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The Potential Relevance of the Multiple Lipid-Independent (Pleiotropic) Effects of Statins in the Management of Acute Coronary Syndromes

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Emerging data suggest that acute presentations of coronary artery disease may involve a complex interplay between the vessel wall, inflammatory cells, and the coagulation cascade. Although a culprit thrombotic lesion may be treated effectively by antithrombotic therapy and revascularization, this will have little effect on the global processes that determine recurrent events at non-culprit sites. Thus, additional systemic treatment is required to modulate the adverse biological features that are the hallmark of acute coronary syndromes (ACS). Statins possess multiple beneficial effects that are independent of low-density-lipoprotein cholesterol (LDL-C) lowering and that have favorable effects on inflammation, the endothelium, and the coagulation cascade. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, differences were seen based on achieved LDL-C that could be further discriminated by the achieved C-reactive protein level. Studies of non-vascular disease such as multiple sclerosis have shown that statins reduce inflammation, supporting the presence of lipid-independent effects of statins. This review focuses on the potential importance of these effects in the management of ACS. (J Am Coll Cardiol 2005;46:1425–33) © 2005 by the American College of Cardiology Foundation

Acute coronary syndromes (ACS) are increasingly recognized to be secondary to a diffuse process involving the entire coronary vasculature (1). Although multiple vulnerable or ruptured plaques may be present at a given point in time, only a few of these ultimately lead to an acute presentation. It is now suggested that a complex interplay between the pathological vascular triad of inflammation, endothelial dysfunction/activation, and thrombosis exists (Fig. 1) that individually or collectively determines an individual's propensity to develop an ACS. Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is central not only to cholesterol metabolism (via the liver) but which also plays a key role in cell signaling in many vascular cells. Inhibition of HMG-CoA reductase in vascular cells by statins rapidly modulates a number of cellular responses implicated in ACS in a dose-dependent manner.

LIPID-DEPENDENT EFFECTS OF STATINS

Low-density lipoprotein-C (LDL-C) is intrinsically linked to atherothrombosis and is oxidized by free radicals to oxidized LDL-C (ox-LDL-C), which in turn has a number of deleterious effects. Hence, reductions in the circulating LDL-C pool will likely reduce the amount of the LDL-C substrate available for oxidation and therefore potentially have beneficial early effects (2). Non-statin therapies that lower LDL-C, such as ileal bypass or use of bile acid sequestrants, require five to seven years to show a clinical effect, in contrast to the earlier benefits observed in statin trials (3). Although statins reduce LDL-C and markers of inflammation such as C-reactive protein (CRP), the correlation coefficient between LDL-C and CRP is weak (approximately 0.13) (4), suggesting that the reductions in CRP cannot be explained by reductions in LDL-C alone. Additionally, patients receiving statins have lower event rates than that predicted by their achieved LDL-C, raising the possibility of distinct mechanisms beyond cholesterol reduction (cholesterol-independent effects). Moreover, these lipid-independent effects may be particularly relevant to the early benefit in ACS. In the A to Z trial, an intensive statin regimen was associated with a 60-mg/dl LDL-C difference at four months, but no clinical benefit was seen (and no CRP difference was shown at one month). In contrast, the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) trial had less LDL-C difference (32 mg/dl) but a greater CRP difference and early benefit (5). These data suggest strongly that the early benefits of statins in ACS are mediated by a lipid-independent process. The LDL-C−dependent benefits of statins are summarized in Table 1.

Abbreviations and Acronyms

ACS	=	acute coronary syndromes
CAD	=	coronary artery disease
CRP	=	C-reactive protein
HMG-CoA	=	3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA)
ICAM	=	intercellular adhesion molecule
IL	=	interleukin
LDL-C	=	low-density lipoprotein cholesterol
NO	=	nitric oxide
PAI-1	=	plasminogen activator inhibitor
PROVE IT-TIMI 22	=	Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22
TF	=	tissue factor
TM	=	thrombomodulin
tPA	=	tissue plasminogen activator
vWF	=	von Willebrand factor

LIPID-INDEPENDENT EFFECTS OF STATINS

Inhibition of HMG-CoA reductase by statins inhibits the generation of proteins called isoprenoids (geranyl-geranyl pyrophosphate and farnesyl pyrophosphate) in vascular cells (Fig. 2). The binding of isoprenoids to a number of signaling proteins (Rho and Ras) enables them to function in inflammatory signaling pathways. Rho activates a number of nuclear transcription factors such as nuclear factor-kappa B, which promote a number of inflammatory responses, and also reduces endothelial nitric oxide synthetase, which serves as a protective factor in vascular disease. Statins promote anti-inflammatory pathways by inhibiting Rho, and also by up-regulating endothelial nitric oxide synthetase. The lipid-independent, diverse biological effects produced by the inhibition of isoprenoid synthesis have been collectively referred to as pleiotropic effects. As this review shows, this term may be an oversimplification because statins have distinct effects on each component of the vascular triad implicated in atherothrombosis (Fig. 1, Table 1).

THE ENDOTHELIUM IN ACS

The normal endothelium synthesizes nitric oxide (NO), which gives the vessel wall its vasodilator and antithrombotic properties (6). Under resting conditions, the endothelium presents a non-adherent surface expressing very little in the way of adhesion molecules such as E-selectin and intercellular adhesion molecule (ICAM)-1. The surface is also non-thrombotic, expressing high levels of thrombomodulin (TM) and small amounts of tissue factor (TF). A small amount of von Willebrand factor (vWF) is constitutively released, and the net balance of tissue plasminogen activator (tPA)/plasminogen activator inhibitor (PAI-1) favors fibrinolysis (6).

Endothelial dysfunction is an independent predictor of clinical risk in patients with coronary artery disease (CAD).

The normal endothelium is distorted in ACS (Fig. 3). In response to inflammatory cytokines, the endothelium down-regulates TM and up-regulates TF. There is also enhanced release of vWF and a reduction in the tPA/PAI-1 ratio, which combined with the reduction in NO release favors thrombosis and vasoconstriction. Increased local expression of adhesion molecules on the endothelial surface (7), together with increased local levels of chemoattractants (e.g., monocyte chemoattractant protein-1 [MCP-1]), result in the adhesion and transmigration of inflammatory cells to potentially vulnerable sites within the vessel wall (8). Here, inflammatory cells can further propagate inflammation through the release of inflammatory cytokines. Acute coronary sydrome is associated with elevations in soluble markers of endothelial activation such as vWF, E-selectin, and ICAM-1, and a reduction in these markers seems to correlate with a reduction in cardiovascular mortality/morbidity (9). Hence, treatments that lead to a reduction in endothelial activation may be biologically beneficial.

EFFECT OF STATINS ON ENDOTHELIAL ACTIVATION/FUNCTION

Statins have beneficial effects on endothelial function independently of effects on lipid lowering, and these are related to a rapid increase in NO bioavailability (10). In stable patients, improvements in flow-mediated dilatation have been observed as early as three hours (11), i.e., well before the effects of hepatic HMG-CoA reductase inhibition are
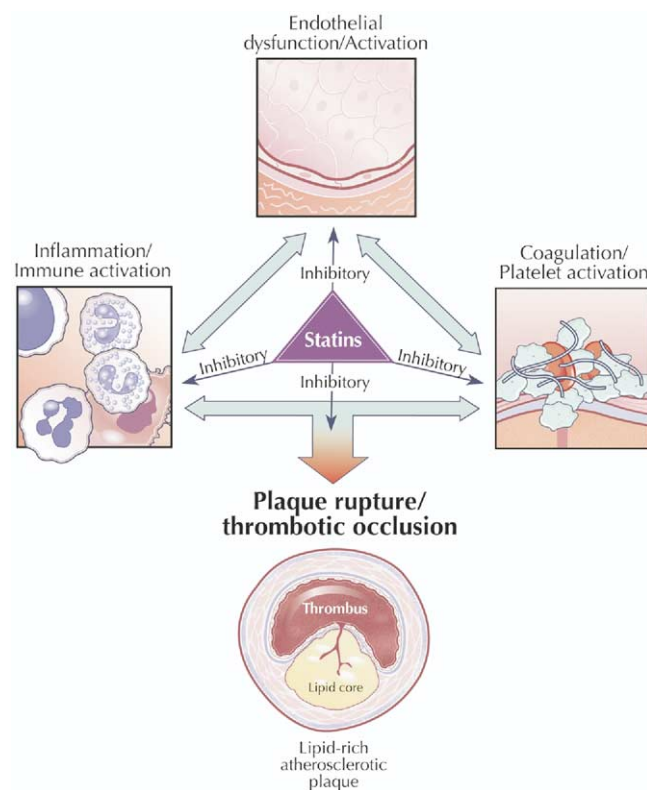
Figure 1. "Pathological vascular triad" implicated in acute coronary syndrome. Illustration by Rob Flewell.

Table 1. Pathways By Which Statins Can Modulate the Pathological Changes in ACS

HMG-CoA Reductase Dependent		HMG-CoA Reductase Independent
Cholesterol Dependent	**Cholesterol Independent**	
↓ LDL-C and ↓ oxidized LDL-C	↓ Prenylation ↓ Isoprenoid synthesis Down-regulation of Rho/rhokinase ↓ NFκB and inflammatory signalling	
↓ Foam cell formation	↓ Expression of MCP-1 by endothelial cells	Binding to the lymphocyte function associated antigen, thus preventing binding of lymphocyte to endothelial counter ligand ICAM-1
↓ Macrophage number	↓ Binding of lymphocytes to endothelial receptor ICAM-1	
↓ Cholesterol rafts for inflammatory signalling	Down-regulation of Th-1 lymphocytes	
↓ Expression of inflammatory cytokines	Cytokine switching from Th-1 to Th-2 type phenotype in lymphocytes ↓ Inflammatory cytokine production/CRP immune modulation	
↑ Nitric oxide levels by stabilizing m-RNA	↑ Nitric oxide production	
↓ Oxidative stress	↓ Oxidative stress	
↓ Expression of adhesion molecules	↓ Endothelial adhesion molecule expression	
↓ Platelet activation	↑ Increased TM expression ↓ Tissue factor expression ↑ tPA/PAI-1 ratio ↓ Coagulation factors	? Inactivation of factor Va

ACS = acute coronary syndromes; CRP = C-reactive protein; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; ICAM = intercellular adhesion molecule; LDL-C = low-density lipoprotein cholesterol; MCP = monocyte chemoattractant protein; NFκB = nuclear factor kappa B; PAI = plasminogen activator inhibitor; TM = thrombomodulin; tPA = tissue plasminogen activator.

likely to have impacted on plasma LDL-C. Statins also reduce the endothelial expression of endothelin-1 (12), further favoring vasodilatation. Because CRP reduces e-NOS and impairs flow-mediated dilatation (13), some of the beneficial effects on endothelial function may be indirectly mediated by the ability of statins to lower CRP.

Erosion of the endothelial surface and exposure to circulating blood may trigger thrombosis, and patients with highest circulating coagulation factors are at greatest risk. Repair of the damaged endothelium is therefore important, and may occur in two ways: firstly by migration of adjacent endothelial cells or secondly from mobilization of circulating endothelial progenitor cells derived from the bone marrow. Statins increase the number and the survival of circulating endothelial progenitor cells, and mobilize them to sites of injury (14), thus accelerating re-endothelialization (15) as rapidly as one week after treatment (16). Senescence of endothelial progenitor cells contributes to reduced endothelial reparative capacity. Statins also inhibit senescence and increase cell proliferation by effects on cell cycle genes (17), hence statins may reduce recurrent events at sites of superficial erosions by having favorable effects on cellular repair.

In large prospective studies of patients with CAD, elevations in levels of adhesion molecules predict adverse clinical events in a manner analogous to that of CRP (18). Statins reduce the expression of adhesion molecules such as E-selectin and ICAM-1 on the surface of endothelial cells in response to various stimuli, at the level of gene transcription (19), resulting in fewer inflammatory cells binding to an activated endothelium and thus increasing the stability of vulnerable plaques. In small clinical studies, statins have been shown to reduce circulating levels of adhesion molecules (20). Therefore, part of the cardiovascular benefit of statins may be mediated by reducing the activation of the endothelium.

The endothelium produces a number of inflammatory cytokines that may activate inflammatory cells and platelets, including interleukin (IL)-1, IL-6, and CD40 ligand and its receptor (CD40). In endothelial cells, statins reduce IL-1 and IL-6 production at the level of gene transcription (21), and also the expression of CD40 ligand and CD40, suggesting that statins play a potent role in mediating inflammation within endothelial cells by directly reducing local cytokine production or by inhibiting cytokine binding (22,23) (Table 2).

PROTHROMBOTIC CHANGES IN ACS

Inflammation is intrinsically related to ACS and results in a down-regulation of TM and up-regulation of TF on the surface of the endothelium, favoring thrombosis. A reduction in circulating soluble TM has been implicated in the development of incident CAD (24), and recently circulating TF has emerged as a possible risk factor for ACS, with observations that classical risk factors and ACS are associated with higher TF levels (25,26). Elevated fibrinogen and factor VII levels have been associated with increased cardiovascular risk in stable and unstable CAD (27,28). Thus, treatments that reduce procoagulant factors or that increase
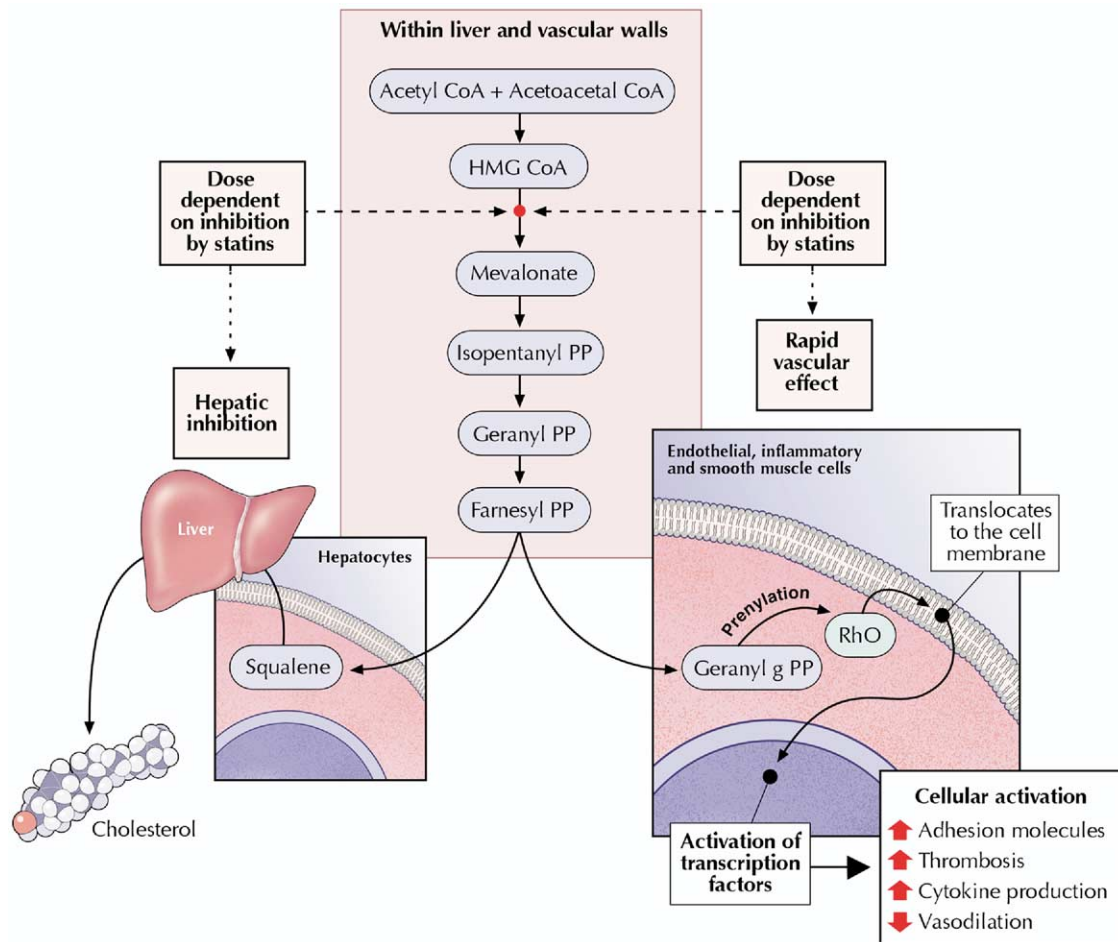
Figure 2. Molecular pathway. Inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibits cholesterol synthesis and isoprenoid production (geranyl-geranyl pyrophosphate and farnesyl pyrophosphate). This in turn reduces prenylation of G proteins such as Rho, and hence membrane binding. Illustration by Rob Flewell.

natural anticoagulants would be expected to have favorable effects on thrombosis.

## EFFECT OF STATINS ON MARKERS OF COAGULATION

Statins increase TM expression on the cell surface (29) and reduce TF expression on endothelial cells directly by inhibiting the Rho/Rho kinase pathways (30). This not only reduces thrombin generation, but the binding of thrombin to TM also activates protein C, stimulating the intrinsic anticoagulation cascade. In addition, statin therapy reduces circulating levels of vWF (31) and tends to alter the balance of PAI-1 to tPA back in favor of fibrinolysis (32), possibly via the reduction in circulating levels of proinflammatory cytokines as an intermediate step. CD40 ligand and CRP are powerful inducers of tissue factor expression by the monocyte/macrophage system, and a reduction in these mediators by statins could result in a second, indirect method by which statins could reduce TF (33).

In addition to effects mediated by the vessel wall, statins have systemic effects on coagulation, including reductions in factor VII antigen levels (34), prothrombin activation, factor Va generation, and factor XIII activation, as well as an

increased rate of factor Va inactivation (35). The mechanisms behind this are unclear, but could reflect an effect on protein transcription within the liver, the activation of catalytic enzymes, both, or some other mechanism yet to be identified. These effects are cholesterol-independent and may serve to reduce clot formation or the stability of fibrin clots. These data suggest that statins improve markers of coagulation by both endothelium-dependent and non-endothelium-dependent mechanisms (Table 2).

THE ROLE OF INFLAMMATION IN ACS

Patients with ACS have heightened focal inflammation within the vessel wall as well as evidence of a systemic inflammatory response (summarized in Table 3). In particular, T-lymphocytes present in the plaque produce a number of inflammatory proteins (cytokines), including interferon (IFN)-gamma, which lead to a decrease in collagen production by vascular smooth muscle cells. Activated macrophages produce large quantities of matrix metalloproteinases and elastases, which degrade collagen and elastin, resulting in a weakening of the fibrous cap. In the systemic circulation, evidence of immune activation also can be
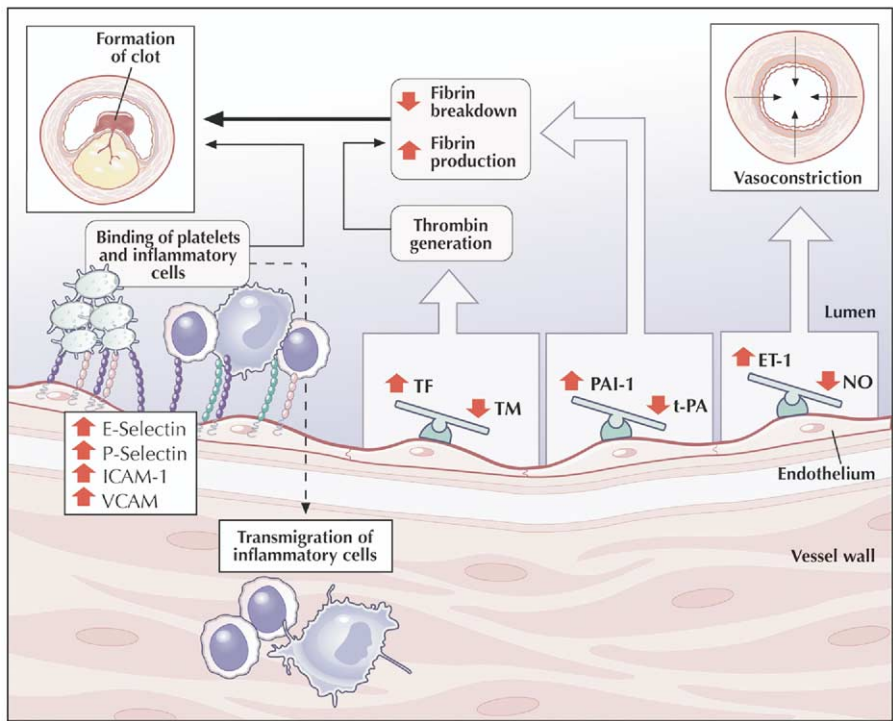
Figure 3. Endothelial abnormalities in acute coronary syndrome. ET = endothelin; ICAM = intercellular adhesion molecule; NO = nitric oxide; PAI = plasminogen activator inhibitor; t-PA = tissue plasminogen activator; TF = tissue factor; TM = thrombomodulin; VCAM = vascular cellular adhesion molecule. Illustration by Rob Flewell.

observed (Fig. 4) (36–40), resulting in the production of proinflammatory cytokines (Table 1). Suppressing the activity of inflammatory cells therefore represents an important therapeutic target for the management of ACS (Fig. 4).

Acute coronary syndrome is associated with an increase in non-specific markers of systemic inflammation, such as CRP,

Table 2. Endothelial and Coagulation Abnormalities Implicated in ACS and the Effect of Statins on Endothelial and Coagulation Markers

	Health	Changes Implicated in ACS	Effect of Statins
Endothelial function			
Vasomotor function	↑	↓	↑
NO bioavailability	↑	↓	↑
eNOS	↑	↓	↑
Endothelial activation			
Adhesion molecule expression	↓	↑	↓
Endothelial repair			
Progenitor cell number	↑	↓	↑
Progenitor cell senescence	↓	↑	↓
Coagulation			
Tissue factor	↓	↑	↓
Thrombomodulin	↑	↓	↑
PAI-1	↓	↑	↓
tPA	↑	↓	↑
vWF	↓	↑	↓
Factor VII	↓	↑	↓
Va	↓	Unknown	↓

eNOS = endothelial nitric oxide synthetase; NO = nitric oxide; vWF = von Willebrand factor. Other abbreviations as in Table 1.

and those with the highest levels have the worst clinical outcomes (41). Hepatic production of CRP is largely driven by increased release of cytokines, e.g., interleukins (IL-1, IL-6, IL-18) and tumor necrosis factor-alpha, which themselves also predict cardiovascular risk (42–45). Hence, cardiovascular risk could be reduced by treatments that have direct anti-inflammatory effects. In contrast, ACS is associated with low circulating levels of the anti-inflammatory cytokines, e.g., IL-10, and recent observations suggest that high IL-10 levels attenuate the risk associated with an elevated CRP (46), reflecting a dynamic relationship between pro-inflammatory and anti-inflammatory processes. Another emerging prognostic marker also elevated in ACS is CD40-ligand (47), which has been shown to regulate plaque stability (48), and its potential modulation could be an important target for future systemic therapy.

MODULATION OF INFLAMMATION BY STATINS

Recently, statins have been shown to directly bind to receptors on the lymphocyte cell surface (lymphocyte function associated antigen), preventing binding to the counter-receptor on the endothelial surface (ICAM-1) (49). Additionally, statins reduce the production of chemoattractants (e.g., MCP-1) by the vessel wall. These direct anti-inflammatory effects are important and distinct from effects on LDL-C, and result in a reduction in the net number of inflammatory cells within plaques (50). In addition, statins reduce the activation of the monocyte/macrophage system,
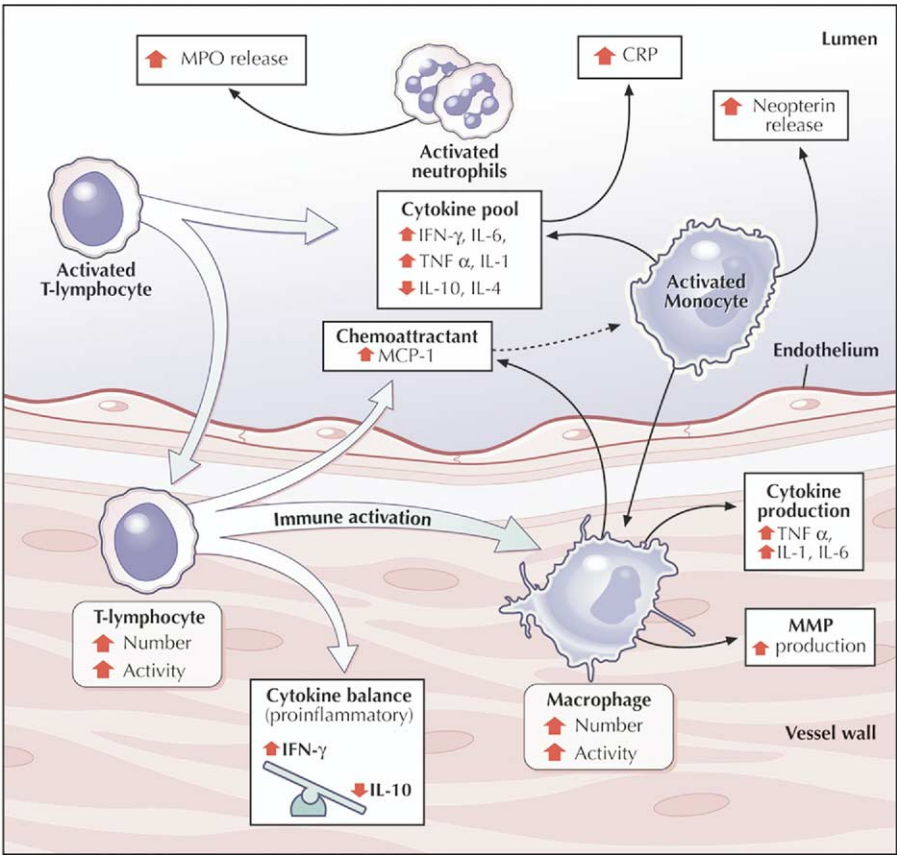
Figure 4. Inflammatory changes in acute coronary syndrome. CRP = C-reactive protein; IFN = interferon; IL = interleukin; MCP = monocyte chemoattractant protein; MMP = matrix metalloproteinases; MPO = myeloperoxidase; TNF = tumor necrosis factor. Illustration by Rob Flewell.

resulting in a reduction in the release of proteolytic enzymes (matrix metalloproteinases) (51). Statins also have many favorable effects on T-lymphocytes, which include reducing their cytotoxicity (52). T-helper cell subclasses that promote inflammation (Th-1 subclass) are inhibited by statins. In contrast, T-helper subclasses that promote anti-inflammatory effects (Th-2 subclass) are stimulated by statins (53), resulting in a net "switching" of cytokine production among T-cells from the production of pro-inflammatory cytokines such as interferon-gamma to the production of anti-inflammatory cytokines such as IL-4 or IL-10 (54). The net result of these effects would be to promote plaque stabilization (Table 3). Statins diminish the proinflammatory activity of monocytes (55) and their ability to bind to the vessel wall. The latter is mediated by a reduction in the expression of endothelial adhesion molecules such as ICAM-1 on the endothelial surface and their counter ligand (CD11a/CD18) on the monocyte (56), which are dependent on the Rho/Rho kinase pathways. Hence, statins modify the immune response in ACS via reductions in inflammatory cell number, adhesion, and activation at potentially vulnerable sites along the wall.

Statins reduce the production and release of cytokines involved in the inflammatory cascade (IL-6, IL-8, tumor necrosis factor-alpha, and CD40 ligand) (57), and thus reduce CRP independently of their effects on LDL-C. C-reactive protein has a number of direct pathological

effects on atherosclerosis progression (4), endothelial dysfunction (58), and thrombosis (59). Hence, by lowering CRP, statins potentially negate many of the pathological effects of inflammation.

Cholesterol rafts are cholesterol-rich regions of the cell membrane where many receptors involved in cell signaling preferentially accumulate. A novel and increasingly recognized effect of statins is their ability to deplete the lipid

Table 3. Inflammatory Changes Implicated in ACS and the Effect of Statins on Components of Inflammation

	Changes Implicated in ACS	Effect of Statins
Changes within the plaque		
Inflammatory cells infiltrate plaque	↑	↓
Inflammatory cells activated	↑	↓
Systemic effects		
T-cell activation	↑	↓
Monocyte activation	↑	↓
Neutrophil activation	↑	↓
Cytokine production		
Inflammatory cytokine production	↑	↓
Anti-inflammatory cytokine production	↓	↑
Non-specific markers of inflammation		
CRP	↑	↓
Ischemia/reperfusion injury	↑	↓

Abbreviations as in Table 1.

content of cholesterol rafts and thus alter their function, resulting in reduced inflammatory signaling (60). Other known beneficial anti-inflammatory effects of statins include reducing ischemia reperfusion injury and infarct size in animal and clinical models (61) (Table 3).

Immune modulation in non-vascular disease. In addition to benefits in vascular disease, there is now evidence that statins improve non-vascular diseases that have an inflammatory etiology. In relapsing-remitting multiple sclerosis, high-dose statin therapy reduced gadolinium-enhancing lesions at four to six months on magnetic resonance imaging scans (62). In animal models of relapsing-remitting encephalomyelitis, the use of statin therapy reversed or prevented chronic and relapsing paralysis (63). These beneficial effects were associated with beneficial effects on immunomodulation (cytokine switching). In patients with rheumatoid arthritis receiving disease-modifying drugs, statins reduced disease activity scores by 21% at six months (64), which coincided with a 50% reduction in CRP. In observational studies, statin use is associated with a 60% to 73% lower incidence of Alzheimer disease (65). Although the mechanisms are unclear, it is speculated that reductions in neuronal levels of a peptide implicated in Alzheimer disease (Abeta42) may play a role (66). These data in the setting of non-vascular disease provide even more compelling evidence that statins possess LDL-C–independent effects that become clinically relevant within a relatively short time window.

STATIN SOLUBILITY AND DOSE

The solubility of a statin could potentially influence the magnitude of the LDL-C–independent effects. In particular, hydrophilic statins have been associated with an increase in the collagen and smooth muscle cell content in atherosclerotic lesions compared with lipophilic statins in animal models of atherosclerosis (50). However, lipophilic statins were superior to hydrophilic statins in the ability to reduce cytokine production in endothelial and inflammatory cells via inhibition of Rho (21). Differences in lipid-independent effects between statins possibly resulting from drug solubility have been suggested by recent clinical studies (67). A dose-dependent relationship for the inhibition of Rho-mediated lipid-independent effects exists in vitro. We would therefore predict that higher doses of a lipophilic statin would be associated with the greatest as well as the most rapid effect in vascular cells. Whether there are differences between statins based on solubility that are of biological and clinical relevance warrants further study.

EVIDENCE FROM CLINICAL TRIALS

Several trials have investigated the effects of statins in ACS. The first of these (MIRACL) showed that atorvastatin 80 mg reduced clinical events and CRP at four months compared with placebo (68,69). A trend toward a reduction in soluble CD40-ligand was also observed with atorvastatin

80 mg. In the PROVE IT-TIMI 22 trial, atorvastatin 80 mg lowered CRP at 30 days compared with pravastatin 40 mg, and this was associated with clinically significant benefit by four months (70,71). In contrast, in patients with stable CAD, benefit is delayed. Inspection of the Kaplan-Meier curves shows little detectable separation in the first year (Scandanavian Simvastatin Survial Study [4S] and Long-term Intervention with Pravastatin in Ischemic Disease [LIPID] study) (3) or two years (Cholesterol And Recurrent Events [CARE] trial) (3). These differences suggest that the clinical benefits of intensive statin therapy observed in ACS patients occurred very early, and perhaps before the greater reductions in LDL-C were likely to have had any significant effect on disease progression.

Two recent publications have intensified the debate about choice and dose of statin in ACS. The Pravastatin in Acute Coronary Teatment [PACT] study investigated the use of pravastatin 20 to 40 mg versus placebo within 24 hours of non–ST-segment elevation ACS at 30 days. There seemed to be no difference between the pravastatin 20 mg group and placebo, but benefit tended to be seen only in the pravastatin 40 mg group, in an overall negative trial. In the recent Z phase of the A to Z study, simvastatin 40 mg failed to lower CRP at one month compared with placebo, and in turn no significant clinical benefit was observed within the first four months after randomization. This suggests that the highest statin doses may be important for early clinical benefits in ACS patients.

SUMMARY

Acute coronary syndrome is accompanied by adverse changes in inflammation, the immune system, endothelial function, and coagulation, which may be causative or epiphenomena. Statins improve adverse biological profiles rapidly in a dose-dependent manner in vitro and in animal studies, and thus the lipid-independent effects of statins may contribute to the early reduction in cardiovascular risk observed with intensive statin therapy in ACS patients. These observed biological effects deserve further study in patients regarding the role of statin type and dose, and may open up new avenues beyond statin therapy for other more potent and specific inhibitors of the pathways impacted by statins, as new ways of improving outcomes in ACS.

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