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Scientific Update™

The Role of Statins in Dyslipidemia: Making the Difference

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Clinical trials continue to improve our understanding of the pathophysiology and 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 are 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 CAD

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 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).

Atherogenesis and 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 that results in the increased size of the atherosclerotic plaque. Ample pathologic observations add to this understanding. There is evidence of plaque erosion and clot formation without previous symptoms or diagnosis of CAD in patients who have 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.

One of the important components of atherogenesis is the oxidative process that takes place at endothelial borders, including oxidation of LDL cholesterol particles. It is thought that repetitive injury to the endothelium (eg, from smoking or because of hypertension) results in superoxide particle production which leads to oxidation of LDL, a more avid pick-up of these oxidized particles by macrophages, and the conversion of these to foam cells. Oxidized LDL may also lead to endothelial dysfunction since there is evidence of endothelium-mediated vasodilatation in the presence of oxidized LDL. Evidence of inverse relationships between brachial flow and concentration of antibody to oxidized LDL supports this hypothesis.[1] Interestingly, endothelial cells are the source of superoxide production with an increase in superoxide production in a high cholesterol animal model.[2] Inflammation also appears to play an important role in endothelial dysfunction and leads to expression of leukocyte adhesion molecules. Recent evidence suggests that statin therapy may decrease adhesion molecule production and therefore, may decrease development of atherosclerosis.[3] Similarly,

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

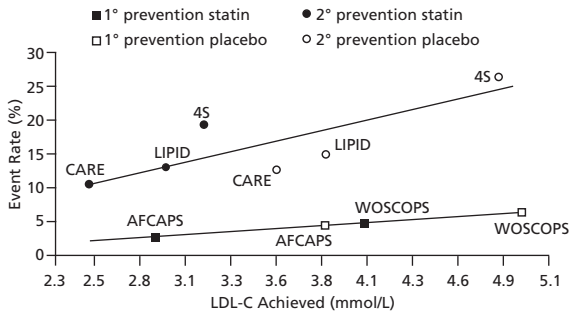

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Table 1: Angiographic evolution to myocardial infarction

	Initial angiographic stenosis			
Study	**n**	**<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%

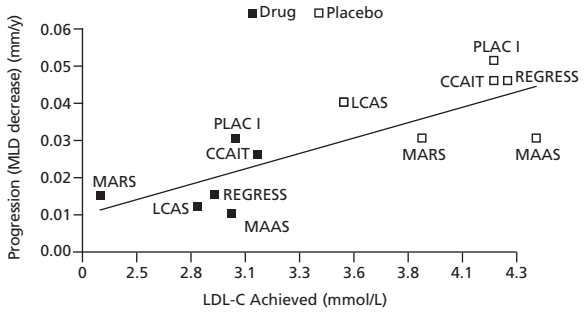
recent evidence suggests that treatment with simvastatin may correct endothelial dysfunction induced by oxidized LDL by increasing nitric oxide production; this may in turn inhibit production of metallaproteinase and leukocyte adhesion factors.[4]

More recently, several studies have indicated improved endothelial function (change from vasoconstriction to vasodilatation in response to acetylcholine) after favorable cholesterol modification through diet or lipid-lowering medication. Anderson et al examined changes in endothelial vasomotion function in response to treatment. There was significant improvement with combination therapy (lovastatin and probucol) as opposed to a lipid-lowering diet alone, while a combination of lovastatin and cholestyramine 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. 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 may in turn result in stabilization of atherosclerotic plaque and reduction in the propensity for rupture and acute ischemic events.

Another important concept that has developed over the past decade has been plaque stabilization. Previous observations suggested that culprit lesions causing coronary occlusion and acute myocardial infarction (MI) frequently arise from previously insignificant lesions, eg, <50% luminal obstruction (Table 1).

Figure 2: Regression analysis of angiographic statin trials



MLD = Minimum lumen diameter

Table 2: 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%

Treatment with HMG-CoA reductase inhibitors (statins) can therefore lead not only to regression of angiographic severity of the disease (Figure 2), but more importantly, to improvement in clinical outcome, most likely based on plaque stabilization and improvement in endothelial function (Table 2). 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 reduction in tissue factor.[5,6] These results suggest that 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 3).

Secondary prevention: Are we doing enough?

Regional variations in the prevalence of cardiovascular disease were evident based on NPHS self-reported data for the planning regions used in 1994/95 when the survey was fielded.

Table 3: 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

Figure 3: Age/sex-adjusted cardiovascular mortality rates per 100,000 population in Ontario, 1981/82-1996/97

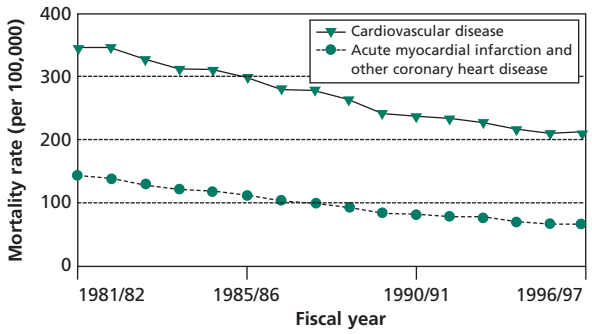
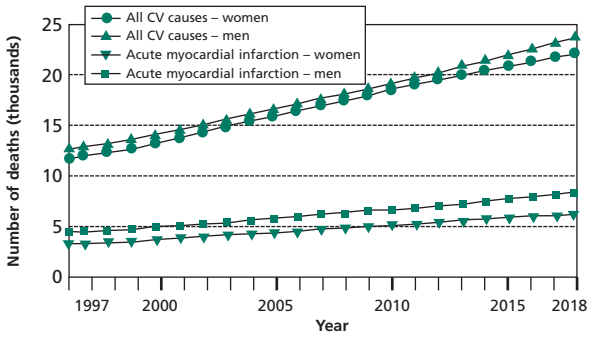


Figure 4: Projected number of deaths from all cause cardiovascular disease and acute myocardial infarction only in Ontario, 1997 to 2018*



*Note: Projected deaths based on assumption that age-sex mortality remains constant from 1996 onwards.

The lowest prevalence was found in the highly industrialized Central West and Central East regions of Ontario, centered around the major Metropolitan areas of Toronto and Hamilton (Table 4). Northern Ontario had a prevalence that was 50% higher than in these regions.

Table 4: Age/sex adjusted cardiac disease prevalence rate

North	6.7
East	6.2
South West	5.1
Central East	4.5
Central West	4.4

Cardiovascular mortality continues to decline steadily. This finding is consistent with previous data that show that cardiovascular disease death rates have been declining steadily in Ontario since the mid-1960s.[7] The 1992 death rates are almost half those of 1969 and this decline applies to all major categories of cardiac diseases for both men and women (Figure 3).

However, based on population projections prepared by the provincial government, the number of deaths in the cardiovascular category would almost double (an increase of 90%) by the year 2018, due to population growth and aging (Figure 4). However, it is possible that the continuing slow decline in mortality rates will blunt the impact of population aging.

One of the ways to approach an evaluation of secondary prevention is to review the frequency with which proven therapies are utilized. Tables 5 and 6 show that even therapies with well-documented benefits such as beta-blockers, ACE inhibitors, and statins, may still not be used optimally.

Update on statins: Focus on clinical efficacy with cerivastatin

A number of cerivastatin-related studies have been undertaken. A North American pivotal study with 0.8 mg was recently completed in hypercholesterolemic patients over a period of 1.5 years of follow-up. In that study, cerivastatin 0.8 mg and 0.4 mg was compared to pravastatin 40 mg following initial treatment with placebo. While the results of the overall study are not available, Canadian data revealed that approximately 120 patients out of 1,170 showed a 43% reduction in LDL cholesterol with the 0.8 mg dose and a 37.4% reduction with the 0.4 mg dose, as compared to a 32% reduction with pravastatin, after 24 weeks of therapy. Total cholesterol was reduced 30%, 25%, and 21%, respectively, while triglycerides

Table 5: Overall and age/sex-specific 90-day post-discharge utilization rates for beta-blockers, ACE inhibitors, statins and calcium channel blockers per 100 acute MI patients aged 65 years and over in Ontario, 1994/95 – 1996/97

	1994/95 – 1996/97								Total
	Women (age)			Men (age)			Overall			1994/95
	65-74	75-84	85+	65-74	75-84	85+	1994/95	1995/96	1996/97	1996/97
# of acute MI patients	5,034	4,813	1,749	8,312	5,076	1,070	8,305	8,579	9,170	26,054
Beta-blocker (%)	58	48	34	57	45	34	48	53	51	51
ACE inhibitor	48	52	53	46	51	49	45	50	52	49
Statin	21	10	2	18	9	2	7	14	20	14
Calcium channel blocker	38	40	32	33	36	32	39	34	34	36

Data Source: Canadian Institute for Health Information, Ontario Drug Benefit Program

Table 6: 90-day post-discharge utilization rates for beta-blockers, ACE inhibitors, statins and calcium channel blockers per 100 acute MI patients aged ≥65 years in Ontario by District Health Council, 1994/95 – 1996/97

District Health Council	Number of acute MI Patients	Utilization rate (%)			Calcium channel blockers
		Beta-blockers	ACE inhibitors	Statins	
Summary statistics	26,054				
Minimum		42	43	9	29
25th Percentile		48	47	11	33
Median		51	49	12	36
75th Percentile		54	51	14	39
Maximum		57	57	18	41

Data Source: Canadian Institute for Health Information, Ontario Drug Benefit Program

were reduced 17%, 16%, and 1%, respectively. HDL cholesterol increased 11%, 14%, and 6%, respectively. Similar results with respect to safety and efficacy of 0.2 mg, 0.3, and 0.4 mg doses of cerivastatin have also been demonstrated in published studies.[8,9] In the study by Ose et al, 494 patients were randomized to receive either 0.2 mg (n=162) or 0.4 mg (n=332). There was a six-week placebo run-in phase followed by a 24-week active treatment phase. Analysis revealed that mean LDL-C was reduced by 38.4 ± 0.7% from baseline in the 0.4 group, compared with a decrease of 31.5 ± 0.9% in the 0.2 group (p=0.0001). Also, there was a significant gender difference in the 0.4 mg group: LDL-C decreased by 44.4 ± 8.9%, with a decrease of 37 ± 0.9% in men (p=0.046). In this study both doses of cerivastatin were well tolerated. Overall meta-analysis involving over 800 patients with over 8 weeks of therapy shows that by comparison to placebo, LDL-cholesterol is lowered 28.3% with the 0.2 mg dose, 30.9% with the 0.3 mg dose, 36% with the 0.4 mg dose, and 41.8% with the 0.8 mg dose, indicating a clear dose response curve.

A number of combination therapy trials have also been undertaken. 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 currently underway will assess the potential benefits 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 a 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.

Combination therapy including a statin and a fibric acid derivative has also been studied by Fournier et al[10] with evidence of successful combination of cerivastatin 0.3 mg and Lipidil 200 mg. Preliminary results have suggested that combination therapy can achieve an LDL cholesterol reduction of over 40%, which is greater than that seen with either 0.3 mg of cerivastatin (27.6%) or Lipidil (21%) alone. The decrease in triglycerides seen with combination therapy (37%) and the increase in HDL (12%) could be attributed to the efficacy of Lipidil.

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.

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