# Intensive Cholesterol Lowering: No Longer a Myth

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Epidemiologic data demonstrate a log-linear relationship between low density lipoprotein-cholesterol levels and risk of coronary heart disease [1,2]. This means that the change in relative risk for a given milligram-per-deciliter change in the low density lipoprotein-cholesterol level, is the same, regardless of the baseline LDL-C level. As a result, the absolute benefit of cholesterol reduction depends on the absolute CHD risk conferred by all the risk factors combined [3].

Until recently, the goal for LDL-C lowering in high risk patients was set at <100 mg/dl [4]. This was because such a goal was considered to be not only the limit of efficacy supported by clinical trial data at the time, but also the practical limit that could be achieved in most high risk patients with the available standard therapy [3].

Recent years have witnessed great advances in the treatment of hypercholesterolemia. New and potent drugs were developed, enabling the lowering of LDL-C levels with the use of more potent statins [5,6] and combination of statins and other lipid-lowering agents [7]. The development of these potent drugs makes an even lower LDL-C goal an attainable option. This prompted research comparing "intensive" with "conventional" cholesterol-lowering strategies.

In last month's issue of *IMAJ,* Shechter and colleagues [8] summarize the current knowledge on intensive cholesterol lowering. The results are remarkably consistent: LDL-C lowering to levels below 70 mg/dl confers greater risk reduction in high risk patients [9–11]. Moreover, this benefit is independent of baseline LDL-C levels [10,12]. Intensive lowering of LDL-C levels reduces (and indeed almost halts) progression of coronary atherosclerosis in coronary arteries [10]. Carotid intima media thickness actually regressed with intensive cholesterol-lowering therapy [13]. Other studies have demonstrated that intensive cholesterol-lowering therapy reduces the mean number of ischemic or viable segments on dobutamine echocardiography, and improves flow-mediated dilatation response of the brachial artery [14].

It is important to note that the advantages of intensive cholesterol lowering are evident mainly for high risk patients. Decisions concerning patients with lower overall risk will have to wait until studies enrolling such patients are published [15]. Recently published trials indicate that the benefit of intensive cholesterol-lowering therapy may not be as impressive for populations at a lower level of risk [16–18].

All the studies on intensive cholesterol-lowering therapy used statins as the hypolipidemic agent. The efficacy of other classes of cholesterol-lowering agents has yet to be investigated. This is important because there is now a considerable weight of evidence to indicate that this class of drugs exerts a range of effects that inhibit the atherosclerotic process beyond their well-documented lipid-lowering action.

HMG-CoA reductase is a ubiquitous enzyme that is present in vascular and inflammatory cells as well as in hepatocytes. Inhibition of HMG-CoA reductase by statins not only inhibits cholesterol biosynthesis but also inhibits the generation of isoprenoids. In endothelial cells, vascular smooth muscle cells and inflammatory cells, the inhibition of HMG-CoA reductase results in inhibition of important signaling pathways (pleiotropic effects), as well as changes in the lipid content of the cell membrane [19]. Isopoprenoids bind a number of G-proteins such as Rho and Ras by a process known as prenylation. Rho activates a number of nuclear transcription factors such as nuclear factor-kappa b that are involved in inflammatory cellular responses, and also reduces endothelial nitric oxide synthase production by endothelial cells [20]. Thus, the inhibition of Rho by statin therapy reduces the expression of transcription factors, which are intrinsic to inflammatory signaling, and this in turn leads to a reduced response to inflammatory stimuli. The use of a powerful/high dose statin is likely to result in the greatest inhibition of Rho, in parallel with the greatest reduction in LDL-cholesterol.

Inflammation is an integral part of the pathogenesis of atherosclerosis, with the accumulation of inflammatory cells such as macrophages and T lymphocytes particularly within vulnerable plaques [21]. Statins have been shown in animal and human studies to reduce both the number and the activity of inflammatory cells within atherosclerotic plaques [22]. Among the favorable phenotypic changes in the vessel wall are the reduction in matrix metalloproteinase production as well as abrogation of pro-inflammatory Th1-type cellular responses, including the reduction in interferon-gamma and IFNγ-mediated monocyte activation. The recent observation that many of the inflammatory cells in atherosclerotic lesions over-express the

LDL-C = low density lipoprotein-cholesterol
CHD = coronary heart disease

IFNγ = interferon-gamma

HMG-CoA reductase gene may explain why statins, and in particular high dose, potent statins, may be beneficial in reducing inflammation within the vessel wall [19].

Consistent with the view of statins as anti-inflammatory agents was the finding in the REVERSAL trial that reductions in both LDL-cholesterol and C-reactive protein levels were significantly correlated to the rate of atherosclerosis progression [23]. Reductions in the levels of atherogenic lipoproteins were not correlated with reductions in CRP levels.

In the PROVE-IT trial, among patients with acute coronary syndromes who were treated with a statin, achieving a target level of CRP of less than 2 mg/L was associated with a significant reduction in cardiovascular events [24]. Patients assigned to receive 80 mg atorvastatin daily were significantly more likely than those assigned to receive 40 mg pravastatin daily to have a decrease in the levels of both LDL-C and CRP to the target values.

Other pleiotropic effects of statins include immunomodulatory effects [19,25], antithrombotic and anticoagulant effects [19,26] and effects on adhesion molecules and endothelial function [19].

We are witnessing the beginning of an exciting new era in atherosclerosis prevention. New potent drugs are costly. As Shechter et al. [8] note, there is a great degree of undertreatment, mainly because of cost concerns. As new potent (and costly) therapies become available, it remains our challenge to make these valuable drugs part of the arsenal used to treat patients at risk of cardiovascular disease – in an increasingly cost-aware environment.

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CRP = C-reactive protein


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