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Fish Oils
(Swimming in a New Direction)

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Disclosures:

I have received honoraria from the following companies:

- Novo-Nordisc
- Amgen
- BI/Lilly
- AstraZeneca
History
PERFECT NUTRITIONAL STORM

- Diet has changed more in past 50 years than in past 10,000
- Increased Consumption of Refined Carbohydrates
- Increased Consumption of Inflammatory Omega6 Vegetable Oils (corn, soy)
- Decreased Consumption of Anti-Inflammatory Omega3 Fatty Acids by 95%

This pro-inflammatory diet is causing gene expression of Paleo genes resulting in rampant chronic illness. Gene Expression can be controlled by diet.
HISTORIC FATTY ACID BALANCE

- **OMEGA3**
- **OMEGA6**

<table>
<thead>
<tr>
<th>Year</th>
<th>OMEGA3</th>
<th>OMEGA6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1900</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>2010</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>PALEO</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>
South African Pilchard Oil

5. THE ISOLATION AND STRUCTURE OF AN EICOSAPENTAENIC ACID FROM SOUTH AFRICAN PILCHARD OIL

By J. M. WHITCUTT† and D. A. SUTTON

National Chemical Research Laboratory, South African Council for Scientific and Industrial Research, Pretoria, South Africa

(Rceived 12 December 1955)

In recent years structural diagnosis of the highly unsaturated fatty acids of natural origin has been facilitated by the increased use of spectral data, and by improvements in the methods of oxidative degradation due to Klenk & Hoeggard (1952). However, there is still considerable disagreement on the polyunsaturated oxidation products of such acids, and probably does occur. Keil & Brown (1952)

† Marine Oils Research Fellow.

From PubMed Database: Earliest Published Papers on Fish Oil (1922) and Omega-3 Fatty Acids (1956)
Dr. Jørn Dyerberg MD, Professor, DMSc

- “Father and Discoverer of Omega 3’s”
- Chief Physician
- World renowned and foremost expert on Omega 3 Fatty Acids
- 350 Publications
- AHA “Recognition of Outstanding Contribution for the Advancement of Heart Health Worldwide”
- Led 5 Expeditions to the Eskimos in Greenland

“The Godfather of Omega-3s”
What Are Fatty Acids

- Long Chain Hydrocarbons with a carboxyl group
- Long Chain Fatty Acids are typically even numbered
- Variable Saturation (single bonded hydrogens)
- Fully Saturated (SF) – no double bonds
  - Ex. Palmitic Acid, Butyric Acid
- Monounsaturated (MUFA) – single double bond
  - Ex. Omega 9s - Oleic Acid
- Polyunsaturated (PUFA) – multiple double bonds
  - Ex. Omega 3s & 6s - Eicosapentaenoic Acid, Docosahexaenoic acid, Alpha-linolenic acid
Background on Omega-3 Fatty Acids

• EPA and DHA are precursors to eicosanoids and provide an anti-inflammatory effect throughout the body.

• These fatty acids are used in the formation and fluidity of cell membranes, which help with maintenance of blood pressure and heart rate, nervous system function, and in hemostatic regulation, consisting of blood clotting and thromboxane production.

• EPA is a long chain fatty acid. It is the single vital nutrient that controls communication between nerve cells and the brain, and vital for functionality of multiple cellular organelles. Ex. nuclear signaling, genetic sequencing, mitochondrial electron transport, ribosomal protein synthesis, cell membrane gas/nutrient/molecular transport, energy metabolism.

• DHA is another long chain fatty acid. It is mostly structural for cell membranes.
Biosynthesis & Metabolism of Polyunsaturated Fatty Acids Leading Towards or Away From Inflammation

**Omega-6**

- Linoleic Acid (LA)
- Arachidonic Acid (AA)
- Desaturases
- Elongases
- Cyclooxygenases
- Lipoxigenases

**Pro-Inflammatory:**
- Eicosanoids
- Prostaglandins
- Leukotrienes
- Thromboxanes

**Omega-3**

- α-Linolenic Acid (ALA)
- Eicosapentaenoic acid (EPA)
- Docosahexaenoic acid (DHA)
- Desaturases
- Elongases

**Minimally Inflammatory:**
- Eicosanoids
- Inflammation Resolving:
  - Resolvins, Protectins
Triglycerides and ASCVD
Postprandial Hepatic Lipid Load

Cholesterol
Safflower oil

• Poor Clearance 6-10 hours postprandial
• Patient Profile:
  • Hypertriglyceridemia
  • Chronic inflammation
  • CHD/risk equivalent
  • Diabetes and/or Metabolic Syndrome
  • Non-HDL >130 mg/dL

Turley S. et al., Am J Physiol Gastrointest Liver Physiol, 2008; 295: G813–G822

Cholesterol
Safflower oil
Ezetimibe

• Normal Clearance 2-4 hours postprandial
• Patient Profile: <2 risk factors
HTG Leads to Dysfunctional sdLDL: ↑LDL Oxidation, ↓LDL Clearance, and ↑Atherogenicity\textsuperscript{1,2}

Abnormal LDL and Macrophage Metabolism

- ↑ LDL oxidation
- ↓ LDL receptor binding (↓LDL clearance)
- ↑Monocyte chemoattraction
- ↑Monocyte adhesion to endothelial cells
- ↑Monocyte chemotaxis (through endothelium into artery wall)
- ↑Monocyte→ macrophage conversion
- ↑LDL uptake by macrophages
- ↑Foam cell formation

High TG and TRL Reflect an Atherogenic State

CE=cholesteryl ester; CETP=cholesteryl ester transfer protein; FFA=free fatty acid; sdHDL=small, dense high-density lipoprotein; sdLDL=small, dense low-density lipoprotein.

Image adapted from Bays and Miller.

Early Results from Omega-3 and Other Related Trials
# What Is the Effect on CV Outcomes?
(in Combination With Statin Therapy)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Key Trials</th>
<th>Key Findings</th>
</tr>
</thead>
</table>
| **Fibrates**           | ACCORD<sup>1</sup>  
FIELD<sup>2</sup> | No improvement in coronary events with fenofibrate monotherapy or addition of fenofibrate to statin therapy in patients with T2DM          |
| **Niacin**             | AIM-HIGH<sup>3</sup>  
HPS2-THRIVE<sup>4</sup> | No improvement in CHD death or risk of major vascular events from addition of niacin or niacin-laropiprant to statin therapy               |
| **EPA + DHA mixtures** | ORIGIN<sup>5</sup>  
RISK & PREVENTION<sup>6</sup>  
OMEGA<sup>7</sup> | No effect of low dose on CV outcomes (≥40% statin therapy at baseline)                                                                       |
| **Pure EPA**           | STRENGTH<sup>8</sup> | Ongoing (Western population)                                                                                                                  |
| **Pure EPA**           | JELIS<sup>9</sup>  
REDUCE-IT<sup>10</sup> | EPA + statin reduced Primary Endpoint MACE 19% (Japan)                                                                                  |
| **Pure EPA**           | REDUCE-IT<sup>10</sup> | Reduced Primary Endpoint 5-Point MACE 25%                                                                                                    |

CV=cardiovascular; ER=extended-release; MCE=major cardiac events; PCI=percutaneous coronary intervention; T2DM=type 2 diabetes mellitus.

Other Recent CVOT in the Omega-3 Class have Reported Negligible Impact on CV Events

- Two large, randomized, placebo-controlled CV outcome trials failed to demonstrate an effect of **low dose** supplementation with OM3FAs on the risk for CV events:
  - ORIGIN Trial: (1g/day); patients with (or at risk for) diabetes\(^1\)
  - RISK & PREVENTION Trial: (1g/day); patients with multiple CV risk factors\(^2\)
- Several meta-analyses of clinical trials of OM3FAs and CV events have been published. The majority have failed to confirm CV benefit from EPA and DHA low-dose supplementation
  
  Note: These were low-dose studies and not in patients with persistent high TGs
- The OM3FA mixtures studied in most omega-3 trials were primarily comprised of EPA, DHA, other omega-3 and omega-6 acids and other constituents

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FDA Withdraws Approval of Indications for Use of Fenofibrates and Niacin ER in Combination With Statins

“...the totality of the scientific evidence no longer supports the conclusion that a drug-induced reduction in TG levels and/or increase in HDL-C levels in statin-treated patients results in a reduction in the risk of CV events...”

“...FDA has determined that the benefits of niacin ER tablets and fenofibric acid DR capsules for coadministration with statins no longer outweigh the risks...”

*Federal Register/Vol. 81, No. 74/ Monday, April 18, 2016*
### 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>
<th>Favors Treatment</th>
<th>Favors Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOIT (2010)</td>
<td>1150 / 800</td>
<td>Dietary supplement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AREDS-2 (2014)</td>
<td>650 / 350</td>
<td>Dietary supplement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU.FOL.OM3 (2010)</td>
<td>400 / 200</td>
<td>Dietary supplement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JELIS (2007)</td>
<td>1800 / NA</td>
<td>Pure EPA Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha Omega (2010)</td>
<td>226 / 150</td>
<td>Margarine with dietary supplement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMEGA (2010)</td>
<td>460 / 380</td>
<td>Rx EPA/DHA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R&amp;P (2013)</td>
<td>500 / 500</td>
<td>Rx EPA/DHA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GISSI-HF (2008)</td>
<td>850 / 950</td>
<td>Rx EPA/DHA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORIGIN (2012)</td>
<td>465 / 375</td>
<td>Rx EPA/DHA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GISSI-P (1999)</td>
<td>850 / 1700</td>
<td>Rx EPA/DHA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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></td>
</tr>
<tr>
<td>Von Schacky, 1999</td>
<td></td>
</tr>
<tr>
<td>Marchioli, 2001</td>
<td></td>
</tr>
<tr>
<td>Yokoyama, 2007</td>
<td></td>
</tr>
<tr>
<td>Einvik, 2010</td>
<td></td>
</tr>
<tr>
<td>Roncaglioni, 2013</td>
<td></td>
</tr>
</tbody>
</table>

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

Favors EPA+DHA  Favors Control

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

JELIS: Rx EPA + Statin Reduced MCE by 19% versus Statin Alone


<table>
<thead>
<tr>
<th>Major Coronary Events</th>
<th>EPA + Statin</th>
<th>Statin (Control)</th>
<th>P Value</th>
<th>HR (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (N=18,645)</td>
<td>2.8%</td>
<td>3.5%</td>
<td>0.011</td>
<td>0.81 (0.69–0.95)</td>
</tr>
<tr>
<td>Primary prevention (n=14,981)</td>
<td>1.4%</td>
<td>1.7%</td>
<td>0.132</td>
<td>0.82 (0.63–1.06)</td>
</tr>
<tr>
<td>Secondary prevention (n=3664)</td>
<td>8.7%</td>
<td>10.7%</td>
<td>0.048</td>
<td>0.81 (0.66–1.00)</td>
</tr>
</tbody>
</table>
Why REDUCE-IT?

No previous CV outcomes trial has been designed to assess treatment of patients with persistent high TG despite statin therapy.
REDUCE-IT: **Reduction of CV Events With Icosapent Ethyl – Intervention Trial**\(^1,2\)

- 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
  - TG ≥200 mg/dL

**Primary endpoint:** Prevention of 1st major CV event

**Study duration** ≈ 4–6 years

- Randomized, double-blind, parallel-group design
- Secondary outcome measures: incidence of additional CV events, lipid and lipoprotein levels, subgroup analyses such as patients with diabetes, etc
- International trial; first patient dosed in December 2011
- Participants enrolled should not be advised to use VASCEPA in place of participation
- Vascepa should not be taken in place of a healthy diet and lifestyle or statin therapy

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Primary Composite Endpoint

Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.2%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

25% RRR
NNT=21

No. at Risk
Placebo  4090  3743  3327  2607  2347  1358
VASCEPA  4389  3787  3431  2951  2563  1439
Bhatt et al., *NEJM* 2019 Jan 3;380(1):11-22

**Pure EPA Reduced Aggregated 5-Point MACE Endpoints by 25%**

Hazard ratio: 0.75
95% CI: 0.68 – 0.83
RRR: 24.7%
ARR: 4.8%
NNT: 21 (95% CI: 15-33)
P = 0.00000001
EPA vs. DHA
Both EPA and DHA have been shown to lower TG...²-⁴,*

...but DHA has also been shown to increase LDL-C in some patients²,³,*

Both the amount and type of omega-3 fatty acid are important for TG-lowering¹

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*Studies were conducted in subjects with varying baseline TG levels. Arrows are not representative of actual effect on TG or LDL-C; individual effects may vary.

**Fig. 2.** Representative examples of the OCT analysis.

In an example from the EPA group (A), the fibrous cap thickness increased (120 μm to 200 μm) and the lipid arc decreased (133 degrees to 119 degrees) over 7.9 months of follow-up. In an example from the control group (B), the fibrous cap thickness decreased (120 μm to 110 μm) and the lipid arc increased (127 degrees to 131 degrees) over 8.1 months of follow-up. The white arrows indicate the fibrous cap thickness. The yellow arrows indicate the lipid arc. OCT = optical coherence tomography, EPA = ethyl eicosapentaenoic acid.
Further, EPA Has Been Shown to Inhibit Oxidative Stress in Small Dense LDL

EPA is believed to block free-radical propagation through the phospholipid monolayer, preventing lipid oxidation and deleterious changes in lipid structural organization.

Adapted from Mason RP, Jacob RF. Diabetes. 2015;64(suppl 1):A178-A179. Poster 705.
Mason RP, Jacob RF. Biochim Biophys Acta. 2015;1848(2):502-509.
Other Potential Cardioprotective Effects of EPA

- Cardioprotective effects of EPA observed in REDUCE-IT and JELIS may be due to multiple mechanisms working together rather than lowering TGs alone.
- EPA may have beneficial effects on multiple atherosclerosis processes\(^1\):
  - endothelial function
  - oxidative stress
  - foam cell formation
  - inflammation/cytokines
  - plaque formation/progression
  - platelet aggregation
  - thrombus formation
  - plaque rupture
- A non-statin drug’s various mechanisms may not translate into a reduced CV risk when used with a statin\(^2\).

Supplements
Dietary Supplement Background

• In the US, fish oil is the most commonly used dietary supplement\(^1\)
  • Dietary supplement fish oils contain a variety of omega-3s e.g. EPA, DHA, omega-6s, saturated fats and other ingredients

• Although omega-3 fatty acid dietary supplements are widely available, their integrity and efficacy remain unverified\(^3\)-\(^6\)

• Dietary Supplement Current Good Manufacturing Practices (cGMPs) are not as strict as CGMP for drugs e.g. No expiration date required

• US Department of Justice has begun an industry-wide sweep of the dietary supplement industry filing 117 actions regarding the safety, content and labeling of various products and the potential risks posed to consumers\(^7\)

Available forms of Omega-3: Rx and Supplement (there are no OTC)

<table>
<thead>
<tr>
<th>FDA Product Classification</th>
<th>Prescription1-2</th>
<th>Dietary Supplements3-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Pre-Approval</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Products</td>
<td>VASCEPA® (icosapent ethyl); generic omega-3 fatty acid EE</td>
<td>Numerous Available (EPA, DHA, Other FAs, Saturated Fat)</td>
</tr>
<tr>
<td>Quantity of OM3/Capsule</td>
<td>VASCEPA: 1 g EPA Generic OM3FA EE: mixed 465mg EPA/ 375mg DHA</td>
<td>Typically 100 mg – 400 mg mixed content</td>
</tr>
<tr>
<td>Capsules to achieve daily dose of Omega-3</td>
<td>4</td>
<td>? : maybe 10-40</td>
</tr>
</tbody>
</table>

FDA=US Food and Drug Administration, EE=Ethyl Ester, FA=Fatty Acids

Representative Fish and Krill Oil Supplements Contain High Amounts of Saturated Fats

2. Mason RP et al. Poster presented at: Academy of Managed Care Pharmacy 2015 Nexus; October 26-29, 2015; Orlando, FL.
Dietary Supplement Fish Oil: A Dose of Saturated Fat for Patients at CV Risk?

- As much as 36% of dietary supplement fish oil fatty acid content is saturated fat.
- Following hydrolysis, dietary supplement fish oil creates a solid mass of saturated fat at room temperature compared to Rx omega-3 fatty acids.

Hydrolyzed content of VASCEPA is pure EPA.

Hydrolyzed content of dietary supplement fish oil is high in saturated fat.

Photo courtesy of R. Preston Mason, PhD.
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.

Omega-3s in Diabetes Mellitus

• Omega-3 therapy improves the ability of muscle cells to take up glucose in the presence of insulin.

• This proves to be beneficial to those with type II diabetes.

• Hypertriglyceridemia (fasting serum TG of 200 mg/dl or higher) is a common lipid abnormality in individuals with Type 2 diabetes

• A number of randomized controlled trials have found that fish oil supplementation significantly lowers serum triglyceride levels in diabetic individuals
Additional Diseases Showing Possible Benefit from Omega-3 Therapy

Diseases of Cellular Dysfunction and/or Tissue Inflammation

- Allergy
- Alzheimers Disease
- Anti-phospholipid Antibodies
- Asthma
- Autism
- Cancers
  - Breast
  - Colon
  - Non-small Cell Lung
  - Prostate
- Dermatologic Disease
  - Atopic Dermatitis
  - Eczema
  - Psoriasis
- Endometriosis
- IgA Nephropathy
- Infection
- Infertility
- Inflammatory Bowel Disease
  - Crohn’s Disease
  - Ulcerative Colitis
- Lupus Erythematosus
- Nonalcoholic Steatic Hepatitis
- Ophthalmic Disease
  - Age-related macular degeneration
  - Astigmatism
  - Dry eye
- Periodontitis
- Psychological Disorders
  - Attention Deficit Hyperactivity Disorder
  - Bipolar Disorder
  - Major Depressive Disorder
  - Schizophrenia
- Rheumatoid Arthritis
- Sepsis/Septic Shock
Across decades and continents, populations with high omega-3 intake have significantly less vascular disease.

Omega-3s are Essential Fatty Acids because the body needs them but cannot synthesize them sufficiently from component molecules.

Omega-3s are known to have multiple cellular mechanisms, and have been shown to provide numerous cellular, tissue, organ, and system benefits:
- Reducing inflammation, especially EPA
- Normalizing cell and tissue function

Because Omega-3s disperse to every cell in the body with no singular locus of action, they must be acquired in relatively large amounts.

Pure high dose eicosapentaenoic acid added to statin therapy has been shown to reduce MACE events in 2 large CVOTs:
- REDUCE-IT Trial showed 25% MACE reduction
- JELIS Trial showed 19% MACE reduction
- No DHA-containing product has shown MACE benefit when added to a statin

Store-bought supplements are not therapeutic, and should not be used for disease treatment or prevention.
References


- Wataru Matsuyama, MD, PhD; Hideo Mitsuyama, MD; Masaki Watanabe, MD, PhD; Ken-ichi Oonakahara, MD; Ikkou Higashimoto, MD, PhD; Mitsuhiro Osame, MD, PhD and Kimiyoshi Arimura, MD, PhD: “Effects of omega-3 polyunsaturated fatty acids on inflammatory markers in COPD” American College of Chest Physicians, 2005, Available at: http://www.chestjournal.org/cgi/content/full/128/6/3817 Accessed on: October, 29, 2007

References

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• Rose DP, Connolly JM. Pharmacol Ther. 1999;83(3):217-244.
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• http://lpi.oregonstate.edu/infocenter/othernuts/omega3fa/index.html
• http://www.google.com/imghp?hl=en&tab=wi&q=
Thankyou