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Prognostic implications of intima-media thickness and plaques in the carotid and femoral arteries in patients with stable angina pectoris

C. Held[1], P. Hjemdahl[2], S. V. Eriksson[1], I. Björkander[1], L. Forslund[3] and N. Rehnqvist[4]

[1]*Department of Medicine, Danderyd Hospital,* [2]*Departments of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Hospital,* [3]*Department of Medicine, Trelleborg Hospital, Trelleborg and* [4]*National Board of Health and Welfare, Stockholm, Sweden*

Background Ultrasonographic assessments of intima-media thickness and plaques in the carotid artery are widely used as surrogate markers for coronary atherosclerosis, but prospective evaluations are scarce and appear to be lacking in patients with coronary artery disease. Ultrasonographic evaluations of femoral vascular changes have not been studied prospectively.

Methods and Results In the Angina Prognosis Study in Stockholm (APSIS), 809 patients with stable angina pectoris were studied prospectively during double-blind treatment with verapamil or metoprolol. Ultrasonographic assessments of intima-media thickness, lumen diameter and plaques in the carotid and femoral arteries were evaluated in a subgroup of 558 patients (182 females) with a mean age of 60 ± 7 years, and related to the risk of cardiovascular death (n=18) or non-fatal myocardial infarction (n=26), or revascularization (n=70) during follow-up (median 3·0 years). Univariate Cox regression analyses showed that carotid intima-media thickness and plaques were related to the risk of cardiovascular death or myocardial infarction. Femoral intima-media thickness was related to cardiovascular death or myocardial infarction, as well as to revascularization, whereas femoral plaques were only related to the latter. After adjustment for age, sex, smoking, previous cardiovascular disease and lipid status, carotid intima-media thickness failed to predict any cardiovascular event, whereas carotid plaques tended ($P=0{\cdot}056$) to predict the risk of cardiovascular death or myocardial infarction. Femoral intima-media thickness ($P<0{\cdot}01$) and plaques ($P<0{\cdot}05$) were also related to the risk of revascularization after adjustments.

Conclusions Carotid and femoral vascular changes were differently related to cardiovascular events. Carotid intima-media thickness was a weak predictor of events, whereas femoral intima-media thickness predicted revascularization. Plaques in the carotid artery were related to cardiovascular death or non-fatal myocardial infarction, whereas plaques in the femoral artery were related to revascularization. Evaluations of plaques provided better prediction than assessments of intima-media thickness in patients with stable angina.

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Key Words: Ultrasound, carotid artery, femoral artery, intima-media thickness, plaques, atherosclerosis, angina pectoris, prognosis, risk factor.

See page 11 for the Editorial comment on this article

Introduction

Ultrasonographic assessment of peripheral arteries has evolved as a promising technique for non-invasive evaluation of atherosclerosis. Intima-media thickness of the carotid artery has been shown to be related to coronary risk factors in epidemiological and cross-sectional studies[1–4], and has even been used as the primary effect variable for the evaluation of progression/regression of atherosclerosis during lipid-lowering[5–7] or

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Correspondence: Claes Held, MD, PhD, Karolinska Institute, Department of Medicine, Danderyd Hospital, S-182 88 Danderyd, Sweden.

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antihypertensive[8] treatment. Relationships between intima-media thickness of peripheral arteries and coronary artery disease manifestations are, however, not well studied. In autopsy studies, a close relationship between carotid and coronary atherosclerosis has been reported, whereas a weaker relationship was found for femoral atherosclerosis[9,10]. Results regarding correlations between carotid intima-media thickness and the severity of coronary artery disease on coronary angiograms[11–14] have been conflicting.

Whether or not ultrasonographic changes in peripheral arteries are good surrogate markers for cardiovascular risk is not well established. One study in healthy men showed that carotid intima-media thickening tended to be related to increased risk of acute myocardial infarction, and that the presence of carotid plaques was significantly related to such events[15]. Semiquantitative assessments of carotid atherosclerosis[16] or intima-media thickness measurements[17] by ultrasound, have been found to be related to the risk of subsequent cardiovascular events in asymptomatic individuals, and to the risk of ischaemic stroke in patients with various manifestations of atherosclerosis[18]. However, there are few data regarding the prognostic importance of intima-media thickness or the occurrence of plaques in the carotid and/or femoral arteries in patients with coronary artery disease. Increased large artery lumen diameters may be a compensatory response in early stages of atherosclerosis, based on patho-anatomical studies[19,20], and ultrasonographic assessments[21,22]. Whether carotid or femoral lumen diameters have prognostic implications is, however, not known. Taken together, there is a need for information regarding the prognostic implications of ultrasonographic findings in patients with coronary artery disease.

The Angina Prognosis Study in Stockholm (APSIS) evaluated the long-term effects of verapamil and metoprolol on cardiovascular prognosis in patients with stable angina pectoris[23]. The aim of the present APSIS substudy was to evaluate how baseline ultrasonographic measurements of intima-media thickness, lumen diameter and/or plaques in the carotid and femoral arteries relate to cardiovascular end-points in patients with stable angina pectoris. In addition, we examined the relationships between vessel wall changes and the presence of clinical coronary risk indicators.

Methods

Subjects

A total of 809 patients (248 women) less than 70 years of age, with a typical history of angina pectoris (effort induced, angina at rest or mixed angina), were included in the APSIS study. The present substudy concerns baseline assessments of the carotid artery in 540 patients (179 females), and of the femoral artery in 536 patients (182 females). The diagnosis of angina pectoris was clinical. When indicated, thorough examinations were performed in order to exclude non-cardiac causes of chest pain[23]. Exclusion criteria were: previous myocardial infarction within 3 years, unstable angina or severe angina with an anticipated need for revascularization within 1 month, coronary artery by-pass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the last year, heart failure despite treatment, systolic blood pressure below 100 mmHg, obstructive pulmonary disease, significant valvular disease or obvious risks for poor compliance. Baseline findings in these patients have been described in detail previously[23,24].

Treatment regimen

The patients were randomized to double-blind treatment with slow-release formulations of either metoprolol (Seloken ZOC; target dose 200 mg once daily) or verapamil (Isoptin SR; target dose 240 mg twice daily). If tolerated, the dosage was increased after 2 weeks on half of the target dose. About half of the patients were on full dose in both treatment groups at the end of the study; the remainder were on half dose. Patients previously treated with beta-blockers or calcium antagonists were switched to minimal doses of either study drug (25–50 mg . day^{-1} of metoprolol or 80 mg . day^{-1} of verapamil, depending on the type of drug used) during a 2-week run-in period. Treatment with long-acting nitrates, acetylsalicylic acid, ACE inhibitors and lipid-lowering drugs was allowed. The use of lipid-lowering drugs and aspirin at baseline was 6% and 39%, respectively.

Ultrasonographic examinations

Ultrasonographic examinations were performed with an Acuson 128 (Mountain View, CA, U.S.A.), equipped with 5 or 7 MHz transducers, with subjects in the supine position. An ECG signal synchronized the image analysis to the end of diastole. The left carotid and femoral arteries were examined. The carotid artery was scanned at the level of the bifurcation with the head turned to the right. The examined region included 30 mm of the common carotid artery, the carotid bulb, and 10 mm each of the internal and external carotid arteries. The femoral artery was examined distally to the inguinal ligament at the bifurcation into the superficial and profound femoral arteries. The area scanned was approximately 30 mm proximal and 10 mm distal to the femoral bifurcation.

The regions were scanned with both longitudinal and transverse projections, in order to assess the occurrence of plaques. Three B-mode images from the longitudinal view, as well as a short sequence of real-time images, were recorded on videotape. Doppler ultrasound was used for information on blood flow velocity and for

vessel identification. Three 'frozen' images were recorded for assessments of intima-media thickness and lumen diameter. Optimal image projection was considered to be achieved when ultrasound beams were perpendicular to the far vessel wall.

All ultrasonographic examinations were performed by two specially trained technicians. In order to standardize the reading procedure of the video-recordings, one technician analysed all examinations of the carotid artery, and the other of the femoral artery. Intra-observer variability was less than 10%.

Assessments of intima-media thickness and lumen diameter

The ultrasonographic images were analysed with a computerized system[25], and blind evaluation was made in terms of treatment. Intima-media thickness was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall. Intima-media thickness was measured in a 10-mm long segment just proximal to the carotid bulb in the common carotid artery and in a 15-mm long segment just proximal to the bifurcation in the femoral artery. The computer program calculated the minimum, maximum and mean values of intima-media thickness from three separate images. Lumen diameter was defined as the distance between the leading edges of the intima-lumen interface of the near wall and the lumen-intima interface of the far wall.

Assessments of plaques

Plaques in the carotid and femoral artery were classified according to a four-graded semi-quantitative scale of the size/severity of plaques. A plaque was defined as a distinct area with an intima-media thickness exceeding twice that of neighbouring sites. The scale was defined as follows: grade 0: no plaque; grade 1: small localized plaque/wall thickening; grade 2: moderate plaque with $<50\%$ lumen diameter stenosis; grade 3: circumferential and/or large plaque with $\geq 50\%$ lumen diameter stenosis. Plaques were registered in the distal part of the common carotid artery, the carotid bulb or in the proximal parts of the internal or external carotid artery. Plaques in the femoral artery were registered if found in the 15 mm section proximal to the bifurcation, in the bifurcation area or in the proximal parts of the superficial and profound femoral arteries.

Follow-up and definitions of end-points

All examinations were performed at baseline. The median follow-up time was 3·0 years, comprising a total of 1679 patient years on an intention-to-treat basis. No patient was lost to follow-up. The primary end-points for follow-up of the APSIS study were death and cardiovascular events, defined as: acute myocardial infarction, incapacitating or unstable angina, cerebrovascular events (including transitory ischaemic events) or peripheral vascular events (threatening or overt gangrene, or surgery for aortic aneurysm). The criteria for myocardial infarction were a typical clinical presentation, a significant rise in cardiac enzymes and/or development of Q waves on the ECG, with or without hospitalization. Incapacitating angina was defined as symptoms which were insufficiently relieved by the study medication, complemented with long-acting nitrates, and severe enough to compromise ordinary life and indicate a revascularization procedure when needed.

Statistical analysis

Continuous variables in different groups were compared by independent two-tailed t-tests. Coefficients of skewness and kurtosis were used to test deviations from a normal distribution. Non-normally distributed variables were logarithmically transformed prior to statistical analysis. Relationships between continuous variables were tested by calculation of Pearson correlation coefficients. Categorical data were compared by chi-squared analyses. In addition, descriptive statistics and graphical methods were employed to characterize the data. Analyses were carried out using Statistica™, version 5.1 (StatSoft, Tulsa, OK, U.S.A.). A P-value $<0{\cdot}05$ was considered significant. Means and standard deviations are given, unless otherwise stated.

Associations between ultrasonographic variables and coronary events were first tested by univariate Cox regression analyses. Follow-up times until various cardiovascular events or the end of the study were used. In analyses of cardiovascular death or non-fatal myocardial infarction, patients were censored at the actual dates of revascularization, since the proportional risk changes considerably with such a procedure. Patients who died of cancer were excluded from the analyses. In a second step, ultrasonographic variables that showed some relationship to coronary events ($P<0{\cdot}1$) were further evaluated with adjustments for factors known (and verified in the present database) to influence prognosis. These factors were: age, sex, a history of previous myocardial infarction, diabetes mellitus, hypertension, smoking habits and lipid status (apolipoprotein A-I for cardiovascular death or myocardial infarction and apolipoprotein B for revascularization, as these were the strongest independent predictors, respectively, among the lipid variables[26]).

Results

Baseline characteristics

The mean age of the patients in this substudy was 60 ± 7 years and 67% were males. Hypertension was present in

Table 1 Deaths and non-fatal cardiovascular events in subgroup with ultrasonographic data

	Carotis	Femoralis
Deaths	23	24
Cardiovascular		
SD	6	6
Acute MI	10	10
Vascular	2	2
Malignancy	5	6
Non-fatal cardiovascular events	137	146
Acute MI	26	26
CABG	54	55
PTCA	14	15
Angiography, no revascularization	25	28
Unstable angina	5	8
Cerebrovascular disease	11	12
Peripheral vascular disease	2	2

SD=sudden death within 2 h; vascular death=pulmonary embolus, cerebrovascular death; MI=myocardial infarction; CABG=coronary artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty.

27%, a history of previous myocardial infarction in 14%, diabetes mellitus in 8%, a previous CABG or PTCA in 6% and intermittent claudication in 4%. Six percent were treated for congestive heart failure, 44% were ex-smokers and 21% were active smokers.

Follow-up

During follow-up, 18 patients suffered a cardiovascular death. The number of non-fatal cardiovascular events differed little among patients in whom data from the carotid and femoral arteries were obtained (Table 1), due to inadequate visualization in some cases. The present analyses focus specifically on the risk of suffering cardiovascular death or myocardial infarction or revascularization in comparison to event-free patients. Analyses regarding other cardiovascular events were not performed.

Influence of age, height and gender

Male and female patients differed with regard to intima-media thickness and lumen diameter in both the carotid and femoral artery (Table 2). The obvious differences in height and weight between genders ($P<0{\cdot}001$) might explain these findings, but most differences remained after adjustment for height (Table 2). Plaques were more common among males compared to females in both the carotid and femoral arteries. Age was correlated to maximal intima-media thickness (r=0·33; $P<0{\cdot}001$) and mean lumen diameter (r=0·21; $P<0{\cdot}001$) of the carotid artery, as well as to the maximal intima-media thickness (r=0·23; $P<0{\cdot}001$) and mean lumen diameter (r=0·12; $P<0{\cdot}01$) of the femoral artery. Height was correlated to mean lumen diameter (r=0·40; $P<0{\cdot}001$) but not to maximal intima-media thickness (r=0·07; $P=0{\cdot}13$) of the carotid artery, and to the maximal intima-media thickness (r=0·16; $P<0{\cdot}001$) and mean lumen diameter (r=0·49; $P<0{\cdot}001$) of the femoral artery. Similar correlations were found for mean intima-media thicknesses (data not shown).

Table 2 Intima-media thickness, lumen diameter and plaques in the carotid and femoral arteries in male and female patients

Variables	Males	Females
Carotid artery	n=361	n=179
Intima-media thickness		
Maximal, mm	0·98 ± 0·33	0·89 ± 0·34***
Mean, mm	0·78 ± 0·26	0·71 ± 0·29***
Mean (height adjusted), mm . m^{-1}	0·44 ± 0·15	0·43 ± 0·18
Lumen diameter		
Mean, mm	6·72 ± 0·84	5·84 ± 0·64***
Mean (height adjusted), mm . m^{-1}	3·81 ± 0·48	3·56 ± 0·40***
Plaque occurrence, %	41·7	24·6**
Femoral artery	n=362	n=174
Intima-media thickness		
Maximal, mm	1·61 ± 0·79	1·22 ± 0·69***
Mean, mm	1·20 ± 0·61	0·88 ± 0·50***
Mean (height adjusted), mm . m^{-1}	0·68 ± 0·34	0·54 ± 0·31***
Lumen diameter		
Mean, mm	10·19 ± 1·41	8·74 ± 1·14***
Mean (height adjusted), mm . m^{-1}	5·77 ± 0·77	5·32 ± 0·18***
Plaque occurrence, %	56·4	27·9***

Values are means ± standard deviation. **$P<0{\cdot}01$; ***$P<0{\cdot}001$.

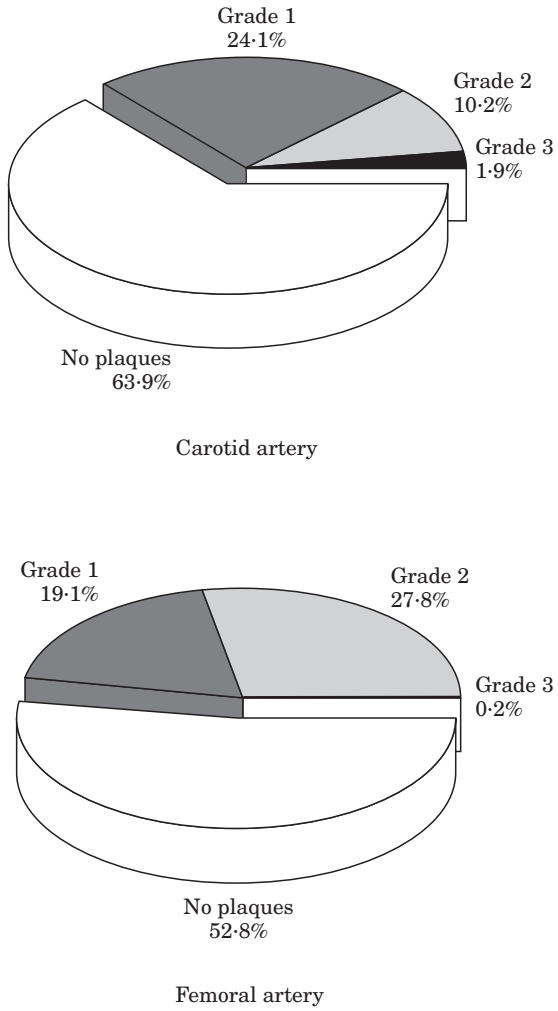

Figure 1 **Occurrence of plaques (percent) grades 0–3 in the carotid and femoral artery, respectively.**

Plaque occurrence

Among the 540 patients who underwent carotid artery examinations, 345 patients had no plaques, 130 had grade 1 plaques, 55 grade 2 plaques and 10 grade 3 plaques (Fig. 1). Plaques were located entirely or partly in the common carotid artery and bifurcation area in 95% of the patients. Eight patients were excluded from assessments of plaques in the femoral artery. Thus, 279 of the 528 evaluable patients had no plaques, 101 had grade 1 plaques, 147 grade 2 plaques and only one had grade 3 plaques (Fig. 1). Of these, 60% were located proximal to the bifurcation site. The presence of plaques in the carotid artery was weakly associated with plaques in the femoral artery; plaques were found only in the carotid artery in 68 patients and only in the femoral artery in 127 patients, whereas 208 patients (39·5%) had no plaque in either the carotid or the femoral artery.

Influence of clinical risk indicators

Patients with histories of previous cardiovascular disease were compared with those without, and smokers were compared to non-smokers (Table 3). These analyses were restricted to male patients in order to avoid confounding by gender related differences (see above). Hypertensives had a greater mean carotid artery lumen diameter ($P<0·05$) and intima-media thickness ($P<0·05$), and greater lumen diameter of the femoral artery ($P<0·05$), than patients without hypertension. Smokers had greater intima-media thickness of both the carotid ($P<0·05$) and femoral ($P<0·001$) artery, and greater mean lumen diameter ($P<0·001$) in the carotid artery, than non-smokers. They more often had plaques in the carotid ($P<0·05$) and femoral ($P<0·001$) arteries than non-smokers. Patients with a previous myocardial infarction had a greater mean lumen of the carotid artery ($P<0·01$) and more often plaques in the femoral artery than patients without a previous myocardial infarction. Among diabetics, however, no increases were observed for lumen diameter or intima-media thickness of the carotid artery. They had a thinner femoral intima-media thickness than non-diabetics, but no other differences.

Intima-media thickness and lumen diameters in patients with different outcomes

Patients suffering cardiovascular death or myocardial infarction had greater maximal and mean intima-media thickness of the carotid ($P<0·05$) and femoral ($P<0·01$) artery than event-free patients (Table 4). In addition, their lumen diameters were greater in both the carotid ($P<0·001$) and femoral ($P<0·01$) arteries, compared with event-free patients. Patients who subsequently underwent CABG or PTCA had greater maximal and mean intima-media thickness of the femoral artery ($P<0·001$), but not of the carotid artery, and a greater mean lumen diameter of the carotid artery ($P<0·05$), but not of the femoral artery than event-free patients.

Prognostic evaluation of intima-media thickness and lumen diameter

Univariate analyses

Cox proportional hazards regression analyses showed a significant relationship between maximal carotid intima-media thickness, as a continuous variable, and cardiovascular death or myocardial infarction ($P<0·01$), but not to the risk of revascularization. However, the increase in risk with increasing intima-media thickness was relatively small and not significant when divided into tertiles (Table 5). Kaplan–Meier curves are shown for intima-media thickness, separated into tertiles (Fig. 2). Femoral maximal intima-media thickness was more clearly related to the risk of cardiovascular death or

Table 3 Intima-media thickness, lumen diameter and presence of plaques in the carotid and femoral artery in relation to previous history of cardiovascular disease and smoking habits in male patients

Variables	Carotid artery			Femoral artery		
	Lumen mean diameter (mm)	IMT mean thickness (mm)	Plaques, %	Lumen mean diameter (mm)	IMT mean thickness (mm)	Plaques, %
Hypertension (+)	6·57 ± 0·93*	0·81 ± 0·26*	45·1	9·94 ± 1·57*	1·25 ± 0·65	59·4
Hypertension (−)	6·37 ± 0·86	0·75 ± 0·25	40·4	9·64 ± 1·46	1·18 ± 0·60	55·3
Previous MI (+)	6·71 ± 0·93**	0·72 ± 0·21	43·1	9·70 ± 1·65	1·24 ± 0·56	71·0**
Previous MI (−)	6·38 ± 0·86	0·78 ± 0·26	41·7	9·71 ± 1·47	1·19 ± 0·62	53·9
Previous DM (+)	6·66 ± 0·83	0·84 ± 0·37	51·5	9·61 ± 1·06	1·01 ± 0·55*	56·3
Previous DM (−)	6·41 ± 0·88	0·76 ± 0·24	40·7	9·73 ± 1·53	1·22 ± 0·62	56·4
Smoker	6·66 ± 0·98***	0·83 ± 0·28*	50·5*	9·79 ± 1·72	1·34 ± 0·63***	71·1***
Non-smoker	6·20 ± 0·75	0·74 ± 0·27	39·4	9·59 ± 1·42	1·03 ± 0·53	39·3

Values are means ± standard deviation.
*P<0·05; **P<0·01; ***P<0·001 denotes differences between groups with presence or absence of disease, or smoking habits.
MI=myocardial infarction; DM=diabetes mellitus; IMT=intima-media thickness.

Table 4 Intima-media thickness and lumen diameter in the carotid and femoral arteries in patients with and without cardiovascular events

Variables	Event-free	CV death or MI	CABG or PTCA
Carotid artery	n=380	n=44	n=68
Intima-media thickness, mm			
Maximal	0·93 ± 0·32	1·07 ± 0·52*	0·95 ± 0·26
Mean	0·74 ± 0·26	0·84 ± 0·40*	0·75 ± 0·22
Lumen diameter, mm			
Mean	6·35 ± 0·85	6·85 ± 0·77***	6·62 ± 0·84†
Femoral artery	n=375	n=42	n=70
Intima-media thickness, mm			
Maximal	1·37 ± 0·76	1·69 ± 0·72**	1·76 ± 0·80†††
Mean	1·01 ± 0·58	1·27 ± 0·56**	1·31 ± 0·59†††
Lumen diameter, mm			
Mean	9·70 ± 1·46	10·35 ± 1·56**	9·71 ± 1·30

Values are means ± SD.
CV=cardiovascular; MI=myocardial infarction; CABG=coronary artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty.
*P<0·05; **P<0·01; ***P<0·001 for CV death or non-fatal MI vs event-free patients.
†P<0·05; ††P<0·01; †††P<0·01 for CABG or PTCA vs event-free patients.

myocardial infarction (P<0·05) and to the risk of revascularization (P<0·001) (Fig. 3). Mean carotid lumen diameter (P<0·01) and femoral lumen diameters (P<0·05) were significantly related to the risk of cardiovascular death or myocardial infarction, but not to the risk of revascularization.

Adjusted analyses

The importance of intima-media thickness and lumen diameter of the carotid and femoral arteries for cardiovascular outcome was also evaluated with a Cox proportional hazards regression model after adjustment for known risk factors, i.e. a history of previous myocardial infarction, hypertension, diabetes mellitus, smoking habits and lipid status (apolipoprotein A-I or B). As ex-smokers had the best prognosis, followed by non-smokers, we combined these versus current smokers in the adjustment for smoking habits. Age and sex were also included in the model as they were significantly related to both intima-media thickness and lumen diameter.

The influence of the carotid and femoral artery intima-media thickness on the risk of cardiovascular death or myocardial infarction, or revascularization, are shown in Table 5. After adjustment for all above factors, intima-media thickness of the carotid or femoral artery was not related to the risk of cardiovascular death or myocardial infarction. However, both maximal and mean intima-media thickness of the femoral artery independently predicted revascularization during follow-up (P<0·001), whereas intima-media thickness of the carotid artery did not. Increased lumen diameter of

Table 5 Ultrasonographic variables in the carotid and femoral arteries and relation to the risk of cardiovascular death or non-fatal myocardial infarction or revascularization: results from unadjusted and multivariate analyses

	CV death or MI Relative risk (95% confidence interval)		Revascularization Relative risk (95% confidence interval)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Carotid artery				
Maximal IMT				
<0·81 mm	1·00	1·00	1·00	1·00
0·81–1·02 mm	0·86 [0·39–1·93]	0·62 [0·27–1·45]	1·20 [0·65–2·22]	1·06 [0·56–2·02]
>1·02 mm	1·41 [0·70–2·85]	0·78 [0·36–1·70]	1·35 [0·75–2·45]	1·07 [0·56–2·04]
No plaque	1·00	1·00	1·00	1·00
Plaque grade 1	2·59 [1·29–5·20]**	2·00 [0·97–4·12]	1·49 [0·85–2·58]	1·13 [0·63–2·03]
Plaque grade 2–3	3·38 [1·47–7·76]**	1·85 [0·77–4·46]	1·54 [0·73–3·24]	1·36 [0·62–2·98]
Plaque; any type	2·73 [1·45–5·11]**	1·83 [0·96–3·51]	1·44 [0·88–2·37]	1·17 [0·70–1·96]
Femoral artery				
Maximal IMT				
<1·00 mm	1·00	1·00	1·00	1·00
1·00–1·69 mm	2·12 [0·85–5·29]	1·54 [0·60–3·96]	1·62 [0·80–3·28]	1·47 [0·72–3·03]
>1·69 mm	3·31 [1·37–7·98]**	1·98 [0·76–5·16]	3·11 [1·63–5·93]***	2·58 [1·30–5·11]**
Plaque grade 0	1·00	1·00	1·00	1·00
Plaque grade 1	1·73 [0·80–3·71]	1·07 [0·48–2·37]	1·81 [0·91–3·59]	1·53 [0·76–3·08]
Plaque grade 2–3	1·56 [0·75–3·23]	0·71 [0·32–1·59]	2·71 [1·54–4·78]***	2·29 [1·23–4·25]**
Plaque; any type	1·63 [0·87–3·05]	0·86 [0·43–1·71]	2·33 [1·38–3·94]**	1·93 [1·10–3·39]*

Analyses with and without adjustments for age, sex, smoking, previous MI, hypertension, diabetes mellitus and apolipoproteins (A-I, B). CV=cardiovascular; MI=myocardial infarction; IMT=intima-media thickness.
*P<0·05; **P<0·01; ***P<0·001, refers to comparisons to the lowest tertile of IMT or no occurrence of plaques.

either artery was not related to prognosis; there was an inverse relationship between the femoral lumen diameter and the risk of revascularization after adjustment.

Plaque occurrence

Plaques (grades 1–3) in the carotid artery were almost twice as common among patients with subsequent cardiovascular death or myocardial infarction as among event-free patients (P<0·001), and tended to be more frequent among those who were revascularized (P=0·05) (Fig. 4). Femoral artery plaques tended to be more common among those suffering cardiovascular death or myocardial infarction (P=0·06), but were significantly more common among patients who were revascularized (P<0·001), than among event-free patients (Fig. 4). Unadjusted Cox proportional hazards regression analyses showed that carotid artery plaques predicted the risk of cardiovascular death or myocardial infarction (P<0·01), but not the risk of revascularization. Conversely, femoral artery plaques predicted the risk of revascularization (P<0·01), but not the risk of cardiovascular death or myocardial infarction.

After adjustment for risk factors, carotid artery plaques (grades 1–3) tended to predict the risk of cardiovascular death or myocardial infarction (P=0·056) but not of revascularization in the Cox proportional hazards analysis. Conversely, femoral artery plaques (grades 1–3) were positively related to the risk of a subsequent revascularization (P<0·05) but not to the risk of cardiovascular death or myocardial infarction, also after adjustment for risk factors. The relative risks are shown in Table 5. The prognostic impact of more advanced plaques (grade 2 or 3) was analysed separately. Such plaques in the femoral artery were predictive of the risk of revascularization (P<0·01) but not of cardiovascular death or myocardial infarction. However, plaques of grade 2 or 3 in the carotid artery were significantly related to the risk of cardiovascular death or myocardial infarction only in the unadjusted analysis.

A low-risk group, without plaques in either artery, could be identified. Figure 5 shows Kaplan–Meier curves for the risk of cardiovascular death or myocardial infarction (P<0·05), and the risk of revascularization (P<0·001), in relation to the presence of plaques in either the carotid or femoral artery.

Discussion

The present study of patients with stable angina pectoris shows that carotid intima-media thickness and plaques were related to increased risk of cardiovascular death or myocardial infarction in univariate Cox regression analyses. Femoral intima-media thickness was related to both cardiovascular death or myocardial infarction and the risk of revascularization, whereas plaques were only related to the latter. In multivariate analyses, i.e. after adjustments for age, sex, lipids, smoking and previous cardiovascular disease, carotid intima-media thickness failed to predict any cardiovascular event, whereas carotid plaques tended to

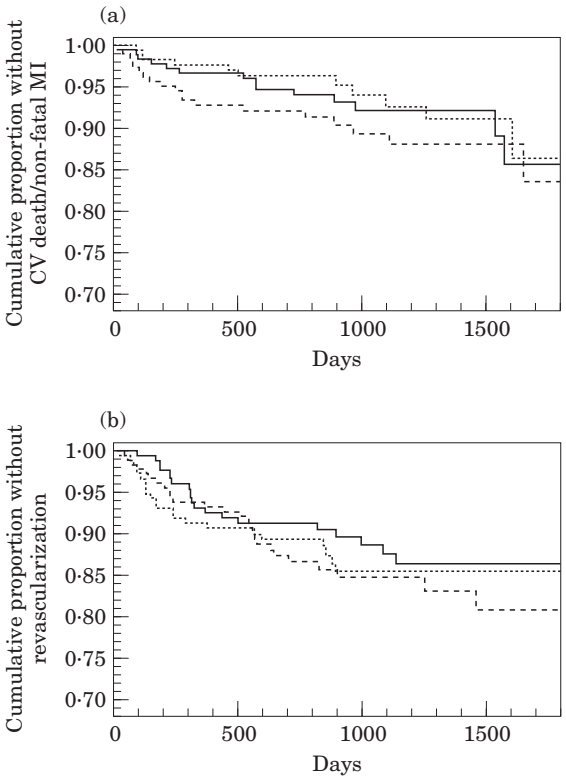

Figure 2 **Kaplan–Meier curves illustrating the likelihood of remaining without cardiovascular death or non-fatal myocardial infarction (a), or without revascularization (b) in relation to mean intima-media thickness (IMT) of the carotid artery divided into tertiles. ——=Carotid artery IMT <0·81 mm, · · ·=IMT of 0·81–1·02 mm, – – –=IMT >1·02 mm. Cox analyses showed no significant prediction for this variable.**

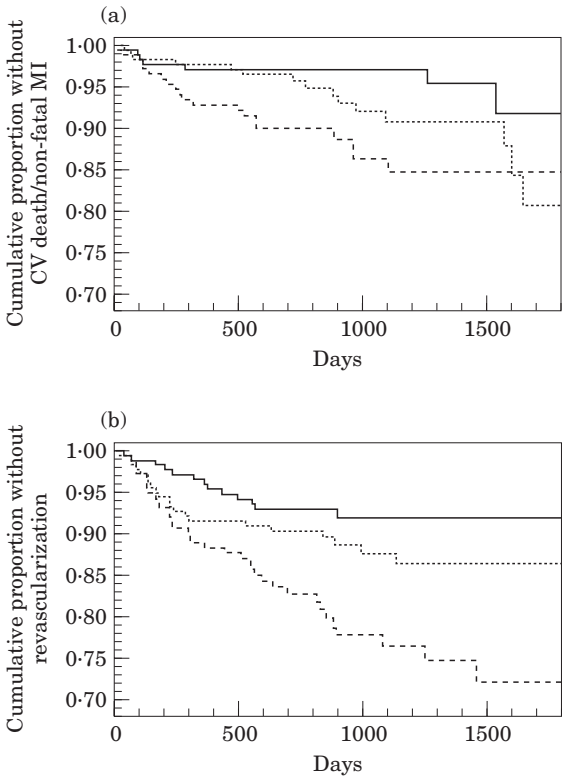

Figure 3 **Kaplan–Meier curves for the likelihood of remaining without cardiovascular death or non-fatal myocardial infarction (MI) (a), or without revascularization (b) in relation to mean intima-media thickness (IMT) of the femoral artery divided into tertiles. ——=Femoral artery IMT <1·00 mm, · · ·=IMT of 1·00–1·69 mm, – – –=IMT >1·69 mm. Cox analyses showed significant prediction of the risk of revascularization (P<0·01).**

predict the risk of cardiovascular death or myocardial infarction. Femoral intima-media thickness and occurrence of plaques, however, were related to the risk of revascularization also after adjustments. It is of interest that carotid and femoral vascular changes were differently related to the type of cardiovascular event. Carotid intima-media thickness was a weak predictor of events, whereas femoral intima-media thickness predicted revascularization. Plaques in the carotid artery tended to predict the risk of cardiovascular death or myocardial infarction, i.e. acute coronary events, whereas plaques in the femoral artery clearly predicted the risk of revascularization.

Little has been published regarding the prognostic impact of vascular changes in peripheral arteries in patients with coronary artery disease. Salonen and Salonen[15] found that plaques in the carotid artery predicted the risk of acute myocardial infarction better than carotid intima-media thickness in 1288 healthy men in an analysis based on 24 events. A later re-analysis with more events (n=36) showed significant prediction of the risk of fatal or non-fatal myocardial infarction by carotid intima-media thickness, but that plaques still were more strongly related to events than intima-media thickness[27]. Even though our analyses are based on a larger number of events, in a cohort of patients with stable angina pectoris, we found no independent relationship between carotid intima-media thickness and any type of cardiovascular event, whereas carotid plaques were related to the risk of cardiovascular death or myocardial infarction. The risk increased with the severity of plaques in the unadjusted analysis only, in contrast to the findings by Salonen and Salonen[27]. However, carotid plaques did not predict the risk of revascularization. Such events were not reported in the previous study[15,27]. In a recent, large prospective study of patients without a history of cardiovascular disease by O'Leary *et al.*[17], carotid intima-media thickness was found to be an independent predictor of both myocardial infarction and stroke. These subjects however, were on average 13 years older and had a higher prevalence of diabetes than our patients. The ultrasonographic methods differed, as O'Leary *et al.* used the means of the near and far wall of the common and internal carotid artery. The Rotterdam study[28], on disease and disability in the elderly, also found associations between common carotid intima-media thickness and the risk of myocardial infarction and stroke. When

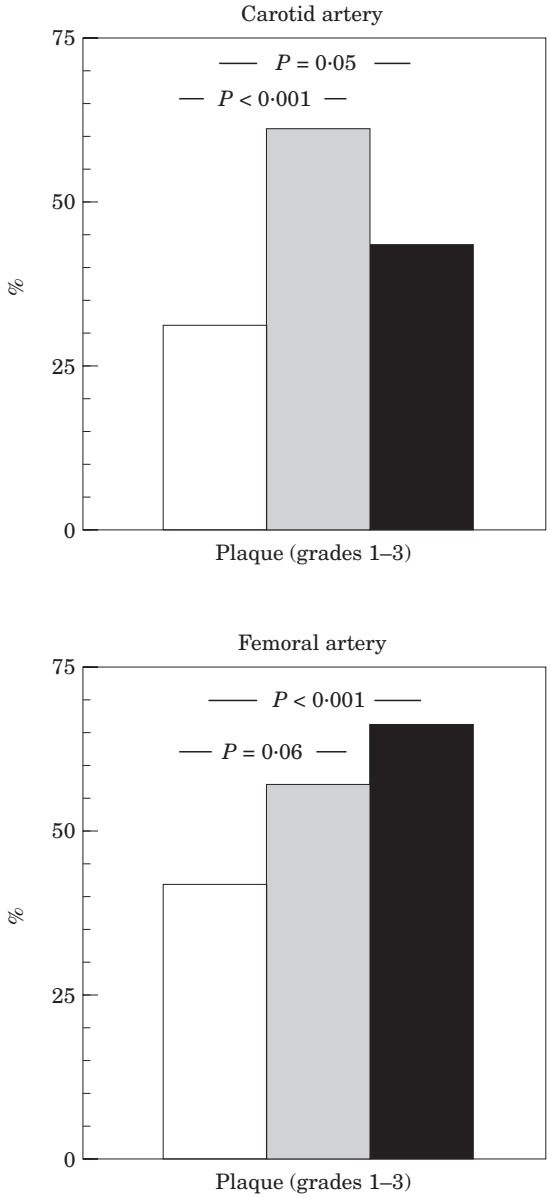

Figure 4 **Frequencies of plaques (grades 1–3) in the carotid and femoral arteries among patients suffering cardiovascular death or non-fatal myocardial infarction combined (■, revascularization (▨) and event-free patients (□).**

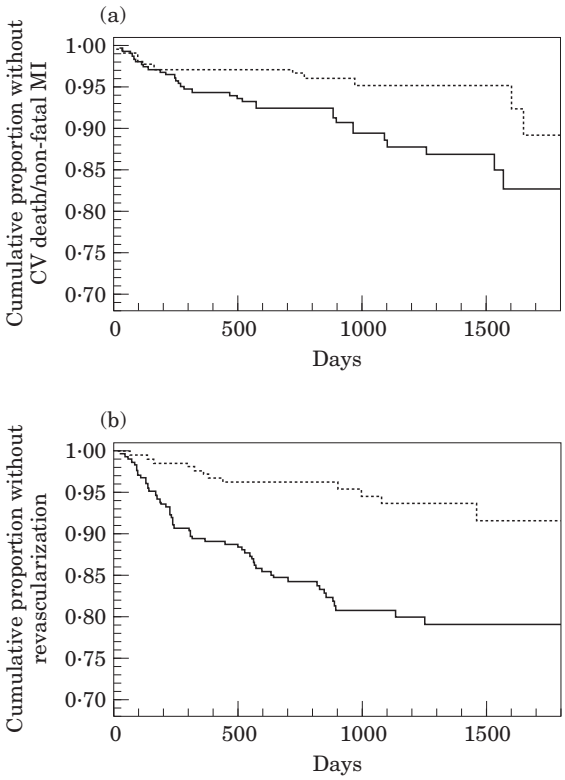

Figure 5 **Kaplan–Meier curves for the likelihood of remaining without cardiovascular death or non-fatal myocardial infarction (a), or without revascularization (b) in relation to presence (——) or absence (· · ·) of plaques in either the carotid or femoral arteries. *P*<0·005 for (a) and <0·001 for (b).**

adjusting for several cardiovascular risk factors, however, these associations were significantly attenuated, as was also the case in our study.

Conflicting results have been presented for correlation between carotid intima-media thickness and coronary atherosclerosis on angiography. One study[13] found a strong relationship, whereas another study[12] concluded that carotid intima-media thickness was only weakly correlated to the extent and severity of coronary artery disease. Macroscopically visible carotid atherosclerosis was, however, related to coronary atherosclerosis[9,10]. Taken together, these studies suggest that intima-media thickness is a less sensitive surrogate variable for the risk of coronary events than the presence of plaques in the common carotid artery. However, in patients without known coronary artery disease, the prevalence of plaques is much smaller, so that intima-media thickness may be a more useful predictor of risk.

The prognostic importance of femoral vascular changes for the risk of coronary events has, to our knowledge, not previously been studied. We found that intima-media thickness in the femoral artery was significantly related to the risk of revascularization, both in unadjusted and adjusted analyses, but not to the risk of cardiovascular death or myocardial infarction. In addition, the occurrence of plaques in the femoral artery predicted the risk of revascularization. This risk increased in proportion to the severity of the plaques, and was more than doubled among patients with the most severe plaques, compared with patients without.

It is interesting to note that carotid and femoral vascular changes predicted different outcomes, i.e. acute cardiac events compared with revascularization differently. Cardiovascular death or myocardial infarction are closely related to plaque rupture and thrombosis, and there is increasing evidence that coronary plaques with less severe angiographic stenosis are more prone to progression/rupture than severely stenotic lesions[29]. In

contrast, revascularization is usually brought about by a slowly growing stenotic lesion, resulting in occlusive symptoms. Thus, the need for revascularization probably reflects the rate of progression of the atherosclerotic disease. Our findings may suggest that carotid plaques reflect vulnerable coronary lesions, whereas femoral vascular changes (intima-media thickness and plaques) reflect the slow progression of coronary atherosclerosis. Different rheological conditions in the carotid and femoral arteries may contribute to the differences presently observed. Salonen and Salonen reported that smoking and fibrinogen were more strongly related to femoral than to carotid intima-media thickening[27]. However, they did not analyse the prognostic implications of femoral vascular changes.

Increased carotid and femoral artery lumen diameter were associated with a higher incidence of cardiovascular death or myocardial infarction in univariate analyses, but not after adjustment for age, sex and height. However, an inverse relationship was observed for femoral mean lumen diameter versus the risk of revascularization. Results from patho-anatomic studies[19,20] have suggested that vessel enlargement may be a compensatory response in early stages of coronary atherosclerosis. Similarly, lumen diameter is related to the presence and extent of plaques in the carotid artery, as assessed by ultrasonography[22]. Males had greater lumen diameters than females, in agreement with previous findings[30]. This may explain why lumen diameter did not carry any prognostic information in the multivariate analysis, since the incidence of cardiovascular events was strongly related to sex. Thus, adjustments for sex and/or height should be performed when prognostic aspects of carotid and femoral lumen diameter are evaluated in patients of both sexes.

We did not find a consistent pattern for clinical risk indicators and intima-media thickness of the carotid and femoral arteries or the presence of plaques in male patients. Hypertensives had a greater intima-media thickness in the carotid artery than normotensives, similar to other findings[2], but at variance with the study of Salonen and Salonen[27]. Smokers had greater carotid and femoral artery intima-media thickness, in agreement with previous findings[27,31], and more plaques than non-smokers. However, a history of previous myocardial infarction was not related to carotid intima-media thickness or plaque occurrence, in contrast to previous findings[32]. Surprisingly, neither carotid intima-media thickness nor plaques were increased among patients with diabetes mellitus, in contrast to other findings[33], and femoral intima-media thickness was even greater in non-diabetics than among diabetics. However, the non-diabetics tended to be older and they were more often current or ex-smokers than the diabetics.

Patients in the APSIS study were treated with lipid-lowering drugs at the discretion of the investigator. The use of lipid-lowering drugs was low (6%) at the beginning and increased slowly during follow-up. It is unlikely that statins influenced the outcome in our study, since follow-up ended in December 1994, only a few months after the 4S study was published[34].

In conclusion, the present analyses suggest that carotid and femoral vascular changes have prognostic implications, but are differently related to the type of cardiovascular event in patients with stable angina pectoris. Increased intima-media thickness and plaques in the femoral artery were the best predictors of the risk of a revascularization, whereas plaques in the carotid artery tended to predict cardiovascular death or myocardial infarction. Carotid intima-media thickness is the most commonly used surrogate variable for atherosclerosis, but was only a weak predictor of events in the present study. Evaluation of plaques in the carotid or femoral arteries appears to provide the best prediction of cardiovascular prognosis in patients with stable angina pectoris.

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References

[1] Wendelhag I, Wiklund O, Wikstrand J. Arterial wall thickness in familial hypercholesterolemia. Ultrasound measurement of intima-media thickness in the common carotid artery. Arterioscler Thromb 92; 12: 70–7.
[2] Bots ML, Hofman A, de Bruyn AM, de Jong PTVM, Grobbee DE. Isolated systolic hypertension and vessel wall thickness of the carotid artery. The Rotterdam Elderly Study. Arterioscler Thromb 93; 13: 64–9.
[3] Salonen R, Seppanen K, Rauramaa R, Salonen JT. Prevalence of carotid atherosclerosis and serum cholesterol levels in eastern Finland. Arteriosclerosis 88; 8: 788–92.
[4] Gnasso A, Pujia A, Irace C, Mattioli PL. Increased carotid arterial wall thickness in common hyperlipidemia. Coronary Artery Dis 95; 6: 57–63.
[5] Crouse JR, Byington RP, Bond MG. Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). Am J Cardiol 95; 75: 455–9.
[6] Salonen R, Nyyssönen K, Porkkala E *et al*. Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. Circulation 95; 92: 1758–64.
[7] Furberg CD, Adams HP, Applegate WB *et al*. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Circulation 94; 90: 1679–87.
[8] Borhani NO, Mercuri M, Borhani PA *et al*. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). A randomized controlled trial. J Am Med Assoc 96; 276: 785–91.
[9] Mathur KS, Kashyap SK, Kumar V. Correlation of the extent and severity of atherosclerosis in the coronary and cerebral arteries. Circulation 63; 27: 929–34.

[10] Young W, Gofman JW, Tandy R, Malamud N, Waters ESG. The quantitation of atherosclerosis: III. The extent of correlation of degrees of atherosclerosis within and between the coronary and cerebral vascular beds. Am J Cardiol 69; 6: 300–8.
[11] Craven TE, Ryu JE, Espeland MA *et al*. Evaluation of the associations between carotid artery atherosclerosis and coronary arterry stenosis. Circulation 90; 82: 1230–42 .
[12] Adams MR, Nakagomi A, Keech A *et al*. Carotid intima-media thickness is only weakly correlated with the extent and severity of coronary artery disease. Circulation 95; 92: 2127–34.
[13] Wofford JL, Kahl FR, Howard GR, McKinney WM, Toole JF, Crouse III JR. Relation of extent of extracranial carotid artery atherosclerosis as measured by B-mode ultrasound to the extent of coronary atherosclerosis. Arterioscler Thromb 91; 11: 1786–94.
[14] Crouse JR III, Craven TE, Hagaman AP, Bond MG. Association of coronary disease with segment-specific intimal-medial thickening of the extracranial carotid artery. Circulation 95; 92: 1141–7.
[15] Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991; 11: 1245–9.
[16] Belcaro G, Nicolaides AN, Laurora G *et al*. Ultrasound morphology classification of the arterial wall and cardiovascular events in a 6-year follow-up study. Arterioscler Thromb Vasc Biol 1996; 16: 851–6.
[17] O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, for the Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999; 340: 14–22.
[18] Handa N, Matsumoto M, Maeda H, Hougaku H, Kamada T, for the Osaka study group. Ischemic stroke events and carotid atherosclerosis. Results of the Osaka follow-up study for ultrasonographic assessment of carotid atherosclerosis (the OSACA study). Stroke 1995; 26: 1781–6.
[19] Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987; 316: 1371–5.
[20] Zarins CK, Weisenberg E, Kolettis G, Stankunavicius R, Glagov S. Differential enlargement of artery segments in response to enlarging atherosclerotic plaques. J Vasc Surg 1988; 7: 386–94.
[21] Losordo DW, Rosenfield K, Kaufman J, Pieczek A, Isner JM. Focal compensatory enlargement of human arteries in response to progressive atherosclerosis. In vivo documentation using intravascular ultrasound. Circulation 1994; 89: 2570–7.
[22] Steinke W, Els T, Hennerichi M. Compensatory carotid artery dilatation in early atherosclerosis. Circulation 1994; 89: 2578–81.
[23] Rehnqvist N, Hjemdahl P, Billing E *et al*. Effects of metoprolol vs verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS). Eur Heart J 1996; 17: 76–81.
[24] Held C, Hjemdahl P, Rehnqvist N *et al*. Haemostatic markers, inflammatory parameters and lipids in male and female patients in the Angina Prognosis Study In Stockholm (APSIS). A comparison with healthy controls. J Intern Med 1997; 241: 59–69.
[25] Wendelhag I, Gustavsson T, Suurkula M, Berglund G, Wikstrand J. Ultrasound measurements of wall thickness in the carotid artery: fundamental principles and description of a computerized analysing system. Clin Physiol 1991; 11: 565–77.
[26] Held C, Hjemdahl P, Rehnqvist N *et al*. Cardiovascular prognosis in relation to apolipoproteins and other lipid parameters in patients treated with verapamil or metoprolol. Atherosclerosis 1997; 135: 109–18.
[27] Salonen JT, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. Circulation 1993; 87 (Suppl II): II-56–II-65.
[28] Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction. The Rotterdam study. Circulation 1997; 96: 1432–7.
[29] Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992; 326: 242–50.
[30] Crouse JR, Goldbourt U, Evans G, *et al*., for the ARIC investigators: arterial enlargement in the Atherosclerosis Risk in Communities (ARIC) cohort. In vivo quantification of carotid arterial enlargement. Stroke 1994; 25: 1354–9.
[31] Salonen R, Salonen JT. Determinants of carotid intima-media thickness: a population-based ultrasonography study in Eastern Finnish men. J Intern Med 1991; 229: 225–31.
[32] Salonen R, Tervahauta M, Salonen JT, Pekkanen J, Nissinen A, Karvonen MJ. Ultrasonographic manifestations of common carotid atherosclerosis in elderly eastern Finnish men. Prevalence and associations with cardiovascular diseases and risk factors. Arterioscler Thromb 1994; 14: 1631–40.
[33] Wei M, Gonzalez C, Haffner SM, O'Leary DH, Stern MP. Ultrasonographically assessed maximum carotid artery wall thickness in Mexico City residents and mexican americans living in San Antonio, Texas. Association with diabetes and cardiovascular risk factors. Arterioscler Thromb Vasc Biol 1996; 16: 1388–92.
[34] Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383–9.