Editorial

Early treatment with high-potency statins in patients with acute coronary syndrome—an example of personalized medicine

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Statins, together with aspirin, are the cornerstone of secondary prevention treatment in stable coronary artery disease (CAD) and acute coronary syndrome (ACS). The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study was one of the first randomized controlled trials which demonstrated a benefit of high-potency statin therapy in the setting of ACS (1). Compared with placebo, atorvastatin 80 mg given during the first days after an ACS decreased the rate of major adverse cardiovascular events (MACE) (1). This effect was observed as early as 6 weeks after randomization and was significant at 16 weeks. The prompt effect that was observed with high-potency statins is one of the cornerstones of the plaque stabilization hypothesis, in which a clinical effect is demonstrated well before the low levels of low density lipoprotein-cholesterol (LDL-c) can affect plaque progression. This "pleiotropic" effect of statins was addressed by numerus studies suggesting various mechanisms of action such as anti-inflammatory effect, and improved endothelial and platelet function. The effect of high *vs.* low potency statins in ACS was examined by the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) trial and other studies which demonstrated a dose-response relationship between LDL-c level and MACE (2,3). The PCI PROVE IT, a sub-study of the PROVE IT-TIMI 22 trial, demonstrated that in patients who underwent percutaneous coronary intervention (PCI), those who were treated with high-potency statins had a significantly lower rate of target vessel revascularization [odds ratio (OR) 0.74, P=0.015] even after adjusting to LDL-c levels (4).

Current European and American guidelines recommend the administration of high-potency statins as early as possible in ACS, but preloading before PCI is not fully addressed and the timing of statin treatment is a matter of debate (5-8). The concept of loading statins before PCI was addressed in several randomized controlled trials such as the Atorvastatin for Reduction of MYocardial Damage during Angioplasty (ARMYDA) trial which demonstrated a reduction in peri-procedural myocardial infarction (MI) (defined as > X2–X5 rise in CK-MB levels) in patients with stable CAD undergoing PCI (9). The ARMYDA-RECAPTURE study showed a reduction in 30 days MACE in patients with stable angina or with non-ST elevation MI who were previously treated with statins and were reloaded with high potency statins (10). In a meta-analysis of 20 randomized controlled trials, comprising 8,750 patients, statins given to naïve patients before PCI decreased the rate of MI at 30 days [OR 0.38, 95% confidence interval (CI), 0.24–0.59; P<0.0001], whereas when statins were given post-PCI, their effect was not significant (OR 0.85, 95% CI 0.64–1.13; P=0.28) (11). Similar results with statins prior to PCI were demonstrated with MACE at 30 days (OR 0.35,

Table 1 Major trials examining early high potency statin treatment prior to PCI in patients with ACS

Study	No. of patients	Population	Loading treatment	Time of 1st dose	Primary endpoint	Secondary endpoint	Results	Follow-up
ARMYDA-ACS (12)	171	NSTEMI	Atorvastatin 80 mg *vs.* placebo	12 h prior to PCI	MACE	Increased level of biomarkers > ULN; increase in CRP	Primary endpoint: 5% *vs.* 17%, P=0.01	30 days
ARMYDA-RECAPTURE (10)	383	Stable angina and NSTEMI	Atorvastatin 80 mg *vs.* placebo	12 h prior to PCI	MACE	Increase level of biomarkers > ULN; increased CRP; MACE	Primary endpoint: 3.7% *vs.* 9.4%, P=0.037	30 days
Yun *et al.* (13)	445	NSTEMI	Rosuvastatin 40 mg *vs.* placebo	Prior to PCI	Peri-procedural MI	Increase level of biomarkers > ULN or ≥20% increase; hsCRP; MACE	Primary endpoint: 11.4% *vs.* 5.8%, P=0.035	30 days; 12 months
Hahn *et al.* (14)	173	STEMI	Atorvastatin 80 *vs.* 10 mg after PCI	Prior to PCI	Infarct size by SPECT (% of LV)	MBG; ST resolution; MACE related to heart failure ANT 6 months	Primary endpoint: 22.2%±15.5% *vs.* 21.6%±15.4%, P=0.79	30 days; 6 months
Yu *et al.* (15)	81	NSTEMI	Atorvastatin 80 mg *vs.* placebo	12 h prior to PCI	MACE	Death, nonfatal MI, TVR, CABG, biomarkers, CRP	Primary endpoint: 2.4% *vs.* 22.5%, P=0.016	30 days
STATIN STEMI (16)	171	STEMI	Atorvastatin 80 *vs.* 10 mg	Prior to PCI	MACE	cTFC, MBG, and ST resolution at 90 min after PCI	Primary endpoint: 5.8% *vs.* 10.6%, P=0.26	30 days; 9 months
REPERATOR (17)	55	STEMI	Atorvastatin 80 mg *vs.* placebo	Prior to PCI	End-systolic volume index by MRI	LV function, infarct size, biomarkers, TIMI flow, and ST resolution	Primary endpoint: 25.1 *vs.* 25.0 mL/m^2, P=0.74	3 months
Gao *et al.* (18)	117	NSTEMI in Females	Rosuvastatin 20 mg *vs.* placebo	12 h prior to PCI	MACE	Myocardial injury, hs-CRP, IL-1, IL-6, and TNFa	Primary endpoint: 1.69% *vs.* 12.07%, P=0.026	3 months; 6 months
Wang *et al.* (19)	125	NSTEMI	Rosuvastatin 20 mg *vs.* placebo	2–4 h prior to PCI	MACE	Elevation in biomarkers > ULN within 30 days after PCI	Primary endpoint: 8.1% *vs.* 22.2%, P<0.01	30 days
SECURE PCI (20)	4191	ACS—STEMI and NSTE	Atorvastatin 80 mg *vs.* placebo	2–12 h—NSTE. Prior to PCI in STEMI	MACE	Mortality, MI, stroke, revascularization, cardiac death, stent thrombosis, TVR	Primary endpoint: 6.2% *vs.* 7.1%; HR 0.88; 95% CI, 0.69–1.11; P=0.27	30 days

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CRP, C reactive protein; cTFC, corrected TIMI frame count; hsCRP, high sensitive CRP; LV, left ventricle; MACE, major adverse cardiovascular events; MBG, myocardial blush grade; NSTEMI, non-ST elevation myocardial infarction; SPECT, single photon emitted computed tomography; STEMI, ST elevation myocardial infarction; PCI, percutaneous coronary intervention; TVR, target vessel revascularization; ULN, upper limit of normal.

95% CI, 0.20–0.59; P=0.0001) and beyond 30 days (OR 0.52, 95% CI, 0.37–0.73; P=0.002). The meta-analysis did not demonstrate a significant effect of statins on mortality at 30 days or beyond (11). A summary of the sentinel trials on statins use prior to PCI in ACS is depicted on *Table 1*.

The mechanism of the benefit observed with statin loading or re-loading before PCI is probably multifactorial. *In-vitro* models showed that statins given prior to PCI decrease distal embolization and increase circulating endothelial progenitor cells (21), thus potentially increase

endothelial healing following the injury caused by PCI. In addition, patients undergoing elective PCI, which were pre-treated with statins, had less microcirculatory resistance compared to placebo (22). These effects might be responsible for the improved clinical outcomes observed after PCI when preloading with statins, yet other unknown mechanisms are possible.

In the Statins Evaluation in Coronary procedUres and Revascularization (SECURE-PCI) trial published recently in *Journal of the American Medical Association*, two doses of atorvastatin 80 mg prior and 24 h after coronary angiography were examined in a double blind, placebo controlled, multi-center randomized trial in patients with ACS (with or without ST-segment elevation) (20). In this study, which included 4,191 patients, there was no significant difference in the 30-day rate of MACE [hazard ratio (HR), 0.88; 95% CI, 0.69–1.11; P=0.27]. The main results of the trial were consistent among different subgroups, and there was no significant between-groups interaction except for the PCI group. In this pre-specified subgroup analysis, patients who underwent PCI (67% of all patients) and who were randomized to receive early treatment with atorvastatin, had a significant reduction in 30-day MACE (HR 0.72, 95% CI, 0.54–0.96, P interaction =0.02). Furthermore, in a post-hoc analysis of patients with ST-segment elevation MI (STEMI) who underwent PCI, there was a significant reduction in 30-day MACE (HR 0.66, 95% CI, 0.48–0.98; P-interaction with the no-PCI group =0.04) in favor of the loading treatment, whereas in patients with non-STEMI there was no significant interaction by PCI and treatment group. Although the primary outcome of the SECURE-PCI trial was negative, it is certainly reassuring with regards to the safety of early high-potency statin treatment. The results in the PCI sub-group may suggest that in ACS patients undergoing PCI, early statin treatment is more important than in those who are treated medically or by coronary artery bypass graft surgery. The positive results of the post-hoc STEMI sub-group may be related to the fact that the majority of these patients underwent PCI and were not treated conservatively. It might also be influenced by the distal embolization to the microcirculation, which in its extreme form is frequently observed as "no reflow" phenomenon during primary PCI in STEMI.

The choice of "hard" clinical end points in the SECURE-PCI trial and the short-term follow-up, may partially explain the negative results of the study. Unlike biomarkers levels and infarct size, mortality in the first 30 days following MI is usually caused by catastrophic events, such as cardiogenic shock and mechanical complications. The contribution of minor distal embolization events is probably limited. Improved microcirculation following statin loading might influence infarct size, which could theoretically translate to improved long term outcomes, but would be very hard to detect after 30 days. Nonetheless, in the absence of contraindication to statin treatment, there is no reason to defer the treatment and it should probably be given, as early as possible, particularly in patients treated with PCI. The positive results of atorvastatin loading in ACS patients undergoing PCI and particular in STEMI patients should make clinicians consider early statin loading even before primary PCI in the emergency department. This rationale concept of "the sooner the better" in ACS resembles preloading of other medications, such as clopidogrel, in which the added value of preloading is not clear while there are no safety concerns. Nevertheless, it is important to identify patients who might benefit the most from preloading with high-potency statins. Thus, a personalized approach, rather than a generalized one, is probably the take home message from the SECURE-PCI trial. Future prospective studies are needed to further examine specific populations who might benefit the most from high-potency statins preloading in ACS.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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