Heart Health Benefits of EPA and DHA

A White Paper Prepared by AlwaysOmega3s.com

Omega-3s
Always a good idea™

www.alwaysomega3s.com

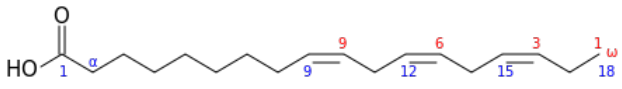
Version 1 • September 2015

Decades of research have uncovered many health benefits of long-chain omega-3 fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

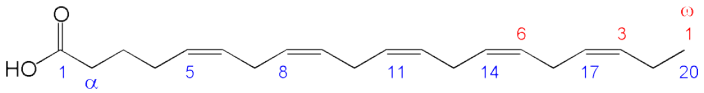
EPA and DHA are both essential building blocks for tissue structures and important biological mediators in health and disease, which is why the Dietary Guidelines for Americans, as well as health advocacy groups from around the globe, recommend eating foods rich in EPA and DHA as part of an overall healthy eating pattern. Yet, there are mixed viewpoints about the cardiovascular benefits of EPA and DHA when taken in supplement form. This document reviews the scientific evidence about EPA and DHA and its association with cardiovascular health and disease risk reduction.

Omega-3 Basics

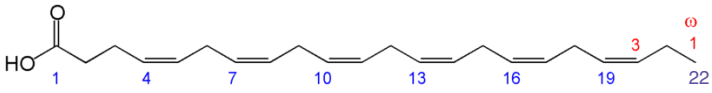
There are three primary omega-3 fatty acids (pictured below) consumed in the diet: alpha linolenic acid (ALA), EPA and DHA. All are polyunsaturated fatty acids with varying lengths of the carbon backbone. ALA has 18 carbon atoms with three



Alpha-Linolenic Acid (ALA)



Eicosapentaenoic Acid (EPA)



Docosohexaenoic Acid (DHA)

double bonds; EPA has 20 carbon atoms and five double bonds; and DHA has 22 carbon atoms and six double bonds. ALA is found in plant foods such as soybeans, black walnuts, flaxseeds, and chia, whereas EPA and DHA are marine-based and found in seafood (especially fatty fish). Sources of EPA and DHA for supplements include sardines, anchovies, certain types of algae and krill.

While the body can elongate ALA into its longer-chain omega-3 fatty acid counterparts, the process is inefficient with less than 5 percent converting to EPA and less than 1 percent to DHA. The best way to get EPA and DHA is by consuming it directly, through foods and supplements.

Why EPA and DHA are Important

The roles and functions of EPA and DHA are distinct but complementary. As precursors to several families of biologically active molecules (resolvins, protectins, maresins, prostaglandins, leukotrienes, etc.), EPA and DHA both help to control inflammatory responses and regulate blood coagulation. They both play a role in determining what genes are turned on and off. DHA, by virtue of its greater presence in cell membranes than EPA, plays an important structural role in cells, helping make cell walls more flexible. This in turn allows the proteins in the membrane to control the inflow and outflow of important cell components, making the cell operate most efficiently. DHA is found in virtually all cells, but it is particularly concentrated in cells of the brain, heart and retina.

EPA and DHA and Heart Health

What Is Known

Scores of research studies support the view that EPA and DHA omega-3s are cardioprotective nutrients. Higher intakes or blood levels of these important fatty acids are associated with reduced risk of mortality from coronary heart disease (CHD) and sudden cardiac death[1]. The USDA's National Evidence Library notes that the evidence supporting EPA and DHA for heart health is "moderate," indicating that some of the evidence is conflicting and more research needs to be done[1]. Importantly, recent meta-analyses of

randomized-controlled studies found that dosages greater than 1 gram (1,000 mg) EPA+DHA per day offer significant cardioprotection[2], reducing risk for CHD by 20% or greater[3]. Even studies with lower intakes found that overall risk for cardiac death is reduced[4] and a recent modeling exercise looking at prospective studies found that intake of EPA+DHA at *any dose level* was associated with reduced risk for any type of CHD event[5].

EPA+DHA, especially at relatively high doses (i.e. >3 g/day), have been shown to lower triglycerides and raise HDL-cholesterol (the "good" cholesterol)[6]. The same study found that in patients with extremely elevated triglyceride levels, fish oil supplementation may also slightly raise LDL-cholesterol, yet total cholesterol remained virtually unchanged. Other studies have also found that EPA+DHA improve blood vessel function[7], reduce inflammation[8], and lower blood pressure[9].

> *"EPA and DHA are cardioprotective nutrients, and calls to abandon their use are premature."*

What is Unclear and Needs More Research

Several major early studies using fish or fish oils to reduce CHD events were favorable. These included DART[10], JELIS[11], and two GISSI[12,13] studies. It was upon the basis of two studies (DART and GISSI-Prevenzione) that most recommendations in the late 1990s and early 2000s for the use of EPA+DHA in secondary prevention were founded.

However, at least six trials published between 2010 and 2014 did not find a benefit for EPA+DHA in patients with known CHD or with risk factors for heart disease[14-19].

These "failed" studies obviously beg the question of whether, in today's world of modern medical care, omega-3 fatty acid supplementation still reduces risk for CHD. It's a reasonable question, because even though the safety of EPA and DHA supplementation is certain, consumers – and their healthcare providers – may express concern about the cost and/or inconvenience of supplementation when the perceived benefits are not as clear. These are valid concerns.

But before any conclusions can be drawn about fish oils and EPA+DHA supplements failing to prevent heart disease, we need to interpret findings of recent clinical studies in context. That is to say that if we are going to accept the findings of these studies, then we must keep in mind the conditions under which they were done. When we do so, we find that fish oils "did not work" in the following settings where patients:

- were given a **< 1 g/day** for about **2-3 years** (i.e., low dose for a short period of time)
- were in their **early 60s**; were typically on **one to five other heart/diabetes medicines** and had been **treated in the hospital immediately after their heart attack to restore blood flow to the heart muscle (which greatly reduces the damage)**
- whose **background omega-3 intake (from diet) was close to a cardioprotective dose already (i.e., around 250 mg/d)**.

In addition, most of these studies included too few of the specific kinds of heart attacks most likely to benefit from omega-3s to draw any valid statistical conclusions. These concerns have been raised by several experts in the field[20-24]. Under these conditions, it is not surprising at all that the addition of a relatively small amount of EPA+DHA had no detectable effect.

The important question is not whether a course of low dose omega-3s given over the short term with other CHD drugs to older people with disease helps, but whether taking either higher doses or taking lower doses for decades (not a couple of years) will be helpful. Potential positive effects of long-term intakes of 1 g or more of EPA+DHA beginning in young adulthood (or even *in utero*) was not addressed in these studies and remains an open question, and it is this question that must be answered before one can conclude that "fish oils don't work." The strong findings of epidemiological studies supporting a cardioprotective effect of higher intakes of EPA+DHA and of higher blood levels of these important fatty acids argues that, in the long-term, EPA and DHA are cardioprotective nutrients, and calls to abandon their use are premature.

In this light, future studies are needed, but they **must be properly powered** (i.e., include enough clinical events to allow for proper statistical analysis), must **measure dietary**

intake and blood levels of all omega-3 fatty acids **before and during** the study, use doses of omega-3 fatty acids **significantly higher than those provided in background diets**, focus on **patient populations with low EPA+DHA** levels, treat for **longer periods of time**, advise taking omega-3s with meals, and consider the effects of these agents in the great majority of patients who are not actually taking the drugs that they were prescribed (which is far more common in the real world than in clinical trials). The strong evidence-base from prospective cohort studies and the ever-deepening understanding of the cellular effects of long-chain omega-3 fatty acids together support the need for these nutrients in reducing cardiovascular risk. Short-term findings from randomized controlled trials need to be interpreted in the light of all the evidence.

Safety of Omega-3 Supplementation

When it comes to recommending omega-3 supplements to patients or consumers, it is important to also consider both safety and costs associated. The good news is that omega-3 supplementation of up to 3 grams per day is generally recognized as safe (GRAS) by the Food and Drug Administration[25]. Omega-3 fish oil supplementation greater than 3 grams per day is possible but should be done only under the care of a physician.

A recent report from Norway concluded that there was no evidence for safety concerns at daily intakes of up to 6.9 g of EPA+DHA per day, a dose that is higher than the currently approved dose for omega-3 prescription drugs (4 g/day, which supplies up to 3.6 g of omega-3 fatty acids). This applies to risk for "excessive bleeding" as well, which is a common misconception among consumers and physicians alike. Fish oils do not increase risk for clinically-significant bleeding[26].

Recommended Amounts of Omega-3s

The Dietary Guidelines for Americans[27], American Heart Association (AHA)[28], the World Health Organization (WHO)[29], the International Society for the Study of Fatty Acids and Lipids (ISSFAL)[30] and other public health groups around the globe recommend dietary patterns that would supply adequate amounts of EPA+DHA, averaging between 250 and 500 mg per day. This can be accomplished by eating two 4-oz servings every week of fatty fish such as salmon, mackerel, trout, halibut, or albacore tuna; or by taking an omega-3 supplement with EPA+DHA (which typically contains 250 to 500 mg per capsule). The Global Organization for EPA+DHA omega-3s (GOED) recommends a minimum intake of 500 mg per day for effective cardiovascular protection.

> "...the weight of the evidence coupled with the low risk and potential high reward [make]...recommending omega-3s a smart strategy."

According to the American Heart Association, people with coronary heart disease should increase their omega-3 intake to about 1 gram per day. Individuals with high triglycerides may require intakes of EPA+DHA in greater amounts and should be done under the care of a physician[28].

Summary

People should be eating fatty fish at least twice a week to get adequate amounts of EPA+DHA to support a healthy heart – as underscored by position pieces from the AHA[28], the Academy of Nutrition and Dietetics[31], and the U.S. government[27]. Yet, the typical American diet is far from ideal, with people consuming only about 3.5 ounces of fish per week – a fraction of which is omega-3-rich fatty fish, and a far cry from the 8 ounce weekly recommendation[32]. Until we can close the gap, health professionals should continue to advocate for increased fish consumption. For those individuals who will not or cannot comply, recommending a high-quality omega-3 supplement to support a healthy lifestyle, including a healthy heart, is reasonable.

It is important to note that omega-3s, as with most supplements, **are not meant to be a proxy for pharmaceutical interventions – they are not drugs**. They are not meant to treat disease (except in the case of severe hypertriglyceridemia), but rather to supplement nutrient gaps in the diet and contribute towards maintaining health and wellbeing. While the science behind omega-3s and cardiovascular disease is not yet conclusive, the weight of the evidence coupled with the low risk and potential high reward associated with supplementation indicates that recommending omega-3s is a smart strategy.

Note: This white paper has been reviewed and approved by the AlwaysOmega3 campaign's Science Advisory Council.

References

1. U.S. Department of Agriculture Nutrition Evidence Library. "What is the relationship between consumption of seafood n-3 fatty acids and the risk of cardiovascular disease?" Accessed October 29, 2015. http://www.nel.gov/evidence.cfm?evidence_summary_id=250321.

2. Wen YT, Dai JH, Gao Q. Effects of Omega-3 fatty acid on major cardiovascular events and mortality in patients with coronary heart disease: a meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis.* 2014;24:470-5.

3. Casula M, Soranna D, Catapano AL, Corrao G. Long-term effect of high dose omega-3 fatty acid supplementation for secondary prevention of cardiovascular outcomes: A meta-analysis of randomized, double blind, placebo controlled trials. *Atheroscler Suppl.* 2013;14:243-51.

4. Trikalinos TA, Lee J, Moorthy D, Yu WW, Lau J, Lichtenstein AH, Chung M. Effects of eicosapentanoic acid and docosahexanoic acid on mortality across diverse settings: systematic review and meta-analysis of randomized trials and prospective cohorts. Technical Review 17, Vol. 4. (Prepared by the Tufts Medical Center Evidence-based Practice Center under Contract No. HHSA 290-2007-10055-1.) AHRQ Publication No. 12-EHC040-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2012.

5. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: A Systematic Review and Meta-analysis. *Ann Intern Med.* 2014; 160:398-406.

6. Eslick GD, Howe PR, Smith C, Priest R, Bensoussan A. Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis. *Int J Cardiol.* 2009;136:4-16.

7. Nestel P, Shige H, Pomeroy S, Cehun M, Abbey M, Raederstorff D. The n-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid increase systemic arterial compliance in humans. *Am J Clin Nutr.* 2002;76:326-30.

8. Li K, Huang T, Zheng J, Wu K, Li D. Effect of marine-derived n-3 polyunsaturated fatty acids on C-reactive protein, interleukin 6 and tumor necrosis factor alpha: a meta-analysis. *PLoS One*. 2014;9:e88103.

9. 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 Hyperten.* 2014;27:885-96.

10. Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet*. 1989;2:757-61.

11. 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;369:1090-8.

12. Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation*. 2002;105:1897-903.

13. Investigators GISSI-Heart Failure Study. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2008;372:1223-30.

14. Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, et al. OMEGA, a randomized, placebo-controlled

trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. *Circulation.* 2010;122:2152-9.

15. Bosch J, Gerstein HC, Dagenais GR, Diaz R, Dyal L, Jung H, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *NEnglJ Med.* 2012;367:309-18.

16. Bonds DE, Harrington M, Worrall BB, Bertoni AG, Eaton CB, Hsia J, et al. Effect of long-chain omega-3 fatty acids and lutein + zeaxanthin supplements on cardiovascular outcomes: results of the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA Intern Med.* 2014;174:763-71.

17. Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. *BMJ*. 2010;341:c6273.

18. Roncaglioni MC, Tombesi M, Avanzini F, Barlera S, Caimi V, Longoni P, et al. n-3 fatty acids in patients with multiple cardiovascular risk factors. *NEnglJ Med.* 2013;368:1800-8.

19. Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. *NEnglJ Med.* 2010;363:2015-26.

20. Harris WS. Are n-3 fatty acids still cardioprotective? *Curr Opin Clin Nutr Metab Care.* 2013;16:141-9.

21. James MJ, Sullivan TR, Metcalf RG, Cleland LG. Pitfalls in the use of randomised controlled trials for fish oil studies with cardiac patients. *Br J Nutr.* 2014;112:812-20.

22. von Schacky C. Omega-3 fatty acids in cardiovascular disease—an uphill battle. *Prostaglandins Leukot Essent Fatty Acids.* 2015;92:41-7.

23. Marchioli R, Levantesi G. n-3 PUFAs in cardiovascular disease. *Int J Cardiol.* 2013;170:S33-8.

24. Wu JH, Mozaffarian D. omega-3 fatty acids, atherosclerosis progression and cardiovascular outcomes in recent trials: new pieces in a complex puzzle. *Heart*. 2014;100:530-3.

25. US Department of Health and Human Services, Food and Drug Administration. 21 CFR part 184 [docket no. 86G-0289]. June 5, 1997.

26. Wachira JK, Larson MK, Harris WS. n-3 Fatty acids affect haemostasis but do not increase the risk of bleeding: clinical observations and mechanistic insights. *Br J Nutr.* 2014;111:1652-62.

27. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2010. 7th Edition, Washington, DC: U.S. Government Printing Office, December 2010.

28. Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation*. 2006;114:82-96.

29. Fatty Acids in Human Nutrition: Report of an expert consultation. FAO Food and Nutrition Paper, 91. November 10-14, 2008. http://www.fao.org/fileadmin/user_upload/nutrition/docs/requirements/fatsandfattacidsreport.pdf.

30. International Society for the Study of Fatty Acids and Lipids (ISSFAL) Report on dietary intake of essential fatty acids. Recommendations for dietary intake of polyunsaturated fatty acids in healthy adults. June 2004.

31. Vannice G, Rasmussen H. Position of the Academy of Nutrition and Dietetics: dietary fatty acids for healthy adults. *J Acad Nutr Diet.* 2014;114:136-53.

32. Papanikolaou Y, Brooks J, Reider C and Fulgoni VL 3rd. U.S. adults are not meeting recommended levels for fish and omega-3 fatty acid intake: results of an analysis using observational data from NHANES 2003–2008. *Nutr J.* 2014;13:31.