responded to the RCGP honorary secretary's call for informed comment last summer. Anyone who feels that they have an important contribution to make to the 'task of the new general practitioner' should send evidence soon to the chairman of the education network at Princes Gate, London, or to the chairman of the joint Welsh Council/Welsh GMSC working group, at the address below. The jury is still out on what is professionally realistic for the new general practitioner in the networking nineties and beyond: the time has come to reconcile the political agenda with professional realism and responsibility.

NIGEL STOTT
Professor of general practice,
University of Wales College of Medicine

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Address for correspondence

Professor N C H Stott, Department of General Practice, University of Wales College of Medicine, Health Centre, Maelfa, Llanedeyrn, Cardiff CF3 7PN.

Does lipid-lowering therapy promote regression of coronary atheroma?

LIPID-LOWERING therapy in patients with high cholesterol levels has been shown to reduce their risk of death from coronary heart disease.[1] Lowering elevated cholesterol levels might therefore be expected to slow down the rate of atheroma progression, but should it also be expected to promote regression? Direct pathological evidence of atheroma regression has been observed in the coronary arteries of animals,[2] but these results cannot necessarily be extrapolated to the human situation, particularly in view of the strictly controlled conditions used in animal experiments. How good is the evidence that lipid-lowering therapy in humans can produce atheroma regression, or is a slowing of disease progression the best that can be achieved? We have conducted a meta-analysis of all randomized controlled trials of lipid-lowering therapy on coronary atherosclerosis to evaluate the evidence for regression in humans with particular reference to the magnitude of any changes in disease and potential problems such as methodological bias, measurement variability and other pathological processes which might lead to an appearance of arterial widening.

Since 1985, the effect of lipid-lowering therapy on underlying coronary atherosclerosis has been reported in six randomized controlled trials.[3-8] Five of these were carried out in the United States of America: the National Heart Lung and Blood Institute (NHLBI) type II coronary intervention study,[3] the cholesterol lowering atherosclerosis study (CLAS),[4] the program on the surgical control of the hyperlipidaemias (POSCH),[5] the familial atherosclerosis treatment study (FATS),[6] and the University of California San Francisco intervention study (UCSF).[7] Only one randomized controlled trial has been performed in the United Kingdom: the St Thomas' atherosclerosis regression study (STARS).[8]

The study methods have varied considerably between the trials. Each study included subjects with hyperlipidaemia and angiographic evidence of disease, but otherwise the clinical groups were quite different. For example, CLAS was restricted to subjects with previous coronary artery bypass grafting,[4] the POSCH study to those who had suffered a myocardial infarction,[5] and STARS to those with angina;[8] women were not included in three of the studies.[4,6,8] The treatments comprised mainly lipid-lowering drugs (either cholestyramine,[3,8] or colestipol combined with niacin[4,6,7] or lovastatin,[6,7] an HMG-CoA reductase inhibitor), but also included partial ileal bypass in the POSCH study,[5] and a dietary regimen in STARS.[8] The duration of follow up ranged from two[6,7] to 10 years.[5] Each study used angiography to estimate the degree of coronary artery disease before and after treatment, combined, in the more recent trials, with a computerized technique to define the amount of atheroma.[6-8] As in most intervention trials there were several methodological problems, particularly selection bias in those studies which recruited only individuals who demonstrated a suitable response to drug therapy,[4,8] together with the incomplete collection of data from around one quarter of subjects entered into each trial. In addition, not all trials were double blind,[4,7,8] and some participants also consumed other drugs,[4,6,7] particularly aspirin which may reduce the progression of plaque by inhibiting platelet function.[9]

Despite the use of different criteria for patient selection, and the varying treatment regimens, the trials consistently showed a significant slowing of disease progression in treated subjects compared with controls. Regression of atheroma was also demonstrated in a minority of patients, between 6%[5] and 39%[6] of those receiving treatment. Analysis of the results in terms of severity of the initial stenoses showed more regression occurring in advanced plaque (greater than 50% reduction in luminal diameter), than in less severe disease.[3,7,8] This might have been expected, as advanced plaque generally has a substantial cholesterol content which could be mobilized by lipid-lowering treatment. In the POSCH study, which examined the relationship between angiographic change and subsequent clinical events, a significant association was found between definite progression of

disease on angiogram and a higher subsequent mortality rate.[10]

The proportion of subjects showing regression in the treatment groups was strongly related to the degree of cholesterol reduction: few subjects exhibited regression when the drop in serum cholesterol level was less than 25%.[3,5] An exception was the dietary intervention group in STARS, in which 28% of subjects showed regression despite a mean fall in serum cholesterol level of only 14%.[8] However, this may have been an exceptional finding, because in other studies where control subjects were advised to follow a lipid-lowering diet, the resultant drop in cholesterol level, and the proportion showing regression, was much smaller than with the STARS diet. The greatest reduction in cholesterol level, and hence most regression, occurred in subjects treated with colestipol combined with lovastatin[6,7] or with cholestyramine (STARS).[8] Cholestyramine was also used in the NHLBI study,[3] at a larger dose than in STARS, but surprisingly the drop in cholesterol level was much smaller.

A potential drawback of these studies is their reliance upon angiography to detect change in atheroma, a technique known to be subject to considerable observer variability.[11] Whenever appreciable variability is present, any measurement may differ considerably from the true value, making it possible for a high estimate to occur on an initial reading, followed by a lower estimate on a second occasion, even if no real change has occurred. Therefore, some of the apparent regression demonstrated in the lipid-lowering trials may simply have been due to measurement variability, when the true situation could have been either no change or slight progression. In each study, however, observer variability was minimized by the use of consensus panels[3-5] or computerized methods.[6-8] Studies using computerized angiography detected more regression than those using consensus panels, possibly because greater variability in panel readings was masking true differences in the degree of atheroma. Nevertheless, variability will also be associated with the procedure itself, rather than with the reading of the results, and this remains unknown and difficult to quantify.

In addition to the problems of measurement variability, several pathological mechanisms may lead to an appearance of arterial widening on angiography.[12,13] 'Pseudoregression' may result from lysis or retraction of superimposed or mural thrombus, relaxation of arterial vasospasm, arterial dilation, or plaque ulceration.[14] The pathological basis of true atheroma regression is unclear in human subjects, but in animals shrinkage of plaque has been observed secondary to depletion of lipids, reduction in cell numbers, and decrease in extracellular material.[12] The removal of lipid is thought to be associated with an increase in high density lipoprotein (HDL)-cholesterol,[12] but in the lipid-lowering trials there was no correlation between HDL-cholesterol levels and regression. Indeed, in STARS 33% of treated subjects demonstrated regression, despite a small decrease in HDL-cholesterol levels.[8]

Lipid-lowering therapy has therefore consistently produced an angiographic improvement in coronary artery disease, but it is impossible to be certain that this was true shrinkage of plaque, or that the results were not biased by the variability of the technique. Regression of coronary atheroma was most likely to occur in more advanced plaque, and in those subjects who had substantially reduced cholesterol levels. Treatment of asymptomatic patients with elevated cholesterol levels in general practice may not produce any substantial regression of atheroma, although the rate of atheroma formation should decline.

G C LENG
Clinical research fellow
F G R FOWKES
Director and reader, Wolfson Unit for the Prevention of Peripheral Vascular Diseases, University of Edinburgh

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Address for correspondence
Dr G C Leng, Wolfson Unit for the Prevention of Peripheral Vascular Diseases, Department of Public Health Sciences, University of Edinburgh, Edinburgh EH8 9AG.