Risk Factors for Progression of Atherosclerosis Measured at Multiple Sites in the Arterial Tree

The Rotterdam Study

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Background and Purpose—Studies investigating determinants of atherosclerotic disease progression are relatively rare. Moreover, although atherosclerotic disease can be assessed noninvasively in different vascular beds, previous studies have not considered progression of atherosclerosis at >1 site. The present study was designed to identify risk factors for progression of atherosclerosis measured at multiple sites in the arterial tree.

Methods—The Rotterdam Study is a population-based cohort study of 7983 men and women ≥55 years of age. Carotid plaques and intima-media thickness were assessed by ultrasound, aortic atherosclerosis by x-ray, and lower-extremity atherosclerosis by the ankle-arm index. Data on progression of atherosclerosis over an average period of 6.5 years were available for 3409 participants. Associations of established cardiovascular risk factors with mild, moderate, and severe progression of atherosclerosis were investigated through multinomial regression analysis.

Results—Age, smoking, total cholesterol, and systolic blood pressure and/or hypertension were strong, independent predictors of moderate and severe progression of atherosclerosis at multiple sites. Diabetes mellitus predicted only severe progression of atherosclerosis. Associations of sex with progression of atherosclerosis were remarkably modest.

Conclusions—Age, smoking, total cholesterol, and systolic blood pressure and/or hypertension strongly predict progression of extracoronary atherosclerosis in the elderly, but sex remarkably does not. These results emphasize the need for prevention of progression of extracoronary atherosclerotic disease in men and women alike. **(*Stroke*. 2003;34: 2374-2379.)**

Key Words: atherosclerosis ■ cohort studies ■ gender ■ risk factors

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Various noninvasive methods are available to detect the presence and severity of atherosclerotic disease. Carotid atherosclerosis assessed by ultrasound, aortic atherosclerosis as shown on abdominal x-ray, and lower-extremity atherosclerosis assessed by the ankle-arm index (AAI) are all important predictors of cardiovascular disease.[1–4] Moreover, they are strongly associated with the presence and amount of coronary calcification[5] and with cardiovascular risk factors.[6–8]

Although the amount of atherosclerosis at 1 point in time is a reflection of lifelong accumulation of atherosclerotic lesions, changes in the extent of atherosclerosis with time give important information about whether, and at what rate, atherosclerotic disease advances. Several studies have reported associations of cardiovascular risk factors with progression of atherosclerosis.[7,9,10] However, none of these studies has yet investigated whether the associations of cardiovascular risk factors with progression of atherosclerosis are consistent across different vascular beds.

Within the Rotterdam Study, a prospective, population-based cohort study among men and women ≥55 years of age, various noninvasive methods were used to assess progression of atherosclerosis over an average period of 6.5 years. We investigated associations of cardiovascular risk factors with progression of atherosclerosis measured at multiple sites in the arterial tree.

Materials and Methods

Study Population

The Rotterdam Study is a prospective, population-based cohort study of 7983 men and women ≥55 years of age. Its aim is to investigate the incidence and determinants of chronic disabling diseases. At phase 1 (baseline; 1990 to 1993), all inhabitants of a suburb of the city of Rotterdam who were ≥55 years of age were invited to participate in an extensive home interview and 2 visits to the research center. The overall response rate was 78%. Phase 3 was conducted in a similar way from 1997 to 1999. Between phases 1 and 3, 25% of the participants had died, and 0.4% were lost to follow-up. Because at phase 2 only a small part of the atherosclerosis measurements were

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performed, data from this phase were not included in the present study. The Medical Ethics Committee of the Erasmus University Medical Center approved the Rotterdam Study, and written informed consent was obtained from all participants.[11]

Of the 7983 participants of the Rotterdam Study, 6505 had never experienced a myocardial infarction, stroke, or revascularization procedure before phase 3. For 6145 of these participants, the extent of atherosclerosis was assessed at baseline at least at 1 site in the arterial tree. For 3506 participants, information on at least 1 measure of atherosclerosis at phase 3 of the Rotterdam Study was also available. Subjects with missing data on >2 cardiovascular risk factors investigated in the present study were excluded (n=97), resulting in a study population of 3409 participants.

Clinical Characteristics

At baseline, a trained investigator visited all participants at home and collected information using a computerized questionnaire. The obtained information included current health status, medical history, drug use, and smoking behavior. Additionally, during 2 visits to the research center, established cardiovascular risk factors were measured, and nonfasting blood samples were obtained.[12] Obesity was defined as body mass index (BMI) ≥30.0 kg/m^2 and/or waist circumference ≥102 cm in men or ≥88 cm in women.[13] We defined hypertension as systolic blood pressure ≥160 mm Hg, diastolic blood pressure ≥100 mm Hg, and/or use of blood pressure–lowering medication with indication of hypertension at phase 1 of the Rotterdam Study. Hypercholesterolemia was defined as serum total cholesterol ≥6.5 mmol/L and/or the use of cholesterol-lowering medication at phase 1. We defined diabetes mellitus as a random or postload serum glucose level ≥11.1 mmol/L and/or the use of blood glucose–lowering medication.

Measures of Atherosclerosis

The extent of atherosclerosis was assessed at phases 1 and 3 of the Rotterdam Study by measuring carotid plaques, carotid intima-media thickness (IMT), aortic atherosclerosis, and lower-extremity atherosclerosis (as indicated by the AAI). Progression of atherosclerosis was divided into 4 categories (no, mild, moderate, severe), except for progression of carotid plaques (3 categories: no, moderate, severe) because of the sample distribution of this measure of progression of atherosclerosis. To be able to compare the different associations of a particular cardiovascular risk factor with progression of the different measures of atherosclerosis, we tried to categorize progression of atherosclerosis in such a way that a specific category (eg, the severe category) included a comparable percentage of the study sample for all of the 4 measures.

Carotid Atherosclerosis

Ultrasonography of both carotid arteries was performed with a 7.5-MHz linear-array transducer and a duplex scanner (ATL Ultra-Mark IV, Advanced Technology Laboratories). The common carotid artery, carotid bifurcation, and internal carotid artery were examined on both the left and right sides for the presence of plaques as described before.[2] A weighted plaque score ranging from 0 to 6 was computed by adding the number of sites at which a plaque was detected, dividing by the total number of sites for which an ultrasonographic image was available, and multiplying by 6 (the maximum number of sites). Progression of carotid plaques was computed by subtracting the plaque score at phase 1 from the plaque score at phase 3. Subjects for whom data on the presence of plaques were not available for at least 4 of the 6 sites examined both at phase 1 and at phase 3 were excluded from analyses. We defined no, moderate, and severe progression of carotid plaques as a change in plaque score of 0, 1 to 2, or ≥3 points, respectively. Subjects with a decrease in plaque score were added to the group with no progression because we considered this to be due mainly to measurement error.

Common carotid IMT was determined as the average of near- and far-wall measurements, and the average of left and right common carotid IMT was computed.[2] Progression of IMT was defined as the difference in mean IMT between phase 3 and phase 1. Subjects were divided into categories of progression of IMT on the basis of their ranking in the sample distribution. Subjects with an increase in IMT below the 30th percentile of the distribution of all subjects with an increase in IMT were considered to have no progression of IMT. Subjects with an increase in IMT above the 30th, 60th, and 90th percentiles of the sample distribution were considered to have mild, moderate, and severe progression of IMT, respectively. We added subjects for whom we found a decrease in IMT to the group with no progression. Because of the limited availability of ultrasonographers at the end of 1992 and in 1993, ultrasound data are missing for some of the subjects who visited the Rotterdam Study research center at phase 1.

Aortic Atherosclerosis

Aortic atherosclerosis was diagnosed by radiographic detection of calcified deposits in the abdominal aorta on a lateral abdominal film.[7] For progression of aortic atherosclerosis, baseline and follow-up films were examined in pairs. Progression was scored on a graded scale (with scores of 0 to 4 corresponding to 0, ≤1, 1 to 2.5, 2.5 to 4.9, and ≥5.0 cm progression, respectively). None of the participants showed a decrease in the extent of aortic atherosclerosis. We defined no, mild, moderate, and severe progression of aortic atherosclerosis as a progression score of 0, 1, 2, and >2, respectively.

Lower-Extremity Atherosclerosis

Systolic blood pressure at the ankles (posterior tibial artery) was measured in the supine position with a random-zero sphygmomanometer and an 8-MHz continuous-wave Doppler probe (Huntleigh 500D, Huntleigh Technology). We computed the ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm to obtain the AAI. Because arterial rigidity prevents arterial compression and therefore will lead to spuriously high values of the AAI, an AAI >1.50 was considered invalid.[12] Progression of lower-extremity atherosclerosis was computed by subtracting the AAI at phase 1 from the AAI at phase 3. For the analyses, we used the leg with the largest decrease in AAI. Subjects with a decrease in AAI below the 30th percentile of the sample distribution of all subjects with a decrease in AAI were considered to have no progression of lower-extremity atherosclerosis. Subjects with a decrease in AAI above the 30th, 60th and 90th percentiles of the sample distribution were considered to have mild, moderate, and severe progression of lower-extremity atherosclerosis, respectively. We added subjects for whom we found an increase in AAI to the group with no progression. Data on progression of carotid plaques, IMT, aortic atherosclerosis, and lower-extremity atherosclerosis were available for 2366, 2622, 2687, and 2756 participants, respectively.

Statistical Analyses

For subjects with missing data on clinical characteristics measured on a continuous scale, we imputed the population mean. Using multinomial logistic regression analysis, we examined the association of cardiovascular risk factors with mild, moderate, and severe progression of atherosclerosis. Analyses with age as the determinant were adjusted for sex and duration of follow-up. Analyses with sex as the determinant were adjusted for age, duration of follow-up, and—to account for the large percentage of ever smokers (84.4%) in men—current and past smoking. Analyses with all other cardiovascular risk factors as the determinant were adjusted for age, sex, duration of follow-up, current and past smoking, BMI, waist-to-hip ratio, total and high-density lipoprotein (HDL) cholesterol, systolic and diastolic blood pressures, diabetes mellitus, and use of cholesterol-lowering and blood pressure–lowering medication at any point in time between phase 1 and phase 3. Analyses on the association of hypertension with progression of atherosclerosis did not include the variables systolic and diastolic blood pressures, and subjects on blood pressure–lowering medication with an indication other than hypertension were excluded.

Results

Table 1 shows baseline characteristics of the study population.

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TABLE 1. Baseline Characteristics of the Study Population

	All Subjects (n=3409)
Age, y	65.4 (6.8)
Men, %	38.3
Current smokers, %	20.1
Past smokers, %	41.9
Body mass index, kg/m^2	26.3 (3.6)
Total cholesterol, mmol/L	6.7 (1.2)
HDL cholesterol, mmol/L	1.4 (0.4)
Systolic blood pressure, mm Hg	135.7 (20.7)
Diastolic blood pressure, mm Hg	73.8 (10.8)
Diabetes mellitus, %	6.0
Cholesterol-lowering medication, %	3.4
Blood pressure–lowering medication, %	23.1
Carotid plaques,* %	51.8
IMT, mm	0.76 (0.14)
Aortic atherosclerosis,† %	59.6
AAI‡	1.12 (0.18)
Duration of follow-up, y	6.5 (0.4)

Data are mean (SD) for continuous variables and percentages for dichotomous variables.

*As indicated by a carotid plaque score >0.

†As indicated by an aortic atherosclerosis score >0.

‡Lowest of both legs.

TABLE 2. Odds Ratios for Progression of Carotid Plaques Associated With Established Cardiovascular Risk Factors

	OR (95% CI) for Progression of Carotid Plaques		
	No (n=1345)	Moderate (n=826)	Severe (n=195)
Age (per SD)*	1.0	1.21 (1.11–1.33)	1.42 (1.22–1.64)
Sex (men)†	1.0	1.23 (1.01–1.50)	1.31 (0.94–1.83)
Current smoking	1.0	1.57 (1.21–2.02)	2.95 (1.89–4.61)
Past smoking	1.0	1.14 (0.92–1.42)	1.65 (1.11–2.47)
BMI (per SD)	1.0	0.88 (0.80–0.98)	1.00 (0.84–1.19)
WHR (per SD)	1.0	1.24 (1.11–1.39)	1.20 (0.98–1.46)
Total cholesterol (per SD)	1.0	1.12 (1.02–1.23)	1.28 (1.09–1.50)
HDL cholesterol (per SD)	1.0	0.94 (0.85–1.04)	0.96 (0.81–1.15)
Systolic BP (per SD)	1.0	1.19 (1.05–1.35)	1.25 (1.01–1.55)
Diastolic BP (per SD)	1.0	0.91 (0.81–1.03)	0.97 (0.79–1.19)
Hypertension (%)‡	1.0	1.44 (1.17–1.77)	1.29 (0.90–1.85)
Diabetes mellitus (%)	1.0	0.81 (0.54–1.21)	1.76 (1.04–2.99)

Data are ORs and 95% CIs adjusted for age, sex, duration of follow-up, current and past smoking, BMI, waist-to-hip ratio (WHR), total and HDL cholesterol, systolic and diastolic blood pressures (BP), diabetes mellitus, and use of blood pressure– and cholesterol-lowering medication.

*Adjusted for sex and duration of follow-up.

†Adjusted for age, current and past smoking, and duration of follow-up.

‡Not adjusted for systolic and diastolic blood pressures; subjects using blood pressure–lowering medication with indication other than hypertension were excluded.

Current smoking was the strongest predictor of progression of carotid plaques (Table 2). Age, total cholesterol, and systolic blood pressure were also strong, independent predictors of both moderate and severe progression. Men seemed to be at a higher risk of carotid plaque progression, but the odds ratio (OR) for severe progression was not statistically significant. Past smoking and diabetes mellitus only, but strongly so, predicted severe progression of carotid plaques. BMI and waist-to-hip ratio had ORs in opposite directions, especially in their association with moderate progression of carotid plaques.

Age and BMI were strong predictors of mild (only BMI), moderate, and severe progression of carotid IMT (Table 3). Sex (inverse association), current (borderline) and past smoking, systolic blood pressure, and hypertension (borderline) were significant predictors of severe but not mild and moderate progression of carotid IMT. Other cardiovascular risk factors did not predict progression of carotid IMT.

TABLE 3. Odds Ratios for Progression of Carotid Intima-Media Thickness Associated With Established Cardiovascular Risk Factors

	OR (95% CI) for Progression of Carotid IMT			
	No (n=1013)	Mild (n=690)	Moderate (n=690)	Severe (n=229)
Age (per SD)	1.0	1.02 (0.92–1.13)	1.16 (1.05–1.28)	1.34 (1.17–1.54)
Sex (men)	1.0	0.99 (0.79–1.23)	1.09 (0.88–1.35)	0.70 (0.50–0.97)
Current smoking	1.0	1.03 (0.78–1.37)	1.18 (0.89–1.57)	1.46 (0.95–2.24)
Past smoking	1.0	1.04 (0.82–1.32)	1.10 (0.87–1.40)	1.46 (1.02–2.07)
BMI (per SD)	1.0	1.14 (1.02–1.27)	1.17 (1.05–1.31)	1.25 (1.06–1.46)
WHR (per SD)	1.0	0.97 (0.86–1.10)	0.89 (0.78–1.01)	1.01 (0.85–1.22)
Total cholesterol (per SD)	1.0	1.02 (0.92–1.13)	1.03 (0.93–2.14)	1.09 (0.94–1.27)
HDL cholesterol (per SD)	1.0	1.02 (0.91–1.13)	0.93 (0.84–1.04)	1.01 (0.86–1.19)
Systolic BP (per SD)	1.0	0.99 (0.86–1.14)	0.99 (0.86–1.14)	1.31 (1.07–1.60)
Diastolic BP (per SD)	1.0	0.98 (0.86–1.12)	0.91 (0.79–1.04)	0.91 (0.75–1.10)
Hypertension (%)	1.0	0.85 (0.67–1.08)	0.93 (0.74–1.17)	1.34 (0.97–1.85)
Diabetes mellitus (%)	1.0	0.80 (0.52–1.23)	0.78 (0.51–1.19)	0.63 (0.33–1.21)

See Table 2 for explanation of variables.

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TABLE 4. Odds Ratios for Progression of Aortic Atherosclerosis Associated With Established Cardiovascular Risk Factors

	OR (95% CI) for Progression of Aortic Atherosclerosis			
	No (n=825)	Mild (n=912)	Moderate (n=765)	Severe (n=185)
Age (per SD)	1.0	1.42 (1.28–1.58)	1.56 (1.40–1.74)	1.84 (1.56–2.17)
Sex (men)	1.0	1.28 (1.03–1.58)	0.96 (0.76–1.20)	0.99 (0.69–1.42)
Current smoking	1.0	1.74 (1.30–2.34)	2.64 (1.95–3.58)	2.45 (1.49–4.02)
Past smoking	1.0	1.31 (1.04–1.65)	1.48 (1.15–1.89)	1.69 (1.13–2.53)
BMI (per SD)	1.0	0.87 (0.78–0.97)	0.85 (0.75–0.95)	0.75 (0.62–0.91)
WHR (per SD)	1.0	1.04 (0.91–1.17)	1.10 (0.96–1.25)	1.05 (0.85–1.30)
Total cholesterol (per SD)	1.0	1.23 (1.11–1.37)	1.28 (1.14–1.43)	1.49 (1.25–1.78)
HDL cholesterol (per SD)	1.0	0.83 (0.75–0.93)	0.81 (0.73–0.91)	0.94 (0.78–1.12)
Systolic BP (per SD)	1.0	1.26 (1.09–1.46)	1.37 (1.17–1.59)	1.29 (1.03–1.63)
Diastolic BP (per SD)	1.0	0.84 (0.73–0.96)	0.85 (0.74–0.98)	0.75 (0.60–0.94)
Hypertension (%)	1.0	1.26 (0.99–1.61)	1.68 (1.31–2.16)	1.84 (1.26–2.70)
Diabetes mellitus (%)	1.0	0.98 (0.63–1.52)	1.03 (0.65–1.63)	1.92 (1.07–3.44)

See Table 2 for explanation of variables.

Table 4 shows that age, smoking habits, total cholesterol, systolic blood pressure, and hypertension were all strong predictors of mild, moderate, and severe progression of aortic atherosclerosis. Sex predicted only mild progression. For BMI and diastolic blood pressure, there was a protective effect, as there was for HDL cholesterol, but the OR for severe progression was not statistically significant for HDL cholesterol. Diabetes mellitus was a strong predictor of severe progression of aortic atherosclerosis.

Current smoking was the strongest predictor of mild, moderate, and severe progression of lower-extremity atherosclerosis (Table 5). Age, total cholesterol, and hypertension also predicted moderate and severe progression of lower-extremity atherosclerosis. Sex was a borderline significant predictor of severe progression of lower-extremity atherosclerosis, but the association with moderate progression was inverse. Diabetes mellitus predicted only severe progression. For BMI and HDL cholesterol, there was a protective effect.

When we excluded subjects with a decrease in carotid plaque score or IMT or an increase in AAI, results were similar to those presented in the tables. In subgroup analyses stratified by sex, we found no major differences between men and women that were consistent across the 4 measures of atherosclerosis. Moreover, no statistically significant interactions between risk factors were consistently found. We did not find evidence of a nonlinear association for any of the associations of continuous variables with progression of atherosclerosis, apart from a modest exponential association of age with progression of carotid IMT (overall value for quadratic term, $P=0.08$; for moderate and severe progression, $P=0.07$ and 0.03, respectively, adjusted for sex and duration of follow-up) and with progression of aortic atherosclerosis

TABLE 5. Odds Ratios for Progression of Lower-Extremity Atherosclerosis Associated With Established Cardiovascular Risk Factors

	OR (95% CI) for Progression of Lower-Extremity Atherosclerosis			
	No (n=1359)	Mild (n=599)	Moderate (n=599)	Severe (n=199)
Age (per SD)	1.0	1.03 (0.93–1.14)	1.10 (1.00–1.21)	1.65 (1.43–1.91)
Sex (men)	1.0	0.86 (0.70–1.06)	0.77 (0.62–0.96)	1.37 (0.98–1.90)
Current smoking	1.0	1.51 (1.14–2.00)	1.55 (1.17–2.05)	3.17 (2.04–4.93)
Past smoking	1.0	1.20 (0.95–1.51)	1.12 (0.89–1.42)	1.35 (0.90–2.03)
BMI (per SD)	1.0	0.93 (0.84–1.04)	0.86 (0.77–0.97)	0.80 (0.67–0.96)
WHR (per SD)	1.0	0.98 (0.86–1.11)	1.05 (0.92–1.18)	1.03 (0.83–1.26)
Total cholesterol (per SD)	1.0	1.05 (0.95–1.17)	1.15 (1.04–1.28)	1.37 (1.18–1.60)
HDL cholesterol (per SD)	1.0	0.92 (0.83–1.03)	0.94 (0.85–1.05)	0.76 (0.64–0.91)
Systolic BP (per SD)	1.0	1.06 (0.92–1.21)	1.04 (0.90–1.19)	1.12 (0.91–1.37)
Diastolic BP (per SD)	1.0	1.00 (0.88–1.15)	0.97 (0.85–1.11)	0.88 (0.72–1.08)
Hypertension (%)	1.0	1.12 (0.89–1.41)	1.27 (1.01–1.60)	1.41 (1.00–2.00)
Diabetes mellitus (%)	1.0	0.81 (0.52–1.27)	0.80 (0.52–1.25)	1.83 (1.10–3.02)

See Table 2 for explanation of variables.

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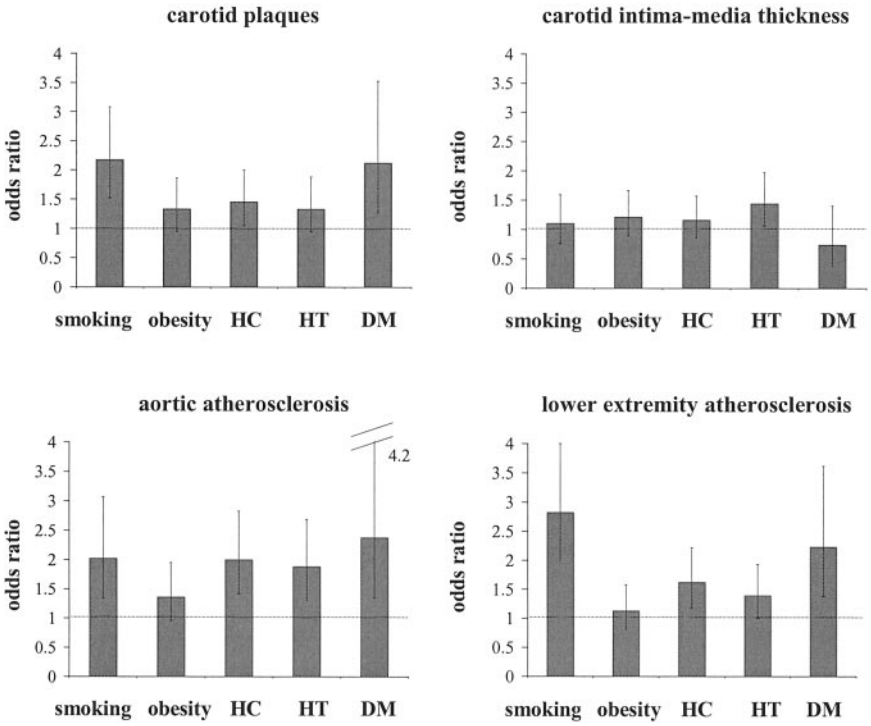

Associations of cardiovascular risk factors with severe progression of atherosclerosis. Bars represent ORs adjusted for age, sex, and duration of follow-up; lines represent 95% CIs. HC indicates hypercholesterolemia; HT, hypertension; and DM, diabetes mellitus.

(overall $P=0.08$; for mild and moderate progression, $P=0.02$ and 0.03, respectively). Addition of the quadratic term for age to the multivariate models did not change any of the ORs associated with the other cardiovascular risk factors.

Finally, the Figure shows ORs for severe progression of all measures of atherosclerosis associated with current smoking, obesity, hypercholesterolemia, hypertension, and diabetes mellitus.

Discussion

The present study shows that age, smoking behavior, total cholesterol, and systolic blood pressure and/or hypertension are strong, independent predictors of progression of atherosclerosis measured at multiple sites in the arterial tree. Diabetes mellitus is a strong predictor of severe but not of mild or moderate progression of atherosclerosis. Sex shows a remarkably modest association with progression of extracoronary atherosclerosis.

The strength of the present study, a relatively large cohort study in a very homogeneous population of elderly people, is the assessment of progression of atherosclerosis at multiple sites. Still, several methodological issues of this study need to be considered. First, subjects with the most severe atherosclerosis at baseline are more likely to have died and therefore are not included in the present study. Although this may have somewhat limited the range of baseline levels of atherosclerosis, it does not affect the validity of the risk estimates. Second, because we defined categories of progression of carotid IMT and the AAI according to percentiles, one should note that the distinction between these categories is not based on clear-cut clinical differences in progression of atherosclerosis. Moreover, our definitions of no, mild, moderate, and severe progression of atherosclerosis depend on the distribution of progression of atherosclerosis within our study population and may therefore be different in other populations. Third, baseline levels of atherosclerosis may influence the association between cardiovascular risk factors and progression of atherosclerosis. However, because of the phenomenon of regression to the mean as a result of measurement error, adjusting for baseline atherosclerosis may introduce bias that leads to an overestimation of the risk estimates.[14] For categorical variables, no statistical model has yet been developed to adjust for baseline values without introducing bias. For continuous variables, both the Atherosclerosis Risk in Communities study and the Cardiovascular Health Study, investigating associations between cardiovascular risk factors and progression of IMT, showed that not adjusting for baseline levels of atherosclerosis gave similar results as adjusting for baseline atherosclerosis while at the same time taking measurement error into account.[15,16] In the present study, we did not adjust for baseline levels of atherosclerosis. Finally, although the measures of atherosclerosis used in the present study were strongly associated with coronary calcification,[5] differences between these measures exist. For the carotid plaque score, we measured distinct atherosclerotic lesions, and radiographically assessed calcification of the abdominal aorta has been shown to specifically represent advanced intimal atherosclerosis.[17] However, changes in IMT and AAI may also be due in part to nonatherosclerotic processes such as fibromuscular hypertrophy, which causes modest increases in IMT, and hemodynamic factors and vascular stiffness, which may influence AAI.

Although for coronary atherosclerosis differences between men and women are pronounced,[18] we report remarkably modest and inconsistent associations between sex and progression of extracoronary atherosclerosis. This finding is in accordance with the fact that the difference between men and women is much smaller for the incidence of stroke than for

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the incidence of myocardial infarction.[19,20] Moreover, we have previously shown that the prevalences of peripheral arterial disease in men and women participating in the Rotterdam Study are similar.[12] It should be kept in mind that these findings could be different in populations with premenopausal women, in whom the protective effects of endogenous estrogens may lead to a slower rate of progression of atherosclerosis than in men.[21] However, because most clinical events related to atherosclerotic disease occur in postmenopausal women, the results from the present study stress the importance of prevention of progression of extracoronary atherosclerotic disease in both men and women alike.

Although we used a standardized protocol for the measurement of IMT both at baseline and at the follow-up visit, a relatively large part of the computed change in IMT over the years may be distorted by measurement error. This may explain why only a few cardiovascular risk factors (smoking habits, BMI, and systolic blood pressure) were significant predictors of progression of carotid IMT, whereas associations of traditional cardiovascular risk factors with progression of carotid plaques were much stronger. Both more precise methods to measure progression of carotid IMT and the assessment of not only the presence but also the volume of carotid plaques will further improve our ability to determine the rate of progression of carotid atherosclerosis.

This population-based study shows that age, smoking behavior, total cholesterol, and systolic blood pressure and/or hypertension are strong predictors of progression of atherosclerosis, regardless of the site of measurement. Sex is not an important risk indicator for progression of extracoronary atherosclerotic disease in men and women ≥55 years of age.

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References

1. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arterioscler Thromb*. 1991;11:1245–1249.
2. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation*. 1997;96:1432–1437.
3. Witteman JC, Kok FJ, van Saase JL, Valkenburg HA. Aortic calcification as a predictor of cardiovascular mortality. *Lancet*. 1986;2:1120–1122.
4. Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. *BMJ*. 1996;313:1440–1444.
5. Oei HH, Vliegenthart R, Hak AE, Iglesias del Sol A, Hofman A, Oudkerk M, Witteman JC. The association between coronary calcification assessed by electron beam computed tomography and measures of extracoronary atherosclerosis: the Rotterdam Coronary Calcification Study. *J Am Coll Cardiol*. 2002;39:1745–51.
6. O'Leary DH, Polak JF, Kronmal RA, Kittner SJ, Bond MG, Wolfson SK Jr, Bommer W, Price TR, Gardin JM, Savage PJ. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study: the CHS Collaborative Research Group. *Stroke*. 1992;23:1752–1760.
7. 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.
8. Fowkes FG, Housley E, Riemersma RA, Macintyre CC, Cawood EH, Prescott RJ, Ruckley CV. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. *Am J Epidemiol*. 1992;135:331–340.
9. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: a population-based ultrasonography study. *Atherosclerosis*. 1990;81:33–40.
10. Howard G, Wagenknecht LE, Burke GL, Diez-Roux A, Evans GW, McGovern P, Nieto FJ, Tell GS. Cigarette smoking and progression of atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) study. *JAMA*. 1998;279:119–124.
11. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol*. 1991;7:403–422.
12. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE. Peripheral arterial disease in the elderly: the Rotterdam Study. *Arterioscler Thromb Vasc Biol*. 1998;18:185–192.
13. *Obesity: Preventing and Managing the Global Epidemic*. Geneva, Switzerland; World Health Organization; 1998. Technical report series 894.
14. Vollmer WM. Comparing change in longitudinal studies: adjusting for initial value. *J Clin Epidemiol*. 1988;41:651–657.
15. Chambless LE, Folsom AR, Davis V, Sharrett R, Heiss G, Sorlie P, Szklo M, Howard G, Evans GW. Risk factors for progression of common carotid atherosclerosis: the Atherosclerosis Risk in Communities study, 1987–1998. *Am J Epidemiol*. 2002;155:38–47.
16. Yanez ND 3rd, Kronmal RA, Shemanski LR, Psaty BM. A regression model for longitudinal change in the presence of measurement error. *Ann Epidemiol*. 2002;12:34–38.
17. Hyman JB, Epstein FH. A study of the correlation between roentgenographic and post-mortem calcification of the aorta. *Am Heart J*. 1954;48:540–543.
18. Hoff JA, Chomka EV, Krainik AJ, Daviglus M, Rich S, Kondos GT. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. *Am J Cardiol*. 2001;87:1335–1339.
19. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, Copper LS, Shahar E. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke*. 1999;30:736–743.
20. Rosamond WD, Folsom AR, Chambless LE, Wang CH. Coronary heart disease trends in four United States communities: the Atherosclerosis Risk in Communities (ARIC) study 1987–1996. *Int J Epidemiol*. 2001;30:S17–S22.
21. Cid MC, Schnaper HW, Kleinman HK. Estrogens and the vascular endothelium. *Ann N Y Acad Sci*. 2002;966:143–57.

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