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# Statins Before Coronary Procedures

## A New Indication for an Old Friend*

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Myocardial infarction (MI), defined as an increase in markers of myonecrosis >2 to 3 times the upper limit of normal, is frequent after coronary procedures and increases mortality (1,2). Several strategies to prevent this outcome have evolved, such as the administration of glycoprotein IIb/IIIa inhibitors during percutaneous coronary interventions (PCIs) (3). Accumulating evidence suggests that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are also of value in preventing post-procedural complications.

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The study of periprocedural statins to prevent cardiac complications is a tale of progressive scientific inquiry. In 2002, Herrmann et al. (4) found that patients who received statins 7 days before PCIs had a lower incidence of MI compared with statin nonusers. In 2004, pre-operative statin therapy was independently associated with a reduction in 30-day all-cause mortality and stroke in a cohort of 1,663 patients undergoing primary coronary bypass graft surgery (5). A subsequent retrospective cohort study found that statin treatment at the time of PCI was associated with reduced 30- and 60-day mortality, suggesting that lowering coronary events around the time of intervention improved survival (6). The ARMYDA (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) trial was the first randomized, prospective study to test whether statin treatment decreased myocardial injury and improved outcomes after coronary angioplasty. In a cohort of 153 statin-naïve patients with chronic stable angina, 40 mg atorvastatin 7 days before PCI reduced post-procedural MI and improved the 30-day composite outcome of death, MI, or the need for repeat revascularization (5% vs. 18%; $p = 0.025$). Multivariate logistic regression showed that atorvastatin pretreatment was independently associated with a reduction in periprocedural creatine kinase-myocardial band elevation (odds ratio: 0.19, 95% confidence interval: 0.05 to 0.57) (7). The ARMYDA–ACS (Atorvastatin for Reduction of Myocardial Damage During Angioplasty–Acute Coronary Syndromes) trial studied this effect in those with unstable coronary syndromes, finding that 80 mg atorvastatin given 12 h before coronary angioplasty decreased the primary composite outcome of death, MI, or revascularization (5% vs. 17%, $p = 0.01$) (8). The incidence of post-procedural MI was 5% among statin users compared with 15% in those on placebo ($p = 0.04$). In 2007, a meta-analysis concluded that the risk of periprocedural myocardial necrosis in those pre-treated with statins was substantially lowered (odds ratio: 0.45, 95% confidence interval: 0.33 to 0.62) (9). More recently, failure to administer pre-operative statins was found to be a predictor of mortality among those undergoing high-risk coronary bypass grafting (10).

Does previous "statin status" affect clinical outcome? In statin-naïve patients, the Italian NAPLES (Novel Approaches for Preventing or Limiting Events) II trial demonstrated that a single pre-procedural 80-mg loading dose of atorvastatin significantly decreased periprocedural MI (9.5% vs. 15.8%, $p = 0.014$) (11). Among those on long-term statin treatment undergoing early PCI for stable angina, the ARMYDA–RECAPTURE study found that acute atorvastatin loading (80 mg 12 h before PCI) reduced the 30-day incidence of cardiac events from 9.4% to 3.7% ($p = 0.037$), principally due to a reduction in MI (12).

How do periprocedural statins protect myocardium? In stable clinical situations, it is thought that statins mediate their primary benefit via low-density lipoprotein reduction. However, in acute situations (such as acute coronary syndromes or coronary interventions), pure low-density lipoprotein reduction cannot explain cardiac protection.

Statins act via inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase. In doing so, they prevent the formation of the cholesterol precursor mevalonate and produce important downstream nonlipid pleiotropic effects. Mevalonate depletion limits isoprenoid production and decreases the formation of Ras and Rho proteins, molecules involved in intracellular signaling pathways (Fig. 1). Specifically, 2 important isoprenoid intermediaries are affected: farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GPP). Both FPP and GPP act as intracellular lipid attachments for the modification of important proteins (guanosine triphosphate-binding molecules), thus function-

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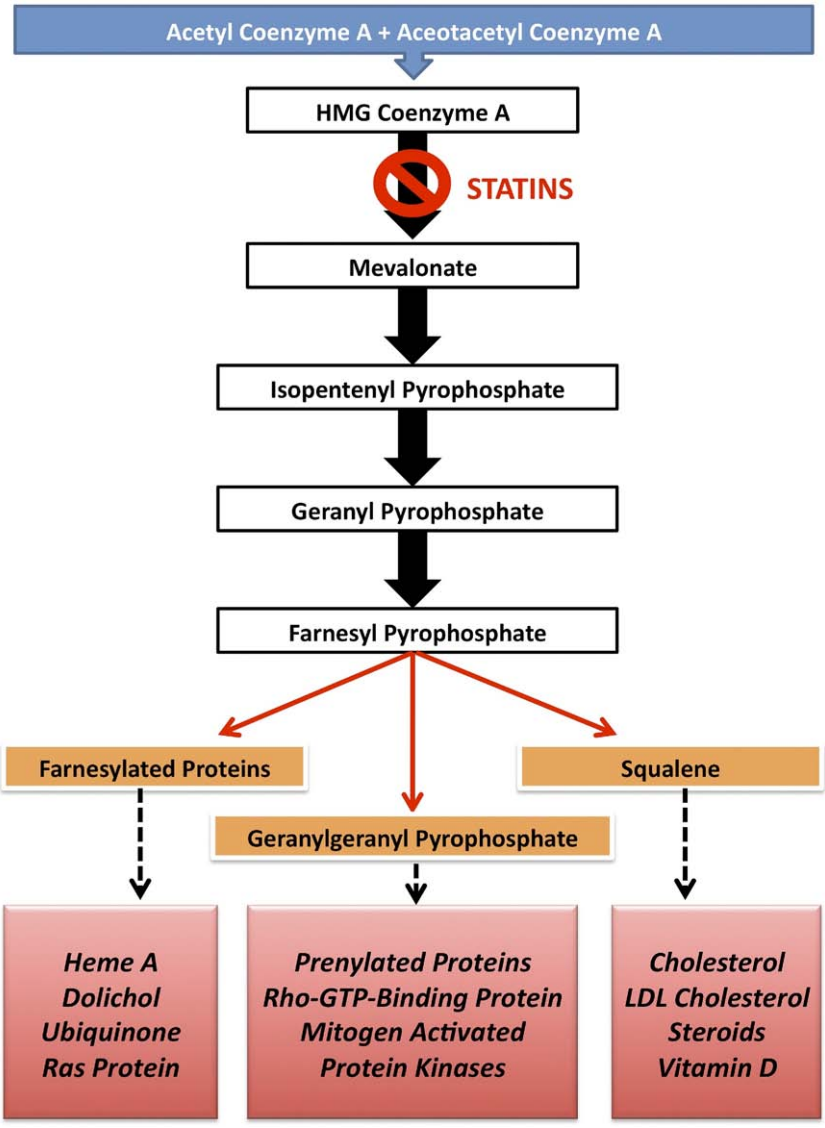


**Figure 1** **Biochemical Basis for the Nonlipid Effects of Statins**

Nonlipid lowering (pleiotropic) effects of statins may be mediated by Rho and/or Ras proteins, which are attenuated via inhibition of 3-hydroxy-3-methylglutaryl (HMG) coenzyme A reductase by statin treatment. LDL = low-density lipoprotein.

ing as on-off switches for a myriad of protein kinases. Depletion of FPP and GPP leads to aberrations in a variety of cellular functions and is believed to be an important mechanism of statin pleiotropicity (13).

The pleiotropic effects of statins are profound. Statins augment endothelial function (by up-regulating endothelial nitric oxide synthase), stabilize vulnerable plaque (by decreasing matrix metalloproteinase activity), reduce adhesion molecules (vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and E-selectin), and decrease circulating biomarkers (e.g., C-reactive protein [CRP]) (13,14). Therefore, before endothelial injury during coronary procedures, statin treatment likely mitigates the inflammatory cascade by decreasing vascular reactivity and stabilizing plaque, both at the site of intervention and at other "vulnerable" lesions. These biological effects are thought to be the basis of periprocedural statin myoprotection.

Should statins routinely be implemented in patients undergoing coronary procedures? The answer appears to be "yes." In their analyses of 4,805 patients in this issue of the *Journal*, Winchester et al. (15) show that statin treatment before coronary procedures decreases rates of post-procedural MI, all-cause mortality, and post-coronary artery bypass graft atrial fibrillation. Their findings are timely and highly relevant in the quest to reduce procedural cardiac complications. However, a number of questions remain.

1. What is the optimal statin dose necessary to achieve periprocedural protection? In a substudy of PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22), patients undergoing PCI who received high-dose atorvastatin fared better than those receiving lower doses. These data support high-dose statin therapy in procedural settings, although clinical trials also found benefit at lower doses (16).
2. Are certain statins better at procedural protection? Theoretically, agents with greater influence on Rho or Ras kinase(s) may be of particular value given the pleiotropism hypothesis. However, this concept remains unproven in a clinical setting.
3. Is the benefit of pre-procedural statins limited to particular cohorts? The NAPLES II study showed that atorvastatin loading reduced periprocedural MI only in those with elevated CRP, not those with normal CRP levels (11). Thus, should CRP elevation guide statin treatment? Further studies are needed to clarify this paradigm.
4. Is there a dark side to periprocedural statins? Unlike beta-blockers and nitrates, statin treatment does not lead to readily detectable clinical effects such as low-output syndromes or bradycardia. Adverse effects may thus be difficult to detect in clinical trials. At this juncture, there is little evidence to suggest that statins plus periprocedural drugs or anesthesia cause liver or muscle injury. However, more data (especially in the elderly and those with pre-existing liver/renal disease), are necessary to further define this dimension.

Despite their multifaceted properties, statins continue to remain underused in the treatment of stable and unstable coronary artery disease. The available evidence creates a convincing argument for statin treatment before coronary procedures. Given the strong biological rationale and the sum of the clinical data, no patient should undergo coronary procedures without statin therapy unless clear contraindications exist. Indeed, it is time to consider a new indication for an old friend.

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**Key Words:** meta-analysis ■ outcomes ■ periprocedural myocardial infarction ■ post-operative myocardial infarction ■ statin.