Protecting the Heart: A Practical Review of the Statin Studies

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Abstract and Introduction

The aim of this review of the landmark HMG-CoA reductase inhibitors (statins) studies is to enable the clinician to draw practical lessons from these trials. The Scandinavian Simvastatin Survival Study (4S) established the importance of treating the hypercholesterolemic patient with established cardiovascular heart disease. The West of Scotland Coronary Prevention Study (WOSCOPS) showed the benefit of treating healthy hypercholesterolemic men who were nevertheless at high risk of developing cardiovascular heart disease in the future. The Cholesterol and Recurrent Events (CARE) study, a secondary prevention trial, proved the benefit of treating patients with myocardial ischemia and cholesterol levels within normal limits.

This conclusion was confirmed by the Long-term Intervention With Pravastatin In Ischemic Disease (LIPID) study, another secondary prevention study that enrolled patients with a wide range of cholesterol levels (4-7 mmol/dL), into which the large majority of patients would belong. The importance of treating patients with established ischemic heart disease (IHD), and those at high risk of developing cardiovascular heart disease, regardless of cholesterol level, was being realized. The Air Force/Texas Coronary Artery Prevention Study (AFCAPS/TexCAPS) then showed that treatment can reduce adverse cardiovascular events even in the primary prevention of patients with normal cholesterol levels.

The Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering (MIRACL) trial showed that hypocholesterolemic therapy is useful in the setting of an acute coronary syndrome, while the Atorvastatin Versus Revascularisation Treatment (AVERT) study showed that agressive statin therapy is as good as angioplasty in reducing ischemic cardiac events in patients with stable angina pectoris.

Finally, the Heart Protection Study (HPS) randomized more than 20,000 patients, and the value of statins in reducing adverse cardiovascular events in the high-risk patient, including the elderly, women, and even in those with low cholesterol levels, is beyond doubt. The emphasis is now on the risk level for developing cardiovascular events, and treatment should target the high-risk group and not be dependent on the actual cholesterol level of the patient. It is interesting to compare the large amount of data on the value and safety of the statins with the much more limited and less convincing data on antioxidant vitamins.

There has been an explosion of data and trials in the 1990s on the role of cholesterol reduction in the management of patients with IHD or those at risk of future development of IHD. It was barely a decade ago that the value of hypolipidemic therapy was questioned and its possible role in increasing noncardiac mortality was raised. In reviewing the developments leading up to the present day, we come to appreciate that many of the questions and suspicions of hypolipidemic therapy have been answered. Yet, many are more attracted to antioxidant therapy, the value of which is not established. We need to familiarize ourselves with the evidence accumulated so that we can appropriately advise patients who may be incorrectly informed by the lay literature or press releases.

The Beginnings: 4S, WOSCOPS, and CARE

4S ushered in the era of megatrials on hypolipidemic therapy. In hindsight, this was a very well conceived trial because it addressed the question for which a positive answer was most likely. It looked at patients who were already suffering from IHD and had definitely elevated cholesterol levels, and investigated whether lowering the cholesterol levels in these patients would bring benefit. A total of 4444 patients with angina or prior myocardial infarction and serum cholesterol between 5.5 and 8.0 mmol/L were put on either simvastatin or placebo and followed up for a median of 5.4 years. Total cholesterol was reduced by 25%, and low-density lipoprotein (LDL) cholesterol by 35% in the treatment group. Treatment with simvastatin reduced major coronary events (defined as coronary death, myocardial infarction, or resuscitated cardiac arrest, relative risk [RR] 0.66, 95% confidence interval [CI] 0.59-0.75), reduced coronary mortality (RR 0.58, 95% CI 0.46-0.73), and reduced total mortality (RR 0.70, 95% CI 0.58-0.85). Furthermore, therapy also reduced the need for coronary revascularization with bypass surgery or angioplasty (RR 0.63, 95% CI 0.54-0.74). There was no difference in noncardiovascular deaths in the treated and placebo groups. This study established clearly that hypolipidemic therapy is safe and it reduces morbidity and mortality in hypercholesterolemic patients with IHD. It is thus reasonable to conclude that all patients with significantly elevated cholesterol levels and known prior cardiovascular heart disease should have their hypercholesterolemia treated to reduce future adverse events. A subsequent substudy confirmed the value of therapy in diabetic patients.

The next major study chronologically, was WOSCOPS. This addressed a different question from 4S and investigated whether hypolipidemic therapy was beneficial in hypercholesterolemic men without a prior history of myocardial infarction. A total of 6595 men aged 45-64 years were put on either pravastatin 40 mg per day or placebo, and followed up over an average of 4.9 years. Total cholesterol was reduced by 20% and LDL cholesterol reduced by 26% with treatment. Although this was a primary
prevention study, the subjects enrolled were actually at high risk for coronary events, being middle-aged men with markedly elevated cholesterol levels (total cholesterol 7.03 +/- 0.57 mmol/L), elevated body mass index (26 +/- 3.1 kg/m²), and more than a third were current smokers. In this high-risk group, pravastatin therapy reduced coronary events by 31% (95% CI 17% to 43%), revascularization procedures by 37% (95% CI 11% to 56%), and cardiovascular mortality by 32% (95% CI 3% to 53%). There was no difference in noncardiovascular mortality, and the reduction in total mortality of 22% was of borderline significance (P = .051). This suggests that in these subjects with no definite prior IHD, treatment of elevated lipid levels does not bring about as great a benefit as it would in a population known definitely to have cardiovascular disease, as in the 4S population. Nevertheless, the reduction of adverse coronary events in WOSCOPS is impressive and the message has been made that the high-risk hypercholesterolemic patient who was not previously known to have IHD would benefit from treatment of hyperlipidemia. The goal post has been moved -- the message is out to seek out the high-risk hypercholesterolemic patient who has now been shown to benefit from statin therapy.

The following year saw the publication of the CARE study.[6] This study was on patients with a past history of a myocardial infarction but who had average cholesterol levels (5.4 +/- 0.4 mmol/L). A total of 4159 patients had a median follow-up of 5 years. Total cholesterol was reduced by 20% and LDL cholesterol by 28%. Compared with placebo, pravastatin therapy reduced the primary end point (defined as coronary death or nonfatal myocardial infarction) by 24% (95% CI 0% to 36%). In this study, there was no significant difference in cardiovascular, noncardiovascular, or total mortality; it was myocardial infarction that was markedly reduced, and this accounted for the significant reduction in primary end point. The need for revascularization procedures and the incidence of strokes were also lowered significantly with pravastatin therapy. The inescapable conclusion was that in patients with a prior myocardial infarction (secondary prevention), hypolipidemic therapy is important even if cholesterol levels are not highly elevated. However, the absence of coronary mortality reduction and the lower percentage reduction of major coronary events in the CARE study compared with 4S suggests that it is the hyperlipidemic and high-risk patient who will benefit most from therapy.

The historical impact of these 3 trials, published over a 2-year period, is especially remarkable when one considers what was available in the 2 decades prior to their appearance. Hypcholesterolemic drug trials achieved only modest reduction of total cholesterol levels of about 10% compared with a 20% to 30% reduction with the statins. These drugs produce significant unpleasant adverse effects, suggested an increase of noncardiac mortality, and appeared to have no impact on total mortality.17-10 The disappointing results of drug trials then made dietary and lifestyle studies appear impressive.11,12 However, dietary and lifestyle changes are difficult to implement and maintain on a large scale. Moreover, the difference between a diet with under 10% of total calories from saturated fat and one with under 7% of total calories from saturated fat may be more significant to the researcher than to the clinician or the patient. Today, we argue for a therapeutic lifestyle and for healthy eating habits, but the safety, efficacy, and tolerability of the statins are so well established that the latest clinical guidelines all devote much more attention to pharmacologic therapy than to dietary advice in the primary and secondary prevention of cardiovascular disease.13-15 It was these 3 statin trials that laid the foundation of our fundamental change in practice habits.

The LIPID study emphasized the importance of hypolipidemic therapy in the secondary prevention setting.[16] Patients enrolled had a history of myocardial infarction or unstable angina with a very broad range of initial total cholesterol levels varying from 4.0-7.0 mmol/L. A total of 9014 patients were enrolled in this placebo-controlled study and followed up over a mean of 6.1 years. The primary end point was coronary mortality and this was reduced with pravastatin therapy by 24% (95% CI 12% to 35%). Total mortality was reduced by 22% (95% CI 13% to 31%). There was also a significant reduction of major coronary events (coronary death and nonfatal infarction) by 24%, coronary revascularization by 20%, and strokes by 19%. A later paper showed that the stroke reduction was due to a reduction of nonhaemorrhagic strokes, with no effect on haemorrhagic strokes.[17] Although subgroup analysis of LIPID showed the benefit of hypolipidemic therapy to extend over all ranges of total cholesterol levels, there was a suggestion that benefit was most in those with the highest LDL cholesterol. It stands to reason that even in secondary prevention, it is those at highest risk of another coronary event who will benefit most from intervention.

The focus returned to primary prevention, and AFCAPS/TexCAPS was a placebo-controlled, randomized trial to investigate the effects of lovastatin therapy on an average-risk healthy population with normal total cholesterol levels (mean 5.71 +/- 0.54 mmol/L).[18] After an average follow-up of 5.2 years in a total of 5608 men and 997 women, the first major coronary event, defined as myocardial infarction, unstable angina, or sudden death, was highly significantly reduced (RR 0.63, 95% CI 0.50-0.79). A similar marked improvement was seen in risk of myocardial infarction, unstable angina, and coronary revascularization. Although no adverse effect of therapy was seen in comparison with the placebo group, there was no difference in the total mortality of the 2 groups.[19] In fact, there were 80 deaths in the lovastatin group and 77 in the placebo group (RR 1.04, 95% CI 0.76-1.42). What was equally striking was that of the total deaths (157) in both the treatment and placebo groups, more than two thirds (115) were from noncardiovascular causes. This emphasizes the point that in a group of people not at high risk of coronary deaths, therapy to lower cholesterol cannot do very much to lower mortality as the patients are more likely to succumb to noncardiovascular causes. Previous experiences with nonstatin hypcholesterolemic drugs have revealed similar findings of a reduction in cardiac end points without total mortality reduction in primary prevention trials. AFCAPS/TexCAPS thus emphasizes the point that in primary prevention, targeting patients at higher risk will bring a bigger impact at lower cost.[20,21] Furthermore, the safety and efficacy of lovastatin is most welcomed given its lower cost compared with the other patented statins.

The 4S recruited patients from throughout the Scandinavian countries. WOSCOPS enrolled Scottish patients, CARE and AFCAPS/TexCAPS were North American studies, and the patients for LIPID were from Australasia. That patients from various regions throughout the world similarly benefit from statin therapy is reassuring, but not surprising. The Seven Countries Study clearly showed that the relationship of increasing cholesterol levels and increasing coronary heart disease mortality holds true across various regions of the world, although different regions are at different absolute risk of disease. Thus, it is reassuring to find that treatment of hypercholesterolemia is also similarly useful in various parts of the world. The challenge for clinicians is to get the correct message from these various statin trials. The publication of LIPID and AFCAPS/TexCAPS confirms that patients at high risk should receive therapy to reduce adverse cardiovascular events, even if their actual cholesterol levels were not in the elevated range. The shifting of concern from the actual cholesterol level to the risk profile of the patient certainly is logical when one remembers that hypercholesterolemia by itself is asymptomatic, and it is the cardiovascular disease to which the hypercholesterolemic patient is prone that brings morbidity and mortality.

Getting Aggressive: MIRACL and ADVERT

Besides lowering cholesterol levels, statins are known to modify endothelial function, stabilize plaques, and reduce inflammation and thrombus formation. The MIRACL study looked at the effect of atorvastatin used early in the acute coronary syndromes. A total of 3086 patients with unstable angina or non-Q wave myocardial infarction were randomly assigned to placebo or atorvastatin 80 mg daily between 24 and 96 hours of admission. After a follow-up of 16 weeks, atorvastatin therapy produced a significant reduction of primary end point, which was defined as death, nonfatal myocardial infarction, cardiac arrest, or recurrent symptomatic ischemia (RR 0.84; 95% CI 0.70-1.00). Unfortunately, there was no significant change in death, nonfatal myocardial infarction, or cardiac arrest, and the benefit is seen in the reduction of recurrent ischemia. Thus, while this study established the safety and efficacy of statins in the acute coronary setting, it also suggests that more benefit will come from other therapeutic intervention when dealing with unstable angina and myocardial infarction.

The AVERT study confirmed, and there is a suggestion that it may be as efficacious as percutaneous intervention in managing patients with stable angina pectoris. In fact, trials of angioplasty vs medical therapy in stable angina pectoris have shown that angioplasty does not reduce the incidence of myocardial infarction and has no effect on coronary mortality. In fact, most myocardial infarctions are due to the sudden disruption of the mildly stenotic lesions, and not the progression of previously severely narrowed plaques. Since angioplasty treats only those severely stenotic lesions and does nothing to the mildly stenotic plaques, it cannot have a big impact in reducing myocardial infarction. Moreover, there is increasing evidence that acute coronary syndromes develop in the setting of a systemic inflammatory state. Since the statins also have an anti-inflammatory and plaque stabilization effect, it stands to reason that they would be better able to prevent plaque rupture than angioplasty, which only targets a local stenotic plaque. Further work is needed in this area, but it does seem that drug therapy has much to offer in preventing the adverse effects of atherosclerosis.

Resolving All Doubts: HPS

The recent publication of the Heart Protection Study (HPS) should firmly establish the benefit of statin therapy in preventing adverse events in patients at high risk of atheromatous disease. Patients recruited were defined as being at high risk of coronary mortality because of prior coronary disease (secondary prevention), presence of noncoronary atheromatous disease, or diabetes. A total of 20,536 patients were enrolled and followed up for an average of 5.5 years. Patients were randomized to receive simvastatin 40 mg per day or placebo. Simvastatin reduced the coronary mortality by 18% (P = .0005) and this resulted in a highly significant reduction in total mortality (P = .0003). Highly significant reduction was also seen in stroke, major cardiovascular events, and need for coronary and noncoronary revascularization (all P < .0001). There was no increase in nonhaemorrhagic stroke and no effect on noncardiac mortality. Benefit was seen clearly in women, in the elderly, in diabetics, and in patients with prior noncardiac atheromatous disease. This benefit extends to those patients with initially low total and LDL cholesterol levels. In fact, the proportional reduction in adverse events was found to be the same in all categories of lipid levels in the patients studied, even in those with initial LDL cholesterol below 3 mmol/L and total cholesterol below 5 mmol/L. There can now be no doubt of the strategy to take. All patients at high risk of atheromatous disease must be given statin therapy, which will reduce adverse coronary and other vascular events. Baseline cholesterol levels are just one of the many risk factors in atheromatous disease, and decision on therapy should be based on an assessment of overall risk and not just the lipid level.

With the publication of the HPS, it is hard to argue with the conclusion that statin therapy is safe. All these statin trials have now randomized well over 50,000 patients, and statin therapy has been available to clinicians for more than 2 decades. No therapy is
free of adverse effects, and the cerivastatin saga highlights the importance of proper patient monitoring and the need for caution with newer formulations and in combining drugs.\textsuperscript{[36]} Nevertheless, the acceptability of the statins contrasts significantly with the poor palatability and high discontinuation rates of niacin and the sequestrant formulations.\textsuperscript{[37]} Although expensive, statin therapy for hyperlipidemia has been shown to be cost effective if the right patient group is targeted.\textsuperscript{[38-41]} The evidence from the trials is that all patients with atheromatous disease or who are at high risk of future atheromatous disease need statin therapy. Less emphasis should be placed on the actual lipid level, and more consideration must be given to the cardiovascular risk profile of the patient. Underutilization of statin therapy is still prevalent today and is a practice that needs to be discouraged as it is far better to prevent coronary disease than to treat its consequences.\textsuperscript{[42]}

It is interesting to contrast briefly the statin story with the evidence on antioxidant vitamins. The HPS also looked at the value of antioxidant vitamin supplementation in preventing adverse events in this large group of high-risk patients.\textsuperscript{[43]} Patients received supplementation with 600 mg vitamin E, 250 mg vitamin C, and 20 mg beta-carotene daily, or matching placebo. Although vitamin supplementation significantly elevated serum vitamin levels, there was no effect on vascular or nonvascular mortality, strokes, major vascular events, and cancer incidence. The disappointing results in the antioxidant vitamin arm of the HPS means we should discourage such therapy that has been proven to carry no benefit. This need for caution with antioxidants is reinforced by a recent angiographic study.\textsuperscript{[44]} A total of 160 patients with coronary artery disease were enrolled in the 3-year double-blind trial and randomly assigned to simvastatin plus niacin, antioxidants, simvastatin-niacin plus antioxidants, or placebo. The average stenosis progressed by 3.9% on placebo, 1.8% on antioxidants, 0.7% on simvastatin-niacin plus antioxidants (P = .004 compared with placebo), and it regressed by 0.4% on simvastatin-niacin alone (P < .0010). Similarly, clinical end point was 24% with placebo, 21% with antioxidants, 14% with simvastatin-niacin plus antioxidants, and only 3% with simvastatin-niacin. The clinical benefit from statin therapy and its ability to induce regression of atherosclerosis is well known.\textsuperscript{[45]} The surprising result is that antioxidants appear to reduce the benefit derived from hypolipidemic therapy. The disappointing effect of vitamin E has been noted in several large studies that have concurrently shown the value of fish-oil, angiotensin-converting enzyme inhibitor, and aspirin in prevention of adverse cardiac events.\textsuperscript{[46-48]} Given this poor record of antioxidants in controlled clinical trials, evidence-based clinical practice means that we should advise patients with IHD to avoid vitamin E and other antioxidants.\textsuperscript{[49]}

### Conclusion

It is important to seek useful lessons for the practicing physician from these statin trials on hyperlipidemia. The beneficial effect of statin therapy in reducing adverse cardiovascular events, as well as reducing coronary mortality and total mortality in high-risk patients, is overwhelming. There has to be a change in emphasis away from the concept of a "normal lipid profile." Instead, the emphasis should be on risk factors predisposing to coronary disease. The actual threshold for the initiation of therapy varies, but the principle remains the same.\textsuperscript{[13-15,50]} The higher the risk, assessed from prior atheromatous disease, diabetes, blood pressure, smoking status, age, and sex, besides the lipid levels, the greater the need to treat and to treat aggressively. Whether statins work by reducing lipid levels or by plaque stabilization or an anti-inflammatory effect is a matter for future researchers to resolve. Present clinicians need to place less emphasis on lipid levels and more importance on risk stratification of the patient. Indeed, a case can be made for all patients with a prior atheromatous disease to be on a statin, regardless of their initial cholesterol level. Equally important, extrapolating especially from the primary prevention trials, the patient not at high risk of cardiovascular events should not be treated merely because of an abnormal lipid profile, as there will not be any significant mortality reduction.

### References


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