

## Review Article

# Where do we Stand with Fish Oil?

**Brenainn Flanagan**<sup>1,2\*</sup><sup>1</sup>Family Medicine Faculty at the Glen Cove Family Medicine Residency Program at Northwell Health System, USA<sup>2</sup>Assistant Professor of Family Medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, USA**\*Corresponding author:** Brenainn Flanagan, Glen Cove Hospital, 101 St Andrews Lane, 516-674-7900, USA**Received:** May 28, 2018; **Accepted:** June 27, 2018;**Published:** July 04, 2018**Abstract**

There is substantial evidence that a higher intake of fish and/or long-chain (LC) n-3 polyunsaturated fatty acids (PUFAs) is associated with health benefits. Fish oil today is one of the largest consumed dietary supplements on the market, with its many health claims touted as improvement in Alzheimers disease and Cardiac disease prevention, both however coming with mixed evidence. Some of the heterogeneity in the results with fish and fish oil in overall health benefits may be explained by substantial variation in the experimental design, including choice of study population, amount of fish, and fish oil administered as well as continually improving standards of care. This Article discusses a series of topics that health care professionals often ask regarding fish oil such as when it is appropriate to use, what are the true benefits of fish oil and lastly, what are the most recent recommendations regarding it use.

**Introduction**

During the 1970s, Danish researchers studying Inuit metabolism suggested that omega-3 fatty acids found in fish were protective against heart disease. This eventually led to the enthusiastic recommendation that people in the United States eat more fish to help prevent heart disease despite the overall increase in animal fat. At around the same time, scientists reported the death rate from coronary artery disease was much lower among Greenland eskimos after noting their diet was mainly due to the consumption of whale lard, seal and fish fat, in contrast to that of American and Danes which did not see seafood as a fundamental component of their diet [1]. The question remains though, whether the observed cardiovascular benefits often found in people who consume fish is truly due to its consumption, or just the overall healthier lifestyle found in those who consume it.

Fish oil today is one of the most utilized dietary supplements and is promoted by mainstream society as ways to lower triglycerides, prevent heart disease and even work as an anti-inflammatory. In observational studies, people who regularly ate fish were less likely to suffer from strokes, heart disease, and cardiac deaths. In view of observational and animal studies, scientists have recognized two types of long chain fatty acids which come from seafood which may have an impact on one's health; they are Eicosapentaenoic Acid and Docosahexaenoic Acid.

Consumption of fish oil increases the EPA and DHA within one's circulation. First, they are absorbed in the gastrointestinal tract and then transported to the liver. They are then processed and released as triglycerides traveling in lipoproteins such as LDL. From LDL, EPA and DHA are stored in cell membrane phospholipids as well as stored as triglycerides in adipose tissue. EPA can be processed to Prostaglandin E<sub>3</sub>, an important mediator in inflammation and in thrombosis. DHA then again is noted to be important in the development of the human brain during pregnancy and the first 2 years of life.

**Effects on the Cardiovascular System**

The physiologic effects of fish oil occur with regular consumption

and as scientists have noted may change cell membrane characteristics and modulate protein receptor function [2].

**Blood lipids**

We know that fish oil consumption lowers serum Triglycerides by approximately 30% and that the amount consumed with regards to change in Triglyceride concentration is dose-dependent. [3-5]. Thus, the more of the fish oil you consume, the linear decrease in serum triglycerides we see. However, still today, we realize that the reduction of triglycerides has not yet been convincingly exhibited to decrease coronary mortality yet we know there is a causal link between high triglycerides and cardiac disease and its mortality. Fish oil additionally has been noted to increase HDL-C concentrations but at the same time increase LDL-C concentrations but lowers the small dense LDL-C particles [6-8]. Thus by lowering the smaller particles, we see an increase in LDL particle size which may in part account for the high LDL-C concentrations, but the overall number of LDL particles (apolipoprotein B) concentration may stay the same [8].

**Blood pressure**

The blood pressure lowering effect of fish oil results from a reduction in systemic vascular resistance, but an unaltered cardiac output [9-10]. It was noted that fish oil consumption increases the metabolites of nitric oxide production, enhancing vasodilatory responses and decreasing the vasoconstrictor responses to nor epinephrine and angiotensin, likely due to protein regulation at the cellular level [11-15]. Thus, It has been widely shown in randomized trials that supplementation with fish oil reduces BP by 1.52mmHg and Diastolic BP by .99mmHg [17].

**Heart rate**

One's resting heart rate is dependent on the vagal and sympathetic activity, the autonomic function of the sinus node as well as cardiac function. It has been suggested that Fish oil may alter indirectly the sinus node activity and or its responsiveness. What we have seen in more than 30 randomized controlled trial is that fish oil consumption, independent of dose, reduced heart rate by 1.6 beats per minute with an even greater decrease in patients who were habitual consumers [16].

### Cardiac relaxation

Abnormalities of early relaxation are some of the signs associated with underlying heart disease whereas decreased compliance is strongly associated with persistent hypertension and or other cardiovascular processes. One study in primates showed after 24 months of fish oil consumption, decreased left ventricular diastolic filling pressure, increasing both end-diastolic volume and stroke volume [18-19]. In an experimental trial with humans, it was noted after seven weeks of fish oil, the early phase of diastolic filling improved within the participants [20]. In a cohort study of older adults, regular fish consumption was associated with a smaller left ventricular mass, size, and hypertrophy [9]. Also noted that patients with established heart failure, fish oil consumption improved their left ventricular ejection fraction, possibly by improving myocardial functions and decreasing oxygen demand without the change in efficacy [21].

### Coagulation and thrombosis

It has always been speculated that high doses of fish oil increase bleeding time, this number is anywhere from 3 gram-15 grams per day, but this has not been associated with higher rates of clinical bleeding [29]. Even with patients taking aspirin and or coumadin, there were no clinical findings of increased bleeding risk with fish oil use [30]. Studies have yet to show any effect on platelet aggregation or factor pathway disruption leading to the increased bleeding time which is suspected. So, doses up to 4 grams a day have not been shown to have any effect on bleeding risk [5].

### Atherosclerosis

There has been some debate with regards to fish oil and atherosclerosis. It has been shown through in a few small studies that modest consumption of fish oil may reduce chronic progression of atherosclerosis. So in essence, the benefits of fish oil could reduce the risk of non-fatal MI. If fish oil decreases the progression of chronic arterial plaques, as well as decreases endothelial dysfunction, it may in fact, decrease overall cardiac events. In one randomized trial of patients undergoing carotid endarterectomy, supplementation with Fish Oil resulted in plaques with no inflammation and thick caps, both beneficial characteristics compared to thin caps with inflammation noted in alternate group. So by lowering triglycerides and possibly countering inflammation, fish oil by itself could decrease cardiac events [32].

In a prospective observational study among Japanese men and women, individuals with the highest consumption (median of 2.1g/day) of fish oil had a 67% lower incidence of nonfatal MI vs those with the lowest consumption (0.3g/day) [33]. However, in 2012 a meta-analysis of 13 randomized controlled trials found a statistically nonsignificant reduction in total fatal and non-fatal MI, so thus it is in question if fish oil has any effect on non-fatal cardiac events [34].

### Sudden cardiac death

Multiple large systematic reviews and meta-analyses of observational studies have shown Fish Oil to decrease the number of sudden cardiac deaths, which are characterized by the physiologic pathway of disease leading to the final a fatal ventricular arrhythmia. The discovery from these studies suggests that fish oil reduces cardiac mortality, but not cardiac events in general. However in a more recent meta-analysis, supplementation with Fish Oil showed no reduction in

cardiac death compared to placebo. As noted above though, previous studies had all showed a significant reduction in cardiac deaths due to fish oil supplementation, so one theory on this new evidence is that fish oil benefits may be diminished in patients already receiving aggressive medical management for secondary prevention of coronary heart disease.

Lastly, in 2018 A meta-analysis demonstrated that omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events. It also provided no support for current recommendations for the use of such supplements in people with a history of coronary heart disease [35].

Further large trial with long-term evaluation is needed to see if supplementation with fish oil may alter the course of cardiac mortality.

### Arrhythmias

There has been a recent concern with regards to fish oil and the effects on recurrent ventricular tachyarrhythmias. A meta-analysis of three trials showed no effect of fish oil on arrhythmias, specifically people with preexisting ventricular arrhythmias or implantable cardioverter-defibrillator [36-39].

There have been no randomized studies so far to say fish oil prevents atrial fibrillation, although there are some observational studies which suggest this [40]. Suggestions have also been reported that fish oil may reduce myocardial susceptibility to atrial fibrillation. Also, it has been shown that fish oil does not affect postoperative atrial fibrillation. Further investigation is needed based on observational studies noted to show decreased risk of new-onset atrial fibrillations, especially in the elderly.

### Heart failure

Heart Failure continues to be significant cause of morbidity and mortality within the United States and trial data still to this day suggests that there is some benefit of fish oil in these people who have existing heart failure. In one trial, patients with existing heart failure were randomly assigned to fish oil versus placebo [41]. After a period of approximately 4 years, those taking fish oil had decreased mortality and overall improvement in ejection fraction [42]. With regards to prevention of heart failure though, there is no sound evidence to date stating that fish oil decreases new-onset heart failure or associated lower incidence of heart failure.

### Stroke

Fish oil as of recent, through large prospective cohort studies and meta-analysis studies have shown that moderate fish consumption has been associated with lower risk of ischemic stroke, however, no significant change in hemorrhagic stroke was identified [43]. This data, however, needs further studies to identify a true cause and evidence that it will decrease stroke, for recent randomized controlled studies have shown no convincing data that fish oil modifies the risk of stroke.

### Inflammation

As one may know, EPA and DHA are precursors to certain eicosanoids and other inflammatory markers. Yet only experimental evidence has shown that the Fish oil metabolites may play some role in the resolution of inflammation [31].

## Other benefits

Some randomized trials in humans have noted that fish oil can lower markers associated with endothelial dysfunction [22-24]. With this finding, nitric oxide-dependent vasodilation was noted to be improved [25]. In experimental studies, fish oil regulation of hepatic gene showed regression of hepatic steatosis, biosynthesis of cholesterol and reduction of hyperinsulinemia [26-28]. Other potential benefits of omega 3 fatty acids which have not been studied as well include the suggested reduction of breast cancer, colorectal cancer and prostate cancer and the possibility of a decreased decline of cognition associated with Alzheimer's disease.

## Safety

The US Food and Drug Administration recommends that distributors of Fish oil supplements suggest more than 2 Grams of EPA and DHA per day and that total intake up to 3g/day are considered safe [44]. The FDA has approved fish oil supplements at a dose of 4 grams/day for prescription therapy of hypertriglyceridemia.

## Contaminants

Fish oil contains small amounts of PCB (polychlorinated biphenyls) and Dioxins but the amount consumed from fish oil is extremely low [45-46]. Also, mercury, more likely found in commercial game has declined but are not negligible [47-48].

## Cancer

Current evidence does not show an association of fish oil on cancer risk.

## Administration

EPA and DHA are found in cold water fish such as salmon, halibut, tuna, and herring. Many over the counter preparations are available but also available in prescription such as Lovaza, Vascepa, and Omnicor in the US. Different fish oil formulations contain a variable amount of EPA and DHA, especially over the counter formulations

## Final Note

Currently, fewer than one in five people in the United States eats fish at least twice a week, as recommended in the dietary guidelines for Americans by the American Heart Association. Recently, the American Heart Association noted that the results of pooled data from 10 randomized controlled trials which found no association of the supplements and lowered risk of death or major cardiac events suggest that the general population should avoid using omega fish oil to prevent heart disease. It, however, suggested that its use was reasonable in patients with heart failure without preserved left ventricular function to reduce mortality and hospitalizations, it, however, does not recommend its use in patients with diabetes and pre-diabetes to prevent heart disease [49].

The AHA also goes on to discourage the use of fish oil in prevention of stroke, recurrent atrial fibrillation and overall cannot make a recommendation of using omega-3 fish oil for primary prevention of cardiovascular disease. It does, however, suggest recommending eating fatty fish at least 2 times a week.

With regards to risk and benefits, to suggest most adults without known coronary heart disease to consume 2 servings of fish per week

and those who don't eat fish to supplement with a fish oil pill 1gram per day provides only benefit with minimal to no harm.

Patients with Coronary heart disease should consume at least 2 servings of fish per week. With the findings of decreased progression of arterial plaques, decreased coronary heart-related deaths, the suggestion of 1 gram/day if unable to get ample fish in diet seems to be only a cardiovascular benefit than a risk factor.

Lastly, physicians should use this information as a guide to make decisions on whether omega-3 fish oil supplements might be appropriate for some patients.

## References

- Bang HO, Dyerberg J. Lipid metabolism and ischemic heart disease in Greenland Eskimos. In: *Advances in nutrition research*, Draper H (Ed), Plenum Press, New York 1980; p. 1-22.
- Siscovick DS, Raguhugathan TE, King I, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA*. 1995; 274: 1363.
- Harris WS. n-3 fatty acids and serum lipoproteins: human studies. *Am J Clinical Nutrition*. 1997; 65: 1645S.
- Balk EM, Lichtenstein AH, Chung M, et al. Effects of omega-3-fatty acids on serum markers of cardiovascular disease risk: a systematic review. *Atherosclerosis*. 2006; 189: 19.
- Wang C, Chung M, Lichtenstein A, et al. Effects of omega-3-fatty acids on cardiovascular disease. *Evid Rep Technol Assess (summ)*. 2004; 1.
- Friedberg CE, Janssen MJ, Heine RJ, Grobbee DE. Fish oil and glycemic control in diabetes. A meta-analysis. *Diabetes Care*. 1998; 21: 494.
- Minihane AM, Khan S, Leigh-Firbank EC, et al. ApoE polymorphism and fish oil supplementation in subjects with an atherogenic lipoprotein phenotype. *Arteriosclerosis Thromb Vascular Biology*. 2000; 20: 1990.
- Griffin MD, Sanders TA, Davies IG, et al. Effects of altering the ratio of dietary n-6 to n-3 fatty acids on insulin sensitivity, lipoprotein size, and post prandial lipemia in men and post menopausal women aged 45-70y: The OPTILIP Study. *Am J Clin Nutrition*. 2006; 84: 1290.
- Mozaffarian D, Gottdiener JS, Siscovick DS. Intake of tuna or other broiled or baked fish versus fried fish and cardiac structure, function and hemodynamics. *Am J Cardiology*. 2006; 97: 216.
- Demaison L, Blet J, Sergiel JP, et al. Effect of dietary polyunsaturated fatty acids on contractile function of hearts isolated from sedentary and trained rats. *Repro Nutr Dev*. 2000; 40: 113.
- Kenny D, Warltier DC, Please JA, et al. Effect of omega-3 fatty acids on the vascular response to angiotensin in normotensive men. *Am J Cardiology*. 1992; 70: 1347.
- Chin JP, Gust AP, Nestel PJ, Dart AM. Marine oil dose dependently inhibit vasoconstriction of forearm resistance vessels in humans. *Hypertension*. 1993; 21: 22.
- Harris WS, Rambjor GS, Windsor SL, Diederich D. n-3 fatty acids and urinary excretion of nitric oxide metabolites in humans. *Am J Clin Nutrition*. 1997; 65: 459.
- Mori TA, Watts GF, Burke V, et al. Differential effects of eicosapentaenoic acid and docosahexaenoic acid on vascular reactivity of the forearm microcirculation in hyperlipidemic, overweight men. *Circulation*. 2000; 102: 1264.
- McVeigh GE, Brennan GM, Cohn JN, et al. Fish oil improves arterial compliance in non insulin-dependent diabetes mellitus. *Arteriosclerosis Thromb*. 1994; 14: 1425.
- Mozaffarian D, Geelen A, Brouwer IA, et al. Effect of fish oil on heart rate in humans: a meta-analysis of randomized controlled trials. *Circulation*. 2005; 112: 1945.

17. Miller PE, Van Elswyk M, Alexander DD. Long-Chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: a meta analysis of randomized controlled trials. *Am J Hypertension*. 2014; 27: 885.
18. Charnock JS, McLennan PL, Abeywardena MY. Dietary modulation of lipid metabolism and mechanical performance of the heart. *Mol Cell Biochem*. 1992; 116: 19.
19. McLennan PL, Barnden LR, Bridle T, et al. Dietary fat modulation of left ventricular ejection fraction in the marmoset duet to enhance filling. *Cardiovasc Res*. 1992; 26: 871.
20. Grimsgaard S, Bonna KH, Hansen JB, Myhre ES. Effects of highly purified eicosapentaenoic acid and docosahexaenoic acid on hemodynamics in humans. *Am J Clin Nutr*. 1998; 68: 52.
21. Peoples GE, McLennan PL, Howe PR, Groeller H. Fish Oil reduces heart rate and oxygen consumption during exercise. *J Cardiovasc Pharmacol*. 2008; 52: 540.
22. Robinson JG, Stone NJ. Antiatherosclerotic and Antithrombotic effects of omega-3 fatty acids. *Am J Cardiology*. 2006; 98: 39.
23. James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr*. 2000; 71: 343.
24. 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.
25. Wang Q, Liang X, Wang L, et al. Effect of omega-3 fatty acids supplementation on endothelial functions: a meta analysis of randomized controlled trials. *Atherosclerosis*. 2012; 221: 536.
26. Jump DB. N-3 polyunsaturated fatty acid regulation of hepatic gene transcription. *Curr Opin Lipidology*. 2008; 19: 242.
27. Giacco R, Cuomo V, Vessby B, et al. Fish oil, insulin sensitivity, insulin secretion and glucose tolerance in healthy people: is there any effect of fish oil supplementing in relation to the type of background diet and habitual dietary intake of n-6 and n-3 fatty acids? *Nutr Metab Cardiovascular Disease*. 2007; 17: 572.
28. Rossmeisl M, Medrikova D, Van Schothorst EM, et al. Omega-3 Phospholipids from fish suppress hepatic steatosis by integrated inhibition of biosynthetic pathways in dietary obese mice. *Biochem Biophys Acta*. 2014; 1841: 267.
29. Knapp HR, Reilly IA, Allesandrini, P, FitzGerald GA. *In vivo* indexes of platelet and vascular function during fish oil administration in patients with atherosclerosis. *N Engl J Med*. 1986; 314: 937.
30. Wang C, Harris, WS, Chung M, et al. n-3 Fatty acids from fish or fish oil supplements, but not alpha linolenic acid, benefit cardiovascular disease outcomes in primary and secondary- prevention studies: a systematic review. *Am J Clin Nutr*. 2006; 84: 5.
31. Spite M, Serhan, CN. Novel Lipid mediators promote resolution of acute inflammation: impact of aspirin and statins. *Circ Res*. 2010; 107: 1170.
32. Theis F, Garry JM, Yaqoob P, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomized controlled trial. *Lancet*. 2003; 361: 477.
33. Iso H, Kobayashi M, Ishihara J, et al. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center Based Study Cohort. *Circulations*. 2006; 113: 195.
34. Rizos EC, Ntzani EE, Bika E, et al. Association between omega-3 fatty acid supplementation and risk for major cardiovascular disease events: a systemic Review and meta-analysis. *Jama*. 2012; 308: 1024.
35. Augn T, Halsey J, Kromhout, D. Associations of Omega-3 Fatty acid supplement use with cardiovascular disease risks: A meta analysis of 10 trials involving 77917 individuals. *JAMA Cardiology*. 2018; 3: 225.
36. Raitt, MH, Connor WE, Morris C, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patient with implantable defibrillators: a randomized controlled trial. *JAMA*. 2005; 293: 2884.
37. Mozaffarian D, Lemaitre RN, King IB, et al. Plasma phospholipid long-chain w-3 fatty acids and total and cause specific mortality in older adults: a cohort study. *Ann Internal Medicine*. 2013; 158: 515.
38. Leaf A, Albert CM, Josephson M, et al. Prevention of fatal arrhythmias in high risk subjects by fish oil n-3 fatty acid intake. *Circulation*. 2005; 112: 2762.
39. Brower IA, Zock PL, Camp AJ, et al. Effect of fish oil on ventricular tachycardiarrhythmia and death in patient with implantable cardioverter defibrillators: the study on Omega -3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. *JAMA*. 2006; 295: 2613.
40. Sakabe M, Shiroshita-Takeshita A, Maguy A, et al. Omega-3 polyunsaturated fatty acids prevent atrial fibrillation associated with heart failure but not atrial tachycardia remodeling. *Circulation*. 2007; 116: 2101.
41. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure: a randomized, double blind, placebo controlled trial. *Lancet*. 2008; 372: 1223.
42. Ghio S, Scelsi L, Latini R, et al. Effects of n-3 polyunsaturated fatty acids and of rouseastatin on left ventricular function in chronic heart failure: A substudy of the GISSI-HF trial. *Eur J Heart Fails*. 2010; 12: 1345.
43. He K, Song Y, Daviglius ML, et al. Fish Consumption and incidence of stroke: A meta analysis of cohort studies. *Stoke*. 2004; 35: 1538.
44. Letter responding to a request to reconsider the qualifiers claim for a dietary supplement health claim for omega-3-fatty acids and coronary heart disease. Office of Nutritional products, Labeling and Dietary supplements, Center for Food safety and applied nutrition, US Food and Drug Administration, 2002.
45. Jimenez B, Wright C, Kelly M, Startin JR. Levels of PCDDs, PCDFs and non-ortho PCBS in dietary supplement fish oil obtained in Spain. *Chemosphere*. 1996; 32: 461.
46. Summary of investigation of dioxins, furans and PCBs in farmed salmon, wild salmon, farmed trout and fish oil capsules. Food safety authority of Ireland. 2002.
47. Mozaffarian D, Rimm EB. Fish intake, contaminants and human health: evaluating the risks and the benefits. *JAMA*. 2006; 296: 1885.
48. Foran SE, Flood JG, Lewandrowski KB. Measurement of mercury levels in concentrated over the counter fish oil preparations: is fish oil healthier than fish? *Arch Pathol Lab Med*. 2003; 127: 1603.
49. Siscovick D, Barringer T, Fretss A, et al. Omega-3 Polyunsaturated Fatty Acid Supplementation and the prevention of clinical cardiovascular disease: A science advisory from the American Heart Association. *Circulation*. 2017; 135: 867.