Relationship of Blood Pressure and Other Factors to Serial Retinal Arteriolar Diameter Measurements Over Time

The Beaver Dam Eye Study

Ronald Klein, MD, MPH; Chelsea E. Myers, MStat; Michael D. Knudtson, MS; Kristine E. Lee, MS; Ronald Gangnon, PhD; Tien Y. Wong, MD, PhD; Barbara E. K. Klein, MD, MPH

Objective: To describe the relationship of blood pressure (BP), antihypertensive medication use, and other factors to serial measurements of retinal arteriolar diameters over time in the Beaver Dam Eye Study.

Methods: Retinal arteriolar diameter was measured by computer-assisted methods and summarized as central retinal arteriolar equivalent (CRAE) in 4573 persons aged 43 to 99 years at 4 examinations (each separated by 5 years) during a 15-year period. Associations of CRAE with risk factors measured concurrently and 5 years previously were determined using multivariate analyses.

Results: While adjusting for image quality, refraction, and lens status, age (per 10 years: β estimate, −0.73; $P<.001$), systolic BP (per 10 mm Hg: concurrent examination, −2.74; $P<.001$; previous examination, −1.75; $P<.001$), smoking status (smoker vs nonsmoker: concurrent examination, 4.29; $P<.001$; previous examination, 1.63; $P=.004$), body mass index (per category: concurrent examination, −0.51; $P=.05$; previous examination, −0.22; $P=.44$), and heavy alcohol consumption (drinking) (current vs past/never heavy drinker: concurrent examination, −2.54; $P=.03$; previous examination, −2.42; $P=.02$) were associated with CRAE. In the same model, there were significant interactions between concurrent and previous systolic BP (0.11; $P=.003$) and between concurrent and previous body mass index (0.12; $P=.04$). Use of calcium channel blockers at both the concurrent and past examination (vs neither examination, 1.59; $P=.01$), but not other classes of antihypertensive drugs, was associated with CRAE.

Conclusions: Retinal arteriolar diameter is independently associated with past and current systolic BP, calcium channel blocker use, smoking status, body mass index, and heavy drinking during 5-year intervals. The relationships with CRAE are stronger for concurrent than for past measures of these variables.

Arch Ophthalmol. 2012;130(8):1019-1027

Author Affiliations: Departments of Ophthalmology & Visual Sciences (Drs R. Klein and B. E. K. Klein, Mss Myers and Lee, and Mr Knudtson) and Population Health Sciences (Dr Gangnon), University of Wisconsin School of Medicine and Public Health, Madison; University of Colorado Anschutz Medical Campus, Aurora (Mr Knudtson); and Singapore Eye Research Institute, National University of Singapore, Singapore, and Centre for Eye Research Australia, University of Melbourne, Victoria, Australia (Dr Wong).

COMPUTER-ASSISTED MEASUREMENT of retinal vessel diameters from fundus photographs has been used increasingly as a tool to study cardiovascular, renal, and other systemic diseases in population-based studies during the past 10 years.[1-19] Retinal arteriolar diameter, measured as the width of the retinal arteriolar blood column, has been shown[1,2,9,13-21] to be associated with past, present, and future blood pressure (BP) and cardiovascular disease morbidity and mortality.

CME available online at www.jamaarchivescme.com and questions on page 970

However, most information regarding associations between BP and other factors related to retinal arteriolar diameters is from cross-sectional studies.[1,2,4,10,13,14,16,22] The purpose of this study was to examine the relationships of past and concurrent values of BP, antihypertensive medication use, and other factors with the central retinal arteriolar equivalent (CRAE). This study used 4 examinations, each separated by 5-year intervals, in the population-based Beaver Dam Eye Study.

METHODS

POPULATION

A private census of Beaver Dam, Wisconsin, was performed in 1987-1988 to identify all resi-

dents aged 43 to 84 years who were eligible to participate in a study of age-related eye conditions and traits.[23] Of 5924 persons identified, 4926 individuals (99% white) participated in the baseline examination in 1988-1990. The cohort was reevaluated at 5-year (n = 3722), 10-year (n = 2962), and 15-year (n = 2375) follow-up examinations. Participation rates exceeded 80% among survivors at each examination.[23-26] Differences between participants and nonparticipants have been presented elsewhere.[23-26] In general, participants at each examination phase were younger, had lower BP, and had fewer comorbid conditions at baseline compared with nonparticipants. All data were collected with institutional review board approval from the University of Wisconsin–Madison in conformity with all federal and state laws, and the study adhered to the tenets of the Declaration of Helsinki.

PROCEDURES

Participants underwent a standardized interview and examination, using the same protocols each time.[27] A questionnaire including questions on the history of physician-diagnosed diabetes mellitus, cigarette smoking, hypertension, and use of medications was administered. Height, weight, and BP were measured using standardized protocols.

Refraction was performed using a modification of the Early Treatment Diabetic Retinopathy Study protocol.[23] Serum total cholesterol and high-density lipoprotein cholesterol levels were determined from unfrozen serum on the day that the samples were collected.[28,29] At all examinations, additional serum samples were obtained and stored at –80°C from the day collected until creatinine and high-sensitivity C-reactive protein tests were performed in 2007. The level of soluble vascular cell adhesion molecule 1 was measured in 2008 on baseline samples.[30,31] Thus, samples from the baseline examination (1988-1990), examination 2 (1993-1995), and examination 3 (1998-2000) were stored frozen for approximately 17 to 19 years, 12 to 14 years, and 7 to 9 years, respectively.

The participants' pupils were pharmacologically dilated. A slit-lamp camera (Topcon America Corporation) was used to photograph the lens of each eye, and the photographs were graded for the presence and severity of nuclear sclerosis.[32] Stereoscopic 30° color fundus photographs centered on the disc (Diabetic Retinopathy Study[33] standard field 1) were obtained for each eye. Age-related macular degeneration (AMD) was graded according to the Wisconsin Age-Related Maculopathy Grading System.[34,35]

Retinal vessels were measured from the digitized images of field 1 slides using a semiautomated computer program designed for this project (IVAN; University of Wisconsin–Madison).[36,37] In brief, the grading protocol required vessel diameters from the 6 largest arterioles and 6 largest venules located in a zone 0.5 to 1.0 disc diameter from the disc margin.[38,39] Every 6 months, the graders remeasured 50 eyes to determine intergrader and intragrader variability. Correlation coefficients were high (>0.90) for both intergrader and intragrader comparisons for both arteriolar and venular measurements (data not shown).

DEFINITIONS

For each eye graded, the measurements of the 6 largest arterioles were combined to calculate the CRAE.[38] Image quality was evaluated as good, fair, or poor. Nuclear sclerosis was graded by comparing images with standard photographs using a 5-step scale and categorized as 2 or less, 3, more than 3, or cataract surgery. Refraction was categorized as moderately to highly myopic (less than –3 diopters [D]), mildly myopic (–3 to –1 D), emmetropic (–1 to 1 D), mildly hyperopic (1 to 3 D), and hyperopic (>3 D). Smokers were defined as persons having smoked 100 or more cigarettes in their lifetime who had not stopped smoking by the time of examination. Nonsmokers were defined as individuals who had either never smoked or who smoked in the past but had stopped by the time of examination. Past smokers and never smokers were combined into a nonsmoker category for all analyses. Pack-years was defined as the average number of cigarettes smoked per day divided by 20, then multiplied by the number of years smoked. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Persons with current heavy alcohol consumption (heavy drinkers) were defined as those who consumed 4 or more servings of alcoholic beverages daily, past heavy drinkers had consumed 4 or more servings of alcoholic beverages on a daily basis in the past but not in the past year, and never heavy drinkers had never consumed 4 or more servings of alcoholic beverages on a daily basis. Past heavy drinkers and never heavy drinkers were combined into a past/never heavy drinker category in all analyses.

Mean arterial BP (MABP) was defined as (systolic BP [SBP] + 2 × diastolic BP [DBP])/3.

STATISTICAL ANALYSIS

The purpose of our analysis was to examine previous (5 years earlier) and concurrent relationships between risk factors (**Table 1**) and CRAE. We hypothesized that previous and concurrent measures of a risk factor would be independently associated with CRAE, that the association would be stronger for concurrent than for previous measures, and that the previous measure of the risk factor would modify the concurrent relationship between that variable and CRAE (ie, there would be a significant interaction). Using SBP as an example, in concurrent analyses (model 1 in **Table 2**), we modeled the relationship of SBP to CRAE at the same examination (ie, SBP at examination 1 to CRAE at examination 1, SBP at examination 2 to CRAE at examination 2, and so on). Rather than creating 4 models (ie, 1 for each examination), we used time-updating covariates to incorporate information from all 4 examinations into 1 model. In model 2 in Table 2, we added a term for each risk factor measured at the previous examination and an interaction term between each risk factor at the examinations previous to and concurrent with the CRAE measurement (ie, SBP at examination 1 + SBP at examination 1 × SBP at examination 2, SBP at examination 2 + SBP at examination 2 × SBP at examination 3, and so on) to determine whether the previous value of the risk factor modified the relationship between the concurrent risk factor and CRAE. Figures were used to show each significant relationship (model 2 in Table 2). In model 3, we created a single multivariate model that included terms for all risk factors for which the previous value or interaction was significantly associated with CRAE.

Results are given for the right eye. Eyes in which 1 of the 6 largest arterioles was ungradable were excluded. Retinal photographs not taken with the preferred cameras (Zeiss; Carl Zeiss International) or eyes with late AMD, photocoagulation, photodynamic or any intravitreal treatment for AMD, retinal vessel occlusions, retinopathy, macular edema, other disease, or that were aphakic or missing lens status were excluded.

All analyses were performed with commercial software (SAS version 9.2; SAS Institute, Inc). Tests for trend over multiple examinations provided in Table 1 were computed using a general linear model. Models with CRAE as the outcome were analyzed using commercial software (SAS Proc Mixed) with unstructured correlation matrices for the error term. Each model also adjusted for image focus, cataract status, and refraction at the examination at which CRAE was measured because these factors may have the largest nondisease effect on the measure-

Table 1. Characteristics of the Beaver Dam Eye Study Cohort at Each Examination

Risk Factor	Mean (SD) 1988-1990, Examination 1 (n=4493)	1993-1995, Examination 2 (n=3223)	1998-2000, Examination 3 (n=2342)	2003-2005, Examination 4 (n=1817)	*P* Value[a]
Age, y	61.3 (10.9)	64.4 (10.1)	67.5 (9.2)	70.5 (8.3)	<.001
Male sex, %	44.1	44.0	43.1	42.3	.16
CRAE, µm	150.0 (14.8)	148.6 (14.9)	148.3 (14.4)	146.6 (14.8)	<.001
CRVE, µm	230.4 (23.0)	224.1 (22.4)	225.5 (22.4)	218.0 (22.5)	<.001
Systolic BP, mm Hg	131.5 (20.2)	128.9 (19.2)	130.8 (18.8)	130.5 (18.2)	.09
Diastolic BP, mm Hg	77.5 (10.9)	76.2 (10.5)	74.4 (10.6)	73.7 (10.9)	<.001
Mean arterial BP, mm Hg	95.5 (12.1)	93.8 (11.8)	93.2 (11.5)	92.7 (11.8)	<.001
Drug therapy, %					
Antihypertensive	36.2	40.8	51.8	62.2	<.001
ACE inhibitor	6.4	11.5	17.0	24.6	<.001
β-blocker	11.5	11.7	18.4	28.1	<.001
Calcium channel blocker	4.1	11.7	14.9	15.9	<.001
Glaucoma drops	1.9	2.5	3.5	5.3	<.001
Intraocular pressure, mm Hg	15.4 (3.3)	15.3 (3.2)	15.2 (3.0)	15.1 (3.3)	<.001
BMI	28.7 (5.4)	29.5 (5.5)	29.9 (5.9)	30.5 (6.0)	<.001
Refraction, D	0.2 (2.3)	0.2 (2.3)	0.2 (2.3)	0.2 (2.3)	.80
Nuclear cataract present, %	12.1	18.3	14.5	18.8	<.001
History of cataract surgery, %	2.9	6.1	9.6	14.5	<.001
Current smoking, %	20.3	15.0	10.4	9.3	<.001
Pack-years smoked	31.7 (28.7)	30.2 (27.3)	28.3 (27.1)	27.0 (25.7)	<.001
Current heavy drinking, %	2.4	2.0	1.5	0.8	<.001
Serum total cholesterol, mg/dL[b]	233.8 (43.9)	239.6 (44.9)	213.8 (40.2)	. . .	<.001
Serum HDL-C, mg/dL[b]	52.2 (17.6)	52.6 (16.5)	50.8 (16.5)	. . .	<.001
Diabetes mellitus, %	7.1	8.3	9.5	12.9	<.001
Serum C-reactive protein, mg/L[c]	4.4 (9.7)	4.6 (11.2)	. . .	. . .	.39
Serum creatinine, mg/dL	0.9 (0.3)	0.9 (0.3)	0.9 (0.2)	0.9 (0.3)	.35
Soluble VCAM-1, ng/mL[c]	821.6 (294.9)	852.2 (278.8)	. . .	. . .	.006

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; D, diopters; HDL-C, high-density lipoprotein cholesterol; VCAM-1, vascular cell adhesion molecule 1.

SI conversion factors: To convert total cholesterol and HDL-C to millimoles per liter, multiply by 0.0259; serum C-reactive protein to nanomoles per liter, multiply by 9.524; and serum creatinine to micromoles per liter, multiply by 88.4.

[a] Test for trend over examination phases.

[b] Measured at examinations 1, 2, and 3.

[c] Measured at examinations 1 and 2.

ment of CRAE. Estimated CRAE and 95% CIs were calculated using the estimate statement in Proc Mixed, assuming age of 65 years, good image focus, absence of cataract or cataract surgery, and emmetropic refraction.

RESULTS

Of the 4926 individuals aged 43 to 86 years seen at baseline, 97 were excluded because they had no retinal photographs of field 1 or photographs were not taken using the preferred camera, 68 because late AMD was present or treatment for late AMD had occurred, 150 because other retinal diseases were present, 30 because of aphakia or unknown lens status, and 88 for having fewer than 6 gradable retinal arterioles, leaving 4493 individuals contributing data at examination 1. Similarly, 3223 of the 3722 participants seen at examination 2, followed by 2342 of the 2962 participants seen at examination 3, and 1817 of the 2373 participants seen at examination 4 contributed data to the cross-sectional analyses. Overall, 4573 unique individuals contributed to the analysis.

Characteristics of these individuals at each interval are reported in Table 1. Participants at later examinations had narrower CRAE, lower DBP, lower serum total cholesterol and high-density lipoprotein cholesterol levels, a lower frequency of current smoking and current heavy drinking, and fewer pack-years smoked. Participants at later examinations had greater BMI, higher frequencies of using antihypertensive medications, and higher frequencies of cataract, cataract surgery, and diabetes mellitus. Systolic BP, refraction, serum creatinine level, and percentages of men and women did not differ significantly between participants at earlier and later examinations.

CONCURRENT RELATIONSHIPS

Model 1 in Table 2 indicates the concurrent relationships between factors listed in Table 2 and CRAE at each examination. After adjustment for cataract status, refraction, and image focus, increasing age, higher SBP, higher DBP, higher MABP, greater BMI, higher levels of serum high-density lipoprotein cholesterol, and current heavy drinking were concurrently associated with narrower CRAE. Current smoking and presence of diabetes were concurrently associated with wider CRAE. There was no

Table 2. Relationship of Risk Factors Measured Previously (5 Years Earlier) and Concurrently (Same Visit) to CRAE in the Beaver Dam Eye Study, 1988-2005

Risk Factor	Model 1[a] β (95% CI)	Model 1[a] *P* Value	Model 2[b] β (95% CI)	Model 2[b] *P* Value	Model 3[c] β (95% CI)	Model 3[c] *P* Value
Associated With Narrower CRAE						
Age, per 10 y	−1.87 (−2.15 to −1.59)	<.001			−0.73 (−1.14 to −0.33)	<.001
Male sex	−0.18 (−0.95 to 0.59)	.65				
Systolic BP, per 10 mm Hg						
Concurrent	−1.34 (−1.46 to −1.22)	<.001	−2.69 (−3.58 to −1.81)	<.001	−2.74 (−3.71 to −1.78)	<.001
5 y previously			−1.78 (−2.66 to −0.90)	<.001	−1.75 (−2.70 to −0.79)	<.001
Concurrent × 5 y previously			0.11 (0.04 to 0.17)	.001	0.11 (0.04 to 0.18)	.003
Diastolic BP, per 5 mm Hg						
Concurrent	−1.16 (−1.26 to −1.05)	<.001	−0.76 (−1.58 to 0.05)	.07		
5 y previously			−0.12 (−0.90 to 0.67)	.77		
Concurrent × 5 y previously			−0.02 (−0.07 to 0.03)	.40		
Mean arterial BP, per 5 mm Hg						
Concurrent	−1.14 (−1.23 to −1.05)	<.001	−1.38 (−2.19 to −0.56)	.001		
5 y previously			−0.67 (−1.46 to 0.12)	.10		
Concurrent × 5 y previously			0.01 (−0.03 to 0.06)	.48		
BMI, per category[d]						
Concurrent	−0.51 (−0.70 to −0.32)	<.001	−1.16 (−1.67 to −0.64)	<.001	−0.51 (−1.02 to 0.00)	.05
5 y previously			−0.56 (−1.12 to 0.01)	.05	−0.22 (−0.77 to 0.34)	.44
Concurrent × 5 y previously			0.20 (0.07 to 0.32)	.002	0.12 (0.00 to 0.24)	.04
Heavy drinking status						
Concurrent	−2.25 (−3.78 to −0.72)	.004	−1.70 (−4.50 to 1.10)	.23	−2.54 (−4.79 to −0.28)	.03
5 y previously			−2.16 (−4.40 to 0.07)	.06	−2.42 (−4.42 to −0.42)	.02
Concurrent × 5 y previously			0.06 (−4.51 to 4.63)	.98		
Associated With Wider CRAE						
Smoking status						
Concurrent	5.03 (4.28 to 5.78)	<.001	5.00 (2.62 to 7.37)	<.001	4.29 (3.02 to 5.56)	<.001
5 y previously			1.55 (0.38 to 2.72)	.01	1.63 (0.53 to 2.74)	.004
Concurrent × 5 y previously			−0.91 (−3.68 to 1.86)	.52		
Not Associated With CRAE						
Antihypertensive medication use						
Concurrent	0.18 (−0.30 to 0.67)	.46	0.02 (−0.69 to 0.73)	.95		
5 y previously			0.69 (−0.81 to 2.18)	.37		
Concurrent × 5 y previously			−0.20 (−1.86 to 1.46)	.82		
Intraocular pressure, per 2 mm Hg						
Concurrent	−0.12 (−0.27 to 0.02)	.10	−0.33 (−1.15 to 0.49)	.43		
5 y previously			−0.15 (−0.94 to 0.65)	.72		
Concurrent × 5 y previously			0.01 (−0.09 to 0.11)	.80		
Total cholesterol level, per category[d,e]						
Concurrent	−0.17 (−0.30 to −0.04)	.01	−0.09 (−0.54 to 0.36)	.70		
5 y previously			0.00 (−0.38 to 0.38)	>.99		
Concurrent × 5 y previously			−0.01 (−0.10 to 0.08)	.82		
HDL-C level, per category[d,e]						
Concurrent	−0.37 (−0.55 to −0.19)	<.001	−0.46 (−0.96 to 0.05)	.08		
5 y previously			−0.15 (−0.63 to 0.33)	.54		
Concurrent × 5 y previously			0.04 (−0.09 to 0.17)	.52		

(continued)

association of sex, intraocular pressure, serum creatinine, vascular cell adhesion molecule 1, antihypertensive medication use, or high-sensitivity C-reactive protein concentration with CRAE measured at the same examination.

RELATIONSHIPS OF PREVIOUS AND CONCURRENT BP AND ANTIHYPERTENSIVE MEDICATION USE TO CRAE

The SBP, DBP, and MABP measured at the previous examination were associated with narrower CRAE independent of concurrent values of these risk variables. Adding BP measured at the previous examination to the model slightly attenuated the relationship between concurrent BP and CRAE, and the effect of the BP from the previous examination was much smaller than that of BP measured at the concurrent examination (β = −0.42 vs −1.32 for SBP, β = −0.34 vs −0.99 for DBP, and β = −0.38 vs −1.07 for MABP) (data not shown). There was a significant interaction between the previous and concurrent SBP but not with the previous and concurrent DBP or MABP (model 2, Table 2). Adding this interaction term strengthened the relationship between both concurrent and previous SBP and CRAE, but concurrent SBP remained more strongly associated with concurrent CRAE than with pre-

Table 2. Relationship of Risk Factors Measured Previously (5 Years Earlier) and Concurrently (Same Visit) to CRAE in the Beaver Dam Eye Study, 1988-2005 (continued)

Risk Factor	Model 1[a] β (95% CI)	Model 1[a] *P* Value	Model 2[b] β (95% CI)	Model 2[b] *P* Value	Model 3[c] β (95% CI)	Model 3[c] *P* Value
HbA_{1c} level, per 1%[f]						
Concurrent	0.30 (0.07 to 0.52)	.01	0.07 (–1.02 to 1.17)	.89		
5 y previously			0.46 (–0.82 to 1.75)	.48		
Concurrent × 5 y previously			–0.01 (–0.14 to 0.13)	.92		
Diabetes mellitus status						
Concurrent	1.36 (0.39 to 2.32)	.01	0.65 (–0.79 to 2.10)	.37		
5 y previously			–0.73 (–4.29 to 2.84)	.69		
Concurrent × 5 y previously			0.98 (–3.10 to 5.06)	.64		
Creatinine level, per quartile						
Concurrent	–0.12 (–0.36 to 0.11)	.29	–0.05 (–0.54 to 0.44)	.84		
5 y previously			–0.22 (–0.74 to 0.31)	.42		
Concurrent × 5 y previously			0.00 (–0.27 to 0.28)	.99		
hsCRP level,[f] per quartile						
Concurrent	0.14 (–0.19 to 0.48)	.40	0.84 (–0.51 to 2.20)	.22		
5 y previously			0.37 (–1.12 to 1.85)	.63		
Concurrent × 5 y previously			–0.03 (–0.75 to 0.69)	.93		
VCAM-1,[f] per quartile						
Concurrent	–0.07 (–0.59 to 0.45)	.79	0.72 (–0.71 to 2.15)	.33		
5 y previously			–0.34 (–1.96 to 1.28)	.68		
Concurrent × 5 y previously			–0.02 (–0.76 to 0.72)	.96		

Abbreviations: BMI, body mass index; BP, blood pressure; CRAE, central retinla arteriolar equivalent; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; VCAM-1, vascular cell adhesion molecule 1.

[a] Adjusts for variable at current visit, age, refraction, cataract, image focus, and systolic BP.

[b] Adjusts for variable at current visit, variable at past visit, interaction between visits, age, refraction, cataract, image focus, and systolic blood pressure interaction.

[c] Adjusts for all variables shown plus refraction, cataract, and image focus.

[d] BMI (calculated as weight in kilograms divided by height in meters squared): less than 20, 20 to less than 23, 23 to less than 26, 26 to less than 29, 29 to less than 32, 32 to less than 35, 35 to less than 38, 38 to less than 41, and 41 or higher. Serum total cholesterol: less than 160, 160 to less than 180, 180 to less than 200, 200 to less than 220, 220 to less than 240, 240 to less than 260, 260 to less than 280, and 280 or more mg/dL. Serum HDL-C: less than 30, 30 to less than 40, 40 to less than 50, 50 to less than 60, 60 to less than 70, 70 to less than 80, 80 to less than 90, and 90 or more mg/dL. See the footnote to Table 1 for SI conversion factors.

[e] Measured at visits 1, 2, and 3.

[f] Measured at visits 1 and 2.

vious SBP. Adding an interaction term to the DBP and MABP models attenuated the associations with the past values of these risk factors and CRAE.

To further explore the relationship of the SBP interaction, we compared estimated values of CRAE for individuals with different previous and concurrent values of SBP as described in the "Methods" section. **Figure 1** shows that the effect of higher and lower concurrent SBP on CRAE depends on whether an individual was normotensive or had moderate or severe hypertension at the previous examination. For example, a 10-mm Hg increase in SBP is associated with a decrease in CRAE in individuals who were previously normotensive but not in individuals who were hypertensive.

Although previous use of any antihypertensive medication was not independently associated with CRAE measured 5 years later (model 2 in Table 2), we hypothesized that previous and concurrent use of specific types of antihypertensive medications would be related to CRAE. Adjusting for age, cataract status, refraction, image focus, and previous and concurrent SBP and their interaction, the history of calcium channel blocker therapy at both examinations was significantly associated and starting calcium channel blocker therapy was borderline significantly associated with wider CRAE compared with individuals who did not take a medication from this class at either examination (**Table 3**). There was no significant association with any other class of antihypertensive medications (eg, β-blockers, diuretics, and angiotensin-converting enzyme inhibitors). There was no relationship between change in glaucoma drop use and CRAE (data not shown).

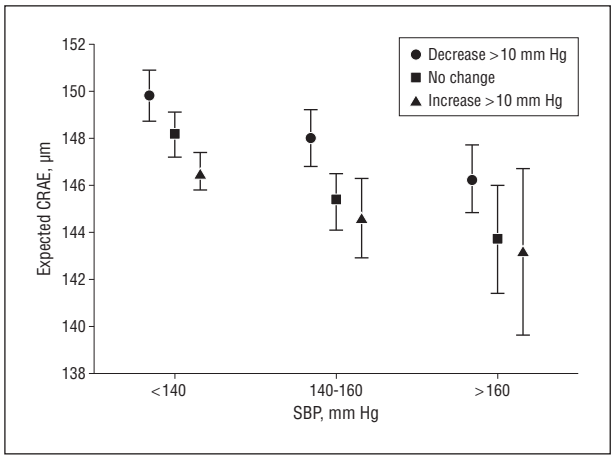

Figure 1. The relationship between change in systolic blood pressure (SBP) during a 5-year period in people at 3 levels of SBP (normotensive, <140 mm Hg; moderate hypertension, 140-160 mm Hg; and severe hypertension, >160 mm Hg) at the start of the period and the expected central retinal arteriolar equivalent (CRAE) at 5-year follow-up (concurrent) examination. Limit lines indicate standard error.

Table 3. Relationship of Changes in Antihypertensive Medication Use to Central Retinal Arteriolar Equivalent

Risk Factor	β Estimate[a] (95% CI)	*P* Value
Diuretics		
Taking at both examinations	−0.12 (−1.05 to 0.82)	.81
Started taking	−0.47 (−1.28 to 0.34)	.26
Stopped taking	0.19 (−0.91 to 1.28)	.74
Not taking at either examination	1 [Reference]	
ACE inhibitors		
Taking at both examinations	−0.27 (−1.42 to 0.88)	.65
Started taking	0.86 (0.04 to 1.68)	.04
Stopped taking	−0.49 (−1.97 to 1.00)	.52
Not taking at either examination	1 [Reference]	
β-Blockers[b]		
Taking at both examinations	0.17 (−0.88 to 1.22)	.75
Started taking	0.33 (−0.50 to 1.17)	.44
Stopped taking	0.69 (−0.68 to 2.06)	.33
Not taking at either examination	1 [Reference]	
Calcium channel blockers		
Taking at both examinations	1.59 (0.32 to 2.85)	.01
Started taking	0.90 (−0.04 to 1.84)	.06
Stopped taking	1.26 (−0.21 to 2.73)	.09
Not taking at either examination	1 [Reference]	

Abbreviation: ACE, angiotensin-converting enzyme.
[a] Adjusts for age, image focus, cataract status, refraction, current systolic blood pressure, past systolic blood pressure, and current × past systolic blood pressure interaction.
[b] Includes glaucoma drops.

RELATIONSHIPS OF PREVIOUS AND CONCURRENT OTHER SYSTEMIC FACTORS TO CRAE

There was a strong positive correlation ($r > 0.70$; $P < .01$) between past and concurrent CRAE. During each 5-year interval, approximately 25% of the participants had a positive change in CRAE (widening by >5 μm), approximately 35% had a negative change in CRAE (narrowing by >5 μm), and approximately 40% had no change in CRAE (widening or narrowing by ≤5 μm). This was consistent across all pairs of examinations.

Both previous BMI and an interaction between previous and concurrent BMI were significantly associated with CRAE (model 2 in Table 2). Adding these terms strengthened the concurrent relationship of BMI and CRAE. The association of the previous BMI was not as large as that of BMI measured at the same examination (β = −1.16 vs −0.56). There was an interaction between previous and concurrent BMI (**Figure 2**). The effect of higher and lower BMI on CRAE at the same examination differed depending on the BMI status at the previous examination. For example, an increase in BMI of least 2 compared with no weight gain was associated with smaller CRAE in individuals who previously had a normal BMI, but an increase in BMI compared with no weight gain was not associated with smaller CRAE in individuals who were previously overweight or obese.

Smoking at both the concurrent and previous examinations was associated with wider CRAE; however, there

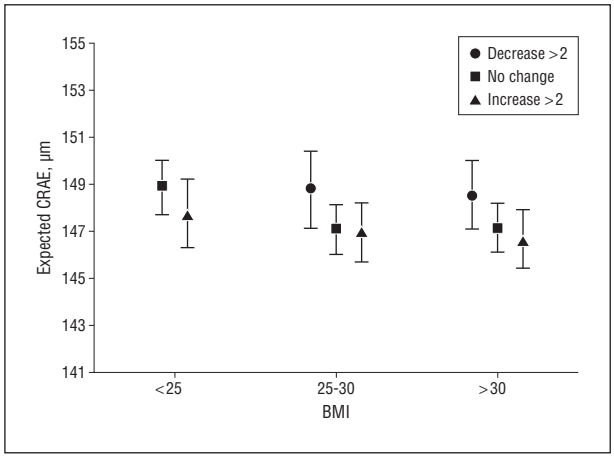

Figure 2. The relationship between change in body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) during a 5-year period in people at 3 levels of BMI (normal weight, <25; overweight, 25-30; and obese, >30) at the start of the period and the expected central retinal arteriolar equivalent (CRAE) at 5-year follow-up (concurrent) examinations. There were too few individuals with a normal BMI who lost weight during a 5-year interval to estimate CRAE. Limit lines indicate standard error.

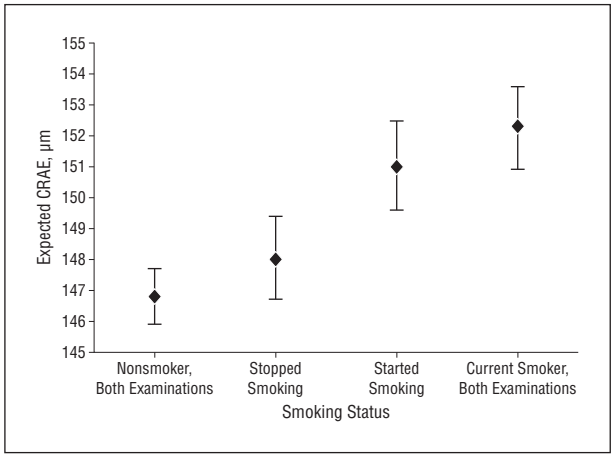

Figure 3. The relationship between change in smoking status during a 5-year period and the expected central retinal arteriolar equivalent (CRAE) at 5-year follow-up (concurrent) examinations. Limit lines indicate standard error.

was no significant interaction between the two (Table 2). The effect size of current smoking at the same examination in which CRAE was measured was approximately 3.25 times larger than that of past smoking (β = 5.00 vs 1.55). Individuals who started smoking during the interval or were smokers at both examinations had significantly wider CRAE than did individuals who stopped smoking or were nonsmokers at both examinations (**Figure 3**).

Having a history of being a heavy drinker at the previous examination was more strongly related to smaller CRAE than being a heavy drinker at the time of the concurrent examination (model 2 in Table 2). There was no interaction between heavy drinking 5 years before CRAE was measured and at the time when CRAE was measured. Individuals who were heavy drinkers at both examinations had narrower CRAE and those who were not heavy drinkers at either examination had wider CRAE than did individuals who either stopped or started drinking heavily (**Figure 4**).

MULTIVARIATE RELATIONSHIPS OF SYSTEMIC FACTORS TO CRAE

Model 3 in Table 2 reports the multivariate relationships of previous and concurrent SBP, antihypertensive medication use, BMI, and smoking status to CRAE. Previous and concurrent SBP, heavy drinking, and BMI were associated with narrower CRAE; previous and concurrent smoking status were associated with wider CRAE. When added to the multivariate model, a history of using a calcium channel blocker at the previous and concurrent examinations compared with a history of not taking a calcium channel blocker at either time was significantly associated with wider CRAE (odds ratio, 1.61; 95% CI, 0.29-2.93).

The risk factors in the full multivariate model explained approximately 19% of the variance of CRAE during the 15-year period.

MULTIVARIATE RELATIONS OF SYSTEMIC FACTORS WHEN MEASURED 10 OR MORE YEARS BEFORE CRAE

We examined the relationship of SBP, BMI, current smoking, and current heavy drinking when they were measured 10 or 15 years before CRAE. None were associated with CRAE (data not shown).

COMMENT

The Beaver Dam Eye Study offered a unique opportunity to examine the associations of the temporal relationships of BP and other factors with retinal arteriolar caliber measured using standardized protocols at multiple examinations during a 15-year period. Systolic BP, smoking status, and heavy drinking measured concurrently and 5 years previously and BMI measured concurrently were independently associated with CRAE (Table 2, model 3). Concurrent levels of these risk factors were more strongly related to CRAE than were those measured 5 or more years before.

The associations of higher SBP with narrower CRAE and interactions of SBP and hypertension with narrower CRAE in our study are consistent with previous findings in both adults and children.[1,2,9,13-19,40] Our finding of a direct effect of both previous and concurrent use of calcium channel blockers but not other antihypertensive medications on CRAE was also consistent with the results of the Anglo-Scandinavian Cardiac Outcomes Trial.[41] In that study, amlodipine treatment was associated with a smaller arteriolar length-diameter ratio than was atenolol treatment, and the association remained significant after adjustment for age, sex, SBP, DBP, and other factors. One year of treatment with amlodipine, but not atenolol, in persons with hypertension led to reduction in the media-lumen ratio of the small arterioles (equivalent to a wider CRAE as measured in our study) despite the similar BP-reducing effect of both agents.[42] It is thought that some calcium channel blockers have a greater effect of vasodilation (and presumably change in media-lumen proportion) of retinal blood vessels and possibly other systemic arterioles without significantly affecting systemic BP.[41,43,44]

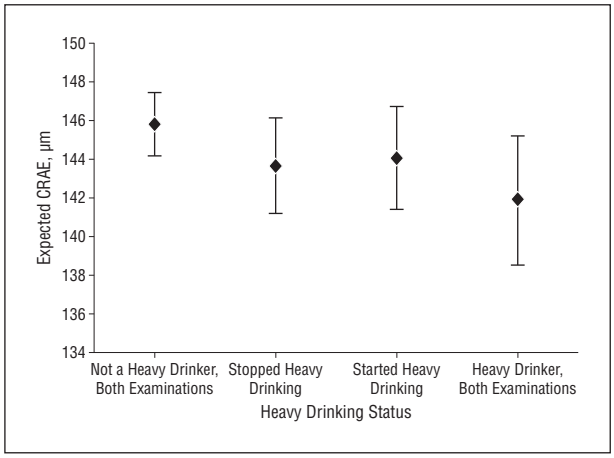

Figure 4. The relationship between change in heavy drinking status during a 5-year period and the expected central retinal arteriolar equivalent (CRAE) at 5-year follow-up (concurrent) examinations. Limit lines indicate standard error.

In our study, starting smoking was associated with a wider retinal arteriolar diameter (increased mean CRAE), whereas stopping was associated with a reduction in arteriolar diameter (decreased mean CRAE), an effect consistent with previously reported associations of current smoking with wider CRAE.[10,37,45,46] Smoking-induced increase in nitrous oxide production, potassium channel activation,[47] and possible elastic tissue degeneration may also explain the association.[48-51] The effect of smoking may also be mediated by an inflammatory effect. Ikram et al[10] hypothesized that disruption of the endothelial surface layer resulting from inflammation secondary to smoking may result in a thinning of this layer, with an increase in the apparent intraluminal caliber of the small retinal blood vessels.

In the Beaver Dam Eye Study, we found an inverse association of BMI with CRAE. The CRAE was narrower in lean persons in whom the BMI increased, and CRAE was wider in obese persons in whom the BMI decreased over time, independent of BP. This relationship was reported for venular diameter but not for CRAE in earlier studies.[10,52] The underlying reasons for these findings are unknown and may involve complex effects on factors not measured in our study, such as changes in endothelial function associated with weight fluctuations.

In the Beaver Dam Eye Study, a history of heavy alcohol consumption was associated with narrower CRAE. This association has been inconsistently found in previous cross-sectional studies.[10,36,46] A similar effect of chronic alcohol ingestion has been reported in both the cerebral and systemic circulations and has been attributed to impaired vasodilation.[53-55]

Although this study has many unique characteristics and strengths, including long-term follow-up, high grader repeatability, and the large population-based study structure, caution is urged in interpreting the findings. One limitation is that the same vessels were not always measured, and, when the same vessels were measured, different lengths may have been measured at different gradings; thus, the CRAE may be an overall summary of

different vessels of the retina at different time points. However, the effect of this is thought to be small, as we have found statistically nonsignificant differences when we did side-by-side grading of the same vessels and compared the results with the standard grading approach used in the study (R.K., unpublished data, October 20, 2010). Second, relationships may have been attenuated by selective survival. Cardiovascular disease and retinal arteriolar narrowing have been shown to be related to mortality in the general population.[10]

In summary, these population-based data show that, while adjusting for refraction, cataract status, and image quality, older age, higher BP, heavy drinking, and greater BMI are independently associated with narrower retinal arterioles and current smoking with wider retinal arterioles. Concurrent measures of these risk factors are more strongly associated than past measures with CRAE, and, after 5 years, the relationships are not statistically significant. These data suggest the importance in adjusting for concurrent BP levels, smoking status, and BMI when examining the relationships of retinal arteriolar diameter as risk indicators of systemic disease over long periods. A clear message from these findings is that current exposure to these modifiable risk factors has a larger effect on the small vessel profile than does previous exposure to the same factors. In other words, it suggests that a change in lifestyle (smoking, drinking) and any other modifiable factor is never too late in affecting the microvasculature. Further study is necessary to evaluate the usefulness of measurements of the retinal vasculature in the care of ocular and systemic disease.

Submitted for Publication: August 9, 2011; final revision received December 19, 2011; accepted January 22, 2012.

Correspondence: Ronald Klein, MD, MPH, Department of Ophthalmology & Visual Sciences, University of Wisconsin School of Medicine and Public Health, 610 N Walnut St, 417 WARF, Madison, WI 53726 (kleinr@epi.ophth.wisc.edu).

Financial Disclosure: None reported.

Funding/Support: National Institutes of Health grant EY06594 (Drs R. Klein and B. E. K. Klein) provided funding for the study, including collection and analyses of data; further support for data analyses was provided by Research to Prevent Blindness (Drs R. Klein and B. E. K. Klein, Senior Scientific Investigator Awards).

Disclaimer: The content is solely the responsibility of the authors and does not necessarily reflect the official views of the National Eye Institute or the National Institutes of Health.

REFERENCES

1. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology*. 1999;106(12):2269-2280.
2. Sharrett AR, Hubbard LD, Cooper LS, et al. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 1999;150(3):263-270.
3. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. *Lancet*. 2001; 358(9288):1134-1140.
4. Klein R, Klein BE, Moss SE, et al. Retinal vascular abnormalities in persons with type 1 diabetes: the Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVIII. *Ophthalmology*. 2003;110(11):2118-2125.
5. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women: the Atherosclerosis Risk in Communities Study. *JAMA*. 2002;287(9):1153-1159.
6. Wong TY, Knudtson MD, Klein R, Klein BE, Hubbard LD. A prospective cohort study of retinal arteriolar narrowing and mortality. *Am J Epidemiol*. 2004;159 (9):819-825.
7. Ikram MK, de Jong FJ, Bos MJ, et al. Retinal vessel diameters and risk of stroke: the Rotterdam Study. *Neurology*. 2006;66(9):1339-1343.
8. Wang JJ, Liew G, Klein R, et al. Retinal vessel diameter and cardiovascular mortality: pooled data analysis from two older populations. *Eur Heart J*. 2007;28 (16):1984-1992.
9. Kawasaki R, Cheung N, Wang JJ, et al. Retinal vessel diameters and risk of hypertension: the Multiethnic Study of Atherosclerosis. *J Hypertens*. 2009;27 (12):2386-2393.
10. Ikram MK, de Jong FJ, Vingerling JR, et al. Are retinal arteriolar or venular diameters associated with markers for cardiovascular disorders? the Rotterdam Study. *Invest Ophthalmol Vis Sci*. 2004;45(7):2129-2134.
11. McGeechan K, Liew G, Macaskill P, et al. Meta-analysis: retinal vessel caliber and risk for coronary heart disease. *Ann Intern Med*. 2009;151(6):404-413.
12. Witt N, Wong TY, Hughes AD, et al. Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke. *Hypertension*. 2006;47(5):975-981.
13. Wong TY, Klein R, Klein BE, Meuer SM, Hubbard LD. Retinal vessel diameters and their associations with age and blood pressure. *Invest Ophthalmol Vis Sci*. 2003;44(11):4644-4650.
14. 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(8):1543-1549.
15. Wong TY, Shankar A, Klein R, Klein BE, Hubbard LD. Prospective cohort study of retinal vessel diameters and risk of hypertension. *BMJ*. 2004;329(7457): 79. doi:10.1136/bmj.38124.682523.55.
16. Leung H, Wang JJ, Rochtchina E, et al. Relationships between age, blood pressure, and retinal vessel diameters in an older population. *Invest Ophthalmol Vis Sci*. 2003;44(7):2900-2904.
17. Wong TY, Klein R, Sharrett AR, et al; Atherosclerosis Risk in Communities Study. Retinal arteriolar diameter and risk for hypertension. *Ann Intern Med*. 2004; 140(4):248-255.
18. Smith W, Wang JJ, Wong TY, et al. Retinal arteriolar narrowing is associated with 5-year incident severe hypertension: the Blue Mountains Eye Study. *Hypertension*. 2004;44(4):442-447.
19. Wang JJ, Rochtchina E, Liew G, et al. The long-term relation among retinal arteriolar narrowing, blood pressure, and incident severe hypertension. *Am J Epidemiol*. 2008;168(1):80-88.
20. Liew G, Wang JJ, Mitchell P, Wong TY. Retinal vascular imaging: a new tool in microvascular disease research. *Circ Cardiovasc Imaging*. 2008;1(2):156-161.
21. Wong TY. Retinal vessel diameter as a clinical predictor of diabetic retinopathy progression: time to take out the measuring tape. *Arch Ophthalmol*. 2011;129 (1):95-96.
22. Klein R, Sharrett AR, Klein BE, et al. Are retinal arteriolar abnormalities related to atherosclerosis? the Atherosclerosis Risk in Communities Study. *Arterioscler Thromb Vasc Biol*. 2000;20(6):1644-1650.
23. Klein R, Klein BE, Linton KL, De Mets DL. The Beaver Dam Eye Study: visual acuity. *Ophthalmology*. 1991;98(8):1310-1315.
24. Klein R, Klein BE, Lee KE. Changes in visual acuity in a population: the Beaver Dam Eye Study. *Ophthalmology*. 1996;103(8):1169-1178.
25. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Chappell RJ. Changes in visual acuity in a population over a 10-year period: the Beaver Dam Eye Study. *Ophthalmology*. 2001;108(10):1757-1766.
26. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Gangnon RE. Changes in visual acuity in a population over a 15-year period: the Beaver Dam Eye Study. *Am J Ophthalmol*. 2006;142(4):539-549.
27. Klein R, Klein BE. *The Beaver Dam Eye Study: Manual of Operations: Revised*. Springfield, VA: National Technical Information Service; 1991:182-227. NTIS publication PB91-149823.
28. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. *Clin Chem*. 1974;20(4):470-475.
29. Lopes-Virella MF, Stone P, Ellis S, Colwell JA. Cholesterol determination in high-density lipoproteins separated by three different methods. *Clin Chem*. 1977; 23(5):882-884.
30. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet

in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999;130(6):461-470.
31. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002; 39(2)(suppl 1):S1-S266.
32. Klein BE, Klein R, Linton KL, Magli YL, Neider MW. Assessment of cataracts from photographs in the Beaver Dam Eye Study. *Ophthalmology*. 1990;97(11):1428-1433.
33. Diabetic Retinopathy Study Research Group. Diabetic retinopathy study: report number 6: design, methods, and baseline results: report number 7: a modification of the Airlie House classification of diabetic retinopathy: prepared by the Diabetic Retinopathy Research Group. *Invest Ophthalmol Vis Sci*. 1981;21(1, pt 2): 1-226.
34. Klein R, Davis MD, Magli YL, Segal P, Klein BE, Hubbard L. The Wisconsin age-related maculopathy grading system. *Ophthalmology*. 1991;98(7):1128-1134.
35. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1992;99(6):933-943.
36. Wong TY, Islam FM, Klein R, et al. Retinal vascular caliber, cardiovascular risk factors, and inflammation: the Multi-Ethnic Study of Atherosclerosis (MESA). *Invest Ophthalmol Vis Sci*. 2006;47(6):2341-2350.
37. Sun C, Liew G, Wang JJ, et al. Retinal vascular caliber, blood pressure, and cardiovascular risk factors in an Asian population: the Singapore Malay Eye Study. *Invest Ophthalmol Vis Sci*. 2008;49(5):1784-1790.
38. Knudtson MD, Lee KE, Hubbard LD, Wong TY, Klein R, Klein BE. Revised formulas for summarizing retinal vessel diameters. *Curr Eye Res*. 2003;27(3): 143-149.
39. Knudtson MD, Klein BE, Klein R, et al. Variation associated with measurement of retinal vessel diameters at different points in the pulse cycle. *Br J Ophthalmol*. 2004;88(1):57-61.
40. Mitchell P, Cheung N, de Haseth K, et al. Blood pressure and retinal arteriolar narrowing in children. *Hypertension*. 2007;49(5):1156-1162.
41. Thom S, Stettler C, Stanton A, et al. Differential effects of antihypertensive treatment on the retinal microcirculation: an Anglo-Scandinavian Cardiac Outcomes Trial substudy. *Hypertension*. 2009;54(2):405-408.
42. Schiffrin EL, Pu Q, Park JB. Effect of amlodipine compared to atenolol on small arteries of previously untreated essential hypertensive patients. *Am J Hypertens*. 2002;15(2, pt 1):105-110.
43. Noguchi M, Mori A, Sakamoto K, Nakahara T, Ishii K. Vasodilator effects of flunarizine on retinal blood vessels in anesthetized rats. *Biol Pharm Bull*. 2009; 32(12):2068-2071.
44. Christensen KL, Mulvany MJ. Vasodilatation, not hypotension, improves resistance vessel design during treatment of essential hypertension: a literature survey. *J Hypertens*. 2001;19(6):1001-1006.
45. Kifley A, Liew G, Wang JJ, et al. Long-term effects of smoking on retinal microvascular caliber. *Am J Epidemiol*. 2007;166(11):1288-1297.
46. Liew G, Sharrett AR, Wang JJ, et al. Relative importance of systemic determinants of retinal arteriolar and venular caliber: the Atherosclerosis Risk in Communities Study. *Arch Ophthalmol*. 2008;126(10):1404-1410.
47. Iida M, Iida H, Dohi S, Takenaka M, Fujiwara H. Mechanisms underlying cerebrovascular effects of cigarette smoking in rats in vivo. *Stroke*. 1998;29(8): 1656-1665.
48. Francès C, Boisnic S, Hartmann DJ, et al. Changes in the elastic tissue of the non–sun-exposed skin of cigarette smokers. *Br J Dermatol*. 1991;125(1):43-47.
49. Rogot E, Murray JL. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Rep*. 1980;95(3):213-222.
50. Sharrett AR, Sorlie PD, Chambless LE, et al. Relative importance of various risk factors for asymptomatic carotid atherosclerosis versus coronary heart disease incidence: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 1999; 149(9):843-852.
51. Sharrett AR, Ding J, Criqui MH, et al. Smoking, diabetes, and blood cholesterol differ in their associations with subclinical atherosclerosis: the Multiethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2006;186(2):441-447.
52. Liew G, Wang JJ. Retinal vascular signs in diabetes and hypertension—review. *Arq Bras Endocrinol Metabol*. 2007;51(2):352-362.
53. Mayhan WG, Didion SP. Effect of chronic alcohol consumption on responses of cerebral arterioles. *Alcohol Clin Exp Res*. 1996;20(3):538-542.
54. Altura BM, Altura BT. Alcohol, the cerebral circulation and strokes. *Alcohol*. 1984; 1(4):325-331.
55. Potter JF, Beevers DG. The possible mechanisms of alcohol associated hypertension. *Ann Clin Res*. 1984;16(suppl 43):97-102.