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Editorial

Should We Intensify Statin Management in ACS Patients with Very Low LDL Cholesterol Levels?

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▸ See the article "Intensity of Statin Treatment in Patients with Acute Myocardial Infarction and Very Low LDL Cholesterol" in volume 8 on page 208.

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Low-density lipoprotein (LDL) cholesterol level in the blood circulation is one of the most powerful and controllable risk factors predicting future atherosclerotic cardiovascular disease (ASCVD) events. Virtually all past trials used fixed doses of specific statins to lower LDL cholesterol levels and the achieved LDL cholesterol level was adopted as a threshold for optimal statin treatment guidelines, with sequential reductions of <100 mg/dL and <70 mg/dL in the case of secondary prevention. However, it remains unclear which of the following factors related to LDL cholesterol levels contributes to ASCVD prevention: the degree of reduction, the achieved level, or the breakthrough of a certain threshold level. In addition, intensive statin treatment itself may directly reduce the event of ASCVD. The 2016 European Society of Cardiology guidelines recommend more aggressive control of LDL cholesterol level using potent statins in secondary prevention, in which LDL cholesterol should be either maintained at <70 mg/dL or lowered by 50% or more when the baseline is 70–135 mg/dL.[1] In the American College of Cardiology/American Heart Association (AHA/ACC) cholesterol management guidelines released in 2013, the concept of management shifted from control of LDL cholesterol levels to the potency of statins, which generally recommends the maximum tolerable dose of statins for effective prevention of ASCVD events, while the use of non-statins is not recommended.[2]

Interestingly, a series of recent randomized control trials (RCTs) provided evidences that more aggressive lowering of LDL cholesterol levels using non-statins (such as cholesterol absorption inhibitors or proprotein convertase subtilisin/kexin type [PCSK] inhibitors) in addition to potent statins produces more favorable results in the prevention of ASCVD. The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study is a double-blind, randomized trial involving 18,144 patients who had been hospitalized for acute coronary syndrome (ACS) within the preceding 10 days and had LDL cholesterol levels of 50 to 100 mg/dL if they were on lipid-lowering therapy or of 50 to 125 mg/dL if they were not receiving lipid-lowering therapy.[3] Combination of simvastatin (40 mg) with a cholesterol absorption inhibitor ezetimibe (10 mg) was compared with simvastatin (40 mg) and placebo. The median time-weighted average LDL cholesterol level in the combination group was 53.7 mg. The benefit of combination treatment was consistently observed in subgroups whose basal LDL cholesterol levels were below the median value or in the first quartile. However, only 34.3%–34.6% of subjects were medicated with statins at baseline, which varies

from Sim's study's[4] demographic profile. The Further cardiovascular OUtcomes Research with PCSK9 Inhibition in patients with Elevated Risk (FOURIER) study is a randomized, double-blind, placebo-controlled trial involving 27,564 patients with ASCVD that tested an evolocumab regimen (either 140 mg every 2 weeks or 420 mg monthly).[5] All subjects had been treated with statins like in Sim's study,[4] but their LDL cholesterol levels were >70 mg/dL at randomization, which varied from Sim's study. The achieved LDL cholesterol level in the evolocumab add-on group was 30 mg/dL, a 59% reduction. The characteristics of ODYSSEY OUTCOMES were similar to the FOURIER trial, in which the achieved LDL cholesterol level in the alirocumab add-on group was 57 mg/dL.[6]

It becomes clear that, at least in the case of secondary prevention, more aggressive control of LDL cholesterol has been advised using statins with/without non-statins. The 2018 American Association of Clinical Endocrinologists and the American College of Endocrinology proposed a new "extreme-risk" category of patients for whom a LDL cholesterol level <55 mg/dL is advised.[7] In the 2018 AHA/ACC cholesterol management guidelines, patients with ASCVD should be treated with high-intensity statins, which can result in a 50% or greater reduction in LDL cholesterol levels.[8,9] Moreover, when LDL cholesterol levels still remain >70 mg/dL, additional management such as intensifying treatment with statins or adding non-statins, such as cholesterol absorption inhibitors or PCSK9 inhibitors, is strongly recommended. These 2018 AHA/ACC guidelines may integrate 2 different concepts in LDL cholesterol management and statin/non-statin treatment. This strongly suggests that LDL cholesterol should be maintained as low as <70 mg/dL through 50% or greater reduction for secondary prevention. In order to achieve this, add-on treatment with non-statins in addition to the maximum-tolerable statin dose are recommended.

The Korean population has a relatively lower concentration of LDL cholesterol in the blood, and the degree of LDL cholesterol reduction after statin medication is greater than seen in other population groups. Therefore, a substantial number of patients with acute myocardial infarction may show a very low LDL cholesterol level (<70 mg/dL) like in Sim's study.[4] Sim et al.[4] analyzed 1,086 patients with acute myocardial infarction with a baseline LDL cholesterol <70 mg/dL who were selected from the Korea Acute Myocardial Infarction Registry (KAMIR)-National Institute of Health database. All subjects were on statin medication upon enrollment and were divided into 2 groups: medicated with less intensive statin (expected LDL reduction <40%, n=302) or more intensive statin (expected LDL lowering ≥40%, n=784). The number of major cardiovascular outcomes within 12 months was monitored. The most impressive finding Sim's study[4] is that more intensive statin group showed lower incidence of target-vessel revascularization (4.6% vs. 1.8%, p=0.027) and MACCE (11.6% vs. 7.0%, p=0.021) during the 12-month observational period. The short duration of study may not be adequate for evaluating cardiovascular mortality, as discussed.

In clinical practice, the question of whether statin treatment should be intensified when LDL cholesterol level is already low (<70 mg/dL) even in patients with ACS including acute myocardial infarction. Indeed, virtually no independent RCT has explored the efficacy of statins in subjects with very low LDL cholesterol level (<70 mg/dL) as either primary or secondary prevention. The 2018 AHA/ACC guideline does not clearly describe those patients as good candidates for statin treatment or requiring more intense LDL cholesterol lowering.[8,9] Sim's study[4] showed that more intensive statin treatment for at least 12 months was more beneficial in maintaining LDL cholesterol at much lower levels, which may further reduce high sensitivity C-reactive protein levels, too. Such favorable findings may eventually contribute to the

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prevention of future ASCVD events. Therefore, in the presence of ACS like acute myocardial infarction, the intensity of statins may be more important than the achieved LDL cholesterol levels. Sim's study[4] suggests that immediate intensification of statin management and maintenance for 12 months after ACS events may be more protective than maintaining low-potency statins even in patients whose LDL cholesterol levels are already <70 mg/dL.

In a previous study by Cho et al.,[10] 9,571 patients (mean age 62.6±12.5 years, 6,967 men) who underwent percutaneous coronary intervention (PCI) with a final diagnosis of acute myocardial infarction in the KAMIR were divided into 5 groups according to LDL cholesterol level: <70, 70–99, 100–129, 130–159, and ≥160 mg/dL and the incidence of ACS was monitored for 12 months. Statins were obviously underused in patients with lower LDL cholesterol levels at baseline and clinical outcomes in hospital and 1 and 12 months after PCI showed worse results, with basal LDL cholesterol levels in lower quintiles. Taken together, a low LDL cholesterol level at the time of ACS suggests poor prognosis, which might be largely attributable to less intensive statin management after PCI. Therefore, aggressive medical treatment including statin medication in ACS patients should not be neglected because of low basal LDL cholesterol (<70 mg/dL).

On the other hand, more attention should be paid to avoiding adverse events when statin treatment is intensified. One of the major concerns is the increase in risk of intracerebral hemorrhagic (ICH) stroke. A meta-analysis performed by McKinney and Kostis[11] demonstrated the opposite finding, in which a total of 91,588 subjects were included in the active statin group and 91,215 in the control group. There was no significant difference in the incidence of ICH observed in the active statin group versus the control group (odds ratio [OR], 1.08; 95% confidence interval [CI], 0.88–1.32; p=0.47). ICH risk was not related to the degree of reduction or achieved levels of LDL cholesterol. Total stroke (OR, 0.84; 95% CI, 0.78–0.91; p<0.0001) and all-cause mortality (OR, 0.92; CI, 0.87–0.96; p=0.0007) were significantly reduced in the active statin group. Recently, concerns about statin-induced new-onset diabetes have been raised. Chun et al.[12] followed 6,048 Koreans who underwent PCI and statin treatment for 3.4 years. New-onset diabetes developed in 11.8%; however, the major adverse cardiovascular event rate was not higher than those who did not develop diabetes (19.5% vs. 20.5%). Therefore, newly diagnosed diabetes during statin treatment may not increase the short-term risk of ASCVD. Virtually all RCTs were limited to 5 years of follow-up. Therefore, more data are required to establish optimal statin management and to minimize life-long risk of ASCVD and statin-induced adverse events.

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