

Lowering Risk Factors Through Cholesterol Treatment: Overview of the Recent Major Trials

By Sidney C. Smith, Jr., MD

Abstract

Recent clinical trials have shown that reducing low-density lipoprotein cholesterol (LDL-C) in patients with coronary heart disease (CHD), or those who are at risk for developing CHD, substantially decreases the risk of total mortality and the financial burden from cardiovascular disease. Before the advent of HMG-CoA reductase inhibitors (statins), large-scale reductions in total cholesterol were not easy to achieve with pharmacotherapy. After statins were introduced, the stage was set for a major advance in the treatment of patients with CHD and those at high risk. All of the recent trials studying the effect of lipid lowering have used statins for their treatment cohorts. The Scandinavian Simvastatin Survival Study (4S), presented in 1994, was the first lipid-lowering trial to demonstrate a highly significant reduction in mortality among patients with documented coronary heart disease. The Cholesterol and Recurrent Events trial extended the findings from 4S to a broader group with statistically average total cholesterol values for the United States population. The Post Coronary Artery Bypass Graft trial, published in 1997, examined the benefit of aggressive LDL-C lowering with statin therapy after coronary bypass surgery. The West of Scotland Coronary Prevention Study, a primary prevention trial, examined the benefits

of lipid lowering with pravastatin in hypercholesterolemic men ages 45 to 64. The Lipoprotein and Coronary Atherosclerosis Study investigated the effect of fluvastatin on men and women within a wide age range who had normal or slightly elevated cholesterol.

(*Am J Man Care* 1997;3(suppl):S23-S28)

During the past 2 decades epidemiologic studies, large-scale clinical trials, and basic research in vascular and molecular biology have resulted in major advances in our understanding of the link between lipid abnormalities and coronary heart disease (CHD). Data from the Framingham Study,¹ the Seven Countries Study,² and the Multiple Risk Factor Intervention Trial³ reveal a clear association between increased dietary intake of saturated fat and cholesterol, elevated plasma cholesterol levels, and morbidity and mortality from CHD. These studies and others provided the foundation that suggests the potential benefits of lowering cholesterol by dietary or drug measures.

Early Trials

Before the advent of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), large reductions in total cholesterol were not easy to achieve with pharmacotherapy. In fact, early trials using drug therapies reduced total cholesterol only 6% to 10%, which failed to demonstrate that treatment could improve total mortality. They did, however, reveal favorable im-

Address correspondence to: Sidney C. Smith, Jr., MD; University of North Carolina School of Medicine, Division of Cardiology; Room 349 Burnett-Womack Building; Chapel Hill, NC 27599-7055.

provement in the incidence of cardiovascular events such as fatal and nonfatal myocardial infarction (MI), and they paved the way for additional clinical trials using interventions that had more powerful lipid-lowering potential. The early studies with lipid-lowering pharmacotherapy also revealed that compliance with certain medications, such as niacin and bile acid resins, was not optimal, thereby further compromising their effectiveness.

The development of statin pharmacotherapy provided a medication that had the power to significantly reduce cholesterol and enhance compliance due to its easy tolerability and few side effects. After statins were introduced, the stage was set for a major advance in the treatment of patients with CHD and those at risk for atherosclerotic vascular disease.

The Program on the Surgical Control of the Hyperlipidemias (POSCH)⁴ was of particular interest and importance among the early trials. This study employed partial ileal bypass surgery to lower lipids. It achieved mean reductions of 23% in total cholesterol and 38% in low-density lipoprotein cholesterol (LDL-C). The POSCH study was not powered to demonstrate a reduction in total mortality, but it did reveal a significant 35% reduction in cardiovascular events. Because POSCH used surgical intervention, the compliance problems seen with early medical therapies were avoided. However, this radical form of therapy holds little appeal to patients or physicians.

Overall, POSCH suggested that when compliance is high, lipid-lowering therapy resulting in 20% to 25% reduction in total cholesterol is possible and might be associated with major benefits for patients with cardiovascular disease and those at high risk.

The development of statin pharmacotherapy provided a medication that had the power to significantly reduce cholesterol and enhance compliance due to its easy tolerability and few side effects. After statins were introduced, the stage was set for a major advance in the treatment of patients with CHD and those at risk for atherosclerotic vascular disease. All of the recent notable trials studying the effect of lipid lowering have used HMG-CoA reductase inhibitors for their treatment cohorts. See Tables 1 and 2 for a summary of the treatments, endpoints, and results of the three largest trials.

4S

The Scandinavian Simvastatin Survival Study (4S),⁵ presented in 1994, was the first lipid-lowering trial to demonstrate a highly significant reduction in total mortality (30%, $P \leq 0.0003$) and CHD mortality (42%, $P \leq 0.00001$) in patients with documented CHD. In this study, 4444 patients aged 35 to 70 years (mean = 58.9) with a history of MI or angina pectoris were randomized to treatment with simvastatin or placebo and followed for a mean interval of 5.4 years. The mean total cholesterol for both groups prior to therapy was 261 mg/dL.

Over the course of the trial, simvastatin lowered total cholesterol by 25%, LDL-C by 35%, and triglycerides by 10%. It also raised high-density lipoprotein cholesterol (HDL-C) by 8%. Simvastatin dosage was started at 20 mg/day; 37% of the subjects had the dosage increased to 40 mg/day while only 2 patients were reduced to 10 mg/day. In addition to the highly significant reductions in total mortality and CHD death, substantial reductions were also observed in the need for revascularization procedures (37%, $P < 0.00001$) and hospital days (34%, $P < 0.0001$). The benefits of statin therapy among those with the lowest quartile of initial LDL-C were similar when compared to those in the highest quartile. Because only 19% of the study population were women and the placebo group mortality rate for

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

	4S	WOSCOPS	CARE
Number of Patients	4444	6595	4159
Gender	81% men; 19% women	100% men	86% men; 14% women
Age	35–70 years	45–64 years	21–75 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%	-28%
HDL-C	+8%	+5%	+5%
Triglycerides	-10%	-12%	-14%

women was less than half that for men, improved survival in women as a subgroup was considered unlikely. Yet across all age groups simvastatin reduced the risk of major coronary events in women with a rate (35%) that was similar to that noted for men. It also improved survival among older patients age 60 or above. A post-hoc analysis revealed a 30% reduction in fatal plus nonfatal cerebrovascular events, confirming the benefits of statin lipid-lowering therapy for patients with CHD. For patients with the comorbidity of diabetes, the reduction in cardiovascular events was even greater. The positive impact of simvastatin therapy on CHD appeared to begin within 1 year of therapy and increased steadily. The benefits were independent of concomitant therapy with aspirin, beta-blockers, or calcium channel blockers.

CARE

The Cholesterol and Recurrent Events (CARE)⁶ trial extended the findings from 4S involving a broader population of patients who had elevated total cholesterol levels that are statistically average values for the United States population. In CARE, the lipid levels were much more in line with what most US clinicians consider “ordinary” cholesterol levels, representing values encountered in the majority of patients with acute MI or those undergoing revascularization procedures. The CARE study is therefore important because it addressed concerns that the findings of 4S might not be applicable to the majority

Table 2. Endpoints (Percent Risk Reduction)

	4S	WOSCOPS	CARE
Nonfatal MI or CHD Death	34% (men) 35% (women)	31% (men only)	46% (women) 20% (men)
PTCA or CABG	37%	37%	27%
CHD Death	42%	33%	20%
Death from any Cause	30%	22%	24%

of US patients with CHD whose mean lipid values (total cholesterol 200 mg/dL to 210 mg/dL) are lower than those who received lipid-lowering therapy in 4S (261 mg/dL). In the CARE study, baseline mean total cholesterol was 209 mg/dL for 4159 men and women randomized to treatment with 40 mg/day of pravastatin or placebo, within 1 or 2 years after MI. Patients, who were between the ages of 21 and 75 (mean age 59 years) were followed for a median of 5 years. The baseline lipid values for total, LDL-C, HDL-C, and triglycerides were 209 mg/dL, 139 mg/dL, 39 mg/dL, and 155 mg/dL, respectively. In the US, where CHD exists in alarming numbers, these are fairly typical national averages.

The CARE results were impressive: treatment with pravastatin led to a 20% reduction in total cholesterol and a 28% reduction in LDL-C. CHD death and nonfatal myocardial infarction were reduced by 24%. As with 4S, there were significant reductions in the incidence of coronary bypass surgery (26%, *P* = 0.005) and coronary angioplasty (23%, *P* =

0.01). Also of note, cerebrovascular events were reduced by 31% ($P = 0.03$), which was similar to the 4S findings. A major benefit for lipid-lowering therapy was observed in women with a 46% reduction in combined CHD death or nonfatal MI, compared to 20% reduction in men. The CARE trial was not powered to examine the effect of lipid-lowering therapy on total mortality. As in 4S, the benefits of lipid-lowering therapy on CHD death and nonfatal MI occurred in the older age group (≥ 65) as well as the younger, and in women as well as in men. Moreover, for women the benefits began to occur after only 6 months of therapy with pravastatin.

A controversial finding based on a post-hoc analysis of the CARE trial was the lack of benefit from lipid lowering therapy in patients with a baseline LDL-C of less than 125 mg/dL. By contrast, significant improvement was seen for those in the two tertiles where LDL-C was greater than 125 mg/dL. This finding contradicts the lowest quartile data from 4S discussed earlier and has prompted vigorous discussion and debate. The American Heart Association (AHA) and American College of Cardiology (ACC) recommend reducing LDL-C to less than 100 mg/dL for all patients who have CHD⁷ and instituting lipid-lowering pharmacotherapy and diet for all patients who have LDL-C levels of greater than 125 mg/dL after MI.⁸

Post-CABG

The Post Coronary Artery Bypass Graft (Post-CABG)⁹ trial, published in 1997, examined the benefit of aggressive LDL-C lowering with statin therapy after coronary bypass surgery. This study, in effect, extends the concepts advanced by 4S and CARE for lipid-lowering therapy on atherosclerosis involving the native coronary circulation to saphenous vein grafts used to bypass coronary obstructions. In the Post-CABG trial, aggressive reduction of LDL-C to mean values of 93 mg/dL to 96 mg/dL using lovastatin with or with-

out cholestyramine therapy was compared to moderate lowering of 134 mg/dL to 136 mg/dL using lower-dose lovastatin with or without cholestyramine therapy over a mean duration of 4.3 years. The trial enrolled 1351 patients 21 to 74 years old (mean age = 61.5), of which 92% were men after bypass surgery and assessed changes in bypass grafts using quantitative angiography.

The primary endpoint in the Post-CABG trial was progression of disease in the bypass grafts while the secondary endpoint was new occlusions. Aggressive treatment resulted in significantly less disease progression (-28%), fewer new occlusions (-40%), fewer new lesions (-52%), and lessened need for revascularization procedures (-29%). The Post-CABG trial also examined the role of anticoagulation with low-dose warfarin to a targeted international normalized ratio of less than 2.0 and showed no benefit over placebo for any of the angiographic or clinical measures.

The Post-CABG trial is important because it extends understanding of the benefits of aggressive LDL-C lowering to saphenous vein grafts. Before its findings were disclosed, many physicians did not accept that lipid-lowering therapy was beneficial in bypass grafts. The study is also important because it includes men and women and patients older than 70 as well as those with diabetes and hypertension. Although the Post-CABG trial was not designed to have sufficient power to confirm clinical outcomes, it is noteworthy that the benefits of aggressive lipid lowering on graft patency were associated with a reduced need for revascularization procedures. As with the 4S and CARE trials, the benefits of lipid lowering in the Post-CABG trial began to occur within 3 years of initiating therapy. The Post-CABG trial supports the National Cholesterol Education Program Adult Treatment Panel - II guidelines¹⁰ and the AHA/ACC recommendations⁷ to reduce LDL-C to less than 100 mg/dL in patients with known CHD.

Taken together, the 4S, CARE, and Post-CABG trials provide convincing evidence that lipid-lowering therapy can reduce total and cardiovascular mortality, as well as the need for recurrent revascularization and hospitalization for patients with CHD, thereby improving quality of life. These impressive results from secondary prevention studies have led to heightened interest in the value of lipid lowering for primary prevention patients—people who are at risk for, but don't yet have, established CHD.

WOSCOPS

The West of Scotland Coronary Prevention Study Group (WOSCOPS)¹¹ was a large-scale primary prevention trial. This study examined the benefits of lipid lowering with pravastatin in 6595 hypercholesterolemic men ages 45 to 64 years (mean age 54.5 years). Mean plasma cholesterol level was 272 mg/dL and LDL-C level was 192 mg/dL prior to randomization to 40 mg pravastatin or placebo once daily. More than 40% were smokers, thus WOSCOPS dealt with a high-risk group. Lipid-lowering therapy reduced total cholesterol 20% and LDL-C 26%. Significant reductions were noted in nonfatal (-31%) and fatal (-33%) CHD while total mortality declined by 22% ($P = 0.051$). As was noted in the secondary prevention studies, the benefits of lipid lowering in WOSCOPS occurred early, within 6 months after initiating treatment. Importantly, the need for expensive revascularization procedures was reduced significantly (-37%). The relative benefits of pravastatin therapy were not affected by age, being similar in those older and younger than 55, nor were they dependent on smoking status.

LCAS

Although severely stenotic lesions are the major cause of symptoms for patients with CHD, mild and moderate stenosis account for the vast majority of MIs. Thus it is important to know whether lipid-lowering therapy reduces the rate of angiographic progression for

mild and moderate coronary obstructions. The Lipoprotein and Coronary Atherosclerosis Study (LCAS)¹² has investigated the effect of fluvastatin (20 mg twice daily) in 429 CHD patients (17% women) ages 35 to 75 (25% were 65 or older) with normal or only slightly elevated cholesterol (LDL 115 mg/dL to 190 mg/dL). Treatment with fluvastatin reduced time to first clinical morbid or any fatal event by 33% and significantly slowed progression of coronary artery disease.¹³ Importantly, lipid lowering with fluvastatin therapy was as beneficial for older as for younger patients, and women responded to treatment as well as or better than men.

Conclusion

In summary, recent notable clinical trials have shown that reducing LDL-C in patients with CHD (or who are at high risk for developing CHD) substantially decreases the risk of total mortality and the financial burden from cardiovascular disease. Unfortunately, lipid-lowering therapies are not widely implemented. It is imperative that the healthcare system be reorganized to place greater emphasis on prevention. The AHA has established a task force whose major emphasis is to review and recommend effective strategies that might be integrated into healthcare systems to improve patient adherence to preventive therapies.¹⁴ They have also held discussions at the national level with representatives from managed care and other third-party funding sources to pursue opportunities to improve implementation of lipid-lowering therapy and other preventive therapies. The benefits to patients and the cost effectiveness of these strategies¹⁵ are a driving force in these discussions.

... REFERENCES ...

1. Castelli WP. Epidemiology of coronary heart disease: The Framingham Study. *Am J Med* 1984;76:4-12.

2. Keys A. Coronary heart disease in seven countries. American Heart Association Monograph #29. *Circulation* 1970;41(Suppl 1):1.
3. Multiple Risk Factor Intervention Trial (MRFIT) Research Group. Risk factor changes and mortality results. *JAMA* 1982; 248:1465-1477.
4. Buchwald H, Varco RL, Matts JP, et al. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia: Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH) *N Engl J Med* 1990;323:946-955.
5. Pedersen TR, Kjekshus J, Berg K, et al, for the Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-1389.
6. Sacks FM, Pfeffer MA, Moye LA, et al, for the Cholesterol and Recurrent Events (CARE) Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335: 1001-1009.
7. Smith SC, Blair SN, Criqui MH, et al. Preventing heart attack and death in patients with coronary disease. *Circulation* 1995; 92:2-4.
8. Ryan TJ, Anderson JL, Antman EM, et al ACC/AHA guidelines for the management of patients with acute myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction) *J Am Coll Cardiol* 1996;28: 1328-1428.
9. The Post Coronary Artery Bypass Graft (Post-CABG) Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. *N Engl J Med* 1997;336:153-162.
10. National Cholesterol Education Program. Second report of the expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel II). *Circulation* 1994;89:1329-1445.
11. Shepherd J, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Prevention Study (WOSCOPS) Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-1307.
12. Herd JA, West MS, Ferlic L, et al. Influence of age and sex on angiographic change in the Lipoprotein and Coronary Atherosclerosis Study (LCAS) [abstract]. *J Am Coll Cardiol* 1997;29:139A.
13. Herd JA, West MS, Ballantyne CM et al. Clinical and all fatal events in the Lipoprotein and Coronary Atherosclerosis Study (LCAS). Fourth International Symposium on Multiple Risk Factors in Cardiovascular Disease. Baylor College of Medicine, Washington DC, April 23-25. *Abstract Book* 1997; 4:26.
14. Houston-Miller N, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: Recommendations for a call to action. *Circulation* 1997;95:1085-1090.
15. Johanneson M, Jonsson B, Kjekshus J, Olsson AG, Pedersen TR, Wedel H, for the Scandinavian Simvastatin Survival Study Group. Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. *N Engl J Med* 1997;336:332-336.