Hypcholesterolemia, particularly an increase in the low-density lipoprotein cholesterol (LDL-C) level, has been established as one of the most important risk factors for coronary artery disease (CAD). Statins revolutionized the treatment of hypercholesterolemia, and many clinical trials have shown that LDL-C-lowering therapy with statins (hydrophilic or lipophilic) can significantly reduce the incidence of CAD in both primary and secondary prevention. These beneficial effects of statins are mainly related to the magnitude of LDL-C level reduction, although statins also have anti-inflammatory and anti-oxidant pleiotropic effects. Moreover, a recent study reported that statin therapy improved mortality rates in patients with heart failure. However, a low LDL-C level is associated with poor prognosis in patients with acute coronary syndrome (ACS) and heart failure. This is called the “cholesterol paradox”.

Although statin-induced rapid reduction of the LDL-C level has been associated with a reduction in short-term mortality in patients with acute myocardial infarction (AMI), another study did not confirm the efficacy of early intensive statin therapy on short-term mortality in patients with ACS. Thus, it is still unclear whether an early reduction of the LDL-C level would improve short-term mortality in patients with ACS.

In this issue of the Journal, Miura et al retrospectively evaluate the 30-day in-hospital all-cause mortality in patients with AMI who were undergoing primary percutaneous coronary intervention. The patients were stratified according to the presence or absence of statin administration in the acute phase, and LDL-C levels on admission of greater than or less than 100 mg/dl. The authors found that the in-hospital all-cause mortality was significantly low in the “statin-treated/LDL-C ≥100 mg/dl” group (3.2%, P<0.001). Multivariate Cox regression analysis showed that the combination of statin treatment and an LDL-C level ≥100 mg/dl was an independent predictor for lower in-hospital mortality (adjusted hazard ratio [HR], 0.211; 95% confidence interval [CI], 0.096–0.462; P=0.0043). Statin-naive/LDL-C <100 mg/dl patients was associated with increased short-term mortality.

Although the mechanisms of the cholesterol paradox are not clearly understood, they may be related to confounding by baseline characteristics. However, in the present study, the combination of statin treatment and LDL-C ≥100 mg/dl was an independent predictor for lower in-hospital mortality after adjustment for general risk factors for CAD and other clinical factors. It is possible that a low LDL-C level may be associated with illness that leads to higher all-cause mortality, and higher LDL-C levels may reflect better nutritional and health status, which are likely related to better tolerance of acute medical stress. In a previous study, lipid-lowering therapy was underused in ACS patients with lower LDL-C levels. Tsai et al evaluated the effects of statin therapy in patients with ACS whose serum LDL-C level was ≤80 mg/dl. The incidence of events in the statin-treated group was 9.5%, which was significantly lower than the 29% incidence in the untreated group. In another study, Lee et al investigated the clinical outcomes of statin therapy in patients with AMI whose LDL-C levels were <70 mg/dl, and found that statin therapy was associated with improved clinical outcome. Consistent with these reports, statin therapy results in better clinical outcomes in AMI patients with lower LDL-C levels. Thus, although low LDL-C on admission may be a marker for worse clinical outcomes, early lipid-lowering therapy with statin during hospitalization may be necessary to improve short-term prognosis in patients with ACS, regardless of their LDL-C levels.

Intensive lipid-lowering therapy with statins significantly reduces the risk of coronary events compared with moderate lipid-lowering therapy. The concept of “the lower, the better” was based on these previous reports, and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines set a value of <70 mg/dl as the therapeutic target for LDL-C for high-risk patients such as those with ACS. However, most randomized controlled clinical trials have compared statin with placebo or compared a high dose of statin with a standard dose of statin. In other words, the statin dosage was fixed, and the study design did not allow for the adjustment of the administered dose toward the therapeutic
target for LDL-C. The results of a meta-analysis with 169,138 patients in 26 randomized trials indicated that the percentage reduction of LDL-C is more important for secondary prevention than for the achievement of a target LDL-C level. Thus, the type or dose of statin, rather than the LDL-C level, becomes an important factor. Accordingly, the recent ACC/AHA and European Society of Cardiology guidelines recommended using high-intensity statin therapy to achieve a percent reduction of LDL-C level instead of a target LDL-C level for secondary prevention. Considering the results of the present study showing that statin administration during hospitalization contributed to better short-term in-hospital outcomes in patients with AMI, regardless of the LDL-C levels on admission, statins should be given to all patients with AMI, whether the LDL-C level would be elevated or not. Thus, this large-scale observational study strengthens the evidence for the benefit of statin therapy during the acute phase in AMI patients. However, this study did not clarify the mechanisms of why statin therapy reduces the short-term mortality, the timing of initiation of statin therapy after the onset of AMI, or the type or dose of statin. A further, large-scale, prospective, randomized trial is necessary to evaluate when statin therapy should be started, and what type or dose should be used in these high-risk patients with AMI.

Disclosures
None.

References