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

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

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 $\geq$5.7 mmol/L or $\geq$5.2 mmol/L in combination with a LDL level of $\geq$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	1.25	−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	2.59	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	4.45	−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.

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, 7.82)
	$I_{1\&2}$	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 cass 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	8.05	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.

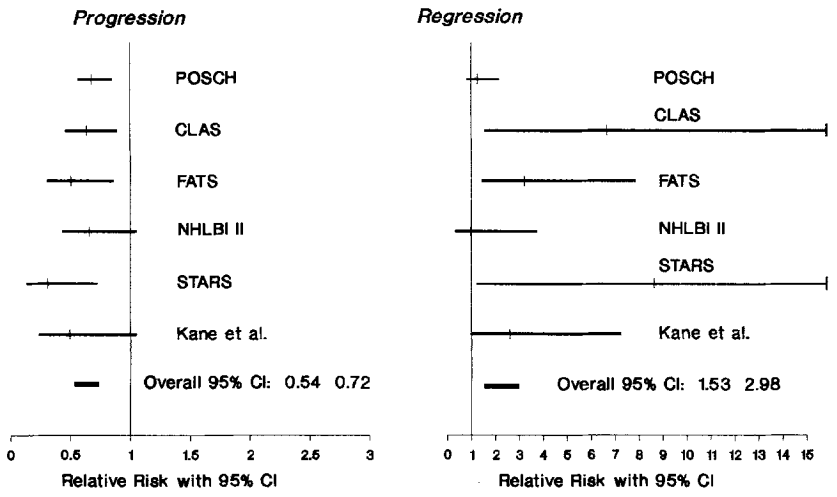


Fig 1. Relative risks for angiographic progression and regression of CAD for each lipid-modifying trial and the overall relative risk. The horizontal bars indicate the 95% confidence interval. For progression the portion left to the line of unity indicates a beneficial effect (reduction in progression);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

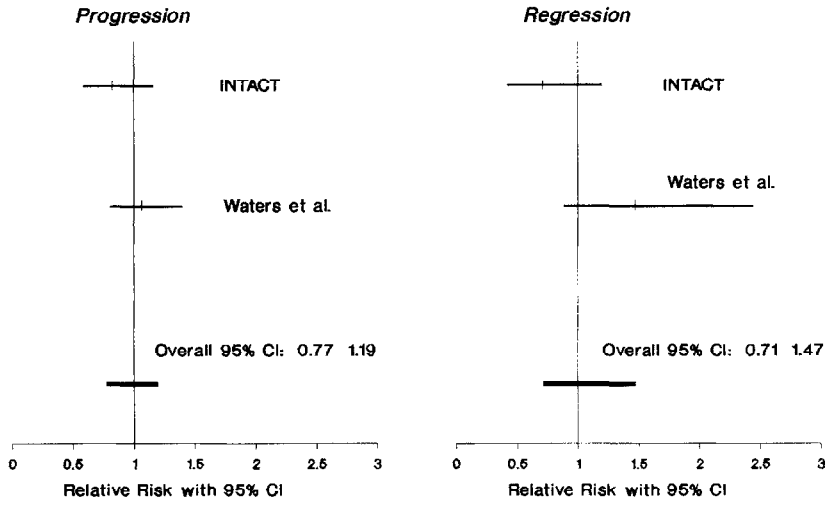


Fig 2. Relative risks for angiographic progression and regression of CAD for both calcium antagonist trials and the overall relative risk. The horizontal bars indicate the 95% confidence interval. For progression the portion left to the line of unity indicates a beneficial effect (reduction in progression);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

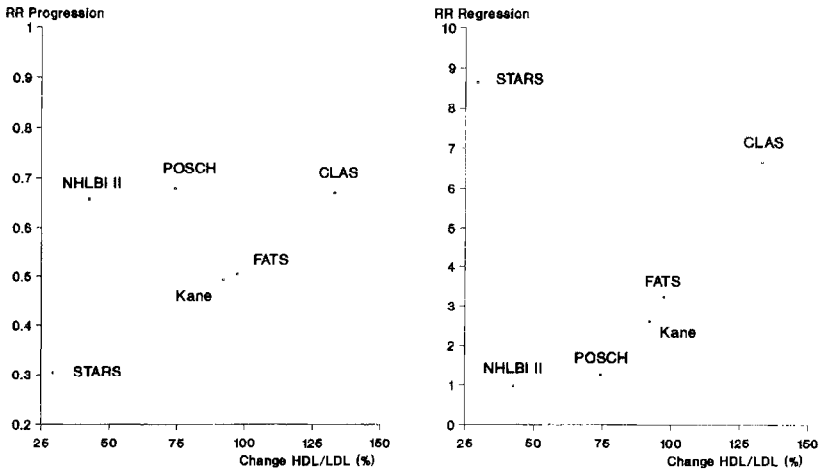


Fig 3. Scatter plot of the difference in change in the HDL/LDL ratio between the placebo and lipid-modified group and the relative risk for progression and regression of CAD. Linear regression analysis did not show a relation between lipid-modifying and angiographic effect among the trials.

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

Study	Total	Number of Patients			Duration (yr)	Type
		Progression (%)	No Change (%)	Regression (%)		
Cohn et al (1975)	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)
Barndt 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

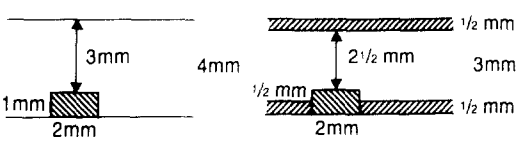
Relative measures, such as percentage diameter stenosis or percentage area stenosis, are dependent of the determination of the normal vessel contour. This normal vessel border at the site of a stenosis is unknown and therefore is traced manually[72] or constructed by computer systems yielding an interpolated 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

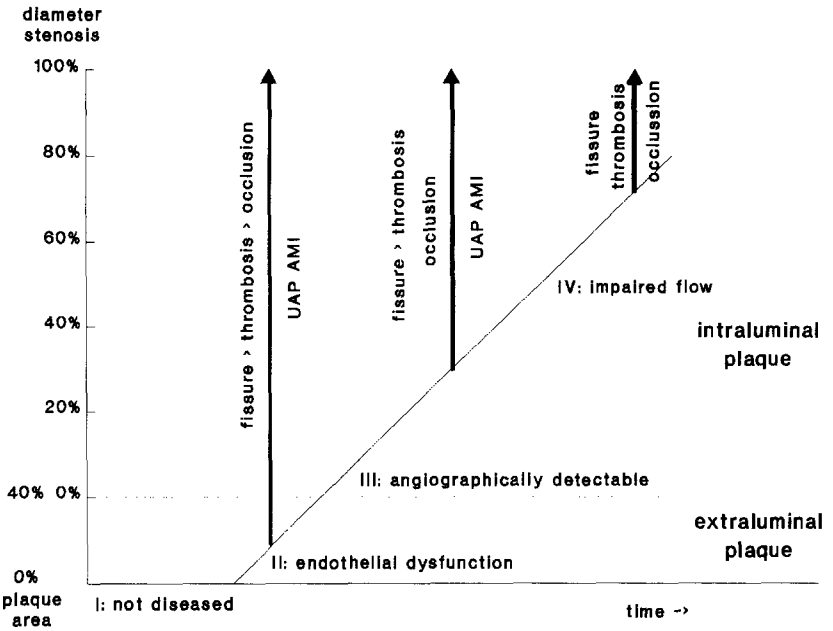


Fig 5. Illustration of the possible natural history of atherosclerotic plaque progression, plaque fissure, thrombosis, and clinical coronary events. Phase I: no atherosclerotic plaque is present, the endothelial function is intact, no thrombosis will occur. Phase II: an atherosclerotic plaque is present, 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

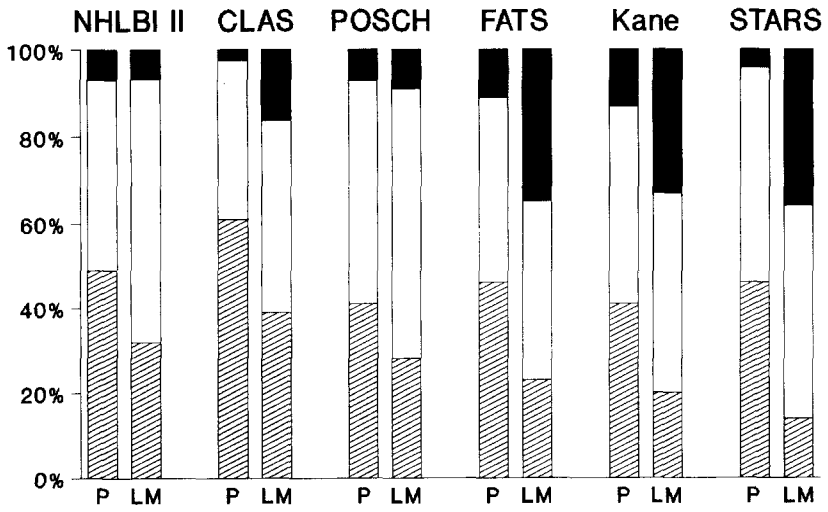


Fig 6. Changes in CAD in five coronary atherosclerosis trial with a lipid-modifying treatment. P, placebo; LM, lipid-modifying treatment; ▨, progression; □, stable or mixed; ■, regression.

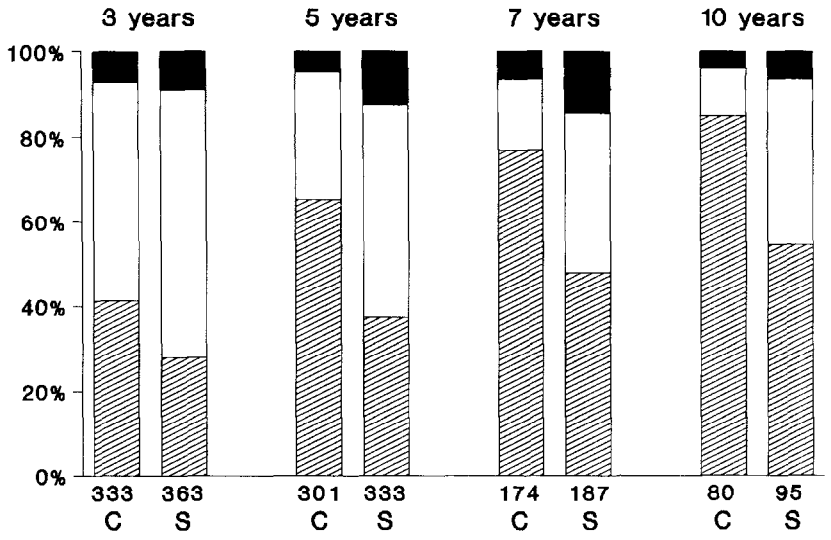


Fig 7. Changes over time in the POSCH trial. Coronary angiography was performed at 3, 5, 7, and 10 years after randomization. Numbers indicate the numbers of patients at each time interval for each treatment group. C, control group; S, partial ileal bypass surgery; ▨, progression; □, stable or mixed;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