Paradise regained: insights into coronary heart disease prevention from recent clinical trials and basic research

ABSTRACT — Many of the uncertainties regarding the place of lipid lowering in the prevention of coronary heart disease have recently been resolved. Some of the newer findings are reviewed, and the scope for a revised clinical approach examined. The results of trials of lipid lowering, based on clinical end-points and particularly on angiographic end-points, and their meta-analyses are discussed. The close relation between coronary-angiographic and clinical outcomes is reviewed in relation to recent advances in understanding of the underlying arterial pathology, and possible underlying mechanisms are proposed. The variables predictive of progression of coronary artery disease, including nutrient intake, are examined. The management of hyperlipidaemia requires that treatment and therapeutic goals are consonant with the patient's cardiovascular risk; for this purpose, clinical and biochemical assessment of risk may be enhanced by angiographic and non-invasive methods to detect potentially-infarctogenic atherosclerotic lesions.

For 25 years the status of lipid-lowering therapy in clinical practice has been famously controversial. Recent findings from many disciplines have done much to illuminate the subject, and it is timely to review the resultant clarification.

In the debates during most of this period, the proposition that cholesterol lowering is a valuable aspect of a strategy to reduce the incidence of coronary heart disease (CHD) rested chiefly on epidemiology and on clinical trials of limited power. Ranged against these has been a succession of different opposing positions. An early but persistent view was that high plasma cholesterol levels were merely an association of atherosclerotic CHD, not a cause. This became untenable in the light of ever more powerful epidemiological studies, experiments on primate models showing atherosclerosis regression, and further affirmative clinical trials. In its place, it was argued that CHD mortality was not significantly reduced in the cholesteryl-lowering trials then available; an ancillary view was that any such reduction was too small to be cost-effective. More recently, there was concern, justified in part by the data then available, that cholesterol lowering did not significantly lessen total mortality; this was attributed, with some initial support from epidemiology and clinical trials, to an increase in non-cardiovascular deaths. At first, low cholesterol levels were thought to increase cancer deaths, but as this became less plausible, attention was directed to depression, suicide and accident proneness.

Quite recently, concordant data from several sources have resolved most of these uncertainties. This paper reviews some of these newer findings, particularly from angiographic trials of lipid lowering and from the growing understanding of the underlying arterial pathology, with a view to resolving outstanding controversies concerning the benefits and safety of cholesterol lowering. It also suggests a clinical approach to lipid-lowering therapy in which the assessment of patients is enhanced by arterial imaging.

Clinical trials of lipid lowering

Coronary heart disease event trials and their meta-analyses

More than 30 controlled trials of lipid lowering have been reported since 1970. By the criteria of statistical power, effectiveness of intervention, and duration, most could be criticised, though all design features showed progressive improvement in later trials. Until 1994, the overall conclusions from this generation of trials were that CHD incidence was reduced in the majority of trials, modestly, in many, but by up to 50% with more effective interventions, while CHD mortality was significantly reduced in relatively few.

Meta-analysis has been of great value in overcoming the limited statistical power of most of these trials but, too, is subject to design problems. Unless most of the trials are included problems of selection bias and generalisation arise, but a degree of exclusiveness is also needed, to maximise homogeneity of design and to avoid distortion of the results by trials of obsolete treatments. Since the effectiveness of treatment has varied so widely among trials, those meta-analyses that take into account the extent of cholesterol lowering are particularly informative; such meta-analyses, based on 21–30 trials, have established that cholesterol-lowering treatments reduce CHD incidence and mortality substantially and highly significantly.

From these meta-analyses it is evident that the
decrease in CHD rates is directly related to the extent of cholesterol lowering. Further, lowering of plasma low-density lipoprotein (LDL) cholesterol is the only evident effect common to the wide range of treatments (diets, several classes of drugs, and surgery), indicating that decreased levels of this lipoprotein must be a major mechanism underlying reduction in CHD.

Two recent trials of effective cholesterol lowering by statin drugs, both in subjects with mild-to-moderate hypercholesterolaemia, have individually been sufficiently powerful to corroborate these conclusions from earlier trials and their meta-analyses. Lowering of LDL cholesterol levels by 35% led to over 40% reduction in non-fatal and fatal CHD events. These are likely to be minimum estimates of the benefit from such treatment in clinical practice because the intention-to-treat principle was employed in both trials. Also, the outcomes do not reflect the use of diet to enhance lipid lowering and reduce overweight, nor do they reveal the further potential benefits of reduction in non-lipid risk factors.

Angiographic trials of lipid lowering (Fig 1)

The direct effect of treatments on atherosclerotic arteries has been measured in serial arteriograms in controlled clinical trials using visual scoring, quantitative coronary angiography (QCA) or ultrasonography. Angiographic trials measure continuously variable end-points and up to 10 coronary artery segments can be measured in each subject, so statistical power is achieved with smaller and shorter trials than are needed to assess clinical outcomes. The effects of 26 lipid-lowering treatments in 24 angiographic trials on human coronary, carotid and femoral arteries have been reviewed.

Among studies on coronary arteries, the sole treatment in one limb of the St Thomas’ Atherosclerosis Regression Study (STARS) was a moderate lipid-lowering diet, diet and exercise were employed in the Heidelberg trial, and the Lifestyle trial used, among other interventions, a vegetarian diet, exercise and weight loss. In all these three trials of health-related behaviour the incidence of progression (defined as reduction in luminal diameter) decreased, while regression (increased diameter) occurred more frequently. CHD events were significantly reduced in two of the trials.

Six of the drug trials employing resins, alone or in combination, documented considerable reduction in progression. The incidence of regression increased in five, including one in subjects with familial hypercholesterolaemia. In the Cholesterol Lowering Atherosclerosis Study (CLAS), native coronary arteries and saphenous vein grafts both showed favourable treatment effects. CHD events significantly decreased in three of the five trials. In the largest and longest trial, Program on the Surgical Control of the Hyperlipidemias (POSCH), partial ileal bypass surgery led to a marked reduction in CHD events. Pronounced reduction in progression and an increase in the low incidence of regression were both significant.

Multiple drugs, diet and management of non-lipid risk factors were used in the Stanford Coronary Risk Intervention Project (SCRIP); reduction in both progression and CHD events was significant. The Harvard Atherosclerosis Reversibility Project (HARP), a smaller trial of multiple interventions, has been the only angiographic trial to date in which no significant treatment effects were seen. In four trials of statins, there was significant reduction of progression as assessed by QCA in three, and in the fourth by visual scoring (but not by QCA).

In treated subjects, regression was observed (significant in two trials). In the largest of these four trials, CHD events decreased significantly, with a smaller trend in the others.

In a further study, LDL apheresis plus simvastatin lowered LDL and lipoprotein(a) in one group; the other group received colestipol plus simvastatin, with similar LDL lowering but no reduction in lipoprotein(a). The angiographic effects were not significantly different.

Four trials based on ultrasonographic measurements of intimal-medial thickness (IMT) in the carotid arteries have been reported. In two, treatment reduced IMT while the control group showed an increase; in one, there was marked reduction in the rate of increase of IMT. In five trials based on femoral arteriography, two showed reduced progression and three, increased regression, but in CLAS, the femoral arteriograms showed favourable changes less frequently than coronary and carotid angiograms in the same subjects.

Regression is seen in some 30% (sometimes 50%) of plaques, and commonly appears most pronounced in the severest stenoses; but in STARS, when the course of disease in arterial segments with mild, moderate, and severe stenoses at entry was compared, reduced progression and increased regression were seen in all groups. The magnitude of regression is usually modest, lumen diameter increasing by 0.1–0.2mm. Regression is less pronounced than in animal models, in which all plaques are lipid-rich and the extent of lipid lowering is greater. In tight coronary stenoses, small changes in lumen size and wall irregularity have a major haemodynamic effect, especially during exercise.

Subset analyses

In five of six trials that included both women and men, favourable angiographic effects were equally evident or more pronounced in women. In diabetics, cholesterol lowering has led to a suggestion of angiographic improvement.

In most angiographic trials the outcome appeared...
### Randomised Controlled Coronary Angiographic Trials

| Trial and lifestyle interventions | Design | LDL-C | TG | HDL-C | Ambient LDL-C (mmol/l) | Outcome Angiographic Change | Outcome Regression | Cardiovascular Events |
|----------------------------------|--------|-------|-----|-------|------------------------|-----------------------------|----------------------|-----------------------|
| LIFESTYLE                        |        |       |     |       |                        |                             |                      |                       |
| Diet and lifestyle interventions |        |       |     |       |                        |                             |                      |                       |
| 41 CHD                           |        |       |     |       |                        |                             |                      |                       |
| QCA 15mo.                        |        |       |     |       |                        |                             |                      |                       |
| STARS (27%en fat                  |        |       |     |       |                        |                             |                      |                       |
| (P>0.8, High-                  |        |       |     |       |                        |                             |                      |                       |
| fibre diet)                      |        |       |     |       |                        |                             |                      |                       |
| QCA 39mo.                        |        |       |     |       |                        |                             |                      |                       |
| HEIDELBERG                       |        |       |     |       |                        |                             |                      |                       |
| (diet, [AHA III]                 |        |       |     |       |                        |                             |                      |                       |
| + exercise)                      |        |       |     |       |                        |                             |                      |                       |
| QCA 12mo.                        |        |       |     |       |                        |                             |                      |                       |
| Multiple interventions           |        |       |     |       |                        |                             |                      |                       |
| SCRIP (diet, wt loss,           |        |       |     |       |                        |                             |                      |                       |
| exercise, smoking cessation,    |        |       |     |       |                        |                             |                      |                       |
| hypolipidaemic drugs             |        |       |     |       |                        |                             |                      |                       |
| vs. lesser diet)                 |        |       |     |       |                        |                             |                      |                       |
| QCA 48mo.                        |        |       |     |       |                        |                             |                      |                       |
| HARP (diet + hypol.             |        |       |     |       |                        |                             |                      |                       |
| drugs vs. lesser diet)           |        |       |     |       |                        |                             |                      |                       |
| QCA 79 CHD                       |        |       |     |       |                        |                             |                      |                       |
| chol<0.5                         |        |       |     |       |                        |                             |                      |                       |
| (diet + hypol.                   |        |       |     |       |                        |                             |                      |                       |
| drugs vs. lesser diet)           |        |       |     |       |                        |                             |                      |                       |
| MARS (lovastatin)               |        |       |     |       |                        |                             |                      |                       |
| 270 CHD                           |        |       |     |       |                        |                             |                      |                       |
| visual score                    |        |       |     |       |                        |                             |                      |                       |
| + QCA 24 mo.                    |        |       |     |       |                        |                             |                      |                       |
| CCAI (lovastatin)               |        |       |     |       |                        |                             |                      |                       |
| 298 CHD                           |        |       |     |       |                        |                             |                      |                       |
| + chol 5.7                      |        |       |     |       |                        |                             |                      |                       |
| QCA 24mo.                        |        |       |     |       |                        |                             |                      |                       |
| MAAS (simvastatin)              |        |       |     |       |                        |                             |                      |                       |
| 345 (24 mo.)                    |        |       |     |       |                        |                             |                      |                       |
| 272 (48 mo.)                    |        |       |     |       |                        |                             |                      |                       |
| CHD + chol 5.5                  |        |       |     |       |                        |                             |                      |                       |
| QCA 48mo.                        |        |       |     |       |                        |                             |                      |                       |
| REGRESS (pravastatin)           |        |       |     |       |                        |                             |                      |                       |
| 653 CHD                           |        |       |     |       |                        |                             |                      |                       |
| + chol 4.8                      |        |       |     |       |                        |                             |                      |                       |
| QCA 24mo.                        |        |       |     |       |                        |                             |                      |                       |
| PLAC I (pravastatin)            |        |       |     |       |                        |                             |                      |                       |
| 320 CHD                           |        |       |     |       |                        |                             |                      |                       |
| av chol 6.0                     |        |       |     |       |                        |                             |                      |                       |
| QCA 36mo.                        |        |       |     |       |                        |                             |                      |                       |
| Resine, niacin, lovastatin       |        |       |     |       |                        |                             |                      |                       |
| 116 CHD                           |        |       |     |       |                        |                             |                      |                       |
| <60% FH; visual score            |        |       |     |       |                        |                             |                      |                       |
| 60mo.                            |        |       |     |       |                        |                             |                      |                       |
| CLAS (colesterol+niacin)         |        |       |     |       |                        |                             |                      |                       |
| 103 CABG                         |        |       |     |       |                        |                             |                      |                       |
| + chol 4.8                      |        |       |     |       |                        |                             |                      |                       |
| visual 48mo.                    |        |       |     |       |                        |                             |                      |                       |
| RATS (colesterol+hova)           |        |       |     |       |                        |                             |                      |                       |
| (colesterol+niacin)              |        |       |     |       |                        |                             |                      |                       |
| 120 CHD                           |        |       |     |       |                        |                             |                      |                       |
| + fam hist; apol B<125           |        |       |     |       |                        |                             |                      |                       |
| QCA 32mo.                        |        |       |     |       |                        |                             |                      |                       |
| UCSF-SCOR (colesterol+niacin,  |        |       |     |       |                        |                             |                      |                       |
| lovastatin)                      |        |       |     |       |                        |                             |                      |                       |
| 72 net, FH                       |        |       |     |       |                        |                             |                      |                       |
| QCA 26mo.                        |        |       |     |       |                        |                             |                      |                       |
| STARS (diet+                      |        |       |     |       |                        |                             |                      |                       |
| cholestryamine)                  |        |       |     |       |                        |                             |                      |                       |
| 75 CHD                           |        |       |     |       |                        |                             |                      |                       |
| chol 6.10                       |        |       |     |       |                        |                             |                      |                       |
| QCA 39mo.                        |        |       |     |       |                        |                             |                      |                       |
| Partial ileal bypass surgery     |        |       |     |       |                        |                             |                      |                       |
| POSCH                            |        |       |     |       |                        |                             |                      |                       |

Fig 1. Results in 17 treatment limbs in randomised controlled trials of cholesterol lowering, based on coronary angiographic change. QCA = quantitative coronary angiography.
to be independent of plasma cholesterol level at entry\textsuperscript{18,26}. An apparent exception is the HARP trial\textsuperscript{3}, in which a pretreatment cholesterol level of below 6.5 mmol/l was specified: despite marked cholesterol lowering, there was no significant benefit. In this study, the control group received lipid-lowering treatment by diet and, in 10 of 39 participants, by drugs, which may have lessened the power of the study to detect a treatment effect. Preliminary findings in the Lipoprotein and Coronary Atherosclerosis Study (LCAS)\textsuperscript{35} have shown that fluvasatin reduces progression of coronary artery disease (CAD) in patients with a mildly elevated LDL cholesterol level (3–5 mmol/l); in a subset studied by positron emission tomography (PET) this was accompanied by improvement in myocardial perfusion. The more favourable results in LCAS compared with HARP may reflect its larger sample size. The outcome of LCAS is consistent with that of the Cholesterol and Recurrent Events (CARE) trial (discussed in the next section). In other angiographic trials the outcome has been compared in groups stratified by cholesterol level at entry. Comparable treatment effects were seen in subsets with entry LDL cholesterol or plasma cholesterol below and above the median level\textsuperscript{18,36}.

\textbf{Implications of the angiographic trials}

The STARS trial and the control group of GLAS provide novel sources of information on the relation between nutrition and atherosclerosis\textsuperscript{32–34}. In STARS, the dietary lipid hypothesis of CHD receives support from the favourable angiographic and clinical effects of diet as the single intervention\textsuperscript{19,37}. Progression of coronary disease in both studies was directly related to the intakes of energy and saturated fat, but there was no evidence that unsaturated fat intake was inversely related to angiographic progression. Multivariate analysis of the STARS data showed progression to be directly and independently related to intakes of the saturated fatty acids palmitate and stearate, and also of trans-fatty acids; consumption of these nutrients ‘explained’ a substantial proportion of the variance in progression\textsuperscript{38}.

Several trials have examined the relation between progression and in-trial levels of lipoproteins and hence the potential pathogenic roles of different lipoproteins. One consistent direct relation is between mean in-trial LDL cholesterol level and progression, evident over a wide range of LDL levels down to 2.5 mmol/l\textsuperscript{14}. In STARS, the strongest independent predictor of progression was the concentration of a subclass of LDL comprising small, dense particles\textsuperscript{41} (elevated levels of which are common in hypertriglyceridaemia as well as in hypercholesterolaemia). Levels of lipoprotein(a) were predictive of progression in one study\textsuperscript{42}, but not in another study when LDL cholesterol was lowered\textsuperscript{43}. Less consistently, progression has been associated with triglyceride levels and ( inversely) high-density lipoprotein (HDL) cholesterol\textsuperscript{48}. Apolipoprotein levels were less predictive than lipoprotein lipids\textsuperscript{42}.

It remains uncertain whether the incidence of regression is maximised by the lowest absolute levels of LDL cholesterol\textsuperscript{19,36} or by the greatest percentage reduction in LDL\textsuperscript{41}. Some studies indicate that a favourable angiographic outcome is not confined to patients with high plasma cholesterol at entry\textsuperscript{18,23,30}. A recent analysis of some of the angiographic trials has shown that the incidence of regression was greatest in studies with higher entry criteria for LDL cholesterol concentration\textsuperscript{45}. In non-diabetic trials, the extent of angiographic improvement is directly and strongly related to the absolute reduction in LDL cholesterol (GF Watts, V Burke, B Lewis; paper in preparation) (Fig 2). Dietary change may influence progression of CAD by mechanisms independent of its effects on LDL cholesterol\textsuperscript{37–40}.

The conclusions from this analysis of angiographic trials about the optimal level of LDL cholesterol are supported by the findings of a clinical end-point trial, CARE, which showed a reduction of coronary events in patients with pre-treatment LDL cholesterol above 3.2 mmol/l, but no benefit in those with entry levels below this value\textsuperscript{46}. A recent trial on post-coronary bypass patients\textsuperscript{17} has given somewhat different results. Angiographic progression in grafts occurred less often in vigorously treated patients with a mean in-trial LDL cholesterol of 2.4 mmol/l than in those treated more conservatively with a mean level of 3.5 mmol/l. Native arteries were not reported on, and clinical event rates were not significantly different. This is in keeping with epidemiological studies, in which the relation between serum cholesterol and CHD incidence shows no discernible threshold. At present, however, the balance of evidence suggests that a large absolute reduction in LDL cholesterol and/or a target level of 3.2 mmol/l are appropriate clinical goals.

Among genetic correlates of progression, one is with the DD allele of the angiotensin-converting enzyme genotype in subjects with low plasma cholesterol\textsuperscript{18}, another with a variant stromelysin gene (discussed later)\textsuperscript{49}.

\textbf{The basis of the relation between angiographic change and clinical coronary heart disease events}

Despite their small magnitude, the angiographic effects of cholesterol lowering in man reflect arterial changes of profound clinical relevance. Among 16 coronary artery trials\textsuperscript{18} a significantly favourable angiographic outcome was associated in seven (with nine intervention groups) with a significant reduction in CHD event rate, and a similar trend was seen in a further three. In HARP, there were no significant effects on either end-point. More striking is the observation in two trials with extended follow-up that favourable angiography outcome in the first 2–3 years
was predictive of a reduction in CHD events rates in the subsequent seven years\textsuperscript{50,51}.

Angiographic evidence of treatment-induced widening of luminal diameter could in theory reflect regression of atherosclerosis, reversal of endothelial dysfunction, lysis of mural thrombi or vascular remodelling. That true regression takes place in man is suggested by analogy with the well documented, histologically-confirmed regression induced by cholesterol lowering in experimental atherosclerosis in primates\textsuperscript{4,52}. Strong support for this interpretation stems from lipid-lowering trials showing reduction of IMT in the human carotid artery\textsuperscript{29,30}. Atherosclerosis, and experimental hypercholesterolaemia without atherosclerosis, attenuate or abolish endotheliump-dependent vasodilatation\textsuperscript{53,54}. This important mechanism is restored by diet\textsuperscript{55,56} or drugs that lower elevated lipid levels. The possible role of vascular remodelling has recently been reviewed\textsuperscript{57}. Cholesterol lowering may also reduce the risk of acute coronary occlusion by decreasing thrombogenicity\textsuperscript{58}.

**Endothelial dysfunction**

Vascular endothelium releases molecules that regulate vasomotor tone, thrombosis, fibrinolysis and chemotaxis of monocytes\textsuperscript{59}. Among these is endothelium-derived relaxing factor (or nitric oxide). The vasodilator effect of acetylcholine, which stimulates synthesis of nitric oxide, is impaired in atherosclerotic coronary arteries, and also in the presence of hypercholesterolaemia or other coronary disease risk factors\textsuperscript{60-62}. Endothelial dysfunction appears to be widespread, as indicated by concordant responses in peripheral and coronary arteries\textsuperscript{63,64}.

There is persuasive evidence that endothelial dysfunction is a pre-atherosclerotic event and that it is mediated by oxidatively-modified LDL\textsuperscript{65}. Reduction of hypercholesterolaemia by resins or statins improves the response to acetylcholine in epicardial coronary arteries within six months\textsuperscript{66-68}. In patients with moderately elevated plasma cholesterol, cholesterol lowering enhanced the endothelial response to forearm reactive hyperaemia, and lessened effort-related myocardial ischaemia within four weeks\textsuperscript{69}. A favourable effect on coronary vasomotion has also been reported in a study of the antioxidant drug probucol\textsuperscript{70}. It is likely that the coronary vasodilatation observed in these studies is accompanied by reduced thrombotic activity and increased fibrinolytic activity, reducing the likelihood of plaque fissuring\textsuperscript{71}. Possibly, therefore, restoration of normal endothelial function contributes to the reduction in coronary event rates in some angiographic and clinical trials (for example, the Pravastatin Multinational Study Group for Cardiac Risk Patients trial\textsuperscript{72}).

**The infarctogenic plaque**

The following discussion addresses the effect of cholesterol lowering on atherosclerotic lesions. There is growing evidence that this is a central process in the reduction in CHD events. Fissuring of the fibrous cap of the atheromatous plaque, leading to thrombotic occlusion, is the basis of most acute coronary events\textsuperscript{73-75}. Only a minority of plaques undergoes this process, however, so the determinants of plaque fissuring have come under scrutiny, and there is now growing insight into the fissure-prone, infarctogenic plaque.
The immediate cause of plaque fissuring is circumferential stress. Computer modelling reveals this to be greatest in plaques with thin fibrous caps and large lipid pools, and stress increases markedly with thinness of the cap.\[^{76,77}\] Circumferential stress is least in severe stenoses. In plaques causing stenoses of more than 75% the presence of a lipid pool is associated with profoundly greater stress.\[^{77}\] In human aortic plaques the presence of a lipid pool occupying more than 40% of cross-sectional area is critical to the presence of fissuring.\[^{78}\] Clinical findings have established that it is plaques of small or moderate size that most often underlie myocardial infarction. In studies of infarct survivors who had fortuitously undergone coronary angiography during the months preceding the event, a plaque in the segment supplying the territory of a subsequent infarct caused a mean 30% stenosis,\[^{79}\] and for Q-wave infarcts a median 34% stenosis.\[^{80}\] Thus, infarctogenic plaques tend to be lipid-rich, thin-capped and of moderate size.

The fibrous caps of fissured plaques have a five-fold greater macrophage content than un fissured plaques\[^{81}\] and an excess of T-lymphocytes,\[^{82}\] while their smooth muscle cell content is reduced.\[^{78}\] Several cell components of human atherosclerotic plaques produce interstitial collagenase, stromelysin and other metalloproteinase enzymes that, in active form, can hydrolyse components of connective tissue matrix.\[^{83}\] In the STARS trial, the GAGA phenotype of the stromelysin promoter was associated with greater progression of CAD.\[^{84}\] Particularly in the shoulder region of human plaques, the common site of fissuring, there is a high activity of enzymes that degrade connective tissue matrix.\[^{83}\] The inflammatory cell content of the plaque cap also appears to mediate a reduction in collagen synthesis. Cytokines released by activated T-lymphocytes inhibit expression of the interstitial collagen gene in arterial smooth muscle cells.\[^{84,85}\] The release of the cytokine interleukin-1 from both monocytes and arterial macrophage-derived foam cells is stimulated by oxidised LDL.\[^{86,87}\] Cytokines can also promote apoptosis (programmed cell death) of smooth muscle cells in culture. These cellular processes underlie the structural features, particularly thinness of the cap, that predispose to fissuring and occlusive thrombosis.

**Hyperlipidaemia, lipid-lowering and the infarctogenic plaque**

The epidemiology of CHD, clinical trials of cholesterol lowering and studies of experimental atherosclerosis all suggest that plasma cholesterol levels play a central role in determining the rate of development of infarctogenic plaques. There is plausible evidence for some of the mechanisms involved. Although its turnover is slow, the cholesterol in plaques is in dynamic equilibrium with that in plasma.\[^{88}\] The rate of influx of LDL cholesterol into arterial intima in man\[^{89}\] and hyperlipidaemic rabbits\[^{90}\] is directly related to plasma LDL level; and plaque size in rabbits correlates both with LDL levels and LDL influx.\[^{90}\] This process is illustrated by the rapid development of atherosclerosis in genetically hypercholesterolaemic rabbits\[^{91}\], an effect prevented by early treatment to lower plasma cholesterol.\[^{92}\] This has its clinical counterpart in the arrest of atherosclerosis progression and the reduction of new lesion formation in angiographic lipid-lowering trials.\[^{93}\]

Lowering of plasma LDL cholesterol level would therefore be expected to lessen uptake of cholesterol into the arterial wall and, if sufficient in extent, to lead to depletion of the plaque’s lipid pool. The time course of this process has been studied in primates with diet-induced atherosclerosis in which a plasma cholesterol-lowering regimen caused the arterial lesions to regress.\[^{94}\] During the first six months of the regression phase the content of macrophage foam cells in the plaque cap was markedly reduced, but with little net change in cholesterol content of the lesions. In the subsequent 18 months, however, there was progressive depletion of cholesterol, with a consequent decrease in arterial wall thickness. Hence, there is experimental support for the view that development of lipid-rich, infarctogenic plaques is promoted by hypercholesterolaemia due to high LDL levels, and that the lipid pool of such lesions is depleted by lowering plasma LDL cholesterol levels, reducing intimal thickness and decreasing circumferential stress. The collagen content of the aorta is relatively conserved during regression of experimental atherosclerosis.\[^{94}\] This appears salutary in view of the relation between thinness of the cap and proneness to fissuring.

It may be that the morphological features of plaques prone to fissuring are the proximate cause of their vulnerability. The large lipid pool includes components that are liquid at 37°C,\[^{95}\] by contrast with the overlying thin fibrous cap. Depletion of, and compositional change within, the lipid pool consequent on plasma lipid lowering may stabilise the plaque by lessening the incompatibility between the physical properties of these elements. Lipid depletion is the main or sole reason for morphological regression.\[^{5,96}\]

Factors influencing the cellular features of the cap of the infarctogenic plaque are incompletely understood. An early event in experimental atherosclerosis due to diet-induced hypercholesterolaemia is the adhesion of macrophages to endothelium, followed by migration of these cells into the subendothelial space; there they take up LDL, so acquiring cholesteryl ester and converting into foam cells.\[^{93}\] However, uptake of native LDL is negligible: modification of the lipoprotein by oxidation or other processes is necessary for macrophages to be converted to foam cells, and thus for the lipid pool to develop.\[^{96}\] Oxidised LDL is also chemotactic to macrophages and other cellular elements in the plaque;\[^{96,97}\] it could play a further important role in activating T-lymphocytes, and thus promoting the inflammatory processes that appear to render the fibrous cap prone to fissuring. It has been speculated that lowering plasma LDL limits the...
inflammatory stimulus provided by oxidised LDL. This could account for the early depletion of macrophages during the regression process. In turn, this could permit accumulation of connective tissue elements in the fibrous cap and so stabilise it against fissuring.

Safety aspects of cholesterol lowering

Clinical trials, supported by animal studies and cell biology, attest to the value of lowering elevated plasma cholesterol levels. Such benefit must be set against possible attendant risks. The topic has received wide attention. Concerns about the hazards of having low plasma cholesterol concentrations arose when some epidemiological studies revealed a ‘J-shaped’ relation between all-cause mortality rates and cholesterol levels. In addition to the expected high mortality (due chiefly to CHD) in the upper part of the cholesterol distribution, increased mortality (due to heterogeneous causes: certain cancers, trauma and non-malignant digestive and respiratory diseases) was also seen when plasma cholesterol was less than 4.1 or less than 3.6 mmol/L. The possibility of untoward effects of cholesterol lowering stemmed from the finding in some trials of more deaths from certain non-cardiovascular causes in treated than in control subjects, although differences within individual trials were not statistically significant nor was there consistency across trials. It was not clear whether such an effect, if real and if causal, was mediated by cholesterol lowering or by a direct effect of a particular treatment.

In some early trials the apparent excess deaths were due to large bowel or lung cancer, but in others they were due to trauma and suicide with no difference in cancer rates.

Several sources of misinterpretation underlie the epidemiological J-curve. One is reverse causality: low plasma cholesterol is a consequence of disease, and early undiagnosed serious illness contributes to the phenomenon (e.g. plasma cholesterol decreases progressively over a 10-year period prior to death from colon cancer). Another is confounding, for example by social class. The J-shape is far from consistent. It is present in many studies based on middle-aged community cohorts, but in long-term studies on initially young people and in studies on persons selected for being in employment (among whom pre-existing undiagnosed serious disease is less likely) the J-shape is absent, and there is no excess of all-cause, cancer, trauma or suicide deaths in the low part of the cholesterol distribution. In fact, one recent study noted an increased rate of suicide in men with higher serum cholesterol levels. The power of confounding was clearly shown in the Whickham Study, in which the initial association between low plasma cholesterol and non-cardiovascular, non-cancer death rates was so attenuated as to become non-significant when adjustment was made for unintentional weight loss, low employment grade and indices of chronic respiratory disease. Each of these confounders is accompanied by lower plasma cholesterol levels.

In the two recent controlled trials of statin drugs, reduction in CHD events was accompanied by lower all-cause mortality, with no excess in non-cardiovascular causes of death. The extent of cholesterol lowering was greater in these trials than in earlier ones and they were larger than most, so they provide persuasive evidence of the safety of decreasing plasma cholesterol. Among earlier, less powerful trials the random play of small numbers may have accounted for some instances of excess non-cardiovascular events. Concerns were aroused, for example, by a non-significant excess of cancer deaths in two trials, but no such trend was present in 10 further trials. In two trials excess suicidal and violent deaths were seen in the intention-to-treat data, but an independent case audit showed this excess to have occurred in subjects non-compliant with medication, who showed little change in plasma cholesterol, had previous psychiatric histories or were passive victims of homicide.

Dose-response effects

If cholesterol lowering were a cause of non-cardiovascular mortality, this should be most pronounced in those trials in which plasma cholesterol reduction was greatest. The two meta-analyses that conformed with the design features described in the section on CHD event trials have shown no such ‘dose-response’ effect: in one, trials with greater cholesterol lowering showed a trend to lower, not higher, total mortality (a trend borne out by the statin trials), and the other showed no significant excess of death from all causes other than CHD, from cancer, accidents or suicide.

Stroke

The relationship between plasma cholesterol concentration and stroke is complex. Many epidemiological studies have found no such association, but when thrombotic and haemorrhagic strokes are distinguished, the incidence of the former is seen to increase with increasing cholesterol level. Cerebral haemorrhage, on the other hand, is over-represented among the small number of persons with plasma cholesterol below 4.1 mmol/L and diastolic blood pressure above 90 mmHg. It has yet to be resolved whether or not this association is causal. Recent trials of the potent cholesterol-lowering statin drugs have shown reductions in total stroke incidence. Clearly, the number of CHD and cerebral thrombosis deaths associated with high plasma cholesterol greatly exceeds the number of deaths from cerebral haemorrhage associated with low plasma cholesterol. In the individual patient, the main clinical implication at present is that hypertension should be effectively treated.
Cell biology

No mechanism has been identified to explain a putative lethal effect of low plasma cholesterol concentration\(^98,99\). Two speculative explanations have been proposed: increased fluidity of plasma membranes\(^108\) and impaired immunosurveillance\(^109\), but neither has been confirmed\(^110,111\). On the other hand, reverse causation, the effect of chronic disease in reducing plasma cholesterol, is readily explained by known effects of cytokines, and of anorexia and weight loss\(^80\).

Most importantly, studies of cholesterol metabolism have led to a fundamental revision of our views on the sources of cell cholesterol. When it appeared that cells met their cholesterol requirements by regulated uptake of LDL cholesterol from tissue fluid and ultimately from plasma, there were some grounds for suspecting that low or lowered plasma cholesterol might compromise this source of supply. Such fears were allayed in part by considerations based on the very high affinity of the cell surface LDL receptor for this cholesterol-rich lipoprotein\(^112\). Direct studies suggested that homeostatic mechanisms maintained normal cell cholesterol content and membrane fluidity\(^113\) even at levels of LDL cholesterol far below those likely to be attainable by lipid-lowering therapy. Most persuasively, meticulous studies have now established in situ synthesis of cholesterol as the main source of the cholesterol content of most cells, including those of the central nervous system\(^115,115\). Lowering of plasma cholesterol is correspondingly unlikely to influence the integrity of the cell.

Implications for preventive strategy

Four concepts relevant to clinical and public health practice stem from recent advances in our understanding of the cholesterol-CHD relation:

1. It is evident both from the new trials\(^16,17\) and from appropriate meta-analyses of older ones\(^14,15\) that reduction of plasma cholesterol substantially decreases the incidence of and mortality from CHD.

2. These trials and meta-analyses, critical analysis of the epidemiology of low plasma cholesterol levels, and biological considerations do not provide grounds for concern that low or lowered cholesterol causes non-cardiovascular diseases\(^98,99\).

3. The strength of the relationship between elevated LDL cholesterol and the risk of major CHD events is underestimated by conventional longitudinal epidemiological studies based on a single baseline plasma cholesterol measurements\(^116\). When corrections are made both for the resultant regression-dilution bias and for the imperfect correlation of total plasma cholesterol with LDL cholesterol level, the risk conferred by increased LDL cholesterol is almost 60\% greater than that suggested by single plasma cholesterol measurements\(^116\). Recommendations for the treatment of hyperlipidaemia require that clinical decisions are based on two or more measurements of lipid and lipoprotein levels\(^117\); hence, this upward revision of the relationship between cholesterol and risk is relevant to clinical practice.

4. The concept that vigorous treatment of hyperlipidaemia should be targeted on patients at substantial risk of cardiovascular disease\(^117\) has long been a feature of expert recommendations, and it obtains support from a meta-analysis of lipid-lowering trials\(^118\). Patients are assigned to the high-risk category and receive active and, if necessary, intensive lipid-lowering therapy when overt cardiovascular disease or multiple risk factors, including significant family history, are present\(^117\).

Arterial imaging in risk assessment

The results of the angiographic trials of lipid lowering combined with increasing insight into the biology of the infarctogenic plaque suggest that vascular imaging techniques should play an increasing part in assessing the need for intensive risk factor reduction. The objectives of lipid-lowering therapy are now seen to be the 'stabilisation' against fissuring of existing plaques, through mechanisms such as those discussed above, and by prevention of new plaque formation.

Coronary angiographic evidence of progression/regression is predictive of CHD event rate\(^60,51\) and the STARS and Familial Atherosclerosis Treatment Study (FATS) trials have shown that plaques producing modest stenoses can show regression or reduced progression during cholesterol lowering\(^19,115\). The detection of plaques causing 15–60\% stenoses during clinically-needed coronary angiography appears to be a strong indication for such therapy, certainly in patients with any degree of hyperlipidaemia; such lesions are likely to include lipid-rich, infarctogenic lesions. Although an angiogram may show no haemodynamically significant stenosis, the presence of lesions of moderate size suggests that vigorous lowering of LDL cholesterol should be considered. Intracoronary ultrasound has the potential to identify infarctogenic plaques, (ie those with large lipid pools and thin fibrous caps)\(^120\), but its predictive power for CHD events remains to be determined. Possible non-invasive approaches to the recognition of coronary atherosclerosis include demonstration of coronary calcification by cine-fluoroscopy\(^121\) or ultrafast computed tomography\(^122,123\). Such calcification correlates with the presence of CAD, but evidence is as yet lacking that it is predictive of CHD events. A further non-invasive approach is PET which has the advantage over angiography of estimating myocardial perfusion\(^124\).

Among non-invasive methods magnetic resonance imaging has successfully been applied in assessing the patency of coronary artery bypass grafts\(^125\). Advances in
the use of this technique show particular promise in discriminating lipid core and fibrous cap in atherosclerotic lesions, as well as normal intima and adventitia, pure calcification, intraplaque haemorrhage and acute thrombosis.

This technique has so far been studied in carotid arteries in vivo, but improvements in resolution may eventually permit its application to other arteries. If so, it will offer a research tool for the study of the evolution of the atherosclerotic plaque and for trials of interventions. It may then become of clinical value in the non-invasive evaluation of arterial disease, and particularly in the identification of infarctogenic plaques.

The value of angiography is limited in assessing coronary atherosclerosis both by its invasive nature and by a lack of direct information concerning the arterial wall. The most promising non-invasive procedures to supplement present methods of risk assessment, and so to assist the clinician in deciding on the need for intensive lipid lowering, appear to be quantitative carotid ultrasonography and ultrasound imaging of the abdominal aorta. Extensive pathological studies have shown strong correlations between the extent of atherosclerosis in the coronary and carotid arteries and the abdominal aorta. The presence of carotid intimal thickening on ultrasound predicts twofold increase in CHD event rate; plaques predict a greater increase and stenoses predict a sixfold higher risk.

In four trials of cholesterol lowering on carotid I/M procedures, favourable angiographic effects were accompanied by a downward trend in CHD event rates in all, but significantly so only in the largest trial Asymptomatic Carotid Artery Progression Study (ACAPS). Ultrasonography also permits non-invasive assessment of endothelial function measured in the brachial artery.

Global cardiovascular risk and lipid-lowering therapy

The vigour with which lipid-lowering therapy is pursued depends on overall (global) cardiovascular risk and also on the individual responsiveness of the patient. Diet should remain the first – and often the only – approach, notwithstanding recent reports of its limited effect. Under controlled conditions, diet can lower LDL cholesterol by 10–25%. Its effect in free-living persons can be substantial and sustained. Unfortunately, much remains to be learnt regarding skills in dietary counselling. Many failures of qualitative dietary change stem from inadequate attention to simultaneous reduction of overweight, which often enhances the fall in LDL cholesterol, reduces plasma triglyceride, and increases HDL cholesterol. In addition to its cost and safety merits, dietary therapy has the value of addressing directly a central cause of both hyperlipidaemia and CHD. The decision to add long-term therapy with a lipid-lowering drug should not be taken lightly, but such drugs often prove necessary in patients at high cardiovascular risk. Insufficient use is made of low-dose drug treatment which can remarkably enhance partial control by diet; both untoward effects and costs are dose related.

Advances during the past few years provide the opportunity to recapture the dynamic of earlier optimism regarding CHD prevention. Only a few years ago the value of lipid-lowering treatment in secondary prevention of CHD could be questioned. Since 1990, when the risk factor status for recurrent CHD of elevated plasma and LDL cholesterol levels and of low HDL cholesterol became clearer, and a meta-analysis of secondary prevention trials showed benefit, there has been a well justified emphasis on secondary prevention as an indication for lipid lowering. There is now a danger of underestimating the case for primary prevention in persons at high risk. Sudden cardiac death remains a common first manifestation of CHD, and first myocardial infarcts carry a finite mortality rate and are followed by significant morbidity. Asymptomatic atherosclerosis, and the presence of severe or multiple risk factors, provide valuable guidelines to appropriate lipid-lowering treatment in persons without overt CHD. Thus, recognition of high risk should take precedence over the distinction between primary and secondary prevention, and is essential in choosing an appropriate level of lipid-lowering therapy.

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