Mechanisms of acute coronary syndromes and the potential role of statins

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Abstract

The conventional concepts of the pathogenesis of acute coronary syndromes are changing. High-risk lesions are not necessarily the angiographically 'tight' stenoses. Rather, vulnerable lesions are those that are unstable, with a large lipid core and a thin fibrous cap. Plaque instability is closely related to the development of inflammation within the intima and acute coronary syndromes result from rupture of a vulnerable atherosclerotic plaque. Stabilization of lesions by modification of structure and content, rather than simple improvement in the luminal diameter, provides a new therapeutic target. Stabilization may be accomplished through lifestyle changes and appropriate pharmacologic therapy. In the past few years, it has become evident that a major beneficial effect of statins is to induce plaque stability and regression. In fact, statins, in addition to lowering low-density lipoprotein cholesterol, have a variety of pleiotropic, or cholesterol-independent, effects that make them a particularly suitable choice in patients with acute coronary syndromes. Among these are improvements in endothelial function, smooth muscle cells, thrombus formation/platelet function, and inflammation. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Atherosclerosis, the underlying cause of acute coronary syndromes (unstable angina and acute myocardial infarction (AMI)), is a chronic disease that may progress silently for many years. However, evidence is emerging that the key factor affecting the risk of coronary events in patients with atherosclerosis is the composition of the plaque rather than its size.

More than a dozen angiographically monitored trials show that lipid lowering with potent agents in combination or with diet alone can decrease the diameter of the fixed stenoses — but very little. At the same time, however, there is a resounding and consistent reduction in the combined events, which averages about 50% across the published studies [1]. Thus, the functional state of the atheroma, not merely its size or the degree of luminal encroachment, determines the propensity for development of acute coronary syndromes. In fact, Falk and colleagues have shown that the infarct-related lesions is usually less than 50% stenosed (Fig. 1) [2].

2. Endothelial dysfunction and the biology of atherosclerosis

Endothelial dysfunction is now recognized as an initiating event in the development of atherosclerosis. All the risk factors for coronary artery disease independently produce endothelial dysfunction, which can be detected well before the presence of anatomic vascular lesions (Fig. 2) [3]. The dysfunctional endothelium produces less nitric oxide (NO), which is the most important endogenous vasodilator. NO also inhibits platelet aggregation and reduces leukocyte adhesion to the endothelium. The dysfunctional endothelium also becomes a prothrombotic surface by an imbalance in the production of plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (tPA) and facilitates interaction with circulating leukocytes through increased expression of adhesion molecules.

In addition to its role in the development of atherosclerosis, recent data suggest that the degree of endothelial dysfunction can predict the risk of future cardiovascular complications, even in patients with only mild coronary disease [4,5].
Biomechanical, molecular, and cellular events may affect the fibrous cap [6]. The evolution of atherosclerosis starts with the T lymphocyte, an inflammatory cell involved in host defenses. The T cell can signal the smooth muscle cell, which is the source of arterial collagen, to decrease synthesis of new collagen molecules. The T cell can also send signals to macrophages, which accumulate in vulnerable lesions, to augment their production of a series of enzymes, including matrix metalloproteinases (MMPs) [7]. When inflammation is due to an excess of inflammatory components in the intima, the collagen fibril and the fibrous cap are in double jeopardy: they may undergo decreased synthesis of new collagen molecules and increased breakdown of structural molecules of the extracellular matrix. These conditions set the stage for acute coronary syndromes [8].

Thrombogenicity is another important aspect in plaque vulnerability; tissue factor is one of the key instigators of thrombus in the core of the atherosclerotic plaque. That is why it is so important to keep the blood from coming into contact with the lipid core — the macrophage foam cells in the atherosclerotic lesion are the overexpressing tissue factor.

The usual soluble cytokines in the atherosclerotic plaques, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), do not induce macrophage tissue factor expression. T cells, however, can induce macrophages to express the tissue factor gene by contact. The CD40 signaling system is important in this process [9–11].

Inflammation constitutes an important component of the developing atheromatous lesions. Plasma markers of inflammation such as C-reactive protein (CRP), serum amyloid A, and interleukin-6 are elevated in acute coronary syndromes. Elevated CRP on admission or at discharge represents an indicator of recurrent events, suggesting that more vulnerable plaques demonstrate ongoing inflammation. Infectious agents such as Chlamydia pneumoniae could contribute to this inflammatory component of atherosclerosis [12–17].

Conventional approaches to restoring viability of stenosed lesions have been revascularization, either surgical or medical. In selected subgroups, revascularization will relieve pain, but it will not prolong life or prevent MI. The phenomenon that we must now tackle is the vulnerable plaque — the plaque that may not cause a narrowing of the artery, and therefore, will not be a target for revascularization. The new therapeutic goal is to stabilize lesions, not to eliminate them, stent them, or squash them.

3. How lipid-lowering agents improve plaque stability

Angiographically monitored trials show that lipid-lowering with potent agents such as statins — but even diet alone — decrease the diameter of fixed stenoses. The angiographic decrease is small, however — perhaps 1–2%. Therefore, other mechanisms must explain why these agents help to improve morbidity and mortality. There is evidence that some statins may also...
inhibit cholesterol accumulation in macrophages, therapy potentially reducing their state of activity [18]. It is clear that lipid lowering results in a reduction in coronary events. However, the statin trials have shown that although different agents achieve similar reductions in LDL cholesterol, they have varying effects in reducing coronary events [19–21]. This may reflect methodologic or demographic differences between studies, but it may also raise the possibility that different statins have varying effects on non-lipid factors involved in plaque stabilization [22].

3.1. Endothelial function

Endothelial function improves during cholesterol-lowering therapy in patients with acute coronary syndromes. In the Reduction of Cholesterol in Ischemia and Function of the Endothelium (RECIFE) trial, 60 patients with acute coronary syndromes were randomly assigned to placebo or to pravastatin during hospitalization. Brachial endothelial function was measured before and after 6 weeks of therapy. Flow-mediated vasodilatation improved in the statin-treated patients but not in the control subjects. Part of this improvement in endothelial function could be related to lowering of cholesterol, especially oxidized LDL (Fig. 3) [23]. Part of it may also be independent of cholesterol reduction, as demonstrated in vascular reactivity studies in monkeys [24] as well as in vitro studies showing an increase in the expression of the enzyme response for NO synthesis, endothelial NO synthetase [25,26].

3.2. Effects on thrombus formation

If plaque rupture occurs, inhibition of platelet aggregation and coagulation and activation of fibrinolytic mechanisms become important in preventing thrombosis. Several studies have investigated the effects of different statins on fibrinogen levels and blood viscosity, both of which are risk factors for coronary events. However, results of these studies are inconsistent and probably reflect problems in accurately measuring levels of acute-phase proteins such as fibrinogen. In one study, pravastatin, but not simvastatin, reduced fibrinogen levels over 6 months [27], whereas in another, more recent, study, pravastatin caused a small increase in fibrinogen levels [28]. Atorvastatin also increased this marker [29]; lovastatin increased fibrinogen over 6 months in one study [30] and decreased it over 12 months in another [31]. Pravastatin has also been found to reduce blood and plasma viscosity [27], whereas simvastatin had no effect on these variables [27,32].

Increased PAI-1 levels are also predictors of coronary disease. Pravastatin has been shown to reduce PAI-1 activity levels [33,34], and to increase tPA levels [34]; with simvastatin [35] and atorvastatin [36], PAI-1 levels have been reported to increase. Lovastatin has been reported to both reduce and increase this marker [36,37], whereas a study of fluvastatin showed no effect on PAI-1 antigen or activity [38].

Due to the inconsistency of these findings and the fact that few investigators have directly compared different statins in the same study, the data from these studies must be interpreted cautiously until further, more consistent data are available. Nevertheless, it appears likely that statins do not have a uniform effect on these variables, i.e. they do not exert a ‘class effect’.

Studies of the effects of statins on platelet aggregability have also yielded inconsistent effects. Lovastatin increased platelet counts and ADP-induced aggregation in one study [30] and reduced it in another [31]. Using an ex vivo bioassay of thrombus formation on a damaged endothelial surface, Lacoste et al. showed that blood from hypercholesterolaemic persons forms a larger platelet thrombus than blood from normcholesterolaemic persons and that this increased platelet aggregation is significantly reduced with pravastatin therapy [39], but not with simvastatin [40] at an equivalent LDL-lowering dose. This antithrombotic effect of pravastatin has been demonstrated in blood from patients with and without overt coronary artery disease and in those receiving and not receiving aspirin [41]. These carefully controlled studies appear, therefore, to support a significant antiplatelet effect of pravastatin, and this may not be common to all statins.

3.3. Inflammation

Atherosclerosis is a low-grade inflammatory process, and high blood levels are markers of inflammation are associated with an increased risk of coronary events. High-sensitivity CRP (hs-CRP), a nonspecific acute-phase reactant, has been studied more extensively than other inflammatory markers. Studies show that elevated levels of hs-CRP impart an increased risk of acute coronary events (Fig. 4) [42].

In the CARE study, the investigators examined whether inflammation after myocardial infarction is a
risk factor for recurrent events and whether pravastatin could reduce the risk. In patients in whom inflammation was present, pravastatin yielded a 54% risk reduction, compared with a 24% risk reduction in the overall trial [15].

The Pravastatin Inflammation CRP Evaluation study (PRINCE), discussed in more detail by Braunwald in this supplement, is examining whether lipid-lowering therapies such as pravastatin can attenuate the inflammatory process. This study should establish the time course of pravastatin’s effect on hs-CRP levels, determine whether an early effect on hs-CRP is independent of pravastatin’s effect on LDL cholesterol, and whether the anti-inflammatory effect of pravastatin in reducing hs-CRP is similar in magnitude among primary- and secondary-prevention patients.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) study will be examining whether early and aggressive lipid-lowering therapy with atorvastatin (80 mg) is superior to pravastatin in terms of morbidity and mortality, but it will also examine the effects of gatifloxacin therapy to determine whether it will affect the inflammatory component of atherosclerosis. This study is in the enrollment phase. The BRAVER substudy of PROVE IT will specifically examine the effects of these statins on endothelial function.

3.4. Smooth muscle cell viability

Early studies in cholesterol-fed rabbits showed that treatment with pravastatin reduces macrophage content and increases the content of smooth muscle cells in atherosclerotic lesions. Williams and colleagues [43] showed that pravastatin reduced macrophage content, calcification, and new vessel formation in atherosclerotic monkeys, without affecting lesion size, independent of its effects on lipids. It is important that smooth muscle cells remain viable because they confer stability to atherosclerotic plaques. Experimental studies have examined the effects of statins on cell viability in cultures of human femoral and rat smooth muscle cells and in carotid arteries of rabbits. These studies showed that pravastatin, which is primarily hydrophilic, has no effect on smooth muscle cell proliferation, even in very large concentrations. Statins that are mainly lipophilic — atorvastatin, cerivastatin, fluvastatin, lovastatin, and simvastatin — decrease cell viability (Fig. 5) [44]. Thus, pravastatin appears to be unique among the statins in not inhibiting smooth muscle cell activity. Theoretically, at least, pravastatin is more likely that the other statins to facilitate smooth muscle cell maintenance of the fibrous cap. The beneficial effect of the smooth muscle repair process on plaque stability may be demonstrated by the experience with balloon angioplasty. This procedure renders the target lesion acutely unstable, requiring aggressive antiplatelet therapy to prevent short-term occlusion and inducing a vigorous, smooth muscle cell-driven repair process that can sometimes lead, in the long term to restenosis. However, a restenotic lesion is rarely if ever unstable.

4. Conclusions

There is encouraging evidence that after an acute coronary syndrome, early therapy with statins can stabilize the process of coronary artery stenosis, improve endothelial function, and — most important — reduce the incidence of further coronary events. Our increased understanding of the cellular interactions in atherosclerosis has emphasized the importance of inflammation in precipitating clinical events and of smooth muscle cells in preventing them. The evidence that atherosclerosis is an inflammatory process also provides us with potential opportunities to use surrogate inflammatory markers such as hs-CRP to identify persons with unstable disease who will benefit from statin treatment. Since statins do not have a uniform effect on the biologic processes contributing to plaque rupture and subse-
quent thrombosis, the potential benefit from treatment with a statin cannot necessarily be presumed or predicted from its lipid-lowering potency alone. Therefore, the use of statins for primary and secondary prevention of cardiovascular events should be confined to those that have been proved to have a net beneficial effect on outcome.

References


