Retardation of Progression of Coronary Atherosclerosis

Vertraging van Progressie van Coronairsclerose

Cover: Changes in quantitative angiographic measurements for 272 patients (129 placebo: contineous line, 143 simvastatin: dotted line) with matched angiograms at baseline, 2 and 4 years. Effect of cholesterol lowering on the progression of diffuse coronary atherosclerosis (mean lumen diameter) in the upper panel and on the progression of focal disease (minimum lumen diameter) in the lower panel. Means and 95% confidence interval. *MAAS investigators. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). Lancet 1994;344:633-638.*

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Chapter 1

INTRODUCTION

Introduction

Atherosclerosis is the leading cause of death and a major contributor to morbidity in the Western World. In the Netherlands approximately 40.000 patients die each year of this disease and 145.000 patients are admitted to a hospital because of it's sequelae.[1] Consequently, atherosclerosis also causes large costs for the community. Within the group of atherosclerotic diseases coronary atherosclerosis is most prominent.[1]

Coronary atherosclerosis is a chronic progressive degenerative disease of the arterial vessel wall.[2] The process begins in early childhood[3] and, usually from the fifth decade on, the advanced stages cause narrowing of the vessel lumen, with plaque fissuring and thrombosis and subsequent occlusion of the vessel.[4] These phenomena are responsible for the clinical sequelae stable and unstable angina pectoris, acute myocardial infarction and sudden death.[4] Also, ischemic heart disease is the most frequent cause of heart failure.[5]

Many effective treatments for either chronic or acute obstructive coronary artery disease have found their place in clinical practice. Medical therapy, percutaneous transluminal coronary angioplasty, coronary artery bypass surgery, and in some patients heart transplantation are applied to treat the consequences of coronary atherosclerosis.[6] These therapies, however, are all basically palliative and do not influence the progressive nature of the disease. Moreover, they only treat the target organ.

Epidemiologic studies have identified qualities associated with an increased risk for coronary artery disease. The most important risk factors are a non-beneficial lipid profile, with a high total cholesterol, high low-density lipoprotein cholesterol (LDL-C), a low high-density lipoprotein cholesterol (HDL-C), and elevated triglycerides; arterial hypertension, smoking, diabetes mellitus, male sex and age.[7] Correction of these factors could lower the risk of coronary artery disease, and might also retard the progression of the disease.

A large body of evidence has made the cholesterol-atherosclerosis link generally accepted.[8] The lipid hypothesis postulates that progression of coronary atherosclerosis can be slowed, stopped or that indeed regression could be induced by lowering plasma cholesterol, which will ultimately result in an improved clinical outcome. For many years evidence has been available that cholesterol enriched diets induce atherosclerosis in animals[9] and that by changing the diet atherosclerotic lesions can regress in these experiments.[10] However, early intervention trials in humans showed a reduction in coronary artery disease related events, but did not demonstrate an effect on total mortality. Therefore, scepticism on the benefit of lipid-lowering interventions remained.[11]

The development of quantitative coronary angiography brought forward an imaging technique that can actually show slowing, arrest and regression of both diffuse and focal coronary atherosclerosis.[12] This development and the evolution of a new class of cholesterol lowering drugs, the HMG-CoA reductase inhibitors,[13] initiated a series of angiographic studies[14] as well as trials with clinical endpoints that finally proved the lipid hypothesis in humans.[15-17]

The present study deals with the effect of cholesterol lowering therapies on the angiographic development of coronary atherosclerosis. It focuses on the effect of simvastatin on coronary atheroma studied by serial quantitative coronary angiography, as investigated in the Multicentre Anti-Atheroma Study: MAAS.[18] A general introduction is provided in the first chapter. Chapter 2 is a review applying meta-analysis techniques of previous angiographic coronary atherosclerosis trials with lipid-lowering therapy, lifestyle changes, and treatment with dihydropyridine calcium antagonists. Also methodological considerations of angiographic trials, and different aspects of coronary angiography are discussed. In chapter 3 the effect of cholesterol lowering therapy with the HMG-CoA reductase inhibitor simvastatin on coronary atheroma is described. This was a randomised, double-blind, parallel group, 4 year angiographic study in 381 patients with mild coronary artery disease. The natural course of both focal and diffuse coronary atherosclerosis is depicted in chapter 4. For 126 patients not on lipid-lowering therapy, 3 consecutive angiograms over a 4 years period were analyzed quantitatively. In chapter 5 a multivariate analysis is reported which selects independent predictors for progression of coronary artery disease from clinical, lipid and angiographic patient characteristics, using data from 345 patients who took part in the MAAS trial. Chapter 6 characterises the incidence and the angiographic patterns of lesion change. This study describes the changes seen in 924 lesions of 272 patients in whom 3 angiograms each 2 years apart were made. The overall reproducibility of the angiographic core laboratory is presented in chapter 7. This is a study performed in 10 patients from whom baseline and follow-up angiograms were analyzed twice. Chapter 8 is a meta-analysis of clinical events in the angiographic trials. A general discussion of the results and implications for clinical practice are presented in chapter 9. It is concluded that cholesterol lowering retards the angiographic progression of coronary atherosclerosis which ultimately results in a reduction of clinical events.

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Chapter 2

RETARDATION AND ARREST OF PROGRESSION OR REGRESSION OF CORONARY ARTERY DISEASE: A REVIEW

Retardation and Arrest of Progression or Regression of Coronary Artery Disease: A Review

Jeroen Vos, Pim J. de Feyter, Maarten L. Simoons, Jan G.P. Tijssen, and Jaap W. Deckers

ATHEROSCLEROSIS is the most common cause of death in the Western world accounting for one half of all deaths.[1] Hypercholesterolemia, smoking, hypertension, diabetes mellitus, obesity, and physical inactivity are identified as risk factors for this disease.[2-6] Control of all these factors is desirable, but cholesterol lowering has showed the greatest promise as regards reduction of cardiac events.[7] Both primary and secondary intervention trials[8-11] have demonstrated that cardiac mortality decreases after lowering of plasma cholesterol levels, although total mortality was not impacted.[12,13]

In animal models atherosclerotic lesions regress after a change in diet or the administration of lipid-lowering drugs.[14-16] Calcium antagonists have been reported to prevent the development of atherosclerosis in animal models.[17] In these experiments lesions characterized by large amounts of intracellular lipids, in contrast to the extracellular lipid accumulations characteristic of human atherosclerosis, were induced in a short time (3 to 24 months) by diets that resulted in excessively high plasma cholesterol levels ($\geq$20 mmol/L).[16] Although these experiments have provided extensive insight into the pathological process, it is not justified to completely extrapolate these results to humans.

To describe the effect of an intervention on the development of coronary artery disease (CAD) a trial with clinical end points only, acute myocardial infarction and cardiac death, is not sufficient. First, lesion growth is often asymptomatic.[18] Second, when progression of atherosclerosis is considered only if it has led to a cardiac event, one is not only monitoring slow progression but many other factors, such as plaque rupture, thrombosis, and vasospasm capable of causing acute progression.[19-23] Third, in such a trial no distinction can be made between arrest, retardation of progression or regression of coronary atherosclerosis, and between diffuse and focal disease.[24]

Many angiographic studies in men have been performed,[25-41] of which some reported regression of atherosclerosis in only a minority of patients, which could be explained by clot lysis in half of the cases.[36] However, these studies were often observational, retrospective, small, uncontrolled, and performed when quantitative coronary angiography was not available.

Currently, the only method that can assess coronary or femoral atherosclerosis over time is repeated angiography.[24] This article reviews the published controlled trials using serial coronary angiography with a lipid-modifying treatment, with calcium antagonists, and with lifestyle changes and the femoral atherosclerosis trials with lipid-modifying therapy.

METHODS

Selection

Studies were considered if they fulfilled the following criteria: (1) the coronary or femoral artery anatomy was the object of the study, (2) repeated coronary or femoral angiography was used, (3) the study had an appropriate control group with which the treatment under study was compared, and (4) the lipid-modifying treatment resulted in a beneficial change of the lipid profile. In order to find trials that could fit these criteria, a computer-assisted literature search was performed, and references of papers were checked. The following trials were selected. Coronary atherosclerosis with a lipid-modifying treatment: National Heart Long Blood Institute type II trial (NHLBI type II),[42] Cholesterol Lowering Atherosclerosis Study (CLAS),[43] Program On the Surgical Control of the Hyperlipidemias (POSCH),[44] Familial Atherosclerosis Treatment Study (FATS),[45] Kane et al,[46] and the St Thomas' Atherosclerosis Regression Study

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(STARS)[47]; coronary atherosclerosis with a change in lifestyle: Lifestyle Heart Study[48,49]; coronary atherosclerosis with calcium anatagonists: International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT),[50] and Waters et al[51]; femoral atherosclerosis with lipid-modifying therapy: Duffield et al,[52] Olsson et al,[53] and CLAS.[54] One study was rejected because no substantial lipid-lowering effect was accomplished,[55] and two studies were not included because the control group was not properly selected. One study[56] compared initial responders with nonresponders to lipid lowering, another trial[57] compared the lipid-modified group with a group of patients from another trial. Three studies were excluded because they did not give sufficient information to make a comparison possible.[58-60]

Statistical Considerations

For each trial, relative risks with 95% confidence intervals for progression and regression of atherosclerosis were calculated.[61] The relative risk is greater than one if the number of patients with progression or regression of CAD is increased in the index group. Because the definitions of change in coronary status differed between the trials, and no common angiographic end point could be defined, the definitions of progression and regression applied by the investigators of each individual study were used. For the FATS and the STARS studies, the two active treatment groups were combined. To obtain an overall measure of effect, the combined relative risks for progression and regression of atherosclerosis were calculated. The selected studies were pooled on the basis of common design characteristics, eg, coronary or femoral atherosclerosis, lipid-modifying therapy or treatment with calcium antagonists and not based on the result of a statistical test on heterogeneity of effect across the trials. The adjusted Mantel-Haenszel relative risk with 95% confidence interval was calculated.[62] To explore the relation between the magnitude of the lipid-regulating effect and the likelihood of progression or regression, linear regression analysis was performed with each trial as a unit of analysis.[63] The relative risks for progression and regression of CAD were taken as dependent variables.

DESCRIPTION OF THE TRIALS

Coronary Atherosclerosis Trials

The design characteristics and the lipid and angiographic results of the selected trials are listed in Tables 1 through 5. Brensike et al[42,64] treated patients with type 2 hyperlipoproteinemia, low-density lipoprotein (LDL) in the upper 10th of the distribution of the general population, and proven CAD with diet alone (N = 72) or with diet and cholestyramine (N = 71) in a randomized double-blind manner. Coronary angiography was performed at baseline and after 5 years. Angiograms were assessed visually by a panel of experts. A decrease of 16% in total cholesterol, 21% in LDL, and an increment of 6% in high-density lipoprotein (HDL) were accomplished. Progression of CAD was noted in 49% of the placebo group and in 32% of the cholestyramine group. Regression was found in 7% in each group. Twelve patients (17%) in the placebo group versus 8 (11%) in the cholestyramine group died or suffered from an acute myocardial infarction (relative risk, 0.68; 95% confidence interval, 0.30, 1.56).

In the CLAS,[43,65] nonsmoking, male patients with previous coronary bypass surgery and plasma cholesterol levels between 4.8 and 9.1 mmol/L were treated with either diet alone (N = 94) or diet, colestipol, and nicotinic acid (N = 94). Patients were recruited by advertising in newspapers, on radio, and on television. Before randomization, all eligible patients were given the lipid-modifying drugs, and only those patients who had a reduction in total cholesterol of $\geq 15\%$ entered the trial. The study was randomized and double-blind for treatment, plasma lipid values, and angiograms. Coronary angiograms were repeated after 2 years of treatment and were judged by a panel of experts. Each patient was classified according to a global score of change, taking into account both the native coronary circulation and the bypass grafts.[66] Total cholesterol decreased by 26%, LDL by 43%, and HDL increased by 37%. Progression of CAD was observed in 61% and regression in 2.4% of the placebo group; for the lipid-modified group, the figures were 39% and 16%, respectively. Twenty-two patients in the placebo group and 21 (both 22%) in the lipid-

Table 1. Coronary Angiographic Atherosclerosis Trials

Study	Analysis	Treatment	Number	Duration (yr)	Type of Patients
Coronary atherosclerosis trials with lipid-modifying therapies					
NHLBI Type II Trial (1984)	Visual panel	R) placebo*	57	5	Proven CAD, 82% NYHA I, type II hyperlipoproteinemia, mean age 48 years
		I) cholestyramine*	59		
CLAS (1987)	Visual panel	R) placebo*	82	2	PostCABG, TC between 4.8-9.1 mmol/L, mean age 54 years
		I) colestipol/niacin*	80		
POSCH (1990)	Visual panel	R) usual care*	333	3	Post MI, TC ≥ 5.7 mmol/L, mean age 51 years
		I) partial ileal bypass surgery*	363	(max 8)	
FATS (1990)	Quantitative and visual	R) conventional*	46	2.5	Apolipoprotein B ≥ 125 mg/dL, 1 lesion ≥ 50%, family history of CAD, 67% angina, mean age 47 years
		I) lovastatin/colestipol*	38		
		I) niacin/colestipol*	36		
Kane et al (1990)	Quantitative	R) placebo/resin*	32	2	Familial hypercholesterolemia: tendon xanthomas, LDL ≥ 5.17 and TG ≥ 3.1 mmol/L, mean age 42 years
		I) colestipol/niacin/lovastatin*	40		
STARS (1992)	Quantitative	R) usual care	24	3	Proven CAD, TC between 6.0-10.0 mmol/L, mean age 51 years
		I_1) lipid-lowering diet	26		
		I_2) diet/cholestyramine	24		
Coronary atherosclerosis trials with lifestyle changes					
Lifestyle Heart Trial (1990)	Quantitative	R) usual care	19	1	Angiographically proven CAD, no lipid-modifying drugs, age 58 years
		I) lifestyle changes	22		
Coronary atherosclerosis trials with calcium antagonists					
INTACT (1990)	Quantitative and visual	R) placebo	175	3	Mild CAD, 1 cardiac risk factor, 63% NYHA I, mean age 53 years
		I) nifedipine	173		
Waters et al (1990)	Quantitative and visual	R) placebo	167	2	5% to 75% stenoses in at least four segments, 62% stable angina pectoris, mean age 61 years
		I) nicardipine	168		

Abbreviations: R, reference group; I, index group; TC, total cholesterol; TG, triglycerides; number, patients with angiographic follow-up.

*Dietary counseling.

modified group had a cardiac event. At the end of the study, patients who were willing to continue entered a 2-year extension of the trial which showed a sustained effect on lipids and angiography at 4 years.[67] Other end points of the CLAS trial were the angiographically assessed change in femoral atherosclerosis and the echo-Doppler evaluation of carotid atherosclerotic disease.

Buchwald et al[44,68,69] performed a large survival trial in patients after they had a first myocardial infarction and who had total cholesterol levels of ≥5.7 mmol/L or ≥5.2 mmol/L in combination with a LDL level of ≥3.6 mmol/L while on a diet. Patients were randomly allocated to diet and partial ileal bypass surgery[70] (N = 421) or diet only (N = 417). All analyses were reported on the basis of the intention-to-

Table 2. Definitions of Progression and Regression of CAD in Coronary Angiographic Atherosclerosis Trials

Study	Definition
Coronary atherosclerosis trials with lipid-modifying therapies	
NHLBI Type II Trial	Definite progression: ≥ 1 lesion with definite progression and no lesion with regression
	Probable progression: ≥ 1 lesion with probable progression and no lesion with regression or definite progression
	Probable regression: ≥ 1 lesion with probable regression and no lesion with definite regression or any progression
	Definite regression: ≥ 1 lesion with definite regression and no progression
	Mixed response: regression and progression: lesion progression and regression in the same patient, whether definite or probable
	No change: no lesion observed as changed by at least two panels
CLAS	CLAS consensus global change score: 0, no change; 1, definitely discernable; 2, moderate; 3, extreme; −, regression; +, progression
POSCH	CLAS consensus global change score: 0, no change; 1, definitely discernable; 2, moderate; 3, extreme; −, regression; +, progression
FATS	Progression: 10% increase in percentage stenosis, regression vice versa
Kane et al	10% increase in percentage stenosis, regression vice versa; change in % area stenosis
STARS	Progression: loss of ≥ 0.17 mm in mean absolute width, regression gain ≥ 0.17 mm
Coronary atherosclerosis trials with lifestyle changes	
Lifestyle Heart Trial	Change in % stenosis as a continuous measure; positive, progression; negative, regression
Coronary atherosclerosis trials with calcium antagonists	
INTACT	Progression: a decrease of > 0.4 mm in minimal lumen diameter, an increase in % stenosis > 20%; regression, vice versa
Waters et al	Progression: a decrease of > 0.4 mm in minimal lumen diameter, an increase in % stenosis of > 10%; regression, vice versa

treat principle. The mean duration of follow-up was 8.7 years. The main end point of the trial was total mortality. Apart from the clinical end points, sequential coronary angiography was performed at baseline and after 3, 5, 7, and 10 years. Angiograms were assessed as in the CLAS trial.[66] Total cholesterol and LDL decreased 32% and 35%, respectively; HDL increased 6%. Total mortality was reduced by 22% (95% confidence interval, 17%, 47%) and cardiovascular death combined with nonfatal acute myocardial infarction was reduced by

Table 3. Lipid Results of Coronary Angiographic Atherosclerosis Trials With Lipid-Modifying Therapies

		Total Cholesterol			LDL Cholesterol			HDL Cholesterol			Triglycerides		
Study	Group	B	T	C(%)	B	T	C(%)	B	T	C(%)	B	T	C(%)
Coronary atherosclerosis trials with lipid-modifying therapies													
NHLBI Type II Trial	R	7.59	7.49	−1	5.93	5.67	−5	1.01	1.01	2	1.48	1.86	26
	I	8.03	6.63	−17	6.27	4.61	−26	0.98	1.06	8	1.76	2.25	28
CLAS	R	6.28	6.00	−4	4.36	4.13	−5	1.13	1.15	2	1.74	1.59	−5
	I	6.35	4.65	−26	4.42	2.51	−43	1.15	1.57	37	1.71	1.26	−22
POSCH	R	6.48	6.14	−5	4.62	4.30	−7	1.05	1.04	−1	2.26	2.17	−4
	I	6.50	4.71	−36	4.62	2.68	−42	1.03	1.08	5	2.33	2.60	12
FATS	R	6.79	6.55	−4	4.53	4.20	−7	0.98	1.04	6	2.69	2.98	15
	I_1	7.12	4.71	−34	5.08	2.77	−45	0.91	1.06	16	2.27	2.07	−9
	I_2	6.99	5.41	−23	4.92	3.34	−32	1.01	1.42	41	2.19	1.55	−29
Kane et al	R	9.49	8.67	−8	7.11	6.27	−12	1.31	1.32	0	1.24	1.29	4
	I	9.79	6.75	−31	7.32	4.45	−39	1.22	1.53	25	1.49	1.17	−21
STARS	R	7.07	6.93	−2	4.82	4.67	−3	1.22	1.21	−1	2.32	2.35	1
	I_1	7.19	6.17	−14	5.00	4.19	−16	1.14	1.14	0	2.31	1.85	−20
	I_2	7.44	5.56	−25	5.26	3.37	−36	1.24	1.19	−4	2.20	2.21	0
Coronary atherosclerosis trials with lifestyle changes													
Lifestyle Heart Trial	R	6.34	6.00	−5	4.32	4.07	−6	1.35	1.31	−3	2.45	2.24	−9
	I	5.88	4.46	−24	3.92	2.46	−37	1.00	0.97	−3	2.38	2.91	22

NOTE. All values are in mmol/L.

Abbreviations: R, reference group; I, index group; B, at baseline; T, during the trial; C, percentage change.

RETARDATION/ARREST OF PROGRESSION OR REGRESSION OF CAD

Table 4. Angiographic Results of Coronary Atherosclerosis Trials: Progression of CAD

Study	Group	Number of Patients (Progression/Total)	Rate (%)	Relative Risk (95% CI)
Coronary atherosclerosis trials with lipid-modifying therapies				
NHLBI Type II Trial	R	28/57	49	0.66 (0.42, 1.03)
	I	19/59	32	
CLAS	R	49/80	61	0.64 (0.46, 0.88)
	I	32/82	39	
POSCH	R	138/333	41	0.68 (0.55, 0.84)
	I	102/363	28	
FATS	R	21/46	46	0.50 (0.30, 0.85)
	$I_{1\&2}$	17/74	23	
Kane et al.	R	13/32	41	0.50 (0.23, 1.04)
	I	8/40	20	
STARS	R	11/24	46	0.31 (0.14, 0.69)
	$I_{1\&2}$	7/50	14	
Overall result				**0.62 (0.54, 0.72)**
Coronary atherosclerosis trials with lifestyle changes				
Lifestyle Heart Trial	R	10/19	53	0.35 (0.13, 0.92)
	I	4/22	18	
Coronary atherosclerosis trials with calcium antagonists				
INTACT (0.4 mm)	R	54/175	31	0.82 (0.59, 1.16)
	I	44/173	25	
Waters et al (0.4 mm)	R	61/167	37	1.06 (0.80, 1.40)
	I	65/168	39	
Overall result				**0.95 (0.77, 1.18)**

Abbreviations: R, reference group; I, index group; 95% CI, 95% confidence interval.

Table 5. Angiographic Results of Coronary Atherosclerosis Trials: Regression of CAD

Study	Group	Number of Patients (Regression/Total)	Rate (%)	Relative Risk (95% CI)
Coronary atherosclerosis trials with lipid-modifying therapies				
NHLBI Type II Trial	R	4/57	7.0	0.97 (0.25, 3.68)
	I	4/59	6.8	
CLAS	R	2/80	2.4	6.67 (1.55, 28.89)
	I	13/80	16.2	
POSCH	R	24/333	7.2	1.26 (0.76, 1.09)
	I	33/363	9.1	
FATS	R	5/46	11	3.20 (1.34, 7.62)
	$I_{1\&2}$	26/74	35	
Kane et al	R	4/32	13	2.60 (0.94, 7.20)
	I	13/40	33	
STARS	R	1/24	4.2	8.64 (1.22, 61.0)
	$I_{1\&2}$	18/50	36	
Overall result				**2.13 (1.53, 2.98)**
Coronary atherosclerosis trials with lifestyle changes				
Lifestyle Heart Trial	R	8/19	42	1.90 (1.11, 3.41)
	I	18/22	82	
Coronary atherosclerosis trials with calcium antagonists				
INTACT (0.4 mm)	R	30/175	17	0.71 (0.42, 1.19)
	I	21/173	12	
Waters et al (0.4 mm)	R	21/167	13	1.47 (0.88, 2.45)
	I	31/168	19	
Overall result				**1.02 (0.72, 1.46)**

Abbreviations: R, reference group; I, index group; 95% CI, 95% confidence interval.

Table 6. Femoral Angiographic Atherosclerosis Trials

Study	Analysis	Treatment	Number	Duration	Type of Patient
Duffield et al (1983)	Quantitative and visual	R) placebo*	12	18 months	Claudicatio intermittens for ≥ 6 months, TC ≥ 6.5 mmol/l and/or TG ≥ 1.8 mmol/l, mean age 55 years
		I) diet, cholestyramine, colestipol, nicotinic acid*	12		
Olsson et al (1990)	Visual	R) placebo;	20	18 months	Hyperlipoproteinemia, no symptoms of cardiovascular disease, TC ≥ 9.5 mmol/L and/or TG ≥ 3.5 mmol/L, mean age 52 years
		I) nicotinic acid, fenofibrate*	23		
CLAS (1991)	Quantitative and visual	R) placebo*	76	2 years	PostCABG, TC between 4.8 and 9.1 mmol/L, mean age 54 years
		I) colestipol-niacin*	77		

Abbreviations: R, reference group; I, index group; TC, total cholesterol; TG, triglycerides; number, patients with angiographic follow-up.

*Dietary counseling.

35% (95% confidence interval, 9%, 53%). Progression of CAD measured after 3 years was found in 41% of the control group versus 28% of the operated group. Regression occurred in 7% versus 9% of the patients.

Brown et al[45,71] reported a randomized study in men with apolipoprotein B levels ≥ 125 mg/dL, proven CAD, and a positive family history of vascular disease. Patients were treated with diet and placebo (N = 27) or colestipol (N = 20), lovastatin and colestipol (N = 38), and nicotinic-acid and colestipol (N = 36). Patients were followed for 2.5 years. The coronary angiograms were analyzed both visually and quantitatively.[72] Total cholesterol was reduced by 30% and 19%, LDL by 38% and 25%, and HDL was increased by 20% and 35% for the colestipol/lovastatin and nicotinic-acid/colestipol groups respectively relative to the conventionally treated group. Angiographic progression was noted in 46%, 21%, and 25%, and regression was noted in 11%, 32%, and 39% for the placebo/colestipol, colestipol/lovastatin, and the nicotinic-acid/colestipol groups, respectively. Less clinical events defined as death, acute myocardial infarction, or new refractory ischemia requiring revascularization were observed in the lipid-modified group: 10 (19%) versus 5 (5%) (relative risk, 0.28; 95% confidence interval, 0.10, 0.77).

Table 7. Definitions of Progression and Regression in Femoral Angiographic Atherosclerosis Trials

Study	Definition
Duffield et al	Visual: change in plaque height Quantitative: a positive or negative change in the edge irregularity index
Olsson et al	A positive or negative change in per segment score (0, no lesion; 1, single plaque <50%; 2, more than 1 plaque <50%; 3, single plaque >50%; 4, more than one plaque >50%) A positive or negative change in overall atherosclerosis score (the average segment score)
CLAS	Progression: progression in at least 1 segment no change in others Regression: regression in at least 1 segment no change in others No change: no change in all segments In case of mixed response: the modal segmental response was taken

In the trial performed by Kane et al,[46] both males and females with heterozygous familial hypercholesterolemia, proven CAD, tendon xanthomas, LDL cholesterol ≥ 5.2 mmol/L, triglycerides ≥ 3.1 mmol/L, or without tendon xanthomas but with a first-degree relative with xanthomas and LDL ≥ 6.5 mmol/L were provided with conservative treatment (N = 49) or a combination of LDL-lowering drugs (N = 48) in a randomized, unblinded fashion. Drugs used were colestipol, resin, nicotinic-acid, and lovastatin. Quantitative coronary analysis was performed at baseline and after 2 years.[72] Total cholesterol, LDL, and HDL were changed by −23%, −37%, and 25%, respectively. Progression of CAD took place in 41% and 20% and regression in 13% and 33% of the placebo and

Table 8. Lipid Results of Femoral Angiographic Atherosclerosis Trials

Study	Group	Total Cholesterol			LDL Cholesterol			HDL Cholesterol			Triglycerides		
		B	T	C(%)	B	T	C(%)	B	T	C(%)	B	T	C(%)
Duffield et al	R	7.72	7.48	3	5.19	5.13	−1	1.20	1.10	−8	3.10	2.87	−7
	I	8.06	6.06	−25	5.41	3.91	−28	1.23	1.55	26	3.25	1.80	−45
Olsson et al	R	8.10	8.00	1	5.74	5.23	−9	1.29	1.33	3	2.67	2.53	−5
	I	9.86	6.37	−35	6.44	3.89	−40	1.47	1.81	23	2.86	1.16	−59
CLAS	R	6.25	5.99	−4	4.34	4.14	−5	1.13	1.13	0	1.74	1.61	−7
	I	6.32	4.62	−27	4.39	2.48	−44	1.13	1.55	37	1.73	1.26	−27

NOTE. All values are in mmol/L.

Abbreviations: R, reference group; I, index group; B, at baseline; T, during the trial; C, percentage change.

the lipid-modified groups, respectively. The mean change in percent area stenosis was −1.53% in the conventional and 0.80% in the lipid-modified group. After stratification for sex, the angiographic benefit expressed in percent area stenosis was statistically significant in females but not in males. Only 1 patient, a control group subject, had a cardiac event.

STARS[47] tested a lipid-lowering diet alone and a diet in combination with cholestyramine to neither diet or medication. In the lipid-lowering diet, total fat intake was reduced to 27% of dietary energy. Saturated fatty acid constituted 8% to 10% of dietary energy. Male patients with total cholesterol levels between 6.0 and 10.0 mmol/L, without previous revascularization procedure, were enrolled in a short trial to test tolerability and responsiveness to cholestyramine. Quantitative coronary angiography was performed at baseline and after 3 years.[73] Ninety patients were recruited. Total cholesterol levels decreased by 12% and 23% and LDL by 13% and 33% in the diet and diet-cholestyramine groups, respectively. HDL remained at the same level in all treatment groups. Progression of CAD was found in 46% and 14% and regression in 4.2% and 36% of the usual care and the lipid-modified groups, respectively. The change in mean coronary diameter was 0.20 mm, 0.03 mm, and 0.10 mm in the usual care, the diet, and the diet-cholestyramine groups, respectively. Ten cardiac events (36%) took place in the usual care group versus four (8%) in the lipid-modified group (relative risk, 0.21; 95% confidence interval, 0.07, 0.61).

The Lifestyle Heart Study[48] investigated whether comprehensive lifestyle changes could influence CAD. Patients with proven CAD were randomly assigned to either a control group (N = 20) or to an experimental group (N = 28) that was exposed to a low-fat vegetarian diet, stress-management techniques, individually prescribed exercise, and twice-weekly (4 hours) group meetings for social support to adhere to the treatment program. Dietary energy consisted of 10% of fat intake, of which less than 50% was unsaturated fat. No lipid-modifying drugs were allowed. Angiograms were assessed quantitatively[74] at baseline and after 1 year. As an indication of overall compliance to the proposed lifestyle changes, a total adherence score was defined. This score was one if the program was followed completely. For the control group the adherence was 0.56 and 0.62 at baseline and after 1 year, respectively. For the experimental group these figures were 0.55 and 1.22 indicating a more than sufficient compliance. Differences between the groups in total cholesterol, LDL, and HDL were −19%, −31%, and 0%, respectively. Both blood pressure and bodyweight decreased in the experimental group. The frequency of anginal attacks decreased in the experimental group (−90%) and increased in the control group (160%). Progression and regression of CAD were observed in 53% and 42% and in 18% and 82% in the usual care and

Table 9. Angiographic Results of Femoral Atherosclerosis Trials: Progression of CAD

Study	Group	Number of Patients (Progression/Total)	Rate (%)	Relative Risk (95% CI)
Duffield et al	R	27/156	17	0.40 (0.20, 0.80)
	I	10/144	7	
Olsson et al	R	10/25	40	0.59 (0.22, 1.57)
	I	4/17	24	
CLAS	R	30/76	40	0.70 (0.44, 1.09)
	I	21/77	27	
Overall result				0.67 (0.44, 1.01)

Abbreviations: R, reference group; I, index group; 95% CI, 95% confidence interval.

Table 10. Angiographic Results of Femoral Atherosclerosis Trials: Regression of CAD

Study	Group	Number of Patients (Regression/Total)	Rate (%)	Relative Risk (95% CI)
Duffield et al	R	7/46	15	2.14 (0.96, 4.76)
	I	15/46	33	
Olsson et al	R	0/25	0	−56%* (−74%, −37%)
	I	15/27	56	
CLAS	R	21/76	28	1.89 (1.23, 2.91)
	I	35/77	52	
Overall result				1.93 (1.27, 2.92)

Abbreviations: R, reference group; I, index group; 95% CI, 95% confidence interval.
*Risk difference.

the lifestyle changes groups, respectively. An additional analysis[49] of the coronary angiograms also showed a beneficial effect of the lifestyle changes on stenosis geometry, which resulted in an increase in the theoretical stenosis flow reserve.[75]

Lichtlen et al[50] reported INTACT in which the antiatherosclerotic properties of the calcium antagonist nifedipine were determined. Patients with proven mild CAD and at least one risk factor were randomized to placebo (N = 211) or nifedipine 80 mg/d (N = 214). Quantitative coronary angiography was performed at baseline and after 3 years.[76] Progression occurred in 31% and 25% and regression in 17% and 12% in the placebo and nifedipine groups, respectively. INTACT showed a reduction in the development of new lesions, defined as new stenosis of ≥ 20% (103 versus 144). This was independent of the effect of nifedipine on blood pressure. More patients died in the nifedipine group (12 versus 2), and the cardiac mortality rate was 2.4% and 0.8% per year.

Waters et al[51,77] studied the effect of the calcium antagonist nicardipine on CAD. Patients with an 80% probability of coronary atherosclerosis progression according to the extent of CAD related to age[78] were randomly allocated in a double-blind fashion to placebo (N = 191) or nicardipine 120 mg/d (N = 192). Angiograms were repeated after 2 years and analyzed quantitatively.[76] Progression and regression of CAD were observed in 37% and 13% and in 39% and 19% in the placebo and the nicardipine groups, respectively.

Femoral Atherosclerosis Trials

The design characteristics and lipid and angiographic results are shown in Tables 6 through 10. Duffield et al[52,79] performed a randomized double-blind controlled trial in patients with symptomatic peripheral atherosclerosis. Patients were provided either usual care (N = 12) or lipid-modifying drugs (N = 12). Femoral angiography was performed at baseline and after 19 months. Total cholesterol was reduced 28%, LDL reduced 31%, and HDL increased by 34%. Angiography was analyzed visually and quantitatively and reported on a segmental basis. Progression was observed in 17% and 7% and regression in 15% and 33% in the placebo and the lipid-modified groups, respectively.

In the trial conducted by Olsson et al,[53] asymptomatic hyperlipidemic middle-aged men were treated with nicotinic-acid, fenofibrate (N = 23), or received dietary advice (N = 20). Angiography was assessed visually at baseline and after 1 year. Total cholesterol decreased 34%, LDL decreased 31%, and HDL increased 19%. Progression and regression were observed in 40% and 0% in the conservatively treated group and in 24% and 29% of the lipid-modified group.

As mentioned previously, CLAS[54] also studied the development of femoral atherosclerosis. Design and treatment are described earlier. The assessment of femoral atherosclerosis was performed quantitatively.[65] Progression of femoral atherosclerosis occurred in 40% versus 27%, and regression occurred in 28% and 52% of the placebo- and lipid-modified groups, respectively.

Relation Between Angiographic Changes Lipid and Nonlipid Factors

In the NHLBI type II study,[80] a decrease in LDL, in total cholesterol, and an increase in HDL were all associated with a lower rate of

CAD progression, although the first two factors were not independent. A decrease in LDL and an increase in HDL, expressed in the HDL/LDL ratio, was related to less progression of CAD. No relation was found between the absolute values of total cholesterol, LDL, and HDL and the changes in CAD. Blankenhorn et al[81] found in univariate analysis that total cholesterol, LDL, HDL, nonHDL cholesterol (LDL and VLDL), apolipoprotein B and C, triglycerides, and diastolic blood pressure were related to progression of CAD. After multivariate analysis, only nonHDL cholesterol in the placebo group and apolipoprotein C (measured in whole serum) in the lipid-modified group were found to be independent determinants of the global change score. In a study on the development of new angiographic lesions in the placebo group,[82] Blankenhorn found that high age at entry and a decrease in systolic blood pressure during the trial were associated with a lower incidence of new lesions. Brown et al[45] found that the change in proximal stenoses was determined by the change in apolipoprotein B or LDL, in HDL, in systolic blood pressure, and the amount of ST segment depression at the baseline exercise test. Kane et al[46] could best predict the change in mean percent area stenosis by the LDL level during the trial. In the STARS trial[47] the change in mean coronary diameter related most strongly to the change in mean blood pressure and the LDL/HDL ratio during the trial. Regression of CAD was strongly related to a LDL level of <3.5 mmol/L.

Pooled Results

For the combined coronary atherosclerosis trials with lipid-modifying regimes, the overall relative risk (ORR) for progression was 0.62 (95% confidence interval, 0.54, 0.72) corresponding with a reduction of 36%. The ORR for regression was 2.13 (95% confidence interval, 1.53, 2.98) (Fig 1). For the two studies using a calcium antagonist, the ORR for progression was 0.95 (95% confidence interval, 0.77, 1.18) and for regression 1.02 (95% confidence interval, 0.72, 1.46) (Fig 2). Of the three studies on femoral atherosclerosis, only two were pooled since the trial of Duffield et al was reported on a segmental and not on a per patient basis. The ORRs were 0.67 (95% confidence interval, 0.44, 1.01) and 1.93 (95% confidence interval, 1.27 = 2.92) for progression and regression, respectively.

Figure 3 shows the relation between the change in HDL/LDL ratio and relative risk for progression and regression of CAD among the different trials. No association could be found between these variables and changes in CAD.

Results of Other Angiographic Studies

Table 11 depicts the angiographic results of studies that were not selected. Progression of CAD occurred in approximately 40% to 80% of the patients. Regression of CAD was found in some of the observational trials but in no more than 8% of the cases.

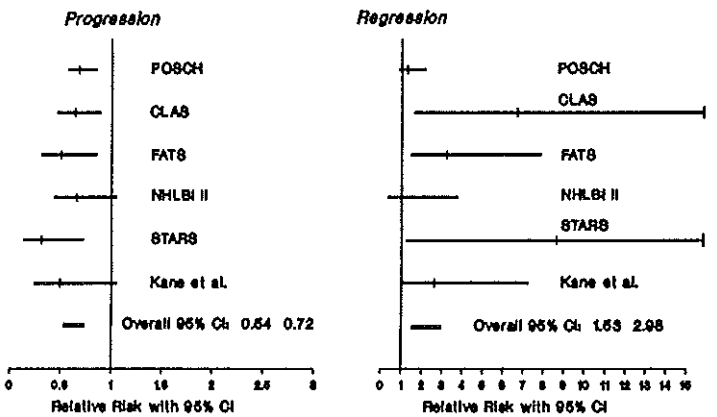


Fig 1. Relative risks for angiographic progression and regression of CAD for each lipid-modifying trial and the overall relative risk. The horizontal bars indicate the 95% confidence interval. For progression the portion left to the line of unity indicates a beneficial effect (reduction in progression); for regression the portion right to the line of unity indicates a beneficial effect (increase in regression).

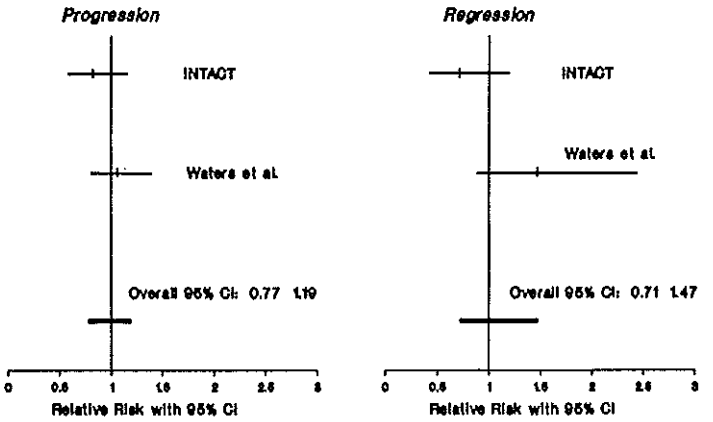


Fig 2. Relative risks for angiographic progression and regression of CAD for both calcium antagonist trials and the overall relative risk. The horizontal bars indicate the 95% confidence interval. For progression the portion left to the line of unity indicates a beneficial effect (reduction in progression); for regression the portion right to the line of unity indicates a beneficial effect (increase in regression).

DISCUSSION

Angiographic Trials

The use of coronary angiography as end point for a trial is attractive. First, it is the only method that can actually document slowing, arrest, or regression of CAD.[24] Second, a trial using angiography needs less patients than one with clinical end points to yield sufficient statistical power.[83-86] Third, the completion time of the study can be shorter, especially in the case of CAD with a low clinical event rate.[86,87] Fourth, accurate and precise measuring methods can be applied.[76,84]

Nevertheless, coronary angiography also has its drawbacks. First, no data are available on patients without an indication for coronary angiography. Second, the assessment of the end point is not continuous as with survival analysis but in most cases only at two moments in time. Third, coronary angiography is an invasive procedure not without risks to the patient.[88] Fourth, angiographic follow-up will never be available for all enrolled patients. Reasons for lack of angiographic follow-up can be independent, eg, a move or refusal for a second angiogram, but also dependent of the patient's clinical status, eg, death, acute myocardial infarction, or other illness. In the latter case this can result in an underestimation of the rate of progression in an observational study. Also, in a clinical trial when a new therapy is effective, underestimation of the treatment effect can occur because more failures in the reference group than in the index group cannot be included in the comparison. In such a case, the angiographic difference will be smaller than the true difference between treatments.

Angiographic trials are a logical step in the

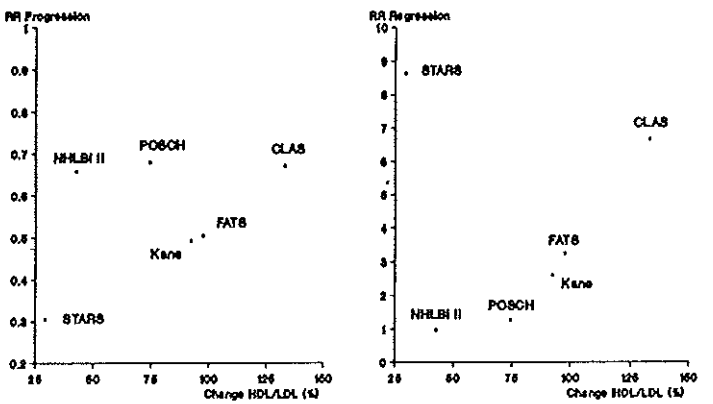


Fig 3. Scatter plot of the difference in change in the HDL/LDL ratio between the placebo and lipid-modified group and the relative risk for progression and regression of CAD. Linear regression analysis did not show a relation between lipid-modifying and angiographic effect among the trials.

Table 11. Angiographic Results of Rejected, Single-Group, and Observational Studies

Study	Total	Number of Patients: Progression (%)	No Change (%)	Regression (%)	Duration (yr)	Type
Cohn et al (1976)	24	15 (69)	9 (31)	0 (—)	1	Control
	16	11 (63)	5 (37)	0 (—)		Lipid-modifying
Nash et al (1982)	17	8 (47)	9 (53)	0 (—)	2	Control
	25	3 (12)	22 (88)	0 (—)		Lipid-modifying
Nikkilä et al (1984)	13	12 (92)	1 (8)	0 (—)	5-7	Control
	28	19 (68)	9 (32)	0 (—)		Lipid-modifying
Loaldi et al (1989)	38	18 (47)	17 (45)	3 (8)	2	Nitrates
	38	19 (53)	14 (39)	3 (8)		Nifedipine
	39	12 (31)	20 (51)	7 (18)		Propranolol
Hahmann et al (1991)	21	21 (100)	0 (—)	0 (—)	2	Control
	21	10 (45)	0 (—)	11 (55)		Lipid-modifying
Schuler et al (1992)	18	6 (33)	11 (61)	1 (6)	1	Control
	18	5 (28)	6 (33)	7 (39)		Lifestyle change
Kuo et al (1979)	25	4 (16)	21 (84)	0 (—)	7	Lipid-modifying
Arntzenius et al (1985)	39	21 (54)	18 (46)	0 (—)	2	Lipid-modifying
Gensini et al (1972)	1,263	985 (78)	276 (22)	2 (0.2)	3	Observational
Bemis et al (1973)	73	38 (52)	35 (48)	0 (—)	3	Observational
Nash et al (1977)	119	106 (89)	13 (11)	0 (—)	2	Observational
Marchandise et al (1978)	22	0 (—)	22 (100)	0 (—)	3	Observational
	26	7 (26)	19 (74)	0 (—)		
Bruschke et al (1981)	256	144 (56)	100 (39)	12 (5)	3	Observational
Kramer et al (1982)	317	148 (47)	154 (49)	15 (5)	3	Observational
Moise et al (1984)	313	139 (44)	162 (52)	12 (4)	3	Observational
Bruschke et al (1988)	168	66 (39)	88 (52)	14 (8)	3	Observational
Öst et al (1967)	28	1 (4)	8 (29)	19 (77)	3	Lipid-modifying (femoral)
Berndt et al (1977)	25	13 (52)	3 (12)	9 (36)	1	Lipid-modifying (femoral)

evaluation of a new treatment because they may provide essential insights into the mechanisms involved. In addition to angiographic benefit, an intervention should also be safe and show clinical benefit, even if a relation clearly exists between the substitute end point and the clinical end point,[86] as in the case of coronary atherosclerosis and angina pectoris, acute myocardial infarction, and sudden cardiac death.[21] Therefore, angiographic trials should be complemented by studies that are large enough to show clinical benefit and can provide sufficient information about the incidence of side effects.

Limitations of Coronary Angiography

Coronary angiography provides shadow images of coronary lumina formed by roentgen ray absorption of contrast medium dissolved in blood.[89] Therefore, no direct information about the arterial wall is obtained. Focal atherosclerotic disease, forming a raised plaque, can be recognized from a narrowing of the contrast column. Diffuse atherosclerotic disease results in a continuous narrowing of the lumen that cannot directly be identified and can only be suspected in the case of an unusual small epicardial vessel. Both clinical investigations[90] and autopsy studies[91] in patients who died from a cardiac cause have shown that diffuse atherosclerosis is a dominant factor as regards atherosclerotic involvement of the coronary arteries,[92] and that up to 90% of the coronary segments are narrowed more than 25% in the cross-sectional area. Early stages of coronary atherosclerosis are accompanied by a compensatory enlargement of the coronary vessel[93-96] or even an overcompensation. Only when 40% of the internal elastic lamina area is occupied by an atherosclerotic lesion is the lumen decreased.[93] This indicates the inability of coronary angiography to detect the early stages of atherosclerosis. Thus, it can be argued that the angiographic definition of a new lesion[97,98] does not exist but is in fact an existing atherosclerotic plaque that begins to encroach on the vessel lumen. The assumptions about the shape of the vessel might not be valid. The shape of the lumen at the side of an atherosclerotic plaque cannot only be

circular but also elliptical or D-shaped,[20] which can cause underestimation or overestimation of the stenosis.

The visual interpretation of coronary angiograms is hampered by a large interobserver and intraobserver variability.[99-103] Quantitative coronary angiography also has sources of error[24] but has a much better reproducibility and is able to give absolute measures of coronary artery dimensions.[76] In conclusion, coronary angiography has specific limitations both in the assessment of early atherosclerotic lesions and diffuse atherosclerosis.

End Points

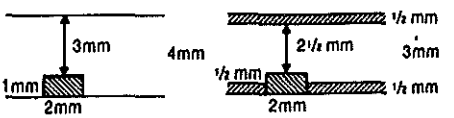
Relative measures, such as percentage diameter stenosis or percentage area stenosis, are dependent of the determination of the normal vessel contour. This normal vessel border at the site of a stenosis is unknown and therefore is traced manually[72] or constructed by computer systems yielding an interpolated reference diameter.[76] Progression of diffuse atherosclerosis at both sides of a stenosis, resulting in a smaller reference diameter, may cause pseudoregression of the lesion itself (Fig 4). In contrast, the mean diameter (mm) of a coronary segment and minimal diameter (mm) of an atherosclerotic lesion are direct measurements independent of the assumed reference diameter. Coronary anatomy should be evaluated by quantitative coronary angiography and should provide absolute measures of both stenosed and nonstenosed segments of the coronary artery, thereby assessing both focal and diffuse atherosclerosis as de Feyter[24] recently proposed (Table 12).

Coronary Angiography, Progression of Coronary Atherosclerosis, and Clinical Events

Observational studies with repeated coronary angiography have shown that a long time period between angiograms,[36,78] severe lesions,[36,78,104-106] irregular ulcerating plaques,[28] large extent of CAD,[78,105] the presence of collaterals,[28] smoking,[28,31] and an abnormal response to ergonovine[107] were associated with atherosclerotic disease progression including the occurrence of total occlusion. However, progression was also less often observed in angiographic normal segments or in lesions $\leq 50\%$. These studies suggested that the progression of CAD does not occur in a linear fashion and is unpredictable.[37,39] Important drawbacks in these observational studies are the retrospective nature and the fact that repeat angiograms were performed for clinical reasons.

Retrospective studies in patients with unstable angina pectoris[108,109] and in survivors of acute myocardial infarction[110-114] have shown these events were caused both by progression of disease in coronary segments that were already severely stenosed and also in coronary segments that contained a nonsevere lesion or were angiographically normal at previous angiography. One study[110] showed that the preexisting lesions associated with Q wave infarction appeared to be less severe than those with non-Q wave infarction. An explanation might be that a chronic severe lesion possibly protects the myocardium during acute occlusion and subsequent sudden ischemia by the already induced collaterals.[115,116] An important bias that invalidates these trials is that no information is available on patients who have died or who did not need to undergo coronary angiography after an acute myocardial infarction.

Endothelial dysfunction and disruption plays an important role in the development of acute ischemic events.[117] Angiography does not directly assess endothelial function. Some studies reported abnormal vasomotor reactivity of angiographically diseased and nondiseased coro-



MEASUREMENTS:		
DS%	25	17
Mean width segm. (mm)	3.75	2.9
Min. lum. diam. (mm)	3.0	2.5
Plaque area (mm.)	2.0	1.0

Fig 4. Diagram of progression of diffuse coronary atherosclerosis in a segment with preexisting stenosis. Relative measurements (DS% relative percent diameter stenosis) suggest regression of severity of lesion, whereas, in reality, absolute measurements (mean width, minimal luminal diameter, and plaque area) show progression of coronary CAD.

Table 12. Significance of Measurements Used to Assess Progression or Regression of Coronary Atherosclerosis

	Diffuse Atherosclerosis	Focal Atherosclerosis	Diffuse and Focal Atherosclerosis
Coronary segment score			
Mean width per vessel segment (mm)	++	+	++
Coronary lesion score			
Absolute measurements	±	++	+
Minimal luminal diameter (mm)			
Minimal cross-sectional area (mm^2)	±	++	+
Plaque area (mm^2)	—	++	+
Relative stenosis measurements			
Relative percent diameter stenosis (%)	—	+	±
Area stenosis (%)	—	+	±
Functional stenosis measurements			
Delta P (mm HG)	—	+	+

NOTE. —, not relevant; ±, more or less relevant; +, relevant; ++, highly relevant.

nary segments after the administration of acetylcholine,[118,119] serotonin,[120,121] and papaverine.[122] Endothelial dysfunction in angiographically normal segments may be caused by diffuse atherosclerosis or extraluminal atherosclerotic lesions. Plaque fissuring and its sequelae can therefore occur in these angiographically normal segments (Fig 5). Clinical benefit from lipid-modifying treatments may not only be mediated through less progression of severe plaques but also by stabilization of less severe lesions and improvement of endothelial function as was shown in animal experiments.[123]

The Angiographic Methods Used in the Selected Trials

The methods used for the assessment of the coronary anatomy in the selected trials were diverse (Table 2). The first investigators, being pioneers in the field, all visually assessed the

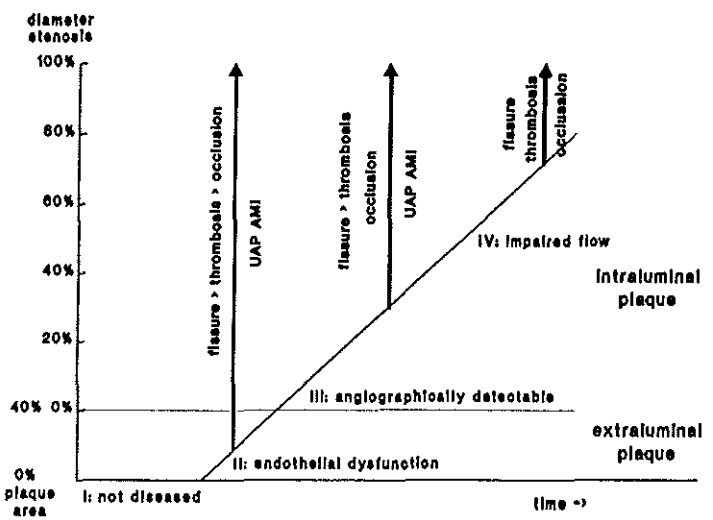


Fig 5. Illustration of the possible natural history of atherosclerotic plaque progression, plaque fissure, thrombosis, and clinical coronary events. Phase I: no atherosclerotic plaque is present, the endothelial function is intact, no thrombosis will occur. Phase II: an atherosclerotic plaque is present, the internal elastic lamina is for ≤40% occupied by atheroma and does not encroach on the lumen, the lesion is not angiographically detectable, plaque fissure, thrombosis and occlusion causing unstable angina pectoris or acute myocardial infarction may occur. Phase III: the internal lamina elastica is ≥40% occupied by an atheroma and encroaches on the lumen, the lesion is angiographically detectable. Phase IV: a severe narrowing of the lumen is present, plaque fissure, thrombosis, occlusion causing unstable angina pectoris or acute myocardial infarction may occur. A severe lesion might induce collaterals that could protect the myocard against sudden ischemia and prevents clinically overt coronary events.

angiograms and used relative percent diameter stenosis as the main criteria. But as knowledge about the assessment of coronary anatomy evolved, investigators began to use quantitative techniques; recent trials all use this technique.

Most assessments were based on the relative percent diameter stenosis of coronary lesions. The criteria used to define clinically significant lesions on patient status change were varied (Table 2). A criterion for lesion change applied by several trials was $\geq 10\%$ in percent relative diameter stenosis. The most recent trial, the STARS study, used mean and minimal vessel diameter as the primary angiographic end points. The diversity of angiographic methods applied illustrates that no consensus as yet exists how to assess coronary artery changes in absolute terms, which hampers the comparison and overview of the trials.

Effect of Lipid-Modifying Therapy on Coronary Anatomy

The common object in these trials was to improve the lipid profile. They all used different therapies to achieve such a shift, ranging from diet and one lipid-modifying drug through multitherapy to partial ileal bypass surgery. All these treatment regimes results in substantial reductions in total cholesterol, LDL cholesterol, and triglycerides up to 36%, 45%, and 29%, respectively; although in some instances an elevation of triglycerides occurred (Table 2). Also large elevations of HDL were observed, whereas in the POSCH and the STARS studies HDL remained unchanged. It can be concluded that the treatment regimes used were very effective in improving the lipid profile. Pooling of the selected trials presents evidence that extensive beneficial changes in the lipid-profile results in retardation, arrest of progression, or regression of CAD. (Fig 6). In the 1,240 patients (666, lipid-modified group; 574, control group) a substantial reduction in the number of patients who showed progression of CAD was noted (184 [28%] in the lipid-modified group versus 261 [46%] in the control group). Furthermore, a less substantial increase in the number of patients who showed regression of CAD (107 [16%] in the lipid-modified group versus 40 [7%] in the control group) was found.

The absolute changes in coronary artery stenosis measured were small and therefore will have little functional importance. On the other hand, when these changes are extrapolated to a longer period, an important functional improvement might occur. POSCH is the only trial that presents data on the long-term effects of lipid-lowering. Figure 7 shows that the angiographic benefit is present after 3 years and remains constant while the absolute incidence of progression increases over the years with a progression rate of more than 85% in the control group and 55% in the operated group after 10 years. The effect on regression increased up to 7 years with 6.3% in the control group and 14.4% in the surgery group.

Data from histological—and physical biochemical studies[124] and epidemiological studies[38] suggest that regression of CAD is mediated by HDL. The STARS study, however, in which

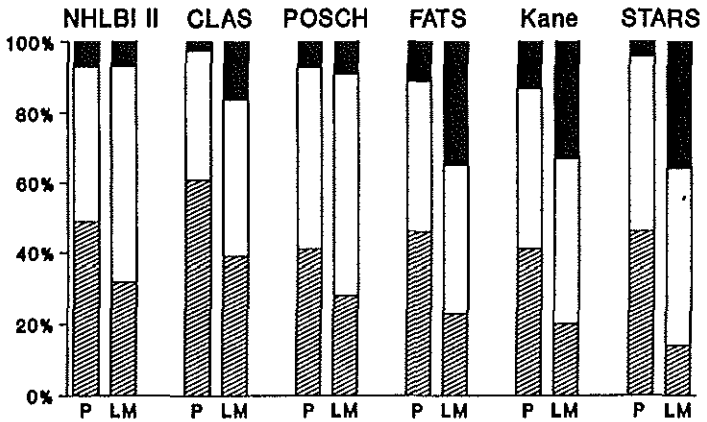


Fig 6. Changes in CAD in five coronary atherosclerosis trial with a lipid-modifying treatment. P, placebo; LM, lipid-modifying treatment; ▨, progression; □, stable or mixed; ■, regression.

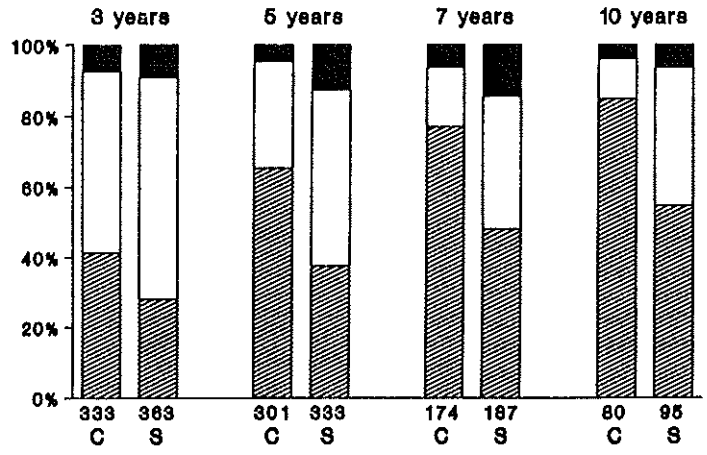


Fig 7. Changes over time in the POSCH trial. Coronary angiography was performed at 3, 5, 7, and 10 years after randomization. Numbers indicate the numbers of patients at each time interval for each treatment group. C, control group; S, partial ileal bypass surgery; ■, progression; □, stable or mixed; ▩, regression.

no change in HDL was seen, shows that regression of CAD can occur in the absence of HDL elevation.

Effect of Diet and Lifestyle Changes on Coronary Anatomy

The Lifestyle Heart Study and the STARS trial provide data on the effect of lifestyle changes and diet on CAD. In the former a combination of diet, daily exercise, and stress management techniques resulted in a substantial improvement of blood lipids, a reduction of anginal complaints, and a 60% reduction in progression of CAD and a twofold increase of regression. In the latter a lipid lowering-diet only was responsible for the largest angiographic benefit: change in mean coronary artery diameter 0.03 mm versus 0.20 mm in the control group. No difference was seen between the 2 intervention groups in categorical progression or regression of CAD and clinical events. The CLAS investigators studied the relation between diet and the occurrence of new lesions in their placebo group.[125] Progression of CAD was associated with a higher consumption of total- and polyunsaturated fat. Patients who compensated for the lower saturated fat intake, prescribed by the diet, by increasing protein intake instead of consuming more polyunsaturated fat, had the lowest risk of developing new atherosclerotic lesions. In the uncontrolled Leiden Intervention Trial,[38] a vegetarian diet was associated with a reduction in body-weight, systolic blood pressure, and total cholesterol. Progression of CAD was stopped in 18 of 39 patients and was related to the total cholesterol/HDL ratio.

The Coronary Atherosclerosis Trials with Calcium Channel Blockade

The two studies by Lichtlen et al. and Waters et al. had similar study designs. Both trials recruited patients with mild to moderate CAD, treated with either placebo or a dihydropyridine calcium antagonist. The analyses of the coronary angiograms were performed with the same quantitative system (CAAS[76]). The pooled results are therefore a precise estimate of the effect of these agents on CAD. Both studies failed to demonstrate an overall effect of calcium channel blockade on progression or regression of CAD. On a segmental level little effect was found on angiographically new- or minimal lesions. INTACT showed a reduction in the occurrence of angiographically new lesions. In a secondary analysis, Waters et al. found less progression of lesions less then 20% diameter stenosis. In the trial by Waters this effect was related to a lowering of blood pressure. The number of cardiac events and deaths were larger in the calcium antagonist groups. Thus, although animal studies have shown antiatherosclerotic properties of several calcium antagonists,[17] no clear benefit of these agents on overall progression of CAD is found in men.

The Femoral Atherosclerosis Trials

The epidemiology of femoral atherosclerosis may be different from that of coronary athero-

sclerosis. The most important risk factors reported are age, pack-years of cigarettes, systolic blood pressure, plasma glucose and obesity. However, the relation between blood lipids and femoral atherosclerosis is inconsistent. Studies showing both an association[126-129] or a lack of association[130] have been reported. Results from pathologic studies suggest the structure of the femoral atherosclerotic plaque may be different from coronary lesions being predominantly fibroproliferative and containing little lipid.[131]

Until now only 3 controlled trials, of which 2 were randomized, with a total of 220 patients have been carried out. Different types of patients were recruited in these trials: patients with symptomatic femoral atherosclerosis, with hyperlipoproteinemia, and patients post-CABG. All trials showed that a lipid-modifying treatment resulted in a reduction of progression of femoral atherosclerosis and an increase of regression.

Generalization of Results

We selected 5 trials testing the lipid hypothesis on coronary atherosclerosis. The kinds of patients enrolled were different, the lipid-modifying treatments varied, different methods of coronary analysis were used and different coronary endpoints were employed. All were secondary prevention trials in patients with elevated blood lipids, with proven CAD, who underwent coronary bypass surgery or who had previously suffered from an acute myocardial infarction. The treatments ranged from monotherapy, combination therapy to accomplish a minimal level of lipid-lowering, to abdominal surgery, and extremely demanding lifestyle changes. This may have consequences for large scale use since patient compliance will be difficult to maintain and treatments will be expensive.

CONCLUSION

The 2 trials testing calcium channel blockade showed no beneficial effect on preexisting atherosclerotic plaques, but this treatment may have an effect on the development of angiographically new lesions. The increased number of clinical events in the calcium antagonist groups emphasizes that safety of an intervention should be taken into account.

The results of several lipid-modifying trials with different designs were pooled. This quantitative overview will, therefore, be hampered by the heterogeneity of these studies. Intensive lipid-modifying treatment in patients with high levels of plasma cholesterol with moderate to severe CAD and at relatively high risk for cardiac events, resulted in large reductions in total cholesterol and elevations of HDL. This was associated with slowing or arrest of progression of CAD in a substantial number of patients (27% versus 46%) and an increase in the incidence of regression of CAD in relatively few patients (17% versus 7%). However, the induced angiographic changes are relatively small and exert only minimal effects on the functional significance of lesions. One should however bear in mind that, apart from the POSCH trial, the interventions were maintained only 1 to 3 years. These effects may be cumulative and functional more impressive if extended for a much larger time period. However, these trial also show that, although patients are submitted to extensive treatment regimes, progression does occur in 14% to 39% after 3 years and 55% after 10 years indicating that lipid-modifying therapy may not be effective in a large number of patients. The 3 femoral atherosclerosis trials showed, although epidemiological data give no clear picture of the risk factors involved, that lipid-modifying treatment may also be beneficial for femoral atherosclerosis.

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Chapter 3

EFFECT OF SIMVASTATIN ON CORONARY ATHEROMA: THE MULTICENTRE ANTI-ATHEROMA STUDY (MAAS)

Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS)

*MAAS Investigators**

Summary

It has yet to be established whether substantial reduction of plasma lipids will lead to retardation, and to what extent and how quickly, of diffuse and focal coronary atheroma.

The Multicentre Anti-Atheroma Study (MAAS) is a randomised double-blind clinical trial of 381 patients with coronary heart disease assigned to treatment with diet and either simvastatin 20 mg daily or placebo for 4 years. Patients on simvastatin had a 23% reduction in serum cholesterol, a 31% reduction in low-density lipoprotein cholesterol, and a 9% increase in high-density lipoprotein cholesterol compared with placebo over 4 years. Quantitative coronary angiography was done at baseline, and after 2 and 4 years. 167 patients (89%) on placebo and 178 (92%) on simvastatin had baseline and follow-up angiograms. In the placebo group there were reductions in mean lumen diameter (−0·08 mm) and in minimum lumen diameter (−0·13 mm). Treatment effects were +0·06 (95% CI 0·02 to 0·10) and +0·08 mm (0·03 to 0·14) for mean and minimum lumen diameter, respectively (combined p = 0·006). Patients on placebo had an increase in mean diameter stenosis of 3·6% and the treatment effect of simvastatin was −2·6% (−4·4 to −0·8). Treatment effects were observed regardless of diameter stenosis at baseline. On a per-patient basis, angiographic progression occurred less often in the simvastatin group, 41 versus 54 patients; and regression was more frequent, 33 versus 20 patients (combined p = 0·02). Significantly more new lesions and new total occlusions developed in the placebo group, 48 versus 28, and 18 versus 8, respectively. There was no difference in clinical outcome. The numbers of patients who died or had a myocardial infarction were 16 and 14 in the placebo and simvastatin groups, respectively. In the placebo group more patients underwent coronary angioplasty or re-vascularisation, 34 versus 23 on simvastatin.

The trial showed that 20 mg simvastatin daily over 4 years reduces hyperlipidaemia and slows progression of diffuse and focal coronary atherosclerosis.

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Introduction

Several randomised controlled trials[1-10] show that progression of coronary atheroma can be slowed by treatment of hypercholesterolaemia, with a combined relative risk for progression compared with controls of 0·62.[11] However, the number in whom atheroma actually regressed has been small and the regression slight. The effects of regression on coronary blood flow and myocardial perfusion, and the clinical relevance of angiographic changes are unclear. Most trials showed the greatest regression in atheroma obstructing more than 50% of the arterial lumen;[12] others reported that smaller obstructions also responded,[8,10] or claimed that the main effect of reducing cholesterol is prevention of new lesions.[10]

The Multicenter Anti-Atheroma Study (MAAS), involving 11 centres in Europe, began a trial in 1987, when there were few angiographic studies in progress, to study the effects on coronary atheroma of reducing lipoprotein concentrations with simvastatin relative to placebo, in patients with moderate hypercholesterolemia and known coronary artery disease. In order to assess the time course of angiographic changes, patients had a baseline and two follow-up angiograms over a 4-year period.

Patients and methods

Trial design

Design, baseline characteristics, randomisation and other procedures have been described.[13] Patients undergoing routine coronary angiography were selected in 11 participating centres. Inclusion and exclusion criteria are shown in table 1. Patients were maintained on a lipid-lowering diet according to the practice of the centre. In some centres, patients were seen regularly by a dietitian; in others, diet-counselling was given by the investigator. In addition, 20 mg simvastatin or matching placebo, once a day immediately before the evening meal, was prescribed.

Randomisation was stratified for clinic and for co-treatment with antiplatelet agents and/or anticoagulants. Compliance was assessed by tablet count. Other medications, except for lipid-lowering drugs, were permitted. Neither the investigators nor the patients were informed about serum cholesterol or other lipid levels. Special procedures were adopted to adjust medication without breaking the double blinding for patients with total cholesterol levels outside the agreed range.[13]

Lipid measurements

Patients were asked to fast before blood sampling. Patient selection was based on local lipid measurements. Two additional baseline and all follow-up measurements of total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and apo-lipoprotein A1 and B were done by standardised methods[14-16] at the MAAS lipid reference laboratory in Rotterdam, Netherlands. Low-density lipoprotein (LDL) cholesterol was calculated with the Friedewald formula.[15] Lipoprotein (a) was measured yearly by the Medical Research Council lipoprotein team, Hammersmith Hospital, London, UK, with enzyme-linked immunosorbent assay (Tint Elize, Biopool, Umeå, Sweden).

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Coronary angiography and quantitative analysis

Coronary angiography was done according to standards required for quantitative analysis,[20] before medication was started and after 2 and 4 years. At the angiographic reference laboratory, all angiograms were assessed by two members of the angiography committee who selected the coronary segments suitable for quantitative analysis, irrespective of the presence of lesions. The intention was to analyse 3 proximal segments in the right coronary artery, 3–4 in the circumflex, and 3 in the left anterior descending and left main stem. This required adequate filling with contrast medium of each segment, acceptable film contrast, and no overlap or foreshortening. The qualifying angiogram was accepted only if at least 5 segments were analysed according to the protocol, otherwise the patient was excluded. At follow-up, all segments that matched the qualifying angiogram were analysed. Segments surgically dilated before randomisation were excluded. If a patient underwent coronary artery bypass grafting (CABG) during the trial, the pre-CABG angiogram was used for the final analysis. When a patient underwent percutaneous transluminal coronary angioplasty (PTCA) before the end of the trial, the pre-PTCA projections of the dilated segment were used for comparison between baseline and follow-up; if no pre-PTCA projections were available, the segments dilated were not included in the final analysis.

Quantitative analyses were done by the computer-assisted Cardiovascular Angiography Analysis System (CAAS)[20] (which allows measurements of diameters in millimetres of coronary segments[21]) without knowledge of trial medication. For each segment the mean lumen diameter (mm) for angiographically diseased segments (diameter stenosis ⩾20%), the minimum lumen diameter, reference diameter, and diameter stenosis (%) were measured. Segments that were patent at baseline but occluded at follow-up were scored: mean and minimum lumen diameter = 0 mm, diameter stenosis = 100%. Segments distal to any subsequent occlusion were not incorporated. In the absence of a 4-year angiogram, 2-year angiographic measurements were carried forward.

Two main efficacy variables were defined[13,21]: *diffuse* coronary atherosclerosis, the per-patient average of mean lumen diameters (mm) of all coronary segments; and *focal* coronary atherosclerosis, the per-patient average of minimum lumen diameters (mm) of all segments that were angiographically atheromatous at baseline, at follow-up, or at both. The per-patient average of the diameter stenosis (%) of all angiographically diseased segments is also reported. Table 2 shows definitions of lesions and responses.

Inclusion criteria	Exclusion criteria
Aged 30–67 years	Myocardial infarction or unstable angina within 6 weeks before qualifying angiogram
At least two coronary artery segments arteriographically atheromatous but not totally occluded	Previous coronary artery bypass surgery
Angioplasty or bypass surgery not considered necessary	Percutaneous coronary angioplasty or major surgery within 3 months before qualifying angiogram
At least 5 segments of initial angiogram suitable for quantitative analysis in two projections	Qualifying angiogram more than 60 days before randomisation
Mean of two successive total serum cholesterol concentrations 5·5–8·0 mmol/L	Congestive heart failure or ejection fraction less than 30%
Mean of two successive fasting serum triglyceride concentrations less than 4·0 mmol/L	Diastolic blood pressure more than 100 mm Hg despite treatment
Informed consent obtained	Fasting plasma glucose concentration more than 7·8 mmol/L or diabetes requiring treatment other than diet
	Secondary hypercholesterolaemia
	Use of lipid-lowering, oestrogen, or steroid medications within 6 weeks before randomisation

Other criteria described in ref 13

Table 1: Main inclusion and exclusion criteria

Lesions	Responses
New: segment with diameter stenosis of ⩾20% at follow-up, diameter stenosis ⩽20% at baseline, and ⩾15% increase in diameter stenosis	**Progress:** at least one segment progressed and none regressed
Disappeared: decrease ⩽15% diameter stenosis in segment with ⩾20% diameter stenosis at baseline, and ⩽20% at follow-up	**Mixed:** one segment regressed and at least one progressed
Progressed: total occlusion of previously patent segment, increase of ⩾15% in diameter stenosis at follow-up of lesion ⩾20% stenosed at baseline, or development of new lesion	**Stable:** no segments progressed or regressed
Regressed: patency in a previously occluded segment, decrease of ⩾15% in diameter stenosis, disappearance of a lesion	**Regressed:** at least one segment regressed and none progressed

Table 2: Definitions of lesions and responses

Analysis

Sample size calculation was based on reproducibility data for the CAAS-system.[20] With SD = 6·5% of the long-term change in diameter stenosis (the original primary efficacy variable), 110 patients per group would enable detection of an absolute difference between treatment groups of 3·2% in change in diameter stenosis at a two-sided significance level of 0·05 with a power of 0·95. To allow for an anticipated loss to angiographic follow-up of one-third, the trial was planned to include 350 patients. Stratification for clinic and for co-treatment with antiplatelet agents and anticoagulants is disregarded in this analysis.

Continuous variables are presented as means and SDs; categorical variables as numbers and percentages; and lipid changes as the difference between each patient's mean lipid concentration over all available follow-up measurements and the mean of their two baseline measurements. Treatment effects are given as the differences between the treatment groups in mean within-patient changes between baseline and follow-up and are reported as point estimates with 95% CI. For pre-specified comparisons of continuous outcomes between treatment groups, unpaired *t* tests were done. The overall significance of the effect on the two main angiographic efficacy variables was determined by a combined test statistic.[22] Segment-based angiographic analyses were done unadjusted (considering each segment as a separate unit of information); and adjusted, (accounting for within-patient associations between multiple measurements by multi-level modelling).[23] For categorical outcomes, rate ratios and 95% CI are reported and χ^2 tests done as appropriate. For all hypothesis tests, a two-sided $p < 0{\cdot}05$ was considered significant. Angiographic outcomes were analysed in all eligible patients with angiographic follow-up, irrespective of trial treatment compliance. Other efficacy and safety analyses were analysed according to intention-to-treat.

Initially, no interim analysis was planned but after 2 years the independent Evaluation Committee recommended that trial medication should not be stopped and another angiogram should be done after a further 2 years, as there was no evidence for a positive effect of treatment (either combined p-value for the two main angiographic efficacy variables of $< 0{\cdot}01$ with $p < 0{\cdot}05$ for at least one main variable, or a $< 0{\cdot}01$ for at least one co-main variable). The blinding of the trial was maintained.

Results

From March, 1988, to October, 1989, 404 patients were randomised. The last follow-up angiogram was in November, 1993. 23 patients were excluded (21 had a baseline angiogram of insufficient quality, 1 had a baseline angiogram more than 6 months before randomisation, and 1 had diabetes). Of these, 12 were randomised to placebo and 11 to simvastatin; none died or had a myocardial infarction during the 4-year follow-up.

Characteristics	Placebo (n = 188)	Simvastatin (n = 193)
Demography		
Mean age (years)	54·9 (7·1)	55·6 (7·3)
Male	165 (88%)	171 (89%)
Current smoker	38 (20%)	53 (27%)
Body mass index ⩾ 30 kg/m²	18 (10%)	15 (8%)
Blood pressure		
Systolic blood pressure (mm Hg)	132 (16)	132 (17)
Diastolic blood pressure (mm Hg)	80 (8)	80 (8)
Current angina:		
None	57 (30%)	65 (34%)
Grade 1 or 2	116 (62%)	117 (61%)
Grade 3 or 4	15 (8%)	11 (6%)
Vessel disease*		
None	60 (33%)	78 (41%)
One	76 (41%)	73 (38%)
Two	39 (21%)	30 (16%)
Three	9 (5%)	10 (5%)
Previous myocardial infarction	101 (54%)	106 (55%)
Previous PTCA	83 (44%)	94 (49%)
Medication at randomisation:		
ACE inhibitor	17 (9%)	9 (5%)
Beta-blocker	80 (43%)	79 (41%)
Calcium channel blocker	82 (44%)	94 (49%)
Long acting nitrates	70 (37%)	80 (41%)
No of these drugs taken:		
None	37 (20%)	36 (19%)
One	70 (37%)	71 (37%)
Two	64 (34%)	67 (35%)
>Three	17 (9%)	19 (10%)
Aspirin	111 (59%)	122 (63%)
Other anti-thrombotic drug	25 (7%)	21 (6%)

*A vessel was considered diseased when there was stenosis of more than 50%.

Table 3: **Baseline characteristics**

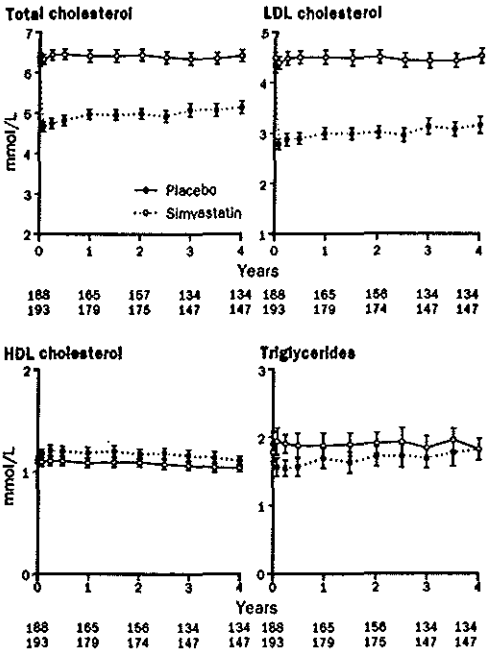

Figure 1: **Total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides for placebo and simvastatin groups during 4-year follow-up**

Means and 95% CI. Numbers of patients below horizontal axes.

Of 381 eligible randomised patients, (193 simvastatin, 188 placebo), 278 (144 simvastatin, 134 placebo) were on medication after 4 years. Baseline characteristics at randomisation are shown in table 3. The treatment groups were well balanced.

The effects of simvastatin on serum lipids are shown in table 4 and figure 1. Compared with placebo, the simvastatin group had a mean reduction in serum total cholesterol of 23% or 1·42 mmol/mL (−1·55 to −1·29) within 1 month. There was reduction of LDL by 31% (−29 to −35). There was also a reduction in apolipoprotein B of 28% (−30·8 to −25·1) in the simvastatin group compared to placebo, but no difference in apolipoprotein-A1 (+2·6% [−1·3 to 6·5]) or lipoprotein (a) (+12·1% [−10·7 to 34·9]). There was no interaction between baseline LDL cholesterol and angiographic treatment effects. There was no significant correlation between the extent of LDL change and the extent of change in minimum lumen diameter. Details will be reported elsewhere.

36 patients (21 simvastatin, 15 placebo) had no second angiogram; 5 due to death, the others mainly unwilling to continue. 345 had a final angiogram (276 at 4 years, 69 at 2 years), and 272 had baseline, 2-year and 4-year angiograms. For 22 patients having PTCA before 4 years, pre-PTCA segments were substituted in either the 2-year or 4-year angiogram. For 13 patients undergoing CABG, pre-procedure angiograms were considered to be the final ones.

In the 345 patients with a final angiogram (167 placebo and 178 simvastatin), 5260 matched projections were analysed of 2678 coronary segments, of which 1555 were

	Placebo			Simvastatin			Treatment effect†	
	N	Baseline*	During†	N	Baseline*	During†	Difference (95% CI)	% effect (95% CI)§
Total cholesterol (mmol/L)	184	6·43 (0·82)	6·45 (0·77)	189	6·35 (0·73)	4·95 (0·75)	−1·42 (−1·55 to −1·29)	−22·7% (−24·7 to −20·7)
LDL cholesterol (mmol/L)	184	4·47 (0·77)	4·50 (0·70)	189	4·38 (0·69)	3·02 (0·68)	−1·39 (−1·49 to −1·25)	−31·4% (−34·6 to −29·2)
HDL cholesterol (mmol/L)	184	1·11 (0·27)	1·08 (0·25)	189	1·10 (0·30)	1·18 (0·31)	0·10 (0·07 to 0·13)	9·1% (6·5 to 11·7)
LDL/HDL ratio	184	4·29 (1·21)	4·42 (1·21)	189	4·22 (1·13)	2·74 (0·86)	−1·61 (−1·76 to −1·45)	−38·7% (−42·0 to −35·5)
Apolipoprotein A1 (g/L)	180	1·59 (0·38)	1·50 (0·25)	188	1·62 (0·39)	1·57 (0·28)	0·04 (−0·02 to 0·10)	2·6% (−1·3 to 6·5)
Apolipoprotein B (g/L)	180	1·62 (0·29)	1·66 (0·25)	188	1·59 (0·27)	1·19 (0·23)	−0·44 (−0·39 to −0·48)	−28·0% (−30·8 to −25·1)
Triglycerides (mmol/L)	184	1·84 (0·85)	1·92 (0·93)	189	1·92 (0·95)	1·68 (0·79)	−0·33 (−0·45 to −0·20)	−17·6% (−24·0 to −11·2)
Lipoprotein(a) (g/L)	158	25·4 (27·6)	28·6 (27·7)	170	25·6 (29·1)	28·8 (32·3)	2·13 (−0·5 to 4·8)	12·1% (−10·7 to 34·9)

N = Number of patients, CI = Confidence interval; standard deviations in brackets.
*Each patient's baseline value is the mean of 2 pre-randomisation measurements.
†Each patient's value during treatment is the mean of all available measurements during 4 years follow-up.
‡All treatment effects are significant ($p < 0.001$) except for apolipoprotein A1 and lipoprotein(a).
§% effect is the difference between simvastatin and placebo groups in the means of patients' % change.

Table 4: **Mean serum lipid levels before and during treatment for all included patients**

Per-patient effect	Placebo			Simvastatin			Treatment effect (95% CI)	Treatment effect (95% CI) (adjusted)*
	No	Baseline (SD)	Change (SD)	No	Baseline (SD)	Change (SD)		
Diffuse disease								
Mean lumen diameter (mm)	167	2·82 (0·41)	−0·08 (0·26)	178	2·84 (0·38)	−0·02 (0·23)	0·06 (0·02 to 0·10)	..
Focal disease								
Minimum lumen diameter (mm)	166	1·91 (0·39)	−0·13 (0·27)	175	1·93 (0·38)	−0·04 (0·25)	0·08 (0·03 to 0·14)	
Diameter stenosis (%)	166	30·6 (6·82)	3·6 (9·03)	175	30·7 (6·41)	1·0 (7·90)	−2·6 (−4·4 to −0·8)	..
Per-segment effect								
Non-diseased segments								
Mean lumen diameter (mm)	652	3·14 (0·89)	−0·03 (0·45)	693	3·12 (0·85)	−0·02 (0·35)	0·06 (0·02 to 0·10)	0·06 (−0·00 to 0·12)
Mild and moderately diseased segments								
Mean lumen diameter (mm)	602	2·52 (0·67)	−0·07 (0·41)	629	2·58 (0·67)	−0·02 (0·38)	0·05 (0·00 to 0·09)	0·04 (−0·02 to 0·09)
Minimum lumen diameter (mm)	602	1·84 (0·53)	−0·06 (0·36)	629	1·88 (0·52)	−0·01 (0·34)	0·05 (0·01 to 0·09)	0·05 (0·00 to 0·10)
Severely diseased segments								
Mean lumen diameter (mm)	47	2·28 (0·63)	−0·24 (0·79)	52	2·42 (0·52)	−0·07 (0·66)	0·17 (−0·12 to 0·46)	0·21 (−0·06 to 0·49)
Minimum lumen diameter (mm)	47	1·17 (0·38)	−0·01 (0·47)	52	1·28 (0·35)	0·19 (0·44)	0·20 (0·02 to 0·38)	0·23 (0·05 to 0·41)

For mean lumen diameter, minimum lumen diameter, and diameter stenosis: p = 0·03, 0·007, and 0·006, respectively.
Mild and moderately diseased: diameter stenosis ≥ 20%—< 50% at baseline, severely diseased: diameter stenosis ≥ 50% baseline.
*Adjusted by multi-level modelling to allow for multiple segments per patient.

Table 5: Changes and treatment effects in quantitative coronary angiographic measurements over 4 years

angiographically diseased. The effects of simvastatin on the angiographic findings are shown in table 5. Simvastatin had a treatment effect of +0·06 mm on mean lumen diameter and of +0·08 mm on minimum lumen diameter. Combining these two co-primary efficacy parameters into a pre-defined single test statistic[13,22] yielded a significant difference between simvastatin and placebo (p = 0·006). An analysis based only on patients who were on trial medication at the final angiogram yielded similar results.

There were 129 patients in the placebo and 143 in the simvastatin groups with matched angiograms at baseline, after 2 years, and after 4 years. Figure 2 shows mean angiographic changes at 2 years and 4 years compared with baseline. All angiographic measures showed similar patterns which are consistent with gradual progression in the placebo group and gradual divergence between the placebo and simvastatin, groups with time. The results for segments with different degrees of stenosis at baseline are shown in table 6. The treatment effect on both mean and minimum lumen diameter was greater in segments with diameter stenosis of 50% or more at baseline. An analysis adjusted for multiple measurements per patient gave the same results.

Table 6 shows that a smaller proportion of patients in the simvastatin group progressed and a higher proportion regressed compared to placebo (combined p = 0·02). Analysis of the interaction between cigarette smoking, simvastatin, and angiographic treatment effects will be the subject of a future report. Categories of never smoked, ex-smokers, and current smokers all benefited from simvastatin. Most patients (111 placebo and 106 simvastatin) were ex-smokers and in these the treatment effects were largest. The benefit was least evident in current smokers, who formed a minority (less than 25%) of both treatment groups. Adjusting for smoking had no significant effect on the estimated overall treatment effect.

Clinical events during follow-up (table 7) are reported on an intention-to-treat basis. Of the cardiac deaths and myocardial infarctions, 11 (3 placebo, 8 simvastatin) occurred within 2 years of randomisation and 11 (5 placebo, 6 simvastatin) occurred after 2 years. None of the differences between groups were statistically significant. 9 patients in the simvastatin group and 16 in the placebo group discontinued treatment because of adverse events. There were no more adverse ophthalmological effects in patients treated with simvastatin compared with those on placebo. No patient in the simvastatin group had myopathy or clinically relevant elevation of transaminases.

Defining progression for all randomised patients taking into account cardiac events and interventions (cardiac death or myocardial infarction, PTCA or CABG in the absence of angiographic follow-up) there was 73 patients randomised

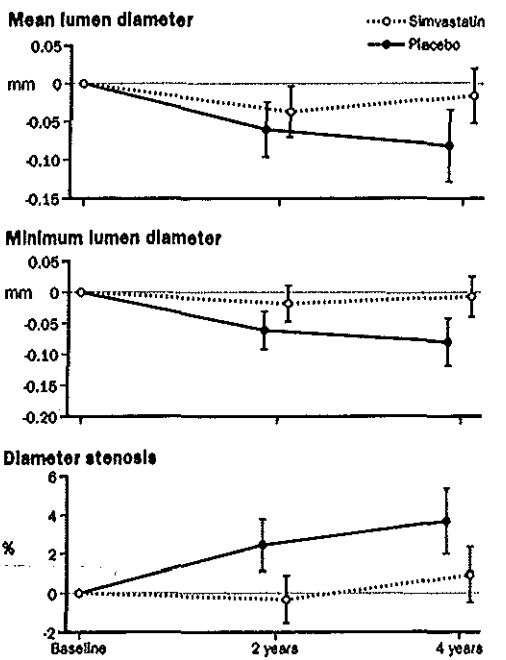

Figure 2: Changes in quantitative angiographic measurements for 272 patients (129 placebo, 143 simvastatin) with matched angiograms at baseline, 2, and 4 years

Means and 95% CI.

	Placebo n %	Simvastatin n %
Classification per patient*		
Progressor	64 (32·3)	41 (23·0)
Mixed responder	21 (12·6)	10 (5·6)
Stable	72 (43·1)	94 (52·8)
Regressor	20 (12·0)	33 (18·6)
Total	167	178
Classification per segment		
Non-diseased at baseline and follow-up	648 (49·8)	706 (51·4)
Diseased at baseline	605 (46·5)	640 (46·6)
Diseased at follow-up	629 (48·3)	638 (46·4)
Total	1301	1374
Lesion		
Progression†	52 (4·0)	43 (3·1)
New	48 (3·7)	28 (2·0)
Stable	506 (38·9)	543 (39·6)
Regression	23 (1·8)	25 (1·8)
Disappeared	24 (1·8)	29 (2·1)

Non-diseased = diameter stenosis < 20%.
*Mantel-Haenszel χ^2 for trend in 3 categories: p = 0·02.
†This includes 18 and 8 new total occlusions in the placebo and simvastatin groups respectively.

Table 6: Classification of segments and patients between baseline and final angiogram

	Placebo (n = 188)	Simvastatin (n = 193)
Deaths	11	4
Cardiac	4	4
Sudden (cause unknown)	1	0
Other causes*	6	0
Myocardial infarction	7	11
Fatal MI	2	1
Non-fatal MI†	3	9
Suspected MI	2	1
CABG	16	8
For symptoms	12	5
Elective	4	3
PTCA‡	22	15
For symptoms	14	12
Elective	8	3
CABG or PTCA	34	23
Hospital admission for unstable angina§	18	15
Patients with at least one of the above cardiac events	51	40

*Aneurysm rupture, cancer (ovary), cancer (lung), cancer (metastatic), pancreatitis with septic shock, complicated cholecystectomy.
†1 patient (simvastatin) had two non-fatal infarcts.
‡5 patients (2 placebo, 3 simvastatin) had more than one PTCA.
§12 patients (5 placebo, 7 simvastatin) had more than one hospital admission for unstable angina.

Table 7: Clinical events during 4-year follow-up

to placebo and 53 to simvastatin who experienced clinical and/or angiographic progression (rate ratio: 0·71 [0·53 to 0·95]).

Discussion

The MAAS trial, with repeated follow-up angiography, allowed assessment of the rate of change in coronary atherosclerosis over time. The trial showed that simvastatin 20 mg daily led to improvements in diffuse and focal coronary atherosclerosis. This was associated with more regression and less progression of lesions, although most patients showed no substantial change. Fewer new lesions and occlusions developed in the simvastatin group. Simvastatin produced no significant side-effects or adverse reactions. It achieved an alteration in lipid profile with reductions of total cholesterol LDL, triglycerides, apolipoprotein-B, and an increase in HDL, which were maintained throughout follow-up.

The reduction of atherosclerosis in the treatment group was small, with an effect on mean lumen diameter of +0·06 mm and on minimum lumen diameter of +0·08 mm, consistent with two other long-term trials. In the Monitored Atherosclerosis Progression Study (MARS) trial[9] of 2 years duration, lovastatin lowered LDL cholesterol by a mean of 38%, with a non-significant difference of 0·03 mm in minimum lumen diameter between treatment and control groups. For a reduction of lumen of 50% or more at baseline, a significant treatment effect of +0·17 mm was found. Regression was twice as frequent in the lovastatin patients. The Canadian Coronary Atherosclerosis Intervention Trial (CCAIT),[10] also of lovastatin over 2 years, showed a 29% reduction in LDL cholesterol and a significant relative improvement of 0·04 mm in minimum lumen diameter. In that trial, the greatest benefit was in the smallest lesions. Progression occurred in 33% of lovastatin patients and 50% of controls, and new lesions developed in 14% and 30%, respectively.

These trials indicate that reduction of atherogenic lipoproteins by a statin slows atherogenesis. MAAS examined the effect of statin treatment on angiographically non-diseased segments and diseased segments. The magnitude of progression and treatment effect in the non-diseased segments were similar to those in the mildly and moderately diseased segments, indicating that both angiographically diseased and non-diseased segments benefit from lowering of serum lipids, although, as in MARS, the treatment effect was greatest in segments with a diameter stenosis of 50% or more. The smaller Familial Atherosclerosis Treatment Study (FATS)[4] (colestipol/niacin or colestipol/lovastatin) and St Thomas Atherosclerosis Regression Study (STARS)[5] (cholestyramine/diet) trials also showed a greater effect on lesions of 50% stenosis or more.

MARS and CCAIT trials showed no significant changes in clinical events. In MAAS there were no non-cardiac deaths in the simvastatin group but more coronary events occurred in this group during the first 2 years. However, none of these trials was designed as a clinical event study and lacked statistical power to detect a difference in cardiovascular events. There are no results available from the large current long-term controlled trials of the use of statins in primary or secondary prevention. The Program On Surgical Control of Hyperlipidaemias (POSCH) study[25] of the effects of ileal bypass surgery showed greater effects on retardation of coronary atherosclerosis over 9·7 years, and a significant reduction in coronary mortality and morbidity.[25]

To what extent an improvement of 2·5% in diameter stenosis is likely to reduce risk of thrombotic occlusion is not known,[26] although the prevention of new lesions, seen in our study and in CCAIT, may be particularly important since lesions that rupture and lead to thrombotic occlusion are often lipid-rich and with a fine fibrous cap.[27,28] There is evidence that such changes eventually have clinical benefit: the angiographic pattern of disease is a risk factor for future clinical events;[29] the results of the POSCH study;[3,25] and long-term primary prevention trials of other lipid-lowering agents,[30-32] which showed significant reductions in coronary events after 5–6 years.[33]

The results of this trial show that reducing atherogenic lipoproteins in blood is associated with slowing of the atherosclerotic process and that these benefits shown by angiography accumulate over time.

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CORRECTION

Effect of simvastatin on coronary atheroma—In figure 1 of the article by MAAS Investigators (3 Sept, p 633), the indicators for placebo and simvastatin were incorrect. Placebo is represented by open circles connected by solid lines and simvastatin by filled circles connected by interrupted lines.

Chapter 4

EVOLUTION OF CORONARY ATHEROSCLEROSIS IN PATIENTS WITH MILD CORONARY ARTERY DISEASE STUDIED BY SERIAL QUANTITATIVE CORONARY ANGIOGRAPHY AT 2 AND 4 YEARS FOLLOW-UP

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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ABSTRACT

AIMS Angiographic studies on the natural course of both focal and diffuse coronary atherosclerosis have not been performed. Quantitative coronary angiography allows to assess both. 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 not on lipid-lowering medication, three coronary angiograms were made each two years apart. 965 angiographically diseased and non-diseased segments were analyzed 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 ≥ 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. CONCLUSIONS Diffuse and focal coronary atherosclerosis progressed at the same rate in the first and second two years in stenosed and non-stenosed segments. The rate of coronary atherosclerosis progression was small and was higher for focal than for diffuse disease. A minority of lesions progressed and spontaneous regression was rare.

INTRODUCTION

Several prospective studies on the angiographic course of coronary atherosclerosis using quantitative coronary angiography (QCA) have been published, but none of these included three angiograms.[1-14] The majority of these studies focused on changes of lesions and only few assessed changes in angiographically non-diseased coronary segments.[7,8,11,13,14] Four other studies[15-18] applied serial coronary angiography (three or more angiograms) allowing description of 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 four years time, in patients with mild to moderate coronary artery disease 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 comparing simvastatin 20 mg daily with placebo, MAAS (Multicentre Anti-Atheroma Study), which was described and reported elsewhere.[19,20] Both male and female patients were enroled from 11 clinics in 6 European countries with at least 2 coronary segments visibly involved with atherosclerosis at angiography, but not requiring a revascularization procedure. Patients were in stable clinical condition. Total cholesterol was between 5.5 and 8.0 mmol/l. Triglycerides were below 4 mmol/l. No lipid-lowering drugs were allowed. All patients were followed for 4 years. Clinical events, death, myocardial infarction, unstable angina pectoris, percutaneous transluminal coronary angioplasty (PTCA) and coronary bypass surgery (CABG), 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 re-

ceived 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 QCA 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 2 and 4 year follow-up. Analyses of the angiograms were performed centrally in a QCA 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 circumflex artery: proximal (11), obtuse marginal (12), distal (13), posterior lateral (14).[23] Totally occluded segments and segments that previously underwent percutaneous transluminal coronary angioplasty were not included in the baseline selection. When a PTCA was performed, the pre-PTCA analysis of dilated coronary segment was used at 2 and 4 your as appropriate. If no pre-PTCA analysis was present, the segment was excluded. For all segments mean lumen diameter (mm) and segment length (mm) were calculated. Furthermore, 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 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 of vessel lumen and therefore indicates progression of atherosclerosis. A segment was considered angiographically diseased when there was a percentage diameter stenosis ≥ 20% at baseline or at follow-up. Progression was defined as an increase ≥

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 number and percentages, and as mean plus or minus standard deviation. QCA measurements at baseline and follow-up are reported as mean plus or minus standard error. The 95% confidence intervals can be calculated as mean plus or minus 1.96 times the standard error. 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 similar results as the analysis per segment, only the latter is reported. Angiographic changes are reported for the group as a whole, stratified for 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 for 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 analyzed, 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 ±44.0 mm and 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 of the patients previously underwent PTCA. 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 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 CABG and 22 PTCA.

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%

Plus-Minus values are means ± standard deviation; LDL-C: Low Density Lipoprotein Cholesterol, HDL-C: High Density Lipoprotein Cholesterol; *: a vessel with a stenosis > 50% was considered diseased.

QUANTITATIVE CORONARY ANGIOGRAPHY: 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. It can be appreciated that most segments do not change significantly over 4 years. For mean lumen diameter 12% progressed, 81% was 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 after 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 the non-diseased segments as in the mildly diseased segments. Progression in diffuse disease was approximately three times larger in the moderately and severely diseased segments.

Stratified for coronary artery and severity of disease

Decrease in vessel lumen was most prominent in the RCA being 5 times as large as in the LAD. 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 largest 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. The severely diseased lesions at baseline showed no progression, but a small and non-significant improvement. As with diffuse disease, progression was largest in the RCA 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 2 and 4 year. The changes in lesion length and plaque area were in the same direction as 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-ste-

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

	Baseline		2 Years		4 Years	
	mean	se	mean	se	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 error; 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%.

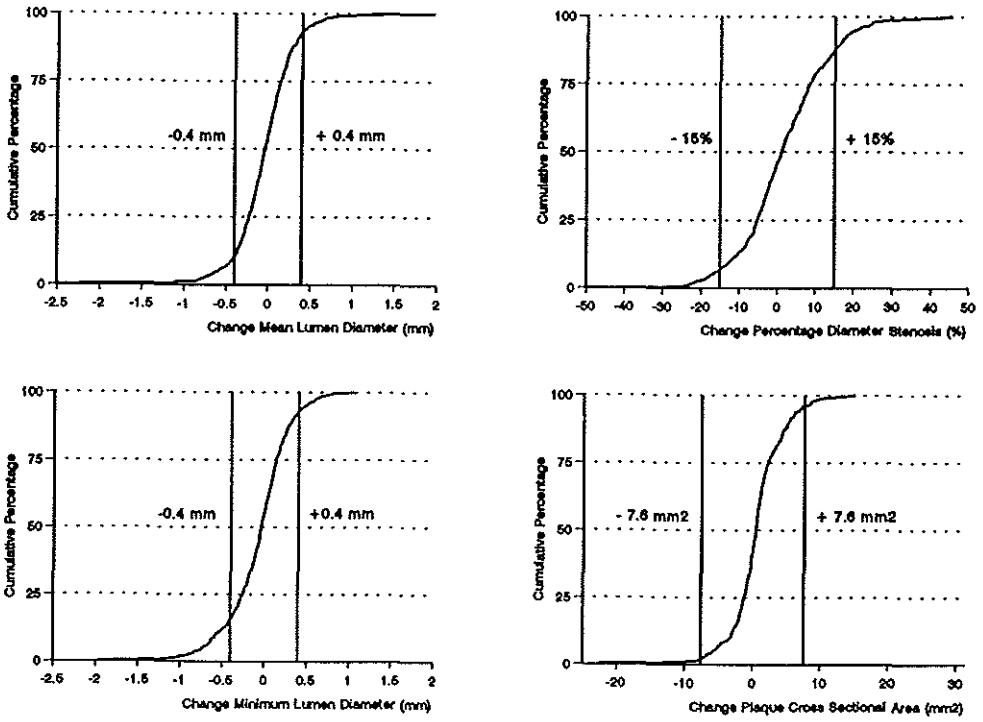

Figure 1 Cumulative distribution curves of change between baseline and 4 year for mean lumen diameter, minimum lumen diameter, percentage diameter stenosis, and plaque area with cut-off points for segment and stenosis change indicating progression of coronary atherosclerosis, stable disease, and regression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

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

Severity of Disease:	Non-Diseased	Mildly	Moderately	Severely
Mean Lumen Diameter (mm)	-0.07 ±0.02	-0.06 ±0.02	-0.13 ±0.05	-0.19 ±0.11
Minium 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
Minium Lumen Diameter (mm)	-0.22 ±0.04	-0.18 ±0.09	-0.07 ±0.02	-0.07 ±0.03

values are means ± standard error; 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%.

nosed parts of these segments.

Changes over time

The overall changes over time are depicted in figure 2. Diffuse atherosclerosis progression was more pronounced in the first two 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 RCA progression was twice as large 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 LAD progression occurred more gradually, whereas the LCX 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 which a total occlusion developed 2 suffered a clinically overt myocardial infarction. The classification per patient showed, that after 4 years 48% of the patients progressed or had a mixed response, which was 38% at 2 years. The percentage of regressors increased from 9% at 2 years to 16% at 4 years. When, as a measure of diffuse atherosclerosis, the criterium 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. The rate of progression of focal atherosclerosis was twice as large 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 differences between the patients included, this might be caused by the fact that we used the average of two orthogonal projections in stead 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 visible assessed changes.

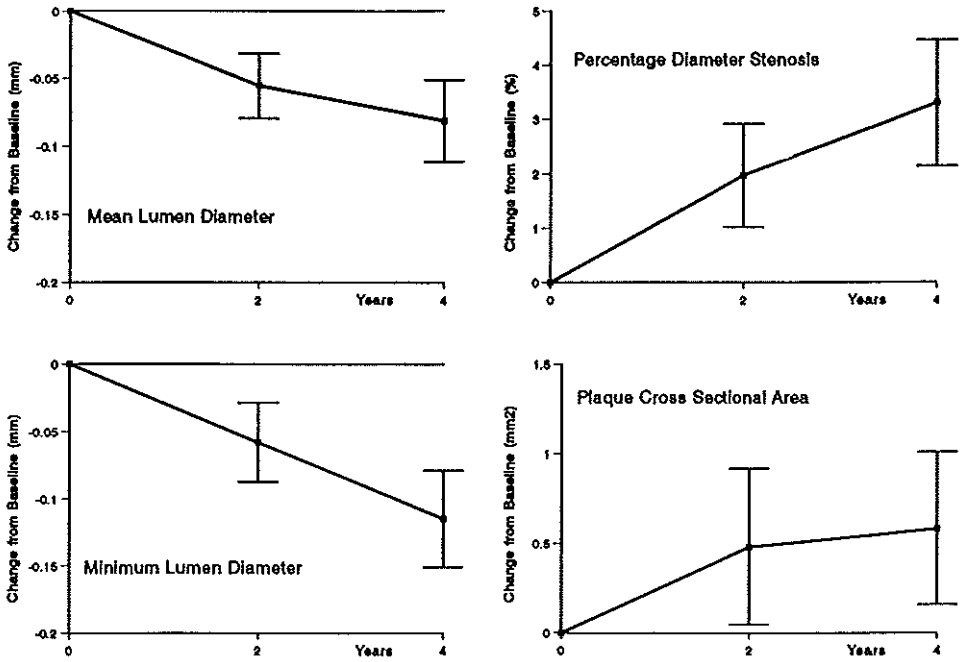

Figure 2 Changes over time from baseline to 2 and 4 year follow-up for mean lumen diameter, minimum lumen diameter, percentage diameter stenosis, and plaque area.

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

	2 year		4 year	
	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)

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, the process of atherosclerosis change is described completely.[22]

The loss in vessel lumen was largest in the RCA as was found by Jost et al.[26] The progression of diffuse atherosclerosis was most prominent in the moderately and severely diseased segments, -0.12 mm and -0.19 mm, respectively.

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 1[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.

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 LCX progressed mainly in the first 2 years and segments in the LAD 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 12 lesion progressed and 1 out 25 regressed. For the per patient classification, however, changes were more pronounced, with 36% of patients stable and 48% progressor or mixed responder. There was a gradual worsening of coronary disease over time in both the per segment as 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 without or with 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 cineangiograms.[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 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 overestimation of the rate of atherosclerosis change.

Clinical Relevance

The rate of progression of coronary atherosclerosis measured by QCA 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.

Albeit the angiographic changes are small, two prospective studies, one analyzed visually[28] and the other using QCA[29] have shown that these small angiographic changes are clinically important because they are predictive of subsequent clinical coronary events as was the absence of angiographic progression for 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 progressor 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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Chapter 5

DIFFUSE CORONARY ATHEROSCLEROSIS AND FOCAL NARROWING ARE CORRELATED WITH SIMILAR CLINICAL, LIPID AND ANGIOGRAPHIC VARIABLES: A 4 YEAR ANGIOGRAPHIC STUDY

Diffuse coronary atherosclerosis and focal narrowing are correlated with similar clinical, lipid and angiographic variables: a 4 year angiographic study

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ABSTRACT

BACKGROUND Coronary atherosclerosis is a not only a focal process producing stenoses, but even more a diffuse disease involving the whole coronary artery. Quantitative coronary angiography can describe the luminal encroaching stages of both focal and diffuse coronary atherosclerosis. Predictors of progression of diffuse coronary atherosclerosis have not yet been identified. PATIENTS AND METHODS In 345 patients with mild coronary atherosclerosis quantitative coronary angiography was performed at baseline and after 4 years. Clinical, lipid and angiographic variables were entered in a multiple linear regression model to select predictors of focal and diffuse coronary atherosclerosis change. Smoking, a larger vessel diameter and a less severe stenosis resulted in more progression for both focal and diffuse coronary atherosclerosis as were a higher total cholesterol during the study and a lower HDL-cholesterol at baseline. Previous successful PTCA was associated with less progression of focal but not diffuse disease. CONCLUSIONS Clinical, lipid and angiographic variables predicting angiographic progression are similar for both focal and diffuse coronary atherosclerosis.

INTRODUCTION

Both visual and quantitative analyses of coronary angiograms have focused on discrete coronary lesions.[1] However, more recently, post-mortem studies[2,3] and in vivo investigations with intracoronary ultrasound[4,5] have shown that coronary atherosclerosis is a diffuse process which insidiously narrows the entire coronary vascular tree. Yet, the significance of diffuse coronary atherosclerosis in the reduction of coronary flow capacity is often not appreciated.[6] The majority of previous angiographic regression trials has investigated changes in focal coronary atherosclerosis,[7-13] while few have paid attention to changes in diffuse coronary disease.[14-17] There are no studies available that describe predictors of progression of diffuse coronary atherosclerosis. The Multicentre Anti-Atheroma Study (MAAS)[15] investigated both focal and diffuse disease in a large number of patients, and the results provide a unique opportunity to compare these manifestations of coronary artery disease. We studied therefore the relationship between patient characteristics, angiographic parameters and lipid measurements and the change over 4 years, in both diffuse and focal coronary atherosclerosis in patients with mild disease. Treatment with simvastatin resulted in retardation of progression of both focal and diffuse coronary atherosclerosis.[15]

METHODS

The patients in this study were originally enroled in a 4 year angiographic trial of lipid-lowering therapy (MAAS) which was reported previously.[15] Male and female patients with a total cholesterol between 5.5 and 8.0 mmol/l (213 and 310 mg/dl) and triglycerides below 4 mmol/l (354 mg/dl), who had at least 2 coronary segments involved with atherosclerosis, were enroled from 11 clinics in 6 European countries. All patients received dietary counselling and were randomized to simvastatin 20 mg daily or matching placebo. Of 404 randomized patients, 23 were excluded. Of the remaining 381, 5 died before a follow-up angiogram was made and 31 refused follow-up angiography. Thus, 345 patients had a follow-up angiogram. Before entering the trial all patients gave informed consent.

Coronary Angiography and Quantitative Coronary Analysis

Coronary angiography was performed according to standards for quantitative analysis at baseline after 2 and 4 years.[19] Prior to angiography all patients received 5 mg isosorbide dinitrate sublingually to induce standardized vasodilation. Angiography was performed via the femoral route, on a fixed table system, and 35 mm cineangiograms were recorded at a minimum speed of 25 frames per second. In each projection the catheter tips not filled with contrast medium were filmed and sent with the angiogram to the QCA

core laboratory for calibration. At baseline all relevant aspects of the angiography procedure were recorded on a case report form to enable exact repetition of the procedure at follow-up. Analyses of the angiograms were performed centrally in the QCA core laboratory using the Coronary Angiography Analysis System (CAAS).[18] From the baseline angiograms orthogonal projections of a maximum of 11 large proximal coronary segments were selected, including both angiographically diseased and non-diseased segments: right coronary artery: proximal, mid, distal; left main coronary artery; left anterior descending artery: proximal, mid, distal; left circumflex artery: proximal, obtuse marginal, distal, posterior lateral.[20] Previous dilated segments were included but totally occluded segments not. For all segments mean lumen diameter (mm) and segment length (mm) were calculated. Furthermore, minimum lumen diameter (mm), reference diameter (mm) and percentage diameter stenosis (%) were estimated for all angiographically diseased segments. The available multiple matched projections were used for the assessment of change over time.

Angiographic Definitions

The mean lumen diameter of all segments was interpreted as measure of *diffuse coronary atherosclerosis*, and the minimum lumen diameter was used as a measure of *focal coronary atherosclerosis*.[21] A negative change in diameter represents a decrease of vessel lumen (progression), a positive change represents widening of the vessel lumen (regression). A segment was considered angiographically diseased when there was a percentage diameter stenosis ≥ 20% at baseline or at follow-up.

Statistical Aspects

The unit of analysis in this study is the patient, hence the segmental measurements were averaged by patient. Continuous variables were reported as mean ± standard deviation, discrete variables as numbers and percentages. Patient characteristics, baseline angiographic parameters and lipid measurements at baseline and during follow-up, which might be related with progression of diffuse and focal coronary atherosclerosis, were first entered in univariate linear regression analysis. This univariate analysis was stratified for simvastatin or placebo. To select independent predictors of atherosclerotic change, stepwise multivariate linear regression analysis was performed.[22] This multivariate analysis was performed on both treatment groups combined. The treatment and its interaction terms were included in the multivariate analysis. Variables predictive in univariate analysis and variables that on the basis of other studies might be related to atherosclerotic change were entered in the multivariate model. Continuous variables were entered as such in the multivariate analysis. For all calculations the SAS statistical software package was used.[23] The changes in mean lumen diameter, representing diffuse disease and minimum lumen diameter, represent-

ing focal disease, were used as dependent variables.

RESULTS

In 345 patients (167 placebo, 178 simvastatin) follow-up angiography was available. In 69 patients in stead of a 4 year angiogram a 2 year angiogram was used as follow-up. The mean age was 55 years, most were males (89%), and 70% had angina pectoris (Table 1). Almost half of the patients had undergone percutaneous transluminal coronary angioplasty (PTCA). Eleven percent of the patients were women, all were postmenopausal and none were on estrogen replacement. Approximately 40 percent of the patients did not have a narrowing of > 50% in any of the epicardial arteries at the baseline angiography, indicating that the patients enroled had mild coronary artery disease. Total cholesterol averaged 6.4 mmol/l (248 mg/dl), LDL-cholesterol 4.5 mmol/l (174 mg/dl). These values were reduced by simvastatin by 23% and 30% respectively. HDL-cholesterol averaged 1.1 mmol/l (43 mg/dl) and increased by 9% in the simvastatin group.

Table 1. Baseline characteristics

		Placebo (N=167)		Simvastatin (N=178)	
Age (years)		55	±6.4	55	±7.3
Systolic Blood Pressure (mmHg)		132	±15.0	132	±16.3
Diastolic Blood Pressure (mmHg)		80	±7.8	81	±8.2
Male		148	(89%)	159	(89%)
Angina Pectoris		117	(70%)	116	(65%)
Smoker		32	(19%)	48	(27%)
Vessel disease*:	none	70	(42%)	69	(39%)
	one	60	(36%)	68	(38%)
	two	26	(16%)	33	(19%)
	three	11	(7%)	8	(5%)
Previous MI		59	(35%)	70	(39%)
Previous PTCA		77	(46%)	87	(49%)
Total Cholesterol (mmol/l)		6.4	±0.83	6.3	±0.72
LDL-Cholesterol (mmol/l)		4.5	±0.78	4.4	±0.67
HDL-Cholesterol (mmol/l)		1.1	±0.27	1.1	±0.30
Triglycerides (mmol/l)		1.8	±0.84	1.9	±0.95

Values are means ± standard deviations and numbers, with percentages in brackets, * visual assessment, a vessel was considered diseased when there was a stenosis of > 50% at baseline angiography. To convert mmol/l values to mg/dl multiply the cholesterol values with 38.7, and the triglycerides values by 88.5.

Simvastatin reduced progression of focal disease over 4 years by 0.08 mm (95% confidence interval 0.03, 0.14) and progression of diffuse coronary atherosclerosis by 0.06 mm (95% confidence interval 0.02, 0.10).[15]

Univariate Analysis: focal coronary atherosclerosis

Table 2 and 3 present the univariate relationships between clinical, lipid and angiographic variables and changes in mean lumen diameter and minimum lumen diameter for the placebo and simvastatin groups, respectively. In the placebo group a relatively high diastolic blood pressure, a low total cholesterol and LDL-C at baseline, a rise in total cholesterol and LDL-C during the trial, a low HDL-C, and a low Apo-A1 were all significantly associated with a greater loss in minimum lumen diameter with time. In the simvastatin group a relatively greater mean and minimum lumen diameter and percentage diameter stenosis at baseline, a low HDL-C, female sex, systolic blood pressure, and smoking were all associated with more progression.

Univariate Analysis: diffuse coronary atherosclerosis

In the patients receiving placebo a relatively low HDL-C and Apo-A1, a high Apo-B, a higher systolic blood pressure, and smoking were associated with more progression. In the simvastatin group patients with a large mean lumen diameter, and smokers showed more progression of diffuse disease.

Multivariate analysis: focal and diffuse disease

Independent predictors for atherosclerosis change in both groups combined are listed in Table 4. Smokers had more progression of both focal and diffuse coronary atherosclerosis. A decrease in total cholesterol during the study and a higher HDL-C at baseline were associated with less progression of both focal and diffuse disease. A larger vessel diameter and a less severe stenosis at baseline resulted in more progression of both focal and diffuse coronary atherosclerosis. The successful performance of PTCA prior to the study was associated with less progression of focal but not diffuse disease.

DISCUSSION

Coronary artery disease is commonly regarded as a focal problem, with single or multiple lesions in a single or several coronary arteries. The angiographically focal lesion is the basis for surgical intervention (bypass of discrete lesions) or angioplasty. However, it should be appreciated that coronary atherosclerosis can also be a diffuse process affecting the whole coronary tree.[3] Some patients exhibit predominantly diffuse disease with narrowed coronary arteries with or without more severe focal stenoses, while in others the clinical picture is dominated by a single severe stenosis resulting in unstable angina pectoris or a sudden large myocardial infarction. Most patients with ischemic heart disease,

Table 2. Results of Univariate Linear Regression Analysis for the placebo group.

	Mean Lumen Diameter			*Minimum Lumen Diameter*		
	Coefficient	se	P-value	Coefficient	se	P-value
Clinical variables:						
Age (years)	0.001	0.003	0.62	0.005	0.002	0.06
Systolic Blood Pressure (mmHg)	-0.005	0.003	0.03	-0.0009	0.001	0.50
Diasystolic Blood Pressure (mmHg)	-0.001	0.001	0.24	-0.005	0.002	0.04
Smokers (no=0, yes=1)	-0.12	0.05	0.01	-0.09	0.05	0.07
Sex (female=0, male=1)	-0.02	0.06	0.49	-0.07	0.06	0.29
Angina Pectoris (no=0, yes=1)	0.02	0.04	0.67	0.007	0.04	0.86
PTCA (no=0, yes=1)	0.04	0.04	0.27	0.04	0.04	0.32
Myocardial Infarction (no=0, yes=1)	0.06	0.04	0.15	0.005	0.04	0.89
Lipid variables:						
Total Cholesterol baseline (mmol/l)	0.05	0.02	0.04	0.06	0.02	0.01
Total Cholesterol change (%)	-0.005	0.002	0.03	-0.006	0.002	0.004
LDL-Cholesterol baseline (mmol/l)	0.04	0.02	0.11	0.05	0.02	0.06
LDL-Cholesterol change (%)	-0.003	0.002	0.06	-0.004	0.001	0.01
HDL-Cholesterol baseline (mmol/l)	0.18	0.07	0.02	0.17	0.07	0.01
HDL-Cholesterol change (%)	-0.002	0.002	0.17	-0.002	0.001	0.17
Triglycerides baseline (mmol/l)	-0.03	0.02	0.17	-0.01	0.02	0.69
Triglycerides change (%)	-0.000	0.000	0.94	-0.0004	0.0005	0.41
Apo-B baseline (g/l)	0.09	0.07	0.19	0.11	0.06	0.09
Apo-B change (%)	-0.002	0.001	0.17	-0.002	0.001	0.09
Apo-A1 baseline (g/l)	0.10	0.05	0.06	0.12	0.05	0.03
Apo-A1 change (%)	0.0002	0.001	0.78	-0.0009	0.001	0.39
Angiographic variables:						
Mean lumen diameter baseline (mm)	-0.08	0.04	0.08	-0.09	0.04	0.07
Minimum lumen diameter baseline (mm)	-0.06	0.05	0.24	-0.11	0.05	0.03
Diameter stenosis baseline (%)	-0.0002	0.003	0.94	0.0004	0.003	0.87

Coefficient: linear regression coefficient; se: standard error.

The linear regression model allows first, to test whether relations between predictors and the lumen change are statistically significant, second it permits to quantify the relation between the predictive value and the change in lumen diameter which is expressed in the regression coefficient. The relation between the change in lumen diameter and the predictive variable is defined as : $Y = A + R * X$, where Y is the change in mean or minimum lumen diameter, A is the intercept, R is the regression coefficient, and X is the value of the predictive variable. For example (the intercept has been deleted from this example): the presence of smoking represents an increase in progression of diffuse disease of 1 * -0.12 mm = -0.12 mm for mean lumen diameter, and a decrease in total cholesterol of 10% represents a -10 * -0.005 mm = +0.05 mm change.

Table 3. Results of Univariate Linear Regression Analysis for the simvastatin group.

	Mean Lumen Diameter			*Minimum Lumen Diameter*		
	Coefficient	se	P-value	Coefficient	se	P-value
Clinical variables:						
Age (years)	-0.0007	0.002	0.78	-0.001	0.002	0.62
Systolic Blood Pressure (mmHg)	0.0008	0.001	0.45	0.0003	0.001	0.75
Diasystolic Blood Pressure (mmHg)	0.001	0.002	0.52	-0.00007	0.002	0.97
Smokers (no=0, yes=1)	-0.10	0.03	0.01	-0.11	0.04	0.005
Sex (female=0, male=1)	-0.04	0.05	0.44	-0.08	0.06	0.17
Angina Pectoris (no=0, yes=1)	0.01	0.03	0.66	-0.008	0.03	0.82
PTCA (no=0, yes=1)	0.02	0.03	0.49	0.06	0.03	0.12
Myocardial Infarction (no=0, yes=1)	-0.004	0.03	0.90	-0.01	0.03	0.78
Lipid variables:						
Total Cholesterol baseline (mmol/l)	0.02	0.02	0.51	0.02	0.02	0.36
Total Cholesterol change (%)	0.001	0.001	0.55	-0.002	0.001	0.30
LDL-Cholesterol baseline (mmol/l)	0.001	0.02	0.96	0.007	0.02	0.79
LDL-Cholesterol change (%)	0.0009	0.001	0.50	-0.002	0.001	0.32
HDL-Cholesterol baseline (mmol/l)	0.08	0.05	0.16	0.09	0.05	0.11
HDL-Cholesterol change (%)	0.0007	0.001	0.62	0.001	0.001	0.38
Triglycerides baseline (mmol/l)	0.001	0.1	0.93	0.008	0.01	0.96
Triglycerides change (%)	-0.0009	0.0006	0.19	-0.001	0.0007	0.17
Apo-B baseline (g/l)	0.003	0.06	0.96	0.03	0.06	0.66
Apo-B change (%)	0.0009	0.001	0.49	-0.001	0.001	0.41
Apo-A1 baseline (g/l)	0.02	0.04	0.78	0.02	0.04	0.63
Apo-A1 change (%)	0.0003	0.0008	0.70	0.0005	0.0009	0.60
Angiographic variables:						
Mean lumen diameter baseline (mm)	-0.13	0.04	0.004	-0.11	0.04	0.01
Minimum lumen diameter baseline (mm)	-0.10	0.04	0.03	-0.27	0.04	0.0001
Diameter stenosis baseline (%)	-0.0003	0.002	0.90	0.01	0.002	0.0001

To convert mmol/l values to mg/dl multiply the cholesterol values with 38.7, and the triglycerides values by 88.5.

Table 4. Results of Multivariate Linear Regression analysis of placebo and simvastatin groups combined.

	Mean Lumen Diameter			*Minimum Lumen Diameter*		
	Coefficient	se	P-value	Coefficient	se	P-value
Intercept	0.12	0.10	0.25	0.10	0.08	0.25
Smokers (no=0, yes=1)	-0.09	0.03	0.002	-0.08	0.03	0.01
PTCA (no=0, yes=1)				0.05	0.02	0.04
Total Cholesterol change (%)	-0.002	0.0009	0.007	-0.004	0.0008	0.0001
HDL-C baseline (mmol/l)	0.10	0.05	0.02	0.05	0.04	0.009
Mean lumen diameter at baseline (mm)	-0.10	0.03	0.002			
Minimum lumen diameter at baseline (mm)				-0.18	0.03	0.0001

Coefficient: linear regression coefficient; se: standard error. To convert mmol/l values to mg/dl multiply the cholesterol values with 38.7, and the triglycerides values by 88.5.

For example, the relation between change in diffuse disease and the independent predictors is:

change in mean lumen diameter (mm) = 0.12 + smoking (no=0, yes=1) * -0.09 + change total cholesterol (%) * -0.002 + baseline HDL-C (mmol/l) * 0.10 + mean diameter at baseline (mm) * -0.10.

A patient who smokes (1), has a reduction in total cholesterol of 20%, a HDL-C of 1.0 mmol/l at baseline, with a mean lumen diameter at baseline of 2.80 mm, has a predicted change in mean lumen diameter of:

0.12 + 2.80 * -0.10 + 1 * -0.10 + -20 * -0.002 + 1.0 * 0.10 = -0.12

a reduction in mean lumen diameter of 0.12 mm over 4 years.

however, exhibit both focal and diffuse disease when studied by appropriate methods such as intracoronary ultrasound.[4] To the human observer, coronary angiography reveals predominantly focal narrowings. However, with the introduction of quantitative coronary angiography both focal and diffuse coronary atherosclerosis can be investigated.[21]

We used as measures of diffuse and focal atherosclerosis the mean and minimum lumen diameter, respectively. The mean lumen diameter also includes in diseased segments a focal narrowing and therefore gives information on focal disease also. However, since the mean lumen diameter is determined in both angiographically diseased segments and non-diseased segments, and it embodies the whole coronary segment and not

only the narrowest point of a stenosis, it predominately represents diffuse disease.[21] In a secondary analysis, which is not presented here, predictors of categorical per patient change[15] were similar as in the present analysis.

In the MAAS trial, the minimum and mean lumen diameter were used as measures of focal and diffuse disease, respectively. Effective lipid-lowering therapy with simvastatin caused retardation of both disease measurements,[15] as has been shown in other angiographic trials.[14,16,17] The present analysis confirms that changes in focal and diffuse disease measurements are related to some of the same clinical characteristics: smoking and baseline HDL-C, and to the same treatment effects, in particular changes in total cholesterol (Table 4). This supports the concept that focal and diffuse atherosclerosis are manifestations of the same pathological process. Pathologic studies have demonstrated that the latter is a continuum ranging from endothelial dysfunction, to plaque formation without encroachment upon the vessel lumen, to diffuse thickening of the coronary arteries over (almost) all segments, but particularly the proximal parts, to advanced atherosclerotic plaque encroachment upon the vessel lumen.[4,25-27] We found that the predictors of focal and diffuse change were similar, suggesting that the pathological processes associated with progression of focal and diffuse disease are identical.

Predictors of coronary atherosclerosis change

Patients enroled in MAAS had on average mild coronary artery disease (Table 1). A large proportion of the patients was selected after successful PTCA without angiographic restenosis at 6 months follow-up. These patients were younger, and represented a subpopulation with a single significant stenosis and probably little diffuse disease. This may explain why PTCA was associated with absence of focal disease progression (Table 4).

The changes in total cholesterol and baseline HDL-C were independent predictors of progression. LDL-C and apolipoprotein-B showed a much less strong relationship, which is somewhat unexpected as simvastatin predominantly influences LDL-particles. No relation was found between the baseline total cholesterol and the angiographic course. This may reflect the limited range of cholesterol level at baseline (between 5.5 and 8.0 mmol/l, 213 and 310 mg/dl) and the marked reduction of total cholesterol in half of the patients. A large baseline diameter was associated with more progression a finding as in the INTACT study,[24] suggesting that the rate of progression might be higher in patients in whom diffuse coronary disease has not yet resulted in a substantial overall narrowing of the coronary tree.

Limitations of the study

The early stages of coronary atherosclerosis are accompanied by a compensatory enlargement of the vessel lumen.[26]

Contrast angiography provides a shadowgram of the vessel lumen, and does not yield information on the vessel wall, as intracoronary ultrasound does. Coronary angiography is therefore hampered in the assessment of the early stages of coronary atherosclerosis.

In an angiographic study of coronary atherosclerosis change, follow-up should be available for all patients. Incompleteness of follow-up will introduce a bias towards less progression of disease when reasons for not performing follow-up angiography are related to a worsening in clinical status.[1] In this long-term angiographic study 91% of patients had a follow-up angiogram, which is relatively high for a 4 year follow-up study, the low drop-out rate would exert minimal effects on the outcome. Because patients with diabetes mellitus and uncontrolled hypertension were excluded from the trial, the influence of these powerful risk factors on progression of coronary atherosclerosis could not be established. As in other trials relatively few women were included in this study and their number was to small to draw any firm conclusions.

The univariate analysis was stratified for treatment allocation since treatment with simvastatin resulted in less progression of coronary atherosclerosis. In multivariate analysis the two treatment groups were pooled since the effect of simvastatin was included in the multivariate model.[22] Since the unit of clinical practice is the patient, we performed a per patient analysis. Consequently, the influence of lesion characteristics on angiographic change is not reported.

Clinical implications

The risk of developing coronary disease in the population is related to the level of total cholesterol, LDL-C and HDL-C.[28] However, in the present study of patients with known coronary atherosclerosis, further disease progression was not significantly related to baseline levels of total cholesterol or LDL-C. In an analogous manner the Scandinavian Simvastatin Survival Study (4S)[29] showed that treatment with simvastatin improves survival and reduces non-fatal cardiovascular events over the entire range of cholesterol levels in the patients selected for the trial (total cholesterol between 5.5 and 8.0 mmol/l, 213 and 310 mg/dl).[30] Accordingly, treatment with a HMG-CoA reductase inhibitor should be considered in all patients with coronary artery disease and mild to moderately elevated cholesterol levels.

Coronary atherosclerosis is a diffuse disease, which often is associated with angiographically focal narrowings. Symptoms caused by these stenoses are often treated by angioplasty or coronary bypass surgery, but these interventions do not affect the underlying diffuse disease process. In contrast, effective lipid modification reduces progression of both focal and diffuse coronary atherosclerosis.[14-17] Development and clinical evaluation of agents which induce even larger lipid changes should thus be encouraged.

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Chapter 6

INCIDENCE OF ANGIOGRAPHIC PATTERNS OF PROGRESSION OR REGRESSION OF CORONARY ATHEROSCLEROSIS: THE IMPORTANCE OF DIFFUSE ATHEROSCLEROSIS. A QUANTITATIVE SERIAL 2-4 YEARS ANGIOGRAPHIC STUDY

Incidence and angiographic patterns of progression or regression of coronary atherosclerosis: the importance of diffuse atherosclerosis. A quantitative serial 2-4 years angiographic study.

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ABSTRACT

BACKGROUND The diffuse nature of atherosclerosis is often not appreciated in clinical practice. Clinical decision making is mainly based on the presence and severity of lesions and angiographic studies of coronary atherosclerosis predominantly report about lesions. With quantitative coronary angiography it is possible to study changes in coronary artery lumen diameters that also reflect diffuse atherosclerosis. METHODS AND RESULTS Angiograms made at baseline, 2 and 4 years follow-up from 272 patients were analyzed using quantitative angiographic techniques. Progression or regression of a coronary stenosis was defined as a change of ≥ 0.4 mm in minimum lumen diameter. A total of 924 lesions were analyzed. Progression occurred in 134 lesions, regression in 90 lesions and 700 lesions were stable. The incidence of progression or regression of lesions was similar within 0 and 2 years and within 2 and 4 years (50%). After progression or regression of a lesion at 2 years the majority of these lesions remained stable in the next 2 years. Progression of lesions was both the result of an increase in plaque size and progression of diffuse atherosclerosis of the segments containing these lesions. Regression of lesions was the result of both a decrease in plaque size and regression of diffuse atherosclerosis. CONCLUSIONS The incidence of progression or regression of lesions and magnitude of change during the first and second 2 year interval was similar. Coronary stenosis progression is accompanied by progression of diffuse atherosclerosis and coronary stenosis regression is accompanied by regression of diffuse atherosclerosis. This emphasizes the importance of diffuse coronary atherosclerosis.

INTRODUCTION

Serial angiographic trials have shown both progression as well as regression of lesions in patients with coronary artery disease.[1] Most studies were designed with two angiograms of 2 to 5 year intervals. In the Multicentre Anti-Atheroma Study (MAAS), angiograms were made at baseline after 2 and again after 4 years follow-up.[2,3] In order to assess the effect of drug intervention, the data in MAAS were presented on a per patient basis. In patients treated with diet and placebo a gradual progression of atherosclerosis was observed. Changes in the per patient averaged minimal and mean lumen diameter after 4 years were approximately twice as large as those after 2 years. Patients receiving simvastatin showed less progression and more often regression of the disease. The MAAS database offers an unique opportunity to assess the serial changes (0-2 years and 2-4 years) of individual atherosclerotic lesions. The current analysis in 272 patients with three serial angiograms (at baseline, after 2 years and after 4 years) specifically addresses two questions. First, what is the relation between changes occurring over time of focal lesion (>20% diameter stenosis) and the lumenal changes of the coronary segment (diffuse coronary atherosclerosis) containing that focal lesion, and second, whether progression or regression of a lesion are gradual processes, with similar changes in the first and second two year period or rather random occurring events.

METHODS

Patients

The patients were originally enroled in the Multicenter Anti-Atheroma Study (MAAS), a coronary angiographic trial of lipid-lowering with the HMG-reductase inhibitor simvastatin 20 mg daily compared to placebo. The design and results of the trial have been described and reported elsewhere.[2,3] Two-hundred-forty-seven male and 25 female patients with mild coronary artery disease in a stable clinical condition and a total cholesterol between 5.5 and 8.0 mmol/l with three serial angiograms were included. The study was approved by the ethical review board of all participating hospitals and all patients gave informed consent before entering the trial.[3]

Coronary Angiography and Quantitative Analysis

Coronary angiography was performed at baseline and after 2 and 4 years. Prior to each procedure patients received 5 mg isosorbide dinitrate sublingually to induce standardized vasodilation. Coronary angiography was performed via the femoral route, on a fixed table system, and 35 mm cineangiograms were recorded at a minimum speed of 25 frames per second. Catheter tips not filled with contrast medium were filmed in each projection and stored with the angiogram for calibration. All relevant aspects of the angiography procedure were recorded on a case report form to enable exact repetition of the procedure

at 2 and 4 year follow-up.

Quantitative analysis of the angiograms was performed centrally in the Cardialysis Core Laboratory for Quantitative Coronary Angiography (QCA) using the Coronary Angiography Analysis System (CAAS).[4] Eleven large proximal coronary segments were selected for analysis. From the right coronary artery (RCA): the proximal, mid and distal segment, the left main coronary artery (LM), the left anterior descending artery (LAD): proximal, mid and distal segment; left circumflex artery (LCX): proximal segment, the obtuse marginal and the posterior lateral.[5]

Of the available views, only the projection in which the stenosis was most severe (the largest percentage diameter stenosis) was used. Totally occluded segments at baseline or at follow-up and segments that previously underwent percutaneous transluminal coronary angioplasty were excluded. The unit of analysis for this study was the coronary lesion.

Quantitative Angiographic Parameters

For all lesions and segments the minimum lumen diameter (mm), interpolated reference diameter (mm), percentage diameter stenosis (%), and plaque diameter (mm) were measured or computed as appropriate (Figure 1a). The minimum lumen diameter was defined as the part of the stenosis with the smallest diameter. The interpolated reference diameter is the value of the reference diameter function taken at the site of the stenosis; this is an automated procedure without any user interaction (Figure 1b).[4] The reference diameter function is the computer estimation of the original diameter values of the vessel segment, assuming there was no coronary disease present, and derived from the available diameter data. To this end, a first degree least squares polynomial is determined through all the diameter values proximal and distal to the obstruction; this polynomial allows the vessel to taper. Next the polynomial is translated upwards until 80 percent of the diameter values are below the polynomial. The resulting polynomial values are then assumed to be a measure for the normal size of the artery at the corresponding points; this polynomial function is denoted the reference diameter and displayed in the diameter function by a straight line. The change of the interpolated reference diameter reflects the change of diffuse atherosclerosis proximal and distal of a lesion in the coronary segment of interest. The percentage diameter stenosis was calculated as: (interpolated reference diameter - minimum lumen diameter) / interpolated reference diameter * 100%. The plaque diameter was defined as the difference between the interpolated reference diameter and the minimum lumen diameter and represents the portion of a plaque that encroaches on the vessel lumen.

Focal disease (the lesion) was defined as stenosis with a percentage diameter stenosis of more than 20%.[2] Coronary segments with a narrowing less than 20% were defined to be angiographically normal and not included in the present

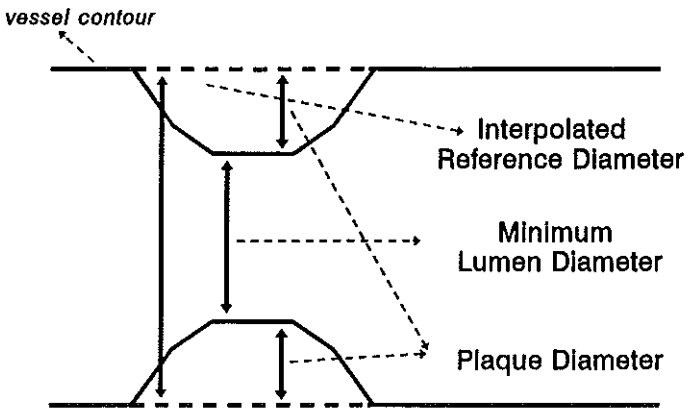

Figure 1a: Illustration of the angiographic parameters used in this study.

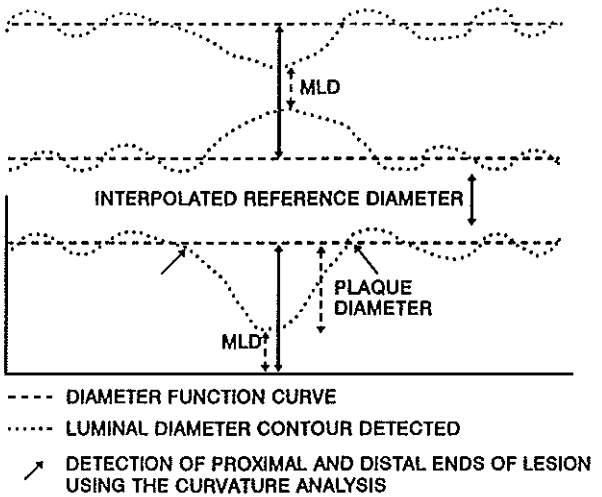

Figure 1b: Graphic representation of the CAAS measurement of the interpolated reference diameter. The actual luminal contour is detected by the edge detection technique. The proximal and distal extremities of the obstructive lesion are determined from the curvature analysis of the detected contour and the thus identified lesion is then excluded from the determination of the interpolated reference diameter. A second degree polynomial function is applied to diameter measurements made from each scanline (every 0.1 mm) of the segment proximal and distal to the lesion, anatomical vessel tapering is taken into consideration and the vessel contours in the area of the lesion are "reconstructed" (as it should appear in the disease free state) and interpolated into the diameter function. The interpolated reference diameter used then is the diametric measurement from the diameter function curve at the point of the minimal luminal diameter.

analysis.

A negative change in minimum lumen diameter is a decrease of vessel lumen and therefore indicates progression of coronary atherosclerosis. Progression of focal disease (of a lesion) was defined as a decrease of $\geq$ 0.4 mm in minimum lumen diameter, regression as an increase of $\geq$ 0.4 mm between baseline and 4 years. Progression or regression of diffuse disease (the segment containing the lesion) was defined as a decrease or an increase in the interpolated reference diameter, respectively. Progression of a coronary plaque was defined as an increase, regression as a decrease in the plaque diameter.

Data Analysis

Baseline characteristics are presented as number and percentages, and as mean plus or minus standard deviation. Average changes of quantitative measurements are reported as mean plus or minus standard deviation. The percentage change from baseline was calculated. For each individual lesion the categorical class of change between 0-2 years and 2-4- years is reported. The angiographic changes were evaluated by means of a paired T-test. A P-value < 0.05 was considered statistically significant. Data are reported for the study population as a whole and stratified by treatment allocation. The SAS statistical software package was used for all analyses.[6]

RESULTS

The baseline characteristics of the whole study group are shown in Table 1. There were no significant differences between the placebo group and the simvastatin group. Nine-hundred-twenty-four lesions were available for analysis. Of these 134 progressed, 90 regressed and 700 remained stable (Table 2).

Relation between focal and diffuse disease

The measurements of interpolated reference-, plaque-, and minimum lumen diameter and percentage diameter stenosis are tabulated at baseline, at 2 years and at 4 years (Table 2). The absolute and relative changes from baseline to 2 years and from baseline to 4 years are tabulated in Table 3.

The magnitude of progression and regression of atherosclerosis is almost similar in the time interval from 0-2 years and from 2-4 years. Lesions that progress have a larger baseline minimum lumen diameter and are located in larger sized coronary segments compared to stable lesions and lesions that regress. The relative magnitude of progression or regression is not statistically different (Table 3). The coronary segments which contained a lesion that progressed also showed a decrease of their entire lumen size which is reflected in a decrease of the interpolated reference diameter (Figure 2). The reverse is seen in coronary segments containing a lesion that regressed, where the entire size of segment increased reflected by an increase in the

Table 1. Baseline characteristics

		Placebo (N=129)		Simvastatin (N=143)	
Age (years)		55.5	±6.6	55.5	±7.5
Systolic Blood Pressure (mmHg)		132	±15.3	132	±16.8
Diastolic Blood Pressure (mmHg)		80	±8.0	80	±8.3
Total Cholesterol (mmol/L)		6.40	±0.8	6.3	±0.7
LDL-Cholesterol (mmol/L)		4.93	±0.8	4.8	±0.7
HDL-Cholesterol (mmol/L)		1.1	±0.3	1.1	±0.3
Triglicerides (mmol/L)		1.8	±0.8	1.8	±0.9
Male		117	(91%)	130	(91%)
Angina Pectoris		90	(70%)	97	(68%)
Smoker		22	(17%)	35	(25%)
Vessel disease*:	none	59	(46%)	55	(39%)
	one	44	(34%)	60	(42%)
	two	19	(15%)	21	(15%)
	three	7	(5%)	7	(5%)
Previous MI		42	(33%)	60	(42%)
Previous PTCA		67	(52%)	71	(50%)
Aspirin		70	(54%)	96	(67%)
ACE-inhibitor		18	(14%)	22	(15%)
Betablocker		54	(42%)	55	(39%)
Calcium Antagonist		82	(44%)	94	(49%)

Figures are means ± standard deviations and numbers with percentages in brackets, * visual assessment, a vessel was considered visually diseased when there was a stenosis of > 50%

interpolated reference diameter (Figure 3). Stable lesions did not, by definition progress or regress, and the coronary segment containing a stable lesion also remained stable (Figure 4). The baseline measurements and absolute and relative changes of 2 and 4 years of the subgroups of patients who were assigned to placebo or simvastatin are tabulated in Tables 4 and 5. By and large the coronary diameter changes occurring in either subgroup were similar to those occurring in the entire study group.

Progression or regression of lesions

Most lesions remained stable between 0 and 2 years (79%), a minority progressed (12%) or regressed (9%) (Figure 5). Eighty-five percent of the stable lesions at 2 years remained stable at 4 years. The

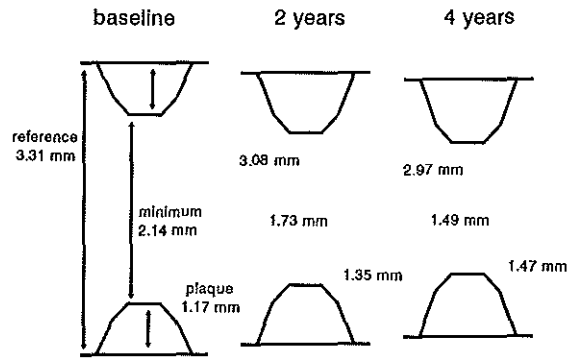

Figure 2: Alteration of minimum lumen-, plaque- and interpolated reference diameter at 2 and 4 years associated with progression of lesions.

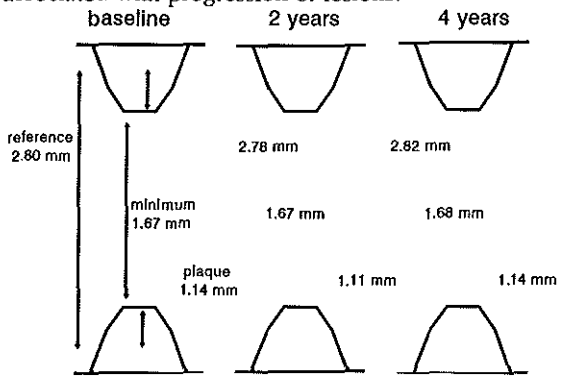

Figure 3: No change of minimum lumen-, plaque- and interpolated reference diameter at 2 and 4 years associated with stability of lesions.

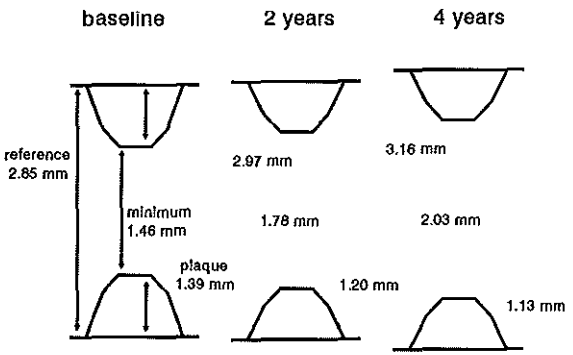

Figure 4: Alteration of minimum lumen-, plaque- and interpolated reference diameter at 2 and 4 years associated with regression of lesions.

Table 2. Results at baseline, 2 years and 4 years stratified by class of change at 4 years.

Variable	baseline	2 years	4 years
Progression (N=134)			
Minimum lumen diameter (mm)	2.14 ± 0.53	1.73 ± 0.56	1.49 ± 0.53
Interpolated reference diameter (mm)	3.31 ± 0.83	3.08 ± 0.86	2.97 ± 0.83
Plaque diameter (mm)	1.17 ± 0.45	1.35 ± 0.60	1.47 ± 0.56
Percentage diameter stenosis (%)	34.7 ± 7.77	43.2 ± 12.8	49.2 ± 11.6
Stable (N=700)			
Minimum lumen diameter (mm)	1.67 ± 0.48	1.67 ± 0.48	1.68 ± 0.45
Interpolated reference diameter (mm)	2.80 ± 0.74	2.78 ± 0.74	2.82 ± 0.75
Plaque diameter (mm)	1.14 ± 0.47	1.11 ± 0.47	1.14 ± 0.50
Percentage diameter stenosis (%)	40.1 ±10.5	39.3 ± 10.4	39.8 ± 10.4
Regression (N=90)			
Minimum lumen diameter (mm)	1.46 ± 0.51	1.78 ± 0.56	2.03 ± 0.54
Interpolated reference diameter (mm)	2.85 ± 0.68	2.97 ± 0.65	3.16 ± 0.65
Plaque diameter (mm)	1.39 ± 0.45	1.20 ± 0.46	1.13 ± 0.33
Percentage diameter stenosis (%)	48.9 ±12.1	40.3 ± 12.4	36.1 ± 8.84

Figures are means ± standard deviation. Progression: decrease ≥ 0.4 mm in minimum lumen diameter, Regression: increase in ≥ 0.4 mm in minimum lumen diameter.

majority of lesions that progressed after 2 years was stable in the second 2 years period (76%), and only few also progressed between 2 and 4 years (5%). Most of the lesions that regressed between 0 and 4 years did so in the first 2 years and stabilized in the second study period (67%), and only few also regressed between 2 and 4 years (2%). The overall incidence of lesion progression and regression was similar in both study periods. Between 0-2 years and 2-4 years 12% and 10% progressed, respectively. For regression the incidence was 9% at 2 years and 8% at 4 years. The differences between the two study periods were not statistically significant.

Between 0 and 4 years 134 lesions progressed, 49% of these changed between 0 and 2 years, 51% between 2 and 4 years (Figure 6). Of the 90 lesions that regressed after 4 years, 41% regressed in the first study period, 59% in the second period.

There was no difference in the angiographic patterns of progression or regression in patients on placebo or on simvastatin treatment, with the exception that

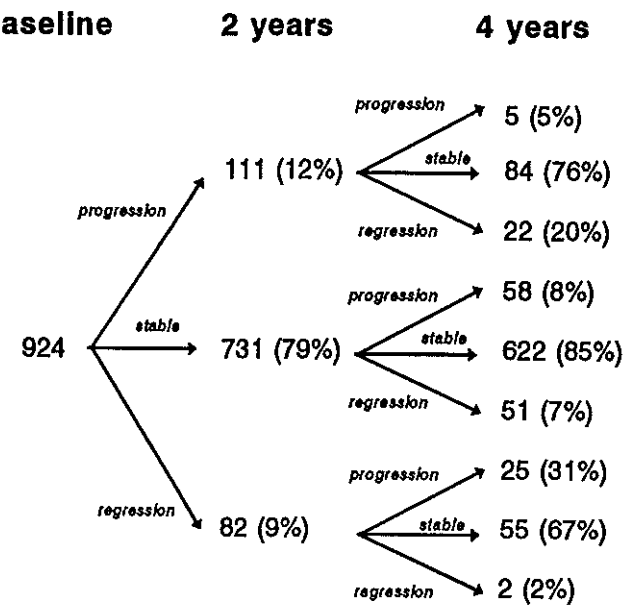

Figure 5. Flowchart of the categorical class of change for individual lesions over and describes the serial changes between 0-2 years and 2-4 years. Numbers of lesions that remain stable, progress or regress with percentages in brackets are depicted.

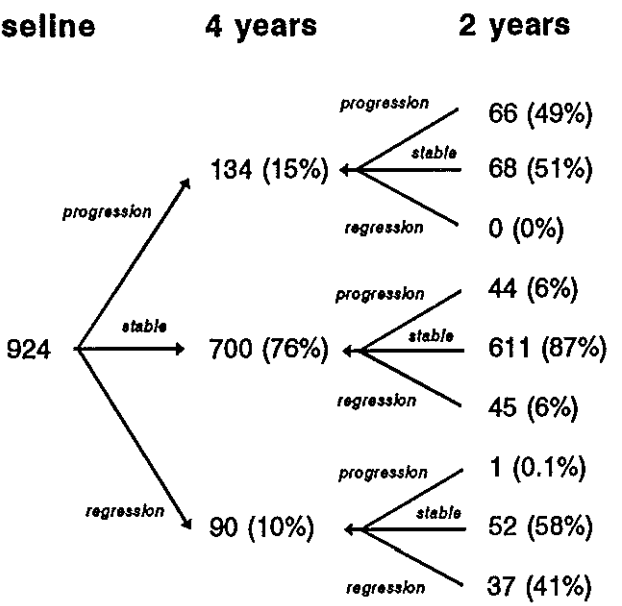

Figure 6. As figure 5. The class of change after 0-2 years is stratified for the class of change after 0-4 years.

Table 3. Changes over time stratified by class of change at 4 years.

Variable	baseline - 2 years		baseline - 4 years	
Progression (N=134)				
Minimum lumen diameter (mm)	-0.42 ±0.36	(-19%)	-0.65 ±0.22	(-30%)
Interpolated reference diameter (mm)	-0.23 ±0.42	(-7%)	-0.34 ±0.43	(-10%)
Plaque diameter (mm)	0.19 ±0.44	(15%)	0.31 ±0.42	(26%)
Percentage diameter stenosis (%)	8.5 ±11.12	(24%)	14.48 ±9.62	(42%)
Stable (N=700)				
Minimum lumen diameter (mm)	0.00 ±0.27	(0%)	0.01 ±0.20	(1%)
Interpolated reference diameter (mm)	-0.03 ±0.42	(-1%)	0.01 ±0.39	(1%)
Plaque diameter (mm)	-0.03 ±0.36	(-3%)	0.00 ±0.37	(0%)
Percentage diameter stenosis (%)	-0.79 ±8.98	(-2%)	-0.31 ±8.53	(-1%)
Regression (N=90)				
Minimum lumen diameter (mm)	0.32 ±0.35	(22%)	0.57 ±0.15	(39%)
Interpolated reference diameter (mm)	0.13 ±0.46	(4%)	0.31 ±0.42	(11%)
Plaque diameter (mm)	-0.19 ±0.49	(-14%)	-0.26 ±0.44	(-19%)
Percentage diameter stenosis (%)	-8.6 ±12.00	(-18%)	-12.8 ±9.61	(-26%)

Figures are means ± standard deviation, percentage change from baseline in brackets. Progression: decrease ≥ 0.4 mm in minimum lumen diameter, Regression: increase in ≥ 0.4 mm in minimum lumen diameter. For progression and regression all repeated changes were statistically significant at the 0.05 level.

more lesions regressed in the simvastatin group compared to the placebo group 34/436 versus 56/488 (relative risk 0.68, 95% Confidence Interval 0.45, 1.02).

DISCUSSION

Progression and regression of focal coronary atherosclerosis measured as the angiographically determined change in minimum lumen diameter is the resultant of alterations of the size of the lesion, remodelling of the coronary artery wall and endothelial function with its effect on basal vasomotor tone.[7-10] In animal experiments it has been shown that regression of coronary atherosclerosis is caused by a) a reduction in the volume of the lesion, b) further remodelling of the arterial wall so that the artery becomes wider and c) restoration of endothelial function with improvement of vascular relaxation.[9,11,12-15] In humans, serial angiographic trials have shown that cholesterol modifying interventions can induce a reduction in the size of a coro-

Table 4. Results at baseline, 2 years and 4 years stratified by class of change and treatment at 4 years.

Variable	baseline	2 years	4 years
PLACEBO			
Progression (N=61)			
Minimum lumen diameter (mm)	2.26 ± 0.52	1.82 ± 0.54	1.60 ± 0.51
Interpolated reference diameter (mm)	3.46 ± 0.89	3.24 ± 0.93	3.08 ± 0.84
Plaque diameter (mm)	1.20 ± 0.52	1.42 ± 0.73	1.48 ± 0.59
Percentage diameter stenosis (%)	34.0 ± 7.65	42.2 ± 13.8	47.3 ±11.1
Stable (N=341)			
Minimum lumen diameter (mm)	1.65 ± 0.46	1.65 ± 0.46	1.65 ± 0.44
Interpolated reference diameter (mm)	2.75 ± 0.69	2.74 ± 0.73	2.75 ± 0.73
Plaque diameter (mm)	1.10 ± 0.44	1.09 ± 0.45	1.10 ± 0.50
Percentage diameter stenosis (%)	39.4 ± 9.92	39.1 ± 9.52	39.2 ±10.4
Regression (N=34)			
Minimum lumen diameter (mm)	1.36 ± 0.47	1.72 ± 0.60	1.94 ± 0.47
Interpolated reference diameter (mm)	2.83 ± 0.69	2.96 ± 0.62	3.05 ± 0.54
Plaque diameter (mm)	1.47 ± 0.46	1.24 ± 0.49	1.11 ± 0.31
Percentage diameter stenosis (%)	52.0 ± 11.3	42.2 ± 13.2	36.7 ± 9.08
SIMVASTATIN			
Progression (N=73)			
Minimum lumen diameter (mm)	2.05 ± 0.51	1.65 ± 0.58	1.40 ± 0.53
Interpolated reference diameter (mm)	3.18 ± 0.76	2.94 ± 0.78	2.87 ± 0.81
Plaque diameter (mm)	1.13 ± 0.40	1.29 ± 0.47	1.47 ± 0.53
Percentage diameter stenosis (%)	35.3 ± 7.88	44.0 ± 11.9	50.7 ±11.9
Stable (N=359)			
Interpolated reference diameter (mm)	2.86 ± 0.78	2.81 ± 0.75	2.88 ± 0.77
Minimum lumen diameter (mm)	1.68 ± 0.50	1.68 ± 0.49	1.70 ± 0.47
Percentage diameter stenosis (%)	40.8 ± 11.0	39.5 ± 11.2	40.4 ± 9.97
Plaque diameter (mm)	1.18 ± 0.49	1.13 ± 0.49	1.18 ± 0.50
Regression (N=56)			
Minimum lumen diameter (mm)	1.51 ± 0.53	1.81 ± 0.54	2.08 ± 0.58
Interpolated reference diameter (mm)	2.85 ± 0.68	2.98 ± 0.67	3.23 ± 0.71
Plaque diameter (mm)	1.34 ± 0.44	1.17 ± 0.45	1.14 ± 0.34
Percentage diameter stenosis (%)	47.1 ± 12.2	39.2 ± 11.9	35.8 ± 8.75

Figures are means ± standard deviation. Progression: decrease $\geq$ 0.4 mm in minimum lumen diameter, Regression: increase in $\geq$ 0.4 mm in minimum lumen diameter.

nary lesion.[1] Preliminary data suggest that regression of atherosclerosis is associated with restoration of endothelial function.[16,17] No data are available on remodelling of the coronary wall during regression.

We found that clinically significant progression of a coronary obstruction, defined as a decrease of the minimum lumen diameter with at least 0.4 mm was not entirely due to an increase of plaque size but also due to progression of diffuse disease of the coronary segment containing that lesion. The magnitude of both components of progression was almost similar, over the time course from 0-2 and 2-4 years. The contribution of each component to the decrease of the minimum lumen diameter was almost equal. Regression of coronary obstruction was due to both a decrease of plaque size and regression of diffuse disease of the coronary segment containing that lesion. The magnitude of both components was almost equal over the time course from 0-2 and 2-4 years. The contribution of each component to the increase of the lumen was by and large equal.

The magnitude of the changes which took place over a 2 years and 4 years time interval may not entirely represent the natural course of coronary atherosclerosis because roughly one half of the patients was taking a cholesterol-lowering drug, which could have influenced the outcome. However, in a separate analysis of patients not taking cholesterol lowering drugs and those with statin therapy we found a similar, although not statistically significant, trend at 2 years and at 4 years interval in both groups.

Our findings are partly in agreement with Gould et al[18] who found that in their placebo patients progression of mild lesions was also associated with a decrease of the reference diameter. However, in their treated patients they found that regression of severe lesions was associated with a decrease of the reference diameter which is opposite to our findings. This may be explained by differences in quantitative methods, duration of intervention (1 year versus 2 and 4 year in our study) or manner of intervention (life-style changes versus lipid-lowering).

In this study a change in the minimum lumen diameter of at least 0.4 mm was considered clinically significant. Although this may appear somewhat arbitrarily, we have chosen this level because it represents almost twice the standard deviation of the variability of repeated measures of the quantitative algorithm used in this study.[4] The same threshold was also chosen by Waters et al,[19] but other investigators have selected lower levels ranging from 0.1 mm to 0.2 mm.[20,21]

It appears that the majority of lesions remains stable. Lesions that have progressed or regressed at 2 years, remain stable over the next two years. The incidence of lesions that progress or regress is similar in the two subsequent time intervals from 0 to 2 years and 2 to 4 years.

Table 5. Changes over time stratified by class of change at 4 years and stratified by treatment.

Variable	baseline - 2 years		baseline - 4 years	
PLACEBO				
Progression (N=61)				
Minimum lumen diameter (mm)	-0.44 ± 0.36	(-18%)	-0.66 ± 0.21	(-29%)
Interpolated reference diameter (mm)	-0.22 ± 0.49	(-6%)	-0.38 ± 0.43	(-10%)
Plaque diameter (mm)	0.22 ± 0.52	(18%)	0.28 ± 0.43	(23%)
Percentage diameter Stenosis (%)	8.18 ± 11.4	(24%)	13.34 ± 9.11	(39%)
Stable (N=341)				
Minimum lumen diameter (mm)	-0.00 ± 0.25	(0%)	-0.01 ± 0.20	(1%)
Interpolated reference diameter (mm)	-0.01 ± 0.40	(-0%)	-0.00 ± 0.41	(0%)
Plaque diameter (mm)	-0.01 ± 0.35	(-1%)	0.00 ± 0.37	(0%)
Percentage diameter stenosis (%)	-0.30 ± 8.82	(-1%)	-0.22 ± 8.60	(-1%)
Regression (N=34)				
Minimum lumen diameter (mm)	0.35 ± 0.43	(27%)	0.57 ± 0.13	(43%)
Interpolated reference diameter (mm)	0.12 ± 0.54	(5%)	0.22 ± 0.48	(8%)
Plaque diameter (mm)	-0.23 ± 0.56	(-16%)	-0.36 ± 0.47	(-25%)
Percentage diameter stenosis (%)	-9.7 ± 12.50	(-19%)	-15.3 ± 9.58	(-30%)
SIMVASTATIN				
Progression (N=73)				
Minimum lumen diameter (mm)	-0.40 ± 0.34	(-20%)	-0.64 ± 0.23	(-32%)
Interpolated reference diameter (mm)	-0.24 ± 0.35	(-8%)	-0.31 ± 0.43	(-10%)
Plaque diameter (mm)	0.16 ± 0.38	(14%)	0.33 ± 0.41	(30%)
Percentage diameter stenosis (%)	8.7 ± 10.93	(25%)	15.42 ± 9.99	(44%)
Stable (N=359)				
Minimum lumen diameter (mm)	0.00 ± 0.29	(0.0%)	0.02 ± 0.20	(1%)
Interpolated reference diameter (mm)	-0.05 ± 0.43	(-1.7%)	0.03 ± 0.38	(1%)
Plaque diameter (mm)	-0.05 ± 0.37	(-4.2%)	0.00 ± 0.36	(0%)
Percentage diameter stenosis (%)	-1.25 ± 9.11	(-3.1%)	-0.39 ± 8.48	(-1%)
Regression (N=56)				
Minimum lumen diameter (mm)	0.30 ± 0.30	(20%)	0.57 ± 0.17	(38%)
Interpolated reference diameter (mm)	0.13 ± 0.40	(5%)	0.37 ± 0.38	(13%)
Plaque diameter (mm)	-0.17 ± 0.44	(-13%)	-0.19 ± 0.42	(-15%)
Percentage diameter stenosis (%)	-7.9 ± 11.74	(-17%)	-11.3 ± 9.38	(-24%)

Figures are means ± standard deviation, percentage change from baseline in brackets. Progression: decrease $\geq$ 0.4 mm in minimum lumen diameter, Regression: increase in $\geq$ 0.4 mm in minimum lumen diameter.

Limitations of the study

Coronary angiography has important limitations to study progression and regression. Coronary angiography is a silhouette technique and detects only coronary lumen changes which are caused by disease of the arterial wall. Remodelling of the coronary arteries resulting in outward growth or displacement of the developing coronary plaque in the earlier stages of the disease preserves the arterial lumen, and therefore occurs unnoticed by angiography. Remodelling falls short when atherosclerosis is progressing and encroachment on the vascular lumen takes place. Thus, angiography allows indirect study of advanced atherosclerosis. Obviously, angiography cannot determine whether an increase or decrease of a coronary segment is due to remodelling of the arterial wall, or due to a change of vasomotor tone subsequent to endothelial dysfunction. In this angiographic study the potential effects of progression and regression on endothelial function and basal vasomotor tone have been masked by the preceding administration of the endothelial-independent vasodilator nitroglycerine to induce standardization of basal coronary vasomotion. It has been shown that in atherosclerotic arteries the cGMP-mediated relaxation to nitrates usually is normal or only modestly impaired. However, extensive arteriosclerotic damage of the artery may produce mechanical dysfunction.[22]

In our study the extent and severity of atherosclerosis was modest, however, we cannot completely rule out the possibility that altered vasomotion may have played a role in the mechanism of progression and regression such as has been shown after cholesterol-lowering treatment.[23,24] Also alterations of local haemodynamic rheological forces associated with significant progression or regression (change of $\geq$ 0.4 mm in a minimal luminal diameter) of a coronary narrowing may have influenced the endothelial dependent vasomotor tone. Progression of a lesion may increase the local shear rate which induces endothelial dependent vasodilation, whereas regression may show the reverse effect.[25] However, in our study plaque progression was associated with additional coronary lumen narrowing and regression with additional coronary lumen widening, thus shear rate effects, if at all present, were obscured.

Conclusion

Progression or regression of atherosclerosis appears to be characterized by long intervals of lesion stability interspersed with periods of change. The majority of lesions remains stable. The incidence of progression or regression of lesions is similar during the subsequent time intervals from 0-2 years and 2 to 4 years. The majority of lesions that has progressed or regressed after 2 years remains stable thereafter. The increase of plaque size is associated with diffuse coronary lumen narrowing which further reduces the obstruction lumen. These data suggest that the coronary artery wall remodels in different fashion during the development

of a plaque. Initially, in the earlier stages of disease, remodelling, with outward growth of the plaque, preserves the vascular lumen diameter. At later stages, after development of a more advanced plaque, this preservation effect is insufficient, and apparently is overruled by progression of diffuse disease which further decreases the vascular lumen diameter.

Of interest is the finding that regression of an advanced plaque is associated with widening of the coronary lumen which further widens the obstruction lumen. This is particular relevant for patients with far advanced coronary atherosclerosis who may benefit from interventions aimed at inducing regression of coronary plaques.

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Chapter 7

OVERALL REPRODUCIBILITY OF QUANTITATIVE CORONARY ANGIOGRAPHY FOR THE ASSESSMENT OF CORONARY ATHEROSCLEROSIS CHANGE

Overall reproducibility of quantitative coronary angiography for the assessment of coronary atherosclerosis change

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ABSTRACT

BACKGROUND The purpose of this study was to assess the overall reproducibility of quantitative coronary angiography in the setting of a multicenter clinical trial. METHODS AND RESULTS From ten patients from different clinics in 6 European countries, baseline and 4 year angiograms were analyzed. All steps of the analysis, selecting coronary segments and projections, computer analysis of cineframes and finally calculating the angiographic outcome parameter, were performed by two different analysis teams. A total of 712 projections, of 170 segments from 20 angiograms were analyzed. CONCLUSIONS Variability decreased from the per projection to the per patient variables.

INTRODUCTION

Several studies have been reported[1-9] which described the variability of quantitative coronary angiography (QCA) with reference to coronary angiographic trials. These studies yielded useful information on sources of measurement variation and provided guidelines to minimize variability.[10] None of these investigations, however, assessed the reproducibility of QCA measurements in the same setting as it is performed during a multicenter coronary atherosclerosis trial, where angiograms are made by different physicians using different equipment, which in most cases are analyzed in a central QCA core laboratory. Furthermore, only the variability of the analysis of coronary lesions was addressed and no data are available on the reproducibility of the quantitative analysis of non-stenosed

coronary segments. To assess the overall variability of the QCA derived endpoints in a multicenter coronary atherosclerosis trial (MAAS)[11,12] the baseline and 4 year follow-up angiograms from 10 patients were analyzed by 2 different analysis teams, which selected the cineframes, performed the computer analysis and approved the QCA analyses. The measurement variability was assessed on a per projection, on a per segment, and on a per patient level.

METHODS

Coronary angiography procedure

Angiography was performed according to standards for quantitative analysis.[2] Before angiography patients received 5 mg isosorbide dinitrate sublingually to induce standardized vasodilation. Coronary angiography was performed via the femoral route, on a fixed table system and 35 mm cineangiograms at a minimum speed of 25 frames per second were recorded. Patients were asked to hold breath in mid-inspiration during filming. In each projection the catheter tips not filled with contrast medium were filmed, cut off and sent with the angiogram to the QCA core laboratory for calibration.[2] The beginning of each angiogram was labelled with a cross to label the zero frame. All relevant aspects of the angiography procedure, sequence of injections, projections, angulation and rotation with frame numbers, type and size of the catheters, were recorded on the case report form to enable exact repetition of the procedure at follow-up.

Selection of projections and coronary segments for quantitative analysis

For this reproducibility study 10 patients were randomly selected from the cohort that participated in the MAAS trial.[11] All patients gave informed consent before participating in the study. In the QCA core laboratory the angiography committee, formed by cardiologists with special expertise in QCA, selected from the baseline angiograms orthogonal projections of 11 large proximal coronary segments both angiographically diseased and non-diseased.[13] Right coronary artery: proximal (1), mid (2), distal (3); left main (5); left anterior descendent: proximal (6), mid (7), distal (8); left circumflex: proximal (11), obtusis marginalis (12), distal (13), posterior lateral (14).[14] Totally occluded segments and segments that previously underwent percutaneous transluminal coronary angioplasty were not included in the baseline selection. For each projection one end-diastolic frame was selected for quantitative analysis. The segments were drawn and the proximal and distal borders were indicated together with the numbers of the selected cineframes. For the follow-up angiogram the same projections and segments were selected as in the baseline angiogram if available. At follow-up the end-diastolic frames were not chosen by a member of the angiography committee but by the senior QCA analyst at the core laboratory. All QCA analyses, baseline and follow-up, were checked by a mem-

ber of the angiography committee. Analyses could be approved, rejected, or reanalysis could be requested. After approval the data were given free for statistical analysis.

In this study the baseline selection of the 11 proximal segments and projections by the angiography committee was performed once. All subsequent procedures were performed by two different teams (A and B) independent of each other. An analysis team was formed by a senior QCA analyst, a CAAS analyst and one member of the angiography committee.

Quantitative Coronary Analysis

For quantitative analysis the Coronary Angiography Analysis System (CAAS) was used which was extensively described and validated previously.[15,16] In short, the region of interest from a cineframe is optically magnified and converted to analog video which is subsequently digitized in a matrix of 512 x 512 pixels with a grey resolution of 256 levels. The cathetertip is digitized and the actual micrometer measurement is combined with the number of pixels into a calibration factor in mm/pixel. The CAAS analyst indicates the centerline of the segment which is then smoothed by the computer. Perpendicular on the centerline the digital data of the pixels are reprocessed and the weighted sum of the first and second derivatives of the brightness function defines the edge of the vessel. An interpolated reference diameter indicating the non-diseased vessel contour is determined after a first degree least square polynomial which is translated upwards until 80% of the diameter values is below the polynomial. The pincushion distortion is corrected.[16] So, the CAAS yields absolute vessel dimensions using the catheter tip as scaling device and relative percentage diameter stenosis from the computer defined interpolated reference diameter. New occlusions at follow-up were assigned a mean and minimum lumen diameter of 0 mm and a percentage diameter stenosis of 100%. Angiographically diseased segments were defined as segments with a percentage diameter stenosis $\geq$ 20% at baseline or at follow-up. The following CAAS parameters are reported. For all segments: mean lumen diameter (mm), length (mm); for angiographically diseased segments also: minimum lumen diameter (mm), percentage diameter stenosis (%). The available multiple matched views were used for the assessment of change over time.[17]

Angiograpic Definitions

Coronary atherosclerosis change was assessed by 2 methods. First, from a continuous approach: the absolute difference in change between baseline and 4 year follow-up in mean and minimum lumen diameter and percentage stenosis. Second, from a categorical approach, where segments were classified according the percentage diameter stenosis at baseline, the change between baseline and 4 year follow-up, and the direction of the change. A segment was considered angiographically diseased when there

was a percentage diameter stenosis ≥ 20%. A true change in disease status was defined as a change ≥ 15% in percentage diameter stenosis, which is approximately two times the standard deviation of the long-term difference measured on a per projection basis.[15] Segments were classified as (1) non-diseased, (2) new lesion, (3) progressed lesion, (4) regressed lesion, (5) disappeared lesion. The categorical per patient classification is not discussed because the small number of patients.

Statistical Aspects

Variability was described by the mean difference and the standard deviation of the differences.[18] The absolute measurements of A and B were plotted against each other, and the mean of A and B was plotted against the difference between A and B to illustrate discrepancies between measurements. To allow comparison of the variability of different QCA parameters with different units coefficients of variation were computed. The following differences were calculated. First, the differences between A and B at baseline: interobserver variability for the same frame. Second, the differences between A and B at follow-up: interobserver variability for the same segments but different frames. Third, the differences between A and B in change between baseline and follow-up: interobserver variability for the endpoint in a clinical trial of atherosclerosis change. The results are reported at three levels: a per projection level, a per segment level for which the available per projection data were averaged, and a per patient level for which the available per segment data were averaged.

RESULTS

From the 10 baseline angiograms 186 projections of 90 segments were selected (Table 1). At 4 year follow-up 170 projections of 86 segments were approved by team A. These figures were 175 and 87 for team B. Sixty-two versus 60 segments were diseased at baseline, and 53 versus 56 at 4 years for teams A and B, respectively. Table 2 depicts the QCA results per projection, per segment and per patient at baseline and 4 years follow-up for both analysis teams. Both teams analyzed per patient approximately 18 ±4.3 cm of the coronary tree at baseline and follow-up. For team A the mean lumen diameter at baseline was 3.05 ±0.93 mm, 2.99 ±0.91 mm, and 3.00 ±0.35 mm per projection, per segment and per patient, respectively. The results at baseline of the minimum lumen diameter for team B were, 1.98 ±0.57 mm, 2.00 ±0.59 mm, and 1.96 ±0.30, respectively. For diameter stenosis the figures were 39.4 ±10.1 %, 32.8 ±10.9 %, and 33.4 ±6.4 %. The results of team B were similar. The coefficients of variation were for all QCA parameters smallest in the per patient analysis, with for team A at baseline for 0.12 for mean lumen diameter , 0.15 for minimum lumen diameter, and 0.19 for diameter stenosis. The results for team B were comparable. The coefficients of var-

Table 1. Angiography and QCA logistics for both analysis teams

	Team A	Team B
Patients	10	10
Number of projections approved		
Baseline	186	186
Follow-up	170	175
Number of segments		
Baseline	90	90
Follow-up	86	87
Number of non-diseased segments		
Baseline	62	60
Follow-up	53	56
Number of diseased segments		
Baseline	28	30
Follow-up	33	31

A segment was defined as diseased when it had a percentage diameter stenosis ≥ 20%.

iation were for all analyses larger at follow-up. Figure 1 shows scatterplots of the measurements at baseline and follow-up combined of team A versus team B for the per projection, the per segment, and the per patient analysis. It can be appreciated that the scatter around the line of identity is smallest for mean and minimum lumen diameter and largest for diameter stenosis.

The differences between team A and team B at baseline, at follow-up, and the differences in change between baseline and 4 year follow-up are listed in table 3. On a per projection basis the differences between team A and B were -0.06 ±0.24 mm, 0.03 ±0.26 mm, and -0.03 ±0.29 mm at baseline, at follow-up, and for the change over time, respectively. For the per segment analysis these figures were 0.04 ±0.20 mm, 0.01 ±0.20 mm, and -0.03 ±0.23 mm. For the per patients analysis the results were 0.04 ±0.09 mm, 0.01 ±0.08 mm, and -0.03 ±0.08 mm. There was a gradual decrease of variability for all 4 QCA variables from the per projection to the per segment and to the per patient analysis. In figure 2 the differences between analysis teams is shown as a function of the average absolute value for the measurements at baseline and follow-up combined. It can be concluded that the variability decreases from the per projection to the per patient analysis. The number of measurements outside the range of mean ± 2 std's is

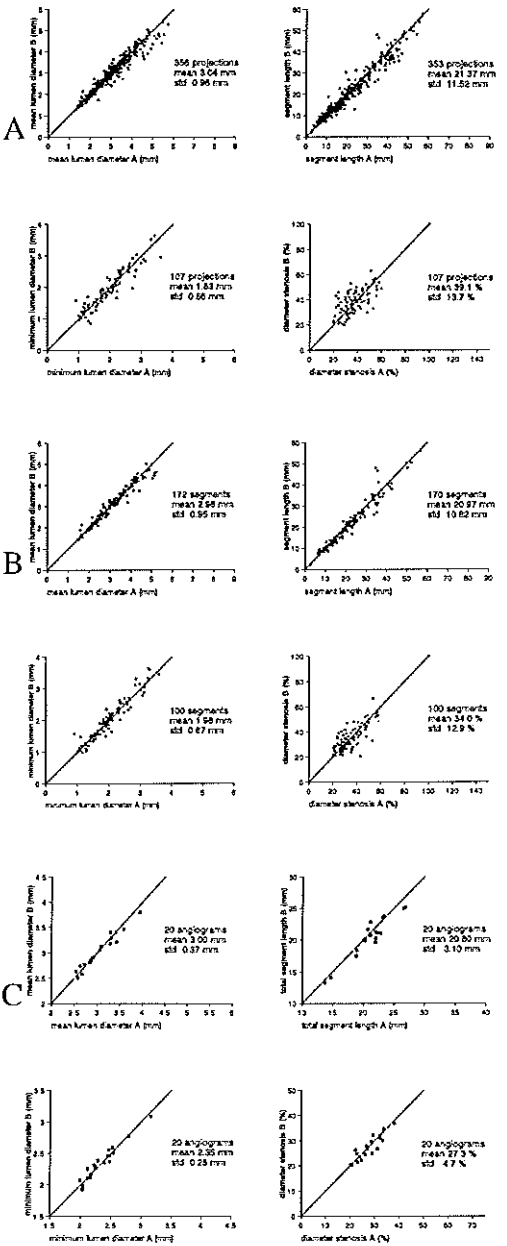

Figure 1. Measurements of Team A plotted versus measurements of Team B with line of equality for mean diameter, segment length, minimum diameter, and percentage diameter stenosis. Results are shown per projection (A), per segment (B) and per patient (C), respectively.

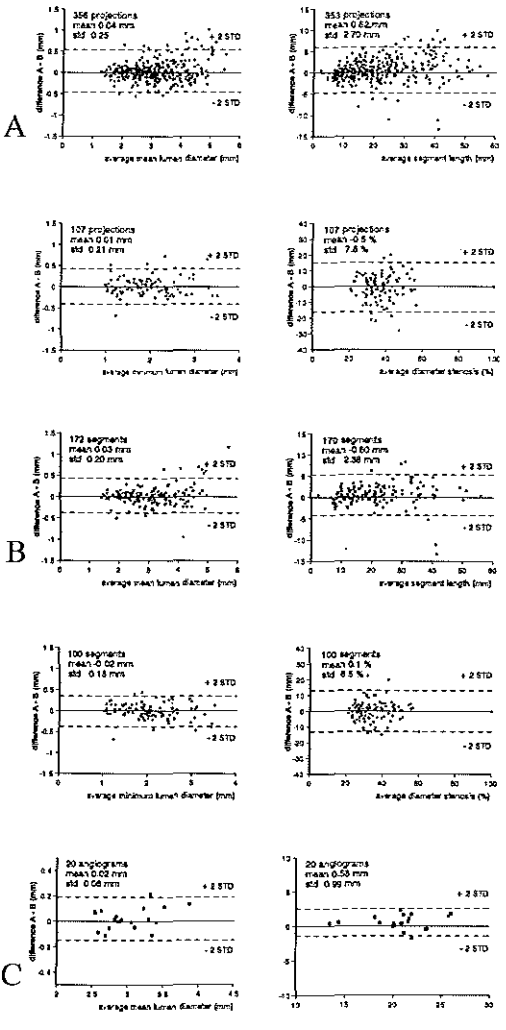

Figure 2. Differences of measurements between Team A and Team B against mean of both measerements for mean diameter, segment length, minimum diameter, and percentage diameter stenosis. Results are shown per projection (A), per segment (B) and per patient (C), respectively.

Table 2. Reproducibility results for measurements at baseline and at 4 year follow-up; per projection, per segment and per patient in multiple matched views.

		Team A				Team B			
		n	mean	std	cv	n	mean	std	cv
Per projection									
Mean Lumen Diameter (mm)	B	170	3.05	0.93	0.30	170	2.99	0.86	0.29
	F	170	3.09	1.06	0.34	170	3.06	0.99	0.32
Minimum Lumen Diameter (mm)	B	59	1.98	0.57	0.29	59	1.96	0.74	0.28
	F	59	1.95	0.74	0.38	59	1.94	0.75	0.39
Percentage Diameter Stenosis (%)	B	59	39.39	10.10	0.26	59	39.54	8.95	0.23
	F	59	41.37	16.51	0.39	59	41.15	17.17	0.42
Segment Length (mm)	B	170	21.78	11.83	0.54	170	21.17	11.22	0.53
	F	167	21.96	12.17	0.54	167	21.18	11.54	0.55
Per segment									
Mean Lumen Diameter (mm)	B	86	2.99	0.91	0.31	86	2.94	0.85	0.30
	F	86	3.02	1.06	0.35	86	3.01	1.01	0.31
Minimum Lumen Diameter (mm)	B	61	2.00	0.59	0.30	59	1.98	0.59	0.30
	F	61	2.04	0.75	0.37	59	2.03	0.74	0.37
Percentage Diameter Stenosis (%)	B	61	32.83	10.91	0.33	59	32.58	10.34	0.32
	F	61	33.78	15.61	0.46	59	34.6	16.22	0.47
Segment Length (mm)	B	86	21.15	10.79	0.51	86	21.26	10.60	0.51
	F	84	21.26	11.14	0.52	84	20.65	10.87	0.53
Per patient									
Mean Lumen diameter (mm)	B	10	3.00	0.35	0.12	10	2.97	0.29	0.10
	F	10	3.04	0.43	0.14	10	3.03	0.42	0.14
Minimum Lumen Diameter (mm)	B	10	1.96	0.30	0.15	10	1.96	0.30	0.15
	F	10	2.00	0.41	0.21	10	1.99	0.41	0.21
Percentage Diameter Stenosis (%)	B	10	33.43	6.39	0.19	10	32.85	4.40	0.14
	F	10	34.21	6.45	0.19	10	35.13	6.03	0.17
Total Length (mm)	B	10	181.89	42.77	0.24	10	179.38	39.84	0.22
	F	10	178.60	44.62	0.25	10	175.28	41.13	0.24

B: at baseline, F: at 4 year follow-up, n: number, std: standard deviation, cv: coefficient of variation (std / mean)

Table 3. Reproducibility results for differences between Team A and B.

		n	Difference A - B mean	std
Per projection				
Mean Lumen Diameter (mm)	B	170	-0.06	0.24
	F		0.03	0.26
	F - B		-0.03	0.29
Minimum Lumen Diameter (mm)	B	59	0.02	0.22
	F		0.01	0.25
	F - B		-0.01	0.35
Percentage Diameter Stenosis (%)	B	59	-0.15	6.75
	F		0.22	7.10
	F - B		0.37	10.47
Segment Length (mm)	B	170	0.61	2.71
	F		0.76	2.65
	F - B		0.19	2.27
Per segment				
Mean Lumen Diameter (mm)	B	86	0.04	0.20
	F		0.01	0.20
	F - B		-0.03	0.23
Minimum Lumen Diameter (mm)	B	56	-0.01	0.20
	F		-0.01	0.19
	F - B		0.01	0.25
Percentage Diameter Stenosis (%)	B	56	0.84	8.12
	F		-0.68	5.66
	F - B		-1.52	9.38
Segment Length (mm)	B	86	0.52	2.27
	F		0.62	2.50
	F - B		0.12	1.77
Per patient				
Mean Lumen Diameter (mm)	B	10	0.04	0.09
	F		0.01	0.08
	F - B		-0.03	0.08
Minimum Lumen Diameter (mm)	B		0.00	0.15
	F		0.02	0.14
	F - B		0.02	0.09
Percentage Diameter Stenosis (%)	B		0.58	4.29
	F		-0.92	2.98
	F - B		-1.52	4.04
Total Length (mm)	B		2.61	7.46
	F		3.32	10.39
	F - B		0.06	0.65

B: at baseline, F: at 4 year follow-up, F - B: change between baseline and 4 year follow-up, n: number, std: standard deviation.

Table 4. Categorical change between baseline and 4 year follow-up for both teams per segment.

	Team A		Team B	
	n	(%)	n	(%)
Per segment:				
Non-diseased	29	(33.7)	30	(34.5)
New lesion	2	(2.3)	3	(3.4)
Stable	46	(53.5)	45	51.7)
Progression	3	(3.5)	4	(4.6)
Regression	4	(4.7)	3	(3.4)
Disappearence	2	(2.3)	2	(2.3)
Total	86		87	

largest for segment length in the per projection analysis and all measurements are within the limits for minimum lumen diameter in the per patient analysis. Table 4 shows the results for categorical change over 4 years per segment. Overall, only minor differences were found between team A and B.

DISCUSSION

In a quantitative coronary angiographic trial 5 factors contribute to the overall variation of the measurements. First, the computer analysis of the cineframe determined by the QCA system used. Second, differences in the X-ray equipment used in the different centers participating in the trials. Third, the angiography procedure: coronary vessel motion, vasomotor tone, respiration phase, projections filmed, contrast agent used. Fourth, the performance of the angiographic core laboratory: differences between analysts, calibration from catheter tips. Fifth, the angiographic committee: selection of projections and coronary segments.

A previous study by Reiber et al[15] has estimated the variability of the CAAS measurements themselves by repeated analysis of the same cineframe and the longest interval of which variability data were published is 90 days. These measurements were obtained in the same QCA laboratory, while only one analyst performed the analysis of all coronary angiograms. The variability of the CAAS itself was 0.11 mm for mean lumen diameter, 0.10 mm for minimum lumen diameter, 2.75 % for diameter stenosis and 0.97 mm for segment length. We assessed the overall variability of QCA measurements in the setting of a core laboratory in a long-term multicenter

study of 4 year duration. Coronary angiograms were obtained by 10 investigators from 6 different countries. In this study the variability of the QCA analysis of the same frame and different CAAS analysts was larger with 0.24 mm, 0.22 mm, 6.75 % and 2.71 mm, respectively (Table 3). The variability for the baseline and 4 year angiograms was identical, indicating that the different selection of cineframes for the 4 year angiograms did not result in additional variability. This might be explained by the finding that selection of an end-diastolic frame is not very critical.[19] Furthermore, the variability in this multicenter 4 years study was comparable with that reported previously after 90 days, with a variability for minimum lumen diameter of 0.23 mm versus 0.36 mm, and for diameter stenosis of 9.4 % versus 6.5 %. for this study and the study of Reiber et al, respectively.[2] The absolute differences in measurements were relatively small when we performed the analysis per projection, per segment or per patient. The measurement variability expressed as the standard deviation of the mean differences gradually decreased from the per projection analysis to the per patient analysis for all variables. Thus averaging the available projections reduced measurement variability of the quantitative parameters.

A reproducibility study will always be limited by the fact that the analysts involved, being aware of the nature of the study, will therefore perform differently than during daily routine, which will result in less variability than during normal practice. Furthermore, in this study only 4 CAAS analysts and 2 cardiologists were involved, who analyzed all angiograms during a 4 week period. In a long-term multicenter coronary atherosclerosis trial that was recently completed by our core laboratory,[12] angiograms were analyzed over a 6 year period by approximately 10 CAAS analysts supervised by 5 cardiologist. Also, in such a setting a learning effect will occur during the startup phase of the study. The variability in this multicenter trial was therefore larger than in this reproducibility study. Although in angiographic multicenter trials much attention has been addressed to the standardization between centers and exact repetition of angiographic procedures, and to standardization of analysis procedures in the QCA core laboratory, measurement variability remains an important issue in the conduction of these trials. This reproducibility study indicates that reduction of measurement variability is still feasible when analysis procedures are performed in a highest standardized manner, and underscores the necessity of an angiographic core laboratory.

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Chapter 8

RETARDATION OF ANGIOGRAPHIC PROGRESSION OF CORONARY ATHEROSCLEROSIS RESULTS IN AN IMPROVED CLINICAL OUTCOME

Retardation of angiographic progression of coronary atherosclerosis results in an improved clinical outcome

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ABSTRACT

BACKGROUND Several angiographic trials of lipid-lowering therapy and of lifestyle changes have shown beneficial effects on the angiographic course of coronary atherosclerosis. Most of these trials were to small to study the effect on clinical outcome. METHODS AND RESULTS All published randomized angiographic trials were pooled using meta-analysis techniques to estimate overall effects on angiographic and clinical outcome. Mean changes in the lipid profile were determined. The overall relative risks for progression and regression of coronary atherosclerosis were calculated. Also, the overall effect on cardiac death and non-fatal myocardial infarction, and on all cardiac events combined including revascularisation procedures, were estimated. A total of 3768 patients were pooled from 15 trials. On average total cholesterol decreased by 23%, LDL-C by 31%, and triglycerides by 8%. HDL-C increased by 8%. In the reference group 44%, and in the lipid-lowering group 32% of the patients had progression of coronary atherosclerosis. A relative reduction of 28% (95% Confidence Interval: 0.66, 0.78). For regression these figures were 10% and 18%, respectively. A relative increase of 84% (95% Confidence Interval: 54, 119). Progression of focal atherosclerosis (minimum lumen diameter) was reduced: 0.05 mm/year versus 0.02 mm/year. Also, diffuse disease (mean lumen diameter) was retarded: 0.03 mm/year versus 0.01 mm/year. The occurrence of death and non-fatal myocardial infarction was reduced by 26% in the lipid lowering group: 5.4% versus 7.3% (95% Confidence Interval: 0.59, 0.94). All cardiac events combined were reduced by 34%: 14% versus 22% (95% Confidence Interval: 0.58, 0.76). CONCLUSIONS Amelioration of the lipid-profile improves the angiographic course of coronary atherosclerosis, which is accompanied by a better clinical outcome. Also, the relationship between lipids, coronary angiography and clinical course is affirmed.

INTRODUCTION

A series of angiographic trials has shown that a substantial amelioration of the lipid-profile, especially lowering LDL-C, results in retardation of the angiographic progression of coronary atherosclerosis.[1] Most of these trials, however, were too small to demonstrate an effect on the clinical course. We therefore performed a meta-analysis to investigate whether the angiographic benefit found in these studies, is accompanied by an improved clinical outcome. In this chapter, we present the trials published since 1992. Furthermore, a novel classification of the angiographic trials is made. The trials are classified according to the lipid-lowering treatment applied, and to the method by which the coronary angiograms were analyzed. Five categories were defined. First, lipid-modifying therapies: visual assessment.[2-4] Second, lipid-modifying therapies: quantitative coronary angiography.[5-9] Third, statin monotherapy: quantitative coronary angiography.[10-15] Fourth, fibrate monotherapy: quantitative coronary angiography.[16] Fifth, lifestyle changes: quantitative coronary angiography.[7,17-19]

METHODS

All randomized angiographic trials that compared an effective lipid-lowering therapy or a lifestyle modification program, with conventional treatment were selected. For each of the studies relative risks for progression and regression of coronary atherosclerosis were calculated. The definitions of disease progression and regression used in each individual trial were applied. To obtain an overall measure of effect the studies were pooled and an adjusted Mantel-Haenszel Relative Risk (RR) was estimated as was described previously.[20] In the same manner the relative risk for the occurrence of clinical events are presented for each trial apart and for all trials combined. The BECAIT[16] study is not included in this quantitative overview, because treatment was not primarily targeted at lowering cholesterol but on reducing triglycerides and fibrinogen.

DESCRIPTION OF THE TRIALS

The studies published before 1992[2-7] are described in chapter 2 and in Tables 1 and 2.

Lipid-modifying therapies: quantitative coronary angiography

The SCRIP[8] study (Stanford Coronary Risk Intervention Project) tested the effect of low-fat diet, lipid-lowering drugs, smoking cessation and exercise on coronary atherosclerosis relative to usual care (Table 1). Three-hunderd males and females with angiographically proven CAD were included, 145 patients in the risk reduction group and 155 patients in the usual care group. Quantitative coronary angiography of both diseased and non-diseased coronary segments was performed at baseline and after 4 years (Table 2). Total cholesterol was reduced

Table 1. Descriptions of angiographic coronary atherosclerosis trials.

Study	Treatment		Number	Duration	Type of Patients
Lipid-modifying therapies: Visual Assessment					
NHLBI	R)	placebo[e]	57	5 years	type II hyperlipoproteinemia
(1984)	I)	cholestyramine[e]	59		mean age 46 years
CLAS	R)	placebo[e]	82	2 years	post-CABG, Total-C 4.8 - 9.1 mmol/l
(1987)	I)	colestipol/niacin[e]	80		mean age 54 years
POSCH	R)	usual care[e]	333	3 years	post-MI, Total-C ≥ 5.7 mmol/l
(1990)	I)	partial ileal bypass surgery[e]	363		mean age 51 years
Lipid-modifying therapies: Quantitative Coronary Angiography					
FATS	R)	conventional[e]	46	2.5 years	apolipoprotein B ≥ 125 mg/dl
(1990)	I_1)	lovastatin/colestipol[e]	38		family history of CAD, 67% angina
	I_2)	niacin/colestipol[e]	36		mean age 47 years
SCOR	R)	placebo/resin[e]	32	2 years	familial hypercholesterolemia
(1990)	I)	colestipol/niacin/lovastatin[e]	40		mean age 42 years
STARS	R)	usual care	24	3 years	Total-C between 6.0 - 10.0 mmol/l
(1992)	I_1)	lipid-lowering diet	26		mean age 51 years
	I_2)	diet/cholestyramine	24		
SCRIP	R)	usual care	127	4 years	coronary artery disease
(1994)	I)	multiple riskfactor reduction	119		mean age 56 years
HARP	R)	placebo[e]	39	2.5 years	mild CAD, Total-C 4.7 - 6.5 mmol/l
(1994)	I)	multiple drug therapy	40		mean age 58 years
Statin Monotherapy: Quantitative Coronary Angiography					
MARS	R)	placebo[e]	124	2 years	Total-C between 4.9 - 7.6 mmol/l
(1993)	I)	lovastatin	123		mean age 58 years
CCAIT	R)	placebo[e]	153	2 years	Total-C between 5.7 - 7.8 mmol/l
(1994)	I)	lovastatin	146		mean age 52 years
MAAS	R)	placebo[e]	167	4 years	Total-C between 5.5 - 7.8 mmol/l
(1994)	I)	simvastatin	178		men and women, mean age 55 years
REGRESS	R)	placebo[e]	330	2 years	CAD, Total-C between 4.0 - 8.0 mmol/l
(1995)	I)	pravastatin	323		mean age 56 years
PLAC I	R)	placebo	202	3 years	CAD, LDL-C between 3.4 - 4.9 mmol/l
(1995)	I)	pravastatin	206		mean age 57 years
Fibrate Monotherapy: Quantitative Coronary Angiography					
BECAIT	R)	usual care	45	5 years	young survivors of myocardial infarction
(1996)	I)	bezofibrate	47		median age 42 years
Lifestyle Changes: Quantitative Coronary Angiography					
Lifestyle	R)	usual care	19	1 year	no lipid-modifying drugs
(1990)	I)	lifestyle changes	22		mean age 58 years
STARS	R)	usual care	24	3 years	Total-C between 6.0 - 10.0 mmol/l
(1992)	I)	lipid-lowering diet	26		mean age 51 years
Heidelberg	R)	usual care	52	1 year	stable angina
(1992)	I)	lifestyle changes	40		mean age 53 years

R: Reference Group; I: Index Group;[e]: Dietary Counselling; Total-C: total cholesterol; TG: triglycerides; Number: patients with angiographic follow-up

Table 2. Definitions of progression and regression of coronary atherosclerosis.

Study	Definition
Lipid-modifying therapies: Visual Assessment	
NHLBI	definite progression: ≥ 1 lesion with definite progression and no lesion with regression probable progression: ≥ 1 lesion with probable progression and no lesion with regression or definite progression probable regression: ≥ 1 lesion with probable regression and no lesion with definite regression or any progression definite regression: ≥ 1 lesion with definite regression and no progression mixed response: regression and progression: lesion progression and regression in the same patient, whether definite or probablem, no change: no lesion observed as changed by at least 2 panels
CLAS	CLAS consensus global change score: 0 = no change, 1 = definitely discernable, 2 = moderate, 3 = extreme; -: regression, +: progression
POSCH	CLAS consensus global change score: 0 = no change, 1 = definitely discernable, 2 = moderate, 3 = extreme; +: regression, -: progression
Lipid-modifying therapies: Quantitative Coronary Angiography	
FATS	progression: 10% increase in percentage diameter stenosis; regression vice versa
SCOR	10% increase in percentage diameter stenosis; regression vice versa; change in percentage area stenosis
STARS	progression: loss of ≥ 0.17 mm in mean absolute width; regression: vice versa
SCRIP	progression: a decrease of > 0.2 mm in minimum lumen diameter; regression: vice versa
HARP	progression: a increase of > 7.8% in percentage diameter stenosis; regression: vice versa
Statin Monotherapy: Quantitative Coronary Angiography	
MARS	progression: change ≥ 12% in diameter percentage stenosis; regression: vice versa, CLAS consensus global change score: 0 = no change, 1 = definitely discernable, 2 = moderate, 3 = extreme; -: regression, +: progression
CCAIT	progression: a decrease of > 0.4 mm in minimum lumen diameter; regression: vice versa
MAAS	progression: a increase of > 15% in percentage diameter stenosis; regression: vice versa
REGRESS	progression: a decrease of > 0.4 mm in minimum lumen diameter; regression: vice versa
PLAC I	progression: a decrease of > 0.4 mm in minimum lumen diameter; regression: vice versa
Fibrate Monotherapy: Quantitative Coronary Angiography	
BECAIT	progression: a decrease of > 0.4 mm in minimum lumen diameter; regression: vice versa
Lifestyle Changes: Quantitative Coronary Angiography	
Lifestyle	change in percentage diameter stenosis as a continuous measure; positive: progression, negative: regression
STARS	progression: loss of ≥ 0.17 mm in mean absolute width; regression: vice versa
Heidelberg	progression: decrease in minimum lumen diameter of ≥ 0.18 mm; regression vice versa

by 14% and LDL-C by 26%. HDL-C was increased by 14% (Tables 3 and 4). Progression of CAD was found in 50% of patients in both treatment groups. Regression was seen in 10% and 20% in the usual care and the intervention groups, respectively (Tables 5 and 6). The minimal luminal diameter of the diseased segments decreased by 0.05 mm and 0.02 mm per years in the usual care and the intervention groups, respectively. In the non-diseased segments a narrowing of 0.02 mm per years was found in both groups. Fewer patients in the intervention group experienced a cardiac event 34 (22%) and 20 (14%), respectively (Tables 7 through 9).

In the Harvard Atherosclerosis Reversibility Project[9] (HARP) the effect of lipid-lowering treatment on the angiographic course of coronary atherosclerosis was studied in normocholesterolaemic patients with a total cholesterol between 4.7 - 6.5 mmol/l. Patients were allocated to placebo (44 patients) or to a stepwise multi-drug treatment (44 patients) to induce a total cholesterol level less than 4.2 mmol and a LDL-cholesterol / HDL-Cholesterol Ratio of less then 2.0. Pravastatin, nicotinic acid, cholestyramin and gemfibrozil were prescribed. Quantitative angiography was performed at baseline and after 2.5 years. In 39 control patients and 40 drug treated patients follow-up angiography was available. Total cholesterol, LDL-C, and triglycerides decreased with 28%, 41%, and 26% respectively. HDL-C increased with 13%. The minimum lumen diameter decreased with 0.14 mm and 0.15 mm in the drug and the placebo groups, respectively. Also no important difference was found for the percentage diameter stenosis with an increase of 2.1 % and 2.4 %, respectively. Ten patients (21%) in the placebo group and 6 patients (14%) in the drugs group experienced a clinical event.

Statin monotherapy: quantitative coronary angiography

In the Monitored Atherosclerosis Regression Study (MARS)[10] Blankenhorn et al assessed the effect of monotherapy with lovastatin on coronary atherosclerosis relative to placebo. Patients with at least two stenoses of which 1 ≥ 50% and with cholesterol levels between 4.9 and 7.6 mmol/l were recruited for the 2 year trial. A total of 270 patients was enroled of which 124 in the placebo group and 123 in the lovastatin group had a follow-up angiogram. Angiograms were analyzed both visually using the global change score[21] and quantitatively.[22] In the lovastatin group total cholesterol, LDL-C, and HDL-C changed by -30%, -37%, and 7%, respectively. Progression of CAD as assessed by quantitative coronary angiography was seen in 41% and 29% in the placebo and lovastatin groups, respectively. For regression of CAD these figures were 12% and 23%. Percentage diameter stenosis increased for the placebo treated patients by 2.2 percentage points and for patients who used lovastatin by 1.6 percentage points. For the lesion ≥ 50% stenosed an increase of 0.9 percentage points was seen in the pla-

Table 3. Lipid results of coronary angiographic atherosclerosis trials.

Study	Group	Total-C		LDL-C		HDL-C		HDL/LDL		Triglycerides	
		B	C	B	C	B	C	B	C	B	C
Lipid-modifying therapies: Visual Assessment											
NHLBI	R	7.59	-1%	5.93	-5%	1.01	1%	0.17	6%	1.48	26%
	I	8.03	-17%	6.27	-26%	0.98	8%	0.16	44%	1.76	28%
CLAS	R	6.28	-4%	4.36	-5%	1.13	2%	0.26	8%	1.74	-5%
	I	6.35	-26%	4.42	-43%	1.15	37%	0.26	142%	1.71	-22%
POSCH	R	6.48	-5%	4.62	-7%	1.05	-1%	0.23	4%	2.26	-4%
	I	6.50	-36%	4.62	-42%	1.03	5%	0.22	82%	2.33	12%
Lipid-modifying therapies: Quantitative Coronary Angiography											
FATS	R	6.79	-4%	4.53	-7%	0.98	6%	0.22	14%	2.59	15%
	$I_{1\&2}$	7.06	-29%	5.00	-39%	0.96	23%	0.19	116%	2.23	-18%
SCOR	R	9.49	-8%	7.11	-12%	1.31	0%	0.18	17%	1.24	4%
	I	9.79	-31%	7.32	-39%	1.22	25%	0.17	100%	1.49	-21%
STARS	R	7.07	-2%	4.82	-3%	1.22	-1%	0.25	4%	2.32	1%
	$I_{1\&2}$	7.31	-20%	5.12	-26%	1.18	-2%	0.23	35%	2.25	-10%
SCRIP	R	5.87	-2%	4.04	-4%	1.10	6%	0.27	11%	1.75	0%
	I	6.03	-16%	4.07	-30%	1.19	12%	0.29	48%	1.77	-19%
HARP	R	5.43	2%	3.49	3%	1.07	0%	0.31	-3%	1.93	1%
	I	5.53	-26%	3.62	-38%	1.08	13%	0.30	83%	1.84	-20%
Statin Monotherapy: Quantitative Coronary Angiography											
MARS	R	6.01	-2%	4.00	-1%	1.11	2%	0.28	4%	1.80	2%
	I	5.97	-32%	3.91	-38%	1.10	9%	0.28	79%	1.80	-22%
CCAIT	R	6.43	-1%	4.44	-2%	1.07	3%	0.24	4%	2.22	-4%
	I	6.46	-21%	4.47	-29%	1.07	7%	0.24	50%	2.22	-8%
MAAS	R	6.43	0%	4.47	1%	1.11	-3%	0.25	-4%	1.84	4%
	I	6.35	-22%	4.38	-31%	1.10	7%	0.25	56%	1.92	-13%
REGRESS	R	6.05	5%	4.31	1%	0.93	4%	0.22	0%	1.80	8%
	I	6.02	-20%	4.30	-29%	0.93	13%	0.22	59%	1.77	-10%
PLAC I*	R	5.97	2%	4.24	1%	1.06	2%			1.87	9%
	I		-19%		-28%		7%				-8%
Fibrate Monotherapy: Quantitative Coronary Angiography											
BECAIT	R	6.90	-6%	4.62	-2%	1.00	-1%	0.19	13%	1.98	3%
	I	6.87	-14%	4.66	-4%	0.89	9%	0.22	1%	2.44	-26%
Lifestyle Changes: Quantitative Coronary Angiography											
Lifestyle	R	6.34	-5%	4.32	-6%	1.35	-3%	0.31	3%	2.45	-9%
	I	5.88	-24%	3.92	-37%	1.00	-3%	0.26	54%	2.38	22%
STARS	R	7.07	-2%	4.82	-3%	1.22	-1%	0.25	4%	2.32	1%
	I_1	7.19	-14%	5.00	-16%	1.14	0%	0.23	17%	2.31	-20%
Heidelberg	R	6.09	0%	4.25	2%	0.91	0%	0.21	0%	2.16	-17%
	I	6.05	-10%	4.24	-9%	0.94	2%	0.22	9%	1.97	-24%

All values in mmol/l; R: Reference Group; I: Index Group; B: at baseline; C: percentage change; Total-C: total cholesterol; *: no other data reported

Table 4. Treatment Effect on lipid parameters.

Study	number	Change			
		Total-C	LDL-C	HDL-C	TG
Lipid-modifying therapies: Visual Assessment					
NHLBI	116	-16%	-21%	7%	2%
CLAS	162	-22%	-38%	35%	-17%
POSCH	734	-31%	-35%	6%	16%
All	***1012***	***-28%***	***-34%***	***11%***	***9%***
Lipid-modifying therapies: Quantitative Coronary Angiography					
FATS	120	-25%	-32%	17%	-33%
SCOR	72	-23%	-27%	25%	-25%
STARS	74	-18%	-23%	-1%	-11%
SCRIP	245	-14%	-26%	6%	-19%
HARP	79	-28%	-41%	13%	-21%
All	***590***	***-20%***	***-30%***	***11%***	***-22%***
Statin Monotherapy: Quantitative Coronary Angiography					
MARS	247	-30%	-37%	7%	-24%
CCAIT	331	-22%	-27%	4%	-4%
MAAS	373	-22%	-32%	10%	-17%
REGRESS	653	-20%	-29%	10%	-7%
PLAC I	408	-21%	-29%	5%	-17%
All	***2012***	***-22%***	***-30%***	***6%***	***-13%***
Lifestyle Changes: Quantitative Coronary Angiography					
Lifestyle	41	-19%	-31%	0%	31%
STARS	50	-16%	-13%	1%	-21%
Heidelberg	113	-10%	-11%	2%	-7%
All	***204***	***-13%***	***-15%***	***1%***	***-3%***
OVERALL	***3768***	***-23%***	***-31%***	***8%***	***-8%***

Total-C: total cholesterol; TG: triglycerides.

cebo group, but in the lovastatin group a decrease by 4.1 percentage points was found. The mean minimal luminal diameter worsened by 0.06 mm and by 0.03 mm after treatment with placebo and lovastatin, respectively. Cardiac events were more frequent in the placebo group, 31 (25%) versus 22 (18%).

In the CCAIT[11,23] (Canadian Coronary Atherosclerosis Intervention Trial) pa-

tients with mild, diffuse coronary atherosclerosis and cholesterol levels between 5.7 and 7.8 mmol/l received dietary counselling (American Heart Association Phase I diet) and lovastatin (N = 165) or matching placebo (N = 166) for 2 years. Coronary angiograms were analyzed quantitatively. Total cholesterol decreased by 20%, LDL-C by 27%, and HDL-C increased by 4% in the lovastatin group relative to placebo. Progression and regression of CAD were noted in 50% and 33% and in 7% and 10% in the placebo and lovastatin groups, respectively. The change in mean minimal luminal diameter was -0.09 mm and -0.05 mm in the placebo and lovastatin groups, respectively. These figures were for stenoses of ≥ 50% 0.01 mm and 0.02 mm and for stenoses < 50% -0.11 mm and -0.06. Eighteen patients (11%) on placebo and 14 patients (9%) randomized to lovastatin experienced a cardiac event.

The Multicentre Anti-Atheroma Study (MAAS)[12,13] studied the effect of simvastatin on the progression of both focal and diffuse coronary atherosclerosis in patients with mild to moderate coronary artery disease. Patients were randomized to placebo (188 patients) and simvastatin 20 mg once daily (193 patients). At baseline and after 2 and 4 years quantitative coronary angiography was performed, allowing to assess the changes in coronary atherosclerosis over time. A follow-up angiogram was available in 167 placebo and 178 simvastatin patients. Treatment with simvastatin reduced total cholesterol by 23%, LDL-C by 31%, and increased HDL-C by 9%. Triglycerides decreased with 18%. Both the progression of diffuse and focal coronary atherosclerosis were reduced in the simvastatin group. With a reduction in loss of mean lumen diameter of 0.06 mm and of 0.08 mm in minimum lumen diameter. There were fewer patients with progression of disease (23% versus 32%) and more patients with regression of disease (19% versus 12%) in the simvastatin group. Fifty-one patients in the placebo group had a cardiac event compared to 40 patients allocated to simvastatin.

The REGRESS[14] (Regression Growth Evaluation Statin Study) investigated the effect of cholesterol lowering treatment in 885 patients with symptomatic coronary artery disease and normal to moderately elevated cholesterol levels (between 4.0 and 8.0 mmol/l). For 330 placebo and 323 pravastatin patients quantitative coronary follow-up angiography was available after 2 years. Total cholesterol decreased by 20%, LDL-C by 29%, and triglycerides by 7% in the patients treated with pravastatin 40 mg once daily relative to the placebo patients. HDL-C increased with 10%. The loss in mean lumen diameter was 0.04 mm less in the cholesterol lowering group. The difference for minimum lumen diameter was 0.06 mm, again in favour for the pravastatin group. Angiographic progression was found in 43% of the placebo group and in 37% of the pravastatin group. For regression the figures were 9% and 17%, respectively. There were fewer clinical events (death, non-fatal myocardial infarction, revas-

Table 5. Angiographic results: Progression of Coronary Atherosclerosis.

Study		Number of patients Progression / Total	Rate	Relative Risk (95% CI)
Lipid-modifying therapies: Visual Assessment				
NHLBI	R	28/57	49%	0.66 (0.42, 1.03)
	I	19/59	32%	
CLAS	R	50/80	61%	0.64 (0.46, 0.88)
	I	32/82	39%	
POSCH	R	138/333	41%	0.68 (0.55, 0.84)
	I	102/363	28%	
All	***R***	***216/472***	***30%***	***0.67 (0.57, 0.78)***
	I	***152/502***	***46%***	
Lipid-modifying therapies: Quantitative Coronary Angiography				
FATS	R	21/46	46%	0.50 (0.30, 0.85)
	$I_{1\&2}$	17/74	23%	
SCOR	R	13/32	41%	0.50 (0.23, 1.04)
	I	8/40	20%	
STARS	R	11/24	46%	0.31 (0.14, 0.69)
	$I_{1\&2}$	7/50	14%	
SCRIP 0.2 mm	R	63/127	50%	1.02 (0.79, 1.31)
	I	60/119	50%	
HARP	R	13/39	33%	0.98 (0.52, 1.83)
	I	13/40	33%	
All	***R***	***121/268***	***45%***	***0.77 (0.63, 0.94)***
	I	***105/323***	***33%***	
Statin Monotherapy: Quantitative Coronary Angiography				
MARS	R	51/124	41%	0.71 (0.50, 1.01)
	I	36/123	29%	
CCAIT	R	76/153	50%	0.66 (0.50, 0.88)
	I	48/146	33%	
MAAS	R	54/167	32%	0.71 (0.50, 1.00)
	I	41/137	23%	
REGRESS	R	140/327	43%	0.86 (0.71, 1.04)
	I	115/314	37%	
PLAC I	R	79/157	50%	0.73 (0.57, 0.94)
	I	60/163	37%	
All	***R***	***400/928***	***43%***	***0.76 (0.67, 0.85)***
	I	***300/924***	***33%***	
Lifestyle Changes: Quantitative Coronary Angiography				
Lifestyle	R	10/19	53%	0.35 (0.13, 0.92)
	I	4/22	18%	
STARS	R	11/24	46%	0.34 (0.12, 0.91)
	I_1	4/26	15%	
Heidelberg	R	9/40	48%	0.47 (0.25, 0.89)
	I	25/52	23%	
All	***R***	***46/95***	***48%***	***0.40 (0.26, 0.63)***
	I	***17/88***	***19%***	
OVERALL	***R***	***772/1739***	***44%***	***0.72 (0.66, 0.78)***
	I	***570/1811***	***32%***	

R: Reference group; I: Index group; 95% CI: 95% Confidence Interval

Table 6. Angiographic results: Regression of Coronary Atherosclerosis.

Study		Number of patients Regression / Total	Rate	Relative Risk	(95% CI)
Lipid-modifying therapies: Visual Assessment					
NHLBI	R	4/57	7%	0.97	(0.25, 3.68)
	I	4/59	7%		
CLAS	R	2/80	2%	6.67	(1.55, 28.89)
	I	13/80	16%		
POSCH	R	24/333	7%	1.26	(0.76, 1.09)
	I	33/363	9%		
All	***R***	***30/472***	***6%***	***1.57***	***(1.02, 2.40)***
	I	***50/502***	***10%***		
Lipid-modifying therapies: Quantitative Coronary Angiography					
FATS	R	5/46	11%	3.20	(1.34, 7.82)
	$I_{1\&2}$	26/74	35%		
SCOR	R	4/32	13%	2.60	(0.94, 7.20)
	I	13/40	33%		
STARS	R	1/24	4%	8.64	(1.22, 61.0)
	$I_{1\&2}$	18/50	36%		
SCRIP 0.2 mm	R	13/127	10%	1.97	(1.05, 3.69)
	I	24/119	20%		
HARP	R	7/39	18%	0.70	(0.24, 2.01)
	I	5/40	13%		
All	***R***	***30/268***	***11%***	***2.03***	***(1.58, 3.35)***
	I	***86/323***	***27%***		
Statin Monotherapy: Quantitative Coronary Angiography					
MARS	R	15/124	12%	1.88	(1.06, 3.35)
	I	28/123	23%		
CCAIT	R	10/153	7%	1.47	(0.67, 3.20)
	I	14/156	10%		
MAAS	R	20/167	12%	1.55	(0.93, 2.59)
	I	33/178	19%		
REGRESS	R	30/327	9%	1.88	(1.23, 2.85)
	I	54/314	17%		
PLAC I	R	24/157	15%	1.37	(0.85, 2.19)
	I	34/163	21%		
All	***R***	***99/928***	***11%***	***1.64***	***(1.31, 2.06)***
	I	***163/924***	***18%***		
Lifestyle Changes: Quantitative Coronary Angiography					
Lifestyle	R	8/19	42%	1.90	(1.11, 3.41)
	I	18/22	82%		
STARS	R	1/24	4%	9.23	(1.28, 66.8)
	I_1	10/26	38%		
Heidelberg	R	9/52	17%	1.88	(0.89, 3.95)
	I	13/40	33%		
All	***R***	***18/95***	***19%***	***2.35***	***(1.54, 3.58)***
	I	***41/88***	***47%***		
OVERALL	***R***	***176/1739***	***10%***	***1.84***	***(1.54, 2.19)***
	I	***330/1811***	***18%***		

R: Reference Group; I: Index group; 95% CI: 95% Confidence Interval

cularization and stroke) in the monostatin group with 59 events compared to 93.

The PLAC I trial[15] (Pravastatin Limitation of Atherosclerosis in the Coronary arteries) reported the effect of pravastatin 40 mg once daily on the progression of coronary atherosclerosis over a period of 3 years was assessed. Four-hundred-eight patients with mildly elevated cholesterol levels were included. In 157 placebo and 163 pravastatin patients follow-up angiography was available. Total cholesterol, LDL-C decreased by 21% and 29 % respectively. HDL-C rose by 5%. The triglyceride level was lowered by 17%. The loss in mean lumen diameter and in minimum lumen diameter was decreased by 0.02 mm / year. In the placebo group more patients had progression of disease, 50% versus 37%. Regression occurred less in the placebo patients, 15% versus 21%.

Fibrate monotherapy: quantitative coronary angiography

The Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT)[16] studied the effect of lipid-modifying and fibrinogen-lowering therapy with bezafibrate 200 mg three times daily in young survivors of an acute myocardial infarction. For 39 placebo patients and 42 bezafibrate patients quantitative coronary angiography was available at baseline and after 2 and 5 years. Total cholesterol, LDL-C, triglycerides, and fibrinogen were reduced by bezafibrate by 9%, 1%, 30% and 14%, respectively. HDL-C increased by 9%. Both the loss in mean lumen diameter and minimum lumen diameter was less in the bezafibrate with a treatment effect of 0.07 mm and 0.11 mm, respectively. More patients had regression and less progression in the lipid-lowering group, 21% versus 13%, and 74% versus 85%, respectively. Eleven out of 45 placebo patients and 3 out of 47 bezafibrate patients suffered a clinical event.

Lifestyle changes: quantitative coronary angiography

For the STARS[7] (St Thomas' Atherosclerosis Regression Study) we compared in this analysis the usual care group (N = 24) with the diet group (N = 26). Blood lipids did not change in the usual care group. In the diet group total cholesterol and LDL-C were reduced by 14% and 16%, respectively; HDL-C remained constant. Progression of CAD was noted in 46% and 15%, regression was seen in 4% and 38% of the usual care and the diet groups, respectively. The change in mean coronary diameter was -0.20 mm, and 0.03 mm in the usual care, and the diet groups, respectively.

The Heidelberg study[18,19] treated patients with stable angina and proven coronary atherosclerosis with usual care (N = 57) or with a low-fat diet and intensive physical exercise (N = 56). The diet applied was the American Heart Association phase 3 diet with < 200 mg cholesterol and fat < 20% energy. Also, they were asked to exercise daily for at least 30 minutes on a cycle ergometer at 75% of their maximal heart rate and to participate in twice-weekly group training

Table 7. Changes in QCA measurements per year.

Study	Group	Number of patients	Change MLD (mm / year)	Change DS (% / year)	Change MD (mm / year)
Lipid-modifying therapies					
FATS	R	46	-0.020	0.8	
(2.5 yrs)	I_1	38	0.005	0.3	
	I_2	36	0.014	0.4	
STARS	R	24	-0.077	1.9	-0.067
(3 yrs)	I_1	26	0.010	-0.4	0.001
	I_2	24	0.039	-0.6	0.034
SCRIP	R	127	-0.046	0.7	-0.016
(4 yrs)	I	119	-0.024	0.5	-0.015
HARP	R	39	-0.068	1.0	
(2.5 yrs)	I	40	-0.048	0.8	
All	***R***	***236***	***-0.048***	***0.9***	***-0.024***
	I	***283***	***-0.010***	***0.3***	***-0.006***
Statin Monotherapy					
MARS	R	124	-0.030	1.1	
(2 yrs)	I	123	-0.015	0.8	
CCAIT	R	153	-0.045	1.5	
(2 yrs)	I	146	-0.025	0.9	
MAAS	R	167	-0.033	0.9	-0.020
(4 yrs)	I	178	-0.010	0.3	-0.005
REGRESS	R	330	-0.050		-0.045
(2 yrs)	I	323	-0.030		-0.015
PLAC I	R	157	-0.050	1.1	-0.040
	I	163	-0.030	0.7	-0.020
All	***R***	***931***	***-0.043***	***1.2***	***-0.037***
	I	***933***	***-0.023***	***0.7***	***-0.014***
Lifestyle Changes:					
Lifestyle	R	19		3.4	
(1 yr)	I	22		-2.2	
STARS	R	24	-0.077	1.9	-0.067
(3 yrs)	I_1	26	0.010	-0.4	0.001
Heidelberg	R	52	-0.130	3.0	
(1 yr)	I	40	-0.010	-1.0	
All	***R***	***95***	***-0.113***	***2.8***	***-0.067***
	I	***85***	***-0.002***	***-1.1***	***0.001***
OVERALL	***R***	***1262***	***-0.047***	***1.2***	***-0.034***
	I	***1301***	***-0.019***	***0.4***	***-0.011***

R: Reference group; I: Index group; MLD: minimum lumen diameter, DS: percentage diameter stenosis, MD: mean lumen diameter.

Table 8. Cardiac mortality and non-fatal myocardial infarction.

Study		Number of patients Event / Total	Rate	Relative Risk (95% CI)
Lipid-modifying therapies: Visual Assessment				
NHLBI	R	12/72	17%	0.68 (0.29, 1.55)
	I	8/71	11%	
CLAS	R	5/94	5%	0.20 (0.02, 1.68)
	I	1/94	1%	
POSCH	R	42/417	10%	0.99 (0.66, 1.49)
	I	42/421	10%	
All	***R***	***59/583***	***10%***	***0.86 (0.60, 1.23)***
	I	***51/586***	***9%***	
Lipid-modifying therapies: Quantitative Coronary Angiography				
FATS	R	0/52	0%	[0]2% (-8%, 5%)
	$I_{1\&2}$	2/94	2%	
SCOR	R	1/49	2%	[0]-2% (-6%, 2%)
	I	0/48	0%	
STARS	R	5/28	18%	0.34 (0.09, 1.30)
	$I_{1\&2}$	3/50	6%	
SCRIP	R	13/155	8%	0.49 (0.19, 1.26)
	I	6/145	4%	
HARP	R	1/40	5%	2.05 (0.19, 21.7)
	I	2/39	3%	
All	***R***	***20/324***	***6%***	***0.56 (0.29, 1.11)***
	I	***13/376***	***4%***	
Statin Monotherapy: Quantitative Coronary Angiography				
CCAIT	R	7/166	4%	1.01 (0.36, 2.81)
	I	7/165	4%	
MAAS	R	16/188	9%	0.85 (0.43, 1.70)
	I	14/193	7%	
REGRESS	R	19/434	4%	0.61 (0.30, 1.24)
	I	12/450	3%	
PLAC I	R	19/202	9%	0.52 (0.25, 1.08)
	I	10/206	5%	
All	***R***	***60/989***	***6%***	***0.70 (0.48, 1.02)***
	I	***43/1014***	***4%***	
Lifestyle Changes: Quantitative Coronary Angiography				
Lifestyle	R	0/19	0%	
	I	0/22	0%	
STARS2	R	5/28	18%	0.42 (0.09, 1.96)
	I	2/27	7%	
Heidelberg	R	3/57	5%	0.83 (0.14, 4.74)
	I	2/46	4%	
All	***R***	***8/77***	***4%***	***0.56 (0.18, 1.73)***
	I	***4/69***	***6%***	
OVERALL	***R***	***143/1954***	***7%***	***0.74 (0.59, 0.94)***
	I	***109/2002***	***5%***	

R: Reference group; I: Index group; 95% CI: 95% Confidence Interval; [0]: risk difference; MARS: not reported

sessions for at least 60 minutes.[18] No lipid-lowering drugs were used. Angiograms were assessed quantitatively after 1 year. Total cholesterol, LDL-C, and triglycerides were reduced by 10%, 11%, and 7%, respectively; HDL-C increased by 3%. Body weight decreased by 5% in the intervention group; blood pressure remained constant. Five patients in the intervention group and 4 in the control group experienced a cardiac event. In an additional analysis[24] a relation was found between the magnitude of the leisure time physical activity and the progression of coronary atherosclerotic lesion. It was found that > 1.400 kcal/week of exercise was necessary to improve cardiovascular fitness and that > 1.530 kcal/week and > 2.200 kcal/week were needed to halt progression or to induce regression, respectively.

POOLED RESULTS

The effects of the different therapies applied in the angiographic trials on the lipid profile are depicted for each individual trial, for each group of trials and for all groups combined.

Treatment effect on lipid profile

Overall the reduction in total cholesterol was 23%, in LDL-C 31% and triglycerides 8%, whereas HDL-C increased by 8%. The average treatment effect in the trials with monostatin therapy was a reduction in total cholesterol of 22%, in LDL-C of 30%, in triglycerides of 13%, and an increase in HDL-C of 6%. (Tables 3 and 4).

Treatment effect on progression and regression

The reduction of the number of patients with progression was significant in almost all of the individual trials and in all five trial groups. Overall progression was reduced by approximately 30%, and regression increased by about 80% (Tables 5 and 6). Monostatin therapy resulted in a relative risk for progression of 0.76 (95% Confidence Interval: 0.67, 0.85). For regression this figure was 1.64 (95% Confidence Interval: 1.31, 2.06).

Treatment effect on focal and diffuse coronary atherosclerosis

Quantitative coronary angiography allows the assessment of both the changes in focal (minium lumen diameter and diameter stenosis) and diffuse coronary atherosclerosis (mean lumen diameter). Progression of diffuse coronary atherosclerosis is often not noted, or underestimated because coronary angiography, particularly when visually evaluated, is an unreliable technique for the detection of diffuse disease. However, the introduction of quantitative coronary angiography allows the accurate measurement of changes caused by diffuse coronary atherosclerosis. The quantitative coronary angiography trials clearly demonstrate that diffuse changes do occur and can be slowed by lipid-lowering interventions (Table 7). The overall treatment effect on the progression of coronary atherosclerosis is small. The minimum lumen diameter (a measure of focal disease) decreased by 0.047 mm per year in the

Table 9. All Cardiac Events: mortality, non-fatal myocardial infarction, CABG and PTCA.

Study		Number of patients Event / Total	Rate	Relative Risk (95% CI)
Lipid-modifying therapies: Visual Assessment				
NHLBI	R	12/72	17%	0.68 (0.29, 1.55)
	I	8/71	11%	
CLAS	R	22/94	22%	0.96 (0.57, 1.61)
	I	21/94	23%	
All	***R***	***34/166***	***21%***	***0.86 (0.55, 1.34)***
	I	***29/165***	***18%***	
Lipid-modifying therapies: Quantitative Coronary Angiography				
FATS	R	11/52	21%	0.25 (0.09, 0.68)
	$I_{1\&2}$	5/94	5%	
SCOR	R	1/49	2%	[9]-2% (-6%, 2%)
	I	0/48	0%	
STARS	R	10/28	36%	0.21 (0.07, 0.61)
	$I_{1\&2}$	4/50	8%	
SCRIP	R	34/155	22%	0.63 (0.38, 1.04)
	I	20/145	14%	
HARP	R	4/40	10%	1.03 (0.28, 3.82)
	I	4/39	10%	
All	***R***	***60/324***	***19%***	***0.48 (0.33, 0.70)***
	I	***33/376***	***9%***	
Statin Monotherapy: Quantitative Coronary Angiography				
MARS	R	31/124	25%	0.72 (0.44, 1.16)
	I	22/123	18%	
CCAIT	R	18/166	11%	0.78 (0.40, 1.52)
	I	14/165	9%	
MAAS	R	50/188	27%	0.78 (0.54, 1.12)
	I	40/193	21%	
REGRESS	R	93/434	21%	0.58 (0.43, 0.79)
	I	56/450	12%	
PLAC I	R	81/202	40%	0.67 (0.50, 0.88)
	I	55/206	27%	
All	***R***	***272/841***	***24%***	***0.67 (0.57, 0.79)***
	I	***187/1137***	***17%***	
Lifestyle Changes: Quantitative Coronary Angiography				
Lifestyle	R	0/19	0%	
	I	0/22	0%	
STARS2	R	9/28	32%	0.35 (0.11, 1.14)
	I	3/27	11%	
Heidelberg	R	4/57	7%	1.55 (0.44, 5.44)
	I	5/46	11%	
All	***R***	***13/85***	***7%***	***0.69 (0.31, 1.53)***
	I	***8/73***	***11%***	
OVERALL	***R***	***371/1661***	***22%***	***0.66 (0.58, 0.76)***
	I	***254/1724***	***15%***	

R: Reference group; I: Index group; 95% CI: 95% Confidence Interval; [9]: risk difference; POSCH: not reported

placebo group versus 0.019 in the treatment group. The mean lumen diameter (a measure of diffuse disease) decreased by 0.034 mm per year in the placebo group versus 0.011 in the lipid-lowering group. Treatment with a HMG-CoA reductase inhibitor reduced the progression of focal disease: minimum lumen diameter by 0.02 mm per year, percentage diameter stenosis by 0.6% per year. Also the progression of diffuse coronary atherosclerosis decreased: treatment effect on mean lumen diameter of 0.03 mm per year.

Treatment effect on clinical events

The treatment effects on mortality and non-fatal myocardial infarction and on all cardiac events including death, myocardial infarction, revascularization procedures, or hospitalization for unstable angina, are presented in Tables 8 and 9. Treatment with a lipid-lowering regime induced a reduction of 26% (95% Confidence Interval: -41%, -6%) of death and non-fatal myocardial infarction. For all cardiac events combined the risk reduction was 34% (95% Confidence Interval: -42%, -24%) (Table 9). For the monostatin group the relative risks were 0.70 (95% Confidence Interval: 0.48, 1.02), and 0.67 (95% Confidence Interval: 0.57, 0.79), respectively.

CONCLUSION

The use of coronary angiography as an end point for a trial studying progression or regression of coronary atherosclerosis is attractive. First, it is a safe, widely available method of studying changes in the vessel lumen in humans. Second, an angiographic trial needs fewer patients and the study duration can be shorter, yet yield insufficient power compared to a trial with clinical endpoints. However, serial coronary angiography to study progression or regression only provides a surrogate endpoint, albeit useful. Slowing of progression or frank regression of a lesion is not necessarily linked with a lesser occurrence of coronary events. Yet, the pooled results of the angiographic trials provide sufficient evidence that retardation of coronary atherosclerosis is associated with an improved prognosis. In the over 3500 patients included in this review, the LDL-C was reduced by 31%, this resulted in a retardation of coronary athero-sclerosis with a reduction of approx-imately 30% in progression and a relative increase of 80% for regression. This angiographic benefit was associated with a reduction of 33% in all cardiac events. These randomized angiographic coronary atherosclerosis trials have demonstrated the beneficial effects of different lipid-lowering treatment regimes on the angiographic course of the disease. Various lipid-modifying therapies were applied, from life-style changes, monodrug and multidrug therapies, to ileal bypass surgery. All of these resulted in substantial improvements of the lipid profile with a reduction in LDL-C as common denominator. The mono statin therapies are the most promising since the use of these compounds

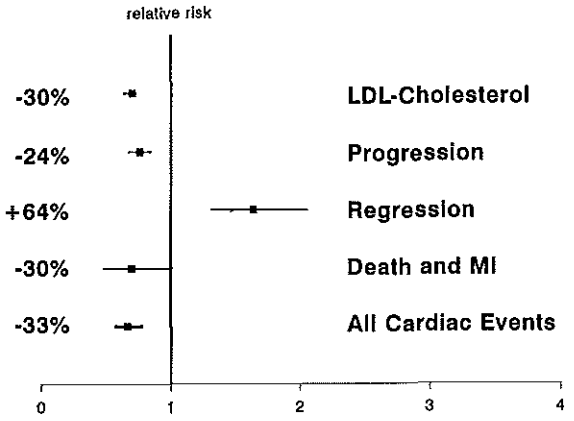

Figure 1. Overview of the lipid, angiographic, and clinical treatment effect in the monostatin trials in over 2012 patients. An average reduction of LDL-C of 30% (range 37% - 27%), results in a reduction of patients with progression of 24% (95% Confidence Interval: -33%, -15%) and an increase of patients with regression of 64% (95% Confidence Interval: 31%, 106%). The improved angiographic course is accompanied by a reduction in death and myocardial infarction of 30% (95% Confidence Interval: -52%, 2%), and of all cardiac events combined (mortality, non-fatal myocardial infarction, CABG and PTCA) of 33% (95% Confidence Interval: -43%, -21%), over an average time period of approximately 3 years.

result in a major amelioration of the serum lipids almost without side-effect.[25,26] Amelioration of the lipid profile, especially lowering LDL-C, induced by the different treatment regimes, resulted in a retardation of progression of coronary atherosclerosis and improved the clinical outcome. At the same time the overview illustrates the relationship between lipids, coronary angiography and clinical course.

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Chapter 9

ANGIOGRAPHIC CORONARY ATHEROSCLEROSIS TRIALS IN PERSPECTIVE

Angiographic coronary atherosclerosis trials in perspective

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The relationship between serum cholesterol levels and the development of coronary artery disease is supported by an overwhelming amount of evidence, so that it has become irrefutable. In animal experiments it has been shown that a diet induced hypercholesterolemia causes atherosclerosis.[1,2] Observational studies in humans, both in-between population studies[3] and within-population studies,[4,5] have clearly demonstrated the association between cholesterol and coronary artery disease. The lipid-hypothesis furthermore maintains, that a reduction of serum cholesterol can retard the progression or can even induce regression of coronary atherosclerosis, which will consequently improve clinical outcome.

Angiographic trials

In recent years a series of angiographic trials has been performed to verify whether interventions aimed at lowering serum cholesterol or otherwise ameliorating the lipid-profile and lifestyle changes, do really result in retardation, arrest or regression of coronary atherosclerosis in humans.[6-22] The use of angiography as an endpoint is appealing, because it is not only able to demonstrate progression or arrest, but can actually show regression of disease. Quantitative coronary angiography can demonstrate changes in focal and diffuse coronary atherosclerosis.[23] Also, fewer patients and a shorter time period are needed to show the effect of an intervention.[24] A clear relationship has been demonstrated between angiographic course and clinical outcome.[25,26] Coronary angiography also has limitations. Since angiography provides shadow images of coronary lumina formed by roentgen ray absorption of contrast medium dissolved in blood, it only yields information on the vessel lumen and not on the vessel wall. Angiography therefore, is unable to study the early stages of the atherosclerotic plaque where remodelling of the vessel preserves the vessel lumen dimensions or even causes an increase of the vessel diameter measured with contrast angiography.[27,28]

Conventional coronary angiography without the administration of vasoactive

compounds, does not yield information on the vasomotor qualities of the coronary artery, a reflection of endothelial function.[29,30] Therefore, classic visual and quantitative angiography does not give data on the effects of lipid-lowering treatment on endothelial function in patients with coronary artery disease.[31,32] Several studies of lipid-lowering, of antioxidant therapies, and of angiotensin-converting enzyme inhibition with quantitative coronary angiography before and after administration of vasoactive compounds, have shown the restoration of normal vasomotor response, which indicates improvement of endothelial function.[33-36]

Apart from the beneficial effect of lipid-lowering interventions on coronary atherosclerosis, several trials have shown advantageous effects on development of atherosclerosis in the carotid[37-40] and femoral arteries.[8,40,41] This salutary indicates that the favourable effects are not only limited to the heart, but extend throughout the arterial system.

Coronary angiography and clinical events

Acute coronary syndromes are caused by rupture of atherosclerotic plaques causing thrombosis with possibly subsequent spasm.[42] Not only the retardation of the development or growth of these lesions detectable by serial angiography, but also the reduction of the propensity of plaques for rupture e.g. plaque stabilization, may be responsible for a part of the reduction of clinical events after lipid-lowering.[43] Figures 1 and 2 illustrate the possible relationship between the angiography of focal and diffuse coronary atherosclerosis and clinical coronary events.

Trials with clinical endpoints

To apply a new treatment in clinical practice, data from trials with intermediate endpoints or results from meta-analyses are not considered sufficient. In addition, direct evidence from larger randomized trials, with a sufficient number of patients to show a beneficial effect on the clinical course, should be available. Before the development of HMG-CoA reductase inhibitors several large trials of lipid-lowering therapy were reported. The primary prevention studies, but also some secondary prevention studies performed, showed a decrease in cardiac morbidity and mortality,[44-46] but were not able to confirm an irrefutable beneficial effect of these lipid-lowering interventions on total mortality.[47,48] Concern about an increase in non-cardiac mortality emerged. Mechanism that related the excess non-cardiac mortality found in these studies with the treatment used or with the actual lipid levels, were not found.[49,50] Recently, only a small increase in risk for haemorraghic stroke has been associated with a lower serum cholesterol, but no other major unwanted effects were found.[51] Furthermore, Gould et al. have demonstrated using meta-analysis techniques, that cholesterol-lowering itself is associated with a lower mortality, and that the excess of non-cardiac mortality is related to specific

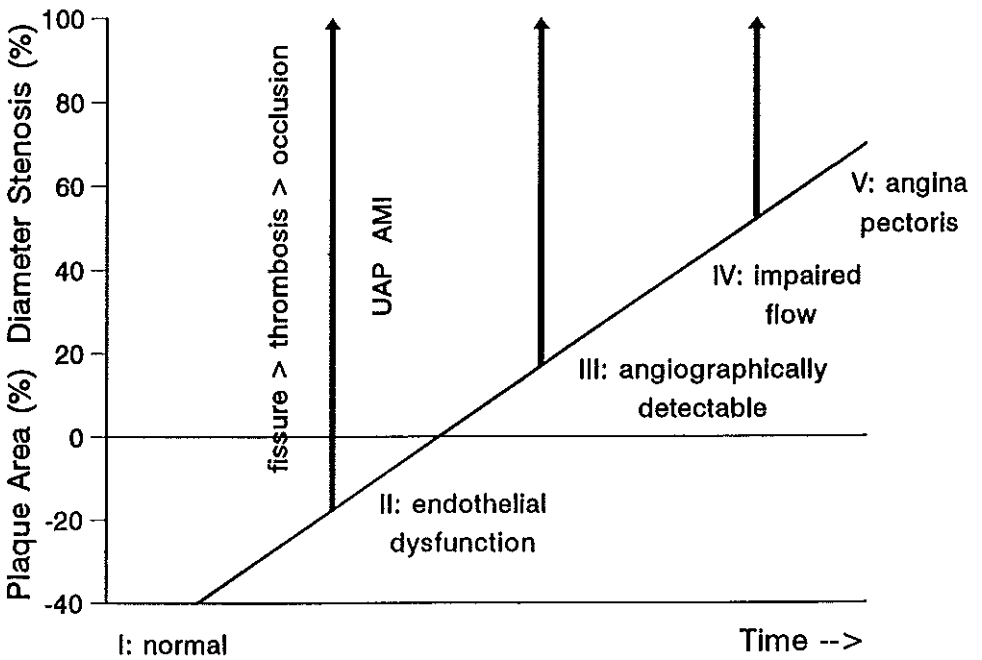

Figure 1. Figure illustrating the possible natural course of focal coronary atherosclerosis, plaque progression, plaque fissure, thrombosis, and ensuing clinical events. ***Phase 1:*** no abnormalities, the endothelium is normal. ***Phase 2:*** a focal atherosclerotic lesion is present, but the internal elastic lamina is less than 40% occupied by atheroma, and because of remodelling does not encroach upon the vessel lumen, making this lesion angiographically undetectable. However, plaque rupture and ensuing clinical events may occur. ***Phase 3:*** The plaque occupies more than 40% of area of the internal elastic lamina, remodelling falls short and the lesion encroaches upon the vessel lumen making this lesion angiographically recognized. Clinically this lesion is silent, but plaque rupture and ensuing acute coronary syndromes may occur. ***Phase 4:*** Plaque growth occurs, which may still be clinically silent. The coronary blood flow reserve (CBFR) is impaired and plaque rupture and it's sequelae may occur. ***Phase 5:*** Plaque growth to an obstruction of more than 50% causes angina pectoris. plaque rupture may occur. The gradually increasing severity of this lesion induces collaterals which may exert protection in the case of plaque rupture and occlusive thrombosis.

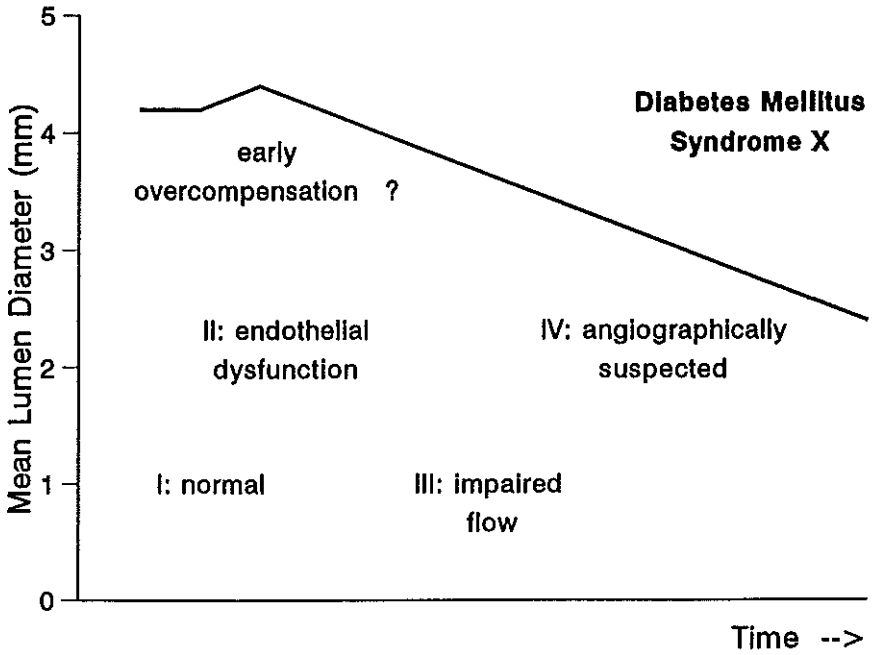

Figure 2. Figure illustrating the possible natural course of diffuse coronary atherosclerosis. ***Phase 1:*** Normal vessel wall, normal endothelium. ***Phase 2:*** Intimal wall abnormalities, undetected by angiography. Endothelial dysfunction may be present as can be demonstrated by abnormal vasoconstrictor response to acetylcholine. ***Phase 3:*** Progression of diffuse disease, still angiographically undetected, may cause endothelial dysfunction and impaired coronary blood flow reserve (CBFR). This may cause angina: Syndrome X, or may be associated with diabetes mellitus. ***Phase 4:*** Further progression of diffuse disease results in the presence of abnormally small caliber epicardial vessels, raising high-suspicion angiographic diffuse disease. Endothelial dysfunction and impaired coronary blood flow are more pronounced. This is often seen in syndrome X and diabetes mellitus.

interventions e.g. fibrates and hormones.[52]

Recently three large trials with clinical endpoints were reported. The West of Scotland Coronary Prevention Study (WOSCOPS) is a prospective randomized double-blind primary prevention study in men with hypercholesterolemia (LDL-C between 4.5 and 6.0 mmol/l) that were allocated to placebo or to treatment with the HMG-CoA reductase inhibitor pravastatin 40 mg once daily.[53] For an average time period of 4.9 years 6595 men (placebo 3293, pravastatin 3302) were followed.[54] Mean age at enrollement was 55 years and the mean total cholesterol was 7.0 mmol/l. Pravastatin lowered total cholesterol by 20%, LDL-C by 26%, and triglycerides by 12%. HDL-C increased by 5%. The primary endpoint, cardiac death and non-fatal myocardial infarction combined, occurred in 7.9% versus 5.9% of the patients in the placebo and lipid-lowering groups, respectively. This is a reduction of 31% (95% Confidence Interval: -43%, -17%). Death from any cause was seen in 4.1% versus 3.2%, a reduction of 22% (95% Confidence Interval: - 40%, 0%). Non-cardiac death and stroke were more frequent in the placebo group. Coronary angiography, percutaneous transluminal coronary angioplasty and coronary artery bypass surgery were reduced by approximately 35%. When patients were dichotomized for smoking status, presence of multiple risk factors, total cholesterol, LDL-C, HDL-C and triglycerides level, no difference was found in the treatment effect. Only in patients aged below 55 years lipid lowering was more effective than in those above 55 years.

The Scandinavian Simvastatin Survival Study (4S)[55] is a prospective randomized double-blind secondary prevention study of both males and females with moderately elevated cholesterol levels (total cholesterol between 5.5 and 8.0 mmol/l, triglycerides beneath 2.5 mmol/l), who were allocated to placebo or simvastatin 20 mg or 40 mg once daily. For a median time period of 5.4 years 4444 patients (placebo 2223, simvastatin 2221) were followed.[56] Mean age was 60 years, mean total cholesterol was 6.75 mmol/l. The goal of treatment was a serum total cholesterol between 3.0 en 5.2 mmol/l. The initial dose was 20 mg of simvastatin but when total cholesterol remained above 5.2 mmol/l the dosage was doubled, which occurred in 37% of the patients. Simvastatin reduced total cholesterol, LDL-C and triglycerides by 25%, 35%, and 10%, respectively. HDL-C increased by 8%. The primary endpoint of the trial was all cause mortality. Twelve percent of the patients in the placebo group died and 8% in the simvastatin group, a reduction of 30% (95% Confidence interval: -42%, -15%). The combined endpoint of cardiac death, non-fatal myocardial infarction and resuscitated cardiac arrest was found in 28% and 18% in the control and lipid-lowering groups, respectively. A risk reduction of 34% (95% Confidence Interval: -41%, -25%). Furthermore, a reduction in the incidence of stroke was observed in the simvastatin group. In sub-

group analyses no difference in efficacy was found for use of aspirin, of beta blockers or of calcium antagonists or not.[57] Also for presence of hypertension or smoking status, gender, and age a similar treatment effects were seen. Only patients with diabetes had a more substantial reduction in risk than non-diabetics. Furthermore, when the baseline cholesterol level was divided in quartiles no difference in treatment efficacy between groups was found, indicating that treatment with simvastatin lowered the risk for clinical events independent of baseline cholesterol within the range of 5.5 to 8.0 mmol/l.[58]

The Cholesterol and Recurrent Events trial (CARE) is a prospective randomized double-blind secondary prevention trial of men and women who experienced a myocardial infarction and with average serum total cholesterol levels (total cholesterol beneath 6.2 mmol/l, LDL-C between 3.0 and 4.5 mmol/l, and triglycerides below 4.0 mmol/l) who were allocated to placebo or pravastatin 40 mg once daily.[59] A total of 4159 patients (placebo 2078, pravastatin 2081) entered the trial and were followed for 5 years.[60] Mean age was 59 years, mean total serum cholesterol was 5.4 mmol/l. Total cholesterol was reduced by 20%, LDL-C by 28%, and triglycerides by 14%. HDL-C rose 5%. The primary endpoint was the combination of cardiac death and nonfatal myocardial infarction. Two hundred sixty nine patients 13.2% in the placebo group and 206 patients (10.2%) in the lipid-lowering group suffered such an event. This represents a reduction of 24% (95% Confidence interval: -36%, -9%). Revascularization procedures were less frequent in the pravastatin group, with 294 (14.1%) versus 391 (18.8%) patients. A reduction of 27% (95% Confidence interval: -37%, -15%). In a subgroup analysis patients were trichomized according to the baseline level of LDL-C, below 3.2 mmol/l, between 3.2 and 3.9 mmol/l, and between 3.2 and 4.5 mmol/l. In the highest stratum a reduction in cardiac events of 35% was seen, in the middle of the range this was 26%, below 3.2 mmol/l, however, no reduction was found. Apart from the beneficial effect on cardiac events, a reduction in stroke was found in the lipid-lowering group, 2.6% versus 3.8%.

Implications for clinical practice

The combined angiographic trials, and the three large trials with clinical endpoints have consistently shown the beneficial effect of predominantly LDL-C lowering in patients with established coronary artery disease with average or moderately elevated cholesterol levels, and for subjects with elevated cholesterol levels in primary prevention. The treatment effect found in the 4S, CARE and WOSCOPS with monostatin therapy is comparable to the risk reduction estimated in the meta-analysis of the angiographic trials presented in chapter 8[61] (Table 1). These studies did not include patients with elevated triglyceride levels, so that an extrapolation of results must be made in patients with a combined

Table 1. Summary of results from the angiographic trials and 4S, CARE and WOSCOPS.

Variable	Angiographic trials	4S	CARE	WOSCOPS
Number	3768	4444	4159	6595
Mean duration (years)	3.0	5.4	5.0	4.9
Treatment	different lipid lowering regimes	simvastatin 20 - 40 mg/d	pravastatin 40 mg/d	pravastatin 40 mg/d
Total cholesterol (mmol/l)	6.5	6.3	5.4	7.0
Lipid changes:				
Total Cholesterol	-23%	-25%	-20%	-20%
LDL-C	-31%	-35%	-28%	-26%
HDL-C	+8%	+8%	+5%	+5%
Triglycerides	-8%	-10%	-14%	-12%
Angiographic changes:				
Progression	-28%			
Regression	+84%			
Non-diseased segments (mm/year)	0.02			
Focal disease (mm/year)	0.03			
Diffuse disease (mm/year)	0.02			
Death and AMI*	5% vs 7%	8% vs 12%	10% vs 13%	6% vs 8%
Relative reduction	-26%	-26%	-24%	-31%
All Cardiac events*	15% vs 22%	18% vs 28%	21% vs 26%	7% vs 10%
Relative reduction	-34%	-34%	-22%	-32%

Non-diseased: mean lumen diameter data from MAAS, Focal disease: minimum lumen diameter, Diffuse disease: mean lumen diameter; *: duration of follow-up differed between groups.

hyperlipidaemia. Also, patients with a poor left ventricular function were excluded from these studies. A group in which the lipid-level is not of special prognostic significance, but where left ventricular function is by far the most important predictor for clinical outcome.[62]

In 4S and WOSCOPS the improvement of the clinical course was found to be independent of the initial cholesterol level. This was also observed in the MAAS[18] (Chapter 5) and REGRESS[20] trials. In the CARE study, however, the treatment effect was less strong in patients with a baseline LDL-C between 3.2 and

3.9 mmol/l, while no reduction in events was seen in those with a LDL-C below 3.2 mmol/l. It might be concluded that the treatment effect of lipid-lowering therapy in patients with clinically overt coronary atherosclerosis and a baseline cholesterol level LDL-C > 3.9 mmol/l, is not dependent on the baseline cholesterol as long as this is decreased substantially, e.g. a reduction of LDL-C of approximately 30%. The treatment effect for patients with a baseline LDL-C between 3.2 and 3.9 mmol/l was still a reduction of 26% in cardiac death and non-fatal myocardial infarction. This suggests that apart from current guidelines for lipid-lowering aiming at certain absolute levels of lipid-values,[63,64] also a substantial relative reduction in cholesterol should be accomplished. Furthermore, the CARE study showed that the beneficial effect of cholesterol lowering decreased with the baseline LDL-C, and is absent in those patients with a LDL-C below 3.2 mmol/l. This implies that also for secondary prevention there might exist a cut-off level, below which lipid-lowering does not result in a better clinical outcome.

The results of these monostatin trials with clinical endpoints have initiated a series of statements underlining the importance of lipid-lowering for clinical practice.[65,66] When prevention with lipid-lowering drugs is being considered, cost-benefit data give important information. When the primary prevention WOSCOPS and secondary prevention 4S are compared, almost identical relative reductions in coronary events by the comparable lipid reductions achieved in these studies, are seen. Since the absolute risk for development of clinical events was substantially higher in 4S than in WOSCOPS, the effectiveness of treatment was considerably larger. For 100 patients treated in 4S during 6 years, 4 deaths, 7 non-fatal myocardial infarctions, and 6 revascularization procedures were prevented. For CARE these figures were 1.1, 2.6, and 6.2 respectively, over a 5 years period. For 100 patients in WOSCOPS approximately 1 death, 2 non-fatal myocardial infarctions, and 1 revascularization procedure were prevented. This illustrates, that treatment with statins has a better cost-benefit ratio in persons with a high risk for developing coronary events (Figure 3). A cost-effective analysis based on data from 4S reported a cost per life year gained of approximately 14,300 Dutch guilders, a figure which is comparable with other well accepted therapies for established coronary artery disease.[67] Cost-benefit analysis analyses for primary prevention based on WOSCOPS have not yet been published, however one can estimate that these will be a factor 3 to 4 less favourable.

Apart from lipid-levels, several other risk factors for developing of progression of coronary artery disease that can be influenced, have been identified. Among these, diabetes mellitus, arterial hypertension, tobacco smoking, obesity, a sedentary lifestyle, and a diet rich of calories and unsaturated fat are most prominent.[68] Reduction of all of these factors is desirable, and lifestyle changes should always

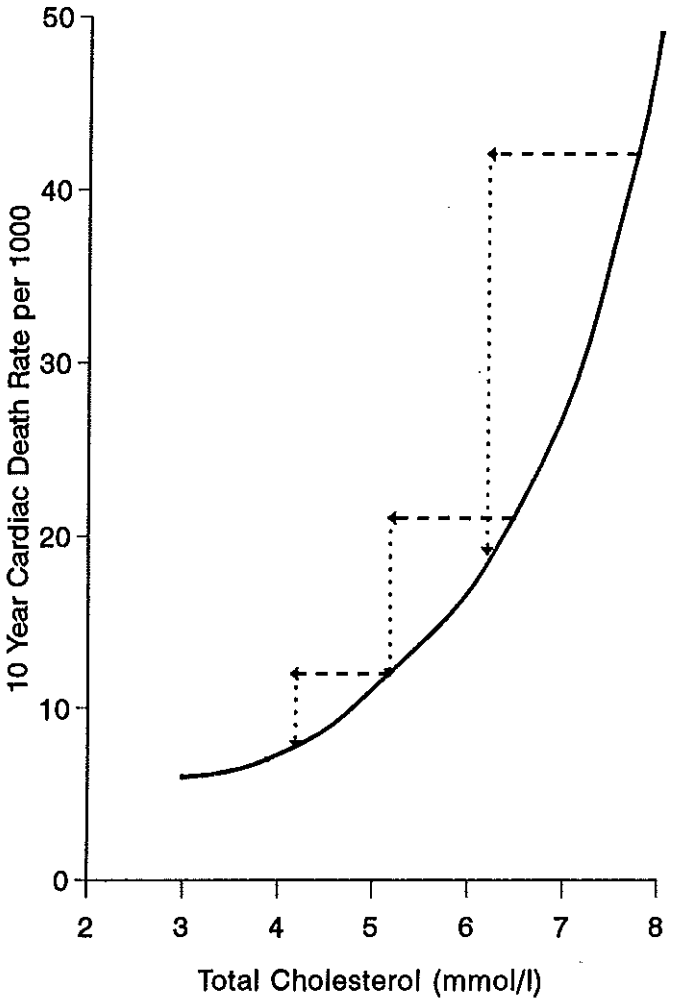

Figure 3. Figure illustrating the theoretical effect of a 20% reduction of total cholesterol (horizontal arrows pointed to the left) on the 10 year cardiac mortality (arrows pointed downward) based on data from MRFIT. It can be appreciated that the same relative reduction in total cholesterol yields a much larger decrease in mortality in the higher range of total cholesterol, with a higher absolute risk on cardiac death, than a similar relative reduction in total cholesterol in the lower range.

be advised when one decides to apply drug therapy. Both European[68] and American[69] recommendations for risk reduction in patients with or without signs of coronary artery disease have stressed the importance of such integrated approach to prevention.

The results from the monostatin trials have demonstrated a clear beneficial effect of lipid-lowering on the occurrence of cardiac events, although in patients with a low LDL-C no clear benefit has been shown. In patients with a moderate or elevated cholesterol level at baseline, who are treated with a HMG-CoA reductase inhibitor, a reduction in clinical events of approximately 30% over 5 years can be expected. When lipid-lowering drugs would be prescribed to all patients with coronary artery disease, those with a low absolute risk on new coronary events would still have a small chance to benefit from treatment. Cost-benefit analyses can provide data to select patient groups that have "sufficient risk", so that the individual patient has a reasonable chance to benefit from drugtherapy. The findings indicate that treatment with a statin should be considered in all patients with established coronary artery disease and applied in most of these, always as part of an integrated program of risk reduction.

Conclusion

Serial coronary angiography is a reliable tool to study the course of coronary atherosclerosis. Quantitative coronary angiography has unquestionably demonstrated it's value for studying the coronary lumen, although specific limitations remain. A clear relationship between angiography and clinical course has been established. The angiographic coronary atherosclerosis trials have shown that a substantial amelioration of the lipid profile results in retardation of progression of coronary atherosclerosis. Meta-analysis of these studies has demonstrated, that the improved angiographic course is accompanied by a better clinical outcome with a reduction in deaths, non-fatal myocardial infarctions and revascularization procedures. Three large, long-term, prospective, randomized trials with clinical endpoints have definitively shown, that statin monotherapy substantially improves the clinical course. The lipid hypothesis, which postulates that an elevated cholesterol level causes coronary atherosclerosis and that lipid-lowering therapy will retard progression of the disease, has been confirmed.

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APPENDIX

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Participating centres, numbers of patients and investigators: Thoraxcenter, Academic Hospital Dijkzigt, Erasmus University, Rotterdam (NL), 69 patients (M.L. Simoons, J.P.M. Saelman, J.W. Deckers); Sint Antonius Hospital, Nieuwegein (NL), 51 patients (J.H. Kingma, M. Quere, A.J. Six, P.H.M.J. Vermeers); Sahlgrenska Hospital, Gothenburg (S), 40 patients (H. Emanuelsson, K. Selin, O. Wiklund); Hammersmith Hospital, London (UK), 38 patients (G.R. Thompson, G. Davies, V. Maher); Universität Erlangen-Nürnberg, Erlangen (G), 33 patients (K. Bachmann, K. Reynen); Tour de Soins Normaux, C.H.U. Sart-Tilman, Liège (Belgium), 31 patients (V. Legrand, C. Martinez); Freie Universität Berlin, Klinikum Rudolf Virchow-Charlottenburg, Berlin (G), 28 patients (H. Schmutzler, W. Rutsch, J. Bott); Johann Wolfgang Goethe-Universität, Frankfurt am Main (G), 29 patients (M. Kaltenbach, W. Schneider, B.R. Winkelmann); Drechtsteden Ziekenhuis, Dordrecht (NL), 25 patients (I. Stoel, J. ten Kate); Klinikum der Medizinischen Hochschule, Hannover (G), 21 patients (W. Rafflenbeul, P. Nikutta); Hôpital Cardio-Vasculaire et Pneumologique Louis Pradel, Lyon (F), 16 patients (J. Delaye, M.P Mathieu-Mulin)

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Sponsor main trial: Merck Sharp & Dohme Research Laboratories, Rahway (USA) and Brussels (B). A. Sweany, W. Malbecq, M. Melino, M. Kiely.

Summary

In this thesis the effect of cholesterol-lowering therapy on the angiographic progression of coronary atherosclerosis is described.

In chapter 1 as an introduction a brief summary is given of the epidemiologic aspects and the treatment of the clinical sequelae of coronary atherosclerosis. Furthermore, the cholesterol-atherosclerosis link and the lipid hypothesis are introduced.

In chapter 2 an overview is provided of the angiographic coronary and angiographic femoral atherosclerosis trials. The trials of cholesterol lowering therapy, medical and surgical, the studies of lifestyle changes, and the trials of dihydropyridin calciumanatagonists completed before 1992 are described. By means of meta-analysis techniques an overall measure of effect of the treatment is calculated. It was found that the different cholesterol lowering treatments show a relative reduction of the number of patients with progression of disease of approximately 35%, and a relative increase in the number of patients with regression of approximately 85%. Very intensive lifestyle changes had a similar effect. No strong evidence was found for a beneficial effect of dihydropyridin calciumanatagonists on the progression of coronary atherosclerosis. The cholesterol lowering treatments also appear to retard the evolution of femoral atherosclerosis. Finally, the epidemiologic aspects of angiographic coronary atherosclerosis trials are discussed, as well as the relation between coronary angiography, stable and unstable angina, and the acute myocardial infarction.

In chapter 3 the effect of cholesterol lowering treatment with the HMG-CoA reductase inhibitor simvastatin on the angiographic progression of coronary atherosclerosis is presented. This is a report of the Multi Centre Anti-Atheroma Study: MAAS. Three-hundred-and-eighty-one patients with mild coronary artery disease, in stable clinical condition, and with a total cholesterol between 5.5 and 8.0 mmol/l, received a cholesterol lowering diet and were randomized to treatment with simvastatin 20 mg once daily or placebo. After 2 years an interim analysis was performed, after which it was decided to prolong the study for another 2 years. Before the start of the study medication, after 2 and after 4 years, quantitative coronary angiography was performed. Treatment with simvastatin resulted in a reduction of total cholesterol of 23%, LDL-C of 31% and triglycerides of 18%. HDL-C increased by 9%. For 167 placebo patients and 178 simvastatin patients a follow-up angiogram was available after 4 years. Simvastatin reduced both the progression of diffuse coronary atherosclerosis, a decrease of

the mean lumen diameter of 0.02 mm versus 0.08 mm, as the progression of focal disease, a decrease of minimum lumen diameter of 0.04 mm versus 0.13 mm. The number of patients with progression was lower in the simvastatin group: 41 versus 45 patients. The number of patients with regression was higher: 33 versus 20 in the placebo group. Simvastatin retards both the progression of diffuse and focal coronary atherosclerosis.

In chapter 4 the angiographic course of coronary atherosclerosis in the placebo group of the MAAS trial is described, for which 3 serial quantitatively analysed coronary angiograms, at baseline, after 2 and after 4 years, were used. The progression of diffuse coronary atherosclerosis, expressed as a decrease in mean lumen diameter, was 0.02 mm/year (0.7%) The progression of focal disease, expressed as a decrease in minimum lumen diameter, was 0.03 mm/year (1.3%). Progression of focal disease was most prominent in new and mild stenoses and in the right coronary artery. In most of the subgroups progression occurred gradually over time. Diffuse and focal coronary atherosclerosis progress gradually over time. Progression of focal atherosclerosis is approximately twice as large as progression of diffuse disease.

In chapter 5 predictors of both diffuse and focal atherosclerosis changes are described. For 345 patients of which half were treated with simvastatin, both independent predictors of progression of diffuse disease, represented by mean lumen diameter, and predictors of focal disease, expressed in minimum lumen diameter of stenosed segments, were selected using multiple linear regression analysis. First, univariate linear regression analysis was performed with clinical, lipid and angiographic parameters. Second, those variables predictive in univariate analysis were entered in a multivariate linear regression model to select independent predictors of disease advancement. Progression of both diffuse and focal coronary atherosclerosis was associated with smoking, a larger mean or minimum lumen diameter at baseline, a higher total cholesterol and a low HDL-C. Also a previous successful PTCA without restenosis was related to less progression of focal disease. The predictors of diffuse and focal coronary atherosclerosis are identical.

In chapter 6 the incidence and angiographic patterns of progression and regression are addressed. In 272 patients 924 stenoses were quantitatively analyzed at baseline, at 2 and at 4 years. Both stenosis parameters and parameters of the whole coronary segment were measured. As a measure of width of the whole coronary segment the interpolated reference diameter was used. To describe changes of the coronary lesion, the minium lumen diameter and the plaque diameter (the difference between interpolated reference diameter and minimum lumen diameter) were used. Most of the

stenoses did not change (79%). After 4 years 12% had progressed, and 9% of the lesions had regressed. Progression, a decrease of the minimum lumen diameter, was equally caused by a reduction of the interpolated reference diameter of the whole coronary segment, as by an increase of the plaque diameter. Regression, an increase of the minimum lumen diameter, was equally caused by an increase of the interpolated reference diameter of the whole coronary segment, as by a decrease of the plaque diameter. Progression is caused by an advancement of both diffuse and focal coronary atherosclerosis. Regression is induced by reversement of both diffuse and focal disease.

In chapter 7 the reproducibility of the quantitative analysis of coronary angiograms as it is performed in a multicenter study with a central analysis laboratory is presented. Of 10 patients from the MAAS trial, baseline and 4 years angiograms were analyzed by 2 different analysis teams. For each team coefficients of variation were calculated for a per projection analysis, a per segment analysis (mean of the projections), and a per patient analysis (mean of the segments). Also the mean differences between teams were calculated. Each team analyzed of 10 patients, 90 coronary segments and 186 projections. The difference between teams for mean lumen diameter was -0.06 ±0.24, 0.04 ±0.20, and 0.04 ±0.09 mm, per projection, per segment and per patient respectively. For minimum lumen diameter these figures were 0.02 ±0.22, 0.01 ±0.20, and 0.00 ±0.15 mm. The measurement variability decrease from the per projection analysis to the per patient analysis.

In chapter 8 a meta-analysis is presented of the clinical endpoints in the angiographic trials. Also, the angiographic trials are discussed, that were published after 1992 and that were not included in chapter 2. The mean effects on the lipid profile were a reduction in total cholesterol of 23%, in LDL-C of 31% and in triglycerides of 8%. HDL-C increased by 8%. The improvement in the lipid-profile resulted in a reduction of 28% in the number of patients with progression, and an increase of 84% in the number of patients with regression. The beneficial effect on the angiographic course was accompanied by a reduction of 26% of patients who died or suffered an acute myocardial infarction, and a reduction of 34% in death, acute myocardial infarction, CABG, PTCA or hospitalization for unstable angina. This beneficial effect on both angiographic and clinical course was also found for the group of monostatin trials alone.

In chapter 9 the results of the angiographic trials are summarized and compared with large clinical endpoint studies. The most important trials with clinical endpoints are discussed. In the first half of this decade the lipid hypothesis has been proven, which postulates that a cholesterol reduction results in a retarda-

tion, arrest of progression or indeed regression of coronary atherosclerosis, which will eventually result in an improved clinical outcome. A large number of angiographic trials with cholesterol lowering therapy has consistently shown, that amelioration of the lipid profile results in a reduction of the number of patients with progression of disease and increase in the number with regression. The improved angiographic course is accompanied with a lower morbidity and mortality, and with a reduction of revascularisation procedures. Three large, long-term studies with clinical endpoints have definitively shown that statin monotherapy substantially improves the clinical course. Examplary in this context are the MAAS and 4S. Treatment of patients with established coronary atherosclerosis and a total cholesterol between 5.5 and 8.0 mmol/l with simvastatin, resulted in the first angiographic trial in a substantial reduction of the number of patients with progression of disease, and in the second study, a large long-term trial with clinical endpoints, in an important reduction in mortality, non-fatal myocardial infarctions and revascularisation procedures.

Samenvatting

Dit proefschrift beschrijft het effect van cholesterol verlagende behandeling op de angiografische progressie van coronairlijden.

In hoofdstuk 1 wordt een korte introductie gegeven van de epidemiologische aspecten en de behandeling van de klinische gevolgen van coronairsclerose. De cholesterol-atherosclerose link en de lipiden hypothese worden geïntroduceerd.

In hoofdstuk 2 wordt een overzicht gegeven van de angiografische coronaire en de angiografische femorale atherosclerose trials verricht tot 1992. Zowel de studies met cholesterol verlagende behandelingen, medicamenteuze en chirurgische, de studies met levensstijl aanpassingen, als de trials met dihydropiridine calciumantagonisten worden beschreven. Met behulp van de meta-analyse techniek wordt een globale effectmaat van de behandelingen op de progressie van coronairsclerose berekend. Het blijkt dat verschillende cholesterol verlagende behandelingen gepaard gaan met een relatieve vermindering van het aantal patiënten dat progressie van de ziekte heeft met ongeveer 35% en een relatieve toename van het aantal patiënten met regressie van 85%. Tevens zijn er aanwijzingen dat hetzelfde geldt voor zeer stringente levensstijlveranderingen. Er werd geen overtuigend bewijs gevonden dat behandeling met een dihydropiridine calciumantagonist een belangrijk effect heeft op de progressie van coronairsclerose. De cholesterol verlagende behandelingen lijken ook een gunstig effect te hebben op de atherosclerose van de femoraalarterien. De epidemiologische angiografische aspecten van coronairsclerose trials worden besproken, en het verband tussen coronairangiografie, stabiele en onstabiele angina pectoris en het acute myocardinfarct wordt behandeld.

In hoofdstuk 3 wordt het effect van cholesterol verlagende behandeling met de HMG-Co reductase remmer simvastatine op de angiografische progressie van coronairsclerose besproken. Dit is een verslag van de Multicentre Anti-Atheroma Studie: MAAS. Driehonderd-en-een-en-tachtig patiënten met mild coronairlijden, in klinisch stabiele conditie, met een totaal cholesterol tussen de 5.5 en 8.0 mmol/l werden naast een dieet behandeld met simvastatine 20 mg per dag of placebo. Na 2 jaar vond een interimanalyse plaats, waarna besloten werd de studieperiode met 2 jaar te verlengen. Voor het begin met de studiemedicatie, na 2 en na 4 jaar werd kwantitatieve coronairangiografie verricht. De behandeling met simvastatine resulteerde in een reductie van het totaal cholesterol met 23%, het LDL-cholesterol van 31%, en triglyceride van 18%. Het

HDL-cholesterol gehalte steeg met 9%. Voor 167 patiënten in de placebogroep en 178 met simvastine behandelde patiënten was een 4 jaars vervolgangiogram beschikbaar. Simvastatine vertraagde zowel de progressie van diffuse coronairsclerose, een afname van de gemiddelde lumen diameter van 0.02 mm tegenover 0.08 mm, als die van focale coronairsclerose, een afname van de minimum lumen diameter van 0.04 tegenover 0.13 mm in de placebo groep. Het aantal patiënten met progressie was lager in de simvastine groep, 41 tegenover 54 patiënten. Het aantal patiënten met regressie was hoger, 33 tegenover 20 patiënten in de placebogroep. Simvastatine vertraagt de progressie van zowel diffuse als focale coronairsclerose.

In hoofdstuk 4 wordt het angiografische beloop van coronairsclerose beschreven in de placebo groep van de MAAS. Hiervoor werden drie kwantitatief geanalyseerde coronairangiogrammen van het begin van het onderzoek, na 2 en na 4 jaar gebruikt. Zowel de veranderingen in diffuse en focale atherosclerose op segment niveau worden gerapporteerd. De toename van diffuse ziekte, uitgedrukt in een afname van de gemiddelde lumen diameter, was 0.02 mm per jaar (0.7%). De voortschrijding van focale ziekte, uitgedrukt in een afname van de minimum lumen diameter was 0.03 mm per jaar (1.4%). Progressie van diffuse ziekte was het grootst in ernstig vernauwde segmenten en in de rechter coronairarterie. Progressie van focale ziekte was het meest uitgesproken in de nieuwe en milde stenosen en in de rechter coronairarterie. In de meeste subgroepen was er een geleidelijke progressie over de tijd. Diffuse en focale coronairsclerose schrijden beide geleidelijk voort over de tijd. Progressie van focale ziekte is ongeveer 2 maal zo groot als de voortschrijding van diffuse coronairsclerose.

In hoofdstuk 5 worden factoren die van invloed zijn op de progressie van coronairsclerose beschreven. Voor 345 patiënten, waarvan de helft met simvastatine behandeld was, werden de voorspellers van progressie van diffuse coronairsclerose, uitgedrukt in de gemiddelde lumen diameter per patiënt, en die van het verloop van focale atherosclerose, vastgelegd in de minimum lumen diameter van de gestenoseerde segmenten per patiënt, geidentificeerd met behulp van lineaire regressie analyse. Hiertoe werden eerst klinische -, lipiden - en angiografische variabelen ieder afzonderlijk in een lineair regressie model ingevoerd. Vervolgens werden die factoren, die van invloed bleken bij de univariate analyse, ingevoerd in een multivariate analyse om onafhankelijke voorspellers van progressie te identificeren. Progressie van zowel diffuse als focale coronairsclerose was geassocieerd met roken, een groter vat of een minder ernstige stenose, een hoog totaal cholesterol en een laag HDL-cholesterol. Daarnaast ging een eerder ondergane succesvolle PTCA zonder restenose gepaard met minder progressie van focale atherosclerose. De voorspellers van

diffuse en focale coronairsclerose zijn dezelfde.

In hoofdstuk 6 worden de incidentie en de angiografische patronen van progressie en regressie behandeld. Voor 272 patiënten werden 924 stenosen kwantitatief geanalyseerd bij begin van het onderzoek, na 2 en na 4 jaar. Zowel stenose parameters als parameters van het hele segment waarin de vernauwing gelegen was, werden berekend. Als maat voor de dimensies van het hele segment, diffuse atherosclerose, werd de geinterpoleerde referentie diameter gebruikt. Om de veranderingen in de lesie te beschrijven werden de minimum lumen diameter en de plaque diameter, het verschil tussen de referentie- en minimum lumen diameter, bepaald. De meerderheid van de stenosen veranderde niet (79%). Na 4 jaar was er progressie van 12% en regressie van 9% van de vernauwingen. Progressie, een afname van de minimum lumen diameter, werd in gelijke mate veroorzaakt door een afname van de geinterpoleerde referentie diameter van het gehele segment, als van een toename van de plaque diameter. Regressie werd in gelijke mate veroorzaakt door een toename van de geinterpoleerde referentie diameter van het gehele segment, als van een afname van de plaque diameter. Deze veranderingen traden gelijkmatig op tussen 0 en 2 jaar en tussen 2 en 4 jaar. Progressie is het resultaat van voortschrijding van zowel focale als diffuse atherosclerose. Regressie wordt veroorzaakt door afname van focale en diffuse coronairsclerose.

In hoofdstuk 7 wordt de reproduceerbaarheid van de kwantitatieve analyse van coronairangiogrammen zoals deze plaatsvindt in een multicenter onderzoek met een centraal analyse laboratorium beschreven. Van 10 patiënten werden het coronairangiogram bij aanvang en na 4 jaar geanalyseerd door 2 verschillende analyse teams. Voor ieder team werden variatie coefficienten berekend voor alle projecties, per segmenten (gemiddelde van de projecties van een segment) en per patiënt (gemiddelde van de segmenten). Tevens werd de gemiddelde verschillen tussen beide teams berekend. Per team werden van 10 patiënten 90 segmenten van 186 projecties geanalyseerd. Het verschil tussen beide teams voor gemiddelde lumen diameter was -0.06 ±0.24, 0.04 ±0.20, en 0.04 ±0.09 mm, achtereenvolgens per projectie, per segment en per patiënt. Voor de minimum lumen diameter waren de cijfers 0.02 ±0.22, 0.01 ±0.20, en 0.00 ±0.15 mm. De de meetvariabiliteit neemt af van de per projectie naar de per patiënt analyse.

In hoofdstuk 8 wordt een meta-analyse van de klinische eindpunten in de verschillende angiografische trials gerapporteerd. Tevens worden de angiografische onderzoeken die sinds 1992 zijn gepubliceerd en niet in hoofdstuk 2 zijn behandeld, beschreven. Het gemiddelde effect van de verschillende angiografische trials is een verlaging van het totaal cholesterol met 23%, het LDL-C met 31%,

en het triglyceride gehalte met 8%. Het HDL-C steeg gemiddeld 8%. Deze verbetering van het lipidenspectrum resulteerde in een reductie van 28% van de patienten met progressie van coronairsclerose en een toename van het aantal patienten met regressie van 84%. Het gunstige effect op de ontwikkeling van coronairsclerose ging gepaard met een reductie van 26% van het aantal patiënten dat overleed of een niet fataal myocardinfarct kreeg, en een reductie van 34% in sterfte, myocardinfarcten, revascularisatie procedures en opnames in verband met onstabiele angina pectoris. Dit gunstige effect op het angiografische en klinische beloop gold ook voor de groep van monostatine trials alleen.

In hoofdstuk 9 worden de resultaten van de verschillende angiografische en klininische onderzoeken samengevat. De belangrijkste trials met klinische eindpunten worden besproken. Begin jaren negentig is de lipiden hypothese bewezen, die stelt dat door cholesterol verlaging progressie van coronairsclerose vertraagd, gestopt of dat zelfs regressie geinduceerd kan worden, wat uiteindelijk een gunstiger klinisch beloop ten gevolge zal hebben. Een groot aantal angiografische studies met cholesterol verlagende behandeling heeft aangetoond, dat deze verbetering van het lipiden profiel resulteert in een vermindering van het aantal patiënten met progressie en een vermeerdering van het aantal met regressie van coronairsclerose. Meta-analyse van deze studies toont aan dat het verbeterde angiografisch beloop van de ziekte gepaard gaat met een lagere mortaliteit en morbiditeit, en met een vermindering van het aantal revascularisaties. Een drietal grote, lange termijn studies heeft definitief aangetoond dat cholesterol verlaging met statine monotherapie het klinisch beloop aanzienlijk verbeterd. De MAAS en de 4S trial zijn hiervoor exemplarisch. Behandeling van patiënten met bewezen coronairlijden en een totaal cholesterol tussen 5.5 en 8.0 mmol/l met simvastatine leidde in het eerste, angiografische, onderzoek tot een substantiele afname van progressie van atherosclerose en in het tweede, een lange termijn studie met klinische eindpunten, tot een belangrijke reductie in sterfte, in niet-fatale infarcten en revascularisatie procedures.

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Curriculum Vitae

Jeroen Vos werd op 20 augustus 1963 te Rotterdam geboren, waar hij van 1967 tot 1975 de Rotterdamse School Vereniging en van 1975 tot 1982 het Gymnasium Erasmianum bezocht. Hierna studeerde hij van 1982 tot 1988 geneeskunde aan de Erasmus Universiteit Rotterdam. Tijdens zijn studie was hij werkzaam op de afdeling Klinische Epidemiologie van het Thoraxcentrum. Van 1988 tot 1992 was hij achtereenvolgens verbonden aan het Centrum voor Klinische Besliskunde van de Erasmus Universiteit Rotterdam, de Société de la Recherche Cardiologique te Nyon Zwitserland, en aan het Thoraxcentrum van het Academisch Ziekenhuis Rotterdam Dijkzigt, gedurende welke periode aan het in dit proefschrift beschreven onderzoek werd verricht. In 1992 is hij begonnen aan de opleiding tot cardioloog aan het Thoraxcentrum te Rotterdam (opleider Prof. dr J.R.T.C Roelandt). Hiertoe volgde hij van 1992 tot 1994 de stage inwendige geneeskunde in het Merwedeziekenhuis te Dordrecht (opleider dr B.A. de Planque). Vanaf 1994 wordt de opleiding vervolgd aan het Thoraxcentrum te Rotterdam.

In 1993 werd hij geregistreerd als epidemioloog. Van 1991 tot en met 1994 werkte hij onder leiding van dr P.J. de Feyter mee aan de Multicentre Anti-Atheroma Study. In 1995 liep hij stage aan de lipid clinic van Prof. Scott M. Grundy, Center for Human Nutrition van de University of Texas Southwestern Medical Center, te Dallas.

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