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HMG-CoA Reductase Inhibition in the Treatment of Atherosclerosis: Effects Beyond Lipid Lowering

W. März¹, B. R. Winkelmann²

Abstract: Treatment with HMG-CoA reductase inhibitors (statins) has proven the most successful strategy to reduce the concentration of LDL in the circulation. These compounds lower LDL cholesterol by inhibiting the mevalonate pathway in the liver, which in turn depletes the regulatory pool of cholesterol and enhances the activity of LDL receptors. Six prospective clinical trials have convincingly demonstrated that HMG-CoA reductase inhibitors can effectively lower the incidence of cardiovascular events in primary and secondary prevention. *Post hoc* analyses of these trials suggest that the clinical benefit brought about by HMG-CoA reductase inhibitors may not entirely be due to their effect on the levels of circulating lipoproteins. A host of actions of statins on the vascular wall including improvement of endothelial function, anti-oxidative, anti-inflammatory, plaque-stabilizing, and anti-coagulant effects have been advocated to explain effects beyond lipid-lowering. LDL are known to impair endothelial dysfunction, produce pro-inflammatory and pro-thrombotic responses of cellular elements, and cause plaque destabilization on their own.

It is hence not entirely clear to which extent the pleiotropic effects of statins contribute to the overall

efficacy of these compounds. Further investigation is therefore necessary in order to determine the relative significance of cholesterol lowering and of ancillary effects on the net clinical benefit of statin treatment. Finally, it is an emerging clinical issue whether or not statin treatment would yield short-term benefit in the management of acute coronary syndromes.

Kurzfassung: HMG-CoA-Reduktasehemmer in der Behandlung der Atherosklerose: Effekte jenseits der Lipidsenkung. Die Behandlung mit HMG-CoA-Reduktasehemmern ist die bisher erfolgreichste Strategie zur Verminderung des LDL-Cholesterins. HMG-CoA-Reduktasehemmer vermindern das LDL-Cholesterin, indem sie den Mevalonat-Stoffwechselweg in der Leber hemmen, den Gehalt an regulatorisch aktivem Cholesterin vermindern und als Folge die Aktivität des LDL-Rezeptors steigern. Sechs prospektive klinische Studien haben überzeugend gezeigt, daß HMG-CoA-Reduktasehemmer effektiv die Häufigkeit kardiovaskulärer Ereignisse in der primären und sekundären Prävention reduzieren. *Post-hoc*-Analysen dieser Studien legen nahe, daß der klinische Nutzen der HMG-CoA-Reduktasehemmer nicht

alleine auf ihren Effekt auf die Lipoproteine des Plasmas zurückzuführen ist. Inzwischen ist eine Vielzahl von Wirkungen der Statine auf die Gefäßwand bekannt, darunter eine Verbesserung der Endothelzellfunktion, antioxidative, antientzündliche, plaquestabilisierende und antikoagulatorische Wirkungen, mit denen man die über die Lipidsenkung hinausgehenden Effekte erklärt. Von den LDL selbst ist aber bekannt, daß sie die endotheliale Funktion beeinträchtigen und proinflammatorische bzw. prothrombotische Funktionsveränderungen der Gefäßwand induzieren und damit eine Destabilisierung von Plaques hervorrufen. Aus diesem Grund ist der Anteil, mit dem die pleiotropen Effekte der Statine zum gesamten klinischen Nutzen dieser Substanzklasse beitragen, unklar. Weitere Untersuchungen sind daher notwendig, um die relative Bedeutung der Cholesterinsenkung und der zusätzlichen Effekte für die klinisch beobachtete Prognoseverbesserung unter Statinbehandlung herauszuarbeiten. Darüber hinaus wird zu untersuchen sein, ob die Behandlung mit Statinen auch einen kurzfristigen Nutzen bei Patienten mit akutem Koronarsyndrom zeitigt. **J Kardiologie 2002; 9: 284–94.**

■ Introduction

Atherosclerosis continues to be a major health care challenge. Despite intensive basic and clinical research, atherosclerosis is a complex process that has yet to be fully understood. One of the most recent advances in the treatment of atherosclerosis is the use of HMG-CoA reductase inhibitors (statins). Evidence from major trials convincingly shows that statins can effectively reduce the incidence of coronary heart disease (CHD) and stroke [1–5]. With the completion of these trials and results from further basic research, there is a growing body of evidence that the effects of some statins go beyond their cholesterol-lowering effects [6]. This article will critically evaluate the extent to which effects of statins may be due to modulation of endothelial function, antioxidant, anti-inflammatory, or anti-thrombotic properties of these compounds.

■ Endothelial Dysfunction, Lipid Deposition, and Inflammation are Major Hallmarks of Atherosclerotic Lesions

According to the modified response-to-injury concept [7], the earliest manifestation of atherosclerosis is endothelial dysfunction. Well-established causes of endothelial dysfunction

include dyslipidemia, insulin resistance, diabetes mellitus, free radicals produced by cigarette smoking, hypertension, and elevated homocysteine concentrations. Almost independent from specific noxious agents, the dysfunctional endothelium is characterised by an enhanced expression of membrane molecules (E-selectin, intercellular adhesion molecule, ICAM, and vascular cell-adhesion molecule, VCAM) that facilitate the adhesion of platelets, monocytes, and T-cells. Furthermore, irritation of endothelial cells shifts the balance of pro- and anticoagulant factors towards coagulation, and the availability of nitric oxide is compromised, resulting in impaired endothelium-mediated vasodilation. As atherosclerosis progresses, the numbers of monocyte-derived macrophages, T-lymphocytes and even mast cells in the lesions increase, and growth factors and chemokines – released by platelets, endothelial cells and macrophages – stimulate the penetration of smooth muscle cells from the media into the intima. Macrophages accumulating large amounts of lipids are themselves activated and eventually undergo necrosis or apoptosis. This transforms the lesion into a complex one characterised by a core of extracellular lipid deposits and cell debris [8], which is separated from the vessel lumen by a fibrous cap containing, in varying proportions, smooth muscle cells, T-lymphocytes and mast cells. Smooth muscle cells exclusively account for the production of matrix components, which strengthen the cap. T-cells, macrophages and mast cells in contrast, are thought to disintegrate the fibrous cap. Activated macrophages do so by releasing metalloproteinases, a group of proteolytic enzymes cleaving components of basement membranes and extracellular matrix constituents [9]. T-cells contribute to the weakening of the fibrous cap by secreting interferon-gamma, which down-regulates collagen synthesis in

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smooth muscle cells [10] and (in combination with IL-1 β and TNF-alpha originating from macrophages) may even induce apoptosis in these cells [11]. The ratio of smooth muscle cells and matrix on the one hand and lipid deposits and inflammatory cells on the other hand is believed to determine the stability of a lesion. Lesions containing a thin fibrous cap are prone to rupture, an event, which brings platelets from the circulating blood into contact with activated macrophages residing within the lipid core, thereby initiating local thrombosis. Not surprisingly, the risk of vascular events in patients with stable atherosclerotic plaques is lower than in those with unstable plaques [9].

■ What Is The Evidence in Humans That Statins Have Effects Beyond Cholesterol Lowering?

To date, six large statin trials have been completed in primary or secondary prevention. The evidence from these trials has been unequivocal in demonstrating the efficacy and safety of statins in reducing cardiovascular morbidity and mortality. The statin trials included a broad range of patients with different cardiovascular risk at baseline. AFCAPS/TexCAPS [1] and WOSCOPS [5] were primary prevention studies in patients with low to moderate risk of CHD. The Heart Protection Study (HPS) examined the effectiveness of simvastatin, with and without antioxidant vitamin supplementation, on total mortality and cause-specific mortality in subjects with coronary heart disease, peripheral vascular disease or stroke, diabetes mellitus, and treated hypertension [12]. CARE [4] and LIPID [3] included patients with previous MI or unstable angina, respectively, with average cholesterol levels, while the Scandinavian Simvastatin Survival Study (4S) [2] was a secondary prevention study in patients with CHD and elevated cholesterol levels. In each of these studies, treatment with statins reduced major cardiovascular events, relative risk reductions ranging between 24 and 40 percent, with reductions in absolute risk ranging from 3 to 10 percent.

Post-hoc subgroup analyses of some of these trials raised questions about the effects of statins beyond cholesterol lowering. Specifically, in WOSCOPS the following questions were addressed: 1) Is it possible to predict the cardiovascular event rates in the pravastatin-treated patients by means of lipid changes using a risk assessment algorithm derived from the Framingham study? and 2) If the clinical benefit was due to lipid-lowering alone, do placebo and statin patients with similar attained LDL cholesterol levels then have similar event rates?

Intriguingly, in the first analysis [13], patients receiving pravastatin experienced greater benefit in WOSCOPS than predicted by the Framingham risk model (based on the lipid changes achieved by pravastatin in the study): Whereas the predicted risk reduction in pravastatin patients was 24 %, the observed risk reduction was 35 %. This difference was statistically significant. The second analysis [13] showed a considerable overlap of on-treatment LDL cholesterol levels in the placebo and in the verum group. In total, approximately 1,100 patients in each treatment arm had LDL cholesterol levels in the range of 140 to 180 mg/dl (3.26 to 4.65 mmol/l). Mean LDL cholesterol in the placebo group was 170 mg/dl (4.38 mmol/l) and 159 mg/dl (4.10 mmol/l) in the pravastatin group.

When the pravastatin patients were compared with placebo patients who had similar LDL cholesterol, the pravastatin group had a significantly 36 % lower risk of cardiovascular events. Together, these results suggest that lipid changes brought about by the study medication may not fully account for the net clinical benefit seen in WOSCOPS.

Results from the angiographically controlled statin trials also demonstrated risk reduction without substantial regression of atherosclerotic plaques. In the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC) I and the Regression Growth Evaluation Statin Study (REGRESS), there was a statistically significant event reduction even though the trials were of short duration. An additional observation from many of these trials was that the degree of LDL-C lowering did not correlate with coronary event reduction [14].

Further arguments for non-lipid mechanisms of statin action relate to the unexpected reduction of stroke observed in the large statin trials. In contrast to hypertension [15], cholesterol is not a major risk factor of stroke in prospective studies, at a first glance suggesting that cholesterol lowering would yield no benefit in the prevention of stroke. Consistently, neither fibrates, resins nor lipid-lowering diet clearly prevent stroke. However, an approximately 24 percent reduction of stroke incidence is seen in trials of statins [16].

■ Statin Treatment Improves Endothelial Function and Vasoreactivity

Hypercholesterolaemia is a pivotal pathogenic factor of endothelial dysfunction. The mechanism by which low density lipoproteins (LDL) modify endothelial function has not completely been elucidated. Atherogenic lipoproteins and in particular its modified derivatives profoundly affect the function of endothelial cells. In addition to diminishing the production [17] and accelerating the decay of nitric oxide [18], oxidised LDL enhance the expression of adhesion molecules (E-selectin, VCAM-1, ICAM-1), of macrophage colony stimulating factor (M-CSF) [19], monocyte chemoattractant protein-1 (MCP-1) [20], transforming growth factor-beta, and of tissue factor (TF) [21] in endothelial cells. Remnants derived from the incomplete catabolism of triglyceride-rich lipoproteins (chylomicrons and LDL) behave much the same as LDL or modified LDL [22], possibly linking delayed clearance of triglyceride-rich lipoproteins to endothelial dysfunction. In genetically modified mice that are deficient in apolipoprotein E (and have hypercholesterolaemia), the expression of ICAM-1 on the surface of the endothelium is increased at lesion-prone sites [23], and VCAM-1, which is absent in normal mice, is expressed at the same sites as ICAM-1 in mice with apolipoprotein E deficiency [23]. Similar findings were reported in hypercholesterolaemic rabbits [24].

Clinical studies have demonstrated that statins improve endothelial function [25–29] and myocardial perfusion [30–35]. Interestingly, Mellwig et al. using positron emission tomography (PET) to assess coronary blood flow showed that abrupt reduction in LDL cholesterol by a single LDL apheresis improved myocardial perfusion overnight [36]. Consistently, a single session of LDL apheresis significantly augmented endothelium dependent vasodilatation, also emphasizing the significance of LDL cholesterol reduction itself [37].

In an attempt to clarify whether or not improvement of endothelial function was related to cholesterol-lowering, Williams and colleagues [29] administered pravastatin to cynomolgus monkeys previously fed an atherogenic diet for two years, followed by a lipid-lowering diet either containing ($n = 14$) or not containing ($n = 18$) pravastatin for an additional two years. The lipid content in the diet of these animals was adjusted to produce exactly the same plasma cholesterol, LDL cholesterol and high density lipoprotein concentrations as in control animals not receiving pravastatin. Examination of endothelial function at the end of the treatment phase revealed that coronary arteries of pravastatin-treated monkeys dilated in response to acetylcholine, whereas those from untreated control monkeys showed considerable vasoconstriction, despite identical lipid concentrations.

One of the major functions of the vascular endothelium is the generation of the endogenous vasodilator *nitric oxide (NO)*. In endothelial cells (ECs), NO is produced from L-arginine by the constitutive endothelial nitric oxide synthase (eNOS). Enhanced bioavailability of NO is probably responsible for the improvement of endothelial dysfunction during statin therapy, as the effect of statins on acetylcholine-mediated stimulation of blood flow is blunted by co-administration of L-NMMA, an inhibitor of endothelial NO production [38, 39].

Lovastatin and simvastatin were shown to enhance NO production in human saphenous vein-derived endothelial cells by stabilizing the mRNA for eNOS [40]. This was proposed to translate into increased cerebral blood flow, reduced cerebral infarct and ameliorated neurological function in a mouse model of cerebral ischaemia. The effect was independent of cholesterol and was completely abolished in mice genetically deficient in eNOS [41, 42] (Figure 1). These findings may help to explain the beneficial effects of statins in the prevention of stroke, which is unexpected in the view of the fact that prospective studies failed to establish a relationship between cholesterol and the incidence of stroke [14, 16].

The mechanisms by which statins enhance NO production are still not entirely clear. Through their inhibitory effect on the mevalonate pathway, statins decrease the availability of farnesylpyrophosphate and geranylgeranylpyrophosphate.

Changes in the concentration of eNOS mRNA were observed after incubation of endothelial cells with lovastatin or simvastatin for 24 hours or longer, a period of time which is sufficiently long to allow for inhibition of the geranylgeranylation of the small *GTP binding protein rho*. As rho enhances the decay of eNOS mRNA, the effects of lovastatin and simvastatin on eNOS stability were ascribed to inhibition of rho function [40, 43, 44].

Recently, an alternative mechanism relating the cellular sterol homeostasis to post-translational regulation of eNOS activity has been identified. Immediate activation of eNOS can result from interaction with calmodulin in the presence of Ca^{2+} [45]. The binding of calmodulin to eNOS is antagonized by *caveolin-1* [46–48]. The caveolin promoter contains two sterol regulatory element-like components that mediate inhibition of caveolin transcription upon binding of sterol regulatory element binding protein-1 (SREBP-1) [49]. Caveolin-1 expression is thus enhanced by free cholesterol [50]. As expected, exposure of endothelial cells to LDL inhibits basal and stimulated NO release [51] and atorvastatin, by virtue of its ability to decrease the cellular content of sterols, reduces caveolin-1 abundance and promotes basal and agonist-stimulated eNOS activity [52].

Pravastatin has been reported to be roughly twice as effective in stimulating the formation of NO than simvastatin at the same molar concentration [53]. It is, however, unlikely that pravastatin acts by down-regulating rho function or caveolin expression. Pravastatin, the most hydrophilic among the currently available statins, is taken up into cells by an active transport process involving a sodium-independent bile acid transporter which is exclusively expressed on the surface of hepatocytes [54]. Hence pravastatin poorly penetrates non-hepatic cells and does not substantially compromise the generation of isoprenoid intermediates of the mevalonate pathway like farnesyl and geranylgeranyl pyrophosphate in these cells. Pravastatin (and simvastatin) enhanced NO release as early as after eight minutes of exposure of aortic rings to the compounds [53], a period of time too short to modify the cellular sterol pool or the function rho. It is therefore likely that different mechanisms exist by which statins enhance the generation of NO.

It has been shown that eNOS is activated by phosphorylation of serine 1179 [55–59]. Phosphorylation of eNOS at serine 1179 is mediated by an activation of the *phosphatidylinositol-3-OH-kinase (PI(3)K) and Akt (protein kinase B) pathway* of signal transduction [58, 59]. To examine whether statins might affect eNOS activity through phosphorylation, we incubated ECs with ^{32}P -phosphoric acid in the presence or absence of pravastatin (10^{-5} M) or simvastatin (10^{-5} M) for 3 h and measured radioactivity associated with immunoprecipitated eNOS. These experiments showed that both pravastatin and simvastatin stimulated eNOS phosphorylation by more than 200 %, and Ly294002, a specific inhibitor of phosphatidylinositol-3-OH-kinase blunted the release of NO into the culture medium [März et al. unpublished]. Thus, it seems likely that statins activate phosphatidylinositol-3-OH-kinase leading to the phosphorylation of the protein kinase Akt

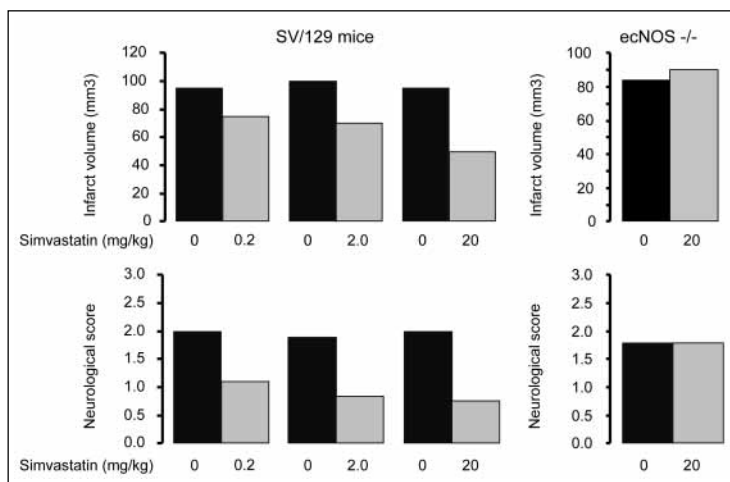


Figure 1: Left panel: Effect of increasing doses of simvastatin administered for two weeks on the volume of cerebral infarcts and a neurological sensory-motor score in mice induced by occlusion of the main carotid artery. Right panel: The effect is abolished in mice lacking endothelial nitric oxide. Modified according to Endres et al. [41].

and, consecutively, of eNOS. Together three synergistic pathways are thus emerging which might explain the beneficial effects of statins of NO production.

Beyond disturbances of the L-arginine and NO pathway an excess of *endothelin-1* has been implicated in endothelial dysfunction associated with atherosclerosis. Endothelin-1 is a 21 amino acid peptide, produced stepwise by proteolytic cleavage of pre-pro endothelin-1 and big endothelin. It is among the most effective vasoconstrictors known so far. In bovine aortic endothelial cells, atorvastatin and simvastatin inhibited pre-pro endothelin-1 mRNA expression reduced immunoreactive endothelin-1 levels, effects which were maintained in the presence of oxidized LDL [60]. *In vivo*, however, statin treatment has so far not been shown to lower ET-1 concentrations [28].

In view of their distinct vascular effects statins might in the future attain a role as adjunctive therapeutics in the management of hypertension. Small studies indicating that blood pressure reduction was more effective in patients receiving a statin on top of an angiotensin converting enzyme (ACE) inhibitor than in those receiving an ACE inhibitor alone have previously been reported [61–63]. It is in line with these observations that statin treatment decreases the responsiveness to vasoconstrictors in patients with hypercholesterolaemia. Straznicky et al. [64] found that the amounts of norepinephrine and angiotensin II required to raise diastolic blood pressure by 20 mmHg was significantly higher than during treatment with pravastatin than before, and Nickenig and colleagues provided evidence that overexpression of angiotensin II type 1 receptors in hypercholesterolaemia [65] was reversed by treatment with statins [66].

■ Are Statins Antioxidants?

LDL isolated from patients receiving statins [67–72] are less susceptible to oxidative modification *in vitro*. One of the primary effects of statins on lipoprotein metabolism is that they enhance the turnover of LDL. Since the residence time of LDL in the plasma is inversely related to its susceptibility to oxidation, an increase in the resistance of LDL to oxidation may be secondary to the acceleration of the metabolism of LDL. However, statins may also have direct antioxidative properties. This has been shown for simvastatin [72, 73], fluvastatin [70, 74], but apparently does not apply to pravastatin, a hydrophilic compound [74]. Aviram et al. [75] reported that para- and ortho-hydroxymetabolites of atorvastatin, but not the parent compound, protected LDL, HDL and HDL associated paraoxonase against oxidation. The relevance of these findings to the situation *in vivo*, however, is not clear. *In vitro*, statins have substantial anti-oxidative effects at concentrations that are hardly reached systemically (i.e. 10^{-5} mol/l and more). Of further interest, LDL from patients treated with pravastatin reveals reduced susceptibility to oxidation *ex vivo* [69], albeit pravastatin is ineffective as an antioxidant *in vitro* [74]. This discrepancy may point at the importance of an enhanced turnover of LDL as a major determinant of LDL oxidizability *ex vivo*. Finally, the negative results of prospective trials [76] looking at the effect of antioxidant vitamins on clinical events, make it unlikely that any anti-oxidative properties of statins contribute to their clinical efficacy.

■ Statin Treatment Has Anti-Inflammatory Effects

Recent years have seen approaches to redefine atherosclerosis as a chronic inflammatory process. In fact, atherosclerosis shares many characteristics with chronic inflammatory diseases like cirrhosis, rheumatoid arthritis or glomerulosclerosis [7]. It is consistent with the concept of atherosclerosis as an inflammatory disease, that systemic markers of inflammation such as leukocyte count, fibrinogen, *C-reactive protein* (CRP) [77], serum amyloid A (SAA), soluble ICAM-1 [78] or interleukin (IL)-6 [79] are predictive of clinical events of cardiovascular disease in patients with stable or unstable coronary disease, and perhaps more important, in individuals not yet having experienced a clinical event.

Disturbances of lipoprotein metabolism may themselves trigger inflammatory processes. Interestingly, CRP has been shown to complex to enzymatically modified LDL, thus promoting the uptake of cholesterol into macrophages and the generation of foam cells in atherosclerotic lesions [80]. Zwaka and colleagues could demonstrate the potential role of CRP in mediating the uptake of native LDL by macrophages. This process seems to depend on the activity of a specific CRP-receptor on the macrophage surface, FC-gammaRIIA [81]. These latter findings are remarkable because the do not require any kind of oxidative modification of LDL particles to explain deposition of LDL derived lipids in macrophages, thus providing an additional link between circulating lipoproteins and inflammatory responses at the level of the vessel wall.

The anti-atherogenic effects of high density lipoproteins, in contrast may in part come from anti-inflammatory actions. Paraoxonase, which is transported as a component of HDL inhibits the oxidative modification of LDL [82, 83]. Lipids oxidized in LDL can be transferred to HDL by cholesteryl ester transfer protein (CETP) [84]. Once these lipids have become components of HDL, they can be reduced by the formation of methionine sulphoxides in apo A-I and apo A-II [85]. HDL has been shown to inhibit platelet activation [86], bind and neutralize pro-inflammatory lipopolysaccharides [87], and to inhibit expression of adhesion molecules in endothelial cells [88–92].

A substudy of the CARE trial examined two markers of inflammation, CRP and SAA, to evaluate the relationship between pravastatin, inflammation, and the risk of recurrent coronary events. Pre-treatment levels of CRP and SAA were measured in 391 patients who developed a recurrent non-fatal MI or a fatal coronary event. This group was compared to a control group consisting of 391 gender-matched patients who remained event-free. Levels of CRP and SAA were significantly higher among subjects with recurring events than in control subjects. Further, 708 of the 782 participants had plasma levels of both CRP and SAA above the 90th percentile cut points for each parameter, or below. These 708 subjects with concordant CRP and SAA levels were divided into 4 groups based on the levels of both markers and based on randomisation to pravastatin or placebo (Figure 2). Upon analysis according to treatment (pravastatin or placebo), a significant relationship was seen between the presence of inflammation (elevation of both CRP and SAA) and coronary risk of patients randomised to placebo. This association, however,

was attenuated and no longer significant in those patients randomized to pravastatin. In patients with signs of systemic inflammation, the relative risk reduction by pravastatin was approximately twice as large as in the group without elevated markers of inflammation, thus raising the possibility that pravastatin has anti-inflammatory effects beyond lipid lowering [93].

Most recent data from the AFCAPS/TexCAPS trial in primary prevention showed that lovastatin also effectively reduced cardiovascular endpoints in individuals with LDL cholesterol above 150 mg/dl, with or without elevated CRP (above 1.65 mg/L). Interestingly, lovastatin was equally effective in reducing clinical endpoints in those with high CRP but with LDL cholesterol levels less than 150 mg/dl [94].

In additional analyses the CARE investigators examined whether pravastatin treatment could actually lower CRP long-term [95]. CRP was measured at baseline and at 5 years in another 472 participants of CARE who remained free of recurrent coronary events during follow-up. Statistically significant differences were observed at 5 years between the pravastatin and placebo groups in mean and median CRP levels (Figure 2). Of interest, these effects persisted after adjustment for confounders like age, body mass index, smoking status, blood pressure, and baseline lipid levels, and there was no correlation between the changes in CRP and changes in LDL cholesterol.

These results were recently confirmed prospectively in the Pravastatin Inflammation/CRP Evaluation (PRINCE) study [96], which included 1702 individuals without history of cardiovascular disease and 1182 patients with known cardiovascular disease. Pravastatin given at 40 mg daily reduced CRP roughly 15 percent. Remarkably, there was virtually no correlation of the changes in CRP with any of the lipoprotein levels examined (i.e. LDL cholesterol, HDL cholesterol and triglycerides). A smaller trial also showed that statin treatment lowers CRP [97].

Further arguments for an anti-inflammatory effect of statins come from clinical observations in transplant recipients. In heart and kidney allograft recipients, pravastatin reduced both the incidence of acute rejection episodes, the development of transplant vasculopathy, at the same time lowering natural killer cells *in vivo* [98, 99]. Similar results could be achieved with simvastatin [100].

Together, these observations may point to the existence of anti-inflammatory properties of statins. Nevertheless the data should be interpreted with caution. As mentioned above, atherogenic lipoproteins, in particular LDL, represent potent pro-inflammatory stimuli, and it would not be surprising if measures effectively lowering the concentrations of these lipoproteins normalise systemic inflammation markers. The absence of a correlation between LDL cholesterol changes and CRP [95] does not completely rule out such relationship. There is considerable biological variation of CRP at concentrations below 10 mg/l, which makes it difficult to detect such a link by statistical means. Finally, it would lend further support to the contention of a direct anti-inflammatory effect of statins if other markers of inflammation (white blood cells, SAA, IL-6) behaved similar to CRP during statin treatment; and if it could be shown that statins lower CRP by affecting the inflammatory reactions in the vessel wall, rather than merely modulating hepatic CRP synthesis. It is of interest in this respect, that statin treatment did not affect IL-6 levels and soluble IL-6 receptor levels in the study by Jialal et al. [97] and that in patients with familial hypercholesterolaemia, lipopolysaccharide-induced release of cytokines (including interleukin 1a, interleukin 1β, interleukin 6, and tumor necrosis factor α) from peripheral blood mononuclear cells was not altered by simvastatin or atorvastatin [101]. One communication reporting diminished cytokine production during pravastatin administration included six patients only and might hence be inadequately powered [102].

HDL opposes many of the pro-inflammatory effects of LDL, and statins have consistently been shown to increase HDL cholesterol. In a recently published small study of simvastatin and atorvastatin [103] decreases of CRP were significantly associated with changes in HDL cholesterol ($r = -0.45$) and apolipoprotein A-I ($r = -0.40$), but not with changes in LDL cholesterol or triglycerides. The change in HDL cholesterol explained 20 percent of the change in CRP during statin treatment, raising the possibility that anti-inflammatory properties of statins might stem from their effect on HDL rather than on LDL metabolism. Results of other recently published studies, however, argue against this hypothesis [96, 104]. In the study of patients with combined hyperlipidaemia by Jialal et al. [97], CRP reduction was unrelated to changes in both LDL cholesterol and HDL cholesterol. A

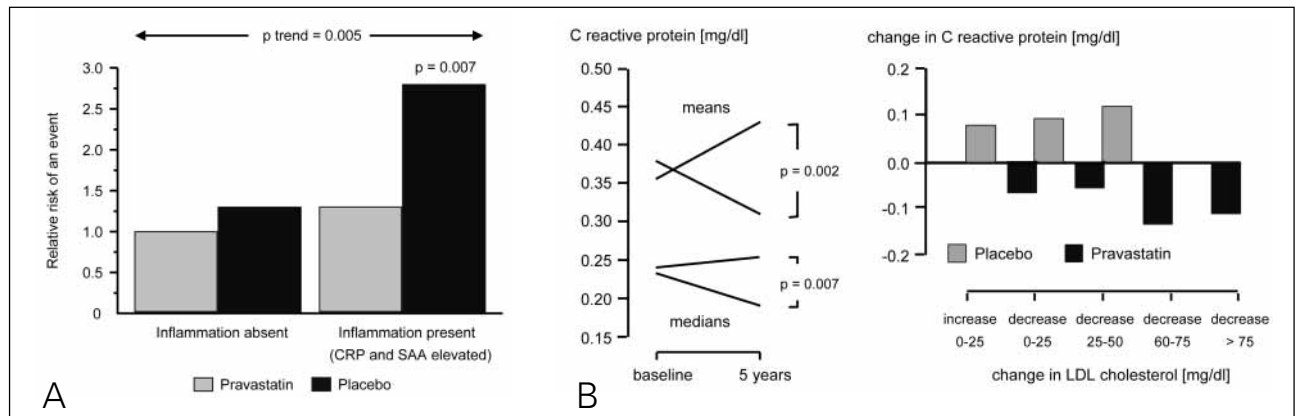


Figure 2: Pravastatin and C-reactive protein. **A.** Relative risks of recurrent coronary events in patients with previous MI in the CARE trial according to the presence (both C-reactive protein and serum amyloid A (> 90th percentile) or absence of systemic inflammation and according to treatment group [93]. **B.** C-reactive protein in a subset of 472 participants of the CARE study who remained free of coronary event during the trial. Left panel: Median and mean values at baseline and at 5 years of follow-up. Right panel: Mean changes over time stratified according to changes in LDL cholesterol in the placebo and in the pravastatin group. Modified according to [95].

strong correlation ($r = 0.59$) was, however, seen between the changes of triglycerides and CRP, alluding to the possibility that triglyceride-rich particles contribute to the inflammatory processes in patients at high risk of coronary events.

An attempt to dissociate lipid and non-lipid anti-inflammatory effects of pravastatin on atherosclerosis was made in the study by Williams and colleagues [29]. Cynomolgous monkeys received an atherogenic diet for two years, followed by a lipid-lowering diet either containing or not containing pravastatin for an additional two years. Diets were adjusted in order to produce identical plasma total cholesterol, LDL and HDL cholesterol concentrations in both groups during the treatment phase. Histochemical analysis of atherosclerotic lesions indicated that arteries from pravastatin-treated monkeys had significantly less macrophages in the intima and media, and also less calcification and neovascularization in the intima, despite similar lipoprotein concentrations in both groups.

A host of laboratory data has become available during recent years supporting direct *immunomodulatory effects* of statins. Lovastatin inhibits the proliferation of mitogen-stimulated T-lymphocytes [105, 106] and natural killer cell cytotoxicity [107–109]. Statins may also have a role in immunomodulation by virtue of their ability to repress the induction of the class II major histocompatibility (MHCII) complex in antigen presenting cells. MHCII is a heterodimer of two peptide chains, alpha and beta. In antigen presenting-cells, peptides derived from the proteolysis of antigens are complexed to MHCII and the resulting heterotrimeric complex is then translocated to the cell surface where it activates T-lymphocytes via interaction with the T-cell receptor. Very recent evidence indicates that statins inhibit the expression of MHCII induced by IFN in primary cultures of human macrophages, endothelial cells and smooth muscle cells. No such effect was seen in cell types constitutively expressing MHCII such as B lymphocytes. A detailed analysis of the underlying molecular mechanism revealed that statins down-regulated the non-DNA binding MHCII transactivator CIITA by inhibiting promoter IV. The effects of statins on MHCII were alleviated by supplementation with mevalonate, suggesting that promoter IV function depends on the geranylgeranylation or farnesylation of proteins [110].

In endothelial cells, pravastatin, simvastatin, fluvastatin, and cerivastatin significantly reduced the expression of IL-1 β , IL-6, cyclooxygenase-2, and p22phox and p47phox subunits of nicotine adenine dinucleotide phosphate (NADPH) oxidase [111]. This study by Inoue and colleagues bears a further interesting aspect, namely that all statins tested induced peroxisome proliferator-activated receptor alpha (PPAR- α) and PPAR- γ mRNA and protein levels in both endothelial cells and hepatocytes. Since PPAR- α activation has been shown to up-regulate the NF- κ B inhibitor I κ -Ba [112, 113], reduction of NF- κ B activity by statins might thus be mediated by PPAR- α . Metabolic links between HMG-CoA reductase inhibition and activation of PPARs might also explain some of the yet unexplained metabolic effects of statins such as the increase in hepatic apo A-I production and a decreased incidence of type 2 diabetes occurring during treatment with statins [114].

Additional evidence for anti-inflammatory effects of statins also comes from a variety of studies in experimental animals [115–122] and cell models [123–127].

Most of these effects are unlikely to be related to changes in plasma cholesterol [117, 119, 121]. Cholesterol represents the end product of the mevalonate pathway [128]. This pathway yields a series of intermediate isoprenoid compounds, including farnesyl and geranylgeranyl pyrophosphate. Normally, these intermediates are covalently attached to GTP proteins involved in cellular signal transduction and proliferation. Complete inhibition of HMG-CoA reductase will, therefore, interfere not only with the synthesis of cholesterol but also with the provision of mevalonate-derived compounds essential to cellular functions [128]. *In vitro*, anti-inflammatory and immune-modulatory effects of statins could be reverted by provision of mevalonate, suggesting that the depletion of mevalonate-derived intermediates is crucial [110, 117, 124, 126]. It is, however, an open question whether significant shortage of mevalonate derived products can be produced in non-hepatic tissues in humans. Concentrations of statins needed to compromise farnesylation and geranylgeranylation of proteins are probably much higher than those needed to reduce cholesterol biosynthesis because enzymes at the branch-points to non-sterols have lower Michaelis constants than those involved in sterol production [129]. In addition, if enough sterols (provided by LDL) are available to the cell, enzymes serving the production of sterols distal to mevalonate are suppressed so that mevalonate is mainly diverted to non-sterol pathways. Together, these considerations could explain why anti-proliferative or anti-inflammatory actions of statins are usually not observed below 10^{-6} mol/l *in vitro*. Such concentration is hardly reached in humans on standard doses of a statin, in particular because of the almost complete hepatic first-pass extraction after oral dosage.

Weitz-Schmidt et al. [130] showed that statins inhibit leukocyte function antigen-1 (a heterodimer of CD11a and CD18, known as aM- β 2), which is also involved in binding to ICAM-1. Intriguingly, the effect was independent from inhibition of HMG-CoA reductase and was mediated by direct interaction of statins with an allosteric site within LFA-1 on the cell membrane. Based on detailed structural information on the statin binding pocket on the LFA-1 molecule, a derivative compound was designed, which was more potent in inhibiting LFA-1 function, but less potent in inhibiting sterol synthesis.

Statins obviously have the capacity to modulate the inflammatory response of the vessel wall, either by virtue of their cholesterol-lowering effect or due to direct immuno-modulation. It remains an open question whether or not individuals with elevated CRP should be treated with statins irrespective of their cholesterol levels in the primary prevention of coronary disease.

■ Statin Treatment Stabilizes Vulnerable Plaques

The salient features of vulnerable lesions include vast lipid deposits, an increased number of inflammatory cells, few smooth muscle cells, and a thin fibrous cap. As expected, lowering LDL cholesterol therapy depletes lipids from vulnerable plaques [131]. Of interest is, however, the question whether this is merely a consequence of systemic lipid-lowering or whether statins are capable of actively modifying the lipid balance of the vessel wall.

Lipid deposits of unstable lesions originate from degenerated or apoptotic foam cells. For more than two decades, research has focused on the question how macrophages accumulate cholesteryl esters derived from LDL. Macrophages incubated with native LDL do not accumulate lipids, and lipid storage is seen in vascular macrophages of patients completely deficient in LDL receptors. These observations excluded LDL receptors from being involved in foam cell formation. In 1979, Goldstein and Brown demonstrated that LDL previously modified by acetylation was avidly taken up into monocyte-derived macrophages [132, 133]. The receptors mediating this process were named scavenger receptors. In contrast to LDL receptors, the activity of scavenger receptors is not subject to feedback regulation by the cellular content of sterols, thus allowing for nearly unlimited influx of lipids. It is now known that there are many membrane molecules having broad and partially overlapping ligand specificities, which can all assume the function of scavenger receptors. Equally important, not only acetylation, but a series of other modifications have been recognized to convert LDL into ligands of the scavenger pathway. These include modification with malondialdehyde [134], oxidation [135] mediated by cellular lipoxygenases and phospholipases, glycation, incorporation into complexes with immunoglobulins, complexation with proteoglycans, self-aggregation, and enzymatic modification.

Statins may indeed have direct effects on *foam cell formation* by down-regulating macrophage scavenger receptors. For instance, lovastatin reduces the expression of the scavenger receptor CD36 on human monocytic U937 [136], inhibits type I scavenger receptor A in human monocyte-like THP-1 cells [137], and decreases the abundance of mRNA for the lectin-like oxidized LDL receptor 1 (LOX-1) in human monocyte-derived macrophages [138]. Further, simvastatin reduces cholesteryl ester uptake triggered by aggregated LDL [139] in both platelet-derived growth factor-stimulated and unstimulated vascular smooth muscle cells.

The more lipophilic statins like simvastatin, lovastatin or atorvastatin, but not pravastatin, decrease the proliferation [140, 141] and elicit apoptosis of *smooth muscle cells* [142, 143]. It is still a matter of debate, whether inhibition of smooth muscle cell proliferation would yield clinical benefit.

Smooth muscle cells may be considered important for plaque stability, as they strengthen the fibrous cap and regulate the synthesis of interstitial collagen. It is also not clear whether the differences between statins regarding their effects on smooth muscle cell viability will ultimately be of clinical importance.

Abundant production of *matrix metalloproteinases* (MMP) by macrophages has been implicated in the weakening of the fibrous cap in unstable plaques. Exposure to oxidized LDL increases matrix metalloproteinase-9 and decreases tissue inhibitor of metalloproteinase-1 (TIMP-1) in human monocyte-derived macrophages [144]. Statins may contribute to plaque stabilization by modulating metalloproteinase expression. Bellosa et al. [145] found that fluvastatin decreased constitutive and phorbol ester stimulated gelatinase B (MMP-9) activity. In Watanabe heritable hyperlipidaemic (WHHL) rabbits, cerivastatin diminished accumulation of macrophages in aortic atheroma and macrophage expression of MMP-1, MMP-3, MMP-9 decreased with cerivastatin treatment [122].

In rabbits, macrophage accumulation and interstitial collagenase (matrix metalloproteinase-1, MMP-1) expression in atheroma were also reduced by lowering the lipid content of the diet. At the same time, the aortic content of interstitial collagen increased in the lipid-lowering group compared with hyperlipaemic groups. These results obviously raise the possibility that plaque stabilization is a result of lipid modification rather than an effect specific to statins [146].

In an elegant prospective study, the effect of oral pravastatin (40 mg daily for 3 months prior to carotid endarterectomy) on plaque composition was investigated in 11 patients with symptomatic carotid artery stenosis of > 70 % in diameter [147]. The control group consisted of 13 patients with the same degree of stenosis who underwent routine carotid endarterectomy but without statin therapy. Analysis of the carotid plaques obtained during operation (Figure 3) showed that pravastatin reduces the lipid content of human plaques, reduces oxidized LDL, decreases the number of inflammatory cells (i.e. macrophages and T cells), matrix metalloproteinase 2 (MMP-2) expression, and also decreases cell death. In contrast, TIMP-1 immunoreactivity and collagen content were found to be increased [147].

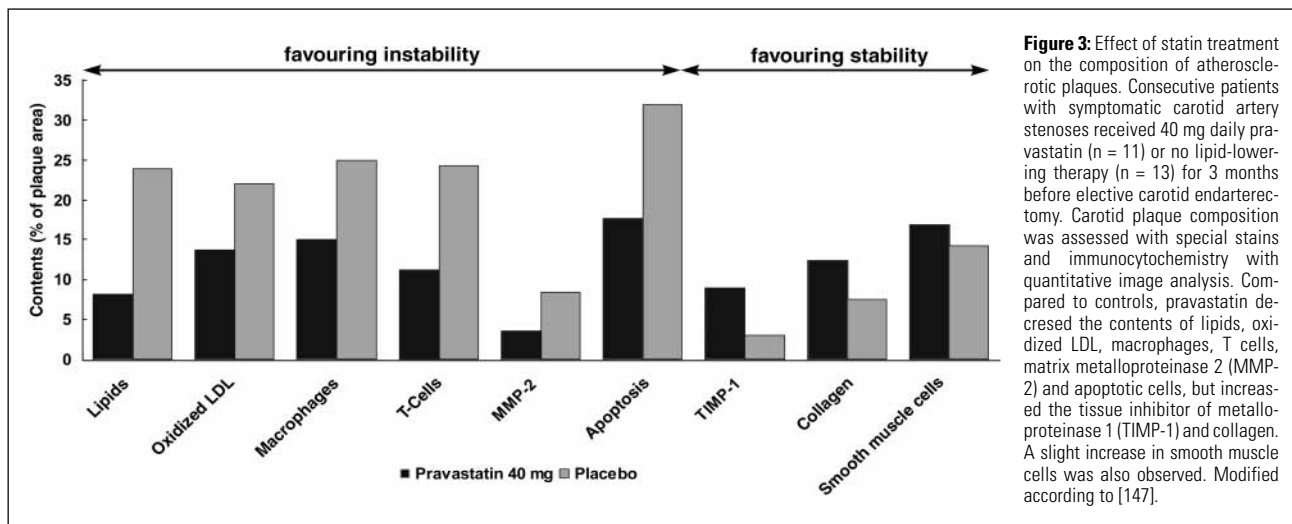


Figure 3: Effect of statin treatment on the composition of atherosclerotic plaques. Consecutive patients with symptomatic carotid artery stenoses received 40 mg daily pravastatin (n = 11) or no lipid-lowering therapy (n = 13) for 3 months before elective carotid endarterectomy. Carotid plaque composition was assessed with special stains and immunocytochemistry with quantitative image analysis. Compared to controls, pravastatin decreased the contents of lipids, oxidized LDL, macrophages, T cells, matrix metalloproteinase 2 (MMP-2) and apoptotic cells, but increased the tissue inhibitor of metalloproteinase 1 (TIMP-1) and collagen. A slight increase in smooth muscle cells was also observed. Modified according to [147].

■ Statin Treatment Affects Blood Coagulation

It has been known for long that hypercholesterolaemia enhances platelet reactivity [148, 149]. It would therefore not be surprising if statin treatment demonstrated effects on *platelet activity*. At a dose of 40 mg daily, fluvastatin reduced platelet aggregation within four weeks of treatment [150]. Interestingly, in this study incubation *in vitro* of platelets with increasing concentrations of fluvastatin resulted in a dose-dependent reduction in platelet aggregation, suggesting a direct effect of fluvastatin on platelets. Aviram et al. [151] demonstrated that lovastatin therapy was associated with a similar mechanism of action. In cholesterol-fed pigs, in which atherosclerotic lesions were induced by mechanical injury, Alfon et al. [152] found a reduction in platelet deposition on a mildly damaged vessel wall by both fluvastatin and lovastatin. In hyperlipidaemic rabbits the same group found an effect of atorvastatin, but not simvastatin on platelet thrombus formation [153] *ex vivo*.

Further, in an *ex vivo* model, the effect of pravastatin on thrombus formation was evaluated in patients with stable coronary disease. Platelet thrombus formation was measured in 16 hypercholesterolaemic patients before and after a mean of 2.5 months of therapy and in 16 normocholesterolaemic controls. At baseline, platelet thrombus formation was higher in the hypercholesterolaemic patients compared with the normocholesterolaemic patients. After pravastatin therapy, however, platelet thrombus formation in hypercholesterolaemic patients was similar to normocholesterolaemic patients [154]. A similar comparative study of pravastatin and simvastatin evaluated platelet thrombus formation in patients with stable coronary disease taking 325 mg of aspirin per day. Thrombus formation was assessed before and after 2 to 3 months of statin therapy. On the background of similar reductions of LDL cholesterol in both groups, platelet thrombus formation was significantly reduced by pravastatin but not simvastatin [155]. It is currently not clear whether this finding of a differential effect of statins on thrombus formation bears any clinical significance.

Tissue factor plays a pivotal role in the initiation of thrombus formation in acute coronary syndromes [156]. In monocyte-derived macrophages the lipophilic compounds fluvastatin and simvastatin, but not pravastatin reduced tissue factor activity *in vitro* [157] and *ex vivo* [158]. This effect appeared dependent on an inhibition of the mevalonate pathway, as it was completely reversed by providing mevalonate [157, 158]. Interestingly, fluvastatin has been shown to lower tissue factor pathway inhibitor (TFPI), a lipoprotein-bound negative regulator of tissue factor activity [159].

Studies of fibrinogen are highly inconsistent. Basically, there are studies in which fibrinogen remained unchanged [160–170], increased [171–175] and decreased [166, 171, 176] with no consistent differences between individual statins. Similarly, reports on the effects of statins on plasminogen activator inhibitor-1 (PAI-1), a modulator of plasminogen activation, which is increased in diabetes mellitus and hypertriglyceridemia, are equivocal. Studies with pravastatin demonstrated reductions in PAI-1 [177, 178], whereas others suggest minimal changes with fluvastatin [179] or increases with simvastatin [170]. In cultured endothelial cells and in smooth muscle cells, all currently available statins reduced the expression of PAI-1, and in smooth

muscle cells these statins enhanced t-PA production, suggesting an overall anti-coagulant effect of the compounds (180).

■ Clinical Implications

As atherosclerosis progresses slowly it has been argued that long-term administration of lipid-lowering drugs was required to substantially lower the risk of major cardiovascular events. In the major trials of statins, improvement of clinical outcome emerged after one to two years of treatment. The angiographically controlled trials of statins indicated risk reduction without evidence of substantial plaque reduction [181].

However, improvement of endothelial function and myocardial perfusion occurs even within several weeks [30, 31, 38], even in patients with acute coronary syndromes [28]. Regardless of whether the immediate effects of statin therapy result from LDL cholesterol reduction or from pleiotropic effects, they might advocate the *early use of statins in acute coronary syndromes*. The major secondary prevention trials of statins only included patients who had suffered coronary syndromes three to six months prior to recruitment and once they were again in a clinically stable condition. Prospective data are now emerging which support a role of statins in the management of acute coronary syndromes.

A retrospective analysis of the GUSTO IIB and PURSUIT trials by Aronow and colleagues compared mortality in patients with acute coronary syndromes who were discharged on lipid-lowering agents ($n = 3653$) following the initial hospitalisation with those who did not receive these agents ($n = 17,156$). Lipid-lowering therapy was associated with a smaller proportion of deaths at 30 days (0.5 % versus 1.0 %, $p = 0.001$) and at 6 months (1.7 % versus 3.5 %, $p < 0.0001$) [182]. Among 19,599 patients of the prospective Swedish Register of Cardiac Intensive Care, who were discharged alive from the hospital, were 5528 who received statins at or before discharge and 14,071 who did not [183]. At 1 year, unadjusted mortality was 9.3 % in the no-statin group and 4.0 % in the statin treatment group. In addition, several small-scale studies demonstrated that the early initiation of statin treatment might be beneficial [184].

MIRACL, the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering study, is the first large-scale prospective study designed to provide evidence that initiation of statin therapy in the early post-acute coronary syndrome period is beneficial in reducing the risk of early recurrent ischaemic events [185]. The primary end-point was a composite including death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischaemia with objective evidence and requiring emergency rehospitalization. Within four months, atorvastatin at 80 mg daily resulted in a 16 percent ($p = 0.048$) improvement in the incidence of the primary endpoint.

■ Conclusions

Treatment with statins clearly is one of the most exciting advances in the prevention and treatment of atherosclerosis. Clinical observations raise the possibility that the benefit of statin therapy cannot solely be explained by LDL cholesterol reduction. *In vitro*, statins enhance the production of NO, exert anti-oxidative, anti-inflammatory, immuno-modulatory and anti-throm-

botic effects. How these findings apply to the *in vivo* situation in humans is, at the time being, still an open question. Because reduction of LDL cholesterol on its own might elicit many of the functional changes seen, plenty of work will be required to precisely distinguish the direct effects of statins on plaque structure and composition from those merely attributable to a negative cholesterol balance in the vessel wall. It is further an open question whether or not those effects related to the depletion of cellular mevalonate (and consequently ubiquinone, dolichol, geranylgeraniol and farnesol) should be coined "pleiotropic" as they reflect the primary mode of action of statins. With the number of statins in the marketplace increasing, differences between these compounds regarding their actions beyond cholesterol lowering may well emerge in the future.

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References

- Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TEXCAPS Air force/texas coronary atherosclerosis prevention study. *JAMA* 1998; 279: 1615–22.
- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344: 1383–9.
- The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; 339: 1349–57.
- Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and recurrent events trial investigators. *N Engl J Med* 1996; 335: 1001–9.
- Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995; 333: 1301–7.
- Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins. *JAMA* 1998; 279: 1643–50.
- Ross R. Atherosclerosis - an inflammatory disease. *N Engl J Med* 1999; 340: 115–26.
- Stary HC, Chandler AB, Glagov S, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the committee on vascular lesions of the council on arteriosclerosis, American Heart Association. *Circulation* 1994; 89: 2462–78.
- Libby P. Molecular bases of the acute coronary syndromes. *Circulation* 1995; 91: 2844–50.
- Amento EP, Ehsani N, Palmer H, Libby P. Cytokines and growth factors positively and negatively regulate interstitial collagen gene expression in human vascular smooth muscle cells. *Arterioscler Thromb* 1991; 11: 1223–30.
- Geng YJ, Wu Q, Muszynski M, et al. Apoptosis of vascular smooth muscle cells induced by *in vitro* stimulation with interferon-gamma, tumor necrosis factor-alpha and interleukin-1 beta. *Arterioscler Thromb Vasc Biol* 1996; 16: 19–27.
- Collins R for the MRC/BHF Heart Protection Study Collaborative Group. Main results of the MRC/BHF heart protection study. Presented at the clinical trials hotline session at the scientific sessions 2001 of the American Heart Association, Anaheim, U.S.A., Tuesday, November 14, 2001 (slides with main results: <http://www.Ctsu.Ox.Ac.Uk/~hps/>).
- West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study. *Circulation* 1998; 97: 1440–5.
- Rossouw JE. Lipid-lowering intervention in angiographic trials. *Am J Cardiol* 1995; 76: 86C–92C.
- Prospective studies collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. *Lancet* 1995; 346: 1647–53.
- Bucher HC, Griffith LE, Guyatt GH. Effect of HMG CoA reductase inhibitors on stroke. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 1998; 128: 89–95.
- Tanner FC, Noll G, Boulanger CM, Lüscher TF. Oxidized low density lipoproteins inhibit relaxations of porcine coronary arteries: Role of scavenger receptor and endothelium derived nitric oxide. *Circulation* 1991; 83: 2012–20.
- Galle J, Mülsch A, Busse R, Bassenge E. Effects of native and oxidized low density lipoproteins on formation and inactivation of endothelium derived relaxing factor. *Arterioscler Thromb* 1991; 11: 198–203.
- Rajavashith TB, Andalibi AS, Territo MC, et al. Induction of endothelial cell expression of granulocyte and macrophage colony stimulating factors by modified low-density lipoproteins. *Nature* 1990; 344: 254–7.
- Navab M, Imes SS, Hama SY, et al. Monocyte transmigration induced by modification of low density lipoprotein in cocultures of human aortic wall cells is due to induction of monocyte chemoattractant protein 1 synthesis and is abolished by high density lipoprotein. *J Clin Invest* 1991; 88: 2039–46.
- Drake TA, Hannani K, Fei H, Lavi S, Berliner JA. Minimally oxidized LDL induces tissue factor expression in cultured endothelial cells. *Am J Pathol* 1991; 138: 601–8.
- Doi H, Kugiyama K, Oka H, et al. Remnant lipoproteins induce proatherothrombogenic molecules in endothelial cells through a redox-sensitive mechanism. *Circulation* 2000; 102: 670–6.
- Nakashima Y, Raines EW, Plump AS, Breslow JL, Ross R. Upregulation of VCAM-1 and ICAM-1 at atherosclerosis-prone sites on the endothelium in the apo E-deficient mouse. *Arterioscler Thromb Vasc Biol* 1998; 18: 842–51.
- Sakai A, Kume N, Nishi E, Tanoue K, Miyasaka M, Kita T. P-selectin and vascular cell adhesion molecule-1 are focally expressed in aortas of hypercholesterolemic rabbits before intimal accumulation of macrophages and T lymphocytes. *Arterioscler Thromb Vasc Biol* 1997; 17: 310–6.
- Egashira K, Hirooka Y, Kai H, et al. Reduction in serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with hypercholesterolemia. *Circulation* 1994; 89: 2519–24.
- Anderson TJ, Meredith IT, Yeung AC, Frei B, Selwyn AP, Ganz P. The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. *N Engl J Med* 1995; 332: 488–93.
- Treasure CB, Klein JL, Weintraub WS, et al. Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. *N Engl J Med* 1995; 332: 481–7.
- Dupuis J, Tardif JC, Cernacek P, Theroux P. Cholesterol reduction rapidly improves endothelial function after acute coronary syndromes. The RECIFE (reduction of cholesterol in ischemia and function of the endothelium) trial. *Circulation* 1999; 99: 3227–33.
- Williams JK, Sukova GK, Herrington DM, Libby P. Pravastatin has cholesterol-lowering independent effects on the artery wall of atherosclerotic monkeys. *J Am Coll Cardiol* 1998; 31: 684–91.
- Eichstädt HW, Eskötter H, Hoffman I, Amthauer HW, Weidinger G. Improvement of myocardial perfusion by short-term fluvastatin therapy in coronary artery disease. *Am J Cardiol* 1995; 76 (Suppl.): 122A–5A.
- Gould KL, Martucci JP, Goldberg DI, et al. Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole in patients with coronary artery disease. A potential noninvasive marker of healing coronary endothelium. *Circulation* 1994; 89: 1530–8.
- Aengevaeren WR, Uijen GJ, Jukema JW, Brusckhe AV, van der Werf T. Functional evaluation of lipid-lowering therapy by pravastatin in the regression growth evaluation statin study (REGRESS). *Circulation* 1997; 96: 429–35.
- Huggins GS, Pasternak RC, Alpert NM, Fischman AJ, Gewirtz H. Effects of short-term treatment of hyperlipidemia on coronary vasodilator function and myocardial perfusion in regions having substantial impairment of baseline dilator reserve. *Circulation* 1998; 98: 1291–6.
- Baller D, Notohamiprodjo G, Gleichmann U, Holzinger J, Weise R, Lehmann J. Improvement in coronary flow reserve determined by positron emission tomography after 6 months of cholesterol-lowering therapy in patients with early stages of coronary atherosclerosis. *Circulation* 1999; 99: 2871–5.
- Yokoyama I, Momomura S, Ohtake T, et al. Improvement of impaired myocardial vasodilatation due to diffuse coronary atherosclerosis in hypercholesterolemics after lipid-lowering therapy. *Circulation* 1999; 100: 117–22.
- Mellwig KP, Baller D, Gleichmann U, et al. Improvement of coronary vasodilatation capacity through single LDL apheresis. *Atherosclerosis* 1998; 139: 173–8.
- Tamai O, Matsuoka H, Itabe H, Wada Y, Kohno K, Imaizumi T. Single LDL apheresis improves endothelium-dependent vasodilatation in hypercholesterolemic humans. *Circulation* 1997; 95: 76–82.
- O'Driscoll G, Green D, Taylor RR. Simvastatin, an HMG-Coenzyme A reductase inhibitor, improves endothelial function within 1 month. *Circulation* 1997; 95: 1126–31.
- John S, Schlaich M, Langenfeld M, et al. Increased bioavailability of nitric oxide after lipid-lowering therapy in hypercholesterolemic patients. A randomized, placebo-controlled, double-blind study. *Circulation* 1998; 98: 211–6.
- Laufs U, Liao JK. Post-transcriptional regulation of endothelial nitric oxide synthase mRNA stability by rho GTPase. *J Biol Chem* 1998; 273: 24266–71.
- Endres M, Laufs U, Huang Z, et al. Stroke protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase. *Proc Natl Acad Sci USA* 1998; 95: 8880–5.
- Laufs U, Endres M, Stagliano N, et al. Neuroprotection mediated by changes in the endothelial actin cytoskeleton. *J Clin Invest* 2000; 106: 15–24.
- Laufs U, La Fata V, Liao JK. Inhibition of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase blocks hypoxia-mediated down-regulation of endothelial nitric oxide synthase. *J Biol Chem* 1997; 272: 31725–9.
- Laufs U, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG-CoA reductase inhibitors. *Circulation* 1998; 97: 1129–35.
- Ju H, Zou R, Venema VJ, Venema RC. Direct interaction of endothelial nitric-oxide synthase and caveolin-1 inhibits synthase activity. *J Biol Chem* 1997; 272: 25437–40.
- Michel JB, Feron O, Sacks D, Michel T. Reciprocal regulation of endothelial nitric-oxide synthase by Ca^{2+} -calmodulin and caveolin. *J Biol Chem* 1997; 272: 15583–6.
- Michel JB, Feron O, Sase K, Prabhakar P, Michel T. Caveolin versus calmodulin: Counterbalancing allosteric modulators of nitric oxide synthase. *J Biol Chem* 1997; 272: 25907–12.
- Feron O, Saldana F, Michel JB, Michel T. The endothelial nitric-oxide synthase-caveolin regulatory cycle. *J Biol Chem* 1998; 273: 3125–8.
- Bist A, Fielding PE, Fielding CJ. Two sterol regulatory element-like sequences mediate up-regulation of caveolin gene transcription in response to low density lipoprotein free cholesterol. *Proc Natl Acad Sci USA* 1997; 94: 10693–8.
- Fielding CJ, Bist A, Fielding PE. Caveolin mRNA levels are up-regulated by free cholesterol and down-regulated by oxysterols in fibroblast monolayers. *Proc Natl Acad Sci USA* 1997; 94: 3753–8.
- Feron O, Dessy C, Moniotte S, Desager JP, Balligand JL. Hypercholesterolemia decreases nitric oxide production by promoting the interaction of caveolin and endothelial nitric oxide synthase. *J Clin Invest* 1999; 103: 897–905.
- Feron O, Dessy C, Desager JP, Balligand JL. Hydroxy-methylglutaryl-coenzyme A reductase inhibition promotes endothelial nitric oxide synthase activation through a decrease in caveolin abundance. *Circulation* 2001; 103: 113–8.
- Kaesemeyer WH, Caldwell RB, Huang J, Caldwell RW. Pravastatin sodium activates endothelial nitric oxide synthase independent of its cholesterol-lowering actions. *J Am Coll Cardiol* 1999; 33: 234–41.
- Ziegler K, Stunkel W. Tissue-selective action of pravastatin due to hepatocellular uptake

- via a sodium-independent bile acid transporter. *Biochim Biophys Acta* 1992; 1139: 203–9.
55. Chen ZP, Mitchellhill KI, Michell BJ, et al. AMP-activated protein kinase phosphorylation of endothelial nitric oxide synthase. *FEBS Lett* 1999; 443: 285–9.
56. Garcia-Cardena G, Fan R, Stern D, Liu J, Sessa WC. Endothelial nitric oxide synthase is regulated by tyrosine phosphorylation and interacts with caveolin-1. *J Biol Chem* 1996; 271: 27237–40.
57. Corson MA, James NL, Latta SE, Nerem RM, Berk BC, Harrison DG. Phosphorylation of endothelial nitric oxide synthase in response to fluid shear stress. *Circ Res* 1996; 79: 984–91.
58. Fulton D, Gratton J-P, McCabe TJ, et al. Regulation of endothelium-derived nitric oxide production by the protein kinase Akt. *Nature* 2000; 399: 597–601.
59. Dimmeler S, Fleming I, Fisslthaler B, Hermann C, Busse R, Zeiher AM. Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation. *Nature* 2000; 399: 601–5.
60. Hernandez-Perera O, Perez-Sala D, Navarro-Antolin J, et al. Effects of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, atorvastatin and simvastatin, on the expression of endothelin-1 and endothelial nitric oxide synthase in vascular endothelial cells. *J Clin Invest* 1998; 101: 2711–9.
61. Nazzaro P, Manzari M, Merlo M, et al. Distinct and combined vascular effects of ACE blockade and HMG-CoA reductase inhibition in hypertensive subjects. *Hypertension* 1999; 33: 719–25.
62. Sposito AC, Mansur AP, Coelho OR, Nicolau JC, Ramires JA. Additional reduction in blood pressure after cholesterol-lowering treatment by statins (lovastatin or pravastatin) in hypercholesterolemic patients using angiotensin-converting enzyme inhibitors (enalapril or lisinopril). *Am J Cardiol* 1999; 83: 1497–9, A8.
63. Abetel G, Poget PN, Bonnabry JP. Hypotensive effect of an inhibitor of cholesterol synthesis (fluvastatin). A pilot study. *Schweiz Med Wochenschr* 1998; 128: 272–7.
64. Straznicki NE, Howes LG, Lam W, Louis WJ. Effects of pravastatin on cardiovascular reactivity to norepinephrine and angiotensin II in patients with hypercholesterolemia and systemic hypertension. *Am J Cardiol* 1995; 75: 582–6.
65. Nickenig G, Sachinidis A, Michaelsen F, Bohm M, Seewald S, Vetter H. Upregulation of vascular angiotensin II receptor gene expression by low-density lipoprotein in vascular smooth muscle cells. *Circulation* 1997; 95: 473–8.
66. Nickenig G, Baumer AT, Temur Y, Kebben D, Jockenhovel F, Bohm M. Statin-sensitive dysregulated AT1 receptor function and density in hypercholesterolemic men. *Circulation* 1999; 100: 2131–4.
67. Aviram M, Dankner G, Cogan U, Hochgraf E, Brook JG. Lovastatin inhibits low-density lipoprotein oxidation and alters its fluidity and uptake by macrophages: In vitro and in vivo studies. *Metabolism* 1992; 41: 229–35.
68. Kleinveld HA, Demacker PN, De Haan AF, Stalenhoef AF. Decreased in vitro oxidizability of low-density lipoprotein in hypercholesterolaemic patients treated with 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors. *Eur J Clin Invest* 1993; 23: 289–95.
69. Salonen R, Nyyssonen K, Porkkala-Sarataho E, Salonen JT. The Kuopio Atherosclerosis Prevention Study (KAPS): Effect of pravastatin treatment on lipids, oxidation resistance of lipoproteins, and atherosclerotic progression. *Am J Cardiol* 1995; 76: 34C–39C.
70. Hussein O, Schlezinger S, Rosenblatt M, Keidar S, Aviram M. Reduced susceptibility of low density lipoprotein (LDL) to lipid peroxidation after fluvastatin therapy is associated with the hypocholesterolemic effect of the drug and its binding to the LDL. *Atherosclerosis* 1997; 128: 11–8.
71. Bredie SJ, de Bruin TW, Demacker PN, Kastelein JJ, Stalenhoef AF. Comparison of gemfibrozil versus simvastatin in familial combined hyperlipidemia and effects on apolipoprotein-B-containing lipoproteins, low-density lipoprotein subfraction profile, and low-density lipoprotein oxidizability. *Am J Cardiol* 1995; 75: 348–53.
72. Girona J, La Ville AE, Sola R, Plana N, Masana L. Simvastatin decreases aldehyde production derived from lipoprotein oxidation. *Am J Cardiol* 1999; 83: 846–51.
73. Giroux LM, Davignon J, Naruszewicz M. Simvastatin inhibits the oxidation of low-density lipoproteins by activated human monocyte-derived macrophages. *Biochim Biophys Acta* 1993; 1165: 335–8.
74. Suzumura K, Yasuhara M, Tanaka K, Suzuki T. Protective effect of fluvastatin sodium (XU-62-320), a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, on oxidative modification of human low-density lipoprotein in vitro. *Biochem Pharmacol* 1999; 57: 697–703.
75. Aviram M, Rosenblatt M, Bisgaier CL, Newton RS. Atorvastatin and gemfibrozil metabolites, but not the parent drugs, are potent antioxidants against lipoprotein oxidation. *Atherosclerosis* 1998; 138: 271–80.
76. The Heart Outcomes Prevention Evaluation Study Investigators. Vitamin E supplementation and cardiovascular events in high risk patients. *N Engl J Med* 2000; 342: 154–60.
77. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: Prospective study and updated meta-analyses. *BMJ* 2000; 321: 199–204.
78. Ridker PM, Hennekens CH, Rietman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. *Lancet* 1998; 351: 88–92.
79. Rohde LE, Lee RT, Rivero J, et al. Circulating cell adhesion molecules are correlated with ultrasound-based assessment of carotid atherosclerosis. *Arterioscler Thromb Vasc Biol* 1998; 18: 1765–70.
80. Bhakdi S, Torzewski M, Klouche M, Hemmes M. Complement and atherogenesis: Binding of CRP to degraded, nonoxidized LDL enhances complement activation. *Arterioscler Thromb Vasc Biol* 1999; 19: 2348–54.
81. Zwaka TP, Hombach V, Torzewski J. C-reactive protein-mediated low density lipoprotein uptake by macrophages: implications for atherosclerosis. *Circulation* 2001; 103: 1194–7.
82. Mackness MI, Abbott C, Arrol S, Durrington PN. The role of high-density lipoprotein and lipid-soluble antioxidant vitamins in inhibiting low-density lipoprotein oxidation. *Biochem J* 1993; 294: 829–34.
83. Mackness MI, Arrol S, Durrington PN. Paraoxonase prevents accumulation of lipoperoxides in low-density lipoprotein. *FEBS Lett* 1991; 286: 152–4.
84. Christison JK, Rye KA, Stocker R. Exchange of oxidized cholesteryl linoleate between LDL and HDL mediated by cholesteryl ester transfer protein. *J Lipid Res* 1995; 36: 2017–26.
85. Garner B, Waldeck AR, Witting PK, Rye KA, Stocker R. Oxidation of high density lipoproteins. II. Evidence for direct reduction of lipid hydroperoxides by methionine residues of apolipoproteins AI and AII. *J Biol Chem* 1998; 273: 6088–95.
86. Nofer JR, Walter M, Kehrel B, et al. HDL3-mediated inhibition of thrombin-induced platelet aggregation and fibrinogen binding occurs via decreased production of phosphoinositide-derived second messengers 1,2-diaclylglycerol and inositol 1,4,5-tris-phosphate. *Arterioscler Thromb Vasc Biol* 1998; 18: 861–9.
87. Baumberger C, Ulevitch RJ, Dayer JM. Modulation of endotoxic activity of lipopolysaccharide by high-density lipoprotein. *Pathobiology* 1991; 59: 378–83.
88. Xia P, Vadas MA, Rye KA, Barter PJ, Gamble JR. High density lipoproteins (HDL) interrupt the sphingosine kinase signaling pathway. A possible mechanism for protection against atherosclerosis by HDL. *J Biol Chem* 1999; 274: 33143–7.
89. Baker PW, Rye KA, Gamble JR, Vadas MA, Barter PJ. Phospholipid composition of reconstituted high density lipoproteins influences their ability to inhibit endothelial cell adhesion molecule expression. *J Lipid Res* 2000; 41: 1261–7.
90. Dimayuga P, Zhu J, Oguchi S, et al. Reconstituted HDL containing human apolipoprotein A-1 reduces VCAM-1 expression and neointima formation following periaortic cuff-induced carotid injury in apoE null mice. *Biochem Biophys Res Commun* 1999; 264: 465–8.
91. Cockerill GW, Huehns TY, Weerasinghe A, et al. Elevation of plasma high-density lipoprotein concentration reduces interleukin-1-induced expression of E-selectin in an in vivo model of acute inflammation. *Circulation* 2001; 103: 108–12.
92. Theilmeier G, De Geest B, Van Veldhoven PP, et al. HDL-associated PAF-AH reduces endothelial adhesiveness in ApoE^{-/-} mice. *FASEB J* 2000; 14: 2032–9.
93. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and recurrent events (CARE) investigators. *Circulation* 1998; 98: 839–44.
94. Ridker PM, Rifai N, Miles JS, et al. Lovastatin 20–40 mg/day lowers high sensitivity C-reactive protein levels in AFCAPS/TEXCAPS. *Circulation* 2000; 102 (Suppl): II-833.
95. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol And Recurrent Events (CARE) investigators. *Circulation* 1999; 100: 230–5.
96. Albert MA, Danielson E, Rifai N, Ridker P. Effect of statin therapy on C-reactive protein levels. *JAMA* 2001; 286: 64–70.
97. Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devaraj S. Effect of hydroxymethyl glutaryl coenzyme A reductase inhibitor therapy on high sensitive C-reactive protein levels. *Circulation* 2001; 103: 1933–5.
98. Katznelson S, Wilkinson AH, Kobashigawa JA, et al. The effect of pravastatin on acute rejection after kidney transplantation—a pilot study. *Transplantation* 1996; 61: 1469–74.
99. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after transplantation. *N Engl J Med* 1995; 333: 621–7.
100. Wenke K, Meiser B, Thiery J, et al. Simvastatin reduces graft vessel disease and mortality after heart transplantation. A four-year randomized trial. *Circulation* 1997; 96: 1398–402.
101. de Bont N, Netea MG, Rovers C, et al. LPS-induced cytokine production and expression of LPS-receptors by peripheral blood mononuclear cells of patients with familial hypercholesterolemia and the effect of HMG-CoA reductase inhibitors. *Atherosclerosis* 1998; 139: 147–52.
102. Rosenson RS, Tangney CC, Casey LC. Inhibition of proinflammatory cytokine production by pravastatin. *Lancet* 1999; 353: 983–4.
103. Strandberg TE, Vanhanen H, Tikkanen MJ. Associations between change in C-reactive protein and serum lipids during statin treatment. *Ann Med* 2000; 32: 579–83.
104. Ridker PM, Rifai N, Lowenthal SP. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. *Circulation* 2001; 103: 1191–3.
105. Chakrabarti R, Engleman EG. Interrelationships between mevalonate metabolism and the mitogenic signaling pathway in T lymphocyte proliferation. *J Biol Chem* 1991; 266: 12216–22.
106. Cutts JL, Bankhurst AD. Suppression of lymphoid cell function in vitro by inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase by lovastatin. *Int J Immunopharmacol* 1989; 11: 863–9.
107. Cutts JL, Scallen TJ, Watson J, Bankhurst AD. Role of mevalonic acid in the regulation of natural killer cell cytotoxicity. *J Cell Physiol* 1989; 139: 550–7.
108. Cutts JL, Bankhurst AD. Reversal of lovastatin-mediated inhibition of natural killer cell cytotoxicity by interleukin 2. *J Cell Physiol* 1990; 145: 244–52.
109. McPherson R, Tsoukas C, Baines MG, et al. Effects of lovastatin on natural killer cell function and other immunological parameters in man. *J Clin Immunol* 1993; 13: 439–44.
110. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. *Nat Med* 2000; 6: 1399–402.
111. Inoue I, Goto S, Mizotani K, et al. Lipophilic HMG-CoA reductase inhibitor has an anti-inflammatory effect: Reduction of mRNA levels for interleukin-1 β , interleukin-6, cyclooxygenase-2, and p22phox by regulation of peroxisome proliferator-activated receptor alpha (PPAR- α) in primary endothelial cells. *Life Sci* 2000; 67: 863–76.
112. Delerive P, De Bosscher K, Besnard S, et al. Peroxisome proliferator-activated receptor alpha negatively regulates the vascular inflammatory gene response by negative cross-talk with transcription factors NF- κ B and AP-1. *J Biol Chem* 1999; 274: 32048–54.
113. Delerive P, Gervois P, Fruchart JC, Staels B. Induction of I- κ B α expression as a mechanism contributing to the anti-inflammatory activities of peroxisome proliferator-activated receptor- α activators. *J Biol Chem* 2000; 275: 36703–7.
114. Freeman DJ, Norrie J, Sattar N, et al. Pravastatin and the development of diabetes mellitus: Evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* 2001; 103: 357–62.
115. Kimura M, Kurose I, Russell J, Granger DN. Effects of lovastatin on leukocyte-endothelial cell adhesion in hypercholesterolemic rats. *Arterioscler Thromb Vasc Biol* 1996; 17: 1521–6.
116. Bustos C, Hernandez-Presa MA, Ortego M, et al. HMG-CoA reductase inhibition by atorvastatin reduces neutrophilic inflammation in a rabbit model of atherosclerosis. *J Am Coll Cardiol* 1998; 32: 2057–64.
117. Romano M, Diomedea L, Sironi M, et al. Inhibition of monocyte chemotactic protein-1 synthesis by statins. *Lab Invest* 2000; 80: 1095–100.
118. Lefler AM, Campbell B, Shin Y-K, Scalia R, Hayward R, Lefler DJ. Simvastatin preserves the ischemic-reperfused myocardium in normocholesterolemic rat hearts. *Circulation* 1999; 100: 178–84.
119. Pruefer D, Scalia R, Lefler AM. Simvastatin inhibits leukocyte-endothelial cell interactions and protects against inflammatory processes in normocholesterolemic rats. *Arterioscler Thromb Vasc Biol* 1999; 19: 2894–900.
120. Stanislaus R, Pahan K, Singh AK, Singh I. Amelioration of experimental allergic encephalomyelitis in Lewis rats by lovastatin. *Neurosci Lett* 1999; 269: 71–4.

121. Sparrow CP, Burton CA, Hernandez M, et al. Simvastatin has anti-inflammatory and antiatherosclerotic activities independent of plasma cholesterol lowering. *Arterioscler Thromb Vasc Biol* 2001; 21: 115–21.
122. Aikawa M, Rabkin E, Sugiyama S, et al. An HMG-CoA reductase inhibitor, cerivastatin, suppresses growth of macrophages expressing matrix metalloproteinases and tissue factor in vivo and in vitro. *Circulation* 2001; 103: 276–83.
123. Kreuzer J, Bader J, Jahn L. Chemotaxis of the monocyte line U937: Dependence on cholesterol and early mevalonate pathway products. *Atherosclerosis* 1991; 191: 90: 203–9.
124. Weber C, Erl W, Weber KS, Weber PC. HMG-CoA reductase inhibitors decrease CD11b expression and CD11b-dependent adhesion of monocytes to endothelium and reduce increased adhesiveness of monocytes isolated from patients with hypercholesterolemia. *J Am Coll Cardiol* 1997; 30: 1212–7.
125. Pahan K, Sheikh FG, Namboodiri AM, Singh I. Lovastatin and phenylacetate inhibit the induction of nitric oxide synthase and cytokines in rat primary astrocytes, microglia, and macrophages. *J Clin Invest* 1997; 100: 2671–9.
126. Ortego M, Bustos C, Hernandez-Presa MA, et al. Atorvastatin reduces NF- κ B activation and chemokine expression in vascular smooth muscle cells and mononuclear cells. *Atherosclerosis* 1999; 147: 253–61.
127. Kothe H, Dalhoff K, Rupp J, et al. Hydroxymethylglutaryl coenzyme A reductase inhibitors modify the inflammatory response of human macrophages and endothelial cells infected with *Chlamydia pneumoniae*. *Circulation* 2000; 101: 1760–3.
128. Goldstein JL, Brown MS. Regulation of the mevalonate pathway. *Nature* 1990; 343: 425–30.
129. Brown MS, Goldstein JL. Multivalent feedback regulation of HMG-CoA reductase, a control mechanism coordinating isoprenoid synthesis and cell growth. *J Lipid Res* 1980; 21: 505–17.
130. Weitz-Schmidt G, Welzenbach K, Brinkmann V, et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. *Nature Med* 2001; 6: 687–92.
131. Brown BG, Zhao XQ. Importance of endothelial function in mediating the benefits of lipid-lowering therapy. *Am J Cardiol* 1998; 82: 49T–52T.
132. Brown MS, Goldstein JL, Krieger M, Ho YK, Anderson RGW. Reversible accumulation of cholesteryl esters in macrophages incubated with acetylated lipoproteins. *J Cell Biol* 1979; 82: 597–613.
133. Goldstein JL, Ho YK, Basu SK, Brown MS. Binding site on macrophages that mediates uptake and degradation of acetylated low density lipoprotein, producing massive cholesterol deposition. *Proc Natl Acad Sci USA* 1979; 76: 333–7.
134. Haberland ME, Fogelman AM, Edwards PA. Specificity of receptor-mediated recognition of malondialdehyde-modified low density lipoproteins. *Proc Natl Acad Sci USA* 1982; 79: 1712–6.
135. Steinbrecher UP, Parthasarathy S, Leake DS, Witztum JL, Steinberg D. Modification of low-density lipoprotein by endothelial cells involves lipid peroxidation and degradation of low density lipoprotein phospholipids. *Proc Natl Acad Sci USA* 1984; 81: 3883–7.
136. Pietsch A, Erl W, Lorenz RL. Lovastatin reduces expression of the combined adhesion and scavenger receptor CD36 in human monocytic cells. *Biochem Pharmacol* 1996; 52: 433–9.
137. Umetani N, Kanayama Y, Okamura M, Negoro N, Takeda T. Lovastatin inhibits gene expression of type-I scavenger receptor in THP-1 human macrophages. *Biochim Biophys Acta* 1996; 1303: 199–206.
138. Draude G, Hrboticky N, Lorenz RL. The expression of the lectin-like oxidized low-density lipoprotein receptor (lox-1) on human vascular smooth muscle cells and monocytes and its down-regulation by lovastatin. *Biochem Pharmacol* 1999; 57: 383–6.
139. Llorente-Cortes V, Martinez-Gonzalez J, Badimon L. Esterified cholesterol accumulation induced by aggregated LDL uptake in human vascular smooth muscle cells is reduced by HMG-CoA reductase inhibitors. *Arterioscler Thromb Vasc Biol* 1998; 18: 738–46.
140. Negre-Aminou P, van Vliet AK, van Erck M, van Thiel GC, van Leeuwen RE, Cohen LH. Inhibition of proliferation of human smooth muscle cells by various HMG-CoA reductase inhibitors; comparison with other human cell types. *Biochim Biophys Acta* 1997; 1345: 259–68.
141. Bellosta S, Bernini F, Ferri N, et al. Direct vascular effects of HMG-CoA reductase inhibitors. *Atherosclerosis* 1998; 137 (Suppl): S101–9.
142. Guijarro C, Blanco-Colio LM, Ortego M, et al. 3-hydroxy-3-methylglutaryl coenzyme A reductase and isoprenylation inhibitors induce apoptosis of vascular smooth muscle cells in culture. *Circ Res* 1998; 83: 490–500.
143. Tan A, Levrey H, Dahm C, Polunovsky VA, Rubins J, Bitterman PB. Lovastatin induces fibroblast apoptosis in vitro and in vivo. A possible therapy for fibroproliferative disorders. *Am J Respir Crit Care Med* 1999; 159: 220–7.
144. Xu XP, Meisel SR, Ong JM, et al. Oxidized low-density lipoprotein regulates matrix metalloproteinase-9 and its tissue inhibitor in human monocyte-derived macrophages. *Circulation* 1999; 99: 993–8.
145. Bellosta S, Via D, Canavesi M, et al. HMG-CoA reductase inhibitors reduce MMP-9 secretion by macrophages. *Arterioscler Thromb Vasc Biol* 1998; 18: 1671–8.
146. Aikawa M, Rabkin E, Okada Y, et al. Lipid lowering by diet reduces matrix metalloproteinase activity and increases collagen content of rabbit atheroma: A potential mechanism of lesion stabilization. *Circulation* 1998; 97: 2433–44.
147. Crisby M, Nordin-Fredrickson G, Shah PK, Yano J, Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques. Implications for plaque stabilization. *Circulation* 2001; 103: 926–33.
148. Davi G, Averna M, Catalano I, et al. Increased thromboxane biosynthesis in type IIa hypercholesterolemia. *Circulation* 1992; 85: 1792–8.
149. Badimon JJ, Badimon L, Turotto VT, Fuster V. Platelet deposition at high shear rates is enhanced by high plasma cholesterol levels: In vivo study in the rabbit model. *Arterioscler Thromb* 1991; 11: 395–402.
150. Osamah H, Mira R, Sorina S, Shlomo K, Michael A. Reduced platelet aggregation after fluvastatin therapy is associated with altered platelet lipid composition and drug binding to the platelets. *Br J Clin Pharmacol* 1997; 44: 77–83.
151. Aviram M, Hussein O, Rosenblat M, Schlezinger S, Hayek T, Keidar S. Interactions of platelets, macrophages, and lipoproteins in hypercholesterolemia: Antiatherogenic effects of HMG-CoA reductase inhibitor therapy. *J Cardiovasc Pharmacol* 1998; 31: 39–45.
152. Alfón J, Royo T, Garcia-Moll X, Badimon L. Platelet deposition on eroded vessel walls at a stenotic shear rate is inhibited by lipid-lowering treatment with atorvastatin. *Arterioscler Thromb Vasc Biol* 1999; 19: 1812–7.
153. Alfón J, Pueyo Palazon C, Royo T, Badimon L. Effects of statins in thrombosis and aortic lesion development in a dyslipemic rabbit model. *Thromb Haemost* 1999; 81: 822–7.
154. Lacoste L, Lam JY, Hung J, Letchacovski G, Solymoss CB, Waters D. Hyperlipidemia and coronary disease. Correction of the increased thrombotic potential with cholesterol reduction. *Circulation* 1995; 92: 3172–7.
155. Lacoste L, Lam YT. Comparative effect of pravastatin and simvastatin on platelet-thrombus formation in hypercholesterolemic coronary patients. *J Am Coll Cardiol* 1996; 27 (Suppl A): 413A.
156. Misumi K, Ogawa H, Yasue H, et al. Comparison of plasma tissue factor levels in unstable and stable angina pectoris. *Am J Cardiol* 1998; 81: 22–6.
157. Collis S, Eligini S, Lalli M, Camera M, Paoletti R, Tremoli E. Vastatins inhibit tissue factor in cultured human macrophages. *Arterioscler Thromb Vasc Biol* 1997; 17: 265–72.
158. Ferro D, Basili S, Alessandri C, Mantovani B, Cordova C, Violi F. Simvastatin reduces monocyte-tissue-factor expression type IIa hypercholesterolaemia. *Lancet* 1997; 350: 1222.
159. Lorena M, Perolini S, Casazza F, Milani M, Cimminiello C. Fluvastatin and tissue factor pathway inhibitor in type IIa and IIb hyperlipidemia and in acute myocardial infarction. *Thromb Res* 1997; 87: 397–403.
160. Koppensteiner R, Minar E, Ehringer H. Effect of lovastatin on hemorheology in type II hyperlipoproteinemia. *Atherosclerosis* 1990; 83: 53–8.
161. Bo M, Bonino F, Neirotti M, et al. Hemorheologic and coagulative pattern in hypercholesterolemic subjects treated with lipid-lowering drugs. *Angiology* 1991; 42: 106–13.
162. Illingworth DR, Bacon S, Pappu AS, Sexton GJ. Comparative hyperlipidemic effects of lovastatin and simvastatin in patients with heterozygous familial hypercholesterolemia. *Atherosclerosis* 1992; 96: 53–64.
163. Branchi A, Rovellini A, Sommariva D, Gugliandolo AG, Fasoli A. Effect of three fibrate derivatives and of two HMG-CoA reductase inhibitors on plasma fibrinogen level in patients with primary hypercholesterolemia. *Thromb Haemost* 1993; 70: 241–3.
164. Farnier M, Bonnefous F, Debbaas N, Irvine A. Comparative efficacy and safety of micro-nized fenofibrate and simvastatin in patients with primary type IIa or IIb hyperlipidemia. *Arch Intern Med* 1994; 154: 441–9.
165. Tsuda Y, Satoh K, Kitadai M, Takahashi T, Izumi Y, Hosomi N. Effects of pravastatin sodium and simvastatin on plasma fibrinogen level and blood rheology in type II hyperlipoproteinemia. *Atherosclerosis* 1996; 122: 225–33.
166. Davidson MH, Nawrocki JW, Weiss SR, et al. Effectiveness of atorvastatin for reducing low-density lipoprotein cholesterol to national cholesterol education program treatment goals. *Am J Cardiol* 1997; 80: 347–8.
167. Davidson M, McKenney J, Stein E, et al. Comparison of one-year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia. Atorvastatin study group. *Am J Cardiol* 1997; 79: 1475–81.
168. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol* 1998; 81: 582–7.
169. Kario K, Matsuo T, Hoshida S, et al. Lipid-lowering therapy corrects endothelial cell dysfunction in a short time but does not affect hypercoagulable state even after long-term use in hyperlipidemic patients. *Blood Coagul Fibrinolysis* 1999; 10: 269–76.
170. Mitropoulos KA, Armitage JM, Collins R, et al. Randomized placebo-controlled study of the effects of simvastatin on haemostatic variables, lipoproteins and free fatty acids. The Oxford cholesterol study group. *Eur Heart J* 1997; 18: 235–41.
171. Davi G, Averna MR, Catalano I, Barbagello CM, Mogavero A, Notorbartolo A. Plasma fibrinogen in hypercholesterolemia: Effects of simvastatin therapy. *Curr Ther Res* 1991; 50: 79–83.
172. Voster HH, Venter CS, Jerling JC, Oosthuizen W, Kruger HH, Vermaak JH. Changes in plasma fibrinogen during six months of successful hypolipidemic treatment. 3rd International Symposium on multiple risk factors in cardiovascular diseases 1994.
173. Wierzbicki AS, Lumb PJ, Semra YK, Crook MA. Effect of atorvastatin on plasma fibrinogen [letter]. *Lancet* 1997; 351: 569–70.
174. Marais AD, Firth JC, Bateman ME, Byrnes P, Martens C, Mountney J. Atorvastatin: An effective lipid-modifying agent in familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol* 1997; 17: 1527–31.
175. Gottsater A, Anwar I, Lind P, Mattiasson I, Lindgarde F. Increasing plasma fibrinogen, but unchanged levels of intraplatelet cyclic nucleotides, plasma endothelin-1, factor VII, and neopterin during cholesterol lowering with fluvastatin. *Blood Coagul Fibrinolysis* 1999; 10: 133–40.
176. Mayer J, Eller T, Brauer P, et al. Effects of long-term treatment with lovastatin on the clotting system and blood platelets. *Ann Hematol* 1992; 64: 196–201.
177. Wada H, Mori Y, Kaneko T, et al. Hypercoagulable state in patients with hypercholesterolemia: Effects of pravastatin. *Clin Ther* 1992; 14: 829–34.
178. Szczekielik A, Musial J, Undas A, et al. Inhibition of thrombin generation by simvastatin and lack of additive effects of aspirin in patients with marked hypercholesterolemia. *J Am Coll Cardiol* 1999; 33: 1286–93.
179. Tan KC, Janus ED, Lam KS. Effects of fluvastatin on prothrombotic and fibrinolytic factors in type 2 diabetes mellitus. *Am J Cardiol* 1999; 84: 934–7, A7.
180. Wiesbauer F, Kaun C, Zorn G, Maurer G, Huber K, Wojta J. HMG-CoA reductase inhibitors affect the fibrinolytic system of human vascular cells in vitro: A comparative study using different statins. *Br J Pharmacol* 2002; 135: 284–92.
181. Byington RP, Jukema JW, Salonen JT, et al. Reduction in cardiovascular events during pravastatin therapy. Pooled analysis of clinical events of the pravastatin atherosclerosis intervention program. *Circulation* 1995; 92: 2419–25.
182. Aronow HD, Topol EJ, Roe MT, et al. Effect of lipid-lowering therapy on early mortality after acute coronary syndromes: An observational study. *Lancet* 2001; 357: 1063–8.
183. Stenestrand U, Wallentin L. Early statin treatment following acute myocardial infarction and 1-year survival. *JAMA* 2001; 285: 430–6.
184. Arntz HR, Agrawal R, Wunderlich W, et al. Beneficial effects of pravastatin (+/- colestyramine/niacin) initiated immediately after a coronary event (the randomized lipid-coronary artery disease [L-CAD] study). *Am J Cardiol* 2000; 86: 1293–8.
185. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: The MIRACL study: A randomized controlled trial. *JAMA* 2001; 285: 1711–8.

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