Blood Pressure, Atherosclerosis, and the Incidence of Age-Related Maculopathy: The Rotterdam Study

Redmer van Leeuwen,[1] *M. Kamran Ikram,*[1] *Johannes R. Vingerling,*[1,2] *Jacqueline C. M. Witteman,*[1] *Albert Hofman,*[1] *and Paulus T. V. M. de Jong*[1,3,4]

Purpose. To determine whether blood pressure and subclinical atherosclerosis are associated with incident age-related maculopathy (ARM).

Methods. The study was performed within the Rotterdam Study, a population-based, prospective cohort study in Rotterdam, The Netherlands. A total of 4822 subjects who at baseline were aged 55 years more, were free of ARM, and participated in at least one of two follow-up examinations after a mean of 2 and 6.5 years, were included in the study. At baseline, blood pressure and the presence of atherosclerosis were determined. ARM was assessed according to the International Classification and Grading System and defined as large, soft drusen with pigmentary changes; indistinct drusen; or atrophic or neovascular age-related macular degeneration.

Results. After a mean follow-up of 5.2 years, incident ARM was diagnosed in 417 subjects. Increased systolic blood pressure or pulse pressure was associated with a higher risk of ARM. Adjusted for age, gender, smoking, total and high-density lipoprotein cholesterol, body mass index, and diabetes mellitus, odds ratios (OR) per 10-mm Hg increase were 1.08 (95% confidence interval [CI]: 1.03–1.14) and 1.11 (95% CI: 1.04–1.18), respectively. Moreover, different measures of atherosclerosis were associated with the risk of ARM. An increase in carotid wall thickness (OR per 1 SD, 1.15; 95% CI: 1.03–1.28) increased the risk of ARM. The lowest compared with the highest tertile of ankle–arm index had an OR of 1.32 (95% CI: 1.00–1.75). A weak association was found between aortic calcifications and the risk of ARM.

Conclusions. Elevated systolic blood or pulse pressure or the presence of atherosclerosis may increase the risk of development of ARM. (*Invest Ophthalmol Vis Sci.* 2003;44:3771–3777) DOI:10.1167/iovs.03-0121

In a recent report, the National Eye Institute estimated that currently 1.6 million Americans have from age-related macular degeneration (AMD), the most common cause of incurable blindness and visual impairment in industrialized countries.[1,2] Because of the aging of the population, the institute expects this number to double over the next 30 years. At this moment, treatment options include thermal laser and photodynamic therapy, but they are effective in a minority of patients only.[3,4] Prevention of AMD is hampered by a lack of knowledge about etiology and modifiable risk factors.[5] Only high-dose supplementation with specific antioxidant nutrients has been shown to slow the development of AMD.[6]

Decades ago, in 1937, Verhoeff and Grossman postulated that systemic vascular factors may be involved in the pathogenesis of AMD.[7] More recently, interest in this potential relationship has grown,[8] and a vascular model has been proposed in which a process that resembles atherosclerosis causes an accumulation of lipids and subsequently an increase in choroidal vascular resistance.[9] This process would interfere with the high metabolic rate of the retinal pigment epithelium and lead to the development of subretinal deposits (drusen), pigment abnormalities, and, finally, the blinding late stages of atrophic or neovascular AMD. Collectively, these early and late fundus signs are called age-related maculopathy (ARM), according to an international consensus.[10]

Most epidemiologic studies have addressed the vascular hypothesis by studying the classic risk factors for cardiovascular disease, such as blood pressure, serum cholesterol, and smoking, as well as clinical manifestations of atherosclerosis, such as myocardial infarction. Except for smoking, the results have been inconclusive.[11–20] However, very few of these studies were population based and prospective in design. Only two prevalence studies, including a cross-sectional analysis of the Rotterdam Study, used direct measurements of atherosclerosis.[21,22]

To explore further the vascular hypothesis, we studied, in a population-based cohort, the association of systemic blood pressure and subclinical atherosclerosis with the risk of ARM. We used noninvasive techniques for the measurement of atherosclerotic changes and prospectively studied the development of ARM.

Methods

Population

Information on the identification and description of the baseline study population has appeared in previous reports.[23] Briefly, the Rotterdam Study is a population-based prospective cohort study of the frequency and determinants of common cardiovascular, locomotor, neurologic, and ocular diseases.[24] The eligible population (n = 10,275) consisted of all inhabitants aged 55 years or more in a suburb of Rotterdam, The Netherlands. Of these, 7983 (78%) subjects agreed to participate in the study. Because the ophthalmic part of the study became operational

From the Departments of [1]Epidemiology and Biostatistics and [2]Ophthalmology, Erasmus Medical Center, Rotterdam, The Netherlands; [3]The Netherlands Ophthalmic Research Institute, Royal Academy of Arts and Sciences (KNAW), Amsterdam, The Netherlands; and [4]Department of Ophthalmology, Academic Medical Center, Amsterdam, The Netherlands.

Presented in part at the annual meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, Florida, May 2003.

Supported by Optimix Foundation, Amsterdam; Netherlands Organization for Scientific Research (NWO), The Hague; The Netherlands Society for the Prevention of Blindness, Doorn; Blindenhulp Foundation, The Hague; Rotterdamse Blindenbelangen Foundation, Rotterdam; OOG Foundation, The Hague; Topcon Europe BV, Capelle aan de IJssel; and The Edward and Marianne Blaauw Foundation, Amsterdam, The Netherlands.

Submitted for publication February 5, 2003; revised May 19, 2003; accepted May 29, 2003.

Disclosure: **R. van Leeuwen**, None; **M.K. Ikram**, None; **J.R. Vingerling**, None; **J.C.M. Witteman**, None; **A. Hofman**, None; **P.T.V.M. de Jong**, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Paulus T. V. M. de Jong, The Netherlands Ophthalmic Research Institute, Meibergdreef 47, 1105 BA Amsterdam, The Netherlands; p.dejong@ioi.knaw.nl.

after the screening of participants had started, a smaller portion (n = 6780) participated in the ophthalmic examination. The study was conducted according to the tenets of the Declaration of Helsinki, and the medical ethics committee of the Erasmus Medical Center approved the study protocol. Written informed consent was obtained from all participants. Baseline interviews and examinations were performed from 1990 to mid-1993, followed by a first follow-up examination from 1993 to 1994. A second follow-up screening took place from mid-1997 to the end of 1999.

Diagnosis of Age-Related Maculopathy

A detailed description of the diagnostic procedures has been presented elsewhere.[23] Participants underwent a full eye examination, including stereo 35° fundus photography (TRV-50VT fundus camera; Topcon Optical Corp., Tokyo, Japan) centered on field 2 (the fovea) after pharmacologic mydriasis. The resultant transparencies were graded with 12.5× magnification, according to the International Classification and Grading System for ARM and AMD.[10] In this system, all ARM fundus signs within a standard circular area (diameter 6000 μm) around the fovea are recorded. Two graders, trained according to the Wisconsin ARM grading system and having 8 years experience, first graded the follow-up transparencies, after which the grades were compared with grades of those taken at baseline. The grading procedures and definitions, as well as the graders, were identical at baseline and at follow-up. Consensus sessions were conducted, and between-grader comparisons were performed regularly. Weighted κ statistics were 0.72 for soft distinct drusen, 0.80 for hyperpigmentation, and 0.58 for hypopigmentation.

ARM was defined as the presence of large ($\geq$63 μm), soft, distinct drusen with pigmentary irregularities, or indistinct ($\geq$125 μm) or reticular drusen, or atrophic or neovascular AMD. Atrophic AMD was defined as any sharply demarcated round or oval area of apparent absence of the RPE, larger than 175 μm, irrespective of distance from the foveola but within the grid, with visible choroidal vessels and no neovascular AMD. Neovascular AMD was defined as the presence of a serous or hemorrhagic neuroretinal or RPE detachment, and/or a subretinal neovascular membrane, and/or a subretinal hemorrhage, and/or a periretinal fibrous scar. Lesions that were considered to be the result of generalized disease, such as diabetic retinopathy, chorioretinitis, high myopia, trauma, congenital diseases, or photocoagulation for reasons other than for neovascular AMD, were excluded from ARM diagnosis.

Exposure Measurement

Information on smoking habits and current use of medication was derived from the baseline interview. Smoking was categorized as never, former, or current. At the research center, height and weight were determined, and nonfasting blood samples were obtained. Serum total cholesterol and HDL-cholesterol levels were measured by an automated enzymatic procedure. Diabetes mellitus was considered to be present when subjects currently used oral blood-glucose–lowering medication or insulin, or had a nonfasting or postload glucose level above 11.0 mM.

Blood pressure was measured with a random-zero sphygmomanometer at the right brachial artery with the subject in a sitting position, and two consecutive measurements were averaged. Pulse pressure was calculated by taking the difference between systolic and diastolic blood pressure. The systolic blood pressure level of the posterior tibial artery was measured at both sides using an 8-MHz continuous-wave Doppler probe (500 D; Huntleigh, Sussex, UK) and a random-zero sphygmomanometer. The ankle–arm index was calculated by taking the ratio of the systolic blood pressure at the ankle to the systolic pressure at the arm. The ratio was calculated for each leg, and the lowest index was used in the analyses. An ankle–arm index $<$ 0.90 was considered to indicate peripheral atherosclerosis.

The wall thickness of the carotid artery was assessed by ultrasonography using a 7.5-MHz linear-array transducer (Ultra-Mark IV; ATL, Bethel, West Australia), in accordance with the Rotterdam Study ultrasound protocol.[25] Briefly, the intima-media thickness was measured on a longitudinal, two-dimensional ultrasound image of the common carotid artery, the carotid bifurcation, and the internal carotid artery at both the left and right side. When an optimal image of the interface of the anterior (near) and posterior (far) walls was obtained, it was frozen on the R-wave of the electrocardiogram (ECG), stored on videotape, and digitized by additional dedicated software. Next, the interfaces of the common carotid artery, the carotid bifurcation, and the internal carotid artery were marked across a length of 10 mm. The computer calculated the mean and maximum intima-media thickness for both near and far walls. For the analyses, the wall thickness was determined as the mean of the maximum intima-media thickness of near- and far-wall measurements of both the left- and right-side arteries. The thicknesses of each of the three arterial segments were combined after standardization. The ultrasonographers and readers of the images were masked to the case status of the subject.

The common carotid artery, bifurcation, and internal carotid artery were also examined for the presence of atherosclerotic plaques. Plaques were defined as focal thickening of the vessel wall relative to adjacent segments, composed of calcified or noncalcified components. The plaque score reflected the total number of locations where plaques were found, and it ranged from zero to six (left- and right-side common carotid artery, bifurcation, and internal carotid artery).

Aortic atherosclerosis was diagnosed by detecting calcified deposits in the abdominal aorta on lateral radiographic films of the lumbar spine, as described previously.[26] Calcification was considered present when linear densities were seen in an area parallel and anterior to the lumbar spine (L1–L4). The extent of calcification was classified according to the length of the involved area (0, 0.5 to $<$1, 1 to $<$2.5, 2.5 to $<$5, 5 to $<$10, and $\geq$10 cm). We considered the first classification to be the reference; the second and third to be mild to moderate; and the fourth, fifth, and sixth to be severe calcification.

Finally, a composite score of atherosclerosis was constructed with both the continuous (ankle–arm index and carotid wall thickness) and categorical measurements (number of carotid plaques and aortic calcifications). To do so, we transformed all variables to a 10-point scale. For the continuous variables, deciles were created, and subjects received 1 point per decile. For the categorical variables, we determined what percentage of the study population was in a less-severe category, and this percentage was converted to points. For example, a person with an ankle–arm index of 1.1 (6th decile), a carotid wall thickness of 0.8 mm (6th decile), carotid plaques at two locations (57% of the population had less than two locations), and 1 cm to less than 2.5 cm of aortic calcifications (43% had less than this), had a score of 6 + 6 + 5.7 + 4.3 = 22.

Study Sample

Of the 6780 participants in the ophthalmic part of the baseline study, 6477 (95.5%) persons underwent fundus photography and 6418 (94.7%) persons had gradable fundus transparencies in at least one eye. Prevalent ARM was diagnosed in 582 (9.1%) subjects, including 106 cases of AMD. This resulted in a cohort of 5836 subjects at risk who were free of ARM (i.e., subjects with no drusen, only hard or distinct drusen, or pigmentary abnormalities only). Of this cohort, 283 (4.8%) subjects died before the first follow-up examination and another 789 (13.5%) subjects died before the second follow-up. Of those alive at the first screening (n = 5553), 46 subjects were lost to follow-up, 905 refused to participate, and 13 had ungradable photographs. Of those alive at the second follow-up (n = 4764), 15 subjects were lost to follow-up, 1267 refused to participate, and 47 had ungradable photographs. In total, 4822 subjects (83% of those at risk) participated in at least one follow-up examination. Among them, blood pressure measurements were missing in 50 participants, ankle–arm index in 394 participants, carotid wall thickness in 770 participants, plaques in carotid artery in 1572 participants, and aortic calcifications in 497

TABLE 1. Baseline Characteristics of Subjects at Risk for ARM

	Participants (n = 4822)	Nonparticipants* (n = 1014)
Age (y)	67.1 ± 0.1	73.9 ± 0.3†
Female (%)	59.1 ± 0.01	59.0 ± 0.02
Body mass index (kg/m^2)	26.4 ± 0.1	26.1 ± 0.1‡
Smoking (%)		
Never	35.2 ± 0.01	30.5 ± 0.01†
Former	43.3 ± 0.01	38.6 ± 0.02†
Current	21.6 ± 0.01	30.9 ± 0.01†
Diabetes mellitus (%)	9.8 ± 0.4	13.5 ± 1.0†
Mean total cholesterol (mM)	6.67 ± 0.02	6.56 ± 0.04‡
Mean HDL cholesterol (mM)	1.35 ± 0.01	1.34 ± 0.01
Systolic blood pressure (mm Hg)	138.6 ± 0.3	140.4 ± 0.7‡
Diastolic blood pressure (mm Hg)	73.8 ± 0.2	74.1 ± 0.4
Antihypertensive medication (%)	30.9 ± 0.01	34.7 ± 0.02‡
Ankle–arm index	1.08 ± 0.003	1.02 ± 0.007†
Wall thickness common carotid artery (mm)	0.79 ± 0.002	0.81 ± 0.005†
Carotid plaques (%)		
0 plaques	40.9 ± 0.01	40.1 ± 0.02
1–3 plaques	44.7 ± 0.01	38.7 ± 0.02†
4–6 plaques	14.4 ± 0.01	21.2 ± 0.02†
Atherosclerosis composite score	26.2 ± 0.02	28.4 ± 0.04†

Values are age-adjusted means or percentages ± SE.
* Not participating, but alive at the moment of screening.
† $P < 0.01$.
‡ $P < 0.05$.

participants. The main cause of missing data on ultrasonography was restricted availability of technicians, which was irrespective of a subject's exposure and disease status.

Incidence of ARM was defined as absence of ARM in either eye at baseline and presence of ARM in at least one eye at follow-up.

Data Analysis

Analysis of variance, adjusted for age and gender, was used to compare baseline characteristics of eligible subjects participating in at least one follow-up examination with those who were alive at the time of examination but did not participate.

We studied the associations of baseline blood pressure and atherosclerosis with incident ARM in subjects with no ARM at baseline. Logistic regression analysis was used with time of follow-up included in every model. Systolic blood pressure, diastolic blood pressure, and pulse pressure were entered in the model, as either a continuous or categorical variable. In the first case, the regression coefficient was expressed per 10-mm Hg increase. In the second case, three dummy variables were defined based on absolute blood pressures with predefined cutoff points. To detect a J-shaped relationship, the second category of diastolic blood pressure (65–74 mm Hg) was used as the reference. Ankle–arm index was analyzed with the predefined cutoff point of 0.9, as well as in tertiles. We studied wall thickness of the carotid artery both as a continuous variable (per SD) and as a categorical variable (tertiles). Plaques in the carotid artery were analyzed both continuously (in number of plaques) and in categories. Aortic calcifications were studied in categories only, and the atherosclerosis composite score was analyzed in quartiles.

Initially, the regression analysis was adjusted for age and gender (model 1). In model 2, additional adjustment was made for smoking (current, former, or never), diabetes mellitus (yes/no), total cholesterol and HDL-cholesterol (per mM), and body mass index (kilograms per square meter). In model 3, we also adjusted for the composite score of atherosclerosis in the blood pressure analyses, and for systolic and diastolic blood pressure in the atherosclerosis analyses. The associations are presented as odds ratios (ORs), which can be interpreted as relative risks, with 95% confidence intervals (CIs). All analyses were performed on computer (SPSS, ver. 11; SPSS Inc., Chicago, IL).

RESULTS

The baseline characteristics of the eligible study cohort, adjusted for age and gender, are presented in Table 1. Of the eligible subjects who were alive at the time of follow-up examination, 1014 (17.4%) did not participate. Compared with participants, these subjects were significantly older, included more current smokers, more often had diabetes mellitus, used more antihypertensive medication, and had more severe atherosclerosis at baseline.

The average time between baseline and first follow-up examination was 2.0 years, and between baseline and the second follow-up, 6.5 years. Follow-up of all participants was on average 5.2 years, with a range of 1.0 to 9.7 years (median, 6.3). During this period, incident ARM was diagnosed in 419 subjects, of whom most had early ARM and 14 had AMD (4 atrophic and 10 neovascular AMD). Incident cases of early ARM involved large, soft drusen with pigmentary irregularities (n = 261) or indistinct drusen without (n = 109) or with (n = 35) pigmentary irregularities. Incident AMD had developed in one of the participants at the first follow-up examination and in 13 at the second. Six of these cases involved soft distinct drusen or pigmentary abnormalities at baseline, whereas eight showed early ARM at the first follow-up examination. The incidence of ARM did not differ between the study sample and participants with missing data on atherosclerosis (P = 0.17, adjusted for age and gender).

In Table 2, the odds ratios (OR) of incident ARM associated with baseline blood pressure are shown. When adjusted for age and gender, elevated systolic blood pressure was associated with an increased risk of ARM (OR per 10-mm Hg increase: 1.06, 95% CI: 1.01–1.12). When additional adjustments were made for smoking, total and HDL cholesterol, body mass index, diabetes mellitus, and the composite score of atherosclerosis, the association remained statistically significant. Diastolic

TABLE 2. Adjusted ORs of Incident ARM Associated with Baseline Blood Pressures

			Adjusted OR (95% CI)		
	Subjects (*n*)	Cases (*n*)	Model 1*	Model 2†	Model 3‡
Systolic BP (per 10-mm Hg increase)	4772	416	1.06 (1.01–1.12)	1.08 (1.03–1.14)	1.07 (1.01–1.13)
Systolic BP categories (mm Hg)					
<120	977	52	1.00	1.00	1.00
120–139	1689	143	1.47 (1.06–2.05)	1.61 (1.14–2.27)	1.63 (1.12–2.37)
140–159	1366	140	1.70 (1.22–2.39)	1.86 (1.31–2.66)	1.81 (1.23–2.67)
≥160	740	81	1.85 (1.27–2.69)	2.07 (1.40–3.07)	2.08 (1.36–3.20)
Diastolic BP (per 10-mm Hg increase)	4772	416	1.05 (0.96–1.15)	1.07 (0.97–1.17)	1.07 (0.97–1.18)
Diastolic BP, categories (mm Hg)					
<65	940	86	1.05 (0.79–1.39)	1.03 (0.77–1.38)	0.92 (0.67–1.27)
65–74	1675	144	1.00	1.00	1.00
75–84	1367	114	1.02 (0.79–1.32)	1.04 (0.80–1.36)	0.97 (0.73–1.29)
≥85	790	72	1.23 (0.91–1.67)	1.27 (0.93–1.73)	1.23 (0.88–1.71)
Pulse pressure (per 10-mm Hg increase)	4772	416	1.09 (1.02–1.15)	1.11 (1.04–1.18)	1.08 (1.00–1.16)
Pulse pressure, categories (mm Hg)					
<50	1013	54	1.00	1.00	1.00
50–64	1610	140	1.45 (1.04–2.02)	1.50 (1.07–2.11)	1.26 (0.88–1.81)
65–79	1309	129	1.51 (1.07–2.12)	1.54 (1.08–2.19)	1.41 (0.97–2.06)
≥ 80	840	93	1.59 (1.09–2.30)	1.73 (1.18–2.54)	1.41 (0.92–2.15)

* Adjusted for age and gender.
† Additional adjustment for smoking, total and HDL cholesterol, body mass index, and diabetes mellitus.
‡ Additional adjustment for a composite score of atherosclerosis (see text).

blood pressure was also associated with ARM, but this did not reach statistical significance (OR per 10-mm Hg increase: 1.05, 95% CI: 0.96–1.15, adjusted for age and gender). Additional adjustment did not change this relationship. Also, taking the lowest category as reference instead of the second did not change the risk estimates. Pulse pressure was positively associated with the risk of ARM, both as a continuous and as a categorical variable. Adjustment for the composite score of atherosclerosis, however, attenuated the association with categories of pulse pressure to nonsignificant levels. Excluding subjects who used blood pressure-lowering medication at baseline did not substantially alter the results (data not shown).

Table 3 presents the association between ankle–arm index and risk of ARM. Peripheral atherosclerosis was not associated with ARM. However, when the ankle–arm index was analyzed in tertiles, the lowest compared with the highest tertile showed a borderline significantly increased risk of ARM (OR: 1.32, 95% CI: 1.00–1.75). The association was a little stronger when additional adjustments were made, but became nonsignificant when adjusted for systolic and diastolic blood pressure.

Table 4 shows the relationship between measures of atherosclerosis in the carotid artery and risk of ARM. Increased wall thickness of the common carotid artery, both as a continuous (per standard deviation) and as a categorical variable, significantly increased the risk of ARM. Per SD (0.15 mm) of wall thickness, the OR was 1.15 (95% CI: 1.03–1.29; adjusted for age and gender). The highest tertile of carotid wall thickness compared with the lowest tertile had an OR of 1.45 (95% CI: 1.07–1.97). Additional adjustment for cardiovascular risk factors (model 2), including systolic and diastolic blood pressure (model 3) did not substantially alter the results. Plaques in the carotid artery were also associated with an increased risk of ARM. Compared with no plaques, four to six plaques in the right and left carotid artery increased the risk of ARM nearly 50% (OR: 1.46, 95% CI: 1.02–2.09, adjusted for age and gender). Additional adjustment for systolic and diastolic blood pressure decreased this risk estimate to a slight extent.

The relation between calcification of the abdominal aorta and ARM is shown in Table 5. A positive but not statistically significant association was found between aortic calcification and the incidence of ARM. Adjusted for all potential confounders, severe calcifications compared with none carried an OR of 1.39 (95% CI: 0.98–1.98).

Finally, in Table 6, the analysis of the composite score of atherosclerosis is presented. The highest score compared with the lowest carried an OR of 1.53 (95% CI: 1.08–2.18). Additional adjustment for cardiovascular risk factors only marginally

TABLE 3. Adjusted ORs of ARM Associated with Ankle–Arm Index

			Adjusted OR (95% CI)		
	Subjects (*n*)	Cases (*n*)	Model 1*	Model 2†	Model 3‡
Ankle–arm index, categories					
≥0.9	3833	326	1.00	1.00	1.00
<0.9	595	54	0.90 (0.66–1.24)	0.90 (0.64–1.25)	0.81 (0.52–1.27)
Ankle-arm index, tertiles					
1st (highest)	1604	118	1.00	1.00	1.00
2nd	1560	133	1.17 (0.90–1.52)	1.17 (0.89–1.54)	1.10 (0.83–1.45)
3rd (lowest)	1264	129	1.32 (1.00–1.75)	1.39 (1.04–1.84)	1.26 (0.94–1.69)

*,† For adjustments in models, see Table 2.
‡ Additional adjustment for systolic and diastolic blood pressure.

TABLE 4. Adjusted ORs of ARM Associated with Carotid Artery Wall Thickness and Presence of Plaques

			Adjusted OR (95% CI)		
	Subjects (*n*)	Cases (*n*)	Model 1*	Model 2†	Model 3‡
Wall thickness carotid artery, per SD	4052	357	1.15 (1.03–1.28)	1.15 (1.03–1.29)	1.11 (0.99–1.25)
Wall thickness carotid artery, tertiles					
1st	1489	94	1.00	1.00	1.00
2nd	1381	127	1.26(0.95–1.68)	1.33 (0.99–1.79)	1.30 (0.96–1.75)
3rd	1182	136	1.45(1.07–1.97)	1.53 (1.12–2.11)	1.42 (1.03–1.97)
Plaques in carotid artery, per plaque	3250	290	1.06 (0.98–1.14)	1.06 (0.98–1.15)	1.04 (0.96–1.13)
Plaques in carotid artery, categories					
0	1377	107	1.00	1.00	1.00
1–3	1429	127	1.02 (0.77–1.34)	1.02 (0.77–1.35)	0.97 (0.72–1.29)
4–6	444	56	1.46 (1.02–2.09)	1.49 (1.03–2.17)	1.36 (0.93–1.99)

*,†,‡ For adjustments in models, see Table 3.

reduced this risk estimate, but adjustment for blood pressure made it nonsignificant (OR: 1.41, 95% CI: 0.95–2.09).

DISCUSSION

In this prospective cohort study, we observed that high systolic blood pressure or high pulse pressure and the presence of atherosclerosis were associated with an increased risk of ARM. The association was overall not altered when adjusted for confounders and was strongest for atherosclerosis in the carotid artery.

In this study, we used the combination of early and late signs of ARM as incident outcome. Because subjects with early stages at baseline were excluded, AMD developed in very few ($n = 14$) within the 5-year follow-up period and the large majority (97%) of incident cases were of early ARM. When participants with incident AMD were excluded from the analysis, the same results were obtained (data not shown). We may therefore conclude that blood pressure and atherosclerosis promote the development of drusen and other signs of early ARM and not (only) the progression of early ARM to neovascular AMD, as has been suggested by some investigators.[27] A separate analysis of those cases of only neovascular AMD as an outcome was not possible because of the small sample. Given the well-documented risk of early ARM to progress to the blinding stage of AMD, it seems justified to assume that risk factors of early ARM also increase the risk of AMD.[28,29]

A concern in this as well as other follow-up studies is selective nonresponse. Because the international standard for the diagnosis of ARM in epidemiologic studies relies on fundus photography,[10] follow-up depends on a subject's participation in the eye examination. According to the analysis of baseline characteristics, subjects who did not participate in the follow-up examinations had more cardiovascular risk factors and more atherosclerosis. Therefore, subjects with severe atherosclerosis were underrepresented in the studied sample. This reduction in the range of atherosclerosis severity made it more difficult to find an association.

Sixteen percent of participants had missing data on carotid wall thickness and plaques, which was mainly due to logistic problems and to technical difficulties in visualization of the carotid artery. Because these reasons were not related to carotid wall thickness, we do not think that this biased our results. Still, it is possible that some error occurred in the measurement of atherosclerosis. Such a measurement error would have led to an underestimation of the true relationship with ARM, provided that the error occurred to the same extent among subjects with ARM and those without. Another question to be discussed is whether ankle–arm index and ultrasonographic measurement of carotid wall thickness are true indicators of atherosclerosis. The relation between ankle–arm index and atherosclerosis seems well established.[30] Increase in the carotid intima-media thickness may also reflect hypertrophy of the vessel wall as a response to hypertensive stress. Because many studies have shown that increased carotid wall thickness is associated independently of hypertension with both cardiovascular risk factors and cardiovascular events, it can be regarded as a valid indicator of atherosclerosis.[25,31]

An association between blood pressure or hypertension and prevalent AMD was reported earlier in three case–control studies: the Eye Disease Case–Control Study,[12] the AMD Risk Factors Study,[15] and the Age-Related Eye Disease Study.[14] Also, the Framingham Eye Study found an association between prevalent ARM and hypertension diagnosed 25 years before.[11] On the contrary, no association between blood pressure and prevalence of ARM was found in several population-based studies.[16–21] The only prospective, population-based study of this association so far, the Beaver Dam Eye Study, found that both systolic blood pressure and hypertension were significantly related to the incidence of retinal pigment epithelial depigmentation, but not of drusen.[13] Loss of power may be the expla-

TABLE 5. Adjusted ORs of ARM Associated with Aortic Calcifications

			Adjusted OR (95% CI)		
	Subjects (*n*)	Cases (*n*)	Model 1*	Model 2†	Model 3‡
Aortic calcification, categories					
No	1556	85	1.00	1.00	1.00
Mild to moderate	1574	127	1.24 (0.93–1.66)	1.24 (0.92–1.68)	1.36 (0.98–1.88)
Severe	1195	108	1.23 (0.90–1.68)	1.28 (0.92–1.76)	1.39 (0.98–1.98)

*,†,‡ For adjustments in models, see Table 3.

TABLE 6. Adjusted ORs of ARM Associated with a Composite Score of Atherosclerosis

			Adjusted OR (95% CI)		
	Subjects (*n*)	Cases (*n*)	Model 1*	Model 2†	Model 3‡
Composite score of atherosclerosis, quartiles					
1st	975	60	1.00	1.00	1.00
2nd	1092	87	1.16 (0.82–1.65)	1.24 (0.87–1.78)	1.17 (0.82–1.69)
3rd	1041	96	1.20 (0.85–1.70)	1.27 (0.88–1.84)	1.14 (0.78–1.67)
4th	1040	127	1.53 (1.08–2.18)	1.63 (1.12–2.37)	1.41 (0.95–2.09)

*,†,‡ For adjustments in models, see Table 3.

nation, because the number of incident cases of early ARM in their cohort was about half that in our study.

The association between ultrasonographically determined atherosclerosis, and the incidence of ARM has not yet been studied, as far as we know. Klein et al.[21] have studied the prevalence of ARM in the population-based Atherosclerosis Risk in Communities (ARIC) study, in which data on carotid intima-media wall thickness and carotid plaques were available. They found a statistically significant association between carotid plaques and retinal depigmentation, but, referring to the large number of associations studied, they concluded that atherosclerosis was unrelated to ARM overall. Also, they used nonstereoscopic 45° fundus photographs taken through a nonpharmacologically dilated pupil of only one eye, which may have resulted in a decreased detection of ARM.[32] In an earlier cross-sectional analysis of data from the Rotterdam Study, we found that subjects with plaques in the carotid bifurcation were 4.5 times more likely to have AMD.[22] Also, an ankle–arm index below 0.9 was significantly (OR: 2.0; 95% CI: 1.2–3.2) associated with the presence of AMD. However, in the latter study, the early signs of ARM were not included, and the number of AMD cases were low with corresponding wide confidence intervals. Moreover, given the cross-sectional design no causal inferences could be made.

Not all measures of atherosclerosis yielded the same results. The strongest association with ARM was observed for carotid wall thickness and carotid plaques, whereas no association was found for calcifications in the abdominal aorta and peripheral arterial disease. Considering this difference, one might hypothesize that atherosclerosis of the cerebral circulation is more important for the risk of ARM than atherosclerosis of the aorta or peripheral arteries.

There are several ways in which atherosclerosis may be related to ARM. Carotid atherosclerosis may lead to stenosis and, in the end, to a diminished blood flow to the ophthalmic artery and in the choroidal and retinal circulation. Considering the low prevalence of carotid stenosis in our cohort, this explanation seems implausible. It is more likely that the atherosclerosis we measured reflects a similar process in the choroidal vessels under the retina. Thickening and stiffening of the vessel wall results in a decreased lumen diameter, an increased blood flow resistance, and a decreased tissue perfusion. This process may then either directly impair the functioning of the retinal pigment epithelium, which is responsible for the metabolism of rod and cone outer segments, or may lead to leakage and deposition of proteins and lipids due to elevated hydrostatic pressure, as was proposed by Friedman.[9] A decreased choriocapillary density was demonstrated in aging human eyes, especially in those with ARM.[33] Moreover, in patients with ARM, reduced choroidal perfusion was shown by direct measurement of the choroidal blood flow.[34–37] In summary, multiple lines of evidence suggest a role for atherosclerosis in the pathophysiology of ARM.

The question should be answered of whether high blood pressure is a risk factor for ARM in itself or high blood pressure is a risk factor for ARM only through its association with atherosclerosis. To disentangle this relationship, we put both determinants in the same model. Adjustment for the composite score of atherosclerosis did not change the association between systolic or diastolic blood pressure and ARM. The association with pulse pressure was somewhat attenuated, possibly indicating that pulse pressure has more overlap with atherosclerosis. Additional adjustment for systolic and diastolic blood pressure altered only to a slight degree the risk estimates for the association of atherosclerosis with ARM. The interpretation of these analyses may be that high blood pressure and atherosclerosis, independent of each other, increase the risk of ARM. However, because both determinants are strongly linked and both were measured at the same time, the previous analyses are not sufficient to determine the exact order of the pathophysiological pathway.

The level of oxidative defense could disturb the association between atherosclerosis and ARM. Because oxidative stress is implicated both in the etiology of ARM[38] and in the pathogenesis of atherosclerosis,[39] antioxidants may act as a confounder in the observed association. However, this confounder is less likely to explain the relationship between blood pressure and ARM, which was independent of atherosclerosis.

In conclusion, in this large prospective cohort study we showed that high systolic blood pressure, high pulse pressure, or the presence of subclinical atherosclerosis increases the risk of ARM. The magnitude of the risk estimates varied, with a maximum OR of 2.1. Because of the high prevalence of hypertension and atherosclerosis in the population, the impact of these factors on the total incidence of ARM may still be large. Our results suggest that a reduction in the occurrence of hypertension and atherosclerosis may add to the prevention of this blinding disease.

Acknowledgments

The authors thank Irene M. van der Meer, MD, PhD, who developed the atherosclerosis composite score, for assistance in the study.

References

1. Friedman DS, Congdon NG, Kempen J, Tielsch JM, O'Colmain B. *Vision Problems in the U. S.*: *Prevalence of Adult Vision Impairment and Age-Related Eye Disease.* Schaumburg, IL: Prevent Blindness America; 2002.
2. Klein R, Wang Q, Klein BE, Moss SE, Meuer SM. The relationship of age-related maculopathy, cataract, and glaucoma to visual acuity. *Invest Ophthalmol Vis Sci*. 1995;36:182–191.
3. Macular Photocoagulation Study Group. Argon laser photocoagulation for neovascular maculopathy: five-year results from randomized clinical trials. *Arch Ophthalmol*. 1991;109:1109–1114.
4. Bressler NM. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2. *Arch Ophthalmol*. 2001;119:198–207.
5. Evans JR. Risk factors for age-related macular degeneration. *Prog Retinal Eye Res*. 2001;20:227–253.

6. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol.* 2001;119:1417–1436.
7. Ryan SJ, Mittl RN, Maumenee AE. The disciform response: an historical perspective. *Albrecht Von Graefes Arch Klin Exp Ophthalmol*. 1980;215:1–20.
8. Snow KK, Seddon JM. Do age-related macular degeneration and cardiovascular disease share common antecedents? *Ophthalmic Epidemiol*. 1999;6:125–143.
9. Friedman E. The role of the atherosclerotic process in the pathogenesis of age-related macular degeneration. *Am J Ophthalmol*. 2000;130:658–663.
10. The International ARM Epidemiological Study Group. An international classification and grading system for age-related maculopathy and age-related macular degeneration. *Surv Ophthalmol.* 1995; 39:367–374.
11. Sperduto RD, Hiller R. Systemic hypertension and age-related maculopathy in the Framingham Study. *Arch Ophthalmol*. 1986; 104:216–219.
12. The Eye Disease Case-Control Study Group. Risk factors for neovascular age-related macular degeneration. *Arch Ophthalmol.* 1992;110:1701–1708.
13. Klein R, Klein BE, Jensen SC. The relation of cardiovascular disease and its risk factors to the 5-year incidence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1997; 104:1804–1812.
14. Age-Related Eye Disease Study Research Group. Risk factors associated with age-related macular degeneration: a case-control study in the age-related eye disease study: age-related eye disease study report number 3. *Ophthalmology.* 2000;107:2224–2232.
15. Hyman L, Schachat AP, He Q, Leske MC. Hypertension, cardiovascular disease, and age-related macular degeneration. Age-Related Macular Degeneration Risk Factors Study Group. *Arch Ophthalmol*. 2000;118:351–358.
16. Vinding T, Appleyard M, Nyboe J, Jensen G. Risk factor analysis for atrophic and exudative age-related macular degeneration: an epidemiological study of 1000 aged individuals. *Acta Ophthalmol* (*Copenh*). 1992;70:66–72.
17. Klein R, Klein BE, Franke T. The relationship of cardiovascular disease and its risk factors to age-related maculopathy: The Beaver Dam Eye Study. *Ophthalmology*. 1993;100:406–414.
18. Hirvela H, Luukinen H, Laara E, Laatikainen L. Risk factors of age-related maculopathy in a population 70 years of age or older. *Ophthalmology*. 1996;103:871–877.
19. Smith W, Mitchell P, Leeder SR, Wang JJ. Plasma fibrinogen levels, other cardiovascular risk factors, and age-related maculopathy: the Blue Mountains Eye Study. *Arch Ophthalmol*. 1998;116:583–587.
20. Delcourt C, Michel F, Colvez A, Lacroux A, Delage M, Vernet MH. Associations of cardiovascular disease and its risk factors with age-related macular degeneration: the POLA study. *Ophthalmic Epidemiol*. 2001;8:237–249.
21. Klein R, Clegg L, Cooper LS, et al. Prevalence of age-related maculopathy in the Atherosclerosis Risk in Communities Study. *Arch Ophthalmol*. 1999;117:1203–1210.
22. Vingerling JR, Dielemans I, Bots ML, Hofman A, Grobbee DE, de Jong PTVM. Age-related macular degeneration is associated with atherosclerosis: The Rotterdam Study. *Am J Epidemiol*. 1995;142: 404–409.
23. Vingerling JR, Dielemans I, Hofman A, et al. The prevalence of age-related maculopathy in The Rotterdam Study. *Ophthalmology*. 1995;102:205–210.
24. Hofman A, Grobbee DE, de Jong PTVM, van den Ouweland FA. Determinants of disease and disability in the elderly: The Rotterdam Elderly Study. *Eur J Epidemiol*. 1991;7:403–422.
25. Bots ML, Hofman A, De Jong PTVM, Grobbee DE. Common carotid intima-media thickness as an indicator of atherosclerosis at other sites of the carotid artery: The Rotterdam Study. *Ann Epidemiol*. 1996;6:147–153.
26. Witteman JC, Grobbee DE, Valkenburg HA, van Hemert AM, Stijnen T, Hofman A. Cigarette smoking and the development and progression of aortic atherosclerosis: a 9-year population-based follow-up study in women. *Circulation*. 1993;88:2156–2162.
27. Macular Photocoagulation Study Group. Risk factors for choroidal neovascularization in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Arch Ophthalmol.* 1997;115:741–747.
28. Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1997;104:7–21.
29. Van Leeuwen R, Klaver CC, Vingerling JR, Hofman A, De Jong PTVM. The risk and natural course of age-related maculopathy: follow-up at 61/2 years in The Rotterdam Study. *Arch Ophthalmol*. 2003;121:519–526.
30. Feinstein SB, Voci P, Pizzuto F. Noninvasive surrogate markers of atherosclerosis. *Am J Cardiol*. 2002;89:31C–43C; discussion 43C–44C.
31. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arterioscler Thromb*. 1991;11:1245–1249.
32. Klein R, Meuer SM, Moss SE, Klein BE. Detection of drusen and early signs of age-related maculopathy using a nonmydriatic camera and a standard fundus camera. *Ophthalmology*. 1992;99: 1686–1692.
33. Ramrattan RS, van der Schaft TL, Mooy CM, de Bruijn WC, Mulder PG, de Jong PTVM. Morphometric analysis of Bruch's membrane, the choriocapillaris, and the choroid in aging. *Invest Ophthalmol Vis Sci*. 1994;35:2857–2864.
34. Harris A, Chung HS, Ciulla TA, Kagemann L. Progress in measurement of ocular blood flow and relevance to our understanding of glaucoma and age-related macular degeneration. *Prog Retinal Eye Res*. 1999;18:669–687.
35. Grunwald JE, Hariprasad SM, DuPont J, et al. Foveolar choroidal blood flow in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 1998;39:385–390.
36. Pauleikhoff D, Spital G, Radermacher M, Brumm GA, Lommatzsch A, Bird AC. A fluorescein and indocyanine green angiographic study of choriocapillaris in age-related macular disease. *Arch Ophthalmol*. 1999;117:1353–1358.
37. Friedman E, Krupsky S, Lane AM, et al. Ocular blood flow velocity in age-related macular degeneration. *Ophthalmology*. 1995;102: 640–646.
38. Beatty S, Koh H, Phil M, Henson D, Boulton M. The role of oxidative stress in the pathogenesis of age-related macular degeneration. *Surv Ophthalmol*. 2000;45:115–134.
39. Iuliano L. The oxidant stress hypothesis of atherogenesis. *Lipids*. 2001;36(suppl):S41–S44.