The Role of Omega-3 Fatty Acids in Cardiovascular Disease Prevention

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Disclosures

Consultant:
- Bristol Myers Squibb
- Pfizer
- Boehringer-Ingelheim
- Amgen
- Sanofi
- Regeneron
- Amarin Pharma
- Upsher Smith
- Kowa Pharma
- DSM

Speakers’ Bureau:
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Fish Oil in Cardiovascular Prevention

Fish oil is a *whale* of a story that not surprisingly gets *bigger* with every telling.

### Daily Intake

<table>
<thead>
<tr>
<th></th>
<th>Moderns</th>
<th>Foragers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>200-300 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>Fats</td>
<td>30%</td>
<td>35%</td>
</tr>
<tr>
<td>Saturated Fats</td>
<td>14%</td>
<td>7%</td>
</tr>
<tr>
<td>Omega-3</td>
<td>110 mg</td>
<td>660 – 3000 mg</td>
</tr>
</tbody>
</table>

### Norway: Exceptional Life Expectancy

Obtained from Internet

### Omega-3 and CV Diseases

- Fish oil is obtained in human diet by eating oily fish (e.g., herring, mackerel, salmon, albacore tuna, sardines) or by fish oil supplements.
- Fish do not naturally produce these oils, but they obtain them from micro-organisms.

Omega-3 and CV Diseases

Background:
• Sinclair in 1944 described the rarity of CHD in Greenland Eskimos, who ate a diet high in whale, seal and fish
• Bang and Dyberg in the 70s described the diet and risk of MI in Greenland Eskimos compared with Danes
• Data from Japan, Holland, Norway and the US have extended this seminal work

Adapted with permission from Lavie CJ et al. JACC 2009;54:585-594.

Cardiovascular Diseases That May Benefit From Omega-3 Polyunsaturated Fatty Acids
• Post MI
• Hypercholesterolemia
• Heart Failure
• Hypertriglyceridemia
• Atherosclerosis
• Atrial Fibrillation
• Complex Ventricular Arrhythmias
• Hypertension


Potential EPA and DHA Effects
• Anti-arrhythmic Effects
• Improvements in Autonomic Function
• Decreased Platelet Aggregation
• Vasodilation
• Decreased Blood Pressure
• Anti-inflammatory Effects
• Improvements in Endothelial Function
• Plaque Stabilization
• Reduced Atherosclerosis
• Reduced Free Fatty Acids and Triglycerides
• Up-regulate Adiponectin Synthesis
• Reduces Collagen Deposition

The GISSI-Prevenzione Trial: Post MI

- Total Number of Patients: 11,324
- Omega 3: 5666
- Vitamin E: 2830
- Control: 5658
- Omega 3: 2836
- Vitamin E: 2830
- Control: 2828

• 172 centers in Italy involved, managed by the Mario Negri Institute
• The effect of omega-3 PUFA on the risk of pancreatitis in patients with very high TG levels has not been evaluated. The effect of omega-3 PUFA on cardiovascular mortality and morbidity in patients with very high TG levels has not been determined.

GISSI=Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico; MI=myocardial infarction.

GISSI-Prevenzione Investigators [published correction appears in Lancet. 2001;357:642].

Fish Oil and Post-MI Prognosis-The GISSI Prevenzione

- Total Mortality
- Sudden Death

Fish Oil and Post-MI Prognosis-The GISSI Prevenzione

CHD Mortality

- $\omega-3$ PUFA
- Control

0.82 (0.40-0.98) p<0.040
0.72 (0.49-1.05) p=0.065

0 30 60 90 120 150 180 210 240 270 300 330 360 Days

Cardiovascular Mortality

- $\omega-3$ PUFA
- Control

0.64 (0.44-0.94) p<0.024
0.70 (0.51-0.98) p=0.030

0 30 60 90 120 150 180 210 240 270 300 330 360 Days

Omega-3 and CVD - JELIS

- 18,645 patients (14,981 primary prevention and 3,664 secondary prevention)
- Statin alone or statin and EPA 1,800 mg/d
- EPA had 19% reduction in major CV events
- No reduction in SCD

Yokoyama M et al. Lancet 2007;369:1090-1098
Japan EPA Lipid Intervention Study - JELIS
(Yokoyama et al. Lancet 2007;369:1090-98)

16,645 Japanese (70% women, 61 yrs) randomized to statin alone or statin+EPA (1.8 g/d) and followed for 5 years

Entire Cohort N=18,645
1st Prevention=14,981
2nd Prevention=3,664

MCE = Major coronary events considered to be sudden cardiac death, fatal and nonfatal MI, unstable AP, and angioplasty/stenting or CABG

Omega-3 and CHD

• Many other positive studies
• Negative studies, notably OMEGA trial and recent margarine study in NEJM
• Some studies were underpowered, underdosed or both


Omega-3 and CVD – What About ALA?

• ALA is found in flaxseed, canola, olive oil, walnuts, other tree nuts, and in trace amounts in green leafy vegetables
• Humans typically convert <5% of ALA to EPA and much less to DHA
• Some studies with ALA have been positive, whereas many are negative
• Overall evidence is much less than for EPA and DHA

Cardiovascular Health Study
- Population-based study
- 5,000 men and women
- Followed for over 12 yrs
- Consumption of broiled/baked fish
- Associated with a lower incidence of congestive HF

Mozaffarian D et al. JACC 2005;45:2015-2021

Atherosclerosis Risk In Community Study
- 3,500 pts
- Followed for 14 years
- Inverse relationship between intake of PUFA and incidence of HF in women, but not in men.

Japanese Epidemiological Study
- Largest prospective, observational study
- 60,000 men and women
- Followed for 13 years
- Inverse association between omega-3 consumption and CV mortality, including HF mortality

Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial
n. 3494 patients
n-3 PUFA 1g daily
n. 3481 patients
Placebo
n. 2285 patients
Rosuvastatin 10 mg daily
n. 2289 patients
Placebo
4574 patients (eligible for rosuvastatin randomization)
n. 2401 patients not eligible for rosuvastatin:
1572 ruled with statin
395 contraindications to statins
430 Investigator decision

3.9-years median follow-up
(6 patients have been lost to follow-up)

Fish Intake and HF Survival-GISSI-HF

GISSI-HF Design

Fish Intake and HF Survival-GISSI-HF

GISSI-HF. Lancet 2008;372:1223-1230

Fish Intake and HF Survival-GISSI-HF

GISSI-HF. Lancet 2008;372:1223-1230
Although these benefits seem to be only modest, they translate into 56 patients needed to be treated for 4 years to avoid 1 death or hospital CV admission. Importantly, this therapy is safe, inexpensive, and well-tolerated.

GISSI-HF. Lancet 2008;372:1223-1230

The Evidence for Omega-3 Benefit in CHD Is Robust

- Thousands of research studies support the cardio-protective benefits of EPA and DHA. Higher intakes and/or blood levels of these fatty acids are associated with reduced risk of mortality from coronary heart disease (CHD) and sudden cardiac death.


- A 2013 meta-analyses of RCTs found that dosages greater than 1 g/day of EPA-DHA offer significant cardioprotection, reducing the risk for CHD by 20% or greater.

Omega 3 for Triglyceride Rx

Omega-3 at 4 grams/day Reduces Triglycerides Nearly 50% in Severe HTG

HS-Omega-3 Index

A measure of the amount of EPA+DHA in red blood cell membranes expressed as the percent of total fatty acids

There are 64 fatty acids in this model membrane, 3 of which are EPA or DHA
3/64 = 4.6%
HS-Omega-3 Index = 4.6%
Proposed HS-Omega-3 Index Risk Zones

Relative Risk for Death from CHD

USA/EU

Japan

Undesirable
Intermediate
Desirable

4%
8%

Percent of EPA+DHA in RBC


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

Midrange RBC EPA+DHA by Quartile

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

Relative Risk of Sudden Cardiac Death and Blood Omega-3 Levels

Physicians' Health Study

Blood Omega-3 FA (%) by Quartile

Vanitt CH et al. J. Enol J Med 2003;346:2119-2119
Regions with high EPA and DHA blood levels (>8%) include the Sea of Japan, Scandinavia, and areas with indigenous populations or populations not fully adapted to Westernized lifestyles. Very low levels (≤4%) were observed in North America, Central and South America, Europe, the Middle East, Southeast Asia, and Africa. This increase in variability may have implications on the global risk for chronic disease.

**EPA+DHA in dietary supplements**

<table>
<thead>
<tr>
<th>Supplement Facts</th>
<th>Serving Size 1 Softgel</th>
<th>Servings Per Container 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total EPA+DHA content</td>
<td>300 mg per 1 softgel</td>
<td>= 600 mg per 2 softgels</td>
</tr>
</tbody>
</table>

- Fish Oil Concentrate 2400 mg
- Total Omega-3 Fatty Acids 720 mg
  - Omega-3 EPA (Eicosapentaenoic Acid) 360 mg
  - Omega-3 DHA (Docosahexaenoic Acid) 240 mg
  - Omega-3 Other 120 mg

**Fortified foods typically contain 30-100 mg EPA+DHA**

- Milk & Yogurt: 32 mg DHA
- Eggs: 57 mg DHA
- Orange juice: 50 mg EPA+DHA
Minimal recommendation for everyone

Patients who need to lower triglyceride level and modulate inflammation:
- Fish and fortified foods
- Supplements

All patients with documented CHD:
- Continuum of Cardioprotection
- Omega-3 Recommendation
- Primary prevention recommendation

EPA+DHA intake: Continuum of Cardioprotection

- Level 4: ≥ 2000-4000 mg EPA+DHA
- Therapeutic Intervention
- Level 3: ≥ 1500 mg EPA+DHA
- Level 2: ≥ 1000 mg EPA+DHA
- Level 1: ≥ 250 mg EPA+DHA

Primary Prevention recommendations

Secondary Prevention recommendations

Tertiary Prevention recommendations

Diabetic patients with documented coronary artery disease:
- Maintain fasting plasma triglycerides ≤ 150 mg/dL

Omega-3 and Prostate Cancer: Examining the Pertinent Evidence


A Higher Dietary Ratio of Long-Chain Omega-3 to Total Omega-6 Fatty Acids for Prevention of COX-2-Dependent Arteriosclerosis

James J. D'Onofrio

Departments of Medicine and Nutrition Science, University of Kansas School of Medicine, Kansas City, KS 66160-7231, USA

Target Omega 3 Intake: EPA+DHA

- 1st Prevention: 500 mg/d
- 2nd Prevention: 1000 mg/d
- Triglyceride Rx: 3,000 to 6,000 mg/d

Safety of Omega-3

- Prolonged bleeding times with “hyper-Eskimo” doses (eg over 20 g/d)
- No increased bleeding with up to 7g EPA/DHA
- Concern about mercury and other contaminants
  - FDA advised children and pregnant or nursing women to avoid fish with high mercury (eg swordfish, tile fish, big mackerel, and shark)
  - Salmon, sardines, trout, oysters, herring are quite low in mercury

Summary and Outlook

- Prevention in CVD is a realistic opportunity
- Diet is a modifiable risk factor that can be influenced by the individual with your guidance
- There is robust evidence for omega-3 benefits in cardiovascular health
- Omega-3 intake and status is in the very low to low range for most of the globe; including for the United States
- Supplementation with Omegas-3s provides benefits for the individual and the society
- Omega-3 intake via regular fish consumption and/or supplements should be part of prevention strategies
Fish Oil In Cardiovascular Prevention

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