

Retinal Vessel Diameters and Risk of Hypertension

The Rotterdam Study

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Abstract—Generalized retinal arteriolar narrowing is an important sign of systemic hypertension, and a lower arteriolar:venular diameter ratio predicts the risk of hypertension. We investigated whether this association was based on arteriolar or venular diameters or both. This study was based on the prospective population-based Rotterdam Study (1990–1993) and included 1900 participants (≥ 55 years of age) of whom 739 persons had normal blood pressure (systolic < 120 mm Hg and diastolic < 80 mm Hg) and 1161 prehypertension (systolic 120 to 139 mm Hg or diastolic 80 to 89 mm Hg). For each participant, retinal arteriolar and venular diameters were measured on digitized images of 1 eye. After a mean follow-up of 6.6 years, 808 persons developed hypertension, defined as either systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or use of antihypertensive medication. Adjusted for age, gender, follow-up time, body mass index, smoking, diabetes mellitus, total and high-density lipoprotein cholesterol, C-reactive protein, and intima-media thickness, arteriolar narrowing was associated with an increased risk of hypertension (odds ratio per SD: 1.38; 95% CI, 1.23 to 1.55); for venular narrowing this was less striking (OR: 1.17; 95% CI, 1.04 to 1.32). Each SD decrease in the arteriolar:venular diameter ratio significantly increased the risk of hypertension by 24%. To examine the effect of baseline blood pressure, we stratified persons into those with “normal blood pressure” or “prehypertension.” Within these strata, arteriolar narrowing was still related to incident hypertension. These data show that both retinal arteriolar and venular narrowing may precede the development of systemic hypertension. (*Hypertension*. 2006;47:189-194.)

Key Words: population ■ risk factors ■ arterioles ■ vasoconstriction ■ hypertension

Increased peripheral vascular resistance, a hallmark of hypertension, is mainly determined by arteriolar narrowing.^{1–3} It remains uncertain whether generalized arteriolar narrowing antedates high blood pressure or occurs as a secondary adaptation.² A primary role has been attributed to impaired renal sodium homeostasis, leading to fluid expansion and, subsequently, to increased cardiac output and blood pressure.^{3,4} According to this hypothesis, physiological and morphological alterations in the peripheral circulation arise as a secondary reaction.

In recent years, other hypotheses, postulating alterations in arterioles as the initiating event in the development of hypertension, have gained support.² Thus far, evidence is largely based on animal models.^{2,5} Spontaneously hypertensive rats had decreased arteriolar diameters compared with control rats before the onset of hypertension.^{6,7} Studies in humans suggested that persons with familial predisposition had arteriolar narrowing in the prehypertensive stage.⁸

Recently, a semiautomated system was developed to non-invasively measure retinal vessel diameters in vivo.⁹ To avoid

a potential problem of magnification differences because of refractive errors of an eye, an arteriolar:venular ratio (AVR) was used. A lower AVR thus obtained in a population-based study was suggested to reflect generalized arteriolar narrowing and was associated with an increased risk of hypertension within 3 years.¹⁰ We showed recently that retinal venular diameters vary in the presence of several cardiovascular risk factors, making it difficult to interpret the AVR.¹¹ Therefore, we suggested that arteriolar and venular diameters should be examined separately, especially in etiologic research. So far, prospective data on the relationship between retinal arteriolar diameters and hypertension are scarce. We examined the relation between baseline retinal vessel diameters and incident hypertension in a prospective population-based setting.

Methods

Study Population

This study was performed as part of the Rotterdam Study, a population-based cohort study on chronic diseases in the elderly.¹² A total of 7983 participants, aged ≥ 55 years, living in a district of

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Rotterdam, agreed to participate (response rate, 78%). Because the ophthalmic part became operational after the screening of randomly invited participants had started, 6780 participants had an eye examination. The study was conducted according to the tenets of the Declaration of Helsinki, and the medical ethics committee of the Erasmus University approved the study protocol. Written informed consent was obtained from all of the participants. Baseline interviews and examinations were performed from 1990 to 1993 followed by follow-up examinations, and the last one with complete data for these analyses was from 1997 to 1999.

Retinal Vessel Measurements

Simultaneous stereoscopic color transparencies centered on the optic disc (pharmacological mydriasis using tropicamide 0.5% and phenylephrine 5%, 20° field, Topcon Optical Company) were taken at baseline (Figure). These transparencies were digitized, and for each participant, the image of 1 eye with the best quality was analyzed with a semiautomated system (Retinal Analysis; Department of Ophthalmology and Visual Science, University of Wisconsin-Madison).¹¹ For 1 eye of each participant, a sum value was calculated for the arteriolar blood column diameter and 1 for the venular (in micrometers). We used the improved Parr-Hubbard formula to compute the summary vessel measures.¹³ Because eyes may have a different magnification in the case of changes attributed to corneal curvature and refractive errors differences, we corrected this summary vessel measure for possible magnification variations with Littmann's formula to approximate absolute measures.¹⁴ The AVR was defined as the ratio of arteriolar:venular diameters.

In a random subsample of 100 participants, we found no differences between the right and left eyes for the arteriolar and venular diameters. Four trained graders performed all of the measurements masked for participant characteristics. Both intergrader and intragrader studies (n=40) showed good-to-excellent agreement (intra-class correlation coefficient, 0.49 to 0.95)

Ascertainment of Incident Cases of Hypertension

Both at baseline and follow-up, trained examiners took 2 blood pressure measurements with a random-zero sphygmomanometer with appropriate adult cuff size and the participant in sitting position. The average of these 2 measurements was taken. To classify blood pressure, we applied the guidelines as suggested by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.^{15,16} Persons with systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg were considered to be normotensive.^{15,16} Prehypertension was defined as systolic blood pressure between 120 and 139 mm Hg or diastolic blood pressure between 80 and 89 mm Hg. Hypertension was defined as systolic blood pressure \geq 140 mm Hg, diastolic blood pressure \geq 90 mm Hg, or use of antihypertensive medication. Hypertension was additionally subdivided into stage 1 hypertension, defined as either systolic blood pressure 140 to 159 mm Hg or diastolic blood pressure 90 to 99 mm Hg and stage 2 hypertension, defined as systolic blood pressure \geq 160 mm Hg, diastolic blood pressure \geq 100 mm Hg, or use of antihypertensive medication. Exposure to medication was assessed at baseline and follow-up by means of a standardized interview. Participants were asked to bring their medications to the examination center for verification. Incident hypertension was defined as being normotensive or prehypertensive at baseline and having hypertension stage 1 or 2 at follow-up.

Assessment of Confounders

Potential confounders were assessed at baseline. Information on smoking (categorized as current, former, or never) was obtained during the home interview. Because the eye examination was performed at the end of the 2-hour visit to the research center with no-smoking policy, there was a gap of at least of 2 hours between the eye examination and smoking of a cigarette. Body mass index was computed as weight divided by height squared. Nonfasting serum total cholesterol was determined by an enzymatic procedure, and high-density lipoprotein (HDL) was measured similarly after precip-

itation of the non-HDL fraction.¹⁷ Diabetes mellitus was present when participants reported use of antidiabetic medication or when random or postload serum glucose level was >11.0 mmol/L. Intima-media thickness (in mm) was assessed by ultrasonography of the common carotid arteries.¹⁸ Serum levels of C-reactive protein (CRP) were determined by the Rate Near Infrared Particle Immunoassay method (Immagine high-sensitive CRP, Beckman Coulter).

Study Sample

Of the 6780 participants in the ophthalmic part of the Rotterdam Study, 6436 persons had optic disc photographs, and, in 5674 persons (84%), these were gradable for retinal vessel measurements. Excluding participants who had missing data on blood pressure (n=84) and those with prevalent hypertension (stage 1 or 2; n=2871), a total of 2719 participants remained at risk for incident hypertension. During follow-up, 317 participants died (33% cardiovascular mortality), and 502 refused or were unable to participate in the follow-up examination, leaving 1900 participants for the current analyses.

Statistical Analyses

Analyses were started by examining the linear association between baseline retinal vessel diameters and change in blood pressure using linear regression models. For all of the additional analyses, persons who developed hypertension stage 1 or 2 were considered incident cases of hypertension, except when mentioned otherwise. We calculated odds ratios (ORs) with corresponding 95% CIs of incident hypertension per SD difference in baseline retinal vessel diameters through logistic regression analysis adjusted for age, gender, and follow-up time. Additional adjustments were made for baseline levels of smoking, body mass index, diabetes mellitus, total and HDL cholesterol, CRP, and atherosclerosis as measured by the carotid intima-media thickness. Subsequently, the analyses were repeated with the retinal vessel diameters categorized into quartiles of their distribution.

In order to reanalyze whether the association between retinal vessel diameter and incident hypertension was influenced by baseline blood pressure, we stratified blood pressure in 2 subcategories, namely "normal" and "prehypertension," as suggested by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.¹⁶ Finally, we repeated the analyses with a more stringent definition: being normotensive or prehypertensive at baseline and developing hypertension stage 2 during follow-up, excluding persons who had incident hypertension stage 1. All of the analyses were performed with SPSS Windows, version 11.0 (SPSS Inc).

Results

Table 1 presents the baseline characteristics of our study population. Nonparticipants were older, more often women, more often current smokers, and had a slightly higher CRP level compared with participants. Persons who died during follow-up had a worse cardiovascular risk profile compared with participants. Table 2 shows the baseline characteristics for the participants after stratifying on baseline blood pressure. After a mean follow-up of 6.6 years (range, 5.2 to 9.6 years), 808 persons were diagnosed with incident hypertension, including 504 persons with stage 1 and 304 with stage 2 hypertension. The mean blood pressure at follow-up was 148/77 mm Hg for stage 1 hypertension and 155/80 mm Hg for stage 2 hypertension. A total of 281 persons received antihypertensive medication during follow-up.

Each SD decrease in baseline arteriolar diameters was linearly and significantly related to an increase of 1.1 mm Hg (95% CI, 0.3 to 1.9) in systolic and 0.6 mm Hg (95% CI, 0.1 to 1.1) in diastolic blood pressure. Similarly, 1 SD decrease in

TABLE 1. Baseline Characteristics of the Study Population Presented as Unadjusted Means (SD) or Percentages

Baseline Characteristics	Participants	Nonparticipants*	Adjusted Differences† (95% CI)	Died§	Adjusted Differences† (95% CI)
No.	1900	502		317	
Age (y)	64.3 (6.5)	68.2 (8.3)	3.9 (3.2 to 4.6)‡	74.5 (9.0)	10.2 (9.4 to 11.1)‡
Gender (% female)	57.0	65.0	7.8 (2.8 to 12.7)‡	45.0	−13.0 (−19.5 to −6.6)‡
Diabetes mellitus (%)	4.0	7.0	2.1 (−3.3 to 4.5)	18.0	10.4 (7.2 to 13.5)‡
Systolic blood pressure (mm Hg)	121.7 (11.8)	122.7 (11.7)	0.2 (−1.0 to 1.4)	122.0 (12.4)	−2.3 (−3.8 to −0.7)‡
Diastolic blood pressure (mm Hg)	68.6 (8.4)	68.2 (8.8)	0.6 (−0.3 to 1.4)	65.2 (9.3)	−1.3 (−2.4 to −0.2)‡
Smoking (%)					
Current	24.3	28.5	8.4 (4.1 to 12.8)‡	32.4	16.4 (10.7 to 22.1)‡
Past	45.1	41.5	−1.6 (−6.4 to 3.2)	42.1	−8.5 (−14.7 to −2.2)‡
Body mass index (kg/m ²)	25.7 (3.4)	25.8 (3.7)	0.0 (−0.4 to 0.3)	25.3 (3.8)	−0.6 (−1.0 to −0.1)‡
Total serum cholesterol (mmol/L)	6.60 (1.16)	6.67 (1.13)	0.07 (−0.04 to 0.19)	6.18 (1.25)	−0.24 (−0.39 to −0.09)‡
Serum HDL cholesterol (mmol/L)	1.37 (0.35)	1.38 (0.38)	0.00 (−0.03 to 0.04)	1.28 (0.37)	−0.02 (−0.07 to 0.02)
Serum CRP (mg/L)	2.40	2.99	0.55 (0.06 to 1.04)‡	4.95	2.25 (1.60 to 2.89)‡
Carotid artery intima-media thickness (mm)	0.74 (0.13)	0.77 (0.14)	0.01 (−0.003 to 0.003)	0.83 (0.15)	0.01 (−0.003 to 0.003)
Retinal arteriolar diameter (μm)	149.5 (14.0)	148.6 (14.7)	−0.2 (−1.6 to 1.2)	146.8 (14.3)	−1.0 (−2.8 to 0.9)
Retinal venular diameter (μm)	223.8 (19.9)	221.5 (21.5)	−0.4 (−2.5 to 1.6)	220.9 (21.5)	0.4 (−2.2 to 3.1)
Retinal AVR	0.67 (0.05)	0.67 (0.06)	0.001 (−0.005 to 0.006)	0.67 (0.06)	0.005 (−0.013 to 0.017)

*Refused at follow-up (compared to participants).

†Age and gender adjusted if applicable.

‡Significant ($P < 0.05$).

§Persons who died before the follow-up examination (compared with participants).

venular diameters resulted in a nonsignificant rise of 0.2 mm Hg (95% CI, −0.6 to 1.0) in systolic and 0.4 mm Hg (95% CI, −0.1 to 0.9) in diastolic blood pressure. Additional adjustments for other cardiovascular risk factors did not alter these results.

Table 3 presents the associations between retinal vessel diameters and incident hypertension, both per SD and in quartiles. One SD decrease in retinal arteriolar diameters at baseline was associated with a 42% increased risk of incident hypertension. Smaller venular diameters were less markedly associated with incident hypertension. Each SD decrease in the resulting AVR showed a 29% increase in the risk of incident hypertension. Additional adjustments for other cardiovascular risk factors did not affect these associations.

Participants in the lowest quartile of baseline arteriolar diameters had a >2-fold increased risk of hypertension compared with those in the highest one. Stratification on baseline blood pressures revealed that persons with a normal blood pressure and smaller arteriolar diameters were already at an increased risk of developing hypertension with decreasing arteriolar diameters (Table 4). After additional adjustments, the relative risk remained unaltered, albeit borderline significant (OR, 1.21; 95% CI, 0.97 to 1.51).

With the more stringent definition of incident hypertension, each SD decrease in retinal arteriolar diameters was

related to an increased risk of hypertension (Table 5). Finally, stratification on cardiovascular risk factors did not significantly alter any of the above-mentioned results.

Discussion

Generalized retinal arteriolar narrowing at baseline increased the risk of hypertension in a general elderly population and even more so than could be inferred from the AVR only. This association persisted after adjusting for other cardiovascular risk factors and was independent of baseline blood pressure.

In this study, we confirm the association between smaller arteriolar diameters and incident hypertension. Because smaller venular diameters also increased the risk of hypertension, the magnitude of the association with the AVR was smaller than with the arteriolar diameters only. Thus, our data suggest that in order to determine the risk of hypertension, arteriolar sum values are more sensitive than the AVR. In a clinical setting, arteriolar diameters are usually gauged at ophthalmoscopy against venular ones to estimate generalized arteriolar narrowing. Our data imply that this approach may underestimate the extent of arteriolar narrowing and thereby the risk of hypertension, because the venules also narrow with increasing blood pressure.

Until recently, prospective data from population-based studies were lacking mainly because of difficulties in reliably

TABLE 2. Baseline Characteristics of Participants (n=1900) Stratified According to Their Baseline Blood Pressure, Presented as Unadjusted Means (SD) or Percentages

Baseline Characteristics	Normal*	Prehypertension†	Adjusted Differences‡ (95% CI)
No.	739	1161	
Age (y)	62.9 (5.7)	65.2 (6.7)	2.3 (1.7 to 2.9)§
Gender (% female)	60.0	54.0	-6.0 (-10.0 to -1.4)§
Diabetes mellitus (%)	2.4	5.5	2.6 (0.7 to 4.5)§
Systolic blood pressure (mm Hg)	109.5 (7.8)	129.4 (5.8)	19.6 (19.0 to 20.2)§
Diastolic blood pressure (mm Hg)	64.0 (7.0)	71.5 (8.0)	8.1 (7.4 to 8.7)§
Smoking (%)			
Current	27.9	21.9	-4.5 (-8.5 to -5.1)§
Past	43.5	46.1	0.4 (-4.1 to 4.9)
Body mass index (kg/m ²)	25.1 (3.0)	26.1 (3.5)	0.9 (0.6 to 1.3)§
Total serum cholesterol (mmol/L)	6.58 (1.17)	6.61 (1.16)	0.08 (-0.03 to 0.19)
Serum HDL cholesterol (mmol/L)	1.40 (0.37)	1.35 (0.34)	-0.03 (-0.06 to 0.00)
Serum CRP (mg/L)	2.16	2.55	0.29 (-0.06 to 0.64)
Carotid artery intima-media thickness (mm)	0.72 (0.13)	0.76 (0.13)	0.03 (0.01 to 0.04)§
Retinal arteriolar diameter (μm)	151.9 (13.6)	148.0 (14.1)	-3.7 (-5.0 to -2.4)§
Retinal venular diameter (μm)	225.3 (19.4)	222.8 (20.2)	-2.1 (-3.9 to -0.2)§
Retinal AVR	0.68 (0.05)	0.67 (0.05)	-0.01 (-0.02 to -0.005)§

*Systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg.

†Systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg.

‡Age and gender adjusted if applicable.

§Significant ($P<0.05$).

assessing general arteriolar narrowing. Several cross-sectional studies, using a semiautomated system to measure retinal vessel diameters, appeared showing an inverse relationship between retinal arteriolar diameters and blood pressures.^{9,11,19,20} Also, retinal venular diameters showed a significant, although weaker, inverse association with blood pressures.^{11,19} Because of the cross-sectional nature of these

studies, it was not possible to distinguish cause and consequence.

Our ORs for incident hypertension according to baseline vessel diameters were comparable to other incidence studies. The Atherosclerosis Risk in Communities Study published data showing a relationship between smaller AVR at baseline and 3-year incidence of hypertension (n=5628; OR per SD decrease: 1.12; 95% CI, 1.03 to 1.21).¹⁰ The same authors confirmed this finding in data from the Beaver Dam Eye Study (n=2451; OR per SD decrease: 1.31; 95% CI, 1.18 to 1.45).²¹ The Blue Mountains Eye Study (n=1319) reported a slightly stronger association between separate arteriolar diameters, without adjustment for refractive changes, and incident hypertension (OR first versus fifth quintile: 2.4; 95% CI, 1.6 to 3.5).²²

Generalized arteriolar narrowing may be caused by abnormalities in the endothelium, vascular smooth muscle cells, or the neuromuscular junction.^{1,2} Local endothelial NO synthesis (eNOS) in vascular beds as the retinal and renal ones plays an important role in determining the vessel diameters. NO is a potent vasodilator and also prevents smooth muscle cell proliferation.²³ In normotensive persons, administration of *N*-mono-methyl-L-arginine, an inhibitor of eNOS, resulted in elevated systemic blood pressure and decreased retinal blood flow.²⁴ In contrast, no change occurred in hypertensive patients, suggesting that eNOS was already lower in these patients. Impaired local production of other vasoactive agents (angiotensin II and endothelin-1) could also contribute to an altered peripheral vascular resistance. Hypersensitivity of



Diameters of arterioles and venules that cross the area bounded by the dotted and outermost circle were measured.

TABLE 3. ORs of Incident Systemic Hypertension* in Quartiles of Baseline Retinal Vessel Diameters or AVR

Retinal Vessel Measurements	Model I†	Model II‡
Retinal arteriolar diameters (μm)		
Per SD decrease	1.42 (1.29 to 1.57)	1.38 (1.23 to 1.55)
Quartiles [range]		
4 [157.7 to 204.7]	1.0 (reference)	1.0 (reference)
3 [148.6 to 157.6]	1.10 (0.84 to 1.44)	1.00 (0.73 to 1.36)
2 [140.2 to 148.5]	1.31 (1.01 to 1.71)	1.15 (0.84 to 1.58)
1 [95.0 to 140.1]	2.22 (1.71 to 2.89)	2.15 (1.58 to 2.93)
Retinal venular diameters (μm)		
Per SD decrease	1.16 (1.05 to 1.28)	1.17 (1.04 to 1.32)
Quartiles [range]		
4 [236.5 to 296.4]	1.0 (reference)	1.0 (reference)
3 [223.1 to 236.4]	1.24 (0.96 to 1.61)	1.24 (0.90 to 1.70)
2 [210.2 to 223.0]	1.27 (0.98 to 1.65)	1.33 (0.97 to 1.83)
1 [135.1 to 210.1]	1.41 (1.08 to 1.83)	1.39 (1.01 to 1.91)
Retinal AVR		
Per SD decrease	1.29 (1.17 to 1.43)	1.24 (1.10 to 1.40)
Quartiles [range]		
4 [0.70 to 0.94]	1.0 (reference)	1.0 (reference)
3 [0.67 to 0.69]	1.19 (0.92 to 1.55)	1.04 (0.76 to 1.42)
2 [0.63 to 0.66]	1.33 (1.02 to 1.72)	1.11 (0.81 to 1.51)
1 [0.50 to 0.62]	1.89 (1.45 to 2.46)	1.73 (1.27 to 2.35)

*Hypertension stage 1 and 2 pooled.

†Age, gender, and follow-up time adjusted.

‡Additionally for body mass index, smoking, diabetes mellitus, total and HDL cholesterol, CRP, and intima-media thickness.

smooth muscle cells to these vasoactive agents could be another mechanism.²⁵ Hypertensive patients manifest greater vasoconstrictor responses to infused norepinephrine than normotensive persons.²⁶ Moreover, vasoconstrictor responsiveness is increased in normotensive offspring of hypertensive parents, suggesting that hypersensitivity of these cells may be primary in origin.²⁶ Finally, disturbed sympathetic activity in arterioles manifested by greater release of neurotransmitters,²⁷ altered neuronal neurotransmitter reuptake,²⁸ or sympathetic neuromodulation by angiotensin II²⁹ may contribute to the development of hypertension. We cannot, however, distinguish which of the above-mentioned mechanisms may lead to arteriolar narrowing based on the retinal intraluminal diameters that we measured.^{10,21,22}

Previously, we showed that smaller arteriolar diameters were also cross-sectionally related to hypertension.¹¹ It could be that the associations we described in this study were explained by the fact that some of the incident cases already had hypertension at baseline but were misclassified as normotensive or prehypertensive because of large within-subject variability of blood pressures. In our study, the SD of within-subject variability for blood pressure was 10.8 mm Hg. If there was any misclassification, this most probably affected those who were classified as normotensive

TABLE 4. ORs of Incident Systemic Hypertension* per SD Decrease in Baseline Retinal Vessel Diameters or AVR Stratified on Baseline Blood Pressure

Retinal Vessel Measurements	Baseline Blood Pressure	
	Normal† (189/739)§	Prehypertension‡ (619/1161)§
Retinal arteriolar diameters, per SD decrease		
Model III	1.29 (1.08 to 1.56)	1.37 (1.22 to 1.56)
Model II#	1.21 (0.97 to 1.51)	1.38 (1.20 to 1.59)
Retinal venular diameters, per SD decrease		
Model III	1.06 (0.88 to 1.27)	1.17 (1.03 to 1.32)
Model II#	1.02 (0.81 to 1.28)	1.21 (1.05 to 1.40)
Retinal AVR, per SD decrease		
Model III	1.25 (1.04 to 1.50)	1.24 (1.09 to 1.41)
Model II#	1.22 (0.98 to 1.53)	1.21 (1.05 to 1.39)

*Hypertension stage 1 and 2 pooled.

†Systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg.

‡Systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg.

§No. of incident hypertension cases/total no. of persons within stratum.

||Adjusted for age, gender, and follow-up time.

#Additionally for body mass index, smoking, diabetes mellitus, total and HDL cholesterol, CRP, and intima-media thickness.

or prehypertensive at baseline and who had hypertension stage 1 at follow-up. Hence, we excluded these persons and repeated the analyses by taking only those who developed hypertension stage 2 at follow-up. The association between baseline retinal vessel diameters and incident hypertension remained present.

A limitation of this study may be the number of nonparticipants at follow-up. Although nonparticipants were older, more often women, more often current smokers, and had a higher CRP compared with participants, there were no major differences in other cardiovascular risk factors between these groups. Baseline blood pressures and retinal vessel diameters especially did not show any differences, suggesting that there was no selective nonresponse. Another limitation is that photographs were not taken synchronized on the cardiac cycle, leading to variation in vessel diameter because of pulsatility. A variation of 2% to 17% in vessel diameter has

TABLE 5. ORs of Incident Systemic Hypertension* per SD Decrease in Baseline Retinal Vessel Diameters or AVRs

Retinal Vessel Measurements	Model I†	Model II‡
Retinal arteriolar diameters, per SD decrease	1.60 (1.39 to 1.86)	1.62 (1.36 to 1.92)
Retinal venular diameters, per SD decrease	1.18 (1.03 to 1.34)	1.22 (1.03 to 1.44)
Retinal AVR, per SD decrease	1.43 (1.24 to 1.66)	1.40 (1.17 to 1.66)

*Hypertension stage 2.

†Age, gender, and follow-up time adjusted.

‡Additionally for body mass index, smoking, diabetes mellitus, total and HDL cholesterol, CRP, and intima-media thickness.

been described.³⁰ However, because photography was independent of any participant characteristics, this will have caused random misclassification. Strengths of our study are the prospective population-based design with a long follow-up, identical examination procedures at baseline and follow-up for blood pressure measurement, and detailed and standardized evaluation of retinal arteriolar diameters on higher-magnification images with correction for refractive errors.

In conclusion, data from this prospective population-based study in an elderly population provide additional evidence that generalized retinal arteriolar narrowing may precede the development of systemic hypertension. Isolated generalized retinal arteriolar narrowing was more strongly related to the risk of hypertension than the AVR. The clinical implications of these data might be that, in elderly persons (semi-), automated measurement of retinal arterioles may play a role in the prediction of their risk of hypertension.

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