LDL-lowering Independent Effects of Early Pre-treatment with High-dose Statins in Patients Undergoing Percutaneous Coronary Interventions

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ABSTRACT
Statins exert beneficial effects on the endothelium, inflammation and the coagulation cascade that are independent of cholesterol lowering. The main mechanism underlying these effects is inhibition of isoprenoid synthesis, modulating the inflammatory cascade and the endothelial activation reliable of atherosclerosis.

Different studies demonstrated that statins improve endothelial function in patients with stable atherosclerotic plaque and that this effect is dose-dependent. Statins may modulate endothelial expression of adhesion molecules, as demonstrated in the ARMYDA-CAMS, and may enhance mobilisation of endothelial progenitor cells.

Elevated C-reactive protein levels, an inflammatory marker that also plays a direct pathogenetic role in the atherosclerotic process, have been correlated with worse outcome in patients with cardiovascular disease. Multiple studies demonstrated that statin attenuates the rise of inflammatory markers and improves clinical outcome in patients with stable angina, unstable angina and non-Q wave acute myocardial infarction.

During percutaneous coronary intervention randomised trials showed a beneficial effect of statin pre-treatment in reducing peri-procedural myocardial damage probably by plaque stabilisation and inhibition of microembolisation phenomena during stent implantation. The ARMYDA study and the NAPLES II trial demonstrated this beneficial effect in patients undergoing coronary revascularisation for stable angina. Also in patients with ACS, receiving invasive strategy, the role of statins in preventing peri-procedural damage was demonstrated in the ARMYDA-ACS study by the administration of an acute high loading-dose with atorvastatin. In patients already on chronic statin therapy at the time of the procedure, an acute drug reload before stenting would have cardioprotective effects, like demonstrated in the ARMYDA RECAPTURE study.

INTRODUCTION
Statins inhibit hepatic 3-hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA) reductase with consequent suppression of cholesterol biosynthesis. The advent of these drugs has significantly impacted the treatment of cardiovascular disease with well documented benefit in primary and secondary prevention. However, several clinical and basic science investigations suggested that the beneficial effects of statins may extend beyond their cholesterol lowering effects, the so-called “pleiotropic effects”; these include improving endothelial function, inhibiting vascular inflammation and oxidation.

Anti-inflammatory properties of statins: mechanisms of action
The main mechanism underlying the pleiotropic effects of statins is the inhibition of isoprenoid synthesis (farnesyl pyrophosphate and geranyl-geranyl pyrophosphate), which leads to the blockage of small G proteins (i.e. Rho and Ras) and subsequent suppression of nuclear transcription factors activation involved in pro-inflammatory mechanisms. In particular, inhibition of Rho and its downstream target Rho kinase (ROCKs) may mediate the positive effects of statins on the vascular wall.
In fact, ROCK upregulates pro-inflammatory molecules including activating protein-1, NF-κB, NAD(P)H, IL-6, monocyte chemotactrant protein-1, macrophage migration inhibitory factor and interferon-γ, all involved in the inflammatory endothelial response and in the pathogenesis of atherosclerosis. On the other hand, activated ROCK downregulates endothelial NO synthase (eNOS) with subsequent endothelial dysfunction. Moreover, ROCK mediates neo-intimal proliferation via recruitment of circulating leukocytes and infiltration of inflammatory cells into the vessel wall, and upregulates thrombogenic molecules such as plasminogen activator inhibitor-1 and tissue factor.

Thus, the anti-inflammatory properties of statins, inhibiting Rho protein isoprenylation and preventing the subsequent activation of downstream effectors such as ROCK, may modulate all stages of the inflammatory cascade and endothelial activation leading to atherosclerosis. Nohira et al. demonstrated that statins inhibit ROCK’s activity and improve endothelial function in patients with stable atherosclerosis. In this study, atorvastatin 80 mg/day significantly reduced ROCK activity (p=0.002 vs placebo), with a rapid decline within two weeks of treatment. The inhibition of ROCK by atorvastatin remained significant even after controlling for changes in low-density lipoprotein cholesterol and triglycerides (p=0.01). Of note, this effect has been demonstrated to be dose-dependent; in fact, high-dose statins (40 mg/day) mono-therapy achieved greater inhibitory effects on ROCK activity and improved endothelial function than low-dose statin plus ezetimibe (10/10 mg/day) in a prospective, randomised, observer-blinded study on dyslipidemic subjects without cardiovascular disease.

Furthermore, statins can directly enhance the phosphatidyl inositol-3 kinase (PI3K) and the serine/threonine kinase (Akt) pathways, increasing eNOS activity and nitric oxide (NO) availability. They may modulate endothelial expression of adhesion molecules, as demonstrated in the Atorvastatin for Reduction of Myocardial Damage during Angioplasty – Cell Adhesion Molecules (ARMYDAMAS) study, where pre-treatment with atorvastatin significantly attenuated post-procedural elevation of intercellular cell adhesion molecule-1 (ICAM-1) and E-selectin in patients undergoing percutaneous coronary intervention (PCI), confirming the protective actions of statins on endothelial function.

Furthermore, statins may exert beneficial non-cholesterol effects through enhancing the mobilisation of endothelial progenitor cells and thus increasing angiogenesis, and attenuating vascular smooth muscle cells proliferation in coronary arteries. Finally, these drugs inhibit platelet activation by reducing cholesterol levels and increasing eNOS activity in platelets and inhibit tissue factor expression by macrophages.

Inhibition of inflammation by statins, especially reflected by C-reactive protein (CRP) levels reduction, has been clinically demonstrated in several studies. CRP, in addition to be an inflammatory marker, plays a direct pathogenetic role in the atherosclerotic process. Moreover, CRP levels have been repeatedly correlated with outcome in patients with cardiovascular disease and lowering CRP levels was associated with reduction of subsequent cardiovascular events.

Ostadal et al. demonstrated that a single dose of cerivastatin at the time of admission attenuates the inflammatory markers enhancement in patients with acute coronary syndromes (ACS) (CRP and IL-6 at 24 hours). Correia et al. found a significant anti-inflammatory effect of short term, high-dose (80 mg), atorvastatin load in patients with unstable angina or non-Q wave acute myocardial infarction, as expressed by reduction of CRP levels (compared to 188% increase of CRP in the placebo group). Finally, in the JUPITER study, the 2-year Kaplan Meier estimated event rate for the primary combined end point (death, nonfatal MI or recurrent symptomatic myocardial ischemia requiring hospitalisation) in the Pravastatin or Atorvastatin Evaluation and Infection Therapy - Thrombolysis in Myocardial Infarction 22 trial (PROVE-IT TIMI 22), an intensive statin therapy (atorvastatin 80 mg/day) improved 30-day clinical outcome compared to a moderate-dose statin treatment (pravastatin 40 mg/day) in patients with ACS.

Several studies evaluated the role of an early, intensive therapy with statins in patients with ACS treated medically or receiving an invasive strategy. In the randomised Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, treatment with atorvastatin (80 mg/day), initiated 24 to 96 hours after an acute coronary event, reduced the risk of recurrent ischemic events over a 16-week treatment period in patients with unstable angina or non-Q wave acute MI (14.8% vs 17.4% in placebo group; p=0.048); in particular, the authors demonstrated a 16% relative risk reduction of the primary combined end point (death, non-fatal MI or recurrent symptomatic myocardial ischemia requiring hospitalisation). In the Pravastatin or Atorvastatin Evaluation and Infection Therapy - Thrombolysis in Myocardial Infarction 22 trial (PROVE-IT TIMI 22), an intensive statin therapy (atorvastatin 80 mg/day) improved 30-day clinical outcome compared to a moderate-dose statin treatment (pravastatin 40 mg/day) in patients with ACS.

In the subgroup of patients who underwent PCI (PCI-PROVE IT study), the 2-year Kaplan Meier estimated event rate for the primary composite end point (death, MI, unstable angina requiring rehospitalisation and revascularisation by angioplasty or surgery bypass at least 30 days after randomisation and stroke) was 21.5% in patients treated with atorvastatin and 26.5% in those receiving pravastatin, with a 22% relative risk reduction (HR=0.78, 95%CI 0.67-0.91, p=0.001). Amonow et al. investigated the effects of statin therapy prescribed at the time of hospital discharge on short-term clinical outcome in unstable patients randomised in two trials, the Global Use of Streptokinase or t-PA for Occluded Coronary Arteries Illb (GUSTO Illb) and Platelet Glycoprotein Illb/lla in Unstable Angina: Receptor Suppression Using Integrelin Therapy (PURSUIT) studies.

In this post-hoc analysis, statin treatment was associated with a significant survival benefit at six months (1.7% mortality rate in statin-treated patients vs 3.5% in statin-naive; p=0.0001). A recent meta-analysis from 12 randomised trials comparing early (<14 days) statin therapy versus placebo or usual care after an ACS, reported similar overall incidence of major adverse cardiac events (death, MI, stroke) at 4 months in the two groups, with lower recurrence of unstable angina in patients receiving statins (4.8% versus 6.0%, p=0.05).
Interestingly, a recent study by Mensah et al.\textsuperscript{32} demonstrated that cardioprotective effects of statins may be lost over longer treatment periods. In this study, atorvastatin (20 mg/die), although reducing infarct size when given < 3 days before ischemia/reperfusion in an animal model, lost its benefit when administered for one or two weeks before ischemia/reperfusion. These results may be explained by an upregulation of phosphatase and tensin homologue (PTEN), a potent inhibitor of PI3K/Akt pathways, associated with chronic statin treatment. As a result, although acute statin administration might increase PKB/Akt activity, chronic statin use might counteract PKB/Akt activation by increasing PTEN expression. However, the anti-inflammatory effects of statins may be "recaptured" in patients on chronic statin treatment by a reloading with high doses of these agents, providing significant clinical benefit.

**Inflammation and myocardial damage during percutaneous coronary intervention**

The major etiologies of periprocedural MI after PCI include dissection, compromise of side branches due to plaque shifting, thrombosis, no-reflow phenomenon, distal microembolisation of plaque components related to plaque burden instability and enhanced inflammatory state. Despite successful coronary interventions and optimal management directed toward mechanical and thrombotic complications, the rate of this complication is still high (10-40% of cases) and may be associated with higher long-term mortality.\textsuperscript{33,34} The role of inflammation in the pathogenesis of periprocedural myocardial damage is also confirmed by a number of studies that documented the prognostic role of CRP levels after coronary intervention in terms of early and late cardiovascular complications.

In patients with stable angina who underwent coronary stenting, the incidence of major adverse cardiac events (MACEs) during short- and long-term follow-up is significantly higher in those with a significant increase in high sensitivity (hs)-CRP (>3 mg/L) after PCI (18% vs 2.2% at 1 year and 37% vs 3.4% at a mean of 6.6 years, respectively). A hs-CRP increase induced by PCI yields a higher predictive value for MACEs than the absolute hs-CRP value before or after PCI considered separately.\textsuperscript{35}

In this setting, statins may prevent periprocedural myocardial damage probably by plaque stabilisation and inhibition of microembolisation phenomena during stent implantation, especially in patients with ACS, in whom the elevated inflammatory state and the thrombotic plaque composition predispose to rupture and embolisation of particulate matter into the microcirculation with subsequent peri-procedural myocardial necrosis.

**STRATEGIES AND EVIDENCE**

**Statin pretreatment during percutaneous coronary interventions**

Several observational prospective and retrospective studies demonstrated decreased periprocedural MI after statin administration. Herrmann et al.\textsuperscript{36} observed that patients undergoing PCI treated with different statins for at least one week, had a lower incidence of MI (0.4% vs 6%; p=0.03) compared with the non statin group. Chan et al.\textsuperscript{37} demonstrated in a larger series of patients that statins treatment at the time of PCI was associated with a lower 30-day and six-month all cause mortality. In 1552 patients undergoing coronary angioplasty, a lower incidence of postprocedural MI (5.7% vs 8.1%; p=0.038) and one-year mortality (3.4% vs 6.9%; p=0.003) was observed in patients who were on statins at the time of procedure.\textsuperscript{38}

The Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty (ARMYDA) study\textsuperscript{39} was the first randomised, placebo-controlled, double-blind, prospective study demonstrating a beneficial effect of statins in the prevention of myocardial damage after PCI in patients undergoing coronary revascularisation for stable angina. This study enrolled 153 statin-naïve patients randomised to placebo (n=77) or atorvastatin 40 mg (n=76), starting seven days before the planned intervention. A significant reduction of post-procedural MI (defined as an increase of CK-MB >2 times the upper normal limit - UNL) was detected in patients receiving atorvastatin (5% vs 18%; p=0.025) (Figure 1). Multivariate logistic regression analysis demonstrated that pretreatment with atorvastatin was independently associated with lower risk of periprocedural CK-MB increase (OR 0.19; 95% CI 0.05 to 0.57).

**Figure 1: A**RMYDA Trial.

These results were then confirmed by other experiences. In the randomised study by Briguori et al.\textsuperscript{40}, statin administration started > 3 days before PCI resulted in a significant prevention of periprocedural MI in 451 patients undergoing elective PCI (8.0% vs 15.6% in the no-statin group; OR=0.47; 95% CI=0.26-0.86; p=0.012). A meta-analysis by Mood et al.\textsuperscript{41}, collecting data from six randomised trials, showed a reduced incidence of MI in patients pre-treated with statins undergoing PCI (3.0% vs 5.2%; OR 0.57, 95% CI 0.42 to 0.78, p<0.0001); also the incidence of all-cause mortality was 2.3% in the statin arm versus 3.0% in the placebo arm (OR 0.74, 95% CI 0.50 to 1.1, p=0.14).

However, in the studies previously described, statin administration was started at least three to seven days before the procedure. The more recent randomised Novel Approaches for Preventing or Limiting Events (NAPLES) II trial\textsuperscript{42}, enrolling 668 patients scheduled for elective PCI, demonstrated that even a single high (80 mg) loading dose of atorvastatin administered within 24 hours before stenting is effective in reducing the rate of periprocedural MI. In this study, the incidence of a CK-MB elevation > 3 UNL was 9.5% in the atorvastatin group and 15.8% in the control group (OR: 0.56; 95% CI: 0.35 to 0.89; p=0.014).
A post hoc analysis suggested that the cardioprotective effect of atorvastatin was more pronounced in the subgroup of patients with high CRP levels at baseline.

In patients with non ST segment elevation ACS receiving invasive strategy the role of statins has been also largely investigated. Chang et al.43 observed that unstable patients who were on statin therapy had a lower incidence of periprocedural myocardial necrosis compared to patients who were not (2% vs 19%, p=0.04), with a significant better event-free survival at six months (19% vs 31%; p=0.015). However, the ARMYDA-ACS44 was the first randomised, placebo-controlled trial, evaluating the effects of an acute high-dose loading with atorvastatin on 30-day clinical outcome in statin-naive patients with acute coronary events undergoing early (<48 hours) PCI. A total of 171 patients were randomised to receive placebo (n=85) or pre-treatment with atorvastatin (n=86, 80 mg loading dose given a mean of 12 hours before coronary angiography, with a further 40 mg dose approximately two hours before the procedure).

The primary composite end-point, 30 day incidence of MACEs (death, MI, target vessel revascularisation), occurred in 5% of patients in the atorvastatin and in 17% of those of the placebo group (p=0.01) (Figure 2). This difference in MACEs at one month was mostly driven by a higher incidence of peri-procedural myocardial infarction in the control arm (15% vs 5% in the statin treated group, p=0.04).

**Figure 2: ARMYDA ACS Trial.**

![Incidence of primary composite end point (30 day death, myocardial infarction and target vessel revascularization) in atorvastatin group versus placebo group (MACE=major adverse cardiac events, TVR=target vessel revascularization). Modified from Patti G et al.44](image)

The secondary end point, i.e. proportion of patients with post-procedural elevation of CK-MB and troponin I above the UNL, was also significantly lower in the atorvastatin group (CK-MB: 7% vs 27%, p=0.001; troponin I: 41% vs 58%, p=0.039). Cardioprotection by atorvastatin load was paralleled by attenuation of percent increase of CRP levels after PCI. Multivariate analysis revealed 88% risk reduction of MACEs at 30 days (OR 0.12, 95% CI 0.05 to 0.50; p=0.004) (Figure 3) and 70% risk reduction of periprocedural MI in the atorvastatin group: according to these data, 10 patients should be treated with atorvastatin to avoid one case of myocardial infarction (NNT=10).

**Figure 3: ARMYDA ACS Trial.**

![Results of multivariate analysis (MACE=major adverse cardiac events, NSTEMI=non-ST segment elevation myocardial infarction, LVEF=left ventricular ejection fraction, ACE=angiotensin-converting enzyme). Modified from Patti G et al.44](image)

Those results were confirmed in the study by Yun et al.45, in which clinical outcome was improved by a single high-dose of rosuvastatin (40 mg) given an average of 16 hours prior to PCI in patients with unstable syndromes; in fact, 30-day incidence of MACEs was significantly lower in the statin arm (6.7% vs 15.9% in controls, p=0.002); again, this benefit was mainly due to prevention of peri-procedural myocardial MI.

However, the majority of patients undergoing PCI is already on statins therapy at the time of the procedure. Thus, the next step, in light also of the experimental data previously reported, was to investigate whether an acute statin reload before coronary stenting in patients on top of chronic statin use would have cardioprotective effects, especially in the setting of ACS. For this reason, the ARMYDA study group designed the ARMYDA RECAPTURE study46; it was a multicentre, randomised, prospective, double-blind trial enrolling statin-treated patients (> 30 days) with stable angina or non-ST segment elevation acute coronary syndromes undergoing PCI. Eligible patients (n=383) were randomised to receive placebo (n=191) or atorvastatin (n=192, 80 mg loading given a mean of 12 hours before coronary angiography, with a further 40 mg dose approximately two hours before the procedure). The primary end point (30-day MACEs: cardiac death, MI, target vessel revascularisation) was observed in 3.7% of patients in the atorvastatin reload and in 9.4% in the placebo arm (p=0.037).
This beneficial effect of atorvastatin was essentially due to reduction of periprocedural MI (3.7% vs 8.9%; 2.4-fold reduction). Interestingly, subgroup analysis revealed that benefit of atorvastatin reload was highly significant in patients treated for an acute coronary event (MACEs incidence: 3.3% vs 14.8% in the placebo group; OR=0.18, 95% CI 0.10-0.33, RRR=82%; p=0.027), whereas event rates in patients with stable angina were not different (4% vs 4.9%; OR=0.74, 95% CI 0.20-2.90; p=0.70) (Figure 4). Multivariate analysis identified atorvastatin reload as a predictor of decreased risk of MACEs at 30 days (OR: 0.50, 95% CI: 0.20 to 0.80; 50% relative risk reduction; p=0.039) (Figure 5); according to these data 17 patients should be reloaded with atorvastatin in order to prevent one adverse event (NNT=17).

**Figure 4: ARMYDA RECAPTURE Trial.**

Incidence of major adverse cardiac events at 30 days according to clinical presentation (stable angina versus acute coronary syndromes) (ACS= acute coronary syndromes). Modified from Di Sciascio G et al.46

**Figure 5: ARMYDA RECAPTURE Trial.**

Results of multivariate analysis (LVEF=left ventricular ejection fraction). Modified from Di Sciascio G et al.46

**CONCLUSIONS**

The pleiotropic effects of statins, including inhibition of inflammation, modulation of endothelial function and attenuation of thrombosis, may explain the benefit of these drugs in patients with coronary artery disease, especially in those with ACS, treated medically or receiving an invasive strategy. In particular, in the setting of PCI, early high-dose statins treatment is associated with a significant reduction in peri-procedural myocardial damage. Controlled, randomised trials, such as the studies of the ARMYDA group, demonstrated that pre-treatment with statins before PCI reduces the incidence of this complication in statin-naïve patients with both stable and unstable syndromes. Moreover, even in the background of chronic therapy with statins, a short-term, high-dose reload with atorvastatin may give an adjunctive beneficial effect on cardiovascular events, mainly in patients presenting with ACS. All these pieces of evidence strongly support an “upstream” administration of high dose statins in all patients PCI.

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