for acute MI with PCI. On-going concerns regarding excessive major bleeding seem to have been allayed by the use of lower doses of intravenous heparin. Whether the small molecule glycoprotein IIb/IIIa inhibitors (eptifibatide, tirofiban) or the intravenous direct thrombin inhibitors (lepirudin) are effective in the setting of PCI and acute MI has not yet been clarified by clinical trial data. In addition, abciximab's metabolizing independent of renal function makes it the ideal agent for use in patients with chronic renal insufficiency. In patients undergoing PCI for acute MI, the clinical data clearly support the adjunctive use of abciximab.

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Percutaneous Interventions

Statins: Adjunctive Pharmacotherapy for Percutaneous Coronary Intervention?

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HMGCoA reductase inhibitors (statins) have recently been shown to possess direct, white-cell-mediated, anti-inflammatory effects that are distinct from (and operate in addition to) their well established low-density lipoprotein cholesterol-lowering effects. Indeed, statins directly impede leukocyte adhesion, rolling, and transmigration in addition to upregulating endothelial nitric oxide synthase activity (producing nitric oxide)[1,2] and downregulating neutrophil-monocyte, CD llb/18 (MAC-1) receptor expression.[3] The degree of mononuclear cell plaque infiltrate has been directly correlated with the presence of plaque rupture,[4] clinical disease activity (unstable syndromes),[5] and the propensity for restenosis following percutaneous coronary intervention (PCI).[6] The administration of either atorvastatin (80 mg daily) or simvastatin (40 mg daily) orally for 1 to 4 months prior to carotid endarterectomy significantly reduces the degree of macrophage and activated T-lymphocyte infiltration observed in excised plaque.[7,8] Thus, "plaque stabilization" appears to occur rapidly following the initiation of statin therapy. Observational studies have previously suggested that statin treatment prior to PCI (especially stent deployment) reduces the frequency and magnitude of periprocedural myocardial infarction as reflected by CK-MB or troponin measurements.[9-11] Clinically, statin treatment (vs. no statin treatment) has been associated with a reduction in hospital length-of-stay and 6-month and 1-year mortality following coronary stent deployment.[12-14] However, neither the requisite minimum time course required for pretreatment with statins, nor proof of efficacy derived from a placebo controlled randomized trial of statin administration prior to PCI, have been defined.

Randomized Trial of Atorvastatin for Reduction of Myocardial Damage During Coronary Intervention. Results from the ARMYDA (Atorvastatin for Reduction of Myocardial Damage during Angioplasty) Study.

Pasceri V, Patti G, Nusca A, et al. on behalf of the ARMYDA investigators.

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The Atorvastatin for Reduction of Myocardial Damage during Angioplasty (ARMYDA) study randomly assigned 153 patients with stable angina undergoing elective PCI to receive either atorvastatin (40 mg, po, daily, n = 76) or placebo (n = 77) for 7 days prior to the procedure. Markers of myocardial injury (CK-MB, troponin I, and myoglobin) were assessed systematically prior to and following PCI. All patients received aspirin (100 mg/d) and either ticlopidine (250 mg, po, twice daily) for at least 3 days prior to PCI or clopidogrel (300 mg, po) at least 6 hours before PCI. All patients continued either oral ticlopidine, 250 mg twice daily, or oral clopidogrel, 75 mg

daily, for 1 month (6 months for patients treated with drug-eluting stents) following PCI. Procedurally, patients received weight-adjusted unfractionated heparin intravenously to target an in-lab activated clotting time (ACT) of greater than 300 seconds (without adjunctive platelet glycoprotein [GP] IIb/IIIa blockade) and 200-300 seconds with additional GP IIb/IIIa blockade, which was administered at the operator's discretion. Multivariate analysis (adjusted for age; gender; ß-blocker, angiotensin-converting enzyme inhibitor, or GP IIb/IIIa inhibitor therapy; diabetes; lipid status; hypertension; American College of Cardiology/American Heart Association target lesion classification; multi-lesion intervention; stent length, direct stenting strategy; duration of balloon catheter inflation; use of high pressure post dilatation) showed that treatment with atorvastatin significantly reduced the risk of periprocedural myocardial injury (Figure 1). Indeed, preprocedural treatment with atorva-statin reduced both the frequency and magnitude of periprocedural infarction as assessed by CK-MB or troponin elevation (Figure 2).

This is the first placebo-controlled, randomized trial to demonstrate that pretreatment with atorvastatin decreases the incidence of myocardial injury during PCI. Several remarkable aspects of this study deserve mention. First, the rapidity of atorvastatin's clinical effectiveness (within 7 days of initiating therapy) is noteworthy and may be substantiated by other recent observations with

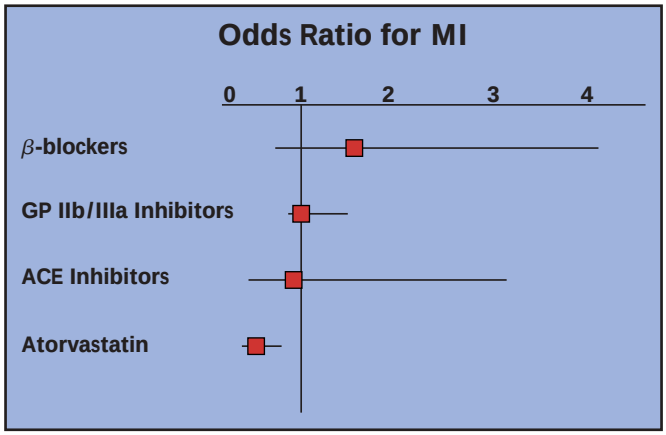
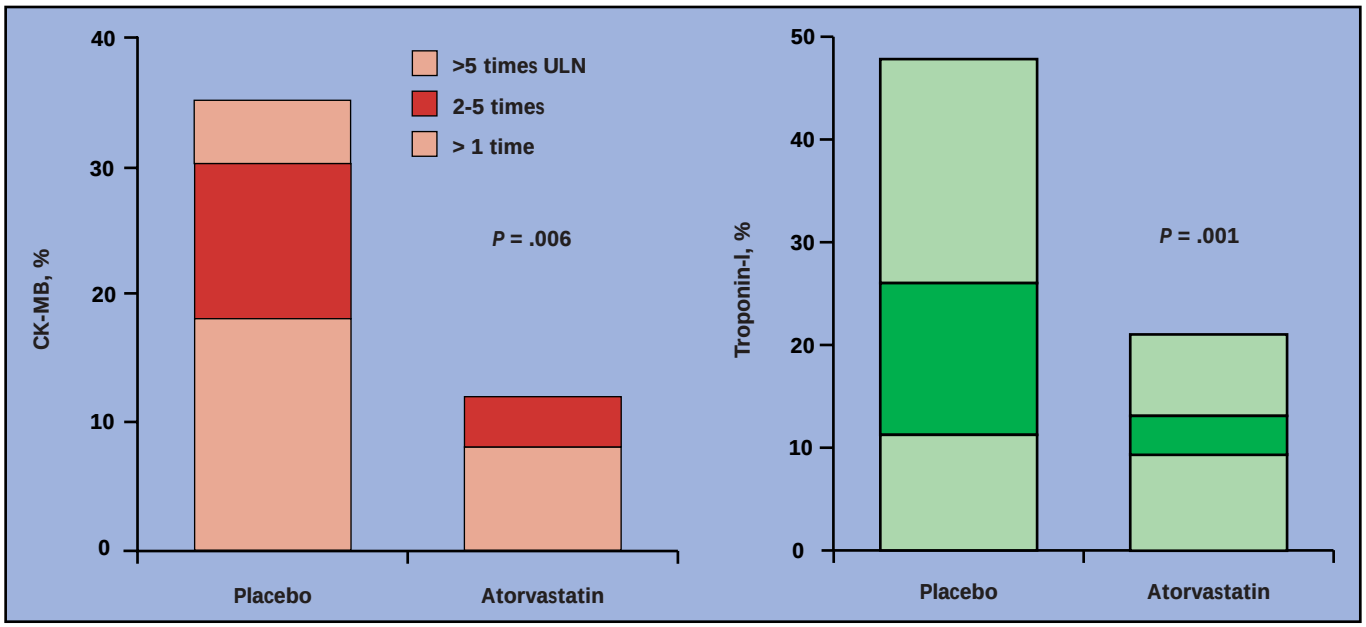


Figure 1. *Odds ratio and 95% confidence intervals for adjunctive pharmacotherapy administered prior to or during percutaneous coronary intervention. Reproduced with permission from Pasceri et al.*

statins. Simvastatin demonstrated a dose-dependent reduction in staph-aureus ß-toxin-induced leukocyte adhesion and rolling within 30 minutes and leukocyte transmigration within 120 minutes of administration in a rat mesenteric venule model.[1] Rousvastatin also inhibited the white-cell-inflammatory response to thrombin stimulation over the same time frame in the same model.[2] Furthermore, prolonged survival of mice randomly assigned to simvastatin (vs placebo) therapy following an

Figure 2. *Atorvastatin (40 mg orally daily) administered for 7 days prior to percutaneous coronary intervention was associated with a reduction in the frequency and magnitude of periprocedural myocardial injury as reflected by CK-MB or troponin-I measurements. ULN, upper limit of normal. Reproduced with permission from Pasceri et al.*



experimental bowel perforation was recently demonstrated.[15] Finally, atorvastatin administered immediately following coronary stent deployment suppressed the subsequent increment in hsCRP observed over 48 hours when compared with patients not treated with statins.[16] Taken together, these observations derived from basic science, animal, and clinical sources support an immediate, white-cell-mediated, anti-inflammatory effect of statin therapy.

Secondly, the benefit derived from atorvastatin to reduce periprocedural infarction was accrued in addition to that derived from other adjunctive pharmacotherapies that were administered. All study patients were adequately pretreated with oral thienopyridines, which have been shown to reduce periprocedural major adverse cardiovascular events.[17] In addition, the benefit of atorvastatin therapy pre-PCI was independent of periprocedural adjunctive platelet GP IIb/IIIa inhibitor use.

Lastly, all patients enrolled into the ARMYDA study had chronic stable angina and were scheduled for elective PCI. These patients would be expected to comprise a much lower risk cohort for PCI than patients who present with acute coronary syndromes (ACS). Indeed, a growing body of literature suggests that statin therapy is beneficial when administered early to patients who present with ACS.[18-20] In both the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study and the Pravastatin or Atorvastatin Evaluation in Infection Therapy (PROVE-IT) study, ACS patients randomly assigned to early and aggressive statin therapy (vs either placebo or less aggressive lipid-lowering therapy) derived clinical benefit, which was evident within 1-4 months of initiating treatment. Importantly, neither MIRACL or PROVE-IT systematically evaluated patients undergoing PCI. The putative benefit to be derived from early and aggressive statin therapy prior to PCI may be even greater for ACS patients than was observed in these stable patients undergoing elective PCI in the ARMYDA study.

Based on the results of the ARMYDA study and in the context of the supportive data previously cited, it would appear reasonable to initiate moderate- to high-dose statin therapy (atorvastatin, 40-80 mg) as early as possible prior to PCI. Whether therapy lasting less than 7 days will confer a similar degree of benefit is a point for further study. The reduction in both frequency and magnitude of periprocedural myocardial infarction associated with atorvastatin therapy prior to PCI may have far-reaching implications. Indeed, a direct relationship has been demonstrated between the magnitude of periprocedural CK-MB elevation and subsequent mortality in late follow-up post-PCI.[21] Thus, the early biochemical benefit of statin therapy may contribute to the late survival advantage observed in previous non-randomized studies.[13,14] Early and aggressive statin therapy should be appropriately incorporated into guideline recommendations for the care of patients who present with ACS and/or those who require PCI. ■

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