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Evolution of coronary atherosclerosis in patients with mild coronary artery disease studied by serial quantitative coronary angiography at 2 and 4 years follow-up

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Aims Angiographic studies on the natural course of both focal and diffuse coronary atherosclerosis have not been performed before, but can both be assessed by quantitative coronary angiography. The objective of this study was to describe the natural course of focal and diffuse coronary atherosclerosis over time.

Methods and results In 129 patients with mild coronary artery disease, but not on lipid-lowering medication, three coronary angiograms were made each 2 years apart. Nine hundred and sixty five angiographically diseased and non-diseased segments were analysed by quantitative coronary angiography. Mean lumen diameter and minimal lumen diameter were used as measures of diffuse and focal coronary atherosclerosis.

Mean lumen diameter and minimum lumen diameter decreased by 0·02 and 0·03 mm per year. The rate of progression was similar in the angiographically non-diseased, as in the mildly and moderately diseased segments. Progression of diffuse coronary atherosclerosis was largest in severely stenosed lesions (percentage diameter stenosis $\geq 50\%$) and in the right coronary artery with a loss of 0·19 mm and 0·16 mm in mean lumen diameter. Progression of focal disease was most prominent in new and mild lesions and the right coronary artery, with a decrease in minimum lumen diameter of 0·34 mm and 0·22 mm. In most subgroups, progression occurred gradually over time. On a per segment level, progression and the occurrence of new lesions occurred in 4·4% and 4·2%. Regression and disappearance of a lesions was found in 2·3% and 1·9%. On a per patient level, 36% were progressors, 12% had a mixed response, 36% were stable, and 16% were regressors.

Conclusion Diffuse and focal coronary atherosclerosis progressed at the same rate in the first and second 2 years in stenosed and non-stenosed segments. The rate of coronary atherosclerosis progression was small, but was higher for focal than for diffuse disease. A minority of lesions progressed and spontaneous regression was rare.
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Key Words: Coronary atherosclerosis, quantitative coronary angiography, natural history.

Introduction

Several prospective studies on the angiographic course of coronary atherosclerosis using quantitative coronary angiography have been published, but none of these included three angiograms[1–14]. The majority of these studies focussed on lesion changes and only a few assessed changes in angiographically non-diseased coronary segments[7,8,11,13,14]. Four other studies[15–18] used serial coronary angiography (three or more angiograms) which described angiographic changes over time. In three of these investigations, however, the coronary angiograms were assessed visually. We performed a prospective quantitative coronary angiographic study with three serial coronary angiograms over 4 years, in patients with mild to moderate coronary artery disease

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not treated by lipid-lowering drugs or revascularization procedures. We assessed the angiographic evolution of diffuse and focal coronary atherosclerosis in non-stenosed (angiographically normal) and stenosed coronary segments.

Methods

Patients

The patients constituted the placebo group of an angiographic trial, (the MAAS, Multicenter Anti-Atheroma Study), which compared simvastatin 20 mg daily with placebo, and has been described and reported elsewhere[19,20]. Both male and female patients were enrolled from 11 clinics from six European countries. At angiography, in each participant, at least two coronary segments were visibly atherosclerotic, but they did not require revascularization. The patients were in a stable clinical condition, and no lipid-lowering drugs were allowed. Total cholesterol was between 5·5 and 8·0 mmol . l^{-1}, and triglycerides were below 4 mmol . l^{-1}. All patients were followed for 4 years. Clinical events, death, myocardial infarction, unstable angina pectoris, percutaneous transluminal coronary angioplasty and coronary bypass surgery were evaluated centrally by a clinical events committee.

Coronary angiography and quantitative coronary analysis

Coronary angiography was performed according to standards for quantitative analysis at baseline and after 2 and 4 years. Prior to angiography, patients received 5 mg isosorbide dinitrate sublingually to induce standardized vasodilation. In each projection, the catheter tip not filled with contrast medium was filmed and sent with the angiogram to the quantitative coronary angiography core laboratory for calibration. All relevant aspects of the angiography procedure (sequence of injections, projections, angulation and rotation, type and size of the catheters) were recorded on a case report form to enable exact repetition of the procedure at the 2- and 4-year follow-up.

Analyses of the angiograms were performed centrally in a quantitative coronary angiography core laboratory using the Coronary Angiography Analysis System (CAAS)[21]. From the baseline angiograms, orthogonal projections of 11 large proximal coronary segments, both angiographically diseased and non-diseased, were selected[22]: right coronary artery: proximal (1), mid (2), distal (3); left main coronary artery (5); left anterior descending artery: proximal (6), mid (7), distal (8); left cirumflex artery: proximal (11), obtusis marginalis (12), distal (13), posterior lateralis (14)[23]. Totally occluded segments and segments that had previously undergone percutaneous transluminal coronary angioplasty were not included in the baseline selection. When percutaneous transluminal coronary angioplasty was performed, the pre-angioplasty analysis of the dilated coronary segment was used at 2 and 4 years as appropriate. If no pre-angioplasty analysis was present, the segment was excluded. For all segments, mean lumen diameter (mm) and segment length (mm) were calculated. In addition, minimum lumen diameter (mm) and percentage diameter stenosis (%) were estimated for all angiographically diseased segments. In the subgroup of segments with a narrowing of at least 20% in a projection in all three angiograms, additional stenosis parameters were computed: interpolated reference or normal vessel diameter (mm), stenosis length (mm), and plaque area (mm^2) which is calculated as the area between the interpolated normal vessel contour constructed by the computer and the measured vessel contour at the site of a stenosis[21]. The plaque area represents the longitudinal cross-sectional area of the plaque that encroaches on the vessel lumen. The available multiple matched projections were used for the assessment of change over time[24]. In the present study, only the most severe stenosis in a segment was taken into account. New occlusions at 2 and 4 year follow-up were assigned a mean and minimum lumen diameter of 0 mm and a percentage diameter stenosis of 100%.

Angiographic definitions

The mean lumen diameter of all segments was interpreted as the measure of diffuse coronary atherosclerosis, and the minimum lumen diameter of stenosed segments as the primary measure of focal atherosclerosis[22]. A negative change in diameter is a decrease in vessel lumen and therefore indicates progresssion of atherosclerosis. A segment was considered angiographically diseased when there was a percentage diameter stenosis $\geq 20\%$ at baseline or at follow- up. Progression was defined as an increase $\geq 15\%$ in percentage diameter stenosis, regression as a decrease of 15%. At follow-up, segments were classified as (1) non-diseased, (2) new lesion, (3) stable lesion, (4) progressed lesion, (5) regressed lesion, (6) disappeared lesion. From this classification of segments, patients were classified as (1) progressor: at least 1 segment progressed, (2) mixed responder: both progressed and regressed segments, (3) stable: only stable segments, (4) regressor: at least 1 segment regressed. For change in diffuse coronary atherosclerosis, segments and patients were classified according to a change in mean lumen diameter of 0·4 mm, a cutoff point also used for change in minimum lumen diameter[2].

Statistical aspects

Baseline characteristics are presented as numbers and percentages and as mean ± SD. Quantitative coronary angiography measurements at baseline and follow-up are reported as mean ± SE. The 95% confidence intervals can be calculated as mean ± 1·96 × SE. Changes over time were evaluated by paired analysis of variance.

A *P*-value <0·05 was considered statistically significant. All analyses are presented on a per segment basis. To test whether dependence of segments within patients influenced the results, a nested analysis within patients was performed. Since this yielded results similar to the analysis per segment, only the latter is reported. Angiographic changes are reported for the group as a whole, stratified according to the severity of disease at baseline: percentage diameter stenosis <20% (non-diseased), ≥20%–<35% (mildly diseased), ≥35%–<50% (moderately diseased), ≥50% (severely diseased), and stratified according to the coronary artery. For each subgroup, changes are reported for diffuse coronary atherosclerosis (mean lumen diameter) and focal disease (minimum lumen diameter).

Results

The study population consisted of 188 patients with an approved baseline angiogram. For 59 patients no complete angiographic follow-up was available, thus 129 patients (69%) had both a 2- and a 4-year follow-up angiogram. Reasons for not having follow-up angiography were death (11 patients), intercurrent coronary bypass surgery (9 patients), insufficient quality for quantitative analysis (1 patient), and refusal (38 patients). In the 129 patients with complete angiographic follow-up, 1753 projections of 965 segments were analysed, of which 614 were angiographically diseased. In 541 projections of 341 segments, stenosis parameters were calculated. The mean total length of segments per patient was 164·2 mm (±44·0). This did not change significantly at 2- and 4-year follow-up. Of the 129 patients with complete angiographic follow-up, one third had a history of myocardial infarction and half had previously undergone percutaneous transluminal coronary angioplasty. Half of the patients had no significant disease (a diameter stenosis of >50%) at visual assessment (Table 1).

Clinical events

Of the initial 188 patients, 137 (73%) had no clinical event during the 4-year follow-up. There were 11 (5·9%) deaths of which 5 were cardiac (2 fatal myocardial infarction, 1 sudden death and 2 congestive heart failure). Furthermore, 5 (2·7%) non-fatal myocardial infarctions occurred, and 18 (9·6%) patients were hospitalized for unstable angina. There were 38 (20·2%) revascularization procedures: 16 coronary bypass surgery and 22 percutaneous transluminal coronary angioplasty.

Quantitative coronary angiography: development of diffuse and focal coronary atherosclerosis

Distribution of angiographic changes

Figure 1 shows the distribution of angiographic changes on a per segment basis between baseline and 4 years.

Table 1 Baseline characteristics for 129 patients with complete angiographic follow-up

Age (years)	55·5	±6·6
Males	117	91%
Systolic blood pressure (mmHg)	132	±15·0
Diastolic blood pressure (mmHg)	80	±8·0
Previous MI	42	33%
Previous PTCA	67	52%
Current angina	112	70%
Current smoker	22	17%
Vessel disease (visual assessment*)		
None	59	46%
One	44	34%
Two	19	15%
Three	7	5%
Total cholesterol	6·40	±0·81
LDL-C	4·47	±0·79
HDL-C	1·11	±0·29
Triglycerides	1·80	±0·84
Long-acting nitrate	48	37%
Beta-blocker	54	42%
Calcium antagonist	57	44%
ACE inhibitor	18	14%
Aspirin	70	54%

Values are means ± standard deviation; MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty; LDL-C=low density lipoprotein cholesterol; HDL-C=high density lipoprotein cholesterol; ACE=angiotensin converting enzyme.
*A vessel with a stenosis >50% was considered diseased.

Most segments do not change significantly over 4 years. For mean lumen diameter 12% progressed, 81% were stable and 7% of segments regressed. For minimum lumen diameter 12% of angiographically diseased segments progressed, 79% were stable and 9% regressed.

Diseased and non-diseased segments

Table 2 shows the quantitative coronary angiography results at baseline, 2 and 4 years. Mean lumen diameter, a measure of diffuse atherosclerosis, decreased by 0·06 mm and 0·08 mm and 2 and 4 years, respectively (Table 3). Both the disease progression from baseline to 2, and from 2 to 4 years were significant. These changes represent a decrease of mean vessel diameter of 2·8% over 4 years. The magnitude of loss in mean lumen diameter was similar in both the non-diseased and mildly diseased segments. Progression in diffuse disease was approximately three times greater in the moderately and severely diseased segments.

Stratification for coronary artery and severity of disease

Decrease in vessel lumen was most prominent in the right coronary artery, being 5 times as great as in the left anterior descending coronary artery. Minimum lumen diameter, a measure of focal atherosclerosis, decreased by 0·06 mm and 0·12 mm after 2 and 4 years, respectively. This is a decrease of 6·0% over 4 years. Progression of focal atherosclerosis was greatest for the lesions non-stenosed at baseline: a decrease of 0·34 mm in minimum lumen diameter and an increase of 12·4% in percentage diameter stenosis. The rate of progression decreased with the severity of the lesions at baseline.

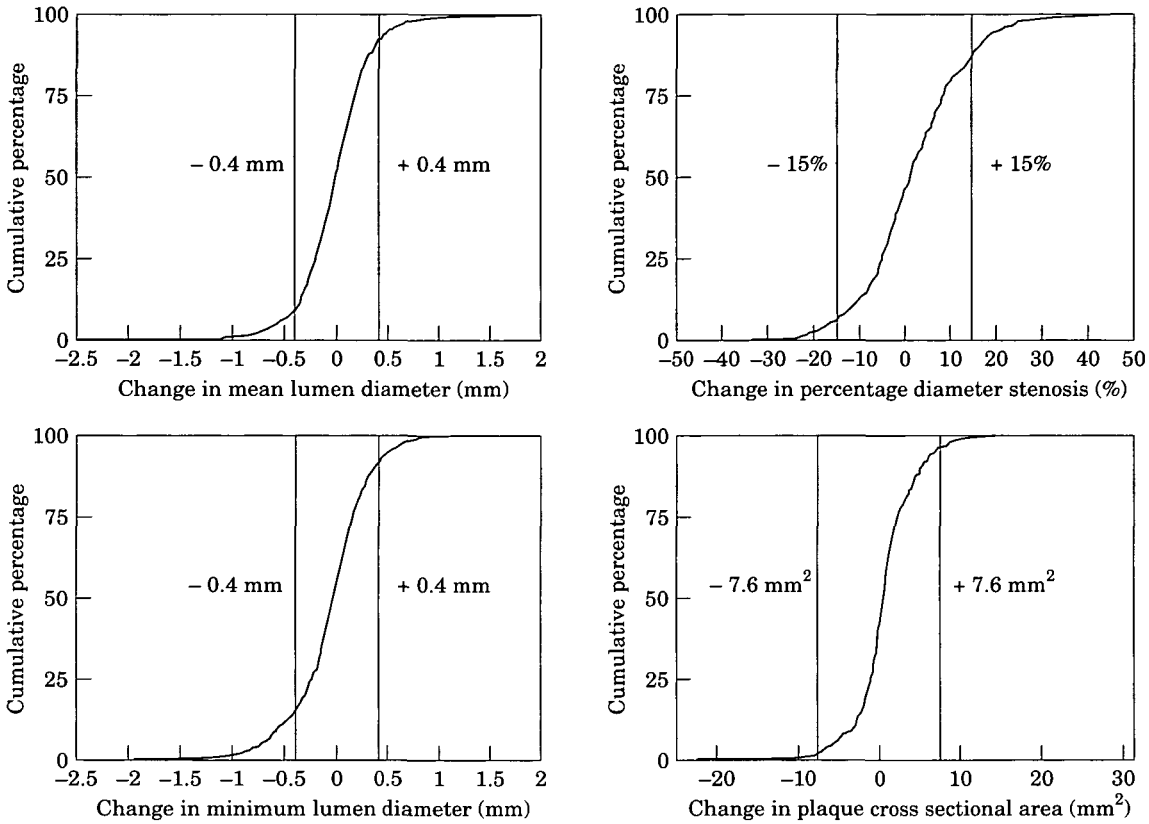

Figure 1 **Cumulative distribution curves for mean lumen diameter, minimum lumen diameter, percentage diameter stenosis, and plaque area (of changes between baseline and 4 years) with cut-off points for segment and stenosis change indicating progression of coronary atherosclerosis, stable disease, and regression of coronary atherosclerosis.**

Severely diseased lesions at baseline showed no progression, but a small and non-significant improvement. As with diffuse disease, progression was greatest in the right coronary artery with a loss in minimum lumen diameter of 0·22 mm and an increase of percentage diameter stenosis of 6·1%.

Stenosis parameters

Table 2 also shows the results for the subgroup of 341 segments in which stenosis parameters were calculated at baseline and at 2 and 4 years. The changes in lesion length and plaque area were in accordance with the changes in minimum lumen diameter. In the combined mildly and moderately diseased segments, minimum lumen diameter decreased by 0·13 mm, the percentage diameter stenosis increased by 14·5%, the length of the stenosis by 0·43 mm, and the plaque area by 0·58 mm^2. There was a small but significant decrease of 0·05 mm in the normal segment diameter, suggesting that progression of diffuse atherosclerosis occurred in the non-stenosed parts of these segments.

Changes over time

The overall changes over time are depicted in Fig. 2. Diffuse atherosclerotic progression was more pronounced in the first 2 years in the non-diseased and severely diseased segments. For the segments with mild and moderate disease (percentage diameter stenosis between 20% and 50%), loss in vessel lumen developed mostly in the last 2 years of the study. In the right coronary artery, progression was twice as great in the second half of the study, with a decrease of 0·10 mm and 0·22 mm in minimum lumen diameter in the first and second half of the study, respectively. In the left anterior descending coronary artery, progression occurred more gradually, whereas the left circumflex artery showed marked progression in the first half and some regression in the second half of the study.

Categorical changes

Half of the segments remained non-diseased after 2 and 4 years (Table 4). Progression was seen in 6% and 9% and regression in 3% and 4% of segments after 2 and 4 years, respectively. After 2 years 10 (1·0%) new total occlusions occurred and after 4 years 16 (1·7%) in 15 patients (11%). One total occlusion at 2 years re-opened at 4 years. In these 15 patients, in whom total occlusion developed, two suffered an overt clinical myocardial infarction. The classification per patient showed that after 4 years 48% of the patients had progressed or had a mixed response, which was 38% at 2 years. The percentage of regressors increased from 9% at 2 years to

Table 2 Quantitative angiographic measurements at baseline, 2 year and 4 year follow-up

	Baseline mean SE	2 years mean SE	4 years mean SE
All segments (n=965)			
Mean lumen diameter (mm)	2·85 ± 0·03	2·79 ± 0·03	2·77 ± 0·03
Minimum lumen diameter (mm)	1·93 ± 0·02	1·87 ± 0·03	1·82 ± 0·03
Percentage diameter stenosis (%)	29·62 ± 0·47	31·59 ± 0·58	32·92 ± 0·64
Length of stenosis (mm)	6·25 ± 0·16	6·52 ± 0·17	6·63 ± 0·17
Plaque area (mm^2)	4·99 ± 0·20	5·44 ± 0·26	5·51 ± 0·22
Non-diseased segments at baseline (n=489)			
Mean lumen diameter (mm)	3·18 ± 0·04	3·11 ± 0·05	3·10 ± 0·05
Minimum lumen diameter (mm)	2·39 ± 0 05	2·16 ± 0·05	2·06 ± 0·05
Percentage diameter stenosis (%)	15·87 ± 0·26	25·33 ± 0·98	28·28 ± 1·20
Mildly diseased segments at baseline (n=295)			
Mean lumen diameter (mm)	2·54 ± 0·04	2·53 ± 0·04	2·48 ± 0·04
Minimum lumen diameter (mm)	1·93 ± 0·03	1·91 ± 0·03	1·86 ± 0·03
Percentage diameter stenosis (%)	27·10 ± 0·24	27·68 ± 0·54	28·99 ± 0·69
Length of stenosis (mm)	6·38 ± 0·24	6·47 ± 0·26	6·68 ± 0·25
Plaque area (mm^2)	4·02 ± 0·23	4·77 ± 0·39	5·16 ± 0·31
Moderately diseased segments at baseline (n=146)			
Mean lumen diameter (mm)	2·50 ± 0·05	2·45 ± 0·06	2·37 ± 0·07
Minimum lumen diameter (mm)	1·66 ± 0·04	1·66 ± 0·04	1·61 ± 0·05
Percentage diameter stenosis (%)	41·39 ± 0·37	39·96 ± 1 17	40·21 ± 1·40
Length of stenosis (mm)	6·03 ± 0·23	6·57 ± 0·24	6·58 ± 0·24
Severely diseased segments at baseline (n=35)			
Mean lumen diameter (mm)	2·36 ± 0·11	2·12 ± 0·19	2·17 ± 0·18
Minimum lumen diameter (mm)	1·23 ± 0·07	1·27 ± 0·12	1·29 ± 0·11
Percentage diameter stenosis (%)	56·39 ± 1 02	54·73 ± 3·55	53·99 ± 3·39
Length of stenosis (mm)	6·59 ± 0·58	6·57 ± 0·61	6·65 ± 0·67
Plaque area (mm^2)	7·24 ± 0 92	6·81 ± 0·82	6·66 ± 0·89
Right coronary artery (n=274)			
Mean lumen diameter (mm)	3·07 ± 0 04	3·01 ± 0·05	2·91 ± 0·05
Minimum lumen diameter (mm)	2·20 ± 0·05	2·11 ± 0·05	1·99 ± 0·05
Percentage diameter stenosis (%)	29·32 ± 0·93	32·44 ± 1·12	35·41 ± 1·37
Left main coronary artery (n=100)			
Mean lumen diameter (mm)	4·13 ± 0·02	4·08 ± 0·08	4·02 ± 0·08
Minimum lumen diameter (mm)	2·62 ± 0·14	2·63 ± 0·12	2·44 ± 0·07
Percentage diameter stenosis (%)	21·90 ± 11·26	23·53 ± 9·26	25·48 ± 3·81
Left anterior descending artery (n=309)			
Mean lumen diameter (mm)	2·51 ± 0·04	2·49 ± 0·04	2·47 ± 0·04
Minimum lumen diameter (mm)	1·82 ± 0·03	1·81 ± 0·04	1·75 ± 0·03
Percentage diameter stenosis (%)	27·68 ± 0·70	28·40 ± 0·75	29·71 ± 0·78
Left circumflex artery (n=282)			
Mean lumen diameter (mm)	2·55 ± 0·04	2·46 ± 0·04	2·50 ± 0·05
Minimum lumen diameter (mm)	1·76 ± 0·04	1·68 ± 0·04	1·69 ± 0·04
Percentage diameter stenosis (%)	31·19 ± 0·81	34·36 ± 1·10	34·14 ± 1·15

SE=standard effort; angiographically non-diseased=percentage diameter stenosis <20%; mildly diseased=percentage diameter stenosis ≥20%–<35%; moderately diseased=percentage diameter stenosis ≥35%–<50%; severely diseased=percentage diameter stenosis ≥50%.

16% at 4 years. When, as a measure of diffuse atherosclerosis, the criterion of 0·4 mm change in mean lumen diameter was applied, then 27% of the patients progressed, 10% had a mixed response, 46% were stable and 19% regressed.

Discussion

The findings show that coronary atherosclerosis progressed gradually over 4 years, but that the rate of progression of focal atherosclerosis was twice as great as for diffuse disease. Progression was larger in severely diseased segments and in the right coronary artery.

Angiographic changes

The extent of progression was small, with a loss of 0·02 (0·7%) mm and 0·03 mm (1·5%) per year for mean and minimal lumen diameter as measures for diffuse and focal atherosclerosis, respectively. The loss in vessel lumen size in our study was smaller than that found in other angiographic trials (Table 5). Apart from the

Table 3 Changes at 4 years stratified for severity of disease at baseline and for vessel

	Severity of disease			
	Non-diseased	Mildly diseased	Moderately diseased	Severely diseased
Mean lumen diameter (mm)	−0·07 ± 0·02	−0·06 ± 0·02	−0·13 ± 0·05	−0·19 ± 0·11
Minimal lumen diameter (mm)	−0·34 ± 0·05	−0·07 ± 0·02	−0·05 ± 0·03	0·06 ± 0·08
	Coronary vessel			
	RCA	LM	LAD	LCX
Mean lumen diameter (mm)	−0·16 ± 0·04	−0 11 ± 0 06	−0·03 ± 0·02	−0·05 ± 0·03
Minimal lumen diameter (mm)	−0·22 ± 0·04	−0·18 ± 0·09	−0·07 ± 0·02	−0·07 ± 0·03

Values are means ± SE; non-diseased = percentage diameter stenosis <20%, mildly diseased = percentage diameter stenosis ≥20%–<35%; moderately diseased = percentage diameter stenosis ≥35%–<50%; severely diseased = percentage diameter stenosis ≥50%. RCA = right coronary artery; LM = left main; LAD = left anterior descending; LCX = left circumflex.

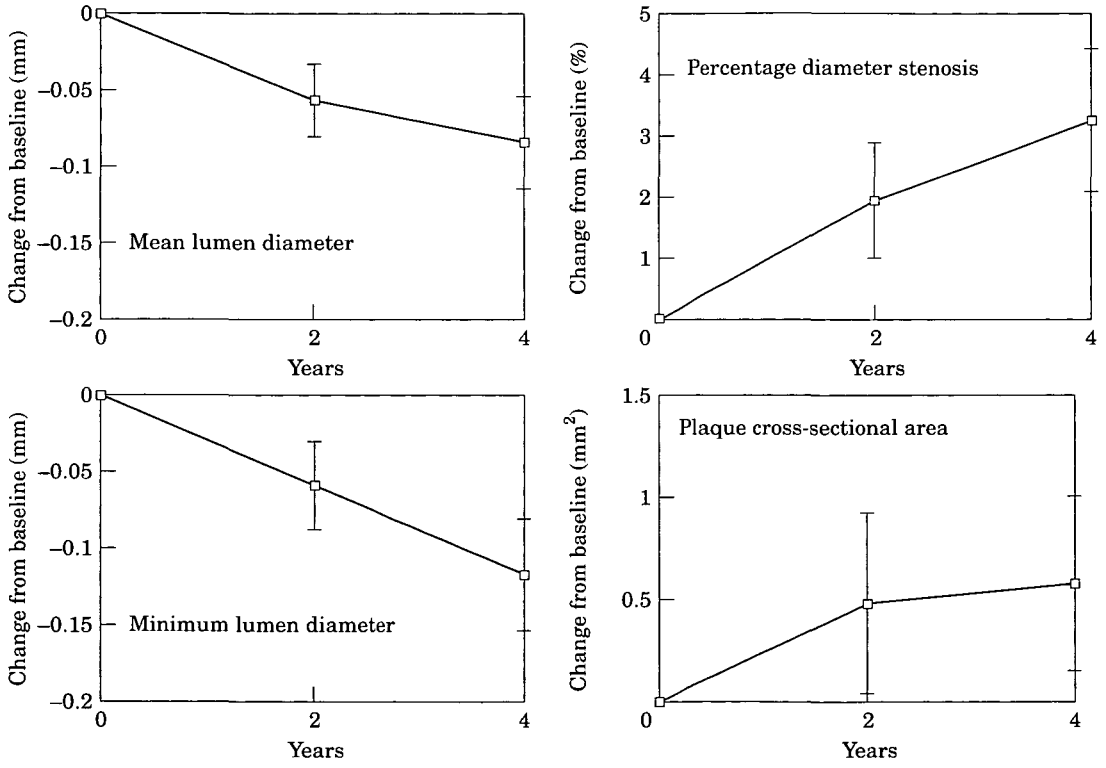

Figure 2 **Changes over time from baseline to 2- and 4-year follow-up for mean lumen diameter, minimum lumen diameter, percentage diameter stenosis, and plaque area.**

differences between the patients included, this might be caused by the fact that we used the average of two orthogonal projections instead of one projection in which the stenosis was most severe. Furthermore, we selected coronary segments at baseline and not by inspection of the baseline and follow-up angiogram together, so that we included segments that showed no visibly assessed changes.

We have shown that the rate of progression of focal atherosclerosis is similar in angiographically non-diseased segments as in the mildly and moderately diseased sections of the coronary tree. This finding supports the hypothesis that assessment of lesion change alone is not sufficient in describing progression of coronary atherosclerosis. Only when the change in mean lumen diameter of all coronary segments, angiographically diseased and non-diseased, is measured, is the process of atherosclerosis change described completely[22].

The loss in vessel lumen was largest in the right coronary artery, as was found by Jost *et al.*[26]. The progression of diffuse atherosclerosis was most

Table 4 Categorical classification of change between baseline, 2- and 4-year follow-up

	2 years		4 years	
	Number	(%)	Number	(%)
Segment classification (n=965)				
Progression of lesion	30	(3·1)	42	(4 4)
New lesion	30	(3·1)	40	(4·2)
Stable lesion	377	(39·1)	354	(36·7)
Regression of lesion	20	(2·1)	22	(2·3)
Disappeared lesion	9	(0·9)	18	(1·9)
Non-diseased segment	499	(51·7)	489	(50·1)
Patient classification (n=129)				
Progressor	39	(30·2)	47	(36·4)
Mixed responder	10	(7·8)	15	(11·6)
Stable	68	(52·7)	47	(36·4)
Regressor	12	(9·3)	20·(15·5)	

prominent in the moderately and severely diseased segments, −0·12 mm and −0·19 mm, respectively. The minimum lumen diameter in these subgroups, however, did not change significantly so that the segments containing the more severe lesions only showed progression of diffuse disease. The progression of focal disease appeared to be largest in the segments with a percentage diameter stenosis <20% at baseline, suggesting that progression of focal atherosclerosis is more prominent in angiographically new lesions that begin to encroach on the vessel lumen.

Most subgroups showed gradual progression of both diffuse and focal atherosclerosis over time. However, segments located in the left circumflex artery mainly progressed in the first 2 years, and segments in the left anterior descending coronary artery between 2 and 4 years. The categorical classification of progression/regression per segment showed that 87% of segments did not change substantially over 4 years and that only 1 out of 12 lesions progressed and 1 out of 25 regressed. For the per patient classification, however, changes were more pronounced, with 36% of patients stable and 48% progressors or mixed repondes. There was a gradual worsening of coronary disease over time in both the per segment and the per patient classification.

Limitations of the study

The results of our study were biased, as in all angiographic trials[25], since follow-up angiography was not available in patients who had a clinical event or refused angiography, which in some cases might be related to their clinical status. The rate of progression found will therefore underestimate the actual tempo of atherosclerosis progression. We only included patients with proven coronary artery disease of a severity not requiring revascularization and with moderately elevated cholesterol levels. Studies on the angiographic course of coronary atherosclerosis in patients with or without severe disease are not feasible since it is unethical to perform angiography in the former and to withhold therapy in the latter.

Angiographic methods

The use of validated quantitative coronary analysis techniques has become mandatory in assessing coronary atherosclerosis change from cinangiograms[22]. We used orthogonal multiple matched views[24] which is different from other studies in which only the projection in which the stenosis was most severe was used[10]. Our method will therefore be more specific though less sensitive to angiographic changes of the lumen. The selection of coronary segments was made at baseline where, when possible, orthogonal projections of 11 proximal

Table 5 Overview of quantitative coronary angiography studies with changes per year

Study	Number of patients	Change MLD (mm/year)	Change DS (%/year)	Change MD (mm/year)
FATS[4]	42	−0·020	0·8	
MARS[9]	124	−0·030	1·1	
STARS[7]	24	−0·053	1·9	−0·043
CCAIT[10]	146	−0·045	1·1	
SCRIP[11]	127	−0·045	0·7	−0·027
The present study	129	−0·029	0·8	−0·020
HARP[8,12]	39	−0·048	0·8	−0·037
PLAC I[13]	157	−0·050	1·1	−0·040
REGRESS[14]	327	−0·045		−0·050
BECAIT[18]	39	−0·034	0·9	−0·016
Overall*	1154	−0·039	1·0	−0·036

MLD=minimum lumen diameter; DS=percentage diameter stenosis; MD=mean lumen diameter; *weighted mean.

segments were taken. Other investigators selected frames for quantitative analysis at the end of the study with both the baseline and follow-up angiograms available[9,10,17]. The latter method of selection will result in a bias towards projections and segments that are changed and might therefore result in an over-estimation of the rate of atherosclerotic change.

Clinical relevance

The rate of progression of coronary atherosclerosis measured by quantitative coronary angiography was small. Combining the information of the prospective angiographic trials yielded an annual loss of 0·04 mm in minimum lumen diameter, and a loss of 0·03 mm in mean lumen diameter. However, all angiographic studies were short relative to the time course of coronary atherosclerosis[27], and one should keep in mind that when this progression rate is taking place over 10 to 20 years, important reductions in vessel lumen will occur. Although the angiographic changes are small, in two prospective studies, one analysed visually [28] and the other using quantitative coronary angiography[29] the small angiographic changes are shown to be clinically important because they are predictive of subsequent clinical coronary events; similarly the absence of angiographic progression was predictive of an uneventful course.

Conclusion

The rate of angiographic progression of coronary atherosclerosis in this cohort of patients with mild coronary artery disease was relatively small and more prominent in focal than in diffuse disease, with an annual loss of 0·03 mm in minimum and 0·02 mm in mean lumen diameter, respectively. Only a small minority of lesions progressed and few new lesions developed. The distribution of progressed lesions, however, was equally distributed over patients, so that the number of patients classified as progressors was substantial. Spontaneous regression was rare both on a segmental as on a patient level. Serial quantitative angiography showed that diffuse and focal coronary atherosclerosis gradually progressed over time in non-stenosed and stenosed coronary segments.

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Appendix

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