Inflammation, Immunity, and HMG-CoA Reductase Inhibitors: Statins as Antiinflammatory Agents?

Uwe Schönbeck, PhD; Peter Libby, MD

Abstract—According to traditional thinking, atherosclerosis results from passive lipid deposition in the vascular wall. Thus, therapies predominantly targeted lipid metabolism. The contemporary view of atherosclerosis, however, has broadened to include an active and complex role for inflammation, orchestrated in part by mediators of the immune system. This recognition prompted the question of whether antiinflammatory interventions might provide a novel avenue for the treatment of atherosclerosis. Uncertainties about the type of antiinflammatory regimen and appropriate patient selection currently hamper clinical investigation. Yet cardiovascular scientists have begun to address these questions at the bench, in experimental models, and indirectly in humans. Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A HMG-CoA reductase (statins) have emerged as promising tools with dual functions. Originally designed to target elevated lipids, the “traditional” cause of atherosclerosis, statins might also confer cardiovascular benefit by directly or indirectly modulating the inflammatory component of this prevalent disease. Yet controversy persists regarding the (clinical) relevance of these potential non–LDL-lowering “pleiotropic” functions of statins. This overview addresses the controversy by reviewing in vitro and in vivo evidence regarding statins as antiinflammatory agents. (Circulation. 2004;109[suppl II]:II-18–II-26.)

Key Words: antiinflammatory ■ atherosclerosis ■ pleiotropic ■ statins

Cardiovascular Benefits of Statins Beyond Lipid Lowering: Hints From Clinical Trials

In 1994, the landmark Scandinavian Simvastatin Survival Study (4S) established the benefits of a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) on mortality in patients with atherosclerosis.¹ In accord with traditional acceptance of atherosclerosis as a consequence of lipid disorders, post-hoc analysis of the 4S trial suggested that the benefit provided by simvastatin in individual patients indeed related to the magnitude of change in low-density–lipoprotein cholesterol (LDL-C).³ Subsequent studies, however, differed with this conclusion even as they affirmed the clinical benefits of statins as a class on cardiovascular (CV) morbidity and mortality in patients with or without established atherosclerotic disease. In one post-hoc analysis of the West of Scotland Coronary Prevention Study (WOSCOPS) population, the Framingham coronary heart disease model accurately predicted the risk in placebo-treated subjects but underestimated the CV benefit to the statin-treated group predicted by the degree of LDL lowering.³ In the Cholesterol and Recurrent Events (CARE) study, pravastatin-mediated lowering of cholesterol and triglycerides appeared to account for most but not all of the benefits, lending further support to the hypothesis that statins provide CV benefit beyond lipid lowering.¹¹ Indeed, analysis of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study,⁵ the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial,⁶ and the Heart Protection Study (HPS)⁷ suggested that treatment effects in certain subjects might not depend on LDL-C lowering alone and that the benefit conferred by statins is independent of baseline LDL-C levels, even those <100 mg/dL. Similarly, statins reduce the risk of stroke and transplantation-associated coronary vasculopathy, complications inconsistently associated with elevated lipid levels.⁸–¹¹ The observation that lipid lowering by means other than statins, such as ileal bypass surgery, requires markedly more time to manifest clinical benefits lent additional support to the relevance of the potential “pleiotropic” functions of this drug class.¹²

Finally, the hypothesis that statins reduce CV risk by mechanisms beyond mere lipid lowering drew support from the recognition that inflammation and immunity are central contributors to atherosclerosis, and that reduction in risk by statins may derive from modulation of the composition and biology of the plaque rather than merely the degree of stenosis. Such modulations might render atheroma less prone to rupture and thus may lower the risk of thromboembolic complications of atherosclerosis, independently of alterations in luminal caliber.¹³–¹⁶ Indeed, subjects with persistent inflammation, as marked by higher quantities of plasma levels of C-reactive protein, interleukin 6 (IL-6), serum amyloid A,
soluble intercellular adhesion molecule-1 (ICAM-1), or P-selectin, have elevated CV risk, raising questions and even confusion regarding the role of inflammatory markers as therapeutic targets.\textsuperscript{17–22} Notably, statins diminish levels of these inflammatory markers seemingly independently of their lipid-lowering function.\textsuperscript{23–25}

Despite these hints from the bedside, we lack direct clinical evidence that distinguishes the lipid-lowering–dependent functions of HMG-CoA reductase inhibitors. Moreover, the degree to which the lipid-lowering–dependent functions of statins derived from changes in plasma or cell-associated lipids remains uncertain. Similarly, it remains to be determined whether lipid-lowering–independent functions depend on their inhibition of HMG-CoA reductase rather than on direct interference with inflammatory pathways.

**In Vitro Studies Suggest Lipid-Lowering–Independent Antiinflammatory Functions of Statins in Cell Types Implicated in Atherosclerosis**

In contrast to the clinical data outlined above, in vitro studies uniformly support antiinflammatory roles of statins. Administration of agents of this drug class to cultures of cells that participate in atherosclerosis, including endothelial cells (ECs) and smooth muscle cells (SMCs), monocytes/macrophages, and T lymphocytes, diminishes proinflammatory functions implicated in atherogenesis. This section will discuss potential lipid-lowering–independent antiinflammatory functions of statins in processes that underlie the formation, progression, and clinical complications of atherosclerosis (an order arbitrarily chosen and not related to importance or strength of evidence).

Leukocyte/endothelial interaction and accumulation of inflammatory cells occur early during atherogenesis. Statins can interfere with this proinflammatory pathway of adhesion and migration at the levels of protein expression and function. For example, the HMG-CoA reductase inhibitors lovastatin and cerivastatin diminish the expression of the integrin dimer CD11b (Mac-1, the cognate ligand of ICAM-1 on endothelium and other cells) on monocytes and inhibit adhesion of leukocytes to ECs (Table).\textsuperscript{26–28} Reduction in adhesion molecule synthesis also applies to other cell types (eg, E-selectin and vascular adhesion molecule-1 on EC).\textsuperscript{26–28} Recent studies shed further light on the potential molecular mechanisms underlying the reduced rates of adhesion of inflammatory cells to the endothelium after statin treatment. Statins can selectively inhibit leukocyte adhesion by direct interactions with the leukocyte-function antigen-1 (LFA-1); definitive evidence for functions independent of lipid lowering.\textsuperscript{29} By binding to a novel allostERIC site within this $\beta_2$ integrin, rather than targeting HMG-CoA reductase, statins block the adhesion of lymphocytes to the endothelium to a degree sufficient to suppress the inflammatory response in peritonitis in mice.\textsuperscript{29}

HMG-CoA reductase–independent functions of statins might extend beyond interactions with LFA-1. In a murine autoimmune disease model, atorvastatin significantly reduced inflammatory infiltration, abrogated the T\textsubscript{H}1 immune responses (a pathway that operates in human and experimental atheroma),\textsuperscript{30} and diminished T-cell proliferation, probably via direct engagement of the T-cell receptor.\textsuperscript{31} The type of immune response supported may also depend on the ability of statins to induce the release of the T\textsubscript{H}2-promoting cytokines (eg, IL-4, IL-5, IL-10, or transforming growth factor–$\beta$), and diminish secretion of the T\textsubscript{H}1 subtype (eg, IL-2, IL-12, or interferon $\gamma$ [IFN-$\gamma$]).\textsuperscript{32} The T\textsubscript{H}2 cytokines IL-4 and IL-10 have antiatherogenic properties, and their overexpression protects against atherosclerosis.\textsuperscript{33–38} In support of this hypothesis, statins diminish the expression and function of proatherogenic cytokines such as IL-6, IFN-$\gamma$, or tumor necrosis factor–$\alpha$ (TNF$\alpha$) in macrophages.\textsuperscript{37–39} Statins may also repress the activation of T lymphocytes by inhibiting major histocompatibility complex class II antigen expression.\textsuperscript{40}

After adhesion to the vascular endothelium, leukocytes migrate to subendothelial sites of inflammation, a process controlled by a cytokine subclass known as chemokines.\textsuperscript{41,42} Notably, HMG-CoA reductase inhibitors also regulate the expression and function of these mediators. Atorvastatin, lovastatin, pravastatin, fluvastatin, and simvastatin reduce expression of the chemokine monocyte chemoattractant protein-1 (MCP-1), IL-8, and regulated on activation normally T-cell expressed and secreted (RANTES) in cultured monocytes, ECs, and SMCs and also within experimental atheroma, in association with reduced macrophage accumulation.\textsuperscript{43–47} Interestingly, inhibition of sterol synthesis via squalestatin in these studies was not comparable, suggesting that the in vivo regulation of cytokine/chemokine production by statins depends on the biosynthesis of nonsterol compounds arising from mevalonate (Figure 1).\textsuperscript{45}

In addition to the inflammatory infiltration, proliferation, and migration of ECs (eg, probably yielding formation of neovessels) and SMCs (promoting formation of the plaque’s fibrous cap) occurs during the formation and progression of atherosclerotic lesions. Currently, however, the implications of HMG-CoA reductase inhibitors in neovascularization remain somewhat controversial. After initial reports demonstrating that simvastatin promotes angiogenesis,\textsuperscript{48} subsequent studies implied inhibition of this process by cerivastatin.\textsuperscript{49,50} These disparities may result from the administration of different statin concentrations rather than compound-specific functions.\textsuperscript{51} Atorvastatin or cerivastatin (10 to 100 nmol/L) promoted the migration of ECs and neovessel formation, whereas concentrations in the supratherapeutic range (>100 nmol/L) limited growth-factor–induced angiogenesis. In contrast, modulation of vascular SMC proliferation and migration by statins appears to be more consistent. Cerivastatin and simvastatin diminish the migration of unstimulated and growth-factor–activated vascular SMCs of arterial or venous origin in vitro as well as ex vivo.\textsuperscript{52,53} Similar inhibitory functions apply to the proliferation of SMCs; however, interpretation of these data requires care, in view of the potential toxic, proapoptotic effects of HMG-CoA reductase inhibitors on these cells.

After initial reports that statins induce apoptosis in a range of tumor cell lines, several studies expanded this concept to include cell types implicated in atherogenesis, originally SMCs, and, more recently, ECs and macrophages.\textsuperscript{54–56} Nev-
Nevertheless, concerns remain regarding the specificity of the proapoptotic function of statins. Early studies in particular utilized high concentrations of drugs (in the millimolar range), which suggested toxicity, rather than a specific process, as a likely explanation for increased cell death. However, more recent mechanistic insights suggest that HMG-CoA reductase inhibitors indeed might mediate apoptosis specifically. Concentrations of statins as low as 10 nM induce the expression of the proapoptotic enzymes caspase-3 and -9, and furthermore, limit expression of Bcl-2, an inhibitor of apoptosis.55,57 In addition, HMG-CoA reductase inhibitors sensitize SMCs to FasL (CD95)-induced apoptosis by yet-undetermined mechanisms.58 Although the role of statins in apoptosis remains uncertain, mevalonic acid, the product of HMG-CoA reductase, serves as the precursor of isoprenoids required for the activation of the G-protein Ras, a promoter of cell survival. Indeed, statins might promote programmed cell death by interfering with Ras prenylation. Exposure of SMCs to atorvastatin, simvastatin, or lovastatin diminished prenylation of p21RhoB, a central regulator of

<table>
<thead>
<tr>
<th>Process/Pathway</th>
<th>Mediator</th>
<th>Cell type</th>
</tr>
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<tbody>
<tr>
<td>Adhesion ↓</td>
<td>Mac-1, LFA-1 (also via direct binding), ICAM-1 (also plasma sICAM-1), VCAM-1 (also plasma sVCAM-1), E-selectin, L-selectin</td>
<td>MØ and T cells to endothelium; peripheral blood</td>
</tr>
<tr>
<td>Migration ↓</td>
<td>MCP-1, IL-8, RANTES</td>
<td>EC, SMC, MØ, T cells</td>
</tr>
<tr>
<td>Proliferation ↓</td>
<td>EC (via p21(Waf1/Cip1))</td>
<td>EC, SMC, MØ</td>
</tr>
<tr>
<td>Endothelial function ↑</td>
<td>eNOS, LDL oxidation, Endothelin-1</td>
<td>EC</td>
</tr>
<tr>
<td>Matrix degradation ↓</td>
<td>Interstitial collagenases MMP-1-13, Gelatinases MMP-2/-9, Stromelysin MMP-3, TIMP-1</td>
<td>EC, MØ</td>
</tr>
<tr>
<td>Apoptosis ↑</td>
<td>Caspase-3, Caspase-9, prenylation of p21RhoB</td>
<td>EC, SMC, MØ</td>
</tr>
<tr>
<td>Thrombosis ↓</td>
<td>Tissue factor, Factor Vila, Platelet aggregation, Fibrinogen, PAI-1, PGI2, Thrombocytosis, TF, TxA2, TxB2</td>
<td>EC, MØ, platelets; peripheral blood</td>
</tr>
<tr>
<td>Inflammatory mediators ↓</td>
<td>CD40/CD40L, sCD40L, IL-1β, IL-6, TNF-α, C-reactive protein, Cyclooxygenase 2, Serum amyloid A, PPAR-γ, Th1 (IFN-γ, IL-12), Th2 (IL-4, IL-10, TGF-β), MHC II</td>
<td>EC, MØ; peripheral blood</td>
</tr>
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Arrows indicate enhanced (↑) or diminished (↓) activation/expression of the pathway and/or mediator after statin administration. EC indicates endothelial cell; ENOS, endothelial nitric-oxide synthase; ICAM-1, intercellular adhesion molecule-1; IL-8, interleukin-8; LDL, low-density lipoprotein; LFA-1, leukocyte-function antigen-1; MCP-1, monocyte chemotactic protein-1; MHC II, major histocompatibility complex class II; MMP, matrix metalloproteinase; MØ, macrophage; PAI, plasminogen activator inhibitor-1; PG2, prostaglandin I2; PPAR-γ, peroxisome proliferator activated receptors; RANTES, regulated upon activation, normal T cell expressed and secreted; sCD40L, soluble CD40L; SMC, smooth muscle cell; sVCAM-1, soluble vascular adhesion molecule-1; TGF-β, transforming growth factor-beta; TIMP-1, tissue inhibitors of metalloproteinase; TNF-α, tumor necrosis factor-alpha; T-PA, tissue plasminogen activator; TXA2, thromboxane A2; and VCAM-1, vascular adhesion molecule-1.
apoptosis. Consideration of the relevance of statin-induced cell death should take into account multiple roles for this process in atherogenesis: it probably promotes formation of the lipid core by the death of foam cells and also influences SMC content in the fibrous cap. Of note, induction of apoptosis by statins appears restricted to the lipophilic members, such as simvastatin, lovastatin, fluvastatin, and atorvastatin, because the hydrophilic statin pravastatin lacks this function in vitro and reportedly diminished cell death in human carotid plaques.

The migration of monocytes/macrophages as well as vascular wall cells, such as endothelial and SMCs, depends, in addition to adhesion molecules and chemokines, on the activity of matrix-degrading enzymes, namely matrix metalloproteinases (MMPs). This protease family may also participate in weakening of the fibrous cap, rendering atherosclerotic lesions prone to rupture. These enzymes localize prominently in the plaques’ shoulder, a common site of rupture. Proinflammatory cytokines, such as IL-1, TNF-α, or CD40L, regulate expression and activation of MMPs. In accord with studies that suggest that statins reduce the migration of cells found in atheroma, and furthermore, render lesions less likely to rupture, these drugs diminish the expression of several matrix-degrading enzymes implicated in these processes. Indeed, HMG-CoA reductase inhibitors lower the expression and function of a broad range of MMPs, including interstitial collagenases (MMP-1, MMP-13), gelatinases (MMP-2 and MMP-9), and stromelysin (MMP-3), in most, if not all, cell types involved in atherogenesis, including macrophages, a major source of MMPs in lesions. Moreover, reduction of MMP expression by statins may apply to animals and humans in vivo. The enzymatic activity of MMPs depends not only on the expression of the protease but also on its interaction with the endogenous tissue inhibitors of MMP (TIMPs). Statins augment the expression of TIMP-1 in human vascular SMCs as well as macrophages, a function that should limit extracellular matrix breakdown and thus might render lesions less prone to rupture. The mechanisms underlying regulation of MMP/TIMP expression and activity remain uncertain but may involve modulation of nuclear factor-κB (NF-κB) activity and prenylation of small signaling Rho proteins.

Rupture of atherosclerotic plaques exposes the procoagulant lipid core to blood, eventually triggering the process of thrombosis. Statins can interfere on several levels with this process by modulating lesional procoagulant activity and platelet function. Simvastatin, cerivastatin, and fluvastatin diminish expression of the major procoagulant tissue factor in macrophages and ECs in vitro and in experimental animals in vivo. In addition, statins promote fibrinolytic activity by diminishing the expression of plasminogen activator inhibitor 1 and enhancing that of tissue-plasminogen activator in endothelial and SMCs. Furthermore, statins modulate platelet function. Although the underlying mechanism remains undefined, statins inhibit fibrinogen expression and thrombin formation in vitro and reduce platelet aggregation and deposition in diseased vessels in vivo. Reduced expression of cyclooxygenase 2 (COX-2), thromboxane A2 (TXA2), or TXB2 and enhanced synthesis of prostacyclin caused by statin treatment may contribute to diminished platelet activation.

Statins may also regulate other aspects of the inflammatory response underlying atherogenesis, including endothelial vasodilatation via enhanced expression of endothelial nitric oxide synthase (eNOS), reduced blood viscosity, and diminished oxidative modification of LDL via their potential antioxidant properties.

**Figure 1.** Implications of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase mevalonate pathway in atherosclerosis.
geranylglyceranlylation). Mechanisms for enhanced expression of the respective proteins might include modulation of mRNA stability. For example, mevalonate destabilizes eNOS mRNA, and statins increase its half-life by blocking mevalonate synthesis. However, statins also directly induce eNOS expression via activation of the phosphatidylinositol kinase 3 and protein kinase Akt pathway. This signaling pathway may also be involved in other functions of statins, such as angiogenesis (via the differentiation of endothelial progenitor cells), apoptosis (probably acting on p21 (Wif1/Cip1), and p27 (Kip1) or tissue-factor expression (by acting on Rho signaling).

Furthermore, recent studies suggest that statins might provide benefit in atherosclerosis by diminishing activity of NF-κB and AP-1, transcription factors implicated in regulating genes involved in a wide range of inflammatory pathways considered central to atherosclerotic pathology. However, it remains undetermined whether statins diminish NF-κB directly or through modulating the peroxisome proliferator activated receptors (PPAR) α, γ, and δ as has been suggested by recent studies. This nuclear receptor family modulates numerous inflammatory processes that characterize atherogenesis.

**Cardiovascular Benefit of HMG-CoA Reductase Inhibitors: a Combination of LDL Lowering and Pleiotropic Mechanisms?**

A review of the recent in vitro as well as in vivo studies supports the hypothesis on LDL-lowering–independent anti-inflammatory functions of HMG-CoA reductase inhibitors:

- The degree of CV benefits observed in patients treated with statins in most analyses appears unaccounted for by the reductions in LDL levels alone.
- Statins seem to benefit patients independently of their baseline lipid profile. Furthermore, statin-mediated protection against stroke and transplantation-associated vasculopathy end points is inconsistently associated with elevated lipids but modulated by mediators of the immune system and inflammation.
- Statins diminish plasma levels of markers of inflammation without apparent regard to the degree of lipid lowering achieved.
- Statins modulate inflammatory processes characterizing atherogenesis specifically, enhancing the expression and activity of antiinflammatory mediators, and, on the other hand, diminishing that of proinflammatory functions in vitro and in experimental animals, without altering lipid profiles.
- Statins may interfere with proatherogenic processes by directly binding to proinflammatory mediators (LFA-1, T-cell receptor), independently of their interaction with HMG-CoA reductase.

Despite suggestive evidence, however, the hypothesis that statins exert antiinflammatory properties independent of their LDL-lowering functions remains unproven. Future studies addressing this issue must confront current uncertainties and concerns, among them:

- Several of the antiinflammatory (and plaque-stabilizing) attributes of statins, such as reduced expression of MMPs and procoagulants, as well as proliferation and migration of SMCs, occur in animals in response to dietary lipid-lowering alone (in the absence of statins).
- Concentrations of statins needed to produce direct effects in vitro are not likely achievable in the clinic.
- Lipophilic and hydrophilic statins both confer clinical benefits, yet they differ in their antiinflammatory capabilities in vitro, eg, the induction of apoptosis (in accord with the prediction that hydrophilic compounds will enter cells slowly if at all).
- Administration of antiinflammatory regimens other than statins (eg, COX-2 inhibitors) do not appear to provide CV benefit, an issue requiring careful interpretation because the range of antiinflammatory compounds tested and the knowledge regarding their functional spectrum (and potentially benefit-masking adverse effects) are still limited.

We interpret available information as showing that statins likely reduce CV events in a dual fashion involving LDL-lowering and LDL-independent functions. Lipid-lowering functions of statins probably extend beyond LDL-C, affecting cholesterol required for the fluidity and function of cell membranes. Indeed, early studies demonstrated that HMG-CoA reductase inhibitors decrease platelet-membrane cholesterol content, which may alter signaling capabilities. More recent studies implicated statin-mediated alterations in transbilayer cholesterol distribution of endothelial cell membranes in the translocation of signal transducers such as Akt. Therefore, it appears necessary to distinguish statin-mediated functions that are dependent on or are independent of the lowering of (1) plasma lipids, (2) cellular cholesterol, or (3) cellular isoprenoids from functions that are irrelevant to interactions with HMG-CoA reductase itself. Several or all of these antiatherogenic functions can apply to the same pathway, as outlined below.

**CD40 Signaling as a Case Study for the Potential Dual Benefits of Statins**

The example of CD40 signaling illustrates the operation of LDL-C–lowering and “pleiotropic” functions (Figure 2). CD40L, through its receptor CD40, mediates a wide range of proatherogenic processes that promote the formation and progression of atherosclerotic lesions as well as thrombotic complications. Interruption of CD40 signaling diminishes the extent of atherosclerotic lesions in hypercholesterolemic mice, modulates the composition and biology of existing plaques toward phenotypically more stable lesions, and affects thrombus formation. In accord with a potentially pivotal role in atherogenesis, elevated plasma levels of soluble CD40L (sCD40L) predict future CV risk. HMG-CoA reductase inhibitors interfere with CD40/CD40L signaling at several levels. Statin administration decreases plasma levels of sCD40L in patients with hypercholesterolemia. The majority of plasma sCD40L probably derives from platelets, although other sources may also contribute. Indeed, statins also diminish the expression of cell-surface CD40L and CD40 on ECs and SMCs, mono-
Interestingly, total cholesterol and LDL-C plasma levels correlate independently and lipid-lowering functions of statins, probably including signaling via the NF-κB pathway. Interestingly, the reductions of plasma and cell-surface lipids/lipoprotein oxidation reduces expression of one category of CD40/CD40L ligand dyad independent of the stimulus, extending from modified lipids to growth factors and cytokines.

These findings imply that statins might affect expression of CD40/CD40L ligand in a dual fashion. Lowering lipids and lipoprotein oxidation reduces expression of one category of stimulators of CD40 and/or CD40L, whereas the reduction of cytokine-induced CD40L/CD40 expression likely requires plasma lipid/cholesterol-independent functions of statins, probably including signaling via the NF-κB pathway. Interestingly, the reductions of plasma and cell-surface CD40L appear to follow different time courses.

In contrast, reduction in plasma levels of sCD40L requires 6 months or more of statin therapy. Interestingly, total cholesterol and LDL-C plasma levels correlate with soluble CD40L concentrations but not monocyte cell-surface CD40, suggesting that statins distinctly modulate the release of (presynthesized) sCD40L (eg, in platelets) and the de novo synthesis of the membrane-associated form of the receptor/ligand dyad.

Conclusions

In our view, the answer to the question posed in the title of this article, based on currently available information, should be “Yes, but . . . .” Although statins certainly exert antiinflammatory functions, both lipid-lowering–dependent and –independent functions appear to be responsible. Lowering LDL levels in blood attenuates functions of lipoproteins in their native or oxidatively modified form as proinflammatory, atherogenic stimuli. On the other hand, the “lipid-lowering–independent” antiinflammatory properties of statins probably include various distinct mechanisms that may or may not involve the HMG-CoA reductase/mevalonate pathway. These functions encompass those that require the synthesis of cholesterol (eg, regulating membrane function), those that require protein prenylation (eg, by FPP or GGPP), or those that do not involve interactions with HMG-CoA reductase (eg, by direct interaction with LFA-1, T-cell receptor). The antiinflammatory role of statins becomes even blurrier as several or all of these pathways can converge, as outlined above for CD40/CD40L.

LDL-C indubitably represents a modifiable key risk factor for atherosclerosis, and lowering LDL-C blood levels certainly diminishes CV risk in the long term. The current flurry of interest in the so-called pleiotropic functions of statins should in no way deter practitioners from aggressive management of dyslipidemia, a long-established risk factor, as mandated by current guidelines. Yet the prospect that some of the benefits conferred by statins may accrue independently of their effects on lipid profiles remains intellectually intriguing. Further study of the pleiotropic functions of statins may provide insights into the biology of atherosclerosis that can yield benefits in terms of both targeting therapy and developing novel strategies that will address the residual burden of atherosclerotic complications that plague even those individuals who have achieved current lipid goals.

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References


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