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™

Lowering of LDL cholesterol with statins: New insights

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Satellite symposium and late-breaking clinical trials session
71st Scientific Sessions of the American Heart Association

Dallas, Texas, November 8-11, 1998

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HMG-CoA reductase inhibitors (statins) are a breakthrough in the treatment of high serum cholesterol. Several recent clinical trials demonstrate that statins can substantially reduce both morbidity and mortality from coronary heart disease; however, there is disagreement on whether currently available data has identified a lower threshold cholesterol level below which no further benefit is achieved. This important topic was debated by 4S principal investigator Dr. Terje Pedersen (the "lower" proponent) and CARE co-principal co-investigator Dr. Lemuel Moye (the "threshold" proponent) at a satellite symposium during the 1998 American Heart Association Scientific Sessions. In addition, the preliminary results of a randomized comparison of aggressive lipid-lowering therapy with atorvastatin as compared to percutaneous coronary revascularization (the AVERT study) were presented; this trial suggests that atorvastatin therapy can reduce recurrent hospitalization with angina.

Cholesterol and CHD risk

By the late 1980s, there was strong epidemiologic evidence of a continuous association between plasma cholesterol levels and the risk of coronary heart disease (CHD). Clinical trials testing the "lipid hypothesis" (ie, that lowering plasma cholesterol levels would decrease the risk of CHD) led to a modest reduction in coronary mortality that was often partially counterbalanced by an excess of deaths from non-coronary causes. Furthermore, the impact of first-generation lipid-lowering agents was modest (cholesterol reduced approximately 10%-15%) and general tolerability was less than ideal.

However, definitive proof that lipid-lowering treatment could reduce cardiovascular mortality and improve overall survival became available in the 1990s based upon trials using a new class of agents. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, have proven to be both safe and effective in the management of patients with established CHD (secondary prevention)[1-4] and in those without evident CHD (primary prevention).[5,6]

How low to go?

Despite the safety and effectiveness of this group of therapies, there is still some uncertainty as to whether these large-scale trials justify the consensus guidelines for lipid management developed in North America by the Working Group on Hypercholesterolemia and Other Dyslipidemias[7] in Canada and the National Cholesterol Education Program (NCEP)[8] in the United States. Indeed, none of the reported trials specifically addressed optimal goals for therapy to lower low-density lipoprotein (LDL) cholesterol, and although future trials might address this issue, it will be several years before an answer is available. In the meantime, more detailed analysis of data from recent statin trials may shed some light on optimal goals for LDL cholesterol.[9]

Earlier prospective studies[10-12] suggested that risk for new-onset CHD changed little up to a total cholesterol level of 5.18 mmol/L; above this threshold, risk apparently began to rise (Figure 1A). A total cholesterol level of 5.18 mmol/L corresponds to an LDL-cholesterol level of approximately 3.37 mmol/L. However, a different relationship was obtained in follow-up of screenees of the MRFIT study.[13] By greatly expanding the population base compared with earlier studies,

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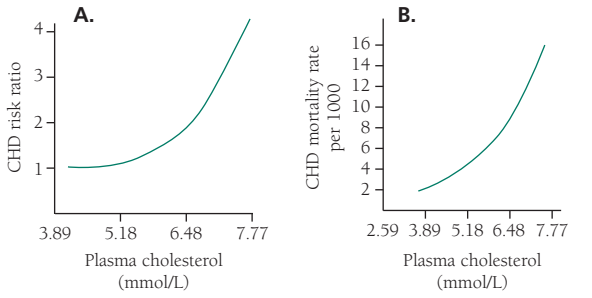
The topics presented in *Cardiology Scientific Update* are independently determined and the content authored exclusively by physician-members of the Division of Cardiology, St. Michael's Hospital. This publication is made possible by unrestricted funding from the publisher, Snell Medical Communication Inc., which has received educational grants from the pharmaceutical industry in support of this work.

Figure 1: Relationship between serum cholesterol levels and CHD in male subjects without established CHD at entrance into prospective study. Figure 1A relates serum cholesterol levels to relative risk (risk ratio) for developing clinical CHD in earlier prospective studies.[10-12] These surveys suggest a threshold relationship. Figure 1B plots association between serum cholesterol levels and CHD mortality for 356 222 male screenees of MRFIT.[13] A curvilinear relationship was observed.



(Adapted from Grundy[9])

a curvilinear relation was uncovered between serum cholesterol levels and CHD risk; in the MRFIT follow-up, no evidence for threshold level was observed (Figure 1B).

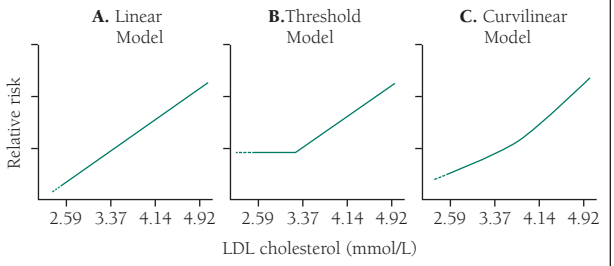
Retrospective subgroup analyses of two secondary prevention trials – The Scandinavian Simvastatin Survival Study (4S)[14] and the Cholesterol and Recurrent Events (CARE) trial[15] – and one primary prevention trial – the West of Scotland Coronary Prevention Study (WOSCOPS)[16] – have been published during the past year. What is surprising is that the prospective association between serum cholesterol levels and recurrent coronary events in patients with existing CHD is even less well-established than for populations without CHD, although some investigations previously indicated a positive relationship.

Grundy[9] has proposed three possible explanations for the fact that lowering serum LDL cholesterol concentrations reduces the relative risk for recurrent CHD:

• According to the *linear model* (Figure 2A), progressive lowering of LDL-cholesterol would reduce CHD risk linearly. If this model pertains for secondary prevention, the lower the LDL level the better. As a consequence, reducing LDL-cholesterol levels even less than 2.59 mmol/L could be advantageous.

• In contrast, if a *threshold model* holds (Figure 2B), no incremental benefit would be achieved by reducing LDL-cholesterol concentrations below the threshold value. This model is analogous to that suggested by earlier prospective studies (Figure 1A).

Figure 2: Theoretical models for effects of reducing serum LDL cholesterol concentrations on relative risk for recurrent coronary heart disease. Model A shows linear relationship; model B, threshold relationship; and model C, curvilinear relationship.



(Adapted from Grundy[9])

• A third possibility, the *curvilinear model* (Figure 2C), gives results analogous to the relationship reported in the large MRFIT follow-up[13] (Figure 1B). Accordingly, progressive lowering of LDL-cholesterol to very low values should yield increasing benefit, but with diminishing returns at lower levels.

4S: The curvilinear model

In 4S, simvastatin therapy reduced LDL-cholesterol levels by an average 35% from a mean of 4.87 to 3.16 mmol/L.[1] This change was associated with a 34% decrease in major coronary events. Although the goal of therapy in 4S was to lower total cholesterol to 5.18 mmol/L or less (LDL-cholesterol <3.37 mmol/L), many patients experienced even greater reductions in serum cholesterol levels. Thus, in 4S subgroup analysis, the decline in cholesterol levels compared with the decrease in risk for recurrent major coronary events is best explained by the curvilinear model[14] (Figure 2C). In other words, greater cholesterol reductions gave continuous, but progressively smaller decrements in CHD risk.

Although the analysis did not specify an LDL cholesterol goal, Pedersen et al[14] concluded that the goal for secondary prevention proposed by current guidelines is appropriate. However, it was speculated that little would be gained by driving LDL to extremely low concentrations.

CARE: The threshold model

A different result was reported by Sacks and Moye et al[15] from subgroup analysis of the CARE trial.[2] Pravastatin therapy lowered LDL cholesterol from an average 3.60 to 2.54 mmol/L; major coronary events decreased by 24%. Subgroup analysis revealed that CHD event rates decreased progressively as LDL-cholesterol levels fell from 4.51 to 3.24 mmol/L; however, from 3.24 to 1.84 mmol/L, CHD events

did not decline further. This finding supports the threshold model (Figure 2B) and speaks against the linear model (Figure 2A).

There is some concern that the CARE subgroup analysis might not have had the power to distinguish between the threshold (Figure 2B) and curvilinear (Figure 2C) models. This is consistent with one of the main limitations of subgroup analysis; that is, the more a set of data is dissected into its components, the less will be the statistical power to precisely define a relationship.

4S vs. CARE: Curvilinear vs. threshold

While debating the topic "Dramatic Lowering of LDL: Increased Benefit?", Pedersen cited the 4S finding that each additional 1% reduction in LDL-cholesterol reduces major coronary event risk by 1.7% (95% confidence interval, 1%-2.4%; p<0.00001). He argued that this is supported by results of examining CARE-type screenees in the 4S trial. Indeed, for those patients in 4S (n≈1,000) who would have met the entry criteria for CARE and had an LDL-cholesterol level of <4.53 mmol/L, there was a 37% risk reduction (p=0.03) in major coronary events in simvastatin-treated patients at 8-year follow-up.[17] Pedersen further argued that the recent AFCAPS/TexCAPS study in primary prevention[6] indicated comparable relative risk reductions in those whose baseline LDL cholesterol was <3.68 mmol/L as compared to those with LDL cholesterol >3.68 mmol/L.

Moye rebutted these arguments by noting that the recently-published LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) study[4] demonstrated an apparent threshold (<3.50 mmol/L) baseline LDL cholesterol value below which no apparent statistical reduction in risk was seen. In addition, the WOSCOPS subgroup analysis[16] in primary-prevention patients indicated a threshold level; maximal risk reduction occurred when LDL cholesterol concentrations fell by 24%, but greater lowering of LDL gave no additional reduction in risk. While the WOSCOPS group recognized the possibility that the true response might have been curvilinear (as in 4S), their data seem to fit the threshold model better.

In summary: Recent statin trials support consensus guideline approaches of adjusting intensity of cholesterol-lowering therapy to absolute risk. While these trials were not specifically designed to define optimal goals for LDL cholesterol in primary and secondary prevention, subgroup analysis does not negate current goals of therapy. These trials do, however, emphasize the need to use clinical judgment as to whether to intensify therapy in patients whose LDL cholesterol levels are already nearing these goals. Future trials will be examining moderate (eg, simvastatin 20 mg/day) versus aggressive (atorvastatin 80 mg/day) lipid lowering to shed further light on this key question of how low to go.

AVERT: Preliminary results

To evaluate whether aggressive lipid lowering reduces cardiac events, the Atorvastatin VErsus Revascularization and Treatments (AVERT) study randomized 341 patients to either treatment with atorvastatin (80 mg/day) or percutaneous coronary intervention followed by usual care (which could include lipid lowering).[18] Inclusion criteria included the recommendation for percutaneous revascularization, ≥50% coronary stenosis in ≥1 major artery, LDL cholesterol ≥115 mg/dL (≥2.98 mmol/L), and ability to exercise ≥4 minutes on treadmill (Bruce protocol) or bicycle. Main exclusion criteria included triple vessel disease, left main disease, unstable angina, and left ventricular ejection fraction <40%.

The AVERT study was conducted at 37 centers in 9 countries. Baseline characteristics were similar between the two treatment groups: mean age of 58 years; 40% with Canadian Cardiovascular Society (CCS) class-I angina, 40% with CCS classes II or III, 20% asymptomatic; mean LDL cholesterol of 152 mg/dL (3.94 mmol/L); 42% with double vessel disease; and 81% mean stenosis of the target lesion. All patients were followed for 18 months for the occurrence of an ischemic event, defined as cardiac death or arrest, myocardial infarction (MI), stroke, bypass surgery, percutaneous revascularization, or worsening angina requiring hospitalization.

The study had 85% power to detect a drop in the estimated ischemic event rate ranging from 35% in the percutaneous revascularization arm to 20% in the atorvastatin-treated arm. Since inclusion to the study required initial referral for percutaneous revascularization and, by study design, only half would undergo this procedure, there were two interim safety analyses performed to ensure that atorvastatin-treated patients were not experiencing events at a significantly greater rate than the intervention-treated patients; this resulted in a slight lowering of the traditional two-sided p value (significance level) to 0.045.

Patients in the percutaneous revascularization arm were allowed to receive lipid-lowering therapy at the discretion of the physician, and this likely contributed to the observed overall 18% lowering of LDL cholesterol from 152 to 119 mg/dL (3.94 to 3.08 mmol/L) in this group. In contrast, there was a significantly greater lowering among atorvastatin-treated patients from 152 to 77 mg/dL (3.94 to 1.99 mmol/L).

Improvement in CCS class was noted in 54% of the revascularization group as compared to 41% in the atorvastatin group (p<0.05). There was a trend toward lowering of the primary composite end-point (death, MI, revascularize-

tion, or worsening angina requiring hospitalization) in the atorvastatin group as compared with the percutaneous-revascularization-treated group (13% versus 21%; relative risk reduction 36%, 95% confidence interval, 5%, 61%; p=0.048). The time to first ischemic event was delayed in the atorvastatin group as compared with the percutaneous intervention group (p=0.027). The individual components of the composite end-point occurred infrequently; they were similar between the two treatment groups, with the exception of a higher incidence of worsening angina requiring hospitalization in the percutaneous intervention group as compared with the atorvastatin-treated group: 25 patients (14.1%) versus 11 patients (6.7%).

The overall safety of atorvastatin was good with only 4 patients (2.4%) experiencing transaminase (liver) enzyme elevations of greater than three times the upper limits of normal.

Conclusion

The AVERT study is the first to examine the important question of whether aggressive lipid lowering is a better approach in stable angina patients than percutaneous revascularization. Preliminary results in a small number of patients (relative to other secondary prevention trials), followed for 18 months indicate reduction in ischemic events/-procedures with high-dose atorvastatin.

Although there have been clear demonstrations of the effect of cholesterol lowering with statins on recurrent coronary events in patients with CHD, little direct information is available on "how low to go." Subgroup analyses of recent large-scale lipid-lowering trials support different hypotheses regarding the optimal goal for LDL cholesterol in secondary prevention. However, both the 4S and CARE trials do suggest some attenuation of benefit when LDL levels drop well below 3.4 mmol/L. CARE results reveal no further risk reduction when LDL cholesterol falls below 3.2 mmol/L; conversely, 4S results suggest continuing benefit below this level, but with diminishing returns. Consequently, for secondary prevention, it seems reasonable to lower LDL levels to ≤2.6 mmol/L if this goal can be achieved with moderate doses of statins.

References

1. 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.
2. Sacks FM, Pfeffer MA, Moye LA, et al for the Cholesterol and Recurrent Events 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.
3. The Post Coronary Artery Bypass Graft 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.
4. The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-1357 (abstract).
5. Shepherd J, Cobbe SM, Ford I, et al for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-1307.
6. Downs JR, Clearfield M, Weis S, et al for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/-TexCAPS. *JAMA* 1998;279:1615-1622.
7. Frolich J, Fodor G, McPherson R, et al for the Dyslipidemia Working Group of Health Canada. Rationale for and outline of the recommendations of the Working Group on Hypercholesterolemia and Other Dyslipidemias: Interim report. *Can J Cardiol* 1998;14:17A-21A.
8. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993;269:3015-3023.
9. Grundy SM. Statin trials and goals of cholesterol-lowering therapy. *Circulation* 1998;97:1436-1439.
10. Kannel WB, Castelli WP, Gordon T, McNamara PM. Serum cholesterol, lipoproteins, and the risk of coronary heart disease: The Framingham Study. *Ann Intern Med* 1971;74:1-12.
11. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the Pooling Project Research Group. *J Chronic Dis* 1978;31:201-306.
12. Goldbourt V, Holtzman E, Neufeld HN. Total and high density lipoprotein cholesterol in the serum and risk of mortality: Evidence of a threshold effect. *Brit Med J* 1985;290:1239-1243.
13. Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986;256:2823-2828.
14. Pedersen TR, Olsson AG, Faergeman O, et al for the Scandinavian Simvastatin Survival Study Group. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1998;1453-1460.
15. Sacks FM, Moye LA, Davis BR, et al. Relationship between plasma LDL concentration during treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events trial. *Circulation* 1998;97:1446-1452.
16. West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation* 1998;97:1440-1445.
17. Pedersen TR, Wilhelmsen L, Faergeman O, et al. Extended follow-up of patients in the Scandinavian Simvastatin Survival Study (4S) shows increased survival benefit of simvastatin therapy. *Circulation* 1998;98:I-451 (Abstract).
18. Pitt B, Waters D, Brown V, et al. Results of the Atorvastatin VErsus Revascularization Treatments (AVERT) study: An 18-month study of aggressive lipid lowering in patients with stable coronary artery disease indicated for catheter-based revascularization (CR). *Circulation* 1998;98:I-636 (Abstract).