Hypertension
Journal of the American Heart Association

Blood Pressure Load Does Not Add to Ambulatory Blood Pressure Level for Cardiovascular Risk Stratification

Yan Li, Lutgarde Thijs, José Boggia, Kei Asayama, Tine W. Hansen, Masahiro Kikuya, Kristina Björklund-Bodegård, Takayoshi Ohkubo, Jørgen Jeppesen, Christian Torp-Pedersen, Eamon Dolan, Tatiana Kuznetsova, Katarzyna Stolarz-Skrzypek, Valérie Tikhonoff, Sofia Malyutina, Edoardo Casiglia, Yuri Nikitin, Lars Lind, Edgardo Sandoya, Kalina Kawecka-Jaszcz, Jan Filipovský, Yutaka Imai, Hans Ibsen, Eoin O'Brien, Jiguang Wang and Jan A. Staessen on behalf of the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) Investigators*

Hypertension. 2014;63:925-933; originally published online February 17, 2014;
doi: 10.1161/HYPERTENSIONAHA.113.02780
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

Blood Pressure Load Does Not Add to Ambulatory Blood Pressure Level for Cardiovascular Risk Stratification

Yan Li, Lutgarde Thijs, José Boggia, Kei Asayama, Tine W. Hansen, Masahiro Kikuya, Kristina Björklund-Bodegård, Takayoshi Ohkubo, Jørgen Jeppesen, Christian Torp-Pedersen, Eamon Dolan, Tatiana Kuznetsova, Katarzyna Stolarz-Skrzypek, Valérie Tikhonoff, Sofia Malyutina, Edoardo Casiglia, Yuri Nikitin, Lars Lind, Edgardo Sandoya, Kalina Kawecka-Jaszcz, Jan Filipovský, Yutaka Imai, Hans Ibsen, Eoin O'Brien, Jiguang Wang, Jan A. Staessen, on behalf of the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) Investigators*

See Editorial Commentary, pp 913–914

Abstract—Experts proposed blood pressure (BP) load derived from 24-hour ambulatory BP recordings as a more accurate predictor of outcome than level, in particular in normotensive people. We analyzed 8711 subjects (mean age, 54.8 years; 47.0% women) randomly recruited from 10 populations. We expressed BP load as percentage (%) of systolic/diastolic readings ≥135/≥85 mm Hg and ≥120/≥70 mm Hg during day and night, respectively, or as the area under the BP curve (mm Hg×h) using the same ceiling values. During a period of 10.7 years (median), 1284 participants died and 1109 experienced a fatal or nonfatal cardiovascular end point. In multivariable-adjusted models, the risk of cardiovascular complications gradually increased across deciles of BP level and load (P<0.001), but BP load did not substantially refine risk prediction based on 24-hour systolic or diastolic BP level (generalized R^2 statistic ≤0.294%; net reclassification improvement ≤0.28%; integrated discrimination improvement ≤0.001%). Systolic/diastolic BP load of 40.0/42.3% or 91.8/73.6 mm Hg×h conferred a 10-year risk of a composite cardiovascular end point similar to a 24-hour systolic/diastolic BP of 130/80 mm Hg. In analyses dichotomized according to these thresholds, increased BP load did not refine risk prediction in the whole study population (R^2≤0.051) or in untreated participants with 24-hour ambulatory normotension (R^2≤0.034). In conclusion, BP load does not improve risk stratification based on 24-hour BP level. This also applies to subjects with normal 24-hour BP for whom BP load was proposed to be particularly useful in risk stratification. **(*Hypertension*. 2014;63:925-933.)** ● **Online Data Supplement**

Key Words: ambulatory blood pressure monitoring ■ epidemiology ■ risk factors

Among risk factors, the 24-hour blood pressure (BP) level is an important predictor of cardiovascular morbidity and mortality.[1] However, several experts in the field of ambulatory BP monitoring proposed BP load as a more accurate predictor of outcome than the ambulatory BP level.[2–4] BP load is the proportion of BP readings above set thresholds, indicating ambulatory

Received November 6, 2013; first decision December 2, 2013; revision accepted January 3, 2014.

From the Center for Epidemiological Studies and Clinical Trials, Shanghai Institute of Hypertension, Shanghai Key Lab of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China (Y.L., J.W.); Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, Department of Cardiovascular Sciences, University of Leuven, Belgium (L.T., K.A., T.K., J.A.S.); Centro de Nefrología and Departamento de Fisiopatología, Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay (J.B.); the Research Center for Prevention and Health and Steno Diabetes Center, Gentofte, Denmark (T.W.H.); Tohoku University Graduate School of Pharmaceutical Science and Medicine, Sendai, Japan (K.A., M.K., Y.I.); Division of Cardiovascular Medicine, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden (K.B.B.); Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan (T.O.); Copenhagen University Hospital, Copenhagen, Denmark (J.J.); Department of Health Science and Technology, Aalborg University, Aalborg, Denmark (C.T.-P); Cambridge University Hospitals, Addenbrook's Hospital, Cambridge, United Kingdom (E.D.); First Department of Cardiology and Hypertension, Jagiellonian University Medical College, Kraków, Poland (K.S.S., K.K.J); Department of Clinical and Experimental Medicine, University of Padova, Padova, Italy (V.T., E.C.); Institute of Internal Medicine, Novosibirsk, Russian Federation (T.K., S.M., Y.N.); Section of Geriatrics, Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden (L.L.); Asociación Española Primera de Socorros Mutuos, Montevideo, Uruguay (E.S.); Faculty of Medicine, Charles University, Pilsen, Czech Republic (J.F.); the Aarhus University and Division of Cardiology, Holbak Hospital, Holbak, Denmark (H.I.); Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland (E.O'B.); and the Department of Epidemiology, Maastricht University, Maastricht, The Netherlands (J.A.S.).

*The IDACO Investigators are listed in reference 10.

This paper was sent to David A. Calhoun, Guest editor, for review by expert referees, editorial decision, and final disposition.

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.113.02780/-/DC1.

Correspondence to Jan A. Staessen, Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Campus Sint Rafaël, Kapucijnenvoer 35, block D, Box 7001, BE-3000 Leuven, Belgium. E-mail jan.staessen@med.kuleuven.be or ja.staessen@maastrichtuniversity.nl

hypertension or the area under the curve delineated by BP values and ceiling values for daytime, nighttime, or 24-hour ambulatory BPs.[4] Previous studies suggested that BP load compared with BP level was closer associated with signs of target organ damage,[4–8] such as left ventricular mass[5–7] or microalbuminuria.[8]

Most studies promoting BP load as risk stratification factor were small, included only selected patients, or had a cross-sectional design.[5–8] Several reports supporting risk stratification based on BP load did not account for the high degree of collinearity between the 24-hour BP level and load.[5,6,8,9] Notwithstanding these limitations, most manufacturers of ambulatory monitors currently implement BP load in their analysis software, making it an integral part of a patient's ambulatory BP report. In the present study, we investigated whether BP load refines risk stratification over and beyond the 24-hour BP level. We analyzed the International Database on Ambulatory BP in relation to Cardiovascular Outcomes while carefully addressing the problem of collinearity between level and load.

Methods

Study Population

As described in detail elsewhere,[10,11] we constructed the International Database on Ambulatory BP in relation to Cardiovascular Outcomes, which at the time of writing of this report included 11 785 participants enrolled in 11 prospective population studies. All studies received ethical approval and adhered to the principles of the Declaration of Helsinki, and participants gave informed written consent. Details on the sampling frame for each cohort are shown in Table S1 in the online-only Data Supplement. For the present analysis, we selected studies in which all the necessary data including ambulatory BP, biochemical measurements, and outcome data were available, leaving 10 cohorts (details and references provided in the online-only Data Supplement) and 10 805 subjects for possible analysis. As in previous analyses,[11] we excluded 2094 participants because they were <18 years (n=250), their nighttime BP has not been recorded (n=1354), or their ambulatory BP recordings did not comply with predefined quality standards[10] and included <10 daytime or 5 nighttime readings (n=490).[10] Thus, the number of subjects included in the present analysis totaled 8711.

BP Measurement

We programmed portable monitors to obtain ambulatory BP readings at 30-minute intervals throughout the whole day or at intervals ranging from 15 to 30 minutes during daytime and from 20 to 45 minutes at night. The detailed information on the time intervals between readings and the numbers of programmed and recorded readings in each cohort is shown in Table S2. According to our predefined criteria,[10] recordings with <10 daytime readings or <5 nighttime readings were not considered for analysis. For detailed methods used for conventional and ambulatory BP measurement, see Expanded Methods available in the online-only Data Supplement. Hypertension was a conventional BP of ≥140 mm Hg systolic or 90 mm Hg diastolic or the use of antihypertensive drugs.[12]

In our main analyses, we defined daytime as the interval ranging from 0800 to 2200 hours in people from Europe and South America and from 0600 to 2000 hours in Asian participants. The corresponding nighttime intervals ranged from 2200 to 0800 hours and from 2000 to 0600 hours, respectively. BP load was either the percentage of BP values reaching or exceeding 135 mm Hg systolic or 85 mm Hg diastolic[12] during daytime or 120 mm Hg systolic or 70 mm Hg diastolic during nighttime, or the area under the BP curve, using the same ceiling levels for systolic and diastolic BPs (Figure S1).[4] Time intervals and thresholds used in sensitivity analyses appear in the Expanded Methods in the online-only Data Supplement.

Other Baseline Measurements

For the details of other baseline measurements, including body mass index, serum cholesterol, blood glucose, questionnaire survey on smoking and drinking habits, and the definition of diabetes mellitus, see Expanded Methods in the online-only Data Supplement.

Ascertainment of Events

We ascertained vital status and the incidence of fatal and nonfatal diseases from the appropriate sources in each country as described in previous publications[10,11] and in the Expanded Methods in the online-only Data Supplement. In analyses of fatal combined with nonfatal outcomes, we only considered the first event within each disease cluster.

Statistical Analysis

For database management and statistical analysis, we used the Statistical Analysis System software, version 9.3 (SAS Institute, Cary, NC). For the methods applied for normality test and comparisons of means and proportions, see Expanded Methods in the online-only Data Supplement. In exploratory analyses, we plotted incidence rates by quartiles of the distributions of BP level and load while standardizing by the direct method for center, sex, and age (≤40, 40–60, and ≥60 years).[13] We computed hazard ratios (HRs) for BP level and load, which express the risk for a 1-decile increase in the explanatory variable. We also plotted the 10-year risk of all-cause mortality and cardiovascular events across deciles of the 24-hour BP level and load. HRs and the 10-year risk estimates were adjusted for sex, age, body mass index, smoking and drinking status, antihypertensive drug intake, total cholesterol, history of cardiovascular complications, and diabetes mellitus. In Cox regression, we accounted for cohort as a random effect using the RANDOM statement as implemented in the Statistical Analysis System 9.3 PROC PHREG procedure. To account for cohort, we also pooled participants recruited in the context of the European Project on Genes in Hypertension (Kraków, Novosibirsk, Padova, and Pilsen).

In the next step of the analysis, we added BP load to Cox models already including the 24-hour BP and other covariables. We tested whether load improved risk stratification by performing the log likelihood ratio test and computing the generalized R^2 statistic,[14] the net reclassification improvement,[15] and the integrated discrimination improvement.[15] In the final part of our analyses, we determined outcome-driven thresholds for BP load (details provided in the Expanded Methods in the online-only Data Supplement). We used Kaplan–Meier survival function estimates and the log-rank test to compare incidence rates and multivariable-adjusted Cox models with a class variable (0, 1) coding for increased load.

Results

Baseline Characteristics

The study population consisted of 5396 Europeans (61.9%), 1877 Asians (21.6%), and 1438 South Americans (16.5%). Of the 8711 participants, 4096 were women (47.0%). Age averaged (±SD) 54.8±15.1 years. The prevalence of hypertension was 44.1% on conventional BP measurement and 44.6% on 24-hour ambulatory monitoring. At enrolment, 2491 participants (28.6%) were smokers and 4126 (47.4%) reported intake of alcohol. Figures S2 and S3 show the distributions of the levels and loads derived from the 24-hour systolic and diastolic BPs, respectively. There was a close correlation ($P<0.001$) between level and load for systolic ($r\geq0.91$), as well as diastolic ($r\geq0.88$), ambulatory BP measurements.

Table 1 shows the baseline characteristics of the participants by quartiles of the systolic BP load expressed in percentage. Most risk factors, including male sex, age, 24-hour systolic BP, body mass index, blood glucose, serum cholesterol, and drinking alcohol, increased ($P\leq0.0076$) with higher category of BP load.

Incidence of Events

In the overall study population, median follow-up was 10.7 years (5th–95th percentile interval, 2.5–15.4 years). During

Table 1. Baseline Characteristics of Participants by Quartiles of Systolic Blood Pressure Load in Percentage

Characteristics	Low	Medium–Low	Medium–High	High
Limits, %	<10.9	10.9–30.2	30.3–58.2	≥58.3
No. of subjects, %	2174	2179	2178	2180
European	1088 (50.1)	1366 (62.7)	1445 (66.4)	1497 (68.7)
Asian	507 (23.3)	486 (22.3)	478 (22.0)	406 (18.6)
South American	579 (26.6)	327 (15.0)	255 (11.7)	277 (12.7)
Women	1408 (64.8)	1073 (49.2)	874 (40.1)	741 (34.0)
Smokers	567 (26.1)	655 (30.1)	657 (30.2)	612 (28.1)
Drinking alcohol	721 (33.2)	1007 (46.2)	1159 (53.2)	1239 (56.8)
Hypertension	271 (12.5)	627 (28.8)	1131 (51.9)	1813 (83.2)
On antihypertensive treatment	193 (8.9)	337 (15.5)	555 (25.5)	814 (37.3)
Diabetes mellitus	78 (3.6)	111 (5.1)	186 (8.5)	247 (11.3)
Cardiovascular disorders	138 (6.4)	155 (7.1)	209 (9.6)	258 (11.8)
Mean characteristic (SD)				
Age, y	45.8 (14.5)	53.0 (14.8)	58.0 (14.0)	62.3 (11.7)
Body mass index, kg/m^2	24.0 (3.8)	25.1 (4.0)	26.0 (4.2)	26.7 (4.3)
Conventional blood pressure				
Systolic, mm Hg	115.3 (13.1)	125.0 (14.5)	135.2 (16.6)	150.4 (18.8)
Diastolic, mm Hg	72.6 (8.9)	77.6 (9.4)	81.4 (10.2)	88.1 (11.7)
24-h blood pressure				
Systolic, mm Hg	108.5 (5.2)	118.1 (3.9)	127.1 (3.9)	143.2 (10.1)
Diastolic, mm Hg	66.8 (5.1)	71.1 (5.4)	75.1 (5.9)	82.2 (8.2)
Blood glucose, mg/dL	207 (42.8)	218 (44.7)	225 (46.1)	226 (44.4)
Serum cholesterol, mg/dL	89.3 (19.2)	91.0 (20.2)	96.0 (27.0)	99.6 (30.2)

Hypertension was a conventional blood pressure of ≥140 mm Hg systolic or 90 mm Hg diastolic or use of antihypertensive drugs. All differences across quartiles were significant (P≤0.0076).

87 203 person-years of follow-up, 1284 participants died (14.7 per 1000 person-years) and 1109 experienced a fatal or nonfatal cardiovascular event (13.2 per 1000 person-years). The online-only Data Supplement provides information on the overall and cause-specific number of fatal and nonfatal events.

We plotted event rates standardized for center, sex, and age groups across quartiles of the 24-hour BP level and load expressed as percentage or area under the curve. Total and cardiovascular mortality and incidence of fatal combined with nonfatal cardiovascular events increased with higher 24-hour systolic level and load (Figure 1). The P values for linear trend were significant (P<0.001) with exception of that for noncardiovascular mortality (P≥0.65). Findings for the 24-hour diastolic level and load were similar (Figure S4).

Risk Associated With 1-Decile Increase in Level or Load

Systolic BP

In multivariable-adjusted Cox models, not including BP load (Table 2), the 24-hour systolic BP predicted (P≤0.001) total and cardiovascular mortality and all fatal combined with nonfatal cardiovascular events but not noncardiovascular mortality (P=0.46). A 1-decile increase in the level of the 24-hour systolic BP conferred a risk increase ranging from 5% (all-cause mortality; P=0.0002) to 19% (stroke; P<0.0001). Findings were similar for the 24-hour systolic BP load expressed as percentage or area under the curve. Figure 2 illustrates this observation for the composite cardiovascular end point. However, when 24-hour systolic BP load was added to multivariable-adjusted models that already included the 24-hour systolic BP level (Table 2), load expressed as percentage only predicted the composite cardiovascular end point (HR for a 1-decile increase, 1.10; P=0.027; R^2, 0.056%) and cardiac events (HR, 1.13; P=0.039; R^2, 0.049%). Systolic load expressed as area under the curve independently predicted the composite cardiovascular end point (HR, 1.15; P=0.001; R^2, 0.124%) and stroke (HR, 1.15; P=0.040; R^2, 0.048%). Adding systolic load either expressed as percentage or area under the curve to multivariable-adjusted models that already included 24-hour systolic BP level resulted in <1% (net reclassification improvement, –0.01% to 0.28%) improvement in the prediction of mortality and cardiovascular events and <0.01% (integrated discrimination improvement, –0.002% to 0.009%) increase in the difference of the average predicted probabilities between cases (who developed events) and noncases (who did not develop events). Sensitivity analyses of systolic BP load using varying time intervals and thresholds (Expanded Methods in the online-only Data Supplement) appear in Tables S3 to S8. In general, these sensitivity analyses were confirmatory that BP load expressed as percentage or area under the curve was a weak or nonsignificant predictor once BP level was accounted for.

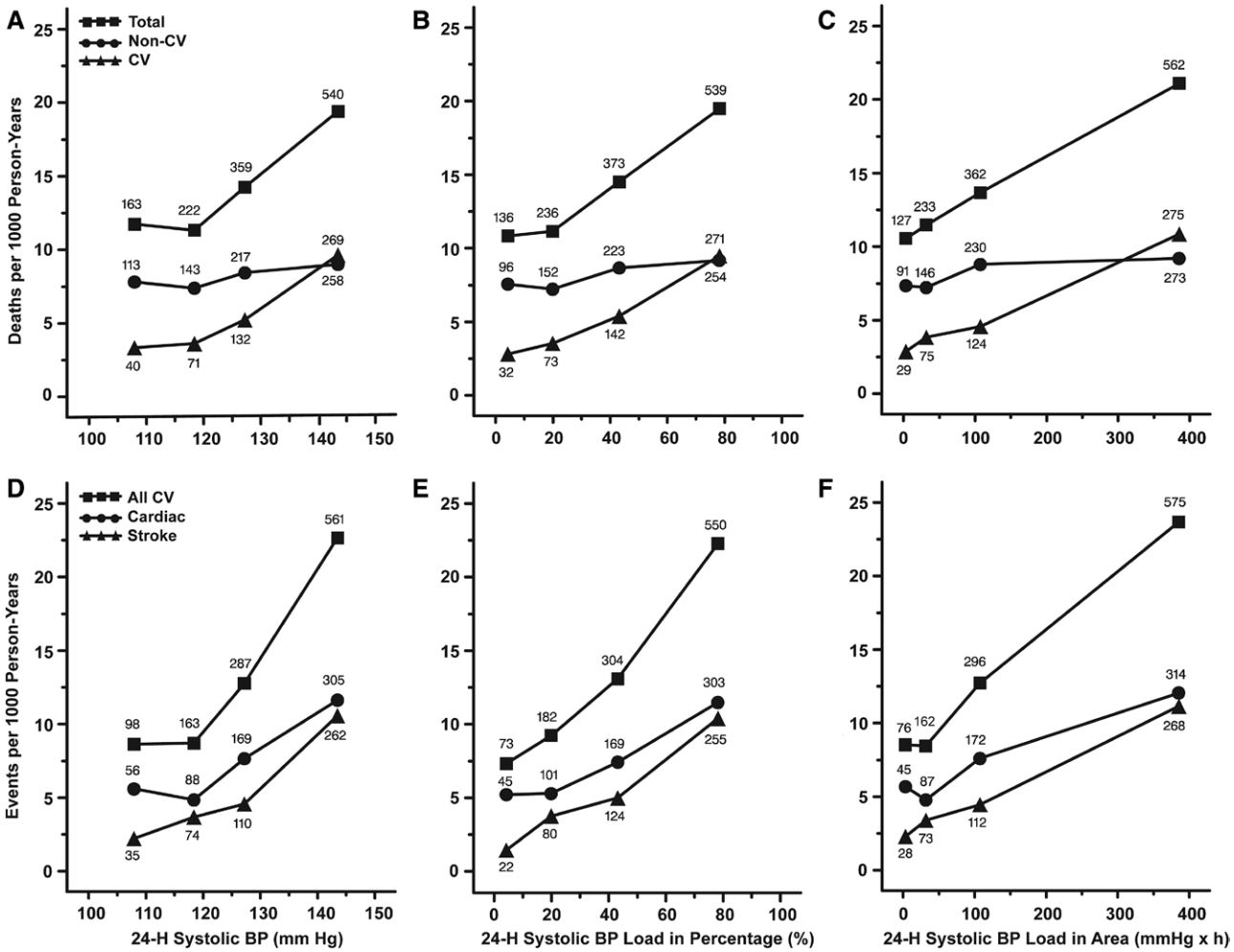

Figure 1. Incidence of mortality (**A**–**C**) and cardiovascular (CV) events (**D**–**F**) across quartiles of the 24-hour systolic blood pressure (BP) level (**A** and **D**) and the 24-hour BP load expressed as percentage (**B** and **E**) or as area under the curve (**C** and **F**). Incidence rates were standardized for center, sex, and age group (<40, 40–60, ≥60 years) by the direct method. The number of events contributing to the rates is presented. All *P* values for trend were significant ($P<0.001$) except those for noncardiovascular mortality ($P\geq0.65$).

Diastolic BP

In multivariable-adjusted Cox models, not including BP load (Table S9), the 24-hour diastolic BP predicted ($P\leq0.001$) total and cardiovascular mortality and all fatal combined with nonfatal cardiovascular events but not noncardiovascular mortality ($P=0.33$). Findings were similar for the 24-hour diastolic load expressed as percentage or area under the curve. Figure S5 illustrates this observation for the composite cardiovascular end point. When 24-hour diastolic BP load expressed in percentage was added to multivariable-adjusted models already including the 24-hour diastolic BP (Table S9), it only predicted all-cause mortality (HR, 1.07; $P=0.035$; R^2, 0.051%) and cardiovascular mortality (HR, 1.12; $P=0.028$; R^2, 0.055%). Diastolic load expressed as area under the curve independently predicted mortality and all fatal combined with nonfatal cardiovascular events ($1.10\leq HR\leq1.21$; $P\leq0.038$; $0.049\%\leq R^2\leq0.294\%$).

Risk Associated With Elevated Versus Normal BP Load

The 10-year risk of a composite cardiovascular end point associated with 24-hour ambulatory hypertension was 7.0% for a systolic level of ≥130 mm Hg and 7.5% for a diastolic pressure of ≥80 mm Hg. These risk estimates were obtained while adjusting for cohort as random effect and standardizing to the midpoint of the distributions in all participants (mean or ratio) of sex, age, body mass index, smoking and drinking status, antihypertensive drug intake, total cholesterol, history of cardiovascular complications, and diabetes mellitus. The risk of BP load in percentage exceeded that of 24-hour ambulatory hypertension when it was 40.0% systolic or 42.3% diastolic. The risk associated with BP load computed as area under the curve exceeded that of 24-hour ambulatory hypertension when load was 91.8 mm Hg×h systolic or 73.6 mm Hg×h diastolic. Among all participants, 4004 (46.0%) reached these systolic or diastolic thresholds expressed as a percentage and 4010 (46.0%) for load expressed as area under the curve. Among 4825 people with 24-hour ambulatory normotension, 761 (15.8%) and 770 (16.0%) reached the systolic or diastolic thresholds expressed in percentage or as area under the curve, respectively.

Table 3 shows that increased BP load as a categorical variable did not refine risk stratification over and beyond BP level in all 8711 participants, irrespective of whether load was expressed

Table 2. Multivariable-Adjusted Hazard Ratios for a 1-Decile Increase in Level and Load of 24-Hour Systolic Blood Pressure

		Basic Model	Full Models									
		BP Level	BP Load in Percentage					Area Under the Curve, mm Hg×h				
Outcome	No. of Events/ Person-Years)	HR (CI)	HR (CI)	R^2, %	NRI, %	IDI, %	*P* Value	HR (CI)	R^2, %	NRI, %	IDI, %	*P* Value
Mortality												
Total	1284/87 203	1.12 (1.02–1.07)*	1.02 (0.94–1.10)	0.002	0.13	<0.001	0.71	1.07 (0.99–1.14)	0.035	0.07	0.002	0.080
Cardiovascular	501/87 203	1.12 (1.07–1.16)*	1.12 (0.98–1.28)	0.033	0.22	0.004	0.091	1.10 (0.97–1.24)	0.026	0.13	0.004	0.13
Noncardiovascular	742/87 203	1.01 (0.98–1.04)	0.96 (0.87–1.06)	0.007	–0.02	<0.001	0.44	1.05 (0.96–1.14)	0.012	-0.01	0.002	0.30
Fatal and nonfatal events combined												
All cardiovascular	1109/83798	1.14 (1.11–1.17)*	1.10 (1.01–1.21)†	0.056	0.27	0.002	0.027	1.15 (1.06–1.24)‡	0.124	0.19	0.008	0.001
Cardiac	618/85 371	1.11 (1.07–1.15)*	1.13 (1.00–1.28)†	0.049	0.28	0.004	0.039	1.10 (0.99–1.23)	0.036	0.09	0.003	0.075
Coronary	445/85941	1.09 (1.05–1.14)*	1.09 (0.95–1.26)	0.019	0.27	–0.002	0.20	1.06 (0.94–1.21)	0.012	0.03	<0.001	0.30
Stroke	481/85 545	1.19 (1.15–1.24)*	1.11 (0.97–1.27)	0.023	0.25	<0.001	0.15	1.15 (1.01–1.30)†	0.048	0.22	0.009	0.040

Hazard ratios (HR) given with 95% confidence interval (CI) express the risk associated with a 1-decile increase in 24-h systolic blood pressure level or load and were estimated from a Cox proportional hazards model. All models were randomized for cohort and adjusted for sex, age, body mass index, smoking and drinking, antihypertensive drug intake, serum cholesterol, history of cardiovascular disease, and diabetes mellitus. The basic model also includes the level of the 24-h systolic blood pressure. Full models include the aforementioned covariables and both level and an index of blood pressure load. The generalized R^2 statistic, the continuous net reclassification improvement (NRI), and the integrated discrimination improvement (IDI) are measures for the refinement in risk prediction over and beyond a model including the 24-h blood pressure level and the other covariables. *P* indicates the significance of the log likelihood ratio test comparing the model including the 24-h blood pressure level and covariables and a model additionally including blood pressure load. The cause of death was unknown in 41 cases. Significance of the hazard ratios:

*$P \leq 0.001$,

†$P \leq 0.05$, and

‡$P \leq 0.01$.

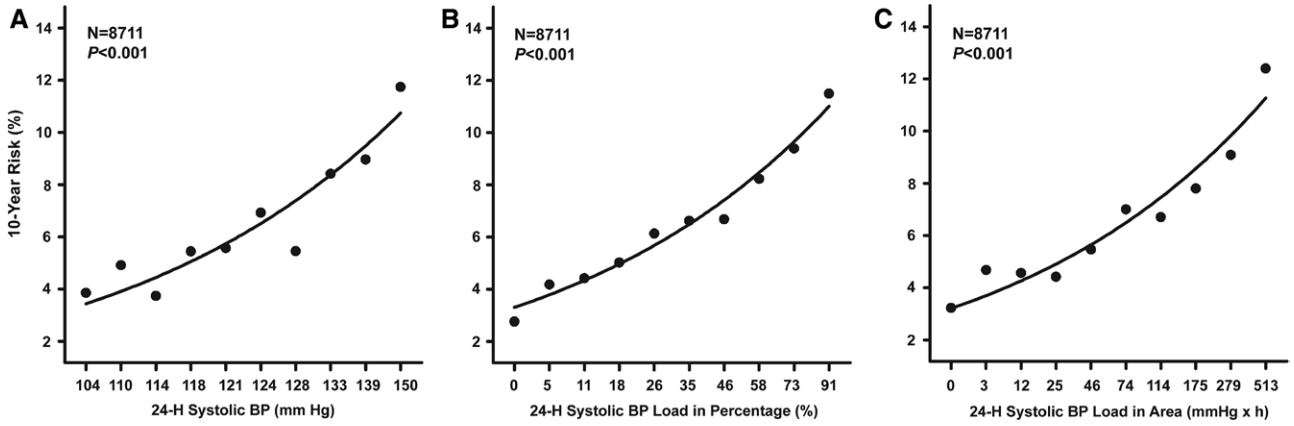

Figure 2. Ten-year risk (%) of a composite cardiovascular end point in relation to 24-hour systolic blood pressure (BP) level (**A**) and load expressed in percentage (**B**) or as area under the curve (**C**). The median of each decile group was plotted along the horizontal axis. Dots represent the risks in deciles of systolic BP level or load. These risk estimates were derived from a multivariate-adjusted Cox regression model including 9 dummy variables coding for deciles. The fitted curve is the risk plotted by an ordinal variable coding for the deciles of systolic BP level or load.

as percentage or area under the curve. These observations were consistent in untreated patients whose 24-hour ambulatory BP was <130 mm Hg systolic and 80 mm Hg diastolic (Table 4). Similarly, the sensitivity analysis based on the composite cardiovascular end point and stratified for sex, age (<60 versus ≥60 years), and antihypertensive treatment status at baseline or ethnicity showed no refinement in risk stratification by using BP load added to the 24-hour BP level (Table S10).

Discussion

The key finding of our study was that BP level and load expressed as percentage or as area under the curve equally predicted cardiovascular risk. However, BP load did not clinically meaningfully refine the risk prediction based on the 24-hour BP level. These findings were consistent for systolic and diastolic BP and in sensitivity analyses.

The concept of BP load was introduced by pioneering reports published in the early 1990s by Zachariah et al[2,3] and Dr White.[4] Zachariah et al[2,3] hypothesized that BP load might provide unique information for the diagnosis of hypertension in cases when mean level of 24-hour ambulatory systolic or diastolic BPs would be misleadingly low.[16] He referred to 1 study in which the diastolic BP load in several patients was ≈50%, whereas the 24-hour diastolic level was still <90 mm Hg.[3] Dr White[4] refined the definition of BP load by recommending to compute load separately for the awake and sleeping periods of the day.[4] Next, several investigators proposed to calculate the area under the curve rather than the number of readings exceeding the thresholds of normality for the awake and sleeping periods of the day.[17] BP load expressed in percentage is a semiquantitative index that reflects how frequently ambulatory readings surpass set thresholds without providing

Table 3. Multivariable-Adjusted Hazard Ratios Associated With Increased 24-Hour Blood Pressure Load in 8711 Participants

	BP Load in Percentage (Systolic/Diastolic ≥40.0/42.3%)					Area Under the Curve (Systolic/Diastolic ≥91.8/73.6 mm Hg×h)				
Outcome	No. of Events (N/E)	Person-Years (N/E)	HR (CI)	R^2, %	*P* Value	No. of Events (N/E)	Person-Years (N/E)	HR (CI)	R^2, %	*P* Value
Mortality										
Total	469/815	48 101 /39 102	1.03 (0.87–1.22)	0.001	0.72	446/838	47 921 /39 282	1.14 (0.97–1.34)	0.027	0.12
Cardiovascular	144/357	48 101 /39 102	1.01 (0.77–1.32)	<0.001	0.98	141/360	47 921 /39 282	1.01 (0.77–1.32)	<0.001	0.94
Noncardiovascular	305/437	48 101 /39 102	1.08 (0.87–1.34)	0.005	0.52	286/456	47 921 /39 282	1.26 (1.01–1.56)*	0.051	0.035
Fatal and nonfatal events combined										
All cardiovascular	321/788	47 069 /36 729	1.15 (0.96–1.38)	0.024	0.15	319/790	46 860 /36 938	1.11 (0.93–1.33)	0.014	0.27
Cardiac	171/447	47 584 /37 787	1.28 (1.00–1.63)	0.043	0.053	171/447	47 376 /37 995	1.17 (0.92–1.49)	0.019	0.19
Coronary	128/317	47 726 /38 215	1.28 (0.96–1.71)	0.034	0.086	123/322	47 547 /38 394	1.32 (0.99–1.76)	0.043	0.053
Stroke	139/342	47 570 /37 975	1.00 (0.76–1.32)	<0.001	0.97	138/343	47 377 /38 168	0.99 (0.75–1.30)	<0.001	0.93

Among the 8711 participants, 4004 (46.0%) and 4010 (46.0%) had an increased load expressed as percentage or as area under the curve, respectively. No. of events and person-years of follow-up are given for participants with normal/elevated (N/E) blood pressure load. Hazard ratios (HR) given with 95% confidence interval (CI) express the risk associated with an elevated blood pressure load and were estimated from a Cox proportional hazards model. All models were randomized for cohort and adjusted for sex, age, 24-h systolic and diastolic blood pressure, body mass index, smoking and drinking, antihypertensive drug intake, serum cholesterol, history of cardiovascular disease, and diabetes mellitus. The R^2 statistic is a measure for the refinement in risk prediction over and beyond a model including the 24-h level of systolic and diastolic blood pressures and the other covariables. *P* indicates the significance of the log likelihood ratio test comparing the model including the 24-h blood pressure level and covariables and a model additionally including blood pressure load. The cause of death was unknown in 41 cases. Significance of the hazard ratio:
*$P \leq 0.05$.

Table 4. Multivariable-Adjusted Hazard Ratios Associated With Increased 24-Hour Blood Pressure Load in 4825 Participants With 24-Hour Ambulatory Normotension

	BP Load in Percentage (Systolic/Diastolic ≥40.0/42.3%)				Area Under the Curve (Systolic/Diastolic ≥91.8/73.6 mm Hg×h)			
Outcome	No. of Events (N/E)	HR (CI)	R^2, %	*P* Value	No. of Events (N/E)	HR (CI)	R^2, %	*P* Value
Mortality								
Total	326/87	0.85 (0.63–1.13)	0.028	0.25	308/105	1.05 (0.80–1.37)	0.002	0.73
Cardiovascular	85/26	0.72 (0.41–1.24)	0.028	0.25	83/28	0.75 (0.44–1.26)	0.018	0.35
Noncardiovascular	229/59	0.86 (0.60–1.22)	0.017	0.37	214/74	1.14 (0.82–1.57)	0.013	0.44
Fatal and nonfatal events combined								
All cardiovascular	202/70	1.00 (0.71–1.40)	<0.001	0.99	201/71	0.87 (0.62–1.20)	0.011	0.46
Cardiac	117/41	1.05 (0.67–1.64)	0.001	0.86	118/40	0.82 (0.53–1.26)	0.015	0.40
Coronary	85/28	1.07 (0.63–1.82)	0.002	0.77	83/30	1.00 (0.60–1.67)	<0.001	0.93
Stroke	83/26	0.77 (0.45–1.32)	0.019	0.34	82/27	0.71 (0.42–1.19)	0.034	0.20

Of the 4825 untreated participants with ambulatory normotension, 761 (15.8%) and 770 (16.0%) had an increased blood pressure load expressed as percentage or as area under the curve, respectively. Ambulatory normotension was a 24-h blood pressure <130 mm Hg systolic and 80 mm Hg diastolic in untreated participants. Number of events are given for participants with normal/elevated (N/E) blood pressure load. Hazard ratios (HR) given with 95% confidence interval (CI) express the risk associated with an elevated blood pressure load and were estimated from a Cox proportional hazards model. All models were randomized for cohort and adjusted for sex, age, 24-h systolic and diastolic blood pressure, body mass index, smoking and drinking, antihypertensive drug intake, serum cholesterol, history of cardiovascular disease, and diabetes mellitus. The R^2 statistic is a measure for the refinement in risk prediction over and beyond a model including the 24-h level of systolic and diastolic blood pressures and the other covariables. *P* indicates the significance of the log likelihood ratio test comparing the model including the 24-h blood pressure level and covariables and a model additionally including blood pressure load. The cause of death was unknown in 14 cases.

any information to what extent readings were higher than the ceiling values. Conversely, area under the curve expressed in mm Hg×h provides quantitative information on how long and how much BP is elevated above the set thresholds, thus theoretically offering information more close to that provided by average BP levels.

Several small studies, most with a cross-sectional design, addressed the relationship between target organ damage and BP load.[5–8] In 60 untreated patients with mild to moderate hypertension,[6] diastolic BP load was the ambulatory BP index closest correlated with left ventricular mass index. The correlation coefficients were 0.38 and 0.32 for 24-hour systolic and diastolic BP and 0.41 and 0.51 for systolic and diastolic BP load calculated as the percentage of readings exceeding 140 mm Hg systolic or 90 mm Hg diastolic, respectively.[6] Mulè et al[7] subdivided 130 untreated patients with hypertension(mean age, 45.8 years; 30.0% women) according to the median values of systolic and diastolic BP load. Patients with a high systolic BP load had greater relative myocardial wall thickness, higher peripheral vascular resistance, higher prevalence of hypertensive retinopathy, and lower midwall fractional shortening and lower cardiac index.[7] In 126 octogenarians, Andrade et al[9] reported that the daytime systolic BP load defined as the percentage of readings exceeding 135 mm Hg predicted the incidence of cardiovascular complications. However, follow-up in this prospective study was limited to 23.0 months and only 12 cardiovascular events occurred.[9]

As already highlighted by the experts who proposed the concept of BP load,[2–4] the assessment of its true predictive value remains elusive because of the high degree of correlation of BP level with load, irrespective of whether load is expressed in percentage or as area under the curve. BP level and load are conceptually and pathophysiologically linked measures. In our current study, the correlation coefficients between level and load were all >0.88. Few previous studies,[5–9] if any,[7] explicitly addressed this problem of collinearity. Moreover, the distributions of BP load substantially deviated from normality, being skewed to the right. For these reasons, we did not enter the 24-hour BP level and load as a continuous variables in our Cox models. We generated multivariable-adjusted risk estimates for a 1-decile increase in BP level and load. Furthermore, we assessed the refinement of risk prediction by load over and beyond level by the log likelihood ratio test and the generalized R^2 statistic, which are not influenced by collinearity. Basically, our analyses based on deciles showed that BP level and load were equally predictive of total and cardiovascular mortality and fatal combined with nonfatal events. However, adding BP load, either as percentage or as area under the curve, to models already including BP level only marginally refined prediction.

The Mayo Clinic's Group proposed that a BP load of 15% should be the upper limit in normotensive subjects.[3] However, estimates for this diagnostic threshold varied widely extending up to 45% systolic and 19% diastolic.[2] To our knowledge, our study is the first that attempted to derive an outcome-driven thresholds for BP load. We considered the 10-year risk of a composite cardiovascular end point associated with the 24-hour BP of 130 mm Hg systolic or 80 mm Hg diastolic as a reference. This risk threshold (≈7%) was exceeded when BP load expressed in percentage was ≥40.0% systolic or 42.3% diastolic; for BP load expressed as area under the curve the corresponding thresholds were 91.8 mm Hg×h and 73.6 mm Hg×h, respectively.

Using the above mentioned thresholds, we dichotomized the whole study population in participants with normal versus elevated BP load. As in our analyses based on deciles, BP load dichotomized into categories did not refine risk stratification once the 24-hour BP level was accounted for. BP load was initially introduced to improve risk stratification in normotensive people in whom the BP averages for 24 hours might be

normal, but BP might be substantially elevated during some parts of the day.[2,4] For this reason, we repeated our analyses of BP load as dichotomized variable in >4000 participants with ambulatory normotension at baseline. Once again BP load did not add to the prediction of risk when BP level was accounted for. BP load, in particular in normotensive people, might reflect BP variability.[2,4] Our current findings are, therefore, in line with previous International Database on Ambulatory BP in relation to Cardiovascular Outcomes reports[18] in which we demonstrated that reading-to-reading BP variability added <1% to the prediction of cardiovascular events in models including the 24-hour ambulatory BP level.

The present findings should be interpreted within the context of some potential limitations. First, our study included participants from different cohorts whose ambulatory BP recordings were not standardized in terms of device type, daytime and nighttime periods, and the frequency of BP measurements, which may have constituted a source of bias in the analysis of ambulatory BP indices. However, for the current analysis, the same Statistical Analysis System macro processed all recordings to compute BP load and time-weighted BP means for each individual. Second, the power to demonstrate a significant interaction in Cox regression is generally low. In sensitivity analyses, we stratified for sex, age, antihypertensive treatment, or ethnicity. We cannot exclude that age <60 years BP load might improve the prediction of risk based on BP level. The HRs were 1.59 and 1.41 for load expressed in percentage or as area under the curve, respectively. Third, our analyses rested on 10 population-based cohorts with an overrepresentation of Europeans and might, therefore, not be representative for other ethnic groups, in particular blacks. Fourth, across cohorts, median follow-up ranged from 2.6 to 13.3 years. However, the crude rates of a cardiovascular death or a composite cardiovascular end point were not correlated with median follow-up time ($P \geq 0.18$). Finally, in spite of repeated attempts, we did not succeed in collecting reliable follow-up data on serum creatinine and microalbuminuria or albuminuria. However, the International Database on Ambulatory BP in relation to Cardiovascular Outcomes does include information on end-stage renal disease requiring replacement therapy. However, the number of fatal and nonfatal renal events, 18 and 17, respectively, was too small to allow a meaningful analysis of these end points.

Perspectives

Our current study showed that BP load did not refine risk stratification based on 24-hour BP level. These findings were consistent in participants with ambulatory normotension for whom the concept of BP load was originally conceived. From a clinical point of view, our results suggest that there is no need to compute complex statistics such as area under the curve when a simple arithmetic average provides the similar prognostic information. We would suggest that reports of ambulatory BP recordings put emphasis on BP level rather than load as the main prognosticator. In our study population, applying thresholds for BP load would have led to the initiation of antihypertensive drug treatment in ≈16% of participants with 24-hour ambulatory normotension as assessed by BP level. There is currently no clinical trial evidence showing that instituting or adjusting antihypertensive treatment based on BP load would improve prognosis.

Acknowledgments

We gratefully acknowledge the expert clerical assistance of Sandra Covens and Annick De Soete (Studies Coordinating Centre, Leuven, Belgium).

Sources of Funding

The European Union (grants IC15-CT98-0329-EPOGH, LSHM-CT-2006-037093 InGenious HyperCare, HEALTH-F4-2007-201550 HyperGenes, HEALTH-F7-2011-278249 EU-MASCARA, HEALTH-F7-305507 HOMAGE, and the European Research Council Advanced Research Grant 294713 EPLORE) and the Fonds voor Wetenschappelijk Onderzoek Vlaanderen, Ministry of the Flemish Community, Brussels, Belgium (G.0734.09, G.0881.13 and G.088013) supported the Studies Coordinating Centre (Leuven, Belgium). The European Union (grants LSHM-CT-2006-037093 and HEALTH-F4-2007-201550) also supported the research groups in Shanghai, Kraków, Padova and Novosibirsk. The Danish Heart Foundation (grant 01-2-9-9A-22914) and the Lundbeck Fonden (grant R32-A2740) supported the studies in Copenhagen. The Ohasama study received support via Grant-in-Aid for Scientific Research (22590767, 22790556, 23249036, 23390171, and 23790242) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan; Health Labor Sciences Research Grant (H23-Junkankitou [Seishuu]-Ippan-005) from the Ministry of Health, Labour, and Welfare, Japan; Japan Arteriosclerosis Prevention Fund; and a Grant from the Central Miso Research Institute, Tokyo, Japan. The National Natural Science Foundation of China (grants 30871360, 30871081, 81170245, and 81270373), Beijing, China, and the Shanghai Commissions of Science and Technology (the Rising Star program 06QA14043 and 11QH1402000) and Education (the Dawn project) supported the JingNing study in China. The Comisión Sectorial de Investigación Científica de la Universidad de la República (Grant I+D GEFA-HT-UY) and the Agencia Nacional de Innovación e Investigación supported research in Uruguay.

Disclosures

None.

References

1. Staessen JA, Wang J, Bianchi G, Birkenhäger WH. Essential hypertension. *Lancet*. 2003;361:1629–1641.
2. Zachariah PK, Sheps SG, Bailey KR, Wiltgen CM, Moore AG. Age-related characteristics of ambulatory blood pressure load and mean blood pressure in normotensive subjects. *JAMA*. 1991;265:1414–1417.
3. Zachariah PK, Sheps SG, Ilstrup DM, Long CR, Bailey KR, Wiltgen CM, Carlson CA. Blood pressure load–a better determinant of hypertension. *Mayo Clin Proc*. 1988;63:1085–1091.
4. White WB. Blood pressure load and target organ effects in patients with essential hypertension. *J Hypertens Suppl*. 1991;9:S39–S41.
5. Bauwens F, Duprez D, De Buyzere M, Clement DL. Blood pressure load determines left ventricular mass in essential hypertension. *Int J Cardiol*. 1992;34:335–338.
6. Grossman E, Alster Y, Shemesh J, Nussinovitch N, Rosenthal T. Left ventricular mass in hypertension: correlation with casual, exercise and ambulatory blood pressure. *J Hum Hypertens*. 1994;8:741–746.
7. Mulè G, Nardi E, Andronico G, Cottone S, Raspanti F, Piazza G, Volpe V, Ferrara D, Cerasola G. Relationships between 24 h blood pressure load and target organ damage in patients with mild-to-moderate essential hypertension. *Blood Press Monit*. 2001;6:115–123.
8. Viazzi F, Leoncini G, Ratto E, Vaccaro V, Tomolillo C, Falqui V, Parodi A, Conti N, Deferrari G, Pontremoli R. Microalbuminuria, blood pressure load, and systemic vascular permeability in primary hypertension. *Am J Hypertens*. 2006;19:1183–1189.
9. Andrade SS, Serro-Azul JB, Nussbacher A, Giorgi D, Pierri H, Gebara O, Wajngarten M. Daytime systolic blood pressure load and previous stroke predict cardiovascular events in treated octogenarians with hypertension. *J Am Geriatr Soc*. 2010;58:2232–2234.

10. Thijs L, Hansen TW, Kikuya M, et al; IDACO Investigators. The International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome (IDACO): protocol and research perspectives. *Blood Press Monit*. 2007;12:255–262.
11. Fan HQ, Li Y, Thijs L, et al. Prognostic value of isolated nocturnal hypertension in 8711 subjects from 10 populations. *J Hypertens.* 2010;28:2036–2045.
12. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) *J Hypertens.* 2007;25:1105–1187.
13. Naing NN. Easy way to learn standardization: direct and indirect methods. *Malays J Med Sci*. 2000;7:10–15.
14. Gillespie BW. Use of generalized R-squared in Cox regression. *APHA Scientific Session and Event Listing*. 2006. https://apha.confex.com/apha/134am/techprogram/paper_135906.htm. Accessed February 8, 2014.
15. Cook NR, Ridker PM. The use and magnitude of reclassification measures for individual predictors of global cardiovascular risk. *Ann Intern Med*. 2009;150:795–802.
16. Zachariah PK, Sumner WE 3rd. The clinical utility of blood pressure load in hypertension. *Am J Hypertens*. 1993;6(6 Pt 2):194S–197S.
17. Nobre F, Mion D Jr. Is the area under blood pressure curve the best parameter to evaluate 24-h ambulatory blood pressure monitoring data? *Blood Press Monit*. 2005;10:263–270.
18. Hansen TW, Thijs L, Li Y, et al. Prognostic value of short-term blood pressure variability over 24 hours in 8938 subjects from 11 populations. *Hypertension*. 2010;55:1049–1057.

Novelty and Significance

What Is New?

- No previous study has ever addressed in a prospective manner whether blood pressure (BP) load truly refines risk stratification over and beyond the 24-hour BP level.

What Is Relevant?

- In our study, BP load did not substantially add to risk stratification based on the 24-hour ambulatory BP level. This particularly applied to untreated subjects with average 24-hour ambulatory BP <130 mm Hg systolic and 80 mm Hg diastolic in whom the use of BP load is recommended.

Summary

What really matters for risk stratification is the 24-hour BP level. We would suggest that reports of ambulatory BP recordings put emphasis on BP level rather than load as the main prognosticator.

HYPERTENSION

Supplemental Material

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

Supplement to:
Li Y *et al*. Blood Pressure Load Does Not Add to Ambulatory Blood Pressure Level for Cardiovascular Risk Stratification

Expanded Methods

Study Population

The 8711 analyzed participants included: 1127 from Noorderkempen, Belgium;[1] 351 from the JingNing county, China;[2] 165 from Pilsen, the Czech Republic;[3] 2142 from Copenhagen, Denmark;[4] 310 from Padova, Italy;[3] 1526 from Ohasama, Japan;[5] 308 from Kraków, Poland;[3] 244 from Novosibirsk, the Russian Federation;[6] 1100 older men from Uppsala, Sweden;[7] and 1438 subjects from Montevideo, Uruguay.[8]

Blood Pressure Measurement

Conventional blood pressure was measured by trained observers with a mercury sphygmomanometer,[1-4,6,7] with validated auscultatory[5] (USM-700F, UEDA Electronic Works, Tokyo, Japan) or oscillometric[8] (OMRON HEM-705CP, Omron Corporation, Tokyo, Japan) devices, using the appropriate cuff size, with participants in the sitting[1-6,8] or supine[7] position. Conventional blood pressure was the average of 2 consecutive readings obtained either at the person's home[1-3,6] or at an examination center.[4,5,7] Office hypertension was a conventional blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or the use of antihypertensive drugs.[9]

We programmed portable monitors to obtain ambulatory blood pressure readings at 30 minute intervals throughout the whole day,[5] or at intervals ranging from 15[3,4,6] to 30[5] minutes during daytime and from 20[7] to 45[2] minutes at night. The detailed information on the time intervals between readings, numbers of programmed and recorded readings in each cohort are shown in Supplement Table S2. The devices implemented an auscultatory algorithm (Accutracker II) in Uppsala[7] or an oscillometric technique (SpaceLabs 90202 and 90207, Nippon Colin, and ABPM 630) in the other cohorts.[1-6,8] The same SAS macro processed all ambulatory recordings, which generally stayed unedited. The Ohasama recordings were edited sparsely according to previously published criteria.[10] According to our predefined criteria,[11] recordings with less than 10 daytime readings and/or less than five nighttime readings were not considered for analysis. Within individual subjects, we weighted the means of the ambulatory blood pressure by the interval between readings.[11]

Time Intervals and Thresholds for the Ambulatory Blood Pressure

In sensitivity analyses confined to systolic blood pressure, we also applied short fixed clock time intervals with daytime and nighttime ranging from 1000 h to 2000 h and from midnight to 0600 h in Europeans and South Americans, and 0800 h to 1800 h and from 2200 h to 0400 h in Asians. Narrow fixed clock time intervals eliminate the transition periods in the morning and evening when blood pressure changes rapidly.[12] We previously demonstrated in Europeans[12] and Chinese[2] that narrow intervals provide estimates of daytime and nighttime blood pressure that are within 1–2 mm Hg of the awake and asleep levels. We used as daytime and nighttime thresh-

olds either 135 and 120 mm Hg, as proposed in European guidelines,[9] or previously derived outcome-driven thresholds of 130 and 110 mmHg.[13] We also did sensitivity analyses based on a single systolic threshold for the whole day, either 130 mmHg[9] or 125 mm Hg.[13]

Other Baseline Measurements

We used the questionnaires originally administered in each cohort to obtain information on each participant's medical history and smoking and drinking habits. Body mass index was body weight in kilograms divided by height in meters squared. We measured serum cholesterol and blood glucose by automated enzymatic methods. Diabetes mellitus was the use of antidiabetic drugs, a fasting blood glucose concentration of at least 7.0 mmol/L,[1-8] a random blood glucose concentration of at least 11.1 mmol/L,[1,2,5] a self-reported diagnosis,[1,5,8] or diabetes documented in practice or hospital records.[8]

Coding of Events

Outcomes were coded according to the international classification of diseases (ICD). Fatal and nonfatal stroke (ICD8/9 430-434 and 436, ICD10 I60-I64 and I67-I68) did not include transient ischemic attacks. Coronary events encompassed death from ischemic heart disease (ICD8 411-412, ICD9 411 and 414, ICD10 I20 and I24-I25), sudden death (ICD8 4272 and 795, ICD9 4275 and 798, ICD10 I46 and R96), nonfatal myocardial infarction (ICD8/9 410, ICD10 I21-I22), and coronary revascularization. Cardiac events comprised coronary events and fatal and nonfatal heart failure (ICD8 428 and 4271-4272 and 4290, ICD9 428 and 429, ICD10 I50 and J81). Hospitalizations for unstable angina were coded as ischemic heart disease. In the Danish[4] and Swedish[7] cohorts, the diagnosis of heart failure required admission to hospital. In the other cohorts,[1-3,5,6,8] heart failure was either a clinical diagnosis or the diagnosis on the death certificate, but in all cases it was validated against hospital files or records held by family doctors. The composite cardiovascular event included all aforementioned events plus cardiovascular mortality (ICD8 390-448, ICD9 3900-4599, ICD10 I00-I79 and R96).

Statistical Analysis

For database management and statistical analysis, we used the Statistical Analysis System (SAS) software, version 9.3 (SAS Institute, Cary, NC). Departure from normality was evaluated by Shapiro-Wilk's statistic and skewness by the computation of the coefficient of skewness, the third moment about the mean divided by the cube of the standard deviation.[14] For comparison of means and proportions, we applied the large-sample z-test and the χ^2-statistic, respectively.

In the final part of our analyses, we determined outcome-driven thresholds for BP load. First, we determined the 10-year risk of a composite cardiovascular endpoint associated with a 24-hour BP of 130 mm Hg systolic or 80 mm Hg diastolic. Next, using a bootstrap procedure,[15] we determined the lowest decile of load associated

with a 10-year risk of a cardiovascular event larger than the risk conferred by the aforementioned thresholds for 24-hour ambulatory hypertension. The lower limit separating this decile from the preceding one was used as cut-off limit in dichotomized analyses contrasting an elevated with normal BP load. We used Kaplan-Meier survival function estimates, and the log-rank test to compare incidence rates and multivariable-adjusted Cox models with a class variable (0,1) coding for increased load.

Expanded Results

Mortality included 501 cardiovascular and 742 noncardiovascular deaths and 41 deaths from unknown cause. Considering cause-specific first cardiovascular events, the incidence of fatal and nonfatal stroke amounted to 145 and 391, respectively. Cardiac events consisted of 176 fatal and 442 nonfatal events, including 76 fatal and 214 nonfatal cases of acute myocardial infarction, 32 deaths from ischemic heart disease, 28 sudden deaths, 40 fatal and 171 nonfatal cases of heart failure, and 57 cases of surgical or percutaneous coronary revascularization.

References

1. Staessen JA, Bieniaszewski L, O'Brien ET, Imai Y, Fagard R. An epidemiological approach to ambulatory blood pressure monitoring : the Belgian population study. *Blood Press Monit.* 1996;1:13-26.
2. Li Y, Wang JG, Gao HF, Nawrot T, Wang GL, Qian YS, Staessen JA, Zhu DL. Are published characteristics of the ambulatory blood pressure generalizable to rural Chinese ? The JingNing population study. *Blood Press Monit.* 2005;10:125-134.
3. Kuznetsova T, Staessen JA, Kawecka-Jaszcz K, Babeanu S, Casiglia E, Filipovský J, Nachev C, Nikitin Y, Peleská J, O'Brien E, on behalf of the EPOGH Investigators. Quality control of the blood pressure phenotype in the European Project on Genes in Hypertension. *Blood Press Monit.* 2002;7:215-224.
4. Hansen TW, Jeppesen J, Rasmussen S, Ibsen H, Torp-Pedersen C. Ambulatory blood pressure and risk of cardiovascular disease : a population based study. *Am J Hypertens.* 2006;19:243-259.
5. Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, Matsubara M, Hashimoto J, Hoshi H, Araki T, Tsuji I, Satoh H, Hisamichi S, Imai Y. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure : the Ohasama study. *J Hypertens.* 2002;20:2183-2189.
6. Kuznetsova T, Malyutina S, Pello E, Thijs L, Nikitin Y, Staessen JA. Ambulatory blood pressure of adults in Novosibirsk, Russia : interim report on a population study. *Blood Press Monit.* 2000;5:291-296.
7. Ingelsson E, Björklund K, Lind L, Ärnlöv J, Sundström J. Diurnal blood pressure pattern and risk of congestive heart failure. *JAMA.* 2006;295:2859-2866.
8. Schettini C, Bianchi M, Nieto F, Sandoya E, Senra H, Hypertension Working Group. Ambulatory blood pressure. Normality and comparison with other measurements. *Hypertension.* 1999;34 (part 2):818-825.

9. Mancia G, De Backer G, Dominiczak A, et al. 2007 guidelines for the management of arterial hypertension : The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens.* 2007;25:1105-1187.
10. Ohkubo T, Imai Y, Tsuji I, Nagai K, Ito S, Satoh H, Hisamichi S. Reference values for 24-hour ambulatory blood pressure monitoring based on a prognositic criterion. The Ohasama Study. *Hypertension.* 1998;32:255-259.
11. Thijs L, Hansen TW, Kikuya M, et al. The International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO) : protocol and research perspectives. *Blood Press Monit.* 2007;12:255-262.
12. Fagard R, Brguljan J, Thijs L, Staessen J. Prediction of the actual awake and asleep blood pressures by various methods of 24 h pressure analysis. *J Hypertens.* 1996;14:557-563.
13. Kikuya M, Hansen TW, Thijs L, Björklund-Bodegård K, Kuznetsova T, Ohkubo T, Richart T, Torp-Pedersen C, Lind L, Ibsen H, Imai Y, Staessen JA, on behalf of the International Database on ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO) investigators. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-year cardiovascular risk. *Circulation.* 2007;115:2145-2152.
14. Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). Biometrika. 1965; 52:591–611.
15. Hesterberg T, Moore DS, Monaghan S, Clipson A, Epstein R. Bootstrap methods and permutation tests. In: Introduction to the Practice of Statistics. New York, NY: WH Freeman & Co; 2005:14-1–14-70.

Table S1. Population Sampling Methods in IDACO Cohorts

Catchment Area	Sampling Frame	Starting Point to Recruit Sample	Participation Rate (%)	Nº in IDACO Database	Analyzed
Nooderkempen, Belgium	Family-based random sample	Address list	78	2542	1127
JingNing, Zhejiang, China	Family-based random sample	Villages, all inhabitants invited	62	360	351
Pilsen, Czech Republic	Family-based random sample	Address list	82	174	165
Copenhagen County, Denmark	Stratified random sample of women and men aged 30, 40, 50 and 60 years	Population registry	83	2311	2142
Mirano (Venice), Torrebelvicino (Vicenza), Valli del Pasubio (Vicenza), Italy	Population-based sample of women and men ≥18 years	Address list	73	310	310
Ohasama, Iwate prefecture, Japan	People aged ≥40 years	Address list	78	1535	1526
Niepolomice, Kràkow, Poland	Family-based random sample	Address list	54	321	308
Octyabrsky district, Novosibirsk, Russian Federation	Family-based random sample	Address list	68	250	244
Montevideo, Uruguay	Age-stratified random sample	Members of a health insurance organization	78	1859	1438
Uppsala, Sweden	Men aged ≥50 year	Population census	80	1143	1100
Allied Irish Bank Study	Bank employees working at branches across Ireland	All invited	14	981	0

Table S2. Number of 24-H Ambulatory Blood Pressure Readings in IDACO Cohorts

IDACO Cohorts	Nº of Subjects	Programmed Interval between Readings (minutes)		Nº of Programmed Readings	Nº of Recorded Readings				
		Daytime	Nighttime		Median	P5	P25	P75	P95
Nooderkempen, Belgium	1127	20	40	55	55	39	51	57	59
JingNing, Zhejiang, China	351	20	45	65	56	52	55	56	57
Pilsen, Czech Republic	165	15	30	76	76	56	71	80	82
Copenhagen County, Denmark	2142	15	30	80	80	68	78	81	83
Mirano (Venice), Torrebelvicino (Vicenza), Valli del Pasubio (Vicenza), Italy	310	15	30	76	77	67	74	78	84
Ohasama, Iwate prefecture, Japan	1526	30	30	48	45	36	42	48	50
Niepolomice, Kraków, Poland	308	15	30	76	75	62	72	77	79
Octyabrsky District, Novosibirsk, Russian Federation	244	15	30	76	72	56	65	75	78
Montevideo, Uruguay	1438	20	40	60	37	30	34	40	42
Uppsala, Sweden	1100	20	20	72	65	44	52	75	85

Table S3. Multivariable-Adjusted Hazard Ratios for a 1-Decile Increase in 24-H Systolic Blood Pressure Level and Load (Defined According to the Cut-off of 135 mmHg Daytime and 120 mmHg Nighttime)

Outcome (Number of Events)	Basic Model Including Level	Full Model, Including Level and Load					
		Load, %			Load, mm Hg × h		
	HR (CI)	HR (CI)	R^2,%	*P*	HR (CI)	R^2,%	*P*
Mortality							
Total (1284)	1.05 (1.02–1.07)‡	1.02 (0.96–1.09)	0.004	0.55	0.99 (0.94–1.05)	0.001	0.79
Cardiovascular (501)	1.12 (1.07–1.16)‡	1.05 (0.94–1.18)	0.010	0.36	0.97 (0.88–1.07)	0.003	0.59
Noncardiovascular (742)	1.01 (0.98–1.04)	1.00 (0.92–1.09)	0.000	0.99	1.00 (0.93–1.07)	0.000	0.95
Fatal and nonfatal events combined							
All cardiovascular (1109)	1.14 (1.11–1.17)‡	1.05 (0.97–1.12)	0.016	0.23	1.04 (0.98–1.12)	0.018	0.20
Cardiac (618)	1.11 (1.07–1.15)‡	1.03 (0.93–1.13)	0.004	0.56	1.03 (0.94–1.13)	0.007	0.45
Coronary (445)	1.09 (1.05–1.14)‡	1.01 (0.91–1.14)	0.001	0.79	1.02 (0.92–1.13)	0.003	0.64
Stroke (481)	1.19 (1.15–1.24)‡	1.08 (0.97–1.21)	0.020	0.19	1.04 (0.94–1.15)	0.006	0.48

Daytime and nighttime was defined using short clock-time intervals (for details, see Methods). All models are randomized for cohort and adjusted for sex, age, body mass index, smoking and drinking, antihypertensive drug intake, serum cholesterol, history of cardiovascular disease and diabetes mellitus. The basic model also includes the level of the 24-h systolic blood pressure. Full models include the aforementioned covariables and both level and an index of blood pressure load. Hazard ratios (HR) given with 95% confidence interval (CI) express the risk associated with a 1-decile increase in 24-h systolic blood pressure level or load. The R^2 statistic is a measure for the refinement in risk prediction over and beyond a model including the 24-h blood pressure level and the other covariables. *P* indicates the significance of the log likelihood ratio test comparing the model including the 24-h blood pressure level and covariables and a model additionally including blood pressure load. The cause of death was unknown in 41 cases.
Significance of the hazard ratios: * $P \leq 0{\cdot}05$; † $P \leq 0{\cdot}01$; and ‡ $P \leq 0{\cdot}001$.

Table S4. Multivariable-Adjusted Hazard Ratios for a 1-Decile Increase in 24-H Systolic Blood Pressure Level and Load (Defined According to the Cut-off of 130 mmHg Daytime and 110 mmHg Nighttime)

Outcome (Number of Events)	Basic Model Including Level	Full Model, Including Level and Load					
		Load, %			Load, mm Hg × h		
	HR (CI)	HR (CI)	R^2,%	*P*	HR (CI)	R^2,%	*P*
Mortality							
Total (1284)	1.05 (1.02–1.07)‡	0.95 (0.89–1.02)	0.024	0.15	1.04 (0.97–1.11)	0.012	0.30
Cardiovascular (501)	1.12 (1.07–1.16)‡	0.93 (0.84–1.03)	0.021	0.17	1.05 (0.93–1.18)	0.006	0.47
Noncardiovascular (742)	1.01 (0.98–1.04)	0.99 (0.91–1.08)	0.002	0.70	1.04 (0.95–1.13)	0.008	0.41
Fatal and nonfatal events combined							
All cardiovascular (1109)	1.14 (1.11–1.17)‡	1.00 (0.93–1.07)	0.000	0.87	1.08 (0.99–1.17)	0.041	0.06
Cardiac (618)	1.11 (1.07–1.15)‡	0.95 (0.86–1.04)	0.013	0.28	1.06 (0.95–1.17)	0.012	0.30
Coronary (445)	1.09 (1.05–1.14)‡	0.95 (0.85–1.06)	0.010	0.36	1.05 (0.93–1.18)	0.006	0.46
Stroke (481)	1.19 (1.15–1.24)‡	1.08 (0.97–1.21)	0.023	0.16	1.10 (0.97–1.24)	0.023	0.16

Daytime and nighttime was defined using short clock-time intervals (for details, see Methods). All models are randomized for cohort and adjusted for sex, age, body mass index, smoking and drinking, antihypertensive drug intake, serum cholesterol, history of cardiovascular disease and diabetes mellitus. The basic model also includes the level of the 24-h systolic blood pressure. Full models include the aforementioned covariables and both level and an index of blood pressure load. Hazard ratios (HR) given with 95% confidence interval (CI) express the risk associated with a 1-decile increase in 24-h systolic blood pressure level or load. The R^2 statistic is a measure for the refinement in risk prediction over and beyond a model including the 24-h blood pressure level and the other covariables. *P* indicates the significance of the log likelihood ratio test comparing the model including the 24-h blood pressure level and covariables and a model additionally including blood pressure load. The cause of death was unknown in 41 cases.
Significance of the hazard ratios: * $P \leq 0{\cdot}05$; † $P \leq 0{\cdot}01$; and ‡ $P \leq 0{\cdot}001$.

Table S5. Multivariable-Adjusted Hazard Ratios for a 1-Decile Increase in 24-H Systolic Blood Pressure Level and Load (Defined According to the Cut-off of 130 mmHg for All the 24-H Readings)

Outcome (Number of Events)	Basic Model Including Level	Full Model, Including Level and Load					
		Load, %			Load, mm Hg × h		
	HR (CI)	HR (CI)	R^2,%	*P*	HR (CI)	R^2,%	*P*
Mortality							
Total (1284)	1.05 (1.02–1.07)‡	1.00 (0.93–1.07)	0.000	0.95	0.97 (0.91–1.04)	0.007	0.43
Cardiovascular (501)	1.12 (1.07–1.16)‡	1.03 (0.91–1.16)	0.003	0.64	1.01 (0.90–1.14)	0.001	0.78
Noncardiovascular (742)	1.01 (0.98–1.04)	1.00 (0.91–1.09)	0.000	0.89	0.95 (0.87–1.03)	0.016	0.24
Fatal and nonfatal events combined							
All cardiovascular (1109)	1.14 (1.11–1.17)‡	1.06 (0.98–1.15)	0.019	0.20	1.10 (1.02–1.18)*	0.066	0.02
Cardiac (618)	1.11 (1.07–1.15)‡	1.04 (0.94–1.16)	0.006	0.49	1.05 (0.95–1.17)	0.013	0.28
Coronary (445)	1.09 (1.05–1.14)‡	1.05 (0.93–1.19)	0.006	0.47	1.03 (0.92–1.16)	0.004	0.58
Stroke (481)	1.19 (1.15–1.24)‡	1.07 (0.95–1.21)	0.016	0.25	1.14 (1.01–1.28)*	0.049	0.04

All models are randomized for cohort and adjusted for sex, age, body mass index, smoking and drinking, antihypertensive drug intake, serum cholesterol, history of cardiovascular disease and diabetes mellitus. The basic model also includes the level of the 24-h systolic blood pressure. Full models include the aforementioned covariables and both level and an index of blood pressure load. Hazard ratios (HR) given with 95% confidence interval (CI) express the risk associated with a 1-decile increase in 24-h systolic blood pressure level or load. The R^2 statistic is a measure for the refinement in risk prediction over and beyond a model including the 24-h blood pressure level and the other covariables. *P* indicates the significance of the log likelihood ratio test comparing the model including the 24-h blood pressure level and covariables and a model additionally including blood pressure load. The cause of death was unknown in 41 cases.
Significance of the hazard ratios: * $P \leq 0{\cdot}05$; † $P \leq 0{\cdot}01$; and ‡ $P \leq 0{\cdot}001$.

Table S6. Multivariable-Adjusted Hazard Ratios for a 1-Decile Increase in 24-H Systolic Blood Pressure Level and Load (Defined According to the Cut-off of 125 mmHg for All the 24-H Readings)

Outcome (Number of Events)	Basic Model Including Level	Full Model, Including Level and Load					
		Load, %			Load, mm Hg × h		
	HR (CI)	HR (CI)	R^2,%	*P*	HR (CI)	R^2,%	*P*
Mortality							
Total (1284)	1.05 (1.02–1.07)‡	1.00 (0.93–1.08)	0.000	0.97	0.99 (0.92–1.07)	0.000	0.84
Cardiovascular (501)	1.12 (1.07–1.16)‡	1.05 (0.93–1.18)	0.006	0.45	1.05 (0.92–1.20)	0.007	0.42
Noncardiovascular (742)	1.01 (0.98–1.04)	0.99 (0.90–1.09)	0.001	0.82	0.96 (0.87–1.06)	0.007	0.43
Fatal and nonfatal events combined							
All cardiovascular (1109)	1.14 (1.11–1.17)‡	1.07 (0.99–1.16)	0.027	0.12	1.12 (1.03–1.23)†	0.078	0.009
Cardiac (618)	1.11 (1.07–1.15)‡	1.08 (0.97–1.20)	0.018	0.21	1.06 (0.94–1.19)	0.013	0.29
Coronary (445)	1.09 (1.05–1.14)‡	1.12 (0.99–1.26)	0.032	0.10	1.07 (0.93–1.22)	0.010	0.34
Stroke (481)	1.19 (1.15–1.24)‡	1.07 (0.95–1.20)	0.017	0.23	1.18 (1.03–1.35)*	0.058	0.02

All models are randomized for cohort and adjusted for sex, age, body mass index, smoking and drinking, antihypertensive drug intake, serum cholesterol, history of cardiovascular disease and diabetes mellitus. The basic model also includes the level of the 24-h systolic blood pressure. Full models include the aforementioned covariables and both level and an index of blood pressure load. Hazard ratios (HR) given with 95% confidence interval (CI) express the risk associated with a 1-decile increase in 24-h systolic blood pressure level or load. The R^2 statistic is a measure for the refinement in risk prediction over and beyond a model including the 24-h blood pressure level and the other covariables. *P* indicates the significance of the log likelihood ratio test comparing the model including the 24-h blood pressure level and covariables and a model additionally including blood pressure load. The cause of death was unknown in 41 cases.
Significance of the hazard ratios: * $P \leq 0{\cdot}05$; † $P \leq 0{\cdot}01$; and ‡ $P \leq 0{\cdot}001$.

Table S7. Multivariable-Adjusted Hazard Ratios for a 1-Decile Increase in Level and Load of Daytime Systolic Blood Pressure

Outcome (Number of Events)	Basic Model Including Level	Full Model, Including Level and Load					
		Load, %			Load, mm Hg × h		
	HR (CI)	HR (CI)	R^2,%	*P*	HR (CI)	R^2,%	*P*
Mortality							
Total (1284)	1.02 (0.99–1.05)	1.05 (1.01–1.09)*	0.059	0.02	1.05 (1.01–1.10)*	0.055	0.03
Cardiovascular (501)	1.08 (1.03–1.13)‡	1.09 (1.02–1.16)*	0.069	0.01	1.12 (1.04–1.19)†	0.117	0.001
Noncardiovascular (742)	0.99 (0.96–1.03)	1.01 (0.96–1.06)	0.001	0.79	0.99 (0.93–1.05)	0.002	0.65
Fatal and nonfatal events combined							
All cardiovascular (1109)	1.13 (1.09–1.16)‡	1.09 (1.04–1.14)‡	0.166	<0.001	1.12 (1.07–1.17)‡	0.255	<0.001
Cardiac (618)	1.09 (1.05–1.14)‡	1.08 (1.02–1.15)†	0.084	0.007	1.10 (1.04–1.17)†	0.117	0.001
Coronary (445)	1.08 (1.03–1.14)‡	1.04 (0.97–1.12)	0.017	0.22	1.08 (1.00–1.15)*	0.048	0.04
Stroke (481)	1.19 (1.14–1.25)‡	1.11 (1.04–1.19)†	0.097	0.004	1.14 (1.06–1.22)‡	0.148	<0.001

All models are randomized for cohort and adjusted for sex, age, body mass index, smoking and drinking, antihypertensive drug intake, serum cholesterol, history of cardiovascular disease and diabetes mellitus. The basic model also includes the level of the daytime systolic blood pressure. Full models include the aforementioned covariables and both level and an index of blood pressure load. Hazard ratios (HR) given with 95% confidence interval (CI) express the risk associated with a 1-decile increase in daytime systolic blood pressure level or load. The R^2 statistic is a measure for the refinement in risk prediction over and beyond a model including the daytime blood pressure level and the other covariables. *P* indicates the significance of the log likelihood ratio test comparing the model including the daytime blood pressure level and covariables and a model additionally including blood pressure load. The cause of death was unknown in 41 cases.
Significance of the hazard ratios: * $P \leq 0{\cdot}05$; † $P \leq 0{\cdot}01$; and ‡ $P \leq 0{\cdot}001$.

Table S8. Multivariable-Adjusted Hazard Ratios for a 1-Decile Increase in Level and Load of Nighttime Systolic Blood Pressure

Outcome (Number of Events)	Basic Model Including Level	Full Model, Including Level and Load					
		Load, %			Load, mm Hg × h		
	HR (CI)	HR (CI)	R^2,%	*P*	HR (CI)	R^2,%	*P*
Mortality							
Total (1284)	1.06 (1.04–1.09)‡	1.03 (0.99–1.08)	0.021	0.18	1.06 (1.01–1.10)*	0.064	0.02
Cardiovascular (501)	1.11 (1.07–1.15)‡	1.12 (1.03–1.22)†	0.088	0.006	1.14 (1.05–1.23)†	0.118	0.001
Noncardiovascular (742)	1.04 (1.01–1.07)*	0.98 (0.93–1.04)	0.004	0.58	1.00 (0.95–1.06)	0.000	0.99
Fatal and nonfatal events combined							
All cardiovascular (1109)	1.12 (1.09–1.15)‡	1.02 (0.97–1.07)	0.005	0.50	1.06 (1.01–1.11)*	0.055	0.03
Cardiac (618)	1.09 (1.06–1.13)‡	1.03 (0.97–1.11)	0.011	0.33	1.05 (0.99–1.13)	0.026	0.13
Coronary (445)	1.07 (1.03–1.11)‡	1.05 (0.97–1.14)	0.019	0.19	1.08 (0.99–1.17)	0.042	0.06
Stroke (481)	1.16 (1.12–1.21)‡	1.02 (0.94–1.10)	0.002	0.68	1.05 (0.97–1.13)*	0.015	0.26

All models are randomized for cohort and adjusted for sex, age, body mass index, smoking and drinking, antihypertensive drug intake, serum cholesterol, history of cardiovascular disease and diabetes mellitus. The basic model also includes the level of the nighttime systolic blood pressure. Full models include the aforementioned covariables and both level and an index of blood pressure load. Hazard ratios (HR) given with 95% confidence interval (CI) express the risk associated with a 1-decile increase in nighttime systolic blood pressure level or load. The R^2 statistic is a measure for the refinement in risk prediction over and beyond a model including the daytime blood pressure level and the other covariables. *P* indicates the significance of the log likelihood ratio test comparing the model including the daytime blood pressure level and covariables and a model additionally including blood pressure load. The cause of death was unknown in 41 cases.
Significance of the hazard ratios: * $P \leq 0{\cdot}05$; † $P \leq 0{\cdot}01$; and ‡ $P \leq 0{\cdot}001$.

Table S9. Multivariable-Adjusted Hazard Ratios for a 1-Decile Increase in Level and Load of 24-H Diastolic Blood Pressure

Outcome (Number of Events)	Basic Model Including Level	Full Model, Including Level and Load					
		Load, %			Load, mm Hg × h		
	HR (CI)	HR (CI)	R^2,%	*P*	HR (CI)	R^2,%	*P*
Mortality							
Total (1284)	1.04 (1.02–1.06)‡	1.07 (1.00–1.14)*	0.051	0.035	1.15 (1.09–1.21)‡	0.294	<0.001
Cardiovascular (501)	1.08 (1.05–1.12)‡	1.12 (1.01–1.24)*	0.055	0.028	1.21 (1.11–1.32)‡	0.212	<0.001
Noncardiovascular (742)	1.01 (0.99–1.04)	1.03 (0.95–1.12)	0.007	0.45	1.11 (1.03–1.18)†	0.093	0.004
Fatal and nonfatal events combined							
All cardiovascular (1109)	1.10 (1.07–1.12)‡	1.05 (0.98–1.12)	0.019	0.20	1.16 (1.09–1.23)‡	0.263	<0.001
Cardiac (618)	1.07 (1.04–1.10)‡	1.03 (0.93–1.13)	0.004	0.57	1.11 (1.02–1.20)*	0.069	0.014
Coronary (445)	1.06 (1.02–1.10)†	1.03 (0.92–1.15)	0.003	0.63	1.11 (1.01–1.22)*	0.049	0.038
Stroke (481)	1.14 (1.10–1.18)‡	1.05 (0.95–1.17)	0.009	0.37	1.18 (1.08–1.30)‡	0.150	<0.001

All models are randomized for cohort and adjusted for sex, age, body mass index, smoking and drinking, antihypertensive drug intake, serum cholesterol, history of cardiovascular disease and diabetes mellitus. The basic model also includes the level of the 24-h diastolic blood pressure. Full models include the aforementioned covariables and both level and an index of blood pressure load. Hazard ratios (HR) given with 95% confidence interval (CI) express the risk associated with a 1-decile increase in 24-h diastolic blood pressure level or load. The R^2 statistic is a measure for the refinement in risk prediction over and beyond a model including the 24-h blood pressure level and the other covariables. *P* indicates the significance of the log likelihood ratio test comparing the model including the 24-h blood pressure level and covariables and a model additionally including blood pressure load. The cause of death was unknown in 41 cases.
Significance of the hazard ratios: * $P \leq 0{\cdot}05$; † $P \leq 0{\cdot}01$; and ‡ $P \leq 0{\cdot}001$.

Table S10. Multivariable-Adjusted Hazard Ratios Associated with Increased 24-H Blood Pressure Load in Participants within Different Strata for Fatal and Nonfatal Combined Cardiovascular Events

Strata	At Risk (n)	Events (n)	Load in Percent (systolic/diastolic ≥40.0/42.3%)			Area Under the Curve (systolic/diastolic ≥91.8/73.6 mm Hg × h)		
			HR (CI)	R^2,%	*P*	HR (CI)	R^2,%	*P*
All participants	8711	1109	1.15 (0.96–1.38)	0.024	0.15	1.11 (0.93–1.33)	0.014	0.27
Women	4096	334	0.95 (0.68–1.33)	0.003	0.72	0.82 (0.59–1.15)	0.038	0.22
Men	4615	775	1.19 (0.96–1.47)	0.048	0.14	1.20 (0.96–1.48)	0.054	0.12
<60 years	4868	190	1.57 (1.01–2.43)	0.089	0.038	1.45 (0.95–2.23)	0.060	0.086
≥60 years	3843	919	1.06 (0.87–1.29)	0.006	0.62	1.03 (0.84–1.25)	0.001	0.81
Untreated	6812	611	1.09 (0.86–1.37)	0.006	0.54	1.02 (0.81–1.29)	<0.001	0.89
Treated	1899	498	1.18 (0.89–1.56)	0.060	0.29	1.19 (0.90–1.57)	0.069	0.25
Asian	1877	255	0.94 (0.64–1.38)	0.006	0.75	0.99 (0.68–1.46)	<0.001	0.97
European	5396	733	1.22 (0.98–1.53)	0.050	0.10	1.14 (0.92–1.42)	0.020	0.30
South American	1438	121	1.02 (0.55–1.88)	<0.001	0.96	0.99 (0.54–1.83)	<0.001	0.97

All models are randomized for cohort and adjusted for sex, age, 24-h systolic and diastolic blood pressure, body mass index, smoking and drinking, antihypertensive drug intake, serum cholesterol, history of cardiovascular disease and diabetes mellitus. Hazard ratios (HR) given with 95% confidence interval (CI) express the risk associated with an elevated blood pressure load. The R^2 statistic is a measure for the refinement in risk prediction over and beyond a model including the 24-h level of systolic and diastolic blood pressure and the other covariables. *P* indicates the significance of the log likelihood ratio test comparing the model including the 24-h blood pressure level and covariables and a model additionally including blood pressure load.

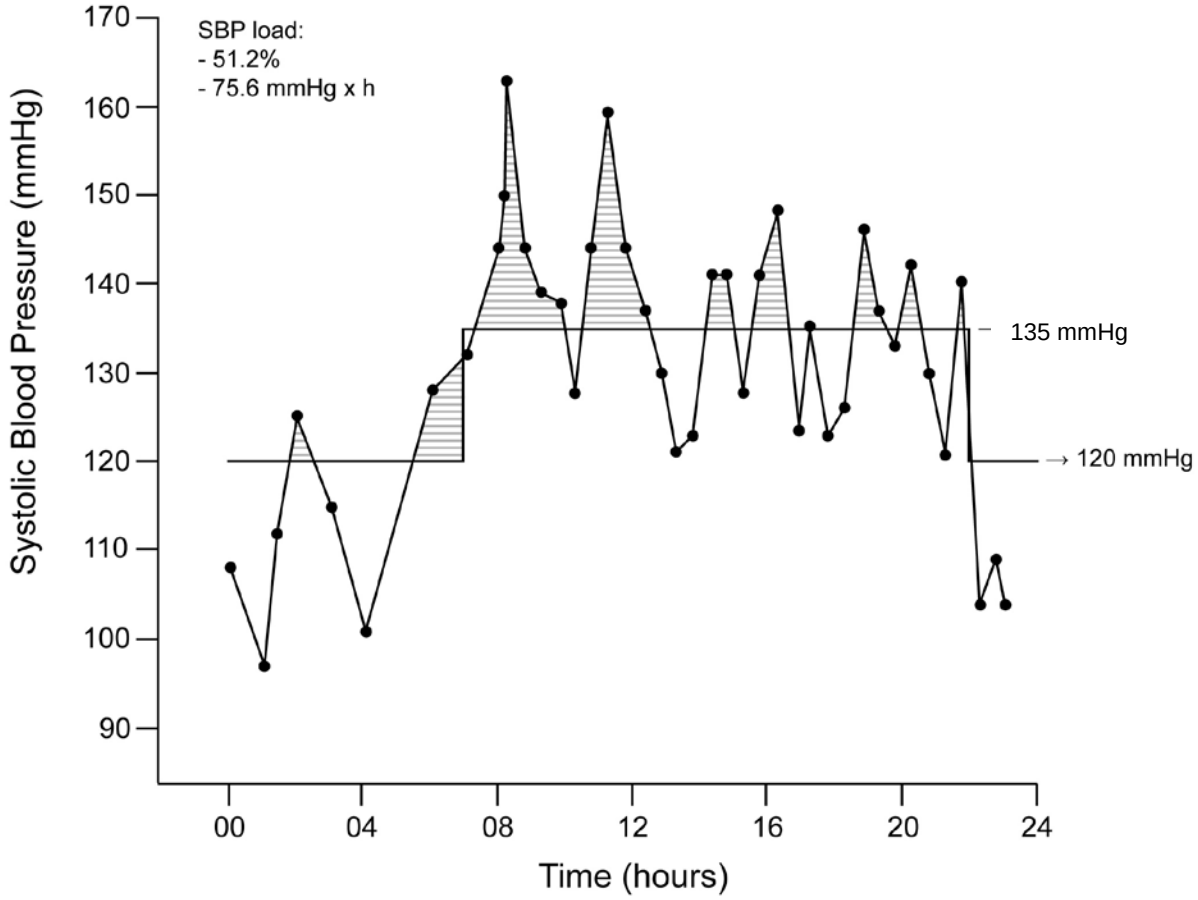

Figure S1. Graph of a 24-h ambulatory recording illustrating the calculation of systolic blood pressure load expressed in percent or as area under the curve.

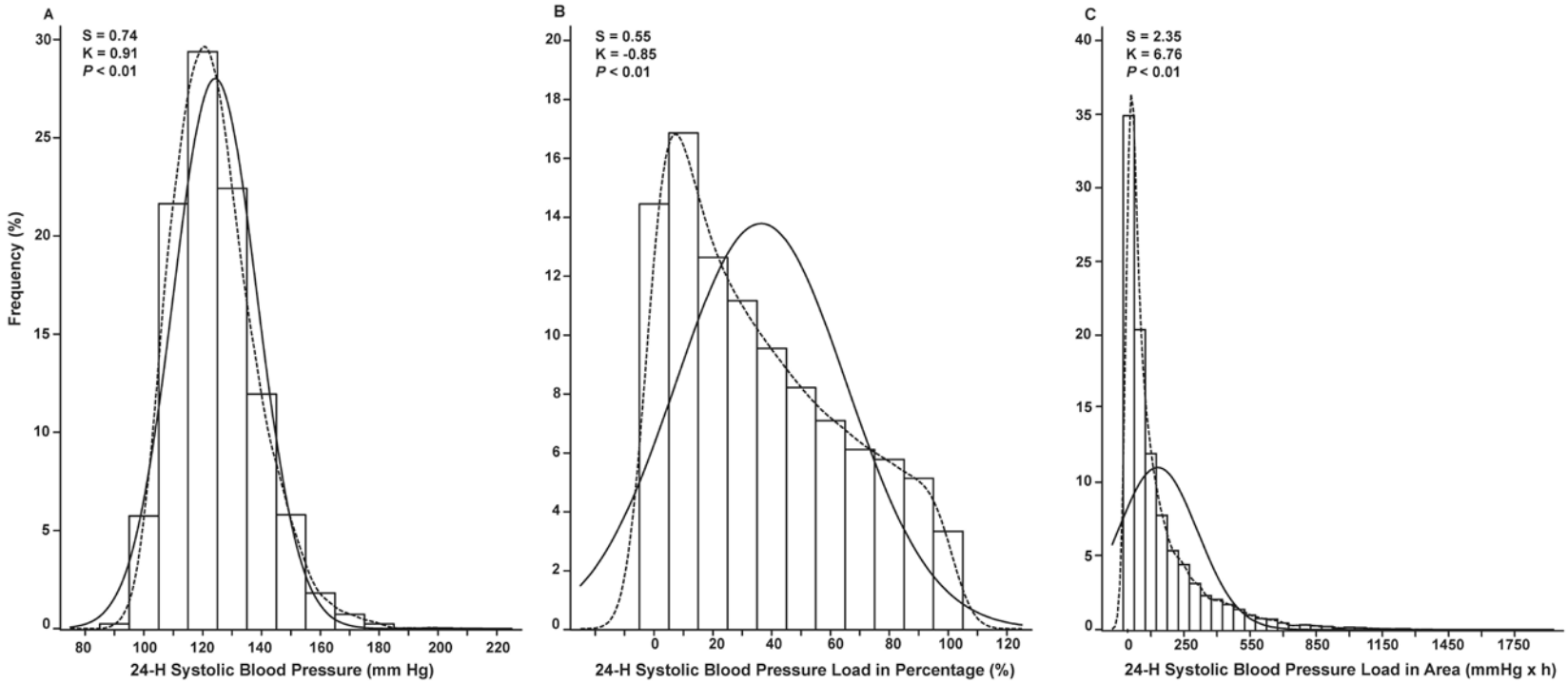

Figure S2. Frequency distribution of the 24-h systolic blood pressure level (A) and load expressed as percent (B) or area under the curve (C) in 8711 participants. S and K are the coefficients of skewness and kurtosis, respectively; the *P* value is for departure of the actually observed distribution (full line) from normality (dotted line).

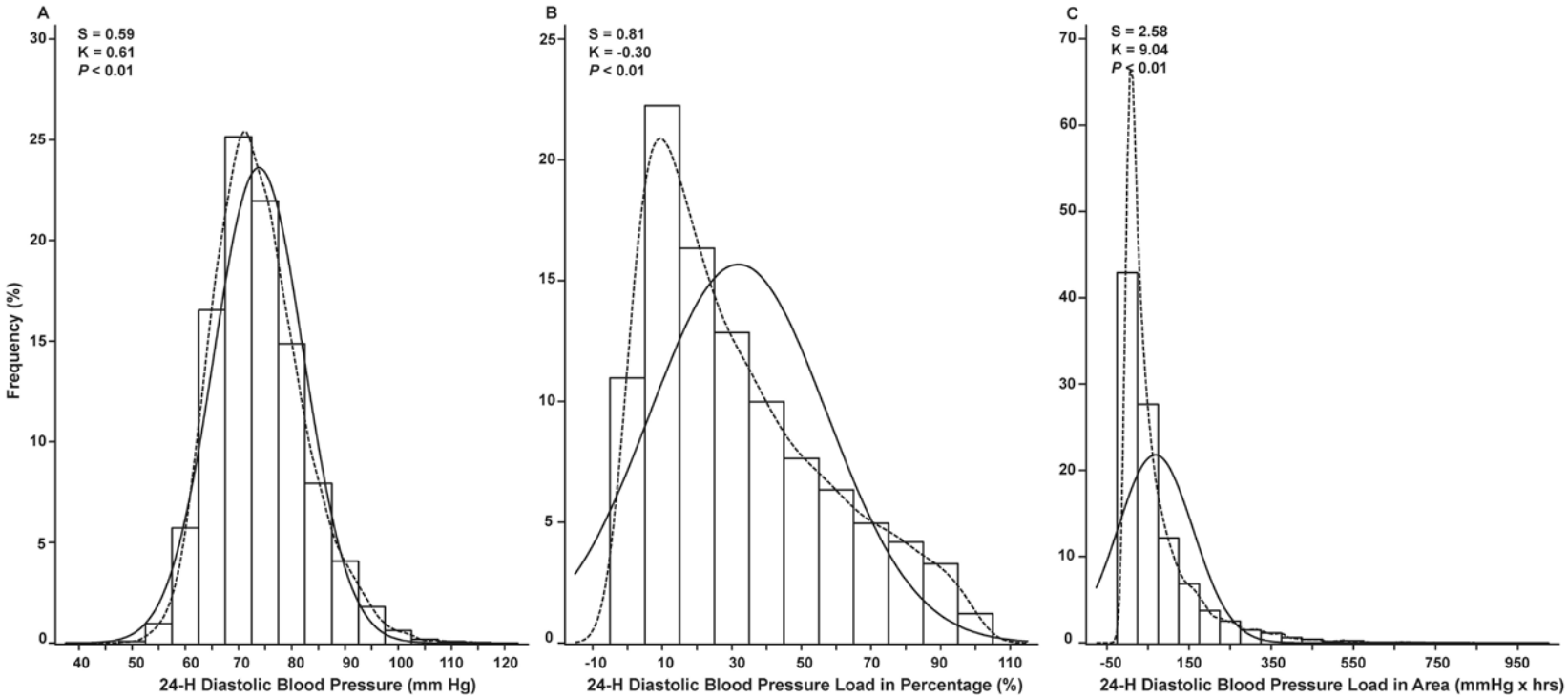

Figure S3. Frequency distribution of the 24-h diastolic blood pressure level (A) and load expressed as percent (B) or area under the curve (C) in 8711 participants. S and K are the coefficients of skewness and kurtosis, respectively; the *P* value is for departure of the actually observed distribution (full line) from normality (dotted line).

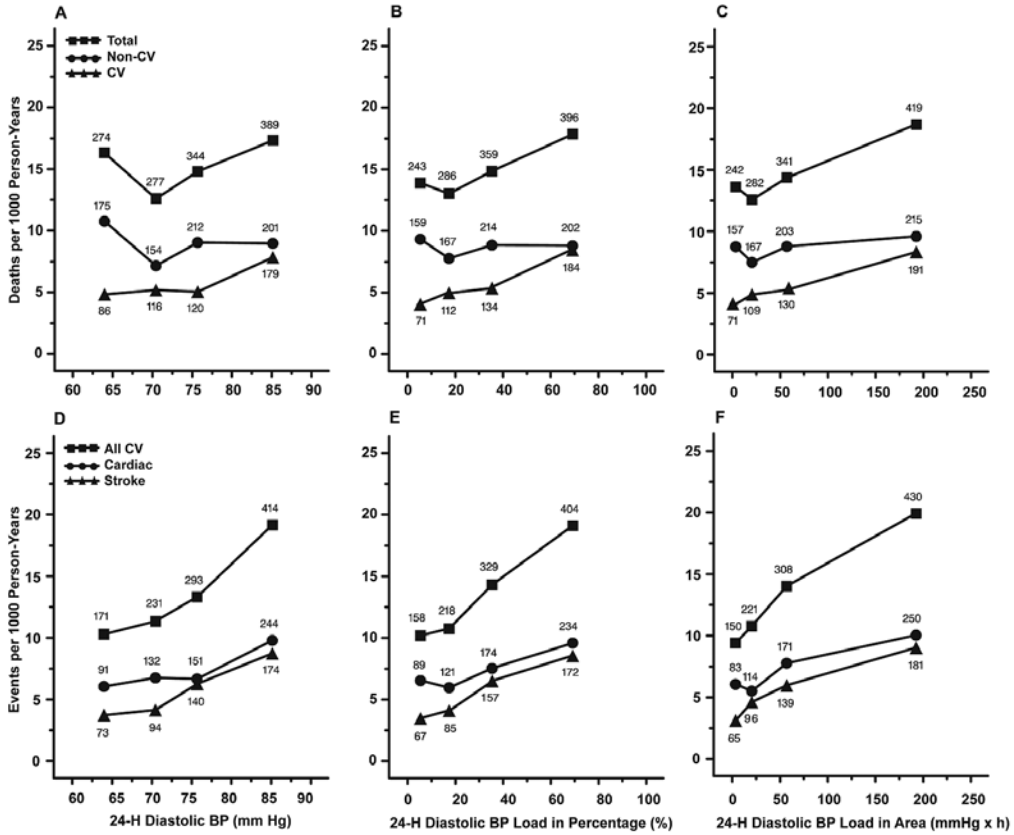

Figure S4. Incidence of mortality (A, B, C) and cardiovascular events (D, E, F) across quartiles of the 24-h diastolic blood pressure (BP) level (A, D) and the 24-h BP load expressed as percent (B, E) or as area under the curve (C, F). Incidence rates were standardized for center, sex, and age group (<40, 40-60, ≥60 years) by the direct method. The number of events contributing to the rates is presented. All *P*-values for trend were significant ($P<0.001$) except those for noncardiovascular mortality ($P\geq0.16$).

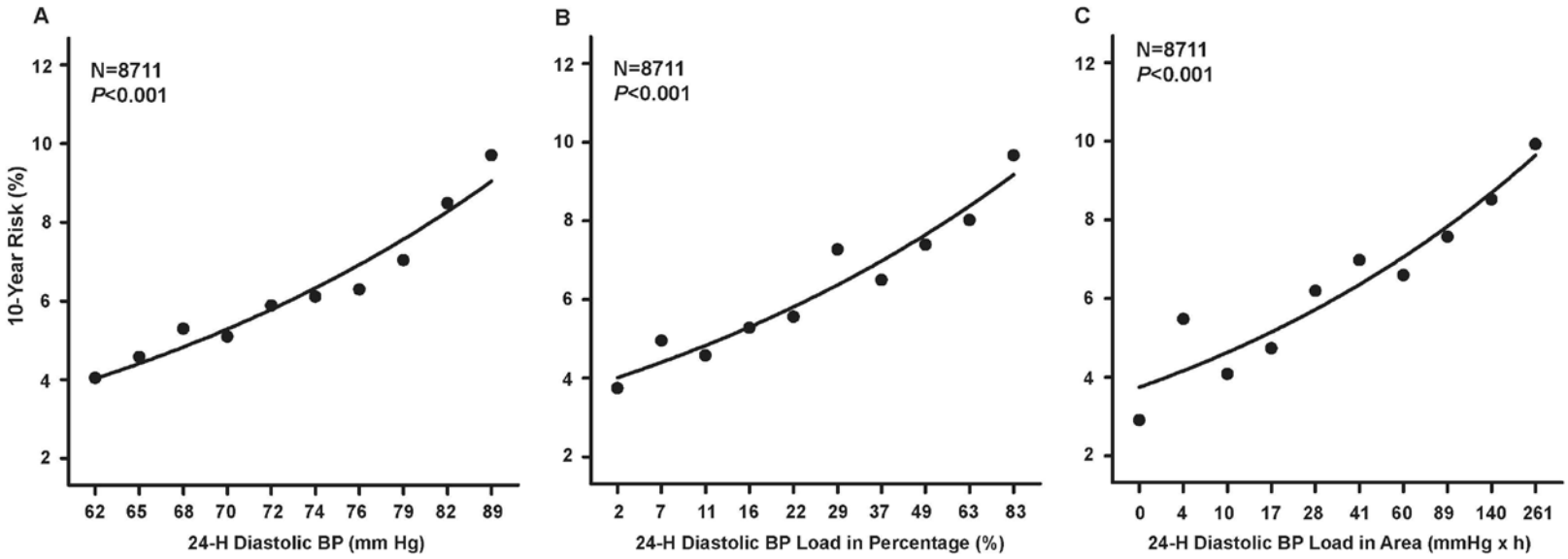

Figure S5. 10-year risk (%) of a composite cardiovascular endpoint in relation to 24-h diastolic blood pressure (BP) level (A) and load expressed in percent (B) or as area under the curve (C). The median of each decile group was plotted along the horizontal axis. Dots represent the risks in deciles of diastolic BP level or load. These risk estimates were derived from a Cox regression model including 9 dummy variables coding for the deciles. The fitted curve is the risk plotted by an ordinal variable coding for the deciles of diastolic BP level or load. All risk estimates were randomized for cohort and standardized to the midpoint (mean or ratio) of the distributions in all participants of sex, age, body mass index, smoking and drinking status, antihypertensive drug intake, total cholesterol, history of cardiovascular complications and diabetes mellitus.