Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: a meta-analysis of 7030 individuals

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Objective To investigate the multivariate-adjusted predictive value of systolic and diastolic blood pressures on conventional (CBP) and daytime (10–20 h) ambulatory (ABP) measurement.

Methods We randomly recruited 7030 subjects (mean age 56.2 years; 44.8% women) from populations in Belgium, Denmark, Japan and Sweden. We constructed the International Database on Ambulatory blood pressure and Cardiovascular Outcomes.

Results During follow-up (median = 9.5 years), 932 subjects died. Neither CBP nor ABP predicted total mortality, of which 60.9% was due to noncardiovascular causes. The incidence of fatal combined with nonfatal cardiovascular events amounted to 863 (228 deaths, 326 strokes and 309 cardiac events). In multivariate-adjusted continuous analyses, both CBP and ABP predicted cardiovascular, cerebrovascular, cardiac and coronary events. However, in fully-adjusted models, including both CBP and ABP, CBP lost its predictive value ($P \geq 0.052$), whereas systolic and diastolic ABP retained their prognostic significance ($P \leq 0.007$) with the exception of diastolic ABP as predictor of cardiac and coronary events ($P \geq 0.21$). In adjusted categorical analyses, normotension was the referent group (CBP<140/90 mmHg and ABP<135/85 mmHg). Adjusted hazard ratios for all cardiovascular events were 1.22 [95% confidence interval (CI) = 0.96–1.53; $P = 0.09$] for white-coat hypertension ($\geq$140/90 and <135/85 mmHg); 1.62 (95% CI = 1.35–1.96; P<0.0001) for masked hypertension (<140/90 and $\geq$135/85 mmHg); and 1.80 (95% CI = 1.59–2.03; P<0.0001) for sustained hypertension ($\geq$140/90 and $\geq$135/85 mmHg).

Conclusions ABP is superior to CBP in predicting cardiovascular events, but not total and noncardiovascular mortality. Cardiovascular risk gradually increases from normotension over white-coat and masked hypertension to sustained hypertension. *J Hypertens* 25:1554–1564 © 2007 Lippincott Williams & Wilkins.

Introduction

Current guidelines define normotension and sustained hypertension as a consistently normal or elevated blood pressure on both conventional office and ambulatory measurement [1,2]. White-coat hypertension is a raised conventional blood pressure in the presence of a normal daytime blood pressure, whereas masked hypertension is an elevated daytime blood pressure with normal conventional blood pressure [1,2]. Several prospective studies have addressed the cardiovascular risk associated with white-coat [3–12] and masked hypertension [9,11–13]. Most studies involved hypertensive patients [3–7], including [3,6] or excluding [4,5,7] a normotensive control group. Fewer reports were population-based [9,11–13] or pooled hypertensive patients with randomly recruited subjects [10]. The interpretation of previous studies on white-coat [3–12] and masked [9,11–13] hypertension is difficult, due to divergent thresholds for ambulatory hypertension, and because, in some studies, most patients were followed up when they were on antihypertensive drug treatment [4,7], and/or because of the relatively low incidence of events [5,7,8], short duration of follow-up [3,5–7] or restriction of follow-up to mortality [12].

We constructed an international database of population studies with the goal to investigate the relation between fatal and nonfatal outcomes and the ambulatory and conventional blood pressures based on long-term follow-up and a large number of events, while adjusting for cardiovascular risk factors [14,15]. In the present study, we assessed risk associated with the conventional and ambulatory blood pressures analysed as continuous exposure variables. We also reported estimates of risk associated with white-coat and masked hypertension, relative to normotension and sustained hypertension.

Methods
Study population
We constructed the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) [14,15]. Studies were eligible for inclusion, if they involved a random population sample, if information on the conventional and ambulatory blood pressures and cardiovascular risk factors were available at baseline, and if the subsequent follow-up included fatal and nonfatal outcomes. An electronic search of the English literature, using 'ambulatory blood pressure monitoring' and 'population' as search terms identified eleven studies [11–13,16–23]. Seven were excluded because follow-up was still ongoing [17,19–23] or because follow-up did not include nonfatal events [12].

For the current analysis, we considered 2311 residents from Copenhagen, Denmark [11], 2542 subjects recruited from Noorderkempen, Belgium [18], 1535 inhabitants of Ohasama, Japan [16], and 1221 men from the population of Uppsala, Sweden [13]. Thus, on 30 April 2006, the number of subjects available for analysis totalled 7609. All studies included randomly selected population samples and the participation rates were 70.2% in Copenhagen [11], 70.0% in Belgium [18], 77.1% in Ohasama [16] and 72.6% in Uppsala [13]. All studies contributing to the IDACO database received ethical approval and have been described in detail [11,13,16,18]. All participants provided their informed written consent. Of the 7609 subjects, 579 were excluded because their conventional ($n = 220$) or daytime ambulatory blood pressure ($n = 79$) was not measured, because their daytime ambulatory blood pressure was the average of fewer than ten readings ($n = 53$), or because they were younger than 18 years at enrolment ($n = 227$). Thus, the number of subjects included in the present analyses totalled 7030.

Conventional and ambulatory blood pressure measurement
Experienced observers measured the conventional blood pressure with a standard mercury sphygmomanometer [11,13,18] or a validated [24] auscultatory device (USM-700F; UEDA Electronic Works, Tokyo, Japan) [16], using the appropriate cuff size, after the subjects had rested for at least 2 min in the sitting [11,16,18] or supine [13] position. The conventional blood pressure was the average of two consecutive readings obtained either at the subjects' homes [18] or at an examination centre [11,13,16].

We programmed portable blood pressure monitors to obtain daytime readings at intervals ranging from 15 min [11] to 30 min [16]. The devices implemented an auscultatory algorithm (Accutracker II; Suntech Medical Instruments Inc., Morrisville, North Carolina, USA) [25] in Uppsala [13] or an oscillometric technique (SpaceLabs 90202 and 90207; SpaceLabs Inc., Redmond, Washington, USA) [26,27] in Noorderkempen [18]. The Takeda TM-2421 recorders (A&D, Tokyo, Japan) [28] and the ABPM-630 devices (Nippon Colin, Komaki, Japan) [29], used in Copenhagen [11] and Ohasama [16], respectively, implemented both techniques, but only the oscillometric readings were analyzed.

To achieve a high degree of standardization, the same SAS macro (SAS software, version 9.1; SAS Institute, Cary, North Carolina, USA) processed all individual recordings, which stayed either unedited [11,13,18] or were only minimally edited [16], according to previously published criteria [30]. We calculated the averaged daytime blood pressure weighted for the time interval between consecutive readings. Accounting for the pattern of the daily activities of the study participants, we defined daytime as the interval ranging from 1000 h to 2000 h in Europeans [11,13,18], and from 0800 h to 1800 h in Japanese [16]. Pulse pressure was the difference between the systolic and diastolic blood pressure. Mean arterial pressure was diastolic blood pressure plus one-third of pulse pressure.

In line with current guidelines for the diagnosis and management of hypertension [1,2], we defined conventional hypertension as a blood pressure equal to or exceeding 140 mmHg systolic or 90 mmHg diastolic. The corresponding thresholds for ambulatory hypertension were 135 mmHg systolic and 85 mmHg diastolic. In line with suggestions by Verdecchia *et al.* [31], we also defined ambulatory hypertension, using 130 and 80 mmHg as systolic and diastolic cut-off limits. Patients on antihypertensive drug treatment were classified according to their treated blood pressure. Normotension and sustained hypertension were a consistently normal or elevated blood pressure on both conventional and ambulatory measurement [1,2]. White-coat hypertension was a raised conventional blood pressure in the presence of a normal daytime blood pressure [1,2]. Masked hypertension was an elevated ambulatory blood pressure with normal conventional blood pressure [1,2].

Other measurements
In all cohorts, a questionnaire was used to obtain detailed information on each subject's medical history, intake of

medications, and lifestyle. We defined smoking and drinking as the current use of tobacco and alcohol. Body mass index was body weight in kilograms divided by height in meters squared (kg/m^2). Previous cardiovascular disease included cardiac disorders, stroke, transient ischemic attack, and peripheral vascular disease. Total serum cholesterol and blood glucose were determined by automated enzymatic methods on venous blood samples. Diabetes mellitus was a self-reported diagnosis, a fasting or random blood glucose level of at least 7.0 mmol/l (126 mg/dl) or 11.1 mmol/l (200 mg/dl), respectively, or use of antidiabetic drugs [32].

Ascertainment of events

We ascertained vital status and the incidence of fatal and nonfatal diseases from the appropriate sources in each country, as previously described in detail [11,13,33,34]. Fatal and nonfatal stroke did not include transient ischemic attacks. Coronary events encompassed death from ischemic heart disease, sudden death, nonfatal myocardial infarction, and surgical and transluminal coronary revascularization. Cardiac events comprised coronary endpoints and fatal and nonfatal heart failure. In the Danish [11] and Swedish [13] cohorts, the diagnosis of heart failure required hospitalization. In the Japanese [16,33] and Belgian [18,34] cohorts, heart failure was either a clinical diagnosis or the diagnosis on the death certificate but, in all cases, validated against hospital records or the records held by general practitioners. 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 9.1 (SAS Institute). For comparison of means and proportions, we applied the standard normal z-test for large samples and the chi-squared test, respectively. We first plotted the incidence of cardiovascular events according to the cross classification of subjects by conventional and ambulatory blood pressure measurement, using Cox models standardized to the sex distribution and mean age of the whole study population. We ascertained that the proportional hazard assumption underlying Cox regression was fulfilled by testing the interaction between follow-up time and blood pressure categories. Next, we modelled the multivariate-adjusted risk associated with the conventional and ambulatory blood pressures treated both as continuous and as categorical variables. In these Cox regression models, we adjusted for cohort, sex, age, body mass index, serum cholesterol, smoking and drinking, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment. We adjusted for cohort by introducing three design variables in the Cox models. We additionally adjusted the Cox models relating outcome to pulse

pressure for mean arterial pressure [35]. For the categorical analyses, we presented hazard ratios as floating absolute risks and calculated their standard errors as described by Easton *et al.* [36]. This approach allows the calculation of a 95% confidence interval (CI) for the relative risk in the referent group. We evaluated differences between hazard ratios, using the test statement in the Cox regression procedure, as implemented in the SAS package. $P < 0.05$ (two-tailed) was considered statistically significant.

Results

Baseline characteristics of the participants

The 7030 subjects included 3148 (44.8%) women and 1520 patients (21.8%) on antihypertensive drug treatment. Mean ± SD values were 56.2 ± 14.4 years for age, 131.8 ± 19.6 mmHg and 79.4 ± 11.3 mmHg for systolic and diastolic blood pressure on conventional measurement, and 131.8 ± 14.9 mmHg and 78.5 ± 9.1 mmHg for systolic and diastolic blood pressure on daytime monitoring. Of the participants, 3473 (49.4%) had normotension, 743 (10.6%) had white-coat hypertension, 1024 (14.6%) had masked hypertension, and 1790 (25.4%) had sustained hypertension. Table 1 shows the baseline characteristics of these four groups. Between-group differences were significant for all variables ($P < 0.0001$). Across cohorts, the prevalence of white-coat hypertension was lowest in Copenhagen and highest in Uppsala (6.7 versus 17.0%), whereas the opposite was true for the prevalence of masked hypertension (20.1 versus 11.3%).

Exploratory analyses

During follow-up (median = 9.5 years; 5th to 95th percentile interval = 2.7–14.0 years), 64 958 person-years accrued. Figure 1 shows the incidence of cardiovascular events in the four blood pressure groups with rates standardized to the sex distribution and mean age of the whole study population. The incidence of cardiovascular events increased from normotension over white-coat and masked hypertension to sustained hypertension (P for trend < 0.0001). The number of events and crude incidence rates expressed in percentage are shown in Table 2 for mortality and in Table 3 for fatal and nonfatal cardiovascular events combined. Cardiac events consisted of 147 fatal and 321 nonfatal events, including 47 fatal and 168 nonfatal cases of acute myocardial infarction, 79 sudden deaths, 21 fatal and 127 nonfatal cases of heart failure, and 26 cases of surgical and percutaneous coronary revascularization. Most revascularization procedures occurred in Belgium ($n = 20$) and a few others occurred in Denmark ($n = 6$).

Adjusted continuous analyses

The multivariate-adjusted hazard ratios (95% CI) associated with each 10-mmHg increase in systolic blood pressure or pulse pressure or each 5-mmHg increase in diastolic blood pressure are shown in Table 2 for

Table 1 Baseline characteristics of participants by cross-classification of conventional and daytime blood pressures

| Characteristic	Normotension (n = 3473)	White-coat HT (n = 743)	Masked HT (n = 1024)	Sustained HT (n = 1790)
Anthropometrics				
Women (n)	1909 (55.0)	300 (40.4)	406 (39.7)	533 (29.8)
Age (years)	50.9 ± 14.7	62.3 ± 12.0	56.5 ± 13.0	63.6 ± 10.6
Body mass index (kg/m^2)	24.5 ± 3.7	26.0 ± 4.4	25.8 ± 3.9	27.0 ± 4.1
Conventional blood pressure (mmHg)				
Systolic	118.9 ± 10.7	148.0 ± 12.8	125.6 ± 9.2	153.8 ± 15.1
Diastolic	73.1 ± 8.1	85.9 ± 9.5	77.5 ± 7.6	90.0 ± 9.9
Pulse pressure	45.7 ± 9.9	62.2 ± 15.7	48.1 ± 10.3	63.7 ± 15.6
Daytime blood pressure (mmHg)				
Daytime systolic	121.4 ± 7.8	126.3 ± 6.5	141.2 ± 8.3	148.7 ± 11.8
Daytime diastolic	73.5 ± 5.9	74.9 ± 6.0	84.0 ± 7.3	86.5 ± 8.7
Pulse pressure	48.0 ± 6.4	51.4 ± 6.9	57.6 ± 9.6	62.4 ± 11.1
Risk factors				
Antihypertensive treatment (n)	421 (12.1)	290 (39.0)	191 (18.7)	618 (34.5)
Current smokers (n)	1093 (31.6)	142 (19.4)	391 (38.4)	507 (28.5)
Current drinkers (n)	1425 (43.4)	316 (51.2)	622 (65.2)	1136 (73.9)
Serum cholesterol (mmol/l)	5.47 ± 1.09	5.86 ± 1.15	5.80 ± 1.11	5.96 ± 1.13
History of cardiovascular disease (n)	213 (6.1)	97 (13.0)	84 (8.2)	199 (11.1)
Diabetes mellitus (n)	157 (4.5)	67 (9.0)	83 (8.1)	184 (10.3)

Data are mean ± SD or number of subjects (%). HT, Hypertension (for conventional and ambulatory thresholds, see Methods). All between-group differences were significant ($P \leq 0.0001$).

mortality and in Table 3 for fatal combined with nonfatal cardiovascular events. We adjusted all analyses for cohort, sex, age, body mass index, serum cholesterol, smoking and drinking, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment. The analyses involving pulse pressure were also adjusted for mean arterial pressure [35]. Fully-adjusted models included blood pressure on conventional as well as daytime ambulatory measurement.

In adjusted and fully-adjusted models, the three blood pressure components on daytime ambulatory measurement, but not on conventional measurement, were significant predictors of cardiovascular mortality, but not of total mortality. Systolic and diastolic blood pressure and pulse pressure on conventional as well as ambulatory measurement did not predict noncardiovascular mortality

in adjusted ($P \geq 0.44$) or fully adjusted ($P \geq 0.49$) models (Table 2). This explains the weak association of total mortality (55.6% due to noncardiovascular causes) with the daytime ambulatory blood pressure in adjusted ($0.014 \leq P \leq 0.30$) and fully-adjusted ($P \geq 0.14$) models (Table 2).

Figure 2 shows the 10-year absolute risk of cardiovascular events in continuous analyses adjusted for cohort and the aforementioned risk factors. In fully-adjusted models, the daytime blood pressure remained a significant predictor for all cardiovascular events over and beyond the conventional blood pressure (Table 3 and Fig. 2). This was also the case for cause-specific cardiovascular endpoints with the exception of the daytime diastolic blood pressure as predictor of cardiac events (hazard ratio, 1.03; $P = 0.45$) and coronary heart disease, including or

Fig. 1
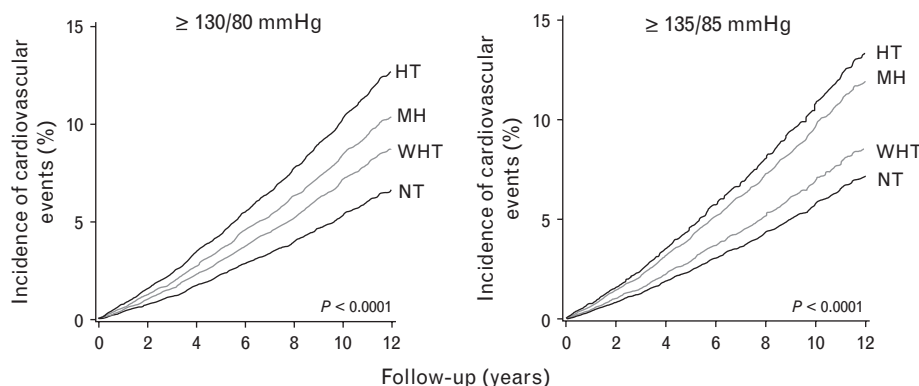
Incidence of cardiovascular events according to the cross classification of subjects by conventional and daytime ambulatory blood pressure. NT, normotension; WHT, white-coat hypertension; MH, masked hypertension; HT, sustained hypertension. The analyses were based on (a) lower ($\geq 130/80$ mmHg) or (b) higher ($\geq 135/85$ mmHg) cut-off limits for daytime ambulatory hypertension. Incidence was standardized to the sex distribution and mean age in the whole study population. The *P*-values are for trend across the blood pressure groups.

Table 2   Multivariate-adjusted hazard ratios for mortality

Label		Total	Noncardiovascular	Cardiovascular
Number of deaths, n (%)		932 (13.3)	524 (7.4)	364 (5.2)
Conventional blood pressure				
Systolic	Adjusted	1.05 (1.00–1.09)*	1.01 (0.95–1.07)	1.10 (1.03–1.17)
	Fully adjusted	1.03 (0.98–1.08)	1.02 (0.95–1.09)	1.03 (0.96–1.11)
Diastolic	Adjusted	1.01 (0.98–1.05)	0.99 (0.94–1.04)	1.05 (0.99–1.11)
	Fully adjusted	1.00 (0.96–1.05)	1.00 (0.95–1.06)	1.00 (0.94–1.07)
Pulse pressure	Adjusted	1.05 (0.99–1.12)	1.03 (0.95–1.12)	1.07 (0.98–1.18)
	Fully adjusted	1.03 (0.97–1.10)	1.03 (0.94–1.13)	1.03 (0.93–1.13)
Daytime blood pressure				
Systolic	Adjusted	1.07 (1.01–1.12)*	0.99 (0.92–1.06)	1.18 (1.09–1.27)‡
	Fully adjusted	1.05 (0.99–1.11)	0.99 (0.90–1.07)	1.16 (1.05–1.27)†
Diastolic	Adjusted	1.02 (0.98–1.07)	0.99 (0.94–1.04)	1.11 (1.04–1.18)†
	Fully adjusted	1.02 (0.96–1.05)	0.98 (0.91–1.05)	1.11 (1.03–1.20)†
Pulse pressure	Adjusted	1.08 (0.99–1.17)	1.04 (0.93–1.17)	1.09 (0.96–1.23)
	Fully adjusted	1.06 (0.97–1.16)	1.02 (0.90–1.16)	1.06 (0.92–1.21)

The cause of death was unknown in 44 cases. Hazard ratios (95% confidence interval) are for the risk associated with 10-mmHg increases in systolic blood pressure and pulse pressure or 5-mmHg increases in diastolic blood pressure. All hazard ratios were adjusted for cohort, sex, age, body mass index, serum cholesterol, smoking and drinking, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment. Hazard ratios for pulse pressure were additionally adjusted for mean arterial pressure. Models including both conventional as well as daytime blood pressure are labelled as fully adjusted. Significance of the hazard ratios: * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.0001$.

excluding the 26 incident cases of coronary revascularization (hazard ratios ≤ 1.05; $P ≥ 0.21$). By contrast, in fully-adjusted models, the conventional blood pressure was not predictive of fatal combined with nonfatal outcomes, over and beyond the ambulatory daytime blood pressure.

Adjusted categorical analyses
Figure 3 shows the hazard ratios (95% CI) for all combined cardiovascular events according to the cross-classification of conventional and daytime ambulatory blood pressure. Cardiovascular risk increased across the hypertensive groups with the highest risk in the patients with sustained hypertension (P-value for trend < 0.0001). These results were consistent in analyses based on the higher (≥ 135/85 mmHg) and lower (≥ 130/80 mmHg) [31] cut-off limits for daytime ambulatory hypertension.

Compared to normotension, white-coat hypertensive patients had a slightly increased risk, but none of the hazard ratios reached significance (0.63 ≥ P ≥ 0.09; Fig. 3). Using 135/85 mmHg as the cut-off limit, white-coat hypertensive patients had higher daytime blood pressures than the normotensive reference group. The differences averaged 4.9 mmHg systolic and 1.4 mmHg diastolic (no P-values calculated because the classification rested on blood pressure). After additional adjustment for the daytime systolic blood pressure, the hazard ratios associated with white-coat hypertension were 1.16 (95% CI = 0.91–1.47; $P = 0.23$) for all cardiovascular events, 1.03 (95% CI = 0.72–1.49; $P = 0.87$) for stroke, and 1.22 (95% CI = 0.87–1.69; $P = 0.24$) for cardiac events. The hazard ratios, relative to normotension, were similar for masked hypertension and sustained hypertension (P ≥ 0.14) with the exception of the hazard ratio for

Table 3   Multivariate-adjusted hazard ratios for fatal and nonfatal events combined

Label		All events	Stroke	Cardiac	CHD+	CHD−
Number of events, n (%)		863 (12.3)	397 (5.7)	468 (6.7)	353 (5.0)	333 (4.7)
Conventional blood pressure						
Systolic	Adjusted	1.12 (1.08–1.17)‡	1.13 (1.07–1.20)‡	1.12 (1.06–1.19)‡	1.10 (1.03–1.18)†	1.11 (1.04–1.19)†
	Fully adjusted	1.05 (1.00–1.10)	1.05 (0.98–1.12)	1.06 (0.99–1.13)	1.02 (0.94–1.11)	1.03 (0.95–1.12)
Diastolic	Adjusted	1.07 (1.03–1.11)‡	1.09 (1.03–1.14)‡	1.08 (1.02–1.13)*	1.09 (1.03–1.15)†	1.09 (1.02–1.16)†
	Fully adjusted	1.03 (0.99–1.07)	1.02 (0.96–1.08)	1.06 (0.99–1.13)	1.05 (0.98–1.13)	1.06 (0.98–1.14)
Pulse pressure	Adjusted	1.08 (1.01–1.15)*	1.06 (0.97–1.16)†	1.10 (1.01–1.19)*	1.01 (0.92–1.12)	1.02 (0.92–1.13)
	Fully adjusted	1.02 (0.96–1.09)	1.01 (0.92–1.11)	1.02 (0.93–1.12)	0.94 (0.85–1.05)	0.95 (0.85–1.06)
Daytime blood pressure						
Systolic	Adjusted	1.21 (1.15–1.27)‡	1.25 (1.16–1.34)‡	1.18 (1.10–1.26)‡	1.19 (1.10–1.29)‡	1.20 (1.11–1.30)‡
	Fully adjusted	1.17 (1.10–1.24)‡	1.21 (1.12–1.32)‡	1.13 (1.04–1.23)‡	1.17 (1.07–1.29)‡	1.18 (1.07–1.30)†
Diastolic	Adjusted	1.11 (1.07–1.15)‡	1.17 (1.10–1.23)‡	1.07 (1.01–1.13)*	1.09 (1.03–1.17)†	1.09 (1.02–1.17)*
	Fully adjusted	1.09 (1.04–1.14)‡	1.15 (1.08–1.23)‡	1.03 (0.96–1.10)	1.06 (0.98–1.15)	1.05 (0.96–1.15)
Pulse pressure	Adjusted	1.14 (1.05–1.23)†	1.06 (0.94–1.20)	1.22 (1.10–1.35)‡	1.16 (1.02–1.31)*	1.17 (1.03–1.33)*
	Fully adjusted	1.11 (1.02–1.21)*	1.03 (0.90–1.33)	1.19 (1.06–1.33)†	1.17 (1.02–1.33)*	1.18 (1.03–1.35)*

CHD+/CHD− indicate coronary heart disease including/excluding coronary bypass surgery and percutaneous transluminal coronary angioplasty. Hazard ratios (95% confidence interval) are for the risk associated with 10-mmHg increases in systolic blood pressure and pulse pressure or 5-mmHg increases in diastolic blood pressure. All hazard ratios were adjusted for cohort, sex, age, body mass index, serum cholesterol, smoking and drinking, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment. Hazard ratios for pulse pressure were additionally adjusted for mean arterial pressure. Models including both conventional as well as daytime blood pressure are labelled as fully adjusted. Significance of the hazard ratios: * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.0001$.

Fig. 2
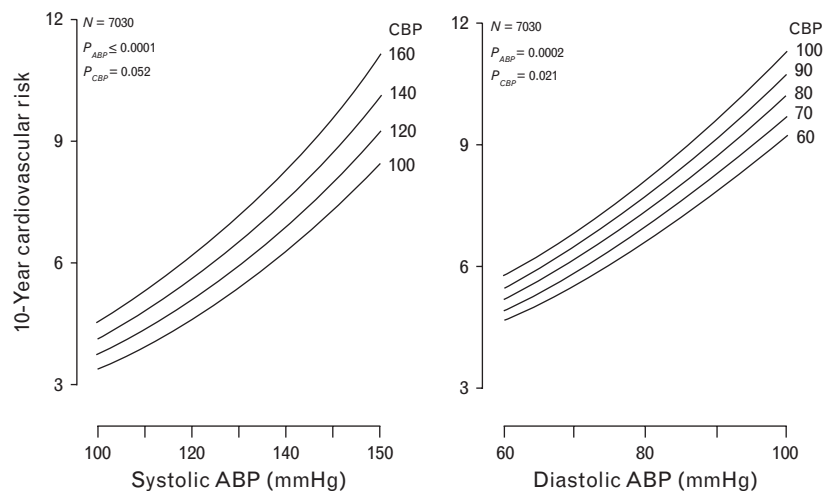
Absolute 10-year risk of a cardiovascular event in relation to the conventional and daytime ambulatory blood pressure. ABP, Ambulatory daytime blood pressure; CBP, conventional blood pressure. Risk estimates are for (a) systolic blood pressure and (b) diastolic blood pressure and were adjusted for cohort, sex, age, body mass index, serum cholesterol, smoking and drinking, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment. *P*-values are for the independent contributions of ABP and CBP to risk.

all cardiovascular events based on the lower definition ($\geq 130/80$ mmHg) of ambulatory hypertension (1.44 versus 1.77; $P = 0.036$; Fig. 3).

With all fatal and nonfatal cardiovascular events as outcome, we performed sensitivity analyses (Table 4), which we adjusted as before and which were based on the higher cut-off limit for ambulatory hypertension ($\geq 135/85$ mmHg). The results in women and men, at younger (< 60 years) and older (≥ 60 years) age, and in subjects taking or not taking antihypertensive drugs at baseline, were consistent (*P*-values for interaction ≥ 0.18) and confirmed the observations in all subjects (Table 3 and Fig. 2). Moreover, analyses from which we excluded subjects with previous cardiovascular disease or from which we excluded one cohort at a time were also confirmatory (Table 4). Thus, previous cardiovascular disease or one particular cohort did not drive our main results. Similarly, when we excluded incident cases of surgical and percutaneous coronary revascularization, our conclusions also remained unchanged (Table 4).

By censoring the adjusted Cox models for all cardiovascular events at 6, 9 and 12 years [10], we furthermore explored whether the risk of white-coat hypertension, compared to normotension, changed with longer follow-up. For the higher threshold of ambulatory hypertension ($\geq 135/85$ mmHg), the hazard ratios were 1.08 (95% CI = 0.61–1.88; $P = 0.79$), 1.20 (95% CI = 0.86–1.69; $P = 0.29$) and 1.30 (95% CI = 1.01–1.68; $P = 0.043$), when censoring at 6, 9 and 12 years. The corresponding hazard ratios for white-coat hypertension compared to sustained

hypertension were 0.64 (95% CI = 0.37–1.12; $P = 0.11$), 0.65 (95% CI = 0.46–0.91; $P = 0.013$) and 0.73 (95% CI = 0.57–0.94; $P = 0.014$), respectively. For the entire follow-up period (without censoring), the hazard ratio for white-coat hypertension compared to sustained hypertension was 0.68 (95% CI = 0.52–0.87; $P = 0.003$).

Discussion
Our current meta-analysis of individual subject data included over 7000 people randomly recruited from four populations and covered approximately 10 years of follow-up with more than 800 new cardiovascular endpoints. The key finding was that ambulatory blood pressure monitoring was by far superior to conventional blood pressure measurement in the prediction of cardiovascular events and risk stratification. These results rested primarily on continuous analyses unbiased by the application of arbitrary blood pressure thresholds. Furthermore, categorical analyses confirmed the superiority of ambulatory monitoring over conventional blood pressure and demonstrated that the risks conferred by white-coat hypertension and masked hypertension were intermediate to those associated with normotension and sustained hypertension. Finally, we noticed that, over a prolonged period of follow-up, the risk of white-coat hypertension remained significantly less than that of sustained hypertension.

In 1983, Perloff *et al.* [37] reported for the first time that the portion of the daytime ambulatory blood pressure, which was not already explained by systolic or diastolic clinic blood pressure, could discriminate high-risk from

Fig. 3
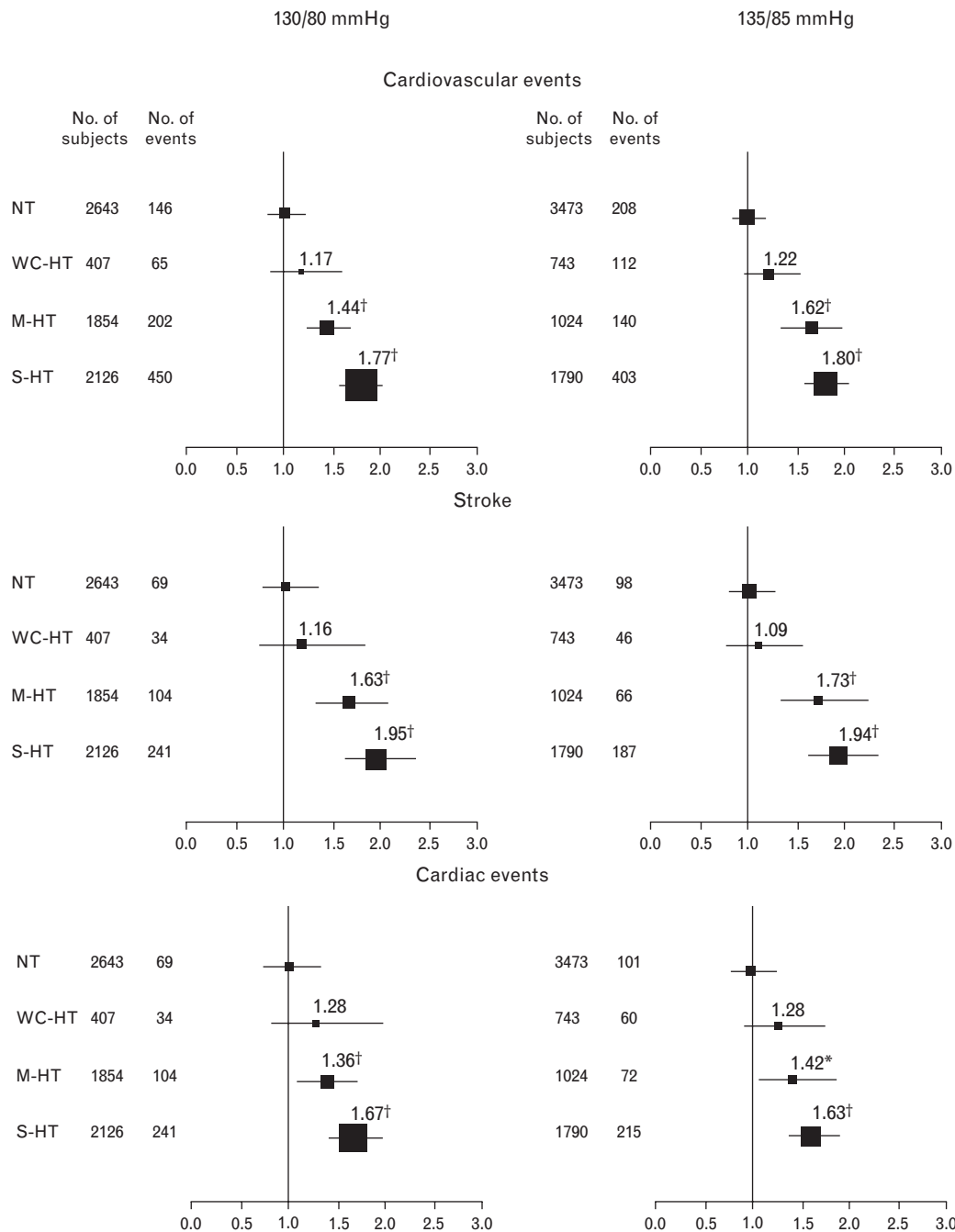
Hazard ratios for cardiovascular events according to the cross-classification of conventional and daytime ambulatory blood pressure. NT, normotension; WC-HT, white-coat hypertension; M-HT, masked hypertension; S-HT, sustained hypertension. NT is the reference group (*$P < 0.01$; †$P < 0.001$). The analyses were based on (a) lower ($\geq 130/80$ mmHg) or (b) higher ($\geq 135/85$ mmHg) cut-off limits for ambulatory hypertension and were adjusted for cohort, sex, age, body mass index, serum cholesterol, smoking and drinking, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment. Squares are proportional to the number of events per group. Horizontal lines denote the 95% confidence interval.

low-risk hypertensive patients. These results obtained by life-table analysis from semi-automated recordings in 1076 hypertensive patients were later confirmed by Cox regression in a subgroup of 761 patients, who were all untreated at baseline [38]. Subsequently, several studies replicated Perloff's seminal observations in hypertensive patients [3–7,39–42] or population cohorts [9,11–13]. On balance, these studies confirmed that ambulatory blood pressure monitoring provided better prognostic accuracy than conventional blood pressure

Table 4 Hazard ratios for cardiovascular event in subgroups with daytime blood pressure threshold set at 135/85 mmHg

Stratification	At risk (n)	Events (n)	White-coat HT	Masked HT	Sustained HT
Baseline characteristic					
Women	3148	211	0.90 (0.53−1.53)	1.85 (1.23−2.77)‡	1.74 (1.22−2.49)‡
Men	3882	652	1.37 (0.99−1.89)	1.53 (1.13−2.07)‡	1.83 (1.43−2.33)‡
< 60 years	3555	118	0.68 (0.28−1.67)	1.79 (1.16−2.76)‡	2.20 (1.48−3.29)‡
≥ 60 years	3475	745	1.27 (0.95−1.70)	1.57 (1.20−2.06)‡	1.74 (1.40−2.17)‡
Untreated	5510	489	1.25 (0.86−1.82)	1.58 (1.17−2.12)‡	1.91 (1.48−2.45)‡
Treated	1520	374	1.15 (0.76−1.75)	1.69 (1.12−2.57)†	1.65 (1.19−2.30)‡
No history of CVD	6437	659	1.19 (0.91−1.57)	1.72 (1.40−2.12)‡	1.90 (1.65−2.19)‡
History of CVD	593	204	1.23 (0.74−2.05)	1.34 (0.79−2.28)	1.55 (1.04−2.30)*
Excluded cohort					
Copenhagen	4735	595	1.26 (0.91−1.74)	1.64 (1.18−2.27)‡	1.87 (1.43−2.44)‡
Noorderkempen	4755	746	1.18 (0.86−1.63)	1.64 (1.26−2.13)‡	1.68 (1.34−2.12)‡
Ohasama	5711	712	1.27 (0.93−1.74)	1.56 (1.18−2.07)‡	1.82 (1.45−2.29)‡
Uppsala	5896	536	1.14 (0.82−1.58)	1.63 (1.24−2.12)‡	1.86 (1.47−2.35)‡
Incident CABG and PTCA					
Included	7030	863	1.23 (0.93−1.63)	1.67 (1.31−2.13)‡	1.83 (1.48−2.25)‡
Excluded	7030	843	1.23 (0.92−1.63)	1.68 (1.31−2.15)‡	1.83 (1.49−2.26)‡

HT, Hypertension; CVD, cardiovascular disease; CABG, coronary artery bypass surgery; PTCA, percutaneous transluminal coronary angioplasty. The hazard ratios (95% confidence interval) express the risk versus normotension and are adjusted, as appropriate, for cohort, sex, age, body mass index, serum cholesterol, smoking and drinking, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment. Significance of the hazard ratios: *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

measurement. However, many studies [3–8], although outcome-driven, were difficult to interpret because blood pressure was not analyzed as a continuous variable [3–7], because some studies did not include a normotensive control group [4,5,7], or because investigators did not subdivide the normotensive controls into those with normal or elevated ambulatory blood pressure [3,6,8].

The current literature illustrates that expert opinion over the prognostic significance of white-coat hypertension remains widely divided [3–12]. For example, an early study by Verdecchia *et al.* [3] included 1187 subjects with essential hypertension and 205 healthy normotensive control subjects, who all underwent baseline off-therapy 24-h ambulatory blood pressure monitoring. In the hypertensive patients, the prevalence of white-coat hypertension, defined as an average daytime blood pressure lower than 131/86 mmHg in women and 136/87 mmHg in men, was 19.2%. After adjustment for traditional markers of cardiovascular risk, the incidence of morbidity over a mean follow-up of 3.2 years did not differ between the normotensive subjects and the white-coat hypertensive group ($P = 0.83$) [3]. Among 2051 subjects recruited from a general Italian population [12], the PAMELA (Pressione Arteriose Monitorate e Loro Associazione) investigators found a significant sex and age-adjusted increasing trend in the risk of cardiovascular mortality from normotension over white-coat hypertension and masked hypertension, to sustained hypertension. They suggested that the risk associated with white-coat hypertension and masked hypertension is not prognostically innocent [12]. However, the adjusted risk conferred by white-coat and masked hypertension did not significantly differ from that associated with normotension [12]. In the PAMELA publication, the threshold for ambulatory hypertension was a 24-h blood pressure of 125 mmHg systolic or 79 mmHg diastolic [12]. A recently published

meta-analysis [10] included three cohorts of hypertensive patients and one population sample. After 6 years of follow-up, patients with white-coat hypertension experienced a substantial increase in the incidence of stroke so that, by the ninth year of follow-up, they had attained the same stroke rate as patients with sustained hypertension [10]. However, over the whole follow-up, the multivariate-adjusted hazard ratio for stroke for white-coat hypertension compared to normotension (1.14; 95% CI = 0.61–2.16; $P = 0.66$) was not significant [10]. In our current analyses, the risk of stroke associated with white-coat hypertension versus normotension did not increase with the duration of follow-up.

The counterpart of white-coat hypertension is masked hypertension, a disorder characterized by a normal conventional blood pressure confirmed on repeated clinic visits, and an elevated daytime ambulatory blood pressure [43]. Three studies [9,11,13] defined masked hypertension based on an awake or daytime blood pressure of at least 135 mmHg systolic or 85 mmHg diastolic. Although the adjusted hazard ratio associated with masked hypertension was not significant [11] or not formally compared with that of sustained hypertension [9,11,13], the three reports concluded that masked and sustained hypertension conferred similar cardiovascular risk. Based on an at least ten-fold larger number of composite cardiovascular endpoints, we found that, with proper adjustments applied, the risk of masked hypertension and sustained hypertension was of the same order of magnitude. The only exception was the lower risk of the composite cardiovascular endpoint in masked compared with sustained hypertension (hazard ratio = 1.44 versus 1.77), when we applied levels of 130 mmHg systolic and 80 mmHg diastolic as thresholds for the daytime ambulatory blood pressure. Fewer events and a lack of statistical power probably explain why at the lower

daytime thresholds the hazard ratios for stroke and cardiac events did not significantly differ between masked and sustained hypertension. In adolescents, masked hypertension is a forerunner of sustained hypertension and is also associated with increased left ventricular mass, and therefore warrants follow-up [44].

In the current meta-analysis, we pre-emptively opted not to combine hypertensive patients and subjects randomly recruited from the general population [14]. We considered that, in hypertensive patients, blood pressure-lowering treatment might be a confounder with too large an impact to adjust for [14]. Indeed, in the older patients with isolated systolic hypertension randomized to placebo ($n = 393$) in the Systolic Hypertension in Europe (Syst-Eur) trial [41], the 24-h, daytime (1000 h to 2000 h) and night-time (0000 h to 0600 h) systolic blood pressures all predicted the incidence of cardiovascular complications, even after further adjustment for conventional blood pressure. By contrast, in the active treatment group ($n = 415$), systolic blood pressure at entry did not significantly predict cardiovascular endpoints, regardless of the technique of blood pressure measurement [41]. In our current meta-analysis, only one-fifth of the subjects were on antihypertensive drug treatment at baseline. The sensitivity analysis in untreated subjects substantiated our overall conclusions and exemplified that antihypertensive drug treatment at baseline was not a major confounder. In addition, the generalizability of population-based results is obviously larger than those emerging from selected cohorts of hypertensive patients. Furthermore, in contrast to other studies [12,39] relating cardiovascular outcomes to conventional and ambulatory blood pressure measurements, we chose to analyze both fatal and nonfatal outcomes. The introduction of stroke units and the wide availability of invasive coronary care and thrombolysis recently reduced the case-fatality rate of most cardiovascular complications of hypertension. Not accounting for nonfatal events therefore limits the generalizability of some previous reports [12,33,39].

Current guidelines for the management of hypertension move away from the concept of blood pressure as an isolated risk factor and increasingly introduce the concept of the management of global cardiovascular risk [45]. From this point of view, our current findings have implications for clinical practice. The prevalence of white-coat hypertension, as evaluated by either ambulatory monitoring [11,12] or blood pressure self-measurement [46,47], varies from 11.5% [11] to 17.5% [12] in the general population, and from 13.3% [46] to 43.0% [47] among hypertensive patients. Hypertension and associated risk factors are age dependent. Any man normotensive at 50 years has a probability of over 90% to become hypertensive during the remainder of his lifetime [48]. The aging of populations is a worldwide phenomenon,

which is putting increasing demands on limited healthcare resources. Superior risk stratification is a way of objectively informing treatment decisions and rationally distributing medical care. A 6-month clinical trial has already proved that optimizing antihypertensive drug treatment on the basis of ambulatory monitoring is feasible and cost-effective [49]. Our present findings therefore suggest that ambulatory blood pressure monitoring should become routine in the risk stratification of patients with hypertension.

Our study must be interpreted within the context of its potential limitations. First, our present analysis rested only on four population-based cohorts and might not be representative for non-European or non-Japanese subjects. Second, anthropometric characteristics differed between cohorts. Third, most participants had their conventional blood pressure measured while seated at an examination centre. By contrast, the conventional blood pressure was measured in the supine position in Uppsala [13] and at home in Noorderkempen [18,34]. Due to regression to the mean, the most recent consensus [2] states that a diagnosis of white-coat hypertension requires measurement of a conventional blood pressure of 140 mmHg systolic or 90 mmHg diastolic or higher on at least three occasions. Furthermore, ambulatory blood pressure monitoring was not standardized in terms of device type and intervals between successive readings. On the other hand, using a single SAS macro ensured that daytime was always defined in the same fashion, using short fixed clock-time intervals [50], and that the time-weighted means were calculated identically across cohorts. The inclusion of cases of surgical and percutaneous coronary revascularization among the coronary and cardiovascular events might have limited the generalizability of the results because these procedures are subject to considerable regional variation in practice. However, our analyses only included 26 such cases and their exclusion confirmed our results for coronary heart disease, as well as all cardiovascular events. Finally, we did not adjust for antihypertensive drug treatment as a time-dependent covariate. However, the proportion of our patients on antihypertensive treatment at baseline was only 21.6%. During the course of follow-up, the proportion of treated patients, giving the poor rates of treatment in the general population [51] and the poor persistence of treatment in some clinical studies [52], must have been considerably lower than in cohorts of referred hypertensive patients, followed up at specialized hypertension centres [3–7,40] or started on antihypertensive treatment at enrolment [4,7,40].

In conclusion, ambulatory monitoring is superior to conventional blood pressure measurement in the prediction of cardiovascular events. Cardiovascular risk gradually increases from normotension over white-coat hypertension and masked hypertension to sustained hypertension.

Risk charts combining ambulatory and conventional blood pressure measurements along with established other risk factors are under construction and might improve risk stratification and the targeted administration of medical care.

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Acknowledgements

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