Pre-treatment with High-Dose Statins: Improved Outcomes for Acute Coronary Syndrome

**Presenter:** Germano Di Sciascio, MD, Campus Bio-Medico University, Rome, Italy

In patients with acute coronary syndrome (ACS) who undergo early invasive percutaneous coronary intervention (PCI), giving high-dose statins for a short term may improve outcomes.

The original ARMYDA trial (Atorvastatin for Reduction of Myocardial Damage during Angioplasty) evaluated seven-day pre-treatment with atorvastatin (Lipitor, Pfizer). At a dose of atorvastatin 40 mg/day, an 81% risk reduction (5% with atorvastatin vs. 18% with placebo; \( P = 0.025 \)) in periprocedural myocardial infarction (MI) was observed. All patients had stable angina and were undergoing elective PCI.

The subsequent ARMYDA–ACS trial included 171 statin-naive patients with non–ST-elevation (NSTEMI) ACS, all of whom had undergone early angiography less than 48 hours after hospital admission. They were randomly assigned to receive placebo or atorvastatin 80 mg 12 hours before angiography and another dose of 40 mg two hours before angiography. Afterward, 86 patients received PCI and atorvastatin therapy, and 85 patients received PCI and placebo. On hospital discharge, all patients were maintained with atorvastatin 40 mg.

The primary combined endpoint was death at 30 days, MI, or the need for target-vessel revascularization.

In the atorvastatin group, patients were slightly younger (64 years of age vs. 67 years), and multivessel coronary artery disease (CAD) was slightly less prevalent (34% vs. 46%; \( P = 0.14 \)).

The composite primary endpoint was reported in 5% of patients receiving atorvastatin and in 17% of patients receiving placebo (\( P = 0.01 \)). Among the primary endpoint components, the greatest difference was in periprocedural MI (5% with atorvastatin, 15% with placebo; \( P = 0.04 \)). No patients died, and target-vessel revascularization was needed in one of the 85 patients receiving placebo.

Among the secondary endpoints, cardiac markers significantly favored atorvastatin (\( P = 0.002 \) for creatine kinase-MB, \( P = 0.028 \) for troponin-I). After PCI, C-reactive protein (CRP) levels increased by 147% from baseline values in the placebo patients but only by 63% from baseline in the atorvastatin group.

Dr. Di Sciascio concluded, “The ARMYDA–ACS trial indicates that even a short-term atorvastatin treatment prior to PCI may improve outcomes in patients with unstable angina and NSTEMI.”

Bivalirudin in Acute Coronary Syndromes

**Presenter:** Gregg W. Stone, MD, Cardiovascular Research Foundation, New York, New York

Finding the pharmacological agent or the combination of agents that successfully balances the risks of thrombosis and bleeding is a complex challenge in many clinical trials of ACS. Thirty-day bleeding was reduced, and one-year mortality and composite ischemia were similar with bivalirudin (Angiomax, The Medicines Company) alone, when compared with either unfractionated heparin (UFH) or enoxaparin (Lovenox, Sanofi-Aventis) in the large-scale, randomized Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. The composite ischemia endpoint consisted of death, MI, and unplanned revascularization for ischemia.

In ACUITY, according to Dr. Stone, 13,819 patients with moderate-risk and high-risk ACS underwent an early invasive strategy with glycoprotein (GPIIb/IIIa) inhibitors (GPIs). The patients received unfractionated heparin (UFH)/enoxaparin plus a GPI (the current standard), bivalirudin plus a GPI, or bivalirudin monotherapy before angiography to determine whether they were to undergo PCI, bypass surgery, or medical therapy.

Before presenting the final one-year results, Dr. Stone noted that 30-day major bleeding had been significantly lower with bivalirudin plus a GPI (5.3%) than with UFH/enoxaparin plus a GPI (5.7%) (\( P < 0.001 \)). At one year, the primary endpoint of ischemic complications was similar for all groups:

- UFH/enoxaparin plus a GPI, 16.3%
- bivalirudin plus a GPI, 16.5%
- bivalirudin alone 16.4%
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Ischemic complications included death, MI, and unplanned revascularizations for ischemia. Results were also similar with all treatments: MI (6%–7%), mortality (4%), unplanned revascularizations (9%), and stent thrombosis (2.2%).

The significance of reduced 30-day major bleeding, Dr. Stone pointed out, was underscored by the fact that a greater one-year mortality hazard ratio (HR) was conferred by bleeding (HR = 2.89) than by MI (HR = 2.47). The fact that there was not a significant mortality benefit for bivalirudin, despite the reduction in bleeding, he said, was attributable to the sample size. He suggested that if ACUITY had included 30,000 to 40,000 patients, a difference in mortality would have been detected.

In a landmark analysis, Dr. Stone also drew attention to a late increased divergence in mortality curves, with a nearly 1% reduction favoring bivalirudin alone versus UFH/enoxaparin at 365 days. The curves, he added, appeared to diverge further out, to 390 days. The analysis, however, was questioned by Marc Cohen, MD, Chief of the Division of Cardiology at Beth Israel Medical Center in Newark, New Jersey.

“There’s no foundation for looking at the 30 days following 360 days when the treatment duration was four hours,” said Dr. Cohen. He described the one-year mortality curves as “super-imposable.”

Dr. Stone concluded that bivalirudin was an acceptable substitute for either UFH or enoxaparin in this moderate-risk to high-risk ACS population.

Rosuvastatin and Carotid Artery Intima Media Thickness

**Presenter:** John R. Crouse III, MD, Wake Forest University School of Medicine, Winston-Salem, North Carolina

In ASTEROID (A Study To Evaluate the effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden), measuring carotid artery intima media thickness (CIMT) with intravascular ultrasound (IVUS) was a reliable means of assessing atherosclerosis, itself a predictor of the risk for cardiovascular events. High-risk patients with CAD, as documented by angiography, received rosuvastatin 40 mg (Crestor, AstraZeneca). As assessed by IVUS, aggressive statin therapy helped to promote regression of atherosclerosis.

Dr. Crouse’s trial, called Measuring Effects on Intima–Media Thickness: an Evaluation of Rosuvastatin (METEOR), also investigated intensive statin therapy but in low-risk patients.

Subjects from 61 centers in the U.S. and Europe were randomly assigned to receive rosuvastatin 40 mg or placebo. These patients (mean age, 57 years) had low-density lipoprotein-cholesterol (LDL-C) levels between 120 and 190 mg/dL, with no risk factors for coronary heart disease (CHD) other than age, or their LDL-C levels were between 120 and 160 mg/dL, with more than one risk factor, triglyceride levels below 500 mg/dL, and a maximum CIMT of at least 1.2 mm at any site and less than 3.5 mm in all sites. A low-risk population was chosen, Dr. Crouse said, in order to allow a placebo comparison.

The primary endpoint was the rate of change (in millimeters per year) in maximum CIMT in all carotid artery measurements.

Dr. Crouse presented two-year data from among 530 patients receiving rosuvastatin and from among 208 patients receiving placebo. Highly significant reductions in all lipid parameters were reported. Although LDL-C levels declined by 0.3% with placebo, they were lowered by 48.8% with rosuvastatin.

For the primary endpoint of CIMT at all sites, the reduction in the rate of change of –0.0014 mm/year with rosuvastatin was also highly significant, compared with an increase of 0.0131 mm/year noted for placebo (P < 0.0001). However, absolute CIMT regression, when compared with placebo, was not significant with rosuvastatin (P = 0.32).

Dr. Crouse explained that the lower-risk status of this patient population probably accounted for the absence of atherosclerotic regression in METEOR. He concluded that rosuvastatin basically halted the progression of atherosclerosis during the two-year treatment period.

Commenting on METEOR, Christopher P. Cannon, MD, from Harvard Medical School, stated that the trial was a useful mechanistic study that identified a high-risk population presently thought of as low-risk. For those patients, he said, “We can now offer the benefits already documented for all statins.”

Optimal Medical Therapy with and without Percutaneous Coronary Intervention

**Presenter:** William E. Boden, MD, Professor of Medicine and Public Health, University of New York at Buffalo School of Medicine and Biomedical Sciences, Buffalo, New York

A trial called Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) attempted to determine whether adding PCI to optimal medical therapy would reduce death, MI, or hospitalizations among patients with acute coronary syndrome (ACS). Dr. Bowden, the lead investigator, said that even though PCI had proved effective in lowering the frequency of angina and in improving exercise performance in the short term, there was no evidence that it could reduce death, MI, or hospitalization. By far, he said, most of the one million PCIs performed each year in the U.S. are of a non-emergency nature in patients with stable CAD.

COURAGE was conducted at 50 North American hospitals among 2,287 patients with a mean age of 62 years. The patients were randomly assigned to undergo PCI plus optimal medical therapy or optimal medical therapy alone. Medications included:

- antiplatelet agents: aspirin plus clopidogrel bisulfate (Plavix, Bristol-Myers Squibb/Sanoﬁ-Aventis)
- a statin: simvastatin with or without ezetimibe or extended-release niacin
- an angiotensin-converting enzyme (ACE)–inhibitor or an angiotensin-receptor blocker (ARB): lisinopril (e.g., Zestril, AstraZeneca) or losartan (Cozaar, Merck)
- a beta-blocker: long-acting metoprolol (Toprol, AstraZeneca)
- a calcium-channel blocker: amlodipine besylate (e.g., Norvasc, Pfizer)
- a nitrate: isosorbide 5-mononitrate (e.g., BiDil, NitroMed)
Intensive optimal medical therapy and lifestyle interventions, as indicated by American College of Cardiology/American Heart Association guidelines, were prescribed for both groups. Goals focused on reducing these risk factors:

- smoking
- dietary fat and dietary cholesterol intake
- serum cholesterol levels (LDL-C), a primary concern
- serum cholesterol (HDL-C) and triglyceride levels, a secondary concern
- physical inactivity
- body mass index
- hypertension
- diabetes, with the aim of obtaining a glycosylated hemoglobin (HbA1c) value below 7%

The mean follow-up period was 4.6 years. The primary endpoint was death or nonfatal MI.

The primary analysis included 1,149 patients with a mean age of 62 years who received PCI plus optimal medical therapy and 1,138 patients with a mean age of 62 years who received optimal medical therapy alone. Patients had heart disease involving one to three vessels, and all patients were eligible for PCI, with Canadian Cardiovascular Score (CCS) Class I to III angina and objective evidence of ischemia at baseline. Results were as follows:

- Freedom from all-cause death or MI was similar for both groups (HR = 1.05), favoring optimal medical therapy (P = 0.62).
- ACS hospitalization-free survival was similar (HR = 1.07), favoring PCI plus optimal medical therapy (P = 0.50).
- MI-free survival was similar (HR = 1.13), favoring medical therapy.
- Freedom from angina favored PCI plus medical therapy at one year (66% vs. 58%) but not at five years (74% for PCI vs. 72% for optimal medical therapy).

Although patients receiving optimal medical therapy alone were more likely to need revascularization (32.6%) than those receiving PCI plus optimal medical therapy (21.1%), the median time to revascularization was similar for both groups (10 months for optimal medical therapy with PCI and 10.8 months for optimal medical therapy alone).

Dr. Bowden concluded:

As an initial management strategy, PCI did not reduce the risk of death, MI, or other major cardiovascular events when added to optimal medical therapy. The COURAGE results give us more options and take away from the sense that if we offer optimal medical therapy we are offering something less than the best medical care.

In a follow-up interview, he added:

I’ve heard it said that COURAGE does not represent the ‘real world,’ and that these kinds of results can’t be achieved in clinical practice because it’s too hard—my response is, ‘That’s rubbish!’ Fundamentally, there was no difference between what patients got in COURAGE and what you are entitled to receive through Medicare, an HMO, or any private practice plan.

### Antithrombotic Therapy: Reducing Clinical Events without Increasing Bleeding

**Presenter:** David J. Moliterno, MD, University of Kentucky College of Medicine, Lexington, Kentucky

As the lead investigator of the Thrombin Receptor Antagonist in Percutaneous Coronary Intervention (TRA–PCI) trial, Dr. Moliterno also took up the recurring theme that for patients undergoing PCI, new agents intended to further reduce clinical events without adding a tendency to cause bleeding have been elusive so far.

His study evaluated a novel thrombin receptor antagonist (TRA, SCH 530348, Schering-Plough), derived from the bark of the Australian rhododendron plant. He pointed out that MIs or other adverse ischemic events occur in 4% to 8% of patients undergoing PCI, even with the optimal use of antiplatelet, anticoagulant, and antithrombotic agents.

Among patients undergoing non-urgent PCI or coronary angiography (with the intent to undergo PCI), the oral, selective TRA was given in a double-blind fashion as a pre-PCI loading dose (10 mg, 20 mg, 40 mg, or placebo) and as a post-loading PCI dose as daily maintenance therapy for 60 days (0.5 mg, 1 mg, 2.5 mg, or placebo).

All of the patients (422 receiving TRA, 151 receiving placebo) were given aspirin. Those undergoing PCI received clopidogrel (Plavix) and an antithrombin agent (heparin, bivalirudin [Angiomax], or a GPIIb/IIIa inhibitor).

The primary endpoint was safety (TIMI [Thrombosis in Myocardial Infarction] major bleeding plus minor bleeding). The secondary endpoint was efficacy (death or major adverse cardiac events).

The endpoint of TIMI major or minor bleeding was reported in 3.3% of placebo patients and in 2.8% of patients receiving TRA (P = 0.77). TIMI major bleeding was similar for TRA 40 mg (0.6%) and for placebo (3.3%); however, overall major and minor bleeding was slightly higher with the highest TRA dose: 4% for TRA vs. 3.3% for placebo (P = 0.73).

The incidence of death or major adverse cardiac events was 8.6% with placebo, 5.9% with all doses of the study drug, and 4.6% with TRA 40 mg (a 46% reduction; P = 0.15).

At 60 days, the rates of death or MI were 7.3% with placebo and 4% with TRA 40 mg (P = 0.20). The rate of MI was reduced by 52% with TRA 40 mg (for 7.3% of patients receiving placebo and for 3.5% of patients receiving TRA 40 mg).

Even though these efficacy endpoints demonstrated favorable trends for TRA, Dr. Moliterno cautioned that the TRA–PCI trial was not adequately powered to evaluate efficacy. He concluded that a large-scale phase 3 trial was warranted. ■