Statin Therapy in Acute Coronary Syndromes
Mechanistic Insight Into Clinical Benefit
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Abstract—Randomized trials have established that statin treatment reduces coronary events in primary prevention and in patients with stable coronary artery disease. In unstable coronary artery disease, however, the pathophysiological background is distinct, and the potential benefits of statin therapy have not been evaluated until recently. Data from animal models and clinical studies indicate that statin treatment can influence a spectrum of molecular and cellular mechanisms that are intimately related to the pathogenesis of acute coronary syndromes; these include the reduction of circulating levels of atherogenic lipoproteins (very low density lipoprotein, very low density lipoprotein remnants, intermediate density lipoprotein, and low density lipoprotein) and thus of arterial lipid deposition and the attenuation of inflammation, modulation of thrombogenesis and thrombolysis, improvement of endothelial dysfunction, and reduction of ischemia/reperfusion injury. Indeed, findings from prospective and observational studies have demonstrated that statin treatment significantly improves clinical outcome after acute coronary syndromes. Therefore, early initiation of statin therapy after an acute coronary event not only enhances adherence to treatment but also preempts the occurrence of new events. In this review, we discuss recent important developments in our knowledge of the clinical evidence of the beneficial effects of early statin therapy in acute coronary syndromes and the biological mechanisms that underlie them. (Arterioscler Thromb Vasc Biol. 2002;22:●●●●●●.)

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Large clinical trials have demonstrated that statin treatment reduces the risk of coronary events and total mortality in patients with stable coronary artery disease (CAD). After an acute coronary event, an enhanced incidence of new events occurs over a prolonged period of time, and as a consequence, there is a higher mortality. In fact, compared with patients with stable disease, patients after an acute coronary event have a 2- to 6-fold higher incidence of recurrent events.1 Recently, the early introduction of statin treatment during the acute phase of a coronary event has been highlighted as a possible therapeutic approach for improving the outcome in patients with unstable disease. However, distinct clinical, biochemical, and histological features have indicated that these 2 clinically distinct forms of CAD, ie, unstable and stable forms, are derived from distinct pathophysiological backgrounds. Indeed, several clinical investigations have been undertaken to clarify the mechanisms by which lipid-lowering treatment can minimize the risk of recurrence after an initial coronary event.

By competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is a key enzyme of cholesterol biosynthesis, statins reduce cellular cholesterol content, notably in liver cells (Figure 1). Indeed, hepatocytes respond to sterol depletion by activating nuclear sterol regulatory element–binding protein-2, which upregulates the transcription of key genes implicated in cholesterol metabolism, including HMG-CoA reductase and the LDL receptor.2 Thus, the cholesterol-lowering effect of statins is principally mediated by the upregulation of LDL receptor activity, which leads to enhanced hepatic uptake of atherogenic apoB-containing lipoproteins (VLDL, VLDL remnants, IDL, and LDL), and to a lesser extent, the cholesterol-lowering effect of statins is mediated by partial inhibition of hepatic VLDL synthesis. In fact, in patients with acute coronary syndromes, rapid and major lowering of LDL cholesterol levels (−29%) was observed after just 5 days of treatment with high-dose statin.3 In addition, a small but significant elevation in antiatherogenic HDL cholesterol has been observed after statin treatment.4 Consequently, statin therapy positively influences the equilibrium between atherogenic and antiatherogenic lipoproteins, favoring reverse cholesterol transport and leading to beneficial changes in the composition, structure, and stability of atherosclerotic plaques (Figure 1).5 Furthermore, a wide spectrum of statin-mediated actions on inflammation, thrombogenesis, and arterial vasomotor properties may also contribute to the potential benefit of such therapy in patients with acute coronary syndromes. Such multiple actions have been termed collectively as pleiotropic effects6 and could result from (1) action dependent...
on lipid lowering; (2) action independent of lipid lowering but dependent on inhibition of HMG-CoA reductase, such as that resulting from cellular mevalonate depletion; (3) actions independent of HMG-CoA reductase inhibition; or (4) distinct combinations of these actions. In the present review, we shall discuss recent important developments in our knowledge of the clinical impact of statin therapy in patients with unstable CAD and, to an equal extent, the biological mechanisms that underlie these beneficial effects.

**Statin-Mediated Effects on Inflammation**

The most striking difference between patients with unstable versus stable clinical presentation of CAD is the higher incidence of new coronary events in the unstable group. Surprisingly, almost half (46%) of such recurrent events are unrelated to the initial culprit lesion but arise from complications in other segments of the coronary artery system. In patients with acute coronary syndromes, transcoronary neutrophil activation is a marker of the inflammatory process occurring in the coronary vasculature. In a recent novel study, transcoronary neutrophil activation was evaluated in patients with unstable angina and occurred to a similar degree in coronary arteries in the presence or absence of the culprit lesion, thereby suggesting widespread coronary inflammation. Moreover, in angiographic studies, an accelerated and diffuse progression of coronary lesions has been observed after an acute coronary event in the entire coronary circulation. Angioscopic evaluation of these patients has revealed that all 3 major coronary arteries are widely diseased and display multiple, non-disrupted, potentially vulnerable atherosclerotic plaques. In necropsy studies, disrupted plaques typically display a large lipid core, thin fibrous caps, large numbers of monocyte-derived macrophages, macrophage foam cells, and activated T cells, and a reduced number of smooth muscle cells. Such cellular content is indicative of a sustained inflammatory reaction. Indeed, inflammatory characteristics have typically been used to histologically define the vulnerable lipid-rich plaque. In contrast to the histological description of the stable disease, the coronary arteries of patients who died after an acute coronary event typically display several nondisrupted plaques with vulnerable features in segments not related to the causal event. Taken together, these findings suggest that an intense inflammatory process occurs simultaneously at multiple sites and that it is maximal at the culprit lesion. After an acute coronary event, the inflammatory activity in the coronary arteries is further intensified by ischemic and reperfusion injuries, which may then contribute to the increased incidence of recurrent events.

It is now abundantly clear that statin treatment can result in local inflammatory modification. In one prospective study, hypercholesterolemic patients with symptomatic carotid artery stenosis received pravastatin at a dose of 40 mg/d for 3 months before scheduled carotid endarterectomy. Histological and immunohistochemical analyses revealed significant reductions in the numbers of macrophages and T cells and in metalloproteinase-2 expression; by contrast, increases in the content of collagen and tissue inhibitor of metalloproteinases-1 were observed when carotid plaques of treated patients were compared with those of nontreated subjects. Histological and immunohistochemical analyses revealed significant reductions in the numbers of macrophages and T cells and in metalloproteinase-2 expression; by contrast, increases in the content of collagen and tissue inhibitor of metalloproteinases-1 were observed when carotid plaques of treated patients were compared with those of nontreated subjects. In a rabbit model of diet-induced atherosclerosis, lipid lowering by diet or statin treatment reduced the content and activation of macrophages in atherosclerotic plaques. In the same model, lipid lowering equally promoted the accumulation of mature smooth muscle cells and collagen in the atherosclerotic intima, thereby increasing tensile strength within the plaque. Despite such stabilizing changes that have been observed after either dietary and/or statin treatment, some statin-mediated effects on plaque compo-

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**Figure 1.** Mechanism of action of statins on lipid metabolism. Statins inhibit endogenous cholesterol synthesis, particularly in liver cells, thereby depleting cellular cholesterol content and upregulating LDL receptor activity. Enhanced catabolism of circulating apoB-containing lipoproteins (VLDL, IDL, and LDL) via the LDL receptor pathway and elevation of HDL attenuate the disequilibrium between atherogenic and antiatherogenic lipoproteins, favoring reverse cholesterol transport and leading to favorable changes in the composition, structure, and stability of atherosclerotic plaques.
Fig. 2. Anti-inflammatory actions of statins. (1) Statins inhibit lymphocyte adhesion to intercellular adhesion molecule-1 (ICAM-1) and impair T-cell stimulation by directly binding to the lymphocyte function-associated antigen-1 (LFA-1) site by a mechanism independent of HMG-CoA reductase inhibition. (2) By inhibiting HMG-CoA reductase, statins inhibit the mevalonate pathway and, consequently, reduce the intracellular pool of isoprenoids, thereby downregulating the prenylation process. Reduced prenylation of the Rho protein, in turn, downregulates activation of NF-κB and increases the transcription of NO synthase (NOS), which, in combination with increased stability of NOS mRNA, induces elevation in the endothelial production of NO. (3) Statins reduce plasma LDL levels, thereby decreasing substrate available for generation of oxidized LDL; oxidized LDL can inactivate NO and equally downregulate endothelial NOS expression (not shown). By reduction of LDL substrate and also by a direct mechanism (see 2 above), statin treatment increases NO bioavailability and decreases monocyte adhesion to endothelial cells.

Recently, Weitz-Schmidt et al.32 reported an anti-inflammatory property of statins that is not related to HMG-CoA reductase inhibition and is thus independent of reduction in intracellular cholesterol or mevalonate levels. They demonstrated that several statins can inhibit lymphocyte adhesion to intercellular adhesion molecule-1 and, equally, can impair T-cell stimulation by directly binding to the lymphocyte function-associated antigen-1 site on leukocytes. Such potent anti-inflammatory action may explain some of the immunoregulatory effects of statins observed in transplant patients.33–35

Significantly, systemic markers of inflammatory activity are attenuated after statin treatment. Indeed, clinical trials in the context of primary and secondary prevention have shown that statin therapy reduces plasma levels of C-reactive protein (CRP), which is a marker of overall systemic inflammation.36–38 In the Cholesterol and Recurrent Events (CARE) trial, pravastatin-treated patients displayed progressive reduction of CRP levels (up to −37.8%) during the 5-year follow-up period, indicating that this anti-inflammatory effect is progressive and maintained over a prolonged period.39 The effect of statins on systemic inflammatory markers results potentially from lipid-lowering–dependent and –independent actions.40 Arterial wall macrophages, stimulated by oxidized LDL, secrete proinflammatory cytokines, such as interleukin-6, which, in turn stimulate hepatic production of CRP and other acute-phase reactants.40 Statins reduce the residence time of LDL particles in the circulation and, consequently, the substrate available for generation of oxidized LDL, thereby reducing the inflammatory stimulus. Equally, statins can directly attenuate the inflammatory response via mechanisms related to the inhibition of mevalonate synthesis but also via mechanisms independent of HMG-CoA reductase inhibition.25–28,32 These mechanisms, involving lipid-lowering–dependent and –independent ac-
tions, are not mutually exclusive and thus operate concomitantly. It is not clear whether there may be a preponderance of one these mechanisms in the statin-induced reduction in plasma CRP levels. Studies involving pravastatin, cerivastatin, lovastatin, simvastatin, and atorvastatin treatments in dyslipidemic patients have consistently demonstrated a decrement in plasma CRP levels in a manner unrelated to their effects on LDL or HDL cholesterol levels.46–49 However, estimation of proinflammatory or anti-inflammatory actions of lipoproteins is not fully reflected in the determination of their cholesterol content. For example, LDL particles differ in their susceptibility to oxidation as a function of their physicochemical properties (eg, size and chemical composition), raising the possibility that LDL particle phenotype may be intimately related to the magnitude of the inflammatory stimulus.41–43 Thus, the potential association between statin-induced modifications in LDL particle phenotype44 and variation in the circulating levels of acute-phase reactants requires further study. Finally, in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),38 statin therapy reduced coronary event rates in subjects with high LDL cholesterol and low CRP levels as well as in those subjects displaying low LDL cholesterol and high CRP levels. These findings suggest that lipid-dependent and -independent mechanisms are clinically relevant and that the predominant mechanism may not be the same in patients with distinct clinical presentations.

Considered together, the above-discussed findings provide evidence that statin treatment may modify plaque composition, reducing inflammatory activity and favoring lesion stability in patients with low-grade chronic inflammation, such as patients with stable atherosclerotic disease. However, during the acute phase of coronary syndromes, an intense augmentation of inflammation is observed, and it is closely related to the incidence of recurrent events.45 By consequence, the anti-inflammatory effect of statins in patients with acute coronary syndromes and augmented inflammatory activity requires a separate consideration. In a randomized double-blind trial with 36 patients in the acute phase of unstable angina or myocardial infarction without ST-segment elevation, we observed a 5% decrease of CRP levels during the first 5 days of treatment with atorvastatin (80 mg/d) compared with an 188% increase in CRP levels in placebo-treated patients (L.C. Correia, unpublished data, 2002). In a substudy of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, 16-week treatment with atorvastatin (80 mg/d) compared with placebo significantly reduced CRP levels.46 Therefore, modulation of the inflammatory response can be obtained after a short period of treatment and may constitute an argument for the early introduction of statin therapy in acute coronary syndromes.

**Statin-Mediated Modulation of Thrombogenesis**

The amount of thrombus generated on plaque disruption is a decisive event in the genesis of an acute coronary syndrome. When the endothelial surface of a coronary plaque is eroded or denuded, the exposure of blood to procoagulant elements triggers the coagulation cascade, platelet aggregation, and fibrin deposition, which may lead to occlusive or semioclusive thrombus formation. The intensity of this thrombogenic process determines clinical outcome, which may vary from the absence of a clinical event to myocardial infarction or even sudden death. In necropsy studies, disrupted plaques without thrombosis are found in 9% to 16% of the subjects who die suddenly of noncardiac causes.14–16 Therefore, the thrombogenic response is considered a major determinant of clinical outcome on plaque rupture.

After plaque disruption or ulceration, the thrombogenic response is determined by several factors, including the presence of procoagulant elements in the vessel wall, local blood flow properties, and circulating coagulation factors. Tissue factor (TF) is a transmembrane protein of the vessel wall that does not normally come into contact with blood until vascular injury occurs. Once in contact with blood, TF rapidly activates the extrinsic coagulation pathway, thus initiating the thrombogenic response. TF in plaque has been suggested as being an essential element for the initiation of intravascular thrombus formation. Histological evaluation of coronary atherectomy specimens has revealed the presence of thrombus only in plaques that express TF.33 Moreover, TF concentration and activity are higher in plaques taken from patients with acute coronary syndromes than in those taken from patients with stable disease.48 These findings highlight the difference between unstable and stable forms of CAD and indicate that TF expression may modulate the thrombogenic response after plaque rupture. In fact, the infusion of anti-TF monoclonal antibodies prevents thrombus formation on injured carotid arteries and the femoral artery in eversion graft models in rabbits.49,50

Recently, Aikawa et al21 have shown that treatment with cerivastatin reduces TF expression in cultured human macrophages and in aortic atheroma of rabbits. Similar results have been observed after incubation of human macrophages with fluvastatin and simvastatin.51,52 In hypercholesterolemic subjects, Ferro et al52 showed that simvastatin inhibited TF expression in monocytes in a dose-dependent manner. Moreover, an equivalent reduction of plasma cholesterol levels by dietary intervention also provoked a significant reduction in TF expression and activity in aortic atheroma of rabbits.19 This finding is consistent with experimental data showing that TF expression by macrophages is stimulated by intracellular accumulation of free cholesterol.53 Thus, the effect of statin treatment on TF is at least partially associated with its lipid-lowering action (Figure 3).

Once exposed to the bloodstream and to circulating plasma factors, TF binds to factor VII, generating the activated factor VII–TF complex, which initiates the extrinsic pathway of the coagulation system. In addition, the factor VII–TF complex can trigger the intrinsic pathway through activation of factor IX and can participate together with factor V and X in the generation of thrombin at the final stage of coagulation.54 In the Northwick Park Heart Study, subjects who exhibited enhanced plasma factor VII coagulant activity equally displayed a higher incidence of fatal cardiac events in 5-year and 16-year follow-up periods.55,56 The plasma concentration and activity of factor VII are modulated by genetic factors and by
plasma lipoproteins. Factor VII activity and mass are positively correlated with the cholesterol content of all lipoprotein fractions and with triglyceride plasma levels. However, the association of factor VII with triglyceride levels is stronger, and even transitory elevations of triglycerides in the postprandial period are followed by a proportional increase in factor VII coagulant activity. Lipid lowering after dietary, fibrate, or statin treatment has been shown to significantly reduce factor VII coagulant activity and mass. Recently, statin-induced reduction of prothrombin activation has also been associated with inhibition of factor V activation, as well as an increase in factor Va inactivation. Thus, statin action on factors V and VII results in a synergistic effect in reducing thrombin generation. In addition, statins inhibit the activation of factor XIII, which cross-links fibrin polymers to form a stable clot.

The activity of TF is physiologically inhibited by the TF pathway inhibitor (TFPI), which binds to the factor VII–TF complex, thereby inhibiting activation of the coagulation cascade. Intravenous infusion of recombinant TFPI prevented thrombus formation in a swine model of coronary injury. Circulating TFPI is transported by LDL and Lp(a), and increased TFPI levels are observed in patients with familial hypercholesterolemia. TFPI-bound LDL may penetrate the subendothelial space, and the accumulation of such LDL might exert an antithrombotic effect. Nevertheless, even a minimal oxidative modification of LDL inactivates LDL-associated TFPI. Pietzsch et al. observed that statin-mediated reduction in the residence time of LDL in the circulation lowers the rate of intravascular oxidation of these particles. Therefore, statin treatment may theoretically reduce the rate of inactivation of LDL-associated TFPI. However, in clinical studies performed with hypercholesterolemic patients, statin treatment decreased TFPI levels without affecting free TFPI concentrations, factor VII coagulation activity, or activated factor VII concentration. Thus, the clinical significance of plasma-free TFPI levels and of the role of statin treatment in this system remains unclear.

Additional elements implicated in thrombus formation after an acute coronary event have been demonstrated to be modifiable by lipid-lowering treatment. This is the case for platelet aggregation and plasma levels of fibrinogen. Platelets drawn from patients with high cholesterol levels are more sensitive to aggregating agents than are platelets from normocholesterolemic subjects. Cholesterol enrichment of platelet membranes and elevated production of thromboxane A2 constitute the potential mechanisms for the hyperaggregability associated with hypercholesterolemia. Statin treatment reduces platelet aggregation, possibly by reducing thromboxane A2 production and the cholesterol content of platelet membranes. The antithrombotic effect of statins is attenuated by concomitant treatment with aspirin, consistent with the demonstrated effect of statin treatment on thromboxane A2 production. Elevated fibrinogen levels increase plasma viscosity and the propensity for thrombosis and indicate the intensity of an inflammatory process. In clinical studies, plasma fibrinogen levels allow stratification of cardiovascular risk in subjects with or without CAD and are positively correlated with LDL cholesterol, Lp(a), and triglyceride levels. Nevertheless, despite the documented correlation with LDL cholesterol, a significant reduction of plasma fibrinogen levels was observed only after treatment with certain fibrates; by contrast, no clear effect was detected after statin treatment.

Overall, an enhanced thrombogenicity has been observed in patients who develop an acute coronary event compared with those who display a stable evolution. Such increased tissue or blood thrombogenicity could result from interaction between inflammatory, lipid, and genetic factors, representing a key element in the clinical outcome of patients with acute coronary syndromes. Overall blood thrombogenicity has been estimated in an ex vivo model in which a patient’s blood passes through a perfusion system that includes a small segment of arterial wall. In this model, a significant reduction was observed in thrombus formation after a 3-month period of treatment with either pravastatin or simvastatin, even in patients already treated with aspirin. Tissue thrombogenes strain results from plaque TF expression, and statin treatment attenuates such expression. Therefore, statin ther-
apy influences the process of thrombus formation by a combination of actions on blood and tissue thrombogenicity (Figure 3).

**Statin Action on Endothelial Dysfunction**

Rapid and sustained restoration of coronary blood flow represents a major goal in the treatment of patients with acute coronary syndromes. The precocity and magnitude of coronary flow restoration will determine infarct size, ventricular function, and mortality. After reperfusion therapy, residual stenosis on infarct-related plaque constitutes the major restriction for coronary flow. The degree of residual stenosis is determined by the interaction between hemodynamic status, the thrombus remaining on the plaque, and coronary vasodilator reserve. Intracoronary pressure opposes arterial wall elasticity and vasomotor tone, thereby opposing the collapsing force within the stenotic segment. In addition, thrombus size and the functional adaptation of the coronary wall interact to generate the luminal stenosis. A paradoxical constriction or adaptive dilation of the stenotic segment has been observed in stable CAD patients according to the functionality of the coronary endothelium.

Endothelial integrity is necessary for adequate vasomotor function and dynamic accommodation of lumen diameter to the coronary flow demand. In necropsy studies, the great majority of epicardial coronary plaques are eccentric, leaving part of the arterial wall relatively uninvolved. The presence of such uninvolved segments may explain the observed dynamic behavior of coronary stenosis. Moreover, in conduit vessels, such as epicardial coronary arteries, blood flow resistance has a fourth-power dependence on luminal diameter at the stenosis. Thus, even small variations of stenotic segment diameter may promote substantial modifications of coronary blood flow.

In CAD patients, the presence of epicardial coronary stenosis induces a proportionate decrease in microvascular resistance, whose role is to preserve myocardial perfusion at a level appropriate for the oxygen demand. Such compensatory microvascular dilation is proportional to the severity of the coronary stenosis and to myocardial oxygen demand and is mainly controlled by the endothelium. Endothelial dysfunction causes impairment of endothelium-dependent vasodilator response not only in conduit vessels but also in microvascular resistance vessels. By consequence, the ischemic threshold and resting poststenotic flow are reduced and are closely related to a fixed coronary stenosis. In patients without obstructive coronary stenosis, reduced endothelium-dependent microvascular function may decrease the ischemic threshold and myocardial perfusion during stress. Furthermore, inappropriate constriction of microvessels may cause angina with transient ST-segment elevation and an acute-onset form of dilated cardiomyopathy in patients without obstructive CAD.

In patients with hypercholesterolemia, endothelium-dependent vasodilator function is impaired in coronary and systemic arteries. The proposed mechanism for such dysfunctional vasomotion involves an enhanced inactivation and decreased production of NO by endothelial cells. Vasomotor dysfunction is extended to conduit and small resistance vessels and can be ameliorated after some weeks of statin treatment or immediately after LDL apheresis. Furthermore, as discussed above, statin therapy reduces the residence time of LDL particles in the circulation, thereby decreasing substrate available for the generation of oxidized LDL. Oxidized LDL downregulates endothelial NO synthase expression through a combination of transcriptional inhibition and posttranscriptional mRNA destabilization. Thus, statins may increase the bioavailability of NO via their LDL cholesterol-lowering effect as well as by a direct inhibition of the production of superoxide anion and the upregulation of the endothelial expression of NO synthase. In addition, statins might influence vascular tone by modulating the expression of endothelial vasoactive factors, such as endothelin-1, or by their direct effects on calcium inflow response in vascular myocytes.

After plaque disruption or erosion, the loss of the endothelial cell monolayer can predispose the epicardial coronary arteries to paradoxical constriction. Therefore, coronary reendothelialization is a limiting step in the improvement of arterial function and myocardial perfusion after plaque disruption. In addition, arterial reendothelialization may also prevent thrombus formation, a potential consequence of the exposure of the subendothelial surface to platelets and circulating factors. Reendothelialization can result from the migration and proliferation of neighboring endothelial cells and equally from the homing of circulating endothelial progenitor cells (EPCs) derived from bone marrow to sites of endothelial disruption. Recently, Walter et al observed that statin treatment accelerates the reendothelialization of balloon-injured arterial segments in rats via mechanisms related to the phosphatidylinositol 3-kinase/Akt pathway. The Akt protein kinase is a multifunctional regulator involved in cell growth, survival, and glycogen synthesis. Statins rapidly induce phosphorylation of Akt at serine residue 473, which increases its protein kinase activity and, as a consequence, increases EPC proliferation, survival, and mobilization to sites of endothelial denudation. Furthermore, Walter et al also observed a 5-fold increase in the number of EPCs on the reendothelialized luminal surface of statin-treated rats compared with control rats. In men, statin therapy is associated with a significant increase in the number of circulating EPCs after 1 week of treatment. Thus, given the established role of circulating EPCs in endothelial repair, the differentiation and mobilization of EPCs after short-term statin treatment may potentially contribute to the rapid amelioration of endothelial function after an acute coronary event. Additionally, Akt signaling activates endothelial cell production of NO via the phosphorylation of endothelial NO synthase at serine residue 1179 or 1177 and, in this way, regulates vasomotion and flow in intact arteries in vivo. Therefore, enhanced activation of the Akt pathway may influence coronary vasomotor reactivity via the acceleration of reendothelialization and increased bioavailability of NO and may represent a potential benefit of early initiation of statin therapy after an acute coronary event.

During acute coronary events, the thrombogenesis-induced release of serotonin, ADP, and thrombin causes a paradoxical vasoconstriction of the dysfunctional endothelium. As a
consequence, endothelial dysfunction is further intensified, and the impairment of coronary vasodilator function is aggravated. Reduction in vasodilator function occurs even in areas that are not supplied by the infarct-related artery and persists for an average of 6 months. In the infarct-related artery, the release of vasoactive mediators, such as serotonin, ADP, and thromboxane, from activated platelets can constrict epicardial coronary arteries surrounding the site of the thrombus and distal resistance vessels, intensifying the ischemic injury (Figure 4). In addition, the overall commitment of the coronary microvascular bed may favor the appearance of inappropriate constrictions and ischemia at the periphery of the infarcted area, thereby extending myocardial injury.

An early initiation of statin treatment after a coronary event may theoretically attenuate the endothelial dysfunction and improve myocardium perfusion. However, clinical data are still lacking to confirm such a hypothesis. In the Reduction of Cholesterol in Ischemia and Function of the Endothelium (RECIFE) trial, 60 hypercholesterolemic patients were randomized to initiate pravastatin or placebo treatment in the first week after an acute coronary event. Endothelial function was measured by brachial ultrasonography before and 6 weeks after treatment. Endothelium-dependent flow-mediated dilation of the brachial artery was significantly improved in statin-treated patients but not in control subjects. A good correlation has been observed between coronary and brachial endothelial function in patients with stable CAD. Moreover, in prospective studies in patients with stable CAD, the presence of endothelial dysfunction at enrollment discriminated those patients who ultimately developed an acute coronary event from those who did not. Besides inadequate coronary vasomotion, a lack of normal metabolic activity in the vascular endothelium favors thrombogenesis, leukocyte adhesion to the vessel wall, and inhibition of vascular smooth muscle cell growth. Therefore, it seems highly probable that endothelial dysfunction is involved in the pathophysiological basis of unstable CAD.

Figure 4. Effects of statin on endothelial dysfunction. During acute coronary events, several stimuli, such as thrombin, platelet-released serotonin and ADP, and low intracoronary blood pressure, may cause paradoxical vasoconstriction of the dysfunctional endothelium, which intensifies ischemic injury. Statin-mediated reduction in atherogenic lipoprotein levels and elevation in antiatherogenic HDL, in addition to effects independent of lipid lowering, result in amelioration of endothelial function. In consequence, the coronary artery responds to those stimuli with an adaptive dilation, thereby attenuating the ischemic insult.

Statin-Mediated Myocardial Protection

Rapid and effective reperfusion is a key factor minimizing myocardial injury after an acute coronary event. However, reperfusion itself may promote an inflammatory response and enhance myocardial injury. During reperfusion, activated leukocytes infiltrate the myocardium, releasing proteases, proinflammatory cytokines, and oxygen-derived free radicals, thereby increasing vascular endothelium and cardiomyocyte damage. In an animal model, reperfusion injury and ventricular dysfunction were significantly reduced in rats treated with statins 18 hours before the induction of myocardial ischemia. In addition, the researchers found a lower adherence of polymorphonuclear leukocytes to vascular endothelium and lower infiltration in the ischemic myocardium from statin-treated rats. This attenuation in neutrophil-endothelium interaction seems to be the consequence of a reduction in the expression of adhesion molecules from endothelial cells and an inhibition of neutrophil activation after statin treatment.
The myocardial protective effect of statins is also detectable in the absence of neutrophils. The addition of the active form of simvastatin to the perfusion medium of isolated rat hearts reduces ischemia/reperfusion injury. In addition, statin treatment partially prevents endothelial NO synthase reduction induced by ischemia/reperfusion injury; this cardioprotective effect of statins is completely abolished by simultaneous treatment with an NO synthase inhibitor. These findings in animal models suggest that acute treatment with statins could potentially attenuate ischemia/reperfusion injury by a lipid-lowering independent mechanism. Despite the relevance of these findings, further studies are awaited to clarify this statin-mediated mechanism.

Clinical Trials of Statins in Acute Coronary Syndromes

On the basis of the above data, there is abundant evidence to predict clear clinical benefit from statin treatment in patients with acute coronary syndromes. The remaining major question concerns the period required from initiation of statin treatment to the detection of clinical benefit. In the retrospective RIKS-HIA study, 5528 patients who received statins at or before discharge after an acute myocardial infarction were compared with 14 071 patients who did not. The authors found a 1-year lower mortality in the statin treatment group even after adjusting for confounding factors (95% CI 0.63 to 0.89, \( P = 0.001 \)). Interestingly, this significant difference in mortality after a 1-year follow-up is suggestive of an early split in the survival curves compared with the typical 2-year split observed in statin trials with stable CAD patients.

Data from 20 809 patients of the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO-IIb) and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trials were analyzed to compare all-cause mortality among patients with acute coronary syndromes who were discharged on lipid-lowering agents (n=3653) with those who were not (n=17 156). A smaller proportion of deaths at 30 days and at 6 months was found for patients who were discharged on lipid-lowering treatment. Several confounding factors could be present in such retrospective analysis. For example, the group on lipid-lowering therapy involved younger patients and higher rates of obesity, hypertension, diabetes mellitus, peripheral vascular disease, previous myocardial infarction, previous coronary revascularization procedures, and severe angina before admission. However, after adjustment for the propensity to prescribe lipid-lowering agents and other potential confounders, patients receiving lipid-lowering agents at discharge displayed a reduced risk of death at 6 months (95% CI 0.48 to 0.95, \( P = 0.023 \)). Despite the possible drawbacks of retrospective analysis, these large observational studies clearly suggest that clinical benefit may result from early initiation of statin treatment.

The first randomized double-blind trial that addressed the comparison between the early versus later introduction of statin treatment was the MIRACL study. In this trial, early treatment with high-dose atorvastatin (80 mg/d) after an episode of unstable angina or non-Q-wave infarction significantly reduced the combined end point of death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or worsening symptomatic myocardial ischemia over a 16-week treatment period. The study had a small sample size (n=3086) and was not powered to detect small differences in 16-week mortality. However, the documentation of a 2.6% absolute reduction in combined events after 16 weeks of statin treatment is far greater than the reduction observed during a comparable period in trials with stable CAD patients.

Thus, when taken together, the findings of MIRACL and observational studies indicate that the benefit of statin treatment may be observed over a shorter period of time in patients with unstable CAD than in those with chronic stable disease.

Many of the actions of statins, including the effects on inflammatory markers, thrombogenesis, and endothelial dysfunction, have been demonstrated after a 12-week period of treatment. Patients who manifest an acute coronary syndrome experience increased mortality in the first 12 months after the initial event. By implication, a longer follow-up period would be necessary to evaluate the difference between early and late initiation of statin treatment after an acute coronary event. In addition, a better estimation of sample size could be possible on the basis of the results of the MIRACL study. New clinical trials that are more appropriately sized and with longer follow-up are currently being conducted to clarify the impact of early initiation of statin treatment after an acute coronary event. The Aggrastat to Zocor (A to Z) trial was designed to include patients with unstable angina or non–ST-elevation myocardial infarction, all treated with tirofiban and then randomized to enoxaparin or unfractionated heparin. In the second phase, 4500 patients, including the initially randomized subjects plus patients with ST-elevation myocardial infarction, will be randomized to either simvastatin (40 mg/d) or to placebo. After 1 month, patients in the simvastatin arm will adjust the dose to 80 mg/d, and at 4 months, patients in the placebo arm will initiate simvastatin at 20 mg/d. The trial will continue until the occurrence of 970 primary end-point events (a composite of cardiovascular death, myocardial infarction, readmission for acute coronary syndrome, and stroke). In this context, the use of such a composite clinical end point is consistent with the assumption that many of the beneficial effects of statins on the vascular bed and on thrombogenesis could be extended to the prevention of stroke and, potentially, vascular dementia. In fact, randomized clinical trials have suggested that statin treatment can reduce the risk of stroke by up to 25%, and in 1 observational study, statin treatment was associated with a lowered risk of the development of dementia. However, populations at high risk for CAD enrolled in statin trials are not always representative of the overall stroke population. Thus, the effects of statin on cerebrovascular disease will be more clearly evaluated in the ongoing Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trial, which has been designed to prospectively evaluate the effects of atorvastatin (80 mg/d) on cerebrovascular events in patients who have had a previous stroke or transient ischemic attack but who have no prior history of CAD.
Conclusion and Perspectives

Until recently, introduction of statin therapy during hospitalization has been proposed as a strategy to improve the long-term compliance of patients to statin treatment. However, a growing body of evidence suggests that early initiation of statin therapy may also provide significant clinical benefits for patients in acute coronary syndromes. Clinical benefits, such as reduction of recurrent ischemic events, have been documented in a recent prospective study after short-term treatment with statins. Mechanistic explanations of the benefits are derived not only from the actions of statin on atherogenic lipoproteins (VLDL, IDL, and LDL) but equally benefits are derived not only from the actions of statin on inflammation, endothelial dysfunction, myocardial protection, and thrombogenesis.

Despite substantial data supporting the early initiation of statin therapy after an acute coronary event, many questions remain unanswered. The reduction in cardiovascular mortality documented in observational studies requires prospective evaluation. The impact of the potentially wider spectrum of benefit from the use of high-dose statin in patients already treated with standard doses requires assessment. Elucidation of the role of such treatment among patients with poor prognosis after an acute coronary event, such as diabetic patients, is equally necessary. Therefore, new large prospective clinical trials are critically required to shed light on these questions and to provide a more comprehensive view of the clinical benefit of early statin treatment in patients with acute coronary syndromes.

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