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

W. März[1], B. R. Winkelmann[2]

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, antioxydative, 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 Kardiol 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-1β 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 tomograpgy (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 homoestasis 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 pyrophophosphate 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.

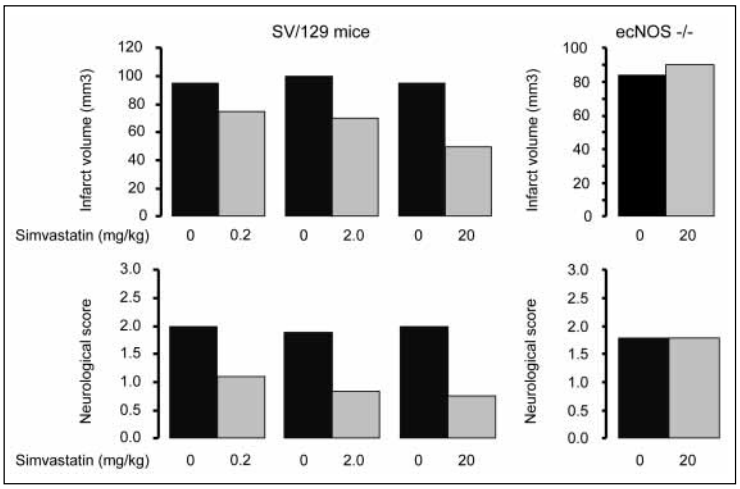

Figure 1: Left panel: Effect of increasing doses of simvastatin administered for two weeks on the volume of cerebral infarcts and a neurological sensory-motor score in mice induced by occlusion of the main carotid artery. Right panel: The effect is abolished in mice lacking endothelial nitric oxide.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

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

and, consecutively, of ecNOS. 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 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 oxidizablity *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 glomeruloslerosis [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 Ml 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 hypoercholesterolaemia, 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

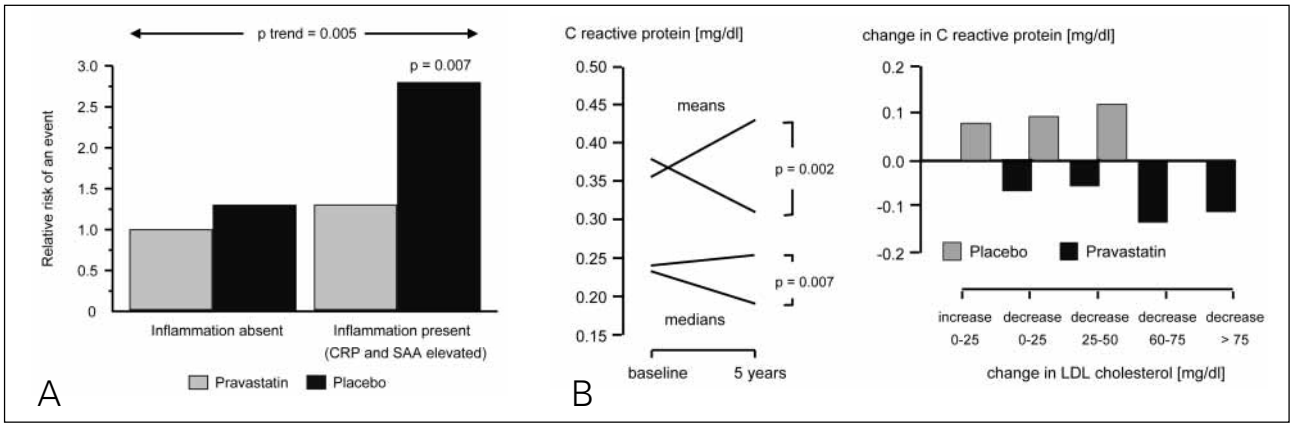

Figure 2: Pravastatin and C-reactive protein. **A.** Relative risks of recurrent coronary events in patients with previous MI in the CARE trial according to the presence (both C-reactive protein and serum amyloid A (> 90th percentile) or absence of systemic inflammation and according to treatment group [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-1β, 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-κB inhibitor Ik-Ba [112, 113], reduction of NF-κB 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 pyrophophosphate. 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 heterdimer of CD11a and CD18, known as aM-β2), 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. Bellosta 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].

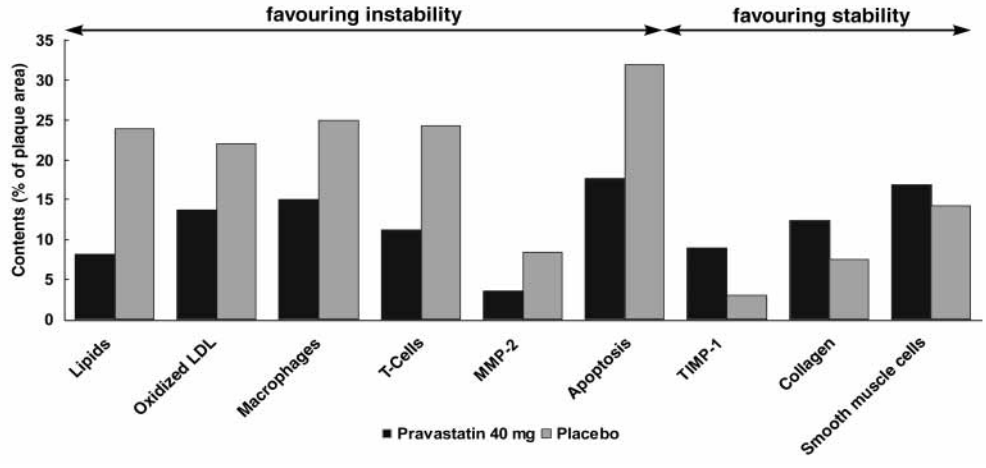

Figure 3: Effect of statin treatment on the composition of atherosclerotic plaques. Consecutive patients with symptomatic carotid artery stenoses received 40 mg daily pravastatin (n = 11) or no lipid-lowering therapy (n = 13) for 3 months before elective carotid endarterectomy. Carotid plaque composition was assessed with special stains and immunocytochemistry with quantitative image analysis. Compared to controls, pravastatin decresed 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 normocholesterolemic 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 completey 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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