

Commentary – Omega-3 fatty acids and cardiovascular disease: do placebo doses give placebo results?

B. Sears

Inflammation Research Foundation, Peabody, MA, USA

Corresponding Author: Barry Sears, Ph.D; e-mail: bsears@drsears.com

A Science Advisory from the American Heart Association (AHA) was recently published providing a relatively tepid endorsement on the use of omega-3 supplements for secondary prevention of myocardial infarction and existing heart failure, but did not recommend their use for primary prevention in patients with diabetes or pre-diabetes, patients with high cardiovascular disease risk, recurrent atrial fibrillation, or stroke¹. Is it possible such equivocal results presented in the Science Advisory are the consequence of using potentially placebo doses of omega-3 fatty acids used in the studies? I believe the answer may be yes.

It is well recognized that heart disease is an inflammatory condition². What is not well known is that there are two phases of inflammation. One is the initiation of the inflammatory response, and the other is the resolution of the same response. Both are active phases that are intimately linked to each other³. Omega-3 fatty acids have two distinct mechanisms of action on each distinct phase of the inflammatory response. The first mechanism is a weak reduction of the initiation phase of inflammation and the second mechanism is a strong acceleration of the resolution phase of the inflammation. Each of these mechanisms is unique, dose-dependent, and mediated by unique hormones derived from omega-3 fatty acids. At low doses of omega-3 fatty acids in the blood, the hormones (known as eicosanoids) derived from omega-3 fatty acids act as weak anti-inflammatory agents similar to low-dose aspirin. At much higher levels in the blood, the omega-3 fatty acids can generate an exceptionally powerful new group of hormones (known as resolvins) that promote the resolution phase of inflammation. Therefore the efficacy of omega-3 fatty acids in the treatment and prevention of cardiovascular disease will be highly dose-dependent on the levels of the omega-3

fatty acids in the blood. Low levels of omega-3 fatty acids in the blood will generate essentially placebo results since the levels of resolvins will also be at placebo levels. Interestingly, there was no mention of resolvins in the Science Advisory from the AHA.

Resolvins are exceptionally difficult to measure in the blood due to their very low levels and extremely short half-life. However, the levels of certain fatty acids in the blood can be used as surrogate markers for resolvins. The two best markers for the potential of generating resolvins are either the omega-3 index consisting of the summation of the long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) or the ratio of the long-chain omega-6 fatty acid arachidonic acid (AA) to EPA. The omega-3 index indicates the levels of the precursors of resolvins, whereas the AA/EPA ratio provides an indication of the balance of precursors of the initiation of inflammation relative to the resolution of inflammation. Either marker may be a better surrogate marker of cardiovascular disease than is LDL-cholesterol. Since this is a rather bold statement, let me support it.

The goal of all cardiovascular treatment is to reduce the incidence and ultimately the mortality from such a chronic disease. From that perspective, the most successful cardiovascular study to date has been the Lyon Diet Heart Study⁴. This study was a secondary prevention trial using supplemental omega-3 fatty acids combined with dietary changes to better reflect the Mediterranean diet. This meant the French participants in the active arm were instructed to consume more vegetables, more fruit more fish, as well as less meat and less butter than those in the control group. The active group also consumed high levels of the short-chain omega-3 fatty acid, alpha-linolenic acid (ALA) in

a margarine containing 5% trans fatty acids. This was because the French participants in the active group would not consume extra-virgin olive oil. It should be noted that ALA is slowly converted into EPA, but not at all converted into DHA⁵. Therefore, under this protocol, the EPA levels would be expected to increase, but not the DHA levels. At the end of the 27 months, the all-cause mortality in the active group was reduced by 70%. As striking as the results, there were no changes in the total cholesterol, HDL cholesterol, LDL cholesterol, weight, BMI, blood pressure, or triglycerides between the two groups. The only marker that changed between the two groups was AA/EPA ratio. This ratio was reduced from 9.0 in the control group to the 6.2 in the active group. This 30% reduction in the AA/EPA ratio appeared to be the only clinical marker that could be correlated with the 70% reduction in all-cause mortality, the 76% reduction in cardiovascular mortality, and the 73% reduction in primary cardiovascular end points so strongly stressed in the AHA Science Advisory statement as for the relative ineffectiveness of omega-3 fatty supplementation in treating cardiovascular conditions. Yet nothing the medical literature has matched the efficacy of the Lyon Diet Heart Study nor was that study mentioned in Science Advisory statement.

The Lyon Diet Heart Study was published before the introduction of statins. Perhaps the efficacy of the reduction of the AA/EPA ratio would be overwhelmed in the presence of statins. This was addressed in the JELIS study⁶. In this secondary prevention study, more than 18,000 Japanese cardiovascular patients were placed on a statin. Half were provided with supplemental EPA, and the other half received supplemental olive oil for three and a half years. The starting AA/EPA ratio in both groups was 1.6 (much lower than in the Lyon Diet Heart Study). The subjects receiving the additional EPA lowered their AA/EPA ratio to 0.8 during the course of the study whereas the control group remained unchanged at 1.6. However, that reduction in the AA/EPA ratio resulted in an additional 20% reduction in the incidence of cardiovascular events suggesting that lowering the AA/EPA ratio was synergistic to statins and not overwhelmed by them. Subsequent *ad hoc* analysis of the JELIS data indicated that the AA/EPA ratio is associated with a 38% reduction in sudden cardiac death or fatal/nonfatal myocardial infarction⁷.

Another trial has indicated that the AA/EPA ratio is an excellent predictor of the potential rupture of soft vulnerable plaques⁸.

The importance of the AA/EPA ratio in predicting cardiovascular mortality was pointed in a 2012 study that looked at the AA/EPA ratio in various nationalities and compared that ratio to the overall cardiovascular mortality rate in their respective countries⁹. In Table 1 the data is shown comparing Americans to Japanese.

Table 1. Comparison of Japanese and American Populations.

Parameter	Japanese	Americans
CHD Mortality/100,000	46	160
LDL cholesterol (mg/dL)	132	135
% Smokers	49	8
AA/EPA ratio	2.6	11

It is difficult to explain the 70% reduction in cardiovascular mortality between the two populations based on the differences in their LDL cholesterol levels. Likewise, it is difficult to invoke more than a 600% increase in smokers as an explanation of the differences in cardiovascular mortality rates in the two countries. However, the 74% reduction in the AA/EPA ratio between the two populations does correlate well with the differences in national cardiovascular mortality rates.

The omega-3 index is another measure of adequate levels of omega-3 fatty acids in the blood to generate resolvins. Whereas the AA/EPA ratio looks at the balance of precursors to eicosanoids and resolvins, the metabolism of the EPA into DHA means that the total omega-3 index will always be at least twice the EPA level. Thus either marker will indicate if adequate omega-3 fatty acids are present in the blood to provide the substrates required to make resolvins. A recent publication has suggested that an omega-3 index between 8 and 11 percent of total fatty acids is required to see significant cardiovascular protection¹⁰. The omega-3 index of the subjects in most of studies referenced in Science Advisory statement is far lower than required to observe cardiovascular protection. This suggests that with supplementation with low-dose omega-3 fatty acids will never impact, using either the omega-3 index or the AA/EPA ratio enough to get them to a therapeutic range required to influence the course of cardiovascular disease. This would explain the equivocal results observed with

most intervention trials quoted in the Science Advisory statement. This point was emphasized in a recent study of mortality in more than 6,000 postmenopausal American women¹¹. Both the omega-3 index and AA/EPA ratio was measured in this population. It was demonstrated that either increasing the omega-3 index or decreasing the AA/EPA ratio was strongly correlated with the decreasing all-cause mortality as well as decreasing cardiovascular mortality during a 15-year follow-up.

The levels of omega-3 supplementation using adequate levels of EPA and DHA needed to move the omega-3 index or AA/EPA ratio into their target ranges (8-11% for the omega-3 index or to 1.5 to 3 for the AA/EPA ratio) is considerable for Americans. With normal American males, it was demonstrated that 5 grams of EPA and DHA per day for a 10-week period was necessary to reduce the AA/EPA ratio from 23 to 2.5¹². This level of supplementation was far greater than used in any of the quoted trials in the Science Advisory statement. Likewise, it has been demonstrated that it requires between 5 and 7.5 grams of EPA and DHA to reduce the AA/EPA to less than 2 in normal American females¹³. Unless these target goals are met for either marker, it is highly unlikely that sufficient resolvins can be produced that will generate a significant reduction in either cardiovascular events or cardiovascular mortality. To support that statement, one the trials quoted in the Science Advisory statement indicated that at low levels of EPA and DHA supplementation (1 gram per day) had no benefits in the treatment of dry age-related macular degeneration¹⁴. However, when a much higher omega-3 fatty acid dose (5 grams of EPA and DHA per day) was used in another study, significant improvements were demonstrated in dry age-related macular degeneration¹⁵.

This leads me back to my earlier contention that non-therapeutic doses of omega-3 fatty acids will fail to significantly change either the AA/EPA ratio or the omega-3 index, thus generating placebo effects. On the contrary, therapeutic doses of omega-3 fatty acids will bring the same surrogate markers into their appropriate target ranges, generating therapeutic effects.

Before the use of higher blood levels of omega-3 fatty acids can be accepted by the cardiovascular community, it requires displacing the current focus on using LDL cholesterol levels as the best surrogate marker for cardiovascular disease progression. This marker has become more suspect as it was

recently shown in a recent meta-analysis study that the LDL cholesterol levels are either not or even inversely correlated with all-cause mortality in after age 60¹⁶.

In summary, it is proposed that new markers are needed for determining therapeutic levels of required omega-3 fatty acid supplementation for reducing cardiovascular risk and increasing the efficacy of any therapeutic intervention if the goal is the reduction of both cardiovascular disease and all-cause mortality.

FINANCIAL DISCLOSURES:

Dr. Sears is the President of Zone Labs; a medical food company that produces omega-3 fatty acid concentrates.

REFERENCES

1. Siscovick DS, Barringer TA, Fretts AM, Wu JH, Lichtenstein AH, Costello RB, Kris-Etherton PM, Jacobson TA, Engler MB, Alger HM, Appel LJ, Mozaffarian D; American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease: A Science Advisory From the American Heart Association. *Circulation* 2017 Mar 13. pii: CIR.0000000000000482. doi: 10.1161/CIR.0000000000000482. [Epub ahead of print].
2. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2012; 32: 2045-2051.
3. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol* 2008; 8: 349-361.
4. de Lorgeril M, Renaud S, Mamelle N, Salen P, Martin J-P, Monjaud I, Guidoliet J, Touboul P, Delaye J. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994; 343: 1454-1459.
5. Brenna JT, Salem N, Sinclair AJ, Cunnane SC. Alpha-linolenic acid supplementation and conversion to n-3 long-chain polyunsaturated fatty acids in humans. *Prostaglandins Leukot Essent Fatty Acids* 2009; 80: 85-91.
6. 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. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 2007; 369: 1090-1098.
7. Matsuzaki M, Yokoyama M, Saito Y, Origasa H, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Matsuzawa Y. Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. *Circ J* 2009; 73: 1283-1290.

8. Yamano T, Kubo T, Shiono Y, Shimamura I, Orii M, Tanimoto T, Matsuo Y, Ino Y, Kitabata H, Yamaguchi T, Hirat K, Tanaka A, Imanishi T, Akasaka T. Impact of eicosapentaenoic acid treatment on the fibrous cap thickness in patients with coronary atherosclerotic plaque: an optical coherence tomography study. *J Atheroscler Thromb* 2015; 22: 52-61.
9. Sekikawa A, Steingrimsdottir L, Ueshima H, Shin C, Curb JD, Evans RW, Hauksdottir AM, Kadota A, Choo J, Masaki K, Thorsson B, Launer LJ, Garcia ME, Maegawa H, Willcox BJ, Eiriksdottir G, Fujiyoshi A, Miura K, Harris TB, Kuller LH, Gudnason V. Serum levels of marine-derived n-3 fatty acids in Icelanders, Japanese, Koreans, and Americans--a descriptive epidemiologic study. *Prostaglandins Leukot Essent Fatty Acids* 2012; 87: 11-16.
10. von Schacky C. Omega-3 index and cardiovascular health. *Nutrients* 2014; 6: 799-814.
11. Harris WS, Luo J, Pottala JV, Espeland MA, Margolis KL, Manson JL, Wang H, Brasky TM, Robinson JG. Red blood cell polyunsaturated fatty acids and mortality in the Women's Health Initiative Memory Study. *J Clin Lipidology* 2017; doi.org/10.1016/j.jacl.2016.12.013
12. Endres S, Ghorbani R, Kelley VE, Georgilis K, Lonnemann G, van der Meer JW, Cannon JG, Rogers TS, Klempner MS, Weber PC. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *N Engl J Med* 1989; 320: 265-271.
13. Yee LD, Lester JL, Cole RM, Richardson, JR, Hsu JC, Li Y, Leman A, Belury MA, Clinton SK. Omega-3 fatty acid supplements Fatty acid supplements in women at high risk of breast cancer have dose-dependent effects on breast adipose tissue fatty acid composition. *Amer J Clin Nutr* 2010; 91: 1885-1194.
14. Bonds DE, Harrington M, Worrall BB, Bertoni AG, Eaton CB, Hsia J, Robinson J, Clemons TE, Fine LJ, Chew EY. Effect of long-chain -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: 763-771.
15. Georgiou T, Neokleous A, Nikolaou D, Sears B. Pilot study for treating dry age-related macular degeneration (AMD) with high-dose omega-3 fatty acids. *PharmaNutrition* 2014; 2: 8-11.
16. Ravnskov U, Diamond DM, Harma R, Hamazaki T, Hammarskjold B, Hynes N, McCully KS, Ogushi Y, Okuyama H, Rosch PJ, Schersten T, Sultan S, Sundberg R. Lack of an association or an inverse association between low-density lipoprotein cholesterol and mortality in the elderly. *BMJ Open* 2016; 6: e010401.