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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

# Scientific Update™

## New Perspectives in Atherosclerosis Prevention and Treatment

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**Clinical trials continue to improve our understanding of not only the pathophysiology but also the treatment of coronary artery disease (CAD). Despite this new knowledge, CAD continues to be the leading cause of mortality in Canada and the rest of the Western world. The etiology of coronary disease is multifactorial, but there is already a wealth of evidence for a causal relationship between the level of plasma LDL cholesterol and the risk of CAD. The benefits of reducing cholesterol have now been established beyond a reasonable doubt. There is also strong research data suggesting that the risk of CAD can be significantly reduced by modification of other risk factors such as smoking, hypertension, and diabetes.**

### LDL cholesterol and beyond

Overwhelming evidence from epidemiologic and clinical studies has demonstrated that low-density lipoprotein (LDL) cholesterol is a key element in the development of atherosclerosis, and that reduction of LDL cholesterol levels results in a lower risk of coronary artery disease (CAD). Recent studies using the HMG-CoA reductase inhibitors (statins), have demonstrated substantial reductions in cholesterol and associated reductions in coronary and all-cause mortality (Figure 1). The benefit of HMG-CoA reductase inhibitors may well extend beyond LDL cholesterol lowering and beyond a modest reduction in triglycerides or an increase in high-density lipoprotein (HDL) cholesterol. The potential benefits of HMG-CoA reductase inhibitor therapy are summarized in Table 1.

While the benefit of LDL cholesterol reduction has clearly been established, there is a greater recognition of the importance of triglycerides and HDL as independent risk factors in CAD. A recent meta-analysis of 17 prospective studies[1] has shown that an elevated serum triglyceride level is an independent risk factor for CAD. An increase in relative risk of 1.32 was observed in men with elevated triglycerides, with the risk being somewhat lower when adjusted for HDL cholesterol and other risk factors in the multivariate analysis. This implies that a rise in triglycerides of 1 mmol/L will increase the relative risk

**Figure 1: Reductions in coronary and all-cause mortality with statins**

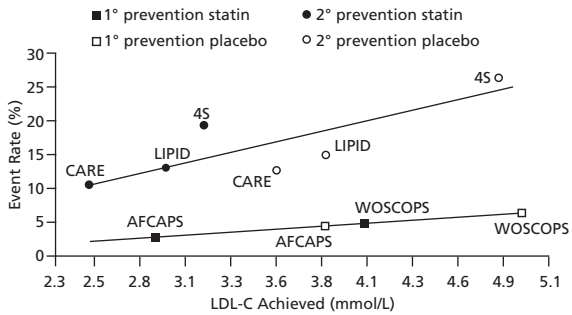




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**Table 1: Potential benefits of Lipid lowering**

- Endothelial function normalization
- Plaque stabilization
  - ↓ extracellular lipid deposits
  - ↓ macrophages in intima and media
  - ↑ collagen and collagen/lipid ratio
  - ↑ smooth muscle cells
  - ↓ calcification and neovascularization in the intima
- Antiinflammatory effects
- Modification of thrombogenic response: ↓ tissue factor, ↓ PAI-I, ↑ Lp(a), ↑ platelet aggregation
- Effect on blood-flow properties (± fibrinogen and ± viscosity)

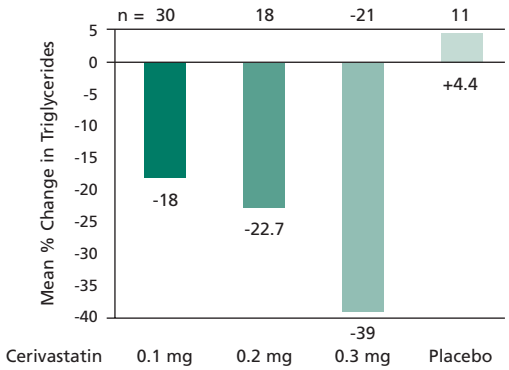
of CAD in men by approximately 32% on univariate analysis and 14% on multivariate analysis. Triglycerides were found to be an even more powerful risk factor in women: The relative risk for CAD in women with elevated triglycerides was 1.76 in the univariate analysis and 1.37 in the multivariate analysis. The relationship between raised triglycerides and risk of cardiovascular disease is likely due to the presence of atherogenic particles, such as triglyceride-rich lipoproteins, rather than the atherogenicity of triglycerides themselves.

In patients with high baseline triglyceride values (≥ 3.95 mmol/L), it has been demonstrated in two small, separate studies that atorvastatin and cerivastatin significantly reduced triglycerides. The results of these trials are shown in Figures 2 and 3.

Further research into the atherogenicity of LDL cholesterol has demonstrated the importance of a particular atherogenic profile associated with the presence of small, dense LDL particles, that is seen more frequently in patients with hypertriglyceridemia. Evidence from the Quebec Cardiovascular Study indicates a relationship between these small, dense LDL particles and the occurrence of CAD.[2]

The contribution of elevated triglyceride levels to CAD risk is further compounded by the ratio of total cholesterol to HDL cholesterol. Low plasma concentrations of HDL cholesterol can be attributed to genetics as well as to a variety of exogenous factors including obesity, diabetes mellitus, hormonal imbalance, hypertriglyceridemia, or cellular lipid storage disease (such as Tangier disease).

**Figure 2: European Pivotal 16-wk Study in mixed HLP patients treated with cerivastatin with baseline TG ≥ 3.95 mmol/L**



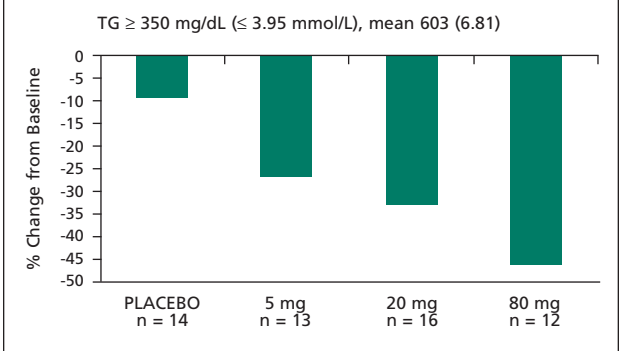

Source: Farnier M, et al

## Acute coronary syndromes

Atherosclerotic CAD is thought to progress not in a linear fashion, with a slow and monotonous increase in the lipid pool, but rather through intermittent plaque rupture or erosion, clot formation, and integration of the clot through lesion remodeling resulting in the increased size of the atherosclerotic plaque. Ample pathologic observations add to this understanding. There is evidence of plaque erosion and clot formation in patients without previous symptoms or diagnosis of CAD who died from other instantaneous causes such as a motor-vehicle accident. There is also evidence of different ages of clots within the same mature atherosclerotic plaque, suggesting that plaque rupture and then lesion stabilization has occurred on more than one occasion.

Another important concept developed over the past decade has been plaque stabilization. Previous observations suggested that culprit lesions causing coronary occlusion and acute myocardial infarction frequently arise from previ-

**Figure 3: Atorvastatin dose-response study in hypertriglyceridemia (4 weeks)**




Source: Bakker-Arkema RG et al.

**Table 2: Angiographic evolution to myocardial infarction**

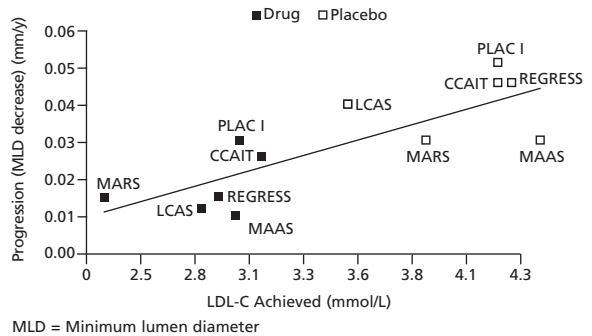
| Study | n | Initial angiographic stenosis <50% | 51-70% | >70% |
|---|---|---|---|---|
| Ambrose et al | 23 | 48% | 30% | 22% |
| Little et al | 29 | 66% | 31% | 3% |
| Nobuyoshi et al | 39 | 59% | 15% | 26% |
| Giroud et al | 92 | 78% | 9% | 13% |
| Hackett et al | 10 | 90% | 10% | 0% |

ously insignificant lesions, eg, < 50% luminal obstruction (Table 2).

Treatment with HMG-CoA reductase inhibitors (statins) can therefore lead not only to regression of angiographic severity of the disease (Figure 4), but more importantly, to improvement in clinical outcome, most likely based on plaque stabilization and improvement in endothelial function (Table 3). Further plaque stabilization can be achieved with lipid lowering, which reduces the number of inflammatory cells and increases the thickness of the fibrous cap. Cap thickness is a major determinant of plaque stability as thinner caps are more affected by shear stress resulting in plaque rupture.

These effects are also observed in hypercholesterolemic rabbit models treated with cerivastatin. Treatment produces a drop in macrophage numbers, decreased activity of metalloproteinases (ie, less macrophage activation), increased collagen content, as well as a reduction in tissue factor.[3,4] These results suggest lipid-lowering with cerivastatin may lead to stabilization of vulnerable lesions and further plaque stabilization. Because of these considerations, aggressive treatment of LDL cholesterol with statins is now mandated (Table 4).

**Figure 4: Regression analysis of angiographic statin trials**




MLD = Minimum lumen diameter

**Table 3: Cholesterol reduction: Association between small angiographic benefit and greater clinical benefit**

| Study | % regression in controls | % regression in treated | % event reduction |
|---|---|---|---|
| NHLBI II | 7% | 7% | 33% |
| POSCH (5 yrs) | 6% | 14% | 35% (62%) |
| Lifestyle | 32% | 41% | 0 vs 1 |
| FATS (niacin + colestipol) | 11% | 25% | 80% |
| FATS (lovastatin + colestipol) | — | 22% | 70% |
| STARS (diet) | 4% | 38% | 69% |
| STARS (diet + cholestyramine) | — | 33% | 89% |
| SCRIP | 10% | 21% | 50% |

## Endothelial function research

The endothelium plays a key role in the regulation of coronary vasoreactivity. Vasodilatation is the predominant response in health, while vasoconstriction is the response to a wide range of physical or chemical stimulants and is the predominant response in endothelial dysfunction. Other important functions of the endothelium include modulation of matrix remodeling, leukocyte adhesion, platelet aggregation, and a number of other antiatherogenic effects. Thus, endothelial function and regulation of nitric oxide synthesis is pivotal in prevention of atherosclerosis.

Other mechanisms impairing nitric oxide synthases in hypercholesterolemic subjects have recently been elucidated.[5] There is evidence that nitric oxide synthetase activity is targeted to the area of small invaginations of cell membranes, the caveola. Caveolin inhibits activity in caveola in response to intracellular calcium concentration. When plasma cholesterol is increased, there is up-regulation of caveolin, resulting in further inhibition of nitric oxide synthetase activity and, therefore, production of nitric oxide.

There is also evidence that oxidized LDL greatly reduces production of nitric oxide. The vasorelaxation frequently seen in response to, for example, serotonin is significantly modified by oxidized LDL.

## Endothelium: A target of therapy

More recently, several studies have indicated improved endothelial function (change from vasoconstriction to vasodilatation in response to acetylcholine) after favorable

**Table 5: NCEP guidelines for treatment based on LDL-C levels**

| | Intervention based on LDL-C | | |
|---|---|---|---|
| | Diet | Drug | Goal |
| *Primary prevention* | | | |
| < 2 risk factors | ≥ 4.1 mmol/L | ≥ 4.9 mmol/L | < 4.1 mmol/L |
| 2 risk factors | ≥ 3.4 mmol/L | ≥ 4.1 mmol/L | < 3.4 mmol/L |
| *Secondary prevention* | | | |
| | > 2.6 mmol/L | ≥ 3.4 mmol/L | ≤ 2.6 mmol/L |

cholesterol modification through diet or lipid-lowering medication. Anderson et al examined changes in endothelial vasomotor function in response to treatment.[6] There was significant improvement with combination therapy (lovastatin and probucol) as opposed to a lipid-lowering diet alone. A lovastatin and cholestyramine combination produced only a trend in improvement. These findings further support the importance of oxidative stress as a mechanism contributing to endothelial dysfunction.

Treasure et al studied changes in coronary endothelial function in moderately hypercholesterolemic patients treated with lovastatin or placebo.[7] After a mean of 5.5 months of therapy, there was significant improvement in the lovastatin group, with a significant reduction in LDL cholesterol (-33%). Findings from this and other studies clearly indicate the potential for improvement in endothelial function following a reduction in cholesterol. This in turn may result in stabilization of atherosclerotic plaque and therefore reduce the propensity for rupture and acute ischemic events.

## The ENCORE trials

In view of the suggestive evidence for the use of CCBs and the very good evidence for the use of statin drugs, the ENCORE (Evaluation of Nifedipine and Cerivastatin On Recovery of Endothelial dysfunction) trial now under way will assess the potential benefit of combining a CCB (nifedipine) with a statin (cerivastatin) to prevent worsening of CAD following percutaneous transluminal coronary angiography in 400 patients. A companion study – ENCORE II – will compare the results in patients taking cerivastatin alone with those in patients treated with a combination of cerivastatin followed by nifedipine. The evaluation will be over a two-year period; results of intravascular ultrasound and quantitative coronary angiography will determine the end points. The two ENCORE trials will, therefore, examine the hypothesis that the combination of CCBs and lipid-lowering therapy has a better effect on endothelial function and structure than either therapy alone. In addition, the studies will allow a comparison of quantitative coronary angiography and intravascular ultrasound as ways of measuring the effects of therapies intended to prevent or ameliorate CAD.

## Conclusion

Our understanding of the pathophysiology of atherosclerosis now includes abnormalities in vasomotion associated with serum cholesterol levels; a relationship between endothelial dysfunction and synthesis of nitric oxide; increased adhesion of molecules; increased platelet activation and aggregation; and increases in smooth muscle cell proliferation. Elucidation of these mechanisms and understanding how we can modify them favorably will bridge the gap between scientific evidence and clinical practice.

### References


1. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: A meta-analysis of population-based prospective studies. *J Cardiovasc Risk* 1996;3:213-219.
2. Lamarche B, et al. Fasting insulin and apolipoprotein B levels and low-density lipoprotein particle size as risk factors for ischemic heart disease. *JAMA* 1998;279(24):1955-1961.
3. Aikawa M, Voglic SJ, Rabkin E, Shiomi M, Libby P. An HMG-CoA reductase inhibitor (cerivastatin) suppresses accumulation of macrophages expressing matrix metalloproteinases and tissue factor in atheroma of WHHL rabbits. *Circulation* 1998;98(17):Abstract 231.
4. Aikawa M, Voglic SJ, Rabkin E, Taubman MB, Fallon JT, Libby P. Lipid lowering by diet reduces tissue factor expression in rabbit atheroma. *Circulation* 1998;98(17):Abstract 195.
5. Michel T, et al. Nitric oxide synthases: Which, where, how, and why? *J Clin Invest* 1997;100(9):2146-52.
6. Anderson TJ, Meredith IT, Yeung AC, et al. The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. *N Engl J Med* 1995;332:488-493.
7. Treasure CB, Klein JL, Weintraub WS, et al. Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. *N Engl J Med* 1995;332:481-487.