Original Article

Impact of Age and Target-Organ Damage on Prognostic Value of 24-Hour Ambulatory Blood Pressure

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Abstract—Markers of target-organ damage and 24-hour ambulatory blood pressure (BP) measurement improve cardiovascular risk stratification. The prevalence of target-organ damage and raised BP increases with aging. The study aim was to evaluate the impact of age and target-organ damage on the prognostic value of ambulatory BP. Markers of target-organ damage and ambulatory BP were measured in 1408 healthy people aged 41 or 51 (middle-aged group), and 61 or 71 (older group) years. The primary outcome was cardiovascular events after 16 years of follow-up, with data obtained from national registries. The prognostic value of BP was evaluated with Cox regression models, adjusted for traditional risk factors and target-organ damage, including left ventricular mass, pulse wave velocity, carotid plaques, and urine albumin/creatinine ratio. A total of 323 events were observed. In comparison with traditional risk factors, adding systolic BP and presence of target-organ damage improved risk stratification by increasing concordance index from 0.711 to 0.728 (P=0.01). In middle-aged subjects with target-organ damage, increment in pulse pressure (hazard ratio, 1.70; 95% confidence interval, 1.31–2.21; P<0.01) and increment in average real variability (hazard ratio, 1.29; 95% confidence interval, 1.05–1.59; P=0.02) were associated with a greater risk of cardiovascular disease compared with subjects without target-organ damage: hazard ratio, 1.04 (95% confidence interval, 0.74–1.46; P=0.81); P for interaction, 0.02; and hazard ratio, 0.89 (95% confidence interval, 0.69–1.14; P=0.36); P for interaction, 0.01. Target-organ damage may be a marker of individual susceptibility to the harmful effects of pulse pressure and BP variability on the cardiovascular system in middle-aged individuals. (***Hypertension*****. 2017;70:00-00. DOI: 10.1161/HYPERTENSIONAHA.117.09173.)** ● **Online Data Supplement**

Key Words: blood pressure monitoring, ambulatory ■ cardiovascular system ■ follow-up studies ■ registries ■ risk factors

Current guidelines for patients with hypertension include 24-hour ambulatory blood pressure (BP) measurements (24hABPM) and assessment of subclinical target-organ damage for cardiovascular risk stratification.[1,2] Markers of subclinical target-organ damage and hemodynamic components derived from 24hABPM improve cardiovascular risk stratification beyond traditional risk factors.[3–6] However, whether the combination of measurements of target-organ damage and 24hABPM in healthy individuals leads to additional predictive benefit is uncertain. The presence of target-organ damage may simply carry an additive risk on top of 24hABPM. Alternatively, hypertension-related target-organ damage could reflect individual susceptibility to the harmful effects of hypertension,[7] that is, elevated BP might be most harmful in subjects with target-organ damage, which would in theory result in a stronger association between 24hABPM and cardiovascular outcome in subjects with target-organ damage than in subjects without. The prognostic value of hemodynamic components obtained from 24hABPM may be modified by age as well.[8] The aim of this study was to evaluate the impact of age and target-organ damage on the prognostic value of 24-hour systolic BP (24hSBP), 24-hour diastolic BP (24hDBP), 24-hour pulse pressure (24hPP), 24-hour heart rate (24hHR), and systolic average real variability. Specifically, we wanted to test the hypothesis that target-organ damage is a marker of individual susceptibility to the harmful effects of hypertension.

Methods

Study Population

During 1982 to 1984, a random sample of the residents of Copenhagen County aged 30, 40, 50, and 60 years were invited to participate in a population survey. The invitations were accepted by 3785 individuals, who attended an examination, where traditional risk markers were measured and lifestyle measures were obtained by questionnaires. In 1993 to 1994, all previous participants were reinvited for a follow-up examination, of whom 2656 (70.2%) attended. The age groups were now 41, 51, 61, and 71 years, and for this study, we stratified all individuals into 2 groups: a middle-aged group including subjects aged 41 or 51 years and an older group comprising of subjects aged 61 or 71 years. A total of 2062

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subjects underwent 24hABPM. Of these, we excluded patients with a history of cardiovascular disease (CVD) or diabetes mellitus (known diabetes mellitus, fasting plasma glucose ≥7.0 mmol/L), and patients taking antidiabetic, antihypertensive, or lipid-lowering drugs (total n=686). To ensure optimal data quality of the ABPM, patients with no registered measurements or <48 valid measurements were excluded (n=533). To further ensure that the calculations of variability were not influenced by wear time, subjects who did not have a valid measurement for a period of >120 consecutive minutes were excluded (n=29) as well, thus leaving 1408 subjects eligible for the present study.

Investigations

All participants completed a questionnaire, in which they provided information on medication, medical history, and lifestyle. After an overnight fast, blood samples were obtained. On the same day, pulse wave velocity, echocardiography, and ultrasound of the carotid arteries were acquired by a trained operator. A trained nurse measured weight, height, office BP, and waist and hip circumferences.

We have described previously how measurements of target-organ damage were obtained.[9]

Atherosclerotic plaque was assessed over both carotid arteries with B-mode ultrasound (Bruel and Kjær 3535, Nærum, Denmark). Plaques were defined as a local thickening of the intima–media layer of >50% or a local, sharp increase in echo density with shadowing.

Pulse wave velocity was calculated as the distance between 2 piezoelectrical pressure transducers (Hellige GmbH Freiburg, Germany) placed over the common carotid artery and the femoral artery, divided by the pulse wave transit time between the 2 transducers. Increased pulse wave velocity was defined as pulse wave velocity >12 m/s, which is the accepted value for this method.[10]

Urine albumin concentration was analyzed using a turbidimetric method (Hitachi 717 analyzer; Roche Diagnostics, Mannheim, Germany) on a single morning urine specimen. Urine creatinine was analyzed using the Jaffé reaction without deproteinizing and then quantified by a photometric method (Hitachi 717 analyzer). Increased urine albumin–creatinine ratio was defined using cutoff points of 0.73 mg/mmol for men and 1.09 mg/mmol for women, corresponding to the 90th percentile in a healthy reference population.[11]

Left ventricular mass was assessed with echocardiography using M mode according to standard guidelines.[12] Left ventricular mass index was calculated as left ventricular mass divided by body surface area, calculated by DuBois formula. Left ventricular hypertrophy was defined as left ventricular mass index >125 g/m^2 for men and left ventricular mass index >110 g/m^2 for women, according to the European Society of Hypertension guidelines.[13]

Oscillometric ABPM was recorded using a Takeda TM-2421 (A&D, Tokyo, Japan) device. BP recordings were made every 15 minutes between 700 and 2300 hours and every 30 minutes between 2300 and 700 hours. Weighted means of ABPM were computed, taking into account the varying time intervals between consecutive measurements.[14] PP was calculated by subtracting mean diastolic BP from the corresponding mean systolic BP. Systolic BP variability was evaluated by calculating average real variability. The average real variability averages the absolute differences of consecutive measurements and as such, accounts for the order in which the BP measurements are obtained.[15] By calculating differences of consecutive measurements, the interference of day to night fluctuations is avoided.

The study was conducted in accordance with the Helsinki declaration and approved by the regional ethical committee on health research (record number: KA 93054). All participants provided oral and written informed consent.

End-Point Classifications

Information on cardiovascular outcome was obtained from national registries after 16 years of follow-up. Data on death and migration status, cause of death, and hospitalization were obtained from the civil registration system, the Danish cause of death register, and the Danish national patient register, respectively, with last follow-up on December 31, 2010. The overall data quality from the national registries has been reviewed recently, and in samples from 2003, the proportion of incorrect registrations was 3%.[16] The primary composite end point for evaluation was major adverse cardiovascular events, which comprised of cardiovascular death, myocardial infarction (I21-24), arrhythmia (I44-47, I49, except I456), cerebrovascular disease (I60-I61, I621, I629 and I63-I67, except I607A, I671+5+7), peripheral and central arterial disease (I70-74, N280, K551-K552, and K558-K559), atherosclerotic eye disease (H340-H342), or sudden death (R96-99). Angina pectoris (I20), atrial fibrillation (I48), heart failure (I50), transient cerebral ischemia (G45), chronic ischemic heart disease (I25), and sequelae after cerebrovascular disease (I69) were defined as an end point if coded as the primary diagnosis during hospitalization.

Statistical Analyses

Continuous variables are summarized by means and SDs (approximately normally distributed variables) and medians and interquartile ranges (non-normally distributed variables); categorical variables are presented by frequencies and corresponding percentages.

To assess which individual component from 24hABPM most accurately predicted incident CVD, we used Cox proportional hazards regression models for each component, adjusted for traditional risk factors (age, sex, office systolic BP, total cholesterol, and smoking), and with time to first major adverse cardiovascular events event as the underlying timescale. Model performance was assessed using Harrell concordance index (C index), and comparisons were made using the somersd package in Stata, as described by Newson.[17] The C index is a measure of predictive discrimination of a regression model[18] and reflects the probability of the model estimating a higher risk score for a randomly selected individual having an event compared with an individual not having an event. It ranges from 0.5 to 1 with a value of 0.5 equaling random chance and a value of 1 indicating perfect prediction.

The impact of age on the predictive capability of 24hABPM was evaluated by constructing models, including 24hSBP, 24hDBP, 24hPP, 24hHR, and average real variability, age group (41/51 and 61/71, respectively), and the interaction term between the 2 as independent variables. Similarly, to test whether the presence of target-organ damage modified the predictive capability of 24hABPM, models were constructed with the hemodynamic component, target-organ damage, and the interaction term between the 2 as independent variables, stratified by the 2 age groups. Finally, we created different risk models combining the traditional risk factors, target-organ damage, and combinations of components obtained from 24hAMBP, which had been associated with the highest C indices on the aforementioned analyses and showed significant interaction with either target-organ damage or age. Hazard ratios (HRs) for CVD were evaluated per SD increment of components derived from 24ABPM with 95% confidence interval (CI).

The proportional hazard assumption was tested using Schoenfeld residuals. All analyses were performed using Stata 13 (StataCorp, College Station, TX). A 2-sided P value <0.05 was considered as statistically significant.

Results

The study population was divided into 2 age categories, that is, 842 middle-aged (41 or 51 years) and 566 older (61 or 71 years) subjects, with baseline characteristics summarized in Table 1. From 1993 to 2010 (median follow-up time 16 years, mean 13.9 years, SD 3.9), we observed 323 composite events, that is, 123 (14.6%) events in the middle-aged group and 200 (35.3%) events in the older group. Types of events are shown in Table 5.

Impact of Age

There were no significant interactions between age and the association between hemodynamic components obtained from 24hABPM and later CVD in the population overall. However, in the subgroup of subjects with target-organ damage, there was a significant prognostic interaction between age and 24hPP (P=0.02), indicating that the association between

Table 1. Baseline Characteristics, Including Markers of Target-Organ Damage and Components From 24-h Ambulatory Blood Pressure Measurement

	Middle Aged	Elderly
Age Group	41 or 51 y	61 or 71 y
General characteristics		
N	842	566
Male sex, %	431 (51.2)	305 (53.9)
Proportion of smokers, %	419 (49.8)	235 (41.5)
Body mass index, kg/m^2	25.3±3.9	26.0±3.8
Total cholesterol, mmol/L	5.9±1.0	6.4±1.1
Office SBP, mm Hg	122±16.1	138±19.0
Office DBP, mm Hg	81±10.4	84±11.5
Office HR, bpm	64±9.7	66±10.3
24hABPM		
24hSBP, mm Hg	125±11.1	130±13.0
24hDBP, mm Hg	75±8.2	74±8.4
24hPP, mm Hg	50±6.6	56±9.5
24hHR, bpm	73±8.4	71±8.3
SARV, mm Hg	11.9±2.8	12.5±2.5
Measurements of TOD		
LVMI, g/m^2	80±18.7	86±23.6
PWV, m/s	9.5 (8.6–10.6)	11.9 (10.4–14.3)
UACR, mg/mmol	0.22 (0.08–0.42)	0.26 (0.10–0.52)
Patients with carotid plaque, %	100 (11.9)	245 (43.3)

Data are presented as median and interquartile range for continuous variables and proportions and number of categorical variables if not otherwise specified. 24hABPM indicates 24-h ambulatory blood pressure measurement; 24hDBP, 24-h diastolic blood pressure; 24hHR, 24-h heart rate; LVMI, left ventricular mass index; N, number; 24hPP, 24-h pulse pressure; PWV, pulse wave velocity; SARV, systolic average real variability; SBP, systolic blood pressure; and UACR, urine albumin creatinine ratio.

24hPP and later CVD was higher in middle-aged (HR, 1.73; 95% CI, 1.33–2.26; P<0.001) than in older subjects (HR, 1.24; 95% CI, 1.09–1.42; P=0.001) per SD of 24hPP.

Impact of Target-Organ Damage on the Association Between 24-Hour ABPM and CVD

24hSBP was associated with incident CVD in both middle-aged and older subjects in multivariable analysis (Table 3). The presence of target-organ damage did not modify this association (Figure [A] and [B]). However, in middle-aged subjects without target-organ damage, 24hSBP was not significantly associated with incident CVD (Table 2)

Similarly, 24hDBP was associated with CVD in both middle-aged and older subjects in multivariable analysis (Table 3), without any modification by target-organ damage.

24hPP was associated with CVD in both middle-aged and older subjects in multivariable analysis. In middle-aged subjects, the association between 24hPP and CVD was further modified by target-organ damage (P=0.02 for interaction; Table 2). When further adjusted for 24hSBP, increment per SD of 24hPP remained significant in predicting CVD (HR, 1.61; 95% CI, 1.09–2.36; P=0.02) in the subgroup of middle-aged patients with target-organ damage. Group comparisons are shown in Figure S1 in the online-only Data Supplement.

24hHR was only associated with CVD in middle-aged subjects without target-organ damage in multivariable regression analysis (Table 3). In the same subgroup, 24hHR remained significant in predicting CVD, when further adjusted for 24hSBP (HR, 1.45; 95% CI, 1.09–1.93; P=0.01).

Finally, in middle-aged subjects with target-organ damage, average real variability was associated with later CVD in multivariable analysis (Table 3). Average real variability was not associated with CVD in middle-aged participants without target-organ damage (P=0.01 for interaction). Group comparisons are shown in Figure S2. In elderly subjects, average real variability was associated with CVD, but this association became nonsignificant when stratifying by target-organ damage. In middle-aged subjects with target-organ damage, increment per SD of average real variability remained significantly associated with CVD (HR, 1.24; 95% CI, 1.01–1.53; P=0.04) after adjusting for 24hSBP.

Target-Organ Damage

The presence of target-organ damage was associated with incident CVD in both middle-aged and older subjects in univariable analysis and remained significant after adjusting for both traditional risk factors and 24hSBP in middle-aged (HR, 2.22; 95% CI, 1.53–3.23; P<0.01) and older subjects (HR, 1.78; 95% CI, 1.18–2.67; P<0.01).

The association between target-organ damage and CVD was not modified by sex in either age group (Figure [A] and [B]). In middle-aged subjects, target-organ damage was significantly associated with CVD in all hemodynamic subgroups, with a greater HR for CVD in subjects with 24hPP >50 mm Hg compared with subjects with 24hPP ≤50 mm Hg (Figure [A]). Likewise, a higher HR for the association between target-organ damage and CVD in subjects with average real variability >11.5 mm Hg compared with subjects with average real variability ≤11.5mm Hg resulted in a significant interaction between average real variability and target-organ damage (Figure [A]).

In older subjects, the presence of target-organ damage was not significantly associated with later CVD when 24hDBP >75 mm Hg or 24hHR >72 bpm (Figure [B]). However, we did not observe any significant interactions between hemodynamic components and the presence of target-organ damage (Figure [B]).

Predictive Capability of Individual Components of 24-Hour Ambulatory BP Measurements

24hSBP together with traditional risk markers yielded the numerically highest predictive capability (C index, 0.721), followed by 24hPP (C index, 0.712), 24hDBP (C index, 0.711), 24hHR (C index, 0.708), and average real variability (C index, 0.700), respectively.

Risk Model Comparisons

Evaluation of different risk models combining the traditional risk factors, target-organ damage, and combinations of hemodynamic components obtained from 24hABPM are shown in Table 4. Combining target-organ damage with traditional risk

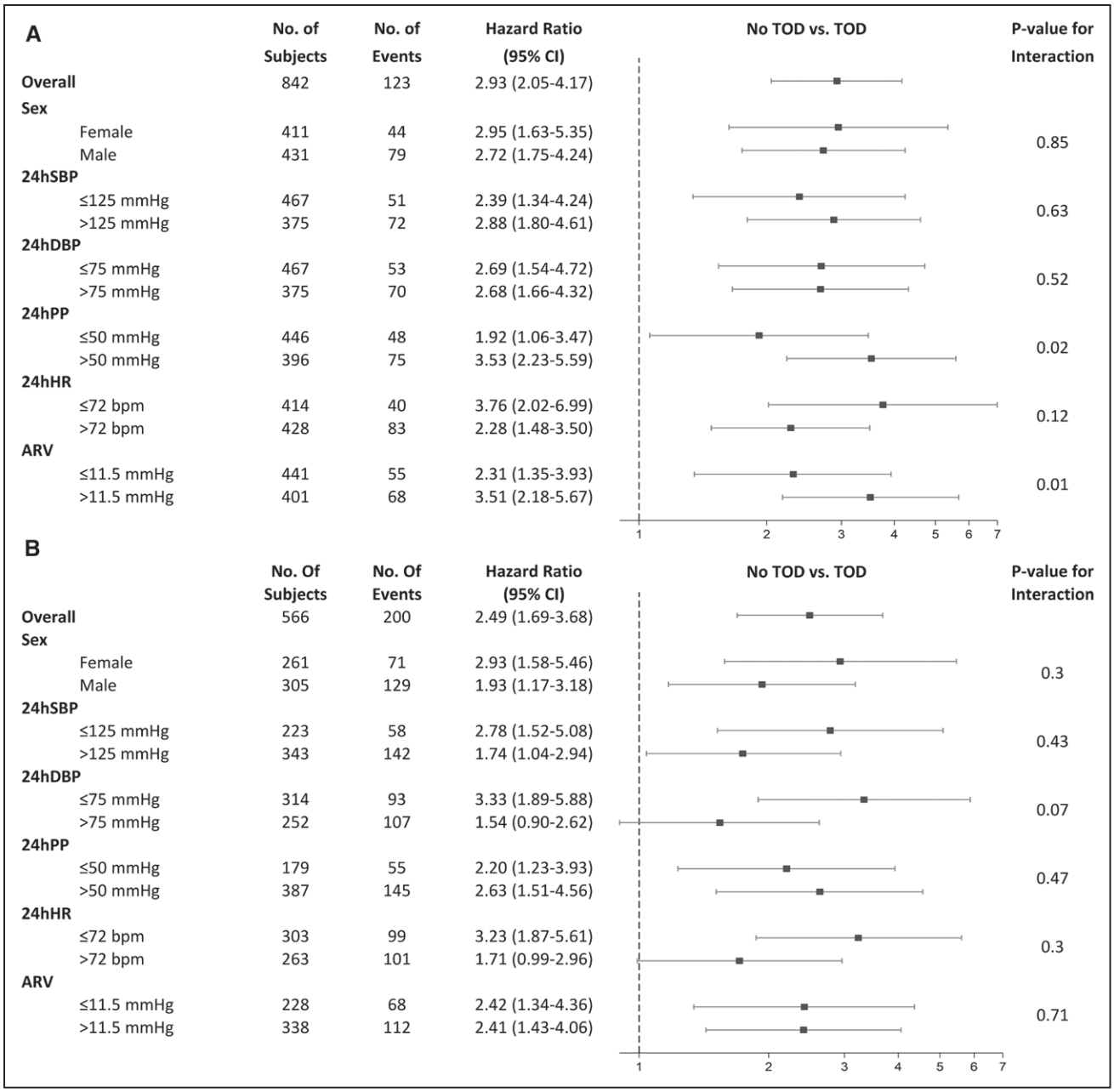

Figure. Shown are the results of Cox regression analysis of data for subgroups of subjects aged 41 or 51 y (**A**) and subjects aged 61 or 71 y (**B**) with respect to major cardiovascular events. Interaction was evaluated by target-organ damage (TOD) as a dichotomous variable and 24-h ambulatory blood pressure measurements as continuous variables. ARV indicates average real variability; CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate; PP, pulse pressure; and SBP, systolic blood pressure.

factors did not significantly improve the predictive capability (C index, 0.701 versus 0.718; *P*=0.06). Similar results were obtained when substituting office SBP with 24hSBP, that is, no significant improvement in C index (0.711 versus 0.722; *P*=0.06). Combining target-organ damage with traditional risk factors yielded similar predictive capability compared with a model with traditional risk factors where office SBP was substituted with 24hSBP evaluated by C index (0.720 versus 0.721; *P*=0.36). However, the model with 24hSBP combined with target-organ damage and traditional risk factors increased the C index from 0.711 to 0.728 (*P*=0.01), when compared with the model consisting solely of traditional risk factors. The highest C index was observed in a model consisting of traditional risk factors, 24hSBP, 24hPP, 24hHR, target-organ damage, and a 3-way interaction term between age, 24hPP, and target-organ damage (C index, 0.737). Adding average real variability to this latter model did not improve the C index (0.737; *P*=0.72).

Discussion

The main results of our study were (1) the presence of subclinical target-organ damage significantly strengthened the prognostic associations of 24hPP and average real variability in middle-aged, but not in older, apparently healthy individuals and (2) the addition of 24hABPM BP levels, but not BP variability, to target-organ damage improved risk prediction slightly, and this risk prediction was further improved when

Table 2. Unadjusted HR for Major Cardiovascular Events Stratified in Age Groups

	Age 41 or 51 y		Age 61 or 71 y	
24hABPM	Hazard Ratio per SD (95% CI)	*P* Value	Hazard Ratio per SD (95% CI)	*P* Value
24hSBP (all)	1.55 (1.32–1.82)	<0.01	1.56 (1.38–1.76)	<0.01
24hSBP (without TOD)	1.28 (0.96–1.72)	0.10	1.62 (1.11–2.38)	0.01
24hSBP (with TOD)	1.40 (1.14–1.72)	<0.01	1.45 (1.26–1.67)	<0.01
24hDBP (all)	1.38 (1.18–1.61)	<0.01	1.44 (1.26–1.64)	<0.01
24hDBP (without TOD)	1.30 (1.00–1.69)	0.05	1.79 (1.23–2.61)	<0.01
24hDBP (with TOD)	1.16 (0.95–1.43)	0.15	1.31 (1.14–1.51)	<0.01
24hPP (all)	1.51 (1.22–1.85)	<0.01	1.31 (1.17–1.47)	<0.01
24hPP (without TOD)	1.04 (0.75–1.44)	0.80	1.06 (0.72–1.57)	0.77
24hPP (with TOD)	1.73 (1.33–2.26)	<0.01	1.24 (1.09–1.42)	<0.01
24hHR (all)	1.18 (0.97–1.43)	0.10	1.04 (0.90–1.20)	0.62
24hHR (without TOD)	1.33 (1.01–1.74)	0.04	1.18 (0.79–1.75)	0.42
24hHR (with TOD)	0.98 (0.75–1.29)	0.89	0.94 (0.80–1.11)	0.48
ARV (all)	1.10 (0.94–1.29)	0.23	1.19 (1.02–1.37)	0.02
ARV (without TOD)	0.89 (0.69–1.14)	0.36	1.18 (0.77–1.81)	0.44
ARV (with TOD)	1.35 (1.09–1.67)	0.01	1.09 (0.93–1.28)	0.30

24hABPM indicates 24-h ambulatory blood pressure measurement; ARV, average real variability; CI, confidence interval; 24hDBP, 24-h diastolic blood pressure; 24hHR, 24-h heart rate; 24hPP, 24-h pulse pressure; 24hSBP, 24-h systolic blood pressure; and TOD, target-organ damage.

interactions between age, 24hPP, and target-organ damage were considered. To our knowledge, this study is the first to suggest an interaction between 24hPP, average real variability, and target-organ damage, in relation to cardiovascular outcome.

The effect of aging on the prognostic importance of overall hemodynamic composition has been evaluated in both hypertensive subjects[8] and population based cohorts,[19–21] with similar findings. 24hDBP generally seems to be a superior predictor of future CVD in young subjects (≤60 years), whereas 24hSBP and 24hPP are better predictors of incident CVD in older subjects (>60 years).[8,19]

The Prognostic Interaction Between Average Real Variability and Target-Organ Damage in Middle-Aged Subjects

The prognostic interactions between 24hPP, average real variability, and target-organ damage support our original hypothesis that target-organ damage might be a marker of individual susceptibility to the harmful cardiovascular effects of elevated BP. BP variability is a complex physiological marker affected by neurological, humoral, and behavioral factors.[22–24] During the last decades, different measures of BP variability have been proposed to be associated with the presence, progression, and severity of target-organ damage, independently of average 24hSBP,[25,26] and perhaps more so in patients with high CVD risk compared with patients with low-to-intermediate risk.[27] Arterial stiffening may be augmented by increased BP variability and vice versa.[28] This could result in a vicious circle, where the combination of stiffened large arteries and increased BP variability convey increased and dynamic pulsatile load to the peripheral arteries, causing accelerated organ damage and triggering cardiovascular events.[29] The prognostic interaction between average real variability and target-organ damage in middle-aged subjects may have been strengthened by the fact that subjects with increased average real variability without target-organ damage had increased average real variability because of other mechanisms than increased arterial stiffness not as closely associated with later cardiovascular events, for example, increased physical activity during the measurement.

The Prognostic Interaction Between 24hPP and Target-Organ Damage in Middle-Aged Subjects

It has been proposed that PP can induce vascular damage by both inflammatory and mechanical mechanisms.[30,31] PP is determined by 3 major components: (1) arterial stiffness, (2) stroke volume, and (3) peripheral vascular resistance. Given the known effects of vascular aging, increased PP most likely reflects aortic stiffening in older subjects,[32,33] whereas an increased PP in young-to-middle-aged subjects may merely reflect increased stroke volume,[34] which, per se, is not associated with increased CVD risk. Therefore, 1 explanation for the prognostic interaction between 24hPP and target-organ damage in middle-aged subjects may simply be that increased PP in subjects without target-organ damage is not a marker of increased arterial stiffness. In a recent meta-analysis examining PP and cardiovascular or all-cause mortality,[35] it was noted that only few studies had reported age-specific relative risk. Although PP seems to be a better predictor of cardiovascular outcome in older subjects, several studies have shown that PP actually carries a higher relative risk in younger subjects compared with older subjects.[36–38] This study confirmed that increase in 24hPP is associated with a higher risk for CVD in middle-aged compared with older individuals.

Table 3. Adjusted* HR for Major Cardiovascular Events Stratified in Age Groups

	Age 41 or 51 y		Age 61 or 71 y	
24hABPM	Hazard Ratio per SD (95% CI)	*P* Value	Hazard Ratio per SD (95% CI)	*P* Value
24hSBP (all)	1.50 (1.27–1.77)	<0.01	1.53 (1.35–1.74)	<0.01
24hSBP (without TOD)	1.20 (0.88–1.65)	0.25	1.49 (1.02–2.18)	0.04
24hSBP (with TOD)	1.40 (1.14–1.72)	<0.01	1.46 (1.27–1.69)	<0.01
24hDBP (all)	1.30 (1.11–1.54)	<0.01	1.39 (1.21–1.59)	<0.01
24hDBP (without TOD)	1.20 (0.91–1.59)	0.19	1.67 (1.11–2.51)	0.02
24hDBP (with TOD)	1.16 (0.93–1.44)	0.18	1.29 (1.11–1.49)	<0.01
24hPP (all)	1.51 (1.23–1.86)	<0.01	1.33 (1.19–1.49)	<0.01
24hPP (without TOD)	1.04 (0.74–1.46)	0.81	1.09 (0.76–1.57)	0.64
24hPP (with TOD)	1.70 (1.31–2.21)	<0.01	1.29 (1.13–1.47)	<0.01
24hHR (all)	1.28 (1.05–1.55)	0.02	1.13 (0.97–1.31)	0.11
24hHR (without TOD)	1.47 (1.11–1.95)	<0.01	1.34 (0.90–1.99)	0.15
24hHR (with TOD	1.02 (0.78–1.34)	0.87	1.01 (0.86–1.19)	0.92
ARV (all)	1.10 (0.94–1.29)	0.24	1.16 (1.00–1.35)	0.04
ARV (without TOD)	0.89 (0.69–1.15)	0.38	1.17 (0.76–1.79)	0.47
ARV (with TOD)	1.29 (1.05–1.59)	0.02	1.08 (0.92–1.27)	0.34

24hABPM indicates 24-h ambulatory blood pressure measurement; ARV, average real variability; CI, confidence interval; 24hDBP, 24-h diastolic blood pressure; 24hHR, 24-h heart rate; 24hPP, 24-h pulse pressure; 24hSBP, 24-h systolic blood pressure; and TOD, target-organ damage.

*Adjusted for sex, total cholesterol, and smoking status.

Absence of Interaction Between 24hPP, Average Real Variability, and Target-Organ Damage in Older Subjects

The absence of interactions between 24hPP, average real variability, and target-organ damage in the older subgroup can be explained either by an age-associated increase in the impact of other nonhemodynamic risk factors on target-organ damage,[39] attenuating the association between hemodynamic risk factors and target-organ damage, or by survival and treatment selection bias because of inclusion of only untreated subjects without prior CVD because it is likely that subjects with prior CVD more often had both elevated BP and target-organ damage. Finally, the absence of interaction in the older subgroup could be the result of an insufficient statistical power to detect differences in outcome because of the relatively small sample size and associated number of events.

Table 4. Comparison of Predictive Capability of Cox Regression Models

Model	Harrell C Index (95% CI)	Model Comparison
1	0.711 (0.683–0.738)	Model 1 vs model 2, *P*=0.06
2	0.720 (0.693–0.748)	Model 2 vs model 4, *P*=0.05
3	0.721 (0.693–0.748)	Model 1 vs model 3, *P*=0.06
4	0.728 (0.701–0.755)	Model 1 vs model 4, *P*=0.01
5	0.737 (0.711–0.764)	Model 4 vs model 5, *P*=0.01

Model 1: age, sex, office SBP, total cholesterol, and smoking status. Model 2: age, sex, office SBP, total cholesterol, smoking status, and TOD. Model 3: age, sex, 24hSBP, total cholesterol, and smoking status. Model 4: age, sex, 24hSBP, total cholesterol and smoking status, and TOD. Model 5: age, sex, 24hSBP, total cholesterol, smoking status, TOD, 24hHR, 24hPP, and the 3-way interaction between age, 24hPP, and TOD. CI indicates confidence interval; 24hHR, 24-h heart rate; 24hPP, 24-h pulse pressure; 24hSBP, 24-h systolic blood pressure; and TOD, target-organ damage.

Cardiovascular Risk Prediction

The improvement of risk prediction was similar when adding 24hABPM or target-organ damage to traditional risk factors. However, the combination of both 24hABPM and target-organ damage resulted in further model improvement. This reaffirms previous findings in this cohort,[3] namely that 24hABPM cannot replace the assessment of subclinical cardiovascular damage, even when extending follow-up time. Several epidemiological and interventional studies have shown previously that the basal cardiovascular risk of subjects may modulate the effect of BP levels on cardiovascular risk during follow-up.[40,41] BP reduction causes a similar relative risk reduction at each baseline CVD risk level. This in turn corresponds to larger absolute reductions in CVD risk among high-risk subjects compared with low-risk subjects.[42] In this study, we find that middle-aged subjects with target-organ damage with increasing PP and average real variability have an increased relative risk of CVD compared with middle-aged subjects without target-organ damage.

Perspectives

The combination of 24hABPM and presence of target-organ damage improved risk prediction based on traditional risk factors. Although the C index is considered a rather conservative measure, it is reasonable to question the clinical significance of the observed effect sizes. Still, the results highlight

Table 5. Major Adverse Cardiovascular Events Stratified in Age Groups and Presence of Target-Organ Damage

	Age 41 or 51		Age 61 or 71	
Cardiovascular Events	Without TOD	With TOD	Without TOD	With TOD
No. of subjects	614	228	155	411
Cerebrovascular disease	14	12	6	56
Peripheral and central arterial disease*	10	9	2	25
Myocardial infarction	5	10	4	16
Atrial fibrillation	11	5	3	17
Arrhythmia	4	5	7	16
Angina pectoris	6	10	5	6
Transitory cerebral ischemia	6	3	0	6
Sudden death	4	3	0	11
Heart failure	1	2	1	11
Chronic ischemic heart disease	1	2	2	6
Total events, %	62 (10.1)	61 (26.8)	30 (19.4)	170 (41.4)

TOD indicates target-organ damage.

*Includes coronary and cerebrovascular revascularization procedures if no other diagnosis was present.

that progression to target-organ damage and subsequent overt CVD is more complex than simple BP load and that considerations including pulse pressure and perhaps BP variability should be considered. Future studies examining age-dependent interactions between target-organ damage and hemodynamic variables with respect to cardiovascular outcome are warranted. Because PP and, to some degree, BP variability seem to carry additional prognostic information, and different antihypertensive drug classes may have varying effects on them,[43,44] they might be alternative therapeutic targets in cardiovascular prevention, especially in middle-aged subjects with subclinical target-organ damage.

Limitations

There are some limitations to this study. A fairly high number of subjects were excluded because of none or nonvalid 24ABPM measurements (n=533), highlighting the difficulties associated with the AMBP technique and might limit the reliability of especially negative findings in this study. However, the inclusion of excluded subjects with 1 to 47 valid measurements (n=97) did not influence our main finding of a significant positive interaction between target-organ damage and both 24hPP and average real variability in younger subjects.

The rationale for the original study design was to determine cardiovascular risk in different age groups (30-, 40-, 50-, and 60-year olds) in 1983 but also to evaluate impact of aging within each age group when re-evaluated in 1993 to 1994. This age selection must be taken in to account if our results are to be generalized to a broader population.

Finally, we did not adjust for multiple testing in our analyses. As such, and because of relative few events in this overall low-risk population, our findings are to be considered hypothesis-generating, and some positive results because of chance cannot be ruled out.

Conclusions

In apparently healthy, untreated subjects, both presence of target-organ damage and BP levels, but not BP variability, obtained from 24hABPM carried additive risk on top of traditional risk factors. In the subgroup of middle-aged subjects, the associations of 24hPP and average real variability with incident CVD were strengthened by the presence of subclinical target-organ damage, suggesting that target-organ damage may be a marker of individual susceptibility to the harmful effects of increased pulse pressure and BP variability on the cardiovascular system. The slightly improved risk prediction by the combination of 24hSBP and presence of target-organ damage was further improved when interactions between age, 24hPP, and target-organ damage were taken into account.

Disclosures

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Novelty and Significance

What Is New?

- The associations of 24-hour pulse pressure and systolic blood pressure variability with cardiovascular events were strengthened in subjects with subclinical target-organ damage suggesting that target-organ damage may be a marker of individual susceptibility to the harmful cardiovascular effects of increased 24-hour pulse pressure and average real variability.
- The combination of 24-hour systolic blood pressure and presence of target-organ damage improved risk prediction more when taken into account their interactions with age.

What Is Relevant?

- The prognostic importance of 24-hour pulse pressure and average real variability was more pronounced in middle-aged subjects with target-organ damage compared with older subjects without target-organ damage.

Summary

24-hour ambulant blood pressure measurements and target-organ damage improve risk prediction when their interactions with age are taken into account.

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Impact of Age and Target-Organ Damage on Prognostic Value of 24-Hour Ambulatory Blood Pressure

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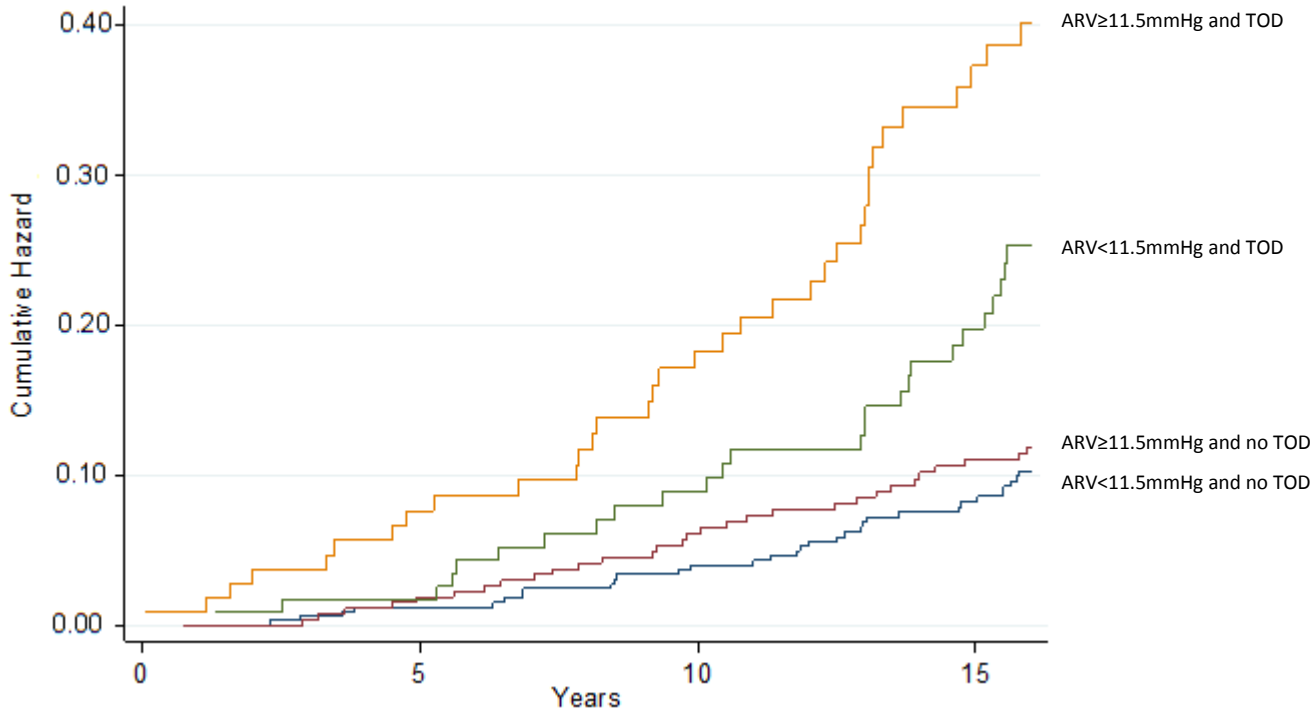
Supplemental figure S1 – Risk of MACE in middle-aged subjects (aged 41 or 51)

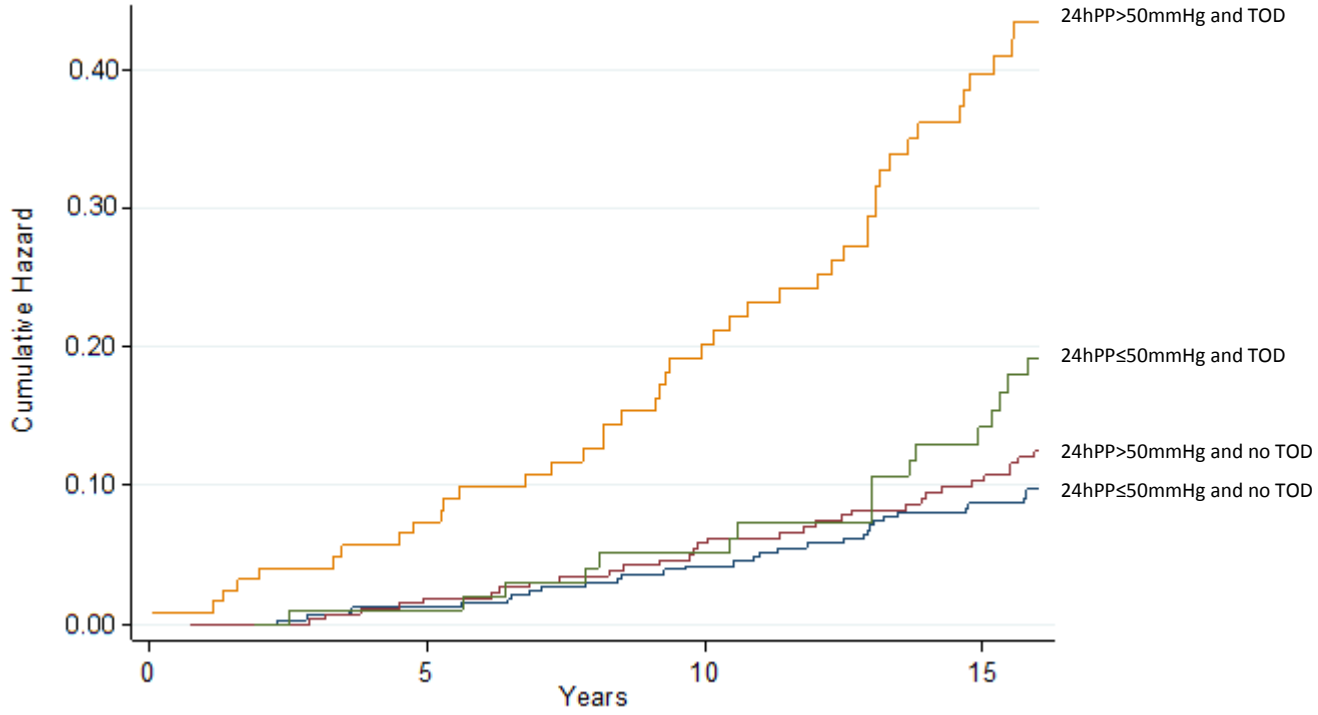


Model	ARV<11.5mmHg and no TOD	ARV≥11.5mmHg and no TOD	ARV<11.5mmHg and TOD	ARV≥11.5mmHg and TOD
No	339	275	119	109
Hazard ratios (95% CI)	1	1.17 (0.71-1.92)	2.44 (1.46- 4.10)	4.40 (2.48-6.47)

Nelson-Aalen cumulative hazard estimates and hazard ratios of MACE in subgroups according to ARV and presence of TOD. Subjects without TOD and ARV<11.5mmHg were the reference group.

Abbreviations: ARV, average real variability; TOD, target organ damage.

Supplemental figure S2 – Risk of MACE in middle-aged subjects (aged 41 or 51)



Model	24hPP≤50mmHg and no TOD	24hPP>50mmHg and no TOD	24hPP≤50mmHg and TOD	24hPP>50mmHg and TOD
No	344	270	102	126
Hazard ratios (95% CI)	1	1.28 (0.78-2.10)	1.92 (1.06-3.46)	4.53 (2.86-7.17)

Nelson-Aalen cumulative hazard estimates and hazard ratios of MACE in subgroups according to 24hPP and presence of TOD. Subjects without TOD and 24hPP≤50mmHg were the reference group.

Abbreviations: 24hPP, 24 hour pulse pressure; TOD, target organ damage.