Retinal Arteriolar Narrowing Is Associated With 5-Year Incident Severe Hypertension: The Blue Mountains Eye Study

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The Blue Mountains Eye Study

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Abstract—We assessed whether retinal arteriolar narrowing and structural abnormalities independently predicted 5-year incident severe (grade 2 or 3) hypertension in an older population-based cohort. The Blue Mountains Eye Study baseline (1992 to 1994) examined 3654 residents aged 49 and older in 2 postal code areas, west of Sydney. Of the 2335 participants (75.1% of survivors) who returned at the 5-year examinations, 1319 were normotensive or had mild (grade 1) hypertension at baseline. Baseline retinal photographs were graded for focal retinal vessel wall signs and vessel diameters were measured. Participants were classified as having normal, high-normal blood pressure [BP] (systolic BP 121 to 139 mm Hg and/or diastolic BP 81 to 89 mm Hg), mild hypertension (systolic BP 140 to 159 mm Hg and/or diastolic BP 90 to 99 mm Hg), or severe hypertension if they had a previous diagnosis of hypertension and were receiving antihypertensive medications or had systolic BP ≥160 mm Hg and/or diastolic BP ≥100 mm Hg at examination. Incident severe hypertension was defined in persons who were free of severe hypertension at baseline but classified as having severe hypertension at the 5-year examinations. Of the 1319 baseline subjects at risk, 390 (29.6%) developed severe hypertension. After adjusting for age, sex, body mass index, smoking, glucose, and total cholesterol, generalized retinal arteriolar narrowing at baseline was associated with increased risk of incident severe hypertension (odds ratio 2.6; 95% confidence interval, 1.7 to 3.9) when comparing the narrowest versus widest quintile. This association remained significant after further adjustment for baseline mean arterial BP or BP status. Our findings support the hypothesis that small vessel structural changes may precede the development of severe hypertension. **(*Hypertension*. 2004;44:442-447.)**

Key Words: arterioles ■ hypertension, detection and control

Retinal microvascular signs are frequently seen in persons with hypertension.[1–11] These changes, sometimes referred to as hypertensive retinopathy, include generalized[12] and focal retinal arteriolar narrowing,[12,13] arteriovenous (AV) nicking,[4] and retinopathy (retinal microaneurysms, hemorrhages, soft or hard exudates).[3,10] However, it is unclear when these signs develop in the course of the evolution of hypertension, because a graded detrimental effect of blood pressure (BP) is found even in persons with high-normal or mild (grade 1) hypertension.[14,15] It is possible that retinal vessel wall signs may occur before the clinical expression of severe hypertension, reflecting an antecedent systemic arteriolar pathology.[16,17]

In the Atherosclerosis Risk in Communities (ARIC) Study, normotensive persons aged 49 to 73 years with generalized or focal retinal arteriolar narrowing were 60% more likely to have incident hypertension develop within 3 years than persons without these signs, independent of vascular risk factors.[18] Few other population-based data are available. In addition, it is not clear whether this association is present in older people, in whom the prevalence of severe hypertension is higher.

We aimed in this report to explore whether retinal vessel wall signs predict the development of severe (grade 2 or 3) hypertension in a population-based cohort of older normotensive or mild (grade 1) hypertensive persons aged 49 to 97 years.

Methods

The Blue Mountains Eye study is a population-based cohort study of vision, common eye diseases, and other health outcomes in an urban population aged 49 years or older. Baseline participants (1992 to

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1994, n=3654) represented 82.4% of those eligible living in 2 postal codes of the Blue Mountains, west of Sydney, Australia. During 1997 to 1999, 2335 (75.1%) of surviving participants were reexamined. The study was approved by the Western Sydney Area Human Research Ethics Committee, with written informed consent obtained from all participants.[19]

All participants attending both the baseline and 5-year follow-up surveys had face-to-face interviews, with eye examinations after pupil dilatation, including stereoscopic retinal photographs (30-degree) of the macula and other retinal fields of both eyes,[20] using a Zeiss FF3 fundus camera (Carl Zeiss). We obtained gradable retinal photographs of both eyes from 98% of study participants.

Detailed grading of focal arteriolar narrowing and AV nicking and measurement of retinal vessel diameters were described previously.[11]

At each examination, we measured systolic BP and diastolic BP (SBP and DBP) once using a single mercury sphygmomanometer with appropriate adult cuff size, after seating the participants for at least 10 minutes. We applied the 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) guidelines to classify blood pressure[21] as high-normal if systolic BP 121 to 139 mm Hg or diastolic BP 81 to 89 mm Hg, grade 1 (mild) hypertension if systolic BP 140 to 159 mm Hg or diastolic BP 90 to 99 mm Hg, and grade 2 or above (severe) hypertension if the subject previously had hypertension diagnosed and was using antihypertensive medications, or had a systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg at examination. We defined incident severe hypertension as present in persons who were free of severe hypertension at baseline but who then had severe hypertension diagnosed before, or at, the 5-year follow-up examination. We calculated mean arterial BP (MABP) as 0.33 (SBP)+0.67 (DBP).

We measured serum total cholesterol and glucose from fasting blood samples. Diabetes was diagnosed either by history or by fasting blood glucose ≥7.0 mmol/L. Body mass index (BMI) was calculated as measured weight (kg)/measured height (m^2). Smoking status was determined by interview and classified as never, past, and current (which included those who had ceased smoking within the past year).

Statistical Methods

Only persons at risk for severe hypertension (baseline normotensives or mild hypertensives) were included in this report. Incident severe hypertension was the dependent variable. Generalized or focal arteriolar narrowing and AV nicking were independent variables. Potential confounders of the association between retinal vascular disease and hypertension were adjusted for in the stepwise logistic regression models using Statistical Analysis System (SAS version 8.0). The covariables included age and sex, or age, sex, BMI, smoking status, glucose, and serum total cholesterol (model 1). Further models included baseline MABP (model 2) or baseline BP status (model 3). We tested interaction terms between age and retinal vessel diameter, and between age and AV nicking. Odds ratios (ORs), 95% confidence intervals (CIs), and adjusted *P* values for trend are presented.

Results

Of the 3627 baseline participants with complete blood pressure and hypertension data, 1645 (45.4%) had severe (grade 2 or 3) hypertension, 950 (26.2%) had mild (grade 1) hypertension, and 1032 (35.9%) were normotensive, including 154 at normal and 878 at high-normal level. Of the 1982 baseline participants at risk for severe hypertension, 1319 returned for the 5-year examinations. Table 1 shows the proportion with retinal microvascular changes and baseline BP by age group. We detected focal retinal arteriolar narrowing in 61 (4.7%), mild and moderate to severe AV nicking were found in 488 (37.3%) and 83 (6.3%) participants, respectively. The proportions of persons with generalized arteriolar narrowing, focal arteriolar narrowing, and mild AV nicking were all strongly age-related. Age did not increase severe AV nicking.

Of the 1319 participants, 390 (29.6%) had severe hypertension develop over the 5 years. Baseline hypertension status was a strong predictor of progression into severe hypertension. Of those with normal BP at baseline, 23.2% (95% CI 15.3% to 32.8%) progressed to grade 1 and 6.1% (2.3% to 12.7%) progressed to grade 2 hypertension, respectively. Of those with high-normal BP at baseline, the corresponding proportions were 41.2% (37.2% to 45.3%) and 19.7% (16.5% to 23.1%), respectively. Of those with mild (grade 1) hypertension at baseline, 42.4% (38.6% to 46.5%) progressed to severe (grade 2 or 3) hypertension in 5 years.

After excluding a further 50 subjects with missing or poor-quality (not gradable) retinal photographs, we were left with 1269 subjects who had complete data available for analyses of the association with retinal microvascular signs. These 1269 subjects included 370 with incident severe hypertension and 899 who remained either normotensive or mildly hypertensive. We compared the baseline characteristics of these 2 groups in Table 2. Participants with incident severe hypertension were significantly more likely at baseline to have higher mean BMI and higher systolic BP, generalized retinal arteriolar narrowing, or narrower mean central retinal arteriolar equivalent (CRAE) and lower arteriole-to-venule ratio (AVR).

Table 3 shows the relation between baseline retinal microvascular signs and 5-year incident hypertension. Persons with the narrowest quintile of CRAE or AVR, focal arteriolar narrowing, and moderate to severe AV nicking were more likely to have severe hypertension develop than were those with the widest quintile of CRAE or AVR and without focal arteriolar narrowing and AV nicking. After adjusting for age and sex, and after further adjusting for BMI, smoking, blood glucose, and serum cholesterol levels (model 1), persons with generalized retinal arteriolar narrowing at baseline were more likely to have severe hypertension develop (OR, 2.6 for CRAE; OR, 2.4 for AVR). Persons with focal arteriolar narrowing (OR, 1.8) or with moderate to severe AV nicking (OR, 1.6) were also more likely to have severe hypertension develop. After additional adjustment for baseline MABP (model 2) or for baseline BP status (model 3), the associations with CRAE and AVR remained significant, but the association with focal arteriolar narrowing and AV nicking became nonsignificant.

In model 3, we adjusted simultaneously for retinal arteriolar narrowing (CRAE or AVR), baseline BP status, and other covariables, and both arteriolar narrowing and baseline BP status contributed independently and significantly to the development of severe hypertension (Table 3).

Stratification of model 1 by gender resulted in little change in the direction or magnitude of the detected associations between generalized arteriolar narrowing and incident severe hypertension (OR, 1.8; 95%, CI 1.2 to 2.8 for women; OR, 2.0; 95% CI, 1.3 to 3.2 for men; adjusted for covariables in model 1).

Interaction between age and retinal vessel diameter, but not between age and AV nicking, was significant in the models.

TABLE 1. Retinal Vessel Wall Signs and Blood Pressure by Age Among Normotensive or Mild Hypertensive Baseline Participants Who Returned for the 5-Year Examinations

		% by Age Group, y			
Baseline Characteristics	All Ages (n=1319)	<60 (n=512)	60–69 (n=534)	70–79 (n=231)	80+ (n=42)
Central retinal arteriolar equivalent					
Mean (SD)		200.9 (19.4)	196.2 (19.5)	190.7 (21.7)	182.2 (18.5)
Quintile					
Widest		23.7	19.5	15.1	5.7
Fourth		23.9	20.2	13.3	2.9
Third		22.1	19.7	16.5	17.1
Second		17.3	20.0	25.2	25.7
Narrowest		12.9	20.6	29.8	48.6
Arteriole-to-venule ratio					
Mean (SD)		0.88 (0.08)	0.87 (0.08)	0.86 (0.08)	0.85 (0.09)
Quintile					
Widest		21.7	19.9	16.5	20.0
Fourth		21.9	19.3	18.8	11.4
Third		21.3	20.4	17.0	14.3
Second		17.7	21.4	21.6	22.9
Narrowest		17.3	19.1	26.2	31.4
Focal retinal arteriolar narrowing					
Present	61 (4.7)	1.6	3.8	10.4	21.4
AV nicking					
Mild	488 (37.3)	30.2	41.4	40.4	53.4
Moderate to severe	83 (6.3)	4.4	7.7	7.8	4.8
BP, mm Hg		Mean (95% CI)			
Mean arteriolar BP		97.7 (97.0–98.5)	98.2 (97.5–98.9)	99.0 (98.0–100.0)	97.8 (95.7–100.0)
Mean systolic BP		131.7 (130.6–132.8)	135.9 (134.8–137.0)	139.3 (137.8–140.8)	137.8 (134.3–142.4)
Mean diastolic BP		81.0 (80.4–81.7)	79.7 (79.0–80.3)	79.2 (78.1–80.2)	78.2 (76.0–80.4)

Age stratification revealed stronger associations between generalized retinal arteriolar narrowing and incident severe hypertension among persons aged younger than 65 years (OR, 2.4; CI, 1.5 to 3.7) and a weaker association in those aged 65 years or older (OR, 1.5; CI, 1.0 to 2.4). In contrast, the adjusted association between moderate to severe AV nicking and incident hypertension among persons aged 65 years or older (OR, 2.7; CI, 1.3 to 5.6) was significant; but not among those aged younger than 65 years (OR, 0.9; CI, 0.4 to 1.9).

We repeated these analyses using 160/95 mm Hg as the dividing line above which we classified subjects as manifesting incident hypertension. This yielded very similar results to the models in which we used 160/100 as the dividing line.

Discussion

In this older population-based cohort, we found that generalized retinal arteriolar narrowing was significantly associated with subsequent 5-year incident severe (grade 2 or 3) hypertension, independent of other known risk factors for hypertension and baseline BP status. This association was stronger for younger (younger than 65 years) than older (65 years or older) participants. By contrast, the associations of focal arteriolar narrowing and moderate to severe AV nicking with incident severe hypertension became nonsignificant once we adjusted for baseline BP. These data support the notion that generalized structural changes in small blood vessels, visualized in the retina, may precede the development of clinical severe hypertension.

The strengths of our study include its prospective design, our use of a population-based sample with high participation rate, the objective grading of retinal photographs using a standardized protocol, and well-documented information on potential confounding variables. A fair follow-up of 75% of the original sample was seen at the 5-year examinations.

The study also has several limitations. Those who did not return were older and had a slightly higher prevalence of retinal microvascular signs, attributes that define an increased risk of mortality[22] (data not shown). Our findings thus could have underestimated the association between retinal arteriolar narrowing and incident hypertension. The use of single measures of blood pressure, which exhibited significant terminal digit preference, may have meant that we misclassified some subjects as having hypertension when they did not and that we missed some who did. This nondifferential misclassification is likely to bias our observed association

TABLE 2. Baseline Characteristics (95% CI) Stratified by Incident Severe Hypertension Status

Baseline Characteristics	5-Year Examinations: Incident Severe Hypertension (n=390)	5-Year Examinations: No Incident Severe Hypertension (n=929)
Demographics and risk factors		
Mean age, y	63.9 (63.0–64.7)	62.1 (61.6–62.7)
Women, %	59.2 (54.2–64.1)	52.7 (49.5–56.0)
Mean BMI	26.4 (25.9–26.8)	25.5 (25.3–25.8)
Mean total cholesterol, mmol/L	6.09 (5.98–6.20)	5.98 (5.91–6.05)
Diabetes, %	6.4 (4.2–9.3)	5.0 (3.6–6.5)
Current smoker, %	13.0 (9.8–16.8)	15.1 (12.9–17.7)
Retinal vessel wall signs		
Generalized retinal arteriolar narrowing defined by CRAE, %	27.6 (23.1–32.4)	16.8 (14.4–19.4)
Generalized retinal arteriolar narrowing defined by arteriole-to-venule ratio, %	28.1 (23.6–33.0)	16.6 (14.2–19.2)
Mean central retinal arteriolar equivalent, mm	192.0 (190.0–194.1)	198.6 (197.3–199.9)
Mean arteriole-to-venule ratio	0.85 (0.84–0.86)	0.88 (0.87–0.88)
Focal retinal arteriolar narrowing, %	7.0 (4.7–10.0)	3.7 (2.6–5.1)
AV nicking, %		
Mild	38.4 (33.6–43.5)	36.8 (33.7–40.0)
Moderate to severe	8.8 (6.2–12.1)	5.3 (3.9–6.9)
BP, mm Hg		
Mean arteriolar BP	101.9 (101.2–102.6)	96.6 (96.1–97.1)
Mean systolic BP	141.2 (140.2–142.3)	132.3 (131.5–133.1)
Mean diastolic BP	82.6 (81.8–83.3)	79.0 (78.5–79.5)

between retinal vascular disease and incident hypertension toward the null. Our findings thus would be an underestimate of the true association between retinal vascular disease and hypertension. By way of sensitivity analysis, we repeated the principal analyses using diastolic BP ≥95 mm Hg, ≥105 mm Hg, and ≥110 mm Hg at examination instead of ≥100 mm Hg; and using systolic BP ≥155 mm Hg, ≥165 mm Hg, and ≥170 mm Hg at examination instead of ≥160 mm Hg, and found essentially the same results (data not shown).

Our study suggests that generalized structural abnormalities in retinal blood vessels are prospectively associated with subsequent risk of severe hypertension in a representative general population. These findings add support to a long-standing hypothesis about the pathogenesis of hypertension. Others have found from animal studies[16,23] and cross-sectional studies in highly selected human subjects[17] that arteriolar constriction and narrowing may play a critical role in the earliest stages of hypertension development. In addition to their association with hypertension, the retinal vessel wall signs evaluated here have been associated with systemic markers of inflammation.[24] This is consistent with recent studies that suggest inflammation may also play a role in the development of hypertension.[25,26]

Our data are comparable to those from the ARIC study.[18] The 2 studies used identical methods to define retinal arteriolar narrowing from digitized photographs. The magnitude of the association of generalized retinal arteriolar narrowing and incident hypertension in this study was similar to the ARIC study, although the latter was conducted in a younger population (49 to 73 years versus 49 to 97 years) with a shorter follow-up (3 years versus 5.1 years) and examined incident mild (grade 1) hypertension. Taken in totality, the close concordance of the findings in these 2 populations provides consistent evidence that microvascular narrowing may contribute to the development of clinical hypertension.

Two additional observations deserve further comments. First, when we controlled for baseline MABP (model 2) or baseline BP status (model 3), the associations between retinal arteriolar wall signs and incident hypertension attenuated for generalized narrowing and were no longer significant for AV nicking and focal arteriolar narrowing. However, because of the close association of long-term BP levels and retinal vessel wall signs,[11] controlling for baseline BP may have resulted in overadjustment. By including baseline BP in the model, we demonstrated that the contribution from retinal vessel signs to the outcome (incident severe hypertension) could add incrementally to the contribution from baseline BP.

Second, we found somewhat stronger associations between generalized retinal arteriolar narrowing and weaker associations between AV nicking with incident severe hypertension in younger than in older persons. This may reflect the

TABLE 3. Retinal Arteriolar Narrowing and Vascular Signs at Baseline and 5-Year Incident Severe Hypertension in the Blue Mountains Eye Study Population Aged 49 Years and Older

Baseline Characteristics	Mean (SD) Retinal Width (mm)	OR (95% CI) 5-Year Incident Severe Hypertension (n=370/1269)				
				Multivariate Adjusted		
		% Affected	Age- and Sex-Adjusted	Model 1*	Model 2†	Model 3‡
Central retinal arteriolar equivalent						
Quintile						
Widest (n=254)	224.4 (9.7)	21.3	1.0	1.0	1.0	1.0
Fourth (n=254)	207.5 (3.1)	23.6	1.2 (0.8–1.7)	1.3 (0.8–2.0)	1.2 (0.8–1.9)	1.3 (0.8–2.0)
Third (n=254)	196.7 (2.9)	28.4	1.4 (1.0–2.2)	1.5 (1.0–2.3)	1.3 (0.8–2.0)	1.4 (0.9–2.1)
Second (n=254)	186.3 (3.3)	32.3	1.7 (1.2–2.6)	1.8 (1.2–2.8)	1.5 (0.9–2.3)	1.6 (1.0–2.5)
Narrowest (n=253)	168.5 (12.0)	40.3	2.4 (1.6–3.5)	2.6 (1.7–3.9)	1.9 (1.2–2.9)	2.1 (1.4–3.3)
P for trend		<0.0001	<0.0001	<0.0001	0.0037	0.0005
Narrowest quintile vs others			1.8 (1.3–2.4)	1.9 (1.4–2.5)	1.5 (1.1–2.1)	1.6 (1.2–2.2)
Baseline BP status						
Normal						1.0
High-normal BP						3.1 (1.3–7.4)
Grade 1 hypertension						8.9 (3.8–21.0)
Arteriole-to-venule ratio						
Quintile						
Widest (n=254)	0.98 (0.04)	22.8	1.0	1.0	1.0	1.0
Fourth (n=254)	0.91 (0.01)	23.6	1.0 (0.7–1.6)	1.2 (0.7–1.8)	1.1 (0.7–1.7)	1.1 (0.7–1.8)
Third (n=254)	0.87 (0.01)	26.4	1.2 (0.8–1.8)	1.3 (0.8–2.0)	1.1 (0.7–1.8)	1.2 (0.8–1.9)
Second (n=254)	0.83 (0.01)	31.9	1.5 (1.0–2.3)	1.6 (1.0–2.4)	1.2 (0.8–1.9)	1.4 (0.9–2.2)
Narrowest (n=253)	0.76 (0.04)	41.1	2.4 (1.6–3.5)	2.4 (1.6–3.6)	1.7 (1.1–2.6)	2.0 (1.3–3.0)
P for trend		<0.0001	<0.0001	<0.0001	0.0095	0.0011
Narrowest quintile vs others			2.0 (1.5–2.7)	1.9 (1.4–2.6)	1.5 (1.1–2.1)	1.6 (1.2–2.3)
Baseline BP status						
Normal						1.0
High-normal BP						3.1 (1.3–7.2)
Grade 1 hypertension						8.8 (3.7–20.6)
Focal retinal arteriolar narrowing						
Absent (n=1248)		28.7	1.0	1.0	1.0	1.0
Present (n=61)		44.3	1.7 (1.0–2.9)	1.8 (1.0–3.2)	1.3 (0.7–2.5)	1.6 (0.9–2.9)
AV nicking						
Absent/questionable (n=738)		27.5	1.0	1.0	1.0	1.0
Mild (n=488)		30.3	1.1 (0.8–1.4)	1.0 (0.8–1.3)	1.0 (0.7–1.3)	1.0 (0.7–1.3)
Moderate to severe (n=83)		41.0	1.7 (1.1–2.7)	1.6 (1.0–2.6)	1.3 (0.8–2.2)	1.3 (0.8–2.2)

*Adjusted for age, sex, BMI, smoking, glucose, and serum cholesterol (continuous variables).
†Additionally adjusted for baseline MABP.
‡Additionally adjusted for baseline BP status (normal, high-normal, and grade 1 hypertension).

complex associations of small vessel wall signs with several factors other than BP (eg, hormonal status, obesity, insulin resistance, inflammatory marker status) that change as people age. Alternatively, there may be a survivor cohort effect. For example, if there is a differential early cardiovascular mortality among those with retinal arteriolar narrowing, the association between retinal arteriolar narrowing and incident severe hypertension will be less evident among older people who survive.

Although findings from our study and the ARIC study suggest that retinal microvascular signs may identify individuals at greater risk for clinically severe hypertension developing, the variability in the measurements of arteriolar caliber currently limits their applicability to predicting hypertension in individuals seen in clinical practice. The development of automated methods to quantify retinal vessel wall signs may well improve the clinical usefulness of these findings.

In conclusion, this prospective study found that retinal arteriolar wall signs predicted 5-year incident severe hypertension, independent of known vascular risk factors and baseline BP. These data support the hypothesis that structural micro-arteriolar damage, visible in the retina, precedes the development and progression of severe hypertension.

References

1. Svardsudd K, Wedel H, Aurell E, Tibblin G. Hypertensive eye ground changes. Prevalence, relation to blood pressure and prognostic importance. The study of men born in 1913. *Acta Med Scand*. 1978;204: 159–167.
2. Tso MO, Jampol LM. Pathophysiology of hypertensive retinopathy. *Ophthalmology*. 1982;89:1132–1145.
3. Klein R, Klein BE, Moss SE, Wang Q. Blood pressure, hypertension and retinopathy in a population. *Trans Am Ophthalmol Soc*. 1993;91: 207–222.
4. Klein R, Klein BE, Moss SE, Wang Q. Hypertension and retinopathy, arteriolar narrowing, and arteriovenous nicking in a population. *Arch Ophthalmol*. 1994;112:92–98.
5. Klein R, Klein BE, Moss SE. The relation of systemic hypertension to changes in the retinal vasculature: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc*. 1997;95:329–348.
6. Hubbard LD, Brothers RJ, King WN, Clegg LX, Klein R, Cooper LS, Sharrett AR, Davis MD, Cai J. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology*. 1999;106: 2269–2280.
7. Sharrett AR, Hubbard LD, Cooper LS, Sorlie PD, Brothers RJ, Nieto FJ, Pinsky JL, Klein R. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 1999;150:263–270.
8. Wong TY, Hubbard LD, Klein R, Marino EK, Kronmal R, Sharrett AR, Siscovick DS, Burke G, Tielsch JM. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. *Br J Ophthalmol*. 2002;86:1007–1013.
9. Wong TY, Klein R, Sharrett AR, Manolio TA, Hubbard LD, Marino EK, Kuller L, Burke G, Tracy RP, Polak JF, Gottdiener JS, Siscovick DS. The prevalence and risk factors of retinal microvascular abnormalities in older persons: The Cardiovascular Health Study. *Ophthalmology*. 2003;110:658–666.
10. Yu T, Mitchell P, Berry G, Li W, Wang JJ. Retinopathy in older persons without diabetes and its relationship to hypertension. *Arch Ophthalmol*. 1998;116:83–89.
11. Wang JJ, Mitchell P, Leung H, Rochtchina E, Wong TY, Klein R. Hypertensive retinal vessel wall signs in a general older population: the Blue Mountains Eye Study. *Hypertension*. 2003;42:534–541.
12. Parr JC. Hypertensive generalised narrowing of retinal arteries. *Trans Ophthalmol Soc N Z*. 1974;26:55–60.
13. Stokoe NL, Turner RW. Normal retinal vascular pattern. Arteriovenous ratio as a measure of arterial calibre. *Br J Ophthalmol*. 1966;50:21–40.
14. Lundstrom M, Barry P, Leite E, Seward H, Stenevi U. 1998 European Cataract Outcome Study: report from the European Cataract Outcome Study Group. *J Cataract Refract Surg*. 2001;27:1176–1184.
15. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr, Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.
16. Rizzoni D, Castellano M, Porteri E, Bettoni G, Muiesan ML, Agabiti-Rosei E. Vascular structural and functional alterations before and after the development of hypertension in SHR. *Am J Hypertens*. 1994;7: 193–200.
17. Norrelund H, Christensen KL, Samani NJ, Kimber P, Mulvany MJ, Korsgaard N. Early narrowed afferent arteriole is a contributor to the development of hypertension. *Hypertension*. 1994;24:301–308.
18. Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, Klein BE, Hubbard LD, Nieto FJ. Retinal arteriolar diameter and risk for hypertension. *Ann Intern Med*. 2004;140:248–255.
19. Attebo K, Mitchell P, Smith W. Visual acuity and the causes of visual loss in Australia. The Blue Mountains Eye Study. *Ophthalmology*. 1996;103: 357–364.
20. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. *Ophthalmology*. 1995;102:1450–1460.
21. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens*. 2003;21:1983–1992.
22. Wong TY, Klein R, Nieto FJ, Klein BE, Sharrett AR, Meuer SM, Hubbard LD, Tielsch JM. Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. *Ophthalmology*. 2003;110:933–940.
23. Bautista LE, Lopez-Jaramillo P, Vera LM, Casas JP, Otero AP, Guaracao AI. Is C-reactive protein an independent risk factor for essential hypertension? *J Hypertens*. 2001;19:857–861.
24. Klein R, Sharrett AR, Klein BE, Chambless LE, Cooper LS, Hubbard LD, Evans G. Are retinal arteriolar abnormalities related to atherosclerosis? The Atherosclerosis Risk in Communities Study. *Arterioscler Thromb Vasc Biol*. 2000;20:1644–1650.
25. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. *JAMA*. 2003; 290:2945–2951.
26. Folkow B. Physiological aspects of primary hypertension. *Physiol Rev*. 1982;62:347–504.