Omega-3 Fatty Acid Blood Levels
Clinical Significance and Controversy

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The relationship of fish and dietary omega-3 fatty acids and cardiovascular disease (CVD) has been investigated in numerous studies and comprehensive reviews and recommendations exist, but guidance on blood concentrations is missing.[1–4] Some prospective fish oil treatment investigations report a significant reduction in CVD events but others do not.[5–7] A recent meta-analysis did not find a statistically significant relationship between omega-3 consumption and CVD mortality, but it failed to take into account the implications of variability in individual blood levels of omega-3 fatty acids.[8]

Blood levels of omega-3 fatty acids can be influenced by dietary intake of omega-3 fatty acids and intake with oral supplements. The Multiple Risk Factor Intervention Trial reported in 1995 that serum omega-3 fatty acids blood levels were inversely correlated with coronary heart disease (CHD).[9] An association of dietary sources of nonfried fish and blood levels of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) were reported in the Atherosclerosis Risk In Communities (ARIC) investigation and the Multi-Ethnic Study of Atherosclerosis (MESA) investigations.[10,11]

Blood levels of dietary omega-3 fatty acids can vary based on geography and diet habits. For example, Japanese living in Japan have higher blood omega-3 fatty acid levels than whites living in Pennsylvania and Japanese Americans living in Honolulu. The lower 5th percentile of blood omega-3 fatty acids in the Japanese living in Japan is higher than the mean levels in whites and Japanese Americans even though total fat is comparable.[12]

The purpose of this review is to explore insight derived from clinical investigations reporting blood or plasma levels of omega-3 fatty acids and the relationship to CHD risk that may shed light on the fish oil controversy. A National Library of Medicine PubMed search was conducted with the key words omega-3, coronary artery disease, and blood concentration. One hundred eighty-five citations were identified and reviewed for relevance to coronary atherosclerosis and data on omega-3 supplementation type and dose, duration of treatment, laboratory methodology, cardiovascular associations, and blood, plasma, or serum measurements. Twenty-nine reports were identified for inclusion, and 13 reports using doses of fish oil supplements between 1 and 6.7 g/d were identified (Table 1).

Variability of Individual Blood Level Response to Omega-3 Supplementation

Blood levels of fatty acids can be determined by different laboratory methods. The Red Blood Cell method heats a Red Blood Cell aliquot with boron trifluoride methanol, and the fatty acid methyl esters are extracted and analyzed by gas chromatography. The sum of EPA+DHA, as a percentage of total fatty acids, is referred to as the omega-3 index, and patients have been classified as having a low (high-risk) omega-3 index if the index is <4%. The clinical evidence using the Red Blood Cell method has been reviewed.[40] Chromatography is a laboratory method based on the differential rate of separation of compounds and typically involves plasma lipid extraction and methylated fatty acids analyzed by using a gas chromatograph and a capillary column.[41] Mass spectrometry separation is a third method in which plasma fatty acid concentration is determined by the use of a liquid chromatography mass spectrometric method.[42]

Individual differences in response to a fixed dose of fish oil can vary considerably. This variation makes prediction of an individual patient's blood level response to a specific dose problematic. If the blood level response of a population is normally distributed, ≈68% of the individuals will have a value within 1 standard deviation (SD) of the mean with 16% >1 SD and 16% <1 SD. Figure 1 illustrates EPA blood level ranges (mean±SD) pre- and postdosing in studies for which information is reported. Figures 2 and 3 summarize the pre- and postdosing values for DHA and EPA/arachidonic acid (AA), respectively.

Short-Term Studies

A short-term 48-hour metabolic ward fish oil feeding study in healthy volunteers fed 4 g of fish oil reported that the baseline EPA was 0.54% of phospholipid fatty acids and, at 8 hours, had increased between 62% and 80%.[31] The authors concluded that a large variability in fatty acid blood levels was observed. A slightly longer 28-day fish oil study

Table 1.   Investigations Reporting Plasma, Serum, or Whole Blood Measurements of Omega-3 Fatty Acids

Author (ref)	n	Subjects	Study Method	Sample Type	Findings
Anderson[13]	174	Random population without DM	Follow-up study	Plasma	Omega-3 fatty acids predict CV mortality independent of pulse wave velocity.
Albert[14]	281	Healthy men 17-y follow-up	Observational	Blood	Reduction in sudden death related to EPA+DHA+DSA%
Baylin[15]	3338	MI vs control	Case control genetic study	Plasma	EPA and DHA higher in carriers of *FADS2 T* allele but not related to CHD status.
Chung[11]	900	MESA study	Observational	Blood	EPA and DHA correlated with nonfried fish consumption
DiStasio[16]	36	Healthy subjects	Dosing study	Plasma	1 g/d omega-3 increases blood levels 2- to 3-fold in 1 wk
Donadio[17]	73	IgA nephropathy	Randomized, open label, 2 y, 2 doses 3.35 or 6.70 g/d	Plasma	3.35 g/d increased EPA from 0.8% to 3.6% and DHA from 3.7% to 6.7% 6.7 g/d increased EPA from 0.9% to 4.9% and DHA from 3.5% to 7.4%
Donadio[18]	73	IgA nephropathy	Randomized open label, 2 y, 2 doses 3.35 or 6.70 g/d	Plasma	Omega-3 supplementation slowed the rate of renal loss
Hayakawa[19]	206	Stable angina pectoris	Observational	Plasma	Complex coronary lesions associated with lower plasma EPA/AA
Hogg[20]	96	IgA nephropathy	Randomized, double-blind 12-mo trial	Plasma	Superiority of omega-3 fatty acids over placebo in slowing progression of renal disease
Itakura[5]	16 397	TC >250 mg/dL	JELIS. Low-dose statin, then randomized to omega-3 or not.	Plasma	Coronary event risk reduced when plasma EPA >150 μg/mL or EPA/AA >0.75
Khaw[21]	3841	EPIC-Norfolk	Nested case control	Plasma	Omega-3 plasma fatty acids inversely related to CHD but no longer significant after multivariate adjustment
Laidlaw[22]	31	Healthy women	Randomized trial	Serum	4 g EPA+DHA per day increased omega-3 fatty acids 5.6% to 14.4% fatty acids by weight and the EPA/AA from 0.12 to 0.88
Lockyer[23]	100	Free living	Genetic diet and supplement intervention study	Plasma	Increase in EPA but no difference based on ApoE genotype
Lindberg[24]	254	Acutely ill elderly	Follow-up study	Plasma	Mortality higher in patients with EPA in lowest quartile
Matsuzaki[25]	3664	MI, AP, or PCI with LDL-C >170 mg/dL	JELIS. Low-dose statin, then randomized to omega-3 or not.	Plasma	Cardiac death or MI was significantly lower in the group with the highest EPA/AA ratio vs the lowest ratio
Moyers[26]	992	VA hospital	Observational Heart & Soul Study	Whole blood	EPA+DHA associated with exercise capacity and HR recovery
Mozaffarian[27]	2692	Older healthy	Prospective cohort	Plasma	Omega-3 fatty acids associated with fewer CV events
Nigam[28]	734	Acute coronary syndrome	Observational	Plasma	Metabolic syndrome patients had lower EPA and DHA levels vs those without the metabolic syndrome
Poppitt[29]	95	Ischemic stroke patients	Randomized, double-blind trial omega-3 and CVD and mood	Serum	Following a 30% increase in omega-3 fatty acids for 12 wk, no effect was seen
Porttala[30]	956	CHD in older men, Heart & Soul Study	Observational	Blood	EPA+DHA <3.6% revealed greater mortality *P*=002
Raatz[31]	10	Healthy adults	Randomized, crossover 48-h absorption study	Plasma	Emulsified fish oil had enhanced absorption compared with capsular fish oil
Rupp[32]	11	Healthy	Dosing study	Whole blood	EPA 0.6% to 1.4% within 10 days, DHA 2.9% to >4.3%, after withdrawal returned to baseline in 10 days
Schaeffer[33]	727	German Health Survey	Genetic study	Serum	FADS polymorphisms associated with AA, EPA, and DPA
Shintani[34]	43	JELIS CAD patients with angiography	Abstract 2012 ACC Randomized to EPA or ezetimibe	Blood	Reduction in soft plaque when EPA/AA increased from 0.40 to 1.34
Simon[35]	188 men	Multiple Risk Factor Intervention Trial	Nested case control	Serum	DPA inversely associated with CHD risk
Vedin[36]	16	Alzheimer's disease patients	Genetic study	Plasma	Omega-3 supplementation affects expression of genes influencing inflammation.

(*Continued*)

Table 1.   Continued

Author (ref)	n	Subjects	Study Method	Sample Type	Findings
Virtanen[37]	1857	No CHD, Kuopio Ischaemic Heart Disease Risk Factor Study	Observational	Serum	DHA associated with sudden cardiac death but only in subjects with lower hair mercury content
Virtanen[38]	2174	Kuopio Ischaemic Heart Disease Risk Factor Study	Observational	Serum	DHA associated with reduced AF risk
Wang[2]	2909	Atherosclerosis Risk in Communities Study	Observational	Plasma	Incidence of DM positively associated with palmitic, palmitoleic, and dihomo-g-linolenic acids and inversely with linoleic acid
Wu[39]	3326	Free of CHD and >65 y of age	Observational	Plasma	Higher levels of DHA associated with lower AF risk

AA indicates arachidonic acid; ACC, American College of Cardiology; AF, atrial fibrillation; ApoE, apolipoprotein E; CAD, coronary artery disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DM, diabetes mellitus; DPA, docosapentaenoic acid; DSA, docosapentaenoic acid; EPA, eicosapentaenoic acid; HR, heart rate; IgA, immunoglobulin A; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TC, total cholesterol.

involved 31 healthy subjects who were supplemented with 4 g/d EPA+DHA and mean (±SD) plasma levels of EPA increased from 1.12±0.37% to 6.36±1.47%, and plasma levels of DHA increased from 3.41±0.71% to 6.37±0.62%.[22] If the response is normally distributed, this implies that ≈68% of the subjects would increase the EPA to a range of 4.89% to 7.83% with 16% of the subjects <4.89% and 16% of the subjects >7.83%.

Another short-term 10-day study in 11 subjects fed a lower, and more common clinical dose of 1 g/d EPA, revealed that the blood EPA level increased from approximately 0.6±0.4% to 1.4±0.5% of total fatty acids.[32] The total EPA+DHA blood levels increased from a mean of 3.6% to 5.4%, but ≈16% would have achieved an EPA+DHA blood level <4.8%. Rupp et al[32] have suggested that an EPA+DHA level >3.5% is the range in which sudden coronary death reduction can be observed and a dramatic reduction when EPA+DHA > 5% is achieved. These studies indicated that individual variability in blood levels could leave a substantial number of patients at elevated CHD risk because of failure to achieve a therapeutic blood level.

Intermediate to Long-Term Studies

Longer-term studies range from 2 months to 4 years. In response to a diet supplemented with 6 g/d DHA-enriched fish oil capsule for 8 weeks, DHA rose from ≈4% of total fatty acids to 8.3% with a SD of 4.4%.[23] The effect of 1, 2, and 4 g/d n-3 polyunsaturated fatty acid (PUFA) ethyl esters was reported

in 36 healthy individuals treated for 12 weeks.[16] Plasma n-3 PUFA increased from a mean 5.06 mol% to 10.40±1.70 in the 1 g/d group, 5.67 mol% to 12.11±2.15 in the 2 g/d group, and 5.54 mol% to 16.15±2.08 in the 4 g/d group. The investigators noted individual variability in baseline DHA levels that varied between 1.0 and 6.3 mol%. This study was unique in that blood levels were assessed after 4 weeks of supplement wash out, at which time blood levels had returned close to baseline values.

Intermediate-term studies have been reported in populations with immunoglobulin A nephropathy, ischemic stroke, and Alzheimer's disease. In patients with immunoglobulin A nephropathy, 2 years of treatment with either 3.35 g/d total omega-3 fatty acids increased EPA from 0.8±0.5% to 3.1±1.3% after treatment and increased DHA from 3.7±1.6% to 6.5±1.3%. Treatment with 6.70 g/d total omega-3 fatty acids increased EPA from 0.9±0.6% to 5.2±1.8% and DHA from 3.5±1.4% to 7.1±1.6%.[18] Patients with Alzheimer's disease treated with a lower dose of 2.3 g/d total omega-3 fatty acids increased DHA from ≈4.7±1.8% to 8.1±2.0% after treatment, and EPA increased from ≈2.1±1.5% to 5.3±1.8% after treatment.[36] Finally, in stroke patients treated with a more common clinical dose of 1.2 g/d total omega-3 fatty acids, EPA increased from 1.24±0.91% to 1.63±0.72%, DHA increased from 3.90±1.12% to 5.29±1.31%, and compliance was reported to be 90%.[29] The wide range of blood levels in these studies reflects the substantial individual variability in response to a fixed dose.
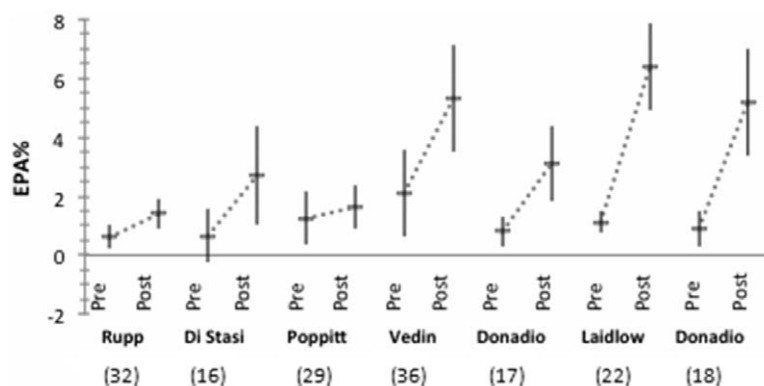

Figure 1. Blood levels (mean±SD) of EPA as a percentage of total fatty acids pre- and postdosing. Data points are identified by author and ranked by daily dose (low to high). Fish oil doses were as follows: Rupp, 1 g/d[32]; Di Stasi, 1 g/d[16]; Poppitt, 1.2 g/d[29]; Vedin, 2.3 g/d[36]; Donadio, 3.35 g/d[17]; Laidlow, 4 g/d[22]; Donadio, 6.7 g/d[18]. EPS indicates eicosapentaenoic acid; and SD, standard deviation.
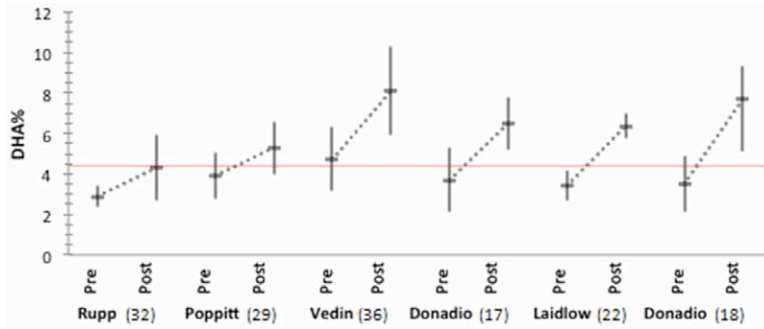
Figure 2. Blood level (mean±SD) of DHA as a percentage of total fatty acids pre- and postdosing. Red line indicates the level, suggested by Wu et al,[39] above which atrial fibrillation risk may be reduced. DHA indicates docosahexaenoic acid; and SD, standard deviation.

EPA/AA Ratio as Therapeutic Goal

The blood EPA/AA ratio may be a clinically relevant measurement and also has substantial individual variability (Figure 3). An EPA/AA ratio >0.75 has been associated with a significantly lower number of major coronary events in a Japanese population.[5] In the 28-day dosing investigation noted above, the mean EPA/AA ratio increased from ≈0.12 to 0.9[22]. Approximately 68% of the subjects would obtain an EPA/AA between 0.78 and 1.02, whereas 16% would be <0.78. Even with 4 g/d omega-3 supplementation, ≈16% of subjects would not have achieved the putative EPA/AA goal.[5] In patients with immunoglobulin A nephropathy, treated with 4 gm/d fish oil, the mean EPA/AA increased from ≈0.09±0.07 to 0.45±0.40 with a wide range of individual variability.[17,18,20] In coronary artery disease (CAD) patients treated with 1.8 g/d EPA, the EPA/AA ratio increased from a mean of 0.40±0.20 to 1.34±0.34 (P<0.001).[34] Finally, in the 4-year Japanese EPA Lipid Intervention Study (JELIS), consumption of 1.8 g/d EPA resulted in an EPA/AA ratio increase from ≈0.6 to 1.3 with a SD of 0.3[25]. These reports indicate that a large segment of the population treated with 2 to 4 g/d fish oil would not achieve the reputedly beneficial goal of EPA/AA >0.75.

Genetic Polymorphisms

Genetic polymorphisms may help to explain part of the observed individual variability in blood levels. Three single-nucleotide polymorphisms in the FADS1 FADS2 gene cluster are related to PUFA proportions in plasma phospholipids.[44] The d-5 and d-6 desaturases, encoded by FADS1 and FADS2 genes, are key enzymes in PUFA metabolism. The C allele of rs174546, in the FADS gene cluster, appears to be associated with high total and high-density lipoprotein cholesterol in subjects with a high dietary intake of n-6 PUFA but not in those with low intake.[45] In subjects with

and without CAD carrying FADS haplotypes, the number of FADS risk alleles appears to be related to CAD risk.[46] Depending on genetic variants, requirements of dietary PUFA intake to achieve comparable biological effects may differ. The consumption of omega-3 fatty acids may also affect the expression of genes that influence inflammatory processes and play a role in CAD risk such as the anaphase-promoting complex subunit 5 (*ANAPC5*) and Ras homolog gene family member B (*RHOB).*

The impact of genetic polymorphisms in the cytochrome P450 system may also have clinical relevance for omega-3 fatty acids in the setting of dual-antiplatelet therapy. The OMEGA-PCI study investigated the effect of adding 1 g of omega-3 ethyl esters in patients treated with aspirin and clopidogrel.[47] The investigators reported that the addition of the omega-3 ethyl ester significantly reduced maximal platelet aggregation by 13.3% (P=0.026). Upon further evaluation, at least 1 loss-of-function variant of CYP2C19*2 was found in 30% of the patients, and, in these patients, maximal platelet aggregation was reduced by 21.4% (P=0.006). There was no difference in platelet aggregation in patients with the 1*/1* variant.

Clinical Implications of Blood Omega-3 Plasma Values

There are at least 3 plasma or blood omega-3 values that appear to have clinical utility in predicting CVD risk or benefit. Values can be reported as an absolute amount in micrograms per milliliter, as a percentage of total fatty acids, or as a ratio such as EPA/AA. Uncertainty remains as to which value is the most clinically relevant for what type of patient, or disorder. This issue is complicated by the fact that various clinical trials have used different populations with different dietary habits, different proportions of omega-3 fatty acid supplements, different doses, and different time lengths of treatment.
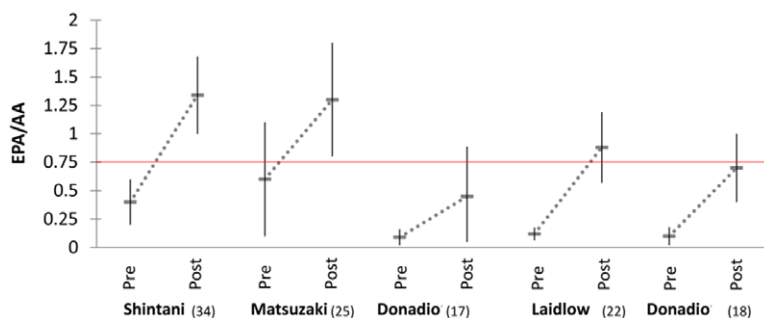

Figure 3. Blood levels (mean±SD) of EPA/AA at baseline and after treatment. Studies are ranked by daily dose low to high. Doses were as follows: Shintani, 1800 mg/d[34]; Matsuzaki, 1800 mg/d[25]; Donadio, 3.5 g/d[17]; Laidlow, 4.0 g/d[22]; Donadio, 6.7 g/d[18]. The red line indicates a risk level suggested by Itakura et al.[5] EPA/AA indicates eicosapentaenoic acid/arachidonic acid; and SD, standard deviation.

Primary Prevention

Determination of omega-3 blood levels appears to help identify high-risk groups in a primary prevention population (Table 2). In the Kuopio Ischaemic Heart Disease Risk Factor study, among the n-3 fatty acids, DHA was most strongly associated with a reduced risk of sudden cardiac death.[37] In a Japanese population (n=15 534), fish oil supplementation (1.8 g/d) did not significantly reduce events in primary prevention patients.[48] However, in the subgroup that achieved plasma EPA concentration >133 μg/mL and an EPA/AA ratio > 0.75, a significant reduction in major coronary events was observed.[5] The investigators suggested an EPA >150 μg/mL and EPA/AA ratio >0.75 as clinical goals for reduced cardiovascular risk in primary prevention. In the Physician Health Study higher blood levels of EPA+DHA+docosapentaenoic acid was associated with a significant reduction (P=0.007) in sudden death from cardiac causes after adjustment for confounders.[14] The lowest quartile of EPA+DHA (<3.45%) indicated high risk, the second quartile (3.46%–4.16%) indicated a 45% reduction in risk, the third quartile (4.17%–4.98%) indicated a 72% reduction in risk, and the fourth quartile (>4.98%) indicated a 81% reduction in risk (EPA+DHA data by communication with the authors). The EPIC-Norfolk prospective study reported that, of the fish oil fatty acids, docosapentaenoic acid was significantly inversely associated with CHD (odds ratio, 0.72; P<0.00001).[21] In an older primary prevention population study of 2692 individuals, and 30 829 person-years, higher plasma levels of omega-3 fatty acids were associated with significantly fewer total and cardiovascular deaths, and individuals in the highest quintile lived an average of 2.2 years more after the age of 65 years.[27] Of the fatty acids, DHA was most strongly associated with fatal CHD and arrhythmic CHD death, illustrating the complexity of fatty acid type and relationship to cardiovascular disease. This study is also of relevance because few other studies have revealed a beneficial effect on mortality in an older population that is related to dietary variables.

Secondary Prevention and Peripheral Vascular Disease

Once CAD is diagnosed, measures of future CVD risk have important prognostic implications. Lower levels of n-3 fatty acids in coronary artery phospholipids have been associated with autopsy-documented CAD.[49] The Alpha Omega Trial reported that a margarine supplemented with 400 mg/d EPA+DHA had no effect on cardiovascular end points in patients with a myocardial infarction history but did not report blood levels.[50] The UCSF Heart and Soul prospective study, conducted in CHD patients, revealed that EPA+DHA levels >3.6% of total fatty acids were significantly associated with reduced all-cause mortality over 5.9 years.[30] Similarly, in Korean acute myocardial infarction patients, an EPA+DHA >4.74% was associated with reduced all-cause and CVD mortality, and a low EPA (<1.26%) was associated with high risk.[51] In JELIS, CHD patients an EPA/AA ratios >1.06 was associated with the lowest cardiac death or myocardial infarction rates, and major coronary events were significantly reduced with EPA treatment (P=0.048).[25,48] In the peripheral artery disease population, EPA supplementation reduced major coronary events 55% in comparison with 18% in the non–peripheral artery disease group, and the number needed to treat was 11 with the blood level of EPA increasing from a mean of 2.8 to 5.6 mol%.[52] Table 3 summarizes fatty acid ranges reported to be associated with risk in secondary prevention populations.

Arteriographically Defined CAD

In postmenopausal CAD women, DHA levels above the median (2.50 mol%) revealed significantly (P=0.009) less

Table 2. Summary of Blood or Plasma Fatty Acids and Ranges Reported to be Associated With Risk by the Investigators in Primary Prevention Populations

Fatty Acid	Range	Risk
EPA		
Itakura[5]	>150 μg/mL	Lower risk (suggested goal)
DHA		
Sekikawa[12]	<1.0%	Highest IMT thickness in US whites
	<4.0%	Highest IMT thickness in Japanese
Virtanen[37]	>2.66%	Reduced SCD risk
Virtanen[38]	>2.85%	Reduced AF risk
Wu[39]	>3.54%	Reduced AF risk
EPA+DHA		
Albert[14]	<3.45%	High risk (lowest quartile)
Sekikawa[12]	>12.3%	Less coronary calcium in Japanese living in Japan
	>6.49%	Less coronary calcium in Japanese Americans
	>5.23%	Less coronary calcium in whites
Sandesara[43]	4.35%	Achieving EPA+DHA level did not prevent post-CABG surgery AF
EPA/AA		
Itakura[5]	>0.75	Lower risk of MCE (suggested goal)

AA indicates arachidonic acid; AF, atrial fibrillation; CABG, coronary artery bypass grafting; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IMT, intima-media thickness; MCE, major coronary event; and SCD, sudden cardiac death.

Table 3. Summary of Blood or Plasma Fatty Acids and Ranges Reported to Be Associated With Risk by the Investigators in Secondary Prevention Populations

Fatty Acid	Range	Risk
EPA		
Lee[40]	<1.26%	High risk
Hayakawa[19]	>111 μg/mL	Least complex coronary lesions
Ishikawa[52]	5.6%	Mean EPA% in treatment group and associated with reduced MCE.
EPA+DHA		
Pottala[30]	>3.6%	Reduced all-cause mortality
Lee[51]	>4.74%	Reduced all cause and CVD mortality
EPA/AA		
Hayakawa[19]	>0.88	Least complex coronary lesions
Matsuzaski[25]	>1.06	Lowest cardiac death or MI

AA indicates arachidonic acid; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MCE, major coronary event; and MI, myocardial infarction.

atherosclerosis progression after 3.2 years of follow-up as determined by quantitative coronary angiography.[53] In patients with stable angina pectoris, an EPA/AA ratio >0.88 has been associated with the least complex lesions.[19] The investigators suggested that the blood EPA/AA ratio is an appropriate target in patients with stable angina pectoris, and an EPA/AA >0.88 was associated with fewer complex coronary lesions.

Plaque Volume

A low serum content of EPA, DHA, and DPA has been associated with percent lipid volume and percent fibrous volume in 116 patients undergoing intravascular ultrasound.[54] In an arteriographic study of 43 patients, change in the EPA/AA ratio was related to a significant reduction in soft plaque volume, and the effect of EPA on plaque volume was independent of low-density lipoprotein cholesterol levels.[34]

Atrial Fibrillation

Studies have assessed the association of omega-3 fatty acids with incident atrial fibrillation (AF) by estimating dietary intake without determining the actual blood levels, and mixed results have been reported.[55–57]

The Kuopio Ischemic Heart Disease Study assessed blood levels of omega-3 fatty acids in 2174 men for 17.7 years and reported that the highest blood levels of DHA+EPA+DPA were associated with a 50% lower risk of AF (P=0.02), and DHA was responsible for this effect.[38] This observation was confirmed in the Cardiovascular Health Study in 3326 US men and women over the age of 65 years who were initially free of AF or heart failure and followed for 14 years and were not taking fish oil supplements.[39] In these older healthy individuals, a DHA level in the 4th quartile (>4.37%) was associated with a significant 23% reduction in AF risk. These 2 studies suggest that it is the specific type of omega-3 fatty acid (DHA) that is associated with reduced AF risk.

Omega-3 fatty acids may be relevant for post–heart surgery AF. Early studies suggested that omega-3 supplementation may have reduced postoperative AF.[58,59] Recent investigations have reported no significant effect of 1 to 6 g/d fish oil several days before surgery, continuing postsurgery for 7 to 10 days, and achieving a mean EPA+DHA of 4.35%.[43,60,61] This suggests that supplementation around the time of heart surgery does not significantly reduce postoperative AF.

Coronary Calcification

The Rotterdam Study reported that fish consumption was correlated with coronary calcium scores.[62] In the Honolulu Heart Study, Japanese living in Japan had 2-fold higher blood levels of omega-3 fatty acids than both whites living in Pennsylvania and Japanese Americans living in Honolulu.[12] The prevalence of coronary artery calcium in Japanese living in Japan was 9.3%, in whites it was 26.1%, and in Japanese Americans it was 31.4%. The highest median EPA+DHA% was associated with the lowest coronary artery calcium prevalence. Although significant differences in coronary artery calcium prevalence between Japanese in Japan and whites was present, these differences became nonsignificant after adjusting for serum omega-3 fatty acid levels.

Carotid Intima-Media Thickness

Estimates of dietary intake of omega-3 fatty acids and nonfried fish have been reported to be inversely related to subclinical atherosclerosis as assessed by carotid intima-media thickness (CIMT) (odds ratio, 0.69; P<0.01).[63] Plasma measurements of omega-3 fatty acids in a cross-sectional study of 487 Swedish men 61 years of age reported that plasma levels of EPA, but not DHA, were inversely associated with carotid and femoral intima-media thickness.[64]

Ethnicity and environment may impact the relevance of omega-3 fatty acid measurements and CIMT. In a study comparing randomly selected Japanese men living in Japan and white American men living in the United States, CIMT correlated with DHA (P=0.032) but not EPA.[65] The Japanese men had 2-fold higher levels of DHA and EPA in comparison with white Americans, but only DHA levels revealed an inverse association with CIMT in both Japanese and white men. In Spanish dyslipidemic patients, the observation of a significant inverse relationship between DHA and CIMT was confirmed.[66]

Conclusions

This review evaluated the evidence studying the relationship between blood levels of omega-3 fatty acids and CVD risk. Individual blood level response to omega-3 oral doses demonstrated significant variability. Study results demonstrated beneficial effects of omega-3 supplementation on CVD risk that appears to be concentrated in subjects who achieved the highest blood levels. This suggests that conclusions regarding the benefit of omega-3 fatty acids, based on studies that did not assess blood levels, may be confusing and misleading because of the inclusion of subjects who did not achieve a therapeutic blood level.[8] For example, in the JELIS investigation, the risk of major coronary events was significantly decreased in the group with high (>150 µg/mL) on-treatment plasma EPA levels, but ≈39% of subjects did not achieve that level despite 1800 mg/d EPA supplementation.[5]

The clinical significance of this information is that (1) there are physiological and genetic reasons for individual variability in blood levels achieved following a fixed dose of fish oil, (2) evidence exists supportive of the concept that the higher the blood level, the greater the effect on atherosclerosis and, owing to individual variability, the blood levels of omega-3 fatty acids may be better markers of CVD risk/benefit than simple assignment to a fixed dose of omega-3 supplementation, and (3) inclusion of subjects achieving less than therapeutic blood levels may have diluted the beneficial effect of omega-3 supplementation on clinical end points. In primary prevention patients, the JELIS study suggests an EPA blood level >133 µg/mL or an EPA/AA ratio >0.75 is most protective (Table 2). In the United States, the Physician Health Study suggests an omega-3 index (EPA+DHA) > 4.17% reflects a 72% reduction in CVD risk.[5,14] The clinical implications in secondary prevention include the UCSF Heart and Soul study that reported an omega-3 index >3.6% is associated with reduced all-cause mortality; in Korean acute myocardial infarction patients an omega-3 index > 4.74% was associated with reduced all cause and CVD mortality; and in Japanese patients, an EPA/AA ratio >1.06 is associated with the lowest

cardiac death or myocardial infarction rates (Table 3).[25,30,51] Determination of blood omega-3 levels may help guide the appropriate use of dietary fish or omega-3 supplements in a personalized heart disease prevention strategy.

Disclosures

Dr Superko is Chief Medical Officer of Celera, a gene discovery company and part of Quest Diagnostics that provides an omega-3 fatty acid blood test. The other authors report no conflicts.

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