Cholesterol Reduction Therapy: A Double-edged Knife

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Summary

Cholesterol reduction reduces ischaemic cardiovascular morbidity and mortality in the asymptomatic healthy population as well as in those with known coronary artery disease. Angiographic studies have also demonstrated regression of atherosclerotic plaques as well as retardation of new atheroma formation with such therapy. Yet, there is a consistent inability to reduce overall mortality in cholesterol-lowering drug trials. An excess of suicide, homicide and violence has been attributed to cholesterol reduction interfering with membrane lipids and receptors, leading to aggressive behaviour. The risk and benefits of cholesterol reduction must thus be weighed in the individual patient; it is more useful in those with known coronary artery disease who are at high risk of subsequent ischaemic cardiovascular events.

Key words: Cholesterol reduction, cardiovascular disease.

Introduction

Hypercholesterolemia is a major risk factor for coronary artery disease. It is increasingly being accepted that cholesterol reduction is useful in the primary and secondary prevention of ischaemic cardiovascular events and can result in regression of atheromatous plaques[1,2,3]. However, reviewing the major trials of hypocholesterolemic pharmacotherapy suggests that therapy has its own risks with an unexplained increase in non-cardiac mortality[4,5]. Practicing physicians must be cautious in interpreting the results of drug trials so as to minimise risk and maximise the benefits for any individual patient[6].

Primary prevention of ischaemic heart disease

The World Health Organisation's trial in the primary prevention of ischaemic heart disease using clofibrate was the first large-scale primary prevention drug trial to be published[7]. The reduction in total cholesterol with 1.6 g of clofibrate was 9%. The major end points were fatal ischaemic heart disease and non-fatal myocardial infarction. There were 167 end points in the treatment group and 208 in the control group, a reduction of 20% ($p<0.05$). The difference was mainly due to the reduction in non-fatal myocardial infarction. This study on 15,745 men, over 5.3 years, also had a third control group of patients who had inherently low cholesterol levels. The incidence of major ischaemic end points in this low cholesterol control was significantly less than in the 2 high cholesterol groups, whether treated with clofibrate or not. This suggests that reducing high blood cholesterol with drugs may not be equivalent to a naturally occurring low cholesterol state.

The Lipid Research Clinic's coronary primary prevention trial studied 3,806 asymptomatic middle-aged men with primary hypercholesterolemia[8]. Treatment with cholestryamine 24 g per day reduced total cholesterol by 13.4% and LDL-cholesterol by 20.3%. The primary end point was either coronary heart disease death or non-

fatal myocardial infarction. Over the 7 years of study, there were 155 end points in the cholestyramine group and 187 in the placebo group, a reduction in risk of 19% ($p<0.05$). Inclusion of patients with possible coronary deaths and possible non-fatal myocardial infarction did not change the results. Similarly, other cardiac events such as the development of angina, of new positive exercise tests and the incidence of coronary bypass surgery were all lower in the treatment group.

The Helsinki Heart Study was a randomised, double-blind trial on 4,081 asymptomatic men who either received gemfibrozil 600 mg twice daily or a placebo[9]. Therapy reduced the total cholesterol by 11%, the LDL-cholesterol by 10% and increased the HDL-cholesterol by over 10%. Cardiovascular end points were defined as fatal and non-fatal myocardial infarction and cardiac deaths. At the end of 5 years, there were 56 cardiac end points in the treated group and 84 in the placebo group. The overall reduction in cardiac end points was 34% (95% confidence interval 8.2% to 52.6%; $p<0.02$). The greatest reduction was in the incidence of non-fatal myocardial infarction.

A review of the mortality data of 6 primary prevention trials totalling 24,847 men followed up for 119,000 person-years was published in 1990[10]. Two of the trials involved only dietary manipulation while the other 4 involved pharmacological cholesterol reduction. Mortality from coronary heart disease was lower in the treatment groups (169 deaths treatment group compared to 197 deaths placebo group; $p=0.06$). However, if only the drug trials were analysed, the reduction reached statistical significance (89 deaths treatment group compared to 113 deaths placebo group; $p=0.04$). Cholesterol-lowering pharmacotherapy thus seems to be useful in the primary prevention of coronary mortality.

Secondary prevention of ischaemic heart disease

In contrast to these large primary prevention studies, there have been surprisingly fewer and smaller secondary prevention trials. The Stockholm Ischaemic Heart Disease Secondary Prevention Study recruited consecutive survivors of a myocardial infarction under 70 years of age into either a control group or for treatment with clofibrate and nicotinic acid[11]. Serum cholesterol was reduced by 13% and triglycerides by 19%. Over a 5 year period, ischaemic heart disease mortality was reduced by 36% and there was also a significant reduction of non-fatal cardiovascular events. Hypertriglyceridemia (50%) was more common then hypercholesterolemia (13%) amongst the population in this study and the decrease in ischaemic heart disease death was directly related to the degree of triglyceride lowering.

The results from the Coronary Drug Project are less distinct[12]. A total of 8,341 men were allocated to 1 of 5 lipid-lowering regimes; 3 regimes were discontinued because of excess adverse effects. Clofibrate achieved only a 6% reduction in serum cholesterol and had no effect on ischaemic events. Nicotinic acid, however, reduced cholesterol by 10% and achieved a significant reduction in non-fatal infarction (10.2% nicotinic acid group vs 13.8% control group; $p<0.01$). Although the fatality rate during the 5 years of study with nicotinic acid was not significantly different from that in the control group, long-term follow-up (mean 15 years) showed a significant reduction in the fatality rate of the nicotinic acid group[13]. Two British trials, over-burdened by subset analysis, suggested that the reduction in cardiovascular events with hypocholesterolemic therapy was more in patients with angina rather than in patients with a prior infarction[14,15]. A body of opinion developed that while lipid reduction is important, other factors such as the extent of myocardial damage were of greater importance in preventing further cardiovascular events[2].

Rossouw reviewed 8 cholesterol-lowering secondary prevention trials, 6 of which involved pharmacological therapy[16]. A meta-analysis of the 7,837 patients showed significant reduction of non-fatal (odds ratio 0.75), fatal (odds ratio 0.84) and total (odds ratio 0.78) myocardial infarction. For every 1,000 patients treated, 27 fewer infarctions were prevented compared to 6 fewer infarctions per 1,000 patients in the primary prevention studies. Patients who have ischaemic heart disease are at high risk of subsequent cardiac events and, hence, have most

to gain from the reduction in absolute risks. It was suggested that a more strict goal in cholesterol reduction is justified in these patients; total cholesterol should be reduced to below 5.2 nmol/l and LDL-cholesterol reduced to below 3.4 nmol/l.

Regression of Atheroma

Recently, evidence has accumulated that lowering cholesterol can retard progression of atherosclerosis as well as induce regression of existing lesions. The Cholesterol Lowering Atherosclerosis Study (CLAS) is a placebo-controlled angiographic study using colestipol and niacin on 162 men with previous bypass surgery studied over a 2 year period[6,17]. A 26% reduction in total cholesterol, a 43% reduction in LDL-cholesterol and a 37% elevation of HDL-cholesterol was achieved. Atherosclerotic regression occurred in 16.2% of total patients compared to 2.4% with regression in the placebo group ($p=0.002$). Similarly, lesion progression and new lesions were less common in the treatment group whether in the native coronary vessels or bypass grafts. This was the first angiographic study to demonstrate the value of cholesterol reduction on atherosclerotic lesions; the benefit was noted throughout the whole range of cholesterol levels from 4.8 nmol/l to 9.1 nmol/l.

In the Familial Atherosclerosis Treatment Study (FATS), 120 men with coronary artery disease detected on baseline angiogram completed a 2.5 year double-blind study[18]. Three treatment regimes were implemented, lovastatin and colestipol, niacin and colestipol or conventional treatment with placebo (and colestipol added if LDL-cholesterol is elevated). Placebo treatment reduced LDL-cholesterol by 7% and increased HDL-cholesterol by 5%. On the other hand, lovastatin-colestipol reduced LDL-cholesterol by 46% and increased HDL-cholesterol by 15%, while niacin-colestipol reduced LDL-cholesterol by 32% and increased HDL-cholesterol by 43%. There is a highly significant reduction in atherosclerotic progression and increase in atherosclerotic regression in the treatment group ($p<0.005$). The relative risk of a clinical event in the treatment group was 0.27 (see Table I). The importance of cholesterol reduction on angiographic and clinical improvement in patients with definite coronary artery disease is thus re-emphasised

Ninety men with known coronary artery disease with mean serum cholesterol of 7.23 nmol/l were entered into the St Thomas' Atherosclerosis Regression Study (STARS)[19]. They were randomised to receive the usual care (U), dietary intervention (D) or diet plus cholestyramine (DC). Angiography was carried out at baseline and after about 40 months. Serum cholesterol was reduced to 6.93 nmol/l in the U group, to 6.17 nmol/l in the D group and to 5.56 nmol/l in the DC group. Atherosclerotic progression was retarded and regression induced by both treatment groups. Similarly, cardiovascular events were reduced with intervention (see Table II). Over the study period, the mean absolute width of the coronary segments decreased by 0.201 mm in the control

Table I
Beneficial effects of hypercholesterolemic therapy in the Familial Atherosclerosis Treatment Study

	No of patients	Percentage of patients with		No of clinical events
		Progression	Regression	
Lovastatin	46	21	32	3
Niacin	48	25	39	2
Placebo	52	46	11	10

group, yet increased by 0.03 mm in the D group (p=0.06) and increased by 0.103 mm in the DC group (p<0.001). The authors support cholesterol-lowering therapy in men with known coronary artery disease even if the serum cholesterol is only mildly raised.

Therapy and Mortality

There has been a persistent inability to reduce overall mortality in lipid-lowering trials despite the reduction in cardiovascular events. In the Helsinki Heart Study with gemfibrozil, over a 5 year period, there were 45 deaths in the treated group of 2,051 patients and 42 deaths in the control group of 2,030 patients. In the Lipid Research Clinic coronary primary prevention trial, at the end of seven years, 68 deaths were noted amongst 1,906 treated patients and 71 deaths occurred amongst 1,900 control patients. In the WHO trial on olofibrate, a significant excess of mortality in the treated group was noted (162 deaths in the treatment group compared to 127 deaths in the control group; p<0.05). In Muldoon's review of primary prevention trials, 590 deaths occurred in the 12,457 patients in the treatment group and 557 deaths occurred in the 12,390 patients in the control group.

The Stockholm Ischaemic Heart Disease Secondary Prevention Study did demonstrate a reduction in overall mortality (82 deaths in control, 61 deaths in treatment group; p<0.05). However, other secondary prevention trials supported the contention that total mortality is unchanged when hypercholesterolemia is lowered. In the Coronary Drug Project, during the study period, 5 year overall fatality with clofibrate was 20.0%, with nicotinic acid was 21.9% and with placebo was 20.9%. In Rossouw's review of 7,837 patients in 8 secondary prevention trials, there was no significant reduction in overall mortality. The highly significant increase in the number of non-cancer, non-cardiovascular deaths noted in the treated group (odds ratio 2.10; p<0.01) balance the reduction in cardiovascular mortality.

The excess of non-cardiac mortality with cholesterol reduction is unlikely to be a specific effect of any drug in view of this finding being noted in various trials using different drugs. The narrow confidence limits of the increased non-cardiac mortality and the level of significance reached makes chance an unlikely explanation for this finding[20]. The excess non-cardiac mortality came mainly from violent and accidental deaths. It has been postulated that lowering serum cholesterol levels would in turn lower membrane cholesterol with resulting lowering of membrane serotonin receptors leading to decreased brain serotonin levels and reduced suppression of aggressive impulses. This would, in turn, cause an increase in suicide, homicide and violence[21]. There is some evidence that these adverse effects are noted when drugs, rather than dietary manipulation, are used to lower serum cholesterol levels, and are not noted in dietary trials or in naturally occurring populations with low cholesterol levels[22,23].

Table II
Beneficial effects of hypocholesterolemic therapy in the St Thomas' Atherosclerosis Regression Study

	No of patients	Percentage of patients with lesion		No of clinical events
		Progression	Regression	
Usual care (U)	28	46	4	10
Diet (D)	27	15	38	3
Diet & cholestyramine (DC)	26	12	33	1

Conclusion

Patients presenting with hypercholesterolemia fall into 1 of 2 groups, those with definite ischaemic heart disease and those without evidence of myocardial ischaemia. The data supporting the importance of lipid reduction in patients with atherosclerotic heart disease is irrefutable — it prevents further coronary events, causes regression of existing atheroma and prevents development of new lesions. Thus, an aggressive approach to hypercholesterolemia is required in such patients. A strict dietary regime, supported by drugs if necessary, should be implemented to normalise cholesterol levels (total cholesterol less than 5.2 nmol/l, LDL-cholesterol less than 3.4 nmol/l). On the other hand, the approach to the patient with hypercholesterolemia and no myocardial ischaemia should be more conservative. The large majority of these patients are hypercholesterolemic because of an unhealthy diet and dietary restriction should be the prescribed therapy[3]. In view of the possible risks of hypocholesterolemic drugs, the initiation of drug therapy is not justified in these otherwise healthy patients. The exception to this rule is the patient with familial hypercholesterolemia. These patients have a strong family history of premature atherosclerosis and have very high serum cholesterol levels (usually above 8.9 nmol/l)[24]. The high risk for myocardial ischaemia justifies the usage of cholesterol lowering drugs.

Prescription of hypocholesterolemic drugs has escalated in the United States and the United Kingdom. In Malaysia, we must beware and avoid this trend, which is not only costly but may actually have a deleterious effect on our patients. We should also remember that palm oil is cholesterol-free and favourably affects cardiovascular risk profile[25]. Furthermore, the traditional rural Malaysian diet has a low fat content[26]. Perhaps we can best serve our community by fully digesting the clinical trials of the developed, Western world but strongly advise our patients to stay away from their lifestyle and dietary habits.

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