Atherosclerosis 234 (2014) 114–119

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary thin-cap fibroatheroma

Ryo Nishio, Toshiro Shinke*, Hiromasa Otake, Masayuki Nakagawa, Ryoji Nagoshi, Takumi Inoue, Amane Kozuki, Hirotoshi Hariki, Tsuyoshi Osue, Yu Taniguchi, Masamichi Iwasaki, Noritoshi Hiranuma, Akihide Konishi, Hiroto Kinutani, Junya Shite, Ken-ichi Hirata

Kobe University Graduate School of Medicine, Division of Cardiovascular Medicine, Department of Internal Medicine, Japan

ARTICLE INFO

Article history:
Received 25 December 2013
Received in revised form
18 February 2014
Accepted 20 February 2014
Available online 5 March 2014

Keywords:
Eicosapentaenoic acid
Thin-cap fibroatheroma
Optical coherence tomography
Pentraxin-3

ABSTRACT

Background: The addition of highly purified eicosapentaenoic acid (EPA) to statin therapy prevents cardiovascular events. However, the impact of this treatment on vulnerable plaques remains unclear. The aim of this study was to assess the impact of adding EPA to a standard statin therapy on vulnerable plaques by serial optical coherence tomography (OCT).
Methods: Forty-nine non-culprit thin-cap fibroatheroma (TCFA) lesions in 30 patients with untreated dyslipidemia were included. Patients were randomly assigned to EPA (1800 mg/day) + statin (23 TCFA, 15 patients) or statin only (26 TCFA, 15 patients) treatment. The statin (rosuvastatin) dose was adjusted to achieve a target low-density lipoprotein (LDL) level of <70 mg/dL. Post-percutaneous intervention and 9-month follow-up OCT were performed to evaluate morphological changes of TCFAs. The EPA/arachidonic acid (EPA/AA) ratio and pentraxin-3 (PTX3) levels were also evaluated.
Results: Despite similar follow-up LDL levels, the EPA + statin group had higher EPA/AA ratios and lower PTX3 levels than the statin group. OCT analysis showed that the EPA + statin group had a greater increase in fibrous-cap thickness, with a greater decrease in lipid arc and lipid length. Macrophage accumulation was less frequently detected in the EPA + statin group than in the statin group at follow-up. When the patients were categorized according to their follow-up PTX3 tertiles, fibrous-cap thickness showed significant increase, and the incidence of macrophages accumulation decreased with lower PTX3 levels.
Conclusion: The concomitant use of EPA and rosuvastatin may stabilize vulnerable plaques better than the statin alone, possibly by suppressing arterial inflammation.

1. Introduction

Statin-based lipid lowering therapy reduces cardiovascular events and is recommended for patients with cardiovascular disease or coronary risk factors [1,2]. Some trials, however, have revealed residual cardiovascular risks even after the reduction of low-density lipoprotein cholesterol (LDL) to target levels [3,4]. According to recent studies, the addition of highly purified eicosapentaenoic acid (EPA) to statin therapy provides additional benefits for preventing cardiovascular events [5–7]. However, the impact of the additive EPA treatment with statin therapy on vulnerable plaques remains unclear.

Plaque rupture is the major mechanism of cardiovascular events, and plaque vulnerability is an important predictor of plaque rupture. Pathological studies have revealed that thin fibrous-cap thickness, large lipid pools, and macrophage infiltration near the fibrous-cap characterize vulnerable plaques [8,9]. Optical coherence tomography (OCT) is a feasible imaging technique for detecting thin-cap fibroatheromas (TCFAs) *in vivo* because of its high resolution [10–13]. In addition, arterial inflammation plays an important role in promoting plaque vulnerability, and high-sensitivity C-reactive protein (hs-CRP) and pentraxin-3 have been reported as useful markers of arterial inflammation [14–16].

The aim of this study was to assess the impact of EPA and statin therapy on the stabilization of vulnerable plaques in patients with

* Corresponding author. Kobe University Graduate School of Medicine, Division of Cardiovascular and Respiratory Medicine, Department of Internal Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan. Tel.: +81 78 382 5846; fax: +81 78 382 5859.
E-mail addresses: shinke820@aol.com, shinke@med.kobe-u.ac.jp (T. Shinke).

http://dx.doi.org/10.1016/j.atherosclerosis.2014.02.025
0021-9150/

untreated dyslipidemia, using serial OCT and serum inflammatory marker evaluations.

2. Methods

2.1. Study design

The study was designed as a randomized, open-label study to assess the impact of 9-month combined therapy using EPA and a statin on OCT parameters and serum inflammatory markers in patients with dyslipidemia. Patients who underwent percutaneous coronary intervention (PCI) for stable angina or acute coronary syndrome and having LDL levels >100 mg/dL without lipid-lowering therapy, were candidates for the study. Acute coronary syndrome (ACS) was defined as acute myocardial infarction (MI) or unstable angina pectoris. MI was defined as a recent symptom of ischemia with electrocardiogram abnormalities, depression or elevation of at least 0.1 mV in the ST segment and troponin T or I elevation. Unstable angina was defined as new-onset severe angina, accelerated angina, or angina at rest. Stable angina was defined as an absence of changes in the frequency, duration, or intensity of symptoms within the 4 weeks preceding the PCI [17]. Patients were excluded from the study if they (1) were already using statins or other lipid-lowering therapies, (2) had known hypersensitivity to statins or contrast, (3) had end-stage renal failure (serum creatinine [Cre] ≥ 2.0 mg/dL), (4) demonstrated hemodynamic and respiratory instability (e.g., cardiogenic shock, severe congestive heart failure), or (5) had terminal stage cancer or dementia (serious conditions that may compromise successful study participation).

After successful PCI to the culprit lesion, multi-vessel OCT examinations of the remaining non-culprit lesions with mild-to-moderate stenosis were performed to detect TCFAs. TCFA was defined as a plaque presenting with a fibrous-cap thickness <65 μm and a lipid arc ≥90° [18]. Finally, patients were enrolled in the study if they had TCFAs in non-culprit, mild-to-moderate stenotic lesions; the patients were randomly assigned to 2 groups: EPA + statin and statin only. The EPA + statin group patients received EPA (1800 mg/day) and rosuvastatin; the statin group received rosuvastatin alone.

Blood analyses and planned follow-up OCT examinations were performed 9 months after the index procedure, regardless of symptomology. During the study period, serum LDL levels were evaluated monthly, and the dose of rosuvastatin was adjusted to achieve a target LDL level of <70 mg/dL, in both groups. Also, they received similar dietary counseling until 1 month after the index procedure.

The ethics committee of Kobe University approved this study, and all enrolled study patients provided written informed consent to participate in this clinical trial.

2.2. Lipid profile and inflammatory markers

Serum LDL levels were evaluated monthly to adjust the dose of rosuvastatin in patients in both groups. Other lipid profiles and inflammatory markers were evaluated before the start of lipid-lowering therapy and 9 months after the PCI. The lipid profile also included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and EPA/arachidonic acid (AA) ratios. The extent of arterial inflammation was evaluated by determining hs-CRP and PTX3 levels.

2.3. OCT examination

To evaluate plaque characteristics, we performed multivessel frequency-domain OCT examinations at the time of the PCI and at the time of the 9-month follow-up angiography. In this study, OCT was performed in a standard fashion, as previously reported [19]. Briefly, a C7 Dragonfly™ catheter (LightLab Imaging, Westford, MA, USA) was advanced to the distal end of the target lesion over a 0.014-inch guide wire, followed by the infusion of contrast medium into the coronary artery from the guiding catheter at 3.5 mL/s, serving as a flush to clear the area of blood. The entire lesion was then imaged using an automatic pullback system moving at 20 mm/s.

2.4. OCT analysis

Lipid arcs were evaluated as the largest arc in a signal-pool region, with diffuse borders in the target plaques on the cross-sectional OCT image. Fibrous-cap thickness was defined as the minimum thickness of the signal-rich layer overlying the lipid-rich plaque. Lipid length was defined as the longitudinal length of the lipid-rich plaque (lipid arc ≥90°). Macrophage accumulation was identified as a high-intensity band or bright spots, which exceed the intensity of intra-tissue speckle noise, with high backscattering within the fibrous-cap, as previously reported [13]. Intimal microvessel was defined as a black hole or a tubular structure within a target plaque [11,13]. For each individual target plaque, the thinnest fibrous-cap thickness measurement obtained from three imaging locations was used for analysis (Fig. 1). At the time of follow-up, the plaques were identified based on the distance from the landmarks such as major branches, calcification and stent edge. Interobserver and intraobserver variabilities were assessed by the evaluation of all images by two independent readers who were blinded to the clinical presentations and the time point of image acquisition and by the same reader at two different times to compute an average value, respectively.

2.5. Clinical follow-up

Clinical events were monitored for at least 18 months after the index PCI. Death, MI, clinically driven revascularization for in-stent restenosis (defined as a repeat PCI or coronary artery bypass graft at the site of the implanted stent) were evaluated [17]. Clinically driven target plaque revascularization was defined as PCI or coronary artery bypass graft to the target TCFA lesion. Clinically driven non-target plaque revascularization was defined as repeat PCI or coronary artery bypass graft to a non-target TCFA lesion.

2.6. Statistical analysis

All statistical analyses were performed using Medcalc (version 12.7; Medcalc Software, Mariakerke, Belgium). Continuous variables are presented as means ± SD. Differences between the continuous parameters in the 2 groups were calculated using a Mann–Whitney *U*-test. Categorical variables are presented as frequency counts. Between group comparisons of categorical variables were performed using Fisher's exact test. Values were considered statistically significant at $p < 0.05$.

3. Results

3.1. Study population

Between April 2010 and October 2011, 341 patients underwent PCI at Kobe University Hospital; 117 patients had LDL levels >100 mg/dL and had not received lipid-lowering therapy. Of these 117 individuals, 22 patients were excluded from this study because of participation in other studies. A further 29 patients were excluded due to their inability to tolerate OCT examination or statin administration due to known hypersensitivity to contrast or statins ($n = 3$), end-stage renal failure ($n = 8$), severe heart failure ($n = 5$),

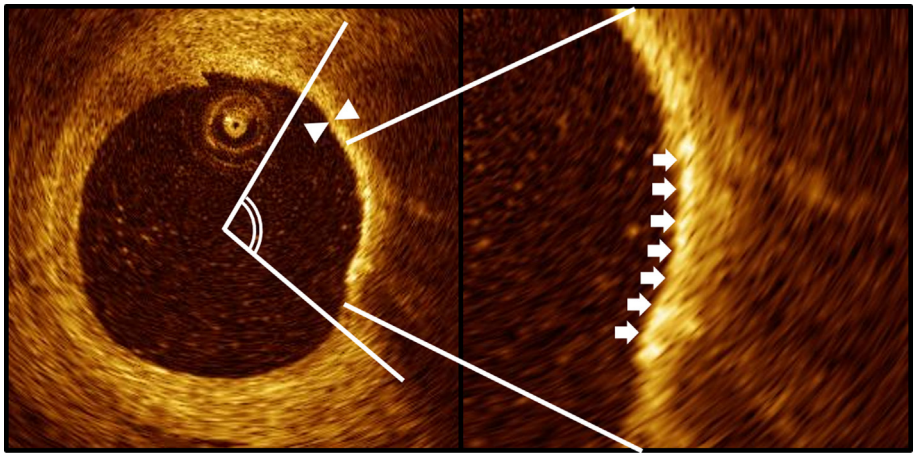

Fig. 1. Representative case of thin-cap fibroatheroma (TCFA) with macrophages accumulation TCFA was defined as a plaque presenting with the thinnest fibrous-cap thickness <65 μm (white arrow head) and a lipid arc ≥90° (white lines). Macrophages accumulation was identified as a high-intensity band within the fibrous-cap (white arrow).

terminal stage cancer ($n = 6$), or dementia ($n = 7$). Nine patients did not provide their consent to participate. Thus, 57 patients underwent multivessel OCT screening to detect TCFAs in non-culprit lesions. According to the OCT examinations, 52 TCFAs were detected in 31 patients and were enrolled in this study. Patients were randomly assigned to the EPA + statin group (16 patients, 25 TCFAs) or statin group (15 patients, 27 TCFAs). Blood analyses and planned follow-up OCT examinations were performed 9 months after the index procedure. During this period, 1 patient in the EPA + statin group rejected follow-up OCT examination; none of the patients dropped out due to side effects caused by EPA or rosuvastatin. One TCFA in each group was disrupted and was removed from the study because its plaque characteristics could not be evaluated in the follow-up OCT. However, the patients with disrupted TCFAs were not excluded because the patients had other TCFAs that could be followed. Ultimately, the final analysis involved 23 TCFAs in 15 patients in the EPA + statin group and 26 TCFAs in 15 patients in the statin group (Supplemental data Fig. 1).

3.2. Patient characteristics

Seventeen patients (56.6%) presented with ACS, and the frequency of ACS was similar between the 2 groups. Similarly, no statistical differences were observed in coronary risk factors or concomitant drug use between the 2 groups (Table 1).

3.3. Lipid profile and inflammatory markers

There were no differences in the baseline lipid profiles or inflammatory markers between the 2 groups (Table 2). Although follow-up TC, HDL, LDL, and TG levels were similar between the 2 groups, the follow-up EPA/AA ratio was higher in the EPA + statin group than in the statin group and the follow-up PTX3 levels were lower in the EPA + statin group than in the statin group (Table 2). Table 2 also shows data on lower hs-CRP levels at follow-up in the EPA + statin group than in the statin group.

3.4. OCT analysis

Although there were no differences in baseline OCT parameters, the follow-up fibrous-cap thicknesses were significantly greater in the EPA + statin group than in the statin group (Table 2). Representative images in each group are shown in Supplemental data Fig. 2. In accordance with this observation, the increase in fibrous-cap thickness during the 9-month follow-up period was greater in the EPA + statin group than in the statin group (Fig. 2A). There were no differences in the follow-up lipid arcs and lipid lengths between the 2 groups; however, the decrease in the lipid arc and lipid length during the follow-up period was significantly greater in the EPA + statin group than in the statin group (Fig. 2B and C). Macrophage accumulation was less frequently detected in the EPA + statin group than in the statin group at the follow-up examination and the presence of intimal microvessel tended to be less frequent in the EPA + statin group than in the statin group at the follow-up (Table 2).

3.5. Correlation analysis

Supplemental data Table 1 describes the correlation between the follow-up EPA/AA ratios and the lipid profiles and inflammatory

Table 1
Patient characteristics at baseline and at the 9-month follow-up.

Variables	EPA[a] + statin group ($n = 15$)	Statin group ($n = 15$)	p-value
Age (year)	61.0 ± 12.6	63.8 ± 9.5	0.46
Men (n; %)	13 (86.7)	13 (86.7)	1.00
BMI[b] (kg/m^2)	26.4 ± 3.6	24.6 ± 3.5	0.24
ACS[c] (n; %)	9 (60.0)	8 (53.3)	0.99
Coronary risk factors			
Hypertension (n; %)	11 (73.3)	10 (66.7)	0.99
Diabetes mellitus (n; %)	5 (33.3)	2 (13.3)	0.39
Smoker (n; %)	12 (80.0)	9 (60.0)	0.43
Family history (n; %)	5 (33.3)	4 (26.7)	0.99
Concomitant drugs			
Aspirin (n; %)	15 (100)	15 (100)	1.00
Clopidogrel (n; %)	15 (100)	15 (100)	1.00
ACE-I[d] or ARB[e] (n; %)	10 (66.7)	9 (60.0)	0.99
Beta-blocker (n; %)	3 (20.0)	3 (20.0)	1.00
Calcium channel blocker (n; %)	2 (13.3)	5 (33.3)	0.39
Anti-diabetic agents (n; %)	5 (33.3)	2 (13.3)	0.39
Other lipid-lowering therapy (n; %)	0	0	1.00
Number of TCFAs[f] (n/patient)	1.53 ± 0.52	1.73 ± 0.96	0.84
Follow-up duration (days)	280.7 ± 38.3	274.4 ± 79.9	0.79
Dose of rosuvastatin at follow-up (mg/day)	3.67 ± 2.08	3.50 ± 3.25	0.27

[a] Eicosapentaenoic acid.
[b] Body mass index.
[c] Acute coronary syndrome.
[d] Angiotensin-converting enzyme inhibitor.
[e] Angiotensin receptor blocker.
[f] Thin-cap fibroatheroma.

Table 2
Blood tests and OCT[a] measurements at baseline and at the 9-month follow-up.

Variables	Baseline			Follow-up		
	EPA + statin group	Statin group	*p*-value	EPA + statin group	Statin group	*p*-value
Blood test						
EPA/AA[b]	0.32 ± 0.15	0.27 ± 0.13	0.37	1.11 ± 0.53	0.42 ± 0.31	0.0001
TC[c] (mg/dL)	207.3 ± 39.1	196.3 ± 40.3	0.34	144.4 ± 36.5	146.3 ± 20.5	0.62
HDL[d] (mg/dL)	40.9 ± 12.0	41.5 ± 7.4	0.97	44.9 ± 9.9	43.6 ± 9.4	0.72
LDL[e] (mg/dL)	138.0 ± 35.3	130.3 ± 34.8	0.41	80.1 ± 29.7	83.2 ± 19.6	0.58
TG[f] (mg/dL)	161.4 ± 50.4	146.8 ± 37.4	0.30	123.5 ± 42.6	131.4 ± 47.9	0.72
hs-CRP[g] (mg/dL)	0.24 ± 0.18	0.22 ± 0.15	0.95	0.06 ± 0.05	0.12 ± 0.11	0.07
PTX3[h] (ng/mL)	4.49 ± 2.25	4.75 ± 2.22	0.60	2.79 ± 0.96	3.84 ± 1.17	0.01
OCT measurements						
Fibrous-cap thickness (μm)	47.5 ± 7.4	46.5 ± 10.9	0.94	102.2 ± 28.8	70.0 ± 10.6	<0.0001
Lipid arc (degree)	159.0 ± 62.0	158.3 ± 63.5	0.98	127.7 ± 44.8	145.6 ± 50.6	0.27
Lipid length (mm)	6.52 ± 3.47	6.17 ± 2.84	0.85	3.87 ± 2.02	4.97 ± 2.39	0.13
The incidence of macrophages accumulation (*n*; %)	16 (69.6)	18 (69.2)	0.99	3 (13.0)	12 (46.2)	0.02
The presence of intimal microvessels (*n*; %)	13 (56.5)	16 (61.5)	0.78	7 (30.4)	15 (57.7)	0.08

[a] Optical coherence tomography.
[b] Eicosapentaenoic acid/arachidonic acid.
[c] Total cholesterol.
[d] High-density lipoprotein cholesterol.
[e] Low-density lipoprotein cholesterol.
[f] Triglyceride.
[g] High sensitivity C-reactive protein.
[h] Pentraxin-3.

marker parameters. The follow-up EPA/AA ratio was significantly correlated with the follow-up TG and PTX3 levels. The follow-up fibrous-cap thicknesses and the presence of macrophage accumulation were also associated with the follow-up PTX3 levels, but not with the follow-up TG levels. When the patients were divided into tertiles according to their follow-up PTX3 levels, fibrous-cap thickness was significantly increased and the presence of macrophage accumulation was decreased in conjunction with lower PTX3 levels (Fig. 3A and B). Receiver-operating curve analyses showed that a PTX3 cutoff value of 3.46 ng/mL predicted fibrous-cap thicknesses of <65 μm with an 87.5% sensitivity and 68.3% specificity; the same cutoff value predicted the presence of macrophage accumulation, as determined by OCT, with 73.3% sensitivity and 73.5% specificity (Supplemental data Fig. 3A and B).

3.6. Clinical events

Supplemental data Table 2 shows clinical events occurring after the index PCI. The median follow-up duration was 725.5 days (95% confidence interval, 553.8–730.8 days). There were no differences in the rates of mortality, MI, in-stent restenosis, target plaque revascularizations, and non-target plaque revascularizations between the 2 groups.

4. Discussion

Previous studies have shown that intensive LDL-lowering therapy involving statins decreases the incidence of future cardiovascular events. At the same time, these studies also described a significant residual cardiovascular risk, even with the intensive statin therapy [3,4]. Among several options to reduce the residual risk, the potential benefit of adding EPA treatment was noted in recent clinical studies [5,6]. A detailed mechanism of EPA's impact on the reduction of cardiovascular events is, however, still unknown.

In the present study, we demonstrated that a combination treatment involving both EPA and rosuvastatin therapy stabilized unstable plaques to a greater degree than did rosuvastatin therapy alone. Serial OCT analyses showed that the EPA + statin group had a larger increase in fibrous-cap thickness and a greater decrease in

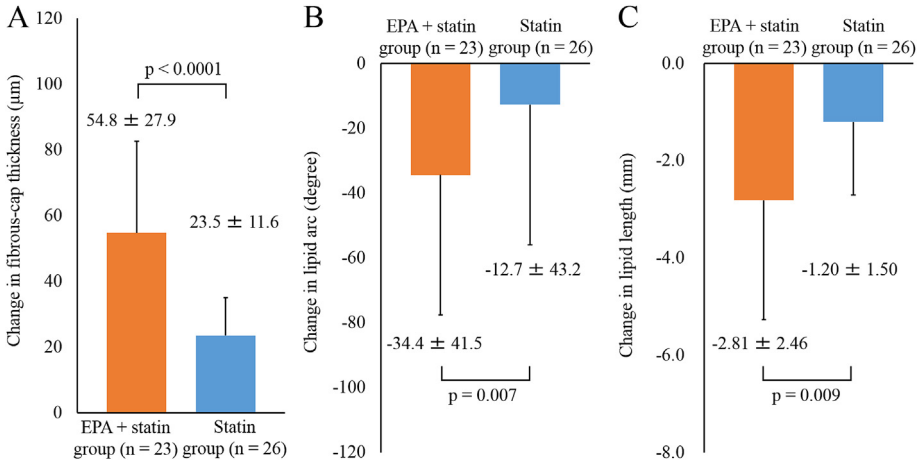

Fig. 2. Changes in optical coherence tomography parameters (A: fibrous-cap thickness; B: lipid arc; C: lipid length) EPA, eicosapentaenoic acid.

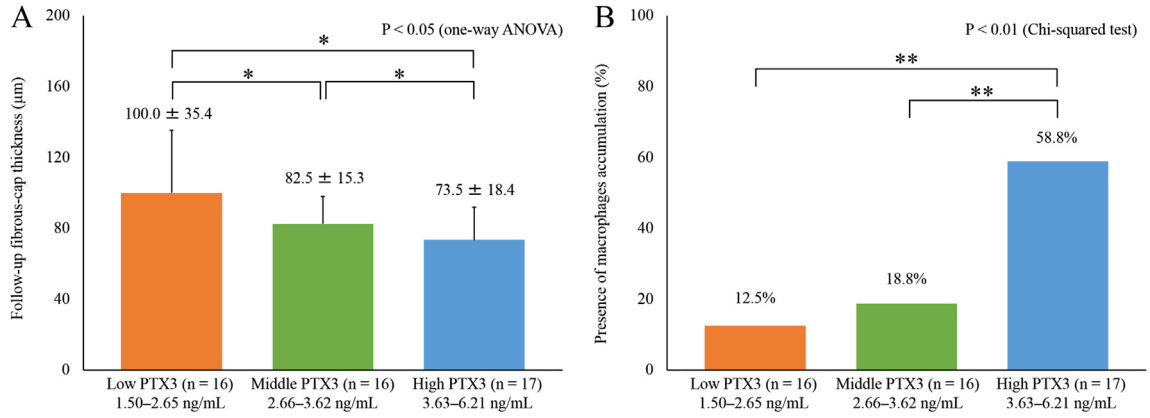

Fig. 3. The relationship between pentraxin-3 (PTX-3) and optical coherence tomography findings at the 9-month follow-up. A: The relationship between PTX3 and fibrous-cap thickness. Differences between the 3 groups were calculated by one-way analysis of variance (ANOVA), and the Tukey–Kramer test was used for post-hoc analysis. $^{*}p < 0.05$. B: The relationship between PTX3 and the incidence of macrophages accumulation. Differences between the 3 groups were calculated by using a chi-squared test, and the Bonferroni test was used as for post-hoc analysis. $^{**}p < 0.01$.

lipid arcs and lipid lengths. Moreover, as evaluated by OCT, the addition of EPA treatment decreased the incidence of macrophage accumulation more strongly compared to the therapy involving statin alone and tended to decrease the intraplaque neovascularization. According to recent pathological studies, important determinants of plaque rupture include the presence of a large lipid pool, the thickness of the fibrous-cap, the extent of macrophage infiltration within the fibrous-cap and intraplaque neovasucularization [8,9,20]. Previous studies revealed the clinical importance of *in vivo* evaluations of vulnerable plaques by intravascular imaging, such as virtual histology intravascular ultrasound (IVUS), integrated backscatter-IVUS, and OCT [21–24]. Histological studies have clearly demonstrated the ability of OCT to detect lipid-rich plaques and macrophage accumulation, as well as its potential for accurately measuring cap thickness [10–13]. Thus, we propose that a larger increase in fibrous-cap thickness and a greater decrease in lipidic components and macrophage infiltration, as determined by OCT in the EPA + statin group, indicates that the concomitant use of EPA and statin stabilizes vulnerable plaques better than statin therapy alone.

Although detailed mechanisms remain unclear, our results suggest that EPA stabilizes TCFAs better than the statin alone therapy through greater suppression of vascular inflammation. In the present study, the added EPA treatment significantly lowered PTX3 levels with a tendency towards greater decreases in hs-CRP levels and decreased macrophage accumulation. PTX3 is produced by macrophages and vascular smooth muscle cells in the vicinity of atherosclerotic lesions in response to inflammatory cytokines, whereas hs-CRP is produced in the liver [25]. Therefore, PTX3 levels reflect local arterial inflammation more directly over the short-term compared to systemic markers of inflammation, such as hs-CRP. A previous study also showed that PTX3 levels are more useful than hs-CRP levels for predicting plaque vulnerability [15]. In the present study, fibrous-cap thickness increased and the frequency of macrophage accumulation decreased along with decreased PTX3 levels. Considering that local inflammatory cytokine levels and macrophage-derived proteolysis promote fibrous-cap thinning [26], we believe that the stabilization associated with EPA therapy involves the suppression of local inflammation and macrophage proteolysis. A previous study showed that orally administered EPA regressed atherosclerosis and decreased the content of macrophages in LDL receptor-deficient mice [27]. Our results are in accordance with previous clinical reports showing the ability of combined EPA and statin treatment to reduce cardiovascular events in patients with coronary artery disease, and these results provide mechanistic support for this hypothesis.

This study has several limitations. First, because of the nature of serial, invasive imaging studies, this study included only a small number of patients, without power to detect possible differences in long-term clinical event rates. Thus, this study failed to show a difference in clinical events between the 2 groups. Second, we only assessed the combination of rosuvastatin and EPA without comparing the results with those of combinations involving other statins or other lipid-lowering therapies. Third, we did not validate the OCT findings with histological findings; therefore, the regions identified as TCFAs, macrophages and neovascularization were not confirmed to be pathologically vulnerable. However, no one-on-one OCT criteria with histological findings have been validated for the identification of pathologically vulnerable plaques. Moreover, the ability of OCT to accurately identify lipidic components and measure cap thickness has previously been validated [10–12]. Therefore, we consider that the information obtained in this study is valid, and a pathological validation of the OCT-based criteria for the identification of vulnerable plaques is warranted to further confirm these results. Finally, this study could not evaluate the presence of positive remodeling, one of the important features of vulnerable plaques, because the near-infrared light irradiated from the OCT catheter only penetrates 1–3 mm into the vessel wall and cannot penetrate through a lipid-rich plaque.

In conclusion, in patients with untreated dyslipidemia, the concomitant use of EPA and rosuvastatin stabilizes vulnerable plaques more effectively than treatment with a statin alone. The present results suggest that the stronger suppression of arterial inflammation associated with the combined therapy might lead to better stabilization of vulnerable plaques.

Conflict of interest

Dr. Shinke, Dr. Shite and Dr. Otake received a consulting fee from St. Jude Medical Japan Co., Ltd. Otherwise, there are nothing to disclose with regard to this manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.atherosclerosis.2014.02.025.

References

[1] Wilt TJ, Bloomfield HE, MacDonald R, et al. Effectiveness of statin therapy in adults with coronary heart disease. Arch Intern Med 2004;164:1427–36.

[2] Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.

[3] Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–504.

[4] LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425–35.

[5] Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007;369:1090–8.

[6] GISSI-Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999;354:447–55.

[7] Matsumoto M, Sata M, Fukuda D, et al. Orally administered eicosapentaenoic acid reduces and stabilizes atherosclerotic lesions in ApoE-deficient mice. Atherosclerosis 2008;197:524–33.

[8] Virmani R, Kolodgie FD, Burke AP, et al. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000;20:1262–75.

[9] Narula J, Nakano M, Virmani R, et al. Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings for the invasive and noninvasive detection of vulnerable plaques. J Am Coll Cardiol 2013;61:1041–51.

[10] Kume T, Akasaka T, Kawamoto T, et al. Assessment of coronary arterial plaque by optical coherence tomography. Am J Cardiol 2006;97:1172–5.

[11] Kubo T, Ino Y, Tanimoto T, et al. Optical coherence tomography imaging in acute coronary syndromes. Cardiol Res Pract 2011;2011:312978.

[12] Kume T, Akasaka T, Kawamoto T, et al. Measurement of the thickness of the fibrous cap by optical coherence tomography. Am Heart J 2006;152:755.e751–754.

[13] Tearney GJ, Regar E, Akasaka T, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. J Am Coll Cardiol 2012;59:1058–72.

[14] Burke AP, Tracy RP, Kolodgie F, et al. Elevated C-reactive protein values and atherosclerosis in sudden coronary death: association with different pathologies. Circulation 2002;105:2019–23.

[15] Koga S, Ikeda S, Yoshida T, et al. Elevated levels of systemic pentraxin 3 are associated with thin-cap fibroatheroma in coronary culprit lesions: assessment by optical coherence tomography and intravascular ultrasound. JACC Cardiovasc Interv 2013;6:945–54.

[16] Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation 2001;104:365–72.

[17] Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634–53.

[18] Kume T, Okura H, Yamada R, et al. Frequency and spatial distribution of thin-cap fibroatheroma assessed by 3-vessel intravascular ultrasound and optical coherence tomography: an ex vivo validation and an initial in vivo feasibility study. Circ J 2009;73:1086–91.

[19] Yoon JH, Di Vito L, Moses JW, et al. Feasibility and safety of the second-generation, frequency domain optical coherence tomography (FD-OCT): a multicenter study. J Invasive Cardiol 2012;24:206–9.

[20] Fleiner M, Kummer M, Mirlacher M, et al. Arterial neovascularization and inflammation in vulnerable patients: early and late signs of symptomatic atherosclerosis. Circulation 2004;110:2843–50.

[21] Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.

[22] Nasu K, Tsuchikane E, Katoh O, et al. Effect of fluvastatin on progression of coronary atherosclerotic plaque evaluated by virtual histology intravascular ultrasound. JACC Cardiovasc Interv 2009;2:689–96.

[23] Takarada S, Imanishi T, Kubo T, et al. Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: assessment by optical coherence tomography study. Atherosclerosis 2009;202:491–7.

[24] Hattori K, Ozaki Y, Ismail TF, et al. Impact of statin therapy on plaque characteristics as assessed by serial OCT, grayscale and integrated backscatter-IVUS. JACC Cardiovasc Imaging 2012;5:169–77.

[25] Savchenko A, Imamura M, Ohashi R, et al. Expression of pentraxin 3 (PTX3) in human atherosclerotic lesions. J Pathol 2008;215:48–55.

[26] Finn AV, Nakano M, Narula J, et al. Concept of vulnerable/unstable plaque. Arterioscler Thromb Vasc Biol 2010;30:1282–92.

[27] Nakajima K, Yamashita T, Kita T, et al. Orally administered eicosapentaenoic acid induces rapid regression of atherosclerosis via modulating the phenotype of dendritic cells in LDL receptor-deficient mice. Arterioscler Thromb Vasc Biol 2011;31:1963–72.