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Is Carotid Intima-Media Thickness Useful in Cardiovascular Disease Risk Assessment?

The Rotterdam Study

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Background and Purpose—We determined the contribution of common carotid intima-media thickness (IMT) in the prediction of future coronary heart disease and cerebrovascular disease when added to established risk factors.

Methods—We used data from a nested case-control study comprising 374 subjects with either an incident stroke or a myocardial infarction and 1496 controls. All subjects were aged 55 years and older and participated in the Rotterdam Study. Mean follow-up was 4.2 years (range, 0.1 to 6.5 years). We evaluated which correlates of coronary heart disease and cerebrovascular disease contribute to the prediction of either a new incident myocardial infarction or a stroke. Logistic regression modeling and the area under the receiver operating characteristic curve (ROC area) were used to quantify the predictive value of the established risk factors and the added value of IMT.

Results—The ROC area of a model with age and sex only was 0.65 (95% CI, 0.62 to 0.69). Independent risk factors were previous myocardial infarction and stroke, diabetes mellitus, smoking, systolic blood pressure, diastolic blood pressure, and total and HDL cholesterol levels. These risk factors increased the ROC area from 0.65 to 0.72 (95% CI, 0.69 to 0.75). This model correctly predicted 17% of all subjects with coronary heart disease and cerebrovascular disease. When common carotid IMT was added to the previous model, the ROC area increased to 0.75 (95% CI, 0.72 to 0.78). When only the IMT measurement was used, the ROC area was 0.71 (95% CI, 0.68 to 0.74), and 14% of all subjects were correctly predicted. There was no difference in ROC area when different measurement sites were used.

Conclusions—Adding IMT to a risk function for coronary heart disease and cerebrovascular disease does not result in a substantial increase in the predictive value when used as a screening tool. **(*Stroke*. 2001;32:1532-1538.)**

Key Words: atherosclerosis ■ cardiovascular diseases ■ carotid arteries ■ risk factors ■ ultrasonics

Carotid intima-media thickness (IMT) measurements are being applied widely as a measure of atherosclerosis in studies on determinants of presence and progression of atherosclerosis and in studies on atherosclerosis as determinant of cardiovascular disease.[1–4] Carotid IMT has been shown to be related to cardiovascular risk factors, prevalent cardiovascular disease, and atherosclerosis in the peripheral, coronary, and femoral arteries. Recently, evidence became available indicating that an increased carotid IMT is a strong predictor of coronary heart disease and stroke.[1,4–7] Therefore, it has been suggested that measurements of carotid IMT may be used to identify high-risk subjects.[8]

The objective of the present study is to evaluate, in elderly subjects of the general population, which established risk factors, such as medical history, blood pressure, and serum lipids, are independent predictors of coronary heart disease and cerebrovascular disease and whether measurement of carotid IMT contributes to the prediction of coronary heart disease and cerebrovascular disease when added to these risk factors. Eventually, we evaluated the predictive ability of the carotid IMT measurement alone when used to replace established risk factors.

Subjects and Methods

Population

The Rotterdam Study is a single-center, prospective follow-up study on disease and disability in the elderly in 7983 subjects, aged 55 years or older, living in the suburb of Ommoord in Rotterdam, Netherlands, as detailed elsewhere.[9] Baseline data were collected from March 1990 to July 1993 during a home interview and 2 visits at the research center. The overall participation rate of those invited for the study was 78%. The study has been approved by the Medical Ethics Committee of Erasmus University, and written informed consent was obtained from all participants.

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Cerebrovascular and Cardiovascular Risk Indicators

At baseline, information about the medical history of myocardial infarction and stroke, current medication, alcohol intake, and smoking habits was obtained by a trained research assistant. At the study center an extensive physical examination was performed, including height and weight measurement, 2 blood pressure measurements (taken with a random zero sphygmomanometer with the subject in sitting position, and averaged), a 12-lead ECG, serum total cholesterol and HDL cholesterol levels, and a nonfasting or postload glucose level.

Presence of hypertension was defined as a systolic pressure $\geq$160 mm Hg or a diastolic pressure $\geq$95 mm Hg or current use of blood pressure–lowering drugs for the indication of hypertension. Diabetes mellitus was considered present when subjects currently used oral blood glucose–lowering drugs or insulin or had a nonfasting or postload glucose level $>$11 mmol/L, assessed after a nonfasting venipuncture.

Incident Cerebrovascular and Cardiovascular Disease

Information on incident fatal and nonfatal events is obtained from the general practitioners working in the district of Ommoord. The general practitioners report all possible cases of myocardial infarction and stroke to the Rotterdam research center. Events are coded according to the International Classification of Primary Care.[10] Information on the vital status of the participants is obtained at regular intervals from the municipal authorities in Rotterdam. When an event or death has been reported, additional information is obtained by scrutinizing information from general practitioner and hospital discharge records in case of admittance or referral. Events are then confirmed by 2 study physicians. Additionally, all data about new cases of myocardial infarction were reviewed by a cardiologist, and all data about stroke cases were reviewed by a neurologist; neither physician actually saw the patient. In case of disagreement, consensus was reached in additional meetings. An incident myocardial infarction was considered to have occurred when the event led to a hospitalization and the hospital discharge record indicated a diagnosis of a new myocardial infarction on the basis of signs and symptoms, ECG recordings, and repeated laboratory investigations during hospital stay. All suspected cerebrovascular events reported by the general practitioners were submitted for review to a neurologist (P.J.K.). The neurologist classified the events as definite, probable, and possible stroke on the basis of all information, including symptoms and signs obtained by interviewing the general practitioner or, in case of hospital referral, hospital data. An incident stroke was considered to have occurred when (1) the event had led to a hospitalization and the hospital discharge record indicated a diagnosis of a new stroke; the clinical diagnosis was based on signs, symptoms, and neuroimaging investigations during hospital stay; or (2) in case of no hospitalization, signs and symptoms associated with the event obtained from the general practitioner were highly suggestive of a stroke according to the neurologist (probable stroke); or (3) in case of out-of-hospital death, when the general practitioner reported that the cause of death was a cerebrovascular accident and a cardiac cause was judged to be highly unlikely. For the analyses, only definite and probable incident strokes were included.

Measurement of IMT

To measure carotid IMT, ultrasonography of the common carotid artery (CCA), carotid bifurcation, and internal carotid artery (ICA) of the left and right carotid arteries was performed with a 7.5-MHz linear-array transducer (ATL Ultra-Mark IV). On a longitudinal, 2-dimensional ultrasound image of the carotid artery, the anterior (near) and posterior (far) walls of the carotid artery are displayed as 2 bright white lines separated by a hypoechogenic space. The distance between the leading edge of the first bright line of the far wall and the leading edge of the second bright line indicates the IMT. For the near wall, the distance between the trailing edge of the first bright line and the trailing edge of the second bright line at the near wall provides the best estimate of the near wall IMT.[11] In accordance with the Rotterdam Study ultrasound protocol,[12] a careful search was performed to obtain the optimal representation of both the near and far walls of the distal CCA, the carotid bifurcation, and the ICA. When an optimal longitudinal image was obtained, it was frozen on the R wave of the ECG and stored on videotape. The actual measurements of IMT were performed offline. From videotape, the frozen images were digitized on the screen of a personal computer with the use of additional dedicated software. This procedure has been described in detail previously.[13,14] In short, with a cursor, or automatically by the computer, the interfaces of the CCA were marked across a length of 10 mm. The computer then calculated the mean IMT and the maximum IMT over the marked length for both near and far walls. We used the average of the measurements of 3 frozen images of both the left and right arteries to obtain mean values of the mean and the maximum thickness for each subject. For the carotid bifurcation and the ICA, the interfaces were marked across a variable length at the thickest part of the measurement site. Then the maximum IMT was calculated over the marked length. For the analyses, the maximum carotid IMT was determined as the mean of the maximum IMT of near and far wall measurements of both the left and right arteries. A composite measure that combined the maximal CCA IMT, the maximal bifurcation IMT, and the maximal ICA IMT, when available, was obtained by averaging the 3 measurements after standardization (subject maximum IMT minus cohort mean of the maximum IMT, divided by cohort SD of the maximum IMT). The readers of the ultrasound images were unaware of the case status of the subject. Results from a reproducibility study of IMT measurements of the CCA among 80 participants of the Rotterdam Study who underwent a second ultrasound of both carotid arteries within 3 months of the first scan have been described elsewhere.[15] In short, mean differences (SD) in far wall IMT of the CCA between paired measurements of sonographers, readers, and visits were 0.005 (0.09), 0.060 (0.05), and 0.033 mm (0.12), respectively. Corresponding intraclass correlation coefficients were 0.63, 0.88, and 0.74, respectively.

Selection of Cases and Controls

Ultrasonography of the carotid arteries was performed in 5965 of the 7983 subjects in the Rotterdam Study. For subjects who had their baseline examination at the end of 1992 and in 1993, ultrasonography could not always be performed because of the restricted availability of ultrasonographers. Since this may be considered a random sample, for the present study the cases and controls were drawn from this cohort of 5965 subjects. For reasons of availability and completeness of information on coronary heart and cerebrovascular events, we restricted the present study to follow-up events registered by general practitioners before May 1996. The mean duration of follow-up was 4.2 years (range, 0.1 to 6.5 years; SD, 1.6). We selected 374 case subjects with incident coronary heart disease and cerebrovascular disease, of whom 194 subjects had a myocardial infarction and 191 subjects had a stroke (11 subjects had both a myocardial infarction and a stroke, for which we used the event that occurred first). For these subjects, data on carotid IMT were obtained from the stored images on videotape. For each case subject, 4 control subjects were drawn. A subject was eligible as a control if he/she was free from myocardial infarction and stroke. The total number of control subjects was 1496, resulting in a total number of 1870 subjects.

Data Analysis

First, data analysis was separately performed for the 2 outcomes (myocardial infarction and stroke) with the same control group. Only subjects with complete data on all risk factors and CCA IMT measurement were included, resulting in a data set of 1721 subjects: 328 cases (174 myocardial infarctions and 165 strokes; 11 had both) and 1393 controls. The association between each risk factor and myocardial infarction was quantified by logistic regression analyses, with adjustment for age and sex. The odds ratio (OR) and 95% CI were used as measure of association. Variables associated with

TABLE 1. Baseline Characteristics of the Study Population

Characteristic	Myocardial Infarction	Stroke	Control Subjects
n	194	191	1496
Age, y	72*	75*	70
Female, %	39*	54*	62
Body mass index, kg/m^2	26.3 (3.4)	26.4 (3.9)	26.6 (3.8)
Current smoking, %	30	28	22
Systolic blood pressure, mm Hg	144 (22.5)*	149 (24.0)*	138 (21.3)
Diastolic blood pressure, mm Hg	72 (12.3)	75 (13.4)*	72 (10.9)
Hypertension, %	41*	52*	34
Total cholesterol, mol/L	6.9 (1.2)*	6.5 (1.2)	6.7 (1.3)
HDL cholesterol, mmol/L	120 (0.28)*	1.31 (0.38)	1.34 (0.38)
Diabetes mellitus, %	13*	14*	7
Previous myocardial infarction, %	31*	23*	12
Previous stroke, %	6	11*	2
Maximum CCA IMT, mm	1.17 (0.29)*	1.22 (0.35)*	1.02 (0.21)
Maximum bifurcation IMT, mm	1.76 (0.68)*	1.83 (0.73)*	1.44 (0.59)
Maximum ICA IMT, mm	1.42 (0.61)*	1.62 (0.81)*	1.15 (0.62)

Values are unadjusted proportions or means, with SD in parentheses.

*$P<0.05$ compared with control subjects, adjusted for differences in age and sex.

myocardial infarction ($P<0.10$) were then included in a multivariate logistic regression model to evaluate the independent contribution in the prediction of myocardial infarction. The first (overall) model included all "univariately" (ie, age and sex adjusted) significant variables from medical history and physical examination. Model reduction was performed by excluding variables that were not significantly related with myocardial infarction (OR with $P<0.10$) from the overall model. Subsequently, the reduced model was extended with carotid IMT measurements to evaluate their added value in the prediction of myocardial infarction. Differences in predictive value between all different prediction models (overall, reduced, and extended) were estimated by comparison of the area under the receiver operating characteristic curve (ROC area) with standard error.[16,17] The ROC curve of a multivariate logistic model plots the sensitivity and 1−specificity at each consecutive threshold in the range of predicted probabilities of the model. The ROC area is a measure of the discriminative or predictive ability of the model that can range from 0.5 (no discrimination between subjects with and without myocardial infarction) to 1.0 (perfect discrimination). In all model comparisons, correlation between the models was taken into account because they were based on the same cases.[18]

The ROC area reflects the overall added value of a model and does not directly indicate its clinical value.[19,20] Therefore, we additionally estimated for the final model the absolute number of correctly predicted patients with and without myocardial infarction. A similar analytical approach was followed for stroke as outcome and for the combined coronary heart disease and cerebrovascular disease outcome (both myocardial infarction and stroke).

A different analysis was performed to evaluate any differences in the predictive value for total coronary heart disease and cerebrovascular disease (ie, myocardial infarction or stroke) between 3 IMT measurement sites and the combined IMT measure with the use of logistic regression analyses in combination with ROC curves. This analysis was done on a restricted data set with complete data for all 3 measurement sites, resulting in a data set of 512 subjects: 156 cases (74 myocardial infarctions and 74 strokes; 8 subjects had both) and 356 controls. Data on IMT at the carotid bifurcation were available in 64% of the 1870 subjects (74% of all myocardial infarction and stroke cases and 61% of controls); data on IMT of the ICA were available in 31% (47% of all cases and 27% of controls); and data on IMT of the CCA were available in 96% (92% of all cases and 97% of controls).

All analyses were performed with the use of SPSS software, version 9.0 (SPSS Inc).

Results

The general characteristics of the study population are given in Table 1. The age- and sex-adjusted associations for all evaluated risk indicators, including the carotid IMT measurements, with myocardial infarction and stroke are given in Table 2. Although the magnitude of the association of each variable with both coronary heart disease and cerebrovascular disease outcomes was different, the same predictors were of importance for both outcomes. Age, male sex, smoking, systolic blood pressure, hypertension, total cholesterol, HDL cholesterol, previous myocardial infarction, previous stroke, and carotid IMT measurements were highly associated with myocardial infarction. For stroke, diastolic blood pressure was also a predictor, while total and HDL cholesterol and diabetes mellitus were much less important predictors.

Table 3 shows, for outcomes of both myocardial infarction and stroke, the ORs of the independent predictors in 2 predictive models. Model 1 has the independent predictors added, such as previous coronary heart disease and cerebrovascular disease, diabetes mellitus, smoking, systolic and diastolic blood pressure, and total and HDL cholesterol. Model 2 is the same model extended with the CCA IMT. For both outcomes almost the same independent predictors were found, except for blood lipids, which were not independent predictors of stroke. In the prediction of myocardial infarction, the ROC area of model 1 was 0.75 (95% CI, 0.72 to 0.79), whereas for the prediction of stroke it was 0.73 (95% CI, 0.69 to 0.77). Because for both outcomes the independent predictors were virtually the same and the ROC areas were also similar, we decided to combine myocardial infarction and stroke as one combined coronary heart disease and cerebrovascular disease outcome. For the prediction of this combined outcome, a model with age and sex only reached a ROC area of 0.65 (95% CI, 0.62 to 0.69). The ROC area of model 1 (Table 3) increased significantly ($P=0.01$) from 0.65 to 0.72 (95% CI, 0.69 to 0.75). When CCA IMT was added to model 1 (Table 3) for the prediction of the combined outcome (model 2), there was a significant increase ($P=0.01$) from 0.72 to 0.75 (95% CI, 0.72 to 0.78). When model 3, a model with age, sex, and CCA IMT only, was used instead of model 2, the ROC area increased ($P=0.01$) from 0.65 to 0.71 (95% CI, 0.68 to 0.74).

In a subgroup analysis on 512 subjects (156 cases and 356 controls), we then evaluated the added contribution of each of the 4 IMT measurements in the prediction of the combined outcome by separately adding them to model 1 (Table 4). In this subset the ROC area of model 1 was 0.72 (95% CI, 0.67 to 0.77). This was increased ($P=0.07$) to 0.74 (95% CI, 0.69 to 0.78) when CCA IMT was added to model 1, to 0.74 (95% CI, 0.69 to 0.78) ($P=0.07$) when bifurcation IMT was added, to 0.75 (95% CI, 0.70 to 0.79) ($P=0.01$) when ICA IMT was added, and to 0.75 (95% CI, 0.71 to 0.80) when the combined IMT measurement was added. The CCA IMT was used for the remainder of the analyses because the increase in ROC

TABLE 2. Association of Risk Factors With Myocardial Infarction and Stroke

Risk Factor	Myocardial Infarction (n=194)	Stroke (n=191)
Characteristics from medical history and physical examination		
Age (year)	1.19 (1.08–1.30)	1.45 (1.33–1.59)
Sex (female)	0.37 (0.27–0.51)	0.64 (0.47–0.89)
Previous myocardial infarction (yes/no)	2.64 (1.85–3.78)	1.61 (1.08–2.40)
Previous stroke (yes/no)	2.18 (1.07–4.46)	4.20 (2.30–7.65)
Smoking		
Current smoking (yes/no)	1.80 (1.10–2.95)	1.90 (1.18–3.05)
Former smoking (yes/no)	1.44 (0.91–2.28)	1.26 (0.82–1.96)
Body mass index (kg/m^2)	1.00 (0.96–1.05)	0.99 (0.95–1.04)
Systolic blood pressure (10 mm Hg)	1.10 (1.02–1.18)	1.18 (1.10–1.27)
Diastolic blood pressure (10 mm Hg)	1.00 (0.87–1.15)	1.31 (1.14–1.50)
Hypertension (yes/no)	1.11 (1.02–1.22)	1.17 (1.08–1.28)
Total cholesterol (mmol/L)	1.31 (1.16–1.49)	0.98 (0.86–1.12)
HDL cholesterol (mmol/L)	0.38 (0.22–0.64)	0.91 (0.58–1.43)
Diabetes mellitus (yes/no)	1.23 (1.03–1.46)	1.13 (0.92–1.39)
Carotid IMT measurements		
Maximum CCA IMT (per SD)	1.51 (1.32–1.74)	1.56 (1.37–1.77)
Maximum bifurcation IMT (per SD)	1.44 (1.22–1.69)	1.51 (1.28–1.77)
Maximum ICA IMT (per SD)	1.27 (1.01–1.59)	1.56 (1.26–1.92)
Combined IMT	1.71 (1.45–2.01)	1.68 (1.44–1.96)

Values are ORs with 95% CIs, adjusted for age and sex (except for age and sex).

area for the different sites did not differ substantially and because it was available for 95% of all 1870 subjects.

To evaluate the difference in predictive value between the model with all independent predictors (model 1) and a model with only CCA IMT added to age and sex (model 3), we obtained an estimate of absolute incidences in the total cohort of the combined outcome (coronary heart disease and cerebrovascular disease) across categories of the model's predicted probability. Initially, the absolute incidence was set by the case-control ratio of 1:4, giving 25%. Therefore, all

TABLE 3. Results of Multivariate Logistic Regression Analyses for Stroke, Myocardial Infarction, and Cardiovascular/Cerebrovascular Disease and ROC Area

	Myocardial Infarction (n=194)	Stroke (n=191)	CVD (Stroke and MI) (n=374)	
Risk Factor	Model 1	Model 1	Model 1	Model 2
Age (per 5y)	1.16 (1.03–1.30)	1.42 (1.26–1.60)	1.28 (1.18–1.40)	1.20 (1.10–1.32)
Sex (women)	0.48 (0.32–0.73)	0.91 (0.60–1.39)	0.63 (0.46–0.85)	
Previous CVD	2.40 (1.65–3.49)	1.94 (1.30–2.89)	2.27 (1.70–3.04)	2.13 (1.58–2.86)
Diabetes mellitus	1.21 (1.00–1.48)	1.15 (0.92–1.45)	1.19 (1.00–1.41)	1.22 (1.03–1.45)
Smoking*				
Current	2.02 (1.18–3.45)	2.11 (1.26–3.53)	1.97 (1.34–2.89)	1.73 (1.17–2.56)
Former	1.44 (0.87–2.38)	1.35 (0.84–2.17)	1.35 (0.94–1.93)	1.29 (0.90–1.85)
Systolic blood pressure (per 10 mm Hg)	1.13 (1.02–1.25)	1.14 (1.03–1.25)	1.14 (1.06–1.23)	1.08 (1.00–1.16)
Diastolic blood pressure (per 10 mm Hg)	0.85 (0.70–1.03)	1.16 (0.97–1.38)	0.98 (0.86–1.13)	1.04 (0.90–1.20)
Total cholesterol (mmol/L)	1.34 (1.17–1.53)	0.99 (0.86–1.15)	1.15 (1.04–1.27)	1.13 (1.02–1.25)
HDL cholesterol (mmol/L)	0.36 (0.20–0.64)	0.84 (0.51–1.38)	0.57 (0.39–0.85)	0.62 (0.41–1.92)
Maximum CCA IMT (mm)				5.72 (3.40–12.6)
ROC area	0.75 (0.72–0.79)	0.73 (0.69–0.77)	0.72 (0.69–0.75)	0.75 (0.72–0.78)

CVD indicates coronary heart disease and cerebrovascular disease. Values are ORs with 95% CIs.

*Included as 2 indicator variables, with no smoking as the reference category.

TABLE 4. Contribution of Different IMT Measures to Model 1 in the Prediction of Coronary Heart Disease and Cerebrovascular Disease

Model	ROC Area (95% CI)
Model 1	0.72 (0.67–0.77)
Model 1+maximum CCA IMT	0.74 (0.69–0.78)
Model 1+maximum BIF IMT	0.74 (0.69–0.78)
Model 1+maximum ICA IMT	0.75 (0.70–0.79)
Model 1+combined IMT	0.75 (0.71–0.80)

*BIF indicates carotid bifurcation.

subjects in the control group were given a weight that was the inverse of the sampling fraction. The sampling fraction was calculated by dividing 1496 controls by the cohort of 5965 subjects minus 374 cases, giving a sampling fraction of 0.27 and a weight of 3.74. Hence, a new data set was created that included all cases and the weighted control group resembling the entire cohort. Table 5 shows the estimated distribution of subjects with and without coronary heart disease and cerebrovascular disease, across selected probability categories of both models 1 and 3. From this table one can directly obtain the predictive value for presence or absence of coronary heart disease and cerebrovascular disease per probability category (reading horizontally). For model 1, for example, of all 3048 subjects with an estimated probability ≤5%, 84 subjects had coronary heart disease and cerebrovascular disease and 2964 did not, yielding a predictive value of coronary heart disease and cerebrovascular disease presence of 84/3048=2.8% and of coronary heart disease and cerebrovascular disease absence of 97.2%. Of 119 subjects with an estimated probability ≥21%, 25 subjects experienced an event and 94 did not, a predictive value of coronary heart disease and cerebrovascular disease presence of 25/119=21%. For model 3, of all 3081 subjects with an estimated probability ≤5%, 82 subjects experienced a coronary heart or cerebrovascular event, a predictive value for coronary heart disease and cerebrovascular disease presence of 2.4%. In the category ≥21%, the predictive value for presence of coronary heart disease and cerebrovascular disease was 20%. Table 5 also enables estimation of the sensitivity and specificity at different probability thresholds (reading vertically). Therefore, a threshold probability must be used above which the probability, as estimated by the model, is considered a "positive" test result. For example, when model 1 is used at an arbitrary threshold probability of 15%, it can be seen that of all 308 (189+119) subjects with a ≥16% risk of coronary heart disease and cerebrovascular disease, 53 (28+25) indeed had a myocardial infarction or stroke, correctly predicting 17% (9%+8%) of all coronary heart disease and cerebrovascular disease patients (ie, the sensitivity or true positive rate), while 255 (161+94) did not, so that only 5% (3%+2%) of all subjects were without coronary heart disease and cerebrovascular disease (ie, 1−specificity or false-positive rate), a specificity of 95%. Using the same threshold of 15% when using carotid IMT (model 3) showed that of all 231 (128+103) subjects with a ≥16% risk, 48 (27+21) indeed experienced a coronary heart or cerebrovascular event (a sensitivity of 14%), while 183 (101+82) did not, resulting in 4% false-positives and a specificity of 96%. Similarly, sensitivity and specificity can be calculated for different threshold probabilities.

Discussion

Despite the observation of a significant association between carotid IMT and risk of future coronary heart disease and cerebrovascular disease, the contribution of a single carotid IMT measurement, which represents the average of the maximum IMT values of the near and far walls of both left and right carotid arteries, to estimate the risk of coronary heart disease and cerebrovascular disease on an individual level is small. Our study showed that clinical coronary heart disease and cerebrovascular disease risk factors obtained with medical history and physical examination, such as blood pressure and cholesterol measurements, can predict the future occurrence of coronary heart disease and cerebrovascular disease reasonably well. Using these parameters facilitates the early prediction of approximately 17% of all future cardiovascular/cerebrovascular disease cases (sensitivity) with only 5% false-positive predictions (95% specificity).

TABLE 5. Distribution of Subjects With and Without Coronary Heart Disease and Cerebrovascular Disease According to Estimated Probability (Risk) by Prognostic Models 1 and 3

Estimated Probability*	Model 1				Model 3			
	CVD %†	N‡	CVD+§	CVD−‖	CVD %†	N‡	CVD+§	CVD−‖
≤5%	2.8	3048 (55)	84 (26)	2964 (57)	2.7	3081 (56)	82 (25)	2999 (58)
6–10%	7.7	1688 (31)	130 (40)	1558 (30)	8.9	1759 (32)	56(48)	1603 (31)
11–15%	12.4	491 (9)	61 (19)	430 (8)	9.1	464 (8)	42 (13)	422 (8)
16–20%	14.8	189 (3)	28 (9)	161 (3)	21.1	128 (2)	27 (8)	101 (2)
≥21%	21.0	119 (2)	25 (8)	94 (2)	20.4	103 (2)	21 (6)	82 (2)
Total		5535	328	5207		5535	328	5207

Values are absolute number of-subjects with percentages of the column total between parentheses, unless stated otherwise.
*Categories of estimated probability of risk, as estimated by the models.
†Actual incidence of coronary heart disease and cerebrovascular disease (CVD) per probability category.
‡Estimated number (percentage, ie, estimated incidence) of patients per probability category.
§Estimated number (percentage) of people with CVD per probability category.
‖Estimated number (percentage) of people without CVD per probability category.

Using the carotid IMT measurement was not substantially worse in the classification of risk of future coronary heart disease and cerebrovascular disease because sensitivity for carotid IMT alone was 14%, while the percentage of false-positives was only 4% (96% specificity). For these estimates we used an arbitrary threshold probability of 15%, above which subjects were classified as future cases of coronary heart disease and cerebrovascular disease. Using risk thresholds other than 15%, as we used, did not yield other results. Whether using sequential measurements will be more useful still needs to be studied.

To appreciate the results of the present analysis, some aspects need to be discussed. First, the estimates of sensitivity, specificity, and predictive values apply to a prognostic setting, with a low baseline risk of the disease, and should not be confused with (the usually much higher) estimates obtained from a diagnostic setting, in which the a priori chance of having the disease under study is much higher. We showed that established risk factors correctly classified 17% of all subjects with coronary heart disease and cerebrovascular disease, while the carotid IMT measurement correctly classified 14%. Thus, performing only a carotid IMT measurement leads to a 3% reduction in correctly predicting the presence of coronary heart disease and cerebrovascular disease. Although the value of carotid IMT as a proxy of atherosclerosis in epidemiological studies is without debate, in daily practice carotid IMT measurement is still a time- and money-consuming investigation, which is not easily performed in primary care. Therefore, its value as a screening tool seems to be limited. Second, CCA IMT was measured only once at baseline. Although studies indicate good reproducibility, automatic edge-detection computer programs may further reduce the measurement error as well as duplicate measurements may. Third, the present analysis was restricted to those 95% of all subjects with complete data on all risk indicators and carotid IMT measurements. It is not likely that the found associations would be different if all those with missing data were not excluded, since there was no reason to believe that the risk indicators and ultrasonography were obtained from a selected sample of the study cohort. This is further exemplified by the analyses on the restricted data set in which the ROC areas were virtually the same. Fourth, because of the case-control design of the present study, the ORs (regression coefficients) of the predictors are correctly estimated, whereas a baseline risk of coronary heart disease and cerebrovascular disease (ie, the intercept or constant of a model) could not be directly estimated. Therefore, we applied a weighting procedure to the control group to obtain Table 5. If one desires to estimate the absolute risk for subjects in a different population, one can directly use the (adjusted) regression coefficients (Table 3), although one must first adjust the constant for the prevalence of coronary heart disease and cerebrovascular disease in the population at hand.

In several studies a high carotid IMT was related to future coronary heart and cerebrovascular events.[4,5,7] Despite the different ultrasound protocols used in these studies, the results for the CCA IMT are remarkably similar. The OR per SD increase in the Atherosclerosis Risk in Communities (ARIC) Study for coronary heart disease was 1.92 (95% CI, 1.66 to 2.22) for women and 1.32 (95% CI, 1.13 to 1.54) for men. In the Cardiovascular Health Study, the relative risk for coronary heart disease and stroke as a combined outcome was 1.35 (95% CI, 1.25 to 1.45). In the Rotterdam Study, the ORs were1.41 (95% CI, 1.25 to 1.82) for stroke and 1.43 (95% CI, 1.16 to 1.78) for myocardial infarction. Recently, Touboul et al[21] found, in cross-sectional analyses on data from the Étude du Profil Génétique de l'Infarctus Cérébral (GÉNIC) study, that an increased CCA IMT was associated with brain infarctions, both overall and in the main subtypes. In all studies, including the present one, the association remained when coronary heart disease and cerebrovascular disease risk factors were accounted for.

In conclusion, the present study indicates that a single carotid IMT measurement is of the same importance as commonly used risk factors in the prediction of coronary heart disease and cerebrovascular disease. Relative to the other easily obtainable and established risk factors, it does not add substantially when used as a screening tool to discriminate subjects with high and low risk of coronary heart disease and cerebrovascular disease.

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