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ORIGINAL ARTICLE

Serum n-3 to n-6 polyunsaturated fatty acids ratio correlates with coronary plaque vulnerability: an optical coherence tomography study

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Abstract A low ratio of eicosapentaenoic acid to arachidonic acid (EPA/AA) has been demonstrated to be associated with a higher risk of cardiovascular events. Optical coherence tomography (OCT) is useful for the assessment of coronary plaque vulnerability. The purpose of this study was to evaluate the association between EPA/AA ratio and coronary plaque vulnerability. This study involved 58 patients with stable angina pectoris undergoing percutaneous coronary intervention. OCT image acquisition was performed before the procedure in the culprit lesions. We assessed lipid-rich plaque length and arc, fibrous cap thickness, frequency of thin-cap fibroatheroma (TCFA), thrombus, ruptured plaque, macrophage infiltration, and microvessels using OCT. Patients were divided into two groups according to the median value of serum EPA/AA ratio: a low-EPA/AA group (n = 29, EPA/AA ratio <0.36) and a high-EPA/AA group (n = 29, EPA/AA ratio ≥0.36). In qualitative analyses, TCFA (35.4 vs 6.9 %, P = 0.0095), macrophage infiltration (48.3 vs 13.8 %, P = 0.0045), and microvessels (44.8 vs 10.3 %, P = 0.0033) were more frequently observed in the low-EPA/AA group. In quantitative analyses, the low-EPA/AA group had wider maximum lipid arc (114.0 ± 94.8° vs 56.4 ± 66.0°, P = 0.0097), longer lipid length (4.8 ± 4.5 vs 1.6 ± 2.6 mm, P = 0.0037), and thinner fibrous cap (69.3 ± 28.3 vs 113.3 ± 46.6 μm, P = 0.005) compared with the high-EPA/AA group. EPA/AA ratio was positively correlated with fibrous cap thickness (r = 0.46, P = 0.007). In a multivariate model, an EPA/AA ratio <0.36 was associated with the presence of TCFA (odds ratio 6.41, 95 % confidence interval 1.11–61.91, P = 0.0371). In our detailed OCT analysis, lower EPA/AA ratio was associated with higher vulnerability of coronary plaques to rupture.

Keywords Eicosapentaenoic acid to arachidonic acid ratio · Vulnerable plaque · Optical coherence tomography

Introduction

Intensive lipid-lowering therapy with statins is regarded as one of the effective treatments for the stabilization of coronary artery plaques, and reduces the risk for coronary events and mortality [1–3]. However, cardiovascular events occur in some patients even with statin therapy. Previous studies have shown that consumption of fish and fish oils was associated with a decreased risk of cardiovascular disease. Fish and fish oil are sources of the omega-3 fatty acid eicosapentaenoic acid (EPA). A high serum ratio of EPA to arachidonic acid (AA) may play an important role in preventing future cardiovascular events and contributing to a better outcome [4–6]. The Japan EPA Lipid Intervention Study (JELIS), a large randomized clinical trial, showed that purified EPA administration along with statin therapy reduced the incidence of coronary events by 19 % compared with statin therapy alone [7].

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Atherosclerosis has an important inflammatory component, and acute cardiovascular events can be initiated by inflammatory processes occurring in vulnerable plaques [8–10]. A major cause of acute coronary syndrome (ACS) is the disruption of vulnerable plaques with superimposed thrombus. The anti-inflammatory effects of marine n-3 polyunsaturated fatty acids (PUFAs) may contribute to their protective actions toward atherosclerosis, plaque rupture, and cardiovascular mortality [11]. Optical coherence tomography (OCT) is a high-resolution imaging technology that can provide a detailed observation of the vulnerable coronary plaque, such as thin-cap fibroatheroma (TCFA), plaque rupture, and intracoronary thrombus.

The purpose of this study was to investigate the association between the serum EPA/AA ratio and plaque vulnerability evaluated by OCT.

Patients and methods

Study patients

This study enrolled 312 consecutive patients with ACS or stable angina pectoris who underwent percutaneous coronary intervention (PCI) and an intracoronary OCT examination. The exclusion criteria were ACS, congestive heart failure, cardiogenic shock, an intercurrent infection or other inflammatory disease, in-stent restenosis, total occluded lesion, lesions with large quantity of thrombus, no blood samples, and poor image quality of OCT for analysis. According to these exclusion criteria, ultimately 58 patients were enrolled into this study. We divided these patients into two groups according to the median value of serum EPA/AA ratio: patients with a low EPA/AA ratio (n = 29, EPA/AA ratio <0.36) and patients with a high EPA/AA ratio (n = 29, EPA/AA ratio $\geq$0.36). OCT findings in the culprit lesions were compared between the two groups.

Blood samples were obtained in the fasting state on admission for measurements of PUFAs (EPA, AA, and docosahexaenoic acid (DHA)). The measurement was performed by gas chromatography at the central laboratory (SRL, Tokyo, Japan). In brief, serum lipids were extracted by Folch's procedure, then fatty acids (tricosanoic acid, C23:0, as the internal standard) were methylated with boron trifluoride and methanol. The methylated fatty acids were then analyzed using a gas chromatograph (GC-2010; Shimadzu, Kyoto, Japan) equipped with a capillary column (TC-70; GL Sciences, Tokyo, Japan).

ACS includes acute myocardial infarction defined by The Joint European Society of Cardiology/American College of Cardiology Committee, and unstable angina pectoris defined according to the Braunwald clinical classification. Hypertension was defined by the Joint National Committee VII, diabetes mellitus by the World Health Organization (WHO) Study Group, and hypercholesterolemia by the Japan Atherosclerosis Society Guidelines. The study was approved by the hospital ethics committee, and informed consent was obtained from all patients before the study.

OCT image acquisition and analysis

OCT imaging was performed before PCI and after the administration of 100–200 mg intracoronary nitroglycerin. In the present study, images were acquired using a time-domain (M2CV OCT Imaging System; LightLab Imaging, Westford, MA, USA) or a frequency-domain (C7-XR OCT Intravascular Imaging System; St Jude Medical, St Paul, MN, USA) OCT system. The intracoronary OCT imaging technique has been described previously [12, 13]. In the M2 system, a 0.016-inch OCT catheter was advanced to the culprit lesion through a 3-F occlusion balloon catheter. To remove the blood from the field of view, the occlusion balloon was inflated to 0.6 atm at the proximal site of the culprit lesion, and Lactated Ringer's solution was infused into the coronary artery from the distal tip of the occlusion balloon catheter at 0.5 mL/s. The entire length of the culprit lesion was imaged using an automatic pullback device moving at 1 mm/s, and the OCT image clearly visualized the culprit lesion. In the C7 system, a 2.7-F OCT imaging catheter (Dragonfly; LightLab Imaging, Westford, MA, USA) is advanced distal to the lesion; automatic pullback was started as soon as the blood was cleared by the injection of contrast media or Dextran. All images were stored digitally for subsequent offline analysis.

OCT image analysis was performed by two experienced observers blinded to the clinical information by using previously established criteria for OCT plaque characterization [14]. OCT analysis was performed in the culprit lesion. The presence of TCFA, plaque rupture, macrophage infiltration, microvessels, and intracoronary thrombus were evaluated. When lipid was present in $\geq$2 quadrants in any of the images within a plaque, it was considered a lipid-rich plaque. In the culprit lesion, maximum lipid arc was measured. Lipid length was defined as length of lipid-rich plaque and measured on longitudinal view. TCFA was defined as a lipid-rich plaque with a fibrous cap thickness measuring $\leq$65 μm. The fibrous cap thickness of lipid-rich plaque was measured at the thinnest part three times, and the average value was then calculated. Plaque rupture was defined as an intimal interruption and cavity formation in the plaque. Macrophage infiltration was defined as bright spots with high OCT backscattering signal variances. A microvessel was defined as a no-signal tubular structure without a connection to the vessel lumen recognized on $\geq$ 3 consecutive cross-sectional images. Thrombus was identified as an

Table 1 Patients' characteristics

	All (n = 58)	Low EPA/AA (n = 29)	High EPA/AA (n = 29)	P value*
Age (years)	69 ± 9	67 ± 9	71 ± 9	0.17
Male, n (%)	39 (67)	19 (66)	20 (69)	0.78
Body mass index (kg/m^2)	24.7 ± 3.4	25.4 ± 2.8	24.0 ± 3.9	0.12
Coronary risk factor, n (%)				
Smoking	35 (60)	16 (55)	19 (66)	0.42
Hypertension	50 (86)	24 (82)	26 (90)	0.45
Diabetes	38 (66)	20 (69)	18 (62)	0.58
Dyslipidemia	44 (76)	22 (76)	22 (76)	1.00
Cardiovascular history, n (%)				
Myocardial infarction	16 (28)	8 (28)	8 (28)	1.00
PTCA or CABG	29 (50)	16 (55)	13 (45)	0.43
Culprit vessel, n (%)				0.18
LAD	28 (48)	15 (52)	13(45)	
LCx	12 (21)	8 (27)	4 (14)	
RCA	18 (31)	6 (21)	12 (41)	
Culprit lesion				
%DS, (%)	67.2 ± 9.9	68.1 ± 10.0	66.3 ± 9.8	0.49
Type B2/C, n (%)	45 (78)	22 (76)	23 (79)	0.75
Medication use, n (%)				
Antiplatelet agent	50 (86)	27 (93)	23 (79)	0.13
β-Blocker	20 (35)	9 (31)	11 (38)	0.58
ACE-I/ARB	33 (57)	15 (52)	18 (62)	0.43
Statin	32 (55)	19 (66)	13 (45)	0.11

EPA/AA eicosapentaenoic acid (EPA) to arachidonic acid (AA) ratio, *PTCA* percutaneous transluminal coronary angioplasty, *CABG* coronary-artery bypass grafting, *LAD* left anterior descending coronary artery, *LCx* left circumflex coronary artery, *RCA* right coronary artery, *%DS* percent diameter stenosis, *ACE-I* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker

* P value for low vs high EPA/AA ratio

irregular high- or low-backscattering mass protruding into the lumen. If there was discordance of diagnosis between the two observers, a consensus diagnosis was obtained using repeated off-line readings.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD). Comparisons were conducted by Student's t test or nonparametric Wilcoxon sum rank test for non-normally distributed variables. Categorical variables were compared by Chi-square test. Multivariate logistic regression analyses were performed to identify independent predictors of OCT-detected vulnerable findings (TCFA, plaque rupture, macrophage infiltration, microvessels, and thrombus) by adjusting for predefined variables. Low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, high-sensitivity C-reactive protein (hsCRP), EPA/AA ratio, and DHA were included in the multivariate logistic model. A P value of less than 0.05 was considered statistically significant. Statistical analysis was performed with JMP, version 10 for windows (SAS Institute, Cary, NC, USA).

Results

Table 1 shows the patients' characteristics. The mean age of all patients was 69 years, and 39 patients (67 %) were men. There were no differences in the patient' characteristics between the two groups. EPA and EPA/AA ratio were significantly lower in low-EPA/AA group than in the high-EPA/AA group. There were no differences in the serum lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) between the two groups. There was no significant difference in hsCRP between the low- and high-EPA/AA groups (0.36 ± 1.24 vs 0.23 ± 0.33, P = 0.58) (Table 2).

The comparison of plaque characteristics by OCT in the low- and high-EPA/AA groups is shown in Table 3. The representative OCT images of the coronary culprit lesions in the low and high-EPA/AA groups are shown in Figs. 1

Table 2 Serum lipid profile and fatty acid composition in low- and high-EPA/AA groups

	Low EPA/AA (n = 29)	High EPA/AA (n = 29)	P value
Serum lipid value, mg/dl			
Total cholesterol	175.8 ± 35.3	175.8 ± 38.0	0.99
LDL cholesterol	101.4 ± 35.4	100.3 ± 29.6	0.90
HDL cholesterol	39.8 ± 12.6	43.1 ± 13.3	0.25
Triglycerides	148.8 ± 75.3	139.7 ± 89.6	0.42
PUFA value, μg/ml			
EPA	47.2 ± 14.5	90.5 ± 36.4	<0.0001
AA	190.2 ± 53.0	160.8 ± 48.4	0.03
DHA	136.1 ± 36.1	164.8 ± 52.7	0.02
EPA/AA ratio	0.26 ± 0.07	0.59 ± 0.26	<0.0001

EPA/AA eicosapentaenoic acid (EPA) to arachidonic acid (AA) ratio, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *PUFA* polyunsaturated fatty acid, *DHA* docosahexaenoic acid

Table 3 Plaque characteristics of optical coherence tomography in low- and high-EPA/AA groups

	Low EPA/AA (n = 29)	High EPA/AA (n = 29)	P value
Minimal CSA, mm^2	1.4 ± 0.8	1.6 ± 0.8	0.26
Lipid-rich plaque, n (%)	14 (48.3)	8 (27.6)	0.10
Maximum lipid arc, (°)	114.0 ± 94.8	56.4 ± 66.0	0.0097
Lipid length, mm	4.8 ± 4.5	1.6 ± 2.6	0.0037
TCFA, n (%)	10 (34.5)	2 (6.9)	0.0095
Fibrous cap thickness, μm	69.3 ± 28.3	113.3 ± 46.6	0.005
Plaque rupture, n (%)	5 (17.2)	1 (3.5)	0.08
Macrophage infiltration, n (%)	14 (48.3)	4 (13.8)	0.0045
Microvessels, n (%)	13 (44.8)	3 (10.3)	0.0033
Thrombus, n (%)	6 (20.7)	4 (13.8)	0.49

EPA/AA eicosapentaenoic acid (EPA) to arachidonic acid (AA) ratio, *CSA* cross-sectional area, *TCFA* thin-cap fibroatheroma

and 2. According to qualitative analysis, TCFA (35.4 vs 6.9 %, $P = 0.0095$), macrophages (48.3 vs 13.8 %, $P = 0.0045$), and microvessels (44.8 vs 10.3 %, $P = 0.0033$) were more frequently observed in the low-EPA/AA group. The frequency of plaque rupture tended to be higher in the low-EPA/AA group (17.2 vs 3.5 %, $P = 0.08$). There were no significant differences in the presence of lipid-rich plaque and thrombus. According to quantitative analysis, the low-EPA/AA group had a wider maximum lipid arc compared with the high-EPA/AA group (114.0 ± 94.8° vs 56.4 ± 66.0°, $P = 0.0097$), longer lipid length (4.8 ± 4.5 vs 1.6 ± 2.6 mm, $P = 0.0037$), and thinner fibrous cap (69.3 ± 28.3 vs 113.3 ± 46.6 μm, $P = 0.005$). The EPA/AA ratio was positively correlated with fibrous cap thickness ($r = 0.46$, $P = 0.007$) (Fig. 2).

In the multivariate logistic regression model including LDL cholesterol, HDL cholesterol, hsCRP, EPA/AA ratio, and DHA, an EPA/AA ratio <0.36 had a significant association with the presence of TCFA (odds ratio 6.41, 95 % confidence interval 1.11–61.91, $P = 0.0371$).

Discussion

The present study showed that the EPA/AA ratio was associated with coronary plaque vulnerability of the culprit lesions by OCT examination in patients with stable angina pectoris. A low EPA/AA ratio had significant association with a thinner fibrous cap, larger lipid-arc length, and higher prevalence of TCFA, macrophages, and microvessels. An EPA/AA ratio <0.36 was a predictor for the presence of TCFA. The EPA/AA ratio was positively correlated with fibrous cap thickness.

Epidemiologic and clinical evidence suggests that an increased intake of marine n-3 PUFAs has protective effects against the cardiovascular events and mortality, including sudden cardiac death [7, 15, 16]. Inflammation is now recognized to play an important role in atherosclerosis [17, 18]. The anti-inflammatory actions of marine n-3 PUFAs may stabilize atherosclerotic plaques by decreasing infiltration of inflammatory and immune cells into the plaques, and by decreasing the activity of those cells once in the plaque [11]. Our study demonstrated that macrophage infiltration was lower in the high-EPA/AA group, which could offer one of the explanations for that mechanism. The protective effects of marine n-3 PUFAs against atherosclerosis have been confirmed in previous animal and human studies [19, 20]. In the animal study, Apolipoprotein E-deficient or low-density lipoprotein receptor-deficient mice were fed a Western-type diet or the same diet plus EPA for 12 weeks. EPA reduced aortic lipid deposition, consistent with earlier animal studies. EPA

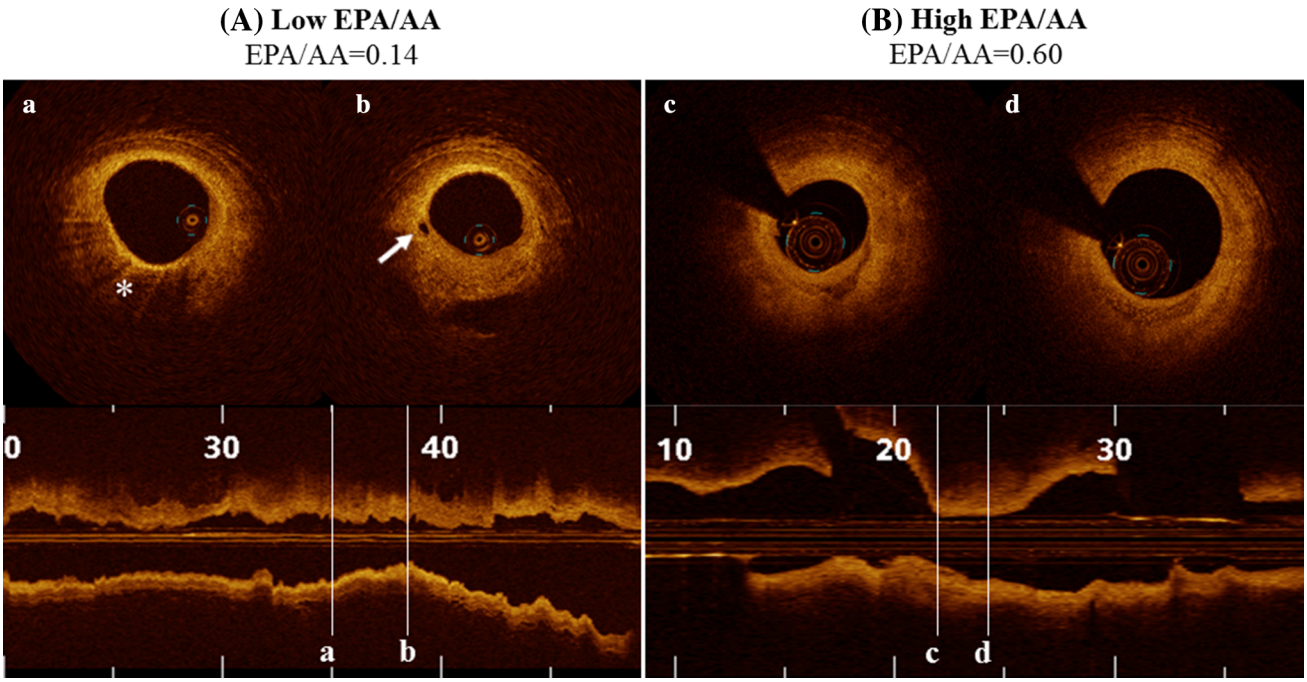

Fig. 1 Representative optical coherence tomography (OCT) images of the culprit lesions. The *left* (**A**) and *right figures* (**B**) are representative OCT images of low- and high-EPA/AA groups, respectively. In the case of the low-EPA/AA group, OCT cross-sectional images show thin-cap fibroatheroma (thickness of the fibrous cap = 63 μm) with macrophage infiltration (*asterisk*) from the 6 o'clock to the 9 o'clock position (**a**) and a microvessel (*arrow*) observed as black holes within a plaque in the 9 o'clock position (**b**). In the case of the low-EPA/AA group, fibrocalcified plaques were observed (**c**, **d**). *EPA/AA* eicosapentaenoic acid to arachidonic acid ratio

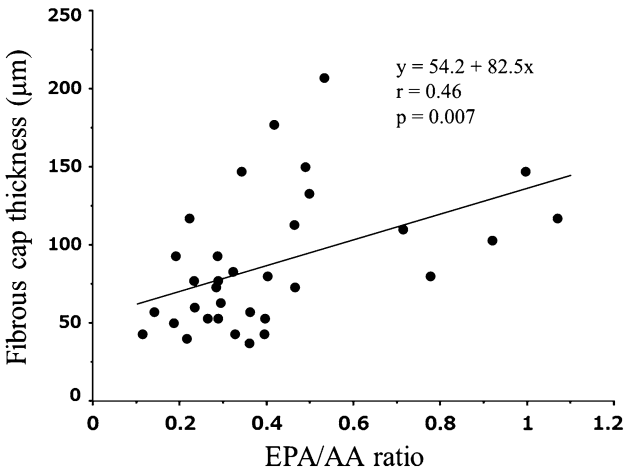

Fig. 2 Correlation between fibrous cap thickness and EPA/AA ratio. There was significant correlation between EPA/AA ratio and fibrous cap thickness identified by optical coherence tomography (r = 0.46, P = 0.007). *EPA/AA* eicosapentaenoic acid to arachidonic acid ratio

resulted in increased plaque collagen and decreased macrophage numbers in the plaque. The human intervention study conducted in patients awaiting carotid endarterectomy showed that marine n-3 fatty acids are incorporated from dietary fish-oil supplements into advanced atherosclerotic plaques, and that this incorporation is associated with structural changes consistent with increased plaque stability including reduced macrophage infiltration. In the present study, coronary plaque vulnerability by OCT was higher in the low-EPA/AA group than in the high-EPA/AA group.

The current understanding of the major cause of ACS is that it results from rupture of a vulnerable plaque [21, 22]. OCT is a high-resolution imaging technology, which can provide detailed observation of the vulnerable coronary plaque. TCFA is recognized as a precursor lesion for plaque rupture. In the present study, multivariate analysis adjusted for LDL cholesterol, HDL cholesterol, hsCRP, EPA/AA ratio, and DHA revealed that a lower EPA/AA ratio (EPA/AA ratio <0.36) was an independent factor for predicting the presence of TCFA. Moreover, the EPA/AA ratio was positively correlated with fibrous cap thickness. Inflammatory cytokine production and expression of adhesion molecules play important roles in the activation of macrophage foam cells, resulting in plaque development and weakening of fibrous cap [8, 23]. n-3 PUFAs have protective effects against coronary plaque vulnerability by inhibiting inflammatory cytokine production and expression of adhesion molecules [24, 25]. These mechanisms might support our results.

To our knowledge, the present study is the first to examine the association between EPA/AA ratios and coronary plaque

vulnerability in patients with stable angina pectoris by OCT. On the basis of a previous report, the results of which are consistent our own, the EPA/AA ratio affects the coronary plaque vulnerability of nonculprit lesions in patients with stable angina pectoris [26]. Even with aggressive statin therapy, a high residual risk of cardiovascular events remains, and draws attention to the need for additional preventive therapies [27, 28]. Additional treatment with n-3 PUFAs in combination with statin therapy may be a therapeutic approach to preventing future cardiovascular events, because increases in serum EPA to AA ratios are associated with low coronary plaque vulnerability.

Study limitations

This study had several limitations. First, the number of subjects included was too small for evaluation of contributing factors to the findings of vulnerable coronary plaque by OCT. Second, owing to the limited axial penetration depth, exact measurements of vessel and plaque area by OCT were not possible. Third, plaque rupture, microvessels, macrophages, and thrombus were only used for qualitative analysis and were not strictly validated. Fourth, images were acquired using two kinds of OCT imaging systems: time-domain or frequency-domain OCT. Fifth, we did not perform OCT analyses in all three coronary vessels.

Conclusions

A lower EPA/AA ratio was associated with higher vulnerability of coronary plaques. Purified EPA administration may have protective effects against vulnerable coronary plaque.

Conflict of interest There are no conflicts of interest to disclose in connection with any commercial associations for any of the authors.

References

1. Deedwania P, Stone PH, Bairey Merz CN, Cosin-Aguilar J, Koylan N, Luo D, Ouyang P, Piotrowicz R, Schenck-Gustafsson K, Sellier P, Stein JH, Thompson PL, Tzivoni D (2007) Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). Circulation 115:700–707
2. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK, Treating to New Targets Investigators (2005) Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 352:1425–1435
3. Lauderdale SA, Sheehan AH (2005) Intensive lipid-lowering therapy in patients with coronary heart disease. Ann Pharmacother 39:329–334
4. Nakamura T, Azuma A, Kuribayashi T, Sugihara H, Okuda S, Nakagawa M (2003) Serum fatty acid levels, dietary style and coronary heart disease in three neighbouring areas in Japan: the Kumihama study. Br J Nutr 89:267–272
5. Domei T, Yokoi H, Kuramitsu S, Soga Y, Arita T, Ando K, Shirai S, Kondo K, Sakai K, Goya M, Iwabuchi M, Ueeda M, Nobuyoshi M (2012) Ratio of serum n-3 to n-6 polyunsaturated fatty acids and the incidence of major adverse cardiac events in patients undergoing percutaneous coronary intervention. Circ J 76:423–429
6. Ueeda M, Doumei T, Takaya Y, Ohnishi N, Takaishi A, Hirohata S, Miyoshi T, Shinohata R, Usui S, Kusachi S (2011) Association of serum levels of arachidonic acid and eicosapentaenoic acid with prevalence of major adverse cardiac events after acute myocardial infarction. Heart Vessels 26:145–152
7. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K (2007) Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 369:1090–1098
8. Hansson GK (2005) Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 352:1685–1695
9. Stoll G, Bendszus M (2006) Inflammation and atherosclerosis: novel insights into plaque formation and destabilization. Stroke 37:1923–1932
10. Libby P (2012) Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol 32:2045–2051
11. Calder PC (2012) The role of marine omega-3 (n-3) fatty acids in inflammatory processes, atherosclerosis and plaque stability. Mol Nutr Food Res 56:1073–1080
12. Onuma Y, Serruys PW, Perkins LE, Okamura T, Gonzalo N, Garcia–Garcia HM, Regar E, Kamberi M, Powers JC, Rapoza R, van Beusekom H, van der Giessen W, Virmani R (2010) Intracoronary optical coherence tomography and histology at 1 month and 2, 3, and 4 years after implantation of everolimus-eluting bioresorbable vascular scaffolds in a porcine coronary artery model: an attempt to decipher the human optical coherence tomography images in the ABSORB trial. Circulation 122:2288–2300
13. Takarada S, Imanishi T, Liu Y, Ikejima H, Tsujioka H, Kuroi A, Ishibashi K, Komukai K, Tanimoto T, Ino Y, Kitabata H, Kubo T, Nakamura N, Hirata K, Tanaka A, Mizukoshi M, Akasaka T (2010) Advantage of next-generation frequency-domain optical coherence tomography compared with conventional time-domain system in the assessment of coronary lesion. Catheter Cardiovasc Interv 75:202–206
14. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, Bouma B, Bruining N, Cho JM, Chowdhary S, Costa MA, de Silva R, Dijkstra J, Di Mario C, Dudek D, Falk E, Feldman MD, Fitzgerald P, Garcia-Garcia HM, Gonzalo N, Granada JF, Guagliumi G, Holm NR, Honda Y, Ikeno F, Kawasaki M, Kochman J, Koltowski L, Kubo T, Kume T, Kyono H, Lam CC, Lamouche G, Lee DP, Leon MB, Maehara A, Manfrini O, Mintz GS, Mizuno K, Morel MA, Nadkarni S, Okura H, Otake H, Pietrasik A, Prati F, Raber L, Radu MD, Rieber J, Riga M, Rollins A, Rosenberg M, Sirbu V, Serruys PW, Shimada K, Shinke T, Shite J, Siegel E, Sonoda S, Suter M, Takarada S, Tanaka A, Terashima M, Thim T, Uemura S, Ughi GJ, van Beusekom HM, van der Steen AF, van Es GA, van Soest G, Virmani R, Waxman S, Weissman NJ, Weisz G, International Working Group for Intravascular Optical Coherence Tomography (2012) 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 59:1058–1072

15. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (1999) Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet 354:447–455
16. Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, Ma J (2002) Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med 346:1113–1118
17. van der Wal AC, Becker AE, van der Loos CM, Das PK (1994) Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation 89:36–44
18. Bogaty P, Poirier P, Simard S, Boyer L, Solymoss S, Dagenais GR (2001) Biological profiles in subjects with recurrent acute coronary events compared with subjects with long-standing stable angina. Circulation 103:3062–3068
19. Matsumoto M, Sata M, Fukuda D, Tanaka K, Soma M, Hirata Y, Nagai R (2008) Orally administered eicosapentaenoic acid reduces and stabilizes atherosclerotic lesions in ApoE-deficient mice. Atherosclerosis 197:524–533
20. Thies F, Garry JM, Yaqoob P, Rerkasem K, Williams J, Shearman CP, Gallagher PJ, Calder PC, Grimble RF (2003) Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. Lancet 361:477–485
21. Virmani R (2011) Are our tools for the identification of TCFA ready and do we know them? JACC Cardiovasc Imaging 4:656–658
22. Kusama I, Hibi K, Kosuge M, Sumita S, Tsukahara K, Okuda J, Ebina T, Umemura S, Kimura K (2012) Intravascular ultrasound assessment of the association between spatial orientation of ruptured coronary plaques and remodeling morphology of culprit plaques in ST-elevation acute myocardial infarction. Heart Vessels 27:541–547
23. Hallenbeck JM, Hansson GK, Becker KJ (2005) Immunology of ischemic vascular disease: plaque to attack. Trends Immunol 26:550–556
24. Calder PC (2003) N-3 polyunsaturated fatty acids and inflammation: from molecular biology to the clinic. Lipids 38:343–352
25. Calder PC (2006) n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am J Clin Nutr 83:1505S–1519S
26. Kashiyama T, Ueda Y, Nemoto T, Wada M, Masumura Y, Matsuo K, Nishio M, Hirata A, Asai M, Kashiwase K, Kodama K (2011) Relationship between coronary plaque vulnerability and serum n-3/n-6 polyunsaturated fatty acid ratio. Circ J 75:2432–2438
27. Ogita M, Miyauchi K, Miyazaki T, Naito R, Konishi H, Tsuboi S, Dohi T, Kasai T, Yokoyama T, Okazaki S, Kurata T, Daida H (2013) Low high-density lipoprotein cholesterol is a residual risk factor associated with long-term clinical outcomes in diabetic patients with stable coronary artery disease who achieve optimal control of low-density lipoprotein cholesterol. Heart Vessels. doi:10.1007/s00380-011-0205-6
28. Kurisu S, Ishibashi K, Kato Y, Mitsuba N, Dohi Y, Nishioka K, Kihara Y (2013) Effects of lipid-lowering therapy with strong statin on serum polyunsaturated fatty acid levels in patients with coronary artery disease. Heart Vessels 28:34–38