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Clinical perspective

Coronary artery disease: prevention of progression and prevention of events

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In patients with coronary artery disease, progression of the disease and clinical events are related in a complex manner. At least two processes can be distinguished (Fig. 1). Endothelial dysfunction initiates gradual growth of plaques. This in turn leads to extraluminal plaques, and the subsequent development of angiographically detectable plaques, followed by impaired flow. At all stages of this development plaque fissuring and plaque rupture can occur, leading to thrombosis and further impairment of flow or coronary occlusion[1]. The development and fissuring of plaques are related to lipid content[2]. Accordingly, lipid modification has been proposed to stabilize plaques, to slow progression of plaque development, and to improve endothelial function[3]. Such intervention may be expected to result in both retardation of plaque development and reduction of clinical events.

Recent studies presented at the 1994 European Congress of Cardiology and American Heart Association Scientific Sessions, and published reports support his concept.

In particular, treatment with 'statins' (inhibitors of hydroxy-methylglutaryl coenzyme A — HMG-co-reductase) has been shown to significantly modify the lipid profile. This has included a marked reduction in low density lipoprotein (LDL) cholesterol and a modest increase in high density lipoprotein (HDL) cholesterol levels, with concomitant retardation of progression of coronary atheroma[4–7] and improved survival in patients with coronary artery disease[8]. In this paper the relationship between angiographic results and clinical outcome with cholesterol-lowering therapy will be discussed.

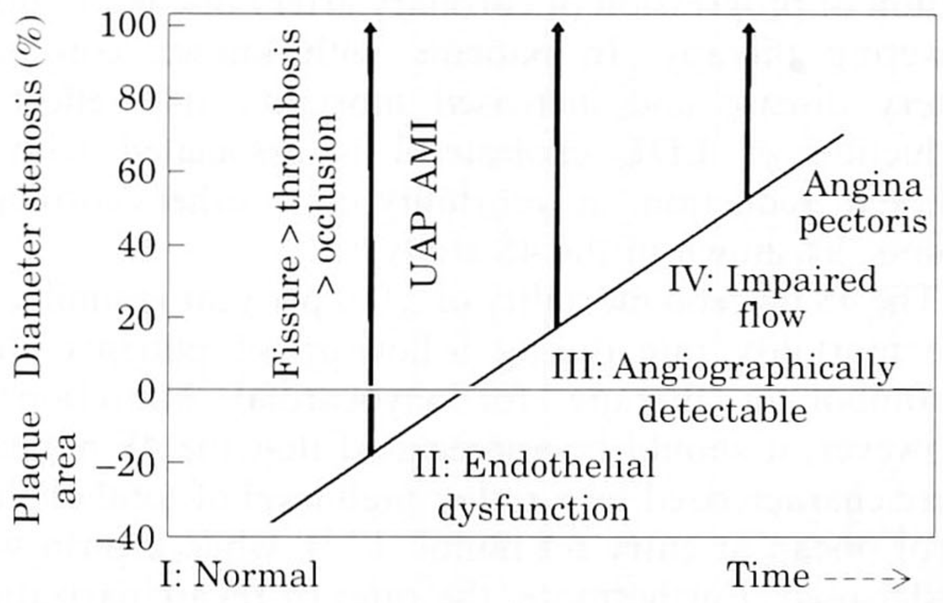

Figure 1 Schematic representation of the development of focal coronary artery disease; modified from[1]. In normal coronary segments (I) no atherosclerotic plaque is present, endothelial function is intact, no thrombosis will occur. Phase II is characterized by endothelial dysfunction and plaque development which does not encroach on the coronary lumen. Lesions are not angiographically detectable. Gradual development progresses to phase III: angiographically detectable lesions without, or with (phase IV) impaired flow. This may lead to (stable) angina pectoris. At all stages of the disease, plaque fissuring may occur leading to thrombosis and (in some cases) thrombotic coronary occlusion. This can result in the clinical syndromes of unstable angina pectoris (UAP) or acute myocardial infarction (AMI).

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Angiographic studies of progression/regression of coronary atheroma

The Multicentre Anti-Atheroma Study (MAAS) is a randomized double-blind trial of 381 patients with angiographically documented coronary artery disease[6]. In spite of dietary advice, no significant changes in lipids were observed in placebo patients during 4 years follow-up. Patients receiving simvastatin (20 mg daily) had a 31% reduction in LDL cholesterol and a 9% increase in HDL cholesterol. In placebo patients a gradual progression of coronary artery disease was observed by quantitative angiography, both in the per patient mean lumen diameter (average reduction 0·02 mm . year^{-1}) and in the minimum lumen diameter of coronary segments (average reduction 0·03 mm . year^{-1}). Changes after 4 years were approximately twice as large as those after 2 years. Patients on simvastatin showed a significantly smaller increase in the mean lumen diameter (difference vs placebo at 4 years 0·06 mm; 95% confidence interval 0·02 to 0·10) and less progression in the minimum lumen diameter (difference 0·08 mm; 0·03 to 0·14).

Overall, angiographic progression occurred less often in the simvastatin group (41 vs 54 patients) and regression was more frequent (33 vs 20 patients; overall $P=0·02$). In the REgression GRowth Evaluation Statin

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Study (REGRESS), presented at the 1994 European Congress of Cardiology, similar lipid changes were reported after pravastatin, while the angiographic differences between patients treated for 2 years with pravastatin vs placebo (653 patients) were very similar to the 2 year changes in MAAS.

These two large angiographic studies confirm and extend previous angiographic studies[1]. In Table 1, salient features of 14 angiographic studies of various modes of lipid-lowering therapy are summarized[4–7,9–18]. The interventions included strict dietary control, various lipid lowering drugs and ileal bypass surgery[9]. The angiograms were analysed either by visual comparison before and after treatment[9–11] or by quantitative analysis[4–7,12–18]. The number of segments analysed per patient varied and different criteria were applied to define progression or regression of coronary lesions. Nevertheless, the results of the studies were remarkably similar: 38% fewer patients showed progression and 84% more patients showed regression (Fig. 2). It should be appreciated, however, that in all studies most patients showed either no change or a mixed response, with some segments progressing and others regressing.

These angiographic studies had insufficient power to assess the effect of lipid lowering therapy on clinical events, but a reduction in cardiovascular events was observed in most studies. In particular, the Program on the Surgical Control of the Hyperlipidemias (POSCH) study showed a significant reduction in coronary events after ileal-bypass during 10 years of follow-up[11]. Furthermore, a reduction in cardiac events was reported in REGRESS after 2 years[7]. A combined analysis of all angiographic trials revealed a 22% reduction (95% confidence interval, 0–40%) in cardiac mortality and non-fatal myocardial infarction and a 34% reduction (22–44%) in all cardiac events during a 2 to 4 years follow-up (Fig. 3).

In summary, these angiographic studies, applying very different lipid interventions, consistently showed retardation of progression and modest regression of coronary artery disease, which was associated with a reduction in myocardial infarction and mortality at follow-up. The consistency among these trials indicates that this effect has indeed been achieved through lowering of LDL cholesterol, which was the common feature among the interventions studied.

Improved survival after cholesterol lowering therapy

The Scandinavian Simvastatin Survival Study (4S) reported improved survival with simvastatin (20 mg daily in 63% and 40 mg daily in 37% of patients) compared with placebo[8]. Four thousand four hundred and forty four patients with angina pectoris or previous myocardial infarction entered the trial with total serum cholesterol between 5·5 and 8·0 mmol . l^{-1}. Six year survival was 87·6% and 91·3% in the placebo and simvastatin groups, respectively. One hundred and eighty-nine coronary deaths were observed in the placebo group and 111 in the simvastatin group, without any increase in non-cardiovascular deaths with simvastatin (49 and 46 deaths respectively).

In addition, there was a reduction in non-fatal cardiac events, a lower rate of coronary surgery or angioplasty and a lower incidence of stroke in patients receiving simvastatin. The benefits of cholesterol lowering therapy were apparent in all patient subgroups. These results should be viewed in the context of other trials of lipid lowering therapy. Previous trials were reviewed by Smith *et al.* in 1993[19]. In this meta-analysis the survival difference after different modes of lipid lowering therapy was presented in relation to mortality in the placebo or reference groups. No benefit, and even a slight negative effect of lipid lowering interventions was observed in trials with a low mortality rate in the control group (<1% per year), while improved survival was apparent in patients with a 3% or greater yearly mortality risk. This important analysis illustrates that negative effects of certain interventions can outweigh the benefit of lipid lowering in low risk populations. This was particularly evident in previous trials using clofibrate. In contrast, the statins, with a more favourable safety profile may already be effective in patient groups with a lower level of risk. In 4S non-cardiovascular mortality was not excessive with simvastatin, and an overall reduction in mortality was apparent in this study, with a mortality rate of 2% per year in the placebo group.

Conclusions and recommendations

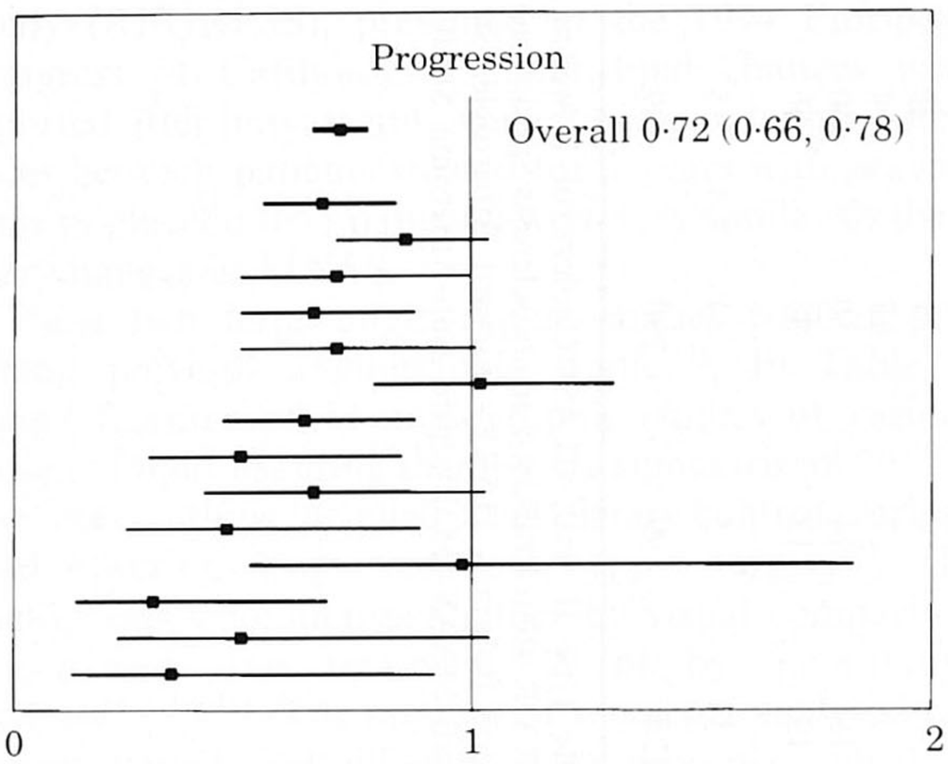
The angiographic studies consistently show retardation of progression of coronary artery disease on lipid lowering therapy. In patients with known coronary artery disease and increased mortality risk, effective reduction of LDL cholesterol is associated with a marked reduction in mortality and other coronary events, as shown in the 4S study.

The 4S placebo mortality of 2·0% per year is similar to the mortality rate during follow-up of patients after thrombolytic therapy for myocardial infarction[20]. However, it should be appreciated that the 4S patients were characterized by a rather high level of total cholesterol (mean at entry 6·8 mmol . l^{-1}), while aspirin was under-used. Furthermore, the rates of revascularization procedures was low in comparison with those in most western European countries. Thus it remains to be determined whether the 4S results can be reproduced in 'more average' post infarction patients. In this regard the CARE (Cholesterol and Recurrent Events) trial in 4200 patients in the U.S.A. will be of great interest. Treatment with statins will not be effective in patients with a restricted life expectancy, less than 5 or 6 years; elderly patients and those with severely impaired left ventricular function. Greatest therapeutic benefit may be expected in patients with intermediate mortality risk. In such patients the cost efficacy ratio will be most favourable. A complete cost-efficacy analysis of 4S, comparing costs of drug therapy in relation to avoidance or delay of coronary interventions and to life expectancy, is eagerly awaited.

Table 1 Selected baseline data and results of 14 angiographic studies of coronary atherosclerosis. For each study is Presented (from left to right) is the name of the study, the reference therapy, cholesterol gained by intervention, criteria for patient selection (focusing on lipid characteristics) mean age, mean change in LDL cholesterol, duration of follow-up, number of patients in the reference and intervention group, respectively, mortality or infarction in the reference and intervention groups respectively, and all cardiac events in the reference and intervention groups=data missing

Study	Reference	Intervention	Patient selection	Age (years)	LDL change	Follow-up (years)	Number of patients		Mortality or infarction		All cardiac events	
									Reference	Intervention	Reference	Intervention
NHLBI, 1984[9]	Placebo	Cholestyramine	Type II hyperlipaemia	46	−21%	5	72	71	12	8	12	8
CLAS, 1987[10]	Placebo	Colestipol/niacin	TC 4·8–9·1	54	−38	2	94	94	5	1	22	21
POSCH, 1990[11]	Usual	Partial ileal bypass	TC>5·7	51	−35	3	417	421	42	42	—	—
FATS, 1990[12]	Usual	Lovastatin/colestipol	Apolip.B>125 mg . dl^{-1}	47	−32	2·5	52	94	0	2	11	5
SCOR, 1990[13]	Placebo/resin	Colestipol/niacin/lovastatin	LDL>5·2	42	−27	2	49	48	1	0	1	0
STARS, 1992[14]	Usual	Cholestyramine	TC 6·0–10·0	51	−23	3	28	50	5	3	10	4
SCRIP, 1994[15]	Usual	Multiple risk reduction	Coronary disease	56	−26	4	155	145	13	6	34	20
HARP, 1994[16]	Placebo	Multiple drugs	TC 4·7–6·5	58	−41	2·5	40	39	1	2	4	4
MARS, 1993[4]	Placebo	Lovastatin	TC 4·9 − 7·6	58	−37	2	124	123	–	–	31	22
CCAIT, 1994[5]	Placebo	Lovastatin	TC 5·7–7·8	52	−27	2	166	165	7	7	18	14
MAAS, 1994[6]	Placebo	Simvastatin	TC 5·5–8·0	55	−32	4	188	193	16	14	50	40
REGRESS, 1994[7]	Placebo	Pravastatin	TC 4·0–8·0	56	−29	2	434	450	19	12	93	56
Lifestyle, 1990[17]	Usual	Lifestyle change	—	58	−3x	1	19	22	—	—	—	—
Heidelberg, 1992[18]	Usual	Lifestyle change	Angina	53	−1x	1	57	46	3	2	4	5
Total of 14 studies					−30		1895	1961	124	99	290	199

TC=total cholesterol; Apolip.B=apolipoprotein B; LDL=LDL cholesterol (mmol . l^{-1}); NHLBI=National Heart Long Blood Institute type II trial; CLAS=Cholesterol Lowering Atherosclerosis Study; POSCH=Program On the Surgical Control of the Hyperlipidemias; FATS=Familial Atherosclerosis Treatment Study; SCOR=San Francisco arteriosclerosis Specialized Center Of Research intervention trial; STARS=St Thomas' Atherosclerosis Regression Trial; SCRIP=Stanford Coronary Risk Intervention Program; HARP=Harvard Atherosclerosis Reversibility Project; MARS=Monitored Atherosclerosis Regression Study; CCAIT=Canadian Coronary Atherosclerosis Intervention Trial; MAAS=Multicentre Anti-Atheroma Study; REGRESS=REgression GRowth Evaluation Statin Study; Lifestyle=Lifestyle Heart Study; Heidelberg=University of Heidelberg Trial.



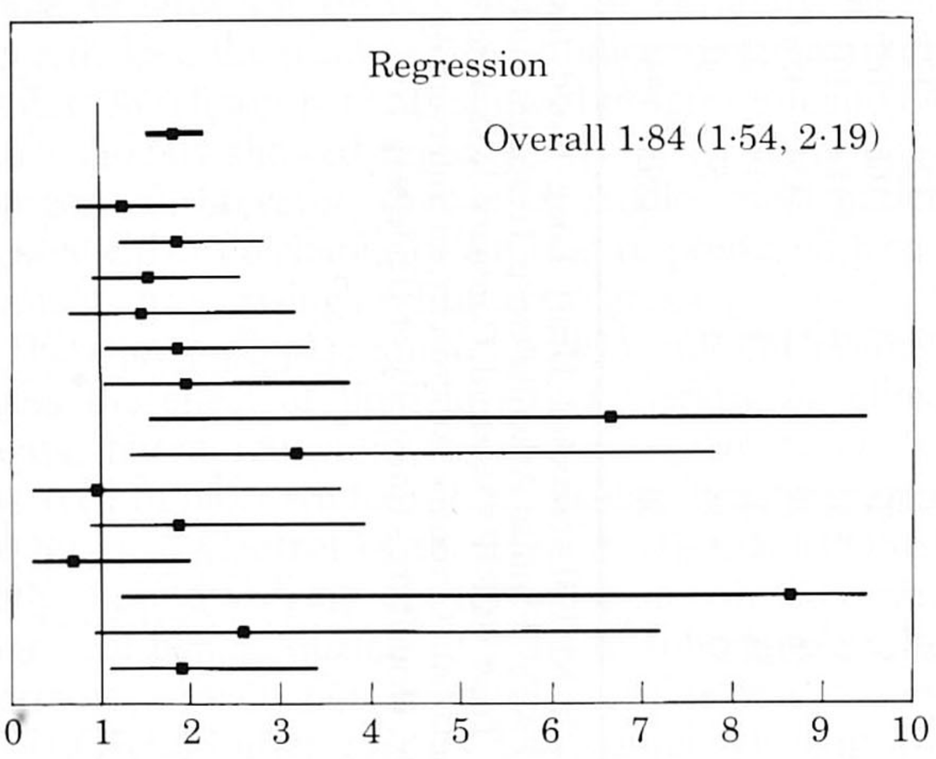


Figure 2 Progression and regression of coronary disease in 14 angiographic studies. Different regimens for lipid lowering were studied, and different criteria for progression and regression were applied. For each study, the rate ratio of progression or regression has been presented with 95% confidence intervals. The overall rate ratios with confidence intervals were computered using definitions as applied in the various studies. There is an overall 28% reduction of progression (rate ratio 0·72) and a 84% increase of regression (rate ratio 1·84) in the combined analysis. The 14 studies have been ordered according to number of patients enrolled (lowest at top), from bottom to top in each figure: Lifestyle[17]; SCOR[13]; STARS[14]; HARP[16]; Heidelberg[18]; NHLBI[9]; FATS[12]; CLAS[10]; SCRIP[15]; MARS[4]; CCAIT[5]; MAAS[6]; REGRESS[7]; POSCH[11].

The cholesterol level (whether total cholesterol or LDL cholesterol) was not a predictor of either events or therapeutic benefit, in either the MAAS study (angiographic progression) or in 4S (survival). Thus, as regards the range of cholesterol values in the patients studied (most patients were between 6·0 and 7·5 mmol . l^{-1}) the actual cholesterol level was apparently not a decisive factor, once significant atherosclerosis had become clinically manifest. Apparently, lowering LDL cholesterol concentration by one third, as in MAAS and 4S, is necessary and more important than the actual lipid levels on treatment.

Accordingly, current guidelines to advise very low LDL levels in every patient may not be correct. Additional studies of 4S and other databases are required to assess whether the lipid response to therapy with a statin drug can be used to distinguish between patients who do and those who are not likely to benefit from therapy. This may allow a more restricted use of statin therapy in selected patients who demonstrate a favourable lipid response. Preliminary, unpublished data from 4S suggest that simvastatin therapy was most effective in patients with a significantly reduced Apo-lipoprotein-B. If this should be confirmed in other analysis, treatment might be discontinued in patients without such a response.

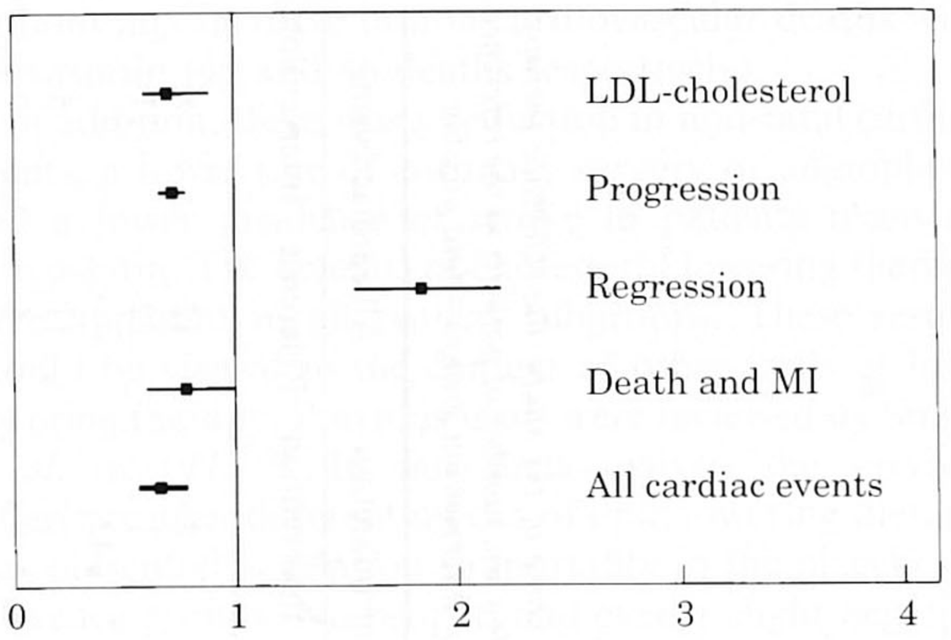


Figure 3 The combined analysis of the 14 angiographic studies of coronary atherosclerosis shows a consistent reduction of LDL cholesterol (mean 30%, range 11–41%) with reduction of progression of coronary disease, an increase of regression (Fig. 2), a reduction of cardiac mortality and non-fatal myocardial infarction (risk ratio 0·78, 95% confidence interval, 0·60–1·00) and reduction of all cardiac events (risk ratio 0·66, 0·56–0·78).

Guidelines for prescription of any drug to prevent or delay future clinical events should consider cost-efficacy. At present, effective lipid modification is by strict dietary control[17] and statins can be recommended in all patients with coronary disease, up to approximately 70 years of age, who are at increased risk for new events (>7% per year) or mortality (>2% per year). Before initiating such therapy other measures should be taken, including stopping smoking, reduction of overweight and treatment of hypertension[21]. Intensive cholesterol lowering therapy is rarely justified in asymptomatic subjects, without evidence of coronary artery disease, since the risk level in those subjects will be low, reducing cost-efficacy of treatment. Existing guidelines for primary and secondary prevention of coronary artery disease should be reviewed to ensure that drug treatment of lipid 'disorders' is prescribed predominantly to patients with known coronary artery disease.

References

[1] Vos J, Feyter PJ de, Simoons ML, Tijssen JGP, Deckers JW. Retardation and arrest of progression or regression of coronary artery disease: a review. Progr Cardiovasc Dis 1993; 35: 435–54.

[2] Small DM. Progression and regression of atherosclerotic lesions. Insights from lipid physician biochemistry. Arteriosclerosis 1988; 8: 103–29.
[3] Harrison DG, Armstrong ML, Freiman PC *et al.* Restoration of endothelium-dependent relaxation by dietary treatment of atherosclerosis. J Clin Invest 1987; 80: 1808–11.
[4] Blankenhorn DH, Azen SP, Kramsch DM *et al.* Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerotic Regression Study (MARS). Ann Intern Med 1993; 119: 969–76.
[5] Waters D, Higginson L, Gladstone P *et al.* for the CCAIT study group. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. Circulation 1994; 89: 959–68.
[6] MAAS Investigators. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). Lancet 1994; 344: 633–8.
[7] REGRESS trial. Presented at the Joint European and World Congress of Cardiology, Berlin 1994.
[8] Scandinavian simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin Survival Study (4S). Lancet 1994; 344: 1383–9.
[9] Brensike JF, Levy RI, Kelsey SF *et al.* Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI Type II Coronary Intervention Study. Circulation 1984; 69: 313–24.
[10] Blankenhorn DH, Nessim SA, Johnson RL *et al.* Beneficial effects of combined colestipol–niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA 1987; 257: 3233–40.
[11] Buchwald H, Varco RL, Matts JP *et al.* and the POSCH Group. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. N Engl J Med 1990; 323: 946–55.
[12] Brown G, Alberts JJ, Fischer LD *et al.* Regression of coronary artery disease as a result of intensive lipid lowering therapy in men with high levels of apolipoprotein B. N Engl J Med 1990; 323: 1289–98.
[13] Kane JP, Malloy MJ, Ports TA *et al.* Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimes. JAMA 1990; 264: 3007–12.
[14] Watts GF, Lewis B, Brunt JNH *et al.* Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St. Thomas' atherosclerosis regression study (STARS). Lancet 1992; 339: 563–9.
[15] Haskell WL, Alderman EL, Fair JM *et al.* Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The Stanford Coronary Risk Intervention Project (SCRIP). Circulation 1994; 89: 975–90.
[16] Sacks FM, Pasternak RC, Gibson CM *et al.* for the Harvard Atherosclerosis reversibility project (HARP) Group. Effect on coronary atherosclerosis of decrease in plasma cholesterol concentrations in normocholesterolaemic patients. Lancet 1994; 34: 1182–6.
[17] Ornish D, Brown SE, Schwerwitz LW *et al.* Can lifestyle changes reverse coronary heart disease? Lancet 1990; 336: 129–33.
[18] Schuler G, Hambrecht R, Schlierf G *et al.* Regular physical exercise and low-fat diet. Effects on progression of coronary disease. Circulation 1992; 86: 1–11.
[19] Smith GD, Song F, Sheldon TA. Cholesterol lowering and mortality: the importance of considering initial level of risk. Br Med J 1993; 306: 1367–73.
[20] Lenderink T, Simoons ML, Es GA van, Werf F van de, Verstraete M, for the European Cooperative Study Group. Benefit of thrombolytic therapy is sustained throughout five years, and is related to TIMI perfusion grade 3 but not grade 2 flow at discharge. Circulation (in press).
[21] Pyörälä K, Backer G de, Graham I, Poole-Wilson P, Wood D, on behalf of the Task Force. Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Eur Heart J 1994; 15: 1300–31.