

## Anti-Thrombotic Effects of Statins in Acute Coronary Syndromes: At the Intersection of Thrombosis, Inflammation, and Platelet-Leukocyte Interactions



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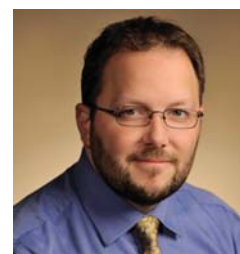
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### ARTICLE HISTORY

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**Abstract:** HMG CoA reductase inhibitors, or statins, are standard of care for preventing cardiovascular disease in at-risk populations. Statins are a well-established therapy proven to reduce long-term cardiovascular mortality and morbidity for prevention of secondary cardiovascular events and have become guideline-recommended therapy following acute myocardial infarction. Emerging data from clinical trials over the last decade indicates that statin therapy may provide broad beneficial effects beyond their primary lipid lowering mechanisms. In coronary heart disease, statins have demonstrated a unique ability to target several cellular pathways, which appear to play an underappreciated role in acute inflammation and subsequent thrombosis. Herein, we review the potential mechanisms where statins may act as antithrombotic agents in the setting of acute coronary syndromes and discuss the clinical implications of these findings.



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**Keywords:** Statin, anti-thrombotic, thrombosis, inflammation, platelets.

### INTRODUCTION

HMG CoA reductase inhibitors, or statins (Table 1), have been used in the treatment of cardiovascular disease for nearly two decades [1, 2]. In numerous clinical trials, reducing LDL cholesterol with statin therapy has been associated with improvements in major cardiovascular events, with a close correlation between the degree of lowering LDL cholesterol and the magnitude of the clinical benefit [1]. In the setting of percutaneous coronary interventions and acute coronary syndromes, early administration of statin therapy may improve cardiovascular outcomes [3, 4] and the protection from recurrent ischemic events may occur before any significant lipid lowering effect [3, 5]. Some proposed mechanisms include anti-inflammatory effects, improvement in endothelial function, decrease in oxidative stress, and inhibition of thrombogenic responses [6]. These LDL cholesterol-independent functions are collectively referred to as the “pleiotropic effects” of statin therapy. More recently, investigators have begun to understand the interplay between these complex signaling pathways. Herein, we review the antithrombotic and anti-inflammatory effects of statins that occur within the first week of administration in the setting of acute coronary syndromes and percutaneous coronary interventions and discuss clinical implications of these findings.

**Table 1. Commonly Prescribed Statins.**

| Generic Name | Trade Name |
|--------------|------------|
| Atorvastatin | Lipitor    |
| Fluvastatin  | Lescol     |
| Lovastatin   | Mevacor    |
| Pravastatin  | Pravochol  |
| Rosuvastatin | Crestor    |
| Simvastatin  | Zocor      |

### PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES AND THE RESPONSE TO ARTERIAL INJURY

Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations ranging from ST-segment elevation myocardial infarctions (STEMI) to non-ST-segment elevation myocardial infarctions (NSTEMI) and unstable angina. These entities are often associated with rupture or erosion of an atherosclerotic plaque resulting in partial or complete occlusion of a coronary artery as a consequence of platelet activation and thrombus formation along the site of vascular injury. In addition to platelet aggregation, cellular adhesion proteins, including P-selectin, are also expressed, recruiting leukocytes to the platelet initiated thrombus. Vasoconstrictors, such as serotonin and thromboxane A<sub>2</sub>, are

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released or generated during platelet activation and this may contribute to reduced blood flow. Other vasoactive substances, extracellular matrix and tissue factor may be exposed [7], and endothelial disruption causes a reduction in endothelial NO synthase (ENOS) with concomitant reduction in nitric oxide (NO). Altogether, these and other changes can reduce coronary flow and potentiate thrombus formation. The response to arterial injury, which occurs following angioplasty or stent deployment, shares features with ACS including rapid platelet accumulation and leukocyte recruitment.

### STATIN THERAPY PRIOR TO PERCUTANEOUS CORONARY INTERVENTIONS

A unique population well suited to assess statin therapy efficacy early in thrombosis is patients undergoing percutaneous coronary intervention (PCI). In this population acute vascular trauma occurs at a planned period (at the time of PCI), therefore statins can be administered for a brief time prior to the injury to study effects on inflammation, thrombosis and outcomes

The ARMYDA investigators examined early atorvastatin dosing in several interventional settings. The initial ARMYDA study examined 7 days of statin dosing prior to undergoing planned PCI in 153 stable angina patients who were statin naive. The study was not powered for clinical events, but evaluated evidence of myocardial necrosis as measured by creatine kinase-muscle and brain (CK-MB), troponin, and myoglobin at 8 and 24 hours. The primary outcome incidence of MI (as measured by CK-MB) was detected after coronary intervention in 5% of patients in the statin group and in 18% of those in the placebo group ( $p=0.025$ ). Peak CK-MB, troponin, and myoglobin, all demonstrated significant reductions in the statin group compared to placebo ( $p<0.01$ ) [8]. Building on these findings, the investigators examined the benefit of repeating a statin “load” prior to PCI in patients on stable statin doses. In this study of 383 patients, the primary endpoint of death, MI, or unplanned revascularization, occurred in 3.7% of patients treated with atorvastatin preload and in 9.4% in the placebo ( $p=0.037$ ). Similarly, reductions in cardiac biomarkers were noted in those patients receiving high dose statin prior to PCI versus routine statin maintenance [9].

The NAPLES II trial examined the potential benefit of a single dose of atorvastatin 24 hours prior to undergoing elective PCI [10]. In their investigation of 668 patients, the incidence of a periprocedural MI was 9.5% in the atorvastatin group and 15.8% in the control group (OR: 0.56; 95% confidence interval: 0.35 to 0.89;  $p=0.014$ ). This resulted in a dramatic 44% relative risk reduction for a single dose of 80 mg of atorvastatin. Overall, thirteen studies have been pooled and observed consistency in the lowering of periprocedural myocardial infarction in the groups that were pretreated with a statin prior to PCI [11].

### EARLY CLINICAL RESPONSE TO STATINS IN ACUTE CORONARY SYNDROMES

The first study of early statin therapy in ACS patients was the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trial [5]. In MIRACL,

3086 participants were randomized to receive high dose atorvastatin (80mg) within 1-4 days of presentation versus placebo. The primary endpoint of death, MI, and recurrent symptomatic myocardial ischemia at 16 weeks occurred in 14.8% in the atorvastatin group and 17.4% in the placebo group (relative risk [RR], 0.84; 95% confidence interval [CI], 0.70-0.999;  $P=.048$ ), although this was primarily driven by symptomatic ischemia (6.2% versus 8.4%; RR, 0.74; 95% CI, 0.57-0.95;  $P=.02$ ). MIRACL demonstrated a clinical benefit of statin in ACS, however, these benefits were thought to be largely driven by a reduction of cholesterol.

Evidence of an acute benefit of statin therapy was observed in the ARMYDA-ACS (Atorvastatin for Reduction of Myocardial Damage during Angioplasty) study. As with MIRACL, the trial studied high-dose atorvastatin (80 mg) in a much smaller population of 171 patients. Statin therapy was initiated upon presentation, at least 12 hours prior to percutaneous coronary intervention (PCI). In this study, major adverse cardiac events occurred in 5% of patients that took atorvastatin versus 17% of those who received placebo ( $p < 0.01$ ), with the majority of the events being post-procedural myocardial infarction. Significant reductions in the cardiac necrosis biomarkers, creatine kinase-MB and troponin-I, were observed in the atorvastatin group versus the placebo indicating a potential acute protective effect of atorvastatin in patients undergoing PCI [12] in the setting of ACS.

Several additional studies of early statin use failed to meet a primary efficacy endpoint, and thus had results that differed from those described above. These studies suffer from premature study termination or low event rates [4, 13, 14]. For example, in the PACT (Pravastatin in Acute Coronary Treatment) trial, more than 10,000 patients were intended to be enrolled, but the study was terminated due to slow enrollment (3408). The primary composite outcome was negative midway through the trial; the pravastatin dose was increased from 20 mg to 40 mg, with a post-hoc analysis suggesting the treatment benefit was present at the higher, but not the lower dose [14].

### EVIDENCE THAT STATINS HAVE AN EARLY EFFECT ON PLATELETS AND BIOMARKERS OF THROMBOSIS

Many of the adverse clinical outcomes associated with ACS and PCI are driven by thrombosis. Given that subclinical, microvascular thrombosis manifests with elevations in cardiac biomarkers, it is reasonable to speculate that the acute clinical benefit observed with statin therapy may be due to the drug's influence on this process. One of the key factors in arterial thrombosis, especially after PCI and in settings of ACS, is platelet function. Early statin therapy has been shown to acutely affect platelet deposition following vascular injury by reducing granule secretion and thromboxane A<sub>2</sub> release, by nearly 30% [15]. In addition, statins may accentuate the inhibitory effect of aspirin on platelet aggregation [16].

One of the first studies to investigate the short-term effect of statin on *in vivo* platelet activation was conducted on a population of 30 hypercholesterolemic patients with 20 age- and sex-matched healthy volunteers. In this study, Sanguigni

*et al.*, [17] investigated CD40, a member of the tumor necrosis factor family that in soluble form (sCD40L) reflects platelet activation and thrombin generation. In 30 hypercholesterolemic patients (LDL-C = 186±13 mg/dL), baseline plasma levels of soluble CD40L (sCD40L) and prothrombin fragments F1+2 were significantly higher than in 20 age- and sex-matched healthy subjects (LDL-C = 112±13 mg/dL). Hypercholesterolemic subjects had mean values of 4.3 ng/mL for sCD40L and 2.0 nM of F1+2 compared to 2.2 ng/mL and 1.3 nM, respectively, in healthy subjects. Furthermore, upon collagen-induced activation of platelets, platelet surface CD40L was significantly increased in patients with hypercholesterolemia (43.9 A.U vs 30.1 A.U). Further, randomization of hypercholesterolemic individuals to diet and atorvastatin (10 mg/d; n=15) for 3 days lowered platelet CD40L (46.3 AU at baseline to 32.2 AU after 3 days treatment), sCD40L (4.1 ng/mL at baseline to 3.0 ng/mL after treatment), and F1+2 (2.0 nM at baseline to 1.4 nM after treatment). In comparison, subjects treated with diet alone (n = 15) had no significant changes between baseline and 3 days. No difference in lipid profile was observed between the groups and, importantly, did not change after 3 days of atorvastatin treatment.

The effect of statin therapy on CD40L was confirmed by a second study performed by Pignatelli and colleagues [18] who studied rosuvastatin in individuals following a Mediterranean diet. A single dose of rosuvastatin (20 mg) was administered to hypercholesterolemic patients and serum collected at 2 and 24 hours. In the diet-alone group, no differences from baseline were observed in platelet activation or in CD40L at the 2- and 24-hour time points, whereas, the addition of one dose of rosuvastatin reduced platelet recruitment by 30% and platelet CD40L by 36% at 2 hours following the dose. Both platelet recruitment as well as CD40L were further reduced at 24 hours in the rosuvastatin-treated group.

The effect of statin therapy on markers and molecules involved in thrombin generation have also been reported. In a study by Undas *et al.*, thrombin generation was measured in-vivo as collected from wounds generated by skin cuts in patients treated with simvastatin (40 mg). Administration of simvastatin for only 3 days resulted in significant reductions in thrombin formation (baseline 0.258 nmol/L/s vs 0.175 nmol/L/sec at 3 days) and decreased factor Va [19]. In an analysis by Atalar *et al.* [20], high dose fluvastatin (80 mg) administered within 6 hours of ACS presentation, resulted in significantly lower levels of soluble endothelial protein C receptor (EPCR), which would be predicted to reduce thrombin activation. Free tissue factor pathway inhibitor (fTFPI), which can reversibly inhibit Factor Xa, also significantly increased in both groups, although the magnitude of the rise was much greater in the fluvastatin group (450% in fluvastatin group compared to 155% in the placebo group). The downstream effects of these inhibitors and receptor interactions can lead to decreased activity of individual components of the clotting cascade. In fact, dosages as low as 10 mg of atorvastatin inhibited the physiologic increase in anti-thrombin III, Factor V, and von Willebrand factor at 1 week after an ACS [21], results that have been confirmed by other investigators [22]. Altogether, these studies point to a rapid, antithrombotic effect of statins on biomarkers within the

coagulation cascade in hypercholesterolemic individuals and in those presenting with ACS.

## EFFECT OF STATINS ON VENOUS THROMBOSIS

In support of an anti-thrombotic role, statin therapy may lower the rate of venous thromboembolism (VTE), including pulmonary embolism and deep vein thrombosis (DVT). In the JUPITER trial, patients with elevated CRP and healthy levels of LDL-cholesterol were given placebo or rosuvastatin (20 mg per day) in order to investigate the preventive role of statin therapy [23]. A secondary analysis revealed that patients randomized to rosuvastatin were less likely to develop VTE. Out of the 17,802 patients enrolled into JUPITER, 94 patients had a VTE within a median follow-up of 1.9 years: 34 patients were in the rosuvastatin branch and 60 in the placebo branch (p = 0.007) [24]. While there is no data to indicate that statins have an acute effect on VTE, in terms of thrombus resolution or prevention of recurrent thrombotic events, the significant reduction of events observed with rosuvastatin in JUPITER supports additional investigations in an acute setting. In a recent review of VTE and statins, the authors hypothesize that DVTs, inflammation, and statins are interrelated [25].

## EARLY EFFECT OF STATINS ON INFLAMMATION

Several studies have demonstrated that statins have the ability to alter inflammation over the course of several weeks and years. In the landmark JUPITER trial, mentioned above, clinical benefit of rosuvastatin was observed in subjects with normal cholesterol levels and elevated hs-CRP [23]. Post-hoc analysis suggested that the greatest benefit was observed in individuals who had both lowering of LDL-cholesterol and CRP. Sposito *et al.*, [26] demonstrated that statins reduce CRP within 24 hours and the days following acute MI in a dose-dependent manner. In their study, patients were divided into 5 groups; no early dose statin, groups receiving early statin therapy at 20 mg/day, 40 mg/day, or 80 mg/day, and the remaining group receiving 80 mg/day, 48 hours after admission. Each patient group maintained their respective doses until 7 days after admission, at which point all patients were switched to 20 mg/day simvastatin. On the second day patients receiving the early statin treatments had significantly less plasma CRP than the no-dose and late dose statin groups. Statin has a dose-dependent effect on CRP, with the lowest CRP levels associated with highest simvastatin doses. Similar dose-dependent reductions were observed in IL-6 and TNF- $\alpha$  at 5 days following treatment. Collectively, these data suggest early dose statins can dampen the inflammatory response that follows myocardial infarction and could be mechanistically important for the acute clinical benefits of early statin therapy. Statins also reduce the production and release of cytokines involved with inflammation (IL-6, IL-8, TNF- $\alpha$ , CD40 ligand) and thus reduce CRP independently of LDL [27].

## PLATELET-LEUKOCYTE AGGREGATES AS A LINK BETWEEN INFLAMMATION AND THROMBOSIS

Interactions between platelets and leukocytes may be important in the cross-talk between inflammation and

Table 2. Studies with acute effects of statins.

| Study                              | Statin                    | Clinical Setting              | Acute Effect   | Time to Observed Effect | Reference number |
|------------------------------------|---------------------------|-------------------------------|--|-------------------------|------------------|
| ARMYDA                             | atorvastatin              | Angina, PCI                   | Lower CK-MB, troponin, and myoglobin following PCI                   | 7 days                  | [8]              |
| ARMYDA-RECAPTURE                   | atorvastatin              | Angina, PCI                   | Lower MACE, CK-MB, and troponin                                      | 12 hours                | [9]              |
| NAPLES II                          | atorvastatin              | elective PCI                  | Lower CK-MB and troponin   | 24 hours                | [10]             |
| ARMYDA-ACS                         | atorvastatin              | ACS, PCI                      | Lower MACE, CK-MB, and troponin                                      | 12 hours                | [12]             |
| Moscardo A, <i>et al.</i> (2005)   | atorvastatin, simvastatin | vascular injury               | Reduced platelet granule secretion and thromboxane A2 release        | <1 hour                 | [15]             |
| Sanguigni V, <i>et al.</i> (2005)  | atorvastatin              | Hypercholesterolemic patients | Reduced CD40L, sCD40L, and F1+2                                      | 3 days                  | [17]             |
| Pignatelli P, <i>et al.</i> (2012) | rosuvastatin              | Hypercholesterolemic patients | Reduced platelet recruitment and platelet CD40L                      | <24 hours               | [18]             |
| Undas A, <i>et al.</i> (2005)      | simvastatin               | Hypercholesterolemic patients | Reduction in thrombin formation                                      | 3 days                  | [19]             |
| Atalar E, <i>et al.</i> (2005)     | fluvastatin               | Unstable angina, NSTEMI       | Reduction in EPCR, increased tTFPI (Factor X <sub>a</sub> inhibitor) | 6 hours                 | [20]             |
| Sposito A. C, <i>et al.</i> (2011) | simvastatin               | ACS                           | Reduction in CRP, IL-6, and TNF- $\alpha$ following acute MI         | 24 hours                | [26]             |
| Sexton T. R, <i>et al.</i> (2015)  | rosuvastatin              | ACS                           | Reduction in interactions between leukocytes and platelets           | 8 hours                 | [34]             |
| Sexton T. R, <i>et al.</i> (2015)  | rosuvastatin              | ACS                           | Reduction in CRP and MPO   | 8 hours                 | [35]             |

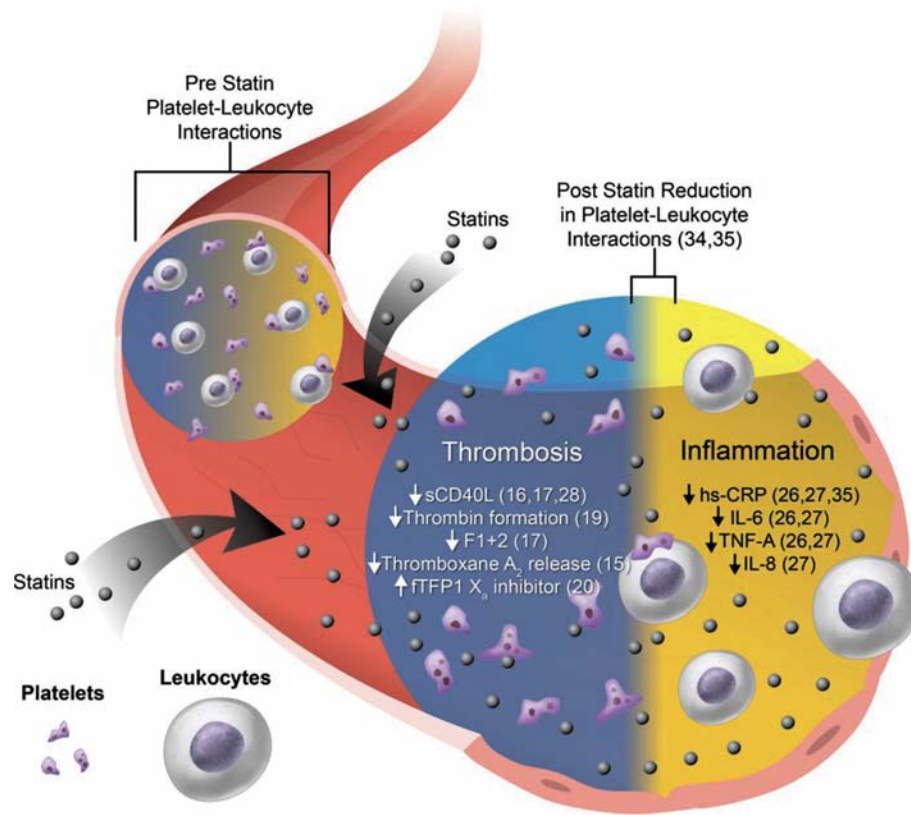
thrombosis. During both inflammatory and thrombotic conditions, platelets and leukocytes physically interact. These interactions are initiated by the platelet surface expression of P-Selectin and by activated  $\beta$ 2-integrins on leukocytes. Platelet-leukocyte aggregations are subsequently stabilized by interactions between GP1b on platelets and  $\alpha$ M $\beta$ 2 integrins on leukocytes. The formation of platelet-leukocyte aggregates increase following acute myocardial infarction [28]. The presence of platelet-leukocyte aggregates correlate with increased CRP and myocardial necrosis in the setting of ACS [29]. Evidence from *in vitro* and animal models indicates that statins decrease interactions between platelets and leukocytes. sCD40, E-Selectin, and ICAM-1 all play a role in the interactions of platelets with leukocytes and endothelial cells and have been shown to be reduced upon statin treatment [17, 30, 31]. In isolated neutrophils and platelets, statins dissociate platelet-neutrophil heterotypic aggregates in a Rho-GTPase-dependent manner [32]. In a rat model of congestive heart failure, rosuvastatin was shown to reduce platelet-leukocyte interactions [33]. More recently, “The Early Use of Rosuvastatin in Acute Coronary Syndrome: Targeting platelet-leukocyte interactions (AVATAR)” trial conducted by our group demonstrated that rosuvastatin reduced interactions between CD11b-expressing leukocytes and platelets within 8 hours of a 40mg dose of rosuvastatin in patients with ACS [34]. Rosuvastatin acutely lowered both monocyte-platelet aggregates and neutrophil-platelet

aggregates [35]. In AVATAR, the reduction in neutrophil- and monocyte-platelet interactions elicited by rosuvastatin were accompanied by acute reductions in plasma CRP and MPO. Importantly, early, high-dose rosuvastatin dampened changes in the myocardial necrosis biomarkers CK-MB and troponin-I as compared to elevated observed in the placebo group [35].

#### CONCLUSIONS – THE ROBUST CLINICAL BENEFIT OF STATIN THERAPY MAY BE MULTIFACTORIAL

In recognition of their benefit, recommendations for early statin therapy has made its way into our clinical guidelines in both acute coronary syndromes and prior to PCI. Compelling evidence exists that clinical outcomes are linked to the drug’s influence on thrombosis, inflammation, and subsequent platelet-leukocyte interactions (Table 2, Fig. 1). The underlying mechanism or mechanisms of the acute effects of statins will likely be elucidated using animal models. Animal models have the distinct advantages over translational and clinical studies of being able to be genetically modifiable as well as having diverse options for *in vivo* study coupled with reduced variability. Still, a further understanding of mechanism coming out of animal models could, in turn, lead to improving how statins are administered clinically.





**Fig. (1). The acute effects of statins on thromboinflammation.** Administration of statins acutely effect the levels of biomarkers for thrombosis and inflammation as well as reduce platelet-leukocyte interactions. References for each biomarker are given in parentheses. Illustration by Matt Hazzard, University of Kentucky, Information Technology.

**DISCLOSURES**

TRS, ELW, and SSS are investigators on the “Early Use of Rosuvastatin in Acute Coronary Syndromes: Targeting Platelet-Leukocyte Interaction” (NCT01241903 on ClinicalTrials.gov).

**CONFLICT OF INTEREST**

The authors confirm that this article content has no conflict of interest.

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Illustration by Matt Hazzard, University of Kentucky, Information Technology.

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