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

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A R T I C L E   I N F O
Article history:
Received 28 December 2015
Received in revised form 30 March 2016
Accepted 16 May 2016
Available online 20 May 2016

Keywords:
Ezetimibe
Statin
Plaque
Intravascular ultrasound
Lipoprotein

A B S T R A C T

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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Members of the PRECISE-IVUS study are listed in Appendix

http://dx.doi.org/10.1016/j.atherosclerosis.2016.05.025
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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 reduce disease 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 ≥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 randomly 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-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 ± 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.
combination compared with statin monotherapy (2.5 (1.9–3.2) mg/100 mg TC vs. 2.1 (1.6–2.5) mg/100 mg TC, p = 0.02) (Table 1, Table 2). Regarding the serial change in LDL-C level during the study period, DLLT showed the significantly stronger (62 ± 16 vs 77 ± 20 mg/dl) and more prompt LDL-C reduction in spite of the lower dose of atorvastatin than statin monotherapy (13.7 ± 4.9 mg/day vs. 20.0 ± 8.8 mg/day) (Fig. 2).

3.2. Coronary atherosclerosis and potential predictors for plaque regression

For IVUS plaque progression/regression parameters, DLLT showed stronger plaque regression than statin alone (−2.3% vs. −0.2% in the absolute change in PAV). Regarding the clinical and laboratory data, higher age, lower serum levels of total cholesterol, LDL-C, triglyceride, and stronger reduction in small-dense LDL-C and cholesterol absorption markers (campesterol, sitosterol) were observed in patients with plaque regression than in those with progression (Table 3). Multivariate logistic regression analysis revealed that achieved LDL-C was the strongest predictor for coronary plaque regression (defined as regression in PAV), followed by age (Table 4).

4. Discussion

4.1. Main results of the subanalysis

The current subanalysis showed that the coronary plaque regression observed in the patients with ACS of the PRECISE-IVUS trial was predominantly derived from lower achieved LDL-C level irrespective of lipid-lowering strategies (DLLT or potent statin therapy).

4.2. LDL hypothesis or statin hypothesis (pleiotropic effects)?

Statins have a complex array of biologic effects (amelioration of endothelial dysfunction, oxidative stress, inflammatory reaction, and increased nitric oxide bioavailability) in addition to their LDL-C-lowering effect [11]. That are sometimes referred to as “pleiotropic effects.” IMPROVE-IT trial showed a clinical benefit of adding

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All n = 100</th>
<th>Statin/ezetimibe n = 51</th>
<th>Statin alone n = 49</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>65 ± 10</td>
<td>64 ± 11</td>
<td>65 ± 10</td>
<td>0.8</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>82 (82%)</td>
<td>41 (80%)</td>
<td>41 (84%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.8 ± 3.2</td>
<td>24.9 ± 3.5</td>
<td>24.8 ± 3.0</td>
<td>0.8</td>
</tr>
<tr>
<td>History of PCI</td>
<td>8 (8%)</td>
<td>3 (6%)</td>
<td>5 (10%)</td>
<td>0.5</td>
</tr>
<tr>
<td>History of PAD</td>
<td>2 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1.0</td>
</tr>
<tr>
<td>History of MI</td>
<td>8 (8%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>66 (66%)</td>
<td>38 (75%)</td>
<td>28 (57%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>70 (70%)</td>
<td>33 (65%)</td>
<td>37 (76%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25 (25%)</td>
<td>12 (24%)</td>
<td>13 (27%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Insulin</td>
<td>3 (3%)</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Non-Insulin</td>
<td>22 (22%)</td>
<td>11 (22%)</td>
<td>11 (22%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Presentation of ACS</td>
<td>100 (100%)</td>
<td>51 (100%)</td>
<td>49 (100%)</td>
<td>0.6</td>
</tr>
<tr>
<td>STEMI</td>
<td>51 (51%)</td>
<td>26 (51%)</td>
<td>25 (51%)</td>
<td>0.1</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>12 (12%)</td>
<td>5 (10%)</td>
<td>7 (14%)</td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>37 (37%)</td>
<td>20 (39%)</td>
<td>17 (35%)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as n (%) or mean ± standard deviation. PCI, percutaneous coronary intervention; PAD, peripheral artery disease; MI, myocardial infarction; ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; UA, unstable angina.
another finding, Puri et al. showed that lower LDL-C levels are associated with lower event rates.

3. Real world lipid-lowering strategy toward the LDL hypothesis

The American College of Cardiology and the American Heart Association 2013 cholesterol treatment guidelines emphasized moderate-to-high-intensity statin therapy as the preferred treatment option for patients with established CV disease, and do not recommend the use of specific targets for LDL-C levels.

### Table 3
Comparison between the patients with regression vs. progression.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regression in PAV (n = 67)</th>
<th>Progression in PAV (n = 33)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual lipid-lowering with atorvastatin and ezetimibe</td>
<td>40 (60%)</td>
<td>11 (33%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age, years</td>
<td>67 (60–74)</td>
<td>63 (51–71)</td>
<td>0.02</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>23.9 (22.4–25.9)</td>
<td>25.3 (22.7–29.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Hemoglobin A1c, %</td>
<td>5.5 (5.1–6.8)</td>
<td>5.5 (5.1–5.8)</td>
<td>0.6</td>
</tr>
<tr>
<td>TC at follow-up, mg/dl</td>
<td>131 ± 24</td>
<td>142 ± 24</td>
<td>0.008</td>
</tr>
<tr>
<td>High-density lipoprotein-cholesterol at follow-up, mg/dl</td>
<td>42 (35–48)</td>
<td>47 (36–53)</td>
<td>0.4</td>
</tr>
<tr>
<td>LDL-C at follow-up, mg/dl</td>
<td>62 ± 14</td>
<td>81 ± 22</td>
<td>0.004</td>
</tr>
<tr>
<td>Triglycerides at follow-up, mg/dl</td>
<td>93 (72–125)</td>
<td>116 (97–152)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lipoprotein (a) at follow-up, mg/dl</td>
<td>16.0 (5.8–32.5)</td>
<td>14.0 (7.0–33.0)</td>
<td>0.3</td>
</tr>
<tr>
<td>MDA-LDL at follow-up, U/l</td>
<td>81 (71–97)</td>
<td>90 (72–96)</td>
<td>0.7</td>
</tr>
<tr>
<td>Remnant-like particle cholesterol at follow-up, mg/dl</td>
<td>2.9 (2.1–4.3)</td>
<td>3.5 (3.1–4.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Δ sdLDL-C, mg/dl</td>
<td>−7.7 (−15.2 to −2.9)</td>
<td>−1.7 (−7.3 to 4.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Δ Lathosterol, µg/100 mg TC</td>
<td>−8.1 (−55.2 to 38.0)</td>
<td>−10.1 (−34.7 to 35.9)</td>
<td>0.96</td>
</tr>
<tr>
<td>Δ Lipoprotein (a), mg/dl</td>
<td>−13.3 (−78.8 to 124.6)</td>
<td>86.4 (−17.7 to 142.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Δ LDL-C, mg/dl</td>
<td>−7.0 (−28.1 to 42.4)</td>
<td>54.5 (−0.4 to 84.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Δ High-sensitivity C-reactive protein, mg/l</td>
<td>−5.3 (−18.9 to 1.11)</td>
<td>−4.5 (−13.7 to 1.13)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Values are presented as n (%) or mean ± standard deviation or median (interquartile range). TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; MDA-LDL, malondialdehyde-modified LDL-C; sdLDL-C, small-dense LDL-C.
However, the guideline simultaneously acknowledge that some patients may have an insufficient response to statin therapy and that in such patients the addition of a nonstatin agent may be considered. The patients with “less-than-anticipated response” to statin therapy and statin-intolerant individuals were frequently observed in real world practice [16]. The clinical benefit of ezetimibe as a nonstatin agent added to statins would be good news for them.

4.4. Limitations

The small sample size of the analysis was one of the inherent limitations. The present sample size might not have enough power to detect some underlying unrevealed predictors for coronary plaque regression (e.g. lipid-lowering strategies, markers for systemic inflammation). Furthermore, the existence of potential confounding variables makes it difficult to establish a clear causal link between clinical latent predictors and coronary plaque regression even if appropriate methods are used to adjust for the influence of the confounders. Our findings thus do not eliminate the possibility that pleiotropic biologic effects contribute to the clinical benefits of statins (e.g. anti-inflammatory effect, antioxidative effect, and preservation of endothelial function). Although the current sub-analysis was planned in advance, the results of the study might be more hypothesis-generating than a conclusive mechanical insight. The future prospective trial targeting the specific targets of LDL-C would be warranted.

5. Conclusion

The strongest lipid predictor of the coronary plaque regression would be achieved LDL-C level at follow-up. Aggressive LDL-C-lowering by DLLT to levels below previous targets might provide additional clinical benefit. Therefore, the DLLT with statin/ezetimibe would be a promising treatment option as a further aggressive lipid-lowering strategy in statin-intolerant or statin-hyporesponsive patients with ACS.

Conflict of interest

Hisao Ogawa has received remuneration for lecture from Bayer, Boehringer Ingelheim, Daiichi Sankyo, MSD, Pfizer, and Takeda, and has received trust research/joint research funds from Bayer, Daiichi Sankyo, and Novartis, and has also received scholarship fund from AstraZeneca, Astellas, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Dainippon Sumitomo Pharma, Kowa, MSD, Otsuka, Pfizer, Sanofi, Shionogi, and Takeda. Masaharu Ishihara has received remuneration for lecture from MSD. The remaining authors declare no conflict of interest.

Trial registration

Clinicaltrials.gov, number NCT01043380.

Appendix

Participating hospitals and collaborators of PRECISE-IVUS trial.

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3. Social Insurance Omuta Tenryo Hospital: K Matsuyama, T Yamashita, M Miura, T Chitose
4. New Tokyo Hospital: S Nakamura, S Mitomo
5. Shin-Beppu Hospital: N Nakamura, K Kikuta, K Watanabe, T Miyazaki
6. Kumamoto City Hospital: Y Morikami, Y Miyazaki, M Fukuda, H Nako
8. Health Insurance Hitozoshi General Hospital: H Oka, S Nakamura
9. Amakusa Medical Center: N Sakaino, S Nakamura, T Nozaki
10. Araw City Hospital: I Kajiwara, Enomoto K, D Sueta
11. Hiroshima City Hospital: M Ishihara, I Inoue, K Ohi
12. Saiseikai Kumamoto Hospital: K Nakao, T Sakamoto, S Miyamoto, E Taguchi, T Fukunaga, T Tokitsu, S Ogawa
15. Kumamoto Central Hospital: S Oshima, K Noda, H Sumida, T Nishijima, K Morihisa
16. National Hospital Organization Kumamoto Medical Center: K Fujimoto, Y Miyao, H Koga, T Honda, M Matsukawa, J Matsubara
17. Japanese Red Cross Kumamoto Hospital: R Tsunoda, T Ito, H Yoshimura, S Fuchigami

Financial support

This work was supported in part by a Grant-in-Aid for Young Scientists B (22790713, 24790769) and a Grant-in-Aid for Scientific Research C (26461075) from the Ministry of Education, Science, and Culture, Japan (to K.T.).

References


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Table 4

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C at follow-up, mg/dl</td>
<td>0.972</td>
<td>0.945–1.000</td>
<td>0.047</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>1.044</td>
<td>0.994–1.096</td>
<td>0.09</td>
</tr>
<tr>
<td>Δd LDL-C, mg/dl</td>
<td>0.976</td>
<td>0.931–1.024</td>
<td>0.3</td>
</tr>
<tr>
<td>Triglyceride at follow-up, mg/dl</td>
<td>0.997</td>
<td>0.990–1.005</td>
<td>0.5</td>
</tr>
<tr>
<td>ΔSitosterol, μg/100 mg TC</td>
<td>9.943 × 10⁻⁸</td>
<td>3.637 × 10⁻⁶ – 2.719 × 10⁻⁸</td>
<td>0.6</td>
</tr>
</tbody>
</table>

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. TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol.


