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Scientific Update™

Update on HMG-CoA reductase inhibitor therapy

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Overwhelming evidence now exists for the importance of early diagnosis and lowering of low-density lipoprotein cholesterol in patients at high risk for cardiovascular events. Current understanding of the pathophysiology of atherosclerosis 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 help us to bridge the gap between scientific evidence and clinical practice. Recent studies of therapy with HMG-CoA reductase inhibitors have demonstrated substantial reductions in cholesterol and associated reductions in coronary and all-cause mortality. Potential benefits of lipid lowering, in particular with HMG-CoA reductase inhibitors, now include improved outcome in cardiac transplant patients. The benefit of HMG-CoA reductase inhibitor therapy might well extend beyond LDL cholesterol lowering, a modest reduction in triglycerides, or an increase in high-density-lipoprotein cholesterol.

Lowering LDL cholesterol improves outcome

The etiology of coronary artery disease (CAD) is multifactorial, but there is a wealth of evidence suggesting a causal relationship between the level of plasma low-density lipoprotein (LDL) cholesterol and the risk of CAD. The benefit of reducing cholesterol has now been established beyond a reasonable doubt, although there is also strong research data suggesting that the risk of CAD can be significantly reduced by modification of other risk factors including smoking, hypertension, and diabetes. Figure 1 shows the evidence from primary and secondary prevention trials.

The mechanism underlying the benefit is thought to relate mostly to plaque stabilization and improvement in endothelial function, although clearly, regression of angiographically-detected CAD can also be achieved with LDL cholesterol-lowering (Figure 2). Because of the importance of LDL cholesterol-lowering, a goal-oriented approach to treatment has been determined (Table 1).

The benefit of reducing LDL cholesterol has clearly been established, and recently there has been greater recognition of the importance of triglycerides and high-density lipoprotein (HDL) cholesterol as independent risk factors in CAD. Further research into the atherogenicity of LDL cholesterol has also demonstrated the importance of a particular atherogenic profile associated with the presence of small, dense LDL particles; this is seen more frequently in patients with hypertriglyceridemia. The contribution of elevated triglyceride levels to CAD risk is further compounded by the ratio of total cholesterol to HDL cholesterol, with low plasma concentrations of HDL cholesterol generally attributed to genetic predisposition as well as a variety of other exogenous factors such as obesity, diabetes mellitus, hormonal imbalance, and hypertriglyceridemia.

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

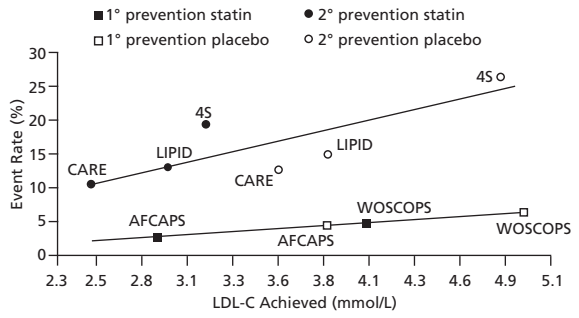
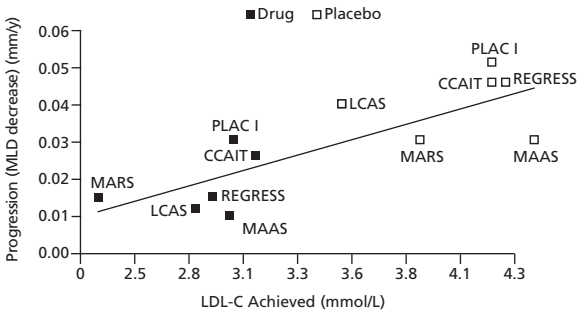


Figure 2: Regression analysis of angiographic statin trials



MLD = Minimum lumen diameter

How low should LDL cholesterol be lowered?

The relationship between LDL cholesterol lowering and reduction in cardiovascular morbidity and mortality continues to be debated. The so-called *linear model* assumes that a progressive lowering of LDL cholesterol would result in linear reduction of CHD risk. However, no single study has demonstrated a similar benefit with respect to reduction of cardiovascular clinical end-points when LDL cholesterol is reduced below 3.0 mmol/L. A more likely scenario is that of a diminishing return, so that with a decrease in the LDL cholesterol below 3.0 mmol/L, there might be some benefit in reducing cardiovascular event, but not at the same rate seen with higher LDL cholesterol levels. Thus, a more likely relationship is that of a *curvilinear* model as suggested by previous prospective cohort studies[1-3] and the results of 4S study.[4]

Another possible relationship between reduction in cardiovascular events and reduction in LDL cholesterol is that of a threshold model as suggested by Grundy[5] and evidence from retrospective analysis[6] of the CARE trial[7] that suggests that there is no incremental benefit in reducing cardiovascular end-point by reducing LDL cholesterol below a threshold value. These observations from the CARE trial were also supported by retrospective analysis of the WOSCOPS[8] and LIPID[9] trials.

It is important to appreciate that none of these trials was specifically designed to define optimal goals for LDL cholesterol lowering for either primary or secondary prevention and therefore, these retrospective analyses attempt to provide an insight into this relationship rather than establish guidelines for clinical practice. Clearly, patients with more significant elevations in LDL cholesterol will benefit the most from more aggressive therapy, as well those with multiple risk factors.

Are all statins created equal?

In a recent review, two subtypes of statins have been identified:[10] the fermentation-derived or natural statins, (eg, lovastatin, pravastatin, and simvastatin) and the synthetic statins (eg, atorvastatin, cerivastatin, and fluvastatin). While the chemical structures of the three natural statins are very similar, those of the synthetic statins differ among themselves, as well

Table 1: NCEP Guidelines for type of treatment based on pre-treatment LDL-C Levels

	Intervention		
	Dietary	**Pharmacologic**	**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

Table 2: 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)

as from the structure of the natural statins. Pharmacokinetically, there is also a difference with lovastatin, simvastatin, atorvastatin, and cerivastatin having a common metabolic pathway through cytochrome P-450 3A4 and cytochrome P-450 2C9 for fluvastatin. Pravastatin appears to have multiple metabolic pathways that do not involve cytochrome P-450.[11] Recently, the Health Protection Branch approved the modification of the pravastatin monograph to state that pravastatin is not primarily metabolized by the P-450 system. The plasma half-life is 2-3 hrs for all statins, except atorvastatin, which has a longer half-life of about 14-20 hrs. The statins also vary in their potency, although its relevance to clinical practice remains uncertain. In general, reductions of 30-50% in LDL cholesterol can be achieved with proper dose titration and in relation to the initial LDL cholesterol levels. The importance of LDL cholesterol lowering and its targets are described in the section above. It is important, however, as emphasized in this editorial, to base our practice of medicine on compounds with proven benefit, as well as evidence of long-term safety, both of which are available mostly for the natural statins, lovastatin, pravastatin and simvastatin.

Beyond LDL cholesterol lowering

Potential benefits of HMG-CoA reductase inhibitor therapy extend beyond LDL cholesterol lowering (Table 2). The beneficial effects of HMG-CoA reductase inhibitors influence multiple steps in the atherogenic cascade, and they bring favorable modifications, not only with respect to reduced LDL cholesterol but also to plaque stabilization.

Pleiotropic effects: Benefits beyond CAD

A recent analysis[12] of over 10,000 patients randomized in secondary prevention trials to treatment with either HMG-CoA reductase inhibitors or placebo revealed a 31% risk reduction in stroke, from 7.3 events/1,000 to 5.1 events/1,000. Thus, successful LDL cholesterol lowering with HMG-CoA reductase inhibitors is associated with a significant impact on the outcome of two of the leading global causes of mortality: ischemic heart disease and stroke.

An analysis of the WOSCOPS data[13] demonstrated that the reduction in event rate with pravastatin therapy exceeded what was expected based solely on cholesterol reduction. The reduction in event rate was from 9.6% in the placebo group to 6.3% in the pravastatin group after 4.4 years of treatment. In other words, a predicted reduction in event rate (based on serum cholesterol level reduction) was 24%, while the observed reduction was 36%, suggesting that additional mechanisms, beyond those associated with LDL cholesterol reduction, may play a role.

While it is clear that the benefits are achieved through a favourable alteration of lipid profiles that reduces that rate of disease progression, it is increasingly recognized that statin medications exert multiple effects beyond lipid-lowering and being anti-atherogenic. Such multiple effects, seen in difference organ systems, are referred to as *pleiotropic effects*. Two pleiotropic effects of note of statins are the associated reduction of stroke risk and of heart transplant graft atherosclerosis.

Recently, at the American College of Cardiology meeting in New Orleans, Keogh et al presented data discussing the effects of pravastatin and simvastatin on reducing heart transplant graft atherosclerosis.[14] HMG-CoA reductase therapy resulted in not only decreased mortality but also fewer rejections. In the study, eighty-seven cardiac transplant recipients received either pravastatin 20 mg or simvastatin 10 mg, starting on day 2 after transplantation. Within this group, 78 patients have completed 12 months of therapy on the mean pravastatin daily dose of 36±8 mg (n=40) or the mean simvastatin daily dose of 18±6 mg

(n=38). No significant differences were observed with respect to rejection or infection rates, liver or renal function tests, or doses of immunosuppressants. Survival in pravastatin-treated patients at 12 months appeared to be better; (95.3% vs. 78.7%, p <.05), however, because of the small number of patients and the preliminary nature of this observation, the data should not be overinterpreted.

Indeed, another prospective study by Mehra et al[15] presented at the meeting found no differences in rejection indices in a cohort of 49 heart transplant recipients who were randomly assigned, within six weeks of surgery, to one year of treatment with simvastatin or pravastatin. It is interesting that a parallel cohort of 37 untreated heart transplant recipients had a mean biopsy rejection score that was significantly higher than that of either treatment group, suggesting that therapy with HMG-CoA reductase inhibitors might reduce rejection episodes, perhaps by inhibiting natural cytotoxicity, T-cell proliferation, and monocyte chemotaxis. In this small study, simvastatin appeared to lower total and LDL cholesterol somewhat more than pravastatin, but there was no correlation between the percent lipid change and the mean biopsy rejection scores. Thus, the important immunomodulatory property of HMG-CoA reductase inhibitors appears independent of the lipid-lowering effects of these agents.

Future challenges

With this overwhelming evidence of benefit from LDL-cholesterol lowering and cardiovascular-event reduction on the one hand, and the possible benefits that might extend beyond the CAD patient population on the other hand, it is disappointing that only 25–30% of suitable patients actually receive HMG-CoA reductase treatment. This may be due, in part, to less-than-optimal screening and detection, the prescribing of fixed doses rather than goal-oriented therapy, and compliance issues.

Cholesterol assessment and lowering is a simple, non-invasive, and universally available intervention. It is usually well-tolerated, with minimal serious side effects, and it can be safely administered in conjunction with other medications.[4]

Not all patients benefit from cholesterol reduction, although clearly it needs to be attempted in everyone at significant risk for CAD. Thus, aggressive and goal-orientated LDL-cholesterol lowering should be a routine part of risk-factor modification. It is also important to modify other risk factors, including smoking, hypertension, glucose intolerance, and other lipid abnormalities. The importance of yet more risk factors such as homocysteine is also emerging and will require further attention.

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