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Cross-sectionally assessed carotid intima–media thickness relates to long-term risk of stroke, coronary heart disease and death as estimated by available risk functions

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Abstract. Bots ML, Hoes AW, Hofman A, Witteman JCM, Grobbee DE (Erasmus University Medical School, Rotterdam; Julius Centre for Patient Oriented Research and Department of General Practice, University Medical Centre, Utrecht, The Netherlands). Cross-sectionally assessed carotid intima–media thickness relates to long-term risk of stroke, coronary heart disease and death as estimated by available risk functions. *J Intern Med* 1999 **245:** 269–76.

Objective. To relate cross-sectionally assessed indicators of carotid atherosclerosis measured in participants of the Rotterdam Study to absolute 10–12 year risks of stroke, coronary heart disease and death estimated by risk functions available from other studies.

Setting. General population living in the suburb of Ommoord in Rotterdam, The Netherlands.

Subjects. A sample of men and women (n = 1683), aged 55 years or over, drawn from participants from the Rotterdam Study (n = 7983).

Main outcomes measures. Three risk scores were used to estimate for each individual the absolute risk of stroke, coronary heart disease and death within 10–12 years as a function of their cardiovascular risk factor profile. Cross-sectionally measured indicators of carotid atherosclerosis (presence of atherosclerotic lesions and common carotid intima–media thickness) were subsequently related to these risk scores.

Results. The 10-year absolute risk of stroke increased linearly from 4.8% (95%CI = 3.8, 5.8) for subjects in the lowest quintile to 16.1% (12.3, 21.9) for subjects in the highest quintile of common carotid intima–media thickness distribution. Similarly, the 10-year absolute risk for coronary heart disease rose from 13.1% (95%CI = 12.0, 14.2) to 23.4% (95%CI = 21.4, 25.4), whereas the risk of death within 11.5 years rose from 15.0% (95%CI = 12.8, 17.4) in the lowest quintile to 46.0% (42.8, 49.3) in the upper quintile. The absolute risks of stroke, coronary heart disease or death rose from 8.8, 15.8 and 26.9% to 14.3, 19.8 and 40.9%, respectively, when plaques in the common carotid artery were present. Similar findings were observed for plaques in the carotid bifurcation.

Conclusion. Common carotid intima–media thickness and carotid plaques are markers for increased risk of stroke, coronary heart disease and death within 10–12 years.

Keywords: atherosclerosis, high risk, prevention, risk stratification.

Introduction

In several prospective follow-up studies, high-resolution B-mode ultrasonography of the carotid arteries for the assessment of intima–media thickness and presence and extent of plaques has been used to study atherosclerosis in populations at large [1–5]. Intervention studies using carotid intima–media thickness as an end-point showed reduced progression of intima–media thickness in subjects treated with lipid-lowering drugs compared with a placebo group [6–9]. There is a growing belief that increased carotid intima–media thickness should be regarded as an indicator of generalized atherosclerosis [10].

Intima-media thickness may be used as an intermediate end-point in observational studies and trials as a suitable proxy for cardiovascular morbidity and mortality. In these studies the underlying assumption is that intima–media thickness predicts future cardiovascular disease. Quantitative information showing that increased intima–media thickness is related to long-term future cerebrovascular and cardiovascular disease is very limited, but urgently needed. Currently, results are becoming available from studies with a short follow-up time showing that an increased carotid intima–media thickness is associated with an increased risk of myocardial infarction [11–14] and stroke [13].

We related indicators of carotid atherosclerosis measured in a sample of 1683 participants of the Rotterdam Study to estimates of individual 10–12 year absolute risk of stroke, coronary heart disease and death. Three risk scores from other studies were used to estimate the individual absolute risk of stroke, coronary heart disease and death as a function of their cardiovascular risk factor profile [15–17].

Methods

Population

The Rotterdam Study is a single centre prospective follow-up study of a cohort of 7983 subjects, aged 55 years or over, living in the suburb of Ommoord in Rotterdam, The Netherlands. The study has been approved by the Medical Ethics Committee of Erasmus University and written informed consent was obtained from all participants. The rationale and design of the Rotterdam Study have been described elsewhere [18]. The overall response rate of those invited to participate was 78%. The present findings come from an analysis of data obtained from a sample of 1683 participants of the Rotterdam Study for whom ultrasound information was available.

Assessment of carotid atherosclerosis

To measure carotid intima–media thickness, ultrasonography of both carotid arteries was performed with a 7.5-MHz linear array transducer using an ATL UltraMark IV duplex scanner [19]. A careful search was performed for all interfaces at the near and far wall of the distal common carotid artery and the image was frozen on the R wave of the electrocardiogram and stored on videotape. This procedure was repeated three times for both sides. The actual measurements of intima–media thickness were performed off-line. From the videotape, the frozen images were digitized and displayed on the screen of a personal computer using additional dedicated software [20]. With a cursor, the interfaces of the distal common carotid artery were marked over a length of 10 mm. The distance from the leading edge of the first bright line of the far wall (lumen–intima interface) to the leading edge of the second bright line (media–adventitia interface) indicates the intima–media thickness [20, 21]. For the near wall, the distance between the trailing edge of the first bright line to the trailing edge of the second bright line at the near wall provides the best estimate of the near wall intima–media thickness. The beginning of the dilatation of the distal common carotid artery served as a reference point for the start of the measurement. For each individual, a common carotid intima–media thickness was determined as the average of near and far wall measurements of both the left and right arteries. Results from a reproducibility study of intima–media thickness measurements have been described elsewhere [22].

The common carotid artery and the carotid bifurcation were evaluated off-line (from tapes) for the presence (yes/no) of atherosclerotic lesions on both the near and far walls of the carotid artery. Plaques were defined as a focal widening relative to adjacent segments, with protrusion into the lumen composed either of only calcified deposits or of a combination of calcified and non-calcified material. No attempt was made to quantify the size or extent of the lesions. A reproducibility study of the assessment of plaques in the carotid artery has been described elsewhere [23].

Cardiovascular risk indicators

In the Rotterdam Study, information on health status, medical history, current drug use and smoking behaviour was obtained using a computerized questionnaire, which included a Dutch version of the Rose questionnaire for assessment of prevalent angina pectoris and intermittent claudication [24]. A previous history of myocardial infarction and stroke was based on the questions 'Did you ever have a myocardial infarction for which you were hospitalized?', and 'Did you ever have a stroke?', respectively. Diabetes mellitus was considered present when subjects were currently using oral blood sugar lowering

drugs or receiving insulin treatment. With respect to smoking behaviour, subjects were categorized into groups of current smokers, former smokers and those who never smoked.

Height and weight were measured and body mass index (kg m^{-2}) was calculated. Sitting blood pressure was measured at the right upper arm using a random-zero sphygmomanometer. Hypertension was defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or current use of antihypertensive drugs for the indication hypertension. An electrocardiogram was made. An automated diagnostic classification system MEANS (Modular Electrocardiogram Analysis System) was used to assess atrial fibrillation and left ventricular hypertrophy (LVH). The diagnosis of LVH was based on voltage, shape and repolarization criteria, as detailed elsewhere [25, 26].

A non-fasting venous blood sample was taken, applying minimal stasis, using a 21 gauge Butterfly needle with tube as described previously [27]. Serum total cholesterol was determined using an automated enzymatic procedure. High-density lipoprotein (HDL) cholesterol was measured similarly, after precipitation of the non-HDL fraction with phosphotungstate-magnesium.

Risk functions for stroke, coronary heart disease and all-cause mortality

A risk function estimates an individual's probability for the occurrence of an event within a certain time span as a function of the individual's level of the risk indicators. Risk functions are derived from analyses on data from longitudinal (cohort) studies, in which the relative and independent contribution of certain risk factors in predicting the occurrence of the event is evaluated.

The risk function for stroke was based on information from 10 years follow-up of participants of the Framingham Heart Study, aged 55–84 years, initially free from stroke at the biannual examinations 9 and 14 [16]. A Cox proportional hazards model was used to estimate the contribution of cardiovascular risk factors to the occurrence of stroke. The report provides detailed information on how an individual's absolute 10-year risk of stroke may be estimated; for men:

$$1–0.9044^{\exp(0.0488 \times \text{age} + 0.0152 \times \text{SBP} + 0.00019 \times \text{HRXSBP} + 0.5460 \times \text{CVD} + 0.7864 \times \text{ECGLVH} + 0.5224 \times \text{smoking} + 0.5998 \times \text{atrial fibrillation} + 0.3429 \times \text{diabetes} - 5.6670)}$$

and for women:

$$1–0.9353^{\exp(0.0699 \times \text{age} + 0.0161 \times \text{SBP} + 0.00026 \times \text{HRXSBP} + 0.4404 \times \text{CVD} + 0.8055 \times \text{ECGLVH} + 0.5219 \times \text{smoking} + 1.1173 \times \text{atrial fibrillation} + 0.5604 \times \text{diabetes} - 7.5766)}$$

where HRXSBP = 0 if systolic pressure < 110 or > 200, otherwise HRXSBP is HRX $\times$ (SBP $-$ 110) $\times$ (200 – SBP) and HRX = 1 when subjects are on antihypertensive treatment.

The risk function predicting 10-year coronary heart disease risk was obtained from data on the Framingham Heart cohort aged 30–74 years and free from cardiovascular disease at baseline [15]. A logistic regression model was used for risk estimation. Risk indicators included in the final model were age, systolic blood pressure, total/HDL cholesterol ratio, left ventricular hypertrophy (on ECG), smoking and diabetes mellitus. In the report, an extensive and detailed description is given of how to arrive at an estimate of the absolute risk of coronary heart disease within 10 years for an individual given a certain set of cardiovascular risk factors.

The risk function to predict an individual's probability of dying within 11.5 years as a function of the levels of cardiovascular risk factors was obtained from findings in a follow-up study amongst 6057 subjects aged 20 years or over, conducted in The Netherlands [17]. A Cox proportional hazards model was used to identify the most relevant cardiovascular factors for death. For each individual, an absolute risk of dying within 11.5 years may be calculated; for men:

$$[1–0.99968^{\exp(0.096 \times \text{age} + 0.004 \times \text{SBP} + 0.009 \times \text{pulse rate} + 0.414 \times \text{smoking} + 0.372 \times \text{antihypertensive drugs} + 0.594 \times \text{diabetes mellitus} + 0.672 \times \text{myocardial infarction} - 0.033 \times \text{BMI})}]$$

and for women:

$$1–0.99945^{\exp(0.081 \times \text{age} + 0.010 \times \text{SBP} + 0.001 \times \text{pulse rate} + -0.119 \times \text{smoking} + 0.160 \times \text{antihypertensive drugs} + 0.700 \times \text{diabetes mellitus} + 0.436 \times \text{myocardial infarction} - 0.036 \times \text{BMI})}$$

Data analysis

First, we calculated for each of the 1683 individuals the absolute risk of stroke, coronary heart disease and death using the approaches described above. Then, we evaluated the association between these risk estimates and common carotid intima–media thickness, and presence of plaques in the common carotid artery and carotid bifurcation using linear regression analyses. In addition, the absolute risks

were compared across quintiles of common carotid intima–media thickness using linear regression analyses with four dummy variables. The beta coefficients resulting from these analyses reflect the difference in absolute risk for the second, third, fourth and fifth quintiles relative to the first quintile (reference group). Since the three risk functions were based on different cohorts in terms of age range and presence or absence of cardiovascular disease, the cut-off points (in mm) for the quintiles of the intima–media thickness distributions were made separately for stroke (0.662, 0.735, 0.808, 0.894), coronary heart disease (0.661, 0.730, 0.807, 0.891) and death (0.667, 0.743, 0.813, 0.902).

Results

Baseline characteristics of the study population are presented in Table 1. Comparison of risk estimates for stroke and coronary heart disease obtained by application of the original Framingham Heart Study risk functions to the participants of the Rotterdam Study data are presented in Table 2. In general, no important differences in risk estimates between the two study populations were observed.

The 10-year absolute risk of stroke increased gradually with increasing common carotid intima–media thickness; absolute stroke risk increased by 4.1% (95%CI = 3.6, 4.6) per standard deviation increase (0.15 mm in intima–media thickness). The 10-year risks of stroke in subjects with and without plaques in the common carotid artery plaques were 14.3 and 8.8%, respectively, with a risk difference of 5.5% (95%CI = 4.1, 6.8). Corresponding stroke risks in those with and without plaques in the carotid bifurcation were 11.5 and 7.7%, respectively, with a risk difference of 3.8% (95%CI = 2.7, 5.0).

The 10-year absolute risk of coronary heart disease increased gradually with increasing common carotid intima–media thickness; absolute coronary heart disease risk increased by 3.7% (95%CI = 2.9, 4.4) per standard deviation increase (0.15 mm in intima–media thickness). The 10-year risks of coronary heart disease in subjects with and without plaques in the common carotid artery plaques were 19.8 and 15.8%, respectively, with a risk difference of

Table 1 General characteristics of the study population

	Men (SD)	Women (SD)
Number	630	1053
Age (years)	69.9 (8.3)	71.7 (9.7)
Body mass index (kg m^{-2})	25.8 (3.1)	26.8 (4.2)
Systolic pressure (mmHg)	137.9 (20.7)	139.0 (22.4)
Diastolic pressure (mmHg)	72.7 (11.0)	71.0 (11.6)
Pulse rate (beats min^{-1})	71.8 (12.1)	74.3 (12.0)
Total cholesterol (mmol L^{-1})	6.3 (1.1)	6.8 (1.2)
HDL cholesterol (mmol L^{-1})	1.21 (0.4)	1.42 (0.34)
Total/HDL ratio	5.56 (1.5)	5.09 (1.62)
Smoking (%)	29.8	17.1
Antihypertensive treatment (%)	15.1	22.0
Diabetes mellitus (%)	4.7	4.8
Myocardial infarction (%)	14.5	5.4
Stroke (%)	6.9	4.2
Cardiovascular disease (%)	23.3	16.6
Atrial fibrillation (%)	2.8	2.9.
Left ventricular hypertrophy (%)	5.8	6.6
Intima-media thickness (mm)	0.82 (0.15)	0.79 (0.16)
Plaques, common carotid artery (%)	23.0	16.6
Plaques, carotid bifurcation (%)	64.3	59.0
10-year risk of stroke (%)[a]	12.8 (9.5)	7.7 (9.0)
10-year risk of coronary disease (%)[a]	23.5 (9.2)	12.0 (6.5)
11.5-year risk of death (%)[a]	42.7 (20.0)	21.7 (18.3)

Values are means (SD). IMT, intima–media thickness.
[a]Number of subjects – stroke risk: free from stroke, 511 men and 821 women (55–84 years); coronary heart disease risk: free from cardiovascular disease, 340 men and 551 women (55–74 years); and death: 588 men and 970 women.

Table 2 Comparison between 10-year risk estimates of stroke and coronary heart disease (as a percentage (95% confidence intervals)) based on application of the Framingham risk score to participants in the Framingham Study and the Rotterdam Study

	Stroke		Coronary heart disease	
	Framingham	Rotterdam	Framingham	Rotterdam
Men				
55–59 years	5.9	6.5 (5.5, 7.4)	16	19.2 (17.3, 21.2)
60–64 years	7.8	8.4 (7.4, 9.3)	21	21.2 (19.3, 23.0)
65–69 years	11.0	11.0 (9.9, 12.1)	30	24.6 (23.1, 26.1)
70–74 years	13.7	15.1 (13.4, 16.8)	24	28.1 (25.8, 30.4)
75–79 years	18.0	21.0 (18.1, 23.9)		
80–84 years	22.3	23.8 (18.7, 28.9)		
Women				
55–59 years	3.0	2.2 (1.9, 2.6)	12	9.8 (8.5, 11.0)
60–64 years	4.7	3.2 (2.9, 3.5)	13	11.3 (10.4, 12.2)
65–69 years	7.2	5.3 (4.7, 5.8)	9	12.9 (12.7, 14.7)
70–74 years	10.9	8.1 (7.3, 8.9)	12	13.7 (11.8, 14.7)
75–79 years	15.5	13.3 (11.2, 15.6)		
80–84 years	23.9	18.8 (16.1, 21.5)		

4.0% (95%CI = 2.1, 5.9). Corresponding coronary heart disease risks in subjects with and without plaques in the carotid bifurcation were 18.2 and 14.5%, respectively, with a risk difference of 3.7% (95%CI = 2.3, 5.0).

The risk of dying within 11.5 years increased by 10.5% (95%CI = 9.4, 11.5) for each standard deviation increase in common carotid intima–media thickness. The risk of dying increased in absolute terms by 13.9% (95%CI = 11.0, 16.9) with presence of common carotid artery plaques and by 13.8% (95%CI = 11.3, 16.2) with presence of plaques in the carotid bifurcation. No major differences were seen between men and women (Table 3).

The 10-year risk of stroke increased linearly from 4.8% (95%CI = 3.8, 5.8) for subjects in the lowest quintile to 16.1% (95%CI = 12.3, 21.9) for subjects in the highest quintile of common carotid intima–media thickness distribution (Fig. 1). Similarly, the 10-year risk for coronary heart disease rose from 13.1% (95%CI = 12.0, 14.2) to 23.4% (95%CI = 21.4, 25.4), whereas the risk of death within 11.5 years rose from 15.0% (95%CI = 12.8, 17.4) in the lowest quintile to 46.0% (95%CI = 42.8, 49.3) in the upper quintile.

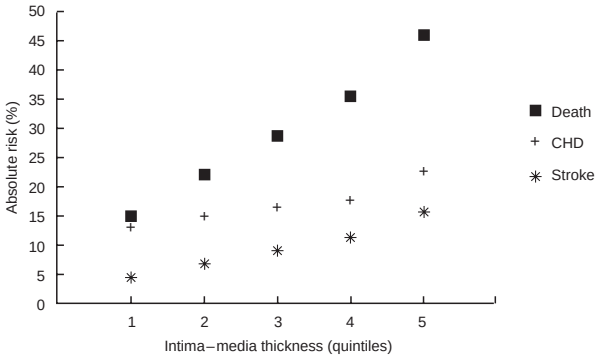

Fig. 1 Absolute 10-year risk of stroke, 10-year risk of coronary heart disease and 11.5-year risk of death by common carotid intima–media thickness (quintiles). Risks are estimated using risk functions [15–17].

Table 3 Absolute increase in risk as a percentage (95% CI) of the change in indicator of carotid atherosclerosis per unit

	Stroke		Coronary heart disease		All cause mortality	
	Men	Women	Men	Women	Men	Women
IMT (0.15 mm)	4.2% (3.4, 5.0)	3.7% (3.1, 4.3)	3.0% (1.8, 4.1)	2.2% (1.5, 2.8)	10.3% (8.4, 12.2)	8.9% (7.9, 10.0)
CCA plaque (Y/N)	3.2% (1.1, 5.3)	6.4% (4.6, 8.1)	1.2% (–1.3,3.9)	3.1% (1.3, 4.9)	9.5% (4.8, 14.4)	13.8% (10.8, 16.8)
BIF plaque (Y/N)	2.7% (0.9, 4.5)	4.1% (2.7, 5.4)	2.3% (0.2, 4.5)	3.3% (2.1, 4.5)	13.8% (9.4, 18.3)	11.9% (9.5, 14.3)

BIF, carotid bifurcation; CCA, common carotid artery; IMT, common carotid intima–media thickness.

Discussion

The present study showed that, cross-sectionally, indicators of carotid atherosclerosis such as plaques and common carotid intima–media thickness are clear markers of an increased absolute risk of stroke, coronary heart disease and death within 10–12 years. Of importance is the fact that, at these levels of intima–media thickness and with by far the majority of these plaques, a haemodynamically significant stenosis was not present.

In a large number of reports presenting results from cross-sectional analyses, an increased common carotid intima–media thickness was associated with unfavourable levels of cardiovascular risk factors, with prevalent cardiovascular disease and with atherosclerosis elsewhere in the arterial system [1–4, 28–30]. From the results of these studies, it has been suggested that an increased common carotid intima–media thickness may be a suitable marker for generalized atherosclerosis and cardiovascular risk. The current results provide support for that notion by showing that an increased common carotid intima–media thickness as such is a marker for long-term cardiovascular disease risk and death. Our findings are in agreement with results described for the British Heart Study risk score, in which a strong positive correlation between common carotid intima–media thickness and risk score was found [31].

Whether increased common carotid intima–media thickness itself reflects atherosclerosis is still subject to debate. It may merely reflect an adaptive response of the vessel wall to changes in shear stress and tensile stress [32], particularly as atherosclerosis is viewed as a disorder which is restricted to the intimal layer of the arterial vessel wall and ultrasound imaging cannot discriminate between the intima layer and the media layer of the vessel wall [33]. The level of intima–media thickness that seems indicative of atherosclerotic involvement has not yet been determined. From other studies it may seem likely that intima–media thickness above a certain level, e.g. 1.0 mm, reflects local atherosclerosis [34, 35]. The present analysis, however, showed that, across the entire distribution, common carotid intima–media thickness is a marker for increased cardiovascular risk and death. Thus, our findings do not support the presence of a clear cut-off level above which the risk increases considerably.

The present analyses, and those in the British Heart Study, did not evaluate the contribution of carotid intima–media thickness measurements relative to other cardiovascular risk indicators as an independent long-term predictor of stroke, coronary heart disease and death. Such data require prolonged periods of follow-up in current running cohort studies; these are now required and are of the utmost importance. Currently, data are emerging based on short-term follow-up periods to indicate that, indeed, an increased carotid intima–media thickness is associated with risk of myocardial infarction and stroke, independent of other cardiovascular risk factors [11–14].

Recently, a number of national and international guidelines for practising physicians have been issued in which the start of treatment in an individual patient is related to the individual's absolute risk of future coronary heart disease and cerebrovascular disease [36, 37]. These guidelines have been triggered by observations that subjects at the highest absolute risk of future cardiovascular events benefit more from, for example, blood pressure or lipid-lowering treatment than those at low or intermediate risk [38–42]. In the context of these guidelines, we have shown that increased intima–media thickness indicates an increased cardiovascular risk and, as such, may be of use to identify high-risk patients and guide therapeutic decisions. However, the extent of the contribution of intima–media thickness measurements to the identification of high-risk subjects relative to other measurable and easily obtainable cardiovascular risk factors remains to be evaluated in future studies.

In conclusion, the results of the present analyses show that common carotid intima–media thickness and carotid plaques are markers of increased risk of stroke, coronary heart disease and death in the decade to come.

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