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Statins and Their Role in Pre-Percutaneous Coronary Intervention

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Abstract Lipid-lowering therapy with statins reduces the risk of cardiovascular events in patients with coronary artery disease. Recent in vitro and in vivo studies demonstrated a low-density lipoprotein-independent action of this class of drugs, which appears to modulate endothelial function, inflammation, and thrombosis. Randomized studies showed a beneficial effect of short-term statin pretreatment in reducing periprocedural cardiac marker release in patients undergoing percutaneous coronary intervention (PCI). In particular, the ARMYDA (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) investigators—initially in stable angina patients, then in patients with acute coronary syndrome, and then in patients already on chronic statin therapy—demonstrated an improvement in 30-day major adverse cardiac event rates, which were driven by a reduced rate of periprocedural myocardial infarction. Moreover, statin therapy at the time of PCI significantly decreased the incidence of contrast-induced nephropathy. These observations support high-dose statin pretreatment in all patients who are candidates for PCI.

Keywords Percutaneous coronary intervention · Statins · Myocardial infarction · Chronic angina · Acute coronary syndrome

Clinical Trial Acronyms

ARMYDA	Atorvastatin for Reduction of Myocardial Damage During Angioplasty
ARMYDA ACS	Atorvastatin for Reduction of Myocardial Damage During Angioplasty—Acute Coronary Syndromes
ARMYDA-CAMS	Atorvastatin for Reduction of Myocardial Damage During Angioplasty—Cell Adhesion Molecules
HPS	Heart Protection Study
MIRACL	Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering
4S	Scandinavian Simvastatin Survival Study

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Introduction

Therapy with statins has become a cornerstone for the prevention of cardiovascular events. This class of molecules is a potent suppressor of cholesterol biosynthesis by inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase in the liver. The effectiveness of statins for secondary cardiovascular prevention was first demonstrated in the 4 S [1], which provided clear evidence of the survival benefit by simvastatin therapy versus placebo. The HPS showed that a reduction of 40 mg/dL in the low-density lipoprotein cholesterol levels was associated with an overall 25% reduction in the incidence of coronary events in individuals at high cardiovascular risk (primary prevention) [2].

The lipid-lowering action of statins might explain most of the beneficial effects of long-term statin use [3]. However, significant changes in serum lipid levels may take days to weeks, and clinical benefit of statins appears to be greater and more rapid than that expected from reduction in lipid levels alone, suggesting effects beyond cholesterol lowering (the so-called "pleiotropic effect"). These noncholesterol-lowering–mediated actions include

inhibition of inflammation, modulation of endothelial function and, antithrombotic effect, and have been demonstrated within a few hours after statin therapy initiation [4, 5].

Percutaneous coronary intervention (PCI) represents a widespread and effective revascularization strategy in patients with coronary artery disease, but some periprocedural complications (eg, periprocedural myocardial infarction [MI] or contrast-induced nephropathy [CIN]) could attenuate the effectiveness of these procedures. Periprocedural MI by cardiac marker elevation (without electrocardiogram changes or impairment of cardiac function) is a relatively frequent complication after PCI, with a reported incidence up to 40% [6–8]. Recent studies have indicated that postprocedural rise of creatine-kinase MB (CK-MB) or troponin I (TnI) is a predictor of future major adverse cardiac events (MACE) (death or MI) in patients undergoing PCI [9], and that the risk of further events is proportional to the amount of cardiac marker elevation after the procedure [10]. Various pharmacologic strategies have been evaluated to prevent periprocedural myocardial ischemic events (eg, nitrate infusion [11], intracoronary β blockers [12], use of glycoprotein IIb/IIIa inhibitors [13], and adenosine [14]), but only glycoprotein IIb/IIIa inhibitors have been demonstrated to provide a definite clinical benefit.

CIN is a nonfrequent complication following contrast exposure, but it is associated with increased early and follow-up morbidity and mortality [15–17]. Both periprocedural MI and CIN have underlying inflammatory mechanisms that could be attenuated by the anti-inflammatory effect of statins.

Statins and Prevention of Periprocedural Myocardial Damage

In light of the recent observation of early pleiotropic effect of statins, in the recent years, various studies have investigated the effects of high-dose statin load on the incidence of periprocedural MI in the setting of PCI.

In an observational study, Herrmann et al. [18] tested the hypothesis that preprocedural statin therapy could be associated with reduction in the extent of procedure-related myocardial injury in patients (n=296) undergoing PCI for de novo coronary stenoses; patients were stratified into statin treated and statin naïve. Statin-treated patients showed a greater than 90% lower post-PCI incidence of CK-MB elevation versus those without statin (0.4% vs 6%; P=0.037); statin therapy was independently associated with a lower risk of CK-MB elevation after the procedure (OR, 0.08; 95% CI, 0.01–0.75; P=0.03). In a larger series of patients receiving elective PCI (n=5052), Chan et al. [19] demonstrated that patients treated with statins at the time of intervention had a significant mortality reduction at 30 days (0.8% vs 1.5% in statin-naïve patients; hazard ratio [HR], 0.53; P=0.048); this benefit was also maintained at 6-month follow-up (2.4% vs 3.6%; HR, 0.67; 95% CI, 0.46–0.99; P=0.046). At multivariate analysis, statin use remained an independent predictor for better survival at 6 months after coronary intervention (HR, 0.65; 95% CI, 0.42–0.99; P=0.045). The same authors reported in a large population (n=1552) that patients who had initiated statin therapy prior to the procedure (39.6%) had lower occurrence of periprocedural MI (5.7% vs 8.1% in statin naïve; P= 0.038) and a mortality benefit at 1 year (3.4% vs 6.9%; P= 0.003); statin pretreatment was predictive of survival mainly among patients in the highest C-reactive protein (CRP) quartile (5.7% vs 14.8%, P=0.009) [20].

The ARMYDA trial [21] was the first randomized, prospective, placebo-controlled, double-blind study that demonstrated a beneficial effect of a statin pretreatment in preventing myocardial damage after coronary stenting. The study population consisted of 153 statin-naïve patients with chronic stable angina undergoing elective PCI, who were randomized to receive placebo (n=77) or atorvastatin 40 mg/d (n=76) starting 7 days before the planned angioplasty. Periprocedural MI was detected in 5% of patients in the atorvastatin versus 18% of those in the placebo group (P=0.025) (Fig. 1a); moreover, post-PCI increase of cardiac markers above upper limits of normal (ULN) was also lower in the atorvastatin arm (CK-MB 12% vs 35%; P=0.001; TnI 20% vs 48%; P=0.0004). At 1-month follow-up, no further cardiac event was observed in the study cohort and benefit of atorvastatin pretreatment on the 30-day composite end point (including death, MI, and repeat coronary revascularization) was essentially due to prevention of periprocedural MI. Multivariate logistic regression analysis showed that use of atorvastatin was associated with 81% relative risk reduction of periprocedural MI (OR, 0.19; 95% CI, 0.05–0.57). As for the anti-inflammatory effects, prevalence of patients with CRP greater than 5 mg/L after 1 week of treatment was significantly lower in the atorvastatin group (10% vs 23%; P=0.02).

The Supposed Mechanism of Benefit of Statin Therapy in Elective PCI

A relationship between the degree of CK-MB elevation after PCI and mortality risk during follow-up has been demonstrated. A recent meta-analysis, pooling data from 23,230 patients, showed that any increase of CK-MB above normal limits is associated with increased mortality; in particular, an elevation of CK-MB of one to three times was

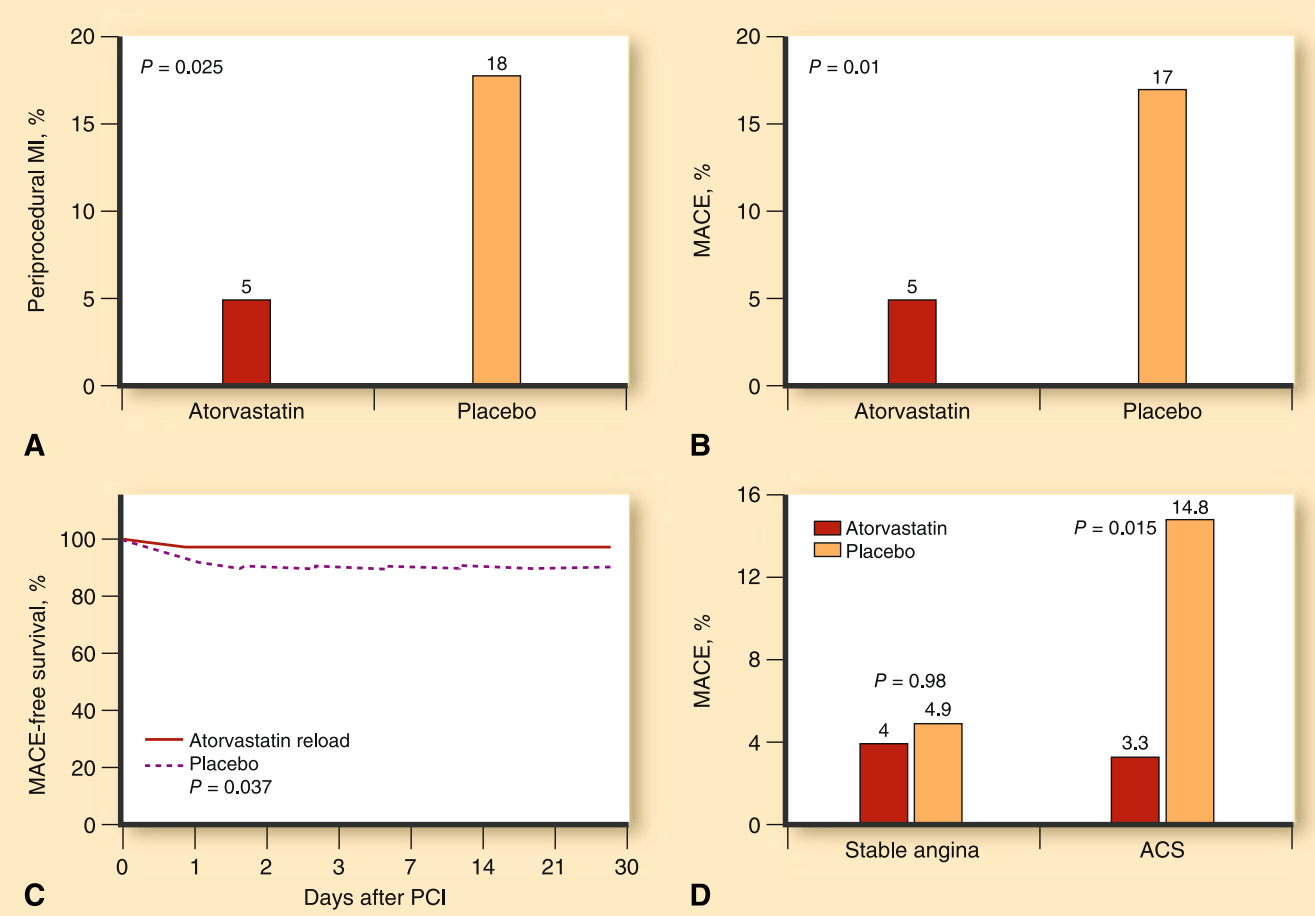

Fig. 1 **a** ARMYDA trial: incidence of periprocedural MI in the atorvastatin versus placebo arm. **b** ARMYDA-ACS trial: incidence of 30-day MACE in the atorvastatin versus placebo arm. **c** ARMYDA-RECAPTURE trial: event-free survival in the atorvastatin reload versus placebo arm. **d** ARMYDA-RECAPTURE trial: incidence of 30-day MACE in the atorvastatin versus placebo arm according to clinical presentation. *ACS*—acute coronary syndrome; *ARMYDA*—Atorvastatin for Reduction of Myocardial Damage During Angioplasty; *ARMYDA ACS*—Atorvastatin for Reduction of Myocardial Damage During Angioplasty—Acute Coronary Syndromes; *MACE*—major adverse cardiac events; *MI*—myocardial infarction; *PCI*—percutaneous coronary intervention; *TVR*—target vessel revascularization

associated with an excess mortality of 1.7% at 1 year; the excess mortality was 2.8% for CK-MB three to five times above the ULN and 7.4% for an increase greater than five times above the ULN [9]. Thus, identification of drugs able to reduce the occurrence and the extent of the myocardial injury during PCI could have an important prognostic relevance.

Statins have anti-inflammatory effects in vitro [22] and in vivo [23], and inflammatory status before angioplasty is associated with higher risk of periprocedural myocardial necrosis [24] and adverse cardiac events during follow-up [25, 26]. The anti-inflammatory action of statins might contribute to reduce myocardial necrosis due to micro-embolization during coronary intervention; this concept is supported by experimental evidence showing protective effects of statins in a model of ischemia/reperfusion, possibly by effects on microcirculation, cell adhesion [27], and platelet function [28].

Statins may induce plaque stabilization by reducing matrix metalloproteinase secretion and may decrease thrombosis by preventing platelet CD40L expression and production of prothrombin fragment F1+2 [29]. Previous studies demonstrated a significant attenuation of inflammatory markers, such as CRP, in acute coronary syndrome (ACS) patients treated with those agents [30]. In the ARMYDA-CAMS study [31], a planned subanalysis of the ARMYDA trial, peripheral levels of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin were blindly measured at randomization, 7 days before PCI, immediately before angioplasty, and after 8 and 24 h. ICAM-1, E-selectin, and VCAM-1 levels were not different at the randomization and before intervention in either arm, whereas compared with placebo, atorvastatin pretreatment significantly attenuated ICAM-1 and E-selectin increase following PCI. A similar post-PCI attenuation of adhesion

molecules peak levels by atorvastatin load was recently demonstrated in ACS patients [32]. This confirms the protective action of atorvastatin on endothelial function.

Improvement of microvessel coronary circulation and endothelial function, with reduction of microembolization events, could represent the mechanism of cardioprotection during coronary intervention provided by statins; those protective effects translate into better clinical outcome.

Statin Cardioprotective Effect in Patients with ACS Undergoing PCI

Patients with ACS present a relatively high risk of recurrent adverse cardiovascular events [33]. Early, intensive use of statins may improve clinical outcome in those patients and such agents have recently been included in the treatment guidelines for ACS [34].

Early benefit by statin therapy in patients with ACS was demonstrated in the MIRACL study [35]; this trial enrolled 3086 patients with non–ST-segment elevation MI, randomized to atorvastatin, 80 mg, versus placebo within 24 to 96 h from hospital admission. In the active treatment arm, there was a 16% risk reduction in the primary composite end point (death, nonfatal MI, cardiac arrest, or recurrent ischemia) at 4 months versus placebo (P=0.048).

A meta-analysis of 12 randomized controlled trials, involving a total of 13,024 patients, evaluated whether early initiation of statin therapy compared with placebo or usual care improved patients outcomes following ACS [36]. Early statin therapy failed to demonstrate significant benefit in the occurrence of death, MI, or stroke (primary composite end point) at 4 months; however, recurrence of unstable angina was reduced (4.8% vs 6.0%; P=0.05). To note, these trials included ACS patients in whom only a minority received coronary intervention (<50% in seven trials, whereas in four trials no patients underwent PCI); moreover, the absolute numbers of revascularization procedures were variable because of different criteria for performing revascularization. Additional meta-analyses of randomized, controlled trials demonstrated that early initiation of statins after ACS improves cardiovascular outcomes, although this benefit takes 6 months for morbid events [37] and 24 months for fatal events [37, 38] to become evident.

The effect of statins in patients with ACS undergoing nonprimary PCI was specifically investigated by Chang et al. [39] in an observational study; the authors evaluated whether the release of CK-MB post-PCI and the incidence of clinical events during follow-up was different in patients who were taking statins at the time of procedure (n=63) versus those statin naïve (n=56). Patients pretreated with statins had a significantly lower incidence of myonecrosis (2% vs 10%; P=0.04) and decreased event rate (death, nonfatal MI unrelated to PCI, target vessel revascularization, unstable angina requiring hospitalization) at 6 months (17% vs 21%; P=0.015). At multivariate analysis, use of statins prior to PCI was associated with an 80% reduction in the risk of clinical events (OR, 0.20; CI, 0.06–0.63; P=0.006). However, in this study the samples size was not powered to evaluate a possible mortality benefit with statins and there was a relevant heterogeneity in the risk profile of the index population; moreover, patients receiving statins were treated with different statins, at variable doses and different duration of therapy.

The ARMYDA ACS randomized 171 patients with ACS to receive placebo (N=85) or atorvastatin (n=86: 80 mg 12 h before coronary angiography and 40-mg dose 2 h before intervention) to evaluate the effects of short-term, high-dose loading with a specific statin, given at a fixed dose, on outcome after PCI [40]••. The primary composite end point was 30-day MACE (death, MI, target vessel revascularization). MACE occurred in 5% of patients in the atorvastatin group versus 17% in the placebo arm (P=0.01) (Fig. 1b); incidence of MACE at 1 month was essentially driven by periprocedural MI in either group (5% vs 15%; P=0.04). At multivariate analysis, pretreatment with atorvastatin was associated with an 88% relative risk reduction of 30-day events. Incidence of patients with any postprocedural elevation of CK-MB and TnI was also significantly lower in the atorvastatin arm (CK-MB: 7% vs 27%; P=0.001; TnI: 41% vs 58%; P=0.039).

Acute Loading with Statin in Patients in Chronic Therapy

Given the extensive use of statins in primary and secondary prevention of cardiovascular events, a large proportion of patients undergoing PCI are already on statin therapy at the time of hospitalization for ACS or elective PCI. The ARMYDA group designed the ARMYDA RECAPTURE study [41]••, a multicenter, randomized, double-blind trial on statin-treated patients (>30 days) with stable angina or non–ST-segment elevation ACS requiring early invasive strategy, to evaluate whether an acute statin reload before intervention would have cardioprotective effects. A total of 383 patients were randomized to receive placebo (N=191) or atorvastatin reload (N=192: 80 mg approximately 12 h before coronary angiography, with an additional 40-mg dose 2 h before intervention). The primary end point (cardiac death, MI, target vessel revascularization at 30 days) was observed in 3.7% of patients in the atorvastatin reload versus 9.4% of those in the placebo arm (P=0.037; 50% risk reduction at multivariate analysis) (Fig. 1c); those results were essentially driven by a 2.4-fold reduction of periprocedural MI in the active treatment

group. Subgroup analysis showed that clinical benefit by atorvastatin reload was confined in patients with ACS (82% risk reduction of 30-day adverse events) (Fig. 1d); the number needed to treat was 17 in the overall cohort and 9 in the ACS subgroup.

Prevention of Contrast-Induced Nephropathy

CIN is an infrequent but clinically important complication after PCI, leading to prolonged hospitalization and increased morbidity and mortality during follow-up. Incidence of CIN is low in patients with normal renal function [15], but it may significantly higher in patients with pre-existing chronic renal failure [16]. Diabetes mellitus, congestive heart failure, advanced age, and high-contrast volume exposure are reported to be other risk factors related to the occurrence of CIN. Although the pathophysiologic mechanisms of this complication are controversial, a combination of medullary ischemic damage due to vasoconstriction, detrimental effects of oxygen-free radicals causing tubular cell alterations, and inflammation may be involved [17, 42].

In a large population (n=29,409), Khanal et al. [43] observed that patients who did receive preprocedural statins had lower incidence of CIN (4.37% vs 5.93%; P<0.0001) and less nephropathy requiring dialysis after PCI (0.32 vs 0.49; P=0.03). At multivariate analysis, statin use was associated with a significant reduction in CIN (OR, 0.87; 95% CI, 0.77–0.99; P=0.03).

Patti et al. [44] prospectively enrolled 434 patients undergoing PCI to evaluate the effects of statins on CIN incidence and long-term outcome. Patients were stratified according to preprocedural statin therapy (260 statin treated, 174 statin naïve) and follow-up was obtained up to 4 years. CIN was defined as a postprocedural increase in serum creatinine of ≥0.5 mg/dL or greater than 25% from baseline. Statin-treated patients had a significantly lower incidence of CIN (3% vs 27% in patients statin naïve; P< 0.0001), corresponding to a 90% risk reduction (OR, 0.10; 95% CI, 0.02–0.18; P=0.0001), and showed better post-intervention creatinine clearance (80±25 vs 65±19 mL/min; P<0.0001). This benefit was maintained in all subgroups, except for patients with pre-existing baseline creatinine clearance less than 40 mL/min (OR for CIN 0.42; 95% CI, 0.1–2.8; P=0.37); this was probably related to the multiple, nonreversible mechanisms of advanced renal dysfunction. Multivariable analysis identified female gender, diabetes mellitus, previous MI, increased baseline serum creatinine level, decreased baseline creatinine clearance, and amount of contrast load as independently associated with increased risk of CIN. At long-term (4-year) clinical follow-up, patients receiving statins at the time of the procedure had a significantly reduced occurrence of cardiovascular events (cardiac death, MI, or repeat coronary revascularization) compared with statin-naïve patients (6% vs 36%; P<0.0001). Actuarial life table analysis showed that 4-year event-free survival was best in patients treated with statins and no CIN (95%, P≤0.015 vs other groups) and worst in statin-naïve patients with CIN (53%, P≤0.018 vs other groups); interestingly, survival of statin-treated patients who developed CIN was similar to those statin-naïve patients who did not develop this complication (72% vs 71%), demonstrating that prevention of CIN by statin use translates into outcome improvement.

Mechanism of Action of Statins in CIN Prevention

The beneficial action of statins on CIN prevention may be explained by different mechanisms. Statins may modulate the kidney hypoperfusion after contrast administration by downregulation of angiotensin receptors and decreased synthesis of endothelin-1 [45, 46]; furthermore, toxic damage on the tubular cells by oxygen-free radicals and proinflammatory cytokines may be decreased by anti-inflammatory effects of statins that inhibit tissue factor expression by macrophages and prevent the activation of nuclear factor-κB [47].

Conclusions

Revascularization with PCI is recognized as an effective therapeutic strategy in patients with coronary artery disease, and it is actually considered the gold standard treatment in a variety of cardiac clinical syndromes. An increase in cardiac biomarkers has been shown to occur in up to 40% of patients after otherwise successful PCI, with subsequent, worse outcome during follow-up. Development of CIN after PCI, even if less frequent, may also negatively impact prognosis in these patients.

Beside improvements of PCI techniques and materials to reduce the incidence of vasal dissection, the compromise of side branches, plaque shifting, no-reflow phenomenon, or high-contrast volume utilization, therapies with antithrombotic and anti-inflammatory actions may provide significant advantages in patients undergoing PCI.

Experimental data have demonstrated that lipid-lowering action of statins may partly explain beneficial effects of these drugs; the so-called “pleiotropic effects” of statins include inhibition of inflammation, modulation of endothelial function, and attenuation of thrombosis, which could provide a clinical benefit in the setting of PCI.

Observational studies, and more recently, controlled, randomized trials, such as the studies of the ARMYDA

group, have demonstrated that pretreatment with statins before PCI reduces periprocedural MI in statin-naïve patients with both stable and unstable syndromes,. Even in the background of chronic therapy with statins, a short-term, high-dose reload with atorvastatin gives an adjunctive beneficial effect on cardiovascular events, mainly in patients presenting with ACS. Also, statins have been demonstrated to prevent CIN post-PCI and prevention of CIN translates into clinical outcome improvement.

Statin pretreatment is a low-risk strategy that results in significant clinical benefit short term and long term in patients undergoing PCI. Thus, current evidence strongly supports a systematic use of statins prior to PCI as an adjuvant pharmacologic therapy.

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