Omega-3 fatty acids and cardiovascular disease: a continuum of nutrition and medicine

Ann C. Skulas-Ray, PhD
Food, Bioactives, & Health Lab

Department of Nutritional Sciences
Department of Immunobiology
Arizona Center on Aging
Physiological Sciences GIDP

No financial disclosures
Outline

- Dose-response considerations
- Nutrition vs. medical
- Disease prevention
- Triglyceride lowering
- What’s next?
### How much?

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>DGA: 2 servings of fish per week</td>
<td>~ 250 mg/d</td>
</tr>
<tr>
<td>2 servings of oily fish per week</td>
<td>Up to 500 mg/d</td>
</tr>
<tr>
<td>1 fish oil capsule</td>
<td>300+ mg</td>
</tr>
<tr>
<td>1 prescription capsule</td>
<td>840 mg EPA + DHA</td>
</tr>
<tr>
<td></td>
<td>or 960 mg EPA</td>
</tr>
<tr>
<td>4 prescription capsules</td>
<td>3.4-3.8 g</td>
</tr>
</tbody>
</table>
Current omega-3 fatty acid intakes

What are the differences between supplements and prescription agents?
### Nutritional/Dietary Supplements
- Subtle effects
- Excellent safety profile
- Recommendations at a population level
- Meant to be consumed for a lifetime
- **Maintain health**
- FDA: safe until evidence otherwise
- Some degree of variability is to be expected

### Medical/Pharmacological
- Consistent, measurable benefits
- Adequate safety profile relative to benefits for indicated use
- Indicated for subset of the population
- Varying duration of use
- **Indication to treat/prevent disease** (or established risk factors)
- FDA: safety demonstrated in clinical trials
- Strict regulatory specs for composition
Health maintenance, disease *prevention*

**INFLAMMATORY RESPONSES**

**ARRYTHMIA**

**COAGULATION**

**BLOOD PRESSURE/HR**

### Nutrition/Dietary Supplements

- Subtle effects
- Excellent safety profile
- Recommendations at a population level
- Meant to be consumed for a lifetime
- **Maintain health**
- FDA: safe until evidence otherwise
- Some degree of variability is to be expected
An apple a day keeps the doctor away

...But we do not have a randomized controlled trial in which apples are proven effective at a specified dose for preventing or treating disease.
How might we evaluate the role of dietary omega-3 fatty acids in PREVENTING disease?

- Randomized controlled trials
- Observational Studies
- Human Translational Studies
- Animal models
- In vitro mechanistic studies
Omega-3 fatty acids and inflammation

<table>
<thead>
<tr>
<th>hs-CRP Value</th>
<th>Cardiovascular Disease Risk Level*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 mg/L</td>
<td>Low risk</td>
</tr>
<tr>
<td>1-3 mg/L</td>
<td>Average risk</td>
</tr>
<tr>
<td>&gt; 3 mg/L</td>
<td>High risk</td>
</tr>
</tbody>
</table>


CRP = C-Reactive Protein
Observational evidence: a marker of habitual omega-3 fatty acid intake is inversely associated with inflammation.

Prostaglandins, Leukotrienes, and Essential Fatty Acids. 2014;91(4):161-168

$r = -0.337, p < 0.001$
We have a biomarker for intake that responds dose dependently.

We have mechanistic evidence of the importance of omega-3 fatty acids in regulating inflammatory responses.

Supplemental EPA and/or DHA

Inflammation signals

EPA + DPA + DHA

Inflammatory eicosanoids (PGE$_2$, TXA$_2$, LTA$_4$)

Less inflammatory eicosanoids (PGE$_3$, TXA$_3$, LTA$_3$)

Pro-resolving lipid mediators (e.g. Resolvins)

Resolution of Inflammation

↑ Inflammation (CRP)
Pharmacological indication

ELEVATED TRIGLYCERIDES*

*ICOSAPENT ETHYL HAS AN ADDITIONAL INDICATION FOR REDUCING THE RISK OF HEART ATTACK, STROKE AND CERTAIN TYPES OF HEART ISSUES REQUIRING HOSPITALIZATION IN ADULTS WITH HEART (CARDIOVASCULAR) DISEASE, OR DIABETES AND 2 OR MORE ADDITIONAL RISK FACTORS FOR HEART DISEASE.
FDA-approved n-3 FA agents

- Omega-3 fatty acid ethyl esters (O3AEE, EPA + DHA)
- Icosapent ethyl (IPE, EPA-only)
- Omega-3 carboxylic acids (O3CA, EPA + DHA)

Skulas-Ray et al. Circulation. 2019; 140
HTG and VHTG

- Normal TG < 150 mg/dL
- Borderline TG = 150 – 199
- High TG (HTG) = 200 – 499
- Very high TG (VHTG) = 500+
Effect of FDA-approved agents in VHTG and HTG (FDA-reviewed studies)

Skulas-Ray et al. Circulation. 2019; 140
### Dietary supplements, fish oil concentrates: HTG

<table>
<thead>
<tr>
<th>Author, year (country)</th>
<th>EPA + DHA per day</th>
<th>n per arm (Active/placebo)</th>
<th>Baseline TG (mg/dL)</th>
<th>Effect of omega-3 on TG</th>
<th>Effect of omega-3 on LDL-C &amp; HDL-C</th>
<th>Effect of omega-3 on non-HDL-C &amp; apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bairati, 1992 (Canada)</td>
<td>4.5 g (2.7 g EPA, 1.8 g DHA)</td>
<td>66 (n-3 FA) 59 (placebo)</td>
<td>205</td>
<td>↓ 39%</td>
<td>↔ /↑ LDL-C 8% ↑ HDL-C 10%</td>
<td>non-HDL-C and apo B not reported</td>
</tr>
<tr>
<td>Minihane, 2000 (United Kingdom)</td>
<td>3 g (1.7 g EPA, 1.3 g DHA)</td>
<td>50 (n-3 FA) 50 (placebo)</td>
<td>220</td>
<td>↓ 35%</td>
<td>↑ LDL-C 7% ↔ HDL-C</td>
<td>non-HDL-C and apo B not reported</td>
</tr>
<tr>
<td>Shaikh, 2014 (Canada)</td>
<td>3.2 g (2.7 g EPA, 0.4 g DHA)</td>
<td>20 (n-3 FA) 22 (placebo)</td>
<td>305c</td>
<td>↓ 48%</td>
<td>↔ LDL-C ↑ HDL-C 9%</td>
<td>↔ non-HDL-C and apo B</td>
</tr>
</tbody>
</table>
Why not use supplements for high TG?

- Supplement concentrations and serving size varies; patients get the dosing wrong even with training
- Potential for a sub-standard product to be sold (FDA regulates supplements post-marketing) or product with additional ingredients that could introduce negative health effects at high doses long-term
- Prescription agents standardized to exact specifications—clinicians can be assured patients receiving exactly what they intend
- Prescription more pragmatic and safest long term solution for patients, insurance should cover
EPA vs DHA effects?

- Lipids and lipoproteins
- Blood pressure / vascular effects
- Arrhythmia risk
- Inflammation
## Takeaways: Effects of n-3 FA for Managing TG

<table>
<thead>
<tr>
<th>TG 200 – 499 mg/dL</th>
<th>20-30% reduction in TG and no LDL-C increase with 4 g/d prescription n-3 FA</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG ≥ 500 mg/dL</td>
<td>≥ 30% reduction in TG with 4 g/d prescription n-3 FA, LDL-C increase with DHA-containing agents</td>
</tr>
<tr>
<td>Children/adolescents</td>
<td>Apparently safe, but more research needed to further evaluate efficacy</td>
</tr>
<tr>
<td>Use with other lipid therapy</td>
<td>Safe and apparently additive TG-reduction with statin therapy. Apparently safe with fibrates or niacin, but more research needed to evaluate efficacy</td>
</tr>
<tr>
<td>Prescription n-3 FA agent</td>
<td>Based on available data, all prescription agents appear comparably effective, but head-to-head comparisons are lacking</td>
</tr>
</tbody>
</table>

Skulas-Ray et al. Circulation. 2019; 140
Beyond Lipids—Evidence from Recent Outcome Trials

**VITAL:** 840 mg/d EPA + DHA for 5 years in 25,871 older adults (primary prevention)

- Risk for heart attack decreased 28%
- Risk for total coronary heart disease decreased by 17%
- Risk for primary composite endpoint decreased significantly in low fish consumers in secondary analyses (overall risk for primary composite endpoint not significant)

**REDUCE-IT:** 3600 mg/d EPA for 5 years in 8,179 people with HTG taking statin

- Risk of composite endpoint decreased by 25%

Manson et al. NEJM 2019; 380(1):23-32
Bhatt et al. NEJM 2019; 380(1):11-22
Food (as well as supplements and drugs) for thought

VITAL results indicated that people who eat < 1.5 serving/week of oily fish could benefit from lower doses of n-3 FA

REDUCE-IT results showed benefit of treating HTG with 4 g/d prescription agent (3.6 g/d EPA-only)

- People were recruited based on fasting TG
- First outcomes trial to administer 4 g/d concentrate (> 3 g/d EPA + DHA)
- Is presence of HTG the defining characteristic of people who most benefit from n-3?
- Would this dose benefit other populations if administered longer term?

Manson et al. NEJM 2009 380(1):23-32
Happy to take questions during our panel discussion