

Pravastatin Event Reduction Analysis

Based on a presentation by James Shepherd, MD, PhD, FRCP

Presentation Summary

In the Pravastatin Event Reduction Analysis based on data from the West of Scotland Coronary Prevention Study (WOSCOPS), investigators sought to determine whether variation of plasma lipid levels at baseline influences efficacy of treatment. They also asked whether the change in low-density lipoprotein cholesterol (LDL-C) is directly related to reduction in coronary heart disease (CHD) risk among patients taking pravastatin and whether LDL-C reduction alone explains the clinical outcome in the WOSCOPS. The analysis divided patients taking placebo and those taking pravastatin into quintiles.

Cardiovascular risk effect of incremental changes in baseline lipids on treatment effect was analyzed with the mean of the two baseline lipid measurements made at the start of the study. Level of LDL-C was shown to be a predictor risk across all quintiles; the higher the baseline LDL-C, the greater was the risk for an event. Level of high-density lipoprotein cholesterol (HDL-C) was shown to be a better predictor of risk than level of LDL-C. However, the

association with risk was negative. It was concluded that risk reduction with pravastatin is independent of baseline lipid phenotype.

To relate change in LDL-C level to reduction in CHD risk among patients taking pravastatin, the percentage change in LDL-C from baseline was calculated for every pravastatin-treated subject and related to the events recorded from 6 months after initiation of the study to study end. The results showed that LDL-C reduction was required for risk reduction but that the maximum benefit was achieved with LDL-C reductions of no more than about 25%. The relation was similar when quintiles of absolute LDL-C reduction were examined.

To establish whether LDL-C reduction alone explains the clinical outcome of the WOSCOPS, overlap and Framingham analyses were conducted. In the overlap analysis, subjects taking pravastatin had significantly greater benefit than that predicted from the Framingham model. These analyses demonstrated that LDL-C reduction alone may not account entirely for the benefits of pravastatin therapy.

After publishing the results of the WOSCOPS,¹ the trial investigators conducted an analysis of pravastatin event reduction based on study data. James Shepherd, MD, PhD, FRCP, Professor of Pathological Bio-

chemistry at Glasgow University's Glasgow Royal Infirmary and one of the WOSCOPS principal investigators, summarized the results during his presentation "The Pravastatin Event Reduction Analysis."

Before the statins were developed, trials conducted with other lipid-lowering therapies began to focus attention on primary prevention of coronary heart disease (CHD). The Lipid Research Clinics Coronary Primary Prevention Trial² with cholestyramine and the Helsinki Heart Study trial with gemfibrozil³ clearly showed that reduction in low-density lipoprotein cholesterol (LDL-C) levels and elevation of high-density lipoprotein (HDL-C) levels had a positive effect on coronary risk reduction. These trials, however, did not add to the literature as much as they could have because of lack of power and shortcomings of the drugs used.

The WOSCOPS, on the other hand, had a larger number of subjects and a very powerful lipid-lowering drug. "That combination allowed us to look at a key question that influences all of our thinking when it comes to lowering cholesterol and preventing coronary heart disease: What is the relationship between LDL-C reduction and risk reduction?" said Dr. Shepherd. The WOSCOPS researchers hypothesized that the link between changes in cholesterol levels and event changes would be linear and that the lower cholesterol levels were driven, the greater the benefit would be.

Two complete lipoprotein profiles were determined for each patient before they were randomized into the trial, according to methods that met the quality criteria set by the United States Centers for Disease Control and Prevention. These profiles allowed the investigators to assess precisely the basal lipid and lipoprotein levels. Lipids and lipoproteins were then measured every 6 months throughout the trial. Thus patients who participated in the trial from beginning to end had measurements taken of LDL-C, HDL-C, and triglyceride levels on nine or more separate occasions.

The analysis was based on mean benefit related to the average of the nine measurements. If a subject experienced a coronary event, his lipid and lipopro-

tein profile measurements were included in the analysis up to the point of that event. These data were used in the calculations to relate lipid reduction to endpoint reduction. Information on patients who had an event within the first 6 months, before the change in lipids from baseline had been measured, was not included.

At study initiation, both the pravastatin group and the placebo group had the same measurements of LDL-C, HDL-C, and triglyceride levels. Lipid measurements revealed that subjects taking pravastatin on average lowered their total cholesterol by 20% and their LDL-C by 26%. Level of HDL-C increased 5% and of triglyceride decreased 12%. Some patients taking pravastatin did not achieve these lipid levels, providing researchers with the opportunity to compare those who benefited most versus those who benefited least.

The pravastatin event reduction analysis had the following three objectives: (1) to determine whether variation in plasma lipid levels at baseline influences efficacy of treatment, (2) to relate changes in LDL-C to reduction in CHD events among patients taking pravastatin, and (3) to explore whether LDL-C reduction alone explains the clinical outcome in the WOSCOPS.

Baseline Lipids and Outcome

Within the framework of the recruitment strategy for the WOSCOPS, it was possible that some patients with a particular baseline lipoprotein profile might have a more favorable response than others with a different baseline lipoprotein profile. Dr. Shepherd pointed out that the investigators were constrained by the ethics committee to enroll only patients with a maximum total cholesterol of 300 mg/dL and a maximum LDL-C of 230 mg/dL. As a result, the LDL-C in both the placebo and pravastatin groups ranged from 155 to 230 mg/dL. The limitation on baseline LDL-C had important implications for the results of the event reduction analysis. There were no caps, however,

on HDL-C or, in essence, on triglyceride levels.

To determine whether variation in plasma lipid levels at baseline influences efficacy of treatment, the frequency of occurrence of events was examined for subjects in the placebo group who began the study with differing baseline lipid levels. The endpoints chosen were all cardiac events, including fatal and nonfatal myocardial infarction (MI), coronary death, and revascularization procedures (coronary artery bypass grafting or percutaneous

transluminal coronary angioplasty). The baseline lipids for the 3293 placebo-treated subjects were divided into quintiles of increasing LDL-C, HDL-C, and triglyceride levels. The effect of change in baseline lipids on the endpoints recorded was analyzed over the duration of the study. The 5-year Kaplan-Meier risk for a cardiac event was determined for each quintile and adjusted with a Cox regression model for baseline covariates.

The results showed that the lowest quintile had an average LDL-C of about 170 mg/dL and that the highest quintile had an average LDL-C of 220 mg/dL (Figure 1). Patients taking placebo in the lowest quintile of baseline LDL-C had an event rate of about 9% over the 5 years of the study. Patients taking placebo in the highest quintile of baseline LDL-C had an event rate of about 12%. "LDL-C was a predictor of risk across these quintiles. As the LDL-C rose, the risk also rose, and the events also rose. But LDL-C per se is not a particularly good predictor of risk," said Dr. Shepherd.

When the analysis was performed for the 3303 pravastatin-treated subjects, again relating events recorded in the trial to baseline lipid levels, it was clear that treatment with the drug reduced the number of events across the board by about 30%. All of the quintiles for patients taking pravastatin demonstrated this one-third risk reduction, even the quintile at the highest risk. "Essentially, it did not really matter where patients started off with their LDL-C. When they got the treatment, they got the same relative benefit," said Dr. Shepherd. The patients at highest absolute risk received the most absolute benefit; thus it is important to think in terms of absolute benefit when applying therapy in this situation. Dr. Shepherd again pointed out that these results included only subjects with LDL-C levels between 155 and 230 mg/dL.

Level of HDL-C was the best lipid predictor of risk in the WOSCOPS, according to Dr. Shepherd (Figure 2). The pattern was reversed; patients who

Figure 1. Baseline Lipids and Outcome:
Baseline LDL-Cholesterol

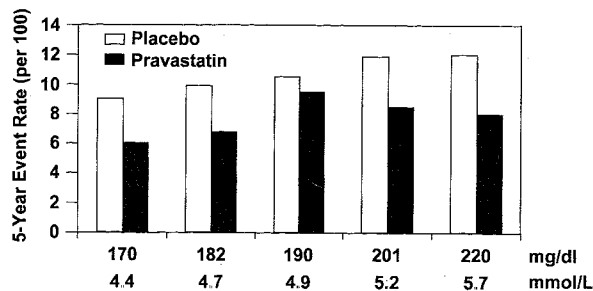
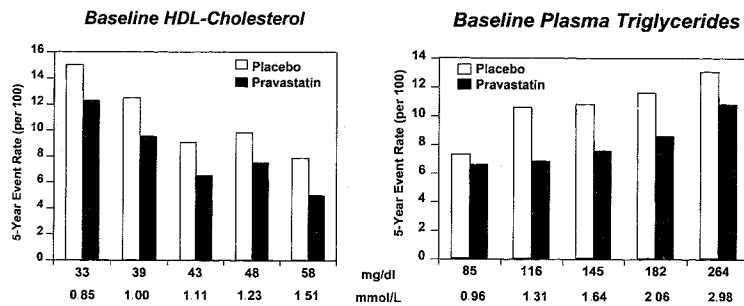


Figure 2. Baseline Lipids and Outcome:
Baseline HDL-Cholesterol and Plasma Triglycerides



had the lowest level of HDL-C had the highest level of risk in the placebo group. Patients taking placebo with an HDL-C of less than 33 mg/dL experienced 15 events per 100 over 5 years. Patients with a high HDL-C were at proportionately lower risk with a negative relation between HDL-C at baseline and event risk. Patients taking pravastatin showed equal relative benefit in all quintiles. There was no level of HDL-C at which relative benefit differed.

Patients who had the lowest level of HDL-C and the highest level of risk in absolute terms benefited most from treatment with pravastatin. "That is why global risk for patients and absolute risk are so important, rather than lipid levels alone. Lipid levels only give you a small element of the total risk spectrum that physicians should be trying to influence," said Dr. Shepherd.

A similar pattern was seen with triglyceride levels. Patients taking placebo with the lowest level of triglyceride, 85 mg/dL, had the lowest level of risk. As triglyceride levels increased in each quintile, so did the risk. Patients taking pravastatin had a proportional risk reduction across the board. "In other words, if you take any individual from the West of Scotland study, no matter what his baseline lipoprotein profile was, and give him treatment with pravastatin, you actually got the same proportionate benefit," said Dr. Shepherd. Patients with the worst baseline total lipoprotein profile had the highest absolute risk and therefore received the most absolute benefit, but in proportional terms, all patients had the same kind of benefit. It was concluded that risk reduction with pravastatin is independent of baseline lipid phenotype. In terms of absolute benefit, subjects at the highest absolute risk had the greatest absolute benefit.

Change in Plasma Lipids and Treatment Effect

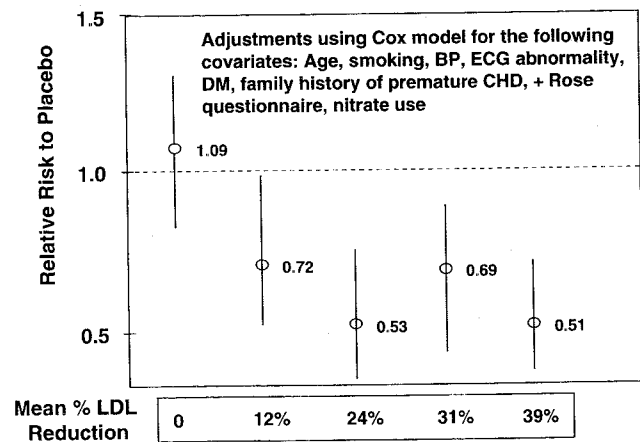
To relate change in LDL-C to reduction in CHD risk among patients taking

pravastatin, the percentage change in LDL-C from baseline was calculated for every patient taking pravastatin. The event profile was quantified from 6 months after study initiation until the end of the study, providing 4.4 years worth of events.

Patients were divided into quintiles according to percentage LDL-C change, and 4.4-year Kaplan-Meier risk for a cardiac event was determined in each quintile. Patients in quintile 1 showed on average no change in LDL-C with a range of plus 20% to minus 4%. There is no doubt that at least some of them were not taking their medicine. At the other end of the spectrum, in quintile 5, which had the highest percentage reduction in LDL-C, the decrease ranged from 34% to 57%, with an average of 39%.

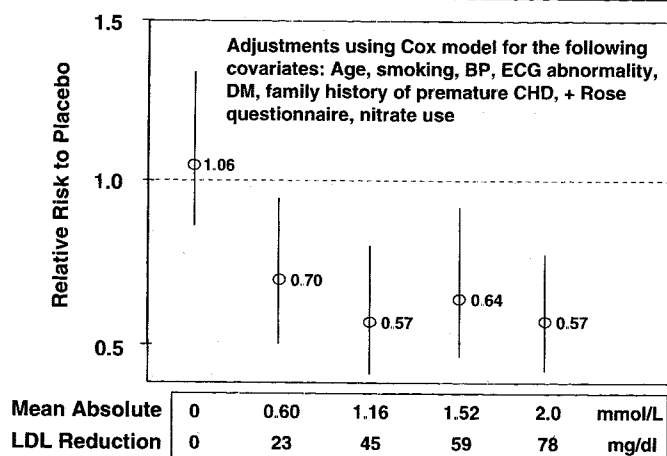
The number of patients in each quintile who had a coronary event was determined. The event rate for the first quintile was 11 per 100 over 4.4 years (Figure 3). Patients who lowered their LDL-C by 39% on average had an event rate about 55% of the basal event rate of quintile 1. Quintile 3, however, although it had an average LDL-C reduction of 24%, showed exactly the same kind of event rate and event reduction

Figure 3. Comparisons of Each Quintile of Percentage LDL Reduction Versus the Placebo Group



from quintile 1 as did quintile 5. "We expected to see a progressive lowering of events across the entire set of quintiles of LDL reduction. We did not get that. If the individuals lowered their LDL-C by about 25%, they got as much benefit as we were ever going to see within the framework of the people in this study," said Dr. Shepherd.

Figure 4. Comparisons of Each Quintile of Absolute LDL Reduction Versus the Placebo Group



Pravastatin-treated patients in quintile 1 who did not show any change in LDL-C had an event rate indistinguishable from that of the placebo group. Patients taking pravastatin who lowered their LDL-C by 40% had an event rate about 50% of that of the placebo group. Patients taking pravastatin who lowered their LDL by 24% also showed 50% risk reduction.

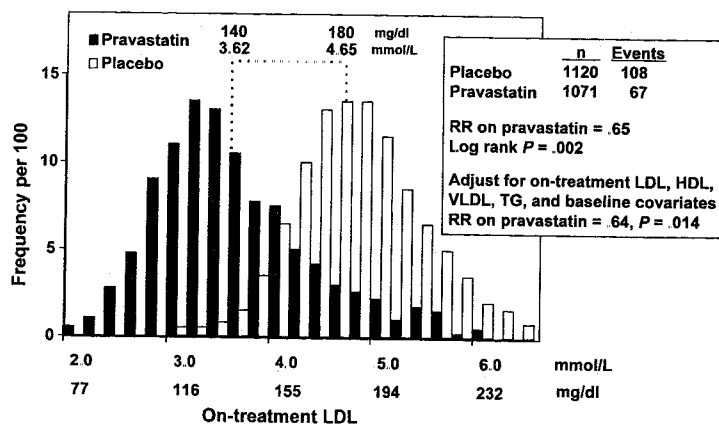
To conduct this analysis, adjustments were made in each quintile for other variables that could have influenced risk. A Cox proportional hazard assessment was conducted for age, smoking, blood pressure, electrocardiographic abnormalities, diabetes mellitus, family history of premature disease in the Rose questionnaire, and nitrate use. Absolute reduction was analyzed with the same results as those for relative risk reduction (Figure 4).

Because this was a posthoc analysis, the investigators sought to prevent accusations of data dredging by looking at the data from every angle. They measured not only the quintiles but also the octiles, tertiles, and deciles. The results always indisputably showed the same trend and led to the same conclusions.

Relation Between Reduction in Low-Density Lipoprotein Cholesterol

To establish whether LDL-C reduction alone explains the clinical outcome in the WOSCOPS, two types of analyses were conducted: overlap and Framingham. The overlap analysis was performed to determine whether the event rates would be the same for patients with the same LDL-C level achieved by some patients through pravastatin therapy and that others in the placebo group had naturally at baseline. The analysis started at 6 months after trial initiation and continued for 4.4 years. Patients who were less than 75% compliant were excluded from analysis, as were those who had cardiac events in the first months of the study, because their cholesterol levels before the cardiac event were unknown.

Figure 5. Overlap Analysis



A substantial number of patients—roughly 1100 in the placebo group and 1070 in the pravastatin group—fell into the overlap. Both groups exhibited overlapping LDL-C levels ranging from 140 to 180 mg/dL. The cardiac events in the overlapping groups were counted, and the numbers were compared. A Cox model was used to adjust for minor differences in baseline risk. There were 108 cardiac events in the placebo group as opposed to 67 cardiac events in the pravastatin group (Figure 5); that is, the pravastatin group had 35% fewer events.

When the analysis was conducted over a narrower range of the cholesterol overlap (150 to 170 mg/dL), the results were the same. At other levels of the overlap, significance was not always achieved because of small numbers, but again, the trend was always there. “We always got better benefit in the pravastatin group than we really would have expected,” said Dr. Shepherd. “Individuals who achieved a specific LDL-C level with pravastatin had significantly fewer CHD events than those in the placebo group.” Why patients taking pravastatin had lower cardiac event rates than patients taking placebo with the same LDL-C is unknown. It is possible that pravastatin was doing something other than just lowering LDL-C, or that when LDL-C is lowered, the resulting biologic modification in coronary risk profile provides greater benefit than might be expected, according to Dr. Shepherd.

In the Framingham study, subjects had their risk factor profiles assessed and then participated in follow-up data collection over time to see how these different risk factors affected their likelihood of having an event. The WOSCOPS investigators compared the risk profile in their placebo- and pravastatin-treated cohorts and the subsequent events observed in these cohorts with the number of events that would have been predicted with the Framingham CHD risk model. Dr. Shepherd pointed out that the Framingham study recorded age, gender, smok-

ing habits, blood pressure, total cholesterol, HDL-C, and LDL-C. The Framingham definition of diabetes differed in detail from that used in the WOSCOPS, and left ventricular hypertrophy was not recorded in the WOSCOPS. Thus not all input to the Framingham equation was available in the WOSCOPS database.

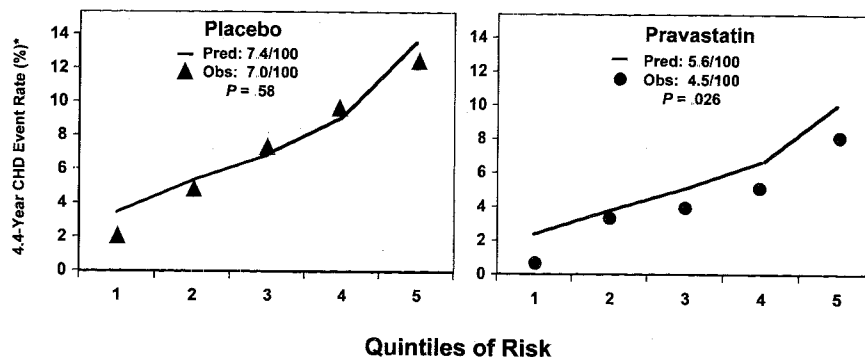
The Framingham equation is based on a regression model used to predict what will happen to any individual over any period of time. The WOSCOPS investigators chose to predict events 4.4 years into the future, which allowed all patients with at least one lipid measurement during treatment in the WOSCOPS to be considered for the analysis. An assessment was made of what would happen to the placebo group and, separately, to the pravastatin group if their coronary risk profile had exposed them to the same likelihood of an event as in the Framingham study.

After adjustment for the large number of patients in the WOSCOPS cohort who had a risk profile outside the Framingham risk equation, 1250 patients in the placebo group and 1803 patients in the pravastatin group met the inclusion criteria for the Framingham study. More patients taking pravastatin met the criteria than those taking placebo because pravastatin lowered LDL-C enough to make them eligible for the Framingham analysis.

Predicted event rates were derived with the Framingham model. Total cholesterol from the WOSCOPS database was used because the Framingham study did not measure LDL-C. The endpoint was definitive nonfatal MI or CHD death plus revascularization. The results for the placebo group showed remarkable agreement between the observed CHD event rate and that predicted with the Framingham model (Figure 6). Patients taking pravastatin, however, experienced a significantly greater benefit than that predicted with the Framingham risk model.

The results of both the overlap analysis and the Framingham analysis sug-

Figure 6. Framingham Predicted Versus Observed Event Rates: Placebo and Pravastatin Groups



*Predicted on the basis of on-treatment levels

gest that pravastatin had a beneficial effect beyond reduction in LDL-C. Dr. Shepherd highlighted two possible explanations for the added benefit: reduced viscosity in the blood and a change in atherogenic profile of lipoproteins in the blood as a consequence of pravastatin therapy. The WOSCOPS investigators measured the viscosity of subjects' blood before and during treatment with pravastatin and found that pravastatin actually reduced the viscosity of whole blood. By extrapolation, this should have improved blood flow through the myocardium. The investigators calculated that the change in viscosity might have accounted for a substantial fraction of the overall benefit seen in the WOSCOPS, a benefit that stemmed from something beyond cholesterol reduction.

Another possibility is that when a statin such as pravastatin is given, it reduces the atherogenicity of the lipoproteins by selectively lowering the circulating mass of atherogenic intermediate density lipoprotein (IDL). The global measurement of LDL-C incorporates IDL cholesterol (IDL-C) into the fraction. Because IDL-C is more atherogenic than LDL-C, a small apparent reduction in LDL-C should translate into a much larger decrease in risk than ex-

pected. The WOSCOPS investigators plan to test this theory using frozen plasma collected from all of the study patients during the course of the project.

Conclusions

The treatment effect of 40 mg of pravastatin is proportionally the same regardless of lipid phenotype. A reduction in LDL-C was necessary to achieve CHD risk reduction, but a reduction of about 25% in LDL-C provided the maximum benefit among patients

taking 40 mg of pravastatin. Reduction in LDL-C does not appear to account entirely for the benefits of pravastatin therapy, as demonstrated by the overlap and Framingham analyses.

FACULTY QUESTION-AND-ANSWER SESSION

Question: *What was your actual target cholesterol level?*

Answer: We had no target. We gave the patients all the same dose of the drug, and we looked for the benefit.

Comment: *The reason I asked was that as the average cholesterol of both groups gets higher, theory might tell us that the gap may get wider and wider and become more statistically valuable.*

Answer: That's a valid point. Within the framework of the lipid levels in the West of Scotland study, these are the results. Twenty-five percent of our population are like the men in the West of Scotland study. What we learn from them will apply to the majority of individuals on statins. We obviously cannot comment on the potential benefits of

treatment outside the lipid range investigated in WOSCOPS. It is reasonable to expect that individuals with lower baseline lipid levels will gain less absolute benefit from cholesterol lowering, and there will come a point below which the benefit will not be measurable.

Question: *What can you say about pravastatin at 10 and 20 mg?*

Answer: No specific endpoint studies have been done using pravastatin at a dose of 20 mg. If the benefit of the drug comes from its LDL-lowering action, 20 mg may be a completely adequate dose. However, if the issue goes beyond cholesterol reduction, we do not know whether a 20 mg dose would be appropriate.

Question: *There are a lot of data becoming available now that look at ApoA and ApoB. Should we be looking at measurements other than LDL?*

Answer: I suspect that we might be looking at the wrong measurements, but you can't rewrite history. Virtually all lipid-lowering trials focus on LDL. The problem with measuring ApoB is that there is no gold standard method, and the variation is something like plus or minus 7%, even in the best laboratories. With LDL, the variation is less than 1%.

Question: *Have you looked at other lipid-lowering studies, either using the same agent or different agents, to see if they arrived at the same magic number that levels off with lowering?*

Answer: We're the first to produce these kind of data. The information that I have is that the CARE [Cholesterol and Recurrent Events] study is going to

turn up something like this. It's too early to say for LIPID [Long-Term Intervention with Pravastatin in Ischaemic Disease Study], because they're just getting their primary database together. The 4S [Scandinavian Simvastatin Survival Study] used a different technology. They didn't measure LDL; they calculated it. So it's difficult for them to reproduce our findings. They've produced tertiles of LDL reduction that don't show, as far as I can see, a linear relationship to event reduction.

Comment: *Your study was done with white Anglo-Saxon males. There are no data on an ethnically diverse population.*

Answer: I think it's completely unreasonable to expect that we should have to do the study on every ethnic group before you start to treat people. You can take this evidence-based medicine so far, but when you try to take it further, it causes damage.

... REFERENCES ...

1. Shepherd J, Cobbe S, Ford I, et al for the West of Scotland Coronary Prevention Study (WOSCOPS) Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-1307.
2. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CCPT) results II: The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA* 1984;251:351-364.
3. Frick MH, Elo O, Haapa K et al. Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia: Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237-1245.