Evaluation of Statins in Decreasing the Early Mortality and Morbidity of Acute Coronary Syndrome

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Abstract

Background- Lipid-lowering therapy with statin reduces the risk of cardiovascular events in acute coronary syndrome (ACS). Preclinical and clinical evidence also indicates that in addition to its lipid-lowering effects, statin may reduce inflammation improve endothelial function and increase plaque stability.

Methods- We enrolled 220 patients who had been hospitalized for an acute coronary syndrome (unstable angina, non-ST elevation MI) within the preceding 30 days and compared 20 mg of simvastatin daily (*group B*) with patients not receiving that (*group A*). The primary end point was a composite of deaths, myocardial infarction, documented unstable angina requiring re-hospitalization, and urgent revascularization (performed at least 30 days after randomization). Follow-up lasted for one month.

Results- Median LDL cholesterol level achieved during treatment was similar; 90 mg/dl in group B and 87.1 mg/dl in group A (P> 0.05). Chi-square and t-test estimates of the rate of the documented unstable angina requiring hospitalization were 26.4 percent in group B and 31 percent in group A (odds ratio= 4.5; 95% CI= 2.4-6; P= 0.01). Revascularization and early angiography was 20.9 percent in group B and 48.2 percent in group A (odds ratio= 3.5; 95% CI= 1.9-6.3; P< 0.001). Group B had a lower risk of myocardial infarction after admission due to acute coronary syndrome (odds ratio= 4; 95% CI= 1.1-6; P<0.001), reflecting a reduction in mortality (0.9% in group B and 2.7% in group A), but this difference was not significant (P= 0.6), at least partially because of the relatively small number of mortalities in this study (1.8%).

Conclusion- Early use of simvastatin in ACS appears to decrease risk for cardiovascular events. We believe statin therapy should be initiated early (at the latest before hospital discharge) in all patients who have been hospitalized for acute coronary syndrome (*Iranian Heart Journal 2007; 8 (2): 6-15*).

Key words: acute coronary syndrome ■ blood lipids ■ statins ■ mortality ■ morbidity

Recent research has shown that inflammation plays a key role in coronary artery disease (CAD) and other manifestations of atherosclerosis.

Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndromes.

It will recount the evidence that atherosclerosis, the main cause of CAD, is an inflammatory disease in which immune mechanisms interact with metabolic risk factors to initiate, propagate, and activate lesions in the arterial tree. A decade ago, the treatment of hypercholesterolemia and hypertension was expected to eliminate CAD by the end of the 20th century. Lately, however, that optimistic prediction has needed revision. Cardiovascular diseases are expected to be the main cause of death globally within the next 15 years owing to a rapidly increasing prevalence in developing countries and Eastern Europe and the rising incidence of obesity and diabetes in the Western world.[1] These facts have led scientists to revisit cardiovascular disease and consider new strategies for prediction, prevention, and treatment.[2]

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.[3] 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 two clinically distinct forms of CAD, i.e., 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. Statin therapy positively influences the equilibrium between atherogenic and anti-atherogenic lipoproteins, favoring reverse cholesterol transport and leading to beneficial changes in the composition, structure and stability of atherosclerotic plaques.[4] 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 effects[13] and could result from: (1) actions dependent on lipid lowering; (2) actions 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.[5]

In the following discussion, we will 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

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. By inhibiting HMG-CoA reductase, statins inhibit the mevalonate pathway and, consequently, reduce the intracellular pool of isoprenoids, thereby down-regulating the prenylation process. Reduced prenylation of the Rho protein, in turn, down-regulates activation of $NF_{-k}B$ 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.

Statins reduce plasma LDL levels, thereby decreasing substrate available for generation of oxidized LDL; oxidized LDL can inactivate NO and equally down-regulate endothelial NOS expression.

By reduction of LDL substrate and also by a direct mechanism, statin treatment increases NO bioavailability and decreases monocyte adhesion to endothelial cells (Fig. 1).
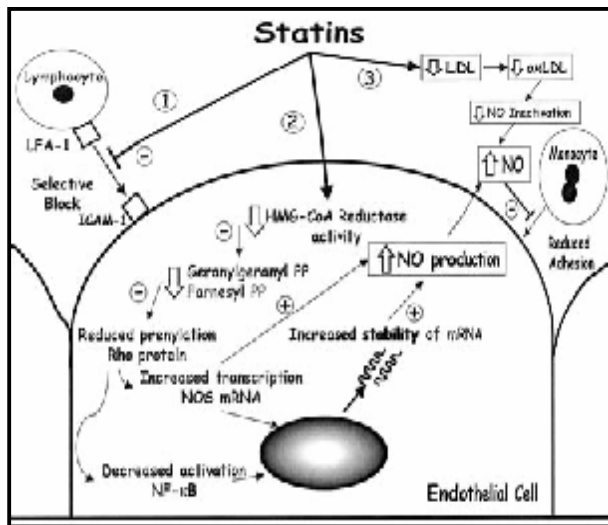

Fig. 1. Anti-inflammatory actions of statins.

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.[6] As a consequence, the anti-inflammatory effect of statins in patients with acute coronary syndromes and augmented inflammatory activity requires separate consideration.[5]

Overall, an enhanced thrombogenicity has been observed in patients who develop an acute coronary event compared with those who display a stable evolution.[4] Such increased tissue or blood thrombogenicity could result from an 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 three-month period of treatment with either pravastatin or simvastatin, even in patients already treated with aspirin.[7,8] Tissue thrombogenesis mainly results from plaque TF expression, and statin treatment attenuates such expression.

Therefore, statin therapy influences the process of thrombus formation by a combination of actions on blood and tissue thrombogenicity (Fig. 2).[5]
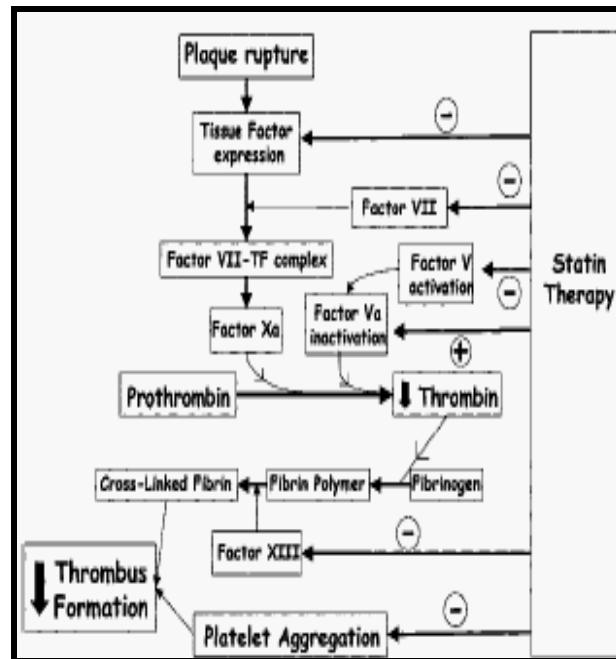
Fig. 2. Effects of statins on thrombus formation. Statin treatment attenuates TF expression on macrophages, reducing activation of the coagulation cascade. Once the cascade is activated, statins reduce thrombin formation by reduction in factor VII coagulation activity and mass, inhibition of factor V activation, and increase in factor Va inactivation. Finally, statins inhibit factor XIII activation, reducing the formation of a stable clot; in addition, statins attenuate platelet aggregability, thereby reducing thrombus formation.

Statin Action 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 anti-atherogenic HDL, in addition to the effects independent of lipid lowering, result in the amelioration of endothelial function.

In consequence, the coronary artery responds to those stimuli with an adaptive dilation, thereby attenuating the ischemic insult (Fig. 3). [5]
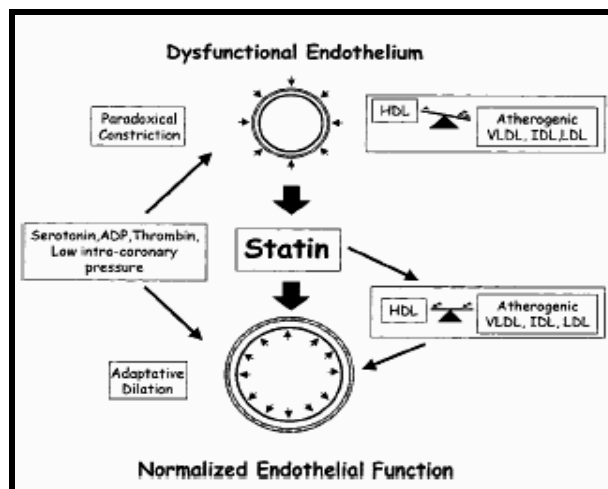
Fig. 3. Effects of statins on endothelial dysfunction.

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.[9,10] 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.[11] 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.[12] 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.[5]

In conclusion, statins are potent inhibitors of cholesterol biosynthesis and exert beneficial effects in the primary and secondary prevention of coronary artery disease. Be that as it may, the overall benefits observed with statins appear to occur much earlier and to be greater than what might be expected from changes in lipid levels alone, suggesting effects beyond simple cholesterol lowering. Indeed, recent studies indicate that some of the cholesterol-independent or "pleiotropic" effects of statins involve improving endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response. Many of these pleiotropic effects are mediated by the inhibition of isoprenoids, which serve as lipid attachments for intracellular signaling molecules. In particular, inhibition of the small guanosine triphosphate–binding proteins Rho, Ras, and Rac, whose proper membrane localization and function are dependent on isoprenylation, may play an important role in mediating the pleiotropic effects of statins.[14]

Blood cholesterol control with statins has been regarded as a long-term strategy to reduce death and ischemic cardiovascular events in patients with stable coronary heart disease, with significant effects evident after approximately 2 years of treatment. However, it is within the early period after an acute coronary syndrome (ACS) that patients experience the highest rate of death and recurrent ischemic events. Recent studies indicate that statins have salutory physiologic effects within weeks. In conjunction with lowering total and low-density lipoprotein (LDL) cholesterol, statins may improve endothelial function,[15] decrease platelet aggregability and thrombus deposition,[16, 17] and reduce vascular inflammation.[18] Each of these mechanisms might be expected to have a favorable impact in the early period following an ACS.

This study, therefore, tested the hypothesis that treatment with simvastatin (20 mg/d), initiated soon after presentation with unstable angina or non-ST elevation MI (NSTEMI), reduces the occurrence of early, recurrent ischemic events and death.

Methods

Study population

Eligible patients were adults aged 20 years or older that were admitted to our center with unstable angina or non-ST elevation MI (NSTEMI). In addition, diagnosis of unstable angina required evidence of myocardial ischemia by at least one of the following: new or dynamic ST-wave or T-wave changes in at least 2 contiguous standard ECG leads; a new wall motion abnormality by echocardiography; a new and reversible myocardial perfusion defect by radionuclide scintigraphy; or elevation of serum creatine kinase or its MB fraction to a level not exceeding 2 times the upper limit of normal (ULN). Diagnosis of NSTEMI required elevation of serum creatine kinase or its MB fraction, or troponin to a level exceeding 2 times the ULN.

Patients were excluded if the serum LDL level at screening exceeded 100 mg/dL. There was no lower limit on LDL level at entry. Patients were excluded if coronary revascularization was planned or anticipated at the time of screening. Other exclusion criteria were: evidence of ST-elevation MI within the preceding 4 weeks; coronary artery bypass surgery within the preceding 3 months; percutaneous coronary intervention within the preceding 6 months; severe congestive heart failure (New York Heart Association class III or IV); concurrent treatment with drugs associated with rhabdomyolysis in combination with statins; severe anemia; renal failure requiring dialysis; hepatic dysfunction (alanine aminotransferase greater than 2 times ULN); pregnancy or lactation.

Study Design

The study was performed in accordance with the ethical principles set forth in the Declaration of Helsinki and was approved by local ethics committees. Written informed consent was obtained from all patients. Between 24 and 48 hours after hospital admission, eligible patients were randomly assigned with stratification by center to double-blind treatment with simvastatin (20 mg/d, group B) or matching patients not receiving that (group A) for 30 days. The protocol did not restrict or specify any other diagnostic or therapeutic measures, except as noted in the exclusion criteria. All patients received instructions and counseling to promote compliance with a National Cholesterol Education Program Step II diet. Patients were seen on follow-up 2 and 4 weeks after the initiation of therapy. Laboratory testing was performed centrally at baseline and at 4 weeks. An independent data and safety monitoring board reviewed the results of 3 planned interim analyses using $P<0.01$ for the primary end point analysis as a statistical stopping guideline. On each occasion, continuation of the study was recommended.

End Points

Patients were monitored for ischemic events for 4 weeks after randomization. The primary combined end point was death, non-fatal acute MI, fatal acute MI, or recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalization or urgent angiography and revascularization due to ongoing ischemia. Cardiac arrest with resuscitation and recurrent symptomatic myocardial ischemia with objective evidence and emergency rehospitalization were diagnosed according to previously published criteria.[19] The latter diagnosis required both exacerbation of the patient's usual symptoms and new objective evidence of ischemia (electrocardiographic, echocardiographic, or scintigraphic).

Statistical Analysis

The initial sample size requirement was 220 patients, based on the assumption of 10-15% occurrence of a primary end point event among treated-untreated patients. The primary combined

end point was analyzed by time of first event, using a Cox proportional hazards model.[20] The occurrence of each end point was analyzed using the Cochran Mantel-Haenszel method,[21] stratified by inclusion event. All end point analyses were performed on an intention-to-treat basis, with all randomized patients included in the analyses. Censoring occurred for patients who did not experience an end point prior to completing the study as planned or prior to early withdrawal from the study. In the case of censoring, the survival time corresponded to the day of final study contact. Interaction of treatment assignment with baseline demographic and clinical characteristics and baseline lipid levels was examined. A significance level of *P=0.01* was used for each interim analysis, with a significance level for the final analysis adjusted to *P=.049* to adhere to the overall type I error rate at *P*=0.05. The testing of all secondary objectives was done at the 2-sided *P= 0 .05* level of significance.

Results

Patient Population

Between April 2004 and April 2005, 220 patients were enrolled; 110 were randomly assigned to receive simvastatin (Group B) and 110 did not receive simvastatin (Group A). Demographic and clinical characteristics of the 2 treatment groups were similar at baseline (Table I).

Table I. Baseline characteristics of the patients.

Characteristic	Control (A Group) (n = 110) No. (%) of Patients	Simvastatin (B Group) (n = 110) No. (%) of Patients	P value
Age, mean (SD), yr	68 (10)	70 (10)	>0.05
Women	37 (33.6)	36 (32.7)	>0.05
Inclusion event: *-Unstable angina* *- NSTEMI*	60 (54.5) 40 (45.5)	60 (54.5) 40 (45.5)	>0.05 >0.05
Time from hospital admission to randomization, mean (SD), hr	31 (12)	31 (12)	>0.05
Coronary risk factors: *-Current smoking* *-Hypertension* *-Diabetes mellitus* *-Family history*	26 (23.6) 45 (40.9) 13 (11.8) 6 (5.5)	31 (28.2) 66 (60) 21 (19.1) 9(8.2)	>0.05 >0.05 >0.05 >0.05

Similar medications were administered to all patients, both prior to and after admission to hospital for the inclusion ischemic event. Aspirin, heparin, low molecular weight heparin (Enoxaparin), nitrates, and beta-blockers were administered to a majority of patients.

Serum Lipid Levels
At the time of randomization, serum LDL levels were nearly identical in both groups and showed similar levels with mean LDL cholesterol level of 87.1 mg/dL in group A and 90 mg/dl in group B (P>0.05).

End Point Events
A total of 23 patients in group B (given 20 mg of simvastatin) and 39 patients in group A had a primary event during the study, representing an event rate of 20.9 percent and 35.4 percent, respectively. This rate was equivalent to an absolute reduction of 14.5 percent in the group given simvastatin.

Outcomes for individual components of the primary end point are shown in Table II. Relative reductions in the risk of death from CAD, myocardial infarction, unstable angina requiring re-hospitalization and early angiography and revascularization due to ongoing ischemia with treatment with 20 mg of simvastatin, as compared with group A were all consistent with the reduction observed for the primary composite outcome. There was no statistical interaction for age or sex in the primary outcome measure.

The rate of the documented unstable angina requiring rehospitalization was 31% in group A and 26.4% in group B (odds ratio= 4; 95% confidence interval, 2.4 to 6; P=0.01). Also, urgent angiography and revascularization due to ongoing ischemia was 20.9 percent in group B and 48.2 percent in group A (odds ratio= 3.5; 95% confidence interval, 1.9 to 6.3; P< 0.001).

The rate of MI after admission due to acute coronary syndrome in the following thirty days was 10.9 percent in group A and 2.7 percent in group B (odds ratio=4; 95 percent confidence interval1.1 to 6; P<0.001).

The risk of death from any cause during the following 30 days was 2.7 percent in group A and 0.9 percent in group B, and it did not differ significantly between the two groups (odds ratio, 1.01; 95 percent confidence interval, 0.85 to 1.19; P=0.6).

No significant increase in adverse events of any type was identified among the patients who had very low levels of LDL cholesterol (less than 70 mg/dl), as compared with those with higher levels (Table II).

Discussion

In this trial, early treatment with simvastatin 20 mg/d reduced recurrent ischemic events over a one-month treatment period among patients with unstable angina or NSTEMI.

Table II. Estimated odds ratio for individual components of the efficacy outcomes.

Outcome	Group B (N= 110) No. (%)	Group A (N= 110) No. (%)	Odds Ratio (95% CI)	P Value
Death	1 (0.9)	3 (2.7)	1.01 (0.8 – 1.1)	0.06
Unstable angina requiring rehospitalization	28 (26.4)	35 (31)	4 (2.4 – 6)	0.01
Early angiography and revascularization	53 (48.2)	23 (20.9)	3.5 (1.9 – 6.3)	<.001
Myocardial infarction	12 (10.9)	3 (2.7)	4 (1.1 – 6)	<.001

There was a 14.5% absolute reduction and a 17% relative reduction in the primary combined end point of death, non-fatal acute MI, or worsening symptomatic myocardial ischemia with objective evidence and emergency re-hospitalization and revascularization. This study was not powered to detect differences between both groups in the individual components of the primary composite end point. Also, our data is reflecting a reduction in mortality (0.9 percent in group B and 2.7 percent in group A), but this difference was not significant (P= 0.6), at least partially because of the relative small numbers of mortality rate in this study (1.8%).

Most of the inter group difference in the combined primary end point resulted from a reduction in recurrent symptomatic myocardial ischemia with objective evidence and emergency rehospitalization (absolute risk reduction 14% in the simvastatin group; P=0.001).

Patients with ST elevation MI were excluded from this study because factors that are unlikely to be affected by cholesterol lowering, such as left ventricular dysfunction, ventricular arrhythmias, and mechanical complications represent the major determinants of short-term outcome.

Patients for whom a coronary revascularization procedure was planned or anticipated at the time of screening were excluded so that adverse events related to the procedures or to restenosis after angioplasty would not complicate assessment of the effect of simvastatin treatment. Despite a low rate of revascularization and rehospitalization, patients in our trial experienced a similar incidence of death as patients in another large, contemporary trial of ACS.[22] In comparing event rates among trials, it is noteworthy that our trial did not include as end points events that occurred during the median 31-hour period between hospital admission and randomization.

There is difficulty in identifying non-lipid statin effects in clinical studies. Because of their excellent lipid-lowering potential, statins always modify serum cholesterol levels to some extent and thus, it is impossible to differentiate possible lipid-independent effects from those associated with lipid reduction, especially if these effects are complementary. Furthermore, analysis of the basic mechanisms behind an observed statin effect (e.g. addition of isoprenoid intermediates to further define the pathways involved in the mechanism responsible for a specific statin effect) may not be possible in the *in vivo* setting. The only way to directly assess effects unrelated to the modification of plasma cholesterol levels is to study the very short-term statin effects which appear within the first days or even hours after initiation of therapy before changes of plasma cholesterol levels occur. On the other hand, we can only assume the existence of non-lipid effects in humans by indirect evidence, by comparing groups which show similar cholesterol levels despite presence or absence of statin treatment, or by treating normo-cholesterolemic patients with these drugs.[23]

In this study, the benefit of treatment with simvastatin was observed in a population with a similar mean baseline LDL cholesterol level (87.1 mg/dl in group A and 90 mg/dl in group B, P= 0.08). Also, follow-up duration was 30 days in this study.

Simvastatin was generally well-tolerated in this patient population. There were no documented cases of myositis, which is the most serious adverse effect of statins. Levels of serum transaminases exceeding 2 times the ULN were not detected in simvastatin-treated patients.

Results from this clinical trial suggest that early administration of simvastatin following an acute coronary syndrome reduces short-term adverse outcomes such as subsequent cardiovascular events (myocardial infarction, unstable angina requiring re-hospitalization, urgent angiography, and revascularization). The potential mechanisms of benefit include improvements in endothelial function and vasomotion, reduction of platelet aggregability and thrombus formation, fibrinolytic and antioxidant activity as well as reduction of inflammation within plaques, reducing matrix degradation due to reduction of macrophage metalloproteinase production and increasing collagen content.

Based on the available evidence and in light of the understanding that statins have pleiotropic effects, especially as a potent anti-inflammatory agent, it might be concluded that patients hospitalized for ACS should be given a statin and the treatment should be initiated as soon as possible.

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Left Ventricular Wall Motion Score Index as an Early Predictor of Hemodynamic State after Myocardial Infarction

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Abstract