Can High-Dose Eicosapentaenoic Acid Get a Place as a Plaque Modifier?

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Despite the established anti-atherosclerotic benefits of lowering low-density lipoprotein-cholesterol (LDL-C) with a statin, atherosclerotic coronary artery disease still remains one of the leading causes of death in developed countries, which underscores the need to modify additional residual risks. The n-3 fatty acids (eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA)) have been considered as a potential therapeutic target to prevent atherosclerotic cardiovascular diseases. Although the JELIS study reported a significant reduction in cardiovascular events with EPA in Japanese subjects,¹ 2 recent randomized controlled trials (RCTs: REDUCE-IT study² and STRENGTH study³) have reported inconsistent findings about the clinical benefits of agents modulating EPA and/or DHA in the secondary prevention setting under statin therapy. In addition, a recent cohort study reported that these contrasting results were driven partly by differences of comparator oils.⁴ These observations indicate further need to conduct dedicated studies for elucidating the efficacy of targeting EPA and/or DHA.

In this issue of the Journal, Motoyama et al⁵ used serial coronary computed tomography angiography (CCTA) to compare atheroma progression in 210 acute coronary syndrome (ACS) statin-treated subjects receiving different doses of EPA/DHA. The main findings of their study are: (1) types of statin differed in the 4 groups, and a lower on-treatment LDL-C level was observed in those treated with high-dose EPA+DHA or high-dose EPA alone, (2) on serial CCTA imaging analysis, the frequency of plaque progression was 0% and 7.1% in the high-dose EPA+DHA and high-dose EPA alone groups, respectively, (3) when patients were stratified into 3 groups according to the dose of EPA, less plaque progression was observed in the high-dose EPA group, (4) the dose of DHA was not associated with the degree of plaque progression, and (5) the use of high-dose EPA more likely induced reduction of fibrous, fibrofatty and low-attenuation plaque volumes with less calcification.

Although this study provides additional clinical data to support the favorable anti-atherosclerotic effect of high-dose EPA, several limitations should be considered when interpreting the findings. First, this was a single-center, observational study, not a randomized controlled clinical trial. The type and dose of statin and the use of EPA/DHA

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agents were decided at each physician's discretion not by randomization. As a consequence, significant differences exist in the type of statin and on-treatment LDL-C among the 4 groups. In particular, given that patients receiving high-dose EPA+DHA and high-dose EPA exhibited a lower on-treatment LDL-C level, this lipid management may slow their plaque progression rate. Second, it is important to evaluate the efficacy of therapies under guideline-recommended LDL-C control, whereas the on-treatment LDL-C level in the current study subjects was >70 mg/dL. Whether high-dose EPA still works even in ACS patients who achieve on-treatment LDL-C <70 mg/dL remains unknown. Third, calcification is considered as a contributor to plaque stabilization, but in the high-dose EPA and high-EPA groups, calcification was not promoted. Further investigation is required into whether high-dose EPA truly stabilizes coronary atherosclerosis after ACS. Further studies are required to clarify whether high-dose EPA favorably modifies plaque quality and quantity in statin-treated ACS patients with optimal LDL-C control.

To date, several RCTs have used a variety of plaque imaging modalities to investigate the efficacy of n-3 fatty acids on coronary atherosclerosis⁶⁻¹⁴ (Table). Although 6 studies reported a reduction of plaque volume or a plaque stabilization effect in those receiving EPA, others did not show any positive findings. In addition, subanalysis of the STRENGTH study reported that achieving a greater EPA level with the agent did not necessarily reduce cardiovascular events.¹⁵ These inconsistent observations indicate the complicated properties of EPA and DHA in vivo. Further elucidation of their physiological and biological effects in circulation is needed to determine whether "high-dose" EPA truly modulates coronary atherosclerosis under statin therapy.

Disclosures

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Table. Randomized Control Trials Evaluating the Effects of n-3 Fatty Acids on Coronary Plaque

Imaging modality	Coronary computed tomography angiography (CCTA)		Intravascular ultrasound (IVUS)		
	Alfaddagh et al ⁶ (2017)	Budoff et al ⁷ (2020)	Niki et al ⁸ (2016)	Ahn et al ⁹ (2016)	Watanabe et al ¹⁰ (2017)
Study	Stable CAD	Patients with coronary artery stenosis on CCTA, with elevated triglycerides	Stable CAD	Stable CAD and ACS	Stable CAD and ACS
Subjects	Stable CAD	Patients with coronary artery stenosis on CCTA, with elevated triglycerides	Stable CAD	Stable CAD and ACS	Stable CAD and ACS
Therapies	126:114 for EPA 1.86 g/day + DHA 1.5 g/day vs. no n-3 fatty acids	31:37 for EPA 4 g/day vs. placebo	29:30 for EPA 1.8 g/day vs. no n-3 fatty acids	38:36 for EPA 1.395 g/day + DHA 1.125 mg/day vs. placebo	97:96 for pitavastatin 4 mg/day + EPA 1.8 mg/day vs. pitavastatin 4 mg/day
Percentage of statin-treated patients	95%	100%	100%	100%	47%
Baseline LDL-C level in each group, mg/dL	78.5 vs. 77.5 (P=0.46)	Not shown but not significantly different between groups	97.7 vs. 100.0 (P=0.85)	127.0 vs. 113.8 (P=0.100)	107.1 vs. 98.6 (P=0.080)
Type of statins	Both high- and low-intensity statins	Not shown	Atorvastatin or rosuvastatin or pitavastatin	Atorvastatin or rosuvastatin	Pitavastatin
On-treatment LDL-C in each group, mg/dL	84.6 vs. 80.4 (P=0.76)	Not shown but increase not significantly different between groups	91.4 vs. 88.3 (Not evaluated)	86.8 vs. 80.8 (P=0.525)	76.9 vs. 76.0 (P=0.796)
Primary outcome	Change in noncalcified plaque volume at 30 months	Change in low-attenuation plaque volume at 18 months	Changes in plaque components assessed by integrated backscatter-IVUS at 6 months	Changes in atheroma volume index and percent atheroma volume at 12 months	Coronary plaque volume and composition assessed by integrated backscatter-IVUS at 6–8 months
Findings	Primary endpoint not significantly different between groups (−2.4% vs. 4.5%, P=0.14)	EPA group reduced low-attenuation plaque volume (−17% vs. +109%, P=0.0061)	EPA group reduced lipid plaque volume (−18.9% vs. +8.4%, P=0.002) and increased fibrous volume (+11.7% vs. −9.2%, P=0.01)	Primary endpoint not significantly different between groups (atheroma volume index: −12.65% vs. −8.51%, P=0.768 and percent atheroma volume: −4.36% vs. −9.98%, P=0.526)	EPA group reduced total atheroma volume (−9.3 mm ³ vs. −1.7 mm ³ , P<0.001). Lipid volume decreased in EPA group only (−3.4%, P=0.045 vs. −1.3%, P=0.429)

Imaging modality	Optical coherence tomography			Cardiac magnetic resonance
	Nishio et al ¹¹ (2014)	Kita et al ¹² (2020)	Sugizaki et al ¹³ (2020)	Nakao et al ¹⁴ (2018)
Study	Stable CAD and ACS	ACS	Stable CAD and ACS, with in-stent neoatherosclerosis	Proven or suspected CAD
Subjects	Stable CAD and ACS	ACS	Stable CAD and ACS, with in-stent neoatherosclerosis	Proven or suspected CAD
Therapies	16:15 for EPA 1.8 g/day + rosuvastatin vs. rosuvastatin only	31:31:35 for EPA 1.86 g/day vs. EPA 0.93 g/day + DHA 0.75 mg/day vs. no n-3 fatty acids	21:21 for EPA 1.8 g/day + rosuvastatin 10 mg/day vs. rosuvastatin 2.5 mg/day	50:50:50 for EPA 0.93 g/day + DHA 0.75 g/day vs. EPA 1.86 g/day + DHA 1.5 g/day vs. no n-3 fatty acids
Percentage of statin-treated patients	0%	53%	61%	100%
Baseline LDL-C level in each group, mg/dL	138.0 vs. 130.3 (P=0.41)	120 vs. 118 vs. 125 (P=0.953)	90 vs. 89 (Not shown but not significant)	On-going
Type of statins	Rosuvastatin	Rosuvastatin	Rosuvastatin	On-going
On-treatment LDL-C in each group, mg/dL	80.1 vs. 83.2 (P=0.58)	78 vs. 82 vs. 78 (Not evaluated)	68 vs. 82 (P<0.001)	On-going
Primary outcome	Morphologic changes of TCFAs at 9 months	Change in minimum fibrous-cap thickness at 8 months	Changes in the lipid index or macrophage grade of native coronary plaques at 12 months	Change in plaque-to-myocardium signal intensity ratio
Findings	EPA+statin group increased fibrous-cap thickness (+54.8 μm vs. +23.5 μm, P<0.001) and decreased lipid arc (−34.4 degrees vs. −12.7 degrees, P=0.007) and lipid length (−2.81 mm vs. −1.2 mm, P=0.009)	Primary endpoint not significantly different between groups (absolute change: 60 μm vs. 20 μm vs. 20 μm, P=0.1491 and percent change: 58.3% vs. 14.3% vs. 20.0%, P=0.1075)	EPA+statin group decreased lipid index (−112 vs. 29, P<0.001) and macrophage grade (−17 vs. 1, P<0.001)	On-going

ACS, acute coronary syndrome; CAD, coronary artery disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LDL-C, low-density lipoprotein-cholesterol.

References

1. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): A randomised open-label, blinded endpoint analysis. *Lancet* 2007; **369**: 1090–1098.
2. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019; **380**: 11–22.
3. Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: The STRENGTH randomized clinical trial. *JAMA* 2020; **324**: 2268–2280.
4. Doi T, Langsted A, Nordestgaard BG. A possible explanation for the contrasting results of REDUCE-IT vs. STRENGTH: Cohort study mimicking trial designs. *Eur Heart J*, doi:10.1093/eurheartj/ehab555.
5. Motoyama S, Nagahara Y, Sarai M, Kawai H, Miyajima K, Sato Y, et al. Effect of omega-3 fatty acids on coronary plaque morphology: A serial computed tomography angiography study. *Circ J*, doi:10.1253/circj.CJ-21-0615.
6. Alfaddagh A, Elajami TK, Ashfaq H, Saleh M, Bistran BR, Welty FK. Effect of eicosapentaenoic and docosahexaenoic acids added to statin therapy on coronary artery plaque in patients with coronary artery disease: A randomized clinical trial. *J Am Heart Assoc* 2017; **6**: e006981.
7. Budoff MJ, Bhatt DL, Kinninger A, Lakshmanan S, Muhlestein JB, Le VT, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: Final results of the EVAPORATE trial. *Eur Heart J* 2020; **41**: 3925–3932.
8. Niki T, Wakatsuki T, Yamaguchi K, Taketani Y, Oeduka H, Kusunose K, et al. Effects of the addition of eicosapentaenoic acid to strong statin therapy on inflammatory cytokines and coronary plaque components assessed by integrated backscatter intravascular ultrasound. *Circ J* 2016; **80**: 450–460.
9. Ahn J, Park SK, Park TS, Kim JH, Yun E, Kim SP, et al. Effect of n-3 polyunsaturated fatty acids on regression of coronary atherosclerosis in statin treated patients undergoing percutaneous coronary intervention. *Korean Circ J* 2016; **46**: 481–489.
10. Watanabe T, Ando K, Daidoji H, Otaki Y, Sugawara S, Matsui M, et al. A randomized controlled trial of eicosapentaenoic acid in patients with coronary heart disease on statins. *J Cardiol* 2017; **70**: 537–544.
11. Nishio R, Shinke T, Otake H, Nakagawa M, Nagoshi R, Inoue T, et al. Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary thin-cap fibroatheroma. *Atherosclerosis* 2014; **234**: 114–119.
12. Kita Y, Watanabe M, Kamon D, Ueda T, Soeda T, Okayama S, et al. Effects of fatty acid therapy in addition to strong statin on coronary plaques in acute coronary syndrome: An optical coherence tomography study. *J Am Heart Assoc* 2020; **9**: e015593.
13. Sugizaki Y, Otake H, Kuroda K, Kawamori H, Toba T, Nagasawa A, et al. Concomitant use of rosuvastatin and eicosapentaenoic acid significantly prevents native coronary atherosclerotic progression in patients with in-stent neoatherosclerosis. *Circ J* 2020; **84**: 1826–1836.
14. Nakao K, Noguchi T, Asaumi Y, Morita Y, Kanaya T, Fujino M, et al. Effect of eicosapentaenoic acid/docosahexaenoic acid on coronary high-intensity plaques detected with non-contrast T1-weighted imaging (the AQUAMARINE EPA/DHA study): Study protocol for a randomized controlled trial. *Trials* 2018; **19**: 12.
15. Nissen SE, Lincoff AM, Wolski K, Ballantyne CM, Kastelein JJP, Ridker PM, et al. Association between achieved ω -3 fatty acid levels and major adverse cardiovascular outcomes in patients with high cardiovascular risk: A secondary analysis of the STRENGTH trial. *JAMA Cardiol* 2021; **6**: 1–8.