

Primary Prevention

Based on a presentation by Stuart M. Cobbe, MD, FRCP

Presentation Summary

The West of Scotland Coronary Prevention Study was the first large primary prevention study of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in coronary heart disease (CHD). It was the first study to examine the relation between lowering low-density lipoprotein cholesterol (LDL-C) and reducing CHD events and to demonstrate early reduction (six months) in clinical events. Patients taking pravastatin, an LDL-C-lowering therapy, demonstrated considerable reductions in the rate of nonfatal myocardial infarction (MI) or CHD death (31%), first MI (31%), and cardiovascular death (32%). The rate of coronary interventions was reduced 37% and total mortality rate 22%. Pravastatin was the first cholesterol-lowering agent to reduce total mortality rate in a primary prevention

setting. The findings suggest that other mechanisms, in addition to LDL-C lowering, may contribute to plaque stabilization and reduction of risk for MI.

The study population was similar to that of many managed care organizations in which patients are eligible for primary prevention of myocardial infarction. The results provided evidence-based risk reduction and showed that use of pravastatin was cost effective under a wide range of risk factors and model assumptions. Risk for CHD events is recommended as the starting point for patient care rather than total or LDL cholesterol.

Identifying patients whose risk exceeds 10% at 5 years but who have not manifested any symptoms of CHD is difficult. Multivariate analysis is the most accurate way to predict risk of CHD.

The West of Scotland Coronary Prevention Study (WOSCOPS) was the first primary prevention trial of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (HMG) therapy to examine the relation between lowering low-density lipoprotein cholesterol (LDL-C) and reducing coronary heart disease (CHD) events. The WOSCOPS was also the longest (5 years) and largest (6596 patients) pri-

mary prevention study of any HMG drug.¹ Stuart M. Cobbe, MD, FRCP, Walton Professor of Medical Cardiology at Glasgow University, Glasgow Royal Infirmary, was coprincipal investigator of the WOSCOPS, the results of which were published in the *New England Journal of Medicine* in 1995. He presented an overview of the study and its results.

The patients in the WOSCOPS were middle-aged men with moderately high

lipid levels and no history of CHD, like many managed care patients (Figure 1).¹ Allowing for the fact that Scotsmen have a greater aggregate of risk factors, the risk for myocardial infarction (MI) in this population is similar to that in the United States. The investigators sought to evaluate the effect of pravastatin therapy in prevention of CHD events and to

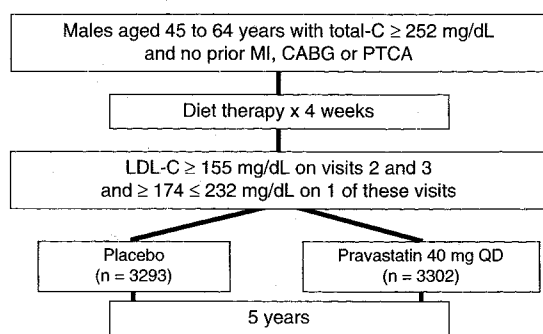
determine whether therapy reduced the combined incidence of nonfatal MI and CHD.

Subjects had no history of MI or coronary revascularization procedures. Still, they were at high risk for coronary events, with a one in 13 chance of having a fatal or a nonfatal MI within 5 years. Men 45 to 64 years of age were recruited in primary care through screening. Those with a total cholesterol greater than 250 mg/dL and with no prior serious coronary events were treated initially with four weeks of dietary therapy equivalent to the American Heart Association Step 1 diet. After a full lipoprotein profile, if fasting LDL-C was in the range of 155 to 232 mg/dL on the second and third visits, and $\geq 174 \leq 232$ mg/dL on 1 of these visits, the patients were recruited into the study and randomized to receive either placebo or a fixed dose of 40 mg of pravastatin daily. Collection of data continued for 5 years.

The mean age at entrance into the study was 55 years for the placebo and pravastatin groups. Five percent of the subjects in both groups had a history of mild stable angina pectoris, 15% had hypertension, and 44% smoked. Both groups were balanced in terms of mean cholesterol, with total cholesterol of 272 mg/dL, LDL-C of 192 mg/dL, high-density lipoprotein cholesterol (HDL-C) of 44 mg/dL, and triglycerides of 163 mg/dL.

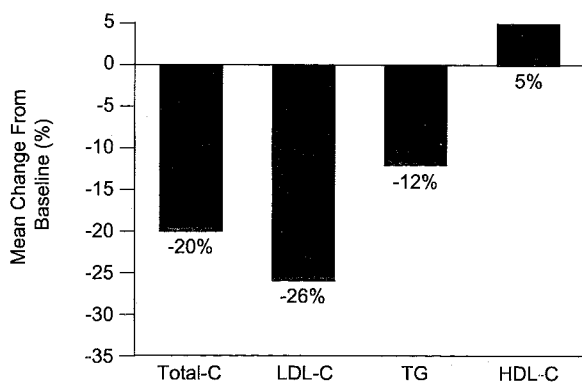
The primary endpoint of WOSCOPS was the combined incidence of nonfatal MI, or CHD death, which included fatal MI or sudden death. Secondary endpoints were separate occurrences of nonfatal MI or CHD death, and other endpoints were cardiovascular death, total mortality rate, and need for revascularization, either percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. The results of the study demonstrated that pravastatin affected all of the lipoproteins in the right direction (Figure 2).¹ Total cholesterol was reduced 20%, LDL-C 26%, and triglycerides 12%. A modest but significant 5% increase in HDL-C was seen.

Figure 1. WOSCOPS Study Design



Shepherd, Cobbe, Ford et al. *N Engl J Med* 1995;333:1301-1307.

Figure 2. WOSCOPS Results: Effect of Pravastatin on Lipid Levels



Shepherd, Cobbe, Ford et al. *N Engl J Med* 1995;333:1301-1307.

The combined incidence of fatal and nonfatal coronary event rates at 5 years was 8% for the placebo group and 5.5% for the pravastatin group. This represented a relative risk reduction of 31%, which was highly significant (Table 1). The event curves began to separate within 6 months of the trial onset and were statistically significant by 18 months. "This speaks very strongly for pravastatin having a stabilizing effect," said Dr. Cobbe. "Had the effect been only on regression of atherosclerosis or prevention of progression of atherosclerosis, we would not have expected to see a benefit in such a short period of time." The incidence of first MI was reduced 31%, and number of coronary interventions was reduced 37%.

The WOSCOPS demonstrated earlier benefits with pravastatin than previous studies of other cholesterol-lowering interventions. The Program on the Surgical Control of Hyperlipidemias (POSCH) study of partial ileal bypass to treat patients who had had an MI,² the Helsinki Heart Study of gemfibrozil,³ and the Lipid Research Clinics Program with cholestyramine⁴ all showed a clear lag period of between 2 and 3 years before there was any evidence of benefit. The early benefits of pravastatin in the WOSCOPS suggest that several mechanisms in addition to LDL-C lowering may contribute to plaque stabilization and reduction in risk for a first event.

Pravastatin demonstrated significant reductions in cardiovascular mortality (32%) and total mortality rate (22%). It is the first cholesterol-lowering agent in a primary prevention study to demonstrate a reduction in total mortality rate, an important consideration because concerns were raised that cholesterol reduction might have adverse effects on noncardiovascular mortality rate. It had been argued that although meta-analysis of the older lipid-lowering trials had confirmed that cholesterol reduction could reduce risk for coronary events, there could be an equal and opposite increase in risk for noncardiovascular death. "The results of our study clearly

indicate that there is no evidence to suggest that that is the case, and indeed, all of the statin trials that have been published are consistent in showing no excess of noncardiovascular mortality," said Dr. Cobbe.

Table 1. Summary of WOSCOPS Results in Primary Prevention with Pravastatin

- Significant 31% reduction in nonfatal MI or CHD death ($P < 0.001$)
- Significant 31% reduction in first MI ($P < 0.001$)
- Significant 32% reduction in cardiovascular mortality ($P = 0.033$)
- 22% reduction in total mortality ($P = 0.051$)
- 37% reduction in coronary interventions ($P = 0.009$)
- Reduction in clinical events begins within first 6 months

Risk and Benefit Assessment

On the basis of the WOSCOPS results, Dr. Cobbe advocates using CHD event risk, not total or LDL cholesterol as the starting point for patient care. He suggested that patients whose event rates exceed 10% at 5 years or 20% at 10 years are at sufficient risk to warrant intervention with lipid-lowering therapy. Some of these patients, those with obvious cardiovascular disease as manifested by MI, unstable angina, or stable angina, are easily identified. The problem is identifying those who have not yet had clinically manifest coronary disease but are at high risk. Twenty-five percent of the patients in the WOSCOPS met this threshold.

Dr. Cobbe demonstrated the CHD event risk concept by identifying the proportion of the population in the WOSCOPS who met this level of risk and then conducting a cost-benefit analysis for both the entire study population and for subgroups at progressively high risk. Multivariate analysis of the baseline risk factors, used in the WOSCOPS, is by far the most sensitive and accurate way to predict risk, accord-

ing to Dr. Cobbe. The risk ratio for pravastatin was 0.68, a 32% reduction in risk. More important, pravastatin reduced risk independently of other risk factors. Thus the 32% relative reduction held for both subjects at high risk and subjects at low risk.

All of the independent and continuous variables of risk were combined, and a risk was assigned to each trial subject. Subjects were then divided into four quartiles of ascending risk from lowest to highest. In quartile 1, the 5-year event rate was 4.4% or less, whereas in quartile 4, it was 9.6% or greater. Forty-five percent of all the coronary events in the WOSCOPS occurred in quartile 4, making their treatment the most cost effective. More than 50% of the coronary events, however, occurred among those at lower risk. "The West of Scotland study tells you that there will be benefit in treating these individuals, even though the cost effectiveness will not be as good as in the highest risk category," said Dr. Cobbe.

The same data can be analyzed according to the National Cholesterol Education Program guidelines, a simpler method. All these people already have some risk factors; they are middle-aged men with hypercholesterolemia. What extra risk factors are necessary to push them across the 10% threshold? Among younger men (45 to 54 years of age), those with minor electrocardiographic abnormalities, vascular disease, or angina, and those who smoke cross

the threshold. Dr. Cobbe pointed out that people with isolated hypercholesterolemia but no additional risk factors are at very low risk. Among older men (55 years of age or older), any additional risk factor pushes them across the 10% threshold. "So even with very simple methods, although they are not as accurate and not as precise as the multivariate analysis, one can come to an assessment of the higher-risk patient," said Dr. Cobbe.

Dr. Cobbe illustrated the concept of benefit estimation with a discussion of four hypothetical individuals with 5-year event risks of 5%, 10%, 15%, and 20%, based on people in the trial who matched these risk profiles (Table 2). Knowing that pravastatin therapy reduces relative risk by 32% regardless of baseline risk, the risk with therapy can be calculated. This figure is subtracted from baseline risk, and absolute risk reduction is calculated. In this case, it is calculated to be as low as 1.6% for subjects at low risk, and as high as 6.4% for subjects at high risk. Another figure commonly used in the literature is the number of people who must be treated to prevent one event, which is simply the reciprocal of absolute risk reduction. In this example, 63 low-risk people and 16 high-risk people must be treated for 5 years to prevent one event in each group.

Compliance is another issue. The benefit of pravastatin was evident among the compliant patients who took 75% or more of the treatment over the 5-year period. The noncompliant patients, however, did not achieve benefit in coronary death or nonfatal MI, and they did not achieve the benefit in avoidance of coronary revascularization.

Table 2. Effect of Underlying Risk on Treatment Benefit

	Definite Nonfatal MI or CHD Death			
5-year risk of event (%)	5	10	15	20
Risk of event on therapy* (%)	3.4	6.8	10.2	13.6
Absolute risk reduction (%)	1.6	3.2	4.8	6.4
Number to treat	63	31	21	16

*Relative risk reduction 32%

Cost Effectiveness of Pravastatin

The cost-effectiveness analysis considered all costs of treating the men for 5 years. Pravastatin prevented 318 cardiovascular disease events per 10,000 treated subjects, and the cost savings of avoided cardiovascular disease events was subtracted from the cost of therapy.

The analysis was based on the United Kingdom healthcare system, because the trial took place in Scotland. Dr. Cobbe also presented some figures relevant to the United States.

Costs in United Kingdom hospitals are substantially lower than they are in the United States. The 318 events avoided were 33 sudden deaths; 138 nonfatal MIs, which led to 35 delayed deaths; 68 angina hospitalizations; 33 revascularizations; and 47 strokes or transient ischemic attacks. That adds to 2460 life-years free from manifest cardiovascular disease, which was attained by means of treatment, or £8,000 undiscounted per life-year gained. When the cost was discounted, weighted according to when the benefits occurred, the cost per life-year gained was rounded up to £20,000. The discount rate was 6% per year, the rate of healthcare inflation in the United Kingdom.

That figure of £20,000 per life-year gained for all the men in the WOSCOPS compares quite favorably with that for other healthcare interventions. The cost of treatment with pravastatin is similar to those of the conventional benchmark, hospital hemodialysis, which costs about £15,000 to £20,000 per life-year gained, and of screening for osteoporosis among postmenopausal women, which costs £22,000 per life-year gained.

When groups at higher risk in the WOSCOPS are separated out, cost effectiveness improves. For example, if pravastatin is given only to people with an event rate of 2% per year or greater, the cost per life-year gained is £5000 undiscounted and £14,000 discounted. If the threshold is set higher and pravastatin is given only to people with an event rate of 3% per year, the figures are reduced to £3900 undiscounted and £9680 discounted.

In the United States, the cost-effectiveness figures would be expected to be even better, because of much higher hospitalization costs and similar unit medication costs. Dr. Cobbe presented a cost-effectiveness analysis of the

WOSCOPS data extrapolated to the United States that was presented by Dr. Joel Hay at the American Heart Association meeting in November 1997. The figures were derived from the WOSCOPS database and from United States vital statistics. The WOSCOPS risk equations were used to model the initial events. The survival effect of these events was derived from United States vital statistics and the Framingham heart study.

The incremental 5-year healthcare costs of the initial cardiovascular events were estimated from health insurer databases. The analyses involved societal and managed care perspectives with a 3% annual discount rate.

The results demonstrated that pravastatin treatment of 1000 patients for 5 years prevented 31 cardiovascular disease events and resulted in 129 life-years gained.⁵ This translated into \$2.2 million in subsequent healthcare costs saved, and a cost-effectiveness figure of approximately \$17,000 per life year.⁵ "The figures from the United States support the analysis we undertook from our own source data in Scotland," said Dr. Cobbe. "Pravastatin remains cost effective under a wide range of risk factors and model assumptions."

Conclusions

Pravastatin in primary prevention has been proved to be both efficacious in definitive clinical outcomes and to be cost effective. The WOSCOPS provided evidence-based risk reduction in disease progression, first MI, cardiovascular death, and coronary interventions. These proved clinical outcomes foster improved treatment decisions, which are based on efficacy in avoiding costly events, rather than on the surrogate marker of LDL-C reduction.

The WOSCOPS study population was similar to the population of patients in managed care organizations—middle-aged men with elevated cholesterol levels and some additional risk factors who are at a high risk for MI within 5 years. Risk stratification of these pa-

tients can be used to refine treatment with pravastatin and streamline costs by targeting the benefit at those who stand to gain the most.

FACULTY QUESTION-AND-ANSWER
SESSION

Comment: You think that patients in the WOSCOPS study are representative of patient populations that would be seen in managed care organizations in the United States. I'm concerned about the representative nature of the study and the use of your significant covariates in the multivariate model as a predictive variable in doing risk assessment of patients.

Answer (Dr. Cobbe): The risk-assessment equations were obviously derived from the population in the study, so you're at liberty to debate whether they apply in other populations. Scotsmen have higher levels of risk, but those are translated into the level of events you would have predicted whether you use our risk equation or other published equations such as Framingham. When the Framingham risk equation was applied to the West of Scotland study, it predicted risk very successfully.

Question: How would you apply risk assessment to Medicare or Medicaid populations that might be in managed care?

Answer (Dr. Cobbe): The result of the study says that you get the same proportionate risk reduction regardless of the baseline risk. The answer will be the same. If you identify higher risk subjects, then the absolute benefit will be proportionately greater.

Question: Where was your multivariate risk analysis published? Have you generated a formula similar to Framingham? I find that very useful in confronting a patient.

Answer (Dr. Cobbe): The multivariate analysis was published in the *American Journal of Cardiology* earlier this year. The paper doesn't give the formula, but it's available. We have a prototype, the WOSCOPSometer, and we're exploring ways to make that widely available.

Question: The question of morbidity with statins has arisen in the popular press. Is it a possibility that statins decrease cerebral function?

Answer (Dr. Cobbe): In WOSCOPS, we looked at cause-specific hospitalizations for all noncardiovascular causes, and there is absolutely no evidence of excess in cause-specific hospitalization.

Comment (Dr. Shepherd): We are confident that there is not a negative effect on cognitive function with pravastatin therapy. The West of Scotland investigators are about to embark on a very large and important study in the elderly that will carefully assess cognitive function in patients on pravastatin and placebo over a period of several years.

Comment (Dr. Cobbe): The elderly study is testing the hypothesis that pravastatin might actually improve cognitive function by avoiding the development of microvascular or multi-infarct dementia.

Question: Is your conclusion that pravastatin therapy is going to cost more money but we'll save by reducing the number of events?

Answer (Dr. Cobbe): At the moment, yes. We may reach the stage where this provides cost saving. Right now, pravastatin therapy prevents events. We're saying the cost is comparable to many justifiable medical costs.

... REFERENCES ...

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