

# The use of high-dose omega-3 fatty acids in the management of cardiovascular disease

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ABSTRACT

High-dose omega-3 fatty acids rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can have significant benefits in the management of cardiovascular disease due to their formation of specialized hormones known as resolvins. The appropriate dose can be determined by the ratio of arachidonic acid (AA) to EPA in the blood. This review will summarize the recent data on reducing the AA/EPA ratio and its effects on cardiovascular outcomes.

## Keywords

Omega-3 fatty acids  
Cardiovascular diseases  
Resolvins  
Omega-3 index,  
AA / EPA ratio

## Introduction

Although there has been much research on omega-3 fatty acids, scientific support for their clinical use in the management of cardiovascular conditions remains equivocal at best. This may be the result of the use of less than therapeutic doses in previous studies. For example, a recently published Science Advisory from the American Heart Association (AHA) mildly endorsed the use of omega-3 supplements for the 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, high cardiovascular disease risk, recurrent atrial fibrillation or stroke [1]. It may be that the equivocal results presented in the Science Advisory are the consequence of using potentially placebo doses of omega-3 fatty acids in the cited studies.

## Understanding inflammation

It is well recognized that heart disease is an inflammatory condition [2]. Inflammation has two phases: initiation of the inflammatory response and resolution of the inflammatory

response. Both are active phases that are intimately linked to each other [3]. Omega-3 fatty acids have two distinct mechanisms of action on 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, 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 is highly dose-dependent on the levels of omega-3 fatty acids in the blood. This is why 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 AHA Science Advisory [1].

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.

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### New markers of inflammation

The two best markers for the potential of generating adequate levels of resolvins are the omega-3 index and the ratio of the long-chain omega-6 fatty acid arachidonic acid (AA) to EPA. The omega-3 index (calculated as the sum of the long-chain omega-3 fatty acids docosahexaenoic acid (DHA) and EPA) indicates the levels of the precursors for 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. The lower the AA/EPA ratio, the better the balance between initiation and resolution of inflammation. Either marker may be a better surrogate marker of future cardiovascular disease and mortality than LDL cholesterol. Support for this statement is discussed below.

### Clinical support for high-dose omega-3 fatty acids

The goal of all cardiovascular treatment is to reduce the incidence of cardiovascular disease and ultimately mortality. The most successful cardiovascular study to date has been the Lyon Diet Heart Study [4] which was a secondary prevention trial using supplemental omega-3 fatty acids combined with dietary changes to better reflect the Mediterranean diet. The French participants in the active arm were instructed to consume more vegetables, more fruit and more fish, as well as less meat and less butter than those in a 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, which is a primary constituent of the Mediterranean diet. It should be noted that ALA is slowly converted into EPA, but extremely poorly converted into DHA [5]. Therefore, under this protocol, EPA levels would be expected to increase, but not DHA levels. At the end of 27 months, the all-cause mortality in the active group was reduced by 70%. However, there were no changes in traditional surrogate markers of heart disease such as 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 the AA/EPA ratio. This ratio was reduced from 9.0 in the control group to 6.2 in the active group. This 30% reduction in the AA/EPA ratio appeared to be the only factor that could be correlated with the 70% reduction in all-cause mortality, in addition to a complete eradication of sudden cardiac death

and a 73% reduction in primary cardiovascular end points so strongly stressed in the AHA Science Advisory as for the relative ineffectiveness of omega-3 fatty supplementation in treating cardiovascular conditions. Nothing in the medical literature has since matched the efficacy of the Lyon Diet Heart Study in treating existing heart disease. It should be noted that the Lyon Diet Heart Study results were not mentioned in the AHA Science Advisory [1].

The Lyon Diet Heart Study was published before the introduction of statins. It may be that the efficacy of treatment of heart disease by a reduction in the AA/EPA ratio would be overwhelmed by statins. This was addressed in the JELIS study [6]. 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 3.5 years. The starting AA/EPA ratio in both groups was 1.6 (much lower than the final AA/EPA ratio in the active group in the Lyon Diet Heart Study). The subjects in the JELIS study receiving the additional EPA lowered their AA/EPA ratio to 0.8 during the course of the study, while that in 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 the action of statins and not overwhelmed by them. Subsequent ad hoc analysis of the JELIS data indicated that lowering the AA/EPA ratio was associated with a 38% reduction in sudden cardiac death or fatal/non-fatal myocardial infarction [7]. Another clinical trial has indicated that the AA/EPA ratio is an excellent predictor of the potential rupture of soft vulnerable plaque, which is the primary cause of cardiovascular mortality [8].

The importance of lowering the AA/EPA ratio in preventing cardiovascular mortality was reinforced 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 countries [9]. Data comparing an American with a Japanese population are shown in Table 1.

Parameter	Japan	America
CHD Mortality/100,000	46	160
LDL cholesterol (mg/dL)	132	135
% Smokers	49	8
AA/EPA ratio	2.6	11
AA, arachidonic acid; CHD, coronary heart disease; EPA, eicosapentaenoic acid.		
<b>Table 1 - Comparison of Japanese and American populations</b>		

It is difficult to explain the 70% lower cardiovascular mortality in Japan despite the much higher percentage of smokers and similar LDL cholesterol levels. However, the 74% reduction in the AA/EPA ratio between the two populations does correlate well with the 70% difference in the national cardiovascular mortality rates of the two countries.

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 continuous metabolism of EPA into DHA means that the total omega-3 index will always be at least twice the EPA level. This is confirmed by studies of global populations [10]. 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% of total fatty acids is required for adequate cardiovascular protection [11]. The omega-3 index of the subjects in most studies referenced in the AHA Science Advisory is far lower than required for cardiovascular protection. This point was further emphasized in a recent study of mortality in more than 6,000 postmenopausal American women [12]. Both the omega-3 index and AA/EPA ratio were measured in this population. It was demonstrated that either increasing the omega-3 index or decreasing the AA/EPA ratio was strongly correlated with decreasing all-cause mortality as well as decreasing cardiovascular mortality during a 15-year follow-up period.

High levels of omega-3 supplementation using adequate levels of EPA and DHA are needed to move the omega-3 index or AA/EPA ratio into their target ranges (8–11% for the omega-3 index or 1.5–3 for the AA/EPA ratio) for Americans.

With normal American males, it was demonstrated that 5 g of EPA and DHA per day for a 10-week period was necessary to reduce the AA/EPA ratio from 23 to 2.5 [13]. This level of supplementation was far greater than used in any of the trials quoted in the AHA Science Advisory. Likewise, it has been demonstrated that between 5 and 7.5 g of EPA and DHA are required to reduce the AA/EPA ratio to less than 2 in normal American females [14]. 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 the statement that therapeutic levels of omega-3 fatty acids are required, one trial quoted in the Science Advisory indicated that low levels of EPA and DHA supple-

mentation (1 g per day) had no benefits in the treatment of dry age-related macular degeneration [15]. However, when a much higher omega-3 fatty acid dose (5 g of EPA and DHA per day) was used in another study, significant improvements were demonstrated in dry age-related macular degeneration [16].

## Potential bleeding

Existing data suggest that at least 5 g of EPA and DHA is required to provide significant cardiovascular benefits. Therefore, the question of potential increased bleeding has to be addressed. It is possible that bleeding may be increased if the AA/EPA ratio becomes too low. This was demonstrated in the JELIS study in which there was a slight increase in bleeding in those subjects whose AA/EPA ratio was below 1 compared to those whose ratio was 1.6 after 3.5 years of intervention [6]. Six-month studies in healthy women indicated that there was no increase in bleeding at 7.5 g of EPA and DHA per day as the AA/EPA ratio remained above 1.2 at that dose [14]. Studies have indicated increased intracerebral bleeding if EPA levels are too low or the AA/EPA ratio is too high [17]. Furthermore, other studies indicate that increased bleeding is not observed in studies with or without anti-coagulant therapy [18–20].

## Conclusion

Before the use of higher blood levels of omega-3 fatty acids can be accepted by the cardiovascular community, the current focus on using LDL cholesterol levels as the best surrogate marker for cardiovascular disease progression needs to change. This surrogate marker for future cardiovascular health has become more suspect since it was shown in a recent meta-analysis that LDL cholesterol levels are not correlated with all-cause mortality after age 60 [21].

This suggests that supplementation with low-dose omega-3 fatty acids will not be sufficient to drive the new clinical markers (the omega-3 index or the AA/EPA ratio) into their appropriate therapeutic ranges required to influence the course of cardiovascular disease. An appropriate dose of EPA and DHA to manage cardiovascular disease is likely to be greater than 5 g per day. Maintaining the AA/EPA ratio above 1.5 ensures the lack of potential bleeding and thus allows fine-tuning of the appropriate dose of high-dose omega-3 fatty acids to maintain a therapeutic range in which the resolution of inflammation is enhanced, while at the same reducing the likelihood of any potential bleeding.

In summary, high-dose omega-3 fatty acid supplementation may have great potential in managing cardiovascular disease, but therapeutic doses have to be used.

### Conflict of interest

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

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