OPEN

Conventional and Ambulatory Blood Pressure as Predictors of Retinal Arteriolar Narrowing

Fang-Fei Wei, Zhen-Yu Zhang, Lutgarde Thijs, Wen-Yi Yang, Lotte Jacobs, Nicholas Cauwenberghs, Yu-Mei Gu, Tatiana Kuznetsova, Karel Allegaert, Peter Verhamme, Yan Li, Harry A.J. Struijker-Boudier, Jan A. Staessen

Abstract—At variance with the long established paradigm that retinal arteriolar narrowing trails hypertension, several longitudinal studies, all based on conventional blood pressure (CBP) measurement, proposed that retinal arteriolar narrowing indicates heightened microvascular resistance and precedes hypertension. In 783 randomly recruited Flemish (mean age, 38.2 years; 51.3% women), we investigated to what extent CBP and daytime (10 AM to 8 PM) ambulatory blood pressure (ABP) measured at baseline (1989–2008) predicted the central retinal arteriolar equivalent (CRAE) in retinal photographs obtained at follow-up (2008–2015). Systolic/diastolic hypertension thresholds were 140/90 mm Hg for CBP and 135/85 mm Hg for ABP. In multivariable-adjusted models including both baseline CBP and ABP, CRAE after 10.3 years (median) of follow-up was unrelated to CBP ($P \geq 0.14$), whereas ABP predicted CRAE narrowing ($P \leq 0.011$). Per 1-SD increment in systolic/diastolic blood pressure, the association sizes were −0.95 µm (95% confidence interval, −2.20 to 0.30)/−0.75 µm (−1.93 to 0.42) for CBP and −1.76 µm (−2.95 to −0.58)/−1.48 µm (−2.61 to −0.34) for ABP. Patients with ambulatory hypertension at baseline (17.0%) had smaller CRAE (146.5 versus 152.6 µm; $P < 0.001$) at follow-up. CRAE was not different ($P \geq 0.31$) between true normotension (normal CBP and ABP; prevalence, 77.6%) and white-coat hypertension (elevated CBP and normal ABP, 5.4%) and between masked hypertension (normal CBP and elevated ABP, 10.2%) and hypertension (elevated CBP and ABP, 6.8%). In conclusion, the paradigm that retinal arteriolar narrowing precedes hypertension can be explained by the limitations of CBP measurement, including nonidentification of masked and white-coat hypertension . **(*Hypertension*. 2016;68:511-520. DOI: 10.1161/HYPERTENSIONAHA.116.07523.)** ● **Online Data Supplement**

Key Words: ambulatory blood pressure monitoring ■ blood pressure ■ hypertension ■ microcirculation ■ population science ■ retina

In 1892, Gunn's pioneering work proposed narrowing of retinal arterioles as an early sign of hypertensive retinopathy and as a prognostic indicator in hypertensive patients.[1] More than a century later, abundant evidence shows that retinal arteriolar narrowing parallels target organ damage in cross-sectional studies[2] and predicts macrovascular complications in longitudinal population surveys.[3,4] At variance with the long established paradigm that retinal arteriolar narrowing trails hypertension, other studies proposed that retinal arteriolar narrowing indicates heightened microvascular resistance[5,6] and precedes the development of hypertension.[7–13] However, in these studies,[7–13] blood pressure was only conventionally measured as a single reading[9,11,13] or as the average of 2 readings,[7,8,10,12] using error-prone devices[14–16] based on an auscultatory[7–11,13] or oscillometric[12] approach.

Guidelines[17] and expert opinion[18,19] currently propose ambulatory blood pressure monitoring as the state-of-the-art method for measuring blood pressure. Compared with the conventional approach, ambulatory monitoring substantially refines risk stratification in hypertensive patients[20–22] and the general population.[23–25] The greater number of readings, the absence of observer bias, and the minimization of the white-coat effect all contribute to its predictive superiority.[17] The combined application of office and

Received March 14, 2016; first decision April 3, 2016; revision accepted May 22, 2016.

From the Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences (F.-F.W., Z.-Y.Z, L.T., W.-Y.Y, L.J., N.C., Y.-M.G., T.K., J.A.S.), Department of Development and Regeneration (K.A.), Centre for Molecular and Vascular Biology, KU Leuven Department of Cardiovascular Sciences (P.V.), University of Leuven, Leuven, Belgium; Center for Epidemiological Studies and Clinical Trials and Center for Vascular Evaluations, Shanghai Institute of Hypertension, Shanghai Key Laboratory of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China (Y.L.); and Department of Pharmacology (H.A.J.S.-B.) and R&D Group VitaK (J.A.S.), Maastricht University, Maastricht, The Netherlands.

This article was sent to Daniel W. Jones, Guest Editor, for review by expert referees, editorial decision, and final disposition.

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.116.07523/-/DC1.

Correspondence to Jan A. Staessen, Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Campus Sint Rafaël, Kapucijnenvoer 35, Box 7001, BE-3000 Leuven, Belgium. E-mail jan.staessen@med.kuleuven.be

ambulatory blood pressure measurement allows stratifying for white-coat and masked hypertension, reproducible conditions[26] characterized by a high conventional and normal ambulatory blood pressure or vice versa. The risk associated with white-coat hypertension is low, whereas it is high for masked hypertension.[25,27] In this article, we analyzed the Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO)[28,29] to assess to what extent conventional and daytime ambulatory blood pressure at baseline predicted retinal arteriolar and venular diameters at follow-up 10 years later.

Methods

Study Population

FLEMENGHO complies with the Helsinki declaration for research in human subjects and the Belgian legislation for the protection of privacy (http://www.privacycommission.be). As described in detail elsewhere,[28,29] from August 1985 to November 1990, a random sample of the households living in a geographically defined area of Northern Belgium was investigated. All household members with a minimum age of 20 years were invited to take part, if the quota of their sex-age group had not yet been satisfied. From June 1996 to January 2004 recruitment of families continued using the former participants (1985–1990) as index persons and including teenagers. The participants were repeatedly followed up. At each contact, participants gave informed written consent.

Of 3343 participants, 2904 had their daytime ambulatory blood pressure measured (1989–2008) and 1285 underwent retinal photography (2008–2015). The participation rate for ambulatory blood pressure monitoring and retinal photography amounted to 94.7% and 76.0%, respectively. In the context of this article, baseline and follow-up, respectively, refer to the dates of daytime blood pressure measurement and retinal imaging (Figure 1). We excluded participants from analysis if conventional and ambulatory blood pressure were measured at an interval >7 days (n=1039), if the daytime ambulatory blood pressure was the mean of <10 readings (n=35), or if the retinal photographs were of too low quality to be reliably graded (n=221). This left 791 participants with both conventional and ambulatory blood pressure measured and with gradable retinal photographs. Finally, we excluded 8 participants because their retinal microvascular diameters were >3 SDs lower than the population mean. Thus, the number of participants statistically analyzed totaled 783.

Imaging of the Retinal Microvasculature

Participants were asked to refrain from heavy exercise, smoking, drinking alcohol, or caffeine-containing beverages for at least 3 hours before retinal imaging. We applied a nonmydriatic approach in a dimly lit room to obtain retinal photographs, 1 image per eye in each participant, with the Canon Cr-DGi retinal visualization system combined with the Canon D 50 digital camera (Canon Inc, Medical Equipment Group, Utsunomiya, Japan). We determined the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent, which represent the retinal arteriolar and venular diameters, respectively. We used the validated computer-assisted program IVAN (Vasculomatic ala Nicola, version 1.1; Department of Ophthalmology and Visual Science, University of Wisconsin-Madison, Madison, WI) based on formulae published by Parr and Spears[30] and Hubbard et al.[31] The IVAN software returns average vessel diameters according to the revised Knudtson formula.[32] The arteriolar:venular diameter ratio (AVR) was CRAE divided by central retinal venular equivalent. For analysis, we averaged each participant's measurements at both eyes. Intraobserver variability according to the Bland and Altman method[33] was 11.7% for CRAE, 9.6% for central retinal venular equivalent, and 12.5% for AVR.[34] The corresponding estimates for interobserver variability were 10.8%, 9.9%, and 14.6%.[34]

Blood Pressure Measurement

Nurses measured each participant's blood pressure at baseline and follow-up by auscultation of the Korotkoff sounds. After the participants had rested for 5 minutes in the sitting position, the observers obtained 5 consecutive blood pressure readings (phase V diastolic pressure) to the nearest 2 mm Hg, using mercury sphygmomanometers. Standard cuffs had a 12×24 cm inflatable portion, but if upper arm girth exceeded 31 cm, larger cuffs with 15×35 cm bladders were used. For analysis, the 5 blood pressure readings obtained at baseline or at follow-up were averaged. From baseline to follow-up, we implemented a stringent quality assurance and quality control program, as described in detail elsewhere.[35,36] We checked digit preference at 6-month intervals. Hypertension on conventional blood pressure measurement was a blood pressure equal to or exceeding 140 mm Hg systolic or 90 mm Hg diastolic.

At baseline, within 1 week of the conventional blood pressure measurements, participants were validated[37] SpaceLabs 90204 or 90207 portable monitors to record their daytime ambulatory blood pressure from 8 AM to 10 PM at 20-minute intervals. As an alternative, they could also opt having their blood pressure monitored >24 hours, but for the current study, only the daytime part of these recordings was analyzed. The recordings were sparsely edited, removing only readings labeled with an error code or with lower systolic than diastolic blood pressure level. For continuous analyses, we computed the daytime blood pressure as the within-individual mean of the readings between 10 AM and 8 PM weighted for the interval between readings. This short definition of daytime eliminates the transition periods in the morning and evening during which blood pressure changes rapidly in most people and approximates within 1 to 2 mm Hg to the wakeful blood pressure recorded by the diary method.[38] In categorical analyses, ambulatory hypertension was a daytime blood pressure of 135 mm Hg systolic or 85 mm Hg diastolic or higher.[17] Normotension and sustained hypertension were a consistently normal or elevated blood pressure on conventional and ambulatory measurement. White-coat hypertension was a raised conventional blood pressure in the presence of a normal daytime blood pressure. Masked hypertension was an elevated ambulatory blood pressure with normal conventional blood pressure. Participants were cross-classified based on blood pressure levels only, irrespective of treatment with antihypertensive drugs.

Other Measurements

The nurses measured the subjects' anthropometric characteristics. Body mass index was weight in kilograms divided by the square of height in meters. They also administered a standardized questionnaire inquiring into each participant's medical history, smoking and drinking habits, and intake of medications. Consumption of alcohol was a daily intake of at least 5 g of ethanol.[39] Plasma glucose and total serum cholesterol were measured using automated methods in a single certified laboratory. Diabetes mellitus was described as a fasting or random glucose level exceeding 126 or 200 mg/dL (7.0 or 11.1 mmol/L) or use of antidiabetic agents.[40]

Statistical Analysis

For database management and statistical analysis, we used SAS software, version 9.4. We compared means and proportions by the standard normal z test or ANOVA and by the χ^2 statistic, respectively. We applied McNemar test to assess changes over time in categorical variables. Statistical significance was a 2-sided significance level of 0.05 on 2-sided tests.

First, in unadjusted analyses, we explored whether the baseline conventional and ambulatory blood pressure, either as continuous variables or by their cross-classification into normotension and white-coat, masked and sustained hypertension predicted the retinal microvascular traits at follow-up. We then searched for covariables of the retinal microvascular diameters, using a stepwise regression procedure with P values for covariables to enter and stay in the models set at 0.15. We standardized the retinal traits to the average in the whole study population (mean or ratio) for significant covariables so identified. In multivariable-adjusted analyses, we assessed conventional and ambulatory blood pressure as continuous variables or their

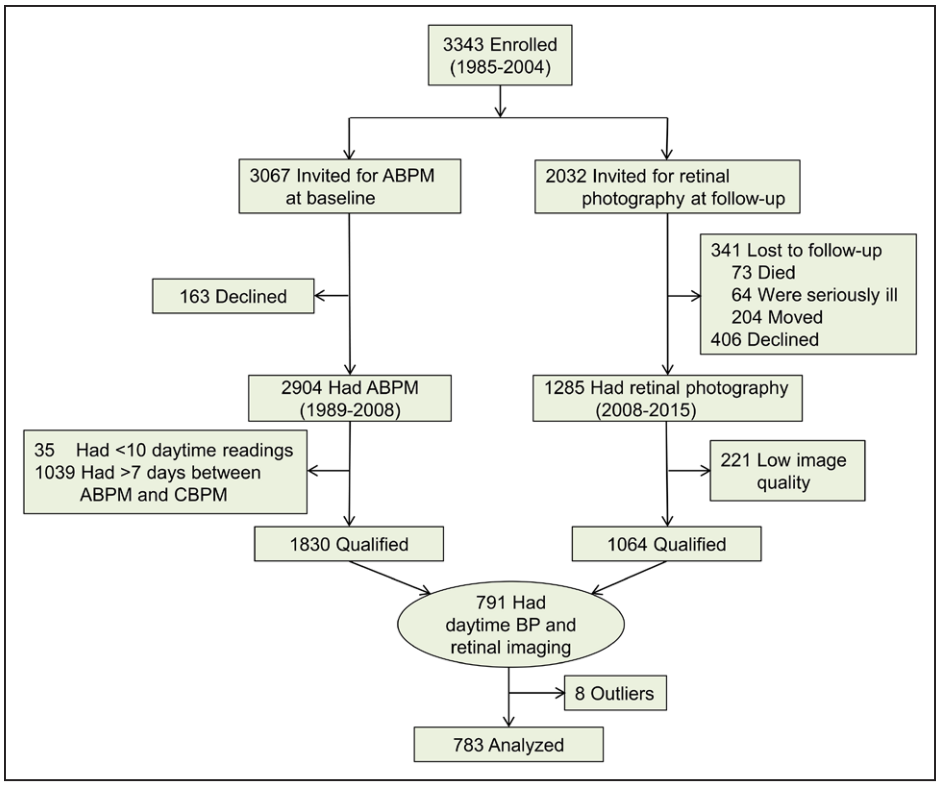

Figure 1. Flowchart for study participants.

cross-classification as predictors of the retinal traits. Fully adjusted analyses accounted for sex, age, body mass index, smoking and drinking, serum total cholesterol, plasma glucose at baseline, duration of follow-up, and 3 indicator variables coding for starting, stopping, or continuing antihypertensive drug treatment from baseline to follow-up. We computed the variance inflation factor for collinearity from regression models including both conventional and daytime blood pressure.[41] The final multivariable analyses relied on mixed models as implemented in SAS 9.4, which accounted for family clusters modeled as a random effect and the other covariables modeled as fixed effects. In sensitivity analyses, we replaced age, body mass index, smoking and drinking, serum total cholesterol, and plasma glucose by the values obtained at follow-up. In addition, we ran models relating CRAE and AVR as continuous traits with daytime blood pressure at baseline and concurrent conventional blood pressure at follow-up.

Results

Quality of the Blood Pressure Measurements

Within-individual participants, there were no missing conventional blood pressure readings in each series of 5. Of the 7830 systolic and diastolic blood pressure readings obtained by auscultation at baseline, 25.9% ended on zero, 17.5% on 2, 19.7% on 4, 18.1% on 6, and 18.8% on 8. At follow-up, these proportions were 22.0%, 19.0%, 19.8%, 19.7%, and 19.4%, respectively. Combining baseline and follow-up, only 6 readings (0.03%) ended on an odd number. The number of participants with 5 identical readings at baseline amounted to 5 (0.64%) for systolic pressure and to 7 (0.89%) for diastolic pressure. At follow-up, these numbers were 2 (0.26%) and 6 (0.77%), respectively. The number of blood pressure readings obtained by ambulatory monitoring ranged from 11 to 43 (median, 32; 5th–95th percentile interval, 19–40).

Characteristics of Participants

All 783 participants were white Europeans, of whom 402 (51.3%) were women. The study population consisted of 124 singletons and 659 related subjects, belonging to 128 one-generation families and to 88 multigeneration pedigrees. In all participants (Table 1), mean values at baseline were 38.2 years for age, 120.7/74.8 mm Hg and 122.8/76.1 mm Hg for systolic and diastolic blood pressure, respectively, on conventional and daytime measurement, and 24.7 kg/m^2 for body mass index. At baseline, participants opting for 24-hour (n=299) instead of daytime (n=484) monitoring had similar sex distribution and prevalence of smoking and drinking ($P \geq 0.21$), but were on average 6.0 years older and therefore had slightly but significantly ($P \leq 0.048$) higher body mass index, blood pressure, serum cholesterol, and plasma glucose.

Median follow-up was 10.3 years (5th–95th percentile interval, 4.8–20.2 years). From baseline to follow-up, the prevalence of smoking decreased from 21.2% to 15.8%, whereas the proportion of people drinking alcohol increased from 27.1% to 40.9%. Body mass index, the prevalence of overweight and obesity, conventional blood pressure, and treatment rates for hypertension and hyperlipidemia increased from baseline to follow-up. On the contrary, serum total cholesterol and plasma glucose decreased over time. At baseline, among 66 participants on antihypertensive drug treatment, 23 (2.9%) were taking diuretics, 53 (6.8%) inhibitors of the renin-angiotensin system (β-blockers, angiotensin-converting enzyme inhibitors, or angiotensin II type-1 receptor blockers) and 12 on vasodilators (calcium-channel blockers or α-blockers). At follow-up, the number of participants on

Table 1. Characteristics of Participants at Baseline and Follow-Up

Characteristic	Baseline	Follow-Up	*P* Value
No. with characteristics (%)	783	783	
Current smoker	166 (21.2)	124 (15.8)	<0.001
Drinking alcohol ≥5 g/d	212 (27.1)	320 (40.9)	<0.001
Overweight	255 (32.6)	305 (39.0)	0.0014
Obesity	78 (10.0)	146 (18.6)	<0.001
Diabetes mellitus	8 (1.0)	26 (3.3)	0.002
Conventional hypertension	95 (12.1)	232 (29.6)	<0.001
Daytime hypertension	133 (17.0)	…	…
On antihypertensive drugs	66 (8.4)	174 (22.2)	<0.001
Lipid-lowering treatment	25 (3.2)	117 (14.9)	<0.001
Mean of characteristic (±SD)			
Age, years	38.2±14.4	49.3±15.0	<0.001
Body mass index, kg/m^2	24.7±4.3	26.4±4.5	<0.001
Conventional blood pressure			
Systolic, mm Hg	120.7±14.1	128.6±15.8	<0.001
Diastolic, mm Hg	74.8±10.6	81.9±9.9	<0.001
Daytime blood pressure			
Systolic, mm Hg	122.8±10.2	…	…
Diastolic, mm Hg	76.1±7.8	…	…
Total cholesterol, mmol/L	5.10±1.02	4.95±0.92	0.002
Plasma glucose, mmol/L	5.05±1.02	4.78±0.74	<0.001

Body mass index was body weight in kilogram divided by height in meters squared. Overweight and obesity refer to a body mass index of 25 to 29.9 and ≥30 kg/m^2, respectively. Conventional hypertension was a blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic. Daytime hypertension was a blood pressure of ≥135 mm Hg systolic or ≥85 mm Hg diastolic. *P* values indicates the significance of the difference between baseline and follow-up.

antihypertensive drugs increased to 174, of whom 60 (7.7%) were on diuretics, 137 (17.5%) on inhibitors of the renin-angiotensin system, and 46 (5.9%) on vasodilators. From baseline to follow-up, the number of patients on combination therapy increased from 22 to 69 (P<0.001).

Of the 783 participants, at baseline, 608 (77.6%) were consistently normotensive based on conventional and daytime blood pressure measurement and 42 (5.4%), 80 (10.2%), and 53 (6.8%) had white-coat, masked, or sustained hypertension (Table 2). Among 42 white-coat hypertensive patients, the conventional blood pressure thresholds were met by 16 participants (38.0%) for systolic pressure, by 19 (45.2%) for diastolic pressure, and by 7 (16.8%) for systolic and diastolic blood pressure. Among the 80 participants with masked hypertension, 27 (33.8%) satisfied the daytime threshold for systolic pressure, 32 (40.0%) the diastolic threshold, and 21 (26.2%) both.

Continuous Analyses

Figure 2 demonstrates that in unadjusted analyses, CRAE decreased (P≤0.003) across sex-specific fourths of the distributions of blood pressure, irrespective of the type of measurement.

Associations of CRAE with conventional and daytime blood pressure, either analyzed separately or introduced together in the same model, appear in Table 3. All analyses in Table 3 accounted for clustering within families. In otherwise unadjusted models, 1-SD increment in the baseline systolic/diastolic blood pressure was associated with a smaller CRAE (P<0.001) at follow-up. The estimates were −3.14/−2.83 µm and by −3.03/−2.79 µm for conventional and daytime blood pressure, respectively. With adjustments applied for the baseline variables sex, age, and smoking, these estimates became −1.68/−1.34 µm and −2.14/−1.72 µm (P≤0.010). Fully adjusted models additionally included as covariables body mass index, serum total cholesterol, plasma glucose, and drinking at baseline, follow-up duration, and 3 indicator variables coding for starting, stopping, or remaining on antihypertensive drug treatment from baseline to follow-up. In fully adjusted models, CRAE at follow-up was 1.89/1.38 µm and 2.21/1.76 µm smaller in relation to the conventional and daytime blood pressure at baseline (P≤0.011).

Next, we introduced the conventional and daytime blood pressure together into the models (Table 3). Although accounting only for family ties, CRAE at follow-up significantly decreased in relation to both baseline conventional and daytime blood pressure with systolic/diastolic estimates amounting to −2.07/−1.86 µm (P≤0.001) and to −1.80/−1.78 µm (P≤0.002). In adjusted models, the associations of CRAE with conventional systolic/diastolic blood pressure lost significance (−0.60/−0.65 µm; P≥0.27), whereas those with daytime blood pressure remained significant (−1.83/−1.43 µm; P≤0.011). Fully adjusted models were confirmatory with effect sizes of −0.94/−0.75 µm (P≥0.14) and of −1.75/−1.46 µm (P≤0.011) for conventional and daytime blood pressure, respectively (Figure 3). In all models including both conventional and daytime blood pressure, the variance inflation factor for collinearity was ≤1.94. Finally, sensitivity analyses, in which we adjusted for covariables measured at follow-up instead of baseline, produced consistent results (Table S1 and Figure S1 in the online-only Data Supplement). The same was true if we additionally replaced baseline conventional blood pressure by concurrent conventional blood pressure (Table S2).

Both before and after adjustment for baseline or follow-up variables, all associations of central retinal venular equivalent with conventional and daytime blood pressure were nonsignificant (0.06≤P≤0.87; Tables S3 and S4); the associations of AVR with blood pressure mirrored those of CRAE, the numerator of AVR (Tables S5 and S6).

Categorical Analyses

Table 4 shows the retinal traits by cross-classification based on the baseline conventional and daytime blood pressure. Patients with ambulatory hypertension at baseline (17.0%) had smaller CRAE (146.5 versus 152.6 µm; P<0.001) and AVR (0.68 versus 0.70; P=0.004) at follow-up. Participants with sustained hypertension had smaller CRAE than those with normotension and white-coat hypertension (P≤0.050), whereas there was no difference between participants with sustained hypertension and masked hypertension (P≥0.31), irrespective of whether

Table 2. Characteristics of Participants at Baseline by Blood Pressure Status

Characteristic	Normotension	White-Coat Hypertension	Masked Hypertension	Sustained Hypertension	*P* Value
No. with characteristics (%)	608 (77.6)	42 (5.4)	80 (10.2)	53 (6.8)	
Women	343 (56.4)	15 (35.7)*	25 (31.2)	19 (35.8)	<0.001
Current smoker	119 (19.6)	8 (19.0)	28 (35.0)	11 (20.8)	0.017
Drinking alcohol ≥5 g/d	144 (23.7)	11 (26.2)	34 (42.5)	23 (43.4)	0.001
Diabetes mellitus	4 (0.7)	1 (2.4)	2 (2.5)	1 (1.9)	0.30
Treated for hypertension	39 (6.4)	5 (11.9)	7 (8.8)	15 (28.3)*	<0.001
Mean of characteristic (±SD)					
Age, years	36.1±14.0	47.2±13.3†	41.1±13.8‡	50.4±11.8†	<0.001
Body mass index, kg/m^2	24.2±4.2	26.2±4.2*	26.0±4.8	26.3±2.8	<0.001
Conventional blood pressure					
Systolic, mm Hg	116.4±10.4	140.5±11.7†	125.2±8.1†	148.1±13.3†	<0.001
Diastolic, mm Hg	72.0±8.9	89.9±6.5†	76.9±7.5†	90.8±9.3†	<0.001
Heart rate, bpm	68.3±9.0	65.6±8.9	69.0±10.4‡	69.6±11.8	<0.001
Daytime blood pressure					
Systolic, mm Hg	119.3±7.2	123.4±7.6†	136.0±6.3†	141.6±9.3†	<0.001
Diastolic, mm Hg	73.7±5.8	76.6±5.9*	85.3±5.3†	89.6±8.4†	<0.001
Heart rate, bpm	76.8±10.8	71.0±10.5†	79.8±11.2†	75.5±12.8‡	<0.001
Total cholesterol, mmol/L	4.98±0.97	5.46±1.06*	5.37±1.06	5.81±1.16‡	<0.001
Plasma glucose, mmol/L	5.00±1.00	5.05±0.89	5.28±1.08	5.30±1.18	<0.001

Body mass index was body weight in kilogram divided by height in meters squared. Normotension and sustained hypertension were a consistently normal or elevated blood pressure on conventional (threshold, 140/90 mm Hg) and daytime ambulatory measurement (threshold, 135/85 mm Hg). White-coat hypertension was a raised conventional blood pressure (≥140/90 mm Hg) with a normal daytime blood pressure (<135/85 mm Hg). Masked hypertension was a normal conventional blood pressure (<140/90 mm Hg) with a raised daytime blood pressure (≥135/85 mm Hg). *P* values for the overall between-group differences were derived by ANOVA.

Significance of the difference with the left adjacent group: *P≤0.01, †P≤0.001, and ‡P≤0.05.

the analyses were fully adjusted (Table 4). Furthermore, participants with sustained hypertension had smaller AVR than normotensive people (P≤0.015), again irrespective of adjustment (Table 4). Sensitivity analyses from which we excluded participants on antihypertensive drug treatment at baseline (Table S7) or accounting for covariables

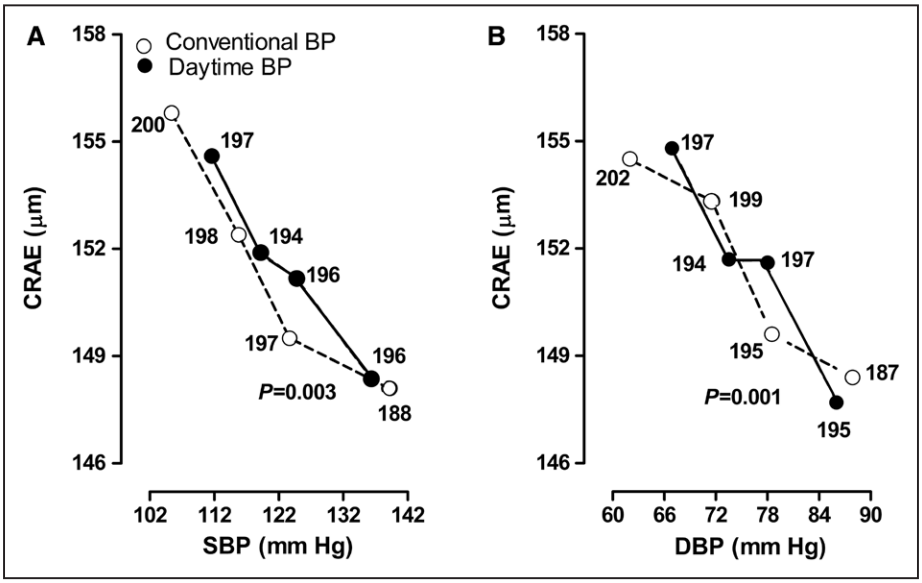

Figure 2. Sex-specific associations of central retinal arteriolar equivalent with conventional and daytime blood pressure. Central retinal arteriolar equivalent (CRAE) by fourths of the sex-specific distributions of systolic (SBP, **A**) or diastolic (DBP, **B**) blood pressures, based on conventional and daytime blood pressure measurements. *P* values for linear trend were all significant (P≤0.003).

Table 3. Central Retinal Arteriolar Equivalent at Follow-Up in Relation to Blood Pressure at Baseline

	Models Including a Single Type of Blood Pressure Measurement		Models Including Both Types of Blood Pressure Measurement	
	Conventional Blood Pressure	Daytime Blood Pressure	Conventional Blood Pressure	Daytime Blood Pressure
Systolic pressure				
Unadjusted	–3.14 (–4.08 to –2.20)*	–3.03 (–3.97 to –2.09)*	–2.07 (–3.23 to –0.91)*	–1.80 (–2.96 to –0.64)†
Adjusted	–1.68 (–2.70 to –0.64)†	–2.14 (–3.11 to –1.17)*	–0.60 (–1.83 to 0.63)	–1.83 (–2.99 to –0.66)†
Fully adjusted	–1.89 (–2.98 to –0.81)*	–2.21 (–3.22 to –1.19)*	–0.94 (–2.19 to 0.31)	–1.75 (–2.93 to –0.57)†
Diastolic pressure				
Unadjusted	–2.83 (–3.77 to –1.88)*	–2.79 (–3.74 to –1.85)*	–1.86 (–2.98 to –0.74)†	–1.78 (–2.90 to –0.66)†
Adjusted	–1.34 (–2.36 to –0.32)‡	–1.72 (–2.70 to –0.74)*	–0.65 (–1.80 to 0.50)	–1.43 (–2.54 to –0.32)‡
Fully adjusted	–1.38 (–2.46 to –0.31)‡	–1.76 (–2.80 to –0.73)*	–0.75 (–1.93 to 0.42)	–1.46 (–2.60 to –0.33)‡

Effect sizes (95% confidence interval) express the changes in the central retinal arteriolar equivalent associated with a 1-SD increase in conventional or daytime blood pressure. All estimates account for clustering within families. Adjusted estimates account for baseline characteristics including sex, age, and smoking. Fully adjusted models were additionally adjusted for body mass index, serum total cholesterol, plasma glucose, and drinking at baseline, for follow-up duration, and for three indicator variables coding for starting, stopping or continuing antihypertensive drug treatment from baseline to follow-up. In all models, the variance inflation factor for collinearity between conventional and daytime blood pressure was ≤1.94. Significance of the associations: *P≤0.001, †P≤0.01, and ‡P≤0.05.

measured at follow-up instead of baseline were confirmatory (Table S8).

Discussion

To our knowledge, our study is the first longitudinal population survey assessing the association of retinal microvascular traits with conventional and daytime ambulatory blood pressure either analyzed as continuous variables or categorized into distinct hypertension subtypes. The key findings can be summarized as follows: (1) CRAE and AVR at follow-up decreased with blood pressure at baseline, irrespective of the type of measurement; (2) in the presence of daytime ambulatory blood pressure, conventional blood pressure did not predict the retinal microvascular traits at follow-up; (3) in the presence of concurrent conventional blood pressure, baseline daytime blood pressure retained its predictive value for CRAE and AVR; (4) masked hypertension had a prevalence of 10% and was associated with the same degree of retinal arteriolar narrowing as sustained hypertension; (5) and white-coat hypertension, being present in 5.4% of participants, was not associated with retinal arteriolar narrowing compared with normotension.

A key question is whether retinal arteriolar narrowing occurs in response to current blood pressure levels or whether it relates to previous blood pressure levels, regardless of the current blood pressure level, and therefore reflects

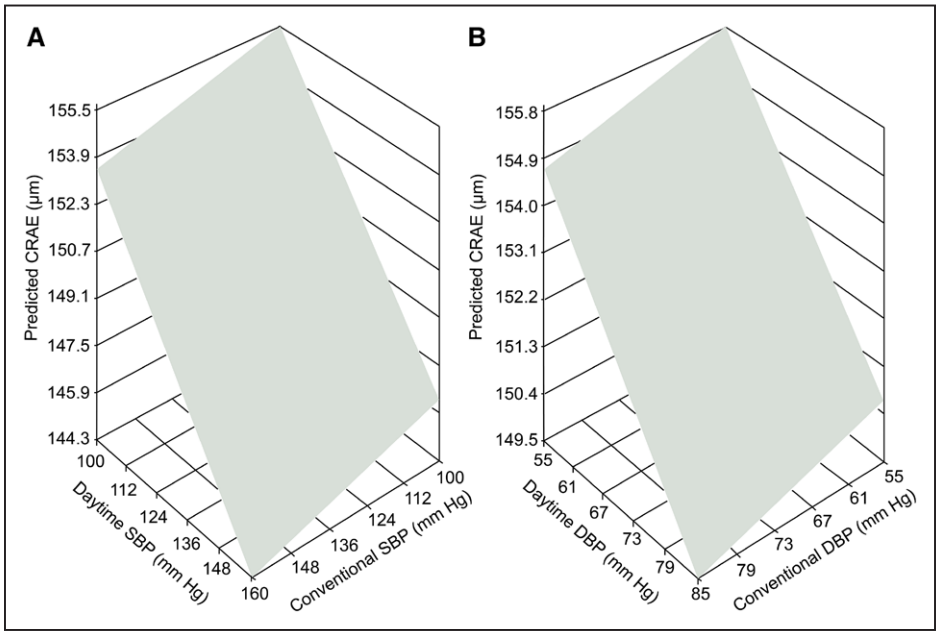

Figure 3. Multivariable-adjusted associations of central retinal arteriolar equivalent with systolic and diastolic blood pressure. The plane shows the independent associations of central retinal arteriolar equivalent (CRAE) with systolic (SBP; **A**) and diastolic (DBP; **B**) blood pressures, based on conventional and daytime measurement. The plotted plane was standardized to the midpoints of the distributions (means or ratios) of sex, age, body mass index, serum total cholesterol, plasma glucose, smoking, and drinking at baseline, to follow-up duration, and to 3 indicator variables coding for starting, stopping, or continuing antihypertensive drug treatment from baseline to follow-up.

Table 4. Retinal Phenotypes at Follow-Up by Hypertension Category at Baseline

Retinal Microvascular Trait	Normotension	White-Coat Hypertension	Masked Hypertension	Sustained Hypertension	P_{NT} Value	P_{WT} Value	P_{MT} Value
Unadjusted							
CRAE, µm	152.7±0.55	150.5±2.1	147.5±1.5	145.0±1.9	<0.001	0.050	0.31
CRVE, µm	218.8±0.78	222.8±3.0	217.5±2.2	216.2±2.6	0.35	0.10	0.70
AVR	0.70±0.003	0.68±0.012	0.68±0.009	0.67±0.011	0.015	0.84	0.62
Adjusted							
CRAE, µm	152.2±0.54	153.1±2.0	148.3±1.5	148.2±1.8	0.032	0.062	0.78
CRVE, µm	218.1±0.76	226.3±2.9	217.8±2.1	220.6±2.6	0.36	0.13	0.38
AVR	0.70±0.003	0.68±0.012	0.68±0.009	0.67±0.011	0.013	0.80	0.40
Fully adjusted							
CRAE, µm	152.2±0.54	152.8±2.0	148.6±1.5	147.6±1.9	0.020	0.049	0.64
CRVE, µm	218.1±0.76	225.8±2.9	217.9±2.1	221.0±2.7	0.34	0.18	0.37
AVR	0.70±0.003	0.68±0.012	0.68±0.009	0.67±0.012	0.006	0.61	0.21

Values are mean±SE. All estimates account for clustering within families. Adjusted estimates account for baseline characteristics including sex, age, and smoking. Fully adjusted models were additionally adjusted for body mass index, serum total cholesterol, plasma glucose, and drinking at baseline, for follow-up duration, and for 3 indicator variables coding for starting, stopping, or continuing antihypertensive drug treatment from baseline to follow-up. AVR indicates arteriole:venule ratio; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; P_{MT}, the significance of the difference between masked hypertension and sustained hypertension; P_{NT}, the significance of the difference between normotension and sustained hypertension; and P_{WT}, the significance of the difference between white-coat hypertension and sustained hypertension.

persisting arteriolar damage. Three previous population studies[42–44] assessed the association between retinal traits from photographs taken at 1 eye[42–44] and concurrent and past blood pressure. The exposure variable was a single blood pressure reading[44,45] or the average of 2 readings,[42,43] obtained with a standard mercury sphygmomanometer[44,45] or with the Hawksley random zero device.[42,43] Previous blood pressure was obtained 3,[42] 5,[44] 6,[42] or up to 8[43] years before retinal imaging. The report of the Atherosclerosis Risk in Communities (ARIC) study[42] included 9300 nondiabetic participants representing 4 communities (age range, 50–71 years; 56.2% women; 19.0% blacks). In multivariable-adjusted analyses, AVR decreased ($P \leq 0.009$) with concurrent and past mean arterial pressure, irrespective of sex and antihypertensive drug treatment. Effect sizes for a 10-mm Hg higher level of mean arterial pressure ranged from −0.010 to −0.018 and from −0.006 to −0.012 for concurrent and past blood pressure, respectively. Among 10 hypertensive retinal signs, 8 were associated with concurrent blood pressure, but arteriovenous nicking was the only retinal abnormality associated with both concurrent and past blood pressure with odds ratios per 10-mm Hg increment in mean arterial pressure of 1.10 (95% confidence interval, 1.00–1.21) and 1.28 (1.15–1.43), respectively.[42] In the Cardiovascular Health Study (CHS),[43] generalized arteriolar narrowing was defined as the lowest fifth of the CRAE distribution. Among 2405 participants, aged ≥65 years (60.0% women; 14.6% blacks; and 14.5% diabetic patients), the odds ratios of arteriolar narrowing, expressed per 10-mm Hg increments in blood pressure level, were 1.11 (1.04–1.18) systolic and 1.17 (1.04–1.31) diastolic for concurrent blood pressure and 1.15 (1.07–1.24) systolic and 1.30 (1.12–1.50) diastolic for past blood pressure.[43] However, with adjustment for concurrent blood pressure, generalized arteriolar narrowing was the only of 4 retinal signs that remained significantly associated with past blood pressure.[43] The Blue Mountains Eye Study (BMES)[44] reported that among 2002 people aged ≥54 years (57.6% women), the multivariable-adjusted slopes of CRAE on systolic/diastolic blood pressure were −0.13/−0.14 µm per mm Hg for concurrent blood pressure and −0.05/−0.09 µm per mm Hg for past blood pressure.[44] For AVR, these estimates were −0.12/−0.15 U per mm Hg and −0.02/−0.10 U per mm Hg, respectively.[44] To summarize, the combined evidence from 3 cohort studies[42–44] demonstrates that, expectedly, concurrent compared with past blood pressure is a stronger correlate of retinal microvascular traits.

Moving from retrospective[42–44] to prospective studies, 7 reports[7–13] suggested that retinal arteriolar narrowing precedes the development of hypertension. Mean follow-up from retinal imaging at baseline to the diagnosis of incident hypertension ranged from 3 years in the Multi-Ethnic Study of Atherosclerosis (MESA)[8] to 10 years in the Beaver Dam Eye Study (BDES)[7] and BMES,[11] and sample size ranged from 1058 in the Funagata Study[13] to 5628 in ARIC.[8] In all,[7,8,10–13] but 1 study,[9] hypertension was a conventional blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic or use of antihypertensive drugs. Incident hypertension in BMES[9] also included untreated severe hypertension with as thresholds 160 mm Hg systolic and 100 mm Hg diastolic. Mean age at enrollment ranged from 57.3[13] to 64.3[10] years. In all[7,8,10–13] but 1[9] study, the multivariable analyses accounted for blood pressure at baseline at the time of retinal imaging. Five studies[7,10–13] expressed the risk of hypertension per 1-SD increment in CRAE,[12,13] AVR,[7] or both.[10,11] In these continuous analyses, the maximally adjusted odds ratios ranged from 1.10 (1.10–1.20)[11] to 1.53 (1.08–2.18)[13] for CRAE and from 1.10 (1.00–1.20)[11] to 1.31 (1.18–1.45)[7] for AVR. In 7 reports,[7–13] investigators

also compared the risk of hypertension between the bottom and top quantile of the distributions of CRAE,[12,13] AVR,[7,8] or both,[9–11] subdivided into thirds,[13] fourths,[7,10,12] or fifths.[8,9,11] In these analyses, odds ratios ranged from 1.47 (1.01–2.14)[12] to 2.15 (1.58–2.93)[10] for CRAE and from 1.50 (1.20–2.00)[11] to 2.00 (1.30–3.00)[9] for AVR. In view of contemporary knowledge,[17–19] not yet available at the time of recruitment for the aforementioned prospective studies,[7–13] blood pressure measurement constitutes a major limitation in their interpretation. Indeed, in all studies,[7–13] blood pressure was the only conventionally measured as a single reading[9,11,13] or as the average of 2 readings,[7,8,10,12] using error-prone devices[14–16] based on auscultatory[7–11,13] or oscillometric[12] techniques. None of the studies reported on digit or number preference. Moreover, a single blood pressure reading or the average of 2 at a single visit is insufficient to differentiate normotension from hypertension.[17,46]

A major contribution of ambulatory blood pressure monitoring to risk stratification is the cross-classification between office and ambulatory blood pressure.[17] The International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcome (IDACO) includes randomly recruited population samples who had office and ambulatory blood pressure and cardiovascular risk factors measured at baseline with a longitudinal follow-up of fatal and nonfatal cardiovascular outcomes.[25,27] Using a daytime threshold of 135/85 mm Hg,[17] the prevalence of normotension and white-coat, masked, and sustained hypertension was 49.4%, 10.6%, 14.5%, and 25.5%, respectively.[25] The multivariable-adjusted risk associated with white-coat hypertension did not differ from normotension, whereas masked hypertension conferred a risk not different from that of sustained hypertension.[25] Among untreated IDACO participants with office normotension (<120/<80 mm Hg[46]) or office prehypertension (120–139/80–89 mm Hg[46]), the multivariable-adjusted hazard ratios associated with masked hypertension in normotensive subjects were 2.11 (1.24–3.60; P=0.007) for a composite cardiovascular end point and 3.02 (1.25–7.32; P=0.01) for stroke.[27] The corresponding hazard ratios associated with masked hypertension in prehypertensive subjects were 2.08 (1.67–2.59; P<0.0001) and 2.97 (2.03–4.35; P<0.0001), respectively.[27] In the reviewed prospective studies,[7–13] normotension at the time of retinal imaging includes masked hypertension, a forerunner of sustained hypertension,[47,48] which as shown in our current study is associated with retinal arteriolar narrowing. Furthermore, hypertension at follow-up in the reviewed studies encompasses white-coat hypertension, of which the prevalence increases with a lower number of conventional readings,[49] higher conventional blood pressure,[49,50] and advancing age.[49,50] Compared with normotension, the cardiovascular risk associated with white-coat hypertension also increases with longer follow-up with a hazard ratio of 1.30 (1.01–1.68; P=0.043) at 12 years of follow-up.[25] Disregarding masked hypertension at baseline and higher conventional blood pressure at baseline as precursor of white-coat hypertension at follow-up,[49,50] in our view, necessitate revision of the hypothesis that retinal arteriolar narrowing precedes true hypertension.[7–13]

In our current study, we did not take photographs at baseline. However, in the retrospective[42–44] and prospective[7–13] studies reviewed above, the conventional blood pressure was always measured at baseline and follow-up, but retinal photographs were lacking at baseline in the retrospective studies[42–44] and at follow-up in the prospective studies[7–13] that proposed that retinal arteriolar narrowing precedes hypertension. We did a sensitivity analysis showing that even in the presence of concurrent conventional blood pressure daytime ambulatory blood pressure at baseline remained a predictor of retinal arteriolar narrowing at follow-up (Table S2). In previous studies based on conventional blood pressure measurement, concurrent compared with past blood pressure was consistently a stronger correlate of the retinal microvascular traits.[42–44] Moreover, retinal arteriolar diameter decreases with aging,[34] making it unlikely that in our current study, we missed retinal arteriolar narrowing already being present at baseline.

Our current study has to be interpreted within the context of other potential limitations and its strengths. First, at baseline, there was a slight overrepresentation of conventional blood pressure readings ending in zero (25.9% versus the expected 20%). However, to our knowledge, FLEMENGHO is among the few studies that reported on the quality of both conventional and ambulatory blood pressure measurement. Second, in line with current practice,[17] we used daytime not 24-hour ambulatory blood pressure to cross-classify our participants. However, previous studies demonstrated that using daytime or 24-h blood pressure yields similar proportions of patients with white-coat and masked hypertension,[48] as well as similar estimates of cardiovascular risk.[27] Third, the prevalence of white-coat hypertension in our study was about half of that in other studies of populations[25,27] and patients.[48] However, our participants were repeatedly followed up by the same team of study nurses living in the catchment area of the study. Familiarization of participants with the study team is a likely explanation of the low prevalence of white-coat hypertension. Fourth, ≈20% of invitees declined retinal imaging at follow-up. However, participants and nonparticipants did not differ (P≥0.16) in age, body mass index, conventional and daytime blood pressure level, or prevalence of hypertension or smoking. Finally, our study included only white Europeans. However, in the international multiethnic IDACO study, there were no differences in the risks associated with blood pressure among Europeans, Asians, and South Americans.[27]

Perspectives

The paradigm that retinal arteriolar narrowing precedes hypertension can be explained by the limitations of conventional blood pressure measurement, including the nonidentification of white-coat and masked hypertension. The take-home message of our current study is that multiple measurements of blood pressure outside the medical environment are superior to fewer measurements by observers and that ambulatory monitoring, as already proposed a decade ago by Pickering et al[18,19] and as reiterated in contemporary guidelines,[17] is the state-of-the-art technique for assessing blood pressure in clinical practice and research.

Acknowledgments

We acknowledge the contribution of the nurses working at the examination center (Linda Custers, Marie-Jeanne Jehoul, Daisy Thijs,

and Hanne Truyens) and the clerical staff at the Studies Coordinating Centre (Vera De Leebeeck, Yvette Piccart, and Renilde Wolfs).

Sources of Funding

The European Union (HEALTH-2011.2.4.2-2-EU-MASCARA, HEALTH-F7-305507 HOMAGE and the European Research Council Advanced Researcher Grant-2011-294713-EPLORE) and the Fonds voor Wetenschappelijk Onderzoek Vlaanderen, Ministry of the Flemish Community, Brussels, Belgium (G.0881.13 and G.088013) currently support the Studies Coordinating Centre in Leuven.

Disclosures

None.

References

1. Gunn RM. Ophthalmoscopic evidence of (1) arterial changes associated with chronic renal disease and (2) of increased arterial tension. *Trans Ophthalmol Soc UK*. 1892;1892:12–124.
2. Chew SK, Xie J, Wang JJ. Retinal arteriolar diameter and the prevalence and incidence of hypertension: a systematic review and meta-analysis of their association. *Curr Hypertens Rep*. 2012;14:144–151. doi: 10.1007/s11906-012-0252-0.
3. Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, Tielsch JM, Klein BE, Hubbard LD. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. *JAMA*. 2002;287:1153–1159.
4. Yatsuya H, Folsom AR, Wong TY, Klein R, Klein BE, Sharrett AR; ARIC Study Investigators. Retinal microvascular abnormalities and risk of lacunar stroke: Atherosclerosis Risk in Communities Study. *Stroke*. 2010;41:1349–1355. doi: 10.1161/STROKEAHA.110.580837.
5. Mulvany MJ. Are vascular abnormalities a primary cause or secondary consequence of hypertension? *Hypertension*. 1991;18(suppl I):I-52–I-57.
6. Rizzoni D, Castellano M, Porteri E, Bettoni G, Muiesan ML, Agabiti-Rosei E. Vascular structural and functional alterations before and after the development of hypertension in SHR. *Am J Hypertens*. 1994;7:193–200.
7. Wong TY, Shankar A, Klein R, Klein BE, Hubbard LD. Prospective cohort study of retinal vessel diameters and risk of hypertension. *BMJ*. 2004;329:79. doi: 10.1136/bmj.38124.682523.55.
8. Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, Klein BE, Hubbard LD, Nieto FJ; Atherosclerosis Risk in Communities Study. Retinal arteriolar diameter and risk for hypertension. *Ann Intern Med*. 2004;140:248–255.
9. Smith W, Wang JJ, Wong TY, Rochtchina E, Klein R, Leeder SR, Mitchell P. Retinal arteriolar narrowing is associated with 5-year incident severe hypertension: the Blue Mountains Eye Study. *Hypertension*. 2004;44:442–447. doi: 10.1161/01.HYP.0000140772.40322.ec.
10. Ikram MK, Witteman JC, Vingerling JR, Breteler MM, Hofman A, de Jong PT. Retinal vessel diameters and risk of hypertension: the Rotterdam Study. *Hypertension*. 2006;47:189–194. doi: 10.1161/01.HYP.0000199104.61945.33.
11. Wang JJ, Rochtchina E, Liew G, Tan AG, Wong TY, Leeder SR, Smith W, Shankar A, Mitchell P. The long-term relation among retinal arteriolar narrowing, blood pressure, and incident severe hypertension. *Am J Epidemiol*. 2008;168:80–88. doi: 10.1093/aje/kwn100.
12. Kawasaki R, Cheung N, Wang JJ, Klein R, Klein BE, Cotch MF, Sharrett AR, Shea S, Islam FA, Wong TY. Retinal vessel diameters and risk of hypertension: the Multiethnic Study of Atherosclerosis. *J Hypertens*. 2009;27:2386–2393. doi: 10.1097/HJH.0b013e3283310f7e.
13. Tanabe Y, Kawasaki R, Wang JJ, Wong TY, Mitchell P, Daimon M, Oizumi T, Kato T, Kawata S, Kayama T, Yamashita H. Retinal arteriolar narrowing predicts 5-year risk of hypertension in Japanese people: the Funagata study. *Microcirculation*. 2010;17:94–102. doi: 10.1111/j.1549-8719.2009.00006.x.
14. O'Brien E, Mee F, Atkins N, O'Malley K. Inaccuracy of the Hawksley random zero sphygmomanometer. *Lancet*. 1990;336:1465–1468.
15. Kronmal RA, Rutan GH, Manolio TA, Borhani NO. Properties of the random zero sphygmomanometer. *Hypertension*. 1993;21:632–637.
16. Ni H, Wu C, Prineas R, Shea S, Liu K, Kronmal R, Bild D. Comparison of Dinamap PRO-100 and mercury sphygmomanometer blood pressure measurements in a population-based study. *Am J Hypertens*. 2006;19:353–360. doi: 10.1016/j.amjhyper.2005.10.020.
17. O'Brien E, Parati G, Stergiou G, et al; European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens*. 2013;31:1731–1768. doi: 10.1097/HJH.0b013e328363e964.
18. Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. *N Engl J Med*. 2006;354:2368–2374. doi: 10.1056/NEJMra060433.
19. Pickering TG, Gerin W, Schwartz JE, Spruill TM, Davidson KW. Franz Volhard lecture: should doctors still measure blood pressure? The missing patients with masked hypertension. *J Hypertens*. 2008;26:2259–2267. doi: 10.1097/HJH.0b013e32831313c4.
20. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A, Santucci C, Reboldi G. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension*. 1994;24:793–801.
21. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA*. 1999;282:539–546.
22. Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, Gheeraert PJ, Missault LH, Braun JJ, Six RO, Van Der Niepen P, O'Brien E; Office versus Ambulatory Pressure Study Investigators. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med*. 2003;348:2407–2415. doi: 10.1056/NEJMoa022273.
23. Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Predictors of all-cause mortality in clinical ambulatory monitoring: unique aspects of blood pressure during sleep. *Hypertension*. 2007;49:1235–1241. doi: 10.1161/HYPERTENSIONAHA.107.087262.
24. Boggia J, Li Y, Thijs L, et al; International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) investigators. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. *Lancet*. 2007;370:1219–1229. doi: 10.1016/S0140-6736(07)61538-4.
25. Hansen TW, Kikuya M, Thijs L, Björklund-Bodegård K, Kuznetsova T, Ohkubo T, Richart T, Torp-Pedersen C, Lind L, Jeppesen J, Ibsen H, Imai Y, Staessen JA; IDACO Investigators. Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: a meta-analysis of 7,030 individuals. *J Hypertens*. 2007;25:1554–1564. doi: 10.1097/HJH.0b013e3281c49da5.
26. Wei FF, Li Y, Zhang L, Shan XL, Cheng YB, Wang JG, Yang CH, Staessen JA. Persistence of masked hypertension in Chinese patients. *Am J Hypertens*. 2016;29:326–331. doi: 10.1093/ajh/hpv106.
27. Brguljan-Hitij J, Thijs L, Li Y, et al; International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome Investigators. Risk stratification by ambulatory blood pressure monitoring across JNC classes of conventional blood pressure. *Am J Hypertens*. 2014;27:956–965. doi: 10.1093/ajh/hpu002.
28. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, Tikhonoff V, Seidlerová J, Richart T, Jin Y, Olszanecka A, Malyutina S, Casiglia E, Filipovský J, Kawecka-Jaszcz K, Nikitin Y, Staessen JA; European Project on Genes in Hypertension (EPOGH) Investigators. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. *JAMA*. 2011;305:1777–1785. doi: 10.1001/jama.2011.574.
29. Liu YP, Gu YM, Thijs L, et al. Inactive matrix Gla protein is causally related to adverse health outcomes: a Mendelian randomization study in a Flemish population. *Hypertension*. 2015;65:463–470. doi: 10.1161/HYPERTENSIONAHA.114.04494.
30. Parr JC, Spears GF. General caliber of the retinal arteries expressed as the equivalent width of the central retinal artery. *Am J Ophthalmol*. 1974;77:472–477.
31. Hubbard LD, Brothers RJ, King WN, Clegg LX, Klein R, Cooper LS, Sharrett AR, Davis MD, Cai J. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology*. 1999;106:2269–2280.
32. Knudtson MD, Lee KE, Hubbard LD, Wong TY, Klein R, Klein BE. Revised formulas for summarizing retinal vessel diameters. *Curr Eye Res*. 2003;27:143–149.
33. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1:307–310.
34. Liu YP, Richart T, Jin Y, Struijker-Boudier HA, Staessen JA. Retinal arteriolar and venular phenotypes in a Flemish population: Reproducibility and correlates. *Artery Res.* 2011;5:72–79.

35. Staessen J, Bulpitt CJ, Fagard R, Joossens JV, Lijnen P, Amery A. Familial aggregation of blood pressure, anthropometric characteristics and urinary excretion of sodium and potassium–a population study in two Belgian towns. *J Chronic Dis*. 1985;38:397–407.
36. Kuznetsova T, Staessen JA, Kawecka-Jaszcz K, Babeanu S, Casiglia E, Filipovsky J, Nachev C, Nikitin Y, Peleskã J, O'Brien E. Quality control of the blood pressure phenotype in the European Project on Genes in Hypertension. *Blood Press Monit*. 2002;7:215–224.
37. Groppelli A, Omboni S, Parati G, Mancia G. Evaluation of noninvasive blood pressure monitoring devices Spacelabs 90202 and 90207 versus resting and ambulatory 24-hour intra-arterial blood pressure. *Hypertension*. 1992;20:227–232.
38. Fagard R, Brguljan J, Thijs L, Staessen J. Prediction of the actual awake and asleep blood pressures by various methods of 24 h pressure analysis. *J Hypertens*. 1996;14:557–563.
39. McFadden CB, Brensinger CM, Berlin JA, Townsend RR. Systematic review of the effect of daily alcohol intake on blood pressure. *Am J Hypertens*. 2005;18(2 Pt 1):276–286. doi: 10.1016/j.amjhyper.2004.07.020.
40. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diab Care*. 2003;26(suppl 1):S5–S20.
41. Kleinbaum DG, Kupper LL, Muller KE. Regression diagnostics. In: *Applied Regression Analysis and Other Multivariate Methods*. Boston, MA: PWS-Kent Publishing Company; 1988:181–227.
42. Sharrett AR, Hubbard LD, Cooper LS, Sorlie PD, Brothers RJ, Nieto FJ, Pinsky JL, Klein R. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 1999;150:263–270.
43. Wong TY, Hubbard LD, Klein R, Marino EK, Kronmal R, Sharrett AR, Siscovick DS, Burke G, Tielsch JM. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. *Br J Ophthalmol*. 2002;86:1007–1013.
44. Leung H, Wang JJ, Rochtchina E, Wong TY, Klein R, Mitchell P. Impact of current and past blood pressure on retinal arteriolar diameter in an older population. *J Hypertens*. 2004;22:1543–1549.
45. Leung H, Wang JJ, Rochtchina E, Tan AG, Wong TY, Klein R, Hubbard LD, Mitchell P. Relationships between age, blood pressure, and retinal vessel diameters in an older population. *Invest Ophthalmol Vis Sci*. 2003;44:2900–2904.
46. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572. doi: 10.1001/jama.289.19.2560.
47. Lurbe E, Torro I, Alvarez V, Nawrot T, Paya R, Redon J, Staessen JA. Prevalence, persistence, and clinical significance of masked hypertension in youth. *Hypertension*. 2005;45:493–498. doi: 10.1161/01.HYP.0000160320.39303.ab.
48. Zhang L, Li Y, Wei FF, Thijs L, Kang YY, Wang S, Xu TY, Wang JG, Staessen JA. Strategies for classifying patients based on office, home, and ambulatory blood pressure measurement. *Hypertension*. 2015;65:1258–1265. doi: 10.1161/HYPERTENSIONAHA.114.05038.
49. Staessen JA, O'Brien ET, Amery AK, Atkins N, Baumgart P, De Cort P, Degaute JP, Dolenc P, De Gaudemaris R, Enström I. Ambulatory blood pressure in normotensive and hypertensive subjects: results from an international database. *J Hypertens Suppl*. 1994;12:S1–12.
50. Conen D, Aeschbacher S, Thijs L, et al. Age-specific differences between conventional and ambulatory daytime blood pressure values. *Hypertension*. 2014;64:1073–1079. doi: 10.1161/HYPERTENSIONAHA.114.03957.

Novelty and Significance

What Is New?

- At variance with the long established paradigm, that retinal arterial narrowing trails hypertension, several longitudinal studies proposed that retinal arteriolar narrowing indicates heightened microvascular resistance and precedes the development of hypertension. In all previous longitudinal studies, blood pressure was conventionally measured. We investigated in 783 randomly recruited Flemish to what extent conventional (CBP) and daytime ambulatory (ABP) blood pressure predict narrowing of the retinal arterioles.

What Is Relevant?

- In multivariable-adjusted models including both baseline CBP and ABP, central retinal arteriolar equivalent after 10.3 years (median) of follow-up was unrelated to CBP, whereas central retinal arteriolar equivalent significantly decreased with the ABP level.
- Patients with ambulatory hypertension at baseline (≥135/85 mm Hg) had smaller central retinal arteriolar equivalent at follow-up.
- Central retinal arteriolar equivalent was not different between true normotension (normal CBP and ABP; prevalence, 78%) and white-coat hypertension (elevated CBP and normal ABP; 5%) and between masked hypertension (normal CBP and elevated ABP; 10%) and hypertension (elevated CBP and ABP; 7%).

Summary

The paradigm that retinal arterial narrowing precedes hypertension can be explained by the limitations of CBP measurement, including nonidentification of masked and white-coat hypertension. The take-home message is that in relation to the retinal microvasculature, multiple measurements of blood pressure outside the medical environment are superior to fewer measurements by observers.