Exploratory “Odyssey” During Pursuit of Plaque Control

Hirohiko Ando, MD, PhD; Hiroaki Takashima, MD, PhD; Tetsuya Amano, MD, PhD

Recent guidelines focus on the importance of lowering low-density lipoprotein cholesterol (LDL-C) levels in patients at high risk of developing atherosclerotic cardiovascular disease.^{1–3} Patients who have presented recently with acute coronary syndrome (ACS) are at a very high risk of experiencing further cardiovascular events,

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and the maximum tolerable dose of high-intensity statin is recommended as the first-line therapy aimed at reaching the LDL-C target <1.8 mmol/L (70 mg/dL) or a 50% reduc-

Figure. Relationship between achieved LDL-C levels and the change in percentage atheroma volume for previous IVUS trials and the ODYSSEY J-IVUS trial. A close relationship between achieved LDL-C levels and the change in PAV on IVUS studies has been reported. The median changes in PAV are plotted. In the GLOGOV trial and the ODYSSEY J-IVUS trial, the mean changes in PAV were plotted. ACS, acute coronary syndrome; Atorva, atorvastatin; IVUS, intravascular ultrasound; LDL-C, low-density lipoprotein cholesterol; PAV, percentage atheroma volume; Prava, pravastatin; SAP, stable angina pectoris. (Modified with permission from Tsujita K, et al.⁹)

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Department of Cardiology, Aichi Medical University, Nagakute, Japan
Mailing address: Hirohiko Ando, MD, PhD, Department of Cardiology, Aichi Medical University, 1-1 Yazakokarimata, Nagakute 480-1195, Japan. E-mail: anhiro@aichi-med-u.ac.jp
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tion in LDL-C. However, despite the fact that monotherapy with high-intensity statins significantly lowers LDL-C, treatment goals often cannot be achieved and cardiovascular events do occur. Consequently, for patients with insufficient LDL-C reduction with statin monotherapy, additional non-statin therapies should be considered and aggressive LDL-C lowering therapy combining statin and non-statin agents, such as ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, are potentially useful approaches to delivering more effective coronary care.

The ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial is a double-blind trial comparing alirocumab with placebo, added to high-intensity or maximum-tolerated statin treatment, after ACS in 18,924 patients.⁴ Over 2.8 years of follow-up, patients who received alirocumab showed a 15% reduction in the primary endpoint (a composite of death from coronary artery disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalization). However, the specific effect on coronary atheroma progression remains unknown.

Under this background, the report by Ako et al⁵ of the ODYSSEY J-IVUS trial, published in this issue of the Journal, offers important findings. This is a landmark study evaluating the efficacy of alirocumab plus statin on coronary atheroma progression in patients hospitalized for ACS, compared with standard of care. Intravascular ultrasound (IVUS) was performed at baseline and at 36-week follow-up. The primary efficacy endpoint was the percent change in normalized total atheroma volume (TAV) from baseline to Week 36, and the key secondary efficacy endpoint was the absolute change in percent atheroma volume (PAV) from baseline to Week 36. A numerically greater percent reduction in normalized TAV was observed with alirocumab vs. standard of care, but it did not reach statistical significance.

In this study, progression and regression of atherosclerosis on IVUS were used as surrogate markers of the outcomes, as has been increasingly used in clinical trials. Several randomized trials investigating the efficacy of intensive statin therapy demonstrated that aggressive lipid modification results in suppression of atherosclerosis progression.^{6–8} Additionally, the degree of plaque change was associated with the LDL-C level or the percentage reduction in LDL-C, supporting the theory that the lower the better. The PRECISE-IVUS (Plaque REGression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by IntraVascular UltraSound) trial investigated the effects of dual lipid-lowering therapy with ezetimibe plus atorvastatin on coronary atherosclerosis progression.⁹ The absolute change in PAV was significantly higher in the dual lipid-lowering therapy group than in the statin alone group (−1.4% vs. −0.3%; $P=0.001$). Also, a significantly greater percentage of patients in the dual lipid-lowering therapy group had coronary plaque regression (78% vs. 58%; $P=0.004$). They also found a larger response in patients with ACS than in those with stable coronary artery disease. The GRAGOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound) trial was the first to compare combination therapy with evolocumab plus statin with statin therapy alone for coronary atherosclerosis.¹⁰ The primary outcome, nominal change in PAV at 78 weeks, was −0.95% in the evolocumab group vs. 0.05% in the placebo group ($P<0.001$

for between-group comparison), further confirming the lower the better theory.

Contrary to these trials, the ODYSSEY J-IVUS trial failed to show additional effectiveness of alirocumab for plaque regression. The lack of a statistically significant difference needs to be considered in the light of several specific features of the study design, such as the limited sample size, the short duration of the treatment period, racial differences, the baseline coronary atheroma volume,¹¹ and the prevalence of ACS patients,⁹ as the investigators stated in their report. The mean change in PAV was −1.3% and −1.4% in the standard of care group and the alirocumab group, respectively (mean difference: −0.2%; nominal $P=0.79$). As compared with the previous trials cited, it should also be noted that sufficient plaque regression was achieved even in the standard of care group, which might have led to no significant difference between groups (Figure). The population covered in the present study comprised patients with ACS, and only one-third of those were taking statins at the onset of ACS; in this subset the effect of statins on plaque regression is considered very high. Furthermore, almost half of the standard of care group took ezetimibe during the study, in which highly effective medical therapy was undertaken. In the standard of care group it seems that sufficient medical treatment had already been introduced for patients in whom it could be expected to be most effective. Under these conditions, alirocumab failed to demonstrate additional effectiveness for plaque regression. Consequently, the ODYSSEY J-IVUS trial should not be interpreted in terms of plaque regression but rather as a study that supports the importance of optimal dual LDL-C reduction therapy instead of monotherapy with statins. Further clinical trials are required to make a final conclusion about the effectiveness of alirocumab for plaque regression.

Conflict of Interest

All authors report that they have no relationships relevant to the contents of this paper to disclose.

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