Original Article

C-Reactive Protein and Future Cardiovascular Events in Statin-Treated Patients with Angina Pectoris: The Extended TRUTH Study

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Aim: The TRUTH trial demonstrated that 8-month statin therapy alters the composition of coronary artery plaque using virtual histology (VH)-intravascular ultrasound (IVUS). The extended TRUTH study was conducted to evaluate the relationship between changes in coronary atherosclerosis and mid-term clinical outcomes and identify the factors associated with cardiovascular events.

Methods: Of 164 patients with angina pectoris who participated in the TRUTH trial, 119 subjects with analyzable IVUS data at both enrollment and the 8-month follow-up were enrolled and observed for at least two years. The primary end point was the time to first occurrence of cardiovascular composite events, including cardiovascular death, nonfatal myocardial infarction, nonfatal cerebral infarction, unstable angina and ischemic-driven revascularization, except for target lesion revascularization.

Results: The frequency of reaching the primary end point was 13% (16/119), with a mean follow-up period of 41.9 ± 9.4 months. Although plaque regression and changes in plaque composition were not associated with future cardiovascular events, the serum high-sensitivity C-reactive protein (hs-CRP) levels at the start of the extended TRUTH study were significantly higher in the event group than in the event-free group (1.43 mg/L vs. 0.58 mg/L, $p=0.01$). A multivariate logistic regression analysis showed that the hs-CRP level was an independent significant predictor of cardiovascular events (odds ratio: 1.69; 95% confidence interval: 1.14-2.50, $p=0.01$).

Conclusions: Coronary artery plaque regression and changes in plaque composition during statin therapy do not predict future cardiovascular events in patients with angina pectoris. Instead, the serum hs-CRP level can be used as a predictor of cardiovascular events.

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Key words: Cardiovascular event, Coronary artery disease, High-sensitivity C-reactive protein, Low-density lipoprotein cholesterol, Statin

Introduction

Data derived from intravascular ultrasound (IVUS) have provided important insights into the progression and regression of coronary atherosclerosis and vessel remodeling^{1, 2}. Serial volumetric measurements of coronary artery plaques obtained with IVUS can be used to evaluate the effects of pharmacological interventions. Recent trials employing IVUS have shown that statins attenuate the progression and/or induce the regression of coronary artery plaques³⁻⁶. A previous IVUS study showed that the burden of coronary atherosclerosis and its progression is associated with an increased risk of adverse cardiovascular events⁷. In contrast, another study demonstrated that coronary plaque regression induced by an intensive statin regimen did not predict future cardiovascular events⁸.

The TRUTH trial showed that 8-month statin therapy alters the composition of coronary artery plaque using virtual histology (VH)-IVUS⁹. IVUS studies of the progression and regression of coronary atherosclerosis and changes in plaque composition have limited these findings to surrogate end points. It is important to evaluate whether the surrogate end point predicts future cardiovascular events. Therefore, we investigated mid-term TRUTH follow-up data in order to evaluate the relationship between mid-term clinical outcomes and plaque regression or changes in plaque composition and identify factors associated with cardiovascular events.

Methods

Patients and Study Design

The extended TRUTH study increased the follow-up period of the TRUTH trial in order to evaluate the relationship between mid-term clinical outcomes and plaque regression or changes in plaque composition and identify factors associated with cardiovascular events. The TRUTH trial was a prospective, open-label, randomized, multicenter trial performed at 11 Japanese centers to evaluate the effects of 8-month treatment with pitavastatin (4 mg/day, intensive lipid-lowering) versus pravastatin (20 mg/day, moderate lipid-lowering) on the composition of coro-

nary artery plaque using VH-IVUS^{9, 10}. This trial showed that 8-month treatment with pitavastatin and pravastatin alters the coronary artery plaque composition by significantly decreasing the fibro-fatty plaque component and increasing the calcified plaque component in patients with angina pectoris⁹. Patients with measurable IVUS data at both enrollment and the 8-month follow-up in the TRUTH trial were enrolled in the extended TRUTH study. The patients were observed for at least two years from the final visit of the TRUTH trial (**Fig. 1**). Among the 164 patients enrolled in the TRUTH trial, 119 comprised the extended TRUTH study cohort. During the extended TRUTH period, the attending physicians decided whether the assigned statin would be continued. The mid-term clinical outcomes were obtained from either a review of the hospital records, telephone calls or the primary care physician in all 119 subjects, with a mean follow-up period of 41.9 ± 9.4 months.

The extended TRUTH study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional ethical committees of all participating institutions, and all patients provided their written informed consent. The study was registered at the University Hospital Medical Information Network (UMIN000004627).

End Points

The primary end point was the time to first occurrence of cardiovascular composite events, defined as cardiovascular death, nonfatal myocardial infarction, nonfatal cerebral infarction, unstable angina requiring urgent hospitalization or ischemic-driven revascularization, except for target lesion revascularization. The secondary end point was all-cause mortality.

The independent Event Assessment Committee evaluated the events (K. H.).

IVUS Examination and Analysis

The details of the IVUS procedures and examinations are documented elsewhere⁹. Briefly, following percutaneous coronary intervention of the culprit lesion, an IVUS examination was performed to evaluate angiographic lesions with $<50\%$ lumen narrowing on the distal and proximal sides of the culprit lesion. An IVUS catheter (Eagle Eye Gold; Volcano Corporation, San Diego, CA) was used, and a motorized pullback device withdrew the transducer at 0.5 mm/s. During pullback, grayscale IVUS was recorded, and raw radiofrequency data were captured at the top of the R wave using a commercially available IVUS console (IVG3; Volcano Corporation)¹¹. After eight months of statin therapy, the IVUS examination was

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Fig. 1. Overview of the extended TRUTH study.

Patients with measurable IVUS data at both enrollment and the 8-month follow-up in the TRUTH trial were enrolled in the extended TRUTH study. The patients were observed for at least two years from the final visit of the TRUTH trial.

Table 1. Mid-term clinical outcomes

	All subjects (<i>n</i> = 119)
Primary end point (cardiovascular composite events)	16 (13%)
Cardiovascular death	3 (3%)
Nonfatal myocardial infarction	1 (1%)
Nonfatal cerebral infarction	0 (0%)
Unstable angina requiring urgent hospitalization	0 (0%)
Revascularization*	13 (11%)
Secondary end point	
All-cause mortality	5 (4%)

The data are expressed as numbers (%). The mean follow-up period was 41.9 ± 9.4 months.

* Ischemic-driven revascularization, except for target lesion revascularization.

repeated in the same coronary artery using the same type of IVUS catheter as that used at baseline.

All baseline and follow-up IVUS core laboratory analyses were performed by an independent and experienced investigator (M. T.) in a blinded manner. Before the IVUS analysis, the baseline and follow-up IVUS images were reviewed side by side on a display, and the distal and proximal ends of the target segment were identified based on the presence of reproducible anatomic landmarks, such as the side branch, vein and stent edge. The target segment of interest had a $\geq 50\%$

plaque burden, according to IVUS^{11, 12}. Plaques close to the percutaneous coronary intervention site (within 5 mm) were excluded. Manual contour detection of the lumen and external elastic membrane (EEM) was performed for each frame. A quantitative IVUS grayscale analysis was performed according to the guidelines of the American College of Cardiology and European Society of Cardiology². All volumetric data were divided by the lesion length to obtain a volume index. The VH-IVUS data analysis was based on grayscale border contour calculation, and the relative and

Table 2. Baseline characteristics of the patients with and without events

	Event (n=16)	Event-free (n=103)	p value
Age (years)*	66 ± 10	68 ± 10	0.42
Male gender	14 (88%)	85 (83%)	>0.99
Body mass index (kg/m ²)*	24.3 ± 2.7	24.2 ± 3.5	0.9
Smoking	1 (6%)	25 (24%)	0.19
Family history of CAD	1 (6%)	9 (9%)	>0.99
Serum creatinine (mg/dL)	0.93 ± 0.24	0.94 ± 0.23	0.87
Treatment allocation			
Pitavastatin/Pravastatin	6 (37.5%) / 10 (62.5%)	52 (50%) / 51 (50%)	0.33
Allocated statin continued	12 (75%)	71 (69%)	0.84
No statin	2 (13%)	16 (13%)	>0.99
Status of coronary artery disease			
Stable AP/Unstable AP	9 (56%) / 7 (44%)	74 (72%) / 29 (28%)	0.21
Target coronary artery			
LAD/LCX/RCA	8 (50%) / 0 (0%) / 8 (50%)	59 (57%) / 5 (5%) / 39 (38%)	0.49
Type of stents			
BMS/DES	1 (6%) / 15 (94%)	19 (18%) / 84 (82%)	0.39
Diabetes mellitus	10 (63%)	40 (39%)	0.07
Hypertension	7 (44%)	68 (66%)	0.09
Medications			
ACE inhibitors or ARBs	7 (44%)	54 (52%)	0.52
Beta-blockers	1 (6%)	12 (12%)	>0.99
Calcium channel blockers	8 (50%)	52 (50%)	0.97
Aspirin	16 (100%)	101 (98%)	>0.99
Thienopyridines	16 (100%)	102 (99%)	>0.99
Insulin	2 (13%)	9 (9%)	0.64
Oral hypoglycemic agents	2 (13%)	14 (14%)	>0.99

The data are expressed as the mean ± SD or number (%).

*Recalculated at the beginning of the extended TRUTH study.

CAD, coronary artery disease; AP, angina pectoris; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; BMS, bare-metal stent; DES, drug-eluting stent; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

absolute amounts of different coronary artery plaque components were measured using the IVUSLab version 2.2 software program (Volcano Corporation).

Statistical Analysis

The statistical analyses were performed using the SAS version 9.2 software package (SAS Institute Inc., Cary, NC). The results are expressed as the mean (SD) or median (interquartile range [IQR]). Differences in continuous variables between the two groups were compared using the unpaired *t*-test or the Wilcoxon rank-sum test. Categorical variables were compared between the two groups using the chi-square test or Fisher's exact test. The variables with a *p* value of <0.2 in the univariate analysis were entered into the multivariate logistic models. Statistical significance was set at *p*<0.05. All analyses were conducted by an independent statistician (T. S.).

Results

Mid-Term Clinical Outcomes

The mid-term clinical outcomes are shown in **Table 1**. There were 16 primary end points (13%) in all subjects (three cardiovascular deaths [3%], one nonfatal myocardial infarction [1%] and 13 revascularizations [11%]). Five patients (4%) met the secondary end point during the follow-up period.

Patient Characteristics

The baseline characteristics of the patients with and without events are shown in **Table 2**. During the TRUTH trial, 58 patients were randomized to receive pitavastatin and 61 were randomized to receive pravastatin. The treatment allocation did not differ between the two groups. Twelve patients (75%) in the event group and 71 patients (69%) in the event-free group

Table 3. Risk factors and IVUS parameters in patients with and without events

	Event (<i>n</i> = 16)	Event-free (<i>n</i> = 103)	<i>p</i> value
Risk factor control			
LDL-C at observation start (mg/dL)	92 ± 28	84 ± 25	0.21
HDL-C at observation start (mg/dL)	47 ± 12	51 ± 13	0.21
TG at observation start (mg/dL)	115 ± 54	117 ± 65	0.92
hs-CRP at observation start (mg/L)	1.43 (0.44-10.40)	0.58 (0.27-1.46)	0.01
SBP at observation start (mmHg)	133 ± 18	134 ± 23	0.9
DBP at observation start (mmHg)	77 ± 8	76 ± 13	0.61
FPG at observation start (mg/dL)	112 ± 33	108 ± 33	0.65
HbA1c at observation start (%)	6.7 ± 1.1	6.2 ± 0.8	0.1
Gray-scale IVUS parameters			
Plaque volume progression	6 (38%)	45 (44%)	0.64
Plaque volume at observation start (mm ³ /mm)	9.61 ± 3.98	8.66 ± 3.08	0.27
EEM volume progression	4 (25%)	42 (41%)	0.28
EEM volume at observation start (mm ³ /mm)	16.46 ± 6.69	16.04 ± 5.10	0.77
VH-IVUS parameters			
DC progression	13 (81%)	73 (71%)	0.39
DC volume at observation start (mm ³ /mm)	0.69 ± 0.55	0.53 ± 0.49	0.24
FI progression	5 (31%)	39 (38%)	0.61
FI volume at observation start (mm ³ /mm)	3.47 ± 1.83	3.08 ± 1.63	0.38
FF progression	3 (19%)	36 (35%)	0.26
FF volume at observation start (mm ³ /mm)	1.08 ± 0.98	0.78 ± 0.69	0.13
NC progression	9 (56%)	65 (63%)	0.6
NC volume at observation start (mm ³ /mm)	0.88 ± 0.65	0.87 ± 0.58	0.97

The data are expressed as the mean ± SD or median [IQR] or number (%).

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; EEM, external elastic membrane; DC, dense-calcium; FI, fibrous; FF, fibro-fatty; NC, necrotic-core.

continued the allocated statins. Two patients (13%) in the event group and 16 patients (13%) in the event-free group were not treated with any type of statin during the extended TRUTH study period. The frequency of diabetes mellitus was generally higher, while that of hypertension was generally lower, in the event group.

Risk Factor Control and IVUS Parameters

The high-sensitivity C-reactive protein (hs-CRP) levels at the start of the extended TRUTH study were significantly higher in the event group than in the event-free group (1.43 mg/L vs. 0.58 mg/L, *p* = 0.01). The serum low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol and hemoglobin A1c levels and the systolic and diastolic blood pressure did not differ between the two groups. Furthermore, the EEM volume, plaque volume and rate of coronary artery plaque progression or regression did not differ between the two groups. The fibro-fatty component volume at the start of the extended

Table 4. Predictors of cardiovascular composite events

	OR	95% CI	<i>p</i> value
Hypertension	0.34	0.10-1.11	0.07
Diabetes mellitus	2.39	0.71-8.01	0.16
FF volume at observation start	1.30	0.60-2.79	0.51
hs-CRP at observation start	1.69	1.14-2.50	0.01

OR, odds ratio; CI, confidence interval; FF, fibro-fatty; hs-CRP, high-sensitivity C-reactive protein.

TRUTH study was generally larger in the event group (**Table 3**).

Predictors of Cardiovascular Composite Events

A multivariate logistic regression analysis showed that the hs-CRP level at the start of the extended TRUTH study was an independent significant predictor of cardiovascular events (odds ratio: 1.69; 95% confidence interval: 1.14-2.50, *p* = 0.01; **Table 4**). When we separated the subjects according to the hs-CRP

Fig. 2. Incidence of cardiovascular composite events according to the hs-CRP level at the start of the extended TRUTH study.

The incidence of cardiovascular composite events gradually increased in association with increases in the hs-CRP level (8.8% for <1.0 mg/L, 14.8% for 1.0-3.0 mg/L, and 29.4% for >3.0 mg/L, $p=0.03$). The p values were calculated using the Mantel test.

level, the incidence of cardiovascular events gradually increased in association with increasing hs-CRP levels (8.8% for <1.0 mg/L, 14.8% for 1.0-3.0 mg/L, and 29.4% for >3.0 mg/L, $p=0.03$; **Fig. 2**).

Discussion

The main findings of the extended TRUTH study are that the hs-CRP level predicts future cardiovascular events, whereas coronary artery plaque regression or changes in the plaque composition do not predict future cardiovascular events in statin-treated patients with angina pectoris. Furthermore, in this study, neither the type of statin (pitavastatin or pravastatin) nor the LDL-C level were associated with the mid-term clinical outcomes.

CRP is an acute-phase reactant demonstrated to be a reliable measurement of underlying systemic inflammation and a strong predictor of future cardiovascular events¹³. Measurement of the hs-CRP level is recommended for risk assessment. A consensus panel suggested that an hs-CRP level of <1.0, 1.0 to 3.0 and >3.0 mg/L corresponds to low, moderate and high cardiovascular risks and that a level of >10 mg/L indicates the presence of other inflammatory diseases¹³. Although the associations between the CRP level and coronary events were substantially reduced following adjustment for conventional cardiovascular risk factors in several studies¹⁴⁻¹⁶, elevated CRP levels

are associated with an increased 10-year risk of coronary artery disease (CAD), regardless of the presence or absence of cardiac risk factors¹⁷ after simultaneously controlling for multiple cardiac risk factors¹⁸. Consistent with these previous reports, the hs-CRP level was found to be an independent significant predictor for future cardiovascular events in statin-treated patients with angina pectoris in this study. Furthermore, when recent clinical guidelines were applied, the frequency of cardiovascular events gradually increased by 8.8% at low CRP concentrations (<1.0 mg/L), by 14.8% at intermediate CRP concentrations (1.0-3.0 mg/L) and by 29.4% at high CRP concentrations (>3.0 mg/L).

Nicholls *et al.* reported a direct relationship between coronary artery plaque progression-regression and future cardiovascular events in patients with stable CAD⁷. The same results were reported in the extended ESTABLISH study in patients with acute coronary syndrome (ACS)¹⁹. However, neither coronary artery plaque regression nor changes in the plaque composition were significant predictors of future cardiovascular events in the present study, consistent with the findings of the extended JAPAN-ACS study⁸. This is because Japanese patients are at low risk for cardiovascular events compared with individuals from other regions²⁰. Furthermore, in this study, the most frequent cardiovascular events were ischemic-driven revascularization (13 of 16 events). Consistent with the

results of a recent trial²¹⁾, the number of cardiovascular events was smaller than expected, especially with respect to acute myocardial infarction (AMI) and unstable angina requiring urgent hospitalization, because statins were the standard treatment. Two previous 3-vessel IVUS studies reported that multiple plaque rupture is observed in patients with ACS²²⁾ or AMI²³⁾. Furthermore, an elevated CRP level is independently associated with plaque rupture in patients with AMI²³⁻²⁵⁾. Burke *et al.* reported that the number of macrophages in thin-cap atheromas is significantly greater in patients with a high CRP level than in those with a low CRP level²⁶⁾. These results suggest that the CRP level reflects the activity of these inflammatory processes, leading to plaque rupture in all coronary arteries. Approximately half of cardiovascular events were judged to be related to non-culprit lesions following percutaneous coronary intervention²⁷⁾. IVUS examinations were performed in the culprit vessel only in the TRUTH trial. Therefore, coronary artery plaque regression or changes in plaque composition could not be used to predict future cardiovascular events in the present study.

Statins are the most effective agents for reducing vascular inflammation. In addition to their lipid-lowering effects, these drugs reduce the CRP level and exhibit potent anti-inflammatory effects mediated by the inhibition of the macrophage function²⁸⁾. Indeed, long-term treatment with pravastatin is associated with a reduction in the serum CRP levels and better clinical outcomes²⁹⁾. Although the ability of statin therapy to reduce the CRP level is clearly a class effect, studies of statins have failed to show correlations between the magnitude of LDL-C reduction and the magnitude of CRP reduction³⁰⁾. However, the hs-CRP levels add prognostic information at all levels of LDL-C³¹⁾. This indicates that measuring the levels of hs-CRP or LDL-C or both may be useful for predicting future cardiovascular events in statin-treated patients with CAD.

Conclusions

Coronary artery plaque regression and changes in plaque composition during statin therapy do not predict future cardiovascular events in patients with angina pectoris. Instead, the serum hs-CRP level serves as a predictor of cardiovascular events.

Limitations

There are several limitations to the present study. First, a small number of patients with angina pectoris

were enrolled. Therefore, the sample size may not be sufficient to validate the hypothesis, and some selection bias may exist. Second, the IVUS examinations were performed in the culprit vessel only. A recent PROSPECT trial performing whole 3-vessel IVUS examinations reported that the characteristics of non-culprit lesions are associated with future events²⁷⁾. Therefore, the use of whole coronary artery evaluations employing IVUS is necessary to predict future clinical events. Third, the hs-CRP levels were measured at enrollment and the 8-month follow-up in the TRUTH trial; however, they were not measured at the end of the extended TRUTH study. Furthermore, other inflammatory markers were not measured. Fourth, two patients (13%) in the event group and 16 patients (13%) in the event-free group were not treated with statins during the extended TRUTH study. These factors may have affected the results of this study. Finally, 41.9 months may be too short to evaluate cardiovascular events. Further large-scale studies involving precise sample size calculation and long-term follow-up clinical trials are needed to clarify the results of the present study.

Conflicts of Interest

None.

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