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CLINICAL RESEARCH
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Ambulatory blood pressure monitoring, European guideline targets, and cardiovascular outcomes: an individual patient data meta-analysis

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Abstract

Background and Aims Hypertension is the predominant modifiable cardiovascular risk factor. This cohort study assessed the association of risk with the percentage of time that the ambulatory blood pressure (ABP) is within the target range (PTTR) proposed by the 2024 European Society of Cardiology (ESC) guidelines for blood pressure (BP) management.

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¶ The International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) investigators are listed at the end of this article.

Methods In a person-level meta-analysis of 14 230 individuals enrolled in 14 population cohorts, systolic and diastolic ABPs were combined to assess 24-h, daytime, and nighttime PTTR with thresholds for non-elevated ABP set at <115/65, <120/70, and <110/60 mmHg, respectively.

Results Median 24-h PTTR was 18% (interquartile range 5–33) corresponding to 4.3 h (1.2–7.9). Over 10.9 years (median), deaths (N = 3117) and cardiovascular endpoints (N = 2265) decreased across increasing 24-h PTTR quartiles from 21.3 to 16.1 and from 20.3 to 11.3 events per 1000 person-years. The standardized multivariable-adjusted hazard ratios for 24-h PTTR were 0.57 (95% confidence interval 0.46–0.71) for mortality and 0.30 (0.23–0.39) for cardiovascular endpoints. Analyses of daytime and nighttime ABP, cardiovascular mortality, coronary endpoints and stroke, and subgroups produced confirmatory results. The 2024 ESC non-elevated 24-h PTTR, compared with the 2018 ESC/European Society of Hypertension non-hypertensive 24-h PTTR, shortened the interval required to reduce relative risk for adverse outcomes from 60% to 18% (14.4–4.3 h). Office BP, compared with 24-h PTTR, misclassified most participants with regard to BP control.

Conclusions Longer time that ABP is within the 2024 ESC target range is associated with reduced adverse outcomes; PTTR derived from ABP refines risk prediction and compared with office BP avoids misclassification of individuals with regard to BP control.

Structured Graphical Abstract

Key Question

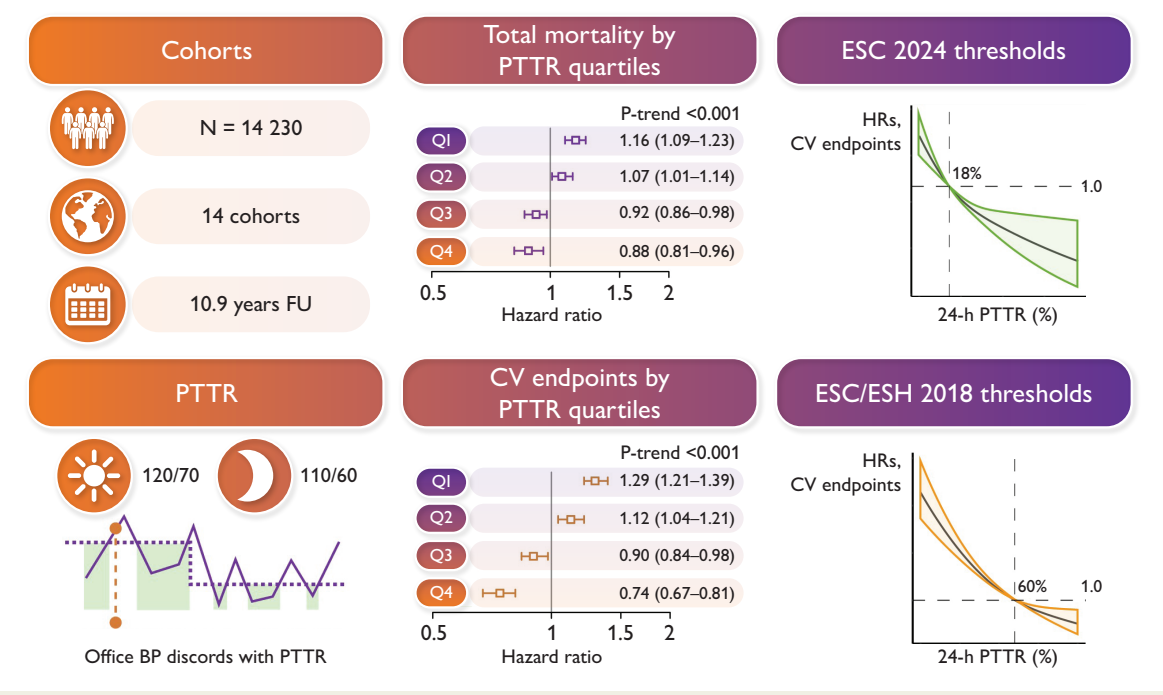
Does the association of adverse health outcomes with the percentage of time that the 24-h ambulatory blood pressure (24-h ABP) is within target range (24-h PTTR) hold true at the low non-elevated 24-h ABP level (<115/65 mmHg) set by the 2024 ESC Guidelines for blood pressure management?

Key Finding

In 14 230 participants followed up for 10.9 years (median), mortality and cardiovascular endpoints were inversely associated with 24-h PTTR. Contrasting the 2024 ESC non-elevated to the 2018 ESC/ESH non-hypertensive 24-h PTTR shortened the interval required to reduce relative risk for adverse outcomes from 60% to 18% (14.4 to 4.3 h). Office BP, compared to 24-h PTTR, misclassified most participants with regard to BP control.

Take Home Message

Longer time that ABP is within the 2024 ESC target range is associated with reduced adverse health outcomes. 24-h PTTR derived from ABP refines risk prediction and compared to office BP avoids misclassification of individuals with regard to BP control.



Keywords Ambulatory blood pressure • Guidelines • Morbidity • Mortality • Population science • Risk stratification

Introduction

The 2024 European Society of Cardiology (ESC) guidelines for the management of blood pressure (BP)[1] introduced a major evidence-based paradigm shift by recommending a target office BP (OBP) of 120–129/70–79 mmHg in most patients in need of treatment with the proviso that in vulnerable or intolerant patients, OBP should be reduced to the lowest level reasonably achievable. Furthermore, the ESC guidelines advice to use out-of-office BP measurement to ascertain that the OBP target is reached, either by ambulatory BP (ABP) or home BP monitoring.[1]

The percentage of time that BP is within the target range (PTTR) is a metric that recently emerged in the literature to assess BP control (see Supplementary material online, *Page S3*). However, of 22 relevant studies,[2–23] all but two community-based studies[19,23] included selected patients with hypertension, diabetes, or severe comorbidities. Most articles disregarded diastolic BP,[4–10,12–15,19–22] and if both systolic and diastolic BPs were reported, both were not combined to define BP control.[2,3,18] Only five studies analysed the out-of-office BP.[11,16,19,22,23] Nine studies presented similar data and are duplicate publications.[2–6,9,10,15,18] In studies focusing on ABP monitoring, thresholds were often not congruent with contemporary guidelines and results for daytime or nighttime BP were not presented.[11,16,22,23] The International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO) consists of 14 longitudinal population studies.[24,25] The objectives of the current person-level meta-analysis were as follows: first, to investigate how at the low 2024 ESC BP thresholds,[1] mortality and cardiovascular endpoints are related to ABP-based PTTR for all periods of the day while simultaneously accounting for both systolic and diastolic BPs; and second, to compare the risks associated with the non-elevated ABP (ESC 2024)[1] and with the non-hypertensive ABP, as defined in most international guidelines,[26–29] including the 2018 ESC/European Society of Hypertension (ESH) recommendations.[29] According to the 2024 ESC terminology,[1] the non-hypertensive ABP includes both the non-elevated and elevated ABPs.

Methods

Study participants

All studies received ethical approval and adhered to the principles of the Declaration of Helsinki. Participants gave written informed consent. Previous publications describe the IDACO database in detail.[24,25] Population studies qualified for inclusion, if information on OBP and ABP and cardiovascular risk factors was available at baseline and collected within a short time interval usually not exceeding 2 weeks, and if follow-up included both fatal and non-fatal outcomes. Of the 17 003 people included in the database, 2773 were excluded, because they were younger than 18 years ($N = 319$) without any adverse health outcome or because their ABP recording included fewer than eight daytime and four nighttime readings ($N = 2454$).[30] Thus, the number of individuals statistically analysed was 14 230. The Supplementary material online, *Pages S3* and *S4* and *Table S1* provide detailed information on the population sampling methods, timelines, and country of recruitment.

Blood pressure and other measurements

At baseline, nurses or physicians measured OBP with a standard mercury sphygmomanometer or with validated auscultatory or oscillometric devices. Hypertension was an OBP of ≥140 mmHg systolic or ≥90 mmHg diastolic[1] or use of antihypertensive drugs. For ABP monitoring (see Supplementary data online, *Table S2*), portable monitors were programmed to obtain BP readings at 30–min intervals during the whole day, at intervals of 15–30 min during daytime, and at intervals ranging from 20 to 60 min during nighttime. For descriptive purposes (*Table 1*), in line with previous IDACO publications,[24,25] daytime ranged from 10:00 to 20:00 h in Europeans and South Americans and from 8:00 to 18:00 h in Asians. The corresponding nighttime intervals went from 24:00 to 6:00 h and from 22:00 to 4:00 h, respectively. These fixed short clock-time intervals exclude the transition periods in the morning and evening when the ABP changes rapidly and approximate within 1–2 mmHg to the awake and asleep periods of the day as determined by the diary method.[31] The expanded methods in Supplementary material online, *Pages S4* and *S5* describe how OBP and ABP were recorded in each cohort and how questionnaire and biochemical data were collected.

Linear interpolation between any two consecutive BP readings was applied to compute PTTR. In contrast to the approach expressing the time-in-target range as the percentage of ABP readings, PTTR considers the actual BP levels and the interval between any two consecutive measured BP readings (see Supplementary data online, *Figure S1*). The weight of the first ABP reading was arbitrarily set at 5 min, assuming that in the clinical setting 5-min elapse before the first test reading.[32]

Ascertainment of endpoints

Vital status and the incidence of fatal and non-fatal endpoints were ascertained from the appropriate sources in each country.[24,25] All endpoints were prespecified and coded according to the International Classification of Diseases (see Supplementary materials online, *Pages S5* and *S6*). The co-primary endpoints were total mortality and a composite cardiovascular endpoint consisting of cardiovascular mortality combined with non-fatal coronary endpoint, heart failure, and stroke. Secondary endpoints included cardiovascular mortality, coronary endpoint, and stroke. All endpoints were validated against hospital files or medical records held by primary care physicians or specialists. In all outcome analyses, only the first event within each category was considered.

Statistical analysis

Full details of the statistical methods and associated references are presented in Supplementary material online, *Pages S6–S9*. Age of the IDACO study population ranged from young adults to the oldest old. Given the age-related change in the risk associated with systolic and diastolic ABPs,[33] both BP components were considered simultaneously and summarized into a single PTTR variable, using <115/65, <120/70, and <110/60 mmHg for the 24–h, daytime, and nighttime ABP as thresholds differentiating non-elevated from elevated BP and hypertension.[1] In analyses related to the second aim of the study, <130/80, <135/85, and <120/70 mmHg, i.e. thresholds differentiating non-hypertensive from hypertensive ABP, were also examined. These 2018 ESC/ESH thresholds[29] include both non-elevated and elevated ABPs. The two sets of thresholds were compared by restricted cubic splines. To avoid omission of the morning and evening ABP readings, the 24–h PTTR was derived with daytime set from 7 to 22 h in Europeans and South Americans and from 5 to 20 h in Asians and nighttime from 22 to 7 h and from 20 to 5 h, respectively (see Supplementary data online, *Figure S1*).

Absolute risk was assessed from the cohort–sex–age-specific (<40, 40–60, and >60 years) incidence rates of endpoints standardized by the direct method and relative risk from hazard ratios (HRs) obtained by proportional hazard regression. Multivariable-adjusted HRs account for cohort (random effect), sex, and baseline characteristics including age, body mass index, smoking (0, 1) and drinking (0, 1), the total-to-HDL serum cholesterol ratio, antihypertensive drug treatment, diabetes, and history of cardiovascular disease. The number of interpolated values for missing covariables is given by cohort in Supplementary data online, *Table S3*. Given that PTTR applies to both systolic and diastolic BPs, models with extended adjustment also included mean arterial pressure (MAP), which is derived from both systolic and diastolic BP. Because of the high correlation between PTTR and MAP, the covariable introduced in Cox models was the residual of MAP (R_MAP) regressed on PTTR (see Supplementary data online, *Figure S2*). In continuous analyses, HRs express the relative risk per 1 SD PTTR increment. In a further categorical analysis, Cox models were constructed by the

Table 1 Baseline characteristics of participants by quartiles of time with non-elevated 24–h ambulatory blood pressure

Characteristic	All participants	Quartiles of time with non-elevated readings				
		Q1	Q2	Q3	Q4	*P*-value
Quartile limits						
Expressed as per cent	…	0–5	5–18	18–33	33–100	…
Expressed as number of hours	…	0–1.2	1.2–4.3	4.3–7.9	7.9–24	…
No. in group	14 230	3558	3557	3558	3557	…
Women, *N* (%)	7072 (49.7)	1483 (41.7)	1455 (40.9)	1733 (48.7)***	2401 (67.5)***	<0.001
Region of enrolment						0.92
Asia, *N* (%)	2387 (16.8)	620 (17.4)	541 (15.2)***	567 (15.9)	659 (18.5)***	
Europe, *N* (%)	9636 (67.7)	2276 (64.0)	2573 (72.3)***	2512 (70.6)	2275 (64.0)***	
South America, *N* (%)	2207 (15.5)	662 (18.6)	443 (12.5)***	479 (13.5)	623 (17.5)***	
Clinical measurements						
Age, median (IQR), y	60.3 (43.5–70.7)	66.0 (53.4–71.5)	62.1 (50.3–71.0)***	56.6 (41.4–70.0)***	50.3 (33.8–66.4)***	<0.001
Age, mean, y	56.4 ± 16.2	62.2 ± 12.6	59.2 ± 14.4***	54.2 ± 16.7***	49.8 ± 17.8***	<0.001
Body height, cm	164.2 ± 11.1	164.0 ± 10.8	165.0 ± 11.0***	165.0 ± 11.3	162.5 ± 11.0***	<0.001
Body weight, kg	70.3 ± 15.5	72.8 ± 16.1	72.9 ± 15.7	70.4 ± 14.8***	64.8 ± 13.7***	<0.001
Body mass index, kg/m^2	25.8 ± 4.5	26.9 ± 4.7	26.5 ± 4.4**	25.6 ± 4.2***	24.3 ± 4.1***	<0.001
BP and heart rate						
Office systolic BP, mmHg	133.1 ± 22.5	149.2 ± 23.9	136.0 ± 19.2***	127.9 ± 17.6***	119.2 ± 17.0***	<0.001
Office diastolic BP, mmHg	79.8 ± 11.9	87.7 ± 12.1	82.0 ± 10.3***	77.7 ± 9.6***	71.9 ± 9.1***	<0.001
Office heart rate, b.p.m.	70.5 ± 11.4	71.1 ± 11.7	69.9 ± 11.5***	70.2 ± 11.2	70.7 ± 11.2	0.29
24–h systolic BP, mmHg	123.6 ± 14.1	139.2 ± 13.0	126.4 ± 8.3***	119.0 ± 7.0***	109.8 ± 6.6***	<0.001
24–h diastolic BP, mmHg	73.5 ± 8.5	82.4 ± 8.1	75.7 ± 5.1***	71.2 ± 4.0***	64.7 ± 4.1***	<0.001
24–h MAP, mmHg	93.4 ± 10.3	105.2 ± 8.7	96.0 ± 5.3***	90.0 ± 4.4***	82.3 ± 4.6***	<0.001
24–h heart rate, b.p.m.	71.4 ± 9.3	71.8 ± 9.6	71.1 ± 9.6**	71.6 ± 9.2*	71.1 ± 8.9*	0.011
Risk factors						
Body mass index ≥ 30 kg/m^2, No. (%)	2242 (15.8)	772 (21.7)	685 (19.3)*	454 (12.8)***	331 (9.3)***	<0.001
Serum cholesterol ≥ 4.9 mmol/L, *N* (%)	8840 (62.1)	2305 (64.8)	2337 (65.7)	2200 (61.8)***	1998 (56.1)***	<0.001
Current smoking, *N* (%)	3175 (22.3)	707 (19.9)	795 (22.3)*	891 (25.0)**	782 (22.0)**	0.004
Use of alcoholic beverages, *N* (%)	6051 (42.5)	1657 (46.6)	1589 (44.7)	1565 (44.0)	1240 (34.8)***	<0.001

Continued

Table 1 *Continued*

Characteristic	All participants	Quartiles of time with non-elevated readings				
		Q1	Q2	Q3	Q4	*P*-value
Office hypertension, *N* (%)	6913 (48.6)	2757 (77.5)	2032 (57.2)***	1313 (36.9)***	811 (22.8)***	<0.001
Diabetes, *N* (%)	1350 (9.5)	478 (14.4)	400 (11.3)**	257 (7.2)***	215 (6.1)	<0.001
Previous cardiovascular disease, *N* (%)	1296 (9.10)	468 (13.2)	327 (9.2)**	253 (7.1)***	248 (7.0)	<0.001
Biochemical measurements						
Blood glucose, mmol/L	5.30 ± 1.45	5.52 ± 1.78	5.37 ± 1.41***	5.21 ± 1.27***	5.05 ± 1.16***	<0.001
Total serum cholesterol, mmol/L	5.43 ± 1.12	5.50 ± 1.15	5.52 ± 1.16	5.44 ± 1.17**	5.28 ± 1.13***	<0.001
HDL serum cholesterol, mmol/L	1.39 ± 0.37	1.36 ± 0.40	1.36 ± 0.41	1.38 ± 0.39	1.43 ± 0.39***	<0.001
Total/HDL serum cholesterol ratio	4.17 ± 1.81	4.27 ± 1.38	4.34 ± 2.81	4.17 ± 1.33***	3.89 ± 1.19***	<0.001
Use of prescription drugs						
Antihypertensive drugs, *N* (%)	3775 (26.6)	1345 (38.4)	1077 (30.3)***	752 (21.2)***	582 (16.4)***	<0.001
Antidiabetic agents, *N* (%)	689 (5.3)	269 (8.0)	228 (6.9)	114 (3.6)***	78 (2.5)*	<0.001

Values are mean ± SD, median (IQR, or number or participants (%). The non-elevated 24–h ABP is <115 mmHg systolic and <65 mmHg diastolic. Office hypertension is a BP of ≥140 mmHg systolic or ≥90 mmHg diastolic or use of antihypertensive medications. Diabetes is the use of antidiabetic drugs, fasting blood glucose of ≥7.0 mmol/L, random blood glucose of ≥11.1 mmol/L, a self-reported diagnosis, or diabetes documented in practice or hospital records. The use of alcohol is the habitual consumption of alcoholic beverages daily or weekly. An ellipsis indicates not applicable. The *P*–value denotes the significance of trend across quartiles. Significance of the difference with the left adjacent quartile: *$P \leq .05$; **$P \leq .01$; and ***$P \leq .001$. BP, blood pressure; IQR, interquartile range; MAP, mean arterial pressure.

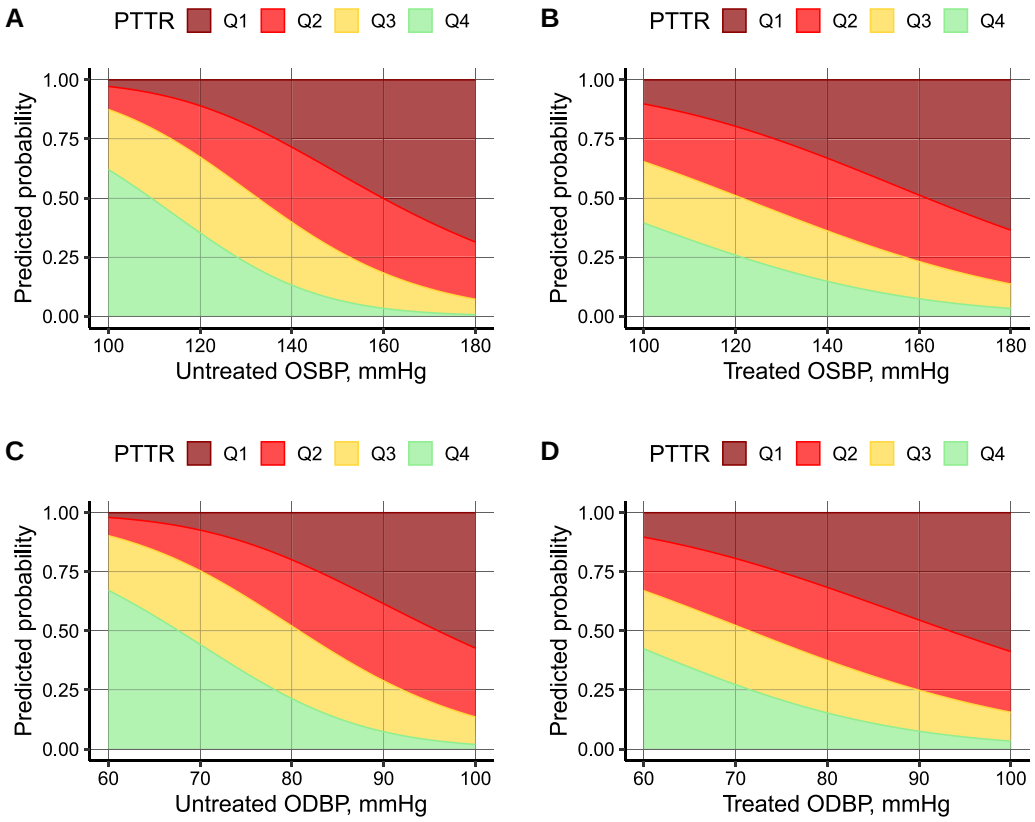


Figure 1 Relation of office blood pressure with the percentage of time that the 24–h ambulatory blood pressure is within target range according to the 2024 European Society of Cardiology guidelines. The probability that individuals belong to one of four decreasing quartiles of 24–h percentage of time with non-elevated ambulatory blood pressure is assessed by multinomial logistic regression analysis over a wide range of systolic (*A*, *B*) and diastolic (*C*, *D*) office blood pressure in untreated (*A*, *C*) and treated (*B*, *D*) study participants. Q1 reflects the worst control of the 24–h ambulatory blood pressure and Q4 the best control. The analysis includes the baseline blood pressure data from 14 230 study participants, of whom 3775 were taking antihypertensive drugs. The non-elevated 24–h ambulatory blood pressure is <115 mmHg systolic and <65 mmHg diastolic. For quartile limits, see *Table 1*. ODBP, diastolic office blood pressure; OSBP, systolic office blood pressure; PTTR, percentage of time that the 24-h blood pressure is within the target range

deviation from mean coding, which compares the risk in each PTTR quartile to the average risk in the whole study population and allows to generate 95% confidence intervals (CIs) for each quartile. To visualize the contribution of PTTR and R_MAP to risk, multivariable-adjusted heat maps were constructed. Performance of PTTR and R_MAP in risk stratification was assessed using nested Cox models and the log-likelihood test, the *C*-index, the integrated discrimination (IDI) and net reclassification (NRI) improvement indexes. In subgroup analyses, the results for the co-primary endpoints were dichotomized by sex, median age, antihypertensive treatment status, or history of cardiovascular disease. A sensitivity analysis excluded one cohort at a time to address the issue of whether any cohort unduly had a disproportionate influence on the HRs. Finally, to assess the relation between the level of OBP and ABP, both measured at baseline, the probability that individuals would fall within one of four decreasing quartiles of PTTR based on the 2024 ESC guidelines[1] was assessed by multinomial logistic regression analysis over a wide range of systolic and diastolic OBP in untreated and treated study participants.

Results

Baseline characteristics of participants

The study population included 7072 women (49.7%), 9636 Europeans (67.7%), 2387 Asians (16.8%), and 2207 South Americans (15.5%). Median age at enrolment was 60.3 years (*Table 1*). In terms of risk factors, 3175 (22.3%) participants were smokers, 6051 (42.5%) reported habitual alcohol intake, 1350 (9.5%) had diabetes, 1296 (9.1%) had a history of cardiovascular disease, and 6913 (48.6%) had office hypertension, of whom 3775 (26.6%) were on antihypertensive drug treatment. Across increasing quartiles of 24–h PTTR (*Table 1*), risk factors decreased in magnitude or prevalence ($P \leq .004$).

The median number (5th–95th percentile interval) of ABP readings was 57 (35–81), 29 (15–41), and 12 (6–13) over 24 h and during daytime and nighttime, respectively (see Supplementary data online, *Table S2*). The correlation between indexes derived from the ABP recordings was high ($-0.815 \leq r \leq 0.921$; $P < .001$), but R_MAP was uncorrelated from PTTR at all time intervals ($r < 0.001$; $P > .99$; Supplementary data online, *Table S4*).

Figure 1 shows the relation at baseline in all participants between systolic and diastolic OBP and 24–h PTTR defined as a 24–h ABP of ≤115 mmHg systolic and ≤65 mmHg diastolic. In 10 455 untreated individuals, the predicted probabilities of belonging to the fourth 24–h PTTR quartile (better 24–h BP control) for OBPs of 120 mmHg systolic or 70 mmHg diastolic were 0.35 (95% CI 0.33–0.37) and 0.44 (0.41–0.47). The probabilities corresponding to untreated OBPs of

Table 2 Cohort–sex–age-specific incidence of endpoints by quartiles of time with non-elevated 24-h ambulatory blood pressure

	Quartiles of time with non-elevated readings				
Endpoints	**Q1**	**Q2**	**Q3**	**Q4**	***P*-value**
Number of participants	3558	3557	3558	3557	
Primary endpoints					
Total mortality					
Number of deaths	1034	842	700	541	
Rate (per 1000 person-years)	21.3 (19.9–22.7)	17.6 (16.3–19.0)	14.8 (13.6–16.2)	16.1 (14.3–18.0)	<0.001
Cardiovascular endpoints					
Number of endpoints	857	604	471	333	
Rate (per 1000 person-years)	20.3 (19.0–21.9)	14.7 (13.5–16.0)	11.7 (10.5–13.0)	11.3 (9.80–12.9)	<0.001
Secondary endpoints					
Cardiovascular mortality					
Number of deaths	457	286	227	160	
Rate (per 1000 person-years)	9.10 (8.26–10.1)	6.13 (5.39–7.03)	4.59 (3.95–5.40)	4.52 (3.69–5.55)	<0.001
Coronary endpoints					
Number of endpoints	374	244	189	132	
Rate (per 1000 person-years)	7.50 (6.72–8.44)	5.46 (4.76–6.33)	4.41 (3.73–5.27)	4.19 (3.37–5.21)	<0.001
Stroke					
Number of strokes	344	270	190	134	
Rate (per 1000 person-years)	8.12 (7.23–9.18)	6.22 (5.45–7.15)	4.38 (3.69–5.25)	3.86 (3.09–4.82)	<0.001

The analysis includes 14 230 study participants. The non-elevated 24–h ABP is <115 mmHg systolic and <65 mmHg diastolic. For quartile limits, see *Table 1*. Rates are given with 95% CI. The *P*-value is for trend across quartiles.

140 or 90 mmHg were 0.13 (0.12–0.14) and 0.07 (0.06–0.08). Among 3775 treated patients, the probabilities were 0.26 (0.23–0.29) and 0.27 (0.24–0.30) for OBPs of 120 mmHg systolic or 70 mmHg diastolic and 0.15 (0.13–0.16) and 0.08 (0.06–0.09) for OBPs of 140 mmHg systolic or 90 mmHg diastolic.

Primary endpoints

Absolute risk

Median follow-up of the whole study population was 10.9 years (5th–95th percentile interval 3.6–25.8) and across cohorts (see Supplementary data online, *Table S1*) ranged from 4.0 years (3.5–7.6) to 24.5 years (8.6–27.8 years). Over 176 021 person-years of follow-up (see Supplementary data online, *Table S5*), 3117 participants died (17.7 per 1000 person-years) and 2265 experienced the co-primary cardiovascular endpoint (12.9 per 1000 person-years). Across increasing quartiles of 24–h PTTR (*Table 2*), mortality declined from 21.3 (95% CI 19.9–22.7) to 16.1 (14.3–18.0) deaths per 1000 person-years and the incidence of the co-primary cardiovascular endpoint from 20.3 (19.0–21.9) to 11.3 (9.80–12.9) endpoints per 1000 person-years ($P < .001$). With cumulative adjustment for cohort, sex, and age, the incidence of co-primary endpoints increased with longer follow-up, but in line with the data in *Table 2* significantly ($P < .001$) declined from the lowest to the highest 24–h PTTR category (see Supplementary data online, *Figure S3*).

Relative risk

In all outcome analyses that follow, the proportional hazard assumption was met ($P > .10$). In unadjusted Cox models and models with basic and extended adjustment, which related total mortality or the co-primary cardiovascular endpoint to PTTR analysed as a continuous variable (*Table 3*), HRs were smaller than unity, indicating lower risk with higher PTTR. These findings were consistent for PTTR assessed over 24 h, daytime, and nighttime, except for mortality in relation to daytime PTTR in adjusted analyses. With full adjustments applied, HRs expressing risk per 1 SD increment in 24–h PTTR were 0.57 (95% CI 0.46–0.71) for total mortality and 0.30 (0.23–0.39) for the co-primary cardiovascular endpoint. For the nighttime PTTR, the corresponding HRs were 0.68 (0.60–0.78) and 0.50 (0.43–0.59), respectively, which were intermediate between the 24-h and the daytime HRs. A further categorical analysis assessing the relative risk across 24–h PTTR quartiles compared with the average risk in the whole population (see Supplementary data online, *Table S6*) produced confirmatory results for both primary endpoints with a significant gradient ($P < .001$) from HRs greater than unity in the lowest PTTR category to HRs lower than unity in the highest PTTR quartile.

Model performance

Heatmaps for the 24-h ABP (see Supplementary data online, *Figure S4*) demonstrated that along the vertical axis, the 10–year risks of the

Table 3 Continuous associations of endpoints with percentage of time with non-elevated ambulatory blood pressure

Endpoints	Unadjusted		Basic adjustment		Extended adjustment	
Period of day	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Primary endpoints						
Total mortality						
24-h	0.23 (0.18–0.28)	<0.001	0.57 (0.46–0.71)	<0.001	0.57 (0.46–0.71)	<0.001
Daytime	0.61 (0.51–0.73)	<0.001	0.87 (0.72–1.05)	0.15	0.91 (0.76–1.09)	0.30
Nighttime	0.41 (0.36–0.47)	<0.001	0.69 (0.60–0.78)	<0.001	0.68 (0.60–0.78)	<0.001
Cardiovascular endpoints						
24-h	0.10 (0.08–0.14)	<0.001	0.28 (0.21–0.37)	<0.001	0.30 (0.23–0.39)	<0.001
Daytime	0.35 (0.28–0.44)	<0.001	0.52 (0.41–0.66)	<0.001	0.59 (0.47–0.74)	<0.001
Nighttime	0.30 (0.25–0.35)	<0.001	0.50 (0.43–0.59)	<0.001	0.50 (0.43–0.59)	<0.001
Secondary endpoints						
Cardiovascular mortality						
24-h	0.10 (0.06–0.14)	<0.001	0.28 (0.19–0.41)	<0.001	0.30 (0.20–0.43)	<0.001
Daytime	0.37 (0.27–0.52)	<0.001	0.53 (0.38–0.74)	<0.001	0.59 (0.43–0.82)	<0.001
Nighttime	0.29 (0.23–0.36)	<0.001	0.52 (0.41–0.65)	<0.001	0.51 (0.41–0.64)	<0.001
Coronary endpoints						
24-h	0.10 (0.06–0.15)	<0.001	0.29 (0.19–0.45)	<0.001	0.30 (0.20–0.46)	<0.001
Daytime	0.30 (0.20–0.44)	<0.001	0.50 (0.34–0.73)	<0.001	0.53 (0.36–0.77)	<0.001
Nighttime	0.32 (0.25–0.41)	<0.001	0.58 (0.45–0.74)	<0.001	0.57 (0.45–0.73)	<0.001
Stroke						
24-h	0.08 (0.05–0.12)	<0.001	0.19 (0.13–0.30)	<0.001	0.22 (0.15–0.34)	<0.001
Daytime	0.31 (0.21–0.44)	<0.001	0.41 (0.28–0.59)	<0.001	0.48 (0.34–0.69)	<0.001
Nighttime	0.24 (0.19–0.31)	<0.001	0.39 (0.30–0.50)	<0.001	0.39 (0.30–0.50)	<0.001

The non-elevated ambulatory systolic/diastolic blood pressure is <115/65 mmHg over 24 h, <120/70 mmHg for daytime, and <110/60 mmHg for nighttime. Unadjusted models account for cohort (random effect). The basic adjustment accounts for sex, age, body mass index, smoking and drinking, the total-to-HDL serum cholesterol ratio, antihypertensive drug treatment, diabetes, and history of cardiovascular disease. The extended adjustment also includes the residual of mean arterial pressure regressed on percentage of time that the 24-h blood pressure is within the target range. Hazard ratios express the relative risk per 1 SD increment in percentage of time that the 24-h blood pressure is within the target range. CI, confidence interval.

co-primary endpoints decreased with greater 24–h PTTR ($P < .001$), while along the horizontal axis, risks increased with 24–h R_MAP ($P < .001$), which to facilitate clinical implication was replaced by the corresponding 24–h MAP ($P < .001$).

For the co-primary endpoints, adding 24–h R_MAP, 24–h PTTR, or both to the base model including all other covariables refined the models as evidenced by the 2 log-likelihood statistic, the *C*–index, and both NRI and IDI (*Table 4*). If both 24–h R_MAP and 24–h PTTR were added to the base model, NRI was 11.8% (95% CI 8.59–16.2) for total mortality and 18.3% (14.4–22.9) for the co-primary cardiovascular endpoint and IDI 0.42% (0.17–0.73) and 1.25% (0.72–1.82), respectively. *Figure 2* shows that the area under the curve (AUC) for total mortality and the co-primary cardiovascular endpoint increases with follow-up time, because of the accrual of deaths and cardiovascular endpoints. Time dependency of the AUC is illustrated for three models: (i) the base model including all covariables; (ii) the base model extended by 24–h R_MAP; and (iii) the base model extended by 24–h R_MAP and 24–h PTTR. The full model including covariables, 24–h R_MAP, and 24–h PTTR resulted in a significantly greater AUC compared with both other models ($P < .001$), albeit that the AUC increments were small as reflected by NRI (*Table 4*).

Subgroup and sensitivity analyses

Compared with the data in *Table 3*, HRs for the co-primary endpoints in relation to the 24–h PTTR were generally consistent across subgroups stratified by age, sex, use of antihypertensive drugs, or history of cardiovascular disease (see Supplementary data online, *Figure S5*). In models with extended adjustment, the HRs were directionally similar in all subgroups, but for both co-primary endpoints, HRs were significantly smaller, indicating lower relative risk, in younger than older individuals and in untreated compared with treated participants ($P \leq .005$). The risk of death was also smaller in women than men ($P = .031$). None of the cohorts had a disproportionate influence on the HRs (see Supplementary data online, *Table S7*).

Table 4 Model refinement in associating the co-primary endpoints with 24-h blood pressure indexes

Endpoint models	−2 Log-likelihood	C-index	NRI (95% CI) (%)	IDI (95% CI) (%)
Total mortality				
Base model	49577.05	0.8180	…	…
+ PTTR	49551.11**	0.8185**	15.2 (9.95–18.7)**	0.11 (0.00–0.33)*
+ MAP	49522.31**	0.8195**	12.8 (9.31–16.4)**	0.39 (0.18–0.70)**
+ R_MAP	49547.34**	0.8192**	5.35 (0.60–8.97)*	0.32 (0.09–0.53)**
+ PTTR & R_MAP	49521.35**	0.8196**	11.8 (8.59–16.2)**	0.42 (0.17–0.73)**
Cardiovascular endpoints				
Base model	37222.89	0.8131	…	…
+ PTTR	37134.86**	0.8165**	19.5 (16.2–23.8)**	0.62 (0.31–1.09)**
+ MAP	37065.38**	0.8196**	18.4 (14.4–22.31)**	1.24 (0.72–1.80)**
+ R_MAP	37147.81**	0.8167**	6.97 (1.42–10.7)*	0.69 (0.27–1.01)**
+ PTTR & R_MAP	37065.37**	0.8196**	18.3 (14.4–22.9)**	1.25 (0.72–1.82)**

The base model included cohort, sex, age, body mass index, smoking and drinking, the total-to-HDL serum cholesterol ratio, antihypertensive drug treatment, diabetes, and history of cardiovascular disease. The non-elevated 24–h ABP is <115 mmHg systolic and <65 mmHg diastolic. An ellipsis indicates not applicable. Significance of the difference with the base model: *$P \leq .05$ and **$P \leq 0.001$.
CI, confidence interval; IDI, integrated discrimination improvement (95% CI); MAP, 24-h mean arterial pressure; R_MAP, residual of MAP regressed on PTTR; NRI, net reclassification improvement (95% CI); PTTR, percentage of time that the 24-h blood pressure is within the target range.

Comparison of 24–h ambulatory blood pressure thresholds

Using 24–h ABP recordings, restricted cubic spline models were constructed for two definitions of PTTR: (i) non-elevated ABP (<115/65 mmHg as per the 2024 ESC Guidelines) and (ii) non-hypertensive ABP, which included the elevated ABP (<130/80 mmHg as per the 2018 ESC/ESH guidelines). The overlayed 24–h PTTR distributions according to the two definitions are shown in Supplementary data online, *Figure S6*. The multivariable-adjusted models showed an inverse association of total mortality and the co-primary cardiovascular endpoint with both definitions of 24–h PTTR. However, removing the elevated 24-h ABP from the non-hypertensive 24–h ABP reduced the 24–h PTTR required to attain reduced relative risk for the co-primary endpoints from ∼60% to ∼18% (*Figure 3*). These findings were consistent in 10 455 participants untreated at baseline (see Supplementary data online, *Figure S7*) and 3775 participants on antihypertensive drug treatment (see Supplementary data online, *Figure S8*).

Secondary endpoints

Over follow-up, 1130 cardiovascular deaths (6.4 per 1000 person-years), 939 coronary endpoints (5.3 per 1000 person-years), and 938 strokes (5.3 per 1000 person-years) occurred (see Supplementary data online, *Table S5*). Across increasing quartiles of 24–h PTTR, rates of the secondary endpoints decreased (*Table 2*). In unadjusted Cox models and models with basic and extended adjustment, which related secondary endpoints to PTTR analysed as continuous variable over 24 h, daytime, and nighttime (*Table 3*), HRs were consistently smaller than unity, indicating lower risk with higher PTTR. Similarly, heatmaps confirmed that along the vertical axis, the risk of secondary endpoints decreased with greater 24–h PTTR and increased with higher 24–h MAP (see Supplementary data online, *Figure S4*). Considering the three secondary endpoints, in line with the co-primary endpoints (*Table 4; Figure 2*), the full model including covariables, 24–h R_MAP, and 24–h PTTR refined model performance (see Supplementary data online, *Table S8*) and resulted in a significantly greater AUC compared with the base model including or not 24–h R_MAP (see Supplementary data online, *Figure S9*).

Multivariable spline models showed that removing elevated from non-hypertensive 24–h ABP shifted the time required to attain median risk for all endpoints from ∼60% to ∼18% while maintaining the non-linear and linear pattern for all-cause mortality and other endpoints, respectively (see Supplementary data online, *Figure S10*).

Discussion

Numerous studies reported that total and cause-specific mortality[25,34,35] and fatal combined with non-fatal cardiovascular complications[25,34] are associated with the ABP level and that these associations were stronger for ABP[25,34,35] and home BP[36] than for OBP. Moving the field forward, this person-level meta-analysis investigated whether at the substantially lower ABP thresholds, proposed by the 2024 ESC guidelines,[1] the incidence of adverse health outcomes remains associated with the ABP level. The PTTR was the metric used, but in contrast to previous studies,[2–23] PTTR included both systolic and diastolic ABPs in a single summary variable and was examined for the 24–h, daytime, and nighttime ABP in a large unbiased population cohort. The key findings can be summarized as follows. First, in continuous and categorical analyses of the co-primary and secondary endpoints, absolute and relative risk decreased with higher 24–h, daytime, and nighttime PTTR. Second, the inverse association of adverse health outcomes with PTTR was robust in multivariable adjusted models and subgroup and sensitivity analyses. Third, with adjustments applied for cohort, multiple risk factors, and 24–h MAP, PTTR improved models

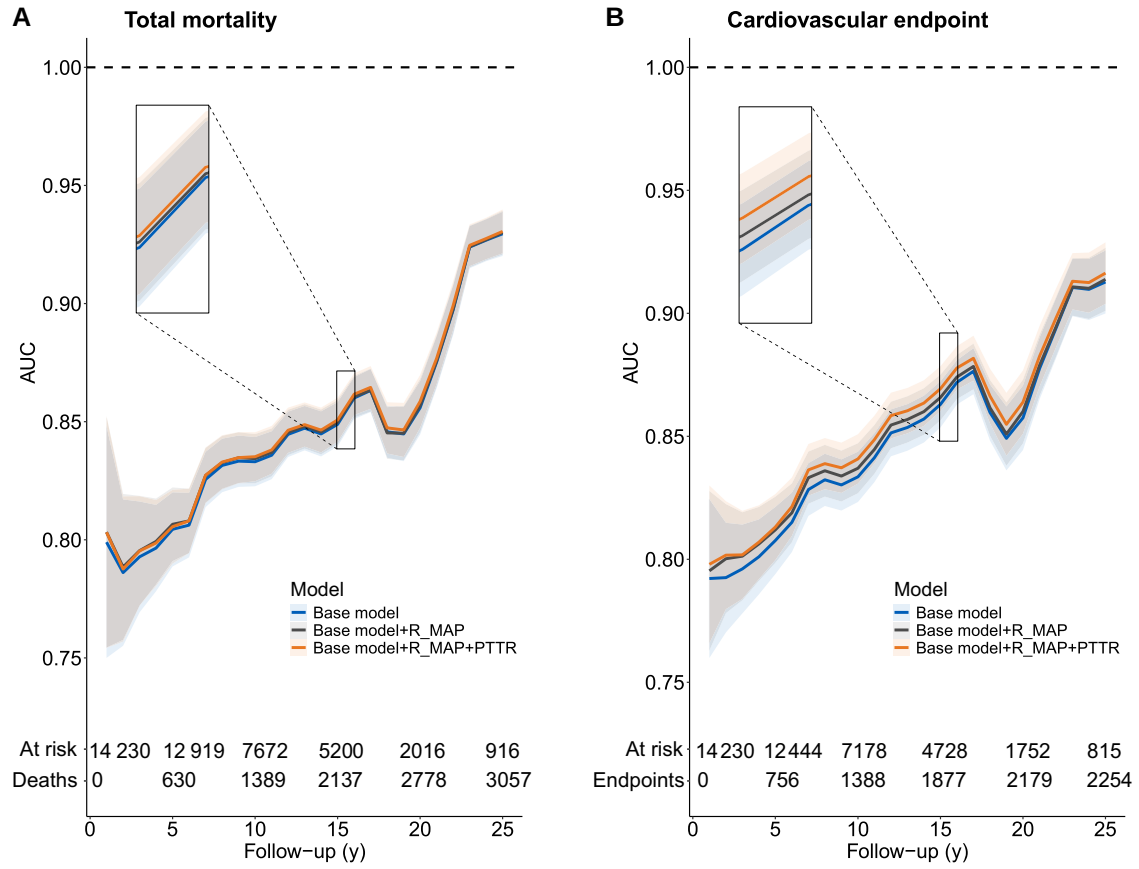


Figure 2 Time-dependent receiver operator characteristic curves for the co-primary endpoints in relation to the percentage of time with non-elevated 24–h ambulatory blood pressure. The non-elevated 24–h ambulatory blood pressure is <115 mmHg systolic and <65 mmHg diastolic. The area under the curve for total mortality (*A*) and the co-primary cardiovascular endpoint (*B*) increases with longer follow-up, because of the accrual of deaths and cardiovascular endpoints. The number of participants at risk and the number of deaths or cardiovascular endpoints is tabulated for 5-year intervals. The area under the curve is plotted for three models: (i) the base model including cohort (random effect), sex, age, body mass index, smoking and drinking, the total-to-HDL serum cholesterol ratio, antihypertensive drug treatment, and history of cardiovascular disease; (ii) the base model extended by the residual of 24–h mean arterial pressure regressed on percentage of time that the 24-h blood pressure is within the target range (R_MAP); and (iii) the base model extended by the residual of 24-h mean arterial pressure regressed on percentage of time that the 24-h blood pressure is within the target range (R_MAP) and percentage of time that the 24-h blood pressure is within the target range (PTTR). The insert is a magnification of the three plotted lines at 15 years of follow-up. The full model including covariables, 24–h residual of mean arterial pressure and 24–h percentage of time with non-elevated ambulatory blood pressure results in a significantly greater area under the curve compared with both other models ($P < .001$). AUC, area under the curve; PTTR, percentage of time that the 24-h blood pressure is within the target range; R_MAP, residual of mean arterial pressure regressed on PTTR

as evidenced by the log-likelihood statistic, the AUC and the IDI and NRI indexes. The 24–h PTTR refined the association with mortality in 15.2% of individuals and with the co-primary cardiovascular endpoint in 19.5%. The statistically significant increase in IDI by 1.25% (for the fullest-adjusted model of cardiovascular endpoints), albeit of small magnitude, reflects the increase in the average sensitivity given no change in specificity. For both endpoints, the addition of 24–h PTTR yielded the greatest increase in NRI and IDI, and PTTR combined with R_MAP the greatest increase in the *C*-index and IDI. Finally, multivariable-adjusted cubic spline models showed an inverse association of all endpoints with 24–h PTTR defined by the current and previous thresholds, i.e. <115/65[1] and <130/80 mmHg,[26–28] respectively. Removing the elevated 24-h ABP from the non-hypertensive 24–h ABP reduced the 24–h PTTR required to attain reduced relative risk for an adverse health outcome from ∼60% to ∼18% (14.4–4.3 h) (*Structured Graphical Abstract*).

The 2024 ESC guidelines for the management of BP[1] considered that the association between adverse health outcomes and BP is continuous with risk increasing from levels of systolic/diastolic OBP as low as 110/70 mmHg. The task force therefore simplified the classification of OBP into non-elevated BP (<120/70 mmHg), elevated BP (120–139/70–89 mmHg), and hypertension (≥140/90 mmHg). In addition to lifestyle measures, antihypertensive drug treatment is indicated in hypertensive patients. In recognition of the multiplicative nature of cardiovascular risk factors,[37] the same recommendation also applies to patients with elevated OBP, if their 10–year cardiovascular risk is ≥10% or in the presence of comorbidities.[1] Furthermore, the 2024 ESC guidelines[1] recommended out-of-office BP monitoring to confirm the classification of patients and to ensure that the OBP target of 120–129/70–79 mmHg is corroborated by the out-of-office BP. Ambulatory BP monitoring is the state-of-the-art method for assessing the

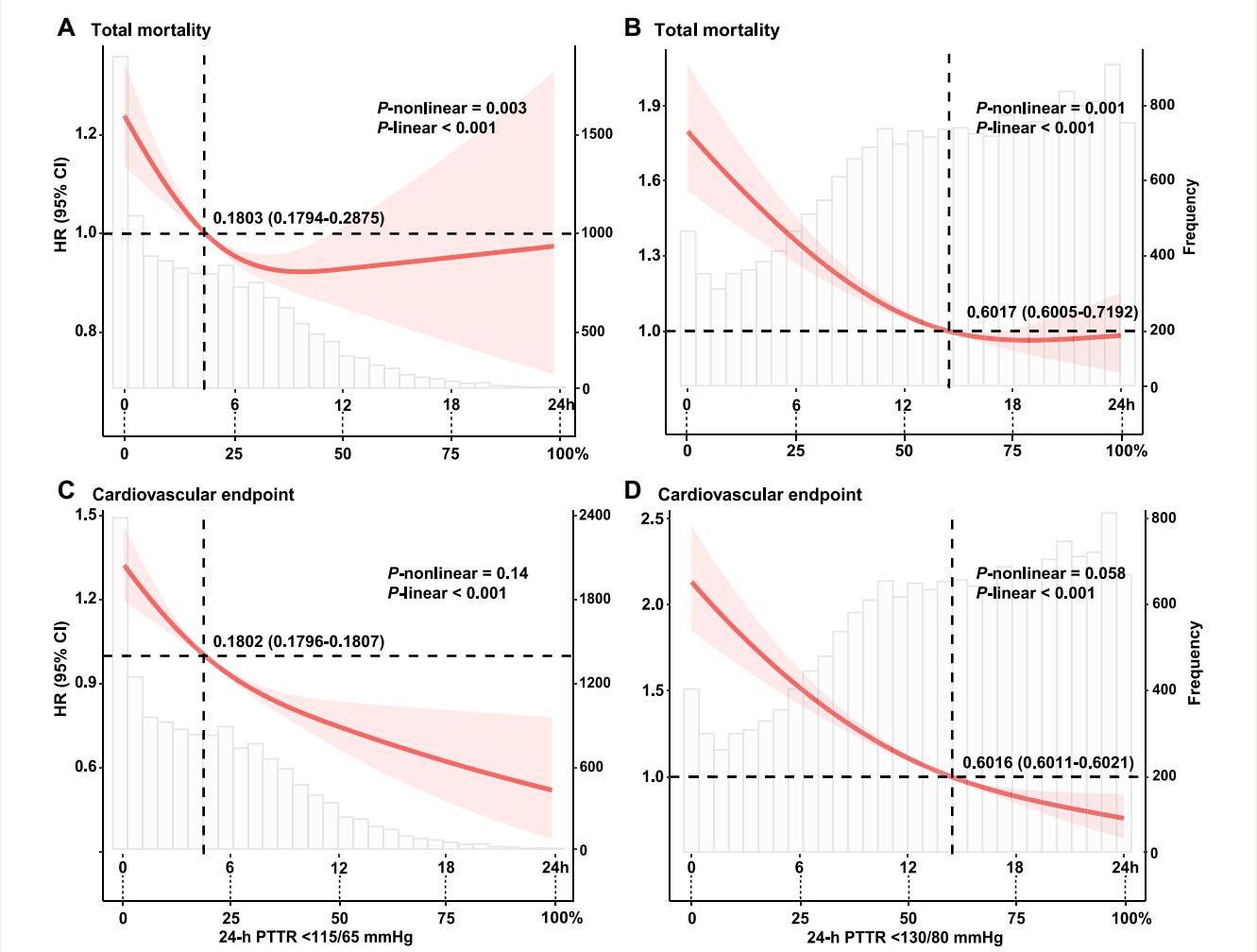


Figure 3 Association between the risk of the co-primary endpoints and the percentage of time with non-elevated or non-hypertensive 24-h ambulatory blood pressure. Hazard ratios are obtained by cubic spline regression for total mortality (*A*, *B*) and the co-primary cardiovascular endpoint (*C*, *D*). The non-elevated 24-h ambulatory blood pressure is currently <115/65 mmHg (*A*, *C*), while the 2018 European Society of Cardiology/European Society of Hypertension non-hypertensive 24-h ambulatory blood pressure, which includes the elevated 24–h ambulatory blood pressure, is <130/80 mmHg (*B*, *D*). Hazard ratios are adjusted for cohort (random effect), sex, age, body mass index, smoking and drinking, the total-to-HDL serum cholesterol ratio, antihypertensive drug treatment, diabetes, history of cardiovascular disease, and the residual of 24-h mean arterial pressure regressed on percentage of time that the 24-h blood pressure is within the target range. Shaded bands represent the 95% confidence interval of the regression line and grey bars the distribution of 24–h percentage of time with non-elevated ambulatory blood pressure (number of individuals). *P*-linear and *P*-non-linear indicate the significance of the linear and non-linear model components. The 2024 European Society of Cardiology non-elevated 24–h percentage of time with non-elevated ambulatory blood pressure, compared with the 2018 European Society of Cardiology/European Society of Hypertension non-hypertensive 24–h percentage of time with non-elevated ambulatory blood pressure, shortened the interval required to reduce relative risk from 60% to 18% (14.4–4.3 h). CI, confidence interval; HR, hazard ratio; 24-h PTTR, percentage of time that 24-h ambulatory blood pressure is within the target range

out-of-office BP.[32,38] The proposed thresholds are <115/65, <120/70, and <110/60 mmHg for the non-elevated 24–h, daytime, and nighttime ABP, respectively. The 2018 ESC/ESH actionable thresholds[29] were ≥130/80, ≥135/85, and ≥120/70 mmHg, i.e. 15/15 mmHg higher for systolic/diastolic 24–h and daytime ABP and 10/10 mmHg higher for nighttime ABP.

Clinical implications

Population studies across all races and ethnicities highlight that hypertension is the major modifiable driver of cardiovascular complications. According to the 2019 Global Burden of Disease Study, hypertension is by far the leading risk factor causing death and disability.[39] Physicians should be made aware that timely prevention before target organ damage becomes symptomatic or irreversible is the way forward. From young to old age, the absolute risk associated with BP increases, as evidenced by the incidence rates of adverse health outcomes,[40] whereas over the same age span, relative risk as quantified by HRs falls. A life-course perspective in the management of elevated BP and hypertension is therefore necessary.[41]

Verdecchia *et al.*[42] recently published a seminal review of randomized clinical trials, comparing lower with higher BP targets. The take-

home message was that the lowest well-tolerated BP is a simple and universally applicable BP target in the management of hypertension, a treatment goal also referred to in the 2024 ESC guidelines[1] as the BP level as low as reasonably achievable. However, in high- and middle-income countries, the rule of halves still applies, indicating halving of the prevalence at each step from being aware of hypertension, being treated, and having BP controlled.[43] Statistics in low-income countries, such as in sub-Saharan Africa,[44] are even much worse.

In a categorical analysis, Cox models were constructed by the deviation from mean coding, which compares the risk in each 24-h PTTR quartile to the average risk in the whole study population and allows to generate 95% CIs for each quartile. For all primary and secondary endpoints, HRs were significantly greater than unity in Q1 and significantly lower than unity in Q4. The *P*-values for a decreasing trend in the risk from Q1 (worst BP control) to Q4 (best BP control) were all significant. These results (see Supplementary data online, *Table S6*), taken together with the average BP values categorized by quartiles of the 24–h PTTR and tabulated in *Table 1*, suggest that patients who are hypertensive by any international criteria[26–28] are at the highest risk and have the most to gain from treatment. Given that the association of adverse health effects with the BP level is log-linear[40] and that risk factors are multiplicative,[37] the delivery of healthcare should prioritize patients with established hypertension and those with elevated BP with a 10–year cardiovascular risk of ≥10%, as highlighted not only in the 2024 ESC guidelines,[1] but in other international recommendations as well.[26–28]

Office BP is the standard method to diagnose and manage hypertension. From this perspective, a supplemental analysis (*Figure 1*) demonstrated that in untreated participants, the predicted probabilities of belonging to the fourth 24–h PTTR quartile (better 24–h BP control) were only 0.35/0.44 and 0.13/0.07 for a systolic/diastolic OBPs of respectively 120/70 and 140/90 mmHg and 0.26/0.27 and 0.15/0.08 in patients on antihypertensive drug treatment. These observations highlight that with regard to optimal 24–h BP control, most patients were misclassified based on OBP. Although recommended by international guidelines[26–29] as the primary approach to verify the OBP level, the technique is not universally available, particularly in low- and middle-income countries and is not readily accepted by all patients, because of the discomfort caused by the cuff inflations and the disturbance of sleep. Home BP measurement is the recommended alternative,[26–29] increases adherence to antihypertensive drug treatment,[45] and is less expensive to set up and therefore applicable in low-income countries.[46]

Strengths and limitations

Several characteristics set the current study apart from previous reports: PTTR assessment accounting for systolic and diastolic BPs in a single variable, the use of ABP, the state-of-the-art method for recording the out-of-office BP,[32,38] and the person-level meta-analysis of unbiased population cohorts enrolled in very diverse regions from the world. This approach is superior to pooling summary statistics from several studies[47] or examining selected patients with hypertension, diabetes, or comorbidities. Nevertheless, the present study has also several limitations. First, the linear interpolation applied to compute PTTR is inferior to beat-to-beat approaches, such as for instance implemented by intra-arterial BP monitoring.[48] Cuffless devices are a non-invasive alternative but are not recommended by the 2024 ESC guidelines.[1] Second, the current meta-analysis, albeit prospective, as all observational studies, remains vulnerable to confounding. However, a wide array of major confounders was considered, albeit that residual confounding is always possible, for instance by renal dysfunction, for which no adjustment was possible given that serum creatinine was not measured in all cohorts. Moreover, the current results are congruent with clinical trials, in which patients were randomized to intensive (<120 mmHg) compared with usual (<140 mmHg) BP control.[49,50] Third, in all participants, OBP and ABP were only measured at baseline. Although the non-elevated ABP (ESC 2024)[1] and non-hypertensive ABP (ESC/ESH 2018)[29] were analysed as benchmarks, the current report cannot be considered as directly supporting the ESC guidelines. Indeed, no information was collected on the change in BP or hypertension status over time nor about the use of antihypertensive drugs and the optimization of BP-lowering treatment, as proposed in the 2024 ESC guidelines.[1] Fourth, potential complications of excessive BP lowering, such as syncope, falls, or acute kidney injury, are unavailable in the IDACO database, thereby limiting the applicability of the findings, in particular to frail patients and the very elderly. However, in the patients randomized in the double-blind placebo-controlled HYVET trial[51] (age range 80–105 years; interquartile range 81.2–85.3 years), active treatment reduced stroke mortality by 39%, all-cause mortality by 21%, and the incidence of heart failure by 64%. On active treatment, BP decreased by 15.0/6.1 mmHg, but compared with placebo did not increase the rate of serious adverse events (358 vs 448). Finally, the IDACO cohort, although ethnically diverse, did not include Black individuals born and living in Africa or individuals of Black ancestry living in other parts of the world, potentially limiting generalizability. However, compared with other racial groups, Blacks are more susceptible to the cardiovascular and renal complication of an elevated BP,[46,52] so that a cautious extrapolation of the current findings is reasonable.

Conclusions

Using the state of the art for out-of-office BP monitoring,[32,38] this person-level meta-analysis applied PTTR as metric to evaluate the ABP thresholds proposed in the 2024 ESC guidelines for the diagnosis and management of elevated BP and hypertension.[1] Higher PTTR, indicative of more time that ABP is within the 2024 ESC target range, is associated with lower rates of adverse health outcomes. Office BP often misclassifies individuals with regard to BP control, if not verified by the out-of-office BP, preferentially by ABP monitoring or otherwise by home BP self-measurement.

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Supplemental material

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. K.A. reported having received a consulting fee from Omron Healthcare Co. Ltd.; T.O. reported having received honoraria for lectures from Omron Healthcare Co. Ltd.

Data Availability

All relevant data are within the paper. Informed consent given by study participants did not include data sharing with third parties. Anonymized data can be made available to investigators for targeted non-commercial research based on a motivated request to be submitted to J.A.S. and pending ethical clearance by each of the 14 participating centres.

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Ethical Approval

The IDACO population studies received ethical approval from the competent Institutional Review Boards in their country of origin. Ethical clearance for the secondary use of anonymized data was waved.

Pre-registered Clinical Trial Number

None supplied.

Appendix

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