Comparison Between Measures of Atherosclerosis and Risk of Stroke

The Rotterdam Study

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Background and Purpose—Several measures of atherosclerosis predict the risk of stroke. However, a comparison between various measures of atherosclerosis is lacking, and limited information exists on the added value of individual measures of atherosclerosis to cardiovascular risk factors. We compared different measures of atherosclerosis in relation to stroke.

Methods—The study was based on the prospective cohort of the Rotterdam Study and included 6913 participants who did not suffer from previous stroke. At baseline, carotid intima-media thickness and plaques, ankle-arm index, and aortic calcifications were assessed; 3996 participants (53%) had measures of all studied markers of atherosclerosis. After a mean follow-up of 6.1 years, 378 strokes occurred. Data were analyzed with Cox proportional-hazards regression and Akaike information criteria scores.

Results—Carotid intima-media thickness and aortic calcifications were related most strongly to the risk of stroke (relative risk, 2.23 and 1.89; 95% confidence interval, 1.48 to 3.36 and 1.28 to 2.80 for highest versus lowest tertile, respectively). The relations between intima-media thickness, aortic calcifications, and carotid plaques and stroke remained after adjustment for cardiovascular risk factors. Intima-media thickness and aortic calcifications were related to the risk of stroke independently of each other. The relation between ankle-arm index and stroke disappeared after adjustment for cardiovascular risk factors.

Conclusions—Carotid intima-media thickness and aortic calcifications are stronger predictors of incident stroke than carotid plaque or ankle-arm indexes. They have additional value to each other and to classic risk factors and may reflect different processes. **(*Stroke*. 2003;34:2367-2373.)**

Key Words: atherosclerosis ■ epidemiology ■ risk factors

Several noninvasive measures of atherosclerosis—including carotid artery intima-media thickness (IMT), carotid plaques, ankle-arm index, and aortic calcifications—are related to the risk of stroke in the population.[1–4] Most studies focused on individual measures of atherosclerosis; few studies have compared measures of atherosclerosis.[5] It is still unclear whether all measures of atherosclerosis reflect the same process. Carotid IMT is considered a marker of generalized atherosclerosis. Carotid plaques can be markers of generalized atherosclerosis and sources of emboli.[6] Recently, it was reported that ankle-arm index may reflect only an unfavorable cardiovascular risk profile.[3] Calcifications in the vessel wall are considered to reflect the extent of atherosclerosis elsewhere.[7] Therefore, measures reflecting the amount of calcification in the atherosclerotic plaque such as aortic atherosclerosis[8] may be strongly related to stroke. Data on the contribution of each individual measure of atherosclerosis to classic cardiovascular risk factors in relation to stroke are limited.[9] We evaluated and compared the strength of the relation between carotid plaques, carotid IMT, ankle-arm index, and aortic calcifications in relation to stroke in a population of elderly subjects.

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Materials and Methods

Population

The study is part of the Rotterdam Study, a population-based cohort study on chronic and disabling diseases in the elderly. All inhabitants of Ommoord, a district of Rotterdam, ≥55 years of age were invited. People living in homes for the elderly were included. Participation rate of those invited for the study was 78%; in total, 7983 subjects participated.[10] The Medical Ethics Committee of Erasmus University Rotterdam approved the study. Written informed consent to retrieve information from treating physicians was obtained from all participants. Baseline measurements were obtained from 1990 through

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1993 and consisted of a home interview and 2 visits to the research center for physical examination. A total of 7721 participants were free of previous stroke. At the baseline visit to the research center, we assessed several measures of atherosclerosis: carotid IMT, carotid plaques, ankle-arm index, and aortic calcifications. The study population consisted of 6913 persons who had assessment of at least 1 measure of atherosclerosis.

Assessment of Atherosclerosis at Baseline

Carotid IMT and Carotid Plaques

Participants underwent B-mode ultrasonography of both carotid arteries. We measured IMT of the common carotid artery and presence of plaques in both carotid arteries according to a standardized protocol as published previously.[1,6,11]

Ankle-Arm Index

The systolic blood pressure of the posterior tibial artery was measured on both sides with an 8-MHz continuous-wave Doppler probe (Huntleigh 500 D, Huntleigh Technology) and a random-zero sphygmomanometer. Sitting blood pressure of the right arm was measured twice with a random-zero sphygmomanometer. Mean blood pressure was used to calculate the ankle-arm index for each leg. In the analyses, we used the lowest measurement. Because of possible measurement artifacts reflecting the presence of rigid or calcified walls, 36 participants with an ankle-arm index >1.5 were excluded.

Aortic Calcification

Aortic calcification was diagnosed by radiographic detection of calcified deposits in the abdominal aorta.[8] At baseline, lateral abdominal films (T12 through S1) were made from a fixed distance while the subject was seated. Aortic calcifications were considered present when linear densities were seen in an area parallel and anterior to the lumbar spine (L1 through L4). Baseline values for the extent of calcification were scored into 5 categories according to the length of the involved area (1 plaque, 0.5 to 1.0 cm; several disseminated plaques, <2.5, 2.5 to 4.9, 5.0 to 9.9, and ≥ 10 cm).

The numbers of participants with data available on carotid IMT, plaques, ankle-arm index, and aortic calcifications were 5479, 5440, 6196, and 5631, respectively. Data on all measurements of atherosclerosis were available for 3996 participants (53% of the 6913 participants without previous stroke). Logistical reasons such as limited availability of ultrasonographers mainly accounted for the fact that not all measurements were available for all participants. Furthermore, x-rays were not taken at the very beginning of the study. Because in most instances a lack of measures of atherosclerosis was not related to participant characteristics, we do not think that restriction to persons with all measurements has caused a serious selection bias. Participants with all measures available were on average 4.6 years younger (95% confidence interval [CI], 4.2 to 5.1), were more often male (41% versus 38%; $P<0.05$ adjusted for age), had 2.6 mm Hg–higher (95% CI, 1.5 to 3.7) systolic blood pressure, and had 0.09-mmol/L-higher (95% CI, 0.0 to 0.1) total cholesterol levels compared with participants with missing values for ≥ 1 measures of atherosclerosis (adjusted for age and/or sex). We observed no differences in diastolic blood pressure, diabetes, smoking, and cholesterol.

Assessment of Stroke

History of stroke or transient ischemic attack at baseline was assessed and verified as described previously.[6] Once subjects enter the Rotterdam Study, they are continuously monitored for major events through automated linkage of the study database with files from general practitioners and the municipality. For reported events, additional information was obtained from hospital records. A neurologist (P.J.K.) reviewed information on all possible strokes and classified the stroke as definite, probable, or possible. A stroke was definite if the diagnosis was based on typical clinical symptoms and neuroimaging excluded other diagnoses. A stroke was considered probable if typical clinical symptoms were present but neuroimaging was not performed. For fatal strokes, other causes of death, especially cardiac, should have been excluded. A stroke was classified as possible if clinical symptoms were less typical and neuroimaging was not performed or if a cardiac cause of death could not be excluded in case of reported stroke. Subclassification into hemorrhagic or ischemic stroke was based on neuroimaging, which was available for 61% of all patients. Follow-up was available for all participants until January 1, 1999.

Cardiovascular Disease Status and Risk Factors

Information on current health status and medical history at baseline was obtained with a computerized questionnaire. All reported myocardial infarctions were verified by medical records. History of intermittent claudication and angina pectoris was assessed through the Rose questionnaire. Nonfasting blood samples were taken, and serum total cholesterol and high-density lipoprotein (HDL) cholesterol were measured with an automated enzymatic procedure. Hypertension was defined as systolic blood pressure of ≥ 140 mm Hg or diastolic blood pressure of ≥ 90 mm Hg. Diabetes mellitus was defined as use of oral blood glucose–lowering drugs or insulin or random or postload serum glucose level >11.0 mmol/L, according to the World Health Organization criteria. Atrial fibrillation was assessed by ECG. A history of cardiovascular disease was coded if participants had a history of transient ischemic attack, myocardial infarction, angina pectoris, intermittent claudication, atrial fibrillation, coronary bypass surgery, and/or coronary angioplasty.

Data Analysis

We evaluated the relationship between carotid IMT, carotid plaques, ankle-arm index, and aortic calcifications and risk of first-ever stroke and cerebral infarction using Cox regression analysis. Data were analyzed in several ways. First, to check for gross deviations from

TABLE 1. Baseline Characteristics of the Study Population

	Study Population (n=6913)
Age, y	69.5 (9.2)
Female sex, %	60.3
Diastolic blood pressure, mm Hg	73.6 (11.7)
Systolic blood pressure, mm Hg	139.2 (22.4)
Total cholesterol, mmol/L	6.6 (1.2)
Hypertension, %	33.9
HDL cholesterol, mmol/L	1.3 (0.4)
Diabetes, %	10.0
Smoking, %	
Current	22.7
Former	41.6
History of cardiovascular disease, %	24.4
History of myocardial infarction, %	11.5
Mean common carotid IMT, mm	0.80 (0.16)
Carotid plaque score	1.4
Ankle-arm index	1.06 (0.23)
Aortic calcifications, %	
None	33.4
0.5–1.0 cm	9.5
1.0–2.5 cm	26.6
2.5–4.9 cm	17.7
5.0–9.9 cm	10.7
≥10 cm	2.2

Values represent means (SD).

TABLE 2. Relative Risk of Stroke in Relation to Measures of Atherosclerosis

Measure of Atherosclerosis	At Risk, n	Patients, n	Relative Risk* (95% CI)	Relative Risk† (95% CI)
Carotid IMT				
Tertiles				
Low	1777	35	1.00	1.00
Intermediate	1820	90	1.66 (1.10–2.51)	1.64 (1.01–2.66)
High	1882	169	2.23 (1.48–3.36)	2.42 (1.51–3.89)
Per-SD increase	5479	294	1.29 (1.15–1.44)	1.28 (1.15–1.44)
Carotid plaques				
Tertiles				
Low	2225	72	1.00	1.00
Intermediate	1826	101	1.24 (0.89–1.71)	1.18 (0.82–1.71)
High	1389	122	1.61 (1.16–2.23)	1.47 (1.02–2.13)
Per-category increase	5440	295	1.13 (1.05–1.21)	1.15 (1.07–1.24)
Ankle-arm index				
Tertiles				
High	2069	78	1.00	1.00
Intermediate	2061	87	1.08 (0.79–1.47)	0.99 (0.66–1.46)
Low	2066	160	1.55 (1.16–2.07)	1.28 (0.87–1.88)
Per-SD decrease	6196	325	1.10 (0.98–1.24)	1.13 (1.00–1.26)
Aortic calcification				
Tertiles				
Low	1881	40	1.00	1.00
Intermediate	2032	96	1.45 (0.99–2.14)	1.21 (1.06–1.52)
High	1718	133	1.89 (1.28–2.80)	1.63 (1.06–2.52)
Per-category increase	5631	269	1.20 (1.09–1.32)	1.21 (1.10–1.33)
Composite score				
Tertiles				
Low	1336	20	1.00	1.00
Intermediate	1263	48	2.05 (1.21–3.48)	1.52 (0.83–2.80)
High	1397	129	4.20 (2.55–6.90)	2.71 (1.50–4.90)
Per-category increase	3996	197	1.24 (1.14–1.35)	1.26 (1.16–1.38)

Ranges for tertiles were <0.72, 0.72–0.84, >0.84 mm for IMT; 0, 1–2, 3–6 for carotid plaques; <1.01, 1.01–1.17, >1.17 for ankle-arm index; 0, 1–2, 3–5 for aortic calcifications; 0–2, 3–4, 5–8 for compound score.

*Adjusted for age and sex.

†Adjusted for age, sex, diabetes mellitus, smoking, systolic and diastolic blood pressures, cholesterol and HDL cholesterol levels, and history of cardiovascular disease.

linearity, we assessed the risks in participants in tertiles, taking the least severe atherosclerosis as the reference. A composite atherosclerosis score was obtained by adding up the scores for the separate measures of atherosclerosis (range, 0 to 8). We further analyzed carotid IMT and ankle-arm index per-SD increase and carotid plaques and aortic calcifications per unit increase. Analyses were adjusted for age and sex and for diabetes mellitus (yes, no), smoking (current, former, never), systolic and diastolic blood pressures, and total and HDL cholesterol levels. Results are presented as relative risks with corresponding 95% CIs.

We used Akaike optimal information criteria (AIC) to evaluate the prognostic ability of the measures of atherosclerosis compared with a reference model.[12] This method allows us to take both follow-up time and differences in numbers of degrees of freedom into account. The height of the AIC score reflects the prognostic value; a positive score indicates that adding the measure of atherosclerosis results in an improvement in the reference model. The AIC was calculated as the χ^2 statistic of the significant change for the extended model compared with a reference model minus 2 times the number of degrees of freedom. For these analyses, we restricted ourselves to participants with information available on all measures of atherosclerosis. We entered carotid IMT and ankle-arm index as continuous variables and carotid plaques and aortic calcifications as categorical variables into the model. First, we used a model including age and sex as reference. Then, the reference model was expanded with diabetes mellitus, smoking, diastolic and systolic blood pressures, total and HDL cholesterol, and history of cardiovascular disease.

We further used stepwise regression analysis to assess which measures of atherosclerosis were independently related to the risk of stroke and cerebral infarction. Age and sex were forced into the model. Finally, we tested for interaction between atherosclerosis and smoking, diabetes, hypertension, and previous myocardial infarction.

TABLE 3. Relative Risk of Cerebral Infarction in Relation to Measures of Atherosclerosis

Measure of Atherosclerosis	At Risk, n	Patients, n	Relative Risk* (95% CI)	Relative Risk† (95% CI)
Carotid IMT				
Tertiles				
Low	1777	22	1.00	1.00
Intermediate	1820	59	2.30 (1.40–3.78)	2.26 (1.34–3.81)
High	1882	82	2.95 (1.79–4.87)	2.30 (1.34–3.94)
Per-SD increase	5479	163	1.33 (1.15–1.54)	1.20 (1.02–1.41)
Carotid plaques				
Tertiles				
Low	2225	42	1.00	1.00
Intermediate	1826	59	1.56 (1.04–2.33)	1.38 (0.91–2.09)
High	1389	63	2.14 (1.42–3.23)	1.55 (1.00–2.40)
Per-category increase	5440	164	1.18 (1.08–1.30)	1.09 (0.99–1.20)
Ankle-arm index				
Tertiles				
High	2069	45	1.00	1.00
Intermediate	2061	42	0.97 (1.16–2.52)	0.77 (0.50–1.20)
Low	2066	78	1.71 (1.16–2.52)	1.02 (0.66–1.56)
Per-SD decrease	6196	165	1.28 (1.12–1.47)	1.09 (0.92–1.28)
Aortic calcification				
Tertiles				
Low	1881	24	1.00	1.00
Intermediate	2032	60	1.95 (1.21–3.15)	1.73 (1.04–2.85)
High	1718	78	2.70 (1.67–4.35)	2.10 (1.26–3.50)
Per-category increase	5631	162	1.30 (1.16–1.45)	1.21 (1.07–1.37)
Composite score				
Tertiles				
Low	1336	14	1.00	1.00
Intermediate	1263	31	2.03 (1.07–3.85)	1.72 (0.90–3.30)
High	1397	74	3.96 (2.16–7.26)	2.63 (1.38–5.05)
Per-category increase	3996	119	1.35 (1.22–1.48)	1.22 (1.10–1.36)

Ranges for tertiles were <0.72, 0.72–0.84, >0.84 mm for IMT; 0, 1–2, 3–6 for carotid plaques; <1.01, 1.01–1.17, >1.17 for ankle-arm index; 0, 1–2, 3–5 for aortic calcifications; 0–2, 3–4, 5–8 for compound score.

*Adjusted for age and sex.

†Adjusted for age, sex, diabetes mellitus, smoking, systolic and diastolic blood pressures; cholesterol and HDL cholesterol levels, and history of cardiovascular disease.

Results

Table 1 shows baseline characteristics of the study population. A total of 378 strokes occurred during a mean follow-up time of 6.1 years (42 272 person-years). Of these, 198 (52%) were cerebral infarctions and 29 (8%) were intracerebral hemorrhages. The number of hemorrhages was too small to analyze them separately. Participants in the highest tertiles of carotid IMT, carotid plaques, and aortic calcification and the lowest tertile of the ankle-arm index had a significantly increased risk compared with those in the reference tertiles (Table 2). We observed a 4-fold–increased risk of stroke for participants in the highest tertile of the composite atherosclerosis score. Additional adjustment for cardiovascular risk factors and history of cardiovascular disease attenuated the risk estimates, but the risks remained significantly increased, except for those related to a low ankle-arm index. Table 3 shows that the results were largely similar for cerebral infarctions. Table 4 shows the additional values for the different measures of atherosclerosis beyond traditional cardiovascular risk factors. It shows that IMT and aortic calcifications had the highest added value to predict stroke compared with a model including age and sex (model 1). The additional value of both measures remained compared with a model with cardiovascular disease (model 2). The AIC scores diminished when the reference model was expanded with history of cardiovascular disease (model 3). Ankle-arm index performed worst of all and lost the additional value for stroke compared with a reference model including age, sex, and cardiovascular risk factors (model 2).

TABLE 4. AIC for the Measure of Atherosclerosis and Percentages of the Maximal AIC Score

		AIC vs Model 1		AIC vs Model 2		AIC vs Model 3	
Outcome	Measure of Atherosclerosis	Percent of Maximal AIC Score	AIC Score	Percent of Maximal AIC Score	AIC Score	Percent of Maximal AIC Score	AIC Score
Stroke	IMT	100	31.84*	100	18.43*	100	11.53*
	Carotid plaques	58	18.38*	34	6.19*	16	1.81†
	Ankle-arm index	36	11.49*	33	0.77‡	0	<0‡
	Aortic calcifications	69	22.09*	66	12.18*	52	5.99*
Cerebral infarction	IMT	95	11.30*	82	4.17†	54	0.97‡
	Carotid plaques	100	11.94*	91	4.63†	100	1.81†
	Ankle-arm index	56	6.68*	12	0.61‡	0	<0‡
	Aortic calcifications	96	11.41*	100	5.09†	31	0.57‡

Model 1 includes age and sex; model 2, age, sex, diabetes mellitus, smoking, systolic and diastolic blood pressures, and cholesterol and HDL cholesterol levels; model 3, age, sex, diabetes mellitus, smoking, systolic and diastolic blood pressures, cholesterol and HDL cholesterol levels, and history of cardiovascular disease.

*$P<0.01$; †$P<0.05$; ‡$P>0.05$.

Subsequently, we analyzed all measures of atherosclerosis in a stepwise regression model in which we forced the variables age and sex. For both stroke and cerebral infarction, carotid IMT and aortic calcifications were included ($P<0.05$).

Finally, we failed to find interactions between carotid IMT and aortic calcifications and diabetes, hypertension, smoking, and previous myocardial infarction ($P>0.05$). The results were similar for stroke and cerebral infarction.

Discussion

In our population-based study of 6943 participants, we found that carotid IMT and aortic calcifications were the strongest predictors of stroke. Carotid plaques and ankle-arm index were less strong predictors. The relation between ankle-arm index and stroke was no longer statistically significant when cardiovascular risk factors were taken into account. Carotid IMT and aortic calcifications predict the risk of stroke independently of each other. This indicates that they may represent different pathophysiological mechanisms. Before we interpret our results, some methodological issues need to be addressed. First, some analyses were restricted to participants with assessment of all measures of atherosclerosis. Because atherosclerosis measures were missing mostly for reasons that were independent of participant characteristics and the overall vascular risk profile was not very different between people with and without complete data on all measures of atherosclerosis, we think that this has not caused a selection bias. Furthermore, misclassification of atherosclerosis could have occurred, and we may have misclassified some strokes or subtypes of stroke. We restricted our analysis to CT- or MRI-confirmed cerebral infarctions to reduce misclassification. However, classification of atherosclerosis was done by researchers blinded to stroke status and vice versa. Hence, if misclassification had occurred, it is likely to be nondifferential, leading to underestimation of the observed effects.

The main issue in our study was to determine which measures of atherosclerosis are strongest predictors of the risk of stroke and cerebral infarction. Carotid IMT and ankle-arm index were continuous measures; carotid plaques and aortic calcifications were categorical measures. Evaluation of relative risks in categories allowed us to compare the relative risks.

IMT has been investigated widely as a measure of generalized atherosclerosis. Our results show the robustness of the relation between IMT and stroke. Presence of aortic calcifications was an important risk indicator for stroke, even when information on carotid IMT or cardiovascular risk factors was taken into account. Two mechanisms could explain the persistence of such association. First, calcifications could reflect arterial stiffness, leading to hypertension and stroke. The relationships remained significant after adjustment for blood pressure, and arterial stiffness has not consistently been shown to be a risk factor for stroke.[13] Still, this hypothesis should not be overlooked because 1 measurement of blood pressure is a poor reflection of the lifetime exposure. Another explanation to consider is that calcifications may represent the presence of atherosclerotic lesions in the aortic arch or carotid arteries from which emboli can be released. A plausible explanation for our finding that IMT and aortic calcifications are related to stroke independently of each other is that both markers of atherosclerosis reflect different processes, as we described. Ankle-arm index was the poorest predictor for stroke because it lost its predictive ability after cardiovascular risk factors were taken into account. This result supports the findings by the other population-based cohort studies in which the relation between ankle-arm index and stroke also diminished after adjustment for cardiovascular risk factors.[14] Our study confirms that ankle-arm index has little prognostic ability beyond traditional risk factors for stroke and cerebral infarction. In summary, carotid IMT and aortic calcifications are the strongest predictors of stroke. Carotid IMT, plaques, and aortic calcifications have additional value to traditional cardiovascular risk factors. The results of our study merit further research on individual stroke risk assessment that includes measures of atherosclerosis. In addition to carotid IMT, information on calcifications in the vessel wall may help in identifying people at high risk of stroke.

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Editorial Comment

Vascular Thickness and Calcification as Markers of Atherosclerotic Burden

The study by Hollander et al[1] provides an uncommon opportunity to directly compare the predictive value of various noninvasive tests of atherosclerotic burden for stroke in community dwellers. The study included a cohort of ≈7000 stroke-free subjects. Slightly more than half of the subjects had a complete set of measures of carotid plaque, carotid intima-media thickness (IMT), ankle-arm index, and aortic calcification. Study participants were followed up for a mean of 6.1 years. On the basis of point estimates, measures of carotid IMT and aortic calcifications were stronger determinants of stroke than measures of carotid plaque and ankle-arm index. Carotid IMT, the most potent risk factor assessed in the study, imparted a relative risk of stroke of 2.23 for values in the highest tertile. Ankle-arm index, the least potent risk factor, imparted a relative risk of stroke of 1.55 for values in the lowest tertile.

Investigators also found that carotid IMT and aortic calcifications were independent risk factors. Statistical independence suggests that different pathophysiological processes may cause IMT and vascular calcifications and that these markers are not simply measures of atherosclerotic burden induced by so-called classic risk factors. B-mode ultrasonographic measurement of IMT of the extracranial carotid arteries assesses at least 2 responses of the blood vessel wall to cardiovascular risk factors. Intimal thickening resulting from cellular accumulation and matrix deposition can be seen in normal aging of the vascular system, even in the absence of atherosclerotic plaque.[2] Medial thickening caused by smooth muscle cell hypertrophy is closely related to arterial hypertension,[3] but the precise stimulus is not known.[4]

Vascular calcification in the form of hydroxyapatite begins early in the atherosclerotic process with microscopic amounts at the preatheroma stage (type III plaque) according to the histological classification system of Stary et al.[5,6] Such calcium deposits commonly occur in the basal aspect of the intima. Bone morphogenetic proteins and noncollagenous matrix proteins associated with bone mineralization are present in atherosclerotic plaques.[7,8] Extracellular matrix vesicles and injured smooth muscle cell organelles may become nidi for calcium precipitation.[9,10] Moreover, plaque mineralization is related to extracellular calcium and phosphate concentrations[11] and may be directly or indirectly induced by oxidized or otherwise modified lipids.[12,13]

There is substantial interindividual variability in the extent of atherosclerosis at every level of exposure to risk factors.[14] Recent studies suggest a genetic basis for developing IMT and

vascular calcification. To determine the extent of the familial aggregation of carotid IMT in the presence of type 2 diabetes, Lange et al[15] studied 252 individuals with type 2 diabetes from 122 families. The age-, sex-, and race-adjusted heritability estimate for carotid IMT was 32%. After further adjustment for total cholesterol, hypertension, and current smoking status, the heritability estimate rose to 41%. Peyser et al[16] quantified the relative contributions of measured risk factors and genetic influences on coronary artery calcification (CAC) measured by electron beam CT in 698 asymptomatic adults from 302 families. Before adjustment for any risk factors, 43.5% of the variation in CAC quantity was attributable to genetic factors. After adjustment for CAC risk factors (age, sex, fasting glucose level, systolic blood pressure, pack-years of smoking, and low-density lipoprotein cholesterol), 41.8% of the residual variation in CAC quantity was attributable to genetic factors. Clearly, the search for genetic factors that influence the susceptibility to cardiovascular risk factors must continue.

Carotid IMT and vascular calcifications are modifiable. Controlled studies show that cholesterol-lowering medications can favorably change both carotid IMT and vascular calcifications. In the Cholesterol Lowering Atherosclerosis Study (CLAS), taking colestipol and niacin caused significant progressive reduction in carotid IMT at 2 and 4 years, whereas placebo-treated patients showed significant increases over the same period.[17] The Asymptomatic Carotid Artery Progression Study (ACAPS) showed that, for patients not taking warfarin, the mean maximum carotid IMT progression curves ran parallel for lovastatin (20 to 40 mg/d) and placebo groups for 6 to 12 months.[18] Thereafter, the curves significantly diverge, and the lovastatin group showed IMT regression (annualized progression rates, −0.009 versus 0.006 mm/year). The Monitored Atherosclerosis Regression Study (MARS) of 188 patients with angiographically defined coronary atherosclerosis confirmed that lovastatin (80 mg/d) can favorably affect carotid IMT.[19]

The effects of cholesterol-lowering drugs on vascular calcification has been less studied. However, a prospective study of patients with low-density lipoprotein cholesterol levels >130 mg/dL showed that the median annualized absolute increase in coronary calcification volume measured by electron beam tomography significantly fell from 25 mm^3 while untreated to 11 mm^3 when treated with cerivastatin.[20] Whether testing for IMT and vascular calcification will become components of routine clinical care depends on whether the results of such testing will have direct therapeutic consequences. At present, there are no pharmacotherapies specifically for vascular wall thickening or calcification beyond what is currently being prescribed for treating classic risk factors like hyperlipidemia and hypertension.

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