The Benefits of Omega-3 Fats for Stabilizing and Remodeling Atherosclerosis

by James J. DiNicolantonio, PharmD & James H. O'Keefe, MD

Vulnerability of the plaque to rupture, rather than the degree of atherosclerosis, is the primary determinant of thrombosis-mediated acute cardiovascular events.[1]

-Cawood AL and colleagues 2010

James J. DiNicolantonio, PharmD, (left), and James H. O'Keefe, MD, (right), MSMA member since 2003, are at Saint Luke's Mid America Heart Institute, Kansas City, Missouri.
Contact: jjdinicol@gmail.com

Abstract

The majority of acute coronary syndromes are caused by the rupture of plaques rendered vulnerable by oxidized lipids, inflammation, and a thin fibrous cap with reduced collagen and smooth muscle cell content.[2] Thus, stabilizing and reversing vulnerable atherosclerotic plaques can help to prevent cardiovascular events. In this regard, long-chain omega-3 fatty acids have a plethora of data for stabilizing vulnerable atherosclerotic plaques as well as reversing atherosclerosis. This review paper will summarize the observational data as well as animal and human studies supporting such a role and further discuss the current controversies around omega-3 supplementation.

Mechanistic Data

Dietary omega-3s, from fatty fish such as salmon, herring, and sardines, are not only building blocks of cellular membranes but are also precursors to eicosanoids or signaling molecules in the body. Whereas the metabolites from omega-6 are generally pro-inflammatory (such as thromboxanes, 2-series prostaglandins and 4-series leukotrienes), the metabolites from marine omega-3s are generally anti-inflammatory. Additionally, several benefits have been noted with marine omega-3 consumption, including reductions in triglycerides, lowered heart rate and blood pressure, improved left ventricular ejection fraction, reduced inflammatory cytokines, anti-thrombotic and anti-arrhythmic effects.[3]

Observational data

The observational data indicate that long-chain omega-3s play an important role in stabilizing atherosclerosis and reducing the risk of cardiovascular events. Indeed, patients with acute coronary syndrome have been documented to have significantly lower serum levels of eicosapentaenoic acid (EPA) and the elongated metabolite of EPA, docosapentaenoic acid (DPA), compared to those without.[4] Low levels of omega-3s in blood, including EPA, DPA, and docosahexaenoic acid (DHA), are also associated with lipid-rich, less fibrous plaques, which are at an increased risk of rupturing.

Low levels of DHA in heart tissue is associated with increased mortality in those who have died from both cardiac and non-cardiac causes.[5] Moreover, patents who have died from sudden cardiac death also have lower levels of omega-3 polyunsaturated fatty acids in their coronary arteries versus patients who have mainly died from traffic accidents.[6] This suggests that eating more long-chain omega-3s may reduce the risk of death from both cardiac and non-cardiac causes.

Table 1: Possible mechanisms for the atherosclerotic plaque stabilizing and remodeling effects of EPA/DHA[3, 25]

- A reduction in adhesion molecule expression on endothelial cells, monocytes, and macrophages
- A reduction in adhesion molecule expression on endothelial cells, monocytes, and macrophages
- A reduction in chemo-attractants (leukotriene B4, platelet-derived growth factor and monocyte chemoattractant protein-1) and matrix metalloproteinases (MMPs)
- A reduction in macrophage number in atherosclerotic plaques
- A reduction in small-dense LDL, triglycerides and inflammationt

Higher dietary intake, as well as increased blood levels of alpha-linolenic acid (ALA), EPA, and DHA are associated with a reduced carotid intimal-medial thickness (CIMT), a lower prevalence of atherosclerotic plaque, and less atherosclerotic plaque progression.[7-10] One study in 487 elderly men found that higher plasma phospholipid EPA was associated with less carotid and femoral intima-media thickness.[11] In a study of 1,920 Japanese patients, higher intakes of long-chain omega-3s (EPA, DHA, and DPA) were significantly and inversely related to CIMT.[8] Additionally, a randomized trial in patients with type 2 diabetes found that supplementation with 1,800 mg of EPA per day significantly decreased CIMT and improved brachial-ankle pulse wave velocity suggesting a reduction in atherosclerosis and improved endothelial function.[12]

Animal Studies

The fat-1 transgenic mouse model, which converts omega-6 to omega-3 producing an omega-6/3 ratio of around 1:1 in tissues and organs, reduces atherosclerotic lesions by inhibiting systemic and vascular inflammation.[13] This is one of the best ways to test the "omega-6/3 hypothesis" of heart disease whereby genetically lowering the omega-6/3 ratio reduces atherosclerosis. Moreover, supplementing mice with EPA reduces aortic atherosclerosis, macrophage infiltration, and matrix metalloproteinases-2 (MMP-2) and MMP-9 mRNA in aortic lesions and increases plaque stability via increased collagen and smooth muscle content.[14] However, the shortcomings of these studies include being in mice, being underpowered, and the genetic background of these mice (APOE-/-). DHA is also hypothesized to inhibit MMP-9 release from human macrophages partially explaining its plaque stabilizing benefits.[15] DHA also reduces NADPH oxidase activity and most, if not all, of the benefits of long-chain omega-3s for reduced inflammatory genes are a result of their inhibition of nuclear factor-kappa beta (NF-kB).[15]

In a mouse model of hyperlipidemia, compared to no EPA supplementation, a diet containing 5% EPA for 13 weeks significantly reduced atherosclerotic lesion formation.[14] Staining of the aorta revealed that EPA not only suppressed atherosclerotic lesion development but also stabilized atherosclerotic plaque by causing an increase in collagen and smooth muscle cells content with less macrophage infiltration. The authors concluded, "EPA may potentially reduce and stabilize atherosclerotic lesions through its anti-inflammatory effects...The atherosclerotic plaques of EPA-treated mice displayed a stabilized morphology that was characterized by less lipid deposition, decreased accumulation of macrophages, more smooth muscle cells, and increased collagen content. EPA also suppressed the expression of adhesion molecules and MCP-1 by endothelial cells and the production of MMPs by macrophages in a PPARalpha-dependent manner."[14]

The ability of fish oil to reduce the formation of atherosclerosis by reducing oxidative stress has also been confirmed by others.[16, 17] In fact, mice fed fish oil, as compared to corn oil, have a significant reduction in atherosclerotic plaque formation possibly due to an increase in antioxidant enzyme activity.[17] In summary, fish oil may reduce atherosclerosis by activating numerous nuclear receptors including PPAR-alpha and PPAR-gamma, by inhibiting the infiltration of macrophages and as the release of MMPs, and by preventing the weakening and rupturing of atherosclerotic plaque.[14,18]

Human Studies

In 30 untreated dyslipidemic patients, supplementation of EPA at 1.8 grams per day on top of rosuvastatin (titrated to achieve an LDL-C $<$ 70 mg/dL) for nine months increased fibrous cap thickness and reduced macrophage accumulation in atherosclerotic plaques versus those on statin therapy alone.[19] The authors concluded, "The concomitant use of EPA and rosuvastatin may stabilize vulnerable plaques better than the statin alone, possibly by suppressing arterial inflammation."[19] In a randomized controlled trial in 193 coronary heart disease patients

who underwent percutaneous coronary intervention the combination of EPA plus high-dose pitavastatin lead to a greater reduction in total atheroma volume compared to pitavastatin alone.[20] Plaque stabilization was also reinforced with the addition of EPA to pitavastatin especially in those with stable angina. The authors concluded, "The addition of EPA is a promising option to reduce residual CHD risk under intensive statin therapy."[20]

In another randomized controlled trial this time in 121 patients awaiting carotid endarterectomy, those who received ~1.5 grams of EPA/DHA for a mean of 21 days prior to surgery had significantly fewer foam cells in their carotid plaque ($p=0.039$).[1] This was thought to be due to the incorporation of EPA into the atherosclerotic plaque phospholipids suppressing inflammation. Indeed, plaques with higher EPA incorporation had less plaque instability ($p=0.0209$), plaque inflammation ($p=0.0108$), number of T cells in plaque ($p=0.0097$) and an overall lower plaque score ($p=0.0425$). More importantly, plaques from patients who supplemented with fish oil had significantly less mRNA for matrix metalloproteinases (MMP)-7 ($p=0.0055$), MMP-9 ($p=0.0048$) and MMP-12 ($p=0.0044$), again which are thought to cause plaque rupture.[21-23] Interleukin-6 (IL-6) and intercellular adhesion molecule-1 (ICAM-1) were also significantly lower in plaques ($p=0.0395$ and $p=0.0142$, respectively) in those who supplemented with long-chain omega-3s suggesting reduced inflammation and increased plaque stability due to their incorporation into atherosclerotic plaques.[24-26] Thus, the more EPA in atherosclerotic plaques, the less inflamed and the more stable the plaques.

In a randomized, investigator-blinded trial, 7 grams of omega-3 fatty acids (EPA 41.4%, DHA 23.6%, providing a total of 4.55 grams of EPA/DHA) reduced platelet-derived growth factor (PDGF)-A and PDGF-B mRNA as well as monocyte chemo-attractant protein-1 (MCP-1) mRNA steady state levels in unstimulated and adherence-activated human mononuclear cells (MNCs).[27] These benefits were not found with omega-6 or omega-9 fatty acids. This demonstrates that omega-3 fatty acids can modulate inflammatory gene expression. MCP-1 induces monocyte activation and attraction and both MCP-1 and PDGF are thought to promote atherosclerosis. Omega-6 PUFA via corn oil (providing LA 50.1%, 12.9% saturated fats) tended to increase PDGF-A and MCP-1 (although not significantly).[27]

In one trial, 188 patients awaiting carotid endarterectomy were randomized to either sunflower oil (providing 3.6 grams of linoleic acid), fish oil or control until surgery with a median duration of treatment being 42 days. Compared to control and sunflower oil, EPA/DHA decreased the prevalence of thin fibrous caps, increased thick fibrous caps, reduced signs of inflammation and reduced the number of macrophages within plaques. The authors concluded, "Atherosclerotic plaques readily incorporate omega-3 PUFAs from fish-oil supplementation, inducing changes that can enhance stability of atherosclerotic plaques. By contrast, increased consumption of omega-6 PUFAs does not affect carotid plaque fatty-acid composition or stability [...]"[25] Interestingly, there was numerically more thin fibrous cap atheroma (29.6% vs. 22.8%), less thick fibrous cap atheroma (53.7% vs. 56.1%) and a greater percentage of plaque rupture (5.6% vs. 3.5%) in the sunflower oil group vs. control, respectively. Although none of these differences were significant the numerical trend for worse plaque morphology with the intake of omega-6 PUFA is concerning. Additionally, what is generally considered stable plaque (calcified nodules and fibrocalcific plaque) tended to be lower in the sunflower group compared to the control group (1.9% vs. 10.5%, $p=0.06$). Some of the possible mechanisms for the ability of EPA/DHA to reduce and stabilize atherosclerotic plaque include are summarized in Table 1.

Clinical Studies Testing Hard Endpoints

Negative Trials

There have been several negative trials testing marine omega-3s, which has caused a recent controversy with omega-3 supplementation. Our group has published several papers discussing potential reasons why these trials have not been successful.[3, 28-30] Table 2 is a summary of those trials and reasons why they likely did not show benefit.

Positive Trials

In the REDUCE-IT study, which randomized 8,179 patients with established cardiovascular disease or diabetes with hypertriglyceridemia with other risk factors to 4 grams of Vascepa (icosapent ethyl) and followed them for 4.9 years.[31] There was a significant 25% reduction in the primary endpoint (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina) in those who were supplemented with 4 grams or Vascepa. High dose marine omega-3s also reduced major adverse cardiovascular events (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) by 26%. Again, these benefits were noted on top of statin therapy (> 99% of participants were on statin therapy).[31]

Table 2. Recent Fish Oil Trial Failures and Reasons Explaining Their Failure[3, 28-30]

Study	Population	Potential reasons for failure
OMEGA	3,851 patients with a history of acute MI	Used a low dose of omega-3 (1 gram), short duration (1 year), inappropriate use of olive oil as a placebo, high baseline intake of fish, unexpected low rate of sudden cardiac death and use of aggressive background medical treatment and the study lacked power to show benefit.
Alpha Omega	4,837 patients with a history of MI	Patients were already receiving antihypertensive, anti-thrombotic, and lipid-modifying therapies.
SU.FOL.OM3 trial		Low dose of omega-3 used (380 mg of EPA/DHA). Small power to detect any positive effect of omega-3s, low major vascular cardiovascular disease events were 15% lower than initially expected, insufficient duration and follow-up. Average time to start omega-3s from cardiovascular event was 101 days compared to 16 days in GISSI-P. Higher use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers at baseline in the placebo vs. the omega-3 group. Higher number of patents with a history of myocardial infarction and current smoker status in the omega-3 group compared to placebo.
ORIGIN	11,119 patients with high risk of cardiovascular disease and impaired glucose tolerance or diabetes	Low dose of omega-3 (1 gram/day) used and high background intake of omega-3 fatty acids in study participants.

A prospective, open-label, blinded endpoint-randomized trial in 241 patients with acute coronary syndrome found that adding 1,800 mg of EPA to pitavastatin 2 mg/day cut the primary endpoint by more than half compared to those given pitavastatin alone (9.2% vs. 20.2%, p=0.02) with a significant reduction in cardiovascular death (0.8% vs. 4.2%, p=0.04).[32] Another prospective, open-label, blinded endpoint, randomized trial in 115 patients with acute myocardial infarction, EPA at 1.8 grams per day given within 24 hours after percutaneous coronary intervention (PCI) significantly reduced (by over 50%) the combined occurrence of cardiac death, stroke, reinfarction, ventricular arrhythmias, or paroxysmal atrial fibrillation at 1-month compared to those not receiving EPA (10.5% vs. 29.3%, p=0.01).[33] Thus, the atherosclerosis plaque stabilizing effects of marine omega-3s also translates into significant reductions in hard endpoints if given soon after an acute coronary syndrome.

Other studies that have found benefit with marine omega-3s include GISSI-P (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico)-Prevenzione trial) and JELIS (the Japan EPA Lipid Intervention Study). GISSI-P was likely successful for several reasons including providing omega-3s early after acute myocardial infarction (average 16 days) as well as being in an Italian population with a notoriously lower background intake of omega-6 compared to the United States.[34] JELIS was likely positive because it used a higher dose of omega-3s (1.8 grams of EPA) and again was in a population with a lower intake of omega-6 versus the United States.[34]

It is important to note that the composition of polyunsaturated fats in the body is not only determined by dietary intake but also metabolism which is controlled by genetic polymorphisms. For example, delta-5 and delta-6 desaturases, otherwise known as FADS1 and FADS2, respectively, influence blood and phospholipid concentrations of omega-6 and omega-3 as they affect the elongation of these fatty acids. Thus, genetics may also play a role in determining the effects of dietary omega-3 intake.[35]

In summary, it is plaque vulnerability, not the degree luminal stenosis, that is the major determinant of the risk of atherothrombotic events.[21] The overall evidence suggests that supplementation with long-chain omega-3s reduces, and can positively remodel, atherosclerotic plaque formation. The totality of evidence also suggests that supplementing high-risk patients with EPA/DHA, either early after an acute coronary syndrome, or using a high dose (4 grams of EPA), reduces the risk of coronary heart disease events and/or coronary heart disease mortality.[3]

References

1. Cawood AL, Ding R, Napper FL, et al. Eicosapentaenoic acid (EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is associated with decreased plaque inflammation and increased stability. Atherosclerosis 2010;212:252-9.
2. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92:657-71.
3. DiNicolantonio JJ, Niazi AK, McCarty MF, et al. Omega-3s and cardiovascular health. The Ochsner journal 2014;14:399-412.
4. Amano T, Matsubara T, Uetani T, et al. Impact of omega-3 polyunsaturated fatty acids on coronary plaque instability: an integrated backscatter intravascular ultrasound study. Atherosclerosis 2011;218:110-6.
5. Chattipakorn N, Settakorn J, Petsophonsakul P, et al. Cardiac mortality is associated with low levels of omega-3 and omega-6 fatty acids in the heart of cadavers with a history of coronary heart disease. Nutrition research (New York, NY) 2009;29:696-704.
6. Luostarinen R, Boberg M, Saldeen T. Fatty acid composition in total phospholipids of human coronary arteries in sudden cardiac death. Atherosclerosis 1993;99:187-93.
7. Djousse L, Folsom AR, Province MA, et al. Dietary linolenic acid and carotid atherosclerosis: the National Heart, Lung, and Blood Institute Family Heart Study. Am J Clin Nutr 2003;77:819-25.
8. Hino A, Adachi H, Toyomasu K, et al. Very long chain N-3 fatty acids intake and carotid atherosclerosis: an epidemiological study evaluated by ultrasonography. Atherosclerosis 2004;176:145-9.
9. Yamada T, Strong JP, Ishii T, et al. Atherosclerosis and omega-3 fatty acids in the populations of a fishing village and a farming village in Japan. Atherosclerosis 2000;153:469-81.
10. Erkkila AT, Lichtenstein AH, Mozaffarian D, et al. Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. Am J Clin Nutr 2004;80:626-32.
11. Lindqvist HM, Sandberg AS, Fagerberg B, et al. Plasma phospholipid EPA and DHA in relation to atherosclerosis in 61-year-old men. Atherosclerosis 2009;205:574-8.
12. Mita T, Watada H, Ogihara T, et al. Eicosapentaenoic acid reduces the progression of carotid intima-media thickness in patients with type 2 diabetes. Atherosclerosis 2007;191:162-7.
13. Wan JB, Huang LL, Rong R, et al. Endogenously decreasing tissue n-6/n-3 fatty acid ratio reduces atherosclerotic lesions in apolipoprotein E-deficient mice by inhibiting systemic and vascular inflammation. Arterioscler Thromb Vasc Biol 2010;30:2487-94.
14. 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.
15. Massaro M, Scoditti E, Carluccio MA, et al. Basic mechanisms behind the effects of n-3 fatty acids on cardiovascular disease. Prostaglandins Leukot Essent Fatty Acids 2008;79:109-15.
16. Renier G, Skamene E, DeSanctis J, et al. Dietary n-3 polyunsaturated fatty acids prevent the development of atherosclerotic lesions in mice. Modulation of macrophage secretory activities. Arterioscler Thromb 1993;13:1515-24.
17. Wang HH, Hung TM, Wei J, et al. Fish oil increases antioxidant enzyme activities in macrophages and reduces atherosclerotic lesions in apoE-knockout mice. Cardiovasc Res 2004;61:169-76.
18. Galis ZS, Sukhova GK, Lark MW, et al. Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques. J Clin Invest 1994;94:2493-503.
19. Nishio R, Shinke T, Otake H, et al. Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary thin-cap fibroatheroma. Atherosclerosis 2014;234:114-9.
20. Watanabe T, Ando K, Daidoji H, et al. A randomized controlled trial of eicosapentaenoic acid in patients with coronary heart disease on statins. J Cardiol 2017;70:537-44.
21. Plutzky J. Atherosclerotic plaque rupture: emerging insights and opportunities. Am J Cardiol 1999;84:15j-20j.
22. Morgan AR, Rerkasem K, Gallagher PJ, et al. Differences in matrix metalloproteinase-1 and matrix metalloproteinase-12 transcript levels among carotid atherosclerotic plaques with different histopathological characteristics. Stroke 2004;35:1310-5.
23. Newby AC, Johnson JL. Genetic strategies to elucidate the roles of matrix metalloproteinases in atherosclerotic plaque growth and stability. Circ Res 2005;97:958-60.
24. Yaqoob P, Calder PC. N-3 polyunsaturated fatty acids and inflammation in the arterial wall. Eur J Med Res 2003;8:337-54.
25. Thies F, Garry JM, Yaqoob P, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. Lancet 2003;361:477-85.
26. Rapp JH, Connor WE, Lin DS, et al. Dietary eicosapentaenoic acid and docosahexaenoic acid from fish oil. Their incorporation into advanced human atherosclerotic plaques. Arterioscler Thromb 1991;11:903-11.
27. Baumann KH, Hessel F, Larass I, et al. Dietary omega-3, omega-6, and omega-9 unsaturated fatty acids and growth factor and cytokine gene expression in unstimulated and stimulated monocytes. A randomized volunteer study. Arterioscler Thromb Vasc Biol 1999;19:59-66.
28. DiNicolantonio JJ, Niazi AK, O'Keefe JH, Lavie CJ. Explaining the Recent Fish Oil Trial "Failures". J Glycomics Lipidomics. 2013: 3: e112. doi:10.4172/2153-0637.1000e112.
29. DiNicolantonio JJ, Meier P, O'Keefe JH. Omega-3 polyunsaturated fatty acids for the prevention of cardiovascular disease: do formulation, dosage & comparator matter? Mo Med 2013;110:495-8.
30. DiNicolantonio JJ, O'Keefe JH, Lavie CJ. The big ones that got away: omega-3 meta-analysis flawed by excluding the biggest fish oil trials. Arch Intern Med 2012;172:1427; author reply -8.
31. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med 2019;380:11-22.
32. Nosaka K, Miyoshi T, Iwamoto M, et al. Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study. Int J Cardiol 2017;228:173-9.
33. Doi M, Nosaka K, Miyoshi T, et al. Early eicosapentaenoic acid treatment after percutaneous coronary intervention reduces acute inflammatory responses and ventricular arrhythmias in patients with acute myocardial infarction: a randomized, controlled study. Int J Cardiol 2014;176:577-82.
34. DiNicolantonio JJ, McCarty MF, Chatterjee S, et al. A higher dietary ratio of long-chain omega-3 to total omega-6 fatty acids for prevention of COX-2-dependent adenocarcinomas. Nutr Cancer 2014;66:1279-84.
35. Simopoulos AP. Genetic variants in the metabolism of omega-6 and omega-3 fatty acids: their role in the determination of nutritional requirements and chronic disease risk. Exp Biol Med (Maywood) 2010;235:785-95.

Disclosure

JJD is author of The Salt Fix, Superfuel, and The Longevity Solution. JHO is Chief Medical Officer and Founder of CardioTabs, a nutraceutical company, and has a major ownership interest in the company. The company, CardioTabs, sells products that contain Omega-3. **MM**