SMH ST. MICHAEL'S HOSPITAL Cardiology
UNIVERSITY OF TORONTO
A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

Lipid Lowering Therapy in Primary and Secondary Prevention: Insights from LIPID and WOSCOPS

Presented by: CHRIS PACKARD, PhD, DSC, ANDREW TONKIN, MD

Satellite Symposium at the 70th Scientific Session of the American Heart Association

Orlando, Florida, November 9-12, 1997

Reported and discussed by:
SHAUN GOODMAN, MD

Clinical trials have demonstrated that inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) greatly reduce cardiovascular-related morbidity and mortality in patients with and without coronary artery disease. The recently presented landmark Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial suggests that even patients with average cholesterol levels may benefit from pravastatin therapy. There is also important new information to suggest that the benefits of pravastatin use in the West of Scotland Coronary Prevention Study (WOSCOPS) and Cholesterol and Recurrent Events (CARE) trials may be effected by more than a simple lowering of circulating LDL cholesterol levels.

The LIPID trial, the largest secondary prevention trial with a statin, examined the role of low density lipoprotein (LDL) cholesterol in reducing coronary events. Design and baseline data were presented at a satellite symposium on November 9th, while the final (preliminary) results were presented for the first time on November 12, 1997

There is now overwhelming evidence from several large-scale clinical trials that therapy with this group of agents leads to less progression and more regression of pre-existing coronary atherosclerotic lesions.[1] Evidence from these trials also suggests fewer subsequent clinical coronary heart disease events among patients with clinically manifest disease.[2-4]

Secondary prevention with statins

In the secondary prevention randomized clinical trial – 4S (Scandinavian Simvastatin Survival Study) – 4,444 men and women, aged 35-70 years, with angina or prior myocardial infarction (MI) and total cholesterol 5.5-8.0 mmol/L, were followed for 5.4 years.[2] Compared with placebo-treated patients, simvastatin (20-40 mg daily) produced a 30% reduction in the relative risk of death from all causes, a 42% reduction in deaths from coronary heart disease, a 34% risk reduction in CHD morbidity, and a 37% risk reduction in myocardial revascularization procedures.

The results of 4S were dramatically extended by the CARE (Cholesterol and Recurrent Events) trial investigators.[4] In a double-blind trial lasting five years, 4,159 men and women with a prior MI (between three and 20 months before randomization), who were 21-75 years of age, had total cholesterol levels less than 6.2 mmol/L and LDL levels of 3-4.5 mmol/L, received either 40 mg of pravastatin per day or placebo. A 24% reduction in the risk of coronary heart disease death or non-fatal MI was seen among pravastatin-treated patients as compared to placebo. In addition, there was a 27% risk reduction with pravastatin in the need for coronary revascularization and a 31% reduction in the risk for stroke. This occurred in the setting of a 32% reduction in the mean level of LDL values. Thus, CARE was able to demonstrate additional benefit in lowering LDL cholesterol levels that had previously been considered "average" with the use of pravastatin.

Preliminary results of the LIPID trial

The LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) study further extends the findings of CARE. The primary objective of LIPID was to investigate whether treatment with pravastatin – in patients with a history of acute MI or hospitalization for unstable angina and a baseline cholesterol in the range of 4-7 mmol/L – would reduce coronary mortality over a period of >5 years.

St. Michael's Hospital
30 Bond St., Suite 701A
Toronto, Ontario M5B 1W8
Fax: (416) 864-5330

LIPID was a double-blind, placebo-controlled trial involving men and women aged 31-75 years. Eligible patients were stratified by diagnosis (MI or unstable angina) and randomized to treatment with diet plus pravastatin (40 mg/day), or to diet plus placebo. A total of 9,014 patients were randomized from 87 centres in Australia and New Zealand. Recognizing that the results of other trials would become available during the course of the long-term follow-up in LIPID, study investigators allowed for the use of unblinded lipid-lowering therapy by the patients' personal physicians and made a specific effort to disseminate information on newly reported studies to investigators, patients, and their physicians. Therefore, 13% of patients initially assigned to placebo commenced some type of lipid-lowering therapy and 18% of patients assigned to the pravastatin group discontinued their study drug treatment over the approximate six years of follow-up.

Randomization into the LIPID study began in June 1990, with the last visit scheduled for September 1997. However, on May 22, 1997, the investigators announced that the LIPID study was closing earlier than projected following communication from an independent monitoring committee that overall survival was significantly improved in patients receiving pravastatin therapy.

Baseline characteristics were similar among the placebo and pravastatin groups.[5] Of note, 17% of the study population (n=1,516) were women, 64% (n=5,754) of patients had a qualifying diagnosis of MI, the median age was 62 years, and importantly, 15% of patients were over 70 years of age at the time of entry into the study. The median baseline values were: total cholesterol 5.65 mmol/L, LDL 3.88 mmol/L, HDL 0.92 mmol/L, triglycerides 1.58 mmol/L, and total cholesterol/HDL ratio 6.08. Pravastatin had a significant effect on lipid fractions over the course of the trial with an average 18% reduction in total cholesterol, 25% reduction in LDL, 12% reduction in triglycerides, and a 6% increase in HDL.

LIPID demonstrated that pravastatin reduces both coronary and total mortality in a broad range of patients with established coronary disease, including a large number with average or below-average cholesterol levels (table 1). The primary endpoint of coronary heart disease mortality was reduced by 24% (p=0.0004). The secondary endpoints of total mortality and stroke were reduced by 23% (p=0.00002) and 20% (p=0.022), respectively, and there was a 24% reduction (p=0.0001) in the need for coronary bypass surgery. The benefits of pravastatin were consistent across all patient subtypes, including gender, inclusion diagnosis (MI or unstable angina), age, smoking status, diabetes, or hypertension. Of note, no lower boundary of total cholesterol was seen; subsequent clinical benefit was demonstrated across the entire study inclusion range of 4-7 mmol/L with pravastatin as compared to placebo treatment.

Pravastatin was safe and well-tolerated and there was no evidence of increased risk for noncardiovascular death. Importantly, the incidence of cancers (including breast) were similar in the placebo- and pravastatin-treated groups. While there was a significantly higher rate of asymptomatic AST and ALT elevation among pravastatin-treated patients (0.9% vs 0.5%, p=0.01), the overall rate was less than one in 100 patients treated, and there were no statistical differences in hepatitis, myalgia, myopathy, rash, and other reported side effects.

The LIPID study results are particularly striking because they were demonstrated in patients with average or below average cholesterol levels who were already receiving established medical therapy (e.g. aspirin in 82%, beta-blocker in

Table 1: Pravastatin reduces both coronary and total mortality in a broad range of patients in LIPID (preliminary results)

Endpoint	Number of events		Relative Risk Reduction	p value
	Placebo (n=4502)	Pravastatin (n=4512)		
Coronary mortality*	373 (8.3%)	287 (6.4%)	24%	0.0004
Total mortality	633 (14.1%)	498 (11.0%)	23%	0.00002
Total stroke	194 (4.3%)	157 (3.5%)	20%	0.022
Fatal CHD/non-fatal MI	706 (15.7%)	554 (12.3%)	23%	0.000002
Cardiovascular mortality	431 (9.6%)	333 (7.4%)	24%	0.0002
Fatal/non-fatal MI	455 (10.1%)	334 (7.4%)	29%	<0.00001
CABG	510 (11.3%)	400 (8.9%)	24%	0.0001

* prespecified primary endpoint

47% of patients). In summary, administering 40 mg of pravastatin daily over six years to patients with a history of MI or unstable angina, whose total cholesterol was between 4 and 7 mmol/L prior to treatment, could be expected to prevent 31 deaths (all cause mortality), 19 coronary heart disease deaths, 34 fatal coronary heart disease deaths or non-fatal MIs, and 8 strokes. Combined, one fatal or serious non-fatal event is prevented among every 20 patients treated with pravastatin 40 mg for six years.

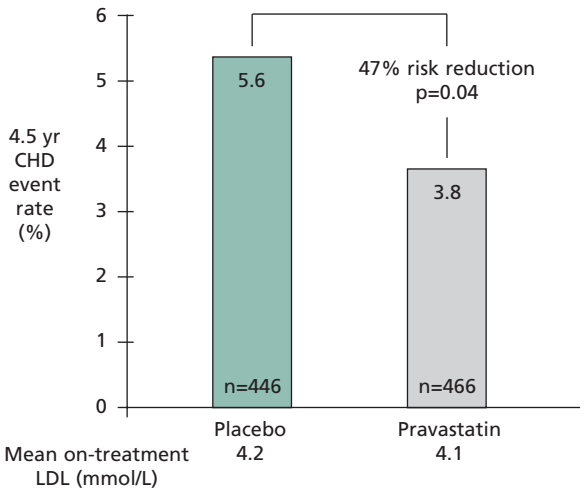
Primary prevention with pravastatin in WOSCOPS

In addition to the dramatic results seen in patients with established coronary heart disease who receive a statin, there is a growing body of evidence that people without overt coronary disease, but with mild or moderate increases in plasma cholesterol, also benefit from lipid-lowering therapy with HMG-CoA reductase inhibitors. The landmark WOSCOPS (West of Scotland Coronary Prevention Study) was published in November, 1995.[3] The trial was conducted in 6,595 hypercholesterolemic (mean total cholesterol 7 mmol/L) men, aged 45-65 years, for a mean of 4.9 years. Most of these men were otherwise healthy, none with previous MI. The criteria for entry to the trial were LDL cholesterol values greater than 4 mmol/L at both screening visits, or greater than 4.5 mmol/L at one screening visit (but less than 6 mmol/L).

Pravastatin 40 mg/day, as compared to placebo, reduced total cholesterol by 20%, LDL cholesterol by 26%, triglycerides by 12%, and raised HDL cholesterol by 5%. In the pravastatin-treated group, the risk of coronary heart disease, death or non-fatal MI, and non-fatal MI alone, was reduced by 31% ($p<0.001$). There were similar reductions in the risk of death from coronary heart disease (definite plus suspected cases: 33% reduction, $p=0.042$), and death from all cardiovascular causes (32% reduction, $p=0.033$). Importantly, the need for coronary angiography was reduced by 31% and for myocardial revascularization by 37% ($p<0.001$). Finally, a 22% reduction in the risk of death from any cause was seen in the pravastatin group ($p=0.051$).

Additional data presented at the AHA from the WOSCOPS database suggests that the dramatic reduction in events seen among pravastatin-treated patients may not be completely explained by LDL lowering alone.[6] In an "overlap analysis," the WOSCOPS researchers eliminated potentially non-compliant subjects (those who had missed at least one-quarter of their trial visits) from the analysis and adjusted for other baseline and on-treatment risk factors, including HDL, VLDL, and triglyceride levels. When comparing the coronary heart disease event rate among patients on placebo and those on treatment with pravastatin with LDL values of between 3.6 and 4.7, there was a 47% risk reduction ($p=0.04$) among those receiving pravastatin,

Figure 1: WOSCOPS on-treatment LDL "Overlap Analysis"

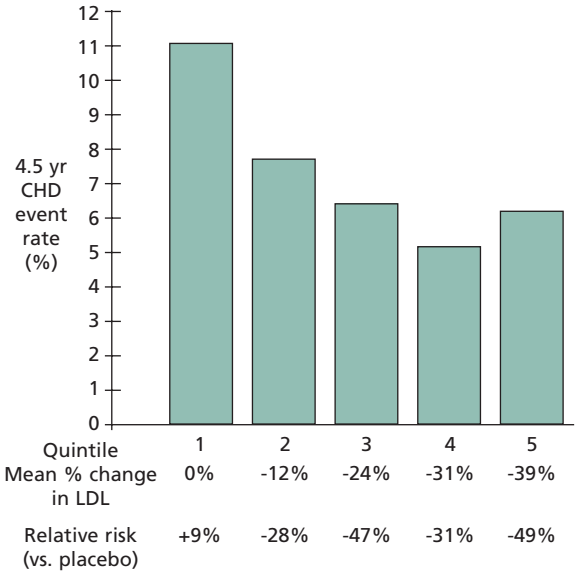


Patients with on-treatment (placebo or pravastatin) LDL values of 3.6-4.7 mmol/L

despite identical LDL levels (figure 1). Thus, patients achieving a specific LDL cholesterol level with pravastatin therapy had a significantly lower coronary heart disease event rate compared to subjects on placebo with the same LDL cholesterol level, suggesting that pravastatin may have effects other than its effect purely on LDL cholesterol.

A "quintile" analysis was next performed to examine the relationship between the reduction in coronary heart disease events and the change in LDL cholesterol induced by pravastatin. These analyses were based on percent change in LDL cholesterol in patients on treatment as compared to baseline. WOSCOPS participants were divided into quintiles on the basis of their baseline LDL levels, which ranged from 4.25 to 6 mmol/L. The 4.5 year event rates in those quintiles showed a consistent reduction in event rates across the LDL baseline range. The pravastatin-treated subjects were then divided into quintiles based on their percent reduction in LDL levels. While the highest event rate occurred in the quintile comprised of patients who showed essentially no change in LDL cholesterol, there was no difference seen among the other four quintiles, regardless of LDL lowering from baseline (figure 2). Thus, LDL reduction was required for relative risk reduction in events with pravastatin therapy; however, the maximum benefit occurred at a mean LDL lowering percentage of 24% (range 19-28%) and there was no further decrease in event reduction even if there was greater percentage LDL reduction (range 34% to 57%). A similar analysis performed in the CARE population show a similar

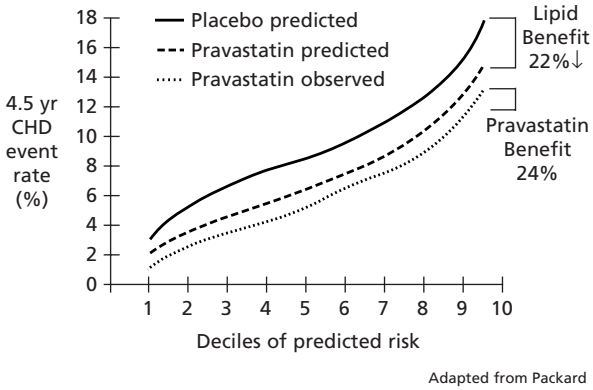
Figure 2: Relationship between CHD event rate with pravastatin and mean % LDL reduction stratified by quintile (≈527 pts in each quintile)



non-linear relationship between LDL levels on treatment and coronary events.[7]

Finally, a Framingham model analysis was performed to compare the predicted coronary heart disease event rates to those actually observed in the West of Scotland Study. The risk factors in the Framingham model include age, gender, smoking, blood pressure, plasma total cholesterol, HDL, and diabetes. The average predicted risk in each group matched the actual risk seen in WOSCOPS in the placebo-treated patients. However, while the Framingham model would have predicted an average 22% reduction in events among the pravastatin as compared to placebo-treated group, the actual reduction in the WOSCOPS pravastatin group averaged 46% (figure 3). Again, this analysis suggests that there is some additional risk reduction in the pravastatin group that is not explained by all of the risk factors in the Framingham model and the on-treatment levels of total and HDL cholesterol that were achieved.

Figure 3: Predicted vs. observed coronary heart disease (CHD) event rate for WOSCOPS using the Framingham Model



Adapted from Packard

The fact that pravastatin had a greater benefit in event reduction in WOSCOPS than could be predicted by the amount of LDL lowering achieved alone implies that there are other mechanisms that account for pravastatin's benefit in this patient population. In addition to its effect on LDL cholesterol, there may be beneficial effects on other cholesterol components (e.g. chylomicrons, VLDL remnants, IDL), improved endothelial function, decreased platelet aggregation, reduced fibrinogen levels and thrombin generation.

Summary

The landmark LIPID study demonstrates that administration of pravastatin to 1000 patients with prior MI or unstable angina with primarily average cholesterol levels for an average of six years prevents 31 deaths, including 19 from coronary heart disease, and 8 strokes. In total, one fatal or serious non-fatal event is prevented among every 20 patients treated with pravastatin 40 mg. The statins were designed to inhibit the rate-limiting enzyme of cholesterol synthesis in the liver. However, the clinical benefit of pravastatin, as demonstrated in additional analyses from WOSCOPS and CARE, appears to be mediated by factors other than those which directly lower LDL cholesterol.

References

1. Rossouw JE. Lipid-lowering interventions in angiographic trials. *Am J Cardiol* 1995;76:86C-92C.
2. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-1389.
3. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-1307.
4. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Eng J Med* 1996;335:1001-1009.
5. The LIPID Study Group. Design features and baseline characteristics of the LIPID Study: A randomized trial in patients with previous acute myocardial infarction and/or unstable angina pectoris. *Am J Cardiol* 1995;76:474-479.
6. Packard CJ. Relationship between LDL-C changes and CHD event reduction with pravastatin in WOSCOPS. *Circulation* 1997;96(8):107.
7. Sacks FM, Moye LA, Davis RB et al. The influence on coronary events of lipid therapy during treatment with pravastatin: The CARE Trial. *Circulation* 1997;96(8):66.