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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Cholesterol and Vascular Biology

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The epidemiological link between hypercholesterolemia and atherosclerosis is well-established. Cholesterol-lowering medications reduce cardiovascular mortality and morbidity in patients with and without established vascular disease. However, whether the benefits of these medications are largely related to a reduction in serum cholesterol or due to other factors is of great interest. Although the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have been shown to slow the progression of coronary atherosclerosis, there is controversy about how they prevent myocardial infarction (MI) and stroke, even at low doses. The statins have been shown to reduce adverse cardiovascular outcomes in a wide range of subjects with different levels of cardiovascular risk. Initially, patients with established cardiovascular disease (CVD) at high risk of further events and with levels of total cholesterol well above the normal range were shown to benefit from statin treatment (Figure 1). More recently, however, patients at risk (those with prior CVD, hypertension, or diabetes), but with average cholesterol levels, have also been shown to have an important reduction in risk for all cardiovascular outcomes. Yet, many questions remain. Is the benefit of statin therapy entirely related to the reduction in cholesterol? Is improvement in endothelial function and the reduction in inflammatory markers with statin therapy important for plaque stabilization and the prevention of acute coronary events? Furthermore, what level should cholesterol be reduced to? Is there a role for combination treatment to lower cholesterol to an even lower nadir? Are there pleiotropic differences between the statin drugs that favour plaque stabilization? This issue of *Cardiology Scientific Update* examines these questions in light of recent clinical trials.

Is patient phenotype more important than lipid levels?

Recent clinical trials have demonstrated that the relative benefit from statin treatment is related to a patient's overall risk for CVD and is independent of the initial cholesterol level. Reductions in cardiovascular events were observed with statin treatment, whether cholesterol was high or at levels previously considered normal.

Established cardiovascular disease

The 4S,[1] CARE,[2] and LIPID[3] trials included patients with known coronary heart disease. While the 4S included only patients with elevated total cholesterol levels, CARE studied patients with "normal" cholesterol. Patients in the LIPID trial had a wide range of baseline cholesterol (4.0-7.0 mmol/L). Despite the wide range of baseline cholesterol levels, the benefits of statin treatment were similar, with a 34% reduction in major coronary events in the 4S study, a 24% reduction in fatal and non-fatal coronary events in the CARE study, and a 31% reduction in fatal and non-fatal cardiac events in the LIPID study.

Post-acute coronary syndromes

In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial,[4] high-dose atorvastatin (80 mg) started within 24-96 hours of admission for patients with unstable angina or non-ST-segment elevation myocardial infarction (MI) reduced recurrent ischemic events (death, non-fatal MI, resuscitated cardiac arrest, or worsening unstable angina) by 16% (p=0.048), over a 16-week period of treatment. The benefit of treatment was independent of baseline lipid levels and the results suggested that all patients with acute coronary syndromes should be considered for immediate statin therapy to attain both short- and long-term benefits.

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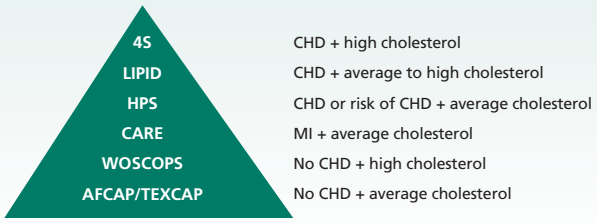
Figure 1: The spectrum of cardiovascular risk and cholesterol levels in the major clinical trials



Diabetes

The Heart Protection Study (HPS)[5] examined the impact of lowering cholesterol in certain specific populations, such as patients with diabetes and hypertension, women, the elderly, and those with peripheral vascular disease and cerebrovascular disease. The entry criteria included a baseline total cholesterol (TC) of >3.5 mmol/L. The results in the nearly 6000 diabetic patients are impressive.[6] Simvastatin (40 mg daily) resulted in a 27% reduction in major cardiovascular events in all diabetic patients (control 18.6%, simvastatin 13.8%, p<0.0003). In the 2912 patients with diabetes, but no evidence of vascular disease, simvastatin reduced major vascular events by 32.9% (p<0.0003). Similar benefits were observed for patients with baseline low-density lipoprotein cholesterol (LDL-C) levels <2.6 mmol/L. The HPS study confirmed for the first time that treatment with a statin could reduce cardiovascular events in diabetic patients without a history of CVD and with "normal" cholesterol levels. The Collaborative Atorvastatin Diabetes Study (CARDS)[7] was recently halted because of a "substantial and highly significant benefit" of atorvastatin (10 mg daily) in diabetic patients with 1 risk factor for coronary heart disease. Diabetic patients with 1 risk factor for CVD have a risk of a future cardiac event that is as high as non-diabetic patients with established CVD. Hence, statin treatment should be considered for most diabetic patients independent of their fasting cholesterol level.

Hypertension

The lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)[8] demonstrated that cholesterol lowering with atorvastatin (10 mg daily) reduced the risk of cardiovascular events in hypertensive patients with normal cholesterol levels (TC <6.5 mmol/L) and 3 risk factors for CVD (male sex, age >55, TC/high-density lipoprotein cholesterol (HDL-C) ratio >6, family history of premature coronary disease, smoking, left ventricular hypertrophy, diabetes, peripheral vascular disease, stroke). The atorvastatin-treated group had a 36% reduction in the incidence of fatal/nonfatal MI (p<0.0005), a 29% reduction in total coronary events (p<0.0005), and a 27% reduction in stroke (p<0.02) during the 3.3 years of treatment. The benefit from atorvastatin was seen during the first year, which is earlier than what has been observed in most trials of statin therapy. It is likely that greater benefits would have been seen if the dose of atorvastatin had been titrated to achieve a greater reduction in LDL-C and the trial had been allowed to continue for the planned duration of 5 years. The ASCOT trial indicates that hypertensive patients with multiple risk factors for CVD, but with "normal" lipid profiles, should be considered for treatment with a statin.

Post-percutaneous coronary intervention (PCI)

The Lescol Intervention Prevention Study (LIPS)[9] revealed that in patients undergoing PCI, fluvastatin (80 mg daily) for up to 4 years significantly reduced the risk of major adverse cardiovascular events (MACE) and prolonged the time to future cardiac events. The range of baseline cholesterol levels was 3.5-7.0 mmol/L. Fluvastatin reduced the risk of cardiac death, non-fatal MI, coronary bypass grafting, or need for repeat PCI by 22% (p<0.013). Patients with multi-vessel disease and diabetes had an amplified benefit from fluvastatin treatment with a 34% (p<0.011) and 47% reduction in MACE, respectively.

In a recent study, troponin levels after PCI[10] were shown to be 2-fold greater in patients not receiving statin therapy, suggesting that statins may have both an early and long-term protective benefit. Although most patients with established coronary artery disease are receiving statin therapy today, the LIPS trial further stresses the need for initiating statin therapy before coronary interventions, irrespective of the baseline cholesterol level.

Increased CRP

C-reactive protein (CRP) is both a marker and a mediator of inflammation in the arterial wall.[11] In apparently healthy men and women, baseline levels of CRP are highly predictive of the risk of sudden death, MI, and stroke.[12] Higher levels of CRP are associated with traditional risk factors for coronary heart disease (eg, obesity, hypertension, smoking, and an inactive lifestyle). More active, thin, and normotensive individuals generally have lower levels of CRP. High sensitivity CRP (hsCRP) is a stronger predictor of future cardiovascular events than LDL-C and improves risk prediction at all levels of LDL-C (Figure 2).[13] The combination of hsCRP and TC/HDL-C ratio provides the best predictor of future cardiovascular events (Figure 3).[14] In patients with the metabolic syndrome, CRP is not only predictive of the risk for coronary artery disease, but also for the development of diabetes.[15]

Statin therapy reduces CRP levels; however, most studies reveal that CRP reduction does not appear to be related to a decrease in lipid levels. In the Pravastatin Inflammation/CRP Evaluation (PRINCE)[16] trial, pravastatin (40 mg daily) reduced CRP levels by 16.9% (p<0.001) in a wide range of subjects independent of sex, age, smoking status, body mass index, baseline lipid levels, presence of diabetes, and use of aspirin or hormone replacement therapy. No associations were observed between baseline CRP and lipid levels, or change in CRP and change in lipids.

Although all statins appear to reduce CRP levels, in the recent REVERSAL trial,[17] atorvastatin (80 mg daily) was associated with no significant change in atherosclerotic plaque volume (as assessed by intracoronary ultrasound) and reduced CRP by 36%. In contrast,

Figure 2: Cardiovascular event-free survival by baseline CRP and LDL cholesterol levels[13]

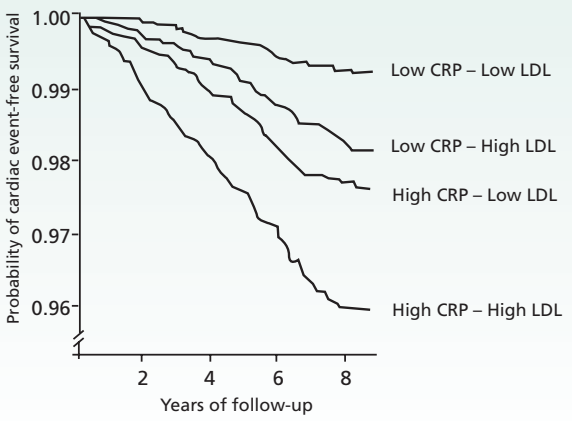
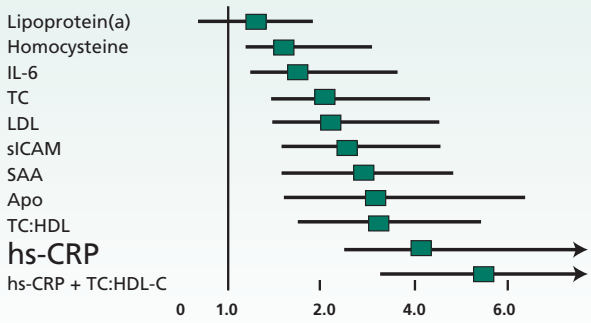


Figure 3: Direct comparison of CRP to other lipid and non-lipid risk factors for cardiovascular disease.[14]



IL-6 = Interleukin 6, TC = Total cholesterol, LDL-C = LDL cholesterol, sICAM = soluble intercellular adhesion molecule-1, SAA = Serum Amyloid A, Apo B = Apolipoprotein B

the comparator, pravastatin (40 mg) was associated with a progression of atherosclerosis and a modest 5% reduction in CRP. Whether these apparently beneficial changes in surrogate endpoints have any relationship to clinical outcomes such as fatal and nonfatal MI is unknown.

For patients with acute coronary syndromes, high-dose atorvastatin in the MIRACL trial potentiated the decline in CRP.[18] By 16 weeks, CRP was 34% lower ($p<0.0001$) with atorvastatin than with placebo. It is suggested that the benefit of atorvastatin may be mediated by a more rapid decline in vascular wall inflammation, which is a known cause for plaque disruption and recurrent acute coronary events.

Higher baseline CRP levels may predict an improvement in outcomes with statin therapy, especially in patients with low or borderline lipid levels. In the Air Force/Texas Coronary Atherosclerosis Prevention study (AFCAPS/TexCAPS),[19] patients had CRP levels that were higher than the median value for patients at high risk by any criteria; therefore, CRP is not necessary to make therapeutic decisions about initiating statin therapy. However, for patients at intermediate risk (ie, with a calculated 10-year Framingham risk between 5% and 20 %), CRP may be of value in helping the clinician to decide about initiating treatment.[12] Although the prognostic value of hsCRP is well-established, we await the results of the Jupiter trial[20] to support the use of hsCRP to direct statin therapy.

Mechanisms of long-term statin therapy

Mechanisms beyond lipid-lowering have been suggested and details of the pleiotropic effects of statins have been discussed in a previous edition of *Cardiology Scientific Update*.[19,21] Statin therapy may stabilize vulnerable atherosclerotic plaque by one of several mechanisms (Table 1). Experimental and clinical evidence support the hypothesis that statin therapy reduces inflammation. Clinical observations suggest that patients with the most inflammation have the greatest benefit from statin therapy, especially when baseline lipid levels are low.[19] Endothelial-dependent vasodilatation is improved by statin therapy in both the brachial[22] and coronary circulation;[23] this is likely a consequence of reduced inflammation and improved availability of nitric oxide.

Current lipid guidelines and phenotypic risk

The 2003 update of recommendations for management of dyslipidemia and prevention of cardiovascular disease[19,24] stratifies patients into 3 categories of risk according to the modified Framingham criteria:

- high (10-year risk of coronary artery disease (CAD) >20%: ie, a history of CAD, diabetes mellitus, chronic kidney disease, or atherosclerosis in any other area)
- intermediate (11%-19%)
- low (<10%).

In the high-risk patient, statin treatment should be started immediately in association with lifestyle and other risk factor modification. Evidence for clinically silent atherosclerosis should

Table 1: Statins and atherosclerotic plaque stabilization

- Reduced inflammation
  - Reduced macrophage and foam cell content
  - Reduced MMP activity
- Improved endothelial function
  - Improved vascular homeostasis
- Reduced plaque lipid and oxidized LDL content
  - More fibrous plaque
- Antithrombotic and pro-fibrinolytic activity
  - Decreased tissue factor activity

MMP = matrix metalloproteinase

be sought in patients at moderate risk by measurement of the ankle-brachial index and performance of carotid ultrasonography and graded exercise testing in men > 40-years-old. A positive test would place the patient in the high-risk category.

The HPS study[5] demonstrates that patients with high risk (diabetes, coronary disease, peripheral vascular disease) benefit from lipid-lowering with simvastatin (40 mg daily) for any level of baseline LDL-C. As a result, the recommendations include a statement that patients at high risk of coronary artery disease should receive the equivalent of simvastatin (40 mg daily) with a minimum target LDL-C of < 2.5 mmol/L.

In patients at moderate risk of CAD, (ie, age > 50 years; TC, 5.20-6.19 mmol/L; HDL-C, 0.9 mmol/L; nonsmoker; systolic blood pressure on treatment 140-159 mm Hg: 12% risk for CAD in next 10 years), the guidelines recommend target levels of LDL-C of <3.5 mmol/L and a TC/HDL-C ratio < 5.0. The ASCOT trial[8] indicates that the hypertensive patient with multiple risk factors (male sex, age >55, TC/HDL-C ratio >6) would benefit from atorvastatin 10 mg daily, irrespective of the baseline lipid profile. The current guidelines state that the ASCOT study "provides strong support for statin therapy in patients at high risk in the primary prevention category."

When deciding about lipid therapy in patients at medium risk, especially those with hypertension, individual risk needs to be carefully assessed. If the patient has 3 risk factors for coronary disease, then the equivalent of atorvastatin (10 mg) should be started irrespective of a lipid profile close to recommended targets. The Working Group did not provide firm recommendations for the application of hsCRP; however, they did state that hsCRP might be clinically useful in identifying patients at higher risk than that predicted by traditional risk factors.

Clinical trials of statin therapy demonstrate that targeting risk is more important than targeting plasma lipids. A high-risk patient should be considered for statin therapy regardless of how low the pre-treatment LDL-C. However, the patient with elevated lipid levels should be treated with the most effective statin therapy to lower LDL-C to below the recommended target of 2.5 mmol/L.

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