

w-3 Fatty Acids and CVD

**w-3 Fatty Acids: Recommendations for
Therapeutics and Prevention**

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Omega-3 Fatty Acids and CVD

- 1. Overview of existing findings**
- 2. Mechanistic explanations**
- 3. Recommendations from existing data**
- 4. Directions for future research**

w-3 Fatty Acids and CVD

- **Greenland Eskimos (1976)**
- **Epidemiological Studies:**
 - Prospective Cohort Studies: 11 beneficial, 5 no effect**
Meta analysis of 11 PC studies suggests benefit for high but not low risk individuals (Marckmann 1999)
 - Case Control Studies: 4 beneficial, 2 no effect**
 - Randomized Control Trials (Secondary Prevention)**
Dart Trial (Burr 1989, 1994)
GISSI-Prevention Study (GISSI-Prevention 1999)

Dart Trial (Burr 1989 & 1994)

- Male MI survivors were encouraged to increase their oily fish intake to provide an additional 500-800 mg/d of w-3 fatty acids.
- Over a 2 year period, this resulted in a 29% reduction in total mortality, with the greatest benefit in fatal MI.
- Of the group randomized to ingest dietary fish, a subgroup chose to ingest 1.5 g/d fish oil capsules containing 450 mg of EPA + DHA.
- The capsule group had a 62% reduction in CHD death and a 56% reduction in all cause mortality, suggesting that the benefits of the fish consumption were in the fish oil fraction.

GISSI-Prevention Study (1999)

- Patients with preexisting CHD were randomized to receive either 300 mg vitamin E, 850 mg w-3 fatty acids (EPA+DHA), both, or neither.
- After 3.5 years, the w-3 group had a 20% reduction in overall mortality, a 30% reduction in coronary mortality, and a 45% reduction in sudden death compared to control.
- Vitamin E had no effect.

Mechanisms whereby w-3 fatty acids might influence CVD

- **Prevent arrhythmias**
- **Lower plasma triglycerides**
- **Decrease blood pressure**
- **Decrease platelet aggregation**
- **Stimulate endothelial-derived nitric oxide**
- **Decrease proinflammatory eicosanoids**

Preventing Arrhythmias

- **Very suggestive evidence that w-3 fatty acids reduce the risk for sudden cardiac death by stabilizing the myocardium.**
- **In studies of rats and dogs EPA and DHA have been shown to have potent antiarrhythmic effects.**
- **In rat ventricular myocytes w-3 fatty acids prevent the induction of tachyarrhythmias.**
- **This appears to be by preventing calcium overload by maintaining the activity of L-type calcium channels during stress and increasing the activity of cardiac microsomal Ca/Mg-ATPase.**

Decreasing Risk Factors

- w-3 fatty acids as fish oil decrease triglycerides (25 to 30%), increase LDL cholesterol (5 to 10%), increase HDL cholesterol (1 to 3%) at a dose of 4 gm/d.
- w-3 fatty acids decrease postprandial hypertriglyceridemia at a dose of less than 2 gm/d.
- w-3 fatty acids are used to treat marked hypertriglyceridemia (>750 mg/dl) at a dose of 3 to 5 gm/d.
- w-3 fatty acids reduce blood pressure in hypertensives by 3.4/2.0 mm Hg at 5.6 gm/d and 5.5/3.5 mm Hg at 3 gm/d.
- w-3 fatty acids do not adversely affect diabetes.

Recommended w-3 Fatty Acid Intake

AHA Nutrition Committee

Kris-Etherton: Circulation 106;2747-2757, 2002

| Population | Recommendation |
|------------------------------|---|
| No documented CHD | Eat fish (pref oily) 2x/wk plus oils and foods rich in α-linolenic acid (flaxseed, canola, soy, walnuts) |
| Documented CHD | Eat ~1gm EPA+DHA/day preferably from oily fish, but can take EPA+DHA supplements in consultation with a physician |
| Triglyceride Lowering | 2 to 4 gm/day as capsules under a physicians care |

Recommendations of Professional Organizations

- **AHA** – Recommends consumption of omega-3s for patients with established CV disease
- **IOM - AMDR** – advises consumption of 133-267mg/day DHA to reduce risk of chronic disease (incl. cardiovascular)
- **NIH/ISSFAL** - recommends 200mg DHA per day for adults

Future Research

Role of w-3 FAs in secondary prevention

- GISSI trial w-3 FAs decreased major CVD events by 20% over 3.5 yrs
- Cardiac death, coronary death, sudden death decreased 30-45% (signif)
- Recurrent non-fatal MI trend to reduction (non signif) and non-fatal stroke no reduction
- Greatest reduction in cardiac mortality in first 9 months after MI, implying w-3 FAs are antiarrhythmic, not plaque stabilizing or antithrombotic
- GISSI trial needs confirmation in short term trials in the immediate post MI period (not primary or long term secondary prevention) major end point cardiac death, include verification of antiarrhythmic effects
- W-3 FAs vs. EPA vs. DHA

Grundy: Circulation 2003;107:1834-1836

Risk for Side Effects From W-3 FAs

| | GI Upset | Clinical Bleeding | Fishy After taste | Worse Glycemia | Rise LDL-C |
|-------------------|-----------------|--------------------------|--------------------------|-----------------------|-------------------|
| < 1 g/d | Very Low | Very Low | Low | Very Low | Very Low |
| 1 to 3 g/d | Moderate | Very Low | Moderate | Low | Moderate |
| > 3 g/d | Moderate | Low | Likely | Moderate | Likely |

Directions for Future Research

- w-6/w-3 ratio
- Vegetable vs. Marine w-3 Oils
- EPA vs. DHA
- Highly controlled GCRC-type metabolic studies
- Clinical anti arrhythmia studies
- Systemic and adipose tissue inflammation
- Immune function

Hypothesis: DHA (2 gm/day) favorably alters CVD risk factors in overweight and obese individuals

Type of Study: prospective, double blind, placebo controlled, dietary supplement

Inpatient #1
(3 weeks)

Avg Am Diet

Placebo A

Outpatient
(4 months)

Low w-3 Diet

Placebo B

or DHA 2gm

Inpatient #2
(3 weeks)

Avg Am Diet

Placebo B

or DHA 2gm

Avg Am Diet: Carb 51%; Fat 34%; Prot 15%; P/S=0.55;
Chol 100mg/KCAL; w-6/w-3=10

Plasma Phospholipid FAs (%)

Placebo

DHA

| | IP-1 | IP-2 | IP-1 | IP-2 | DHA Effect |
|----------------|-------------|-------------|-------------|-------------|-------------------|
| SFA | 40.8 | 40.7 | 40.9 | 41.1 | NC |
| N-9 | 7.7 | 7.8 | 7.8 | 7.3 | NC |
| N-6 | 40.5 | 40.4 | 39.7 | 34.7 | Decr |
| N-3 | 4.3 | 4.3 | 4.7 | 10.4 | Incr |
| 22:6N-3 | 2.7 | 2.7 | 3.0 | 8.8 | Incr |

Inpatient # 1 vs. Inpatient # 2

Placebo vs. DHA Rx

- **Fasting lipids and lipoproteins**
- **NMR lipoprotein analysis**
- **Oral glucose tolerance testing (OGTT)**
- **Supine and upright blood pressure**
- **24 hour blood pressure monitoring**
- **Clotting: PT, PTT, fibrinogen**
- **Inflammation: hsCRP, I-CAM, SAA, IL-6, TNF α , TNFR**
- **Immunology studies: CBC; lymphocyte subsets (T, B, NK); intracellular cytokines (TNF α , IL-1 β); proliferative response; monocyte and neutrophil respiratory burst**
- **FA analysis: plasma phospholipids, adipose tissue triglycerides**