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# Association of Office and Ambulatory Blood Pressure With Mortality and Cardiovascular Outcomes

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**IMPORTANCE** Blood pressure (BP) is a known risk factor for overall mortality and cardiovascular (CV)-specific fatal and nonfatal outcomes. It is uncertain which BP index is most strongly associated with these outcomes.

**OBJECTIVE** To evaluate the association of BP indexes with death and a composite CV event.

**DESIGN, SETTING, AND PARTICIPANTS** Longitudinal population-based cohort study of 11 135 adults from Europe, Asia, and South America with baseline observations collected from May 1988 to May 2010 (last follow-ups, August 2006-October 2016).

**EXPOSURES** Blood pressure measured by an observer or an automated office machine; measured for 24 hours, during the day or the night; and the dipping ratio (nighttime divided by daytime readings).

**MAIN OUTCOMES AND MEASURES** Multivariable-adjusted hazard ratios (HRs) expressed the risk of death or a CV event associated with BP increments of 20/10 mm Hg. Cardiovascular events included CV mortality combined with nonfatal coronary events, heart failure, and stroke. Improvement in model performance was assessed by the change in the area under the curve (AUC).

**RESULTS** Among 11 135 participants (median age, 54.7 years, 49.3% women), 2836 participants died (18.5 per 1000 person-years) and 2049 (13.4 per 1000 person-years) experienced a CV event over a median of 13.8 years of follow-up. Both end points were significantly associated with all single systolic BP indexes ($P < .001$). For nighttime systolic BP level, the HR for total mortality was 1.23 (95% CI, 1.17-1.28) and for CV events, 1.36 (95% CI, 1.30-1.43). For the 24-hour systolic BP level, the HR for total mortality was 1.22 (95% CI, 1.16-1.28) and for CV events, 1.45 (95% CI, 1.37-1.54). With adjustment for any of the other systolic BP indexes, the associations of nighttime and 24-hour systolic BP with the primary outcomes remained statistically significant (HRs ranging from 1.17 [95% CI, 1.10-1.25] to 1.87 [95% CI, 1.62-2.16]). Base models that included single systolic BP indexes yielded an AUC of 0.83 for mortality and 0.84 for the CV outcomes. Adding 24-hour or nighttime systolic BP to base models that included other BP indexes resulted in incremental improvements in the AUC of 0.0013 to 0.0027 for mortality and 0.0031 to 0.0075 for the composite CV outcome. Adding any systolic BP index to models already including nighttime or 24-hour systolic BP did not significantly improve model performance. These findings were consistent for diastolic BP.

**CONCLUSIONS AND RELEVANCE** In this population-based cohort study, higher 24-hour and nighttime blood pressure measurements were significantly associated with greater risks of death and a composite CV outcome, even after adjusting for other office-based or ambulatory blood pressure measurements. Thus, 24-hour and nighttime blood pressure may be considered optimal measurements for estimating CV risk, although statistically, model improvement compared with other blood pressure indexes was small.

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Editor's Note page 420

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 459

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North American,[1,2] European,[3,4] Japanese,[5] and Chinese[6] guidelines unanimously recommend ambulatory blood pressure (BP) monitoring for BP assessment. However, which BP index among the multitude of measurements that can be derived from conventional and ambulatory BP recordings is more closely associated with adverse health outcomes remains unresolved. In several studies, the association between cardiovascular risk and BP was strongest for systolic readings taken at nighttime,[7] an observation subsequently replicated among patients with hypertension[8] or referred for ambulatory BP monitoring.[9] More recently,[10] BP readings via automated office machines was introduced as an alternative to ambulatory monitoring, but the strength of its association with a cardiovascular outcome is unknown. Given the uncertainty left by these previous findings,[7-13] the objective of this study was to evaluate various types of BP measurements and assess the strength of their associations with mortality and adverse cardiovascular outcomes.

### Key Points

**Question** What is the association of office and ambulatory blood pressure with subsequent risk of mortality and cardiovascular outcomes?

**Findings** In a population-based cohort of 11 135 adults, higher 24-hour and nighttime blood pressure readings were significantly associated with greater risks of death and cardiovascular events that included cardiovascular mortality combined with nonfatal coronary events, heart failure, or stroke. This association persisted after adjusting for other blood pressure measurements taken during an office visit or during ambulatory monitoring.

**Meaning** Higher 24-hour and nighttime blood pressure readings were significantly associated with greater risks of death and a composite of cardiovascular outcomes, although statistically the incremental model improvement was small.

## Methods

### Study Participants

All population studies included in the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO)[14] received ethical approval from the responsible institutional review boards in their country of origin and adhered to the principles of the Declaration of Helsinki.[15] Participants provided written informed consent. The IDACO database was constructed and is regularly updated at the Studies Coordinating Centre in Leuven, but does not include any data allowing identification of study participants. In accordance with current national regulations, review boards either waived or provided ethical clearance for secondary use of data to be included in the IDACO resource.

Population studies qualified for inclusion if office and the ambulatory BP measures and cardiovascular risk factors were available at baseline and if follow-up included both fatal and nonfatal outcomes. The Expanded eMethods section and eTable 1 in Supplement 1 provide detailed information on the population sampling methods, timelines, and country of recruitment. Across all studies, enrollment took place from August 1985 until May 2010 (eTable 1 in Supplement 1). For the current study, baseline refers to the first measurement of the conventional and the ambulatory BP measures along with cardiovascular risk factors (May 1988 until May 2010); timing of the last follow-up ranged from August 2006 to October 2016 across studies. References specifying methods in each of the 13 cohorts are available in the Expanded eMethods section in Supplement 1.

### BP Measurement

Nurses or physicians obtained the conventional readings with a standard mercury sphygmomanometer or with validated auscultatory or oscillometric devices. Patients were considered to have hypertension if their conventional BP was 140/90 mm Hg or higher or if they were taking antihypertensive drugs.

For ambulatory monitoring (eTable 2 in Supplement 1), portable monitors were programmed to obtain ambulatory readings at 30-minute intervals throughout the whole day or at intervals of 15 to 30 minutes during daytime and at intervals ranging from 20 to 60 minutes during the nighttime.[16] Daytime readings ranged from 10 AM to 8 PM in European and South American countries and from 8 AM to 6 PM in Asian countries. The corresponding nighttime intervals ranged from midnight to 6 AM in European and South American countries and from 10 PM to 4 AM in Asian countries. For analysis, ambulatory recordings had to include at least 6 daytime and 3 nighttime readings.[17] We used the mean BP recordings taken by automated devices during the first hour patients were being monitored while in a medical environment. The dipping ratio was calculated by dividing the nighttime by the daytime BP level. We focused on systolic BP, because it is the predominant risk factor among older adults and because the mean age of patients in this study was 53.4 years.[18] Diastolic BP was analyzed to replicate findings for systolic BP. In categorical analyses, the dipping ratios were 0.80 or less for extreme dipping, more than 0.80 to 0.90 or less for normal dipping, more than 0.90 to 1.00 or less for nondipping, and more than 1.00 for reverse dipping.[19] The Expanded Methods section in Supplement 1 describes the collection of questionnaire and biochemical data.

### Ascertainment of End Points

We ascertained vital status and the incidence of fatal and nonfatal events from the appropriate sources in each country.[14] All events were prespecified and coded according to the *International Classification of Diseases* (*ICD*).[14] The coprimary end points were total mortality and a composite cardiovascular event consisting of cardiovascular mortality combined with nonfatal coronary events, heart failure, and stroke. Secondary end points included cardiovascular mortality (*ICD-8*, 390-448; *ICD-9*, 390.0-459.9; and *ICD-10,* I00-I79 and R96), coronary events (death from ischemic heart disease [*ICD-8*, 411-412; *ICD-9*, 411 and 414; and *ICD-10*, I20 and I24-I25], sudden death [*ICD-8*, 427.2 and 795; *ICD-9*, 427.5 and 798; and *ICD-10*, I46 and R96], nonfatal myocardial infarction [*ICD-8* or *ICD-9*, 410 and *ICD-10*, I21-I22], and

coronary revascularization), and stroke (*ICD-8* or *ICD-9*, 430-434 and 436; and *ICD-10*, I60-I64 and I67-I68), not including transient ischemic attack. Heart failure (*ICD-8*, 427.0, 427.1, 427.2, 428, 429, 519.1, and 782.4, *ICD-9*, 429, and *ICD-10*, I50 and J81) was included in the composite cardiovascular outcome. Its diagnosis required hospitalization in the Scandinavian cohorts.[20,21] In the other cohorts, heart failure was either a clinical diagnosis or the diagnosis on the death certificate. All outcomes were validated against hospital files or medical records held by primary care physicians or specialists. In all outcome analyses, we only considered the first event within each category. No participant was lost to follow-up.

### Statistical Analysis

We applied the Kolmogorov-Smirnov test for assessing the normality of distributions. For comparison of means and proportions, we applied the large-sample *Z* test and Fisher exact test, respectively. After stratification for cohort and sex, we interpolated missing values of body mass index and serum cholesterol levels from the regression slopes on age. In participants with unknown status of smoking, drinking, antihypertensive treatment, diabetes mellitus, or unknown history of cardiovascular disease, we set the indicator (dummy) variable to the cohort- and sex-specific mean of the codes (0, 1).

We compared the cumulative incidence of the primary and secondary outcomes by dipping status, while adjusting for sex and age, and next for the 24-hour or nighttime BP. In multivariable-adjusted Cox regression, we accounted for cohort (random effect), sex, and baseline characteristics including age, body mass index, smoking and drinking status, serum cholesterol level, antihypertensive drug intake, history of cardiovascular disease, and diabetes mellitus. We expressed hazard ratios (HRs) per increments of 20/10 mm Hg BP and per 0.10-increment in the dipping ratio. In models including 2 BP indexes, we uncorrelated these indexes by regressing one index on the other and using the residual of one index in computing the HRs or in assessing improvement of model performance.[22] We constructed heat maps to visualize the contribution of the 24-hour and nighttime BP measurements in their associations with outcomes. To adjust for cohort, we pooled participants recruited in the framework of the European Project on Genes in Hypertension, Novosibirsk, Russia; Kraków and Gdańsk, Poland; Pilsen, the Czech Republic; and Padova, Italy.[23] We checked the proportional hazards assumption by the Kolmogorov-type supremum test and by testing the interaction between follow-up duration and the BP variables. Sensitivity analyses addressed the use of antihypertensive drug at baseline, the consistency of the results based on a diary approach to define wakefulness and sleep, and the weight of cohorts in the overall pooled results. Improvement in model performance was assessed from change in the area under the curve (AUC).

Dipping status as a categorical variable was analyzed using the deviation from mean coding,[24] which contrasts risk in each group to the average risk in the whole study population and which allows computing confidence intervals for the HR in each group without the need to define a reference group. We did not apply a correction for multiple testing because the outcomes in our study were highly correlated so that each test did not provide an independent opportunity for a type I error.[25] Thus, the analyses of secondary outcomes should be considered as exploratory. For database management and statistical analysis, we used SAS software, version 9.4, maintenance level 5. Statistical significance was a 2-tailed α of ≤.05.

## Results

### Baseline Characteristics of Participants

Of 13 111 people included in the database, we excluded 1976 because they were adolescents without events (n = 493) or because they had an ambulatory BP recording with fewer than 6 daytime or 3 nighttime readings (n = 1483). The study population analyzed statistically (n = 11 135) included 5494 women (49.3%) and consisted of 6929 white Europeans (62.2%), 1887 Asians (17.0%), and 2319 South Americans (20.8%). Missing values were interpolated for body mass index (n = 33), serum cholesterol level (n = 806), smoking status (n = 56), drinking status (n = 805), antihypertensive treatment (n = 16), diabetes mellitus (n = 5), and history of cardiovascular disease (n = 1).

The median age at enrollment was 54.7 years (**Table 1**). The study population included 3022 smokers (27.3%) and 5185 participants (56.3%) reporting alcohol consumption. Of 4866 participants (43.7%) with hypertension on conventional BP measurement, 2262 (46.5%) were taking antihypertensive drug treatment. A total of 849 participants (7.6%) had diabetes and 1291 (11.6%) had a history of cardiovascular disease. There were 9286 participants (83.4%) with 3 automated office BP monitoring readings, 1650 (14.8%) with 2, and 199 (1.8%) with 1. The median number of ambulatory readings was 55 (5th-95th percentile intervals, 33-82) for 24-hours, 28 (5th-95th percentile intervals, 14-41) for daytime, and 11 (5th-95th percentile interval, 5-13) for nighttime readings. eTable 3 in Supplement 1 shows that all BP indexes were highly correlated.

### Primary End Points

#### Incidence of Outcomes

Among 11 135 participants, the median follow-up was 13.8 years (5th-95th percentile interval, 2.5-25.1 years). Across cohorts (eTable 1 in Supplement 1), the median follow-up ranged from 2.4 years (5th-95th percentile interval, 2.3-2.6 years) to 22.8 years (5th-95th percentile interval, 11.1-26.2 years). During 153 140 person-years of follow-up, 2836 participants died (18.5 per 1000 person-years) and 2049 experienced a composite cardiovascular event (13.4 per 1000 person-years). eTable 4 in Supplement 1 lists the number of events by category.

#### Cox Regression

In all outcome analyses that follow, the proportional hazard assumption was not violated and the residual method, as described in the Statistical Analysis section, was used. None of the interaction terms between a BP index under study with any residual of a comparator index reached statistical significance ($P > .09$).

Table 1. Baseline Characteristics of Participants

| Characteristics | Participants |
|---|---|
| No. of participants | 11 135 |
| Sex, No. (%) | |
| Men | 5641 (50.7) |
| Women | 5494 (49.3) |
| Region of enrollment, No. (%)[a] | |
| Europe | 6929 (62.2) |
| Asia | 1887 (17.0) |
| South America | 2319 (20.8) |
| Current smoking, No./total (%)[b,c] | 3022/11 079 (27.3) |
| Drinking alcohol, No./total (%)[b,d] | 5815/10 330 (56.3) |
| Risk factors, No./total (%) | |
| Hypertension[b,e] | 4866 (43.7) |
| Antihypertensive treatment[b] | 2262/11 117 (20.3) |
| Diabetes mellitus[b,f] | 849/11 130 (7.6) |
| History of CVD[a] | 1291/11 134 (11.6) |
| Dipping status, No. (%)[b,g] | |
| Extreme | 2018 (18.1) |
| Normal | 5617 (50.4) |
| None | 2809 (25.2) |
| Reverse | 691 (6.2) |
| Age, median (IQR), y | 54.7 (41.6-67.3) |
| BMI, mean (SD) | 25.5 (4.4) |
| No. | 11 102 |
| Serum cholesterol, mean (SD), mg/dL | 216.3 (45.2) |
| No. | 10 329 |
| Blood pressure, mm Hg[h] | |
| Conventional | |
| Systolic/diastolic, mean | 132.4/79.8 |
| SD | 23.0/11.8 |
| Automated office | |
| Systolic/diastolic, mean | 135.3/82.3 |
| SD | 20.0/11.7 |
| 24 hours | |
| Systolic/diastolic, mean | 123.6/73.7 |
| SD | 14.3/8.5 |
| Daytime | |
| Systolic/diastolic, mean | 129.7/78.7 |
| SD | 15.2/9.2 |
| Nighttime | |
| Systolic/diastolic, mean | 112.6/64.7 |
| SD | 15.5/9.4 |
| Dipping ratio[i] | |
| Systolic/diastolic, mean | 0.87/0.83 |
| SD | 0.08/0.06 |

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; BP, blood pressure; CVD, cardiovascular disease; IQR, interquartile range.

SI conversion factor: to convert cholesterol from mg/dL to mmol/L, multiply by 0.0259; glucose from mg/dL to mmol/L, multiply by 0.0555.

[a] Details provided in eTable 1 in Supplement 1.

[b] Assessed only at baseline.

[c] Use of smoking materials on a daily basis.

[d] Drinking was an average alcohol intake of 5 g or more per day.

[e] A conventional BP of 140/90 mm Hg or higher or use of antihypertensive drugs.

[f] Use of antidiabetic drugs, fasting blood glucose of 126 mg/dL or higher, random blood glucose of 200 mg/dL or higher, a self-reported diagnosis, or diabetes documented in practice or hospital records.

[g] Categorization in extreme dippers (≤0.80), normal dippers (>0.80 to ≤0.90), nondippers (>0.90 to ≤1.00), and reverse dippers (>1.00) was based on the systolic dipping ratio.

[h] Conventional BP was measured using a standard mercury sphygmomanometer or validated auscultatory or oscillometric devices. Automated BP was the average of the ambulatory recordings during the first recording hour, when the monitors were applied in a medical environment. Mean BP levels over the whole day and during day/night (10 AM to 8 PM/midnight to 6 AM for Europeans and South Americans and 8 AM to 6 PM/10 PM to 4 AM in Asians).

[i] The dipping ratio was nighttime divided by daytime BP.

In analyses adjusted for cohort, sex, age, body mass index, smoking and drinking status, serum cholesterol levels, antihypertensive drug treatment use, history of cardiovascular disease and diabetes mellitus (**Table 2**), the association between systolic BP and the primary outcomes were all statistically significant ($P < .001$). Adjusting for 24-hour systolic BP, the HR for the nighttime systolic BP readings for total mortality was 1.24 (95% CI, 1.14-1.36), and for all cardiovascular events, the HR was 1.16 (95% CI, 1.05-1.28; Table 2). Adjusting for 24-hour BP readings, the HR for systolic dipping for total mortality was 1.11 (95% CI, 1.06-1.15), and for all cardiovascular outcomes, it was 1.08 (95% CI, 1.03-1.13; Table 2). After adjusting for the nighttime systolic BP, only conventional systolic BP readings was associated with total mortality (HR, 1.05; CI, 1.01 to 1.10; $P = .02$). Adjustment for the nighttime systolic BP did not

Table 2. Association of Outcomes With Systolic BP Indexes Without or With Adjustment for 24-Hour or Nighttime Systolic BP[a]

| Outcomes | Adjusted | | Additionally Adjusted Systolic BP[b] | | | |
|---|---|---|---|---|---|---|
| | | | 24 Hours | | Nighttime | |
| | Hazard Ratio (95% CI)[c] | *P* Value | Hazard Ratio (95% CI)[c] | *P* Value | Hazard Ratio (95% CI)[c] | *P* Value |
| **Total Mortality (n = 2836)** | | | | | | |
| Systolic BP index | | | | | | |
| Conventional | 1.12 (1.08-1.17) | <.001 | 1.05 (1.01-1.10) | .03 | 1.05 (1.01-1.10) | .02 |
| Automated office systolic BP | 1.08 (1.04-1.12) | <.001 | 0.97 (0.92-1.02) | .23 | 1.00 (0.96-1.05) | .94 |
| Measure times | | | | | | |
| 24 hours | 1.22 (1.16-1.28) | <.001 | NA | NA | 0.98 (0.88-1.08) | .68 |
| Daytime | 1.14 (1.09-1.20) | <.001 | 0.78 (0.69-0.88) | <.001 | 0.98 (0.92-1.05) | .64 |
| Nighttime | 1.23 (1.17-1.28) | <.001 | 1.24 (1.14-1.36) | <.001 | NA | NA |
| Dipping ratio[d] | 1.13 (1.09-1.18) | <.001 | 1.11 (1.06-1.15) | <.001 | 1.02 (0.97-1.07) | .46 |
| **All Cardiovascular Outcomes (n = 2049)** | | | | | | |
| Systolic BP index | | | | | | |
| Conventional | 1.20 (1.15-1.26) | <.001 | 1.05 (1.00-1.11) | .06 | 1.09 (1.04-1.14) | .001 |
| Automated office | 1.19 (1.14-1.24) | <.001 | 0.98 (0.93-1.04) | .58 | 1.07 (1.02-1.12) | .007 |
| Measure times | | | | | | |
| 24 hours | 1.45 (1.37-1.54) | <.001 | NA | NA | 1.25 (1.11-1.41) | <.001 |
| Daytime | 1.33 (1.26-1.41) | <.001 | 0.77 (0.67-0.89) | <.001 | 1.11 (1.03-1.20) | .005 |
| Nighttime | 1.36 (1.30-1.43) | <.001 | 1.16 (1.05-1.28) | .004 | NA | NA |
| Dipping ratio[d] | 1.14 (1.08-1.19) | <.001 | 1.08 (1.03-1.13) | <.001 | 0.92 (0.87-0.98) | .008 |
| **Cardiovascular Mortality (n = 1073)** | | | | | | |
| Systolic BP index | | | | | | |
| Conventional | 1.22 (1.15-1.29) | <.001 | 1.07 (1.00-1.15) | .06 | 1.09 (1.02-1.17) | .008 |
| Automated office | 1.19 (1.12-1.26) | <.001 | 0.97 (0.90-1.05) | .44 | 1.05 (0.98-1.12) | .14 |
| Measure times | | | | | | |
| 24 hours | 1.48 (1.36-1.60) | <.001 | NA | NA | 1.17 (1.00-1.37) | .06 |
| Daytime | 1.34 (1.24-1.45) | <.001 | 0.75 (0.62-0.91) | .003 | 1.09 (0.98-1.20) | .10 |
| Nighttime | 1.41 (1.32-1.50) | <.001 | 1.26 (1.10-1.44) | <.001 | NA | NA |
| Dipping ratio[d] | 1.17 (1.10-1.25) | <.001 | 1.12 (1.05-1.19) | <.001 | 0.95 (0.88-1.03) | .18 |
| **Coronary Outcomes (n = 922)** | | | | | | |
| Systolic BP index | | | | | | |
| Conventional | 1.14 (1.07-1.22) | <.001 | 1.01 (0.94-1.10) | .72 | 1.04 (0.97-1.12) | .30 |
| Automated office | 1.18 (1.11-1.26) | <.001 | 1.04 (0.95-1.13) | .41 | 1.08 (1.00-1.16) | .04 |
| Measure times | | | | | | |
| 24 hours | 1.35 (1.24-1.47) | <.001 | NA | NA | 1.12 (0.94-1.34) | .22 |
| Daytime | 1.27 (1.16-1.38) | <.001 | 0.83 (0.67-1.03) | .09 | 1.07 (0.96-1.20) | .23 |
| Nighttime | 1.30 (1.21-1.40) | <.001 | 1.20 (1.03-1.40) | .02 | NA | NA |
| Dipping ratio[d] | 1.13 (1.05-1.21) | <.001 | 1.09 (1.01-1.17) | .02 | 0.95 (0.87-1.04) | .30 |
| **Stroke (n = 822)** | | | | | | |
| Systolic BP index | | | | | | |
| Conventional | 1.30 (1.21-1.40) | <.001 | 1.11 (1.02-1.21) | .02 | 1.16 (1.07-1.26) | <.001 |
| Automated office | 1.24 (1.16-1.33) | <.001 | 0.99 (0.90-1.08) | .76 | 1.10 (1.02-1.19) | .01 |
| Measure times | | | | | | |
| 24 hours | 1.60 (1.46-1.76) | <.001 | NA | NA | 1.36 (1.14-1.63) | .001 |
| Daytime | 1.45 (1.33-1.58) | <.001 | 0.80 (0.65-1.00) | .05 | 1.19 (1.06-1.33) | .003 |
| Nighttime | 1.46 (1.36-1.58) | <.001 | 1.17 (1.01-1.36) | .04 | NA | NA |
| Dipping ratio[d] | 1.14 (1.06-1.23) | <.001 | 1.08 (1.01-1.16) | .03 | 0.87 (0.80-0.96) | .004 |

Abbreviations: BP, blood pressure; NA, not applicable.

[a] All models accounted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, antihypertensive drug intake, history of cardiovascular disease, and diabetes mellitus.

[b] Models including 2 correlated systolic BP indexes were constructed, using the residual method (see Statistical Analysis section).

[c] Hazard ratios express the risk for increments of 20 mm Hg in systolic BP and 0.10 in the dipping ratio.

[d] The dipping ratio is calculated by dividing nighttime by daytime systolic BP.

Table 3. Association of Outcomes With 24 Hours or Nighttime Systolic Blood Pressure Adjusted for Other Systolic Blood Pressure Indexes

| | Systolic BP[a] | | | |
|---|---|---|---|---|
| | 24 Hours | | Nighttime | |
| Systolic BP Indexes | Hazard Ratio (95% CI)[b] | *P* Value | Hazard Ratio (95% CI)[b] | *P* Value |
| **Total Mortality (n = 2836)** | | | | |
| Conventional systolic BP | 1.17 (1.10-1.25) | <.001 | 1.20 (1.14-1.26) | <.001 |
| Automated office systolic BP | 1.25 (1.17-1.34) | <.001 | 1.22 (1.17-1.29) | <.001 |
| Systolic BP | | | | |
| 24 hours | NA | NA | 1.24 (1.14-1.36) | <.001 |
| Daytime | 1.55 (1.36-1.77) | <.001 | 1.24 (1.17-1.31) | <.001 |
| Nighttime | 0.98 (0.88-1.08) | .68 | NA | NA |
| Dipping ratio[c] | 1.19 (1.13-1.26) | <.001 | 1.21 (1.14-1.28) | <.001 |
| **All Cardiovascular Outcomes (n = 2049)** | | | | |
| Conventional systolic BP | 1.40 (1.31-1.50) | <.001 | 1.31 (1.24-1.38) | <.001 |
| Automated office systolic BP | 1.47 (1.36-1.59) | <.001 | 1.32 (1.25-1.40) | <.001 |
| Systolic BP | | | | |
| 24 hours | NA | NA | 1.16 (1.05-1.28) | .004 |
| Daytime | 1.87 (1.62-2.16) | <.001 | 1.29 (1.21-1.37) | <.001 |
| Nighttime | 1.25 (1.11-1.41) | <.001 | NA | NA |
| Dipping ratio[c] | 1.43 (1.34-1.51) | <.001 | 1.44 (1.35-1.54) | <.001 |
| **Cardiovascular Mortality (n = 1073)** | | | | |
| Conventional systolic BP | 1.41 (1.28-1.55) | <.001 | 1.35 (1.26-1.45) | <.001 |
| Automated office systolic BP | 1.52 (1.37-1.68) | <.001 | 1.38 (1.28-1.48) | <.001 |
| Systolic BP | | | | |
| 24 hours | NA | NA | 1.26 (1.10-1.44) | <.001 |
| Daytime | 1.95 (1.60-2.38) | <.001 | 1.34 (1.23-1.47) | <.001 |
| Nighttime | 1.17 (1.00-1.37) | .06 | NA | NA |
| Dipping ratio[c] | 1.44 (1.33-1.56) | <.001 | 1.46 (1.34-1.59) | <.001 |
| **Coronary Outcomes (n = 922)** | | | | |
| Conventional systolic BP | 1.33 (1.20-1.48) | <.001 | 1.28 (1.18-1.39) | <.001 |
| Automated office systolic BP | 1.30 (1.16-1.47) | <.001 | 1.25 (1.15-1.36) | <.001 |
| Systolic BP | | | | |
| 24 h | NA | NA | 1.20 (1.03-1.40) | .02 |
| Daytime | 1.62 (1.29-2.03) | <.001 | 1.25 (1.13-1.38) | <.001 |
| Nighttime | 1.12 (0.94-1.34) | .22 | NA | NA |
| Dipping ratio[c] | 1.32 (1.21-1.44) | <.001 | 1.35 (1.23-1.48) | <.001 |
| **Stroke (n = 822)** | | | | |
| Conventional systolic BP | 1.50 (1.34-1.67) | <.001 | 1.37 (1.26-1.49) | <.001 |
| Automated office systolic BP | 1.62 (1.44-1.83) | <.001 | 1.40 (1.29-1.53) | <.001 |
| Systolic BP | | | | |
| 24 hours | NA | NA | 1.17 (1.01-1.36) | .04 |
| Daytime | 1.98 (1.58-2.47) | <.001 | 1.34 (1.21-1.47) | <.001 |
| Nighttime | 1.36 (1.14-1.63) | .001 | NA | NA |
| Dipping ratio[c] | 1.57 (1.43-1.73) | <.001 | 1.61 (1.46-1.78) | <.001 |

Abbreviations: BP, blood pressure; NA, not applicable.

[a] All models accounted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, antihypertensive drug intake, history of cardiovascular disease and diabetes mellitus and were constructed, using the residual method (see the Statistical Analysis section).

[b] Hazard ratios express the risk for increments of 20 mm Hg in SBP and 0.10 in the dipping ratio.

[c] The dipping ratio is calculated by dividing nighttime by daytime systolic BP.

remove the statistical significance of the association of the conventional or automated office systolic BP or with the daytime or 24-hour systolic BP with the composite cardiovascular outcomes.

In models including both nighttime and 24-hour systolic BP (**Table 3**), the HRs for 24-hour measures were 0.98 (95% CI, 0.88-1.08) for total mortality and 1.25 (95% CI, 1.11-1.41) for the composite cardiovascular outcomes. In models that adjusted for a systolic BP index different from the nighttime systolic BP (Table 3), the HRs expressing the association of the 24-hour systolic BP with the coprimary outcomes ranged from 1.17 (95% CI, 1.10-1.25) to 1.87 (95% CI, 1.62-2.16). After adjusting for each of the other systolic BP indexes (Table 3), the HRs expressing the association of nighttime systolic BP with the coprimary outcomes ranged from 1.16 (95% CI, 1.05-1.28) to 1.44 (95% CI, 1.35-1.54).

### Sensitivity Analyses

The aforementioned findings were generally consistent for diastolic BP (eTables 5 and 6 in Supplement 1) and in sensitivity analyses—from which 2262 participants (20.3%) taking antihypertensive drug medication at baseline were excluded (eTables 7 and 8 in Supplement 1)—when the diary method was applied to 7133 participants (64.1%) to define periods of wakefulness and sleep (eTables 9 and 10 in Supplement 1), or when cohorts were excluded (eTable 11 in Supplement 1).

### Improvement in Model Performance

Based on the results presented in Table 2 and Table 3 for systolic BP and in eTables 5 and 6 in Supplement 1 for diastolic BP, of 30 possible permutations to compare 2 BP indexes, the 24-hour and nighttime measures were carried forward in further analyses to study improvement in model performance.

Heat maps for systolic BP (**Figure 1**) showed that along the vertical axis the 10-year risks of both primary outcomes were significantly greater with higher nighttime systolic BP readings ($P \leq .03$), but that along the horizontal axis, the risk of death was not significantly associated with the 24-hour systolic BP ($P = .66$). Heat maps for diastolic BP were confirmatory (eFigure 1 in Supplement 1).

In general, adding the 24-hour or nighttime systolic BP (eTable 12 in Supplement 1), or adding 24-hour or nighttime diastolic BP (eTable 13 in Supplement 1) to models including any other systolic or diastolic BP index significantly improved model performance. Base models that included single systolic BP indexes yielded an AUC of 0.83 for mortality and 0.84 for the cardiovascular outcomes, and adding 24-hour or nighttime systolic BP to base models that included other BP indexes resulted in incremental improvements in AUC of 0.0013 to 0.0027 for total mortality and 0.0031 to 0.0075 for the composite cardiovascular outcome. Adding 24-hour systolic BP to nighttime systolic BP did not significantly improve model performance (eTable 12 in Supplement 1) with similar findings for 24-hour diastolic BP plus nighttime diastolic BP (eTable 13 in Supplement 1). Conversely, nighttime systolic or diastolic BP added to 24-hour systolic or diastolic BP improved model performance for the estimation of the 10-year risk of death; the change in the AUC was 0.0013 (95% CI, 0.0001-0.0024) systolic and 0.0012 (95% CI, 0.0002-0.0022) diastolic. Model performance was not significantly improved by adding any other systolic or diastolic BP index to 24-hour or nighttime measures (eTables 14 and 15 in Supplement 1)

### Dipping as Categorical Variable

Based on systolic BP, the study included 2018 extreme dippers (18.1%), 5617 dippers (50.4%), 2809 nondippers (25.2%), and 691 reverse dippers (6.2%). **Figure 2**A and B show the sex- and age-adjusted cumulative incidence of total mortality and cardiovascular outcomes by dipping status. The sex- and age-adjusted cumulative incidence significantly differed ($P < .001$) according to dipping status with the highest rates in reverse dippers and the lowest rates in extreme dippers. For total mortality, the cumulative 10-year incidence amounted to 3.73% (95% CI, 3.3%-4.16%) for extreme dippers, 4.08% (95% CI, 3.69%-4.47%) in normal dippers, 4.62% (95% CI, 4.13%-5.12%) in nondippers, and 5.74% (95% CI, 4.92%-6.55%) in reverse dippers; for the composite cardiovascular outcome, these rates were 4.76% (95% CI, 4.16%-5.34%), 5.27% (95% CI, 4.77%-5.78%), 5.87% (95% CI, 5.21%-6.53%), and 7.77% (95% CI, 6.57%-8.95%), respectively. The difference in the sex- and age-adjusted 10-year cumulative incidence between extreme and reverse dippers was 2.01% (95% CI, 1.08%-2.93%; $P < .001$) for total mortality and 3.02% (95% CI, 1.69%-4.34%; $P < .001$) for the composite cardiovascular outcome.

Additional adjustment for the nighttime systolic BP attenuated these differences to 0.33% (95% CI, −0.53% to 1.18%; $P = .46$) and -0.71% (95% CI, −1.83% to 0.41%; $P = .21$), respectively (Figure 2E and F), whereas these differences retained significance when adjusted for 24-hour systolic BP: 1.62% (95% CI, 0.74% to 2.50%; $P < .001$) for total mortality and 2.00% (95% CI, 0.80% to 3.19%; $P = .001$) for the composite cardiovascular outcome (Figure 2C and D).

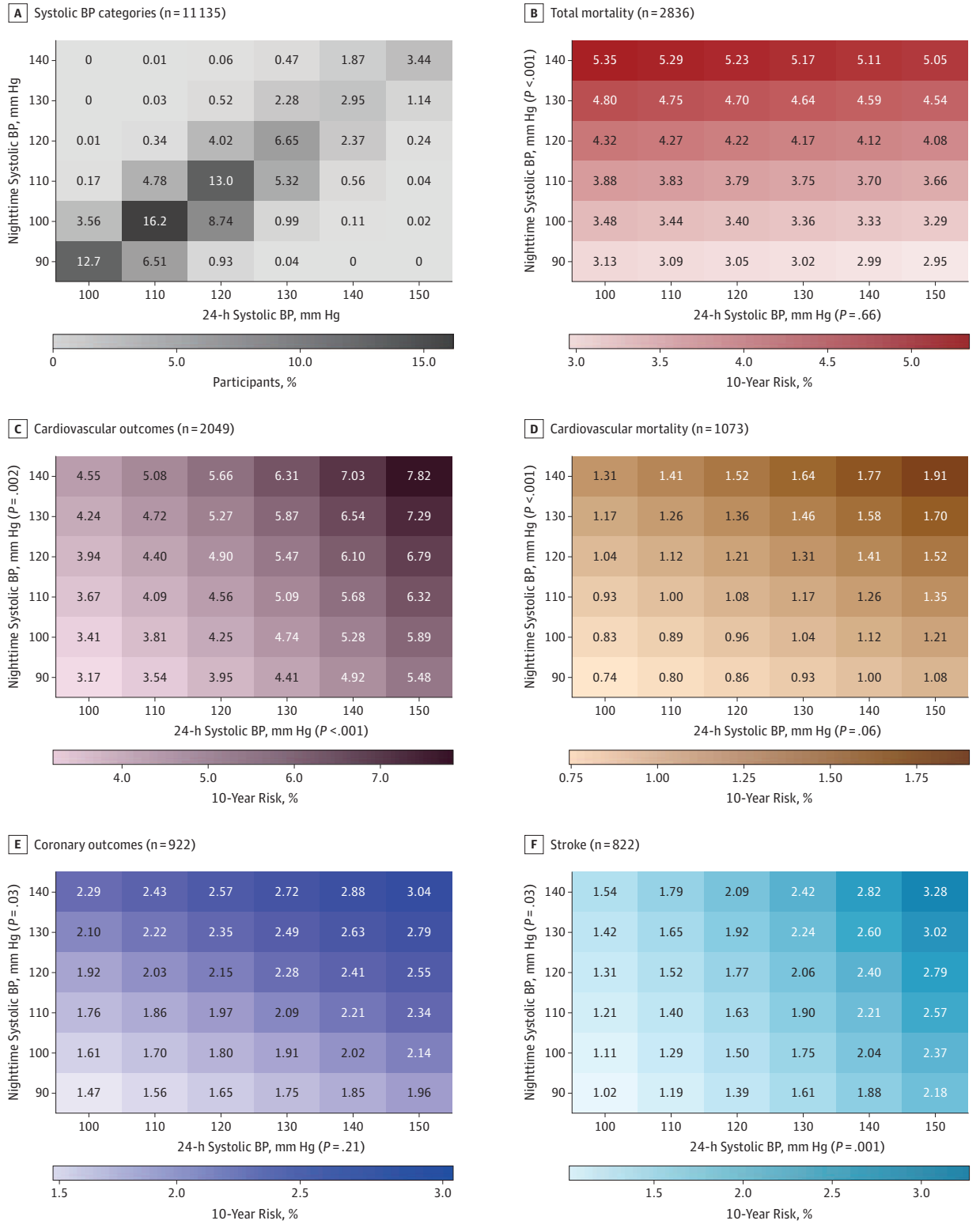
## Secondary Outcomes

During follow-up, cardiovascular mortality accounted for 1073 deaths (7.0 per 1000 person-years). Coronary events occurred in 922 participants (6.0 per 1000 person-years) and 822 (5.4 per 1000 person-years) had a stroke (eTable 3 in Supplement 1). All HRs that associated secondary outcomes with single systolic ($P < .001$) or diastolic ($P \leq .02$) BP indexes were significant (Table 2; eTable 5 in Supplement 1). Findings for the secondary outcomes were consistent with those for the coprimary outcomes (Table 2 and Table 3 for systolic BP; eTables 5 and 6 for diastolic BP in Supplement 1). In models including both 24-hour and nighttime BP measures, secondary outcomes were significantly associated with nighttime BP, whereas for 24-hour BP significance was only retained for stroke (Table 2 for systolic BP; eTable 5 for diastolic BP in Supplement 1; HRs for systolic/diastolic 24-hour BP was 1.36 [95% CI, 1.14-1.63]/1.24 [1.06-1.44]). Sensitivity analyses were confirmatory (eTables 7-11 in Supplement 1). Heat maps for the secondary outcomes and results for improvement in model performance appear in Figure 1 and eTables 12 and 14 for systolic BP and in eFigure 1 and eTables 13 and 15 for diastolic BP. Analyses of the secondary outcomes (eFigure 2 in Supplement 1) according to dipping status produced results comparable with those of the primary outcomes (Figure 2).

## Discussion

In this population-based cohort study, higher 24-hour and higher nighttime BP, compared with other BP indexes, were associated with greater risk of all-cause mortality and a composite cardiovascular outcome. These associations remained significant after adjusting for conventional and automated office BP and after adjusting for the daytime BP and dipping ratio or status. These findings were also largely consistent for secondary outcomes and in sensitivity analyses performed to evaluate the influence of antihypertensive drug treatment at baseline, the use of fixed clock-time intervals vs the diary method to define day and night, and the weight of different cohorts in the overall pooled results.

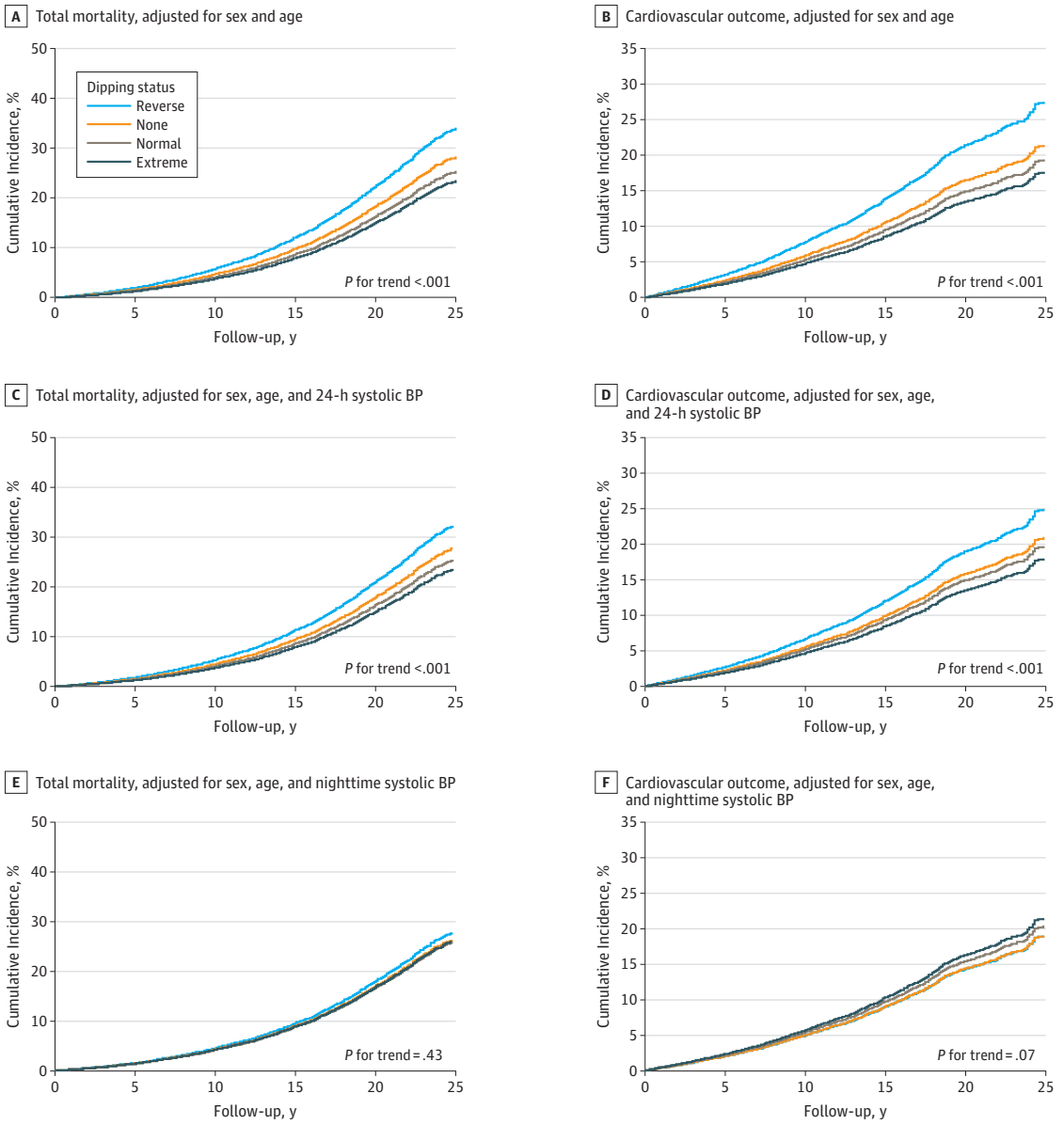
Figure 1. Heat Maps Depicting 10-Year Risk in Relation to 24-Hour and Nighttime Systolic Blood Pressure in 11 135 Study Participants




Derived by Cox proportional hazards regression with 24-hour and nighttime systolic blood pressure (BP) analyzed as continuous variables. Estimates of 10-year risk were standardized to the average of the distributions in the whole study population (mean or ratio) of all covariables. Numbers in the panel A grid represent the percentage of participants within each systolic BP cross-classification category; numbers in the other grids represent the 10-year risk.

See the Results section for *P* values along horizontal and vertical axes. Risks of total mortality, cardiovascular mortality, and a coronary event were not significantly associated with 24-hour systolic BP ($P \geq .06$).

Figure 2. Cumulative Incidence of Total Mortality and the Composite Cardiovascular Outcomes by Dipping Status




| No. of patients | | | | | | |
|---|---|---|---|---|---|---|
| Dipping status | | | | | | |
| Reverse | 691 | 569 | 350 | 167 | 78 | 23 |
| None | 2809 | 2493 | 1693 | 1078 | 445 | 134 |
| Normal | 5617 | 5163 | 3833 | 2717 | 1047 | 302 |
| Extreme | 2018 | 1904 | 1459 | 1042 | 457 | 107 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 691 | 529 | 305 | 136 | 60 | 17 |
| 2809 | 2401 | 1568 | 981 | 402 | 127 |
| 5617 | 5027 | 3606 | 2493 | 914 | 272 |
| 2018 | 1831 | 1372 | 933 | 385 | 94 |

Based on the systolic dipping ratio, ≤0.80 represents extreme dippers; >0.80 to ≤0.90, normal dippers; >0.90 to ≤1.00, nondippers; and >100, reverse dippers. Tabulated data are the number of participants at risk by dipping status at 5-year intervals. *P* values for trend were derived by Cox proportional hazards regression. The 4 lines in panels E and F are superimposed.

Over the past 30 years, ambulatory BP monitoring developed into the recommended technique for BP measurement.[3,19] The current population-based study confirmed previous research, indicating that ambulatory BP monitoring over and beyond measures taken in clinicians' offices improved risk stratification among patients with[7,8] or those suspected of having hypertension.[9] It strengthened the notion that nighttime BP measures carry valuable prognostic information.[7-9] A meta-analysis of both summary statistics and individual-level data, combined studies involving patients with hypertension (n = 23 856) separately from those of individuals randomly recruited from populations (n = 9641).[26] In both patients and populations, in analyses in which nighttime BP was additionally adjusted for daytime BP, and vice versa, nighttime BP was a stronger predictor than was daytime BP.[26] With adjustment for the 24-hour BP, both the dipping ratio and dipping status

remained significantly associated with outcome, but as evidenced by the generalized $R^2$ statistic and in line with the current findings added less than 0.6% to the model fit over and beyond the 24-hour BP readings.[26] Poor reproducibility of the dipping status, intermediate reproducibility of the dipping ratio, and high reproducibility of the nighttime BP might explain the statistically significantly higher predictive value of the nighttime BP.[12,13] Possible explanations for the accuracy of the nighttime BP include minimization of confounding by antihypertensive drug treatment, usually taken in the morning, the standardized conditions during sleep (supine position and absence of movement), and the prognostic value of the basal BP in sedated conditions.[27]

Model performance in the current study was evaluated by change in the AUC. This metric is not very sensitive in model comparisons[28] if the basic model performs well, as was the case in the current study, for which the AUC of the basic model ranged from nearly 0.83 to 0.88 (eTables 12 and 13 in Supplement 1). The prevailing perception among experts is that BP is the strongest modifiable cardiovascular risk factor.[29] The small increments in change in the AUC challenge this concept. Thus, an important issue in the evaluation of an additional risk prediction marker is how to interpret a small AUC increase, which many researchers believe is an imprecise metric because it increases only slightly with the introduction of an additional marker in multivariable-adjusted models, even if the marker under study carries great risk, as reflected by the odds ratio (or HR).[30]

### Limitations

This study has several limitations. First, the diary approach is the gold standard for determining the BP level during wakefulness and sleep.[19] However, the analyses based on short clock-time intervals[16] or confined to 7133 individuals (64.1%) with diary information were confirmatory. Moreover, these short fixed clock-time intervals eliminate the transition periods in the morning and evening when BP changes rapidly, resulting in daytime and nighttime BP levels that are within 1 to 2 mm Hg of the awake and asleep levels.[16] Second, antihypertensive drug treatment was only recorded at baseline and could therefore not be adjusted for as a time-dependent covariable. However, initiation of BP-lowering treatment during follow-up is more likely to weaken rather than to strengthen the associations between baseline BP and outcomes.[7] Third, there might be misclassification bias in the assessment of the cardiovascular study end points.[31] However, all-cause mortality does not require any adjudication, as vital status only involves checking population registries. There was consistency between the findings for total mortality, the composite cardiovascular outcome and the secondary outcomes. Fourth, among some participants, nighttime BP was the time-weighted average of only 3 readings, which is less than proposed by guidelines.[19] However, a recent analysis[17] demonstrated that 6 daytime and 3 nighttime readings are sufficient in large studies to estimate the BP level, to reproducibly cross-classify individuals based on their office and ambulatory BP, and to preserve the association with adverse health outcomes.

## Conclusions

In this population-based cohort study, higher 24-hour and nighttime BP were significantly associated with greater risks of death and a composite cardiovascular outcome, even after adjusting for other office-based or ambulatory blood pressure measurements. Thus, 24-hour and nighttime blood pressure may be considered optimal measurements for estimating cardiovascular risk, although statistically, model improvement compared with other blood pressure indexes was small.

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Editor's Note

# Effective Use of Ambulatory Blood Pressure Monitoring

Philip Greenland, MD

**For almost 100 years,** higher levels of blood pressure (BP) have been recognized as critically important risk factors for clinical disorders of the cardiovascular systems, brain, and kidney.[1] With numerous effective lifestyle and drug treatments available and with clinical trials that convincingly showed the benefits of BP lowering in appropriately selected patients, it is now widely recommended that BP measurement be a routine part of general health screening.[1-6] Evidence favoring the use of ambulatory BP monitoring (ABPM) for measurement of BP has accumulated and guidelines now refer to ABPM as the "best out-of-office measurement method."[1] In addition, the Centers for Medicare & Medicaid Services (CMS) recently proposed to pay for expanded use of ABPM for detection of suspected "white coat" hypertension and detection of masked hypertension.[7]

Related article page 409

Ambulatory BP monitoring is used to obtain out-of-office BP readings at established intervals, usually every 15 to 30 minutes over a period of at least 24 hours. A systematic review conducted by the US Preventive Services Task Force[8] concluded that ABPM provided a better method to predict long-term cardiovascular disease outcomes than did office BP measurements. Therefore, as described in the article by Yang and colleagues,[9] ABPM is considered a preferred method for BP assessment in North American, European, Japanese, and Chinese guidelines.[1-6] However, because ABPM monitoring generates a much larger volume of data than other types of BP measurement, including nighttime BP measurements, it has been uncertain which BP index, or indexes, are more strongly associated with adverse health outcomes. The goal of the study by Yang et al[9] was to examine data from numerous sources to address this clinically important question.

Using a rigorous assessment of ABPM in more than 11 000 adults, higher 24-hour and nighttime BP were significantly associated with greater risks of death and a cardiovascular outcome, consisting of cardiovascular mortality combined with nonfatal coronary events, heart failure, and stroke. The association persisted after adjusting for other office-based or ambulatory monitoring-derived BP measurements, all of which were also associated with the adverse outcomes. This is important information for patients and clinicians as they determine how to use the large amount of BP data from ABPM. Based on these findings, it is reasonable to consider the 2 most clinically relevant measurements from ABPM to be the 24-hour BP and the nighttime BP. Either could be used to justify treatment of BP that is above the treatment threshold. Most important is to obtain accurate measurement from every patient and to initiate and monitor treatment when indicated.

# Supplementary Online Content

Yang W-Y, Melgarejo JD, Thijs L, et al. Association of office and ambulatory blood pressure with mortality and cardiovascular end points. *JAMA*. doi:10.1001/jama.2019.9811



This supplementary material has been provided by the authors to give readers additional information about their work.

*JAMA*

# *Supplement 1*

This Appendix formed part of the original submission and has been peer reviewed.
Supplement to: *Association of Office and Ambulatory Blood Pressure with Mortality and Cardiovascular Outcomes*. *JAMA.* 2019;322(5):1-12. doi:10.1001/jama.2019.9811.

## Table of Contents

## Expanded Methods

### Study Participants

All studies received ethical approval and adhered to the principles of the Declaration of Helsinki.[1] Participants gave written informed consent. Previous publications describe the IDACO database in detail.[2] Population studies qualified for inclusion, if information on the office and the ambulatory blood pressure and cardiovascular risk factors was available at baseline and if follow-up included both fatal and nonfatal outcomes. Of the 13,111 people included in the database, we excluded 1976 because they were teenagers without events (n = 493), or had an ambulatory blood pressure recording with fewer than six daytime and three nighttime readings (n = 1483).[3] Thus, the number of individuals statistically analyzed was 11,135. **eTable 1** provides detailed information on the population sampling methods, timelines and country of recruitment.

### Blood Pressure Measurement

**eTable 2** provides detailed information on blood pressure measurement. Nurses or physicians measured the conventional blood pressure with a standard mercury sphygmomanometers,[4-11] or with validated auscultatory[12] (USM-700F, UEDA Electronic Works, Tokyo, Japan) or oscillometric[13,14] devices (OMRON HEM-705CP, Omron Corporation, Kyoto, Japan; Dinamap 8100, Critikon Inc., Tampa, FL), using the appropriate cuff size, with participants in the sitting[5-9,12-14] or supine[10] position. Hypertension was a conventional blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic or use of antihypertensive drugs.[15]

For ambulatory blood pressure monitoring, portable monitors were programmed to obtain ambulatory readings at 30-minute intervals throughout the whole day,[4,12] or at intervals of

15[7-9,14], 20[5,6,10,11,13] or 30[10] minutes during daytime and at intervals of 20[10], 30[7-9,14], 40[5,13], 45[6,11] or 60[10] minutes during nighttime. All devices had passed validation and only oscillometric measurements were used for analysis. The same SAS macro processed all ambulatory recordings, which remained unedited or were only sparsely edited in Ohasama participants.[12] We defined daytime as the interval from 10 AM to 8 PM in Europeans[4,5,7-11] and South Americans[13,14] and from 8 AM to 6 PM in Asians.[6,12] The corresponding nighttime intervals ranged from midnight to 6 AM[5,7-9,13] and from 10 PM to 4 AM,[6,12] respectively. These short fixed clock-time intervals eliminate the transition periods in the morning and evening when blood pressure changes rapidly, resulting in daytime and nighttime blood pressure levels that are within 1–2 mm Hg of the awake and asleep levels.[16] We weighted the within-subject means of the ambulatory blood pressure by the time interval between successive readings. Furthermore, we also defined the awake and asleep periods of the day in 7133 participants (64.1%), who had kept a diary during ambulatory blood pressure monitoring. Automated office blood pressure was the mean of the ambulatory recordings during the first recording hour, when the monitors were applied in a medical environment.

The dipping ratio was the nighttime divided by the daytime blood pressure level. We focused on systolic blood pressure, because mean age was 53.4 years and in older adults systolic blood pressure is the predominant risk factor.[17] Diastolic pressure was analyzed to replicate findings for systolic pressure. Dipping ratio was defined as nighttime divided by daytime BP. In categorical analyses, extreme dipping, normal dipping, non-dipping and reverse dipping were dipping ratios of ≤0.80, >0.80 to ≤0.90, >0.90 to ≤1.00, and >1.00, respectively.[18]

### Other Measurements

We used the questionnaires originally administered in each cohort to obtain information on each participant's medical history and smoking and drinking habits.[4-14] Body mass index was body weight in kilograms divided by height in meters squared. We measured serum total cholesterol and blood glucose by automated enzymatic methods. Diabetes mellitus was the use of antidiabetic drugs, a fasting blood glucose of ≥126 mg/dL (≥7.0 mmol/L),[5-13] a random blood glucose of ≥200 mg/dL (≥11.1 mmol/L),[5,6,12] a self-reported diagnosis,[5,11-13] or diabetes documented in practice or hospital records.[13]

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**eTable 1. Recruitment and Follow-Up by Cohort**

| Catchment Area | Sampling Frame | Recruitment | | PR (%) | N° of Participants | | Follow-Up | |
|---|---|---|---|---|---|---|---|---|
| | | Timeline (Years) | Invitation | | In Database | Analyzed | Last (Year) | Median in Years (5–95% Interval) |
| Ohasama, Iwate, Japan | People aged ≥40 years | 1988–1994 | Address list | 78 | 1535 | 1535 | 2015 | 21.8 (4.7–26.8) |
| JingNing, Zhejiang, China | Family-based random sample | 2003–2003 | All villagers invited | 62 | 360 | 352 | 2006 | 2.5 (2.3–2.6) |
| Oktyabrsky, Novosibirsk, Russian Federation | Family-based random sample | 1999–2001 | Address list | 68 | 298 | 283 | 2009 | 8.8 (8.0–9.5) |
| Niepolomice, Kraków, Poland | Family-based random sample | 1999–2008 | Address list | 54 | 413 | 355 | 2014 | 13.5 (6.1–14.3) |
| Gdańsk, Poland | Family-based random sample | 2008–2010 | Address list | 90 | 215 | 202 | 2014 | 5.6 (4.7–6.7) |
| Pilsen, Czech Republic | Family-based random sample | 2000–2001 | Address list | 82 | 174 | 159 | 2015 | 14.1 (13.8–14.4) |
| Padova, Italy | Family-based random sample | 1999–2007 | Address list | 73 | 314 | 305 | 2013 | 13.3 (12.5–14.5) |
| Noordkempen, Belgium | Family-based random sample | 1985–2008 | Address list | 78 | 2904 | 1430 | 12016 | 22.8 (7.9–26.2) |
| Uppsala, Sweden | Men aged 69–74 years | 1991–1995 | Population census | 73 | 1143 | 1114 | 2015 | 15.1 (3.5–22.2) |
| Copenhagen County, Denmark | Stratified random sample of women and men aged 30, 40, 50 and 60 years | 1993–1997 | Population registry | 83 | 2311 | 2148 | 2010 | 16.3 (5.1–17.3) |
| Dublin, Ireland | Bank employees working at branches across Ireland | 1989–1991 | All invited | 14 | 981 | 933 | 2007 | 17.6 (16.4–18.2) |
| Maracaibo, Venezuela | City residents aged ≥55 years | 1998–2008 | Population census | 71 | 604 | 590 | 2012 | 8.2 (1.7–13.7) |
| Montevideo, Uruguay | Age-stratified random sample | 1995–1998 | Members of a health insurance organization | 78 | 1859 | 1729 | 2007 | 9.0 (4.2–10.7) |

Abbreviation: PR, participation rate. The European Project on Genes in Hypertension included participants recruited in Novosibirsk, Kraków, Gdańsk, Pilsen and Padova. Participants from Padova were recruited in Mirano in the province of Venice and in Torrebelvicino and Valli del Pasubio in the province of Vicenza.

**eTable 2. Ambulatory Blood Pressure Monitoring by Cohort**

| Study Cohorts | N° of People | Monitoring Device | Programmed Reading Intervals minutes | | N° of Readings | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Day | Night | Programmed | Median | P5 | P25 | P75 | P95 |
| Ohasama, Iwate, Japan | 1535 | ABP-630, Nippon Colin | 30 | 30 | 48 | 45 | 35 | 42 | 48 | 50 |
| JingNing, Zhejiang, China | 352 | 90207, SpaceLabs | 20 | 45 | 65 | 56 | 52 | 55 | 56 | 57 |
| Oktyabrsky, Novosibirsk, Russia | 283 | 90202, SpaceLabs | 15 | 30 | 76 | 71 | 56 | 65 | 75 | 78 |
| Niepolomice, Kraków, Poland | 355 | 90202, SpaceLabs | 15 | 30 | 76 | 74 | 54 | 61 | 77 | 79 |
| Gdańsk, Poland | 202 | TM-2430, A&D | 20 | 45 | 65 | 62 | 50 | 59 | 64 | 64 |
| Pilsen, Czech Republic | 159 | 90202, SpaceLabs | 20 | 45 | 65 | 75 | 54 | 70 | 80 | 82 |
| Padova, Italy | 305 | 90202, SpaceLabs | 15 | 30 | 76 | 76 | 66 | 74 | 77 | 78 |
| Noordkempen, Belgium | 1430 | 90202, SpaceLabs | 20 | 40 | 55 | 53 | 37 | 41 | 56 | 58 |
| Uppsala, Sweden | 1114 | Accutracker II | 20–30 | 20–60 | 41–72 | 65 | 44 | 52 | 75 | 84 |
| Copenhagen County, Denmark | 2148 | TM-2421, A&D | 15 | 30 | 80 | 80 | 67 | 78 | 81 | 83 |
| Dublin, Ireland | 933 | 90202 and 90207, Spacelabs | 30 | 30 | 48 | 46 | 37 | 44 | 48 | 49 |
| Maracaibo, Venezuela | 590 | 90207, SpaceLabs | 15 | 30 | 80 | 67 | 51 | 61 | 71 | 77 |
| Montevideo, Uruguay | 1729 | 90207, SpaceLabs | 20 | 40 | 60 | 37 | 26 | 33 | 39 | 42 |

The TM-2421 and TM-2430 monitors implemented both an auscultatory and an oscillometric technique. However, only oscillometric readings were used for analysis. All devices passed validation.

**eTable 3. Correlation Coefficients between Blood Pressure Measurements**

| | Conventional BP | Automated Office BP | 24-Hour BP | Daytime BP | Nighttime BP |
|---|---|---|---|---|---|
| **Systolic** | | | | | |
| Conventional office BP | — | | | | |
| Automated office BP | 0.71 | — | | | |
| 24-hour BP | 0.67 | 0.78 | — | | |
| Daytime BP | 0.62 | 0.80 | 0.94 | — | |
| Nighttime BP | 0.60 | 0.62 | 0.89 | 0.72 | — |
| Dipping ratio | 0.09 | –0.08 | 0.11 | –0.20 | 0.54 |
| **Diastolic** | | | | | |
| Conventional office BP | — | | | | |
| Automated office BP | 0.62 | — | | | |
| 24-hour BP | 0.62 | 0.74 | — | | |
| Daytime BP | 0.59 | 0.74 | 0.93 | — | |
| Nighttime BP | 0.53 | 0.56 | 0.85 | 0.64 | — |
| Dipping ratio | 0.06 | –0.056 | 0.11 | –0.22 | 0.59 |

Abbreviation: BP, blood pressure. Daytime and nighttime were defined using short fixed clock-time intervals (see Expanded Methods and reference 16). Dipping ratio is nighttime divided by daytime BP.
All correlation coefficients were significant ($P < .001$).

**eTable 4. Incidence of End Points**

| End Point | Number of End Points | | |
|---|---|---|---|
| | End Point | Fatal | Nonfatal |
| Total mortality | 2836 | 2836 | |
| Cardiovascular mortality | 1073 | 1073 | |
| Non-cardiovascular mortality | | 1611 | |
| Death from renal failure | | 45 | |
| Cause of death unknown | | 107 | |
| All cardiovascular Outcomes | 2049 | | |
| Coronary Outcomes | 922 | | |
| Myocardial infarction | | 234 | 441 |
| Coronary revascularization | | | 180 |
| Other ischemic heart disease | | 154 | |
| Sudden death | | 83 | |
| Heart failure | | 154 | 594 |
| Stroke | 822 | 283 | 684 |

Median follow-up of 11,135 participants was 13.8 years (5th to 95th percentile interval, 2.5–25.1 years). The nonfatal events do not add up, because within each category only the first event was analyzed.

**eTable 5. Association of Outcomes With DBP Indexes Without or With Adjustment for 24-Hour or Nighttime DBP**

| Outcomes / DBP Indexes | Adjusted[a] | | Additionally adjusted for 24-Hour DBP[b] | | Additionally Adjusted for Nighttime DBP[b] | |
|---|---|---|---|---|---|---|
| | HR (CI)[c] | *P* | HR (CI)[c] | *P* | HR (CI)[c] | *P* |
| **Total Mortality** (n = 2836) | | | | | | |
| Conventional DBP | 1.07 (1.03 to 1.11) | <.001 | 1.02 (0.98 to 1.07) | .31 | 1.02 (0.98 to 1.06) | .40 |
| Automated office DBP | 1.04 (1.01 to 1.07) | .02 | 0.97 (0.93 to 1.01) | .11 | 0.99 (0.95 to 1.02) | .48 |
| 24-hour DBP | 1.14 (1.09 to 1.19) | <.001 | NA | NA | 0.98 (0.90 to 1.06) | .61 |
| Daytime DBP | 1.09 (1.04 to 1.13) | <.001 | 0.86 (0.78 to 0.96) | .007 | 0.99 (0.94 to 1.05) | .77 |
| Nighttime DBP | 1.16 (1.11 to 1.21) | <.001 | 1.18 (1.09 to 1.27) | <.001 | NA | NA |
| Dipping ratio[d] | 1.09 (1.05 to 1.14) | <.001 | 1.09 (1.04 to 1.13) | <.001 | 1.01 (0.97 to 1.06) | .56 |
| **All CV Outcomes** (n = 2049) | | | | | | |
| Conventional DBP | 1.14 (1.10 to 1.19) | <.001 | 1.03 (0.99 to 1.09) | .17 | 1.06 (1.01 to 1.11) | .02 |
| Automated office DBP | 1.10 (1.06 to 1.14) | <.001 | 0.96 (0.91 to 1.01) | .10 | 1.02 (0.98 to 1.06) | .31 |
| 24-hour DBP | 1.30 (1.24 to 1.37) | <.001 | NA | NA | 1.16 (1.05 to 1.28) | .003 |
| Daytime DBP | 1.21 (1.15 to 1.27) | <.001 | 0.83 (0.73 to 0.93) | .002 | 1.07 (1.01 to 1.14) | .02 |
| Nighttime BP | 1.26 (1.20 to 1.32) | <.001 | 1.13 (1.04 to 1.23) | .005 | NA | NA |
| Dipping ratio[d] | 1.10 (1.05 to 1.15) | <.001 | 1.08 (1.04 to 1.13) | <.001 | 0.95 (0.90 to 1.01) | .07 |
| **CV Mortality** (n = 1073) | | | | | | |
| Conventional DBP | 1.13 (1.07 to 1.20) | <.001 | 1.03 (0.96 to 1.10) | .38 | 1.04 (0.98 to 1.11) | .21 |
| Automated office DBP | 1.07 (1.02 to 1.13) | .007 | 0.92 (0.86 to 0.99) | .02 | 0.98 (0.93 to 1.04) | .56 |
| 24-hour DBP | 1.29 (1.20 to 1.39) | <.001 | NA | NA | 1.09 (0.95 to 1.24) | .22 |
| Daytime DBP | 1.19 (1.12 to 1.28) | <.001 | 0.80 (0.67 to 0.94) | .007 | 1.04 (0.96 to 1.13) | .35 |
| Nighttime DBP | 1.28 (1.20 to 1.36) | <.001 | 1.20 (1.07 to 1.35) | .002 | NA | NA |
| Dipping ratio[d] | 1.13 (1.06 to 1.20) | <.001 | 1.11 (1.04 to 1.18) | <.001 | 0.98 (0.90 to 1.05) | .53 |
| **Coronary Outcomes** (n = 922) | | | | | | |
| Conventional DBP | 1.08 (1.02 to 1.15) | .008 | 1.02 (0.95 to 1.09) | .66 | 1.02 (0.95 to 1.09) | .60 |
| Automated office DBP | 1.07 (1.01 to 1.13) | .02 | 0.98 (0.91 to 1.06) | .66 | 1.01 (0.95 to 1.07) | .79 |
| 24-hour DBP | 1.18 (1.09 to 1.27) | <.001 | NA | NA | 1.02 (0.88 to 1.17) | .82 |
| Daytime DBP | 1.11 (1.04 to 1.20) | .003 | 0.84 (0.70 to 1.01) | .06 | 1.01 (0.92 to 1.10) | .91 |
| Nighttime DBP | 1.18 (1.10 to 1.26) | <.001 | 1.16 (1.03 to 1.32) | .02 | NA | NA |
| Dipping ratio[d] | 1.11 (1.03 to 1.18) | .003 | 1.09 (1.02 to 1.17) | .009 | 1.01 (0.93 to 1.10) | .81 |
| **Stroke** (n = 822) | | | | | | |
| Conventional DBP | 1.19 (1.12 to 1.27) | <.001 | 1.06 (0.98 to 1.14) | .15 | 1.09 (1.01 to 1.17) | .02 |
| Automated office DBP | 1.15 (1.08 to 1.22) | <.001 | 0.98 (0.90 to 1.06) | .58 | 1.05 (0.99 to 1.13) | .11 |
| 24-hour DBP | 1.41 (1.29 to 1.53) | <.001 | NA | NA | 1.24 (1.06 to 1.44) | .006 |
| Daytime DBP | 1.29 (1.19 to 1.39) | <.001 | 0.84 (0.70 to 1.02) | .08 | 1.12 (1.02 to 1.24) | .02 |
| Nighttime DBP | 1.34 (1.24 to 1.44) | <.001 | 1.15 (1.00 to 1.31) | .05 | NA | NA |
| Dipping ratio[d] | 1.10 (1.02 to 1.18) | .013 | 1.07 (1.00 to 1.15) | .05 | 0.89 (0.82 to 0.98) | .01 |

Abbreviations: CI, 95% confidence interval; CV, cardiovascular; DBP, diastolic blood pressure; HR, hazard ratio; NA, not applicable.

[a] All models accounted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, antihypertensive drug intake, history of cardiovascular disease and diabetes mellitus.

[b] Models including two correlated DBP indexes were constructed, using the residual method (see Statistical Analysis).

c Hazard ratios express the risk for increments of 10 mm Hg in DBP and 0.10 in the dipping ratio.

[d] The dipping ratio is calculated by dividing nighttime by daytime DBP.

**eTable 6. Association of Outcomes With 24-Hour or Nighttime DBP Adjusted for Other DBP Indexes**

| Outcomes | 24-Hour DBP[a] | | Nighttime DBP[a] | |
|---|---|---|---|---|
| DBP Indexes Adjusted For | HR (CI)[b] | *P* | HR (CI)[b] | *P* |
| **Total Mortality** (n = 2836) | | | | |
| Conventional DBP | 1.12 (1.06 to 1.19) | <.001 | 1.15 (1.10 to 1.20) | <.001 |
| Automated office DBP | 1.18 (1.11 to 1.25) | <.001 | 1.17 (1.11 to 1.22) | <.001 |
| 24-hour DBP | NA | NA | 1.18 (1.09 to 1.27) | <.001 |
| Daytime DBP | 1.32 (1.17 to 1.48) | <.001 | 1.16 (1.10 to 1.22) | <.001 |
| Nighttime DBP | 0.98 (0.90 to 1.06) | .61 | NA | NA |
| Dipping ratio[c] | 1.13 (1.08 to 1.18) | <.001 | 1.15 (1.09 to 1.21) | <.001 |
| **All CV Outcomes** (n = 2049) | | | | |
| Conventional DBP | 1.27 (1.19 to 1.35) | <.001 | 1.22 (1.16 to 1.29) | <.001 |
| Automated office DBP | 1.36 (1.26 to 1.46) | <.001 | 1.24 (1.18 to 1.31) | <.001 |
| 24-hour DBP | NA | NA | 1.13 (1.04 to 1.23) | .005 |
| Daytime DBP | 1.58 (1.38 to 1.81) | <.001 | 1.21 (1.14 to 1.28) | <.001 |
| Nighttime BP | 1.16 (1.05 to 1.28) | .003 | NA | NA |
| Dipping ratio[c] | 1.29 (1.23 to 1.36) | <.001 | 1.30 (1.23 to 1.38) | <.001 |
| **CV Mortality** (n = 1073) | | | | |
| Conventional DBP | 1.27 (1.16 to 1.38) | <.001 | 1.25 (1.17 to 1.34) | <.001 |
| Automated office DBP | 1.40 (1.27 to 1.54) | <.001 | 1.29 (1.20 to 1.38) | <.001 |
| 24-hour DBP | NA | NA | 1.20 (1.07 to 1.35) | .002 |
| Daytime DBP | 1.63 (1.36 to 1.96) | <.001 | 1.25 (1.15 to 1.35) | <.001 |
| Nighttime DBP | 1.09 (0.95 to 1.24) | .22 | NA | NA |
| Dipping ratio[c] | 1.28 (1.19 to 1.38) | <.001 | 1.30 (1.20 to 1.40) | <.001 |
| **Coronary Outcomes** (n = 922) | | | | |
| Conventional DBP | 1.16 (1.06 to 1.28) | .002 | 1.17 (1.08 to 1.26) | <.001 |
| Automated office DBP | 1.20 (1.08 to 1.33) | <.001 | 1.17 (1.09 to 1.26) | <.001 |
| 24-hour DBP | NA | NA | 1.16 (1.03 to 1.32) | .02 |
| Daytime DBP | 1.40 (1.15 to 1.71) | <.001 | 1.17 (1.08 to 1.28) | <.001 |
| Nighttime DBP | 1.02 (0.88 to 1.17) | .82 | NA | NA |
| Dipping ratio[c] | 1.16 (1.08 to 1.26) | <.001 | 1.17 (1.08 to 1.27) | <.001 |
| **Stroke** (n = 822) | | | | |
| Conventional DBP | 1.35 (1.23 to 1.49) | <.001 | 1.28 (1.18 to 1.39) | <.001 |
| Automated office DBP | 1.44 (1.28 to 1.61) | <.001 | 1.30 (1.20 to 1.41) | <.001 |
| 24-hour DBP | NA | NA | 1.15 (1.00 to 1.31) | .05 |
| Daytime DBP | 1.67 (1.35 to 2.06) | <.001 | 1.25 (1.14 to 1.37) | <.001 |
| Nighttime DBP | 1.24 (1.06 to 1.44) | .006 | NA | NA |
| Dipping ratio[c] | 1.40 (1.28 to 1.52) | <.001 | 1.43 (1.31 to 1.57) | <.001 |

Abbreviations: CI, 95% confidence interval; CV, cardiovascular; DBP, diastolic blood pressure; HR, hazard ratio; NA, not applicable.

[a] All models accounted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, antihypertensive drug intake, history of cardiovascular disease and diabetes mellitus and were constructed, using the residual method (see Statistical Analysis).

[b] Hazard ratios express the risk for increments of 10-mm Hg in DBP and 0.10 in the dipping ratio.

[c] The dipping ratio is calculated by dividing nighttime by daytime DBP.

**eTable 7. Association of Outcomes With SBP Indexes Without or With Adjustment for 24-Hour or Nighttime SBP Among 8873 Untreated Participants**

| Outcomes / SBP Indexes | Adjusted[a] | | Additionally Adjusted for 24-Hour SBP[b] | | Additionally Adjusted for Nighttime SBP[c] | |
|---|---|---|---|---|---|---|
| | HR (CI)[c] | *P* | HR (CI)[c] | *P* | HR (CI)[c] | *P* |
| **Total Mortality** (n = 1754) | | | | | | |
| Conventional SBP | 1.16 (1.10 to 1.22) | <.001 | 1.06 (1.00 to 1.13) | .06 | 1.07 (1.01 to 1.13) | .03 |
| Automated office SBP | 1.14 (1.09 to 1.20) | <.001 | 1.01 (0.95 to 1.08) | .66 | 1.05 (0.99 to 1.11) | .11 |
| 24-hour SBP | 1.29 (1.21 to 1.38) | <.001 | NA | NA | 1.03 (0.90 to 1.18) | .69 |
| Daytime SBP | 1.22 (1.14 to 1.30) | <.001 | 0.84 (0.71 to 0.98) | .03 | 1.03 (0.95 to 1.12) | .45 |
| Nighttime SBP | 1.28 (1.21 to 1.36) | <.001 | 1.26 (1.12 to 1.41) | <.001 | NA | NA |
| Dipping ratio[d] | 1.13 (1.08 to 1.20) | <.001 | 1.10 (1.04 to 1.16) | <.001 | 0.98 (0.92 to 1.05) | .55 |
| **All CV Outcomes** (n = 1227) | | | | | | |
| Conventional SBP | 1.26 (1.19 to 1.34) | <.001 | 1.07 (1.00 to 1.15) | .06 | 1.12 (1.05 to 1.20) | <.001 |
| Automated office SBP | 1.27 (1.20 to 1.35) | <.001 | 1.05 (0.97 to 1.13) | .25 | 1.14 (1.06 to 1.21) | <.001 |
| 24-hour SBP | 1.54 (1.42 to 1.65) | <.001 | NA | NA | 1.37 (1.17 to 1.61) | <.001 |
| Daytime SBP | 1.43 (1.33 to 1.54) | <.001 | 0.90 (0.75 to 1.08) | .26 | 1.20 (1.09 to 1.33) | <.001 |
| Nighttime BP | 1.41 (1.33 to 1.51) | <.001 | 1.11 (0.97 to 1.28) | .12 | NA | NA |
| Dipping ratio[d] | 1.11 (1.04 to 1.19) | <.001 | 1.05 (0.98 to 1.11) | .14 | 0.86 (0.80 to 0.93) | <.001 |
| **CV Mortality** (n = 604) | | | | | | |
| Conventional SBP | 1.27 (1.17 to 1.37) | <.001 | 1.04 (0.94 to 1.14) | .47 | 1.09 (1.00 to 1.19) | .06 |
| Automated office SBP | 1.35 (1.24 to 1.46) | <.001 | 1.08 (0.97 to 1.20) | .17 | 1.17 (1.07 to 1.28) | .001 |
| 24-hour SBP | 1.65 (1.49 to 1.82) | <.001 | NA | NA | 1.36 (1.09 to 1.70) | .006 |
| Daytime SBP | 1.53 (1.38 to 1.68) | <.001 | 0.88 (0.68 to 1.14) | .33 | 1.22 (1.06 to 1.39) | .004 |
| Nighttime SBP | 1.51 (1.39 to 1.65) | <.001 | 1.20 (0.99 to 1.45) | .06 | NA | NA |
| Dipping ratio[d] | 1.16 (1.06 to 1.27) | <.001 | 1.08 (0.99 to 1.18) | .09 | 0.86 (0.77 to 0.96) | .008 |
| **Coronary Outcomes** (n = 566) | | | | | | |
| Conventional SBP | 1.20 (1.10 to 1.30) | <.001 | 1.03 (0.92 to 1.14) | .61 | 1.07 (0.98 to 1.18) | .15 |
| Automated office SBP | 1.26 (1.16 to 1.37) | <.001 | 1.08 (0.96 to 1.22) | .19 | 1.14 (1.03 to 1.26) | .008 |
| 24-hour SBP | 1.44 (1.29 to 1.61) | <.001 | NA | NA | 1.29 (1.01 to 1.64) | .04 |
| Daytime SBP | 1.37 (1.23 to 1.52) | <.001 | 0.91 (0.68 to 1.21) | .53 | 1.17 (1.01 to 1.35) | .04 |
| Nighttime SBP | 1.35 (1.23 to 1.49) | <.001 | 1.11 (0.90 to 1.37) | .31 | NA | NA |
| Dipping ratio[d] | 1.11 (1.01 to 1.22) | .04 | 1.05 (0.95 to 1.15) | .34 | 0.89 (0.79 to 1.00) | .05 |
| **Stroke** (n = 463) | | | | | | |
| Conventional SBP | 1.41 (1.28 to 1.55) | <.001 | 1.18 (1.04 to 1.32) | .007 | 1.23 (1.11 to 1.38) | <.001 |
| Automated office SBP | 1.38 (1.25 to 1.51) | <.001 | 1.11 (0.98 to 1.26) | .10 | 1.21 (1.09 to 1.34) | <.001 |
| 24-hour SBP | 1.69 (1.50 to 1.90) | <.001 | NA | NA | 1.45 (1.12 to 1.87) | .004 |
| Daytime SBP | 1.59 (1.41 to 1.78) | <.001 | 1.03 (0.77 to 1.38) | .84 | 1.30 (1.12 to 1.52) | .001 |
| Nighttime SBP | 1.52 (1.38 to 1.68) | <.001 | 1.16 (0.93 to 1.44) | .18 | NA | NA |
| Dipping ratio[d] | 1.12 (1.02 to 1.24) | .02 | 1.04 (0.94 to 1.15) | .41 | 0.81 (0.72 to 0.92) | .001 |

Abbreviations: CI, 95% confidence interval; CV, cardiovascular; HR, hazard ratio; SBP, systolic blood pressure; NA, not applicable.

[a] All models accounted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, antihypertensive drug intake, history of cardiovascular disease and diabetes mellitus.

[b] Models including two correlated SBP indexes were constructed, using the residual method (see Statistical Analysis).

[c] Hazard ratios express the risk for increments of 20 mm Hg in SBP and 0.10 in the dipping ratio.

[d] The dipping ratio is calculated by dividing nighttime by daytime SBP.

**eTable 8. Association of Outcomes With 24-Hour or Nighttime SBP Adjusted for Other SBP Indexes Among 8873 Untreated Participants**

| Outcomes | 24-Hour SBP[a] | | Nighttime SBP[a] | |
|---|---|---|---|---|
| SBP Indexes Adjusted For | HR (CI)[b] | *P* | HR (CI)[b] | *P* |
| **Total Mortality** (n = 1754) | | | | |
| Conventional SBP | 1.24 (1.14 to 1.34) | <.001 | 1.24 (1.16 to 1.32) | <.001 |
| Automated office SBP | 1.28 (1.17 to 1.40) | <.001 | 1.25 (1.17 to 1.33) | <.001 |
| 24-hour SBP | NA | NA | 1.26 (1.12 to 1.41) | <.001 |
| Daytime SBP | 1.54 (1.30 to 1.82) | <.001 | 1.26 (1.17 to 1.36) | <.001 |
| Nighttime SBP | 1.03 (0.90 to 1.18) | .69 | NA | NA |
| Dipping ratio[c] | 1.27 (1.18 to 1.36) | <.001 | 1.30 (1.21 to 1.40) | <.001 |
| **All CV Outcomes** (n = 1227) | | | | |
| Conventional SBP | 1.45 (1.33 to 1.60) | <.001 | 1.33 (1.24 to 1.43) | <.001 |
| Automated office SBP | 1.47 (1.33 to 1.63) | <.001 | 1.33 (1.23 to 1.43) | <.001 |
| 24-hour SBP | NA | NA | 1.11 (0.97 to 1.28) | .12 |
| Daytime SBP | 1.70 (1.40 to 2.05) | <.001 | 1.27 (1.16 to 1.38) | <.001 |
| Nighttime BP | 1.37 (1.17 to 1.61) | <.001 | NA | NA |
| Dipping ratio[c] | 1.52 (1.41 to 1.64) | <.001 | 1.56 (1.44 to 1.70) | <.001 |
| **CV Mortality** (n = 604) | | | | |
| Conventional SBP | 1.60 (1.42 to 1.81) | <.001 | 1.45 (1.32 to 1.60) | <.001 |
| Automated office SBP | 1.54 (1.34 to 1.77) | <.001 | 1.40 (1.27 to 1.54) | <.001 |
| 24-hour SBP | NA | NA | 1.20 (0.99 to 1.45) | .06 |
| Daytime SBP | 1.86 (1.43 to 2.42) | <.001 | 1.35 (1.20 to 1.52) | <.001 |
| Nighttime SBP | 1.36 (1.09 to 1.70) | .01 | NA | NA |
| Dipping ratio[c] | 1.61 (1.46 to 1.79) | <.001 | 1.67 (1.50 to 1.86) | <.001 |
| **Coronary Outcomes** (n = 566) | | | | |
| Conventional SBP | 1.41 (1.23 to 1.62) | <.001 | 1.30 (1.17 to 1.45) | <.001 |
| Automated office SBP | 1.34 (1.15 to 1.57) | <.001 | 1.26 (1.12 to 1.40) | <.001 |
| 24-hour SBP | NA | NA | 1.11 (0.90 to 1.37) | .31 |
| Daytime SBP | 1.58 (1.17 to 2.11) | .002 | 1.23 (1.08 to 1.41) | .002 |
| Nighttime SBP | 1.29 (1.01 to 1.64) | .04 | NA | NA |
| Dipping ratio[c] | 1.43 (1.27 to 1.59) | <.001 | 1.46 (1.29 to 1.64) | <.001 |
| **Stroke** (n = 463) | | | | |
| Conventional SBP | 1.51 (1.30 to 1.75) | <.001 | 1.38 (1.23 to 1.55) | <.001 |
| Automated office SBP | 1.54 (1.31 to 1.82) | <.001 | 1.39 (1.24 to 1.56) | <.001 |
| 24-hour SBP | NA | NA | 1.16 (0.93 to 1.44) | .18 |
| Daytime SBP | 1.64 (1.21 to 2.22) | .001 | 1.31 (1.15 to 1.50) | <.001 |
| Nighttime SBP | 1.45 (1.12 to 1.87) | <.001 | NA | NA |
| Dipping ratio[c] | 1.67 (1.47 to 1.89) | <.001 | 1.76 (1.55 to 2.01) | <.001 |

Abbreviations: CI, 95% confidence interval; CV, cardiovascular; HR, hazard ratio; SBP, systolic blood pressure; NA, not applicable.

[a] All models accounted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, antihypertensive drug intake, history of cardiovascular disease and diabetes mellitus and were constructed, using the residual method (see Statistical Analysis).

[b] Hazard ratios express the risk for increments of 20 mm Hg in SBP and 0.10 in the dipping ratio.

[c] The dipping ratio is the nighttime divided by the daytime SBP.

**eTable 9. Association of Outcomes With SBP Indexes During Wakefulness and Sleep in 7133 Participants Without or With Adjustment for 24-Hour or Asleep SBP**

| Outcomes / SBP Indexes | Adjusted[a,b] | | Additionally Adjusted for 24-Hour SBP[a,c] | | Additionally Adjusted for Asleep SBP[a,c] | |
|---|---|---|---|---|---|---|
| | HR (CI)[d] | *P* | HR (CI)[d] | *P* | HR (CI)[d] | *P* |
| **Total Mortality** (n = 1566) | | | | | | |
| Conventional SBP | 1.14 (1.08 to 1.21) | <.001 | 1.07 (1.00 to 1.14) | .05 | 1.07 (1.01 to 1.14) | .02 |
| Automated office SBP | 1.11 (1.05 to 1.17) | <.001 | 0.96 (0.89 to 1.04) | .35 | 1.00 (0.94 to 1.07) | .95 |
| 24-hour SBP | 1.28 (1.19 to 1.39) | <.001 | NA | NA | 1.02 (0.87 to 1.19) | .82 |
| Awake SBP | 1.22 (1.13 to 1.32) | <.001 | 0.71 (0.55 to 0.93) | .01 | 1.02 (0.91 to 1.13) | .75 |
| Asleep SBP | 1.29 (1.20 to 1.38) | <.001 | 1.27 (1.10 to 1.47) | <.001 | NA | NA |
| Dipping ratio[e] | 1.14 (1.07 to 1.22) | <.001 | 1.12 (1.05 to 1.20) | <.001 | 1.00 (0.92 to 1.08) | .98 |
| **All CV Outcomes** (n = 1048) | | | | | | |
| Conventional SBP | 1.25 (1.17 to 1.33) | <.001 | 1.06 (0.98 to 1.14) | .15 | 1.10 (1.02 to 1.18) | .009 |
| Automated office SBP | 1.25 (1.17 to 1.33) | <.001 | 0.94 (0.86 to 1.04) | .24 | 1.05 (0.97 to 1.14) | .21 |
| 24-hour SBP | 1.65 (1.50 to 1.80) | <.001 | NA | NA | 1.29 (1.07 to 1.57) | .008 |
| Awake SBP | 1.54 (1.41 to 1.68) | <.001 | 0.69 (0.50 to 0.96) | .03 | 1.19 (1.04 to 1.35) | .009 |
| Asleep BP | 1.57 (1.45 to 1.70) | <.001 | 1.28 (1.08 to 1.52) | .005 | NA | NA |
| Dipping ratio[e] | 1.17 (1.08 to 1.27) | <.001 | 1.13 (1.04 to 1.23) | .004 | 0.89 (0.80 to 0.98) | .02 |
| **CV Mortality** (n = 521) | | | | | | |
| Conventional SBP | 1.32 (1.20 to 1.44) | <.001 | 1.14 (1.02 to 1.27) | .02 | 1.17 (1.06 to 1.29) | .002 |
| Automated office SBP | 1.23 (1.12 to 1.35) | <.001 | 0.92 (0.81 to 1.05) | .22 | 1.02 (0.92 to 1.14) | .67 |
| 24-hour SBP | 1.68 (1.48 to 1.91) | <.001 | NA | NA | 1.21 (0.93 to 1.58) | .16 |
| Awake SBP | 1.55 (1.37 to 1.76) | <.001 | 0.65 (0.42 to 1.01) | .06 | 1.15 (0.96 to 1.38) | .12 |
| Asleep SBP | 1.63 (1.45 to 1.83) | <.001 | 1.40 (1.10 to 1.78) | .006 | NA | NA |
| Dipping ratio[e] | 1.21 (1.08 to 1.35) | .001 | 1.17 (1.04 to 1.31) | .007 | 0.91 (0.79 to 1.04) | .18 |
| **Coronary Outcomes** (n = 409) | | | | | | |
| Conventional SBP | 1.18 (1.06 to 1.31) | .002 | 0.98 (0.86 to 1.11) | .77 | 1.02 (0.91 to 1.15) | .71 |
| Automated office SBP | 1.22 (1.09 to 1.35) | <.001 | 0.93 (0.79 to 1.08) | .34 | 1.01 (0.89 to 1.15) | .83 |
| 24-hour SBP | 1.55 (1.35 to 1.79) | <.001 | NA | NA | 1.15 (0.84 to 1.57) | .39 |
| Awake SBP | 1.46 (1.27 to 1.68) | <.001 | 0.59 (0.34 to 1.04) | .07 | 1.09 (0.88 to 1.36) | .42 |
| Asleep SBP | 1.52 (1.34 to 1.73) | <.001 | 1.36 (1.03 to 1.81) | .03 | NA | NA |
| Dipping ratio[e] | 1.21 (1.06 to 1.39) | .005 | 1.17 (1.02 to 1.34) | .03 | 0.94 (0.80 to 1.11) | .47 |
| **Stroke** (n = 479) | | | | | | |
| Conventional SBP | 1.30 (1.18 to 1.43) | <.001 | 1.08 (0.97 to 1.21) | .17 | 1.13 (1.02 to 1.26) | .02 |
| Automated office SBP | 1.34 (1.22 to 1.48) | <.001 | 1.00 (0.87 to 1.15) | .97 | 1.12 (1.00 to 1.26) | .04 |
| 24-hour SBP | 1.84 (1.61 to 2.10) | <.001 | NA | NA | 1.43 (1.09 to 1.88) | .01 |
| Awake SBP | 1.67 (1.47 to 1.90) | <.001 | 0.62 (0.39 to 0.98) | .04 | 1.25 (1.04 to 1.50) | .02 |
| Asleep SBP | 1.72 (1.52 to 1.94) | <.001 | 1.29 (1.01 to 1.66) | .04 | NA | NA |
| Dipping ratio[e] | 1.18 (1.05 to 1.33) | .005 | 1.14 (1.02 to 1.29) | .03 | 0.85 (0.74 to 0.98) | .03 |

Abbreviations: CI, 95% confidence interval; CV, cardiovascular; HR, hazard ratio; SBP, systolic blood pressure; NA, not applicable.

[a] In this analysis, we defined the awake and asleep periods of the day in 7133 participants (64.1%), who had kept a diary during ambulatory blood pressure monitoring.

[b] All models accounted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, antihypertensive drug intake, history of cardiovascular disease and diabetes mellitus.

[c] Models including two correlated SBP indexes were constructed, using the residual method (see Statistical Analysis).

[d] Hazard ratios express the risk for increments of 20 mm Hg in SBP and 0.10 in the dipping ratio.

[e] The dipping ratio is calculated by dividing asleep by awake SBP.

**eTable 10. Association of Outcomes with 24-Hour or Asleep SBP Adjusted for Other SBP Indexes in 7133 Participants**

| Outcomes | 24-Hour SBP[a] | | Asleep SBP[a] | |
|---|---|---|---|---|
| SBP Indexes Adjusted For | HR (CI)[b] | *P* | HR (CI)[b] | *P* |
| **Total Mortality** (n = 1566) | | | | |
| Conventional SBP | 1.23 (1.12 to 1.34) | <.001 | 1.25 (1.16 to 1.34) | <.001 |
| Automated office SBP | 1.33 (1.19 to 1.48) | <.001 | 1.29 (1.19 to 1.40) | <.001 |
| 24-hour SBP | NA | NA | 1.27 (1.10 to 1.47) | <.001 |
| Awake SBP | 1.81 (1.37 to 2.39) | <.001 | 1.27 (1.15 to 1.41) | <.001 |
| Asleep SBP | 1.02 (0.87 to 1.19) | .82 | NA | NA |
| Dipping ratio[c] | 1.27 (1.17 to 1.37) | <.001 | 1.29 (1.19 to 1.40) | <.001 |
| **All CV Outcomes** (n = 1048) | | | | |
| Conventional SBP | 1.58 (1.42 to 1.76) | <.001 | 1.49 (1.36 to 1.63) | <.001 |
| Automated office SBP | 1.74 (1.53 to 1.98) | <.001 | 1.52 (1.38 to 1.67) | <.001 |
| 24-hour SBP | NA | NA | 1.28 (1.08 to 1.52) | .005 |
| Awake SBP | 2.38 (1.70 to 3.34) | <.001 | 1.39 (1.23 to 1.57) | <.001 |
| Asleep BP | 1.29 (1.07 to 1.57) | .008 | NA | NA |
| Dipping ratio[c] | 1.62 (1.48 to 1.78) | <.001 | 1.68 (1.52 to 1.85) | <.001 |
| **CV Mortality** (n = 521) | | | | |
| Conventional SBP | 1.54 (1.33 to 1.79) | <.001 | 1.52 (1.34 to 1.72) | <.001 |
| Automated office SBP | 1.81 (1.52 to 2.16) | <.001 | 1.61 (1.41 to 1.84) | <.001 |
| 24-hour SBP | NA | NA | 1.40 (1.10 to 1.78) | .006 |
| Awake SBP | 2.60 (1.63 to 4.15) | <.001 | 1.48 (1.25 to 1.75) | <.001 |
| Asleep SBP | 1.21 (0.93 to 1.58) | .16 | NA | NA |
| Dipping ratio[c] | 1.66 (1.45 to 1.88) | <.001 | 1.72 (1.50 to 1.98) | <.001 |
| **Coronary Outcomes** (n = 409) | | | | |
| Conventional SBP | 1.58 (1.32 to 1.88) | <.001 | 1.50 (1.30 to 1.74) | <.001 |
| Automated office SBP | 1.68 (1.36 to 2.07) | <.001 | 1.51 (1.29 to 1.76) | <.001 |
| 24-hour SBP | NA | NA | 1.36 (1.03 to 1.81) | .03 |
| Awake SBP | 2.62 (1.47 to 4.65) | .001 | 1.43 (1.17 to 1.75) | <.001 |
| Asleep SBP | 1.15 (0.84 to 1.57) | .39 | NA | NA |
| Dipping ratio[c] | 1.53 (1.32 to 1.76) | <.001 | 1.57 (1.34 to 1.83) | <.001 |
| **Stroke** (n = 479) | | | | |
| Conventional SBP | 1.74 (1.5 to 2.03) | <.001 | 1.62 (1.42 to 1.84) | <.001 |
| Automated office SBP | 1.83 (1.52 to 2.21) | <.001 | 1.60 (1.39 to 1.84) | <.001 |
| 24-hour SBP | NA | NA | 1.29 (1.01 to 1.66) | .04 |
| Awake SBP | 2.97 (1.84 to 4.80) | <.001 | 1.48 (1.24 to 1.76) | <.001 |
| Asleep SBP | 1.43 (1.09 to 1.88) | .01 | NA | NA |
| Dipping ratio[c] | 1.81 (1.59 to 2.07) | <.001 | 1.88 (1.63 to 2.18) | <.001 |

Abbreviations: CI, 95% confidence interval; CV, cardiovascular; HR, hazard ratio; SBP, systolic blood pressure; NA, not applicable.

[a] In this analysis, we defined the awake and asleep periods of the day in 7133 participants (64.1%), who had kept a diary during ambulatory blood pressure monitoring. All models accounted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, antihypertensive drug intake, history of cardiovascular disease and diabetes mellitus and were constructed, using the residual method (see Statistical Analysis).

[b] Hazard ratios express the risk for increments of 20 mm Hg in SBP and 0.10 in the dipping ratio.

[c] The dipping ratio is calculated by dividing asleep by awake SBP.

**eTable 11. Sensitivity Analysis Excluding Cohorts**

| Outcomes / Population | N° Event/ N° at Risk | 24-Hour SBP | | Nighttime SBP | |
|---|---|---|---|---|---|
| | | HR (CI)[a] | *P* | HR (CI)[a] | *P* |
| **Total Mortality** | | | | | |
| **All Cohorts**[b] | **2836/11,135** | **1.22 (1.16 to 1.28)** | **<.001** | **1.23 (1.17 to 1.28)** | **<.001** |
| Excluding[c] | | | | | |
| Ohasama | 2115/9600 | 1.21 (1.15 to 1.29) | <.001 | 1.22 (1.16 to 1.28) | <.001 |
| Small cohorts | 2787/9479 | 1.22 (1.16 to 1.29) | <.001 | 1.22 (1.17 to 1.28) | <.001 |
| Noordkempen | 2527/9705 | 1.21 (1.14 to 1.27) | <.001 | 1.21 (1.16 to 1.27) | <.001 |
| Uppsala | 1907/10,021 | 1.32 (1.23 to 1.41) | <.001 | 1.33 (1.25 to 1.41) | <.001 |
| Copenhagen | 2297/8987 | 1.19 (1.13 to 1.26) | <.001 | 1.21 (1.15 to 1.27) | <.001 |
| Dublin | 2800/10,202 | 1.22 (1.16 to 1.28) | <.001 | 1.22 (1.17 to 1.28) | <.001 |
| Maracaibo | 2697/10,545 | 1.19 (1.13 to 1.26) | <.001 | 1.20 (1.15 to 1.26) | <.001 |
| Montevideo | 2722/9406 | 1.23 (1.16 to 1.29) | <.001 | 1.23 (1.17 to 1.28) | <.001 |
| **CV Outcomes** | | | | | |
| **All Cohorts**[b] | **2049/11,135** | **1.45 (1.37 to 1.54)** | **<.001** | **1.36 (1.30 to 1.43)** | **<.001** |
| Excluding[c] | | | | | |
| Ohasama | 1681/9600 | 1.42 (1.34 to 1.51) | <.001 | 1.34 (1.28 to 1.42) | <.001 |
| Small cohorts | 1995/9479 | 1.44 (1.36 to 1.53) | <.001 | 1.35 (1.29 to 1.42) | <.001 |
| Noordkempen | 1768/9705 | 1.44 (1.35 to 1.53) | <.001 | 1.35 (1.29 to 1.42) | <.001 |
| Uppsala | 1363/10,021 | 1.62 (1.50 to 1.75) | <.001 | 1.53 (1.43 to 1.64) | <.001 |
| Copenhagen | 1683/8987 | 1.42 (1.34 to 1.52) | <.001 | 1.33 (1.26 to 1.40) | <.001 |
| Dublin | 2030/10,202 | 1.45 (1.37 to 1.54) | <.001 | 1.36 (1.30 to 1.43) | <.001 |
| Maracaibo | 1919/10,545 | 1.45 (1.37 to 1.54) | <.001 | 1.36 (1.29 to 1.43) | <.001 |
| Montevideo | 1904/9406 | 1.45 (1.36 to 1.54) | <.001 | 1.36 (1.30 to 1.43) | <.001 |

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; SBP, systolic blood pressure.

[a] Hazard ratios express the risk per 20 mm Hg increment in 24-hour or nighttime SBP. HRs accounted for cohort (random effect), sex, age, body mass index, smoking and drinking, serum total cholesterol, antihypertensive drug intake, history of CV disease and diabetes mellitus.

[b] The analyses included 11,135 participants.

[c] Identifies the excluded cohort. All cohorts with fewer than 500 participants were excluded in a single run. These cohorts included JingNing (n = 352), Novosibirsk (n = 283), Kraków (n = 355), Gdańsk (n = 202), Pilsen (n = 159) and Padova (n = 305).

**eTable 12. Improvement in Model Performance by Adding 24-Hour or Nighttime SBP to Another SBP Index**

| Outcomes<br>SBP Index to Which 24-Hour or Nighttime SBP Was Added | AUC (CI) Basic Model[a] | ΔAUC (CI)[b] | |
|---|---|---|---|
| | | Adding 24-Hour SBP | Adding Nighttime SBP |
| **Total Mortality** (n = 2836) | | | |
| Conventional SBP | 0.83 (0.82 to 0.85) | 0.0013 (0.0001 to 0.0024) | 0.0024 (0.0010 to 0.0038) |
| Automated office SBP | 0.83 (0.82 to 0.85) | 0.0016 (0.0003 to 0.0029) | 0.0027 (0.0010 to 0.0044) |
| 24-hour SBP | 0.83 (0.82 to 0.85) | *NA* | 0.0013 (0.0001 to 0.0024) |
| Daytime SBP | 0.83 (0.82 to 0.85) | 0.0016 (0.0001 to 0.0032) | 0.0023 (0.0006 to 0.0040) |
| Nighttime SBP | 0.83 (0.82 to 0.85) | *NC*[c] | *NA* |
| Dipping ratio[d] | 0.83 (0.82 to 0.85) | 0.0017 (0.0003 to 0.0032) | 0.0018 (0.0002 to 0.0032) |
| **All CV Outcomes** (n = 2049) | | | |
| Conventional SBP | 0.84 (0.83 to 0.85) | 0.0057 (0.0033 to 0.0082) | 0.0058 (0.0034 to 0.0082) |
| Automated office SBP | 0.84 (0.83 to 0.85) | 0.0048 (0.0025 to 0.0071) | 0.0050 (0.0028 to 0.0072) |
| 24-hour SBP | 0.84 (0.83 to 0.86) | *NA* | 0.0005 (–0.0002 to 0.0012) |
| Daytime SBP | 0.84 (0.83 to 0.86) | 0.0034 (0.0015 to 0.0052) | 0.0031 (0.0014 to 0.0048) |
| Nighttime SBP | 0.84 (0.83 to 0.86) | 0.0006 (–0.0002 to 0.0015) | *NA* |
| Dipping ratio[d] | 0.84 (0.83 to 0.85) | 0.0075 (0.0047 to 0.0103) | 0.0071 (0.0043 to 0.0099) |
| **CV Mortality** (n = 1073) | | | |
| Conventional SBP | 0.87 (0.86 to 0.89) | 0.0037 (0.0012 to 0.0062) | 0.0046 (0.0019 to 0.0073) |
| Automated office SBP | 0.87 (0.86 to 0.89) | 0.0047 (0.0020 to 0.0074) | 0.0052 (0.0022 to 0.0082) |
| 24-hour SBP | 0.88 (0.86 to 0.89) | *NA* | 0.0009 (–0.0004 to 0.0023) |
| Daytime SBP | 0.88 (0.86 to 0.89) | 0.0025 (0.0002 to 0.0048) | 0.0029 (0.0004 to 0.0054) |
| Nighttime SBP | 0.88 (0.86 to 0.89) | *NC*[c] | *NA* |
| Dipping ratio[d] | 0.87 (0.86 to 0.89) | 0.0055 (0.0023 to 0.0087) | 0.0055 (0.0022 to 0.0087) |
| **Coronary Outcomes** (n = 922) | | | |
| Conventional SBP | 0.86 (0.85 to 0.87) | 0.0038 (0.0014 to 0.0063) | 0.0033 (0.0011 to 0.0055) |
| Automated office SBP | 0.86 (0.85 to 0.88) | 0.0023 (0.0002 to 0.0044) | 0.0022 (0.0002 to 0.0042) |
| 24-hour SBP | 0.86 (0.85 to 0.88) | *NA* | 0.0001 (–0.0007 to 0.0009) |
| Daytime SBP | 0.86 (0.85 to 0.88) | 0.0014 (–0.0002 to 0.0029) | 0.0011 (–0.0004 to 0.0027) |
| Nighttime SBP | 0.86 (0.85 to 0.88) | *NC*[c] | *NA* |
| Dipping ratio[d] | 0.86 (0.84 to 0.87) | 0.0049 (0.0018 to 0.0079) | 0.0045 (0.0016 to 0.0074) |
| **Stroke** (n = 822) | | | |
| Conventional SBP | 0.84 (0.82 to 0.86) | 0.0073 (0.0028 to 0.0118) | 0.0068 (0.0025 to 0.0110) |
| Automated office SBP | 0.84 (0.82 to 0.86) | 0.0076 (0.0027 to 0.0124) | 0.0069 (0.0026 to 0.0112) |
| 24-hour SBP | 0.85 (0.83 to 0.87) | *NA* | 0.0002 (–0.0012 to 0.0016) |
| Daytime SBP | 0.85 (0.83 to 0.87) | 0.0037 (0.0004 to 0.0069) | 0.0034 (0.0002 to 0.0066) |
| Nighttime SBP | 0.84 (0.83 to 0.86) | 0.0017 (–0.0004 to 0.0038) | *NA* |
| Dipping ratio[d] | 0.83 (0.82 to 0.85) | 0.0138 (0.0080 to 0.0196) | 0.0135 (0.0077 to 0.0193) |

Abbreviations: AUC, area under the receiver operating characteristic curve for the 10-year absolute risk; CI, 95% confidence interval; CV, cardiovascular; ΔAUC, change in AUC; SBP, systolic blood pressure; NA, not applicable.

[a] Basic models included cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, antihypertensive drug intake, history of cardiovascular disease and diabetes mellitus and another SBP index identified by the row label.

[b] ΔAUC for adding 24-hour or nighttime SBP to a basic model already including covariables and another SBP index. Models were constructed using the residual method (see Statistical Analysis).

[c] NC indicates that the improvement in model performance was not calculated, because the hazard ratio for 24-hour SBP did not attain significance in multivariable-adjusted models already including nighttime SBP (**Table 3**).

[d] The dipping ratio is calculated by dividing nighttime by daytime SBP.

**eTable 13. Improvement in Model Performance by Adding 24-Hour or Nighttime DBP to Another DBP Index**

| Outcomes<br>DBP Index to Which 24-Hour or Nighttime DBP Was Added | AUC (CI) Basic Model[a] | ΔAUC (CI)[b] | |
|---|---|---|---|
| | | Adding 24-Hour DBP | Adding Nighttime DBP |
| **Total Mortality** (n = 2836) | | | |
| Conventional DBP | 0.83 (0.82 to 0.84) | 0.0007 (–0.0001 to 0.0015) | 0.0018 (0.0005 to 0.0030) |
| Automated office DBP | 0.83 (0.82 to 0.85) | 0.0007 (–0.0003 to 0.0017) | 0.0018 (0.0005 to 0.0032) |
| 24-hour DBP | 0.83 (0.82 to 0.85) | *NA* | 0.0012 (0.0002 to 0.0022) |
| Daytime DBP | 0.83 (0.82 to 0.85) | 0.0009 (–0.0001 to 0.0020) | 0.0017 (0.0004 to 0.0030) |
| Nighttime DBP | 0.83 (0.82 to 0.85) | *NC*[c] | *NA* |
| Dipping ratio[d] | 0.83 (0.82 to 0.85) | 0.0009 (–0.0001 to 0.0019) | 0.0011 (0.0001 to 0.0021) |
| **All CV Outcomes** (n = 2049) | | | |
| Conventional DBP | 0.84 (0.83 to 0.85) | 0.0028 (0.0009 to 0.0047) | 0.0034 (0.0014 to 0.0053) |
| Automated office DBP | 0.84 (0.83 to 0.85) | 0.0028 (0.0011 to 0.0045) | 0.0033 (0.0014 to 0.0053) |
| 24-hour DBP | 0.84 (0.83 to 0.85) | *NA* | 0.0006 (–0.0002 to 0.0014) |
| Daytime DBP | 0.84 (0.83 to 0.85) | 0.0025 (0.0007 to 0.0042) | 0.0024 (0.0007 to 0.0041) |
| Nighttime DBP | 0.84 (0.83 to 0.86) | 0.0001 (–0.0006 to 0.0008) | *NA* |
| Dipping ratio[d] | 0.84 (0.83 to 0.85) | 0.0042 (0.0020 to 0.0063) | 0.0039 (0.0018 to 0.0059) |
| **CV Mortality** (n = 1073) | | | |
| Conventional DBP | 0.87 (0.86 to 0.89) | 0.0019 (–0.0000 to 0.0038) | 0.0032 (0.0009 to 0.0056) |
| Automated office DBP | 0.87 (0.86 to 0.89) | 0.0028 (0.0004 to 0.0053) | 0.0038 (0.0011 to 0.0066) |
| 24-hour DBP | 0.87 (0.86 to 0.89) | *NA* | 0.0012 (–0.0002 to 0.0027) |
| Daytime DBP | 0.87 (0.86 to 0.89) | 0.0024 (0.0003 to 0.0044) | 0.0027 (0.0005 to 0.0050) |
| Nighttime DBP | 0.88 (0.86 to 0.89) | *NC*[c] | *NA* |
| Dipping ratio[d] | 0.87 (0.86 to 0.89) | 0.0022 (–0.0002 to 0.0046) | 0.0020 (–0.0003 to 0.0043) |
| **Coronary Outcomes** (n = 922) | | | |
| Conventional DBP | 0.86 (0.85 to 0.87) | 0.0017 (0.0003 to 0.0032) | 0.0016 (0.0002 to 0.0031) |
| Automated office DBP | 0.86 (0.85 to 0.87) | 0.0015 (–0.0001 to 0.0031) | 0.0014 (–0.0001 to 0.0029) |
| 24-hour DBP | 0.86 (0.85 to 0.88) | *NA* | 0.0000 (–0.0008 to 0.0009) |
| Daytime DBP | 0.86 (0.85 to 0.87) | 0.0009 (–0.0005 to 0.0024) | 0.0007 (–0.0006 to 0.0020) |
| Nighttime DBP | 0.86 (0.85 to 0.88) | *NC*[c] | *NA* |
| Dipping ratio[d] | 0.86 (0.84 to 0.87) | 0.0024 (0.0005 to 0.0044) | 0.0022 (0.0004 to 0.0039) |
| **Stroke** (n = 822) | | | |
| Conventional DBP | 0.84 (0.82 to 0.86) | 0.0055 (0.0013 to 0.0096) | 0.0049 (0.0010 to 0.0089) |
| Automated office DBP | 0.84 (0.82 to 0.86) | 0.0054 (0.0014 to 0.0094) | 0.0049 (0.0013 to 0.0085) |
| 24-hour DBP | 0.85 (0.83 to 0.87) | *NA* | 0.0005 (–0.0009 to 0.0019) |
| Daytime DBP | 0.85 (0.83 to 0.87) | 0.0031 (0.0001 to 0.0062) | 0.0028 (–0.0002 to 0.0058) |
| Nighttime DBP | 0.84 (0.83 to 0.86) | 0.0016 (–0.0003 to 0.0034) | *NA* |
| Dipping ratio[d] | 0.83 (0.82 to 0.85) | 0.0094 (0.0045 to 0.0143) | 0.0090 (0.0041 to 0.0140) |

Abbreviations: AUC, area under the receiver operating characteristic curve for the 10-year absolute risk; CI, 95% confidence interval; CV, cardiovascular; ΔAUC, change in AUC; DBP, Diastolic blood pressure; NA, not applicable.

[a] Basic models included cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, antihypertensive drug intake, history of cardiovascular disease and diabetes mellitus and another DBP index identified by the row label.

[b] ΔAUC for adding 24-hour or nighttime to a basic model already including covariables and another DBP index. Models were constructed using the residual method (see Statistical Analysis).

[c] NC indicates that the improvement in model performance was not calculated, because the hazard ratio for 24-hour DBP did not attain significance in multivariable-adjusted models already including nighttime DBP (**eTable 6**).

[d] The dipping ratio is calculated by dividing nighttime by daytime DBP.

**eTable 14. Improvement in Model Performance by Adding a SBP Index to 24-Hour or Nighttime SBP**

| Outcomes<br>SBP Index Added to 24-Hour or Nighttime SBP | Added to 24-Hour SBP | | Added to Nighttime SBP | |
|---|---|---|---|---|
| | **Basic Model AUC (CI)**[a] | **ΔAUC (CI)**[b] | **Basic Model AUC (CI)**[a] | **ΔAUC (CI)**[b] |
| **Total Mortality** (n = 2836) | | | | |
| Conventional SBP | 0.83 (0.82 to 0.85) | 0.0001 (–0.0004 to 0.0007) | 0.84 (0.82 to 0.85) | 0.0000 (–0.0006 to 0.0005) |
| Automated office SBP | 0.83 (0.82 to 0.85) | *NC*[c] | 0.84 (0.82 to 0.85) | *NC*[c] |
| 24-hour SBP | 0.83 (0.82 to 0.85) | *NA* | 0.84 (0.82 to 0.85) | *NC*[c] |
| Daytime SBP | 0.83 (0.82 to 0.85) | 0.0006 (–0.0004 to 0.0016) | 0.84 (0.82 to 0.85) | *NC*[c] |
| Nighttime SBP | 0.83 (0.82 to 0.85) | 0.0013 (0.0001 to 0.0024) | 0.84 (0.82 to 0.85) | *NA* |
| Systolic dipping ratio | 0.83 (0.82 to 0.85) | 0.0010 (–0.0005 to 0.0024) | 0.84 (0.82 to 0.85) | *NC*[c] |
| **All CV Outcomes** (n = 2049) | | | | |
| Conventional SBP | 0.85 (0.83 to 0.86) | *NC*[c] | 0.85 (0.83 to 0.86) | 0.0001 (–0.0007 to 0.0009) |
| Automated office SBP | 0.85 (0.83 to 0.86) | *NC*[c] | 0.85 (0.83 to 0.86) | 0.0003 (–0.0003 to 0.0010) |
| 24-hour SBP | 0.85 (0.83 to 0.86) | *NA* | 0.85 (0.83 to 0.86) | 0.0006 (–0.0002 to 0.0015) |
| Daytime SBP | 0.85 (0.83 to 0.86) | 0.0006 (–0.0003 to 0.0014) | 0.85 (0.83 to 0.86) | 0.0004 (–0.0002 to 0.0011) |
| Nighttime SBP | 0.85 (0.83 to 0.86) | 0.0005 (–0.0002 to 0.0012) | 0.85 (0.83 to 0.86) | *NA* |
| Systolic dipping ratio | 0.85 (0.83 to 0.86) | 0.0010 (–0.0005 to 0.0024) | 0.85 (0.83 to 0.86) | 0.0004 (–0.0003 to 0.0010) |
| **CV Mortality** (n = 1073) | | | | |
| Conventional SBP | 0.88 (0.86 to 0.89) | *NC*[c] | 0.88 (0.86 to 0.89) | 0.0002 (–0.0008 to 0.0012) |
| Automated office SBP | 0.88 (0.86 to 0.89) | *NC*[c] | 0.88 (0.86 to 0.89) | *NC*[c] |
| 24-hour SBP | 0.88 (0.86 to 0.89) | *NA* | 0.88 (0.86 to 0.89) | *NC*[c] |
| Daytime SBP | 0.88 (0.86 to 0.89) | 0.0006 (–0.0006 to 0.0017) | 0.88 (0.86 to 0.89) | *NC*[c] |
| Nighttime SBP | 0.88 (0.86 to 0.89) | 0.0009 (–0.0004 to 0.0023) | 0.88 (0.86 to 0.89) | *NA* |
| Systolic dipping ratio | 0.88 (0.86 to 0.89) | 0.0007 (–0.0002 to 0.0015) | 0.88 (0.86 to 0.89) | *NC*[d] |
| **Coronary Outcomes** (n = 922) | | | | |
| Conventional SBP | 0.86 (0.85 to 0.88) | *NC*[c] | 0.86 (0.85 to 0.88) | *NC*[d] |
| Automated office SBP | 0.86 (0.85 to 0.88) | *NC*[c] | 0.86 (0.85 to 0.88) | 0.0007 (–0.0003 to 0.0017) |
| 24-hour SBP | 0.86 (0.85 to 0.88) | *NA* | 0.86 (0.85 to 0.88) | *NC*[c] |
| Daytime SBP | 0.86 (0.85 to 0.88) | *NC*[c] | 0.86 (0.85 to 0.88) | *NC*[c] |
| Nighttime SBP | 0.86 (0.85 to 0.88) | 0.0001 (–0.0007 to 0.0009) | 0.86 (0.85 to 0.88) | *NA* |
| Systolic dipping ratio | 0.86 (0.85 to 0.88) | 0.0003 (–0.0005 to 0.0011) | 0.86 (0.85 to 0.88) | *NC*[c] |
| **Stroke** (n = 822) | | | | |
| Conventional SBP | 0.85 (0.83 to 0.87) | 0.0004 (–0.0010 to 0.0019) | 0.85 (0.83 to 0.86) | 0.0014 (–0.0006 to 0.0034) |
| Automated office SBP | 0.85 (0.83 to 0.87) | *NC*[c] | 0.85 (0.83 to 0.86) | 0.0009 (–0.0006 to 0.0023) |
| 24-hour SBP | 0.85 (0.83 to 0.87) | *NA* | 0.85 (0.83 to 0.86) | 0.0017 (–0.0004 to 0.0038) |
| Daytime SBP | 0.85 (0.83 to 0.87) | *NC*[c] | 0.85 (0.83 to 0.86) | 0.0014 (–0.0006 to 0.0033) |
| Nighttime SBP | 0.85 (0.83 to 0.87) | 0.0002 (–0.0012 to 0.0016) | 0.85 (0.83 to 0.86) | *NA* |
| Systolic dipping ratio | 0.85 (0.83 to 0.87) | 0.0002 (–0.0012 to 0.0016) | 0.85 (0.83 to 0.86) | 0.0014 (–0.0007 to 0.0034) |

Abbreviations: AUC, area under the receiver operating characteristic curve for the 10-year absolute risk; CI, 95% confidence interval; CV, cardiovascular; ΔAUC, change in AUC; SBP, systolic blood pressure; NA, not applicable.

[a] Basic models included cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, antihypertensive drug intake, history of cardiovascular disease and diabetes mellitus and 24-hour or nighttime SBP.

[b] ΔAUC for adding a SBP index identified by the row label to a basic model already including covariables and 24-hour or nighttime SBP. Models were constructed using the residual method (see Statistical Analysis).

[c] NC indicates that the improvement in model performance was not calculated, because the hazard ratio for the SBP index did not attain significance in multivariable-adjusted models already including either 24-hour or nighttime SBP (**Table 2**).

**eTable 15. Improvement in Model Performance by Adding a DBP Index to 24-Hour or Nighttime DBP**

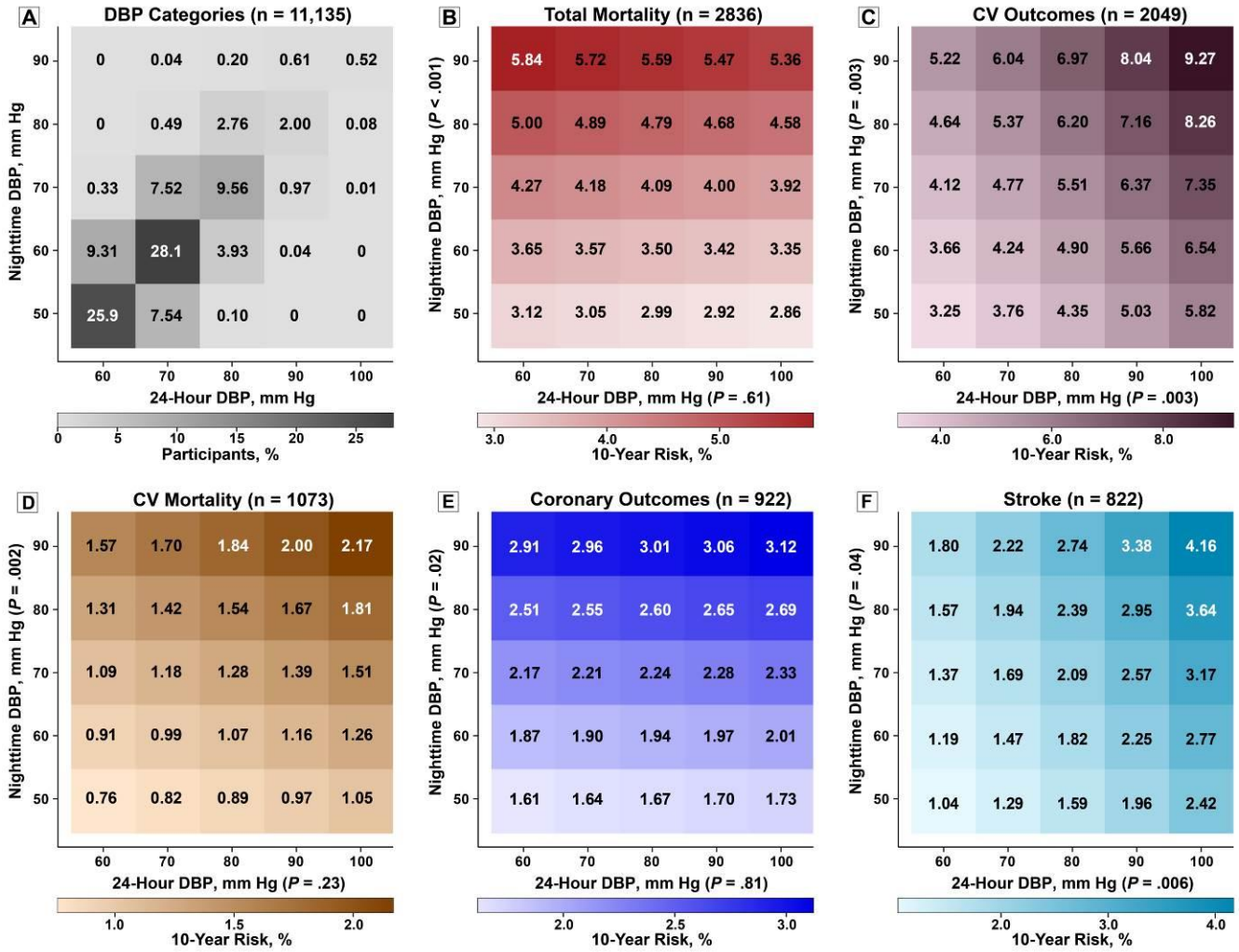
| Outcomes<br>DBP Index Added to 24-Hour or Nighttime DBP | Added to 24-Hour DBP | | Added to Nighttime DBP | |
|---|---|---|---|---|
| | **Basic Model AUC (CI)**[a] | **ΔAUC (CI)**[b] | **Basic Model AUC (CI)**[a] | **ΔAUC (CI)**[b] |
| **Total Mortality** (n = 2836) | | | | |
| Conventional DBP | 0.83 (0.82 to 0.85) | *NC*[c] | 0.83 (0.82 to 0.85) | *NC*[c] |
| Automated office DBP | 0.83 (0.82 to 0.85) | *NC*[c] | 0.83 (0.82 to 0.85) | *NC*[c] |
| 24-hour DBP | 0.83 (0.82 to 0.85) | *NA* | 0.83 (0.82 to 0.85) | *NC*[c] |
| Daytime DBP | 0.83 (0.82 to 0.85) | 0.0004 (–0.0003 to 0.0011) | 0.83 (0.82 to 0.85) | *NC*[c] |
| Nighttime DBP | 0.83 (0.82 to 0.85) | 0.0012 (0.0002 to 0.0022) | 0.83 (0.82 to 0.85) | *NA* |
| Diastolic dipping ratio | 0.83 (0.82 to 0.85) | *NC*[c] | 0.83 (0.82 to 0.85) | *NC*[c] |
| **All CV Outcomes** (n = 2049) | | | | |
| Conventional DBP | 0.84 (0.82 to 0.85) | *NC*[c] | 0.84 (0.83 to 0.86) | 0.0001 (–0.0005 to 0.0006) |
| Automated office DBP | 0.84 (0.82 to 0.85) | *NC*[c] | 0.84 (0.83 to 0.86) | *NC*[c] |
| 24-hour DBP | 0.84 (0.82 to 0.85) | *NA* | 0.84 (0.83 to 0.86) | 0.0001 (–0.0006 to 0.0008) |
| Daytime DBP | 0.84 (0.82 to 0.85) | 0.0006 (–0.0003 to 0.0014) | 0.84 (0.83 to 0.86) | 0.0000 (–0.0005 to 0.0005) |
| Nighttime DBP | 0.84 (0.82 to 0.85) | 0.0006 (–0.0002 to 0.0014) | 0.84 (0.83 to 0.86) | *NA* |
| Diastolic dipping ratio | 0.84 (0.82 to 0.85) | *NC*[c] | 0.84 (0.83 to 0.86) | *NC*[c] |
| **CV Mortality** (n = 1073) | | | | |
| Conventional DBP | 0.87 (0.86 to 0.89) | *NC*[c] | 0.88 (0.86 to 0.89) | *NC*[c] |
| Automated office DBP | 0.87 (0.86 to 0.89) | 0.0005 (–0.0005 to 0.0016) | 0.88 (0.86 to 0.89) | *NC*[c] |
| 24-hour DBP | 0.87 (0.86 to 0.89) | *NA* | 0.88 (0.86 to 0.89) | *NC*[c] |
| Daytime DBP | 0.87 (0.86 to 0.89) | 0.0010 (–0.0003 to 0.0022) | 0.88 (0.86 to 0.89) | *NC*[c] |
| Nighttime DBP | 0.87 (0.86 to 0.89) | 0.0012 (–0.0002 to 0.0027) | 0.88 (0.86 to 0.89) | *NA* |
| Diastolic dipping ratio | 0.87 (0.86 to 0.89) | *NC*[d] | 0.88 (0.86 to 0.89) | *NC*[d] |
| **Coronary Outcomes** (n = 922) | | | | |
| Conventional DBP | 0.86 (0.85 to 0.88) | *NC*[c] | 0.86 (0.85 to 0.88) | *NC*[c] |
| Automated office DBP | 0.86 (0.85 to 0.88) | *NC*[c] | 0.86 (0.85 to 0.88) | *NC*[c] |
| 24-hour DBP | 0.86 (0.85 to 0.88) | *NA* | 0.86 (0.85 to 0.88) | *NC*[c] |
| Daytime DBP | 0.86 (0.85 to 0.88) | *NC*[c] | 0.86 (0.85 to 0.88) | *NC*[c] |
| Nighttime DBP | 0.86 (0.85 to 0.88) | 0.0000 (–0.0008 to 0.0009) | 0.86 (0.85 to 0.88) | *NA* |
| Diastolic dipping ratio | 0.86 (0.85 to 0.88) | *NC*[d] | 0.86 (0.85 to 0.88) | *NC*[c] |
| **Stroke** (n = 822) | | | | |
| Conventional DBP | 0.84 (0.82 to 0.86) | *NC*[c] | 0.85 (0.83 to 0.86) | 0.0011 (–0.0005 to 0.0028) |
| Automated office DBP | 0.84 (0.82 to 0.86) | *NC*[c] | 0.85 (0.83 to 0.86) | *NC*[c] |
| 24-hour DBP | 0.84 (0.82 to 0.86) | *NA* | 0.85 (0.83 to 0.86) | 0.0016 (–0.0003 to 0.0034) |
| Daytime DBP | 0.84 (0.82 to 0.86) | *NC*[c] | 0.85 (0.83 to 0.86) | 0.0012 (–0.0003 to 0.0028) |
| Nighttime DBP | 0.84 (0.82 to 0.86) | 0.0005 (–0.0009 to 0.0019) | 0.85 (0.83 to 0.86) | *NA* |
| Diastolic dipping ratio | 0.84 (0.82 to 0.86) | 0.0005 (–0.0008 to 0.0019) | 0.85 (0.83 to 0.86) | 0.0013 (–0.0004 to 0.0029) |

Abbreviations: AUC, area under the receiver operating characteristic curve for the 10-year absolute risk; CI, 95% confidence interval; CV, cardiovascular; ΔAUC, change in AUC; DBP, Diastolic blood pressure; NA, not applicable.

[a] Basic models included cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, antihypertensive drug intake, history of cardiovascular disease and diabetes mellitus and 24-hour or nighttime DBP.

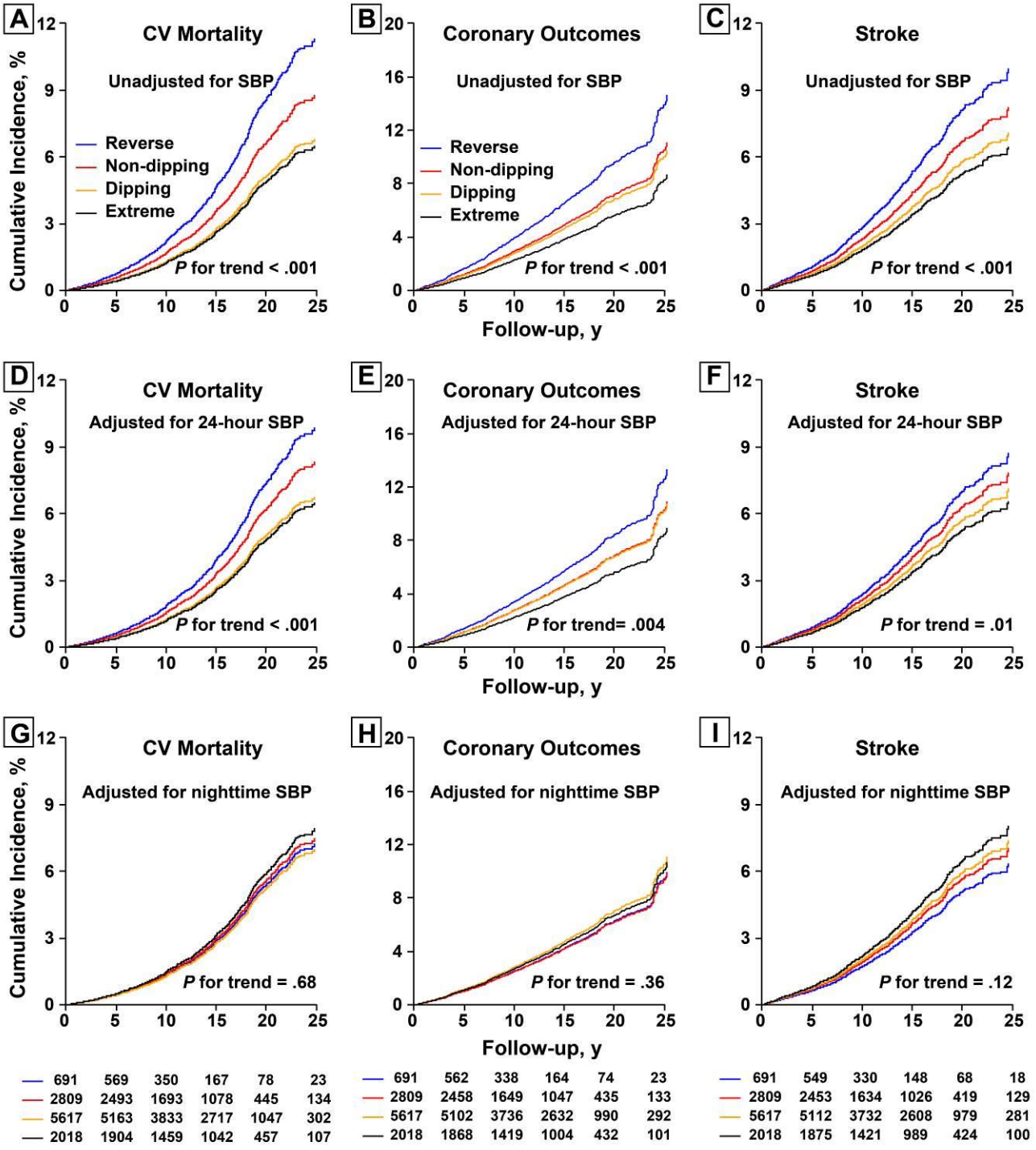
[b] ΔAUC for adding a DBP index identified by the row label to a basic model already including covariables and 24-hour or nighttime DBP. Models were constructed using the residual method (see Statistical Analysis).

[c] NC indicates that the improvement in model performance was not calculated, because the hazard ratio for the DBP index did not attain significance in multivariable-adjusted models already including either 24-hour or nighttime DBP (**eTable 5**).




**eFigure 1. Heat Map Depicting 10-Year Risk in Relation to 24-Hour and Nighttime Diastolic Pressure in 11,135 Study Participants**

Heat maps were derived by Cox proportional hazards regression with 24-hour and nighttime diastolic blood pressure (DBP) analyzed as continuous variables. Estimates of 10-year risk were standardized to the average of the distributions in the whole study population (mean or ratio) of cohort identifier, sex, age, body mass index, smoking and drinking, antihypertensive drug treatment, serum cholesterol, history of cardiovascular (CV) disease and diabetes mellitus. Numbers in the grids in Panel A represent the percent of participants within each cross-classification category. Numbers in colored grids (Panels B–F) the 10-year risk of an end point. Along the vertical axis, the risks of all Outcomes (B–F) were significantly greater with higher nighttime DBP ($P \leq .04$), but along the horizontal axis only the risk of the composite CV outcomes (C; $P = .003$) and stroke (F; $P = .006$) were significantly greater with higher 24-hour DBP. Risks of total mortality (B), CV mortality (D) and coronary outcomes (E) were not significantly associated with 24-hour DBP ($P \geq .23$).




**eFigure 2. Cumulative Incidence of Cardiovascular Mortality, Coronary Outcomes and Stroke by Dipping Status**

Participants were categorized in extreme dippers (≤0.80), normal dippers (>0.80 to ≤0.90), non-dippers (>0.90 to ≤1.00) and reverse dippers (>1.00) based on the systolic dipping ratio. Tabulated data are the number of participants at risk by dipping status at 5-year intervals. *P*-values for trend were derived by Cox proportional hazards regression. All estimates accounted for sex and age (Panels A–I). Additional adjustment for 24-hour SBP (Panels D, E and F) did not remove significance, whereas additional adjustment for nighttime SBP did (Panels G, H and I).