

Recent Clinical Trials and Aggressive Management of Dyslipidemic Patients

Based on a presentation by Donald B. Hunninghake, MD

Presentation Summary

Three recent studies have confirmed the benefit of lipid lowering in reducing morbidity and mortality from coronary disease. These are the Scandinavian Simvastatin Survival Study, the Cholesterol And Recurrent Events trial, and the West of Scotland Coronary Prevention Study. These studies all show the benefit of aggressive lipid management. In addition, a fourth, yet-unpublished study, the Post-Coronary Artery Bypass Grafts study, provides evidence to support lipid lowering to a target low-density lipoprotein cholesterol (LDL-C) of 100 mg/dL or lower.

In today's managed care environment, priorities need to be established as to which interventions will cause the greatest reduction in coronary events. Smoking cessation, lipid management, and aspirin consumption are all effective in-

terventions. In addition to diet, exercise, and other lifestyle changes, patients with coronary disease and LDL-C levels of greater than 130 mg/dL should also receive lipid-lowering therapy, a suggestion that is supported by the aforementioned studies and the National Cholesterol Education Project guidelines.

Patients should be prioritized in terms of those who need drug therapy. The highest priority should be those who have clinical manifestation of atherosclerotic disease. The second priority should be patients who have not had a coronary event but have LDL-C levels above 160 mg/dL or two or more risk factors. In addition, those who stand to benefit the most from aggressive lipid lowering therapy include patients with diabetes, hypertension, high triglycerides, low levels of high-density lipoprotein cholesterol, and those who smoke.

The first priority in lipid management is people with established evidence of coronary heart disease (CHD). Approximately 12 million Americans fall into this category and are thus eligible for lipid-lowering therapy.¹ We are interested in this group of people because they are at high risk for coronary events and death.

Approximately half of the myocardial infarctions (MIs) and about 70% of the

coronary deaths in the United States occur in individuals who have had prior clinical manifestation of cardiovascular disease.² This includes patients with evidence of coronary, cerebral, or lower extremity atherosclerosis. The risk of coronary events and CHD death is similar in patients with cerebral or lower extremity atherosclerosis to those with a prior MI.

Three recent trials have confirmed the benefit of lipid lowering in reducing morbidity and mortality from coronary disease (Tables 1 & 2): The Scandinavian Simvastatin Survival Study (4S),³

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Table 1. Summary: 4S, WOSCOPS, CARE Trials

	4S	WOSCOPS	CARE
Number of Patients	4,444	6,595	4,200
Gender	81% men; 19% women	100% men	86% men; 14% women
Age	35-70 years	45-64 years	24-75 years
Lipid-Lowering Agent	Simvastatin 20-40 mg/day	Pravastatin 40 mg/day	Pravastatin 40 mg/day
Mean Follow-Up	5.4 years	4.9 years	5 years
Changes in Lipid Levels:			
Total Cholesterol	-25%	-20%	-20%
LDL-C	-35%	-26%	-26%
HDL-C	+8%	+5%	+5%
Triglycerides	-10%	-12%	-14%

Table 2. Endpoints (Percent Risk Reduction)

	4S	WOSCOPS	CARE
Nonfatal MI or CHD Death	34% (men)	31%	45% (women)
	34% (women)	(men only)	20% (men)
PTCA or CABG	37%	37%	27%
CHD Death	42%	33%	20%
Death from any Cause	30%	22%	24%

the Cholesterol and Recurrent Events (CARE) trial,⁴ and the West of Scotland Coronary Prevention Study (WOSCOPS).⁵

The 4S Trial

The 4S was a large, well-designed, randomized, placebo-controlled study and it was the first trial to show that lipid-lowering with an HMG-CoA reductase inhibitor (a statin) saves lives. The study enrolled 4,400 patients up to the age of 70 with total cholesterol levels in the range of 209 mg/dL to 304 mg/dL. More than 80% of those entered in this study had experienced prior MI; the rest had angina. All subjects were on a lipid-lowering diet for 8 weeks before going on drug therapy. This trial, as well as the other trials discussed in this paper, shows the benefit of aggressive lipid management.

Patients were randomized to receive either 20 mg simvastatin or placebo. The dose of simvastatin was titrated to 40 mg

if the total cholesterol level remained above 200 mg/dL, with the goal of getting total cholesterol to below 200 mg/dL. However, goal level was not reached in all of the patients. Over the entire course of the study, the low-density lipoprotein cholesterol (LDL-C) reduction was about 35%, and slightly more than a third of these patients were titrated up to 40 mg of simvastatin. The primary endpoint was to show a reduction in total mortality. Total mortality was significantly reduced by 30% with simvastatin. A 42% reduction in risk of coronary deaths was achieved with lipid-lowering therapy as well.

The 4S was the first study that conclusively showed in a prospective fashion that lowering cholesterol in women also reduced the risk. Simvastatin produced a 34% reduction in major coronary clinical events in women. Individuals over the age of 60 and less than 60 also benefited from treatment. Interestingly, 4S achieved a 30% reduction in risk of stroke, even though the numbers are small, which should have a major impact on our thinking about treating older individuals. Other recent trials are also showing a reduction in stroke incidence.

Importantly, there were essentially no significant long-term adverse effects in this trial. There was no change in the incidence of deaths due to cancer or other noncardiovascular causes with lipid-lowering treatment. Transaminase elevations were no greater in the simvastatin group versus placebo.

All of the recent trials have shown the same safety pattern over a 5- or 6-year period of time. The safety of treatment with HMG-CoA reductase inhibitors is an important message to get across to physicians. Many physicians are still afraid of potential toxicity of the statins; they need to know that these drugs are safe to use.

Cost-effectiveness is another issue that is being discussed. Physicians will hear that the statins are cost effective in terms of decreasing the frequency of hospitalizations, which was seen in the 4S and other recent trials.⁶ It is noteworthy that hospitalizations were also reduced for individuals with congestive heart failure (CHF), a very expensive disease to manage.

One analysis projected what the costs would be if 4S were conducted in the US and achieved the same results.⁶ The authors calculated that if this study had been done in the US at that time, it would have cost about \$2.30 a day for the drug, minus \$2.02 for reduced hospitalization costs, with a net daily cost of 28 cents. When additional monitoring costs were added, the net cost of treatment would have been 41 cents per day to achieve these results. There is no argument about the benefits and the cost-effectiveness of lipid management in patients with established coronary disease.

The CARE Study

The 4S trial enrolled patients with elevated cholesterol levels, with a mean baseline of 192 mg/dL. The bulk of patients seen in practice with established CHD tend to have much lower LDL-C levels. Before publication in October, CARE study results were presented at the American College of Cardiology meeting in March of 1996. CARE enrolled 4,200 men and women with a history of prior MI within the past 2 years and LDL-C levels between 115 to 174 mg/dL (median 137 mg/dL), which are more representative of the patients seen in clinical practice than those in the 4S trial. Patients up to the age of 75 were

included, whereas the 4S trial enrolled patients up to age 70. The mean follow-up was 5 years. Patients were randomized to 40 mg of pravastatin or placebo.

In this study, treatment with 40 mg pravastatin achieved a 26% decrease in

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LDL-C, a 24% relative risk reduction in the combined endpoint of fatal and non-fatal MI, a 25% relative risk reduction for MI alone, and a significant risk reduction of 27% in need for coronary bypass surgery and angioplasty compared to placebo.

In the CARE study population, which had lower LDL-C levels and less aggressive LDL-C lowering than in the 4S trial, there was significant benefit. The reduction in fatal or nonfatal MI and the need for revascularization or angioplasty was 20% in individuals who were younger than 60, and 27% in those aged 60 to 65 years. The percent of risk reduction in women was greater than in men: 45% versus 20%. The 4S trial also showed that women benefit from lipid-lowering treatment. Some of the angiographic trials have also provided evidence for benefit in women. Clearly, women with coronary disease benefit from treatment, but more data are needed to determine how that benefit compares to men.

One observation in CARE will be questioned by some cardiologists. CARE results suggested that there was no benefit for individuals with baseline LDL-C levels of less than 125 mg/dL. This observation was part of a subgroup analysis, but epidemiology studies suggest that some benefit should occur with LDL-C levels well below 100 mg/dL. This study did confirm the National Cholesterol Education Project (NCEP) recommendations that CHD patients

with LDL levels of 130 mg/dL should be treated with drug therapy. Future studies will have to determine whether benefit occurs at lower LDL levels.

In the future we will see evidence that aggressive lowering of cholesterol decreases the frequency of anginal episodes and silent myocardial ischemia as seen on Holter monitoring. This provides a rationale for intervening much earlier in terms of cholesterol lowering.

In a managed care environment, one needs to establish priorities in terms of which interventions will cause the greatest reduction in coronary events in patients with CHD. One needs to ask: "What kind of treatment can I give to patients with established CHD to cause the greatest reduction in total number of events?" Smoking cessation would be the first intervention to propose. Lipid management is the second most important intervention, based upon the evidence from the recently reported trials. Lipid management in people with established atherosclerotic disease is an integral part of medical management. Since the word "prevention" sometimes has a negative connotation, lipid lowering therapy can be considered medical management instead of prevention. Aspirin currently falls into third place, but when cost is considered, it will achieve a higher priority.

Currently, it is agreed that individuals with CHD and LDL-C levels of greater than 130 mg/dL should receive lipid-lowering therapy.² There will be a lot of discussion among clinicians about whether individuals with CHD and LDL-C in the range of 100 mg/dL to 129 mg/dL should also receive drug therapy. The CARE results would suggest that drug therapy is not necessary. Some believe that drug therapy should be considered for people who have had an MI or other prior events because they have demonstrated a high-risk profile.

The Post-CABG Trial

Results of the Post-Coronary Artery Bypass Grafts (Post-CABG) trial have

not been published as of this writing. Preliminary results were presented at the March 1996 meeting of the American College of Cardiology. The Post-CABG trial provides evidence for the benefit of aggressive lipid lowering to a target LDL-C goal of 100 mg/dL or lower. Post-CABG was a randomized, double-blind angiographic trial that included 1,351 participants up to age 75, whose last coronary artery bypass graft was 1 to 11 years previously. To date, only the data from the saphenous grafts have been analyzed. This trial was designed in 1987 and has a unique design compared to other trials. It specifically tested whether an aggressive lipid-lowering regimen was more effective than a moderate regimen in preventing progression of obstructive changes in saphenous vein grafts. The study evaluated whether a mean LDL-C of 95 was better than an LDL-C of 135 mg/dL.

[Editor's note: Dr. Hunninghake was a principal investigator for the Post-CABG trial.]

Based on lumen diameter, which reflects the severity of stenosis, the Post-CABG study found increasing narrowing of the lumen was much less severe in the aggressive treatment group compared to the moderately treated group. The aggressively treated group had much less progression in these saphenous vein grafts. There was also a 50% reduction in the number of new lesions in the group that had an LDL-C of 95 mg/dL versus 135 mg/dL. All results were better in the group with the lower LDL-C.

High-risk individuals for death and coronary events were excluded from this particular study, focusing instead on low-risk patients. Enrollment criteria included two patent saphenous veins. Most of the individuals had minimal or no stenosis in their saphenous vein grafts. We wanted to be able to obtain 5-year angiographic follow-up on as many subjects as possible. Although the endpoint of the study was not event rates, there was a 29% reduction in the number of bypasses and a 30% reduc-

tion in the number of PTCAs or CABGs. No positive outcome was seen for combined clinical events, but that was the expectation in the study.

This study does show that in these post-bypass patients, an LDL-C of 95 mg/dL is definitely associated with benefit compared to an LDL-C of 135 mg/dL. There was no difference in revascularization rates between groups in the first 2 1/2 years, but a 30% decrease in PTCA and CABG occurred in the last 2 years of the study. It would be interesting to do a 10- or 15-year trial to see what the results would be. In every trial, curves between treatment groups diverge more widely the longer the study continues.

The WOSCOPS Trial

The 4S, CARE, and Post-CABG trials focused on patients who had evidence of CHD, often referred to as *secondary* prevention. WOSCOPS was a *primary* prevention trial that included 6,595 men aged 45 to 64 years. Mean plasma cholesterol level was 272 mg/dL; mean LDL-C level was 190 mg/dL. Subjects were randomly assigned to receive 40 mg pravastatin or placebo. In this study, patients treated with pravastatin achieved a 26% reduction in LDL-C levels. Significant reductions were achieved in nonfatal MI or CHD death, and for total mortality. The results of WOSCOPS demonstrate lipid-lowering therapy decreased mortality in patients with risk factors for CHD but no evidence of heart disease. In recent trials, the reduction in clinical events appears earlier than in previous studies.

It is noteworthy that in all of these trials, reports of reduction in LDL-C are based upon patients who continued to make clinical visits and were available for follow-up. In all studies, some subjects drop out and do not come for clinical visits. Although they are included in determining the number of clinical events, some of them may not actually be taking the drug. If analysis is limited only to people who faithfully take their medication, results will be better.

The WOSCOPS results can be extrapolated to the United States. It is currently estimated that there are about 24 million people with cholesterol levels greater than 240 mg/dL who have at least one additional risk factor and no prior MI, which is similar to the entry criteria into this study. The best estimate is that currently about 2 million of these people are on some kind of lipid lowering therapy. About 1.5 million people per year are experiencing MIs, and many first CHD events are fatal.¹

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Study Implications and Priorities

The reporting in most clinical trials focuses on the percent reduction in risk (relative risk), but one should also consider the absolute number of events that are prevented. In WOSCOPS, there was a 31% reduction in relative risk for both smokers and nonsmokers. However, nonsmokers were 56% of the total population of the study, but only 41% of the total event reduction occurred in this group. The greater reduction in total number of events experienced by the smokers can be attributed to their higher pretreatment risk profile. The difference between the relative risk and the absolute risk has not been fully appreciated. Some high-risk groups, such as older people, have been excluded from treatment recommendations based only upon relative risk considerations.

The collective evidence from all the trials indicates the percent reduction in risk or the absolute clinical event reduction in risk is at least equal, if not greater, in high-risk groups than in lower risk groups. In fact, the absolute

event reduction in risk may be considerably higher in these groups:

- Patients with diabetes*
- Patients with hypertension
- Patients who smoke
- Patients with high triglycerides
- Patients with low HDL-C levels.

It has also been shown that older individuals, up to the age of 75, benefit from lipid lowering therapy. There is not yet enough data yet to show how the absolute event reduction varies by age group. In many cases the older group is going to have a greater absolute reduction in events. We don't know yet exactly how women compare to men in terms of the absolute event reduction. They certainly appear to benefit as much as men do; some trials suggest that the benefit for women is even greater.

Conclusion

In conclusion, it becomes clear that we should prioritize the group of patients receiving drug therapy. The highest priority is the patient who has any clinical manifestation of atherosclerotic vascular disease; this includes people who have claudication and lower-extremity atherosclerosis. There is little argument that lipid-lowering therapy is cost-effective in this group. Depending on which group you treat, you may actually save healthcare dollars. This is especially true in patients with CHD and elevated cholesterol levels. The cost of managing events is greater than the cost of preventive therapy.

A second priority for lipid-lowering therapy is the patient without a prior MI who has LDL-C levels above 160 mg/dL and two or more risk factors—for so-called primary prevention. Lowering LDL-C levels definitely reduces cardiovascular events in this group. Although the debate on the benefits

versus the cost for this group is still under discussion, most of the data suggest that lipid management compares favorably to other interventions such as mammograms, pap smears, and management of hypertension, in terms of the number of dollars it takes to save 1 year of life.

Treatment for a third group of patients should rely primarily on lifestyle changes. These are individuals with elevated cholesterol levels and fewer than two risk factors, especially young men and premenopausal women. All young people should be screened so that if they have high cholesterol levels, they can begin to make lifestyle changes early in life to maximize benefit.

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*Type II diabetics appear to have greater reductions in both relative risk and absolute events. Lipid control also appears to produce greater reduction in cardiovascular events than does tight glucose control.