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# Lipid profile associated with coronary plaque regression in patients with acute coronary syndrome: Subanalysis of PRECISE-IVUS trial

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ABSTRACT

*Background and aims:* Although dual low-density lipoprotein cholesterol (LDL-C)-lowering therapy (DLLT) with statin-ezetimibe combination showed clinical benefit in patients with acute coronary syndrome (ACS) confirming "the lower, the better," the underlying mechanisms of DLLT are still unknown.
*Methods:* PRECISE-IVUS trial evaluated the effects of DLLT on IVUS-derived coronary atherosclerosis and lipid profile, compared with atorvastatin monotherapy, quantifying the coronary plaque response in 100 ACS patients. We explored the potential predictors of plaque regression.
*Results:* Lower total cholesterol, LDL-C, triglyceride, remnant-like particles cholesterol, and stronger reduction of small dense LDL-C and cholesterol absorption markers were observed in patients with plaque regression compared to those with progression. Multivariate analysis revealed that achieved LDL-C was the strongest predictor for coronary plaque regression (95% CI: 0.944–1.000, $p = 0.05$), followed by age (95% CI: 0.994–1.096, $p = 0.09$).
*Conclusions:* Incremental LDL-C lowering by DLLT was associated with stronger coronary plaque regression, reconfirming that lowering LDL-C to levels below previous targets provided additional clinical benefit.


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[1] Members of the PRECISE-IVUS study are listed in Appendix

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## 1. Introduction

Large-scale randomized clinical trials of secondary preventive measures in patients with stable coronary artery disease (CAD) have shown that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduce cardiovascular (CV) events rates as well as atherogenic lipoproteins (e.g., low-density lipoprotein cholesterol [LDL-C]) [1–3]. Also, the positive correlation between LDL-C levels and incidence of CV events was revealed ("the lower, the better" concept). Accumulating evidence from clinical trials utilizing serial intravascular ultrasound (IVUS) have demonstrated that: 1) intensive statin therapy can halt the progression of coronary atherosclerosis [4] and 2) sometimes induces disease regression [5], 3) indicating strong relationship between achieved LDL-C levels and coronary atherosclerosis progression/regression. As prior meta-analysis evidenced that the degree of coronary plaque progression/regression was significantly associated with CV events [6]. Statins appear to effectively lower LDL-C levels halting coronary plaque progression (or regressing the plaque), and eventually reduce the incidence of future CV adverse outcomes.

Recently, dual lipid-lowering therapy (DLLT) with a combination of statin and ezetimibe has emerged as an aggressive lipid management strategy against the residual risks for CV events. IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) showed that simvastatin taken with ezetimibe led to a significantly lower incidence of the CV events, compared to simvastatin monotherapy [7]. The PRECISE-IVUS (Plaque REgression with Cholesterol absorption Inhibitor or Synthesis inhibitor Evaluated by IntraVascular UltraSound) trial additionally demonstrated the benefit of the DLLT for greater coronary plaque regression [8]. Furthermore, although there has been a close correlation between achieved LDL-C levels and the change in coronary atheroma volume consistently in prior IVUS trials, the plot is located far below the line in the atorvastatin/ezetimibe combination arm of the acute coronary syndrome (ACS) cohort of the PRECISE-IVUS trial, suggesting the potential existence of "beyond-LDL-C-lowering effect" of the DLLT. However, as the intensity of LDL-C-lowering effect is different between statins and ezetimibe, it remains largely-unknown whether the clinical benefit of DLLT is based on the LDL-C-dependent or -independent mechanisms. Therefore, the PRECISE-IVUS database was employed to elucidate the potential "lipid profile" and systemic predictors associated with coronary plaque regression.

## 2. Materials and methods

### 2.1. Study protocol of PRECISE-IVUS trial

The present study is a post-hoc analysis of the PRECISE-IVUS trial. A detailed protocol of the PRECISE-IVUS was described previously [9]. In brief, the PRECISE-IVUS was a prospective, randomized, controlled, assessor-blind, multicenter study to evaluate the effect of ezetimibe addition to atorvastatin on coronary atheroma volume as measured by IVUS in patients with CAD. The eligible patients (LDL-C level at entry $\geq$100 mg/dl) were randomly assigned to receive either atorvastatin alone or atorvastatin plus ezetimibe 10 mg daily. The dosage of atorvastatin was uptitrated with a treatment goal of LDL-C <70 mg/dl. Periodic medical examination and laboratory tests were performed at 3, 6, and 9–12 months after enrollment. In the PRECISE-IVUS trial, patients with both ACS and stable angina had been simultaneously enrolled. Half of the study patients (126 of 246 initially-enrolled patients [51%]) were resultantly enrolled as ACS cohort. After 9–12 months of treatment, 100 of 126 patients (79%) remained for follow-up and underwent repeat IVUS imaging. Among them, 51 were treated with DLLT and 49 with atorvastatin alone (Fig. 1). The study complied with the Declaration of the Helsinki with respect to investigation in humans, was approved by institutional review committees, and conducted in accordance with the guidelines of the ethics committee at participating institutions. Written informed consent was obtained from all patients.

### 2.2. Biomarker assessment

The lipid, glycemic, and inflammatory profile [total cholesterol, LDL-C, triglyceride, high-density lipoprotein, malondialdehyde-modified LDL-C, remnant-like lipoprotein particle cholesterol, small-dense LDL-C, free-fatty acid, apolipoprotein A-I, apolipoprotein B, apolipoprotein C-II, apolipoprotein C-III, lipoprotein(a), fasting insulin level, glycosylated hemoglobin, adiponectin, lathosterol, cholestanol, sitosterol, campesterol, and high-sensitivity C-reactive protein] was assessed during the study period.

### 2.3. IVUS image analysis and exploration of predictor of coronary plaque regression

A detailed image acquisition protocol was described previously [9]. Serial volumetric IVUS was performed at baseline and 9–12 months follow-up to quantify the coronary plaque response. Based on an expert consensus document paper [10], the primary IVUS endpoint was the absolute change in percent atheroma volume (PAV). The lipid and glycemic control profile was compared between patients with and without plaque regression in PAV. In order to explore the potential predictors of plaque regression, univariate and multivariate logistic regression analyses were employed. Candidate variables entered into the multivariate model included significant variables (p value $< 0.05$ in the univariate analysis) except for the confounding factors with potentially internal correlation.

### 2.4. Statistical analysis

Statistical analysis was performed using SPSS Statistics for Windows (version 22.0; IBM Corp., Armonk, New York). After the descriptive statistics, continuous variables (mean $\pm$ SD and medians with interquartile ranges) between the 2 groups were compared using the unpaired Student *t*-test or the Mann-Whitney *U* test. Continuous variables between the baseline and follow-up were compared by 1-sample Student *t* tests or the Wilcoxon signed rank test according to their distributions. Categorical variables (frequencies) were compared using chi-square statistics or the Fisher exact test. The full analysis dataset, in which the patients had measurable IVUS images both at baseline and at follow-up, was used for the primary analyses. A p value $< 0.05$ was considered significant.

## 3. Results

### 3.1. Patients characteristics and laboratory data

There were no between-group differences in clinical background and baseline laboratory data except for the higher baseline campesterol level in patients treated with atorvastatin/ezetimibe