

Effect of Cholesterol-Lowering Treatment on Coronary Heart Disease Morbidity and Mortality: The Evidence from Trials, and Beyond

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Abstract. Evidence from controlled clinical trials shows convincingly that reducing serum cholesterol levels by diet or drug treatment reduces the incidence of coronary heart disease. On a population basis, the most important effect of cholesterol lowering might be postponement of the first symptoms of disease rather than postponement of death, because most cardiac deaths occur at an advanced age. No enhanced cancer mortality is seen either in populations with low serum cholesterol levels or in patients who, through a genetic defect, have a low-density-lipoprotein cholesterol of zero. This makes it unlikely that cholesterol-lowering treatment as such promotes cancer. Still, specific side effects and toxicity of drugs need careful scrutiny, and diet remains the treatment of choice for mild hypercholesterolemia.

Sources of information on the role of serum lipoproteins in the development of disease are diverse (table 1). In the evaluation of drugs, randomized controlled clinical trials are considered indispensable. On the other hand, public health interventions are frequently judged on epidemiologic grounds alone, as was the case regarding the noxious effect of cigarette smoking on the myocardium: the metabolic pathways involved are poorly defined, there are no good animal studies, and, most important, there is no evidence from randomized controlled trials that

cessation of smoking is beneficial; yet, its importance is widely accepted. Nor is there persuasive evidence from randomized controlled trials that obesity, lack of exercise, stress, exposure to radioactivity or air pollution, failure to wear a safety belt or helmet, drunk driving or substance abuse will shorten life expectancy.

On several of these points, e.g. exposure to radioactivity or drug abuse, insistence on trial evidence would be pedantic, because epidemiologic and clinical observations plus common sense should persuade anyone that

they are unhealthy. In the case of obesity or exercise, setting up and running a properly controlled clinical trial would be a formidable and impossible task. On the other hand, the impact of cholesterol lowering on coronary risk has been studied intensively. Still, calculations have shown that a definitive settling of the diet-heart question would require a trial involving 72,000–145,000 subjects treated for at least 5 years [1]. None of the published trials approach these figures. We will thus have to accept the limitations and look at but also beyond trial evidence for the long-term effects of cholesterol reduction on coronary heart disease (CHD) morbidity and mortality.

Effect of Cholesterol Lowering on CHD

There have been many trials to evaluate the role of cholesterol in the etiology of CHD, and their results have not always been consistent – a common phenomenon in biomedical research. A meta-analysis, in which results of all published trials meeting consistent criteria are entered into a single calculation, then becomes helpful. Such analysis can provide a perspective on the extent to which the outcomes of the various trials agree. Single trials have almost uniformly lacked the statistical power to allow firm conclusions.

Although in most trials, treatment of hypercholesterolemia by diet or by drugs reduced the incidence of CHD, the numbers of patients studied were so small that many of these outcomes could have been due to chance if viewed individually. Statisticians express this by saying that the 95% confidence interval for the reduction in incidence did not exclude a zero effect, or that the effect was not significant. Only combining the data

Table 1. Sources of information on the role of cholesterol in disease

Epidemiology
Individuals
Nations
Trends in time
Hereditary hypercholesterolemia and hypocholesterolemia
Metabolic pathways
Animal experiments
Controlled clinical trials

Table 2. Relation between cholesterol lowering and reduction in CHD: meta-analysis of randomized, controlled trials

Cholesterol reduction, %	Reduction in CHD, % ¹
5– 9	8
10–15	19

Adapted from R. Peto [1988, unpubl. analyses].

¹ In these trials, patients who developed CHD had been receiving treatment for an average of 2 years when symptoms first appeared.

compiled for the 40,000 patients studied in the 20–30 trials published hitherto allows the signal to rise above the noise. Such meta-analyses have shown that reducing total or low-density-lipoprotein (LDL) cholesterol levels consistently reduces the incidence of myocardial infarction and coronary death [2, 3]. The effect is graded: the greater the cholesterol reduction, the larger the benefit (table 2). Benefit has been shown to increase with longer duration of treatment (table 3) as well. Table 3 also shows that in this respect the trial evidence fits well with epidemiologic observations. It is therefore a logical conclusion that the duration of exposure of the arterial wall to high LDL concentrations determines the chance that an occluding lesion will occur.

Table 3. Reduction in coronary events associated with a cholesterol reduction of 10% in a meta-analysis of randomized controlled trials

Type of study	Reduction in CHD mean \pm SE, %	Duration of cholesterol reduction until 1st event, years ¹
13 short trials	9 \pm 5	1-2
8 longer (5-7 years) trials	22 \pm 4	3
Comparisons within and between populations	30	~50

Adapted from R. Peto [1988, unpubl. analyses].

¹ At the time when CHD symptoms first appeared, patients had on average been receiving treatment or adhering to a specific diet for the number of years indicated.

Value of Cholesterol-Lowering Strategies

Total Mortality

If treatment of hypercholesterolemia reduces mortality from CHD and does not cause other diseases, then it should be associated with a reduction in total mortality, i.e. patients should live longer. In practice, this has not been proven to occur [3], perhaps because CHD, like cancer, diabetes, and cerebrovascular accidents, is a disease that mainly affects elderly people, who have a limited life expectancy. The average number of years to be gained by prevention of CHD is small, and the gain is diluted by other competing causes of death. Thus, there is a dilemma involved in cholesterol trials: elderly subjects gain little in life expectancy even if CHD is prevented, and younger subjects experience too few CHD deaths during a trial to allow

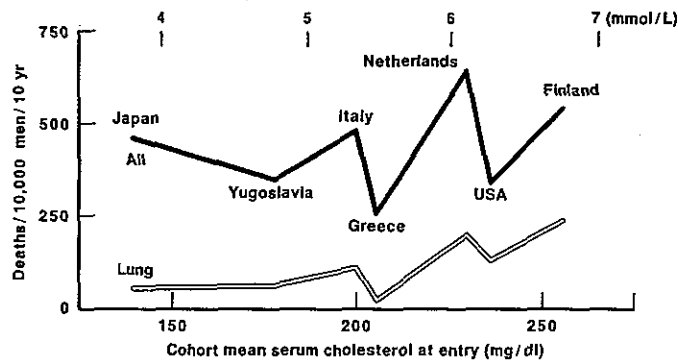
firm conclusions on the benefit of treatment. (The exceptions are patients with familial hypercholesterolemia, in whom CHD mortality is already high in middle age. With the available pharmaceutical treatment for hypercholesterolemia, a dramatic increase in total life expectancy can be assumed to be discernible in the future among these patients.)

With the majority of CHD deaths occurring in elderly people, is an increased average life span a realistic goal in the primary prevention of CHD? In my opinion, increasing life expectancy among populations of the developed world is a pointless effort. The number of people living to 80 years or more is already growing rapidly, and to many the added years are a mixed blessing. Rather than to further postpone death, a more relevant goal is to reduce the burden of disease that makes the last years or even decades of life miserable. The question then becomes: will cholesterol lowering keep patients free from disease for a longer period rather than simply keep them alive longer? This issue of CHD incidence, as opposed to total mortality, has been largely settled by the trials: reduction of LDL and total cholesterol levels leads to a decreased incidence of CHD [2, 3].

Side Effects

A second important question is whether treatment of hypercholesterolemia has significant side effects, i.e., whether it actively causes other diseases, especially cancer. Unfortunately, the trials lack the power to give us reliable information on this aspect. Consider cancer deaths in the Helsinki Heart Study (table 4) [4]. On the face of it, neither this trial nor, for that matter, the Lipid Research Clinics Coronary Primary Prevention Trial [5] showed any evidence that cholesterol lowering promotes cancer. But

Fig. 1. Serum cholesterol levels at entry, and cancer deaths after 6–15 years of follow-up in cohorts of middle-aged men in the Seven Countries Study [7]. Adapted from Katan [8]. Upper curve = total cancer deaths; lower curve = lung cancer deaths.



what if 2 of the 11 patients dying from cancer in the placebo group (table 4) had succumbed just after the trial had finished instead of during the trial, and 2 more of the drug-treated patients had died of cancer during the trial? Instead of a difference of zero, we would then have had an almost 50% excess of cancer deaths in the group receiving active treatment. The reverse holds for the 'accidents and violence' category: simply transfer 3 cases from the drug to the placebo group, and no one would have worried. In statistical terms, it is said that the difference in violent deaths between the drug and placebo groups was not significant. This means it could have been a coincidence; we simply cannot tell. The numbers are too low to allow a reliable answer; even if all the trials are combined, the numbers are still too low.

Thus, the trials cannot settle the cholesterol-cancer issue. Nor are epidemiologic follow-up studies helpful, because by now it is evident that preexisting but undiagnosed tumors caused reduced serum cholesterol levels [6], so that cancer may cause low cholesterol levels instead of the reverse.

However, much more potent and unequivocal evidence on this issue is available. There are hundreds of millions of people who have

Table 4. Number and causes of deaths in the Helsinki Heart Study

Patients	Number	
	placebo (n = 2,030)	gemfibrozil (n = 2,051)
CHD	19	14
Other causes	24	30
Other vascular diseases	4	8
Cancer	11	11
Other medical causes	3	1
Accidents and violence	6	10
Total	43	44

Adapted and corrected from Frick et al. [4]. According to Frick [written comm., 1990], checking of the coding of the patients disclosed some errors in the published [4] mortality data. In the present table 4, there are therefore 1 death less from other medical causes in both groups, and 2 more deaths from accidents and violence in the placebo group than in the original publication.

had low cholesterol levels all their lives. Such people live in countries where the diet is low in saturated fat and cholesterol. As shown in figure 1 [7, 8], there is no evidence that such populations have higher cancer rates than populations with much higher cholesterol levels. If a reduction of cholesterol by 10%

should by itself cause cancer [9], then surely the almost twofold difference in cholesterol levels between Finnish and Japanese men should have caused a perceptibly higher death rate from cancer in the Japanese: this was not the case (fig. 1).

Additional information comes from experiments of nature in the form of genetic disturbances in the regulation of cholesterol levels. That patients with homozygous hyperbetalipoproteinemia (better known as homozygous familial hypercholesterolemia), who have cholesterol levels of 20–30 mmol/l (800–1,200 mg/dl), will often develop myocardial infarctions in the first years of life is well known. It is not always realized that the opposite genetic defect also exists: there are several hundred patients worldwide who suffer from abetalipoproteinemia or homozygous hypobetalipoproteinemia. These patients have an LDL cholesterol level of zero and a total cholesterol level of 0.5–1 mmol/l (20–40 mg/dl). As LDL is the vehicle not only for cholesterol, but also for vitamin E, these patients used to develop massive vitamin E deficiency and its associated neuropathy [10]. Now that this deficiency has been recognized and patients are being treated with megadoses of vitamin E, they live well into their fifties and sixties. The salient point is that excessive cancer rates are not and have never been a feature of these diseases [P.N. Herbert, MD, PhD, pers. comm. October 6, 1987]. This observation is hard to reconcile with any theory that moderate LDL cholesterol lowering will deplete cholesterol from some essential tissues or cells and in that way promote the development of malignant tumors. If that were true, patients with zero LDL cholesterol levels would have rampant tumor growth at an early age, which they do not.

Conclusion and Perspectives for Drug Treatment

Evidence from a number of sources, including trials, shows that reducing serum levels of LDL cholesterol will postpone CHD [2, 3]. The more extensive the lowering, the larger the gain in CHD-free years. In addition, it appears unlikely that a reduction in the level of LDL cholesterol will by itself promote other diseases, especially cancer. However, this does not exclude the possibility that certain forms of cholesterol-lowering treatment may have specific toxic effects. Epidemiologic and trial evidence suggests that diets low in saturated fat and cholesterol are fairly harmless. However, several of the early cholesterol-lowering drugs, including estrogen, dextrothyroxine, and triparanol, caused serious toxicity, and had to be withdrawn. Clofibrate has also been suspected of carcinogenicity, but trials in humans have yielded contradictory evidence for this adverse effect [11, 12].

The new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors have enormous potential for reducing premature CHD and death, and their safety profile to date is satisfactory [13, this issue]. However, no drug is completely free from side effects. There is pressure – from patients more than from physicians – to prescribe reductase inhibitors to very large numbers of people who have only minimal serum cholesterol elevations. In this case, the side effects in the many may outweigh the benefit in the few. This is undesirable not only because of the potential harm to patients not requiring drug therapy, but also because fear of side effects might stop patients with severe hypercholesterolemia from taking these drugs.

Thus, cholesterol lowering as such will probably increase the number of disease-free years for many people in affluent societies. However, the agent used to lower cholesterol should be appropriate to the severity of the hypercholesterolemia, and in the large majority of patients with mild hypercholesterolemia diet is a more appropriate form of treatment than drugs.

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