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Review

Are statins anti-inflammatory?

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Abstract

Large scale clinical trials demonstrate significant reductions in cardiovascular event rates with statin therapy. The observed benefit of statin therapy, however, may be larger in these trials than that expected on the basis of lipid lowering alone. Emerging evidence from both clinical trials and basic science studies suggest that statins have anti-inflammatory properties, which may additionally lead to clinical efficacy. Measurement of markers of inflammation such as high sensitivity C-reactive protein in addition to lipid parameters may help identify those patients who will benefit most from statin therapy.

Keywords: atherosclerosis, C-reactive protein, inflammation, statins

Introduction

Hyperlipidemia is a major risk factor for atherosclerosis, and several large scale trials demonstrate that cholesterol lowering therapy with 3-hydroxy-3-methyl coenzyme A (HMGCoA) reductase inhibitors reduces coronary event rates in both primary and secondary prevention [1–5]. Paradoxes revealed by these trials, however, raise the possibility that statins may have effects that go beyond simple lipid reduction.

Despite large reductions in cardiac event rates, the absolute angiographic change in arterial narrowing observed with statin therapy is small [6]. Second, several trials suggest that the observed clinical benefit of statin therapy is greater than that expected on the basis of low density lipoprotein (LDL) reduction alone. For instance, when the Framingham coronary heart disease model was

applied to the West of Scotland Coronary Prevention Study (WOSCOPS) population, the model accurately predicted risk in the placebo group but underestimated the risk reduction in the pravastatin group [2]. The benefits of LDL reduction with statins also appear to occur earlier than is observed with other cholesterol lowering therapies such as cholestyramine and ileal bypass surgery, even among patients with similar levels of cholesterol after therapy [7,8]. Finally, statins reduce the risk of stroke, but LDL is not an important risk factor for stroke [9].

One additional mechanism by which statins may reduce vascular event rates relates to potential anti-inflammatory effects of these agents. Inflammatory processes, in this regard, play a pivotal role in the pathogenesis of atherosclerosis, and elevated plasma levels of markers of inflammation such as high sensitivity C-reactive protein

eNOS = endothelial nitric oxide synthase; HMGCoA = 3-hydroxy-3-methyl coenzyme A; hs-CRP = high sensitivity C-reactive protein; LDL = low density lipoprotein; MMP = matrix metalloproteinase; TNF- α = tumor necrosis factor- α .

(hs-CRP), serum amyloid A, IL-6 and soluble intercellular adhesion molecule-1 have been shown to predict cardiovascular events [10–16].

Laboratory evidence for anti-inflammatory effects of statins

Unstable plaques are characterized by active inflammation that overwhelms the plaque's capacity for repair [17]. Macrophages and T cells are abundant in the regions of plaque rupture, while smooth muscle cells are few. Stable plaques, conversely, contain few inflammatory cells and abundant smooth muscle cells.

Numerous studies suggest important effects of statins on macrophage function. Macrophages are capable of degrading the extracellular matrix and, by secreting matrix metalloproteinase (MMP), may weaken the fibrous cap and thus predispose an atheromatous plaque to rupture. Fluvastatin and simvastatin have recently been shown to inhibit MMP-9 (gelatinase B) activity and secretion by macrophages [18]. This effect is reversed by the addition of mevalonate, suggesting that it is mediated by HMGCoA reductase inhibition.

MMP-1, or interstitial collagenase, is also thought to play a role in atherosclerotic plaque rupture. Fluvastatin appears to decrease MMP-1 expression in human vascular endothelial cells in a time- and dose-dependent manner [19]. This effect is also seen with lovastatin and again is completely blocked by coincubation with mevalonate. The concentration of fluvastatin required to reduce MMP-1 expression is similar to that seen in clinical practice.

Pravastatin has been shown to cause changes in the composition of atheromatous plaque independent of its cholesterol lowering effect. Pravastatin-treated monkeys have better vasodilator function and favorable changes in the composition of atheromatous plaque compared with control animals with similar changes in lipid profile caused by diet alone [20]. The pravastatin-treated monkeys had fewer macrophages in the intima and media, less calcification and less neovascularization in the intima. Pravastatin may thus serve to stabilize vulnerable plaques by promoting regression of fragile, rupture prone microvessels in the intima.

Oxidized LDL is a key player in the atherogenic pathway. The uptake of oxidized LDL by macrophages generates lipid rich foam cells. Oxidized LDL causes monocyte tissue factor expression, and the proliferation and apoptosis of smooth muscle cells [21,22]. Oxidized LDL also inhibits nitric oxide synthase activity and hence impairs endothelium-dependent vasodilation [23].

Statins reduce the susceptibility of LDL to oxidation by a variety of mechanisms. Statins reduce the cholesterol content of lipoproteins through their hypocholesterolemic

effects, and thus lower the amount of substrate available for oxidation [24]. Simvastatin has been shown to reduce macrophage superoxide formation, thereby decreasing cell oxygen production [25]. Fluvastatin and lovastatin bind to phospholipid on the surface of LDL and thus prevent diffusion into the lipoprotein core of free radicals generated under oxidative stress [26]. Atorvastatin and fluvastatin have also been shown to have direct antioxidant potential [27,28].

Statins can directly upregulate endothelial nitric oxide synthase (eNOS) expression *in vitro* under cholesterol clamped conditions [23]. Both simvastatin and lovastatin upregulate eNOS expression almost fourfold, and completely prevent its downregulation by oxidized LDL. The upregulation of eNOS was reversed by the addition of mevalonate.

A significant increase in endothelium-dependent vasodilation in patients with moderate hypercholesterolemia has been observed after 4 weeks of treatment with simvastatin [29]. The neuroprotective effect of statins is absent in eNOS deficient mice, suggesting that enhanced eNOS activity by statins is a main mechanism by which HMGCoA reductase inhibitors protect against cerebral injury [30].

Hypercholesterolemic rats treated with fluvastatin have attenuated leukocyte adherence responses to platelet activation factor and leukotriene B₄ [31]. Statins inhibit the expression of CD-11b on the cell surface, thus reducing the adhesiveness of macrophages to the vascular endothelium [32]. Atorvastatin reduces monocyte chemoattractant protein-1 levels in the intima and media in hypercholesterolemic rabbits [33]. This decrease in monocyte chemoattractant protein-1 is related to a reduction in nuclear factor κ B activation, a transcription factor involved in the induction of monocyte chemoattractant protein-1 and other proinflammatory cytokines such as IL-1 β and tumor necrosis factor- α (TNF- α).

Statins also cause decreased macrophage expression of soluble intercellular adhesion molecule-1 and lipopolysaccharide-induced secretion of IL-6 and TNF- α by monocytes and macrophages [34–36]. Recent data show that simvastatin therapy for 8 weeks reduces monocyte expression of TNF- α and IL-1 β by 49 and 35%, respectively [37]; this is intriguing data because elevated plasma levels of both soluble intercellular adhesion molecule-1 and IL-6 have been shown to predict risk for myocardial infarction [12,13]. A recent analysis from the Cholesterol and Recurrent Events (CARE) trial showed that plasma concentrations of TNF- α are also persistently elevated among postmyocardial infarction patients at increased risk for coronary events [38]. These findings provide supportive evidence that anti-inflammatory effects of statins may make an important contribution to their clinical efficacy.

In addition to reducing synthesis of cholesterol, HMGCoA reductase inhibitors lower levels of isoprenoids, which are derived from intermediates in the cholesterol biosynthetic pathway. Isoprenoids prenylate a number of cellular proteins that play key roles in cell growth and signal transduction pathways such as G proteins, which have been shown to modulate mitogenic pathways [39].

Statins have been reported to induce apoptosis in cultured vascular smooth muscle cells, and both atorvastatin and fluvastatin increase apoptosis in injured carotid arteries in rabbits [40]. Both simvastatin and fluvastatin inhibit smooth muscle cell proliferation, while pravastatin is devoid of such an effect [41]. The hydrophilic nature of pravastatin may thus limit its diffusion through cell membranes.

Statins also have potentially favorable effects on the coagulation profile. Tissue factor is the primary initiator of the extrinsic pathway. Lipophilic statins (simvastatin and fluvastatin) have been shown to decrease tissue factor expression and activity in cultured human monocyte derived macrophages [42]. Statins also increase tissue plasminogen activator levels and cause a concomitant fall in plasminogen activating inhibitor-1 activity [43].

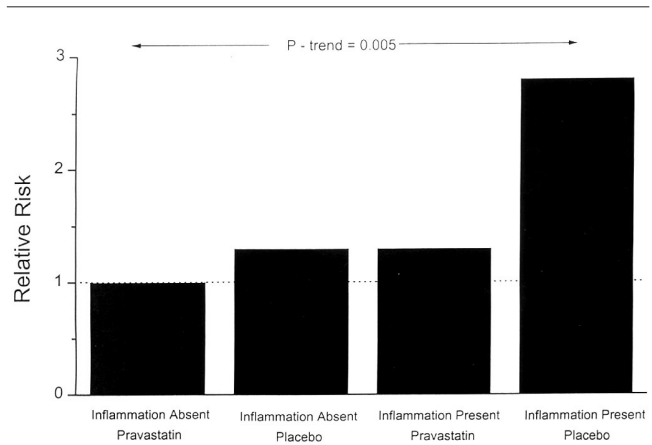
Other *in vivo* effects common to statins include a reduction of platelet aggregation *ex vivo* and *in vitro* [44]. Simvastatin and pravastatin have been shown to reduce thrombus formation and inhibit thrombin generation [45,46].

Pravastatin therapy is associated with a reduction in the number of episodes of rejection following cardiac transplantation. The inhibition of natural killer T cell activity by pravastatin may explain, in part, this beneficial effect [47]. Although transplant vasculopathy is an entity distinct from atherosclerotic disease, similar inflammatory mediators may contribute to plaque instability.

Evidence from clinical trials for anti-inflammatory effects of statins

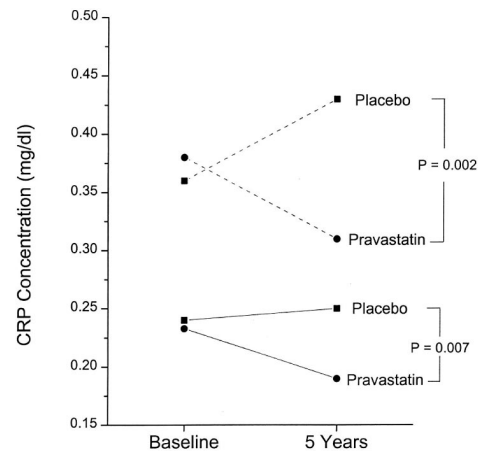
Clinical data regarding the anti-inflammatory role of statins has until recently been limited. Intriguing data from the CARE trial suggests that pravastatin may directly attenuate the adverse effects of inflammation in a process independent of LDL lowering. The CARE trial specifically randomized patients with a prior history of myocardial infarction to receive either 40 mg pravastatin daily or placebo [1]. Patients with evidence of persistent inflammation (as evidenced by elevation of both hs-CRP and serum amyloid A) were at increased risk for recurrent cardiovascular events [48]. The study group with the highest risk of recurrent events was that of patients with persistent evidence of inflammation who were assigned to placebo (relative risk=2.81, $P=0.007$). In a stratified analysis, however, the association between inflammation and risk was significant among those randomized to placebo (relative risk = 2.11, $P=0.048$) but was attenuated and not sig-

Figure 1



Relative risks of recurrent coronary events among postmyocardial infarction patients according to the presence or absence of ongoing inflammation and according to placebo or pravastatin therapy. (Adapted from Ridker *et al* [48].)

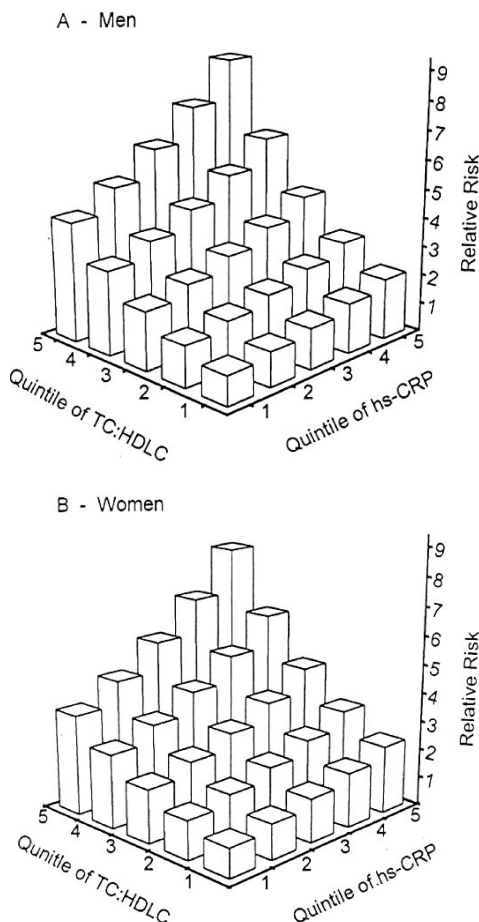
Figure 2



Median (solid lines) and mean (dotted lines) levels of hs-CRP at baseline and at 5 years among participants in the CARE trial, according to placebo or pravastatin assignment. (Adapted from Ridker *et al* [49]).

nificant among those randomized to pravastatin (relative risk=1.29, $P=0.5$). The proportion of recurrent cardiac events prevented by pravastatin was 54% among those patients with persistent evidence of inflammation compared with 25% among those without inflammation (Fig. 1). This difference in benefit was observed despite identical baseline LDL levels in these two groups. Compared with placebo, moreover, pravastatin therapy resulted in a 22% reduction in median hs-CRP levels over a 5 year period (Fig. 2), an effect that was independent of statin-induced changes in LDL [49]. Taken together, these data suggest that, in addition to lowering LDL cholesterol, pravastatin may have clinically important anti-inflammatory properties.

Figure 3



Relative risk of first cardiovascular events in apparently healthy men and women according to baseline levels of the total cholesterol:high density lipoprotein cholesterol (TC:HDLC) ratio and by baseline level of hs-CRP. (Adapted from Ridker *et al* [11,52].)

Atorvastatin and simvastatin have also been shown to reduce CRP levels in a small study of 66 hyperlipidemic patients with coronary artery disease [50]. Simvastatin has been found to reduce CRP levels in type II diabetic patients with hyperlipidemia [51]. The observed change in CRP did not correlate with changes in total cholesterol or high density lipoprotein.

The relative importance of hs-CRP reduction compared with LDL reduction is currently uncertain, and several ongoing studies are directly addressing this issue. What is clear, however, is that markers of inflammation such as hs-CRP appear to add to the predictive value of lipid screening in terms of predicting cardiovascular risk (Fig. 3) [11,52]. It is also clear, at least in secondary prevention, that statins lower hs-CRP levels even in the absence of hyperlipidemia. It has thus been hypothesized that screen-

ing for inflammatory markers may provide an improved method to target statin therapy in primary prevention.

It is not currently known if all statins have clinically relevant anti-inflammatory effects or whether any one agent is more powerful than another is in this regard. Furthermore, the time course of the anti-inflammatory effects of statins is not known. Clinical trials with head to head comparison of statins (such as the PROVE-IT study) and studies designed to examine the time-course of statin therapy on hs-CRP levels (such as the PRINCE trial) will help to resolve these remaining questions [53].

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