Conventional and Ambulatory Blood Pressure as Predictors of Retinal Arteriolar Narrowing

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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 mmHg for CBP and 135/85 mmHg 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 ≤ 0.14), whereas ABP predicted CRAE narrowing (P ≤ 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 ≥ 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.

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

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Guidelines 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 and the general population. The greater number of readings, the absence of observer bias, and the minimization of the white-coat effect all contribute to its predictive superiority. The combined application of office and ambulatory blood pressure monitoring refines risk stratification in hypertensive patients.

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Correspondence to Jan A. Staessen, Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, F-3001, Be-3000 Leuven, Belgium. E-mail jan.staessen@med.kuleuven.be

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ambulatory blood pressure measurement allows stratifying for white-coat and masked hypertension, reproducible conditions 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. In this article, we analyzed the Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO) 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, 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 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 conventional and 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 withgradable 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 and Hubbard et al. The IVAN software returns average vessel diameters according to the revised Knudtson formula. 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 was 11.7% for CRAE, 9.6% for central retinal venular equivalent, and 12.5% for AVR. The corresponding estimates for interobserver variability were 10.8%, 9.9%, and 14.6%.

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 12x24 cm inflatable portion, but if upper arm girth exceeded 31 cm, larger cuffs with 15x35 cm bladders were used. For analysis, the 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. 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 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. In categorical analyses, ambulatory hypertension was a daytime blood pressure of 135 mm Hg systolic or 85 mm Hg diastolic or higher. 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. 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.

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 χ² 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 covariates of the retinal microvascular diameters, using a stepwise regression procedure with P values for covariates 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 covariates so identified. In multivariable-adjusted analyses, we assessed conventional and ambulatory blood pressure as continuous variables or their
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. 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, 18.7% 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 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/m² 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≥0.21), but were on average 6.0 years older and therefore had slightly but significantly (P≤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/m²      | 24.7±4.3 | 26.4±4.5 | <0.001 |
| Conventional blood pressure |          |           |         |
| Systolic, mmHg              | 120.7±14.1| 128.6±15.8| <0.001 |
| Diastolic, mmHg             | 74.8±10.6 | 81.9±9.9  | <0.001 |
| Daytime blood pressure      |          |           |         |
| Systolic, mmHg              | 122.8±10.2| ...      | ...    |
| Diastolic, mmHg             | 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/m², respectively. Conventional hypertension was a blood pressure of ≥140 mmHg systolic or ≥90 mmHg diastolic. Daytime hypertension was a blood pressure of ≥135 mmHg systolic or ≥85 mmHg diastolic. P values indicate the significance of the difference between baseline and follow-up.

Association 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...
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
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

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 | Conventional Blood Pressure | Daytime 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.

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.
persisting arteriolar damage. Three previous population studies assessed the association between retinal traits from photographs taken at 1 eye and concurrent and past blood pressure. The exposure variable was a single blood pressure reading or the average of 2 readings, obtained with a standard mercury sphygmomanometer or with the Hawksley random zero device. Previous blood pressure was obtained or up to 8 years before retinal imaging. The report of the Atherosclerosis Risk in Communities Study to 10 years in the Beaver Dam Eye Study (BMES) reported that among 2002 people aged ≥54 years (56.2% women; 19.0% blacks). In multivariable-adjusted analyses, AVR indicates arteriolar narrowing was the only of 4 retinal signs that remained significantly associated with past blood pressure. The Blue Mountains Eye Study (BMES) 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. For AVR, these estimates were −0.12/−0.15 U per mm Hg and −0.02/−0.10 U per mm Hg, respectively. To summarize, the combined evidence from 3 cohort studies demonstrates that, expectedly, concurrent compared with past blood pressure is a stronger correlate of retinal microvascular traits.

Moving from retrospective to prospective studies, reports 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) to 10 years in the Beaver Dam Eye Study (BMES) and sample size ranged from 1058 in the Funagata Study to 5628 in ARIC. In all but 1 study, 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 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 to 64.3 years. In all but 1 study, the multivariable analyses accounted 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 arteriolar narrowing was the only of 4 retinal signs that remained significantly associated with past blood pressure. The Blue Mountains Eye Study (BMES) 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. For AVR, these estimates were −0.12/−0.15 U per mm Hg and −0.02/−0.10 U per mm Hg, respectively. To summarize, the combined evidence from 3 cohort studies demonstrates that, expectedly, concurrent compared with past blood pressure is a stronger correlate of retinal microvascular traits.

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also compared the risk of hypertension between the bottom and top quintile 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,7,9–11,13 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 reading9,11,13 or as the average of 2 readings7,8,10,12 using error-prone devices14–16 based on auscultatory7–11,13 or oscillometric12 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.17,18

A major contribution of ambulatory blood pressure monitoring to risk stratification is the cross-classification between office and ambulatory blood pressure.25 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.24–27 Using a daytime threshold of 135/85 mm Hg,21 the prevalence of normotension and white-coat, masked, and sustained hypertension was 49.4%, 10.6%, 14.5%, and 25.5%, respectively.23 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 Hg20) or office prehypertension (120–139/80–89 mm Hg20), 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 studies7–13 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.49 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 retrospective42–44 and prospective2–13 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 studies42–44 and at follow-up in the prospective studies7–13 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 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,7 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,46 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 populations25,27 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 al48,49 and as reiterated in contemporary guidelines,17 is the state-of-the-art technique for assessing blood pressure in clinical practice and research.

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Disclosures
None.

Blood Pressure as Predictor of Retinopathy

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Conventional and Ambulatory Blood Pressure as Predictors of Retinal Arteriolar Narrowing

Fang-Fei Wei¹, Zhen-Yu Zhang¹, Lutgarde Thijs¹, Wen-Yi Yang¹, Lotte Jacobs¹, Nicholas Cauwenberghs¹, Yu-Mei Gu¹, Tatiana Kuznetsova¹, Karel Allegaert², Peter Verhamme³, Yan Li⁴, Harry AJ Struijker-Boudier⁵, Jan A. Staessen¹,6

Author Affiliations:

¹ Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium;
² Department of Development and Regeneration, University of Leuven, Belgium;
³ Centre for Molecular and Vascular Biology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Belgium;
⁴ Center for Epidemiological Studies and Clinical Trials and Center for Vascular Evaluations, Shanghai Institute of Hypertension, Shanghai Key Laboratory of Hypertension, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China;
⁵ Department of Pharmacology, Maastricht University, Maastricht, The Netherlands;
⁶ R&D Group VitaK, Maastricht University, Maastricht, The Netherlands

Corresponding Author:
Jan A. Staessen, jan.staessen@med.kuleuven.be or ja.staessen@maastrichtuniversity.nl, Kapucijnenvoer 35, Box 7001, BE-3000 Leuven, Belgium
Supplementary Online Content

This appendix formed part of the original submission and has been peer reviewed. We posted it as supplied by the authors.

Supplement to: “Conventional and Ambulatory Blood Pressure as Predictors of Retinal Arteriolar Narrowing”.

Table S1. CRAE in Relation to Baseline BP — Adjusted for Covariables at Follow-Up p2
Table S2. Retinal Phenotypes in Relation to Baseline Daytime and Concurrent Conventional BPs p3
Table S3. CRVE in Relation to Baseline BP — Adjusted for Covariables at Baseline p4
Table S4. CRVE in Relation to Baseline BP — Adjusted for Covariables at Follow-Up p5
Table S5. AVR in Relation to Baseline BP — Adjusted for Covariables at Baseline p6
Table S6. AVR in Relation to Baseline BP — Adjusted for Covariables at Follow-Up p7
Table S7. Retinal Phenotypes by Hypertension Category — Participants Untreated at Baseline p8
Table S8. Retinal Phenotypes by Hypertension Category — Adjusted for Covariables at Follow-Up p9

Figure S1. Multivariable-Adjusted Associations of CRAE with Baseline SBP and DBP p10
| Blood Pressure Model | 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    |                             |                         |                             |                         |
| Adjusted             | $-1.70 (-2.70$ to $-0.70)\ddagger$ | $-2.15 (-3.11$ to $-1.20)\ddagger$ | $-0.67 (-1.86$ to $0.52)$ | $-1.79 (-2.94$ to $-0.65)\dagger$ |
| Fully adjusted       | $-1.97 (-3.04$ to $-0.91)\ddagger$ | $-2.30 (-3.29$ to $-1.30)\ddagger$ | $-0.95 (-2.19$ to $0.29)$ | $-1.83 (-3.00$ to $-0.66)\dagger$ |
| Diastolic pressure   |                             |                         |                             |                         |
| Adjusted             | $-1.34 (-2.33$ to $-0.34)\dagger$ | $-1.72 (-2.68$ to $-0.76)\ddagger$ | $-0.64 (-1.77$ to $0.48)$ | $-1.42 (-2.52$ to $-0.33)*$ |
| Fully adjusted       | $-1.36 (-2.40$ to $-0.32)\dagger$ | $-1.79 (-2.80$ to $-0.79)\ddagger$ | $-0.68 (-1.82$ to $0.47)$ | $-1.51 (-2.62$ to $-0.39)\dagger$ |

Abbreviations: CRAE, central retinal arteriolar equivalent. Effect size (95% confidence interval) express the risk associated with a 1-SD increase in conventional or daytime blood pressures. All estimates account for clustering within families. Adjusted estimates account for follow-up characteristics including sex, age, and smoking. Fully adjusted estimates were additionally adjusted for body mass index, serum total cholesterol, plasma glucose, and drinking at follow-up, for follow-up duration, and for three indicator variables coding for starting, stopping or continuing antihypertensive drug treatment from baseline to follow-up. Significance of the effect sizes: * $P\leq0.05$, † $P\leq0.01$, and ‡ $P\leq0.001$. 
Table S2. Retinal Phenotypes in Relation to Baseline Daytime Blood Pressure and Concurrent Conventional Blood Pressure

| Blood Pressure Model | Models Including a Single Type of Blood Pressure Measurement | Models Including Both Types of Blood Pressure Measurement |
|----------------------|-------------------------------------------------------------|---------------------------------------------------------|
|                      | Baseline Daytime Blood Pressure | Concurrent Blood Pressure | Baseline Daytime Blood Pressure | Concurrent Blood Pressure |
| Systolic pressure    | CRAE, µm | $-2.30 \ (-3.29 \text{ to } -1.30)\dagger$ | $-3.10 \ (-4.18 \text{ to } -2.03)\dagger$ | $-1.61 \ (-2.63 \text{ to } -0.58)\dagger$ | $-2.60 \ (-3.71 \text{ to } -1.48)\dagger$ |
|                      | AVR    | $-0.011 \ (-0.017 \text{ to } -0.005)\dagger$ | $-0.014 \ (-0.020 \text{ to } -0.007)\dagger$ | $-0.009 \ (-0.015 \text{ to } -0.002)\dagger$ | $-0.011 \ (-0.018 \text{ to } -0.004)\dagger$ |
| Diastolic pressure   | CRAE, µm | $-1.79 \ (-2.80 \text{ to } -0.79)\dagger$ | $-2.74 \ (-3.74 \text{ to } -1.74)\dagger$ | $-1.04 \ (-2.08 \text{ to } -0.004)\ast$ | $-0.007 \ (-0.013 \text{ to } -0.001)\ast$ |
|                      | AVR    | $-0.012 \ (-0.018 \text{ to } -0.006)\dagger$ | $-0.017 \ (-0.023 \text{ to } -0.011)\dagger$ | $-2.40 \ (-3.45 \text{ to } -1.35)\dagger$ | $-0.014 \ (-0.021 \text{ to } -0.008)\dagger$ |

Abbreviations: CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; AVR, arteriole-to-venule ratio. Effect size (95% confidence interval) express the risk associated with a 1-SD increase in baseline daytime or concurrent blood pressures. All estimates account for clustering within families, sex, age, body mass index, serum total cholesterol, plasma glucose, and drinking at follow-up, for follow-up duration, and for three indicator variables coding for starting, stopping or continuing antihypertensive drug treatment from baseline to follow-up. Significance of the effect sizes: $\ast \text{ } P \leq 0.05$, $\dagger \text{ } P \leq 0.01$, and $\ddagger \text{ } P \leq 0.001$. 

Table S3. Central Retinal Venular Equivalent in Relation to Blood Pressure — Adjusted for Covariables at Baseline

| Blood Pressure Model | 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           | $-1.26$ ($-2.60$ to $0.10$) | $-0.93$ ($-2.28$ to $0.42$)          | $-1.09$ ($-2.76$ to $0.59$) | $-0.28$ ($-1.96$ to $1.39$) |
| Adjusted             | $0.96$ ($-0.50$ to $2.43$)  | $-0.11$ ($-1.49$ to $1.27$)          | $1.49$ ($-0.27$ to $3.25$)  | $-0.89$ ($-2.55$ to $0.76$) |
| Fully adjusted       | $0.99$ ($-0.54$ to $2.53$)  | $-0.08$ ($-1.53$ to $1.37$)          | $1.40$ ($-0.38$ to $3.19$)  | $-0.76$ ($-2.44$ to $0.93$) |
| Diastolic pressure   |                               |                                            |                            |                            |
| Unadjusted           | $-0.90$ ($-2.25$ to $0.45$) | $-0.62$ ($-1.97$ to $0.74$)          | $-0.80$ ($-2.41$ to $0.82$) | $-0.18$ ($-1.79$ to $1.43$) |
| Adjusted             | $1.37$ ($-0.07$ to $2.82$)  | $0.75$ ($-0.64$ to $2.15$)          | $1.28$ ($-0.35$ to $2.92$)  | $0.18$ ($-1.40$ to $1.75$) |
| Fully adjusted       | $1.20$ ($-0.32$ to $2.72$)  | $0.69$ ($-0.78$ to $2.15$)          | $1.09$ ($-0.57$ to $2.76$)  | $0.25$ ($-1.36$ to $1.86$) |

Abbreviations: CRVE, central retinal venular equivalent. Effect size (95% confidence interval) express the risk associated with a 1-SD increase in conventional or daytime blood pressures. All estimates account for clustering within families. Adjusted estimates account for baseline characteristics including sex, age, and smoking. Fully adjusted estimates 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. All effect sizes were not significant.
| Blood Pressure Model | Models Including a Single Type of Blood Pressure Measurement | Models Including Both Types of Blood Pressure Measurement |
|----------------------|-----------------------------------------------------------|----------------------------------------------------------|
|                      | Conventional Blood Pressure                              | Daytime Blood Pressure                                   |
| Systolic pressure    |                                                           |                                                          |
| Adjusted             | 0.75 (−0.68 to 2.18)                                     | 1.18 (−0.53 to 2.89)                                     |
|                      | −0.12 (−1.49 to 1.26)                                     | −0.75 (−2.40 to 0.90)                                    |
| Fully adjusted       | 0.91 (−0.60 to 2.43)                                     | 1.41 (−0.38 to 3.20)                                     |
|                      | −0.19 (−1.63 to 1.24)                                     | −0.89 (−2.57 to 0.79)                                    |
| Diastolic pressure   |                                                           |                                                          |
| Adjusted             | 1.22 (−0.20 to 2.63)                                     | 1.10 (−0.51 to 2.71)                                     |
|                      | 0.75 (−0.62 to 2.13)                                     | 0.24 (−1.32 to 1.81)                                     |
| Fully adjusted       | 1.09 (−0.39 to 2.56)                                     | 1.01 (−0.63 to 2.66)                                     |
|                      | 0.60 (−0.83 to 2.03)                                     | 0.17 (−1.43 to 1.76)                                     |

Abbreviations: CRVE, central retinal venular equivalent. Effect size (95% confidence interval) express the risk associated with a 1-SD increase in conventional or daytime blood pressures. All estimates account for clustering within families. Adjusted estimates account for follow-up characteristics including sex, age, and smoking. Fully adjusted estimates were additionally adjusted for body mass index, serum total cholesterol, plasma glucose, and drinking at follow-up, for follow-up duration, and for three indicator variables coding for starting, stopping or continuing antihypertensive drug treatment from baseline to follow-up. All effect sizes were not significant.
Table S5. Retinal Arteriole-to-Venule Ratio in Relation to Blood Pressure — Adjusted for Covariables at Baseline

| Blood Pressure Model | 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           | −0.010 (−0.016 to −0.005)‡ | −0.012 (−0.018 to −0.007)‡ | −0.004 (−0.011 to 0.002)    | −0.010 (−0.016 to −0.003)†          |
| Adjusted             | −0.011 (−0.017 to −0.005)‡ | −0.011 (−0.017 to −0.005)‡ | −0.007 (−0.014 to 0.0005)    | −0.007 (−0.014 to −0.0003)*         |
| Fully adjusted       | −0.012 (−0.019 to −0.006)‡ | −0.011 (−0.017 to −0.005)‡ | −0.009 (−0.016 to −0.001)*    | −0.007 (−0.014 to 0.0000)*          |
| **Diastolic pressure**|                               |                                           |                               |                                           |
| Unadjusted           | −0.010 (−0.015 to −0.004)‡ | −0.012 (−0.017 to −0.006)‡ | −0.005 (−0.011 to 0.002)    | −0.010 (−0.016 to −0.002)†          |
| Adjusted             | −0.011 (−0.017 to −0.004)‡ | −0.012 (−0.018 to −0.006)‡ | −0.006 (−0.013 to 0.0005)    | −0.009 (−0.015 to −0.002)†          |
| Fully adjusted       | −0.010 (−0.017 to −0.004)‡ | −0.012 (−0.018 to −0.006)‡ | −0.007 (−0.014 to 0.0005)    | −0.009 (−0.016 to −0.002)†          |

Abbreviations: AVR, arteriole-to-venule ratio. Effect size (95% confidence interval) express the risk associated with a 1-SD increase in conventional or daytime blood pressures. All estimates account for clustering within families. Adjusted estimates account for baseline characteristics including sex, age, and smoking. Fully adjusted estimates 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. Significance of the effect sizes: * P≤0.05, † P≤0.01, and ‡ P≤0.001.
Table S6. Retinal Arteriole-to-Venule Ratio in Relation to Blood Pressure — Adjusted for Covariables at Follow-Up

| Blood Pressure Model | 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    |                              |                          |                            |                          |
| Adjusted             | -0.010 (-0.016 to -0.004)† | -0.011 (-0.017 to -0.005)† | -0.006 (-0.013 to 0.002)   | -0.008 (-0.015 to -0.0008)* |
| Fully adjusted       | -0.013 (-0.019 to -0.006)† | -0.012 (-0.017 to -0.005)† | -0.009 (-0.016 to -0.001)*  | -0.007 (-0.014 to 0.0000)* |
| Diastolic pressure   |                              |                          |                            |                          |
| Adjusted             | -0.010 (-0.016 to -0.004)† | -0.011 (-0.017 to -0.006)† | -0.005 (-0.012 to 0.001)    | -0.009 (-0.016 to -0.002)† |
| Fully adjusted       | -0.010 (-0.016 to -0.004)† | -0.012 (-0.018 to -0.006)† | -0.006 (-0.013 to 0.001)    | -0.009 (-0.016 to -0.002)† |

Abbreviations: AVR, arteriole-to-venule ratio. Effect size (95% confidence interval) express the risk associated with a 1-SD increase in conventional or daytime blood pressures. All estimates account for clustering within families. Adjusted estimates account for follow-up characteristics including sex, age, and smoking. Fully adjusted estimates were additionally adjusted for body mass index, serum total cholesterol, plasma glucose, and drinking at follow-up, for follow-up duration, and for three indicator variables coding for starting, stopping or continuing antihypertensive drug treatment from baseline to follow-up. Significance of the effect sizes: * P≤0.05, † P≤0.01, and ‡ P≤0.001.
### Table S7. Retinal Phenotypes by Hypertension Category — Participants Untreated at Baseline

| Retinal microvascular trait | Normotension | White-Coat Hypertension | Masked Hypertension | Sustained Hypertension | $P_{NT}$ | $P_{WT}$ | $P_{MT}$ |
|----------------------------|--------------|-------------------------|---------------------|------------------------|---------|---------|---------|
| CRAE, µm                   | 152.9±0.56   | 149.7±2.2               | 147.9±1.6           | 143.9±2.2              | <0.001  | 0.060   | 0.13    |
| CRVE, µm                   | 219.3±0.80   | 224.4±3.1               | 217.8±2.2           | 216.4±3.1              | 0.36    | 0.069   | 0.71    |
| AVR                        | 0.70±0.003   | 0.67±0.012              | 0.68±0.009          | 0.67±0.012             | 0.008   | 0.95    | 0.32    |
| CRAE, µm                   | 152.4±0.54   | 152.5±2.1               | 149.0±1.5           | 146.6±2.1              | 0.009   | 0.047   | 0.36    |
| CRVE, µm                   | 218.8±0.78   | 227.7±3.1               | 218.3±2.2           | 219.6±3.0              | 0.81    | 0.056   | 0.72    |
| AVR                        | 0.70±0.003   | 0.67±0.012              | 0.68±0.009          | 0.67±0.012             | 0.015   | 0.94    | 0.26    |
| CRAE, µm                   | 152.4±0.54   | 152.2±2.1               | 149.3±1.5           | 146.1±2.2              | 0.006   | 0.043   | 0.22    |
| CRVE, µm                   | 218.8±0.78   | 227.0±3.1               | 218.4±2.2           | 219.4±3.1              | 0.85    | 0.081   | 0.78    |
| AVR                        | 0.70±0.003   | 0.67±0.012              | 0.68±0.009          | 0.67±0.013             | 0.012   | 0.84    | 0.17    |

Abbreviations: CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; AVR, arteriole-to-venule ratio. Values are mean ±SE. All estimates account for clustering within families. Adjusted estimates account for follow-up characteristics including sex, age, and smoking. Fully adjusted estimates were additionally adjusted for body mass index, serum total cholesterol, plasma glucose, drinking, and antihypertensive drug treatment at follow-up, and for follow-up duration. $P$-values indicate significance of the difference with sustained hypertension.
Table S8. Retinal Phenotypes by Hypertension Category — Adjusted for Covariables at Follow-Up

| Retinal microvascular trait | Normotension | White-Coat Hypertension | Masked Hypertension | Sustained Hypertension | NT | WT | MT |
|-----------------------------|--------------|-------------------------|---------------------|------------------------|----|----|----|
| CRAE, µm                    | 152.1±0.53   | 153.0±2.0               | 148.7±1.5           | 148.0±1.8              | 0.032 | 0.062 | 0.78 |
| CRVE, µm                    | 218.1±0.76   | 226.0±2.9               | 218.5±2.1           | 220.2±2.6              | 0.42 | 0.12 | 0.59 |
| AVR                         | 0.70±0.003   | 0.68±0.012              | 0.68±0.009          | 0.67±0.011             | 0.018 | 0.81 | 0.50 |

| Retinal microvascular trait | Normotension | White-Coat Hypertension | Masked Hypertension | Sustained Hypertension | NT | WT | MT |
|-----------------------------|--------------|-------------------------|---------------------|------------------------|----|----|----|
| CRAE, µm                    | 152.1±0.54   | 152.9±2.0               | 148.8±1.5           | 147.6±1.9              | 0.022 | 0.047 | 0.62 |
| CRVE, µm                    | 218.0±0.76   | 225.8±2.9               | 218.4±2.1           | 221.2±2.7              | 0.28 | 0.20 | 0.40 |
| AVR                         | 0.70±0.003   | 0.68±0.012              | 0.68±0.009          | 0.67±0.012             | 0.005 | 0.57 | 0.23 |

Abbreviations: CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; AVR, arteriole-to-venule ratio. Values are mean ±SE. All estimates account for clustering within families. Adjusted estimates account for follow-up characteristics including sex, age, and smoking. Fully adjusted estimates were additionally adjusted for body mass index, serum total cholesterol, plasma glucose, and drinking at follow-up, for follow-up duration, and for three indicator variables coding for starting, stopping or continuing antihypertensive drug treatment from baseline to follow-up. \( P \)-values indicate significance of the difference with sustained hypertension.
Figure S1.

Multivariable-Adjusted Associations of Central Retinal Arteriolar Equivalent with Systolic and Diastolic Blood Pressure

The plane shows the independent associations of CRAE (central retinal arteriolar equivalent) with systolic (A) and diastolic (B) blood pressure, based on conventional and daytime blood pressure 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, and drinking at follow-up, to follow-up duration, and to three indicator variables coding for starting, stopping or continuing antihypertensive drug treatment from baseline to follow-up.