New Evidence to Improve Management of Patients with or at High Risk of ASCVD Events

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Omega-3 Fatty Acids
Reducing Risk in ASCVD

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Omega-3 Fatty Acids

- Alpha-linolenic acid (ALA, C18:3, omega-3)
- Eicosapentaenoic acid (EPA, C20:5, omega-3)
- Docosahexaenoic acid (DHA, C22:6, omega-3)
Triglycerides

\[ \text{TG} = \text{Glycerol} + \text{3 Fatty Acids} \]

Lipoprotein Classification
Clinical Trials of Omega-3 Fatty Acids and ASCVD Risk

<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 / 0</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>

ASCEND: Effect of Omega-3 FA Supplements on Serious Vascular Events

- ASCEND - largest and longest duration placebo-controlled randomized trial of OM-3 FA supplementation in diabetics
- No effect on MACE
- No effect on cancer
- No effect on total or cause-specific mortality
- No safety concerns

*1-g capsules containing either n-3 fatty acids (fatty acid group) matching placebo (olive oil) daily.
The VITamin D and OmegA-3 TriaL (VITAL)

- 25,871 participants (primary prevention) median F/U 5.3 yrs
- MACE not significantly different between OM-3 FA and placebo (HR 0.92; p=0.24)
- MI was significantly reduced - HR=0.72 (0.59–0.90)
  - Blacks and lower fish intake
- Major CVD events and total invasive cancer were not significantly reduced by OM-3 FA

REDUCE-IT: Reduction of CV Events with Icosapent Ethyl – Intervention Trial

Participants
- Men and women ≥45 years of age
- Established CHD or at high risk for CHD (diabetes + ≥1 risk factor)
- Atherogenic dyslipidemia
  - All patients required to be on stable statin therapy for at least 4 weeks
  - LDL-C >40 mg/dL and ≤100 mg/dL prior to randomization into the study
- Fasting triglyceride level 135–499 mg/dL

Primary Endpoint
1st major CV event
- CV death
- Nonfatal MI
- Nonfatal stroke
- Coronary revascularization
- Unstable angina requiring hospitalization

Study duration ≈ 4–6 years

N=8179

REDUCE-IT Primary Endpoint
CV Death, MI, Stroke, Coronary Revascularization, Unstable Angina

Primary Endpoint
CV Death, MI, Stroke, Coronary Revascularization, Unstable Angina

- **Placebo**: 23.0%
- **Icosapent Ethyl**: 28.3%

- **Hazard Ratio**: 0.75 (95% CI 0.68–0.83)
- **RRR**: 24.8%
- **ARR**: 4.8%
- **NNT**: 21 (95% CI 15–33)
- **P**: 0.00000001

Key Secondary Endpoint
CV Death, MI, Stroke

- **Placebo**: 16.2%
- **Icosapent Ethyl**: 20.0%

- **Hazard Ratio**: 0.74 (95% CI 0.65–0.83)
- **RRR**: 26.5%
- **ARR**: 3.6%
- **NNT**: 28 (95% CI 20–47)
- **P**: 0.00000006

## Endpoint

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>RRR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite (ITT)</td>
<td></td>
<td>705/4089 (17.2%)</td>
<td>901/4090 (22.0%)</td>
<td>0.75 (0.68–0.83)</td>
<td>25%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Key Secondary Composite (ITT)</td>
<td></td>
<td>459/4089 (11.2%)</td>
<td>606/4090 (14.8%)</td>
<td>0.74 (0.65–0.83)</td>
<td>26%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular Death or Nonfatal Myocardial Infarction</td>
<td></td>
<td>392/4089 (9.6%)</td>
<td>507/4090 (12.4%)</td>
<td>0.75 (0.66–0.86)</td>
<td>25%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatal or Nonfatal Myocardial Infarction</td>
<td></td>
<td>250/4089 (6.1%)</td>
<td>355/4090 (8.7%)</td>
<td>0.69 (0.58–0.81)</td>
<td>31%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent or Emergency Revascularization</td>
<td></td>
<td>216/4089 (5.3%)</td>
<td>321/4090 (7.8%)</td>
<td>0.65 (0.55–0.78)</td>
<td>35%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td></td>
<td>174/4089 (4.3%)</td>
<td>213/4090 (5.2%)</td>
<td>0.80 (0.66–0.98)</td>
<td>20%▼</td>
<td>0.03</td>
</tr>
<tr>
<td>Hospitalization for Unstable Angina</td>
<td></td>
<td>108/4089 (2.6%)</td>
<td>157/4090 (3.8%)</td>
<td>0.68 (0.53–0.87)</td>
<td>32%▼</td>
<td>0.002</td>
</tr>
<tr>
<td>Fatal or Nonfatal Stroke</td>
<td></td>
<td>98/4089 (2.4%)</td>
<td>134/4090 (3.3%)</td>
<td>0.72 (0.55–0.93)</td>
<td>28%▼</td>
<td>0.01</td>
</tr>
<tr>
<td>Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke</td>
<td></td>
<td>549/4089 (13.4%)</td>
<td>690/4090 (16.9%)</td>
<td>0.77 (0.69–0.86)</td>
<td>23%▼</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Hazard Ratio (95% CI)

- **Primary Composite (ITT)**: 0.75 (0.68–0.83)
- **Key Secondary Composite (ITT)**: 0.74 (0.65–0.83)
- **Cardiovascular Death or Nonfatal Myocardial Infarction**: 0.75 (0.66–0.86)
- **Fatal or Nonfatal Myocardial Infarction**: 0.69 (0.58–0.81)
- **Urgent or Emergency Revascularization**: 0.65 (0.55–0.78)
- **Cardiovascular Death**: 0.80 (0.66–0.98)
- **Hospitalization for Unstable Angina**: 0.68 (0.53–0.87)
- **Fatal or Nonfatal Stroke**: 0.72 (0.55–0.93)
- **Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke**: 0.77 (0.69–0.86)

### RRR (Relative Risk Reduction)

- **Primary Composite (ITT)**: 25%
- **Key Secondary Composite (ITT)**: 26%
- **Cardiovascular Death or Nonfatal Myocardial Infarction**: 25%
- **Fatal or Nonfatal Myocardial Infarction**: 31%
- **Urgent or Emergency Revascularization**: 35%
- **Cardiovascular Death**: 20%
- **Hospitalization for Unstable Angina**: 32%
- **Fatal or Nonfatal Stroke**: 28%
- **Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke**: 23%

### P-value

- **Primary Composite (ITT)**: <0.001
- **Key Secondary Composite (ITT)**: <0.001
- **Cardiovascular Death or Nonfatal Myocardial Infarction**: <0.001
- **Fatal or Nonfatal Myocardial Infarction**: <0.001
- **Urgent or Emergency Revascularization**: <0.001
- **Cardiovascular Death**: 0.03
- **Hospitalization for Unstable Angina**: 0.002
- **Fatal or Nonfatal Stroke**: 0.01
- **Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke**: <0.001

**RRR** = relative risk reduction

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Bhatt DL. AHA 2018, Chicago.

## REDUCE-IT: Treatment Emergent Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Icosapent Ethyl (N=4089)</th>
<th>Placebo (N=4090)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at least one TEAE, n (%)</td>
<td>3343 (81.8%)</td>
<td>3326 (81.3%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>1252 (30.6%)</td>
<td>1254 (30.7%)</td>
<td>0.98</td>
</tr>
<tr>
<td>TEAE leading to withdrawal of study drug</td>
<td>321 (7.9%)</td>
<td>335 (8.2%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Serious TEAE leading to withdrawal of study drug</td>
<td>88 (2.2%)</td>
<td>88 (2.2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Serious TEAE leading to death</td>
<td>94 (2.3%)</td>
<td>102 (2.5%)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

### REDUCE-IT: Adverse Events of Interest

**Serious Bleeding and AF**

<table>
<thead>
<tr>
<th></th>
<th>Icosapent Ethyl (N=4089)</th>
<th>Placebo (N=4090)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding related disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>111 (2.7%)</td>
<td>85 (2.1%)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Gastrointestinal bleeding</strong></td>
<td>62 (1.5%)</td>
<td>47 (1.1%)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Central nervous system bleeding</strong></td>
<td>14 (0.3%)</td>
<td>10 (0.2%)</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Other bleeding</strong></td>
<td>41 (1.0%)</td>
<td>30 (0.7%)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

- No fatal bleeding events in either group
- Adjudicated hemorrhagic stroke – no significant difference between treatments (13 icosapent ethyl vs 10 placebo; P=0.55)

**Adjudicated hospitalization for atrial fibrillation/flutter**

<table>
<thead>
<tr>
<th></th>
<th>Icosapent Ethyl (N=4089)</th>
<th>Placebo (N=4090)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>127 (3.1%)</td>
<td>84 (2.1%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Limitations – REDUCE-IT

• Small proportion of patients on ezetimibe
• Concomitant PCSK9 inhibitors prohibited
• LDL-C increased in both arms – 5 mg/dL more in placebo arm
  – Most likely due to mineral oil in placebo
  – LDL-C increase unlikely to account for 25% RRR
  – Benefit of EPA vs placebo consistent with or without increased LDL-C
• Mechanism of EPA benefit cannot be established based on REDUCE-IT
  – Most likely not just TG reduction
  – Consistent benefit across TG range (135–499 mg/dL)
  – Similar benefit at 1-year comparing TG < or > 150 mg/dL
• Cost-effectiveness unknown
  – NNT of 21 – likely cost-effective
Why Did EPA-Only Omega-3 FA Reduce ASCVD Events?

- REDUCE-IT – highest dose among all OM-3 FA cardiovascular outcome trials
- Patient population – higher triglyceride levels
- Differences between EPA and DHA
  - Differ in antioxidant properties and effect on membrane lipid structure and dynamics
  - EPA associates with atherosclerotic plaque membranes
    - Reduces LDL oxidation and free radical propagation
    - Reduces signal transduction associated with inflammation
    - Improves endothelial function as well as HDL functionality
  - DHA associates with neuronal and retinal membranes promoting cholesterol rich membrane domains
    - Essential in neuronal membrane function and fluidity
    - Promote formation of cholesterol-rich extracellular crystals in cell-model membranes
      - Leads to inflammation and cellular apoptosis
Omega-3 FA Products

Prescription

- Omega-3 *fatty acid ethyl esters*
  - Lovaza® + generics
    - 2 g BID with food or 4 g Qday with food

- EPA *ethyl esters*
  - Vascepa®
    - 2 g BID with food

- Omega-3 *carboxylic acids* (free fatty acid form)
  - Epanova®
    - 2-4 g daily with/without food
    - Product currently not available commercially

## Dietary Supplements vs Rx Fish Oil

<table>
<thead>
<tr>
<th></th>
<th>Prescription</th>
<th>Dietary Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Product Classification</td>
<td>Drug</td>
<td>Food</td>
</tr>
<tr>
<td>Clinical Trials Required</td>
<td>Yes</td>
<td>Not required</td>
</tr>
<tr>
<td>Pre-approval</td>
<td></td>
<td>FDA has to prove that a supplement is not safe to restrict use or remove from the market</td>
</tr>
<tr>
<td>FDA Pre-approval</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Proof of efficacy not required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Content and Purity</td>
<td>• Adhere to strict standards for content and purity • Digested content is pure</td>
<td>• Contains variable amounts of OM3-FA • Most do not contain labelled content of OM3-FA • Up to 36% dietary supplement OM3-FA content is saturated fat • Oxidation • Contamination</td>
</tr>
<tr>
<td>Substitution</td>
<td>DHA/EPA combination products are not equivalent to EPA-only products</td>
<td>OM3-FA dietary supplements are not equivalent to and should not be substituted for Rx OM3-FA products</td>
</tr>
</tbody>
</table>
Dietary Supplement Fish Oils Are a By-product of Industrial Extraction Procedures
Dietary Supplement vs Prescription Fish Oil

Supplement

Dietary supplement fish oils
- 30% Omega-3
- 18% EPA
- 12% DHA

Prescription

Omega-3 fatty acid ethyl esters
- ≥96% Omega-3
- 84% Omega-3
- 46.5% EPA
- 37.5% DHA

EPA ethyl esters
- ≥96% EPA
- 0% DHA

Fish oil supplements in New Zealand are highly oxidised and do not meet label content of n-3 PUFA

Benjamin B. Albert\\, José G. B. Derraik\\, David Cameron-Smith\\, Paul L. Hofman\\, Sergey Tumanov\\, Silas G. Villas-Boas\\, Manohar L. Garg\\ and Wayne S. Cutfield

Figure 1 | The actual n-3 PUFA content (EPA + DHA) contained in individual retail fish oil products in relation to the claimed content (dotted line).

Figure 2 | The content of oxidation markers in retail fish oil tested in relation to recommended international thresholds (dotted lines).

Published 21 January 2015
102 products evaluated
- Amount of combined EPA/DHA ranged from 30 mg to 1452 mg per serving.
- The Rx Dose ranged from 3 to 112 doses per day
- Monthly cost ranged from $15 to $700
- Only 22% met our usage criteria

“The amount of EPA and DHA per recommended servings in these products was highly variable. Clinicians should heighten their scrutiny in terms of selection of the appropriate product.”
Knowledge, Perceptions, and Patterns of Fish Oil Use in Cardiac Patients

• Survey to determine cardiac patients’ knowledge and patterns of use of fish oil-derived dietary and Rx products
• 711/1000 respondents
• Reasons for use – general health (34%), heart health (28%), arthritis (9%), lipid disorders (8%)
• 14% advised to take OM-3 FA by a HCP
• 26% knew the active ingredient
• 81% purchased through a non-pharmacy retail outlet

Omega-3 Dietary Supplements

- Pros
  - Few concentrated products are available
  - Some products relatively inexpensive
  - Available at numerous outlets
  - Data indicate most products are within accepted standards for contaminants – mercury, arsenic, dioxin, PCBs
Omega-3 Dietary Supplements

- Cons
  - Low concentrated products require many “pills” – pill burden and calories
  - Liquid products require refrigeration
  - Dosing confusion
  - “Fishy” labeling
    - Pharmaceutical grade”
    - “Tested in FDA-approved laboratory”
    - Provide “Daily recommended intake for EPA and DHA”
    - “Krill Oil” – may contain fish oil
  - Cost often exceeds prescription co-pay
  - Variability – batch-to-batch and seasonal
  - More adverse effects
  - Some products may contain heavy metals, PCBs, and are oxidized
Fish Oil – Prescription

**Pros**
- Pure
- Consistent
- Value of prescription
  - Counseling
  - Monitoring
- Greater adherence
- Adverse effects

**Cons**
- Cost
  - High copay
  - Formulary coverage
- Insurance changes
- Patient perception
- Expanded indication for EPA-only product
- Guideline recommendation for EPA-only product
New Evidence to Improve Management of Patients with or at High Risk of ASCVD Events

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Negative Niacin Outcome Studies (Added to Statin Therapy)

**AIM-HIGH (−29% TG)**

- **Competition Therapy**
- **Monotherapy**

Cumulative % with Primary Outcome vs. Time (years)

- **HR 1.02, 95% CI 0.87–1.21**
- **Log-rank P=0.79**

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1696</td>
<td>1718</td>
</tr>
<tr>
<td>1</td>
<td>1581</td>
<td>1606</td>
</tr>
<tr>
<td>2</td>
<td>1381</td>
<td>1366</td>
</tr>
<tr>
<td>3</td>
<td>910</td>
<td>903</td>
</tr>
<tr>
<td>4</td>
<td>436</td>
<td>428</td>
</tr>
</tbody>
</table>

**HPS2-THRIVE (−26% TG)**

Effect of ERN / LRPT on Major Vascular Events

- **Risk ratio 0.96 (95% CI 0.90–1.03)**
- **Log-rank P=0.29**

<table>
<thead>
<tr>
<th>Years of Follow-up</th>
<th>Placebo</th>
<th>ERN / LRPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15.0%</td>
<td>14.5%</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
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</tr>
</tbody>
</table>


### Negative* Fenofibrate CVOTs (As Statin Adjunct)

<table>
<thead>
<tr>
<th>Study</th>
<th>CV Risk Profile</th>
<th>Statin Use</th>
<th>Daily Intervention</th>
<th>Median Baseline TG Level</th>
<th>Effect on TG Level</th>
<th>Primary Outcome</th>
<th>Primary Outcome Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD (N=5518)</td>
<td>• T2DM • 40-79 yrs w/CVD or • 55-79 yrs w/ ≥2 CV risk factors</td>
<td>All pts: Open-label simvastatin (mean dose: 22 mg/d)</td>
<td>Fenofibrate</td>
<td>162 mg/dL</td>
<td>−26%</td>
<td>• Nonfatal MI or Stroke or CV death (Mean f/u: 4.7 yrs)</td>
<td>• HR=0.92* (95% CI, 0.79-1.08) P=0.32</td>
</tr>
<tr>
<td>FIELD (N=9795)</td>
<td>• T2DM • 50-75 yrs</td>
<td>Added during study in 2547 pts (26%)</td>
<td>Fenofibrate</td>
<td>154 mg/dL</td>
<td>−30% (at 1 yr)</td>
<td>• Nonfatal MI or CHD death Median f/u: 5 yrs</td>
<td>• HR=0.89* (95% CI, 0.75-1.05) P=0.16</td>
</tr>
</tbody>
</table>

*Note that post hoc analysis for both studies found statistically significant benefit in the subgroup of patients with TG≥204 mg/dL & HDL-C ≤34 md/dL (Sacks FM et al. *N Engl J Med*. 2010;363:692-4).