Omega-3 Fatty Acids
Introduction

• What are omega-3 fatty acids/fish oil and how do they fit into treatment for dyslipidemia?
• What are the recommendations and considerations for treatment with omega-3 fatty acids/fish oil?
Supplemental Omega-3 Fish Oil

- Evidence indicates that the consumption of fish oil 2 to 4 g daily can reduce TG by ≥25%, while producing only slight increases in LDL-C levels.
- Because of the demonstrated TG benefits associated with omega-3 fatty acids (EPA and DHA), the AHA supports 2 servings of fatty fish per week for the general population.
- Individuals with ASCVD should consume 1 g of EPA and DHA daily through fatty fish (preferably) or high-quality dietary supplements.

AHA, American Heart Association; ASCVD: atherosclerotic cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Prescription Omega-3 Fish Oil

• Although the benefit of reducing TG levels is uncertain, several studies suggest that TG reduction is associated with a significant decrease in non-fatal MI, with a trend toward reduced ASCVD events.

• OTC omega-3 supplements are not FDA-regulated
  • May not have the quantity of omega-3 listed on the label
  • May contain other ingredients or contaminants
  • May cause mild side effects such as fish burps and upset stomach

• AACE recommends:
  • Prescription omega-3 oil 2 to 4 g daily to treat severe hypertriglyceridemia (TG >500 mg/dL).
  • Dietary supplements are not FDA-approved for treatment of hypertriglyceridemia and generally are not recommended for this purpose.

AACE, American Association of Clinical Endocrinologists; ASCVD: atherosclerotic cardiovascular disease; FDA, U.S. Food and Drug Administration; OTC, over-the-counter; TG, triglycerides.

Omega-3 Fatty Acid Dietary Supplements

- Fish oil: Among the most commonly used dietary supplements by U.S. adults\(^1\)
  - Global sales may reach $3.3 billion by 2020
  - 19 million (8%) took fish oil dietary supplement in previous 30 days\(^2\)
- There are no omega-3 OTC products in U.S. (only prescriptions and dietary supplements)
- Dietary supplements are not FDA-regulated; their content and efficacy often remain unverified.\(^3\)

\(^2\) NIH NCCIH. Available at: https://nccih.nih.gov/health/omega3/introduction.htm

FDA, U.S. Food and Drug Administration; OTC, over-the-counter.
## Prescription vs Dietary Supplement Omega-3 FA

<table>
<thead>
<tr>
<th></th>
<th>Prescriptions</th>
<th>Dietary Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EPA</td>
<td>EPA + DHA</td>
</tr>
<tr>
<td><strong>FDA classification</strong></td>
<td>Drug</td>
<td>Drug</td>
</tr>
<tr>
<td><strong>FDA approval</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Ingredients</strong></td>
<td>EPA</td>
<td>EPA + DHA</td>
</tr>
<tr>
<td><strong>Omega-3 per capsule</strong></td>
<td>0.98 g</td>
<td>0.84 g</td>
</tr>
<tr>
<td><strong>Capsules/day to provide 4 g omega-3</strong></td>
<td>4</td>
<td>~4</td>
</tr>
<tr>
<td><strong>Purity/efficacy and safety tested</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FDA, U.S. Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; PUFA, polyunsaturated fatty acids.
# Prescription Omega-3 Fatty Acid Formulations

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>EPA+DHA EE&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>EPA only EE&lt;sup&gt;3&lt;/sup&gt;</th>
<th>EPA+DHA FFA&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic Available?</strong></td>
<td>Yes&lt;sup&gt;5&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Adjunct to diet to ↓TG levels in adult patients with severe hypertriglyceridemia (≥500 mg/dL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Omega-3 content** | • EPA: 0.465 g  
• DHA: 0.375 g  
• EPA/DHA: 55%/45% | • EPA: 1 g  
• EPA/DHA: 100%/0% | • EPA: 0.55 g  
• DHA: 0.2 g  
• EPA/DHA: 73%/27% |
| **Regimen, capsules** | • 2 BID w/ food or  
• 4 QD w/ food<sup>2</sup> | • 2 BID w/ food | • 2 or 4 QD, meal independent |

BID, twice daily; DHA, docosahexaenoic acid; EE, ethyl ester; EPA, eicosapentaenoic acid; FFA, free fatty acid; QD, once daily.

# Similarities and Differences of Prescription Omega-3 Fatty Acid Formulations

<table>
<thead>
<tr>
<th></th>
<th>EPA+DHA EE(^1,2)</th>
<th>EPA only EE(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand Name</strong></td>
<td>Lovaza</td>
<td>Vascepa</td>
</tr>
<tr>
<td><strong>Lowers TG</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Lowers non-HDL-C</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>** Raises LDL-C**</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

DHA, docosahexaenoic acid; EE, ethyl ester; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

1. Lovaza prescribing information, generics available. 2. Omtryg prescribing information. 3. Vascepa prescribing information. 4. Epanova prescribing information.  
AHRQ Evidence for Clinical Benefit of Omega-3 Fish Oil

• According to a recent U.S. AHRQ technical review:
  • Fish oil supplementation raises HDL-C and LDL-C by ≤2 mg/dL while lowering TG
  • Individuals with high baseline TG levels experience greater benefit than those with lower levels
  • Moderate-to-high evidence exists to indicate that fish oil intake does not affect major CV events, all-cause death, total CHD, sudden cardiac death, coronary revascularization, atrial fibrillation, or blood pressure
  • While randomized controlled trials have not shown improved CV outcomes with fish oil supplementation, observational studies have showed possible benefit

AHRQ, Agency for Healthcare Research and Quality; CHD, coronary heart disease; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

## Meta-analysis of Omega-3 Benefits

“... Omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events.”

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>EPA/DHA Dose (mg/d)</th>
<th>EPA / DHA Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOIT (2010)</td>
<td>1150 / 800</td>
<td>Dietary supplement</td>
</tr>
<tr>
<td>AREDS-2 (2014)</td>
<td>650 / 350</td>
<td>Dietary supplement</td>
</tr>
<tr>
<td>SU.FOL.OM3 (2010)</td>
<td>400 / 200</td>
<td>Dietary supplement</td>
</tr>
<tr>
<td>JELIS (2007)</td>
<td>1800 / NA</td>
<td>Pure EPA Rx</td>
</tr>
<tr>
<td>Alpha Omega (2010)</td>
<td>226 / 150</td>
<td>Margarine with dietary supplement</td>
</tr>
<tr>
<td>OMEGA (2010)</td>
<td>460 / 380</td>
<td>Rx EPA/DHA</td>
</tr>
<tr>
<td>R&amp;P (2013)</td>
<td>500 / 500</td>
<td>Rx EPA/DHA</td>
</tr>
<tr>
<td>GISSI-HF (2008)</td>
<td>850 / 950</td>
<td>Rx EPA/DHA</td>
</tr>
<tr>
<td>ORIGIN (2012)</td>
<td>465 / 375</td>
<td>Rx EPA/DHA</td>
</tr>
<tr>
<td>GISSI-P (1999)</td>
<td>850 / 1700</td>
<td>Rx EPA/DHA</td>
</tr>
</tbody>
</table>

### Source

- **CHD**
  - Nonfatal MI
  - CHD death
  - Any

- **Stroke**
  - Ischemic
  - Hemoerhagic
  - Underclassified/Other
  - Any

- **Revascularization**
  - Coronary
  - Noncoronary
  - Any

- **Any major vascular event**

### Favors Treatment / Favors Control

- CHD: Nonfatal MI, CHD death, Any
- Stroke: Ischemic, Hemoerhagic, Underclassified/Other, Any
- Revascularization: Coronary, Noncoronary, Any
- Any major vascular event

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CHD, coronary heart disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MI, myocardial infarction

JELIS: EPA Reduced Major Coronary Events* in Hypercholesterolemic Patients on Statins

N=18,645 Japanese pts with TC ≥251 mg/dL prior to baseline statin treatment. Baseline TG=153 mg/dL. Statin up-titrated to 20 mg pravastatin or 10 mg simvastatin for LDL-C control.

*Primary endpoint: sudden cardiac death, fatal and non-fatal MI, unstable angina pectoris, angioplasty, stenting, or coronary artery bypass graft.

Randomized Controlled Trials and Prospective Cohort Studies of EPA+DHA and CHD Risk

Subjects with baseline TG levels >150 mg/dL

<table>
<thead>
<tr>
<th>Author, year</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singh, 1997</td>
<td>1.0</td>
</tr>
<tr>
<td>Von Schacky, 1999</td>
<td>0.2</td>
</tr>
<tr>
<td>Marchioli, 2001</td>
<td>0.5</td>
</tr>
<tr>
<td>Yokoyama, 2007</td>
<td>2</td>
</tr>
<tr>
<td>Einvik, 2010</td>
<td>5</td>
</tr>
<tr>
<td>Roncaglioni, 2013</td>
<td></td>
</tr>
</tbody>
</table>

Relative Risk: 0.84 (95% CI: 0.72-0.98)

CHD, coronary heart disease; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; RR, relative risk; TG, triglycerides.

## Ongoing Omega-3 Cardiovascular Outcomes Trials

<table>
<thead>
<tr>
<th></th>
<th>REDUCE-IT</th>
<th>STRENGTH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent Dose</strong></td>
<td>EPA (EE) 4 g/d</td>
<td>EPA+DHA (FFA) 4 g/d</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>International</td>
<td>International</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>~8000</td>
<td>Estimated 13,000</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>≥45 years</td>
<td>≥18 years</td>
</tr>
<tr>
<td><strong>Risk profile</strong></td>
<td>CVD (70%) or ↑CVD risk (30%)</td>
<td>CVD (50%) or ↑CVD risk (50%)</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>4–6 years (planned)</td>
<td>3–5 years (planned)</td>
</tr>
<tr>
<td><strong>Statin use</strong></td>
<td>100% (at LDL-C goal)</td>
<td>100% (at LDL-C goal)</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>Expanded MACE</td>
<td>Expanded MACE</td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td>Powered for 15% RRR</td>
<td>Powered for 15% RRR</td>
</tr>
<tr>
<td><strong>Entry TG</strong></td>
<td>200 to 499 mg/dL</td>
<td>200 to 499 mg/dL</td>
</tr>
<tr>
<td></td>
<td>NONE</td>
<td>&lt;40 mg/dL M, &lt;45 mg/dL W</td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; M, men; MACE, major adverse cardiovascular event; RRR, relative risk reduction; T2D, type 2 diabetes; TG, triglycerides; W, women.

REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial)

**Eligibility criteria:**
- Age ≥45 years with CVD, or ≥50 years with diabetes with ≥1 additional risk factor for CVD
- Fasting TG levels ≥150mg/dL* and <500 mg/dL
- LDL-C >40mg/dL and ≤100mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to randomization

**Primary outcome:** Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina

**Key secondary outcome:** Composite of CV death, nonfatal MI, or nonfatal stroke

**Study design:** Phase 3B, multi-center, randomized, double-blind, placebo-controlled trial with long-term follow-up at 470 centers, worldwide

**Primary objective:** To assess whether treatment with icosapent ethyl reduces ischemic events in statin-treated patients with high TG at elevated CV risk

*RDue to the variability of TGs, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying TG ≥135 mg/dL.*

CV, cardiovascular; CVD, cardiovascular disease, LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TG, triglycerides.

REDUCE-IT: Key Primary Endpoint (CV Death, MI, Stroke, Coronary Revascularization, Unstable Angina)

ARR, absolute risk reduction; CV, cardiovascular; MI, myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction.

REDUCE-IT: Key Secondary Endpoint (CV Death, MI, Stroke)

Hazard Ratio, 0.74
(95% CI, 0.65–0.83)
RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
P=0.0000006

ARR, absolute risk reduction; CV, cardiovascular; MI, myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction.

# FDA-approved Pharmacologic Therapy for Very High TG and Fredrickson Types III & IV

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Very High TG Indications*</th>
<th>Notable Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TG &gt;500 mg/dL</td>
<td>Type III Hyper-lipidemia</td>
</tr>
<tr>
<td><strong>Omega-3 FA (EPA/DHA)</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Omega-3 FA (EPA only)</strong></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Fenofibrate</strong></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Extended-release niacin</strong></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Data from individual product labeling for each drug in patients with very high TG. †AEs: Incidence >Placebo and: ≥3% for ω-3/EPA/DHA; ≥2% for ω-3/EPA, fenofibrate, statins; ≥5% for niacin. a4 g per day. b145 mg per day. c2 g per day. dAtorvastatin, rosuvastatin, simvastatin.

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acids; T2D, type 2 diabetes; TG, triglycerides.

Reported Clinical and Biologic CV Benefits of Omega-3 Fatty Acids

**Anti-arrhythmic**
- ↓ Sudden death (GISSI-P only)
- ↓ AF
- ↓ Protection against ventricular arrhythmias (vs ↑)
  Heart rate variability improvement

**Anti-atherogenic**
- ↓ Non-HDL-C
- ↓ TG and ↓ VLDL-C
- ↓ Chylomicrons
- ↓ VLDL and ↓ chylomicron remnants
- ↑ HDL-C levels (vs ↓ w/ EPA-only)
- ↑ LDL and HDL particle size
  Plaque stabilization

**Antithrombotic**
- ↓ Platelet aggregation
- ↑ Blood rheologic flow

**Anti-inflammatory and endothelial protective effects**
- ↓ Endothelial adhesion molecules
- ↓ Leukocyte adhesion receptor expression
- ↓ Proinflammatory eicosanoids
- ↓ Proinflammatory leukotrienes
  Vasodilation

**↓ Systolic and diastolic BP**

AF=atrial fibrillation; BP, blood pressure; CV=cardiovascular; EPA, eicosapentaenoic acid; FA=fatty acids; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

### Fenofibrate vs Omega-3 vs Niacin for Hypertriglyceridemia: Summary

<table>
<thead>
<tr>
<th></th>
<th>Fenofibrate</th>
<th>Rx Omega-3</th>
<th>Niacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ TG</td>
<td>↓↓↓↓</td>
<td>↓↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Δ LDL-C</td>
<td>↑↑↑↑ to →</td>
<td>↑↑↑↑ to → to ↓</td>
<td>↓ to ↓↓</td>
</tr>
<tr>
<td>Δ Non-HDL-C</td>
<td>→ to ↓</td>
<td>→ to ↓</td>
<td>↓ to ↓↓</td>
</tr>
<tr>
<td>Δ HDL-C</td>
<td>→ to ↑</td>
<td>→ to ↑</td>
<td>↑ to ↑↑</td>
</tr>
<tr>
<td>↓ CVD Efficacy</td>
<td>0 to +</td>
<td>0 to +++</td>
<td>0 to +</td>
</tr>
<tr>
<td>↓ Mortality</td>
<td>0</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Non-CVD Benefits</td>
<td>0 to ++</td>
<td>0 to ++?</td>
<td>0</td>
</tr>
<tr>
<td>Safety</td>
<td>+ to −</td>
<td>+++</td>
<td>− − − to 0</td>
</tr>
<tr>
<td>“Natural”</td>
<td>0</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Access (cost/generic)</td>
<td>+ to ++</td>
<td>− to ++</td>
<td>++ to +++</td>
</tr>
<tr>
<td>Tolerability</td>
<td>++ to −</td>
<td>++ to −</td>
<td>− − −</td>
</tr>
<tr>
<td>Ease of use</td>
<td>+++</td>
<td>+++</td>
<td>− −</td>
</tr>
</tbody>
</table>

CVD=cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.
### Starting Dosages and Dose Ranges

#### Omega-3 Fatty Acids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended starting daily dosage</th>
<th>Dose range</th>
<th>Method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega-3-acid ethyl esters (Lovaza)</td>
<td>4 g per day</td>
<td>4 g per day (1 or 2 doses)</td>
<td>Oral</td>
</tr>
<tr>
<td>Icosapent ethyl (Vascepa)</td>
<td>4 g per day</td>
<td>4 g per day (2 doses)</td>
<td>Oral</td>
</tr>
</tbody>
</table>

Metabolic Effects

Omega-3 Fatty Acids

- Icosapent ethyl ↓ LDL-C 5%, whereas omega-3-acid ethyl esters ↑ LDL-C 45%
- In individuals with severe hypertriglyceridemia, reduces TG 27%-45%, TC 7%-10%, VLDL-C 20%-42%, apolipoprotein B 4%, and non-HDL-C 8%-14%
  - Most likely by reducing hepatic VLDL-TG synthesis and/or secretion and enhancing TG clearance from circulating VLDL particles.
- Other potential mechanisms of action include:
  - Increased β-oxidation
  - Inhibition of acyl-CoA
  - 1,2-diacylglycerol acyltransferase
  - Decreased hepatic lipogenesis
  - Increased plasma lipoprotein activity

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein.

Assess TG levels prior to initiating and periodically during therapy

Omega-3-acid ethyl esters can increase LDL-C levels; monitor LDL-C levels during treatment

Omega-3s may prolong bleeding time; monitor coagulation status periodically in patients receiving treatment with omega-3 fatty acids and other drugs affecting coagulation

Monitor ALT and AST levels periodically during treatment in patients with hepatic impairment; some patients may experience increases in ALT levels only.

Exercise caution when treating patients with a known hypersensitivity to fish and/or shellfish

AF, atrial fibrillation; ALT, alanine transaminase; AST, aspartate aminotransferase; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

The effect of omega-3 fatty acids on CV morbidity and mortality and the risk of pancreatitis has not been determined in patients with severe hypertriglyceridemia.

In patients with paroxysmal or persistent AF, therapy with omega-3-acid ethyl esters may be associated with increased frequency of symptomatic AF or flutter, especially within the first 2 to 3 months after initiation.

Most common adverse events include arthralgia (2.3%), eructation (4%), dyspepsia (3%), and taste perversion (4%); may also experience constipation, gastrointestinal disorders, vomiting, rash, or pruritus.

Omega-3s should be used with caution in nursing mothers and only be used in pregnant women if the benefits of treatment outweigh the potential risk of fetal harm.

AF, atrial fibrillation; CV, cardiovascular.

Conclusion

• Omega-3 fatty acid/fish oil supplementation is highly effective at treating hypertriglyceridemia

• AACE recommends 2g to 4g per day of prescription omega-3 oil in patients with TG >500 mg/dL

• Omega-3 fatty acid/fish oil supplementation may also moderately increase HDL-C and LDL-C
  • LDL-C levels should be monitored

• Evidence suggests that fish oil supplementation does not affect CV events

AACE, American Association of Clinical Endocrinologists; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.