Editorial

Timing of high intensity statin for acute coronary syndrome: how earlier initiation makes better?

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Benefit of early initiation of intensive lipid lowering treatment is established in patients with acute coronary syndrome (ACS). Cholesterol-independent, pleiotropic effects of statin have been widely investigated with regard to suppression of plaque vulnerability (1). Previous studies explored favorable mechanisms of early initiation of statin with plaque modification by reduction of necrotic core in plaques with high risk morphology (2), or in plaques with ACS (3). The other mechanisms including inhibition of inflammatory activity, reduction of lipid accumulation in the plaque, and improving endothelial function have been also suggested as statin effects (4). In the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study, administration of 80 mg atorvastatin within 24 to 96 hours of hospital, compared with placebo, reduced the incidence of cardiovascular events (14.8% *vs.* 17.4%, relative risk 0.84, P=0.048) including death, myocardial infarction, cardiac arrest with resuscitation, and recurrent ischemic symptom within 16 weeks in patients with ACS (5). Compared with moderate intensity, 40 mg pravastatin, 80 mg atorvastatin achieved lower density lipoprotein cholesterol (LDL-C) in patients hospitalized for ACS, which brought favorable clinical outcomes with 16% reduction in major cardiovascular events for 2 years in the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22) study (6). The IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study compared simvastatin plus additional ezetimibe with simvastatin monotherapy (7). Simvastatin-ezetimibe combination was more effective in reducing average LDL-C level than simvastatin monotherapy and it resulted in lower incidences of primary end point [32.7% *vs.* 34.7%, hazard ratio (HR) 0.94, P=0.016] during 7-year follow-up. Current US and European guidelines have emphasized the importance of intensive lipid lowering, which is one of cornerstones for management of atherosclerotic coronary artery disease especially in high risk patients, with using high intensity statin or achieving very low LDL-C concentration (8-12).

Concept of early initiation of statin has been accepted as a manner of starting statin treatment in a patient with stable condition before discharge after index ACS event (8,10). There have been also concerns about safety of high intensity statin administration during early (or unstable) phase of ACS. More importantly, definite evidences supporting administration of statin at very early phase of ACS or before invasive management are limited. Previous trials assessing early lipid lowering strategies enrolled patients during in-hospital period after index ACS event. The MIRACL trial allowed randomization between 1 and 3 days after admission, however, it only included patients with non-ST elevation ACS not planning to undergo coronary revascularization. In both PROVE-IT and

IMPROVE-IT trials including nearly 70% of patients undergoing PCI for treatment of index event, subjects were allowed to be enrolled within 10 days after onset of ACS events and before discharge. The studies tested in-hospital initiation of statin defined by the study protocol and demonstrated meaningful results in favor of more potent lipid lowering treatment. Study protocol of the trials seem to be pragmatic that majority of patients with ACS may be considered for invasive management and that there was no reason to avoid statin initiation for stabilized patients after PCI in clinical practice. However, it had not been revealed whether initiation of statin before PCI or very early phase after event onset may be beneficial or harmful in patients with ACS.

Recently published study, the SECURE-PCI (Statins Evaluation in Coronary Procedures and Revascularization) trial was designed to assess the effect of periprocedural administration of statin in patients with ACS and planned coronary revascularization (13). The investigators sought to test an interesting hypothesis whether high dose atorvastatin before invasive management may reduce adverse cardiac events in ACS. Patients were randomized to receive either loading doses of 80 mg atorvastatin (n=2,087) or placebo (n=2,104) between 2 to 12 hours before PCI and next day, and were to receive 40 mg atorvastatin for 30 days afterward. There was no significant difference in primary outcome, defined as major adverse cardiovascular events including all-cause death, myocardial infarction, stroke, and unplanned coronary revascularization within 30 days, which was occurred in 6.2% in atorvastatin group, and 7.1% in placebo group (HR 0.88, P=0.27). It seems clear that no significant benefit of preprocedural administration of loading dose of atorvastatin compared with control treatment (initiation of 40 mg atorvastatin at day 2 after PCI). Even though assumption of the trial was not satisfied, its overall result has valuable implications in clinical practice: (I) after available evidences, there is no question about that intensive lipid lowering treatment should be started before discharge or within 10 days after ACS events; (II) initiation of high intensity statin within 2 days after PCI is as effective as its initiation within 12 hours before PCI in patients planning PCI. Clinicians do not have to be hasty in initiation of high intensity statin if the timing is just before revascularization; (III) inversely, there seems to be no need to defer preprocedural initiation of high intensity statin—loading dose of atorvastatin before PCI was not associated with periprocedural complications or increasing risk of adverse cardiovascular events.

However, there are still some questions remained. The trial compared timing of statin initiation between relatively narrow time window, 2 days beyond invasive procedure. Current evidences strongly support early initiation of intensive lipid lowering with statin, however the timing has not been definitely determined. It is not clear if it is equivalently effective to start statin as discharge prescription compared with administration at the earliest timing after event. Even though majority of eligible studies were conducted with small number of patients or with stable patients, patient-level meta-analysis of randomized controlled trials supported benefit of preprocedural initiation of high dose statin in patients with planned PCI (14). Another meta-analysis of randomized controlled trials in patients with ACS undergoing PCI demonstrated study-level association between earlier timing of statin initiation and greater clinical benefit within 30 days (15). Despite negative result of primary outcome, the SECURE-PCI study also remains a question if preprocedural administration of high intensity statin may be beneficial in patients undergoing PCI. To understand the role of high intensity statin is still challenging in the patients with unstabilized condition as well as those undergoing PCI after ACS.

Our institute previously reported results of two randomized controlled trials assessing preprocedural high intensity statin at emergency room before PCI. The STATIN STEMI (Efficacy of High-Dose AtorvaSTATIN Loading Before Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction) study compared an effect of 80 mg atorvastatin versus 10 mg atorvastatin before PCI with total 171 patients with ST elevation myocardial infarction. Although study population was limited to reveal statistical significance of differences in major clinical outcomes, a meaningful improvement in immediate coronary flow was noted with high intensity statin treatment before the procedure (16). Another study compared 40 mg rosuvastatin versus placebo as a loading dose before PCI and daily maintenance doses for following 7 days. However, it did not show significant differences in periprocedural coronary flow, infarct burden on cardiac magnetic resonance imaging, or clinical outcomes (17). Considering our clinical experiences and available evidences, we have an insight that initiation of high intensity statin at earlier time during in-hospital management is mostly feasible (even in the setting of urgent or emergency PCI) and not associated with increasing adverse events at worst. We have not hesitated to initiate prescription of high intensity statin in the management of ACS, irrespective of

the timing of PCI, when a patient is available to take oral medication. There is no reason to defer statin treatment at the earliest time after ACS event based on current evidences.

Findings of the SECURE-PCI trial support current strategies for management after ACS with early initiation of high intensity statin. It also implies that periprocedural administration of high intensity statin before invasive management would be acceptable without harm in PCI-eligible patients with ACS. Further investigations are required to clarify whether or how earlier statin initiation has an effect on better clinical outcomes and whether preprocedural high intensity statin truly affect clinical benefits in patients treated by invasive revascularization for ACS.

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Footnote

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

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