The Role of Omega-3 Fatty Acids for the Treatment and Prevention of Cardiovascular Disease

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Disclosures

- Medical Director, Center for Prevention & Wellness, Baptist Health South Florida
- Scientific Advisory Board:
  - Life Extension Foundation
  - Nordic Naturals
- Author:
  - The Great American Heart Hoax
  - Heart Attack Proof
  - The Complete Mediterranean Diet
OBJECTIVES

1 – Discuss the role of omega-3 fatty acids in maintaining cardiometabolic health and reducing residual risk

2 – Cite the clinical trial evidence supporting the use of omega-3 fatty acids in cardiovascular disease prevention

3 – Review the randomized clinical trials currently evaluating the incremental benefit of adding omega-3 fatty acids to statin therapy in high-risk patients with elevated triglycerides
Preventable Causes of Death

Modest consumption of fish or fish oil, together with smoking cessation and regular moderate physical activity, should be among the first-line treatments for prevention of CHD death and sudden cardiac death.
## AHA Recommendations for Omega-3 FA Intake

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without documented CHD</td>
<td>Eat a variety of (preferably oily) fish at least twice a week. Include oils and foods rich in $\alpha$-linolenic acid (flaxseed, canola, and soybean oils; and walnuts)</td>
</tr>
<tr>
<td>Patients with documented CHD</td>
<td>Consume $\sim 1$ g of EPA+DHA per day, preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician</td>
</tr>
<tr>
<td>Patients needing triglyceride lowering</td>
<td>2–4 grams of EPA+DHA per day provided as capsules under a physician’s care</td>
</tr>
</tbody>
</table>

Omega-3 Fatty Acids in Cardiovascular Disease

- Lower triglycerides
- Reduce inflammation
- Lower blood pressure
- Lower resting heart rate
- Improve cardiac diastolic filling
- Increase heart-rate variability
- Increase baroreceptor control
- Reduce the risk of fatal arrhythmias
- Improve insulin sensitivity
- Mildly inhibit platelet function and decrease risk for thrombosis
- Improve endothelial function
- Reduce features of inflammatory atherosclerotic plaque

Raffaele De Caterina, M.D., Ph.D.
Omega-3 Fatty Acids
Onset of Action

• Rapid: n-3 fatty acids cause steric interference with sodium, potassium and calcium channels resulting in an antiarrhythmic effect.

• Slow: incorporating n-3 fatty acids into cell membranes thereby modulating cellular signaling and gene expression resulting in long-acting antiatherogenic and antiinflammatory effects.
Omega-3’s Address the Core Problems of Many Metabolic Disorders

**Metabolic Syndrome**
- Insulin resistance
- High triglyceride levels
- High blood pressure
- Low HDL and High LDL cholesterol
- Excess blood clotting
- Chronic inflammation in fat cells and all tissues

**Omega-3**
- Improves insulin function
- Lowers triglycerides (↓30%)
- Lowers Blood Pressure (slightly)
- ↑HDL; ↑large buoyant LDL
- Improves blood flow and tissue perfusion
- Promotes fat cell fxn / LBM retention (body composition)
- Reduces inflammation in fat cells and all tissues
Omega-3 fatty acids and adipose tissue function in obesity and metabolic syndrome

Abstract:

• The n-3 long-chain polyunsaturated fatty acids (n-3 PUFAs) such as eicosapentaenoic (EPA) and docosahexaenoic (DHA) have been reported to improve obesity-associated metabolic disorders including chronic inflammation, insulin resistance and dyslipidaemia. Growing evidence exits about adipose tissue as a target in mediating the beneficial effects of these marine n-3 PUFAs in adverse metabolic syndrome manifestations. Therefore, in this manuscript we focus in reviewing the current knowledge about effects of marine n-3 PUFAs on adipose tissue metabolism and secretory functions. This scope includes n-3 PUFAs actions on adipogenesis, lipogenesis and lipolysis as well as on fatty acid oxidation and mitochondrial biogenesis. The effects of n-3 PUFAs on adipose tissue glucose uptake and insulin signaling are also summarized. Moreover, the roles of peroxisome proliferator-activated receptor γ (PPARγ) and AMPK activation in mediating n-3 PUFAs actions on adipose tissue functions are discussed. Finally, the mechanisms underlying the ability of n-3 PUFAs to prevent and/or ameliorate adipose tissue inflammation are also revised, focusing on the role of n-3 PUFAs-derived specialized proresolving lipid mediators such as resolvins, protectins and maresins.

Martinez-Fernandez L et al. Prostaglandins and Other Lipid Mediators; Vol 121, 24-41, Sept 2015
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Low-grade inflammation is a key factor for the development of metabolic syndrome.

• Dysfunctional adipose tissue contributes to obesity-associated chronic inflammation.

• Marine n-3 fatty acids can attenuate adipose tissue inflammation and dysfunction.

Martinez-Fernandez L et al. Prostaglandins and Other Lipid Mediators; Vol 121, 24-41, Sept 2015
OMEGA-3 FATTY ACIDS

Triglycerides
Lipoprotein (Sub)Classes

Diameter (nm) vs. Density (g/ml) chart showing the distribution of various lipoprotein subclasses, including Chyomicrons, VLDL, IDL, LDL, HDL2, HDL3, and Lp(a). The chart illustrates the relationship between the size and density of these lipoproteins, with smaller sizes associated with higher densities.
Impact of Triglycerides Beyond LDL-C

PROVE IT: TIMI-22

On-treatment TG 150mg/dL was independently associated with a lower risk of recurrent CHD events, leading support to the concept that achieving lower TG may be an additional consideration beyond low LDL-C in patients with ACS.

ACS=acute coronary syndrome; HR=hazard ratio; MI=myocardial infarction.

Proposed Mechanisms for the Atherogenicity of TG-rich Lipoproteins

LPL = lipoprotein lipase; TRL = triglyceride-rich lipoprotein.
Harris WS, Bulchandani D. Curr Opin Lipidol 2006;17:387-393
Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial.

**BACKGROUND:**
Omega-3 fatty acids in free fatty acid form have enhanced bioavailability, and plasma levels are less influenced by food than for ethyl ester forms.

**OBJECTIVE:**
The aim was to evaluate the safety and lipid-altering efficacy in subjects with severe hypertriglyceridemia of an investigational pharmaceutical omega-3 free fatty acid (OM3-FFA) containing eicosapentaenoic acid and docosahexaenoic acid.

**METHODS:**
This was a multinational, double-blind, randomized, open-patient study. Men and women with triglycerides (TGs) ≥ 500 mg/dL, but <2000 mg/dL, took control (olive oil [OO] 4 g/d; n = 99), OM3-FFA 2 g/d (plus OO 2 g/d; n = 100), OM3-FFA 3 g/d (plus OO 1 g/d; n = 101), or OM3-FFA 4 g/d (n = 99) capsules for 12 weeks in combination with the National Cholesterol Education Program Therapeutic Lifestyle Changes diet.

**RESULTS:**
Fasting serum TGs changed from baseline by -25.9% (P < .01 vs OO), -25.5% (P < .01 vs OO), and -30.9% (P < .001 vs OO) with 2, 3, and 4 g/d OM3-FFA, respectively, compared with -4.3% with OO. Non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol-to-HDL-C ratio, very low-density lipoprotein cholesterol, remnant-like particle cholesterol, apolipoprotein CIII, lipoprotein-associated phospholipase A2, and arachidonic acid were significantly lowered (P < .05 at each OM3-FFA dosage vs OO); and plasma eicosapentaenoic acid and docosahexaenoic acid were significantly elevated (P < .001 at each OM3-FFA dosage vs OO). With OM3-FFA 2 and 4 g/d (but not 3 g/d), low-density lipoprotein cholesterol was significantly increased compared with OO (P < .05 vs OO). High-sensitivity C-reactive protein responses with OM3-FFA did not differ significantly from the OO response at any dosage. Fewer subjects reported any adverse event with OO vs OM3-FFA, but frequencies across dosage groups were similar. Discontinuation due to adverse event, primarily gastrointestinal, ranged from 5% to 7% across OM3-FFA dosage groups vs 0% for OO.

**CONCLUSIONS:**
OM3-FFA achieved the primary end point for TG lowering and secondary end point of non-HDL-C lowering at 2, 3, and 4 g/d in persons with severe hypertriglyceridemia.

Kastelein J et al; J Clin Lipidol; 2014 Jan-Feb;8(1):94-106
Loss-of-Function Mutations in APOC3, Triglycerides, and Coronary Disease

• **BACKGROUND**
  - Plasma triglyceride levels are heritable and are correlated with the risk of coronary heart disease. Sequencing of the protein-coding regions of the human genome (the exome) has the potential to identify rare mutations that have a large effect on phenotype.

• **METHODS**
  - We sequenced the protein-coding regions of 18,666 genes in each of 3734 participants of European or African ancestry in the Exome Sequencing Project. We conducted tests to determine whether rare mutations in coding sequence, individually or in aggregate within a gene, were associated with plasma triglyceride levels. For mutations associated with triglyceride levels, we subsequently evaluated their association with the risk of coronary heart disease in 110,970 persons.

• **RESULTS**
  - An aggregate of rare mutations in the gene encoding apolipoprotein C3 (APOC3) was associated with lower plasma triglyceride levels. Among the four mutations that drove this result, three were loss-of-function mutations: a nonsense mutation (R19X) and two splice-site mutations (IVS2+1G→A and IVS3+1G→T). The fourth was a missense mutation (A43T). Approximately 1 in 150 persons in the study was a heterozygous carrier of at least one of these four mutations. Triglyceride levels in the carriers were 39% lower than levels in noncarriers (P<1×10−20), and circulating levels of APOC3 in carriers were 46% lower than levels in noncarriers (P=8×10−10). The risk of coronary heart disease among 498 carriers of any rare APOC3 mutation was 40% lower than the risk among 110,472 noncarriers (odds ratio, 0.60; 95% confidence interval, 0.47 to 0.75; P=4×10−6).

• **CONCLUSIONS**
  - Rare mutations that disrupt APOC3 function were associated with lower levels of plasma triglycerides and APOC3. Carriers of these mutations were found to have a reduced risk of coronary heart disease.

The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute

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The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute

Omega-3 Ethyl Esters and Lipid Levels in Patients with Triglycerides >500 mg/dL

Baseline (mg/dL)

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<th></th>
<th>TG</th>
<th>HDL-C</th>
<th>Non-HDL-C</th>
<th>Chol</th>
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<th>LDL-C</th>
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<td></td>
<td>816</td>
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<table>
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<tr>
<th></th>
<th>Placebo</th>
<th>Omega-3 Acid Ethyl Esters (4 g/day)</th>
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<tr>
<td></td>
<td>6.7</td>
<td>-45.0</td>
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<tr>
<td></td>
<td>0.0</td>
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<td></td>
<td>9.1</td>
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</tr>
<tr>
<td></td>
<td>-3.6</td>
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<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>-3.6</td>
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<tr>
<td></td>
<td>-13.8</td>
<td>-4.8</td>
</tr>
<tr>
<td></td>
<td>-45.0</td>
<td>45.0</td>
</tr>
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</table>

Median Placebo-Adjusted Change from Baseline for Efficacy End Points (ITT population)

The MARINE Study

COMBination of Prescription Omega-3 With Simvastatin (COMBOS) Study

- N=256 patients receiving a stable dose of a statin (≥8 weeks)
- TG ≥200 mg/dL and ≤500 mg/dL; LDL-C below or within 10% of NCEP ATP III goal
- Multicenter, randomized, double-blind, placebo-controlled, parallel-group study
  - P-OM3 plus simvastatin vs placebo plus simvastatin
- Outcomes
  - Percent change in non—HDL-C from baseline to end of study
- Duration: 8 weeks (after 8-week lead-in)

COMBOS
Primary and Secondary Efficacy Results

Additional changes to baseline simvastatin therapy

*P < .0001 between groups; †P = .0232 between groups; ‡P = .0522 between groups.
Efficacy and Safety of Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Statin-Treated Patients With Persistent High Triglycerides
ANCHOR Study

AMR101 is an ω-3 fatty acid agent containing ≥96% pure icosapent-ethyl, the ethyl ester of eicosapentaenoic acid. The efficacy and safety of AMR101 were evaluated in this phase 3, multicenter, placebo-controlled, randomized, double-blinded, 12-week clinical trial (ANCHOR) in high-risk statin-treated patients with residually high triglyceride (TG) levels (≥200 and <500 mg/dl) despite low-density lipoprotein (LDL) cholesterol control (≥40 and <100 mg/dl). Patients (n = 702) on a stable diet were randomized to AMR101 4 or 2 g/day or placebo. The primary end point was median percent change in TG levels from baseline versus placebo at 12 weeks. AMR101 4 and 2 g/day significantly decreased TG levels by 21.5% (p <0.0001) and 10.1% (p = 0.0005), respectively, and non-high-density lipoprotein (non-HDL) cholesterol by 13.6% (p <0.0001) and 5.5% (p = 0.0054), respectively. AMR101 4 g/day produced greater TG and non-HDL cholesterol decreases in patients with higher-efficacy statin regimens and greater TG decreases in patients with higher baseline TG levels. AMR101 4 g/day decreased LDL cholesterol by 6.2% (p = 0.0067) and decreased apolipoprotein B (9.3%), total cholesterol (12.0%), very-low-density lipoprotein cholesterol (24.4%), lipoprotein-associated phospholipase A2 (19.0%), and high-sensitivity C-reactive protein (22.0%) versus placebo (p <0.001 for all comparisons). AMR101 was generally well tolerated, with safety profiles similar to placebo. In conclusion, AMR101 4 g/day significantly decreased median placebo-adjusted TG, non-HDL cholesterol, LDL cholesterol, apolipoprotein B, total cholesterol, very-low-density lipoprotein cholesterol, lipoprotein-associated phospholipase A2, and high-sensitivity C-reactive protein in statin-treated patients with residual TG elevations.

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Figure 3. Median placebo-adjusted percent change from baseline to week 12 for efficacy end points (intent-to-treat population). *p \textless 0.0001; †p \textless 0.001; ‡p \textless 0.01; §p \textless 0.05. apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; hsCRP...

Christie M. Ballantyne, Harold E. Bays, John J. Kastelein, Evan Stein, Jonathan L. Isaacsohn, Rene A. Braeckman, Paresh N. Soni

**Efficacy and Safety of Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Statin-Treated Patients With Persistent High Triglycerides (from the ANCHOR Study)**


http://dx.doi.org/10.1016/j.amjcard.2012.05.031
Patient subgroup - TG >150mg/dL and HDL <40mg/dL:

Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS)

Atherosclerosis 200 (2008) 135–140

Fig. 3. Effects of EPA on the incidence of MCE for the high TG/low HDL-C group. Hazard ratio and P value adjusted for age, gender, smoking, diabetes, and hypertension. HR, hazard ratio; CI, confidence interval.
Clinical Question

Is there incremental benefit of adding omega-3 fatty acids to high-risk patients with elevated triglycerides who are on optimal statin therapy for LDL-C?
REDUCE-IT

Reduction of CV events with EPA – Intervention Trial

• Multinational, prospective, randomized, double-blind, placebo-controlled study
• Evaluate the effectiveness of AMR 101 in reducing the prevalence of first major cardiovascular events in a high risk patient population
• All patients in the study will be receiving optimized statin therapy. The active arm of the study will involve patients on optimal statin therapy and AMR 101 (4 gm)
• All patients enrolled in the study will have elevated triglyceride levels (>150 mg/dl) and either coronary heart disease or risk factors for coronary heart disease
• Planned enrollment: 8000 patients
• First patient enrolled Dec 2011; planned completion 2017
STRENGTH
Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglycerideridemia

- Randomized, double-blind, placebo-controlled trial
- 13,000 patients with hypertriglycerideridemia (>180 mg/dl and <500 mg/dl) and low HDL and high risk for CVD to be randomized 1:1 to either corn oil + statin or EPA/DHA FFA + statin, once daily, for approximately 3-5 years as determined when the number of MACE outcomes is reached.
OMEGA-3 FATTY ACIDS

HYPERTENSION
Long-Chain Omega-3 Fatty Acids Eicosapentaenoic Acid and Docosahexaenoic Acid and Blood Pressure: A Meta-Analysis of Randomized Controlled Trials

Paige E. Miller, Mary Van Elswyk, and Dominik D. Alexander

BACKGROUND
Although a large body of literature has been devoted to examining the relationship between eicosapentaenoic and docosahexaenoic acids (EPA+DHA) and blood pressure, past systematic reviews have been hampered by narrow inclusion criteria and a limited scope of analytical subgroups. In addition, no meta-analysis to date has captured the substantial volume of randomized controlled trials (RCTs) published in the past 2 years. The objective of this meta-analysis was to examine the effect of EPA+DHA, without upper dose limits and including food sources, on blood pressure in RCTs.

confidence interval (CI) = −2.25 to −0.79) and diastolic blood pressure (−0.99 mm Hg; 95% CI = −1.54 to −0.44) in the meta-analyses of all studies combined. The strongest effects of EPA+DHA were observed among untreated hypertensive subjects (systolic blood pressure = −4.51 mm Hg, 95% CI = −6.12 to −2.83; diastolic blood pressure = −3.05 mm Hg, 95% CI = −4.35 to −1.74), although blood pressure also was lowered among normotensive subjects (systolic blood pressure = −1.25 mm Hg, 95% CI = −2.05 to −0.46; diastolic blood pressure = −0.62 mm Hg, 95% CI = −1.22 to −0.02).

CONCLUSIONS
Overall, available evidence from RCT’s indicates that EPA and DHA reduces systolic and diastolic blood pressure.
Omega-3 EPA and DHA are Effective

<table>
<thead>
<tr>
<th>Lifestyle Intervention</th>
<th>Blood Pressure Reduction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consuming EPA and DHA omega-3s</td>
<td>4.51 mm Hg(^1)</td>
</tr>
<tr>
<td>Reduced dietary sodium</td>
<td>3.6 mm Hg(^6)</td>
</tr>
<tr>
<td>Increased physical activity</td>
<td>4.6 mm Hg(^6)</td>
</tr>
<tr>
<td>Decreased alcohol consumption</td>
<td>3.8 mm Hg(^6)</td>
</tr>
</tbody>
</table>
OMEGA-3 FATTY ACIDS

Cardiac Arrhythmia / Sudden Cardiac Death
Prevention of Sudden Cardiac Death by Dietary Pure ω-3 Polyunsaturated Fatty Acids in Dogs

Abstract

• **Background**—Rat diets high in fish oil have been shown to be protective against ischemia-induced fatal ventricular arrhythmias. Increasing evidence suggests that this may also apply to humans. To confirm the evidence in animals, we tested a concentrate of the free fish-oil fatty acids and found them to be antiarrhythmic. In this study, we tested the pure free fatty acids of the 2 major dietary ω-3 polyunsaturated fatty acids in fish oil: cis-5,8,11,14,17-eicosapentaenoic acid (C20:5ω-3) and cis-4,7,10,13,16,19-docosahexaenoic acid (C22:6ω-3), and the parent ω-3 fatty acid in some vegetable oils, cis-9,12,15-α-linolenic acid (C18:3ω-3), administered intravenously on albumin or a phospholipid emulsion.

• **Methods and Results**—The tests were performed in a dog model of cardiac sudden death. Dogs were prepared with a large anterior wall myocardial infarction produced surgically and an inflatable cuff placed around the left circumflex coronary artery. With the dogs running on a treadmill 1 month after the surgery, occlusion of the left circumflex artery regularly produced ventricular fibrillation in the control tests done 1 week before and after the test, with the ω-3 fatty acids administered intravenously as their pure free fatty acid. With infusion of the eicosapentaenoic acid, 5 of 7 dogs were protected from fatal ventricular arrhythmias (P<0.02). With docosahexaenoic acid, 6 of 8 dogs were protected, and with α-linolenic acid, 6 of 8 dogs were also protected (P<0.004 for each). The before and after control studies performed on the same animal all resulted in fatal ventricular arrhythmias, from which they were defibrillated.

• **Conclusions**—These results indicate that purified ω-3 fatty acids can prevent ischemia-induced ventricular fibrillation in this dog model of sudden cardiac death.

George E. Billman, Jing X. Kang and Alexander Leaf
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George E. Billman, Jing X. Kang and Alexander Leaf
Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest.

OBJECTIVE:
To assess whether the dietary intake of long-chain n-3 polyunsaturated fatty acids from seafood, assessed both directly and indirectly through a biomarker, is associated with a reduced risk of primary cardiac arrest.

DESIGN:
Population-based case-control study.

SETTING:
Seattle and suburban King County, Washington.

PARTICIPANTS:
A total of 334 case patients with primary cardiac arrest, aged 25 to 74 years, attended by paramedics during 1988 to 1994 and 493 population-based control cases and controls, matched for age and sex, randomly identified from the community. All cases and controls were free of prior clinical heart disease, major comorbidity, and use of fish oil supplements.

MEASURES OF EXPOSURE:
Spouses of case patients and control subjects were interviewed to quantify dietary n-3 polyunsaturated fatty acid intake from seafood during the prior month and other clinical characteristics. Blood specimens from 82 cases (collected in the field) and 108 controls were analyzed to determine red blood cell membrane fatty acid composition, a biomarker of dietary n-3 polyunsaturated fatty acid intake.

RESULTS:
Compared with no dietary intake of eicosapentaenoic acid (C20:5n-3) and docosahexaenoic acid (C22:6n-3), an intake of 5.5 g of n-3 fatty acids per month (the mean of the third quartile and the equivalent of one fatty fish meal per week) was associated with a 50% reduction in the risk of primary cardiac arrest (odds ratio [OR], 0.5; 95% confidence interval [CI], 0.4 to 0.8), after adjustment for potential confounding factors. Compared with a red blood cell membrane n-3 polyunsaturated fatty acid level of 3.3% of total fatty acids (the mean of the lowest quartile), a red blood cell n-3 polyunsaturated fatty acid level of 5.0% of total fatty acids (the mean of the third quartile) was associated with a 70% reduction in the risk of primary cardiac arrest.

CONCLUSION:
Dietary intake of n-3 polyunsaturated fatty acids from seafood is associated with a reduced risk of primary cardiac arrest.

Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest.

OBJECTIVE: To assess whether the dietary intake of long-chain n-3 polyunsaturated fatty acids from seafood, assessed both directly and indirectly through a biomarker, is associated with a reduced risk of primary cardiac arrest.

DESIGN: Population-based case-control study.

SETTING: Seattle and suburban King County, Washington.

PARTICIPANTS: A total of 334 case patients with primary cardiac arrest, aged 25 to 74 years, attended by paramedics during 1988 to 1994 and 493 population-based control cases and controls, matched for age and sex, randomly identified from the community. All cases and controls were free of prior clinical heart disease, major comorbidity, and use of fish oil supplements. Spouses of case patients and control subjects were interviewed to quantify dietary n-3 polyunsaturated fatty acid intake from seafood during the prior month and other clinical characteristics. Blood specimens from 82 cases (collected in the field) and 108 controls were analyzed to determine red blood cell membrane fatty acid composition, a biomarker of dietary n-3 polyunsaturated fatty acid intake.

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CONCLUSION: Dietary intake of n-3 polyunsaturated fatty acids from seafood is associated with a reduced risk of primary cardiac arrest.

Risk for Primary Cardiac Arrest and Red Blood Cell EPA+DHA Level

Adapted from Siscovick DS et al. JAMA 1995;274:1363-1367.

Midrange RBC EPA+DHA by Quartile

- 3.0%
- 4.4%
- 5.1%
- 8.2%

90% reduction in risk

*p<0.05 vs Q1
OMEGA-3 FATTY ACIDS

INSULIN RESISTANCE and DIABETES
n–3 Fatty Acids and Cardiovascular Outcomes in Patients with Dysglycemia
The ORIGIN Trial Investigators

• BACKGROUND
  • The use of n–3 fatty acids may prevent cardiovascular events in patients with recent myocardial infarction or heart failure. Their effects in patients with (or at risk for) type 2 diabetes mellitus are unknown.

• METHODS
  • In this double-blind study with a 2-by-2 factorial design, we randomly assigned 12,536 patients who were at high risk for cardiovascular events and had impaired fasting glucose, impaired glucose tolerance, or diabetes to receive a 1-g capsule containing at least 900 mg (90% or more) of ethyl esters of n–3 fatty acids or placebo daily and to receive either insulin glargine or standard care. The primary outcome was death from cardiovascular causes. The results of the comparison between n–3 fatty acids and placebo are reported here.

• RESULTS
  • During a median follow up of 6.2 years, the incidence of the primary outcome was not significantly decreased among patients receiving n–3 fatty acids, as compared with those receiving placebo (574 patients [9.1%] vs. 581 patients [9.3%]; hazard ratio, 0.98; 95% confidence interval [CI], 0.87 to 1.10; P=0.72). The use of n–3 fatty acids also had no significant effect on the rates of major vascular events (1034 patients [16.5%] vs. 1017 patients [16.3%]; hazard ratio, 1.01; 95% CI, 0.93 to 1.10; P=0.81), death from any cause (951 [15.1%] vs. 964 [15.4%]; hazard ratio, 0.98; 95% CI, 0.89 to 1.07; P=0.63), or death from arrhythmia (288 [4.6%] vs. 259 [4.1%]; hazard ratio, 1.10; 95% CI, 0.93 to 1.30; P=0.26). Triglyceride levels were reduced by 14.5 mg per deciliter (0.16 mmol per liter) more among patients receiving n–3 fatty acids than among those receiving placebo (P<0.001), without a significant effect on other lipids. Adverse effects were similar in the two groups.

• CONCLUSIONS
  • Daily supplementation with 1 g of n–3 fatty acids did not reduce the rate of cardiovascular events in patients at high risk for cardiovascular events.
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  Daily supplementation with 1 g of n–3 fatty acids did not reduce the rate of cardiovascular events in patients at high risk for cardiovascular events.
n-3 Fatty Acids in the Treatment of Diabetic Patients

De Caterina R et al.
Diabetes Care April 2007: 30(4): 1012-1026

OM-3:
- Lowers triglycerides
- Improves insulin sensitivity
- Plaque stabilization
- Reduced platelet aggregation
- Improved vascular compliance
Effects of Saturated Fat, Polyunsaturated Fat, Monounsaturated Fat, and Carbohydrate on Glucose-Insulin Homeostasis: A Systematic Review and Meta-analysis of Randomized Controlled Feeding Trials

Abstract

• **Background**
  Effects of major dietary macronutrients on glucose-insulin homeostasis remain controversial and may vary by the clinical measures examined. We aimed to assess how saturated fat (SFA), monounsaturated fat (MUFA), polyunsaturated fat (PUFA), and carbohydrate affect key metrics of glucose-insulin homeostasis.

• **Methods and Findings**
  We systematically searched multiple databases (PubMed, EMBASE, OVID, BIOSIS, Web-of-Knowledge, CAB, CINAHL, Cochrane Library, SIGLE, Faculty1000) for randomised controlled feeding trials published by 26 Nov 2015 that tested effects of macronutrient intake on blood glucose, insulin, HbA1c, insulin sensitivity, and insulin secretion in adults aged ≥18 years. We excluded trials with non-isocaloric comparisons and trials providing dietary advice or supplements rather than meals. Studies were reviewed and data extracted independently in duplicate. Among 6,124 abstracts, 102 trials, including 239 diet arms and 4,220 adults, met eligibility requirements. Using multiple-treatment meta-regression, we estimated dose-response effects of isocaloric replacements between SFA, MUFA, PUFA, and carbohydrate, adjusted for protein, trans fat, and dietary fibre. Replacing 5% energy from carbohydrate with SFA had no significant effect on fasting glucose (+0.02 mmol/L, 95% CI = -0.01, +0.04; n trials = 99), but lowered fasting insulin (-1.1 pmol/L; -1.7, -0.5; n = 90). Replacing carbohydrate with MUFA lowered HbA1c (-0.09%; -0.12, -0.05; n = 23), 2 h post-challenge insulin (-20.3 pmol/L; -32.2, -8.4; n = 11), and homeostasis model assessment for insulin resistance (HOMA-IR) (-2.4%; -4.6, -0.3; n = 30). Replacing carbohydrate with PUFA significantly lowered HbA1c (-0.11%; -0.17, -0.05) and fasting insulin (-1.6 pmol/L; -2.8, -0.4). Replacing SFA with PUFA significantly lowered glucose, HbA1c, C-peptide, and HOMA. Based on gold-standard acute insulin response in ten trials, PUFA significantly improved insulin secretion capacity (+0.5 pmol/L/min; 0.2, 0.8) whether replacing carbohydrate, SFA, or even MUFA. No significant effects of any macronutrient replacements were observed for 2 h post-challenge glucose or insulin sensitivity (minimal-model index). Limitations included a small number of trials for some outcomes and potential issues of blinding, compliance, generalisability, heterogeneity due to unmeasured factors, and publication bias.

• **Conclusions**
  This meta-analysis of randomised controlled feeding trials provides evidence that dietary macronutrients have diverse effects on glucose-insulin homeostasis. In comparison to carbohydrate, SFA, or MUFA, most consistent favourable effects were seen with PUFA, which was linked to improved glycaemia, insulin resistance, and insulin secretion capacity.

Imamura F, Mozaffarian D et al, PLOS 1, July 19, 2016
Effects of Saturated Fat, Polyunsaturated Fat, Monounsaturated Fat, and Carbohydrate on Glucose-Insulin Homeostasis: A Systematic Review and Meta-analysis of Randomized Controlled Feeding Trials

Abstract

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Imamura F, Mozaffarian D et al, PLOS 1, July 19, 2016
OMEGA-3 FATTY ACIDS

Plaque Stabilization and Regression
Comparative Effects of TG-lowering Agents on Cholesterol Domain Formation

Adapted from: Mason RP, Jacob RF. Biochim Biophys Acta. 2015;1848:502-509.
Cellular and Molecular Mechanisms of Atherosclerosis and Effects of O3FA on Early Lesion Development

↑ Antioxidant effects
↓ Cholesterol crystalline domains
↓ Ox-LDL
↓ RLP-C
↑ Improved endothelial function
↓ Adhesion of monocytes
↓ Macrophages
↓ Foam cells

Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomized controlled trial.

Abstract

• **BACKGROUND:**
  N-3 polyunsaturated fatty acids (PUFAs) from oily fish protect against death from cardiovascular disease. We aimed to assess the hypothesis that incorporation of n-3 and n-6 PUFAs into advanced atherosclerotic plaques increases and decreases plaque stability, respectively.

• **METHODS:**
  We did a randomised controlled trial of patients awaiting carotid endarterectomy. We randomly allocated patients control, sunflower oil (n-6), or fish-oil (n-3) capsules until surgery. Primary outcome was plaque morphology indicative of stability or instability, and outcome measures were concentrations of EPA, DHA, and linoleic acid in carotid plaques; plaque morphology; and presence of macrophages in plaques. Analysis was per protocol.

• **FINDINGS:**
  188 patients were enrolled and randomised; 18 withdrew and eight were excluded. Duration of oil treatment was 7-189 days (median 42) and did not differ between groups. The proportions of EPA and DHA were higher in carotid plaque fractions in patients receiving fish oil compared with those receiving control (absolute difference 0.5 [95% CI 0.3-0.7], 0.4 [0.1-0.6], and 0.2 [0.1-0.4] g/100 g total fatty acids for EPA; and 0.3 [0.0-0.8], 0.4 [0.1-0.7], and 0.3 [0.1-0.6] g/100 g total fatty acids for DHA; in plaque phospholipids, cholesteryl esters, and triacylglycerols, respectively). Sunflower oil had little effect on the fatty acid composition of lipid fractions. Fewer plaques from patients being treated with fish oil had thin fibrous caps and signs of inflammation and more plaques had thick fibrous caps and no signs of inflammation, compared with plaques in patients in the control and sunflower oil groups (odds ratio 0.52 [95% CI 0.24-0.89] and 1.19 [1.02-1.57] vs control; 0.49 [0.23-0.90] and 1.16 [1.01-1.53] vs sunflower oil). The number of macrophages in plaques from patients receiving fish oil was lower than in the other two groups. Carotid plaque morphology and infiltration by macrophages did not differ between control and sunflower oil groups.

• **INTERPRETATION:**
  Atherosclerotic plaques readily incorporate n-3 PUFAs from fish-oil supplementation, inducing changes that can enhance stability of atherosclerotic plaques. By contrast, increased consumption of n-6 PUFAs does not affect carotid plaque fatty-acid composition or stability over the time course studied here. Stability of plaques could explain reductions in non-fatal and fatal cardiovascular events associated with increased n-3 PUFA intake.

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Combination Therapy of Eicosapentaenoic Acid and Pitavastatin for Coronary Plaque Regression Evaluated by Intravascular Ultrasonography: A Randomized Controlled Trial

Abstract

- **Introduction:**
  High intensity statin therapy is established for secondary prevention of coronary heart disease (CHD). However, additional therapy is required to reduce residual risk in CHD patients with aggressive lipid-lowering therapy. Eicosapentaenoic acid (EPA) was reported to be beneficial especially in secondary prevention. The aim of this study was to investigate whether coronary plaque regression and stabilization are reinforced by additional administration of EPA to high dose pitavastatin (PTV) therapy.

- **Methods:**
  We enrolled 200 CHD patients who underwent percutaneous coronary intervention in 6 hospitals. Patients were randomly allocated to PTV group (PTV 4 mg/day, n=98) and PTV/EPA group (PTV 4 mg/day and EPA 1800 mg/day, n=102), and prospectively followed for 6 to 8 months. Coronary plaque volume and composition in non-stenting lesion were analyzed by integrated backscatter intravascular ultrasonography at baseline and follow up.

- **Results:**
  EPA / arachidonic acid (AA) ratio was significantly increased in PTV/EPA group compared to PTV group at follow up period. Plaque volume and lipid volume were significantly reduced in PTV/EPA group, but not PTV group. There was a significant inverse correlation between change in EPA/AA ratio and changes in plaque volume (r=-0.332, p<0.001). Plaque regression was defined as percent change in plaque volume more than -14.6% according to previous reports. A multivariate logistic analysis demonstrated that the additional administration of EPA was independently associated with plaque regression after adjustment of confounding factors. The prevalence rate of plaque regression was significantly higher in PTV/EPA group than in PTV group (50% vs. 24%, p<0.001).

- **Conclusions:**
  Additional administration of EPA to high dose PTV therapy significantly reduced coronary plaque volume, suggesting that combination therapy of EPA and PTV might reduce residual risk in CHD patients with aggressive lipid-lowering therapy.

K Ando et al. AHA Scientific Sessions; November 10, 2015
Abstract

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Additional administration of EPA to high dose PTV therapy significantly reduced coronary plaque volume, suggesting that combination therapy of EPA and PTV might reduce residual risk in CHD patients with aggressive lipid-lowering therapy.
Clinical Trials

Primary Prevention of Cardiovascular Disease
US Physicians Health Study

Consumption of at least 1 fish meal per week reduced the risk of sudden cardiac death by 52% compared to those consuming fish once a month.

Nurses Health Study

• 85,000 female nurses free from CVD and cancer were followed for 16 years.

• Higher consumption of fish or omega-3 supplements were associated with lower risk of CHD and CHD death

  *JAMA* 2002;287
Clinical Trials

In 25 studies involving a total of 280,000 participants, there was an inverse association between fish consumption and morbidity or mortality from coronary heart disease.

Importance The role of ω-3 polyunsaturated fatty acids for primary prevention of coronary heart disease (CHD) remains controversial. Most prior longitudinal studies evaluated self-reported consumption rather than biomarkers.

Objective To evaluate biomarkers of seafood-derived eicosapentaenoic acid (EPA; 20:5ω-3), docosapentaenoic acid (DPA; 22:5ω-3), and docosahexaenoic acid (DHA; 22:6ω-3) and plant-derived α-linolenic acid (ALA; 18:3ω-3) for incident CHD.

Data Sources A global consortium of 19 studies identified by November 2014.

Study Selection Available prospective (cohort, nested case-control) or retrospective studies with circulating or tissue ω-3 biomarkers and ascertained CHD.

Data Extraction and Synthesis Each study conducted standardized, individual-level analysis using harmonized models, exposures, outcomes, and covariates. Findings were centrally pooled using random-effects meta-analysis. Heterogeneity was examined by age, sex, race, diabetes, statins, aspirin, ω-6 levels, and FADS desaturase genes.

Main Outcomes and Measures Incident total CHD, fatal CHD, and nonfatal myocardial infarction (MI).

Results The 19 studies comprised 16 countries, 45,637 unique individuals, and 7,973 total CHD, 2,781 fatal CHD, and 7,157 nonfatal MI events, with ω-3 measures in total plasma, phospholipids, cholesterol esters, and adipose tissue. Median age at baseline was 59 years (range, 18-97 years), and 28,660 (62.8%) were male. In continuous (per 1-SD increase) multivariable-adjusted analyses, the ω-3 biomarkers ALA, DPA, and DHA were associated with a lower risk of fatal CHD, with relative risks (RRs) of 0.91 (95% CI, 0.84-0.98) for ALA, 0.90 (95% CI, 0.85-0.96) for DPA, and 0.90 (95% CI, 0.84-0.96) for DHA. Although DPA was associated with a lower risk of total CHD (RR, 0.94; 95% CI, 0.90-0.99), ALA (RR, 1.00; 95% CI, 0.95-1.05), EPA (RR, 0.94; 95% CI, 0.87-1.02), and DHA (RR, 0.95; 95% CI, 0.91-1.00) were not. Significant associations with nonfatal MI were not evident. Associations appeared generally stronger in phospholipids and total plasma. Restricted cubic splines did not identify evidence of nonlinearity in dose responses.

Conclusions and Relevance On the basis of available studies of free-living populations globally, biomarker concentrations of seafood and plant-derived ω-3 fatty acids are associated with a modestly lower incidence of fatal CHD.
ABSTRACT

Importance The role of ω-3 polyunsaturated fatty acids for primary prevention of coronary heart disease (CHD) remains controversial. Most prior longitudinal studies evaluated self-reported consumption rather than biomarkers.

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Conclusion: Biomarker concentrations of seafood and plant-derived ω-3 fatty acids are associated with a modestly lower incidence of fatal CHD.

Del Gobbo L, Mozaffarian et al. JAMA. June 27, 2016
Clinical Trials

Secondary Prevention of Cardiovascular Disease
DART

- Diet and Reinfarction Trial (DART) in men post MI, omega-3 PUFA (either from oily fish or fish oil capsules) reduced 20 year all-cause mortality by 29% (mainly due to a reduction in CHD mortality).

GISSI Prevenzione Trial

- Randomized 11,323 post MI patients with 1 capsule of 850 mg EPA/DHA versus customary care.
- After one year, patients taking the fish oil had a 21% reduction in total mortality and a 30% reduction in CV mortality. In addition, there was a highly significant 45% reduction in sudden cardiac death (SCD) after only 4 months.

Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomized open-label, blinded endpoint analysis.

Abstract

BACKGROUND:
Epidemiological and clinical evidence suggests that an increased intake of long-chain n-3 fatty acids protects against mortality from coronary artery disease. We aimed to test the hypothesis that long-term use of eicosapentaenoic acid (EPA) is effective for prevention of major coronary events in hypercholesterolaemic patients in Japan who consume a large amount of fish.

METHODS:
18,645 patients with a total cholesterol of 6.5 mmol/L or greater were recruited from local physicians throughout Japan between 1996 and 1999. Patients were randomly assigned to receive either 1800 mg of EPA daily with statin (EPA group; n=9326) or statin only (controls; n=9319) with a 5-year follow-up. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. Analysis was by intention-to-treat. The study was registered at ClinicalTrials.gov, number

FINDINGS:
At mean follow-up of 4.6 years, we detected the primary endpoint in 262 (2.8%) patients in the EPA group and 324 (3.5%) in controls-a 19% relative reduction in major coronary events (p=0.011). Post-treatment LDL cholesterol concentrations decreased 25%, from 4.7 mmol/L in both groups. Serum LDL cholesterol was not a significant factor in a reduction of risk for major coronary events. Unstable angina and non-fatal coronary events were also significantly reduced in the EPA group. Sudden cardiac death and coronary death did not differ between groups. In patients with a history of coronary artery disease who were given EPA treatment, major coronary events were reduced by 19% (secondary prevention subgroup: 158 [8.7%] in the EPA group vs 197 [10.7%] in the control group; p=0.048). In patients with no history of coronary artery disease, EPA treatment reduced major coronary events by 18%, but this finding was not significant (104 [1.4%] in the EPA group vs 127 [1.7%] in the control group; p=0.132).

INTERPRETATION:
EPA is a promising treatment for prevention of major coronary events, and especially non-fatal coronary events, in Japanese hypercholesterolaemic patients.

Yokoyama M et al; Lancet, 2007 Mar 31;369(9567):1090-8
Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis.

Abstract

BACKGROUND: Epidemiological and clinical evidence suggests that an increased intake of long-chain n-3 fatty acids protects against mortality from coronary artery disease. We aimed to test the hypothesis that long-term use of eicosapentaenoic acid (EPA) is effective for prevention of major coronary events in hypercholesterolaemic patients in Japan who consume a large amount of fish.

METHODS: 18,645 patients with a total cholesterol of 6.5 mmol/L or greater were recruited from local physicians throughout Japan between 1996 and 1999. Patients were randomly assigned to receive either 1800 mg of EPA daily with statin (EPA group; n=9326) or statin only (controls; n=9319) with a 5-year follow-up. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. Analysis was by intention-to-treat. The study was registered at ClinicalTrials.gov, number

FINDINGS: At mean follow-up of 4.6 years, we detected the primary endpoint in 262 (2.8%) patients in the EPA group and 324 (3.5%) in controls—a 19% relative reduction in major coronary events (p=0.011). Post-treatment LDL cholesterol concentrations decreased 25%, from 4.7 mmol/L in both groups. Serum LDL cholesterol was not a significant factor in a reduction of risk for major coronary events. Unstable angina and non-fatal coronary events were also significantly reduced in the EPA group. Sudden cardiac death and coronary death did not differ between groups. In patients with a history of coronary artery disease who were given EPA treatment, major coronary events were reduced by 19% (secondary prevention subgroup: 158 [8.7%] in the EPA group vs 197 [10.7%] in the control group; p=0.048). In patients with no history of coronary artery disease, EPA treatment reduced major coronary events by 18%, but this finding was not significant (104 [1.4%] in the EPA group vs 127 [1.7%] in the control group; p=0.132).

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Yokoyama M et al; Lancet, 2007 Mar 31;369(9567):1090-8
18,645 Japanese men and women randomized to statin alone or statin + EPA (Epadel) and followed for 5 years

Yokoyama M. The Lancet 2007

JELIS study: Ethyl-EPA reduces Coronary Events

Years

Cumulative Incidence of Major Coronary Events (%)

Control (statin)
EPA (statin+Epadel)

-19% (p=0.011)
Omega-3

Controversial Clinical Trials
n-3 fatty acids and cardiovascular events after myocardial infarction
Alpha Omega Study Group

• BACKGROUND:
Results from prospective cohort studies and randomized, controlled trials have provided evidence of a protective effect of n-3 fatty acids against cardiovascular diseases. We examined the effect of the marine n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and of the plant-derived alpha-linolenic acid (ALA) on the rate of cardiovascular events among patients who have had a myocardial infarction.

• METHODS:
In a multicenter, double-blind, placebo-controlled trial, we randomly assigned 4837 patients, 60 through 80 years of age (78% men), who had had a myocardial infarction and were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy to receive for 40 months one of four trial margarines: a margarine supplemented with a combination of EPA and DHA (with a targeted additional daily intake of 400 mg of EPA-DHA), a margarine supplemented with ALA (with a targeted additional daily intake of 2 g of ALA), a margarine supplemented with EPA-DHA and ALA, or a placebo margarine. The primary end point was the rate of major cardiovascular events, which comprised fatal and nonfatal cardiovascular events and cardiac interventions. Data were analyzed according to the intention-to-treat principle, with the use of Cox proportional-hazards models.

• RESULTS:
The patients consumed, on average, 18.8 g of margarine per day, which resulted in additional intakes of 226 mg of EPA combined with 150 mg of DHA, 1.9 g of ALA, or both, in the active-treatment groups. During the follow-up period, a major cardiovascular event occurred in 671 patients (13.9%). Neither EPA-DHA nor ALA reduced this primary end point (hazard ratio with EPA-DHA, 1.01; 95% confidence interval [CI], 0.87 to 1.17; P=0.93; hazard ratio with ALA, 0.91; 95% CI, 0.78 to 1.05; P=0.20). In the prespecified subgroup of women, ALA, as compared with placebo and EPA-DHA alone, was associated with a reduction in the rate of major cardiovascular events that approached significance (hazard ratio, 0.73; 95% CI, 0.51 to 1.03; P=0.07). The rate of adverse events did not differ significantly among the study groups.

• CONCLUSIONS:
Low-dose supplementation with EPA-DHA or ALA did not significantly reduce the rate of major cardiovascular events among patients who had had a myocardial infarction and who were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy.

n-3 fatty acids and cardiovascular events after myocardial infarction
Alpha Omega Study Group

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• CONCLUSION:
Low-dose supplementation with EPA-DHA or ALA did not significantly reduce the rate of major cardiovascular events among patients who had had a myocardial infarction and who were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy.

Critique of ΑΩ Trial

• Only 378 mg EPA+DHA given
• Median background EPA+DHA intake was 130 mg/d (median in US is 20 mg/d)
• Duration of study: 40 months
• All subjects were received state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy.
• Subgroup analyses in patients with diabetes* and in those not on statins** were positive

Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events: A Systematic Review and Meta-analysis

- **Context** Considerable controversy exists regarding the association of omega-3 polyunsaturated fatty acids (PUFAs) and major cardiovascular end points.

- **Objective** To assess the role of omega-3 supplementation on major cardiovascular outcomes.

- **Study Selection** Randomized clinical trials evaluating the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke.

- **Data Extraction** Descriptive and quantitative information was extracted; absolute and relative risk (RR) estimates were synthesized under a random-effects model. Heterogeneity was assessed using the Q statistic and $I^2$. Subgroup analyses were performed for the presence of blinding, the prevention settings, and patients with implantable cardioverter-defibrillators, and meta-regression analyses were performed for the omega-3 dose. A statistical significance threshold of .0063 was assumed after adjustment for multiple comparisons.

- **Data Synthesis** Of the 3635 citations retrieved, 20 studies of 68,680 patients were included, reporting 7044 deaths, 3993 cardiac deaths, 1150 sudden deaths, 1837 myocardial infarctions, and 1490 strokes. No statistically significant association was observed with all-cause mortality (RR, 0.96; 95% CI, 0.91 to 1.02; risk reduction [RD] −0.004, 95% CI, −0.01 to 0.02), cardiac death (RR, 0.91; 95% CI, 0.85 to 0.98; RD, −0.01; 95% CI, −0.02 to 0.00), sudden death (RR, 0.87; 95% CI, 0.75 to 1.01; RD, −0.003; 95% CI, −0.012 to 0.006), myocardial infarction (RR, 0.89; 95% CI, 0.76 to 1.04; RD, −0.002; 95% CI, −0.007 to 0.002), and stroke (RR, 1.05; 95% CI, 0.93 to 1.18; RD, 0.001; 95% CI, −0.002 to 0.004) when all supplement studies were considered.

- **Conclusion:** Omega-3 PUFA supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke based on relative and absolute measures of association.

Evangelos C. Rizos, MD, PhD, et al

*JAMA.* 2012;308(10):1024-1033
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Evangelos C. Rizos, MD, PhD, et al

*JAMA.* 2012;308(10):1024-1033
Meta-Analysis of Omega-3 Supplementation Studies (including open label trials)

Figure 5. Cumulative Meta-analysis of the Omega-3 Supplements for All-Cause Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Cumulative Sample Size</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacks et al., 1995</td>
<td>59</td>
<td>0.30 (0.01-7.13)</td>
</tr>
<tr>
<td>Leng et al., 1996</td>
<td>179</td>
<td>0.79 (0.20-3.20)</td>
</tr>
<tr>
<td>Marchioli et al., 1999</td>
<td>11,503</td>
<td>0.86 (0.77-0.97)</td>
</tr>
<tr>
<td>von Schacky et al., 1999</td>
<td>11,726</td>
<td>0.86 (0.77-0.97)</td>
</tr>
<tr>
<td>Nilsen et al., 2001</td>
<td>12,326</td>
<td>0.87 (0.77-0.97)</td>
</tr>
<tr>
<td>Leaf et al., 2005</td>
<td>12,726</td>
<td>0.87 (0.78-0.98)</td>
</tr>
<tr>
<td>Raitt et al., 2005</td>
<td>12,928</td>
<td>0.87 (0.77-0.97)</td>
</tr>
<tr>
<td>Brouwer et al., 2006</td>
<td>13,474</td>
<td>0.86 (0.77-0.97)</td>
</tr>
<tr>
<td>Svensson et al., 2006</td>
<td>13,680</td>
<td>0.87 (0.78-0.97)</td>
</tr>
<tr>
<td>Yokoyama et al., 2007</td>
<td>32,325</td>
<td>0.94 (0.84-1.06)</td>
</tr>
<tr>
<td>Tavazzi et al., 2008</td>
<td>39,300</td>
<td>0.94 (0.88-0.99)</td>
</tr>
<tr>
<td>Garbagnati et al., 2009</td>
<td>39,338</td>
<td>0.94 (0.87-1.00)</td>
</tr>
<tr>
<td>Kromhout et al., 2010</td>
<td>44,175</td>
<td>0.94 (0.89-1.00)</td>
</tr>
<tr>
<td>Einvik et al., 2010</td>
<td>44,738</td>
<td>0.94 (0.88-1.01)</td>
</tr>
<tr>
<td>Rauch et al., 2010</td>
<td>48,542</td>
<td>0.96 (0.88-1.04)</td>
</tr>
<tr>
<td>Galan et al., 2010</td>
<td>50,743</td>
<td>0.96 (0.89-1.03)</td>
</tr>
<tr>
<td>ORIGIN, 2012</td>
<td>63,279</td>
<td>0.96 (0.91-1.02)</td>
</tr>
</tbody>
</table>

Rizos et al. Meta-Analysis of Omega-3 Supplementation Studies (including open label trials)

Critical level set at $p=0.006$ to control for multiple comparisons
Too conservative for a safe agent?

Rizos E et al. *JAMA* 2012;308:1024-1032. (Sept 11)
Omega-3 and the Risk of Stroke

Nurses Health Study

- Significant inverse association between omega-3 fatty intake from fish or fish oil supplements and risk of stroke, primarily thrombotic infarction
- 50% reduction in stroke if fish 2x/week

JAMA 2001;285
The Relationship Between Fish Consumption and Stroke Incidence: The NHANES I Epidemiologic Follow-up Study

- **Objective:** To assess the level of fish consumption as a risk factor for stroke.

- **Methods:** Participants were members of the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study, a longitudinal cohort study of a national sample. Included in this analysis were white and black women and men aged 45 to 74 years when examined in 1971 through 1975 who did not report a history of stroke at that time. Average follow-up for survivors was 12 years (maximum, 16 years). The main outcome measure was incident stroke (fatal and nonfatal). Fish consumption at baseline was obtained from a 3-month food frequency questionnaire.

- **Results:** White women aged 45 to 74 years who consumed fish more than once a week had an age-adjusted risk of stroke incidence only about half that of women who never consumed fish. This effect persisted after controlling for multiple stroke risk variables (relative risk, 0.55; 95% confidence interval [CI], 0.32 to 0.93). Fish consumption more than once a week compared with never was not associated with age-adjusted stroke risk in white men aged 45 to 74 years (relative risk, 0.85; 95% CI, 0.49 to 1.46). In black women and men combined aged 45 to 74 years, any fish consumption compared with never was significantly associated with reduced adjusted stroke risk (relative risk, 0.51; 95% CI, 0.30 to 0.88).

- **Conclusions:** White women who consumed fish more than once a week had significantly lower stroke incidence than those who never consumed fish. A similar protective effect was seen in black women and men combined. Further studies are needed to confirm these findings and to elucidate mechanisms for the effect of fish consumption on stroke incidence.

Gillum R, MD et al; *Arch Intern Med.* 1996;156(5):537-542
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The GISSI-HF trial
Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure: a randomised, double-blind, placebo-controlled trial.

Abstract

**BACKGROUND:**
Several epidemiological and experimental studies suggest that n-3 polyunsaturated fatty acids (PUFA) can exert favourable effects on atherothrombotic cardiovascular disease, including arrhythmias. We investigated whether n-3 PUFA could improve morbidity and mortality in a large population of patients with symptomatic heart failure of any cause.

**METHODS:**
We undertook a randomised, double-blind, placebo-controlled trial in 326 cardiology and 31 internal medicine centres in Italy. We enrolled patients with chronic heart failure of New York Heart Association class II-IV, irrespective of cause and left ventricular ejection fraction, and randomly assigned them to n-3 PUFA 1 g daily (n=3494) or placebo (n=3481) by a concealed, computerised telephone randomisation system. Patients were followed up for a median of 3.9 years (IQR 3.0-4.5). Primary endpoints were time to death, and time to death or admission to hospital for cardiovascular reasons. Analysis was by intention to treat.

**FINDINGS:**
We analysed all randomised patients. 955 (27%) patients died from any cause in the n-3 PUFA group and 1014 (29%) in the placebo group (adjusted hazard ratio [HR] 0.91 [95.5% CI 0.833-0.998], p=0.041). 1981 (57%) patients in the n-3 PUFA group and 2053 (59%) in the placebo group died or were admitted to hospital for cardiovascular reasons (adjusted HR 0.92 [99% CI 0.849-0.999], p=0.009). In absolute terms, 56 patients needed to be treated for a median duration of 3.9 years to avoid one death or 44 to avoid one event like death or admission to hospital for cardiovascular reasons. In both groups, gastrointestinal disorders were the most frequent adverse reaction (96 [3%] n-3 PUFA group vs 92 [3%] placebo group).

**INTERPRETATION:**
A simple and safe treatment with n-3 PUFA can provide a small beneficial advantage in terms of mortality and admission to hospital for cardiovascular reasons in patients with heart failure in a context of usual care.

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Omega-3

Should we measure?
Relative Risk of Sudden Cardiac Death and Blood Omega-3 Levels - *Physicians' Health Study*

Blood Omega-3 and Trans Fatty Acids in Middle-Aged Acute Coronary Syndrome Patients

We tested the hypothesis that lower blood omega-3 (ω-3) fatty acids (FAs) and/or higher trans FAs are associated with the risk of an acute coronary syndrome (ACS). Higher levels of ω-3 FA have been associated with decreased risk of sudden cardiac death. However, their association with ACS risk is unclear. Although higher self-reported intakes of trans FAs have been linked to increased coronary risk, the association between blood levels of trans FA and ACS risk is also unknown. We analyzed the FA composition of whole blood from 94 subjects with ACS and 94 age-, gender-, and race-matched controls. Omega-3 and trans FA associations with ACS were assessed using multivariable models after adjusting for smoking status, alcohol use, diabetes, body mass index, serum lipids, and history of myocardial infarction or revascularization. Subjects' mean age was 47 years, 54% were men, and 80% were Caucasian. Whole blood long-chain ω-3 FA content (eicosapentaenoic acid [EPA] plus docosahexaenoic acid [DHA]) was 29% lower in patients than in controls (1.7 ± 0.9% vs 2.4 ± 1.4%, p <0.001), whereas trans FA content was not different (2.1 ± 0.7% vs 2.0 ± 0.9%, p = NS). The multivariable-adjusted odds for case status was 0.67 (95% confidence interval 0.46 to 0.98) for a 1 SD increase in blood EPA + DHA. The inclusion of trans FAs in the EPA + DHA model did not alter this association. In conclusion, low blood EPA + DHA content is an independent predictor of increased risk for ACS, but higher blood trans FA content is not. Blood EPA + DHA may serve as a new, modifiable risk factor for ACS.

Blood EPA and DHA predict all-cause mortality in patients with stable coronary heart disease: The Heart and Soul study.

- **Abstract**

  **BACKGROUND:**
  Omega-3 fatty acid (n-3 FA) blood levels and intake have been inversely associated with risk for sudden cardiac death, but their relationship with all-cause mortality is unclear. The purpose of this study was to determine the extent to which baseline blood n-3 FA levels are associated with reduced risk for all-cause mortality in patients with stable coronary heart disease.

  **METHODS AND RESULTS:**
  The Heart and Soul study used a prospective cohort design with a median follow-up of 5.9 years. Patients were recruited between 2000 and 2002 from 12 outpatient facilities in the San Francisco Bay Area. Standard cardiovascular risk factors, demographics, socioeconomic status, health behaviors, and inflammatory markers were collected at baseline. Fasting blood levels of eicosapentaenoic and docosahexaenoic acids were measured and expressed as a percent of total blood FAs. Vital status was assessed with annual telephone interviews and confirmed by review of death certificates. There were 237 deaths among 956 patients. Cox proportional hazards models were used to evaluate the extent to which blood eicosapentaenoic and docosahexaenoic acids were independently associated with all cause mortality. Compared with patients having baseline eicosapentaenoic and docosahexaenoic acids levels below the median (<3.6%), those at or above the median had a 27% decreased risk of death (hazard ratio, 0.73; 95% confidence interval, 0.56-0.94). This association was unaffected by adjustment for age, sex, ethnicity, center, socioeconomic status, traditional cardiovascular risk factors, and inflammatory markers (hazard ratio, 0.74; 95% confidence interval, 0.55-1.00, P<0.05).

  **CONCLUSIONS:**
  In these outpatients with stable coronary heart disease, blood n-3 FA levels were inversely associated with total mortality independent of standard and emerging risk factors, suggesting that reduced tissue n-3 FA levels may adversely impact metabolism.

Blood EPA and DHA predict all-cause mortality in patients with stable coronary heart disease:

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CONCLUSIONS:
In these outpatients with stable coronary heart disease, blood n-3 FA levels were inversely associated with total mortality independent of standard and emerging risk factors, suggesting that reduced tissue n-3 FA levels may adversely impact metabolism.

Tissue availability of polyunsaturated fatty acids (PUFAs) depends on dietary intake and metabolic turnover and has a major impact on human health. Strong associations between variants in the human genes fatty acid desaturase 1 (FADS1, encoding Delta-5 desaturase) and fatty acid desaturase 2 (FADS2, encoding Delta-6 desaturase) and blood levels of PUFAs and long-chain PUFAs (LC-PUFAs) have been reported. The most significant associations and the highest proportion of genetically explained variability (28%) were found for arachidonic acid (20:4n-6), the main precursor of eicosanoids. Subjects carrying the minor alleles of several single nucleotide polymorphisms had a lower prevalence of allergic rhinitis and atopic eczema. Therefore, blood levels of PUFAs are influenced not only by diet, but to a large extent also by genetic variants common in a European population. These findings have been replicated in independent populations. Depending on genetic variants, requirements of dietary PUFA or LC-PUFA intakes to achieve comparable biological effects may differ. We recommend including analyses of FADS1 and FADS2 polymorphism in future cohort and intervention studies addressing biological effects of PUFAs and LC-PUFAs.

Cardiovascular benefits of omega-3 fatty acids

Abstract

- Cardiac societies recommend the intake of 1 g/day of the two omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for cardiovascular disease prevention, treatment after a myocardial infarction, prevention of sudden death, and secondary prevention of cardiovascular disease. These recommendations are based on a body of scientific evidence that encompasses literally thousands of publications. Of four large scale intervention studies three also support the recommendations of these cardiac societies. One methodologically questionable study with a negative result led a Cochrane meta-analysis to a null conclusion. This null conclusion, however, has not swayed the recommendations of the cardiac societies mentioned, and has been refuted with good reason by scientific societies.

- Based on the scientific evidence just mentioned, we propose a new risk factor to be considered for sudden cardiac death, the omega-3 index. It is measured in red blood cells, and is expressed as a percentage of EPA + DHA of total fatty acids. An omega-3 index of >8% is associated with 90% less risk for sudden cardiac death, as compared to an omega-3 index of <4%. The omega-3 index as a risk factor for sudden cardiac death has striking similarities to LDL as a risk factor for coronary artery disease. Moreover, the omega-3 index reflects the omega-3 fatty acid status of a given individual (analogous to HbA1c reflecting glucose homeostasis). The omega-3 index can therefore be used as a goal for treatment with EPA and DHA. As is the case now for LDL, in the future, the cardiac societies might very well recommend treatment with EPA and DHA to become goal oriented (e.g. an omega-3 index>8%)

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Association of Marine Omega-3 Fatty Acid Levels With Telomeric Aging in Patients With Coronary Heart Disease

• **Context**
  Increased dietary intake of marine omega-3 fatty acids is associated with prolonged survival in patients with coronary heart disease. However, the mechanisms underlying this protective effect are poorly understood.

• **Objective**
  To investigate the association of omega-3 fatty acid blood levels with temporal changes in telomere length, an emerging marker of biological age.

• **Design, Setting, and Participants**
  Prospective cohort study of 608 ambulatory outpatients in California with stable coronary artery disease recruited from the Heart and Soul Study between September 2000 and December 2002 and followed up to January 2009 (median, 6.0 years; range, 5.0-8.1 years).

• **Main Outcome Measures**
  We measured leukocyte telomere length at baseline and again after 5 years of follow-up. Multivariable linear and logistic regression models were used to investigate the association of baseline levels of omega-3 fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) with subsequent change in telomere length.

• **Results**
  Individuals in the lowest quartile of DHA3EPA experienced the fastest rate of telomere shortening (0.13 telomere-to-single-copy gene ratio [T/S] units over 5 years; 95% confidence interval [CI], 0.09-0.17), whereas those in the highest quartile experienced the slowest rate of telomere shortening (0.05 T/S units over 5 years; 95% CI, 0.02-0.08; \( P < .001 \) for linear trend across quartiles). Levels of DHA+EPA were associated with less telomere shortening before (unadjusted \( \beta \) coefficient \( \times 10^{-3} = 0.06; \) 95% CI, 0.02-0.10) and after (adjusted \( \beta \) coefficient \( \times 10^{-3} = 0.05; \) 95% CI, 0.01-0.08) sequential adjustment for established risk factors and potential confounders. Each 1-SD increase in DHA+EPA levels was associated with a 32% reduction in the odds of telomere shortening (adjusted odds ratio, 0.68; 95% CI, 0.47-0.98).

• **Conclusion**
  Among this cohort of patients with coronary artery disease, there was an inverse relationship between baseline blood levels of marine omega-3 fatty acids and the rate of telomere shortening over 5 years.

Harris W et al. JAMA; JAN 20, 2010:303 (3), 250
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Conclusions

• The vast majority of clinical trial evidence supports the use of omega-3 fatty acids to lower CVD risk factors, reduce residual risk and lower major adverse cardiovascular events

• Omega-3 blood levels vary widely due to differences in intake and genetics

• Clinical studies have demonstrated the importance of measuring omega-3 blood levels and suggest that low omega-3 levels can potentially serve as a modifiable CVD risk factor