ORIGINAL ARTICLE

Risk Stratification by Ambulatory Blood Pressure Monitoring Across JNC Classes of Conventional Blood Pressure

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BACKGROUND
Guidelines propose classification of conventional blood pressure (CBP) into normotension (<120/<80 mm Hg), prehypertension (120–139/80–89 mm Hg), and hypertension (≥140/≥90 mm Hg).

METHODS
To assess the potential differential contribution of ambulatory blood pressure (ABP) in predicting risk across CBP strata, we analyzed outcomes in 7,826 untreated people recruited from 11 populations.

RESULTS
During an 11.3-year period, 809 participants died (276 cardiovascular deaths) and 639, 383, and 225 experienced a cardiovascular, cardiac, or cerebrovascular event. Compared with normotension (n = 2,639), prehypertension (n = 3,076) carried higher risk ($P \leq 0.015$) of cardiovascular (+41%) and cerebrovascular (+92%) endpoints; compared with hypertension (n = 2,111) prehypertension entailed lower risk ($P \leq 0.005$) of total mortality (–14%) and cardiovascular mortality (–29%) and of cardiovascular (–34%), cardiac (–33%), or cerebrovascular (–47%) events. Multivariable-adjusted hazard ratios (HRs) for stroke associated with 24-hour and daytime diastolic ABP (+5 mm Hg) were higher ($P \leq 0.045$) in normotension than in prehypertension and hypertension (1.98 vs.1.19 vs.1.28 and 1.73 vs.1.09 vs. 1.24, respectively) with similar trends ($0.03 \leq P \leq 0.11$) for systolic ABP (+10 mm Hg). However, HRs for fatal endpoints and cardiac events associated with ABP did not differ significantly ($P \geq 0.13$) across CBP categories. Of normotensive and prehypertensive participants, 7.5% and 29.3% had masked hypertension (daytime ABP ≥135/≥85 mm Hg). Compared with true normotension ($P \leq 0.01$), HRs for stroke were 3.02 in normotension and 2.97 in prehypertension associated with masked hypertension with no difference between the latter two conditions ($P = 0.93$).

CONCLUSION
ABP refines risk stratification in normotension and prehypertension mainly by enabling the diagnosis of masked hypertension.

Keywords: ambulatory blood pressure monitoring; blood pressure; hypertension; masked hypertension; population science; prehypertension; risk stratification.

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The relationship between cardiovascular outcome and blood pressure (BP) is log linear, without a critical level above which the risk suddenly increases.[1] However, for the diagnosis and management of hypertension, clinicians need operational thresholds.[2,3] Therefore, the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7)[2] and the World Health Organization and the International Society of Hypertension (WHO–ISH)[3] proposed a classification of blood pressure based on conventional measurement into normal, prehypertensive, and hypertensive levels.

Ambulatory blood pressure (ABP) monitoring substantially refines the risk stratification in hypertensive patients[4] and in people randomly recruited from populations.[5,6] Few studies[7–10] have examined whether ABP measurement refines risk stratification to a similar extent within each of the categories of office blood pressure. However, these studies had a sample size that ranged from 591[9] to 942,[8] most included selected patients,[7–10] and all but 1[9] had as outcome variables intermediary outcomes, such as left ventricular mass,[7] pulse wave velocity,[8] and carotid intima-media thickness.[10] To our knowledge, no previous studies have addressed risk stratification by ABP monitoring in large population cohorts across all categories of the conventional blood pressure (CBP) using hard fatal and nonfatal outcomes. To resolve this research question, we analyzed 7,826 untreated participants randomly recruited from 11 populations and enrolled in the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO).[11]

METHODS

Study population

At the time of writing this article, the IDACO database[11] included 11 randomly recruited population cohorts[12–20] and 12,148 participants with available data on conventional and ABP. Details on recruitment of the IDACO cohorts are given in Supplementary Table 1. We excluded 4,322 participants because they were aged <18 years (n = 303), their CBP was not within the database (n = 248), their nighttime blood pressure had not been recorded (n = 1,367[14]), they were taking antihypertensive drugs at baseline (n = 2,156), or their ABP recordings did not comply with recommended[21] and predefined[11] quality standards and covered fewer than 20 hours or included fewer than 10 daytime or 5 nighttime readings (n = 248). Thus, the total number of participants included in the present analysis totaled 7,826.

Blood pressure measurement

Methods used for conventional and ABP measurement are described in detail in the Expanded Methods section. CBP was the average of 2 consecutive readings obtained either at the person's home[14,16–19] or at an examination center.[13,15,20,22] Portable monitors were programmed to obtain ABP readings at 30-minute intervals throughout the whole day[13,20] or at intervals ranging from 15 minutes[22] to 30 minutes[15] during the daytime and from 30 minutes[22] to 60 minutes[15] at night.

We categorized CBP according to the JNC7[2] and WHO–ISH[3] guidelines. Normal blood pressure was a level <120 mm Hg systolic and 80 mm Hg diastolic. Prehypertension encompassed 120–139 mm Hg systolic or 80–89 mm Hg diastolic. Patients who had a blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic were classified as hypertensive. To categorize levels of ABP, we followed the guidelines of the European Societies of Cardiology and Hypertension.[23] Ambulatory hypertension was a 24-hour level of 130 mm Hg systolic or 80 mm Hg diastolic or more; for the daytime blood pressure, these thresholds were 135 mm Hg and 85 mm Hg, and for the nighttime blood pressure they were 120 mm Hg and 70 mm Hg, respectively. Sustained normotension and hypertension were a normal blood pressure or hypertension on both conventional and ambulatory measurement. Masked hypertension was ambulatory hypertension in participants with a normal CBP.

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. Body mass index was measured as 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,[13–16,18,19,22] a random blood glucose concentration of at least 11.1 mmol/L,[13,14,17] a self-reported diagnosis,[14,16,17] or diabetes documented in practice or hospital records.[16]

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.[24–26] Fatal and nonfatal stroke did not include transient ischemic attacks. Coronary events encompassed death from ischemic heart disease, sudden death, nonfatal myocardial infarction, and coronary revascularization. Cardiac events comprised coronary endpoints and fatal and nonfatal heart failure. The composite cardiovascular endpoint included all aforementioned endpoints plus cardiovascular mortality. In all outcome analyses, we only considered the first event within each category.

Statistical analysis

For database management and statistical analysis, we used SAS software, version 9.3 (SAS Institute, Cary, NC). For comparison of means and proportions, we applied the large-sample z test and the χ^2 statistic, respectively. In Cox regression, we adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. To adjust for cohort, we pooled participants recruited in the framework of the European Project on Genes in Hypertension (Kraków,

Novosibirsk, Padova, and Pilsen).[19] We ascertained that the proportional hazard assumption underlying the Cox regression models was fulfilled by testing the interaction between the blood pressure categories and follow-up time. For categorical analyses, we presented hazard ratios (HRs) as floating absolute risks and calculated their standard errors as described by Easton and colleagues.[27] This approach allows calculation of a 95% confidence interval (CI) for the relative risk in the reference group.[27] We compared HRs between groups by testing the significance of the appropriated interaction term. Statistical significance was an α level of <0.05 on 2-sided tests.

RESULTS

Baseline characteristics

The study population consisted of 5,488 Europeans (70.1%), 1,150 Asians (14.7%), and 1,188 South Americans (15.2%). The 7,826 participants included 3,706 women (47.4%). Mean (± standard deviation (SD)) age was 49.9 ± 15.6 years. At enrollment, 2,367 participants (30.2%) were smokers and 3,941 (50.4%) reported intake of alcohol. In the whole study population, CBP averaged (± SD) 126.8 ± 18.7 mm Hg systolic and 78.3 ± 11.0 mm Hg diastolic. The median number of readings averaged to estimate the 24-hour blood pressure was 52 (5th to 95th percentile interval, 35–81; range, 20–99); the 24-hour ABPs were 121.7 ± 13.3 mm Hg and 73.0 ± 8.1 mm Hg, respectively. These levels were 128.2 ± 14.4 mm Hg and 78.3 ± 8.8 mm Hg during daytime and 110.3 ± 13.8 mm Hg and 63.7 ± 8.7 mm Hg at night.

On CBP measurement, according to the JNC7[2]/WHO–ISH[3] criteria, 2,639 (33.7%), 3,076 (39.3%), and 2,111 (27.0%) participants were normotensive, prehypertensive, or hypertensive, respectively. Table 1 lists the characteristics of the study participants by these categories. Using conventional and daytime ABP measurement for cross-classification, the prevalence of masked hypertension was higher ($P < 0.0001$) among prehypertensive patients (n = 900; 29.3%) than those with normotension (n = 198; 7.5%). Supplementary Tables 1 and 2 and the Supplementary Results provide detailed information on the determinants of masked hypertension and their discriminative power in our untreated participants.

Incidence of events

In the overall study population, the median follow-up was 11.3 years (5th to 95th percentile interval, 2.6–18.2 years). Across centers, median follow-up ranged from 2.5 years (5th to 95th percentile interval, 2.3–2.6) in Jingning, China, to 17.8 years (16.6–18.2 years) in Dublin, Ireland. During 87,624 person-years of follow-up, 809 participants died (9.2/1,000 person-years) and 639 experienced a fatal or nonfatal cardiovascular complication (7.5/1,000 person-years). Mortality included 276 cardiovascular and 503 noncardiovascular deaths, 23 deaths from unknown causes, and 7 deaths due to renal failure. Considering cause-specific first cardiovascular events, the incidence of fatal and nonfatal stroke was 42 and 183, respectively. Cardiac events consisted of 39 fatal and 134 nonfatal cases of acute myocardial infarction, 45 deaths from ischemic heart diseases, 6 sudden deaths, 16 fatal and 96 nonfatal cases of heart failure, and 47 cases of surgical or percutaneous coronary revascularization.

Risk associated with categories of CBP

In the first step of our analyses, we assessed, as as internal validation of our dataset, whether as-expected risks increased across increasing categories of CBP. Rates of mortality and fatality combined with nonfatal events increased ($P < 0.0001$) with higher categories of CBP (Table 2). With normotension as the reference (Table 2), prehypertensive participants had a significantly higher risk of a composite cardiovascular endpoint (+41%; $P = 0.01$) and stroke (+92%; $P = 0.02$). With hypertension as the reference (Table 2), the risks of cardiovascular death (−28%; $P = 0.01$), a composite cardiovascular endpoint (−34%; $P < 0.0001$), a cardiac (−33%; $P = 0.0007$) or coronary (−27%; $P = 0.02$) event, or stroke (−47%; $P < 0.0001$) were significantly lower in prehypertensive participants.

Risks associated with ABP by categories of CBP

In the next step of our analyses, we assessed whether the ABP level measured on a continuous scale differentially contributed to risk stratification across increasing categories of the CBP. We expressed HRs for 5-mm Hg and 10-mm Hg increments in the ambulatory diastolic and systolic blood pressures, respectively.

Mortality. In multivariable-adjusted analyses, taking normotension as the reference, the HRs for total and cardiovascular mortality associated with diastolic (+5 mm Hg; Supplementary Table 3) and systolic (+10 mm Hg; Supplementary Table 4) blood pressures as measured by 24-hour daytime and nighttime monitoring did not differ significantly ($P \geq 0.13$) from those in prehypertensive and hypertensive participants. The only exception was the higher HR for total mortality in relation to daytime diastolic blood pressure (DBP) in hypertensive compared with normotensive participants (1.10 vs. 0.92; $P = 0.04$).

Fatal combined with nonfatal endpoints. In multivariable-adjusted analyses, taking normotension as the reference, the HRs for the composite cardiovascular endpoint and cardiac events associated with diastolic (Table 3) and systolic (Table 4) blood pressures as measured by 24-hour daytime and nighttime monitoring did not significantly differ ($P \geq 0.19$) from those in prehypertensive and hypertensive participants. However, the HRs for stroke associated with 24-hour and daytime DBPs were significantly ($0.005 \leq P \leq 0.04$) higher in normotensive participants than in prehypertensive and hypertensive participants. The estimates for 24-hour DBP were 1.98 vs.1.19 vs.1.28 and for the daytime DBP were 1.73 vs.1.09 vs.1.24, respectively (Table 3). A similar trend ($0.04 \leq P \leq 0.11$) was observed for stroke in relation to the 24-hour and daytime systolic blood pressures (SBPs; Table 4). The estimates for 24-hour SBP were 2.27 vs.1.39 vs.1.38 and for daytime SBP were 2.07 vs.1.20 vs.1.37.

Table 1. Baseline characteristics by category of conventional blood pressure

Characteristic	Normotension	Prehypertension	Hypertension
Number (%)			
All participants in category	2,639 (33.7)	3,076 (39.3)	2,111 (27.0)
European	1,765 (66.9)	2,156 (70.1)†	1,567 (74.2)†
Asian	381 (14.4)	535 (17.4)†	234 (11.1)‡
South American	493 (18.7)	385 (12.5)‡	310 (14.7)*
Women	1,676 (63.5)	1,328 (43.2)‡	702 (33.3)‡
Smokers	875 (33.2)	947 (30.1)	545 (25.9)‡
Drinking alcohol	1,172 (45.0)	1,572 (53.6)‡	1,197 (62.7)‡
Diabetes mellitus	73 (2.8)	156 (5.1)‡	140 (6.6)‡
Cardiovascular disorder	96 (3.6)	162 (5.1)‡	145 (6.9)*
Daytime hypertension	198 (7.5)	900 (29.2)‡	1,525 (72.2)‡
Mean ± standard deviation			
Age, years	42.2 ± 13.8	50.2 ± 15.3‡	59.0 ± 13.1‡
Body mass index, kg/m^2	23.5 ± 3.4	25.3 ± 4.0‡	26.6 ± 4.2‡
Conventional pressure (mm Hg)			
Systolic	108.6 ± 7.3	126.4 ± 7.0‡	150.0 ± 14.4‡
Diastolic	69.0 ± 6.3	78.3 ± 6.8‡	89.7 ± 9.7‡
Ambulatory pressure (mm Hg)			
24-hour systolic	112.6 ± 8.5	121.1 ± 9.3‡	133.9 ± 13.5‡
24-hour diastolic	68.3 ± 5.6	72.9 ± 6.4‡	79.1 ± 8.7‡
Daytime systolic	118.5 ± 9.8	127.8 ± 10.5‡	141.0 ± 14.3‡
Daytime diastolic	73.4 ± 6.4	78.2 ± 7.3‡	84.6 ± 9.6‡
Nighttime systolic	102.5 ± 9.3	109.6 ± 10.7‡	121.0 ± 15.6‡
Nighttime diastolic	59.3 ± 6.5	63.5 ± 7.4‡	69.4 ± 9.6‡
Blood glucose, mmol/L	4.8 ± 0.9	5.1 ± 1.1‡	5.4 ± 1.4‡
Serum cholesterol, mmol/L	5.3 ± 1.1	5.6 ± 1.2‡	5.9 ± 1.2‡

Thresholds for the conventional blood pressure were <120/<80 mm Hg for normotension, 120–139/80–89 mm Hg for prehypertension, and ≥140/≥90 mm Hg for hypertension. Daytime hypertension was an ambulatory blood pressure of ≥135/≥85 mm Hg. To convert glucose and cholesterol from mmol/l to mg/dl, multiply by 18.01 and 38.61, respectively. Significance of the difference with the adjacent column as follows: * $P \le 0.05$, † $P \le 0.01$, and ‡ $P \le 0.001$.

Risk associated with masked hypertension

In the last step of our analyses, with sustained normotension as the reference (Figure 1), we first explored the HRs for the composite cardiovascular endpoint and stroke associated with masked hypertension, as defined on the basis of the daytime ABP. Among participants with normotension, 198 (7.5%) had masked hypertension because of an elevated daytime systolic (98 (49.5%)) or diastolic 63 (31.8%)) blood pressure or both (37 (18.7%)). Among participants with prehypertension, 900 (29.3%) had masked hypertension, because of an elevated daytime systolic (391 (43.4%)) or diastolic (216 (24.0%)) blood pressure or both (293 (32.6%)). Compared with true normotension, the HRs associated with masked hypertension in normotensive participants were 2.11 (95% CI, 1.24–3.60; $P = 0.006$) for a composite cardiovascular endpoint and 3.02 (95% CI, 1.25–7.32; $P = 0.01$) for stroke. The corresponding HRs associated with masked hypertension in prehypertensive participants were 2.08 (95% CI, 1.67–2.59; $P < 0.0001$) and 2.97 (95% CI, 2.03–4.35; $P < 0.0001$), respectively. The HRs associated with masked hypertension compared with true normotension were similar among normotensive and prehypertensive participants ($P \ge 0.75$). Compared with prehypertension without masked hypertension, the HRs associated with masked hypertension in prehypertensive participants were 1.53 (95% CI, 1.23–1.91; $P = 0.0001$) for the composite cardiovascular endpoint and 1.48 (95% CI, 1.01–2.16; $P = 0.04$) for stroke (Figure 1).

As shown in the Supplementary Results, the above findings were consistent if we defined masked hypertension based on the 24-hour (Supplementary Figure 1) or nighttime (Supplementary Figure 2) blood pressures.

Table 2. Risk associated with prehypertension vs. normotension or hypertension

	Number of endpoints (rate per 1,000 person-years)			Hazard ratios (confidence interval) associated with prehypertension			
Endpoint	**NT**	**PHT**	**HT**	**vs. NT**	***P***	***vs.* HT**	***P***
Mortality							
Total	126 (4.1)	313 (9.0)	370 (16.6)	1.18 (0.96–1.46)	0.12	0.86 (0.73–1.00)	0.050
Cardiovascular	31 (1.0)	97 (2.8)	148 (6.7)	1.37 (0.91–2.07)	0.13	0.72 (0.55–0.94)	0.012
Noncardiovascular	87 (2.8)	207 (6.0)	209 (9.4)	1.17 (0.90–1.51)	0.24	0.98 (0.80–1.20)	0.84
Fatal plus nonfatal events							
All cardiovascular	77 (2.5)	219 (6.5)	343 (16.1)	1.41 (1.08–1.84)	0.012	0.66 (0.55–0.78)	<0.0001
Cardiac	50 (1.6)	128 (3.7)	205 (9.5)	1.30 (0.93–1.83)	0.12	0.67 (0.54–0.85)	0.0007
Coronary	40 (1.3)	98 (2.9)	145 (6.6)	1.25 (0.86–1.82)	0.25	0.73 (0.56–0.95)	0.020
Stroke	18 (0.6)	76 (2.2)	131 (6.0)	1.92 (1.14–3.24)	0.015	0.53 (0.40–0.72)	<0.0001

Abbreviations: HT, hypertension on conventional blood pressure measurement; NT, normotension on conventional blood pressure measurement; PHT, prehypertension on conventional blood pressure measurement.

NT (<120/<80 mm Hg), PHT (120–139/80–89 mm Hg), and HT (≥140/≥90 mm Hg) were defined according to the JNC7[2]/WHO-ISH[3] criteria. All rates increased from NT to PHT and from PHT to HT ($P < 0.0001$). Hazard ratios, presented with 95% confidence interval, express the risk compared with prehypertension. All Cox models were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus.

Table 3. Multivariable-adjusted hazard ratios for cardiovascular events associated with diastolic ambulatory pressure by category of conventional blood pressure

	24-hour		Daytime		Nighttime	
Endpoint by subgroup	**HR (CI)**	***P***	**HR (CI)**	***P***	**HR (CI)**	***P***
All cardiovascular events						
Normotension	1.32 (1.09–1.60)†	…	1.26 (1.06–1.49)†	…	1.18 (1.00–1.38)*	…
Prehypertension	1.16 (1.04–1.29)†	0.19	1.12 (1.02–1.23)*	0.20	1.10 (1.01–1.21)*	0.37
Hypertension	1.20 (1.12–1.27)§	0.37	1.15 (1.08–1.22)§	0.43	1.15 (1.09–1.21)§	0.67
Cardiac events						
Normotension	1.10 (0.84–1.43)	…	1.10 (0.87–1.38)		1.04 (0.83–1.29)	…
Prehypertension	1.15 (0.99–1.32)	0.93	1.14 (1.00–1.29)*	0.87	1.04 (0.92–1.17)	0.79
Hypertension	1.14 (1.05–1.24)†	0.84	1.10 (1.02–1.18)*	0.83	1.10 (1.03–1.18)†	0.89
Stroke						
Normotension	1.98 (1.44–2.74)§	…	1.73 (1.29–2.32)‡	…	1.61 (1.18–2.20)†	…
Prehypertension	1.19 (0.99–1.43)	0.005	1.09 (0.93–1.27)	0.005	1.21 (1.04–1.40)*	0.12
Hypertension	1.28 (1.16–1.41)§	0.016	1.24 (1.13–1.35)§	0.045	1.20 (1.10–1.31)§	0.13

Normotension (<120/<80 mm Hg), prehypertension (120–139/80–89 mm Hg), and hypertension (≥140/≥90 mm Hg) refer to the classification based on the conventional blood pressure according to the JNC7[2]/WHO-ISH[3] criteria. The number of participants and cardiovascular events per group appear in Table 2. HRs, given with 95% CI, express the risk for a 5-mm Hg increase in diastolic blood pressure and were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. *P* values are for the comparison of the HRs in prehypertensive and hypertensive participants with the HRs in normotensive participants. The differences in the HRs between prehypertensive and hypertensive participants were all nonsignificant ($P \geq 0.074$).

Significance of the HRs: * $P \leq 0.05$; † $P \leq 0.01$, ‡ $P \leq 0.001$, and § $P \leq 0.0001$.

Abbreviations: CI, confidence interval; HR, hazard ratio; ..., not applicable.

Sensitivity analyses

The incidence of endpoints differed among IDACO cohorts according to ethnicity, sex ratio, and age distribution. However, our results, which describe the risk of stroke associated with 24-hour (Supplementary Tables 6 and 8) or daytime (Supplementary Tables 7 and 9) DBP, remained consistent when we excluded 1 cohort at a time (Supplementary Tables 6 and 7) or in analyses stratified by sex, age (<60 vs. ≥60 years), or ethnicity (Supplementary Tables 8 and 9).

Table 4. Multivariable-adjusted hazard ratios for cardiovascular events associated with systolic ambulatory pressure by category of conventional blood pressure

	24-hour		Daytime		Nighttime	
Endpoint by subgroup	**HR (CI)**	***P***	**HR (CI)**	***P***	**HR (CI)**	***P***
All cardiovascular events						
Normotension	1.51 (1.19–1.92)‡	…	1.44 (1.16–1.80)†	…	1.30 (1.07–1.59)†	…
Prehypertension	1.27 (1.10–1.45)†	0.47	1.17 (1.03–1.32)*	0.41	1.17 (1.05–1.31)†	0.42
Hypertension	1.26 (1.18–1.35)§	0.44	1.24 (1.16–1.33)§	0.68	1.17 (1.11–1.24)§	0.36
Cardiac events						
Normotension	1.19 (0.85–1.68)	…	1.15 (0.84–1.57)	…	1.12 (0.84–1.48)	…
Prehypertension	1.16 (0.96–1.41)	0.68	1.11 (0.93–1.32)	0.49	1.04 (0.89–1.22)	0.66
Hypertension	1.21 (1.10–1.32)§	0.66	1.18 (1.07–1.29)‡	0.41	1.14 (1.06–1.23)‡	0.99
Stroke						
Normotension	2.27 (1.43–3.62)‡	…	2.07 (1.36–3.15)‡	…	1.66 (1.13–2.43)*	…
Prehypertension	1.39 (1.12–1.73)†	0.11	1.20 (0.99–1.46)	0.035	1.34 (1.13–1.59)‡	0.44
Hypertension	1.38 (1.24–1.53)§	0.071	1.37 (1.23–1.52)§	0.099	1.22 (1.12–1.32)§	0.16

Normotension (<120/<80 mm Hg), prehypertension (120–139/80–89 mm Hg), and hypertension (≥140/≥90 mm Hg) refer to the JNC classification based on the conventional blood pressure according to the JNC7[2]/WHO-ISH[3] criteria. The number of participants and cardiovascular events per group appear in Table 2. HRs, given with 95% CI, express the risk for a 10-mm Hg increase in systolic blood pressure and were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. *P* values are for the comparison of the HRs in prehypertensive and hypertensive participants with the HRs in normotensive participants. The differences in the HRs between prehypertensive and hypertensive participants were all nonsignificant ($P \geq 0.22$).

Significance of the HRs: * $P \leq 0.05$; † $P \leq 0.01$, ‡ $P \leq 0.001$, and § $P \leq 0.0001$.

Abbreviations: CI, confidence interval; HR, hazard ratio; ..., not applicable.

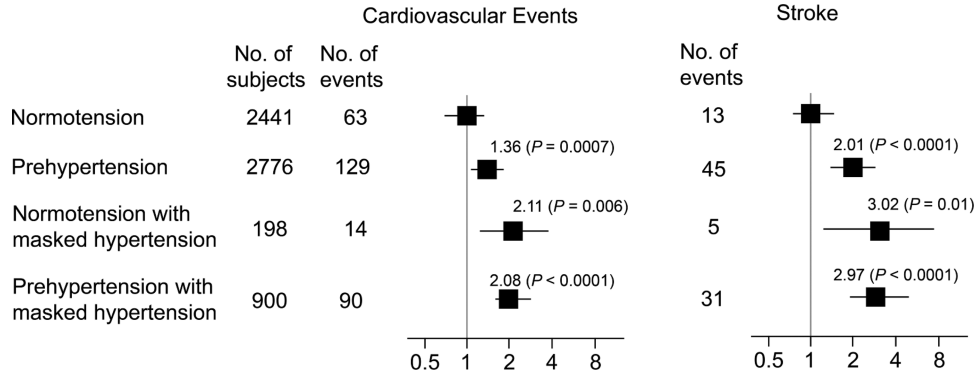

Figure 1. Hazard ratios for cardiovascular events and stroke associated with masked hypertension on daytime blood pressure monitoring in participants with normotension or prehypertension. Participants with sustained normotension are the reference group. Normotension (<120/<80 mm Hg) and prehypertension (120–139/80–89 mm Hg) refer to the classification based on the conventional blood pressure according to the JNC7[2]/WHO-ISH[3] criteria. Thresholds for daytime hypertension were ≥135 mm Hg systolic or ≥85 mm Hg diastolic. The hazard ratios (HRs) were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. Horizontal lines denote the 95% confidence interval (CI). Compared with prehypertension without masked hypertension, the HRs associated with masked hypertension in prehypertensive patients were 1.53 (95% CI, 1.23–1.91; $P = 0.0001$) for the composite cardiovascular endpoint and 1.48 (95% CI, 1.01–2.16; $P = 0.04$) for stroke.

DISCUSSION

Our current metaanalyses of patient-level data included 7,826 people not treated with blood pressure–lowering drugs. They were randomly recruited from 11 populations, and their follow-up covered, on average, 11.3 years. The key finding was that the relative risks associated with a higher ABP were similar across the 3 categories of the CBP for all endpoints under study with the exception of stroke. In normotensive and prehypertensive people with masked hypertension, the risk of cardiovascular events and stroke approximately doubled with each 10-mm Hg systolic or 5-mm Hg diastolic increase in ABP. We recently confirmed these findings in a patient-level metaanalysis of the International Database on Home blood pressure in relation to Cardiovascular Outcome using self-measured home blood pressure instead of ABP as the technique to assess the out-of-the-office blood pressure.[28] The replication of our current findings lends strong support

to the concept that out-of-the-office blood pressure measurement should be applied in normotensive or prehypertensive people with suspected masked hypertension to screen for this high-risk condition. Using the daytime ABP, in our current study, out-of-the-office blood pressure unmasked masked hypertension in 7.5% and 29.3% of participants with normotension or prehypertension on CBP, respectively. However, in the absence of any trial evidence, one can only speculate about the number of events that can be prevented by the early treatment of this condition.

Few other studies[7–10] have addressed the association between health outcomes and the ABP across categories of the CBP, as proposed by US[2] and international[3] guidelines. Most studies were only cross-sectional[7,8,10] or focused only on intermediate signs of target organ damage.[7,8,10] Zhu and colleagues studied 532 white and 410 black twins (mean age, 17.6 years). For youth aged <18 years, prehypertension was a CBP >120 mm Hg systolic or 80 mm Hg diastolic or ranging from the 90th to the 95th percentile after stratification for sex, age, and height;[29] for participants aged ≥18 years, prehypertension was a blood pressure of 120–139 mm Hg systolic or 80–89 mm Hg diastolic.[2,3] The prevalence of prehypertension was 12.0%. Cardiovascular risk factors, including obesity and high pulse wave velocity, clustered in prehypertensive participants.[8]

Manios and coworkers[10] enrolled 807 referred patients whose office blood pressure was <140 mm Hg systolic and 90 mm Hg diastolic. They applied the same criteria as we did to categorize their participants. The prevalence of pure prehypertension and prehypertension with masked hypertension was 59.9% and 19.7%, respectively. With adjustments applied, prehypertensive patients with masked hypertension had higher ($P < 0.01$) carotid intima-media thickness than prehypertensive patients without masked hypertension and normotensive patients (712 vs. 649 vs. 655 μm). Shimbo and colleagues[7] studied 813 untreated participants recruited from a worksite-based population study and obtained 9 blood pressure readings (3 at each of 3 visits over 3 weeks). Among 482 normotensive (<120/<80 mm Hg) and 287 prehypertensive (120–139/80–85 mm Hg) participants, the prevalence of masked hypertension was 3.9% and 34.1%, respectively. In multivariable-adjusted models, participants with prehypertension or masked hypertension (awake blood pressure ≥135/≥85 mm Hg) had greater left ventricular mass index than those with normotension (60.8 vs. 64.2 g/m^2; $P < 0.01$), but left ventricular mass index was not different among prehypertensive participants without and with masked hypertension (66.1 vs. 68.6 g/m^2; $P = 0.19$).

Pierdomenico and colleagues[9] completed the only study that also investigated the incidence of cardiovascular events in prehypertensive patients with (n = 120) and without (n = 471) masked hypertension. The participants were hospital staff, patients referred for reasons other than cardiovascular disease or hypertension, and volunteers. During 6.6 years of follow-up (range, 0.5–15.5 years), 29 fatal and nonfatal cardiovascular events occurred. In prehypertensive patients without and with masked hypertension, the event rates per 100 patient-years were 0.57 and 1.51, respectively. With adjustments applied for covariables, including the CBP, Cox regression showed that cardiovascular risk was significantly higher in masked hypertension than in true prehypertension (masked vs. true prehypertension, relative risk 2.65; 95% CI, 1.18–5.98; $P = 0.018$). Prehypertension and masked hypertension carry great risk to develop into hypertension. In the Flemish Study on Environment, Genes and Health Outcomes,[30] the 4-year progression rates from prehypertension to hypertension were 17.9% and 26.3% in participants aged <50 years and those aged ≥50 years, respectively. In the Copenhagen Monitoring of Trends and Determinants in Cardiovascular Disease,[31] the progression rate over 10 years was 37.3%. In multivariable-adjusted analyses, progression to prehypertension or to hypertension was associated with 10-year cardiovascular risks of 11.1% and 13.9%, respectively.[31]

We[5,32] and other investigators[33–35] demonstrated that masked hypertension carries a risk approaching that of sustained hypertension. However, the novel finding of our current study is that ABP monitoring contributes to risk stratification in people who, on the basis of their CBP, would be categorized as being at low cardiovascular risk and that masked hypertension is the driver of this risk. The present findings therefore suggest that screening for masked hypertension among prehypertensive and even normotensive people might be useful. The relationship between the cardiovascular and renal complications driven by blood pressure is continuous, at least down to a CBP level of 115 mm Hg systolic or 75 mm Hg diastolic.[1] Stroke is the complication of hypertension most closely associated with blood pressure.[36] The continuous nature of the relation with blood pressure not only holds true in hypertensive patients but in normotensive people as well.[1,37] Our current findings clearly show that the relative risk of stroke increases with the ABP in normotensive people at twice the rate observed in patients with hypertension. In addition, we demonstrated that masked hypertension in normotensive and prehypertensive patients contributes to the risk of stroke and cardiovascular complications. Our current findings suggest that ABP monitoring might be indicated in normotensive and prehypertensive people to screen for masked hypertension, a condition that confers a risk approaching that of sustained hypertension.[5] Our current data and the literature show that men, prehypertensive patients, diabetic patients,[32] smokers,[38] alcohol consumers, and individuals with increased cholesterol (≥5.7 mmol/L) are at increased risk of having masked hypertension. However, robust evidence for the routine implementation of ABP monitoring as a screening tool for masked hypertension should come from randomized clinical trials that prove that the early diagnosis of masked hypertension and treatment of this condition reduces the incidence of cardiovascular events.

The strong points of our current study are the use of ambulatory monitoring to assess blood pressure; the relatively large sample size, representing populations from Europe, Asia, and South America; and the removal of treated participants from the analysis. Nevertheless, our study also has limitations. First, the number of strokes was relatively low, so that estimates of stroke risk might be less precise than wished for. We could not differentiate between ischemic and hemorrhagic stroke. On the other hand, the probability of detecting a relation with a predictor variable increases with

the number of events. Thus, that we could already detect a statistically significant difference between normotensive and hypertensive participants in the HRs for stroke associated with the ABP might reflect a true and very strong underlying relation in normotensive people. Second, we did not determine the reproducibility of masked hypertension in the context of our current population study. However, Viera and colleagues reported prevalence rates of masked hypertension among untreated patients with a borderline elevated office blood pressure to be 54% and 53% on first and repeat assessment with an agreement of 73%.[39] Among patients who underwent repeat ambulatory monitoring for a medical indication, Ben-Dov and coworkers reported an agreement of 72%.[40] Third, most participants had their CBP measured while seated at an examination center. By contrast, in other cohorts the CBP was measured in the supine position[15] or at home.[14,17–19] Fourth, ABP monitoring was not standardized in terms of device type and intervals between successive readings, but the same SAS macro ensured that daytime was always defined in the same fashion, using short fixed clock-time intervals,[41] and that the time-weighted means were calculated identically across cohorts. Finally, binning a continuous variable such as the CBP is deemed to lose information.[42] However, we followed the categorization proposed by guidelines[2,3] for use in clinical practice and to be indiscriminately applied to adults of both sexes across the age range.

In conclusion, ABP monitoring contributes to risk stratification in normotension and prehypertension, particularly in the presence of masked hypertension. Further research should address the question whether ABP monitoring might be a cost-effective screening technique to prevent the cardiovascular complications associated with masked hypertension in patients with prehypertension[23] or even in normotensive people in whom unexplained target organ damage is present or who accumulate characteristics often associated with masked hypertension (Supplementary Results).

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

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DISCLOSURE

The authors declared no conflict of interest.

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