Cholesterol Reduction and Coronary Artery Disease
An Overview of Clinical Trials up to 1986

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Summary

The 'cholesterol hypothesis' has been proven in a wealth of experimental, clinical, genetic and epidemiological studies. Cholesterol-lowering trials reviewed here have compared the effects of various treatment modalities on coronary heart disease reduction. They have shown that prevention of coronary heart disease depends on the magnitude and duration of cholesterol reduction, not on the way it was achieved. Collective evidence from all unconfounded trials indicates that most of the benefit of such intervention is achieved within relatively few years of starting the intervention. With the possible exception of adverse effects associated with clofibrate, cholesterol-lowering intervention has not produced any untoward effects that cause concern.

An impressive amount of evidence is now available showing that cholesterol has a major role in the pathogenesis of atherosclerosis. In fact, indications are that the major cholesterol fraction, low density lipoprotein (LDL)-cholesterol, is the most important although not the sole causative agent of atherosclerosis. This has been established beyond doubt in a wide variety of studies in different fields such as experimental pathology, cell biology, clinical genetics and epidemiology. There are, however, many questions which can be answered only by cholesterol reduction intervention trials carried out in man. How soon can a reduction in coronary heart disease (CHD) be achieved? What is the relation between the size and duration of cholesterol reduction and the reduction in CHD? Does it matter by what means cholesterol lowering is achieved, i.e. by diet or any one particular agent? Most of this information can be obtained from analysis of the results of primary and secondary prevention trials. In this review, some of the major prevention trials will be examined and their implications for the therapy of hypercholesterolaemia discussed. Important insights have been obtained by combining the results from different trials and placing them into the context of the basic epidemiological knowledge. A detailed report on the most recent primary prevention trial, the Helsinki Heart Study, appears elsewhere in this issue (p. 32), and the angiographic intervention studies are reviewed separately (p. 37). Also, some important prevention trials based on population intervention rather than individual follow-up (e.g. the Finnish Mental Hospital Study and the European Collaborative Trial) have not been included.

1. Primary Prevention Trials

1.1 Diet Trials

A detailed analysis of all primary prevention trials using diet as a means to reduce plasma cholesterol concentrations is beyond the scope of this
The Oslo Primary Prevention Trial was a 5-year randomised, controlled trial carried out in normotensive middle-aged men at high risk for CHD because of elevated plasma cholesterol concentrations (Hjermann et al. 1981). Intervention consisted of reduced dietary intake of saturated fat and cholesterol and cessation (or reduction) of tobacco smoking. On average during the trial the serum cholesterol concentration was 13% lower in the intervention group than in the control group, and mean tobacco consumption decreased by 45% more in the intervention group than in the control group. The incidence of myocardial infarction (fatal and non-fatal) and sudden death was significantly (−47%) lower in the intervention group than in controls (p = 0.028). The investigators of the Oslo Trial calculated that about 60% of the effect was due to cholesterol lowering. For the general practitioner, the important message from the Oslo Trial is that a remarkable reduction in CHD can be achieved by advising healthy middle-aged men to correct their diet and stop smoking.

The Multiple Risk Factor Intervention Trial (MRFIT) was a multifactorial trial in which intervention consisted of cholesterol lowering by dietary modification, treatment of elevated blood pressure and anti-smoking advice (MRFIT Research Group 1982). This randomised, controlled trial was carried out in middle-aged men at high risk for CHD. Two important considerations must be emphasised with regard to the results of MRFIT: first, the difference in risk factors achieved between the special intervention (SI) group and the control or usual care (UC) group during the trial was smaller than expected, and second, the reduction in CHD anticipated on the basis of the achieved difference in risk factors did not occur. Some important lessons which are applicable to previous or future trials may be learned from the MRFIT study.

The smaller than expected difference in risk factors between the SI and UC groups has several explanations. One is that the increasing awareness among the population of risk factors apparently prompted patients in the UC group to modify their diet, reduce smoking and improve antihypertensive therapy. Cholesterol lowering was the least suc-