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Original Article

A predictor of atheroma progression in patients achieving very low levels of low-density lipoprotein cholesterol

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Abstract: An aggressive reduction in low-density lipoprotein cholesterol (LDL-C) with statins produces regression or stabilization of coronary artery plaques. However, after achieving very low levels of LDL-C, atheroma regression is not observed in all patients. The purpose of the present study was to evaluate the determinants of atheroma progression despite achieving very low levels of LDL-C. The effects of 8-month statin therapy on coronary atherosclerosis were evaluated using virtual histology intravascular ultrasound in the TRUTH study. Of these, 33 patients who achieved an on-treatment LDL-C level of <70 mg/dl were divided into 2 groups according to increase in plaque volume (progressors, n= 16) or decrease in plaque volume (regressors, n= 17) during an 8-month follow-up period. At the 8-month follow-up, serum LDL-C and apolipoprotein B levels were significantly lower in progressors than in regressors; however, significant increases in high-density lipoprotein cholesterol and apolipoprotein AI and decreases in high-sensitivity C-reactive protein and oxidized LDL were observed only in regressors. The changes in the n-3 to n-6 polyunsaturated fatty acid ratios significantly differed between the 2 groups. Multivariate regression analysis showed that a decrease in the eicosapentaenoic acid + docosahexaenoic acid/arachidonic acid ratio was a significant predictor associated with atheroma progression (β= -0.512, p= 0.004). In conclusions, n-3 to n-6 polyunsaturated fatty acid ratios affected coronary artery plaque progression and regression in patients who achieved very low levels of LDL-C during statin therapy.

Keywords: Atheroma, low-density lipoprotein cholesterol, polyunsaturated fatty acid, statin, virtual histology intravascular ultrasound

Introduction

An aggressive reduction in low-density lipoprotein cholesterol (LDL-C) with statin therapy produces regression [1-3] or stabilization [4] of coronary artery plaques and reduces the risk of coronary events [5]. Recent clinical trials have demonstrated an incremental benefit of intensive lipid-lowering therapy compared with moderate lipid-lowering therapy using statins [6, 7], and aggressive reduction in LDL-C levels has been recommended [8]. Current lipid-lowering guidelines focus on LDL-C reduction as a principal target for primary and secondary prevention of cardiovascular disease. The American Heart Association and American College of Cardiology recommended an optimal LDL-C goal of <70 mg/dl for patients with a very high risk of coronary artery disease (CAD) [9]. However, not all patients with an LDL-C level <70 mg/dl show atheroma regression. Some patients show atheroma progression and develop coronary events despite achieving very low levels of LDL-C. Therefore, in this study, we evaluated the determinant of atheroma progression in patients who achieve an LDL-C level <70 mg/dl.

Materials and methods

Patients and study design

The present study was a post-hoc subanalysis of the Treatment With Statin on Atheroma Regression Evaluated by Intravascular Ultrasound With Virtual Histology (TRUTH) study. The TRUTH study is a prospective, open-labeled, randomized, multicenter trial performed at 11 Japanese centers to evaluate the effects of 8-month of treatment with pitavastatin versus pravastatin on coronary atherosclerosis using virtual histology (VH)-intravascular ultrasound (IVUS) [10]. In brief, 164 patients with angina pectoris were randomized to either pitavastatin (4 mg/day, intensive lipid-lowering) or pravastatin (20 mg/day, moderate lipid-lowering) therapy after successful percutaneous coronary intervention (PCI) under VH-IVUS guidance. Follow-up IVUS was performed after 8 months of statin therapy.

The inclusion criteria were analyzable IVUS data obtained at the time of PCI and at the 8-month follow-up as well as an LDL-C level <70 mg/dl after treatment. Thirty-three patients were included in this study. These patients were divided into 2 groups: progressors and regressors. A progressor was defined as a patient whose difference in plaque volume between the 8-month follow-up and baseline was ≥0. A regressor was defined as a patient whose difference in plaque volume between the 8-month follow-up and baseline was <0. We compared the clinical characteristics, risk factor control, and grayscale and VH-IVUS parameters between the progressors and regressors.

The TRUTH trial was conducted in accordance with the Declaration of Helsinki and with the approval of the ethical committees of the 11 participating institutions. Each patient enrolled in the study provided written informed consent.

Intravascular ultrasound examination and analysis

The details regarding the IVUS procedure have been documented [10]. In brief, after PCI of the culprit lesion, IVUS was performed for 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, California) was used, and a motorized pullback device was used to withdraw 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). After 8 months of statin therapy, IVUS was repeated in the same coronary artery using the same type of IVUS catheter 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 IVUS analysis, 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 on the basis of the presence of reproducible anatomical landmarks such as the side branch, vein, and stent edge. Plaques close to the PCI site (<5 mm) were excluded because mechanical interventions affected atheroma measurements. Manual contour detection of the lumen and external elastic membrane (EEM) was performed for each frame. Quantitative IVUS grayscale analysis was performed according to the guidelines of the American College of Cardiology and European Society of Cardiology [11]. VH-IVUS data analysis was based on grayscale border contour calculation, and relative and absolute amounts of different coronary artery plaque components were measured using IVUSLab version 2.2 (Volcano Corporation).

Laboratory determinations

Blood examinations for lipid levels were performed at baseline and at the 8-month follow-up. Levels of serum lipids, apolipoproteins, and high-sensitivity C-reactive protein (hs-CRP) were measured at a central clinical laboratory (SRL, Inc., Tokyo, Japan). The serum levels of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and arachidonic acid (AA) at baseline and at the 8-month follow-up were measured annually by a central laboratory (BML, Inc., Kawagoe, Japan).

Statistical analysis

Statistical analysis was performed using StatView version 5.0 (SAS Institute, Cary, North Carolina). Results are expressed as mean ± SD. Differences in continuous variables between the 2 groups were compared using Student's unpaired t tests when variables showed a normal distribution and Mann-Whitney U tests

Table 1. Baseline clinical characteristics of subjects

	Progressors (n= 16)	Regressor (n= 17)	*p* value
Age (years)	71 ± 9	69 ± 9	0.5
Men	14 (88%)	15 (88%)	>0.99
Body mass index (kg/m^2)	24.2 ± 2.5	24.0 ± 4.7	0.92
Diabetes mellitus	8 (50%)	4 (24%)	0.16
Hypertension	10 (63%)	8 (47%)	0.37
Smoker	6 (38%)	3 (18%)	0.37
Treatment allocation			>0.99
Pitavastatin	13 (81%)	13 (76%)	
Pravastatin	3 (19%)	4 (24%)	
Status of coronary artery disease			0.66
Stable angina pectoris	13 (81%)	15 (88%)	
Unstable angina pectoris	3 (19%)	2 (12%)	
Target coronary artery			0.13
Left anterior descending	7 (44%)	13 (76%)	
Left circumflex	1 (6%)	0 (0%)	
Right	8 (50%)	4 (24%)	
Types of stent			>0.99
Bare metal stent	1 (6%)	1 (6%)	
Drug-eluting stent	15 (94%)	16 (94%)	
Medications			
Aspirin	16 (100%)	16 (94%)	>0.99
Thienopyridines	16 (100%)	16 (94%)	>0.99
ACE-Is or ARBs	8 (50%)	7 (41%)	0.61
β Blockers	2 (13%)	2 (12%)	0.95
Calcium channel blockers	8 (50%)	8 (47%)	>0.99
Follow-up duration (days)	228 ± 39	231 ± 32	0.84

Data are expressed as the mean ± SD or as number (%). ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

when the variables were not normally distributed. Differences in continuous variables within each group were compared using Student's paired t tests when variables showed a normal distribution and Wilcoxon signed-rank-sum tests when the variables were not normally distributed. Univariate regression analysis was performed to determine predictors of percentage changes in plaque volume, including nominal variables (gender, coronary artery disease status, hypertension, diabetes mellitus, and smoking) and numerical variables (age; percentage change in LDL-C, apolipoprotein B, oxidized LDL, high-density lipoprotein cholesterol, and hs-CRP; and change in the EPA + DHA/AA ratio). Variables with a *p* value <0.2 in univariate analysis were entered into multivariate models. Statistical significance was set at $p<0.05$.

Results

Patient characteristics and risk factor control

Baseline characteristics of subjects are listed in **Table 1**. Sixteen patients (48%) were included in the progressor group, and the remaining 17 patients (52%) were included in the regressor group. Thirteen patients (81%) in the progressor group and 13 patients (76%) in the regressor group were treated by intensive lipid-lowering therapy using pitavastatin. There were no significant differences in baseline characteristics between the 2 groups.

Risk factor control at baseline and at the 8-month follow-up is listed in **Table 2**. Significant reductions in levels of total cholesterol, LDL-C, and apolipoprotein B were observed in both groups; however, at the 8-month follow-up,

Table 2. Risk factor control at baseline and at follow-up

	Progressors (n= 16)			Regressors (n= 17)		
	Baseline	Follow-up	*p* value	Baseline	Follow-up	*p* value
TC (mg/dl)	179 ± 25	122 ± 12*	<0.0001	186 ± 28	136 ± 21	<0.0001
% change		-31 ± 10			-26 ± 12	
LDL-C (mg/dl)	107 ± 23	52 ± 11**	<0.0001	117 ± 23	61 ± 6	<0.0001
% change		-51 ± 9			-47 ± 9	
TG (mg/dl)	112 ± 30	83 ± 36	0.01	105 ± 38	110 ± 78	0.76
% change		-23 ± 31			10 ± 57	
HDL-C (mg/dl)	49 ± 13	51 ± 12	0.5	46 ± 10	53 ± 15	0.02
% change		6 ± 20			17 ± 24	
Apo AI (mg/dl)	120 ± 23	127 ± 22	0.12	120 ± 19	143 ± 32	0.003
% change		7 ± 15			20 ± 22	
Apo B (mg/dl)	85 ± 16	49 ± 7**	<0.0001	93 ± 17	59 ± 11	<0.0001
% change		-42 ± 9			-35 ± 13	
hs-CRP (ng/ml)	2687 ± 2729	1564 ± 3172	0.24	3621 ± 3724	1298 ± 2376	0.03
% change		-5 ± 182			-41 ± 95	
Oxidized LDL (U/ml)	9.1 ± 5.2	10.4 ± 14.4	0.76	8.4 ± 3.5	7.0 ± 2.7	0.03
% change		50 ± 271			-13 ± 19	
EPA/AA	0.47 ± 0.18	0.41 ± 0.17*	0.09	0.61 ± 0.51	0.71 ± 0.54	0.03
Change		-0.07 ± 0.15**			0.10 ± 0.16	
DHA/AA	0.96 ± 0.20	0.78 ± 0.22	<0.0001	0.97 ± 0.46	0.97 ± 0.43	0.97
Change		-0.18 ± 0.13**			0.00 ± 0.20	
EPA + DHA/AA	1.44 ± 0.34	1.19 ± 0.35	0.002	1.58 ± 0.92	1.68 ± 0.93	0.17
Change		-0.25 ± 0.25**			0.10 ± 0.27	
Glucose (mg/dl)	116 ± 53	105 ± 33	0.24	105 ± 18	95 ± 13	0.41
SBP (mmHg)	138 ± 22	132 ± 21	0.2	131 ± 20	132 ± 22	0.81
DBP (mmHg)	79 ± 15	77 ± 20	0.57	71 ± 11	74 ± 10	0.37
Heart rate (beats/min)	70 ± 16	73 ± 11	0.31	79 ± 15	69 ± 10	0.54

Data are expressed as mean ± SD. *p<0.05 and **p<0.01 compared with regressors. TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C-reactive protein; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid.

these levels were significantly lower in progressors than in regressors. Significant increases in high-density lipoprotein cholesterol and apolipoprotein AI and decreases in hs-CRP and oxidized LDL were observed only in regressors. The EPA/AA ratio tended to decrease in progressors (mean change, -0.07; p= 0.09), whereas it increased significantly in regressors (mean change, 0.10; p= 0.03). Significant decreases in the DHA/AA ratio (mean change, -0.18; p<0.0001) and EPA + DHA/AA ratio (mean change, -0.25; p= 0.002) were observed in progressors, whereas these decreases were not observed in regressors. There were significant differences in changes in the EPA/AA, DHA/AA, and EPA + DHA/AA ratios between the 2 groups (**Figure 1**).

Intravascular ultrasound analysis

Parameters evaluated using grayscale and VH-IVUS are listed in **Table 3**. In progressors, EEM volume increased, although not significantly, from 15.58 to 15.84 mm^3/mm, and lumen volume decreased from 7.27 to 7.02 mm^3/mm. In contrast, in regressors, EEM volume decreased significantly from 17.70 to 17.05 mm^3/mm and lumen volume increased from 7.82 to 7.90 mm^3/mm. A decrease in the fibro-fatty plaque component and increases in the necrotic-core and dense-calcium components did not differ between the 2 groups. The fibrous plaque component decreased significantly in regressors and increased in progressors. A significant difference was observed in

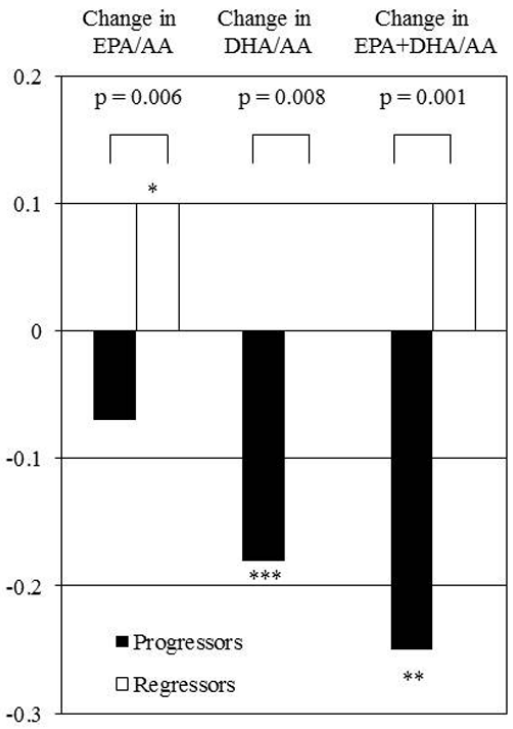

Figure 1. Differences in changes in EPA/AA, DHA/AA, and EPA + DHA/AA ratios between progressors and regressors. There were significant differences in changes in the EPA/AA, DHA/AA, and EPA + DHA/AA ratios between the 2 groups. *p<0.05, **p<0.01, and ***p<0.0001 compared to baseline.

the fibrous component volume change between the 2 groups.

Predictor of atheroma progression

We assessed correlations between percentage change in plaque volume and change in the EPA/AA, DHA/AA, and EPA + DHA/AA ratios (**Figure 2**). We found that percentage change in plaque volume was moderately and negatively correlated with changes in these ratios.

Among n-3 to n-6 polyunsaturated fatty acid (PUFA) ratios, we used the EPA + DHA/AA ratio in the regression model because this ratio produced the greatest correlation coefficient between the n-3 to n-6 PUFA ratios and the percentage change in plaque volume. Multivariate regression analysis showed that a decrease in the EPA + DHA/AA ratio was a significant predictor associated with atheroma progression during statin therapy (β= -0.512, p= 0.004; **Table 4**).

Discussion

The major findings of the present study are as follows: (1) changes in the n-3 to n-6 PUFA ratios differed between progressors and regres-

Table 3. Parameters evaluated using grayscale and virtual histology intravascular ultrasound

	Progressors (n= 16)			Regressors (n= 17)		
	Baseline	Follow-up	*p* value	Baseline	Follow-up	*p* value
EEM volume index (mm³/mm)	15.58 ± 5.06	15.84 ± 5.58	0.39	17.70 ± 5.39	17.05 ± 5.20	0.003
% change		1.5 ± 6.7*			-3.8 ± 4.3	
Plaque volume index (mm³/mm)	8.31 ± 2.39	8.83 ± 2.79	0.003	9.88 ± 3.61	9.15 ± 3.44	<0.0001
% change		5.7 ± 5.4***			-7.8 ± 5.5	
Lumen volume index (mm³/mm)	7.27 ± 2.97	7.02 ± 3.05	0.3	7.82 ± 1.97	7.90 ± 2.21	0.64
% change		-2.7 ± 13.2			0.5 ± 9.3	
Percentage atheroma volume (%)	54.3 ± 6.5	56.5 ± 5.9	0.02	55.1 ± 4.5	53.1 ± 6.8	0.01
Nominal change (%)		2.2 ± 3.3**			-2.1 ± 3.1	
Fibrous volume index (mm³/mm)	3.15 ± 1.65	3.47 ± 1.53	0.06	3.67 ± 2.01	3.07 ± 1.54	0.003
Change (mm³/mm)		0.32 ± 0.64**			-0.60 ± 0.72	
FF volume index (mm³/mm)	0.97 ± 0.59	0.83 ± 0.81	0.38	1.06 ± 0.97	0.81 ± 0.56	0.16
Change (mm³/mm)		-0.14 ± 0.60			-0.25 ± 0.69	
NC volume index (mm³/mm)	0.65 ± 0.31	0.81 ± 0.48	0.26	0.94 ± 0.52	1.04 ± 0.81	0.54
Change (mm³/mm)		0.15 ± 0.52			0.11 ± 0.71	
DC volume index (mm³/mm)	0.35 ± 0.20*	0.45 ± 0.21	0.01	0.65 ± 0.48	0.70 ± 0.66	0.59
Change (mm³/mm)		0.10 ± 0.14			0.06 ± 0.42	
Average length (mm)	26.8 ± 12.7			22.7 ± 10.5		

Data are expressed as mean ± SD. *p<0.05, **p<0.001, and ***p<0.0001 compared with regressors. FF, fibro-fatty; NC, necrotic-core; DC, dense-calcium.

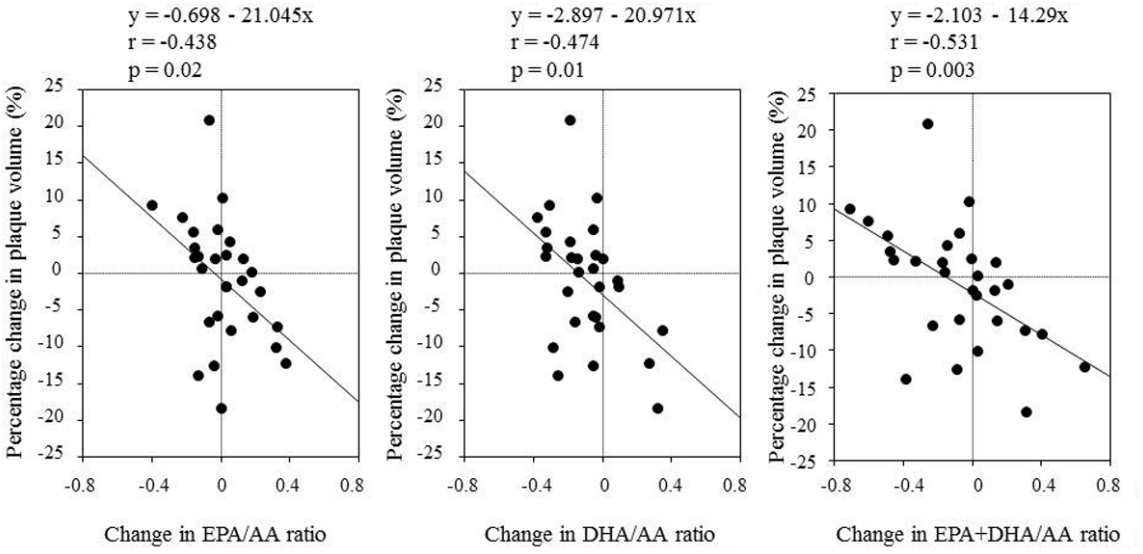

Figure 2. Correlations between percentage change in plaque volume and changes in the EPA/AA, DHA/AA, and EPA + DHA/AA ratios during statin therapy. Percentage change in plaque volume was moderately and negatively correlated with changes in the EPA/AA, DHA/AA, and EPA + DHA/AA ratios during statin therapy. Among n-3 to n-6 PUFA ratios, the EPA + DHA/AA ratio showed the greatest correlation coefficient between the n-3 to n-6 PUFA ratios and percentage change in plaque volume.

Table 4. Predictors of percentage change in plaque volume during statin therapy

	Univariate		Multivariate	
	r	*p* value	β	*p* value
Age	-0.002	0.99		
Gender	0.033	0.85		
Coronary artery disease status	-0.003	0.99		
Hypertension	0.056	0.76		
Diabetes mellitus	0.147	0.42		
% change in LDL-C	-0.177	0.33		
% change in apolipoprotein B	-0.224	0.23		
% change in oxidized LDL	0.031	0.87		
% change in HDL-C	-0.206	0.25		
% change in hs-CRP	0.043	0.82		
Smoking	0.243	0.17	0.209	0.21
Change in EPA + DHA/AA	-0.531	0.003	-0.512	0.004

Male gender, unstable angina, hypertension, diabetes, and smoking were assigned values of 1. Female gender, stable angina, normotension, non-diabetes, and no-smoking were assigned values of 0. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid.

sors, and changes in these ratios were moderately and negatively correlated with percentage change in plaque volume in patients who achieved an on-treatment LDL-C level of <70 mg/dl; and (2) a decrease in the EPA + DHA/AA ratio was a significant predictor associated with atheroma progression in patients who achieved very low levels of LDL-C during statin therapy.

Clinical trials using statins to lower LDL-C have demonstrated that the reduction in cardiovascular events and atheroma progression were related to the magnitude of absolute reductions in LDL-C [6, 7]. Recent IVUS studies have demonstrated regression of coronary atherosclerosis with aggressive LDL-C lowering strategies [1-3]. However, many patients who achieved very low levels of LDL-C subsequently experienced a cardiovascular event or demonstrated atheroma progression in these trials. Surprisingly, in the present study, 48% of patients who achieved LDL-C level <70 mg/dl demonstrated ongoing atheroma progression. This indicates that optimal control of LDL-C represents only 1 component of a strategy for secondary prevention of cardiovascular events in patients with CAD. A recent study reported that low levels of LDL-C and blood pressure are associated with slow progression of coronary

atherosclerosis [12]. Furthermore, pioglitazone prevents progression of coronary atherosclerosis [13], and increasing the levels of high-density lipoprotein cholesterol is an important factor in preventing CAD [14]. These data demonstrate the need for intensive control of global atherosclerotic risk factors to produce atheroma regression and prevent coronary events in these high-risk patients [15, 16]. However, in the present study, levels of LDL-C and apolipoprotein B at the 8-month follow-up were significantly lower in progressors. Furthermore, plasma glucose levels and blood pressure control at baseline and the 8-month follow-up did not differ between the 2 groups. This suggests that the residual risk for atheroma progression despite achieving very low levels of LDL-C during statin therapy is explained in part by n-3 to n-6 PUFA ratios.

Additional important findings of the present study were that correlation coefficients between the percentage change in plaque volume and change in the n-3 to n-6 PUFA ratios were stronger than those in our previous reports [17]. Weak, but significant, negative correlations were observed between percentage change in plaque volume and change in the EPA/AA ratio ($r= -0.190$, $p= 0.05$), DHA/AA ratio ($r= -0.231$, $p= 0.02$), and EPA + DHA/AA ratio ($r= -0.240$, $p= 0.02$) in patients whose LDL-C levels were controlled at mean values of 83 mg/dl [17]. However, the percentage change in plaque volume in patients whose LDL-C level were controlled at <70 mg/dl moderately and negatively correlated with change in the EPA/AA ratio ($r= -0.438$, $p= 0.02$), DHA/AA ratio ($r= -0.474$, $p= 0.01$), and EPA + DHA/AA ratio ($r= -0.531$, $p= 0.003$) in this study. This indicates that n-3 to n-6 PUFA ratios may have greater impact on progression and regression of coronary atherosclerosis, particularly in patients achieving very low levels of LDL-C.

The intake of n-3 PUFAs is associated with a lower risk of cardiovascular disease [18, 19]. Among the n-3 PUFAs, EPA and DHA play important roles in preventing cardiovascular disease [20, 21], because they inhibit platelet aggregation [22], inflammatory cytokine production [23], and adhesion factor expression [24]. The Japan EPA Lipid Intervention Study (JELIS) [20], a large, randomized controlled trial, demonstrated that administration of pure EPA along with statin therapy decreased the incidence of coronary events by 19%. The n-3 to n-6 PUFA ratios decreased in progressors and increased in regressors. We speculate that patients showing decreases in the n-3 to n-6 PUFA ratios during statin therapy should be treated with n-3 PUFAs. Indeed, administration of n-3 PUFAs has been demonstrated to reduce future cardiovascular events [20, 25, 26]. n-3 PUFAs beneficially modify the risk factor profile, which might reduce or slow the progression of atherosclerosis [27, 28] and might affect plaque instability [29, 30]. Previous findings and our results show that serum n-3 to n-6 PUFA ratios have influence the progression and regression of coronary atherosclerosis, particularly in patients achieving very low levels of LDL-C. Additional treatment with n-3 PUFAs may be a therapeutic approach for preventing progression of coronary atherosclerosis in patients with low levels of LDL-C whose n-3 to n-6 PUFA ratios decrease during statin therapy.

Study limitations

This study has several limitations. First, it was a post-hoc subanalysis of the TRUTH trial. Second, patients were not prohibited from making lifestyle changes. Changes in PUFA composition of the diet reflect changes in serum PUFA levels [31]. Third, antidiabetic and antihypertensive medications were not fixed during the study period. Changes in these medications may have affected the present results. Finally, the statistical power was insufficient to characterize the determinants of atheroma progression because of the small number of patients.

Conclusions

In the current relatively small study, n-3 to n-6 PUFA ratios affected coronary artery plaque progression and regression in patients who achieved very low levels of LDL-C during statin therapy.

Disclosure of conflict of interest

None.

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References

[1] Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, Ozaki Y, Kimura K, Saito S, Yamaguchi T, Daida H, Matsuzaki M; JAPAN-ACS Investigators. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitava-statin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol 2009; 54: 293-302.

[2] Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, Daida H. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. Circulation 2004; 110: 1061-1068.

[3] Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, Schoenhagen P, Tim Crowe T, Cain V, Wolski K, Goormastic M, Tuzcu EM; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006; 295: 1556-1565.

[4] Aikawa M, Rabkin E, Sugiyama S, Voglic SJ, Fukumoto Y, Furukawa Y, Shiomi M, Schoen FJ, Libby P. An HMG-CoA reductase inhibitor, cerivastatin, suppresses growth of macrophages expressing matrix metalloproteinases and tissue factor in vivo and in vitro. Circulation 2001; 103: 276-283.

[5] 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 (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352: 1425-1435.

[6] Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004; 350: 1495-1504.

[7] Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grines CL, DeMaria AN; REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004; 291: 1071-1080.

[8] Smith SC, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pasternak RC, Pearson T, Pfeffer MA, Taubert KA. AHA/ACC; National Heart, Lung, and Blood Institute; AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006; 113: 2363-72.

[9] Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ. National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110: 227-239.

[10] Nozue T, Yamamoto S, Tohyama S, Umezawa S, Kunishima T, Sato A, Miyake S, Takeyama Y, Morino Y, Yamauchi T, Muramatsu T, Hibi K, Sozu T, Terashima M, Michishita I. Statin treatment for coronary artery plaque composition based on intravascular ultrasound radiofrequency data analysis. Am Heart J 2012; 163: 191-199.

[11] Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM, Yock PG, Rourke RA, Abrams J, Bates ER, Brodie BR, Douglas PS, Gregoratos G, Hlatky MA, Hochman JS, Kaul S, Tracy CM, Waters DD, Winters WL; American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2001; 37: 1478-1492.

[12] Chhatriwalla AK, Nicholls SJ, Wang TH, Wolski K, Sipahi I, Crowe T, Schoenhagen P, Kapadia S, Tuzcu EM, Nissen SE. Low levels of low-density lipoprotein cholesterol and blood pressure and progression of coronary atherosclerosis. J Am Coll Cardiol 2009; 53: 1110-1115.

[13] Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, Jure M, Larochellière RD, Staniloae CS, Mavromatis K, Saw J, Bo H, Lincoff AM, Tuzcu EM; PERISCOPE Investigators. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 2008; 299: 1561-1573.

[14] Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P,

Koskinen P, Manninen V, Mäenpää H, Mälkönen M, Mänttäri M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjöblom T, Nikkilä EA. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987; 317: 1237-1245.

[15] Bayturan O, Kapadia S, Nicholls SJ, Tuzcu EM, Shao M, Uno K, Shreevatsa A, Lavoie AJ, Wolski K, Schoenhagen P, Nissen SE. Clinical predictors of plaque progression despite very low levels of low-density lipoprotein cholesterol. J Am Coll Cardiol 2010; 55: 2736-2742.

[16] Nozue T, Yamamoto S, Tohyama S, Fukui K, Umezawa S, Onishi Y, Kunishima T, Sato A, Nozato T, Miyake S, Takeyama Y, Morino Y, Yamauchi T, Muramatsu T, Hibi K, Terashima M, Michishita I; TRUTH Investigators. Comparison of arterial remodeling and changes in plaque composition between patients with progression versus regression of coronary atherosclerosis during statin therapy (from the TRUTH study). Am J Cardiol 2012; 109: 1247-1253.

[17] Nozue T, Yamamoto S, Tohyama S, Fukui K, Umezawa S, Onishi Y, Kunishima T, Sato A, Nozato T, Miyake S, Takeyama Y, Morino Y, Yamauchi T, Muramatsu T, Hibi K, Terashima M, Michishita I. Effects of serum n-3 to n-6 polyunsaturated fatty acids ratios on coronary atherosclerosis in statin-treated patients with coronary artery disease. Am J Cardiol 2013; 111: 6-11.

[18] Iso H, Kobayashi M, Ishihara J, Sasaki S, Okada K, Kita Y, Kokubo Y, Tsugane S; JPHC Study Group. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I. Circulation 2006; 113: 195-202.

[19] Mozaffarian D, Lemaitre RN, Kuller LH, Burke GL, Tracy RP, Siscovick DS; Cardiovascular Health Study. Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study. Circulation 2003; 107: 1372-1377.

[20] 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; Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007; 369: 1090-1098.

[21] Rissanen T, Voutilainen S, Nyyssönen K, Lakka TA, Salonen JT. Fish oil-derived fatty acids, docosahexaenoic acid and docosapentaenoic acid, and the risk of acute coronary events: the Kuopio ischaemic heart disease risk factor study. Circulation 2000; 102: 2677-2679.

[22] von Schacky C. Prophylaxis of atherosclerosis with marine omega-3 fatty acids. A comprehensive strategy. Ann Intern Med 1987; 107: 890-899.

[23] Calder PC. N-3 polyunsaturated fatty acids and inflammation: from molecular biology to the clinic. Lipids 2003; 38: 343-352.

[24] Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am J Clin Nutr 2006; 83: 1505S-1519S.

[25] Lavie CJ, Milani RV, Mehra MR, Ventura HO. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. J Am Coll Cardiol 2009; 54: 585-594.

[26] Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Ishikawa Y, Oikawag S, Sasakih J, Hishidai H, Itakuraj H, Kitak T, Kitabatakel A, Nakayam N, Sakatan T, Shimadao K, Shiratop K; JELIS Investigators, Japan. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: subanalysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis 2008; 200: 135-140.

[27] Calder PC. n-3 Fatty acids and cardiovascular disease: evidence explained and mechanisms explored. Clin Sci (Lond) 2004; 107: 1-11.

[28] Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 2002; 106: 2747-2757.

[29] Thies F, Garry JM, Yaqoob P, Rerkasem K, Williams J, Shearman CP, Gallagher PJ, Calder PP. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. Lancet 2003; 361: 477-485.

[30] Matsumoto M, Sata M, Fukuda D, Tanaka K, Soma M, Hirata Y, Nagaia R. Orally administered eicosapentaenoic acid reduces and stabilizes atherosclerotic lesions in ApoE-deficient mice. Atherosclerosis 2008; 197: 524-533.

[31] Seppänen-Laakso T, Vanhanen H, Laakso I, Kohtamäki H, Viikari J. Replacement of margarine on bread by rapeseed and olive oils: effects on plasma fatty acid composition and serum cholesterol. Ann Nutr Metab 1993; 37: 161-174.