Carotid Atherosclerosis Is a Stronger Predictor of Myocardial Infarction in Women Than in Men

A 6-Year Follow-Up Study of 6226 Persons: The Tromsø Study

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Background and Purpose—Ultrasound of carotid arteries provides measures of intima media thickness (IMT) and plaque, both widely used as surrogate measures of cardiovascular disease. Although IMT and plaques are highly intercorrelated, the relationship between carotid plaque and IMT and cardiovascular disease has been conflicting. In this prospective, population-based study, we measured carotid IMT, total plaque area, and plaque echogenicity as predictors for first-ever myocardial infarction (MI).

Methods—IMT, total plaque area, and plaque echogenicity were measured in 6226 men and women aged 25 to 84 years with no previous MI. The subjects were followed for 6 years and incident MI was registered.

Results—During follow-up, MI occurred in 6.6% of men and 3.0% of women. The adjusted relative risk (RR; 95% CI) between the highest plaque area tertile versus no plaque was 1.56 (1.04 to 2.36) in men and 3.95 (2.16 to 7.19) in women. In women, there was a significant trend toward a higher MI risk with more echolucent plaque. The adjusted RR (95% CI) in the highest versus lowest IMT quartile was 1.73 (0.98 to 3.06) in men and 2.86 (1.07 to 7.65) in women. When we excluded bulb IMT from analyses, IMT did not predict MI in either sex.

Conclusions—In a general population, carotid plaque area was a stronger predictor of first-ever MI than was IMT. Carotid atherosclerosis was a stronger risk factor for MI in women than in men. In women, the risk of MI increased with plaque echolucency. **(*Stroke*. 2007;38:2873-2880.)**

Key Words: carotid arteries ■ echogenicity ■ epidemiology ■ myocardial infarction ■ plaque ■ sex ■ ultrasonics

Autopsy and ultrasound studies have shown a close relationship between atherosclerosis in the carotid and coronary arteries.[1,2] B-mode ultrasound of carotid arteries provides measures of intima media thickness (IMT) and the presence of plaques, both widely used as surrogate measures of cardiovascular disease. Although IMT and plaques are highly intercorrelated,[3,4] the role of IMT in the atherosclerotic process has been questioned, especially when measurements include the common carotid artery (CCA) only.[5,6] IMT has usually been measured in the CCA because high measurement precision is easily obtained from this artery. However, plaques are rare in this arterial segment. Plaques usually occur at sites of nonlaminar turbulent flow such as in the carotid bulb and the proximal internal carotid segment.[7] The pathological processes leading to intima media thickening in the distal CCA and to plaque formation may therefore not be similar, and plaque and intima media thickening may reflect different aspects of atherogenesis with distinctive relations to clinical disease.[6,8–10] Diffuse intima media thickening is associated with end-organ disease and probably reflects an adaptive hypertrophic response of mainly medial cells associated with age and hypertension, whereas plaque formation is largely a result of a pathological process in the intima.[10] Studies on the relationship between IMT and coronary heart disease have been conflicting.[11] IMT has been found to be a better predictor of stroke than of ischemic heart disease and myocardial infarction (MI).[6,9] Moreover, IMT has been found to correlate closer with left ventricular mass[12,13] than with coronary artery disease.[5,14] Arterial plaques represent a later stage of atherogenesis related to endothelial dysfunction, oxidation, inflammation, and cell proliferation.[15] Carotid plaque morphology assessed by either ultrasound or angiography is related to coronary plaque morphology and coronary morbidity.[16,17] In this large, prospective population-based ultrasound study, we studied carotid IMT and plaque (area and echogenicity) in relation to first-ever MI.

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Table 1. Risk Factor Level at Baseline (1994) Stratified by Sex (N=6226)

Risk Factor	Men (N=2989)	Women (n=3237)	*P*—Sex Difference
Age, years	59.2 (10.2)	60.6 (10.3)	<0.0001
Ultrasound measures of atherosclerosis			
Plaque present, %	52.9	43.7	<0.0001
Total plaque area, mm^2	12.5 (19.7)	7.6 (13.4)	<0.0001
GSM of total plaque mass	44 (19)	47 (23)	0.0001
IMT, mm	0.895 (0.197)	0.823 (0.173)	<0.0001
Body mass index, kg/m^2	26.0 (3.3)	25.9 (4.4)	0.5
Serum lipids, mmol/L			
High-density lipoprotein cholesterol	1.39 (0.38)	1.67 (0.42)	<0.0001
Total cholesterol	6.54 (1.17)	6.88 (1.30)	<0.0001
Triglycerides	1.73 (0.99)	1.50 (0.81)	<0.0001
Smoking			
Current smoking, %	33.6	31.4	0.06
Past smoking, %	44.1	22.7	<0.0001
Systolic blood pressure, mm Hg	140.2 (18.5)	138.9 (22.3)	0.05
Inflammatory markers			
Fibrinogen, g/L	3.33 (0.90)	3.43 (0.81)	<0.0001
Monocyte count, $\times 10^9$/L	0.63 (0.19)	0.55 (0.17)	<0.0001
White blood cell count, $\times 10^9$/L	7.09 (1.96)	6.83 (1.81)	<0.0001
Use of drugs, %			
Antihypertensive medication	12.0	12.5	0.5
Cholesterol-lowering drugs	1.4	1.5	0.6
Self-reported disease, %			
History of stroke	2.8	2.2	0.1
Diabetes mellitus	2.8	2.9	0.9

Values are age-adjusted means (SD) or percentages.

Methods

Subjects

The Tromsø Study is a population-based prospective study with repeated health surveys in the municipality of Tromsø, Norway. In 1994 to 1995, all men and women aged 55 to 74 years, and 5% to 10% samples of the remaining 5-year birth cohorts aged 25 and above, were eligible for ultrasound examination. This was done in 6727 subjects, 77% of the eligible population. The Regional Committee for Research Ethics approved the study, and informed consent for research was obtained from 6645 of the participants who were scanned with ultrasound. At the baseline examination, 412 persons had a verified MI and were excluded from the study as were 7 persons who attended the survey but were not inhabitants of Tromsø. The remaining 6226 persons were followed from the date of ultrasound examination until December 31, 2000. Mean follow-up was 5.4 years (median, 5.8 years).

Baseline Data

Information about smoking habits, prevalent diabetes mellitus, angina pectoris, previous MI, stroke, and use of antihypertensive- and lipid-lowering drugs was collected from self-administered questionnaires. Standardized measurements of height and weight were done. Specially trained personnel recorded blood pressure with an automatic device (Dinamap Vital Signs Monitor, Tampa, Fla). Nonfasting serum total cholesterol and triglycerides were analyzed by enzymatic colorimetric methods with commercial kits (CHOD-PAP for cholesterol and GPO-PAP for triglycerides; Boehringer-Mannheim). Serum high-density lipoprotein cholesterol was measured after the precipitation of lower-density lipoprotein with heparin and manganese chloride. We measured fibrinogen with the PT-Fibrinogen reagent (Instrumentation Laboratory). Monocytes and white blood cells were counted with automated cell counters by standard techniques. Total cholesterol, high-density lipoprotein cholesterol, triglycerides, and blood pressure were measured twice with an interval of 4 to 12 weeks and the average of these values was used in analyses. The Department of Clinical Chemistry, University Hospital North-Norway, Tromsø, did the blood analyses.

Definition and Ascertainment of End Points

The outcome was first nonfatal or fatal MI. Acute coronary events were categorized according to symptoms, electrocardiographic changes, and levels of cardiac biomarkers. A detailed description of the end point definitions of MI is available in the supplemental Appendix, available online at http://stroke.ahajournals.org. All participants were linked to the Population Registry of Norway to identify subjects who had died and emigrants. Causes of deaths were retrieved from the official Causes of Death Registry. To classify possible out-of-hospital fatal MIs, including sudden death, medical records, death certificates, and autopsy records were reviewed. Nonfatal events were primarily based on review of hospital records. Follow-up time was assigned from the date of screening until December 31, 2000, with date of first MI, death, or migration as censoring dates.

Ultrasonography

Details about the ultrasound methods and reproducibility have been published.[18,19] Briefly, high-resolution B-mode ultrasonography was performed with a duplex scanner (Acuson Xp10 128, ART-upgraded) equipped with a 7.5-MHz linear array transducer. The far and near walls of the right CCA, bulb, and internal carotid artery (6

Table 2. Risk of MI Events Among Persons With and Without Carotid Plaques According to Total Plaque Area

		Plaque, Tertiles of Total Plaque Area			
	No Plaque	1. Tertile	2. Tertile	3. Tertile	*P* Trend
Men					
N	1460	509	510	510	
GSM of total plaque mass, weighted mean	...	44	44	43	0.7
Echolucent plaque by visual classification (class I+II), %	...	45.9	41.9	33.9	0.0002
Person-years follow-up	7986	2728	2693	2606	
Events, n	62	28	49	59	
Event rate per 1000 person-years	7.8	10.3	18.2	22.6	<0.0001
Unadjusted RR (95% CI)	1.00	1.32 (0.85–2.07)	2.34 (1.61–3.41)	2.92 (2.04–4.17)	<0.0001
Age-adjusted RR* (95% CI)	1.00	1.11 (0.71–1.74)	1.85 (1.26–2.71)	2.06 (1.41–3.00)	<0.0001
Multivariate-adjusted RR*† (95% CI)	1.00	1.05 (0.65–1.68)	1.50 (1.00–2.25)	1.56 (1.04–2.36)	0.02
Women					
N	1798	479	479	481	
GSM of total plaque mass, weighted mean	...	50	46	45	0.0007
Echolucent plaque by visual classification (class I+II), %	...	37.9	39.6	27.6	0.001
Person-years follow-up	9979	2630	2596	2559	
Events, n	20	12	25	40	
Event rate per 1000 person-years	2.0	4.6	9.6	15.6	<0.0001
Unadjusted RR (95% CI)	1.00	2.28 (1.11–4.66)	4.81 (2.67–8.65)	7.80 (4.56–13.34)	<0.0001
Age-adjusted RR* (95% CI)	1.00	1.71 (0.83–3.51)	3.21 (1.76–5.87)	4.75 (2.71–8.33)	<0.0001
Multivariate-adjusted RR*† (95% CI)	1.00	1.53 (0.70–3.33)	2.94 (1.57–5.54)	3.95 (2.16–7.19)	<0.0001
P—sex difference					<0.0001

*Adjusted with Cox regression.

†Additionally adjusted for total cholesterol, high-density lipoprotein cholesterol, smoking, systolic blood pressure, white blood cell count, monocyte count, fibrinogen, lipid-lowering and antihypertensive medication.

Plaque area in tertiles, men: 1. tertile (≤11.7 mm^2); 2. tertile (11.8–24.6 mm^2); 3. tertile (>24.6 mm^2).

Plaque area in tertiles, women: 1. tertile (≤9.5 mm^2); 2. tertile (9.6–18.7 mm^2); 3. tertile (>18.7 mm^2).

locations) were scanned for the presence of plaques. For each plaque, a still image was recorded. Still plaque images were digitized using the Matrox Meteor II frame grabber card and Matrox Intellicam v2.07 software at a resolution of 768×576 pixels.[19] After image digitizing, the following steps were performed with the software Adobe Photoshop v7.0: plaque echogenicity was assessed by the gray scale median (GSM) using the histogram function. GSMs of the lumen and adventitia were used as reference structures. Each plaque was then outlined with the Lasso tool, and the cropped image was then standardized against lumen and adventitia using the "levels" function. The plaque areas were calculated as pixel values. For the resolution used in the present study, a plaque area of 167 pixels corresponded to 1 mm^2. In subjects with more than one plaque, the sum of plaque areas was taken as the total plaque area and GSM of the total plaque area was estimated as a weighted mean of the GSM value of each single plaque. Plaque echogenicity was also graded visually from low (1) to high (4) echogenicity.[18] Automated measurement of IMT was performed in the near and far walls of the CCA and the far wall of the bulb.[20] Measurements of IMT were performed in 10-mm segments, and mean IMT from the 3 preselected images was calculated for each location. Plaques were included in measurements of IMT. We used the average of mean IMT of the 3 locations as well as the mean IMT values of the CCA only.

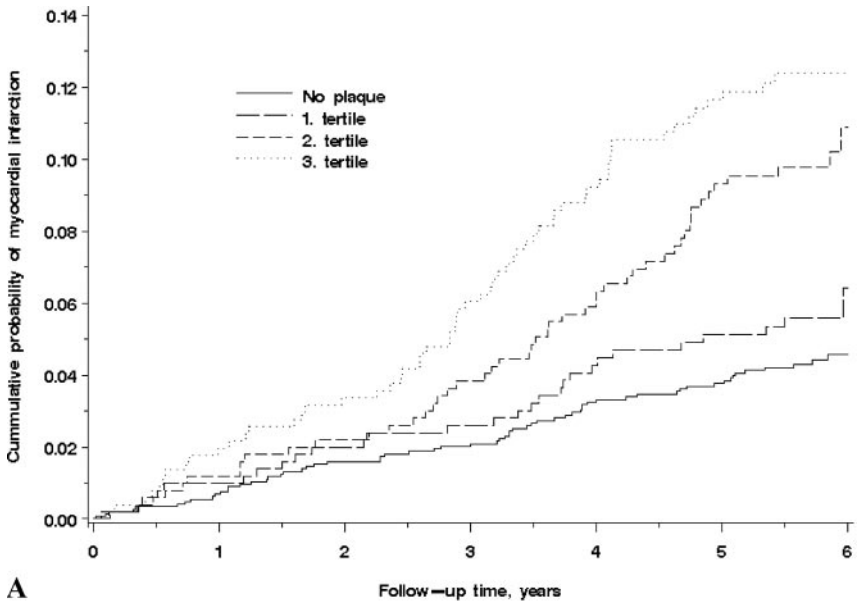
Statistical Analyses

Between-group differences were estimated by analysis of variance. Significance of trends was tested using linear regression. The risk of fatal or nonfatal MI in different plaque groups was compared by life-table analysis and Kaplan-Meier survival analysis. Cox proportional hazards regression models were used to model the outcome MI as a function of ultrasound measurements and baseline cardiovascular risk factors. The interaction between sex and plaque area, plaque echogenicity and IMT were included in the models in separate analyses. The SAS software package was used (SAS, V9). A 2-sided $P<0.05$ was considered statistically significant.

Results

IMT was measured in 2971 men and 3208 women. Plaque(s) was found in 1529 men (53%) and 1439 women (44%; Table 1). The distribution of plaques in different arterial segments was: CCA, 6% in men and 3% in women; bulb, 45% in men and 37% in women; and internal carotid artery, 18% in men and 15% in women. Men had larger total plaque area, lower plaque echogenicity, and a thicker intima media layer than women. Other baseline characteristics are shown in Table 1.

During follow-up, incident MI was registered in 198 (6.6%) men and 97 (3.0%) women. In both sexes, the MI incidence increased by increasing total plaque area (Table 2; Figure 1). The male-to-female ratio for MI was highest in persons without plaques and decreased gradually by increasing plaque area. The sex ratio was somewhat attenuated when adjusting for high-density lipoprotein cholesterol with no further attenuation when adjusting for plaque echogenicity. In men, the unadjusted RR for MI was nearly 3 times higher in the top tertile compared with those without plaques, whereas in women, this risk increased more than 7-fold (Table 2). The



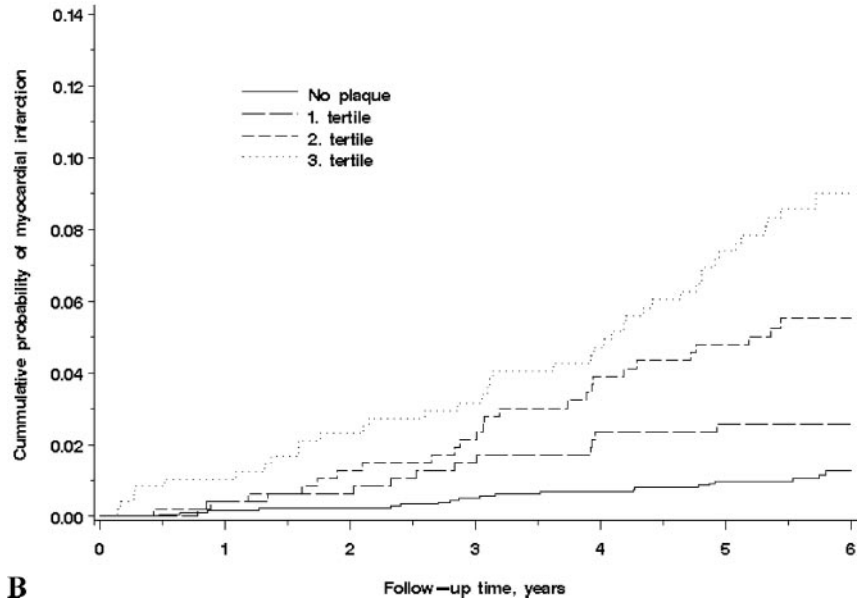


Figure 1. A, Proportion of MI in men according to total plaque area. B, Proportion of MI in women according to total plaque area.

age-adjusted RR (95% CI) was 2.06 (1.41 to 3.00) in men and 4.75 (2.71 to 8.33) in women. In multivariable models, total plaque area was still a significant predictor in both men and women (RR for highest tertile versus no plaque 1.56 [1.04 to 2.36] and 3.95 [2.16 to 7.19], respectively).

GSM of the total plaque mass was associated with plaque area in women, because larger plaques tended to be more echolucent (lower GSM). In women, but not men, there was a slightly higher risk for MI with lower GSM (more echolucent plaques; Table 3). The unadjusted RR for MI was more than 5 times higher in women in the lowest GSM tertile than in women without plaque. The risk estimates remained significant after multivariable adjustment.

In men and women, the risk of MI increased with increasing IMT (Table 4; Figure 2). The unadjusted RR for MI in men was >4 times higher in the upper IMT quartile compared with the lowest, whereas in women, this risk increased more than 9-fold. Adjustment for age weakened the RR to 2.56 (1.51 to 4.36) in men and 3.80 (1.44 to 9.99) in women. In multivariable models, IMT was still a significant predictor in women (RR for highest versus lowest quartile 2.86 [1.07 to 7.65]) and borderline significant in men (RR for highest versus lowest quartile 1.73 [0.98 to 3.06]). In age-adjusted analyses restricted to the CCA–IMT only, CCA–IMT was a significant predictor of MI in men (RR for highest versus lowest quartile 2.88 [1.64 to 5.06]) but not in women (RR 2.05 [0.91 to 4.59]). In fully adjusted models, CCA–IMT did not predict MI either in men or women (P for trend 0.1 and 0.2, respectively).

To study whether sex was an effect modifier in the association between carotid atherosclerosis and MI, the possible interactions between sex and our markers of carotid atherosclerosis (plaque area, plaque echogenicity, and IMT) were tested in full Cox models. Both for plaque area and plaque echogenicity, the interaction term was significant in the sex- and age-adjusted model ($P=0.002$) as well as in the

Table 3. Risk of MI Events Among Persons With and Without Carotid Plaques According to Plaque Echogenicity

		Plaque, Tertiles of GSM			
	No Plaque	3. Tertile	2. Tertile	1. Tertile	*P* Trend
Men					
N	1460	515	510	504	
Echolucent plaque by visual classification (class I+II), %	...	8.1	38.2	75.5	
Person-years follow-up	7986	2652	2652	2726	
Events, n	62	46	53	37	
Event rate per 1000 person-years	7.8	17.4	20.0	13.6	<0.0001
Unadjusted RR (95% CI)	1.00	2.23 (1.53–3.27)	2.57 (1.78–3.71)	1.75 (1.16–2.63)	<0.0001
Age-adjusted RR* (95% CI)	1.00	1.68 (1.14–2.49)	1.92 (1.31–2.81)	1.39 (0.92–2.11)	<0.0001
Age-adjusted RR*† (95% CI)	1.00	1.38 (0.87–2.02)	1.47 (0.97–2.23)	1.10 (0.71–1.72)	0.1
Multivariate-adjusted RR*‡ (95% CI)	1.00	1.17 (0.74–1.83)	1.29 (0.83–2.01)	1.08 (0.68–1.70)	0.7
Women					
N	1798	472	487	480	
Echolucent plaque by visual classification (class I+II), %	...	7.4	31.2	67.1	
Person-years follow-up	9979	2549	2654	2582	
Events, n	20	20	29	28	
Event rate per 1000 person-years	2.0	7.8	10.9	10.8	<0.0001
Unadjusted RR (95% CI)	1.00	3.92 (2.11–7.28)	5.45 (3.08–9.64)	5.41 (3.05–9.60)	<0.0001
Age-adjusted RR* (95% CI)	1.00	2.49 (1.32–4.70)	3.44 (1.92–6.17)	3.69 (2.06–6.61)	<0.0001
Age-adjusted RR*† (95% CI)	1.00	1.87 (0.95–3.70)	2.51 (1.32–4.77)	2.87 (1.54–5.32)	0.0001
Multivariate-adjusted RR*‡ (95% CI)	1.00	1.89 (0.93–3.84)	1.95 (0.98–3.88)	2.79 (1.45–5.37)	0.003
P—sex difference					<0.0001

*Adjusted with Cox regression.

†Additionally adjusted for total plaque area.

‡Additionally adjusted for total cholesterol, high-density lipoprotein cholesterol, smoking, systolic blood pressure, white blood cell count, monocyte count, fibrinogen, lipid-lowering and antihypertensive medication.

GSM in tertiles, men: 1. tertile (<35); 2. tertile (35–49); 3. tertile (>49).

GSM in tertiles, women: 1. tertile (<36); 2. tertile (36–51); 3. tertile (>51).

fully adjusted model ($P=0.01$). The interaction term for IMT was not statistically significant ($P=0.1$, $P=0.4$).

Discussion

The extent of atherosclerosis in the carotid artery, measured either as thickening of the intima media layer or as total plaque area, predicted independently first-ever MI in our study. This confirms previous findings.[10,21,22] However, the association between IMT and MI was weaker, especially in women, than between total plaque area and MI. When the analyses were confined to CCA–IMT, no independent relationship between IMT and MI could be demonstrated in either sex. It has been suggested that measurement of IMT at the CCA alone is a reasonable alternative to more detailed and technically difficult measurements at other arterial sites. Reported findings have demonstrated inconsistent association among IMT, risk factors, and clinical disease depending on which arterial segments are measured.[5,8,11] In cross-sectional studies, CCA–IMT was reported to be strongly associated with risk factors for stroke and with prevalent stroke, whereas IMT measured in the carotid bulb and plaque presence was associated with cardiovascular risk factors and prevalent ischemic heart disease.[6] In our study, the adjusted risk estimates for plaque area and IMT were very similar in men. In contrast, plaque area was a stronger predictor than IMT in women. When analyses were restricted to the CCA–IMT only, the trend was weakened and no longer reached significance either in men or women. This is in line with previous findings[6] and probably reflects the differences in the pathological processes leading to intima media thickening of the distal part of CCA and plaque formation in the coronary arteries, whereas plaque formation in the carotid and coronary arteries are more closely related.[23]

Coronary and carotid plaques are thought to have similar atherogenesis.[24] In a study of asymptomatic hypercholesterolemic patients, carotid plaque demonstrated by B-mode ultrasound significantly improved the diagnostic specificity of exercise electrocardiography in predicting atherosclerotic lesions by coronary angiography.[25] May plaque morphology assessed in one arterial territory reflect the individual's plaque morphology in other arterial territories due to a common underlying systemic factor? This possibility has been suggested earlier.[16,17,26,27] A common inflammatory link for plaque activation in carotid and coronary plaques has been proposed based on high C-reactive protein levels in patients with coronary artery disease and echolucent carotid plaques.[17,28] In women, we observed a trend toward a higher risk of MI with more echolucent plaque, even after adjusting

Table 4. Risk of MI Events in Men and Women According to IMT

	1. Quartile	2. Quartile	3. Quartile	4. Quartile	*P* Trend
Men					
N	742	743	744	742	
Person-years follow-up	4118	4027	3891	3888	
Events, n	20	36	61	80	
Event rate per 1000 person-years	4.9	8.9	15.7	20.6	<0.0001
Unadjusted RR (95% CI)	1.00	1.84 (1.07–3.18)	3.23 (1.95–5.35)	4.24 (2.60–6.92)	<0.0001
Age-adjusted RR* (95% CI)	1.00	1.37 (0.79–2.38)	2.13 (1.26–3.62)	2.56 (1.51–4.36)	<0.0001
Multivariate-adjusted RR*† (95% CI)	1.00	1.20 (0.67–2.14)	1.60 (0.91–2.81)	1.73 (0.98–3.06)	0.03
Women					
N	801	803	802	802	
Person-years follow-up	4414	4457	4355	4387	
Events, n	5	14	33	45	
Event rate per 1000 person-years	1.1	3.1	7.6	10.3	0.0005
Unadjusted RR (95% CI)	1.00	2.77 (1.00–7.70)	6.69 (2.61–17.14)	9.06 (3.60–22.81)	<0.0001
Age-adjusted RR* (95% CI)	1.00	1.78 (0.63–4.97)	3.53 (1.35–9.23)	3.80 (1.44–9.99)	0.002
Multivariate-adjusted RR*† (95% CI)	1.00	1.52 (0.53–4.36)	2.97 (1.13–7.84)	2.86 (1.07–7.65)	0.02
P—sex difference					<0.0001

*Adjusted with Cox regression.

†Additionally adjusted for total cholesterol, high-density lipoprotein cholesterol, smoking, systolic blood pressure, white blood cell count, monocyte count, fibrinogen, lipid-lowering and antihypertensive medication.

Eighteen men had missing values for IMT in whom one person had MI. Twenty-nine women had missing values for IMT in whom none had MI.

IMT in quartiles, men: 1. quartile (0.358–0.751 mm); 2. quartile (0.752–0.859 mm); 3. quartile (0.860–0.995 mm); 4. quartile (0.996–2.090 mm).

IMT in quartiles, women: 1. quartile (0.390–0.706 mm); 2. quartile (0.707–0.804 mm); 3. quartile (0.805–0.925 mm); 4. quartile (0.926–1.786 mm).

for plaque area. No clear relationship between plaque echogenicity and risk of MI was seen in men. This is in contrast to clinical studies demonstrating that echolucent or unstable carotid plaques predicted coronary plaque complexity and the development of future coronary complications in patients with stable coronary artery disease.[17,27] The natural history of an atherosclerotic plaque seems to be that it becomes more fibrous (echogenic) over time.[29] Plaque occurrence in carotid and coronary arteries is highly correlated; however, plaques apparently develop later in life in the carotids than in the aorta and coronary arteries.[30] Therefore, at one point in time, the stage of plaque development in the 2 arterial territories may differ. In our cohort, men and women were of the same age. Men develop atherosclerosis earlier than women and we can therefore assume that the men in this study have more longlasting and fibrous atherosclerosis than women. This might have influenced the plaque stability and the risk for plaque rupture and clinical events in men. Moreover, studies that reported a relationship between carotid and coronary plaque echogenicity were often based on selected patient groups with clinical coronary artery disease, reflecting more advanced atherosclerosis than would be expected in a general population.

Sex-related differences are becoming increasingly recognized as potentially important factors in atherosclerosis.[31] Whereas the prevalence of angina pectoris is similar among men and women, men have a higher incidence of MI and myocardial death than women at any age.[32] This divergence in sex ratios between angina pectoris and MI remains unexplained. For both IMT and plaque area, the RR estimates in our study were stronger in women than in men, although men had more atherosclerosis and MI. When carotid atherosclerosis was present, women seemed to carry a higher risk of future MI than men. This is probably due to the fact that women with little atherosclerosis have a very low risk for MI as compared with men. A previous study found a stronger association between carotid plaque area and the combined outcome of stroke, MI, and vascular death in women than in men.[33] A similar finding was also reported in the ARIC study.[21] As demonstrated in Table 2, the male-to-female ratio for MI was highest in the no-plaque group and lowest tertile and thereafter decreased. In these subjects, other factors than the burden of atherosclerosis may explain the sex difference in MI such as sex differences in plaque properties and interaction among plaque content, platelet activation, and the coagulation system. Previous studies reported higher relative risk ratios for daily smoking and low high-density lipoprotein levels in women than in men.[21,34] In this study, the RR estimate for current versus never smoking were 2.7 (1.8 to 4.0) for women and 1.8 (1.4 to 2.4) for men ($P<0.0001$). For high-density lipoprotein cholesterol <0.9 mmol/L, the corresponding risk estimates were 0.7 (0.1 to 4.8) and 2.2 (1.4 to 3.4).

Strengths of this study are the prospective design, the long follow-up time, few dropouts, and a high quality of the end point registration. A strict definition of MI was used and the end points were verified by meticulous study of hospital records and death certificates by physicians. Both plaque size (area) and echogenicity were measured as continuous variables, and measurement of plaque area provides an accurate

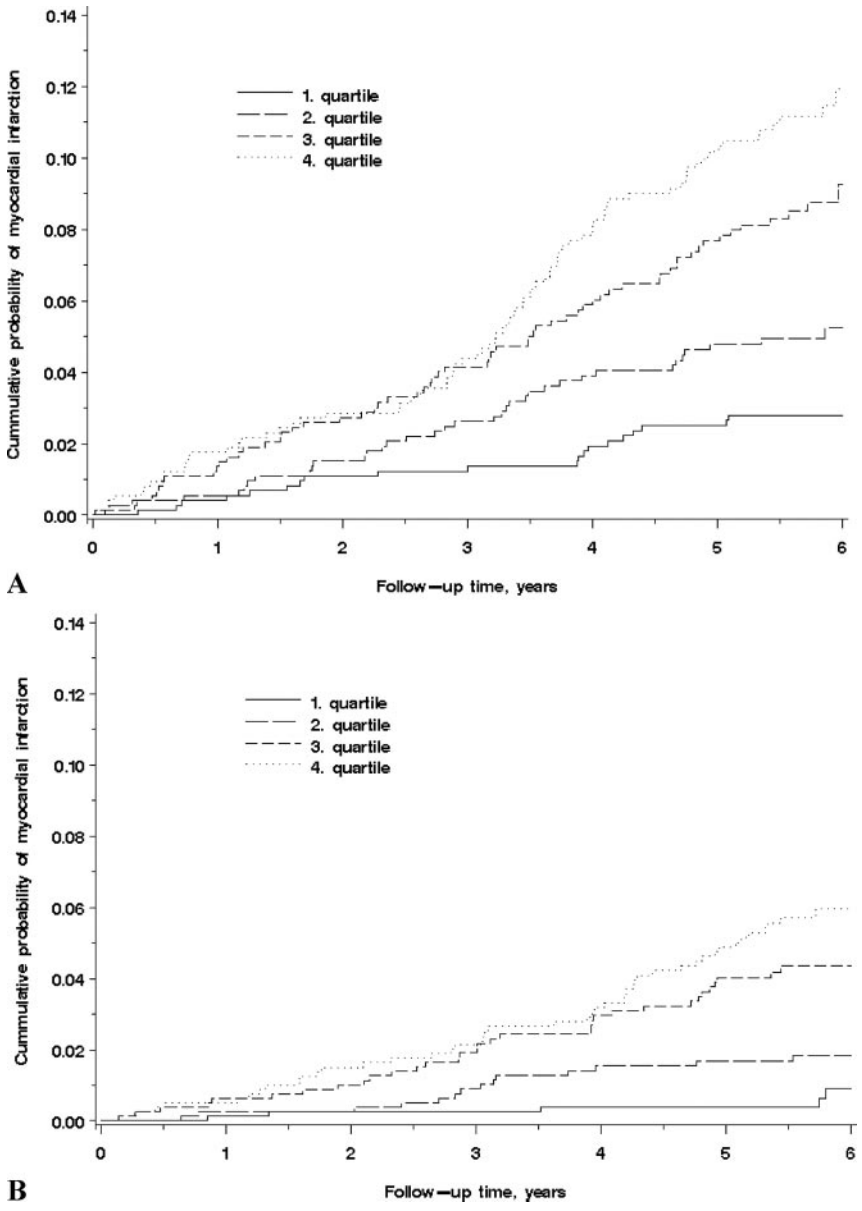


Figure 2. A, Proportion of MI in men according to IMT. B, Proportion of MI in women according to IMT.

and comprehensive measure of atherosclerosis.[10,35] Plaque area may be a more representative measure of the atherosclerotic burden than plaque thickness or IMT because much of the plaque growth occurs longitudinally along the vessel wall.[36] A potential shortcoming of this study is that only one carotid artery was studied. Inclusion of the left carotid and the femoral arteries might have given a better description of the individual plaque burden. The numbers of events are relatively low, especially in women (altogether 97 events in women, plaque features measured in only 44% of them), and the results should therefore be interpreted with some caution.

We conclude that in a general population, carotid plaque area and IMT independently predict the risk of first ever MI. IMT analyses of the CCA only did not predict MI. In women with the most advanced carotid atherosclerosis, the risk of MI compared with those without plaque was more than twice the corresponding risk in men. In women, there was a significant trend toward a higher risk of MI with increasing plaque echolucency. Demonstration of carotid plaques provides important additional information about future risk of coronary events, at least in women.

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Disclosures

None.

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