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Abstract—In previous studies, of which several were underpowered, the relation between cardiovascular outcome and blood pressure (BP) variability was inconsistent. We followed health outcomes in 8938 subjects (mean age: 53.0 years; 46.8% women) randomly recruited from 11 populations. At baseline, we assessed BP variability from the SD and average real variability in 24-hour ambulatory BP recordings. We computed standardized hazard ratios (HRs) while stratifying by cohort and adjusting for 24-hour BP and other risk factors. Over 11.3 years (median), 1242 deaths (487 cardiovascular) occurred, and 1049, 577, 421, and 457 participants experienced a fatal or nonfatal cardiovascular, cardiac, or coronary event or a stroke. Higher diastolic average real variability in 24-hour ambulatory BP recordings predicted ($P \leq 0.03$) total (HR: 1.14) and cardiovascular (HR: 1.21) mortality and all types of fatal combined with nonfatal end points (HR: ≥ 1.07) with the exception of cardiac and coronary events (HR: ≤ 1.02; $P \geq 0.58$). Higher systolic average real variability in 24-hour ambulatory BP recordings predicted ($P < 0.05$) total (HR: 1.11) and cardiovascular (HR: 1.16) mortality and all fatal combined with nonfatal end points (HR: ≥ 1.07), with the exception of cardiac and coronary events (HR: ≤ 1.03; $P \geq 0.54$). SD predicted only total and cardiovascular mortality. While accounting for the 24-hour BP level, average real variability in 24-hour ambulatory BP recordings added $<1\%$ to the prediction of a cardiovascular event. Sensitivity analyses considering ethnicity, sex, age, previous cardiovascular disease, antihypertensive treatment, number of BP readings per recording, or the night:day BP ratio were confirmatory. In conclusion, in a large population cohort, which provided sufficient statistical power, BP variability assessed from 24-hour ambulatory recordings did not contribute much to risk stratification over and beyond 24-hour BP. **(*Hypertension*. 2010;55:1049-1057.)**

Key Words: blood pressure variability ■ ambulatory blood pressure ■ population science ■ risk factors ■ epidemiology

Ambulatory blood pressure monitoring not only provides information on the blood pressure level but on the diurnal changes in blood pressure as well. Blood pressure variability includes both short-term and circadian components, which can be estimated by the SD of the blood pressure values over a defined period of the day or by the night:day blood pressure ratio, respectively. We recently reported in >7000 subjects recruited from 6 populations on the prognos-

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tic accuracy of long-term blood pressure variability.[1] Both daytime and nighttime blood pressure consistently predicted the composite end point of all cardiovascular events. Adjusted for the 24-hour blood pressure, the night:day blood pressure ratio predicted mortality but not fatal combined with nonfatal events.

Although the aforementioned analyses shed light on the association between outcome and long-term blood pressure variability, the predictive value of short-term reading-to-reading blood pressure variability remains uncertain. Possible limitations of previous studies were a lack of statistical power,[2–5] selection of specific groups of patients,[5–7] categorization of variability by arbitrary cutoff points,[2,4,7–9] and sole reliance on fatal end points.[10,11] Moreover, various parameters can capture short-term blood pressure variability over 24 hours, but most studies only considered the SD of systolic[4,6,12] or diastolic blood pressure or both.[8–10] To address the prognostic value of short-term blood pressure variability, we expanded, updated, and analyzed the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome.

Methods

Study Population

Previous publications described the construction of the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome.[1,13–15] Studies were eligible for inclusion if they involved a random population sample, if baseline information on ambulatory blood pressure and cardiovascular risk factors was available, and if the subsequent follow-up included fatal and nonfatal outcomes. At the time of writing this report, the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome included prospective studies from 11 centers (11 785 subjects). All studies received ethical approval and have been reported in peer-reviewed publications. In line with previous reports,[1,13–15] we excluded 252 participants because they were <18 years of age and 1892 participants because they had <10 daytime or <5 nighttime blood pressure readings. For the analyses of the variability, we additionally disregarded 703 subjects because they had missing readings during 3 consecutive hours. The 8938 analyzed participants were 2018 residents from Copenhagen, Denmark[16]; 1086 subjects from Noorderkempen, Belgium[17]; 1069 older men from Uppsala, Sweden[18]; 226 subjects from Novosibirsk, the Russian Federation[19,20]; 1430 inhabitants from Ohasama, Japan[21]; 346 villagers from the JingNing county, China[22]; 1093 subjects from Montevideo, Uruguay[23]; 161 subjects from Pilsen, the Czech Republic[20]; 900 subjects from Dublin, Ireland[24]; 303 subjects from Padova, Italy[20]; and 306 subjects from Kraków, Poland.[20] All participants gave informed written consent.

Blood Pressure Measurements

Conventional blood pressure was measured by trained observers with a mercury sphygmomanometer[16–20,22,24]; with validated auscultatory[21] (USM-700F, UEDA Electronic Works) or oscillometric[23] (OMRON HEM-705CP, Omron Corporation) devices, using the appropriate cuff size; and with participants in the sitting[16,17,19–24] or supine[18] position. Conventional blood pressure was the average of 2 consecutive readings obtained either at the person's home[17,19,20,22,23] or at an examination center.[16,18,21,24] Hypertension was a conventional blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic or the use of antihypertensive drugs.

We programmed portable monitors to obtain ambulatory blood pressure readings at 30-minute intervals throughout the whole day[21,24] or at intervals ranging from 15[16] to 30[18] minutes during daytime and from 30[16] to 60[18] minutes at night. The devices implemented an auscultatory algorithm (Accutracker II) in Uppsala[18] or an oscillometric technique (SpaceLabs 90202 and 90207, Nippon Colin, and ABPM-630) in the other cohorts.[17–24] While accounting for the daily pattern of activities of the participants, we defined daytime as the interval from 10:00 AM to 8:00 PM in Europeans[16–20,24] and South Americans[23] and from 8:00 AM to 6:00 PM in Asians.[21,22] The corresponding nighttime intervals ranged from 12:00 PM to 6:00 AM[16–20,23,24] and from 10:00 PM to 4:00 AM,[21,22] respectively. In dichotomous analyses, we defined systolic and diastolic nondipping as a night:day blood pressure ratio of ≥0.90.[1]

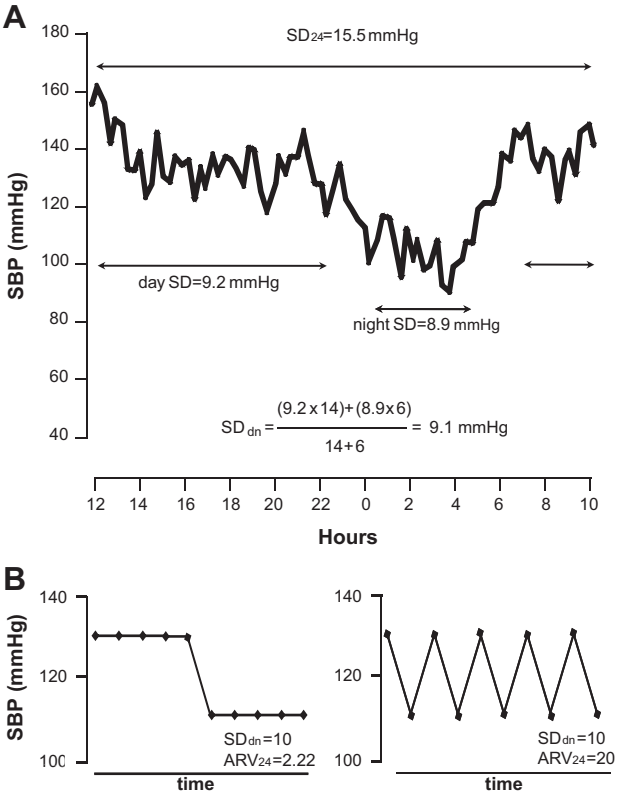

Figure 1. A, Average of the daytime and nighttime SD_{dn} and (B) ARV_{24}. Reproduced with permission from References 25 and 4, respectively. A, Illustrative 24-hour SBP profile. The SD of the 24-hour systolic blood pressure is substantially higher than the corresponding daytime and nighttime SDs, separately computed, because of the contribution of the pronounced nocturnal fall in blood pressure. ARV_{24} averages the absolute differences between consecutive readings and thereby accounts for the order of the blood pressure readings. B illustrates that, for distinct blood pressure signals, SD can be the same, whereas ARV_{24} is not.

As measures of short-term reading-to-reading blood pressure variability, we used the SD over 24 hours weighted for the time interval between consecutive readings (SD_{24}), the average of the daytime and nighttime SDs weighted for the duration of the daytime and nighttime interval (SD_{dn}),[25] and the average real variability weighted for the time interval between consecutive readings (average real variability in 24-hour ambulatory BP recordings; ARV_{24}).[4] The SD_{dn} is the mean of day and night SD values corrected for the number of hours included in each of these 2 periods (Figure 1A), according to the following formula[25]: SD_{dn}=[(day SD×hours included in the daytime)+(night SD×hours included in the nighttime)]/(hours included in daytime+nighttime). This method removes the influence of the day-night blood pressure difference from the estimate of blood pressure variability. The ARV_{24} averages the absolute differences of consecutive measurements and accounts in this manner for the order in which the blood pressure measurements are obtained (Figure 1B). It is calculated by the following formula:

$$ARV=\frac{1}{\sum w}\sum_{k=1}^{n-1} w\times|BP_{k+1}-BP_k|$$

where k ranges from 1 to N−1 and w is the time interval between BP_k and BP_{k+1}. N is the number of blood pressure readings.[4]

Other Measurements

We used the questionnaires originally administered in each cohort to obtain information on each subject's medical history and smoking and drinking habits. Body mass index was body weight in kilograms divided by height in meters squared. We measured serum cholesterol and blood glucose by automated enzymatic methods. Diabetes mellitus was the use of antidiabetic drugs, a fasting blood glucose concentration of ≥7.0 mmol/L,[16–21,23] a random blood glucose concentration of ≥11.1 mmol/L,[17,21,22] a self-reported diagnosis,[17,22,23] or diabetes mellitus documented in practice or hospital records.[23]

Ascertainment of Events

In each cohort, outcomes were adjudicated against source documents described in previous publications.[13,18,21,22,26–28] The adjudication process was the same in the Belgium study[28] and in all of the other studies included in the European Project on Genes in Hypertension (Novosibirsk, Pilsen, Padova, and Kraków).[29] Outcomes were coded according to the international classification of diseases (ICD), as tabulated in the online Data Supplement (Table S1), available at http://hyper.ahajournals.org.

Fatal and nonfatal stroke (ICD8/9 430 to 434 and 436, and ICD10 I60 to I64, I67 and I68) did not include transient ischemic attacks. Coronary events encompassed death from ischemic heart disease (ICD8 411 and 412, ICD9 411 and 414, and ICD10 I20, I24 and I25), sudden death (CD8 427.2 and 795, ICD9 427.5 and 798, and ICD10 I46 and R96), nonfatal myocardial infarction (ICD8/9 410, and ICD10 I21 and I22), and coronary revascularization. Cardiac events were composed of coronary end points and fatal and nonfatal heart failure (ICD8 428, 427.1, 427.2 and 429, ICD9 429, and ICD10 I50 and J81). Hospitalizations for unstable angina were coded as ischemic heart disease. In the Danish and Swedish cohorts, the diagnosis of heart failure required admission to the hospital. In the other cohorts, heart failure was either a clinical diagnosis or the diagnosis on the death certificate, but in all cases it was validated against hospital files or the records held by family doctors. The composite cardiovascular end point included all aforementioned end points plus cardiovascular mortality (ICD8 390 to 448, ICD9 390.0 to 459.9, and ICD10 I00 to I79 and R96). In all outcome analyses, we only considered the first event within each category.

Statistical Methods

For database management and statistical analysis, we used SAS software, version 9.1.3 (SAS Institute). For comparison of means and proportions, we applied the large-sample z test and the χ^2 statistic, respectively. We used a Pearson correlation coefficient to assess the correlations among the 3 measures of short-term blood pressure variability. Statistical significance was an α-level of <0.05 on 2-sided tests. After stratification for cohort and sex, we computed missing values of body mass index (n=916) and serum cholesterol (n=598) from the regression slope on age. In subjects with unknown smoking status (n=38) or drinking habits (n=435 among Swedish men and n=316 among the other cohorts), we set the design variable to the cohort- and sex-specific mean of the codes (0 and 1).

We used Cox regression to compute standardized hazard ratios (HRs). We checked the proportional hazards assumption by the Kolmogorov-type supremum test, as implemented in the PROC PHREG procedure of the SAS package and by testing the interaction terms between follow-up duration and the variable of interest. We first plotted incidence rates by fifths of the distributions of systolic and diastolic blood pressure variability, while standardizing by the direct method for cohort, sex, and age (≤40, 40 to 60, and ≥60 years). We computed HRs while stratifying for cohort and adjusting for sex and baseline characteristics, including age (used as a continuous variable), 24-hour heart rate, body mass index, smoking (0 and 1) and drinking (0 and 1), serum cholesterol, history of cardiovascular disease (0 and 1), diabetes mellitus (0 and 1), and treatment with antihypertensive drugs (0 and 1). In fully adjusted models, we additionally adjusted for the 24-hour systolic or diastolic blood pressure. We tested heterogeneity in the HRs across subgroups by introducing the appropriate interaction term in the Cox model. Finally, we applied the generalized R^2 statistic to assess the risks explained in Cox regression[30] by consecutively entering the 24-hour blood pressure and ARV_{24} as predictor variables into the models for the composite cardiovascular end point.

Results

Baseline Characteristics

The study population consisted of 6069 Europeans (67.9%), 1093 Asians (12.2%), and 1176 South Americans (19.9%). The 8938 participants included 4785 women (46.8%) and 3664 patients with hypertension (41.0%), of whom 1749 (47.7%) were taking blood pressure–lowering drugs. Mean (±SD) age was 53.0±15.8 years. At enrollment, 2558 participants (28.7%) were current smokers, and 4351 (53.1%) reported intake of alcohol.

Table 1 shows the baseline characteristics by quartiles of diastolic ARV_{24}. Across quartiles, all characteristics were significantly different ($P<0.05$). Participants with a higher blood pressure variability were older, had higher blood pressure, were more likely to be male, and were more likely to have diabetes mellitus (Table 1). The ARV_{24}, SD_{24}, and SD_{dn} were highly correlated with one another; the correlation coefficients ranged from 0.75 to 0.81 ($P\leq0.001$) for systolic blood pressure and from 0.71 to 0.79 ($P\leq0.001$) for diastolic blood pressure.

Incidence of Events

In the overall study population, median follow-up was 11.3 years (fifth to 95th percentile interval: 2.5 to 17.6 years). Across cohorts, median follow-up ranged from 2.5 years (fifth to 95th percentile interval: 2.3 to 2.6) in JingNing to 17.6 years (fifth to 95th percentile interval: 16.4 to 18.2 years) in Dublin. During 96 041 person-years of follow-up, 1242 participants died (12.9 per 1000 person-years), and 1049 experienced a fatal or nonfatal cardiovascular complication (11.3 per 1000 person-years). Mortality included 487 cardiovascular and 713 noncardiovascular deaths and 42 deaths from unknown causes (Table 2). Considering cause-specific first cardiovascular events, the incidence of fatal and nonfatal stroke amounted to 138 and 371, respectively. Cardiac events consisted of 172 fatal and 405 nonfatal events, including 72 fatal and 204 nonfatal cases of acute myocardial infarction, 50 deaths from ischemic heart diseases, 13 sudden deaths, 37 fatal and 151 nonfatal cases of heart failure, and 50 cases of surgical or percutaneous coronary revascularization. For comparison, cohort-specific mortality data and country-specific mortality statistics published by the World Health Organization are presented in Table S2.

Risk Associated With Blood Pressure Variability

Figure 2 shows the cohort-, sex-, and age-standardized rates of mortality and fatal combined with nonfatal outcomes across quintiles of systolic and diastolic ARV_{24}. The

Table 1. Baseline Characteristics of Participants

	Quartiles of Diastolic Average Real Variability, Limits, mm Hg			
Characteristic	≤6.9	>6.9 to ≤8.1	>8.1 to ≤9.6	>9.6
Subjects with characteristic				
All subjects in quartile, n	2235	2235	2234	2234
European, n (%)	1428 (63.9)	1586 (71.0)	1575 (70.5)	1480 (66.3)
Asian, n (%)	666 (29.8)	437 (19.6)	347 (15.5)	326 (14.6)
South American, n (%)	141 (6.3)	212 (9.5)	312 (14.0)	428 (19.2)
Women, n (%)	1225 (54.8)	1072 (48.0)	983 (44.0)	905 (40.5)
Antihypertensive treatment, n (%)	331 (14.8)	373 (16.7)	456 (20.4)	589 (26.4)
Smokers, n (%)	644 (28.9)	675 (30.3)	661 (29.7)	578 (26.1)
Using alcohol, n (%)	1065 (51.2)	1182 (56.6)	1181 (57.0)	923 (47.5)
Diabetes mellitus, n (%)	124 (5.6)	136 (6.1)	132 (5.9)	192 (8.6)
Cardiovascular disorder, n (%)	140 (6.3)	135 (6.0)	185 (8.3)	244 (10.9)
Mean±SD of characteristic				
Age, y	50.1±14.8	51.4±15.2	53.4±16.1	57.0±16.2
Body mass index, kg/m^2	24.2±3.6	25.1±4.1	25.9±4.0	26.4±4.4
Ambulatory measurements				
24-hour systolic, mm Hg	118.5±12.1	122.1±12.7	125.0±13.8	128.8± 14.9
24-hour diastolic, mm Hg	71.8±8.0	72.7±8.1	74.0±8.1	75.9±8.6
Daytime systolic, mm Hg	124.6±13.1	128.5±13.6	131.9±15.2	135.0±15.7
Daytime diastolic, mm Hg	76.7±8.6	77.8±8.8	79.3±8.9	81.0±9.6
Nighttime systolic, mm Hg	107.9±12.6	110.6±13.7	112.8±14.5	116.9±16.9
Nighttime diastolic, mm Hg	63.1±8.6	63.6±8.8	64.5±8.9	66.3±9.8
24-hour heart rate, bpm	71.1±8.6	71.7±9.0	72.1±9.0	73.1±9.5
Serum cholesterol, mmol/L	5.4±1.1	5.6±1.2	5.8±1.2	5.7±1.2

Trends across quartiles were significant ($P<0.05$) for all characteristics.

multivariable-adjusted and standardized HRs associated with systolic and diastolic blood pressure variability for mortality and for all fatal combined with nonfatal cardiovascular events appear in Table 2.

Mortality

In adjusted models not including the 24-hour blood pressure level, systolic blood pressure variability predicted both total and cardiovascular mortality ($P\leq0.04$), with the exception of SD_{24} in relation to total mortality ($P=0.17$). We obtained similar results after additional adjustment for the 24-hour systolic blood pressure, with the exception of SD_{24} and SD_{dn}, which no longer predicted cardiovascular mortality ($P\geq0.71$). Diastolic blood pressure variability predicted total and cardiovascular mortality both in adjusted and fully adjusted models ($P\leq0.002$; Table 2). Blood pressure variability did not predict noncardiovascular mortality ($0.14\leq P\leq0.75$).

Fatal and Nonfatal Cardiovascular Events

In adjusted analyses not including the 24-hour blood pressure level, systolic blood pressure variability predicted all of the fatal combined with nonfatal outcomes ($P\leq0.03$) with the exception of coronary events ($P\geq0.07$). However, in fully adjusted analyses, systolic blood pressure variability lost its predictive value with the exception of ARV_{24} in relation to all cardiovascular events combined and stroke (Table 2).

Diastolic blood pressure variability was predictive of all of the combined end points ($P\leq0.03$), with the exception of coronary events ($P\geq0.15$). In fully adjusted models, diastolic blood pressure variability only predicted all cardiovascular events combined (ARV_{24} and SD_{dn}) and fatal plus nonfatal stroke (ARV_{24}). Figure 3 shows the absolute risk of a combined cardiovascular event in relation to the ARV_{24} at different levels of systolic and diastolic 24-hour blood pressure (Figure 3A and 3B) and in relation to 24-hour blood pressure at different levels of the systolic and diastolic ARV_{24} (Figure 3C and 3D). The analyses were standardized to the distributions (mean or ratio) of cohort, sex, age, 24-hour heart rate, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and treatment with antihypertensive drugs. Absolute risk increased with both the 24-hour blood pressure ($P<0.001$) and ARV_{24} ($P\leq0.04$). However, with the 24-hour blood pressure in the model, ARV_{24} added only 0.1% to the explained risk of a composite cardiovascular event (Table 3).

Sensitivity Analyses

In sensitivity analyses, we considered total mortality and all cardiovascular events combined in relation to diastolic and systolic ARV_{24} (Tables S3 and S4). We stratified the study population according to sex; median age (60 years); antihypertensive treatment; the presence or absence of hypertension; European, Asian, or South American origin; numbers of

Table 2. Multivariable-Adjusted Standardized Hazard Ratios Relating Outcome to Blood Pressure Variability

	Systolic Blood Pressure			Diastolic Blood Pressure		
Outcome (No. of Events)	SD_{24}	SD_{dn}	ARV_{24}	SD_{24}	SD_{dn}	ARV_{24}
SD, mm Hg	15.6	12.2	11.2	11.8	9.1	8.5
Mortality						
Total (n=1242)						
Adjusted	1.05 (0.98 to 1.13)	1.13 (1.06 to 1.21)§	1.14 (1.06 to 1.22)§	1.11 (1.04 to 1.19)§	1.17 (1.09 to 1.24)§	1.12 (1.05 to 1.19)§
Fully adjusted*	1.00 (0.94 to 1.07)	1.08 (1.01 to 1.15)†	1.11 (1.04 to 1.18)§	1.09 (1.03 to 1.16)‡	1.16 (1.09 to 1.23)§	1.13 (1.07 to 1.19)§
Cardiovascular (n=487)						
Adjusted	1.11 (1.00 to 1.24)†	1.13 (1.02 to 1.26)†	1.23 (1.11 to 1.36)§	1.21 (1.10 to 1.34)§	1.24 (1.13 to 1.36)§	1.27 (1.17 to 1.38)§
Fully adjusted*	1.03 (0.93 to 1.13)	1.05 (0.95 to 1.17)	1.17 (1.07 to 1.28)†	1.15 (1.05 to 1.26)‡	1.18 (1.08 to 1.29)§	1.21 (1.12 to 1.31)§
Fatal and Nonfatal Events						
Cardiovascular (n=1049)						
Adjusted	1.13 (1.06 to 1.22)§	1.15 (1.07 to 1.24)§	1.19 (1.11 to 1.27)§	1.15 (1.07 to 1.23)§	1.16 (1.09 to 1.24)§	1.16 (1.09 to 1.23)§
Fully adjusted*	1.02 (0.96 to 1.09)	1.04 (0.97 to 1.11)	1.07 (1.00 to 1.14)†	1.05 (0.99 to 1.12)	1.07 (1.01 to 1.14)†	1.07 (1.01 to 1.13)†
Cardiac (n=577)						
Adjusted	1.13 (1.02 to 1.24)†	1.11 (1.01 to 1.23)†	1.11 (1.00 to 1.22)†	1.10 (1.00 to 1.20)†	1.11 (1.02 to 1.21)§	1.10 (1.01 to 1.20)§
Fully adjusted*	1.03 (0.94 to 1.12)	1.01 (0.92 to 1.11)	1.03 (0.94 to 1.13)	1.02 (0.94 to 1.11)	1.03 (0.95 to 1.12)	1.02 (0.94 to 1.11)
Coronary (n=421)						
Adjusted	1.11 (0.99 to 1.24)	1.09 (0.97 to 1.22)	1.06 (0.94 to 1.19)	1.07 (0.96 to 1.19)	1.08 (0.97 to 1.19)	1.07 (0.97 to 1.19)
Fully adjusted*	1.07 (0.96 to 1.18)	1.04 (0.93 to 1.16)	1.03 (0.93 to 1.14)	1.02 (0.93 to 1.13)	1.02 (0.92 to 1.12)	1.02 (0.92 to 1.12)
Stroke (n=457)						
Adjusted	1.13 (1.01 to 1.26)†	1.16 (1.04 to 1.30)†	1.25 (1.13 to 1.39)§	1.22 (1.13 to 1.35)§	1.22 (1.10 to 1.35)§	1.26 (1.14 to 1.38)§
Fully adjusted*	0.98 (0.88 to 1.09)	1.03 (0.92 to 1.14)	1.10 (1.00 to 1.21)†	1.08 (0.99 to 1.19)	1.09 (0.99 to 1.20)	1.14 (1.05 to 1.23)†

Values are standardized hazard ratios (HRs), which express the risk per SD increase in the predictor variables. All HRs (95% confidence interval) were computed by Cox regression stratified for cohort and adjusted for sex, age, 24-hour heart rate, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and treatment with antihypertensive drugs.

*Data were additionally adjusted for the corresponding 24-hour blood pressure level.

†$P<0.05$ HR significance.

‡$P<0.01$ HR significance.

§$P<0.001$ HR significance.

blood pressure readings in individual blood pressure recordings; and dipping status dichotomized by a night:day blood pressure ratio of 0.9. HRs were not statistically different across strata ($0.07<P<0.93$) with 2 exceptions. First, the HR for diastolic ARV_{24} in relation to total mortality was higher in treated than untreated subjects (1.20 versus 1.04; $P=0.02$). Second, the HR for diastolic ARV_{24} in relation to all cardiovascular events was higher in Asians than in Europeans (1.36 versus 1.04; $P=0.009$) but similar in Europeans and South Americans ($P=0.20$). The predictive value of systolic ARV_{24} was similar across all strata (Table S4; $0.07\leq P\leq 0.88$).

Analyses on the basis of daytime and nighttime ARV were confirmative but did not attain the significance levels of ARV_{24} because of the fewer readings included in the daytime and nighttime ARV (data not shown). For SD_{24} and SD_{dn}, none of the interaction terms with the strata shown in Tables S3 and S4 reached significance ($0.08<P<0.97$).

Discussion

Our current meta-analysis of individual data included >8000 people randomly recruited from 11 populations and covered, on average, 11 years of follow-up, during which 1242 people died and 1049 experienced a major cardiovascular complication. The key finding was that, while accounting for the 24-hour blood pressure level and other covariables, blood pressure variability was a significant and independent predictor of mortality and of cardiovascular and stroke events. However, the proportion of the risk explained by the variability index is low.

For most outcomes, ARV_{24} was a better predictor than SD_{24} and SD_{dn}, probably because, as illustrated in Figure 1, subjects with different blood pressure profiles might have similar SDs but different ARV_{24}s. Thus, ARV_{24} might be a more specific measure of blood pressure variability than SD.

Several prospective studies in populations[4,10–12,31] and hypertensive patients[2,3,5–9] searched for association between cardiovascular outcomes and blood pressure variability but reported inconsistent results. This might be because of insufficient sample size, too few events, varying definitions of the outcomes of interest, or the use of different indices of blood pressure variability. To assess blood pressure variability, most studies used ambulatory blood pressure monitoring with intermittent readings at intervals ranging from 15[8] to 30[5] minutes throughout 24 hours. In the Northwick Park Study,[3] the investigators performed continuous intra-arterial recordings but did not fully exploit the potential of this recording technique. Instead of analyzing variability in the frequency

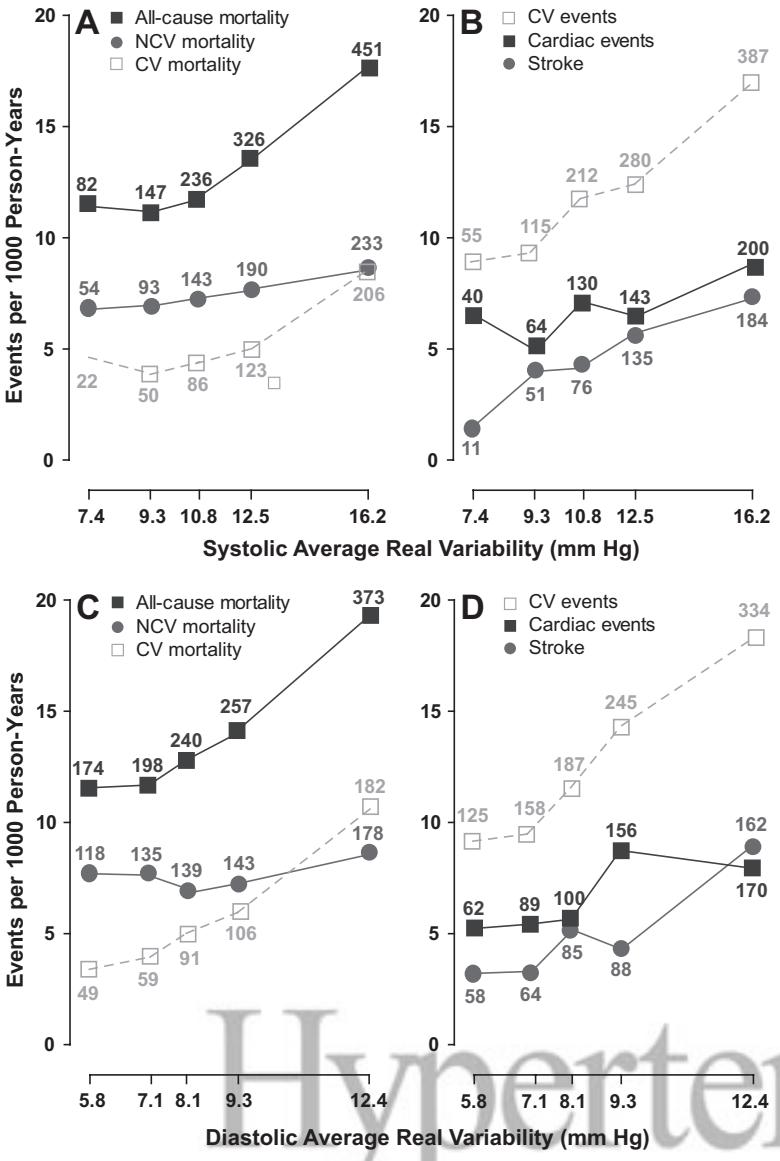

Figure 2. Incidence of mortality (A and C) and cardiovascular events (B and D) by fifths of the distributions of the systolic (A and B) and diastolic (C and D) average real variability in 8938 participants. Incidence rates were standardized for cohort, sex, and age by the direct method. The number of events contributing to the rates is presented. CV and NCV indicate cardiovascular and noncardiovascular, respectively.

domain, they computed hourly means of blood pressure and the within-subject SD of the hourly means as a measure of each participant's blood pressure variability. In the Ohasama Study, investigators used the self-measured blood pressure[31] in addition to ambulatory blood pressure monitoring.[10] In all but 2 studies,[4,7] the researchers used the SD of daytime, nighttime, or 24-hour blood pressure as an index of variability. Four studies[5,8–10] deliberately did not report on the predictive value of the variability in the 24-hour blood pressure, because the diurnal blood pressure profile also includes long-term variability, which is captured by the night:day blood pressure ratio. To address this potential concern, we computed SD_{dn} and ARV_{24} as measures of variability. Only 2 other prospective studies, one in a small general Venezuelan population (312 subjects with 31 composite cardiovascular end points),[4] and one in a hypertensive population,[7] implemented ARV_{24}. Bilo et al[25] were the first to propose SD_{dn}, but to our knowledge there is no prospective study that has used this index of variability.

Diastolic blood pressure variability tended to be a stronger predictor of outcome than systolic blood pressure variability. We can only speculate about the mechanisms underlying this finding, but arterial stiffness might be involved. In normal conditions, systolic and diastolic blood pressures change in parallel in response to physiological stimuli, such as excise or arousal. However, in subjects with stiff arteries, when systolic blood pressure increases, often diastolic blood pressure increases less or even falls,[32,33] giving rise to larger variability. On the other hand, a chance finding cannot be excluded.

From a clinical point of view, our current findings suggest that, although statistically significant, the clinical applicability of blood pressure variability for risk stratification might be limited. First, antihypertensive drug treatment is bound to influence blood pressure variability. Second, the reproducibility of blood pressure variability is poor. In 97 normotensive subjects,[34] the relative repeatability coefficient of the SD of the 24-hour blood pressure in individual recordings, expressed as a percentage of the fifth to 95th percentile interval in all recordings, was 13% systolic and 16% diastolic, whereas for the 24-hour blood pressure these coefficients were 4% and 5%, respectively, lower values, indicating better

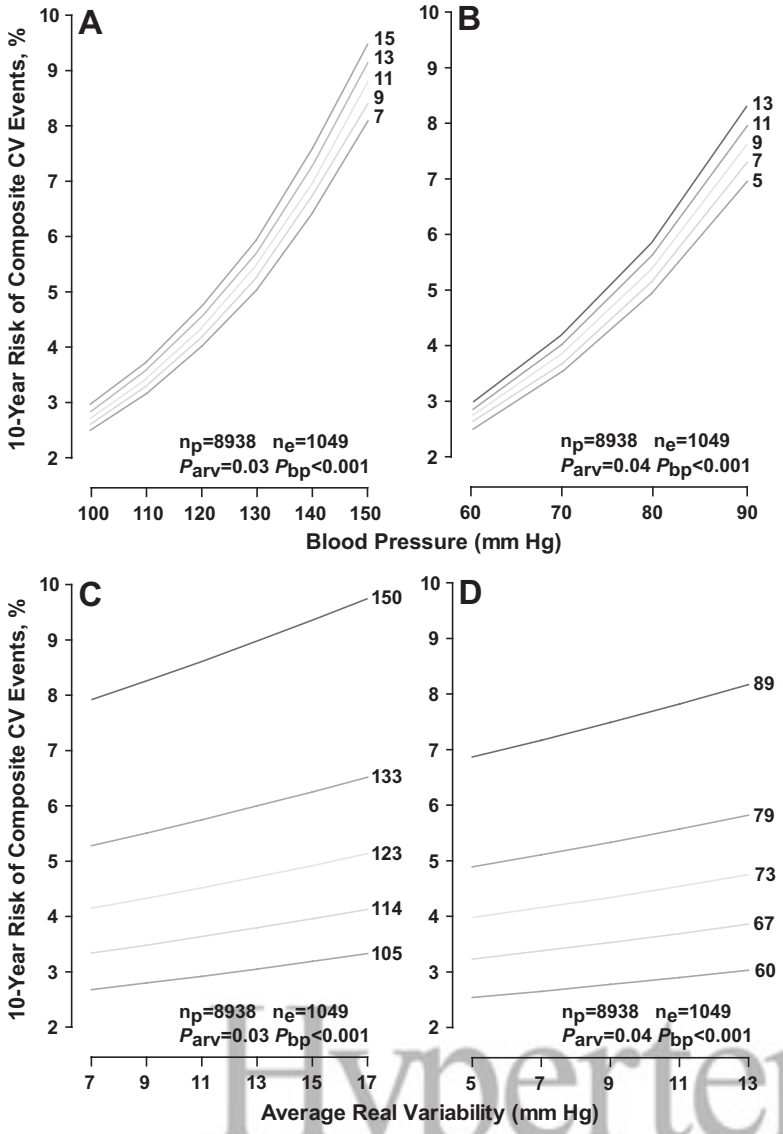

Figure 3. Ten-year absolute risk of combined cardiovascular events in relation to 24-hour blood pressure (A and B) at different levels of systolic and diastolic average real variability over 24 hours (ARV_{24}) and in relation to ARV_{24} (C and D) at different levels of 24-hour systolic and diastolic blood pressure. The analyses were standardized to the distributions (mean or ratio) of cohort, sex, age, 24-hour heart rate, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and treatment with antihypertensive drugs. In panels A and B, the risk functions span the 5th to 95th percentile interval of the 24-hour blood pressure and correspond to the 5th, 25th, 50th, 75th and 95th percentiles of ARV. In panels C and D, the risk functions span the 5th to 95th percentile interval of ARV and correspond to the 5th, 25th, 50th, 75th and 95th percentiles of the 24-hour blood pressure. *P* values are for the independent effect of ARV (P_{arv}) and 24-hour blood pressure (P_{bp}). n_p and n_e indicate the number of participants at risk and the number of events.

reproducibility.[34] Finally, the added value in terms of absolute risk was modest in our population. For example, in adjusted analyses (Figure 3), the increase in the 10-year absolute risk of a composite cardiovascular event associated with an increase from the median to the 75th percentile was 0.21% for systolic ARV_{24} (1.5 mm Hg) and 1.23% for the 24-hour systolic blood pressure (9.8 mm Hg). The corresponding estimates for diastolic ARV_{24} and for 24-hour diastolic blood pressure were 0.16% (2.3 mm Hg) and 1.05% (5.8 mm Hg), respectively.

Notwithstanding the statistical power and the consideration of fatal and nonfatal events, our study has potential limitations. First, the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome is currently composed of 11 population-based cohorts from 3 continents, but our results might not yet be generally applicable, in particular to Africans of black ancestry or African Americans. Second, we and most other investigators applied intermittent techniques of ambulatory blood pressure monitoring, which compared with continuous blood pressure recording, is a less precise technique to capture short-term blood pressure variability. However, intra-arterial recordings or continuous recordings of the arterial signal at the finger are difficult, if not impossible, to implement in large epidemiological studies. Third, in the current meta-analysis of individual data, blood pressure variability turned out to provide independent risk information, and this finding was consistent in stratified sensitivity analyses. However, even in large cohort studies with numerous events, the power to detect heterogeneity across strata is generally low. For example, considering a 2-sided α-level of 0.05, we had only 46% power to detect a 0.24 difference between normotensive and hypertensive subjects in the log-transformed HR of all cardiovascular events.

Perspectives

In line with several[6–8,10,11] but not all[9] previous studies, our current report established that short-term reading-to-reading blood pressure variability is an independent risk factor, but moreover it also highlighted that the level of the 24-hour blood pressure remains the primary blood pressure–related

Table 3. Risk of a Composite Cardiovascular Event Explained by Cox Regression

	Systolic Blood Pressure			Diastolic Blood Pressure		
Models	Likelihood Ratio	*P*	R^2 (%)	Likelihood Ratio	*P*	R^2 (%)
Basic model*	10 307.0	…	9.95	10 307.0	…	9.95
+24-hour blood pressure	10 213.4	< 0.001	11.1	10 258.2	< 0.001	10.6
+24-hour blood pressure and ARV	10 209.4	0.046	11.2	10 250.6	0.006	10.7

P values are for the improvement of the fit across nested models. … indicates not applicable.

*The basic Cox model was stratified for cohort and included as covariables sex, age, 24-hour heart rate, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and treatment with antihypertensive drugs.

risk factor to account for in clinical practice. This caveat also applies to the morning surge in blood pressure, as described in the companion article. Notwithstanding these limitations, in the setting of clinical research, studies of blood pressure variability will continue to generate meaningful information. For research making use of intermittent techniques of ambulatory blood pressure monitoring, our current findings suggest that both SD_{dn} and ARV_{24} might be useful measures, but not the SD computed over the whole day, which also includes the day-night blood pressure difference.

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Disclosures

None.

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Data Supplement

Prognostic Value of Reading-to-Reading Blood Pressure Variability over 24 Hours in 8938 Subjects from 11 Populations.

Short title: Blood Pressure Variability as Risk Predictor

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Table S1. International Classification of Diseases (ICD) Codes Applied in each Cohort

Cohort	Stroke	Myocardial infarction	Angina pectoris	Heart failure
Copenhagen	*ICD8* 430-434 and 436, *ICD10* I60-I64	*ICD8* 410, *ICD10* I21-I22	*ICD8* 411-414, *ICD10* I20 and I23-I25	*ICD8* 427.0, 427.1, 428.0, 429.0, 519.1 and 782.4, *ICD10* I50 and J81
Noorderkempen	*ICD8* 430-434, 436 and 438	*ICD8* 410	*ICD8* 413	*ICD8* 427.0, 427.1, 428.0, 429.0, 519.1 and 782.4
Uppsala	*ICD9* 430-434 and 436, *ICD10* I60-I64	*ICD9* 410, *ICD10* I21	*ICD9* 413 and 411.1, *ICD10* I20	*ICD9* 429, *ICD10* I50
Dublin	*ICD9* 430-434 and 436	*ICD9* 410 and 412	*ICD9* 413, 411.1 and 414	*ICD9* 428
Novosibirsk	*ICD9* 430-434 and 436	*ICD9* 410 and 412	*ICD9* 413 and 411.1	*ICD9* 428
Pilsen	*ICD9* 430-434 and 436	*ICD9* 410 and 412	*ICD9* 413 and 411.1	*ICD9* 428
Padova	*ICD9* 430-434 and 436	*ICD9* 410 and 412	*ICD9* 413 and 411.1	*ICD9* 428
Kraków	*ICD9* 430-438	*ICD9* 410	*ICD9* 413	*ICD9* 428.0-428.4
Montevideo	*ICD10* I60-I64	*ICD10* I21-I22	*ICD10* I20	*ICD10* I50 and J81
Ohasama	*ICD10* I60-I64	……	……	……
JingNing	*ICD9* 430-431 and 434	*ICD9* 410	*ICD9* 413	*ICD9* 428, 427.0 and 427.1

…… Not assessed, because of the low incidence in the Ohasama cohort.

Table S2. Cohort-Specific Mortality Data and Country-Specific Mortality Statistics as Published by the World Health Organization (WHO).

	Observed in cohorts		WHO 2002*
Cohort	All-cause mortality	Cardiovascular mortality	Cardiovascular mortality
Noorderkempen (n=2541)	170/2541(7%)	59/170 (35%)	26%
Copenhagen (n=2311)	393/2311(17%)	136/393 (35%)	26%
Uppsala (n=1143)	315/1143(28%)	140/315 (44%)	33%
Dublin (n=981)	36/981 (4%)	19/36 (53%)	30%
EPOGH† (n=1055)	23/1055 (2%)	6/23 (26%)	37%
Kraków (n=321)	3/321 (1%)	2/3 (67%)	34%
Padova (n=310)	4/310 (1%)	0/4 (0%)	28%
Novosibirsk (n=250)	15/250 (6%)	4/15 (27%)	52%
Pilsen (n=174)	1/174 (1%)	0/1 (0%)	40%
Montevideo (n=1859)	124/1859(7%)	46/124 (37%)	25%
Ohasama (n=1535)	345/1535(22%)	127/345 (37%)	24%
JingNing (n=360)	14/360 (4%)	6/14 (43%)	26%
IDACO total (n=8938)§	1242/8938 (14%)	487/1242 (39%)	25.6%‡

* Country-specific mortality due to ischemic heart disease and cerebrovascular disease, as reported by the World Health Organization (http://www.who.int/countries/en/).
† All 4 centers participating in the European Project on Genes in Hypertension combined.
‡ Deaths related to ischemic heart disease and cerebrovascular disease in high income countries total in 2004 http://www.who.int/mediacentre/factsheets/fs310_2008.pdf.
§ Subjects included in the present analysis.

Table S3. Multivariable-Adjusted Hazard Ratios for Total Mortality and for Fatal and Nonfatal Cardiovascular Events for Diastolic Average Real Variability According to Baseline Characteristics

Strata	At risk (n)	Deaths (n)	Total mortality		Events (n)	Cardiovascular Events	
All participants	8938	1242	1.13 (1.07-1.19)‡		1049	1.07 (1.01-1.13)*	
Women	4186	398	1.19 (1.04-1.36)†		319	1.11 (0.96-1.27)	
Men	4752	844	1.10 (1.02-1.18)*		730	1.10 (1.02-1.19)†	
<60 years	5349	190	1.13 (0.92-1.37)		189	1.04 (0.85-1.24)	
≥60 years	3589	1052	1.11 (1.04-1.19)†		860	1.12 (1.05-1.20)*	
Normotension	5981	605	1.08 (0.97-1.20)		441	1.05 (0.93-1.18)	
Hypertension	2957	637	1.13 (1.04-1.22)†		608	1.13 (1.05-1.22)†	
Nº of readings ≤47	3045	408	1.23 (1.08-1.39)†		330	1.27 (1.12-1.44)†	
Nº of readings 48-71	2891	378	1.13 (1.01-1.26)*		338	1.04 (0.93-1.16)	
Nº of readings >71	3002	456	1.09 (0.96-1.22)		381	1.06 (0.93-1.20)	
Non-dippers	2794	539	1.18 (1.08-1.28)†		428	1.09 (0.99-1.19)	
Dippers	6144	703	1.04 (0.93-1.15)		621	1.12 (1.01-1.24)*	
Untreated	7183	753	1.04 (0.95-1.14)	0.02	586	1.04 (0.95-1.14)	
Treated	1749	488	1.20 (1.10-1.32)‡		463	1.16 (1.06-1.27)‡	
Without ß-blocker	1162	344	1.22 (1.05–1.41)*		321	1.18 (1.02-1.36)*	
With ß-blocker	587	144	1.23 (1.06–1.44)*		142	1.08 (0.92-1.27)	
Asian	1776	331	1.21 (1.04-1.41)*		239	1.36 (1.15-1.62)‡	0.009
European	6069	840	1.08 (1.00-1.17)*		724	1.04 (0.96-1.13)	
South American	1093	71	1.29 (1.01-1.63)*		86	1.19 (0.97-1.47)	

Hypertension was a conventional blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or the use of antihypertensive medications. Nº of readings refers to the number of blood pressure measurements in a single ambulatory recording. Values are standardized hazard ratios (95% confidence interval), which express the risk per SD increase in the predictor variable. All hazard ratios were stratified for cohort and adjusted, as appropriate, for sex, age, 24-hour heart rate, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, treatment with antihypertensive drugs, and the 24-hour diastolic blood pressure. Significance of the hazard ratios: * $P<0.05$; † $P<0.01$; and ‡ $P<0.001$. Braces point to heterogeneity between subgroups (P-value for difference between strata given).

TABLE S4. Multivariable-Adjusted Hazard Ratios for Total Mortality and for Fatal and Nonfatal Cardiovascular Events for Systolic Average Real Variability According to Baseline Characteristics

Strata	At risk (n)	Deaths (n)	Total mortality	Events (n)	Cardiovascular Events
All participants	8938	1242	1.11 (1.04–1.18)‡	1049	1.07 (1.01–1.14)*
Women	4186	398	1.13 (0.99-1.28)	319	1.04 (0.91-1.20)
Men	4752	844	1.10 (1.00-1.19)*	730	1.09 (1.00-1.19)*
<60 years	5349	190	1.15 (0.95-1.38)	189	1.07 (0.89-1.28)
≥60 years	3589	1052	1.09 (1.01-1.18)*	860	1.09(1.01-1.18)*
Normotension	5981	605	1.08 (0.97-1.19)	441	1.02 (0.90-1.15)
Hypertension	2957	637	1.13 (1.02-1.24)†	608	1.13 (1.03-1.24)†
Nº of readings ≤47	3045	408	1.17 (1.03-1.34)*	330	1.21 (1.05-1.39)†
Nº of readings 48-71	2891	378	1.09 (0.95-1.25)	338	1.03 (0.90-1.18)
Nº of readings >71	3002	456	1.09 (0.98-1.22)	381	1.04 (0.92-1.18)
Non-dippers	2794	539	1.16 (1.04-1.28)†	428	1.05 (0.98-1.16)
Dippers	6144	703	1.08 (0.97-1.19)	621	1.14 (1.02-1.26)*
Untreated	7183	753	1.06 (0.96-1.19)	586	1.03 (0.93-1.14)
Treated	1749	488	1.16 (1.05-1.29)†	463	1.13 (1.02-1.25)*
Without ß -blocker	1162	344	1.07 (0.93-1.24)	321	1.14 (0.94-1.27)
With ß-blocker	587	144	1.25 (1.03-1.50)*	142	1.04 (0.88-1.23)
Asian	1776	331	1.12 (0.96-1.30)	239	1.20 (1.01-1.42)*
European	6069	840	1.10 (1.01-1.20)*	724	1.04 (0.95-1.14)
South American	1093	71	1.32 (0.99-1.73)	86	1.10 (0.85-1.42)

Hypertension was a conventional blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or the use of antihypertensive medications. Nº of readings refers to the number of blood pressure measurements in a single ambulatory recording. Values are standardized hazard ratios (95% confidence interval), which express the risk per SD increase in the predictor variable. All hazard ratios were stratified for cohort and adjusted, as appropriate, for sex, age, 24-hour heart rate, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, treatment with antihypertensive drugs, and the 24-hour systolic blood pressure. Significance of the hazard ratios: * $P<0.05$; † $P<0.01$; and ‡ $P<0.001$. There were no statistically significant differences across the strata according to baseline characteristics ($P\geq0.07$).