



ORIGINAL CONTRIBUTIONS

A Prospective Cohort Study of Retinal Arteriolar Narrowing and Mortality

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The authors examined the relation of narrowed retinal arteriolar diameters, a marker of hypertensive damage, to mortality in a population-based cohort of 4,926 persons aged 43–84 years living in Wisconsin. A computer-assisted method was used to measure retinal vessel diameters from digitized retinal photographs taken at the baseline examination (1988–1990). These measurements were summarized as the retinal arteriole-to-venule ratio (AVR), with a smaller AVR indicating narrower arterioles compared with venules. Its relation to 10-year mortality was analyzed by using Cox proportional hazards models, adjusting for age, gender, blood pressure, diabetes, and other risk factors. No relation was found between smaller AVR and increased mortality. In relation to the largest AVR quartile, the adjusted relative risks of all-cause mortality were 0.93 for the smallest AVR quartile, 0.71 for the second AVR quartile, and 0.80 for the third AVR quartile. Results were largely similar in analyses of cause-specific mortality (vascular disease and non-vascular-disease mortality) and in subgroups stratified by age, gender, and diabetes and hypertension status. These data contrast with recent studies showing a relation between narrowed retinal arterioles and increased cardiovascular risk, suggesting that further research is needed to understand the systemic associations of retinal microvascular changes.

arterioles; cardiovascular diseases; hypertension; mortality; retina; venules

Abbreviations: ARIC, Atherosclerosis Risk in Communities; AVR, arteriole-to-venule ratio; HDL, high density lipoprotein.

Direct, noninvasive visualization of the retinal blood vessels provides an opportunity to examine systemic consequences related to structural microvascular damage caused by hypertension (1). Previous studies have linked narrowed retinal arterioles (generalized retinal arteriolar narrowing) with increased risk of coronary heart disease and cardiovascular mortality in persons with hypertension (2–4).

However, these studies have been limited by the imprecision of quantifying retinal arteriolar narrowing associated with a clinical ophthalmoscopic examination (5).

In the Atherosclerosis Risk in Communities (ARIC) Study, we developed a computer-assisted method to define generalized retinal arteriolar narrowing based on measuring retinal vessel diameters from digitized photographs (6). Using this

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approach, we showed that this narrowing was strongly associated with concurrent blood pressure and with blood pressure measured 6 years earlier, suggesting that narrowed retinal arterioles may be a marker of both transient and persistent effects of hypertension (7). In the ARIC Study, narrowed retinal arterioles were associated with incident clinical stroke (8), incident diabetes (9), and incident coronary heart disease in women (10), independent of traditional cardiovascular risk factors. However, subsequent studies in other populations have provided more conflicting evidence. In the Cardiovascular Health Study, retinal arteriolar narrowing was not related to either prevalent stroke or coronary heart disease (11). In an earlier case-control study nested in the Beaver Dam Eye Study, we found a weak association between generalized retinal arteriolar narrowing and cardiovascular (coronary heart disease and/or stroke) mortality for younger persons 43–74 years of age but not for persons aged 75 years or older (12).

In light of these inconsistencies, we examined the relation of retinal vessel diameters to all-cause and vascular-disease-related mortality in the entire Beaver Dam cohort. This paper reports on that examination.

MATERIALS AND METHODS

The Beaver Dam Eye Study is a population-based cohort study described in detail previously (13). In brief, a private census of the population of the town of Beaver Dam, Wisconsin, was performed from fall 1987 to spring 1988. Ninety-nine percent of the population is White. Of 5,924 persons eligible, 4,926 participated in the baseline examination between 1988 and 1990 (13). Photographs to determine retinal vessel diameters for 317 (6.4 percent) of these persons were ungradable, leaving 4,609 who provided data for this study. As reported previously (14), participants whose photographs were ungradable were older. After we controlled for age, we found that participants without gradable photographs were more likely to be women; to have hypertension, cardiovascular disease, diabetes, and cataract; and to have higher levels of serum glucose, glycosylated hemoglobin, and proteinuria. Systolic and diastolic blood pressures were not significantly different for those with and without gradable photographs.

Retinal vessel measurement

The protocol used in the ARIC Study (6), described in detail elsewhere (14, 15), was modified to measure retinal vessel diameters from digitized photographs in the Beaver Dam Eye Study. In brief, 30° color retinal photographs of right eyes were digitized by a high-resolution scanner using standard settings. The diameters of all arterioles and venules coursing through a specified area of one-half to one disc diameter surrounding the optic disc (zone B) were measured by using a computer imaging program (figure 1). The program was based on microdensitometry techniques and measured the width of the blood column (generally equivalent to the width of the vessel lumen). Graders, masked to participant characteristics, performed this measurement. These measurements were combined into summary indices,

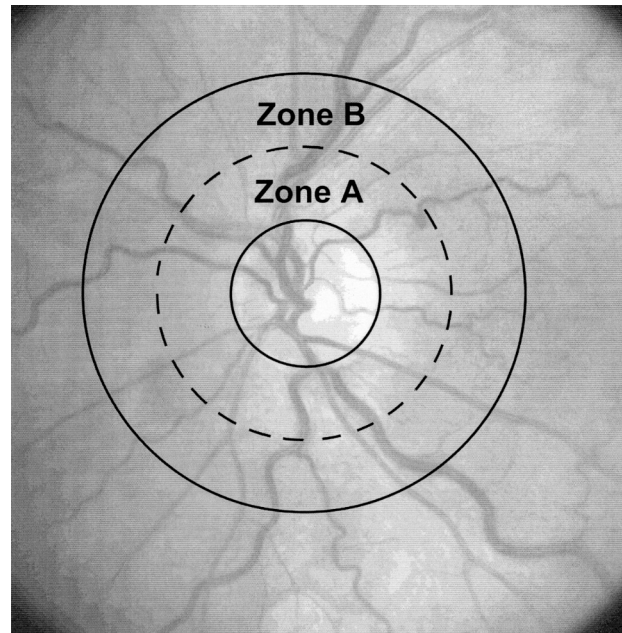


FIGURE 1. Digitized retinal photograph with a superimposed grid showing zones A and B. Retinal vessel diameters were measured in zone B. Beaver Dam Eye Study, Beaver Dam, Wisconsin, 1988–1990.

the central retinal arteriolar and venular equivalents, which represented the average arteriolar and venular diameters of that eye, respectively (14, 15). These diameters were finally expressed as the retinal arteriole-to-venule ratio (AVR). The AVR compensated for possible magnification differences between eyes, and an AVR of 1.0 suggested that arteriolar diameters were, on average, the same as venular diameters in that eye; a smaller AVR suggested narrower arterioles (6). Reproducibility of these retinal measurements has been reported previously (12).

Initially, photographs of the right eyes of all participants were selected for measurement. If a photograph of the right eye was considered ungradable, the left eye was chosen for measurement. In a subset of patients for whom photographs of their right eyes were gradable, we also measured the retinal diameters of their left eyes to determine the correlation between eyes. In this subset, we used the average retinal diameters of both eyes for analysis. Thus, retinal vessel measurements were based on data from the right eyes of 3,397, the left eyes of 383, and the average of both eyes of 829 persons. A previous analysis of the association of retinal vessel diameter with blood pressure showed that results were similar when measurements from one eye or the mean of two eyes were used (14).

Mortality

Ascertainment of mortality involved contacting participants, relatives, and designated physicians annually and reviewing newspaper obituaries daily (16). When a death is

identified in the state of Wisconsin, a request is made to the Wisconsin Center for Health Statistics, Section of Vital Statistics, for death certificate information about the person. Information on persons known to have died outside of Wisconsin as well as on those who we lost contact with (no contact since December 31, 1999) and were not known to have died was submitted to the National Death Index for matching against national death data. We ascertained mortality between the baseline examination in 1988–1990 and December 31, 1999. Cause of death was defined as any contributing cause listed on the death certificate according to *International Classification of Diseases*, Ninth Revision, Clinical Modification and *International Classification of Diseases*, Tenth Revision, Clinical Modification (for deaths after December 31, 1998) codes. Vascular disease mortality was further defined to include deaths from heart disease, stroke, atherosclerosis, and arterial disease according to the following codes: *International Classification of Diseases*, Ninth Revision, Clinical Modification: 391.0–398.9, 402.0–402.9, 404.0–404.9, 410.0–429.9, 430.0–438.9, 440.0–440.9, and 441.0–448.9; and *International Classification of Diseases*, Tenth Revision, Clinical Modification: I01.0–I09.9, I11.0–I11.9, I13.0–I13.9, I20.0–I51.9, I60.0–I69.9, I70.0–I70.9, and I71.0–I78.9. All other cases were classified as nonvascular disease mortality.

Definitions of vascular risk factors

A standardized interview and examination were performed at each study visit (17). Questions were asked relating to household income, history of cardiovascular disease, medication use, and cigarette smoking. Blood pressure was measured with a random zero sphygmomanometer according to the Hypertension Detection and Follow-up Program protocol (18). Pulse pressure was defined as the difference between systolic and diastolic blood pressures. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg, a diastolic blood pressure of ≥ 90 mmHg, or the combination of a self-reported hypertension diagnosis and use of antihypertensive medications at the time of examination. Patients were further classified as those receiving antihypertensive treatment and those not receiving such treatment. Nonfasting blood specimens were obtained from all participants. Serum glucose levels were determined by using the hexokinase method, plasma glycosylated hemoglobin was assessed by using affinity chromatography, and serum total cholesterol and high density lipoprotein (HDL) cholesterol were determined by using enzymatic methods (17).

Diabetes mellitus was defined as having a history of diabetes or being newly diagnosed with diabetes (no previous medical history of diabetes mellitus in the presence of elevated glycosylated hemoglobin and a random blood sugar level of >200 mg/dl) (17). Elevated glycosylated hemoglobin was defined as a value greater than two standard deviations above the mean for a given age-sex group (43–54 years: men, >9.5 percent and women, >9.6 percent; 55–64 years: men, >9.4 percent and women, >10.0 percent; 65–74 years: men, >9.6 percent and women, >9.6 percent; and ≥ 75 years: men, >9.5 percent and women, >9.6 percent). Primary

care physicians were consulted whenever the diagnosis was in doubt.

Statistical methods

Retinal vessel data (AVR and its individual components, retinal arteriolar and venular diameters) were analyzed as both categorical (quartiles) and continuous variables. We used chi-square tests and analysis of variance to compare the association of various baseline characteristics with mortality and AVR quartiles. We used the Kaplan-Meier method to estimate cumulative mortality rates (presented as $100 \times (1 - \text{Kaplan-Meier estimators})$) and Cox proportional hazards models to estimate the relative risk of mortality associated with AVR quartiles. In proportional hazards models, we initially adjusted for age and gender. We constructed two multivariable models, the first adjusting for age, gender, cigarette smoking, history of cardiovascular disease, diabetes, glycosylated hemoglobin, income, and ratio of total to HDL cholesterol (model 1) and the second additionally adjusting for pulse pressure and systolic blood pressure (model 2). In separate models, we substituted systolic blood pressure for diastolic blood pressure and included a quadratic term for systolic blood pressure as an additional covariate because of the strong influence of blood pressure on both retinal arteriolar diameter and mortality. Results of these later models were largely similar (data not shown). Finally, we examined these associations in the cohort stratified by age group, gender, and hypertension and diabetes status.

RESULTS

Table 1 shows the baseline characteristics of participants, comparing those who died ($n = 1,199$) with those still alive as of December 31, 1999 ($n = 3,727$) and comparing the smallest with the largest AVR quartiles. Persons who died were older; more likely to be men; more likely to have a history of myocardial infarction, stroke, hypertension, and diabetes; and more likely to be cigarette smokers. Persons who died were also more likely to have higher systolic blood pressure, lower diastolic blood pressure, and higher glucose, higher glycosylated hemoglobin, lower total cholesterol, and lower HDL cholesterol levels. Similarly, persons for whom the AVR was lower were more likely to be men, have hypertension, and be cigarette smokers. Lower AVR was associated with higher systolic and diastolic blood pressures, higher glucose levels, higher total cholesterol levels, lower HDL cholesterol levels, and higher body mass index.

The relations between retinal AVR and its components with all-cause, vascular-disease-related, and non-vascular-disease-related mortality are shown in table 2. The all-cause cumulative mortality rates were 22.4 percent for persons in the first or smallest AVR quartile, 17.9 percent for persons in the second AVR quartile, 18.3 percent for persons in the third AVR quartile, and 20.7 percent for persons in the fourth or largest AVR quartile. In relation to the fourth AVR quartile, the age- and gender-adjusted relative risks of all-cause mortality were 1.00 for the first AVR quartile, 0.79 for the second AVR quartile, and 0.80 for the third AVR quartile.

TABLE 1. Baseline characteristics of the study population, by mortality status and retinal arteriole-to-venule ratio,* Beaver Dam Eye Study, Beaver Dam, Wisconsin, 1988–1990

Baseline characteristic	Mortality status			Retinal arteriole-to-venule ratio				<i>p</i> value†
	Dead (<i>n</i> = 1,199)	Alive (<i>n</i> = 3,727)	<i>p</i> value†	1st quartile (lowest) (<i>n</i> = 1,200)	2nd quartile (<i>n</i> = 1,087)	3rd quartile (<i>n</i> = 998)	4th quartile (highest) (<i>n</i> = 1,037)	
Age (years)	71 (9.5)	59 (10.1)	<0.001	61 (10.4)	62 (10.6)	62 (11.1)	61 (11.6)	0.78
Gender: men	51	42	<0.001	53	46	43	36	<0.001
History of myocardial infarction	16	4	<0.001	7.0	6.6	5.9	5.9	0.75
History of stroke	10	2	<0.001	3.5	4.0	2.0	2.9	0.09
Hypertension	64	46	<0.001	62	51	44	40	<0.001
Diabetes	17.6	6.4	0.003	8.7	8.4	9.1	7.8	0.71
Systolic blood pressure (mmHg)	138 (23.0)	130 (19.3)	0.02	138 (20.1)	133 (19.4)	130 (19.5)	126 (20.0)	<0.001
Diastolic blood pressure (mmHg)	75 (12.0)	78 (10.5)	<0.001	81 (11.2)	79 (10.5)	76 (10.1)	74 (10.3)	<0.001
Serum glucose (mg/dl)	116 (51.5)	104 (34.1)	<0.001	108 (41.5)	106 (34.6)	107 (43.4)	103 (32.9)	0.01
Glycosylated hemoglobin	6.6 (2.1)	6.0 (1.4)	<0.001	6.2 (1.6)	6.1 (1.6)	6.0 (1.6)	6.0 (1.5)	0.06
Serum total cholesterol (mg/dl)	233 (47.6)	234 (43.1)	0.01	235 (43.4)	235 (46.3)	231 (41.9)	232 (43.9)	0.005
High density lipoprotein cholesterol (mg/dl)	49 (16.9)	53 (17.7)	<0.001	51 (17.4)	51 (17.6)	52 (16.6)	54 (18.2)	0.05
Body mass index (kg/m ²)	28.7 (5.6)	28.8 (5.4)	0.36	29.7 (5.4)	29.0 (5.1)	28.6 (5.5)	27.7 (5.2)	<0.001
Ever cigarette smoker	58	54	<0.001	63	59	52	48	<0.001

* Data are expressed as mean (standard deviation) or percentage.

† Adjusted for age and gender (where appropriate).

These findings did not change substantially after multivariable adjustment (models 1 and 2).

Table 2 also shows that the results were largely similar in analyses of vascular and nonvascular mortality and when the components of AVR (arteriolar and venular diameters) were analyzed separately. Tests for a linear trend of AVR and its components were not statistically significant for all results shown ($p > 0.05$). In analyses repeated by using AVR as a continuous variable, no significant associations with mortality (all cause, vascular, and nonvascular related) were seen (data not shown).

Table 3 shows the associations of retinal AVR with vascular disease mortality in subgroups stratified by age, gender, diabetes and hypertension status, and systolic blood pressure quartiles. In these analyses, decreased AVR was not associated with increased vascular mortality.

DISCUSSION

In this population-based, prospective study, we found no association of narrowed retinal arterioles with either all-cause mortality or vascular-disease- and non-vascular-disease-related mortality specifically. No associations were seen in subgroups stratified by various demographic and vascular factors.

We had hypothesized that narrowed retinal arteriolar diameters (as reflected by a smaller AVR) would be associated with increased mortality. The association between lower AVR and higher blood pressure found in the current

study is consistent with previous investigations (6, 7), but the lack of association between lower AVR and mortality contrasts with studies showing that narrowed retinal arterioles predicted incident cardiovascular disease, including stroke (8), diabetes (9), and coronary heart disease (in women) (10).

In a previous case-control study of the association between hypertensive retinal microvascular changes and cardiovascular mortality nested in the Beaver Dam Eye Study population (413 cases and 1,198 controls), we reported that younger persons aged 43–74 years who died from cardiovascular disease were more likely to have generalized retinal arteriolar narrowing (defined as an AVR in the smallest quintile) than people of the same age without such narrowing (an AVR in the largest four quintiles) (odds ratio = 1.9, 95 percent confidence interval: 1.2, 2.9). This finding was not true for people aged 75 years or older (odds ratio = 1.0, 95 percent confidence interval: 0.6, 1.8). In the current analysis, we did not find an association between retinal arteriolar narrowing and all-cause or vascular-disease-related mortality for younger or older people. Several explanations are possible for the difference between the two analyses. In the case-control analysis, the primary outcome was cardiovascular mortality (coronary heart disease and stroke); in the current study, the definition of vascular-disease-related mortality included deaths from “atherosclerosis” and “arterial diseases.” In the case-control study, we selected three participants per case as controls, matching them by age (5-year intervals) and gender; in the current study, information

TABLE 2. All-cause, vascular disease, and non-vascular-disease mortality associated with retinal arteriole-to-venule ratio and vessel diameters, Beaver Dam Eye Study, Beaver Dam, Wisconsin, 1988–1990

	No. at risk	%*	Age-gender†		All-cause mortality		Multivariable model 1‡		Multivariable model 2§		Vascular disease mortality			Non-vascular-disease mortality		
			RR	95% CI	RR	95% CI	RR	95% CI	%*	Multivariable model 2§		%*	Multivariable model 2§			
										RR	95% CI		RR	95% CI		
Retinal arteriole-to-venule ratio																
1st quartile (lowest)	1,200	22.4	1.00	0.84, 1.19	0.91	0.76, 1.08	0.93	0.78, 1.11	15.6	0.92	0.74, 1.14	8.1	0.96	0.71, 1.31		
2nd quartile	1,087	17.9	0.79	0.66, 0.96	0.71	0.59, 0.85	0.71	0.59, 0.86	11.4	0.63	0.50, 0.80	7.4	0.91	0.66, 1.24		
3rd quartile	998	18.3	0.80	0.66, 0.97	0.79	0.66, 0.96	0.80	0.66, 0.97	12.8	0.79	0.63, 1.00	6.2	0.81	0.59, 1.13		
4th quartile (highest)	1,037	20.7	1.00		1.00		1.00		14.2	1.00		7.6	1.00			
Retinal arteriolar diameter																
1st quartile (lowest)	1,083	21.8	0.81	0.68, 0.97	0.93	0.77, 1.11	0.94	0.78, 1.12	15.6	1.03	0.82, 1.30	7.3	0.78	0.57, 1.07		
2nd quartile	1,070	18.7	0.69	0.57, 0.83	0.78	0.65, 0.94	0.78	0.65, 0.95	12.7	0.84	0.66, 1.06	7.0	0.71	0.52, 0.98		
3rd quartile	1,086	18.9	0.83	0.69, 1.00	0.88	0.73, 1.05	0.88	0.73, 1.06	13.1	0.97	0.77, 1.22	6.6	0.75	0.56, 1.02		
4th quartile (highest)	1,097	20.4	1.00		1.00		1.00		12.9	1.00		5.5	1.00			
Retinal venular diameter																
1st quartile (lowest)	1,056	20.4	0.81	0.67, 0.97	1.04	0.86, 1.26	1.03	0.85, 1.24	14.7	1.12	0.88, 1.41	6.6	0.86	0.62, 1.19		
2nd quartile	1,085	19.8	0.83	0.69, 1.00	0.99	0.82, 1.19	0.99	0.82, 1.19	13.4	1.01	0.80, 1.27	7.3	0.93	0.68, 1.27		
3rd quartile	1,088	19.3	0.92	0.77, 1.11	1.07	0.89, 1.29	1.08	0.90, 1.29	12.3	1.08	0.86, 1.36	7.9	1.06	0.79, 1.43		
4th quartile (highest)	1,095	20.4	1.00		1.00		1.00		13.8	1.00		7.7	1.00			

* Defined as $100 \times (1 - \text{Kaplan-Meier cumulative survival at 10 years})$.

† Relative risk (RR) and 95% confidence interval (CI) adjusted for age and gender.

‡ Model 1: further adjusted for cigarette smoking, history of cardiovascular disease, diabetes, glycosylated hemoglobin, income, and ratio of total to high density lipoprotein cholesterol.

§ Model 2: further adjusted for pulse pressure and systolic blood pressure.

for the entire cohort was included in proportional hazards models. To further examine differences between the two studies, we compared characteristics of the “control” populations. Controls selected for the case-control analysis were more likely to be women and to be younger and, after we adjusted for age and gender, to have lower diastolic blood pressure, lower body mass index, and lower total cholesterol levels compared with “controls” in the current study (participants who did not die). However, cigarette smoking status, HDL cholesterol level, hypertension status, systolic blood pressure, glucose level, and glycosylated hemoglobin level were not significantly different.

On further examination of the data, we found that mortality risk was highest among those for whom the AVRs were in the smallest and largest quartiles compared with the second and third quartiles (refer to tables 2 and 3). After we performed multivariable adjustment, those whose AVRs were in the second quartile versus the largest quartile were 29 percent less likely to die (relative risk = 0.71, 95 percent confidence interval: 0.59, 0.86) and 37 percent less likely to die from a vascular cause (relative risk = 0.63, 95 percent confidence interval: 0.50, 0.80). This pattern appears to suggest that persons whose retinal arteriolar diameters were either smaller or larger were more likely to die than those with moderate-sized diameters. We are unable to fully explain this finding, which was not hypothesized a priori. A

similar U-shaped (or J-shaped) association between blood pressure and cardiovascular risk has been reported in some epidemiologic studies. In these studies, cardiovascular disease risk appears to increase for persons with lower extremes of blood pressure (19–25).

A common explanation for the higher mortality among those with the lower extremes of blood pressure is that this pattern may reflect confounding factors related to poor general health (24, 26). It is possible that similar confounding factors, or others not measured in this study (e.g., inflammation (27)), may contribute to the pattern observed. However, our results are not compatible with the hypothesis of confounding by poor general health, since we would expect a similar U-shaped association with noncardiovascular mortality. Alternatively, overtreatment of hypertension has been suggested to compromise coronary or cerebral blood flow, leading to myocardial or cerebral ischemia (28). This hypothesis is also not supported by the current findings; the U-shaped curve was present for normotensive persons and for hypertensive persons not receiving antihypertensive treatment and was in fact absent for hypertensive persons receiving treatment (table 3). Finally, it is possible that both smaller and larger retinal arteriolar diameters reflect hypertensive damage. Researchers have observed that, in response to elevated blood pressure, retinal arterioles vasoconstrict to regulate the microcirculatory flow in the retinal capillaries (29); however, with a further

TABLE 3. Vascular disease mortality associated with retinal arteriole-to-venule ratio, by hypertension and blood pressure status, Beaver Dam Eye Study, Beaver Dam, Wisconsin, 1988–1990

	Retinal arteriole-to-venule ratio														
	1st quartile (lowest)				2nd quartile				3rd quartile				4th quartile (highest)		
	No. at risk	% death*	RR†	95% CI	No. at risk	% death*	RR†	95% CI	No. at risk	% death*	RR†	95% CI	No. at risk	% death*	RR†
Age group	1,067	11.8	1.04	0.78, 1.39	947	7.2	0.67	0.48, 0.92	857	8.1	0.85	0.61, 1.17	881	8.6	1.00
Younger (43–74 years)															
Older (≥75 years)	133	47.7	0.73	0.51, 1.04	140	40.7	0.63	0.44, 0.91	141	42.7	0.73	0.52, 1.03	156	48.1	1.00
Gender															
Men	644	18.1	0.94	0.70, 1.27	513	14.8	0.63	0.45, 0.88	446	17.3	0.82	0.59, 1.14	374	19.1	1.00
Women	556	12.6	0.87	0.62, 1.21	574	8.3	0.67	0.47, 0.95	552	9.3	0.79	0.56, 1.11	663	11.5	1.00
Diabetes status															
No diabetes	1,097	13.7	0.94	0.73, 1.20	1,001	10.9	0.69	0.53, 0.89	911	10.6	0.72	0.55, 0.94	960	12.5	1.00
Diabetes	103	35.2	0.84	0.50, 1.39	86	17.5	0.37	0.19, 0.71	87	36.6	1.15	0.68, 1.94	77	35.9	1.00
Hypertension status															
Normotensive	450	13.1	1.19	0.82, 1.74	531	6.6	0.59	0.38, 0.91	567	7.6	0.75	0.51, 1.13	629	8.7	1.00
Untreated hypertensive	324	12.1	0.56	0.34, 0.94	238	10.5	0.39	0.23, 0.69	178	15.5	0.62	0.37, 1.05	127	19.8	1.00
Treated hypertensive	426	20.9	0.93	0.67, 1.29	314	20.1	0.90	0.64, 1.28	253	22.5	0.90	0.63, 1.28	278	23.8	1.00
Systolic blood pressure (mmHg)															
<120	205	15.3	0.94	0.58, 1.55	277	5.5	0.56	0.30, 1.02	322	7.7	0.66	0.39, 1.09	424	9.3	1.00
120–139	480	14.0	1.30	0.89, 1.90	461	10.1	0.86	0.57, 1.29	409	11.3	0.93	0.62, 1.39	383	11.9	1.00
140–159	365	15.9	0.64	0.42, 0.98	248	15.7	0.49	0.31, 0.77	196	19.4	0.79	0.51, 1.22	163	25.6	1.00
≥160	150	20.3	0.78	0.44, 1.39	101	23.2	0.71	0.39, 1.29	71	26.3	0.71	0.38, 1.33	67	31.8	1.00

* Cumulative mortality rate, defined as $100 \times (1 - \text{Kaplan-Meier cumulative survival at 10 years})$.

† Relative risk (RR) and 95% confidence interval (CI) adjusted for covariates in model 2 (age, gender, cigarette smoking, history of cardiovascular disease, diabetes, glycosylated hemoglobin, income, ratio of total to high density lipoprotein cholesterol, pulse pressure, and systolic blood pressure) comparing a specific quartile with the 4th quartile (reference).

increase in blood pressure, the arterioles lose this autoregulatory capacity to vasoconstrict and start to distend instead. In the ARIC Study, a number of participants with uncontrolled hypertension had wider arterioles than would be expected (6). Thus, although hypertension would generally be associated with smaller arteriolar diameters in the majority of people, it may also be associated with larger diameters in those with severely elevated blood pressure. Nevertheless, because we did not find evidence of a U-shaped curve in previous analyses of narrowed retinal arterioles and incidence of stroke, diabetes, or coronary heart disease (8–10), this pattern needs to be confirmed in future studies.

There are a few noteworthy limitations. Cause of death was not validated in this study (e.g., by examining medical records). However, death certificate information appears to be a fairly sensitive indicator of cause-specific mortality (30). Selection bias may have further masked or attenuated some associations; a number of photographs were ungradable because of the presence of cataract. Finally, despite overall high reproducibility in the computer-assisted methods used in our studies, many factors affect the caliber of retinal vessels. Retinal vessel diameters may change with the pulse cycle, and taking photographs at untimed points in the pulse cycle may

result in an unrecognized source of variation in the vessel measurements (31). In addition, longitudinal changes in retinal vessel diameters associated with increasing age and variation in blood pressure or other factors are unknown.

In summary, in contrast to previous studies, we did not find a significant relation between generalized retinal arteriolar narrowing and mortality in this study. Future studies, perhaps using more precise methods, will be important in clarifying the clinical utility of an assessment of retinal vascular caliber for cardiovascular risk prediction.

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