

REVIEW

Angiographic trials of lipid-lowering therapy: end of an era?

Gilbert R Thompson

Glossary

CCAIT = Canadian Coronary Atherosclerosis Intervention Trial, CLAS = Cholesterol Lowering Atherosclerosis Study, FATS = Familial Atherosclerosis Treatment Study, HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A, Lp(a) = lipoprotein(a), MAAS = Multicentre Anti-Atheroma Study, MARS = Monitored Atherosclerosis Regression Study, NHLBI = National Heart, Lung and Blood Institute, POSCH = Program on Surgical Control of Hyperlipidaemia, SCRIP = Stamford Coronary Risk Intervention Project, STARS = St Thomas' Atherosclerosis Regression Study, UCSF SCOR = University of California San Francisco Specialised Center of Research.

Research into the secondary prevention of coronary heart disease (CHD) has been dominated during the past decade by angiographic studies of the effects of lipid lowering therapy, often termed "regression" trials. These had the advantages of needing a smaller number of patients and being of shorter duration than clinical endpoint trials, which meant they cost less. The results suggested that regression of coronary artery disease (CAD) was in fact a much less common outcome of intervention than arrest or slowing of the rate of progression. Yet despite the infrequency of angiographic regression there was a considerable decrease in clinical events in several trials.

Is anything to be gained from undertaking further angiographic trials? Although there may be justification for doing so to answer certain specific questions, the current trend of opinion is that the era of angiographic trials is now over, though clinical endpoint trials are still needed. This review attempts to summarise what has been learned from a dozen or so regression trials during the past 10 years.

Trial design

Table 1 lists the chief characteristics of the major angiographic trials of lipid lowering therapy in hyperlipidaemic individuals with coronary artery disease (CAD) which were published between 1984 and 1994.¹⁻¹⁴ These studies ranged from less than 50 to over 800 subjects and lasted from 1 to 10 years. Most of them involved a randomised comparison of diet alone and diet combined with treatment with lipid lowering drugs. Other forms

of treatment used instead of or in addition to drugs included partial ileal bypass,⁵ exercise,^{8 10 13} and anti-stress measures.⁸ In the earlier trials the anion-exchange resins cholestyramine and colestipol were given either alone^{1 2 9} or combined with nicotinic acid or lovastatin (an HMG CoA reductase inhibitor), or both.^{3 6 7} More recent trials have used monotherapy with HMG CoA reductase inhibitors, either lovastatin^{11 12} or simvastatin.¹⁴ Another recent trend has been the increasing use of quantitative coronary angiography (QCA) rather than visual assessment to measure lesion change. Despite these and other differences, some useful insights into CAD may be gleaned from analysing pooled data from the more than 2700 patients who participated in these trials.

Patients' characteristics

The average age at entry ranged from 41⁷ to 60,⁸ with most patients being in their fifties. Five trials were restricted to men,^{1 3 6 9 10} in the remainder the percentage of women was always less than 20% except in the UCSF SCOR trial,⁷ where they were in the majority. Previous coronary artery bypass grafting (CABG) and angioplasty were permitted in several trials,^{3 5 13} indeed prior CABG was an inclusion criterion for CLAS.³ In MAAS previous angioplasty (but not CABG) was permitted but treated segments were excluded from angiographic analysis.¹⁴ Baseline serum concentrations of total and low density lipoprotein (LDL) cholesterol were highest in the trials which involved patients with familial hypercholesterolaemia (FH)^{1 2 7}; in the UCSF

Table 1 Randomised and controlled lipid lowering regression trials (1984-1994)

Trial	n	Years	Treatment
NHLBI	116	5	Cholestyramine (24 g)
CLAS I	162	2	Colestipol (30 g) + Nicotinic acid (4 g)
II	(103)	(4)	
POSCH	838	9.7	Partial ileal bypass
FATS	120	2.5	(a) Colestipol (30 g) + lovastatin (40 mg) (b) Colestipol (30 g) + nicotinic acid (4 g)
UCSF SCOR	72	2.2	Colestipol (15-30 g) + nicotinic acid (1.5-7.5 g) ± lovastatin (40-60 mg)
Life-Style	48	1	Diet, exercise, and anti-stress
STARS	90	3.25	(a) Diet (b) Diet + cholestyramine (16 g)
Heidelberg	113	1	Diet and exercise
MARS	270	2	Diet + lovastatin (80 mg)
CCAIT	331	2	Diet + lovastatin (37 mg (mean))
SCRIP	300	4	Diet, exercise and lipid lowering drugs
MAAS	381	4	Diet + simvastatin (20 mg)

Lipoprotein Team,
MRC Clinical
Sciences Centre,
Royal Postgraduate
Medical School,
Hammersmith
Hospital, Du Cane
Road, London
W12 0NN
G R Thompson

Table 2 Weighted mean values of serum lipids (mmol/l) in randomised angiographic regression trials (1984–1994)

Lipid	Control group (n=1334)	Treatment group (n=1403)	Difference between groups (%)
Total cholesterol	6.28	4.98	-21
LDL cholesterol	4.36	3.02	-31
HDL cholesterol	1.11	1.17	+5
Triglyceride	2.01	1.96	-2.5

SCOR trial values averaged 9.6 and 7.2 mmol/l respectively. In contrast concentrations were lowest in those trials that used a multifactorial approach,^{8,10,13} where total and LDL cholesterol values averaged approximately 6 and 4 mmol/l at entry.

Effects of treatment on serum lipids

Table 2 shows the weighted mean values of serum lipids in the control and treatment groups during the 12 trials. The most pronounced difference was in LDL cholesterol, which averaged 4.36 mmol/l in the controls compared with 3.02 mmol/l in the treatment groups, a reduction of 31%. High density lipoprotein (HDL) cholesterol was 5% higher in treated patients than controls, this trend being most marked in those who were taking nicotinic acid, whereas the decrease in LDL cholesterol was greatest in patients treated with HMG CoA reductase inhibitors.

Overall the reduction in serum triglycerides in treated patients averaged only 2.5%. Although reductions of 20% or more were seen in some trials^{6,7,9} especially in patients taking nicotinic acid, these were offset by increases in other trials, notably the very large POSCH study.⁵ Partial ileal bypass, like anion-exchange resins, is known to raise triglycerides. If the POSCH data are excluded, the decrease in serum triglyceride in the remaining 11 trials averaged 12.9%.

Lp(a) values were reported in only four of

Table 3 Frequency of progression and regression in patients in 12 angiographic trials (1984–1994)

Group (n)	Progression: patients (%)	Regression: patients (%)
Controls (1216)	536 (44)	108 (9)
Treatment (1293)	381 (29)	236 (18)

Table 4 Changes in quantitative coronary angiographic variables in FATS, STARS, Heidelberg, MARS, CCAIT, SCRIP, and MAAS (weighted mean and SD)

Patient group (n)	Δ Minimal lumen diameter (mm)	Δ Diameter stenosis (%)
Control (674)	-0.09 (0.23)	2.60 (5.80)
Intervention (718)	-0.02 (0.22)	0.69 (7.23)
P	<0.001	<0.001

the trials.^{6,13–15} Values were similar in the control and intervention groups except for a decrease in the nicotinic acid (plus colestipol) subgroup in FATS,⁶ reflecting yet another action of this ubiquitous compound.

Angiographic findings

In several trials most lesions initially showed < 50% diameter stenosis, including 82% of lesions in FATS⁶ and STARS,⁹ and over 75% in CCAIT.¹² This may have had a bearing on the outcome because the response to treatment seems greatest in lesions > 50% stenosed at baseline, as discussed below. The criteria used to define angiographic change varied considerably but in all 12 trials patients were categorised as progressors, regressors, mixed responders or as showing no change in CAD. More patients showed progression than regression but the effect of treatment was to lessen this trend (table 3). Overall, treatment reduced the chances of progression by one third and doubled the chances of regression (fig 1).

Seven trials^{6,9,10–14} used quantitative coronary angiography to measure changes in percentage diameter stenosis and minimal lumen diameter of lesions. On average lesions worsened to a lesser extent in treated patients than in the controls (table 4), but the magnitude of the changes was relatively small. Beneficial effects of treatment on lesions seemed to be greater in females than males.^{7,13}

Figure 2 shows the relation between the baseline severity of lesions and the extent and direction of subsequent angiographic change in five of the trials that used quantitative coronary angiography. It is apparent that milder lesions usually progress, albeit to a lesser extent in treated patients than in controls. The only trial in which treatment actually decreased the percentage diameter stenosis of such lesions was MAAS,¹⁴ and then to only a slight extent. In contrast, severe lesions have less of a tendency to progress than milder lesions in control subjects and improve to a much greater extent than milder lesions in treated patients. Quantitative angiographic changes in STARS⁹ were disproportionately much greater than in the other trials, for reasons that are unclear, and have been omitted from

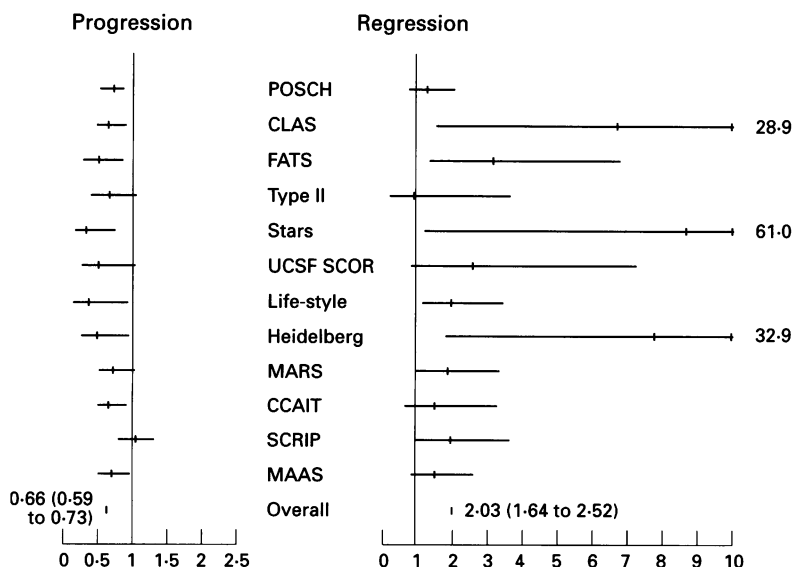


Figure 1 Relative risk of progression and regression (95% confidence interval) occurring in lipid-lowering angiographic trials (updated from Vos, et al, *Progress in Cardiovascular Diseases* 1993;35:435–54).

Figure 2 Lesion change in control and treatment groups in five trials using quantitative coronary angiography according to baseline severity of lesions. C/N and C/L indicate the colestipol/nicotinic acid and colestipol/lovastatin groups in FATS. (adapted from Blankenhorn and Hodis, *Arteriosclerosis and Thrombosis* 1994;14:177-92).

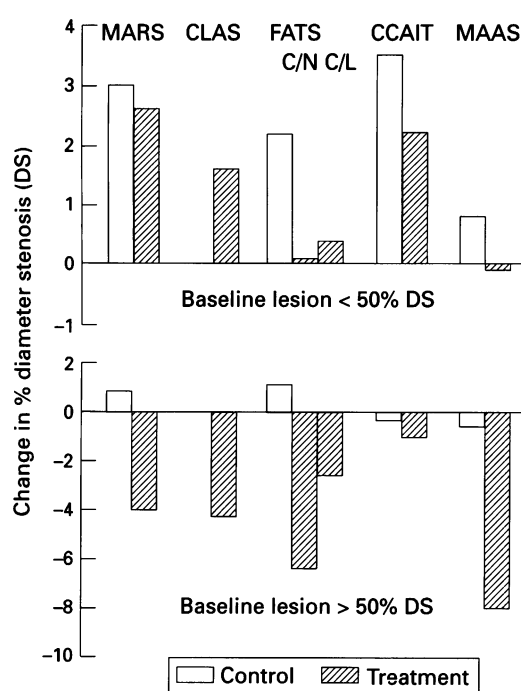


fig 2 on this account. The relevant data from the control group in CLAS are also lacking because they have not yet been published.

The influence of treatment on the development of new lesions was examined in some of the trials. In CLAS II four years of treatment with colestipol and nicotinic acid significantly reduced the frequency of new lesions in vein grafts but not in native vessels.⁴ However, in both CCAIT¹² and MAAS,¹⁴ but not in MARS,¹¹ the rate of appearance of coronary artery lesions was significantly reduced by treatment with HMG CoA reductase inhibitors.

Lipid correlates of angiographic change

There are several subgroup analyses of the relation between lipid abnormalities and lesion change. Thus in the NHLBI Type II intervention trial concentrations of intermediate density lipoprotein (IDL or S_{112-20}) decreased to a significantly greater extent in patients whose lesions did not progress than in those in whom they did.¹⁶ In STARS a univariate correlation between IDL and disease severity was also seen, though this was lost when correlations with small, dense LDL (LDL_s) and HDL_3 were considered.¹⁷ And although IDL was not specifically measured in MARS it undoubtedly contributed to the triglyceride-rich lipoproteins that were identified in that study as correlating with progression of mild lesions.¹⁸ In contrast, progression of more severe lesions correlated best with cholesterol-rich lipoprotein markers such as LDL cholesterol concentration and the LDL:HDL cholesterol ratio.

A recent meta-analysis by Waters suggested that changes in percentage diameter stenosis of lesions correlated better with percentage changes in LDL cholesterol than with the prevailing concentration of LDL cholesterol during diet or drug treatment.¹⁹ In

FATS the percentage change in apoB (another marker of LDL) was the strongest independent correlate of lesion change.⁵ In that trial Lp(a) was also predictive of progression but only in those patients whose LDL cholesterol decreased by less than 10% during the trial.²⁰ There was no relation between baseline concentrations of Lp(a) and disease progression in the Heidelberg trial¹⁵ nor in SCRIP,¹³ both trials being characterised by relatively low LDL concentrations at entry, as noted previously.

Clinical implications

There was a significant reduction in cardiovascular events and the need for re-vascularisation procedures in treated patients in POSCH, FATS, and STARS. This was not seen in the remainder of the trials, as might be expected from the small number of patients involved. Brown *et al* discussed the relation between clinical events and plaque size and concluded that mild to moderate lesions were usually the culprits and were more likely to be responsive to lipid-lowering treatment than severe (>70% stenosed) lesions.²¹ They also claimed that beneficial effects of treatment on lesions were most pronounced in patients with a low pre-treatment LDL cholesterol (<4.1 mmol/l).²² However, a recent study suggests that lipid-lowering treatment is of no benefit if the LDL cholesterol is less than 3.6 mmol/l at baseline.²³

These findings imply that consideration of lipid-lowering treatment in patients with CAD should not be restricted solely to those with severe hyperlipidaemia or those with advanced disease. Furthermore, treatment should be aimed at reducing not only LDL but also triglycerides, as well as raising HDL. Currently, these objectives may often be achieved by monotherapy with simvastatin or pravastatin, which can result in normalisation of triglycerides and HDL cholesterol as well as radical reduction of LDL cholesterol. In some instances, however, it may be necessary to combine an HMG CoA reductase inhibitor with either nicotinic acid or a fibric acid derivative. On the basis of existing evidence there seems no need to lower Lp(a) as long as LDL cholesterol is reduced to ≤ 3.4 mmol/l.²⁴ This being so, it may prove easier to combine one of the statins with bezafibrate²⁵ or fenofibrate rather than nicotinic acid, because nicotinic acid is poorly tolerated. None the less it remains to be shown that fibrates are as effective as adjuvants as is nicotinic acid in retarding the progression of CAD.

Scandinavian simvastatin survival study

The recently published results of the Scandinavian Simvastatin Survival Study (4S) provide impressive confirmation that effective treatment of hypercholesterolaemia can reduce both cardiovascular events and total mortality in patients with coronary heart disease (CHD).²⁶ In this trial a total of 4444

Table 5 Mortality data from the Scandinavian Simvastatin Survival Study (4S), 1994

Deaths	Placebo (n=2223) (%)	Simvastatin (n=2221) (%)
All	256 (11.5)	182 (8.2)*
Cardiovascular	207 (9.3)	136 (6.1)
Non-cardiovascular	49 (2.2)	46 (2.1)

*Relative risk (95% CI) = 0.70 (0.58 to 0.85), P = 0.0003.

patients aged 35 to 70 with angina or post MI, and with serum cholesterol 5.5 to 8 mmol/l and triglyceride less than 2.5 mmol/l after a period of diet treatment, were randomised to receive simvastatin or placebo. More than 80% were men and a similar proportion had a previous MI; less than 10%, however, had undergone myocardial revascularisation.

Simvastatin dosage was aimed at maintaining the serum cholesterol in the range 3.0 to 5.2 mmol/l. Most patients achieved this goal on 20 mg/day, but dosage was increased to 40 mg/day in 37% of patients by the end of the first six months. Over the course of the study simvastatin lowered total cholesterol by 25% from 6.8 mmol/l, LDL cholesterol by 35% from 4.9 mmol/l, triglyceride by 10% from 1.5 mmol/l, and raised HDL cholesterol by 8% from 1.2 mmol/l.

Median duration of treatment was 5.4 years, after which the trial was stopped because of a 30% reduction in overall mortality (P = 0.0003). This was entirely the result of a 42% reduction in mortality from CHD (P < 0.00001): there were no changes in non-cardiovascular causes of death, including cancer and trauma (table 5). The beneficial effect of simvastatin on total mortality emerged after about 1.5 years.

In addition to its effects on mortality, simvastatin significantly reduced the occurrence of major coronary events (353 v 502 with placebo; P < 0.00001), and the need for coronary revascularisation procedures (252 v 383; P < 0.00001). Also, it significantly reduced the number of cerebrovascular events without any increase in cerebral haemorrhage, even though 26% of the patients had hypertension.

The reduction in LDL cholesterol by simvastatin in the 4S resulted in a mean concentration of 3.2 mmol/l, similar to the mean of 3.0 mmol/l in the treatment groups of the 12 regression trials (table 2), which resulted in significantly less progression of coronary disease on angiography. Taken together the findings of these two types of study suggest that a 30–35% reduction of LDL cholesterol by simvastatin leads to changes in atheromatous lesions that render them less likely to cause both fatal and non-fatal clinical events. The nature of the changes which render such lesions less unstable has already been discussed in the *British Heart Journal*.²⁷

Conclusions

Though much has been learned from angiographic trials of lipid lowering treatment dur-

ing the past 10 years any further trials of this type should be restricted to answering specific rather than general questions about the effects of lipid lowering on atherosclerosis, such as the value of reducing the concentration of Lp(a). In contrast, there is still a need for further end point trials, such as the 4S, because these provide vital information concerning the effects of lipid lowering on clinical events and total mortality. Acceptance of the findings of the 4S has important implications for the role of statins in the management of mild to moderately hypercholesterolaemic patients with CHD but leaves unanswered questions concerning the safety and efficacy of other drugs such as the newer fibrates, whether given alone or in combination with one of the statins. For the present, however, simvastatin should probably be used as routinely as aspirin in patients with CHD whose serum cholesterol remains above 5.5 mmol/l despite diet, since its use could be expected to prevent four out of the nine deaths that would otherwise occur.²⁶

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