SD, mm Hg	13.1 ± 3.3	12.7 ± 3.4	12.5 ± 3.2	13.8 ± 3.2	<0.01	12.9 ± 3.2	13.2 ± 3.3	0.08
Morning SBP surge, mm Hg	13 ± 12	0.3 ± 6	12 ± 3	25 ± 7	<0.01	7 ± 10	20 ± 10	<0.01
Clinic DBP, mm Hg	87 ± 10	86 ± 11	86 ± 10	89 ± 10	<0.01	87 ± 11	88 ± 10	0.05
Daytime DBP, mm Hg	78 ± 9	77 ± 9	78 ± 9	80 ± 9	<0.01	78 ± 9	79 ± 9	<0.01
Nighttime DBP, mm Hg	69 ± 9	71 ± 9	67 ± 9	66 ± 8	<0.01	71 ± 9	64 ± 8	<0.01
24-Hour DBP, mm Hg	75 ± 8	75 ± 8	74 ± 9	75 ± 8	0.25	76 ± 8	75 ± 8	0.10
Weighted DBP SD, mm Hg	8.9 ± 2.1	8.8 ± 2.2	8.8 ± 2.1	9.2 ± 1.9	0.02	8.9 ± 2.1	9.0 ± 2.0	0.41
Morning DBP surge, mm Hg	10 ± 7	4 ± 6	10 ± 5	16 ± 6	<0.01	6 ± 7	13 ± 7	<0.01

Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; LV, left ventricular; SBP, systolic blood pressure; SD, standard deviation.

Table 2. Characteristics of nondippers and dippers according to group-specific tertiles of morning surge of SBP

	Nondippers				Dippers			
	1-Tertile (*n* = 220)	2-Tertile (*n* = 223)	3-Tertile (*n* = 200)	*P*	1-Tertile (*n* = 190)	2-Tertile (*n* = 173)	3-Tertile (*n* = 185)	*P*
Age, years	70±6	69±6	69±6	0.47	68±6	68±7	69±6	0.08
Men, *n* (%)	94 (43)	90 (40)	104 (52)	0.04	73 (38)	68 (39)	77 (42)	0.81
Body mass index, kg/m^2	27±4	28±4	28±4	0.64	28±5	27±4	27±4	0.37
Smokers, *n* (%)	20 (9)	27 (12)	21 (10)	0.58	21 (11)	27 (16)	25 (13)	0.44
Previous events, *n* (%)	19 (9)	22 (10)	23 (11)	0.62	14 (7)	10 (6)	16 (9)	0.58
Diabetes, *n* (%)	31 (14)	28 (13)	28 (14)	0.87	20 (10)	17 (10)	24 (13)	0.61
eGFR, ml/min/1.73 m^2	65±15	62.8±14	65.7±15	0.10	65.4±13	62.3±14	63.5±15	0.12
LDL cholesterol, mg/dl	126±29	126±31	127±30	0.95	129±31	130±30	128±29	0.85
LV hypertrophy, *n* (%)	76 (34)	68 (30)	61 (30)	0.58	52 (27)	48 (28)	64 (35)	0.23
Clinic SBP, mm Hg	147±18	148±16	151±18	0.04	146±17	151±18	159±19	<0.01
Daytime SBP, mm Hg	134±14	133±14	135±15	0.18	133±14	136±13	142±14	<0.01
Nighttime SBP, mm Hg	133±16	127±14	127±14	<0.01	115±12	115±13	119±13	<0.01
24-Hour SBP, mm Hg	133±14	131±13	133±14	0.15	128±13	129±13	135±14	<0.01
Weighted SBP SD, mm Hg	12.9±3.4	12.4±3.1	13.7±2.9	<0.01	11.4±2.8	12.7±3.3	13.9±3.2	<0.01
Morning SBP surge, mm Hg	−3±6	7±3	17±4	<0.01	10±4	19±3	31±7	<0.01
Clinic DBP, mm Hg	85±11	87±10	88±11	0.05	86±10	87±11	91±9	<0.01
Daytime DBP, mm Hg	77±8	78±8	78±9	0.30	78±9	78±9	81±8	<0.01
Nighttime DBP, mm Hg	72±9	70±8	70±9	0.03	64±8	63±9	65±8	0.18
24-Hour DBP, mm Hg	76±8	76±9	76±9	0.98	74±8	74±9	76±8	0.02
Weighted DBP SD, mm Hg	9.0±2.2	8.7±2.2	8.9±2.0	0.28	8.8±2.1	8.7±2.0	9.3±1.8	<0.01
Morning DBP surge, mm Hg	3±6	7±5	12±6	<0.01	9±6	12±5	18±7	<0.01

Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; LVH, left ventricular; SBP, systolic blood pressure; SD, standard deviation.

Univariate analysis was performed to assess the association between risk of coronary events and age, gender, body mass index, smoking habit, previous events, diabetes, estimated glomerular filtration rate, low-density lipoprotein cholesterol, LV hypertrophy, single or double or triple antihypertensive therapy at baseline, antiplatelet therapy, statin therapy, clinic and ambulatory BP values, dipping status, weighted systolic BP SD and MS of systolic BP. The analysis showed that age, 24-hour daytime and nighttime systolic BP, diabetes, previous events, estimated glomerular filtration rate, LV hypertrophy, nondipping and high MS of BP in dippers were significantly associated with risk of coronary events ($P < 0.05$; Table 3). There was no association between risk of coronary events and tertiles of MS of BP in the global population and in nondippers (Table 3). If MS of systolic BP was analyzed as a continuous variable, it was not associated with coronary events in the population as a whole (hazard ratio for 1 mm Hg = 1.004, 95% confidence interval 0.989–1.020, $P = 0.59$). We did not find association between risk of coronary events and weighted systolic BP SD both in the population as a whole and in dippers and nondippers analyzed separately. Considering the impact of dipping on the occurrence of outcome and in view of the different influence of MS in BP on the incidence of coronary events in nondippers and dippers, we built a model including three groups, that is, dippers with MS < 23 mm Hg (first and second tertiles), dippers with MS > 23 mm Hg (third tertile), and nondippers. Dippers with MS > 23 mm Hg and nondippers were at higher risk than dippers with MS < 23 mm Hg (Table 3).

Figure 1 shows coronary event-free survival curves in dippers with MS < 23 mm Hg, in dippers with MS > 23 mm Hg and in nondippers.

When we assessed the impact of antiplatelet/anticoagulant or statin use and number of antihypertensive drugs at follow-up, results were substantially similar.

We included age, 24-hour systolic BP (because of stronger association with risk and because it includes both daytime and nighttime BP), diabetes, previous events, estimated glomerular filtration rate, and LV hypertrophy in the multivariate analysis together with the model including nondippers and dippers with different MS in BP.

Results of multivariate analysis are reported in Table 4. After adjustment for the above-mentioned covariates, the risk of coronary events was significantly and similarly higher in dippers with MS >23 mm Hg and in nondippers than in dippers with MS <23 mm Hg (Table 4). If 24-hour BP was

Table 3. Risk of coronary events in univariate analysis

	HR (95% CI)	*P*
Age (1 year)	1.091 (1.061–1.122)	<0.01
Diabetes (yes vs. no)	1.949 (1.137–3.342)	0.01
Previous events (yes vs. no)	2.689 (1.524–4.742)	<0.01
eGFR (1 ml/min/1.73 m^2)	0.987 (0.975–0.999)	0.03
LV hypertrophy (yes vs. no)	1.677 (1.164–2.418)	<0.01
24-Hour SBP (1 mm Hg)	1.015 (1.002–1.028)	0.02
Daytime SBP (1 mm Hg)	1.013 (1.000–1.025)	0.046
Nighttime SBP (1 mm Hg)	1.014 (1.003–1.026)	0.01
MS (all)		
1-Tertile	1	
2-Tertile	0.874 (0.569–1.344)	0.54
3-Tertile	0.935 (0.604–1.447)	0.76
Nondippers vs dippers	1.453 (1.002–2.107)	0.049
MS (nondippers)		
1-Tertile	1	
2-Tertile	0.852 (0.496–1.463)	0.56
3-Tertile	0.940 (0.543–1.628)	0.82
MS (dippers)		
1-Tertile	1	
2-Tertile	0.828 (0.353–1.940)	0.66
3-Tertile	2.203 (1.107–4.383)	0.02
Subgroups		
Dippers (MS < 23 mm Hg)	1	
Dippers (MS > 23 mm Hg)	2.426 (1.343–4.383)	<0.01
Nondippers	2.058 (1.280–3.308)	<0.01

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LV, left ventricular; MS, morning surge; SBP, systolic blood pressure. We reported variables significantly associated with outcome; we also reported results by tertiles of MS in the global population, in dippers and nondippers and analysis by subgroups.

replaced by daytime or nighttime BP, results remained substantially similar. If weighted systolic BP SD was forced into the model, results remained substantially unchanged.

DISCUSSION

This study shows that, in elderly treated hypertensive patients, MS of systolic BP is an independent predictor of coronary events in dippers, but not in nondippers. However, nondippers remain a group at risk of coronary events. Moreover, the negative prognostic impact of MS in dippers was independent of BP variability, evaluated as weighted systolic BP SD. To the best of our knowledge, there is a single study in the literature specifically evaluating the influence of MS of systolic BP on the incidence of coronary

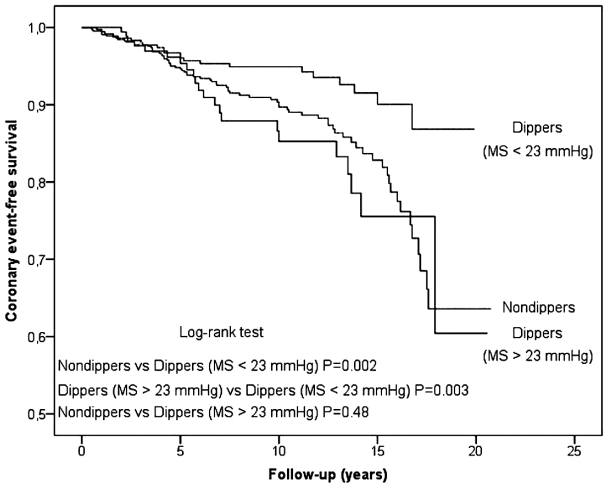

Figure 1. Coronary event-free survival curves in dippers with morning surge (MS) < 23 mm Hg (22 events), in dippers with MS > 23 mm Hg (22 events), and in nondippers (76 events).

Table 4. Risk of coronary events in multivariate analysis by specific subgroups

	HR (95% CI)	*P*
Dippers (MS <23 mm Hg)	1	
Dippers (MS >23 mm Hg)	1.912 (1.048–3.488)	0.03
Nondippers	1.739 (1.074–2.815)	0.02

Abbreviations: CI, confidence interval; HR, hazard ratio; MS, morning surge. Values are adjusted for age, diabetes, previous events, estimated glomerular filtration rate, left ventricular hypertrophy, and 24-hour systolic BP.

events.[14] The above-mentioned study, beyond sleep-trough MS of systolic BP, also studied the prognostic value of pre-awakening MS of systolic BP, as performed in this study. Li *et al.*[14] studied 5,645 subjects who were randomly recruited from general populations in eight countries. Mean age was 53 years, 20% received antihypertensive therapy at entry and 40% had hypertension. Subjects were followed for a median of 11.4 years. During this period, there were 228 coronary events. After adjustment for various covariates, a pre-awakening MS of systolic BP ≥ 28 mm Hg was significantly associated with higher risk of coronary events before (hazard ratio 1.50, 95% confidence interval 1.08–2.09) and more strongly after further adjustment for systolic night:day BP ratio (hazard ratio 1.64, 95% confidence interval 1.16–2.49). In the attempt to define cut-off points for risk stratification, Li *et al.*[14] explored the risk associated with all values of pre-awakening MS of systolic BP within the 5th–95th percentile interval. The overall risk of the global population was used as the reference. For pre-awakening MS of systolic BP, the lower boundary of the 95% confidence interval of the risk function crossed unity of the hazard ratio at 21.5 mm Hg for all cardiovascular events. The results of this and other analyses suggested that a MS of systolic BP < 20 mm Hg is probably not associated with increased risk. Interestingly, in our study subjects with MS of systolic BP > 23 mm Hg had

increased risk of coronary events. Thus, both the study by Li *et al.*[14] performed in a general population and this study performed in an elderly treated hypertensive population suggest that a high MS in systolic BP predisposes to a higher risk of coronary events.

A high MS of systolic BP per se and associated factors could contribute to the increased risk of coronary events. The role of peak systolic BP in predicting coronary events in older patients has been previously described.[23] In addition, it has been reported that high MS in BP is associated with increased oxidative stress,[29] increased markers of inflammation,[30,31] increased platelet aggregation,[3,32] impaired hemostatic activity,[3,33] and coronary microvascular dysfunction.[34] Moreover, we have previously reported that treated overdipper hypertensive patients, who generally show the highest MS in BP, have more nighttime ischemic episodes.[35] Whether this aspect is implicated in the occurrence of type 2 myocardial infarction[27] or predisposes to the occurrence of coronary events in the context of a successive high MS in BP or has no relevance independently of high MS in BP remains unclear. Finally, it has been described that overdipper hypertensive patients, who usually have the highest MS in BP, show greater odds for the presence of coronary artery calcium, a subclinical indicator of coronary atherosclerosis.[36] All the above-mentioned factors could contribute to the occurrence of coronary events in patients with high MS in BP. In nondippers, a persistent 24-hour BP overload and/or altered circadian BP profile could contribute to the occurrence of coronary artery disease. Indeed, it has been reported that nondipping is associated with subclinical coronary atherosclerosis[36] and coronary artery disease both in men and postmenopausal women.[37,38] Moreover, it has been described that nondipping may be associated with alterations in hemostasis or endothelial function[39] and increased platelet activation and inflammatory response.[40] These aspects could contribute to explain increased coronary event risk in nondipper patients compared with dipper ones.

This study has some limitations. First, we studied only Caucasian subjects and our results cannot be applied to other ethnic groups. Second, our data were obtained in elderly treated hypertensive patients and cannot be extrapolated to younger and untreated subjects. Third, it remains unclear whether higher MS of systolic BP reflects an intrinsic characteristic of some subjects or uncontrolled BP because of treatment features (dosage or timing of drug therapy); these aspects, however, do not lessen our findings. Fourth, the lack of association of coronary events with treatment strategy does not mean lack of efficacy of therapy because all subjects were treated with antihypertensive therapy, most of whom received multiple therapy, and patients were not randomized to antihypertensive or antiplatelet or statin therapy. Fifth, we did not specifically design a study to evaluate the risk associated with MS of systolic BP, but this study is part of a prospective assessment of the prognostic value of ambulatory BP parameters and other risk markers in our initially treated hypertensive patients; for subjects recruited from 1992 to 2000, MS was calculated by hourly means because single readings were not available, whereas for those recruited after 2000, we used single readings to calculate MS of systolic BP.

In conclusion, in elderly treated hypertensive patients, high MS of systolic BP predicts coronary events in dippers but not in nondippers. Nondippers, however, show high risk of coronary events independently of MS in BP.

DISCLOSURE

The authors declared no conflict of interest.

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