ORIGINAL RESEARCH

Mid- to Late-Life Time-Averaged Cumulative Blood Pressure and Late-Life Retinal Microvasculature: The ARIC Study

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BACKGROUND: The associations of time-averaged cumulative blood pressure (BP) from midlife to late life with microvasculature expressed as retinal vessel diameters is not well studied. The aim of this study was to evaluate the association of cumulative systolic BP and diastolic BP (DBP) with retinal vessel calibers, focusing on race differences.

METHODS AND RESULTS: The analysis included 1818 adults from the ARIC (Atherosclerosis Risk in Communities) study attending the fifth visit (2011–2013; age 77±5 years, 17.1% Black participants). Time-averaged cumulative BPs were calculated as the sum of averaged BPs from adjacent consecutive visits (visits 1–5) indexed to total observation time (24±1 years). Summarized estimates for central retinal arteriolar equivalent and central retinal venular equivalent at the fifth visit represent average retinal vessel diameters. The arteriole:venule ratio was calculated. We tested for effect modification by race. Results from multiple linear regression models suggested that higher time-averaged cumulative DBP (β [95% CI] per 1-SD increase: −1.78 [−2.53, −1.02], P<0.001 and −0.005 [−0.009, −0.002], P=0.004, respectively) but not systolic BP (−0.52 [−1.30, 0.26], P=0.189 and 0.001 [−0.002, 0.005], P=0.485, respectively) was associated with smaller central retinal arteriolar equivalent and arteriole:venule ratio. The association between time-averaged cumulative DBP and arteriole:venule ratio was strongest in White participants (interaction P=0.007). The association of cumulative systolic BP and DBP with central retinal venular equivalent was strongest in Black participants (interaction P=0.015 and 0.011, respectively).

CONCLUSIONS: Exposure to higher BP levels, particularly DBP, from midlife to late life is associated with narrower retinal vessel diameters in late life. Furthermore, race moderated the association of cumulative BP exposure with retinal microvasculature.

Key Words: blood pressure ■ microcirculation ■ race
Huang et al  Time-Averaged Cumulative BP and Microvasculature

CLINICAL PERSPECTIVE

What Is New?
• Cumulative diastolic blood pressure but not systolic blood pressure from midlife to late life is associated with late-life retinal arteriolar narrowing, and the importance of blood pressure as a risk factor differs between Black individuals and White individuals.

What Are the Clinical Implications?
• The findings suggest that decreased retinal vessel diameters in late life may result from the cumulative effects of elevated blood pressure, particularly diastolic blood pressure, from midlife to late life and underscore the need for targeted interventions based on racial differences.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Description |
|--------------|-------------|
| ARIC         | Atherosclerosis Risk in Communities Study |
| AVR          | arteriole:venule ratio |
| CRAE         | central retinal arteriolar equivalent |
| CRVE         | central retinal venular equivalent |
| DBP          | diastolic blood pressure |
| SBP          | systolic blood pressure |

albumin:creatinine ratio progression\(^{20}\) as well as the risk of coronary heart disease\(^{21}\) and heart failure.\(^{21,22}\) However, limited data exist regarding the relationship of cumulative BP from midlife to late life with late-life retinal vessel diameters. Furthermore, different BP components reflect distinctive hemodynamics and pathophysiologic mechanisms,\(^{23–26}\) and which BP components play a dominant role of the damage to microcirculation is poorly understood. Finally, it has been reported that both retinal vascular caliber and BP levels vary by race.\(^{27–29}\) Racial differences in the impact of elevated BP on CVD and other end points have been shown in previous studies.\(^{24,30–32}\) However, how race affects the relation of BP with microvasculature remains unclear.

Building on this background, in this study we examined the association of time-averaged cumulative BP assessed for 25 years with late-life microvasculature among 1885 adults in the Atherosclerosis Risk in Communities (ARIC) study. In addition, we compared the magnitude and strength of associations of cumulative systolic BP (SBP) with cumulative diastolic BP (DBP) and of White individuals with Black individuals.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The ARIC study’s data and materials are publicly available to qualified investigators.

Study Population

The ARIC study is an ongoing, prospective observational study of CVD and atherosclerosis that recruited a total of 15,792 participants aged 45 to 64 years between 1987 and 1989 (visit 1) from 4 communities in 4 US centers (Forsyth County, NC; Jackson, MS; Minneapolis, MN; and Washington County, MD). The second visit was accomplished in 1990 to 1992, the third in 1993 to 1995, the fourth in 1996 to 1998, and the fifth in 2011 to 2013.\(^{33}\) Participants provided written informed consent, and the study’s protocol was approved by the institutional review board of each participating institution.

Of the 6,538 participants who attended the fifth visit, we evaluated participants who underwent complete BP measurement from visit 1 to visit 5 and had gradable retinal photography with >6 arteries and veins graded at visit 5 (n=2,000). Participants missing data on covariates were excluded (n=115). We also excluded participants with retinal abnormalities in both eyes (retinopathy, macular edema, focal narrowing, arterio-venous nicking, artery or vein occlusions, and other pathologies; n=67), leaving a sample size of 1,818 for final analysis. Table S1 shows the characteristics of included and excluded participants. Compared with participants in the current study, participants excluded for missing or ungradable retinal data were more likely to be young, female, and Black participants who smoked and had high DBP levels.

Imaging of the Retinal Microvasculature

The retinal photography procedure and measurement of retinal vascular caliber were described in detail previously.\(^{34,35}\) Digital, nonmydriatic retinal fundus photographs were taken and evaluated by trained graders at the ARIC Study Retinal Reading Center in the Department of Ophthalmology, University of Wisconsin–Madison. Using a semiautomatic method, the results from image analysis were summarized quantitatively as CRAE and CRVE, representing average arteriolar and venular diameter, respectively.\(^{36,37}\) The arteriole:venule ratio (AVR) was CRAE divided by CRVE, which eliminates the magnification differences between photographs. For analysis, we averaged each participant’s measurements at both eyes. If data were missing from 1 eye, data available from the other eye were selected.\(^{16,38}\)
**BP and Time-Averaged Cumulative BP**

At each examination, BP was measured 3 times with standardized protocols after participants had been seated for 5 minutes and recorded by trained technicians. For all visits except the fourth, an average of the second and the third BP measurements was recorded with a random-zero sphygmomanometer.39

Time-averaged cumulative BPs were calculated as the sum of averaged BPs from adjacent consecutive visits (visits 1–5) indexed to total observation time between visit 1 and 5 (mean time 24±1 years) as follows:

\[
\frac{\text{time}_{1-2} \times (BP_1 + BP_2) + \text{time}_{2-3} \times (BP_2 + BP_3) + \text{time}_{3-4} \times (BP_3 + BP_4) + \text{time}_{4-5} \times (BP_4 + BP_5)}{\text{time}_{1-5}},
\]

where \(BP_1, BP_2, BP_3, BP_4, \text{ and } BP_5\) indicate BP at visits 1, 2, 3, 4, and 5 and \(\text{time}_{1-2}, \text{time}_{2-3}, \text{time}_{3-4}, \text{ and } \text{time}_{4-5}\) indicate the participant-specific time interval between consecutive visits 1 to 5 in years. \(\text{time}_{1-5}\) means total time between visits 1 and 5.

**Definition of Other Variables**

All covariates were assessed at visit 5. Body mass index was calculated as body weight in kilograms divided by height in squared meters. Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg, or BP medicine use in the past 2 weeks. Diabetes was defined as hemoglobin A1C value ≥6.5% or using medication for diabetes or self-report diagnosis of diabetes. Information about age, race, sex, and smoking and drinking status was self-reported.

**Statistical Analysis**

Continuous variables were expressed as mean and SD and compared using Student t tests. Categorical variables were expressed as number and percentage and compared using \(\chi^2\) statistics. We also explored the relationship between tertiles of time-averaged cumulative BP with retinal vessel diameters using ANCOVA.

We used multivariable linear regression models to assess the association between time-averaged cumulative BP from midlife to late life and retinal vessel diameters at visit 5 (all as continuous variables). The primary exposures were measures of time-averaged cumulative SBP and cumulative DBP (z scores). The primary outcome variables were CRAE, CRVE, and AVR. All analyses were performed in 2 models. In model 1, analyses were adjusted for age, sex, race, and body mass index at visit 5. In model 2, analyses were additionally adjusted for smoking status, drinking status, triglycerides, low-density lipoprotein, high-density lipoprotein, prevalence of diabetes, prevalence of hypertension, and antihypertensive medication at visit 5. These covariates were selected as potential confounders because they are known to be related to BP or retinal vessels. In addition, all analyses in model 2 were repeated using visit 1 or visit 5 BP levels as the independent variable to examine the associations of cumulative BP for 25 years compared with BP at a single time point. To test whether race moderates the association of cumulative BP with retinal vessels, we repeated all the analyses in model 2 and tested for interaction (race×cumulative exposure to BP).40 Similarly, effect modifications by hypertension or diabetes were tested using interaction models.

To corroborate our analyses, multivariable logistic regression analysis was used to evaluate the association of cumulative BP with generalized retinal arteriolar narrowing defined as CRAE within the lowest quintile in the population.7,38,41

All statistical analyses were conducted with IBM SPSS Statistics version 26.0, and a \(P<0.05\) was considered statistically significant.

**RESULTS**

**Population Characteristics**

Among the 1818 study participants, the mean (SD) age at the time of visit 5 (2011–2013) was 76.6 (5.2) years, 56.1% were women, and 17.1% were Black participants. The mean (SD) time-averaged cumulative exposure to SBP and DBP in the total cohort was 124.2 (12.7) mm Hg and 69.3 (7.4) mm Hg, respectively. Race-specific clinical characteristics of the included participants are given in Table 1. The time-averaged cumulative SBP, DBP, and mean arterial pressure; CRAE; CRVE; and prevalence of hypertension and diabetes were higher in Black people than in White people. However, age, current drinking status, triglycerides, and AVR were higher in White people than in Black people. In addition, time-averaged cumulative pulse pressure, and smoking status were similar between races.

**Associations Between Time-Averaged Cumulative BP and Microvasculature**

Results from the linear regression models to examine the association between time-averaged cumulative BP exposure and microvasculature are summarized in Table 2. Higher exposure to cumulative DBP was associated with CRAE, CRVE, and AVR in all models. By contrast, cumulative exposure to SBP was not associated with CRAE, CRVE, and AVR in any of the models. Figure 1 shows the adjusted mean (SE) of retinal phenotypes in tertiles of cumulative SBP and DBP. Retinal vessel diameters decreased linearly with increasing cumulative DBP, but did not show an association with cumulative SBP. In multivariable logistic
regression, time-averaged cumulative DBP (adjusted odds ratio [OR; 95% CI] per 1-SD increase, 1.25 [1.09, 1.43]; \( P=0.001 \)), but not SBP (1.06 [0.92, 1.22], \( P=0.443 \)), was associated with the odds of CRAE narrowing (Table S2).

**Associations of Cumulative BP for 25 Years Compared With a Single BP Measurement**

At baseline (visit 1), the mean age of the participants was 53±5 years, mean SBP was 116±16 mm Hg, and mean DBP was 73±10 mm Hg. The progression of BP with increasing age varied by race (Figure S2). Table 3 shows the associations of cumulative BP for 25 years compared with a single BP measurement (at baseline or visit 5) with retinal phenotypes at visit 5. Higher baseline SBP was not associated with any of the retinal phenotypes, and higher baseline DBP was only associated with narrower retinal arterioles. SBP measured at visit 5 was only associated with narrower retinal venule. DBP measured at visit 5 was associated with narrower CRVE and showed no relation to AVR. Cumulative DBP for 25 years had stronger effects on retinal arterioles than baseline or visit 5 BP (unstandardized \( \beta \) in Table 3).
Interaction Between Cumulative BP Exposure and Race

Figure 2 shows the association of cumulative BP with retinal phenotypes stratified by race. The association between cumulative exposure to BP and CRVE was strongest in Black participants (see also Figure S3), whereas the association between time-averaged cumulative DBP and AVR was strongest in White participants (interaction \( P = 0.007 \)). The association between cumulative DBP and CRAE was also stronger in White participants, but the interaction was not statistically significant (interaction \( P = 0.966 \)). There was not significant interaction between cumulative SBP exposure and race, in relation to CRAE, or AVR (interaction \( P = 0.383 \) and \( 0.100 \), respectively). Finally, the association between cumulative BP exposure and retinal vessels did not vary by diabetes or hypertension (Figures S4 and S5).

DISCUSSION

To our knowledge, our study is the first survey assessing the long-term relationship of BP through midlife to late life with late-life microvasculature. We report 2 novel findings. The main finding of this study is that exposure to higher BP starting in midlife is associated with narrower late-life microvasculature, and cumulative DBP plays a dominant role of the damage to microcirculation, especially to the retinal arterioles. Furthermore, we found that higher cumulative DBP for 25 years was associated with narrower retinal arterioles in White participants but not Black participants, whereas higher cumulative BP was associated with narrower retinal venules in Black participants but not White participants.

Cumulative BP From Midlife to Late Life and Late-Life Microvasculature

Previous data documented the independent effects of both current and past BP on small vessel caliber in the retina, suggesting that retinal vessel narrowing may result from the cumulative effects of long-standing hypertension.\(^{15,17,42}\) Consistent with prior studies, our study showed that time-averaged cumulative BP from midlife to late life was associated with narrower retinal vessel caliber. However, past BP was obtained up to 10 years before retinal imaging and measured at a single time point in previous studies.\(^{15–17,42}\) Our study first explored the impact of BP measured for 25 years (baseline BP) before retinal imaging on retinal vessel diameters as well as incorporated the severity and duration of BP exposure for risk assessment in the community.

Accumulating evidence indicates that different components of BP provide some distinctive information about the hemodynamic alterations and may be associated to varying degrees with different cardiovascular outcomes.\(^{43–45}\) Our finding added to the evidence that cumulative DBP but not SBP from midlife to late life was associated with narrower retinal arterioles in late life. This finding was supported by another report of ARIC study, suggesting that higher DBP (OR [95% CI] per 1-SD increase, 1.84 [1.04–3.24]), but not SBP (1.46 [0.90–2.39]), was associated with incident retinopathy for 10 years in participants without diabetes.\(^{46}\)

Potential mechanisms underlying the observed BP components differences may be as follows: DBP reflects a steady-state load of BP, and SBP is an integrated measure of steady and pulsatile pressure load.\(^{23,25,47}\) The impact of both SBP and DBP on CRVE suggests that both increased steady-state load and pulsatile pressure load on vascular structures are important contributors to retinal venules narrowing. By contrast, DBP, but not SBP, was associated with smaller CRAE and AVR, suggesting that higher steady flow instead of pulsatile components of BP contributes to retinal arterioles narrowing. Our study underscores the importance of assessment and management of DBP through early stages of life to prevent and/or delay the progression of microvasculature abnormalities in later stages of life. Further investigations
Racial Differences in Cumulative BP Exposure and Microvasculature

Harris et al.\(^{48}\) found that the effect of BP on risk of retinopathy differed between Black people and White people. The risk of retinopathy increased as BP increased among Black people, but did not reach statistical significance among White people. By contrast, data from the CARDIA (Coronary Artery Risk Development in Young Adults) study\(^{24}\) suggested that DBP at baseline was associated with CVD risk in White people, but was unrelated to CVD risk in Black people. In our study, we observed a stronger association between BP and retinal venules in Black people than in White people, whereas the effect of DBP on retinal arterioles is more obvious in White people than in Black people. One potential mechanism may explain the observed racial differences. The diurnal pattern of BP differed between Black people and White people, and Black people showed less of a decline in BP during sleep than White people.\(^{49,50}\) As a result, the importance of BP as a risk factor may differ between Black people and White people. Based on our study data, we hypothesized that retinal arteriolar and venular calibers were differentially associated with cardiovascular risk factors, such as race and high BP. This hypothesis was further supported by several previous studies.\(^{51-53}\) The major systemic determinant of arteriolar diameters was BP,\(^{51,52}\) whereas the venular calibers were also correlated with cigarette smoking, obesity,\(^{51}\) and systemic inflammation.\(^{51,52}\) Our study underscores the importance of more highly targeted interventions.
For Black adults, both SBP and DBP could potentially serve as a marker of retinal venules narrowing. For White adults, DBP from midlife to late life is more related to retinal arterioles narrowing than SBP and could serve as a potential target for future therapies.

**Limitations**

There are limitations of the current study to consider. First, only 29% of our sample had gradable retinal photography and were included in the analyses. This could have introduced selection bias. However,
participants analyzed and not analyzed had similar baseline characteristics, suggesting that this bias is likely nondifferential and would only attenuate our findings. Second, the results may not be generalizable to individuals from other race or ethnicity cohorts because the ARIC study only consisted of a population of Black and White participants. Although only 17% of our study were Black participants, we still found a stronger association between BP and CRVE in Black participants than in White participants, which only means that our results of interaction between BP and race are robust. Finally, follow-up time between visits in the ARIC study is different, and the time interval between visits 4 and 5 is wider versus visits 1, 2, 3, and 4. However, time-averaged cumulative BP was calculated as previous study described so that BP measured at visits 4 and 5 would not give more weight to the cumulative BP exposure than BP at earlier visits.

**CONCLUSIONS**

Higher time-averaged cumulative BP for 25 years from midlife to late life was independently associated with narrower microvasculature in late life. Of note, cumulative DBP load, rather than SBP, played a role in determining the risk of retinal arteriolar narrowing. Furthermore, the effect of BP on the risk of microvasculature narrowing differed between Black adults and White adults. The findings suggest that decreased retinal vessel diameters in late life may result from the cumulative effects of elevated BP, particularly DBP, from midlife to late life and underscore the need for targeted interventions based on racial differences.

**ARTICLE INFORMATION**

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**Disclosures**

None.

**Supplemental Material**

Tables S1–S2

Figures S1–S5

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Table S1. Comparison of people included and excluded at visit 5 (2011-2013).

| Characteristics | Included in analyses (n=1818) | Excluded from analyses (n=4720) | P-value |
|-----------------|-----------------------------|-------------------------------|---------|
| Age, y          | 76.7 (5.2)                  | 75.4 (5.2)                    | <0.001  |
| Female (%)      | 56.1                        | 58.4                          | 0.047   |
| Black (%)       | 17.1                        | 21.9                          | <0.001  |
| BMI (kg/m²)     | 28.4 (5.6)                  | 28.9 (5.8)                    | 0.003   |
| Current smoking | 4.5%                        | 6.2%                          | <0.001  |
| Current drinking| 50.2                        | 50.7                          | 0.075   |
| SBP (mmHg)      | 129.9 (18.0)                | 130.6 (18.5)                  | 0.155   |
| DBP (mmHg)      | 65.2 (10.5)                 | 66.7 (10.9)                   | <0.001  |
| Triglycerides (mg/dl) | 1.4 (0.6)         | 1.4 (0.8)                     | 0.095   |
| LDL (mg/dl)     | 2.7 (0.9)                   | 2.7 (0.9)                     | 0.067   |
| HDL (mg/dl)     | 1.3 (0.4)                   | 1.3 (0.4)                     | 0.796   |
| TC (mg/dl)      | 4.6 (1.1)                   | 4.7 (1.1)                     | 0.086   |
| FBG (mmol/l)    | 6.3 (1.5)                   | 6.3 (1.6)                     | 0.234   |
| Diabetes (%)    | 29.8                        | 29.9                          | 0.910   |
| Hypertension (%)| 74.3                        | 74.1                          | 0.878   |

Continuous variables are presented as mean (SD). P values were calculated by unpaired t test or χ² test. Abbreviations: SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; FBG, fasting blood glucose.
Table S2. Relationship of time-averaged cumulative blood pressure with generalized arteriolar narrowing defined as narrowest quintile of CRAE.

| Cumulative SBP         | Generalized arteriolar narrowing | P     | Cumulative DBP        | Generalized arteriolar narrowing |
|------------------------|----------------------------------|-------|-----------------------|----------------------------------|
| Lowest quintile        | 1.00 (reference)                 | -     | Lowest quintile       | 1.00 (reference)                 |
| Second quintile        | 1.26 (0.84, 1.87)                | 0.268 | Second quintile       | 1.40 (0.94, 2.10)                | 0.102 |
| Third quintile         | 1.74 (1.16, 2.61)                | 0.007 | Third quintile        | 1.41 (0.94, 2.13)                | 0.096 |
| Fourth quintile        | 1.39 (0.90, 2.14)                | 0.178 | Fourth quintile       | 2.32 (1.54, 3.49)                | <0.001 |
| Highest quintile       | 1.24 (0.79, 1.96)                | 0.383 | Highest quintile      | 1.97 (1.27, 3.05)                | 0.002 |
| Per 1 SD               | 1.06 (0.92, 1.22)                | 0.443 | Per 1 SD              | 1.25 (1.09, 1.43)                | 0.001 |

Analyses were adjusted for age, sex, race, body mass index, visit center, smoking status, drinking status, triglycerides, low-density lipoprotein, high-density lipoprotein, prevalence of diabetes, prevalence of hypertension, and antihypertensive medication at visit 5.

Abbreviations: SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRAE, central retinal arteriolar equivalent.
Figure S1. Definition of time-averaged cumulative systolic blood pressure (SBP).

Time-averaged cumulative SBP over the 5 study visits was area under the curve index to total expose time (time $t_{1-5}$)

Examples:

One patient’s SBP was 100mmHg, 106mmHg, 120mmHg, 124mmHg, and 156mmHg, respectively, from visit 1 to visit 5 ($Y_{1987}, Y_{1990}, Y_{1993}, Y_{1996}, Y_{2011}$)

Time-averaged cumulative SBP = $\frac{3\times(100 + 106)/2 + 3\times(106 + 120)/2 + 3\times(120 + 124)/2 + 15\times(124 + 156)/2}{24} = 129.8$ mmHg
Figure S2. Unadjusted mean systolic blood pressure (SBP), and diastolic blood pressure (DBP) values with increasing age for whites and blacks.
Figure S3. Relationship between time-averaged cumulative blood pressure and CRVE, stratified by race. Model was unadjusted and 95% confidence interval was displayed by dashed lines. Abbreviation: CRVE, central retinal venular equivalent; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Figure S4. Association between cumulative blood pressure over 25 years with retinal phenotypes, stratified by diabetes. The $\beta$ represents unstandardized regression coefficients. Retinal phenotypes were transformed to z-scores. All analyses were adjusted for age, sex, race, body mass index, visit center, smoking status, drinking status, triglycerides, low-density lipoprotein, high-density lipoprotein, prevalence of diabetes, prevalence of hypertension, and antihypertensive medication at visit 5. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; AVR, arteriole: venule ratio.

| Retinal Phenotypes | $\beta$ (95% CI) | $P$ Value | $P$ for interaction |
|-------------------|-----------------|-----------|---------------------|
| CRAE              | -0.655 (-0.100, 0.030) | $0.294$ | $0.699$ |
|                   | -0.655 (-0.100, 0.030) | $0.559$ | $0.643$ |
|                   | -0.427 (-0.091, 0.038) | $0.417$ | $0.929$ |
|                   | -0.103 (-0.204, -0.002) | $0.046$ | $0.512$ |
|                   | -0.086 (-0.071, 0.082) | $0.894$ | $0.512$ |
|                   | 0.011 (0.018, 0.181) | $0.110$ | $0.998$ |

CRAE: central retinal arteriolar equivalent; CRVE: central retinal venular equivalent; AVR: arteriole: venule ratio.
Figure S5. Association between cumulative blood pressure over 25 years with retinal phenotypes, stratified by hypertension. The $\beta$ represents unstandardized regression coefficients. Retinal phenotypes were transformed to $z$-scores. All analyses were adjusted for age, sex, race, body mass index, visit center, smoking status, drinking status, triglycerides, low-density lipoprotein, high-density lipoprotein, prevalence of diabetes, prevalence of hypertension, and antihypertensive medication at visit 5.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; AVR, arteriole: venule ratio.