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Abstract—Evidence-based thresholds for risk stratification based on pulse pressure (PP) are currently unavailable. To derive outcome-driven thresholds for the 24-hour ambulatory PP, we analyzed 9938 participants randomly recruited from 11 populations (47.3% women). After age stratification (<60 versus ≥60 years) and using average risk as reference, we computed multivariable-adjusted hazard ratios (HRs) to assess risk by tenths of the PP distribution or risk associated with stepwise increasing (+1 mm Hg) PP levels. All adjustments included mean arterial pressure. Among 6028 younger participants (68 853 person-years), the risk of cardiovascular (HR, 1.58; P=0.011) or cardiac (HR, 1.52; P=0.056) events increased only in the top PP tenth (mean, 60.6 mm Hg). Using stepwise increasing PP levels, the lower boundary of the 95% confidence interval of the successive thresholds did not cross unity. Among 3910 older participants (39 923 person-years), risk increased (P≤0.028) in the top PP tenth (mean, 76.1 mm Hg). HRs were 1.30 and 1.62 for total and cardiovascular mortality, and 1.52, 1.69, and 1.40 for all cardiovascular, cardiac, and cerebrovascular events. The lower boundary of the 95% confidence interval of the HRs associated with stepwise increasing PP levels crossed unity at 64 mm Hg. While accounting for all covariables, the top tenth of PP contributed less than 0.3% (generalized R^2 statistic) to the overall risk among the elderly. Thus, in randomly recruited people, ambulatory PP does not add to risk stratification below age 60; in the elderly, PP is a weak risk factor with levels below 64 mm Hg probably being innocuous. **(*Hypertension*. 2014;63:00-00.)** ● **Online Data Supplement**

Key Words: ambulatory blood pressure ■ epidemiology ■ population science ■ pulse pressure

The blood pressure wave consists of a steady and pulsatile component, mean arterial pressure, and pulse pressure (PP).[1] Mean arterial pressure, the product of cardiac output with peripheral arterial resistance, is the force driving blood flow.[1] PP, the difference between systolic and diastolic blood pressure, depends on left ventricular ejection, the elasticity of the central arteries, and the timing and intensity of the backward wave originating at refection sites in the peripheral

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circulation. PP widens in the elderly, because systolic blood pressure continues to rise with advancing age, whereas the age-related increase in diastolic blood pressure levels off or even reverses in the fifth decade of life.[2]

Under the premise that systolic blood pressure and PP reflect arterial stiffness, the Framingham investigators demonstrated that with increasing age a gradual shift occurs from diastolic to systolic pressure and then to PP as predictors of coronary heart disease.[3] Several other studies showed that PP, derived from the conventionally measured blood pressure, predicts adverse outcomes in patients with cardiovascular[4] or renal disease[5,6] as well as in populations.[7–11] Compared with the conventionally measured blood pressure, ambulatory monitoring substantially refines risk stratification, but the 5 studies that examined the predictive value of ambulatory PP only included hypertensive patients[12–16] or patients with end-stage renal disease.[5] Although described as a priority in 2006,[17] to our knowledge, current guidelines for the management of hypertension[18–20] do not propose outcome-driven thresholds for PP discriminating normal from abnormal values. We addressed these issues in a subject-level meta-analysis of 9938 people recruited from 11 populations and enrolled in the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO).

Methods

Study Population

Previous publications described the construction of the IDACO database.[21] All studies received ethical approval and qualified for inclusion if they involved a random population sample, contained baseline information on the ambulatory blood pressure and cardiovascular risk factors, and follow-up of fatal and nonfatal outcomes. All participants gave informed written consent. The IDACO database[21] included 12 randomly recruited population cohorts and 12 725 participants, but at the time of writing this report, validated information on outcome was available in only 11 studies (details and references provided in the online-only Data Supplement), leaving 12 148 participants. Of those, we excluded 2210 because they were younger than 18 years (n=74) or had fewer than 10 daytime or 5 nighttime blood pressure readings (n=2136). Thus, the number of subjects included in the present analysis totaled 9938.

Blood Pressure Measurement

Methods used for conventional and ambulatory blood pressure measurement are described in the online-only Data Supplement. Conventional blood pressure was the average of 2 consecutive readings. Hypertension was as a conventional blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic, or use of antihypertensive drugs. Portable monitors were programmed to obtain ambulatory blood pressure readings at 30-minute intervals throughout the whole day, or at intervals ranging from 15 to 30 minutes during daytime and from 15 to 60 minutes at night. Daytime ranged from 10:00 AM to 8:00 PM in Europeans and South Americans, and from 8:00 AM to 6:00 PM in Asians. The corresponding nighttime intervals ranged midnight to 6:00 AM, and from 10:00 PM to 4:00 AM. PP was the difference between systolic and diastolic blood pressure, and mean arterial pressure was diastolic blood pressure plus one third of PP.

Other Measurements

We used questionnaires to obtain information on each participant's medical history and smoking and drinking habits. 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 ≥7.0 mmol/L,[22] a random blood glucose concentration of ≥11.1 mmol/L,[22] a self-reported diagnosis, or diabetes mellitus documented in practice or hospital records.

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[21] and in the online-only Data Supplement. 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 end points and fatal and nonfatal heart failure. The composite cardiovascular end point included all aforementioned end points plus cardiovascular mortality. In all outcome analyses, we only considered the first event within each category.

We informed sample size calculations with the event rate of the composite cardiovascular end point in the IDACO cohort (10.7 per 1000 person-years). We used the one-sample test as implemented in the PROC POWER procedure of the SAS package. To demonstrate a 10% change in the relative risk associated with each 10 mm Hg increase in 24-hour PP, ≈7000 subjects would be needed with the 2-sided α-level set at 0.05 and power at 0.90.

Statistical Analysis

For database management and statistical analysis, we used SAS software, version 9.3 (SAS Institute, Cary, NC). We compared means and proportions using the large-sample z-test and χ^2 statistic, respectively. After stratification for cohort and sex, we interpolated missing values of body mass index (n=46) and total serum cholesterol (n=683) from the regression slope on age. In subjects with unknown drinking (n=813) or smoking habits (n=69), we set the design variable to the cohort- and sex-specific mean of the codes (0,1). Statistical significance was a 2-sided P value of ≤0.05.

To relate outcome to PP, while adjusting for covariables, we applied Cox regression. The baseline characteristics used for adjustment included cohort, sex, age (continuous), mean arterial pressure, heart rate, body mass index (continuous), current smoking and drinking (0,1), serum cholesterol (continuous), history of cardiovascular disease (0,1) and diabetes mellitus (0,1), and antihypertensive drug treatment (0,1). For adjustment, mean arterial pressure and heart rate were derived from the same recordings as PP (24-hour, daytime, nighttime, or conventional measurements).

Because of the Framingham results[23] and the lower age boundary in several randomized clinical trials on antihypertensive treatment in the elderly,[24] we stratified our analyses by 60 years of age. Exploratory analyses demonstrated that the association of end points with 24-hour PP was not always log-linear. To account for this nonlinear association, we applied the deviation from mean coding[25] to compute hazard ratios (HRs) in tenths of the 24-hour PP distribution. This approach expresses the risk in each tenth relative to the overall risk in the whole study population and allows computing 95% confidence intervals (CIs) for the HRs in all tenths without definition of an arbitrary reference group. HRs relating end points to mean arterial pressure expressed the risk associated with a 1-SD increase in the level. We tested heterogeneity in the HRs across subgroups by introducing the appropriate interaction term in the Cox model. We applied the generalized R^2 statistic to assess the risks additionally explained by 24-hour PP over and beyond mean arterial pressure and other covariables.[26] To assess whether collinearity between PP and mean arterial pressure affected our estimates, we applied penalized Cox regression as applied in the RIDGING=RELATIVE model option of the PROC PHREG procedure of the SAS package.

In an attempt to refine the level of PP that was associated with significantly increased risk, we did a stepwise analysis. We calculated HRs for 1-mm Hg increments in PP for thresholds ranging from the 10th to the 90th percentile. These HRs expressed the risk in participants whose PP exceeded the cutoff point versus average risk. We plotted these HRs and their 95% confidence limits versus the increasing cutoff points with the goal to determine at which level the lower confidence limit of the HRs crossed unity.

Results

Characteristics of Participants

The whole study population comprised 6623 Europeans (66.6%), 1877 Asians (18.9%), and 1438 South Americans (14.5%). Of the 9938 participants, 4703 were women (47.3%), 4058 (40.8%) had hypertension on conventional blood pressure measurement, and 1946 (19.6%) were taking blood pressure–lowering drugs. Mean age was 52.7±15.8 years. In the whole study population, average 24-hour blood pressure levels were 123.5±14.0 mm Hg systolic, 73.6±8.3 mm Hg diastolic, 49.9±9.6 mm Hg for PP, and 90.2±9.5 mm Hg for mean arterial pressure. At enrollment, 2789 participants (28.1%) were current smokers, and 4759 (47.9%) reported intake of alcohol.

The Table shows the characteristics of the participants by age group. The median number of readings averaged to estimate the 24-hour PP was 50 (5th to 95th percentile interval, 35–81; range, 21–95) in younger participants and 56 (5th to 95th percentile interval, 35–82; range, 20–99) in the elderly. Table S1 in the online-only Data Supplement additionally lists the conventional blood pressure and the daytime and nighttime blood pressure by age group. All of the differences between age groups were significant ($P \leq 0.0012$) with the exception of the proportion of Asians ($P=0.057$).

Table. Baseline Characteristics of Participants by Age Group

Characteristics	<60 y (N=6028)	≥60 y (N=3910)
Ethnicity		
Asian	953 (15.8)	924 (23.6)
European	4061 (67.4)	2562 (65.5)
South American	1014 (16.8)	424 (10.8)
Women	3239 (53.7)	1464 (37.4)
Cardiovascular risk factors		
Smoking	1857 (30.9)	932 (24.1)
Drinking alcohol	2795 (47.7)	1964 (60.1)
Diabetes mellitus	247 (4.1)	411 (10.5)
Cardiovascular disease	269 (4.5)	521 (13.3)
Hypertension	1529 (25.4)	2529 (64.7)
Antihypertensive drug treatment	619 (10.3)	1327 (34.1)
Age, y	42.5±11.1	68.6±5.6
Body mass index, kg/m^2	25.1±4.3	25.7±4.0
Serum total cholesterol, mmol/L	5.45±1.14	5.83±1.15
Blood glucose, mmol/L	5.01±1.14	5.52±1.60
24-h blood pressure measurements		
Systolic blood pressure, mm Hg	119.4±12.0	129.8±14.5
Diastolic blood pressure, mm Hg	73.0±8.3	74.6±8.3
Pulse pressure, mm Hg	46.4±7.2	55.2±10.5
Mean arterial pressure, mm Hg	88.5±9.1	93.0±9.6
Heart rate, bpm	73.6±8.9	69.9±9.1

Data are No. (%) or mean±SD. Hypertension is a conventional blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic or use of antihypertensive drugs. To convert glucose and cholesterol from mmol/L to mg/dL, multiply by 18.01 and 38.61, respectively. All of the differences between age groups were significant ($P<0.0001$) with the exception of the proportion of Asians ($P=0.057$).

Analyses of Younger Participants

Incidence of End Points

Among 6028 younger participants (<60 years), median follow-up was 12.1 years (5th to 95th percentile interval, 2.5–18.2 years). Over 68 853 person-years, 228 participants died (3.3 per 1000 person-years) and 221 experienced a fatal or nonfatal cardiovascular complication (3.2 per 1000 person-years). The online-only Data Supplement provides information on the overall and cause-specific number of fatal and nonfatal events.

Categorical Analysis of 24-Hour PP

Figure 1 shows the HRs expressing the risk in each tenth of the distribution of the 24-hour ambulatory PP versus average risk. Only in the highest tenth of the PP distribution (threshold, ≥55.6 mm Hg; mean, 60.1 mm Hg) the risk of the composite cardiovascular end point was elevated (HR, 1.58; 95% CI, 1.11–2.25; $P=0.011$) with a similar trend for cardiac end points (HR, 1.52; CI, 0.99–2.33; $P=0.056$). Otherwise, the risks across tenths of the PP distribution (Figure 1) did not deviate from average ($P \geq 0.058$). For stroke, Cox models across tenths of the PP distribution did not converge, because of the low number of events (n=63). The HRs expressing the risk associated with a 1-SD increase in mean arterial pressure were 1.11 (CI, 0.95–1.29; $P=0.19$) for total mortality, 1.40 (CI, 1.09–1.80; $P=0.009$) for cardiovascular mortality, 1.37 (CI, 1.19–1.59; $P<0.0001$) for a composite cardiovascular end point, and 1.40 (CI, 1.18–1.66; $P=0.0001$) for a cardiac event.

Stepwise Analysis of PP

Figure S1 shows the HRs of 24-hour PP levels that stepwise increased by 1 mm Hg from the 10th to the 90th percentile. For all end points under study, the lower boundary of the confidence interval of the successive HRs did not cross unity.

Analyses of Older Participants

Incidence of End Points

Among 3910 older participants (≥60 years), median follow-up was 10.7 years (5th to 95th percentile interval, 2.5–16.1 years). Over 39 923 person-years, 1160 participants died (29.0 per 1000 person-years) and 940 experienced a fatal or nonfatal cardiovascular complication (23.5 per 1000 person-years). The online-only Data Supplement lists the number of fatal and nonfatal events.

Categorical Analysis of 24-Hour PP

Figure 2 shows the HRs expressing the risk in each tenth of the distribution of the 24-hour ambulatory PP versus average risk. The risk of any death, cardiovascular mortality, a composite cardiovascular end point, or a cardiac event was consistently elevated in the top tenth of the PP distribution (threshold, ≥68.8 mm Hg; mean, 76.1 mm Hg). The HRs were 1.30 (CI, 1.09–1.55; $P=0.004$), 1.62 (CI, 1.26–2.10; $P=0.0002$), 1.52 (CI, 1.26–1.83; $P<0.0001$), and 1.69 (CI, 1.33–2.15; $P<0.0001$), respectively. The HR for stroke in the top tenth of the PP distribution was 1.40 (CI, 1.04–1.89; $P=0.028$; Figure S2). For cardiovascular mortality and the composite cardiovascular end point, the HRs were 0.66 (CI, 0.45–0.97; $P=0.033$) and 0.78 (CI, 0.61–0.99; $P=0.040$) in the second and third tenth of the PP distribution, respectively (Figure 2). Otherwise, the risks across tenths of the PP distribution (Figure 2 and Figure S2) did not deviate from average ($P>0.05$). The HRs

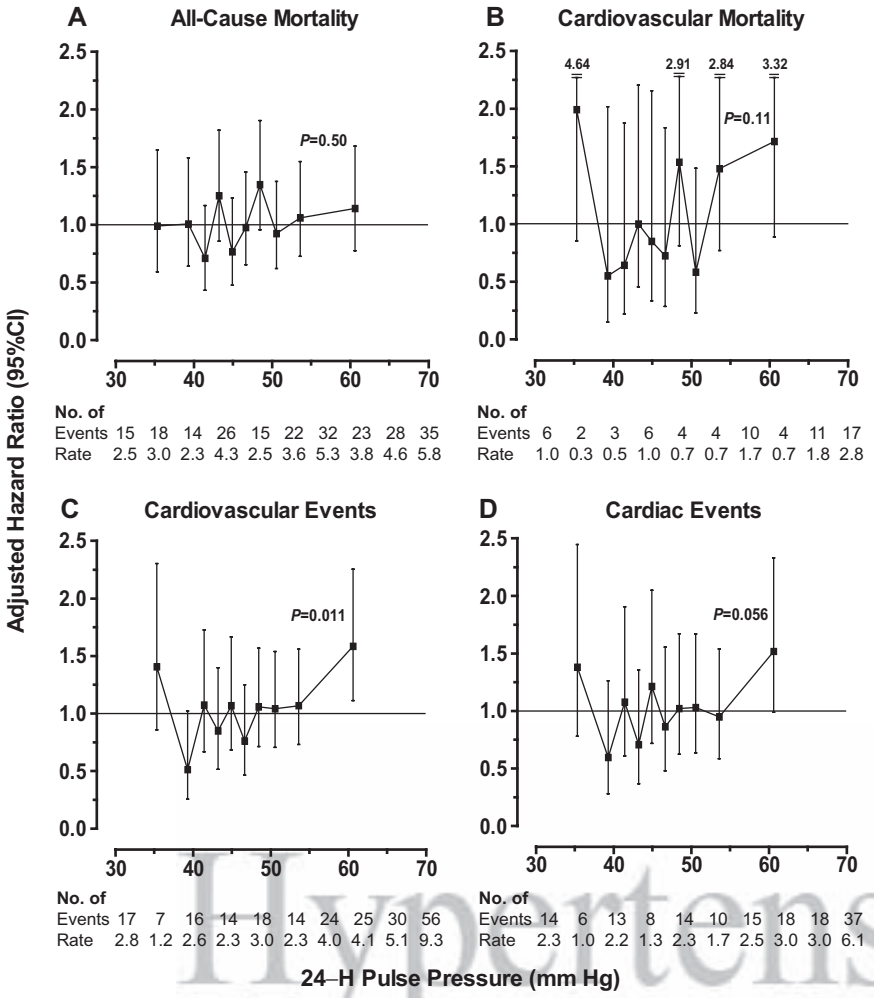

Figure 1. Hazard ratios (HRs) in tenths of the distribution of 24-h pulse pressure (PP) in 6028 younger participants. HRs for total (**A**) and cardiovascular (**B**) mortality and for cardiovascular (**C**) and cardiac (**D**) events express the risk in each tenth compared with average risk. HRs were adjusted for cohort, sex, age, 24-h mean arterial pressure, 24-h heart rate, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease and diabetes mellitus, and antihypertensive drug treatment. Vertical bars denote 95% confidence intervals. For each tenth, the number of events and unadjusted incidence rates (in percent) are given. *P* value refers to the significance of the HR in the top tenth of the 24-h PP distribution.

expressing the risk associated with a 1-SD increase in mean arterial pressure were 1.04 (CI, 0.96–1.12; *P*=0.31) for total mortality, 1.15 (CI, 1.02–1.29; *P*=0.02) for cardiovascular mortality, 1.19 (CI, 1.10–1.29; *P*<0.0001) for a composite cardiovascular end point, 1.07 (CI, 0.96–1.19; *P*=0.22) for a cardiac event, and 1.39 (CI, 1.23–1.58; *P*<0.0001) for stroke. The R^2 statistic for adding a design variable coding for the top tenth of the 24-hour PP distribution to Cox models including all other covariables was 0.10% and 0.12% for total and cardiovascular mortality, and 0.27%, 0.21%, and 0.09% for the composite cardiovascular end point, all cardiac events, and stroke, respectively.

Stepwise Analysis of PP

Figure 3 shows the HRs for 24-hour PP levels increasing by 1-mm Hg steps from the 10th up to the 90th percentile in older participants. For most end points under study (Figure 3) with the exception of stroke (Figure S2), the lower boundary of the confidence interval of the successive HRs crossed the reference line at levels ranging from 64 mm Hg (composite cardiovascular end point) to 69 mm Hg (total mortality and cardiac events).

Sensitivity Analyses

Excluding 1 cohort at a time produced confirmatory results as shown for cardiovascular mortality and composite cardiovascular end point in Table S2. Similarly, when we stratified our analyses in older participants for ethnicity, sex, presence versus absence of conventional hypertension, or use versus nonuse of antihypertensive drugs, the results remained consistent (0.16≤*P*≤0.75 for interaction between subgroups; Table S3). After excluding 863 older participants with a history of cardiovascular disease or diabetes mellitus, the significance of these interaction terms did not materially change (0.37≤*P*≤0.97). Modeling cohort as a random effect in the Cox model instead of adjusting the model for cohort (Figures S3 and S4), applying ridge regression (Table S4), or adjusting for systolic or diastolic blood pressure instead of mean arterial pressure (Table S5) produced consistent results. Finally, when we substituted 24-hour PP by daytime, nighttime, or the conventionally measured PP, the results did not change (Figure 4).

Analyses of Younger and Older Participants Combined

We tested the interaction between 24-hour PP and age modeled as a categorical or continuous variable in 9938 participants. In the categorical analyses (Table S6), using age cutoff limits 50, 55, or 60 years, none of the interaction terms reached significance (0.14≤*P*≤0.72) except for cardiovascular events with 50 years as age cut-off (*P*=0.005). In the continuous analyses, the HRs associated with 10-mm Hg higher 24-hour PP in younger and older participants (<60 versus ≥60 years) were

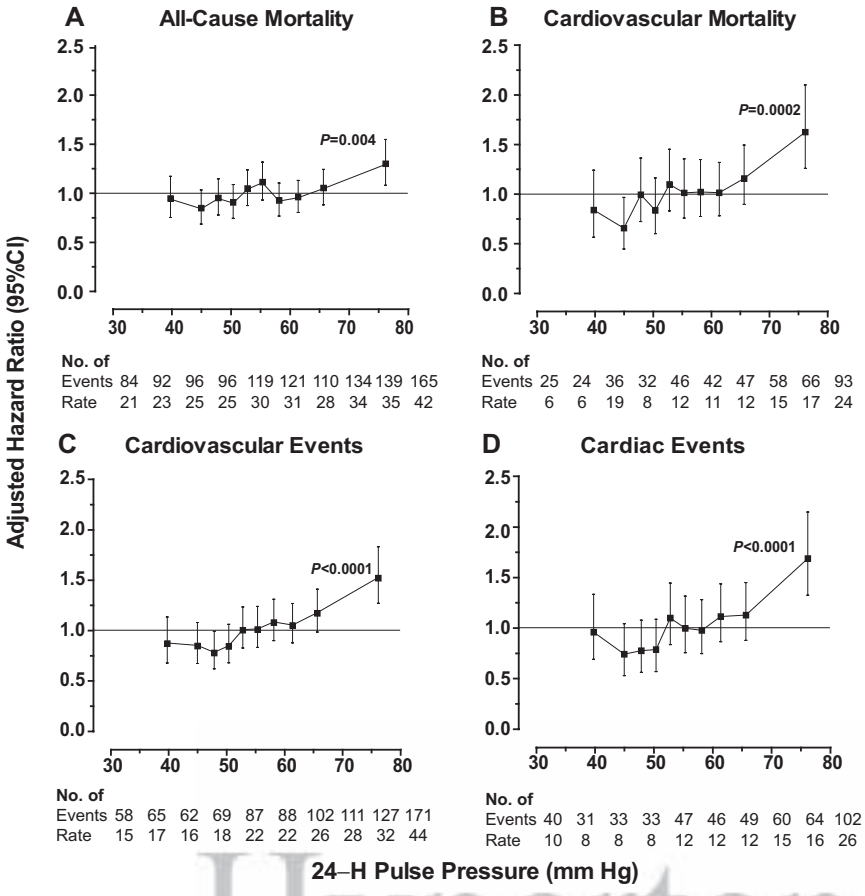

Figure 2. Hazard ratios (HRs) in tenths of the distribution of 24-h pulse pressure (PP) in 3910 older participants. HRs for total (**A**) and cardiovascular (**B**) mortality and for cardiovascular (**C**) and cardiac (**D**) events express the risk in each tenth compared with average risk. The HRs were adjusted as in Figure 1. Vertical bars denote 95% confidence intervals. For each tenth, the number of events and unadjusted incidence rates (in percent) are given. *P* value refers to the significance of the HR in the top tenth of the 24-h PP distribution.

1.12 (CI, 0.91–1.38) versus 1.08 (1.00–1.15) for total mortality (*P* value for difference, 0.085), 1.24 (0.86–1.81) versus 1.13 (1.01–1.25) for cardiovascular mortality (*P*=0.020), 1.28 (1.05–1.57) versus 1.13 (1.05–1.21) for the composite cardiovascular end point (*P*=0.009), and 1.21 (CI, 0.96–1.53) versus 1.17 (1.06–1.28) for cardiac events (*P*=0.22).

Discussion

After more than 2 decades of research,[7] PP remains an elusive cardiovascular risk factor with findings being inconsistent across studies. Previous cohort studies found that peripheral PP, as measured by conventional sphygmomanometry, was an independent risk factor in populations[3,7–11] or in patients with hypertension,[4,27–29] coronary heart disease,[4] or severe renal dysfunction.[5,6] Other population studies failed to confirm the risk associated with PP[30,31] or reported that it was present only in women[7] or in diabetic[10] or treated hypertensive patients.[29] In addition to the conventional method of blood pressure measurement, the aforementioned studies had limitations, because they recorded only fatal end points[5–8,10,11,30,31] or applied recruitment criteria confined to high-risk patie nts,[4,6,27–29,31] a narrow age range,[7,8] or the elderly.[11,28] To address these drawbacks, we applied ambulatory blood pressure monitoring, the current state-of-the-art for blood pressure measurement,[32] and we recorded both fatal and nonfatal end points in randomly recruited populations with age ranging from 18 to 93 years. The key finding of our study was that 24-hour PP did not substantially add to risk stratification below age 60; in the elderly, 24-hour PP was a weak risk factor with levels below 64 mm Hg probably being innocuous. For all end points under study, 24-hour PP remained a significant predictor of outcome with either 24-hour mean arterial pressure or 24-hour diastolic blood pressure as covariable in the Cox models, but it lost significance for all-cause mortality and stroke with 24-hour systolic blood pressure in the model. These findings suggest that systolic blood pressure might be the major blood pressure component driving the risk associated with PP. Using continuous analyses in our current study, the HRs expressing the risk associated with 10-mm Hg wider 24-hour PP, were higher in younger than in older participants for the composite cardiovascular end point (1.28 versus 1.13). However, these HRs only reflect relative risk. The composite cardiovascular end point was running at rates of 3.2 and 23.5 events per 1000 person-years in younger and older participants, respectively. In terms of absolute risk, 24-hour PP, therefore, was a more important predictor in older than in younger participants.

Already in 1971, the Framingham investigators[33] demonstrated that the role of diastolic and systolic blood pressure as risk indicators depends on age. In 2001, they reported that with increasing age there was a gradual shift from diastolic blood pressure to systolic blood pressure and then to PP as predictors of coronary heart disease.[3] In 1989, the Multiple Risk Factor Trial researchers demonstrated that both systolic and diastolic blood pressure determine cardiovascular risk.[34] Also in 1989, Darne et al,[7] by applying principal component analysis, established a steady and pulsatile component of blood pressure, which were unrelated to each other but strongly correlated with mean arterial pressure and PP,

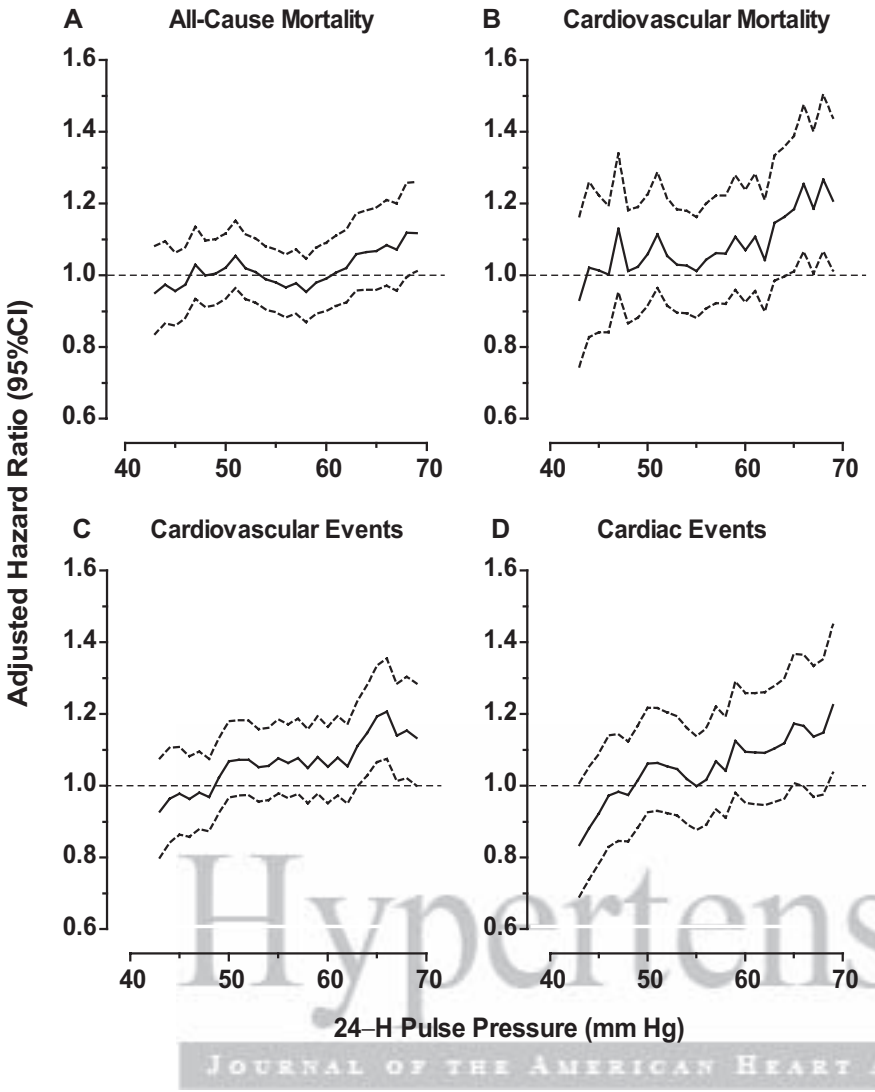

Figure 3. Hazard ratios (HRs) according to 24-h pulse pressure (PP) levels ranging from the 10th to the 90th percentile in 3910 older participants. HRs for total (**A**) and cardiovascular (**B**) mortality and for cardiovascular (**C**) and cardiac (**D**) events express the risk at each level of PP compared with average risk. Solid and dotted lines denote the point estimates and the 95% confidence intervals, respectively. The HRs were adjusted as in Figure 1.

respectively. Guided by these seminal publications,[3,7,33,34] we stratified our main analyses by age (<60 versus ≥60 years) and we modeled PP as risk factor, after accounting for mean arterial pressure.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[18] proposed that PP is only marginally stronger than systolic blood pressure for risk stratification in individuals over age 60, and that under age 60, PP is not predictive. According to the 2007 European guideline,[19] PP is a derived measure, which combines the imprecision of the original systolic and diastolic measurements. The 2007 guideline stated that, although levels of 50 to 55 mm Hg have been suggested,[17] no practical cutoff values separating PP normality from abnormality is available. The 2013 European guideline increased this threshold to 60 mm Hg without any justification.[20] Our current analyses established that below age 60, a 24-hour PP level ≈60 mm Hg might be associated with increased risk, but that a safe threshold could not be established. Among the elderly participants, a 24-hour PP of ≈76 mm Hg was definitely associated with higher risk, and levels below 64 mm Hg were probably safe. Using intra-arterial monitoring, Khattar et al[14] observed that survival rates were highest below age 60, if the 24-hour PP was less than 70 and highest among elderly participants with a 24-hour PP of 70 mm Hg or more. To our knowledge, Khattar's report[14] is the only other study proposing an outcome-driven threshold for 24-hour PP. However, this article does not include any justification why 70 mm Hg was chosen as threshold in a dichotomized analysis. The results rested on an unadjusted Kaplan–Meier survival function analysis, and the study population consisted of patients with essential hypertension, in whom treatment had been withdrawn for 8 weeks.[14] To our knowledge, all other proposals for PP thresholds relied on conventional blood pressure measurement. In analyses adjusted but not stratified for age, 2 studies[9,27] derived a threshold from the 66th percentile of the PP distribution. Madhavan et al[27] proposed 63 mm Hg based on the incidence of myocardial infarction in 2207 hypertensive patients aged 55 years, and Borghi et al[9] suggested 67 mm Hg based on the incidence of cardiovascular disease among 2939 Italian participants (14–84 years). Asmar et al[35] derived a threshold of 65 mm Hg from the mean PP plus 2 SDs in 61 724 French people (16–90 years).

Our current results must be interpreted within the context of some limitations. First, because of the low event rates below the middle age, our analyses did not answer the issue whether

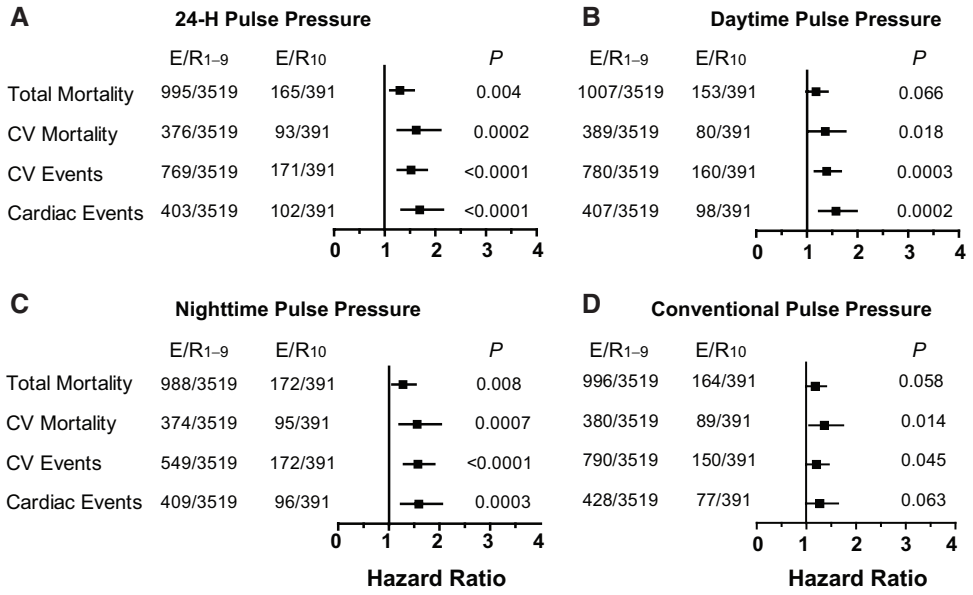

Figure 4. Multivariable-adjusted hazard ratios (HRs) for outcomes in relation to 24-h (**A**), daytime (**B**), nighttime (**C**), and conventional (**D**) pulse pressure (PP) in 3910 older participants. The HRs, presented with 95% confidence interval (CI), express the risk in the top tenth compared with the average risk in the participants. PP thresholds delineating the top tenth were ≥68.8, ≥71.3, ≥66.8, and ≥80.0 mm Hg for 24-h, daytime, nighttime, and conventional blood pressure measurement; the corresponding mean levels of PP in the top tenth were 76.1, 78.8, 75.6, and 89.0 mm Hg, respectively. All models were adjusted for cohort, sex, age, mean arterial pressure and heart rate (on 24-h, daytime, nighttime, conventional measurement in panels **A**, **B**, **C**, and **D**, respectively), body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease and diabetes mellitus, and antihypertensive drug treatment. *P* values are for the risk in the top tenth relative to the overall risk in the whole study population. CV indicates cardiovascular. E/R1–9 and E/R10 indicate the number of events and participants at risk below the 90th percentile of the PP distribution and in the top tenth, respectively.

PP has a different prognostic impact in young compared with older people. However, as reviewed elsewhere,[36] our current study, along with the Framingham report,[3] is one of the few with long-term follow-up of subjects less than 40 years. Second, we did not account for regression dilution bias.[30] However, we previously demonstrated that such correction is not necessary for blood pressure indexes obtained by 24-hour ambulatory monitoring.[37] Third, we had no information on central PP. As demonstrated in Europeans[38] and Chinese participants,[39] with advancing age, systolic augmentation increases and pressure amplification, the difference between peripheral and central systolic blood pressure, decreases. By measuring PP at a peripheral site, we might have underestimated its prognostic significance, in particular in younger people. Finally, oscillometric and auscultatory estimates of PP might differ. However, our findings were consistent regardless of the interval over which the ambulatory blood pressure was measured, as well as on ambulatory (oscillometric) and conventional (predominantly auscultatory) measurements.

Perspectives

Based on our observations in randomly recruited people, PP adds little information on cardiovascular outcomes below age 60. In the elderly participants, ambulatory PP is a risk factor with levels below 64 mm Hg probably being harmless. However, using this threshold in clinical practice might be of little value, because ambulatory PP does not substantially enhance risk stratification over and beyond the steady component of the blood pressure level and other cardiovascular risk factors. We suggest that the threshold proposed for PP in the European 2013 guideline,[20] irrespective of measurement technique, might be revised from the perspective of our current findings.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This is the first population-based study to derive outcome-driven threshold for 24-hour pulse pressure (PP).

What Is Relevant?

- Twenty-four-hour PP does not substantially add to risk stratification below age 60.
- Starting from 60 years onwards, 24-hour PP levels of 70 mm Hg or higher carry an increased cardiovascular risk, whereas levels <64 mm Hg are probably innocuous. However, while accounting for all covariables, having a 24-hour PP in the top tenth of the distribution contributed less than 0.3% to the overall risk among the elderly.
- Findings for daytime, nighttime, and conventional PP were similar to those for 24-hour ambulatory PP.

Summary

The present report is the first to provide outcome-driven thresholds for PP on 24-hour ambulatory measurement. These findings could inform guidelines and be of help to clinicians in diagnosing and managing patients.