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

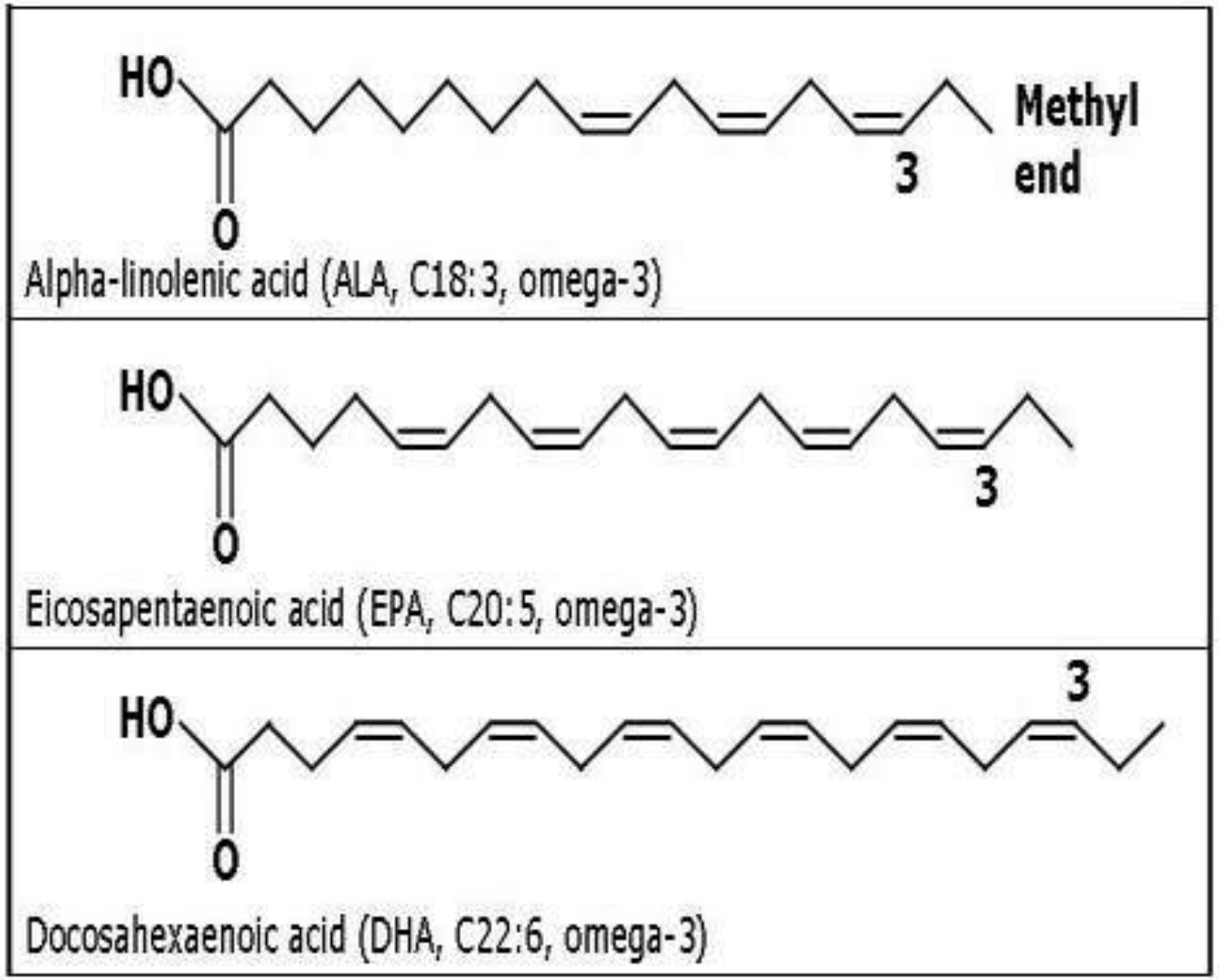
Michael B. Bottorff, PharmD, *Chair*
Professor and Chair
Department of Pharmacy Practice
Manchester College of Pharmacy
Ft. Wayne, IN

Daniel E. Hilleman, PharmD
Professor of Pharmacy Practice
Director, Continuing Education
School of Pharmacy and Health Professions
Creighton University
Omaha, NE

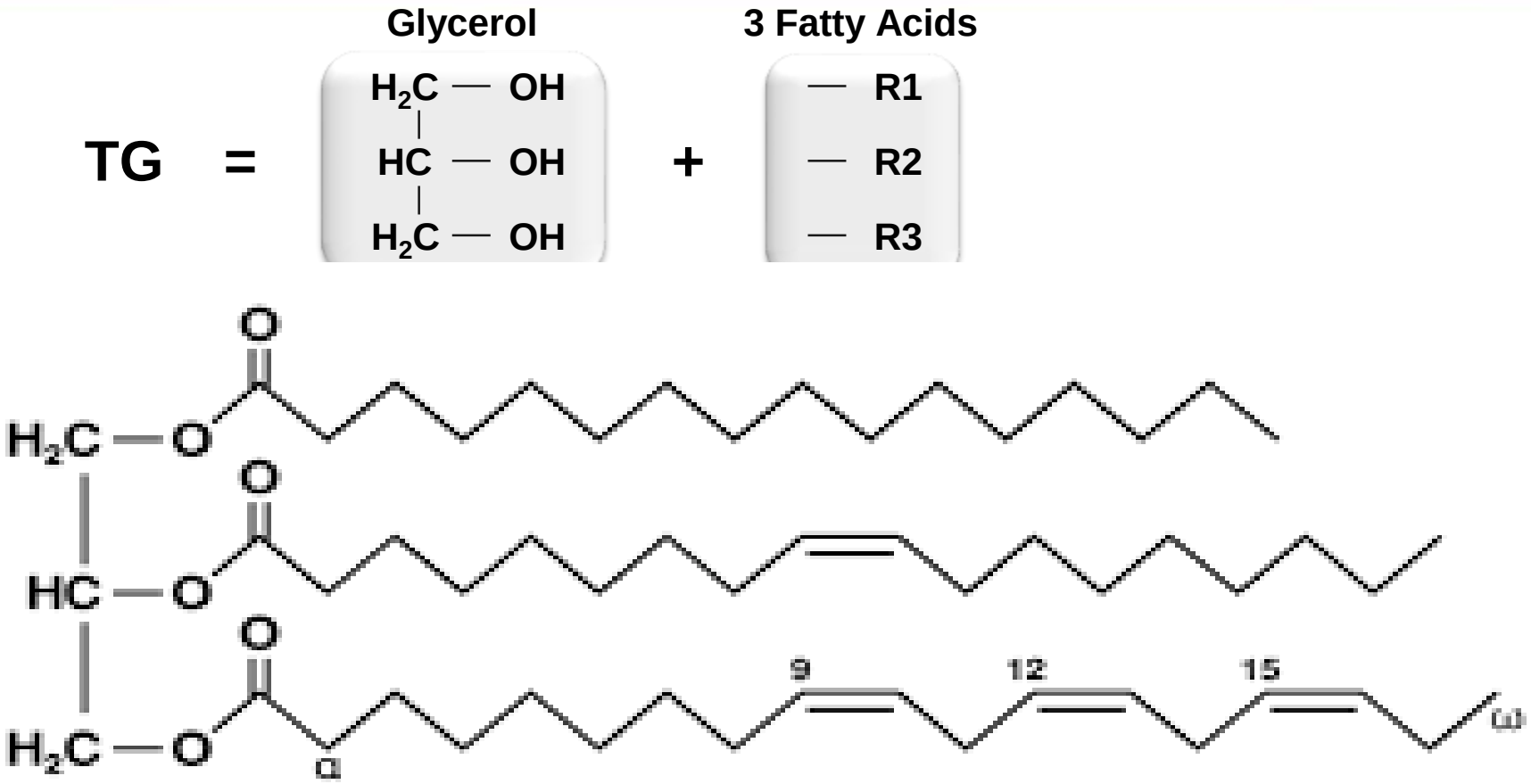
Omega-3 Fatty Acids Reducing Risk in ASCVD

Daniel E. Hilleman, PharmD
Professor of Pharmacy Practice
Director, Continuing Education
School of Pharmacy and Health Professions
Creighton University
Omaha, NE

Omega-3 Fatty Acids

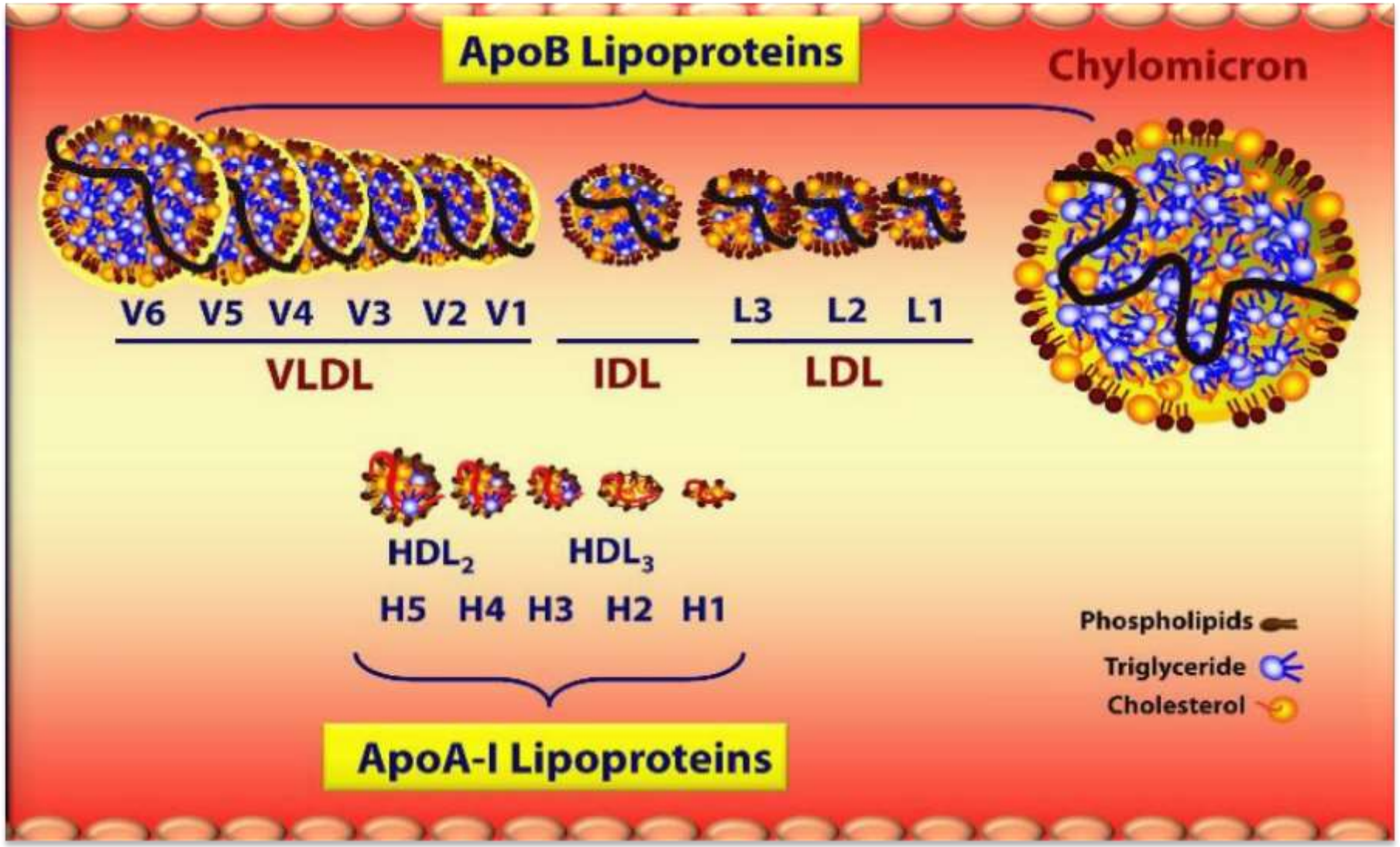


Triglycerides



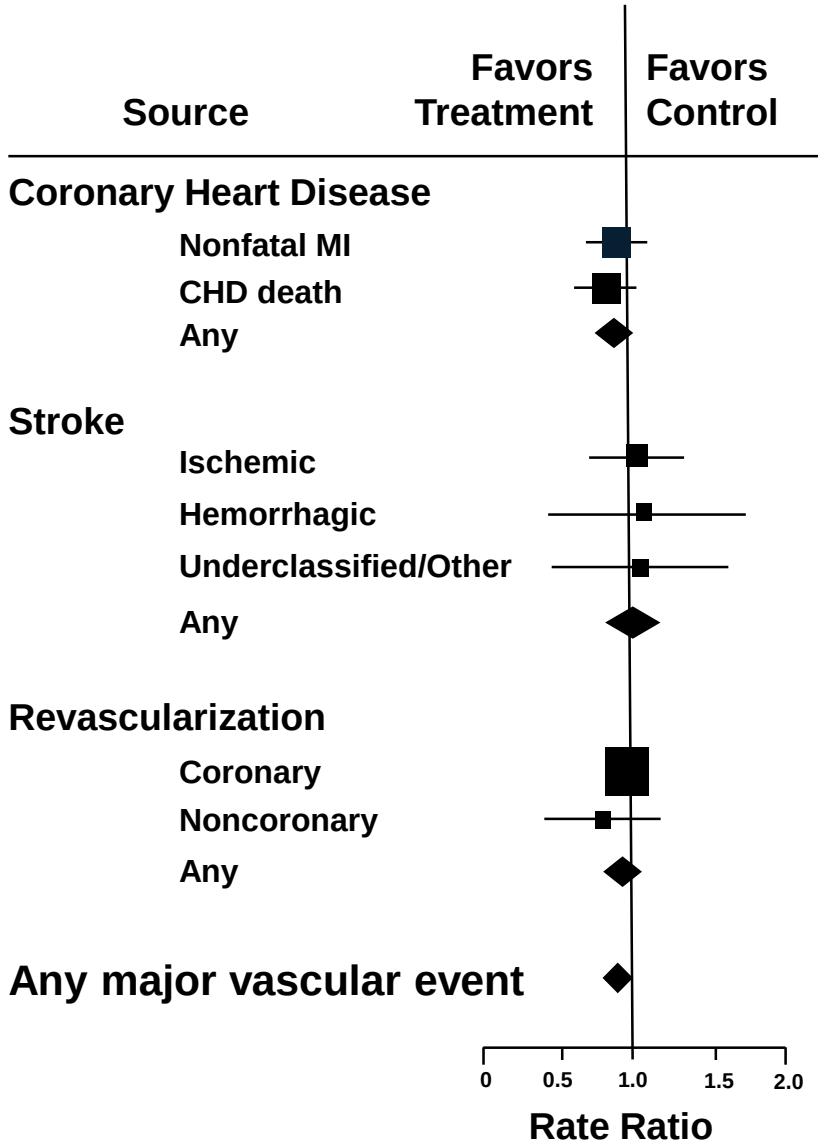
Katan MB et al. A*m J Clin Nutr*. 1994;60(6 suppl):1017S-1022S. Khan-Merchant N et al. *J Nutr.* 2002;132:3256-62.
Choi BG et al. In: Davidson MH, Toth PP, Maki KC, eds. *Therapeutic Lipidology*. 2007:1-22.

Lipoprotein Classification



Clinical Trials of Omega-3 Fatty Acids and ASCVD Risk

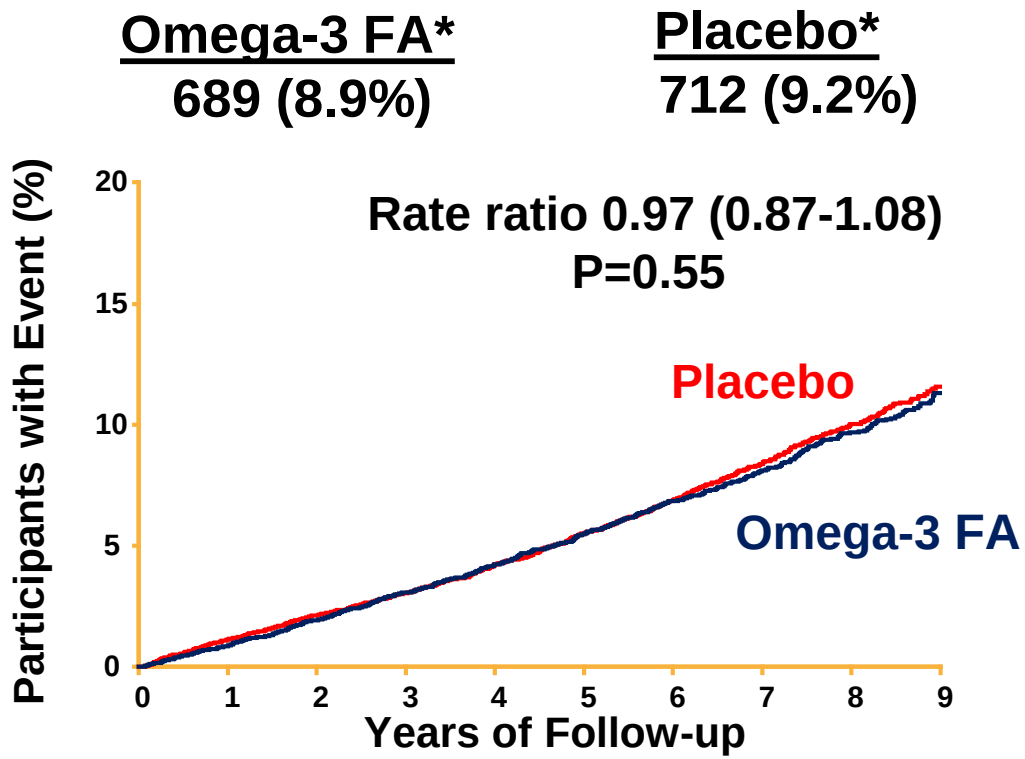
Study (Year)	EPA/DHA Dose (mg/d)	EPA / DHA Source
DOIT (2010)	1150 / 800	Dietary supplement
AREDS-2 (2014)	650 / 350	Dietary supplement
SU.FOL.OM3 (2010)	400 / 200	Dietary supplement
JELIS (2007)	1800 / 0	Pure EPA Rx
Alpha Omega (2010)	226 / 150	Margarine with dietary supplement
OMEGA (2010)	460 / 380	Rx EPA/DHA
R&P (2013)	500 / 500	Rx EPA/DHA
GISSI-HF (2008)	850 / 950	Rx EPA/DHA
ORIGIN (2012)	465 / 375	Rx EPA/DHA
GISSI-P (1999)	850 / 1700	Rx EPA/DHA



Aung T et al. *JAMA Cardiol*. 2018;3:225-34..

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

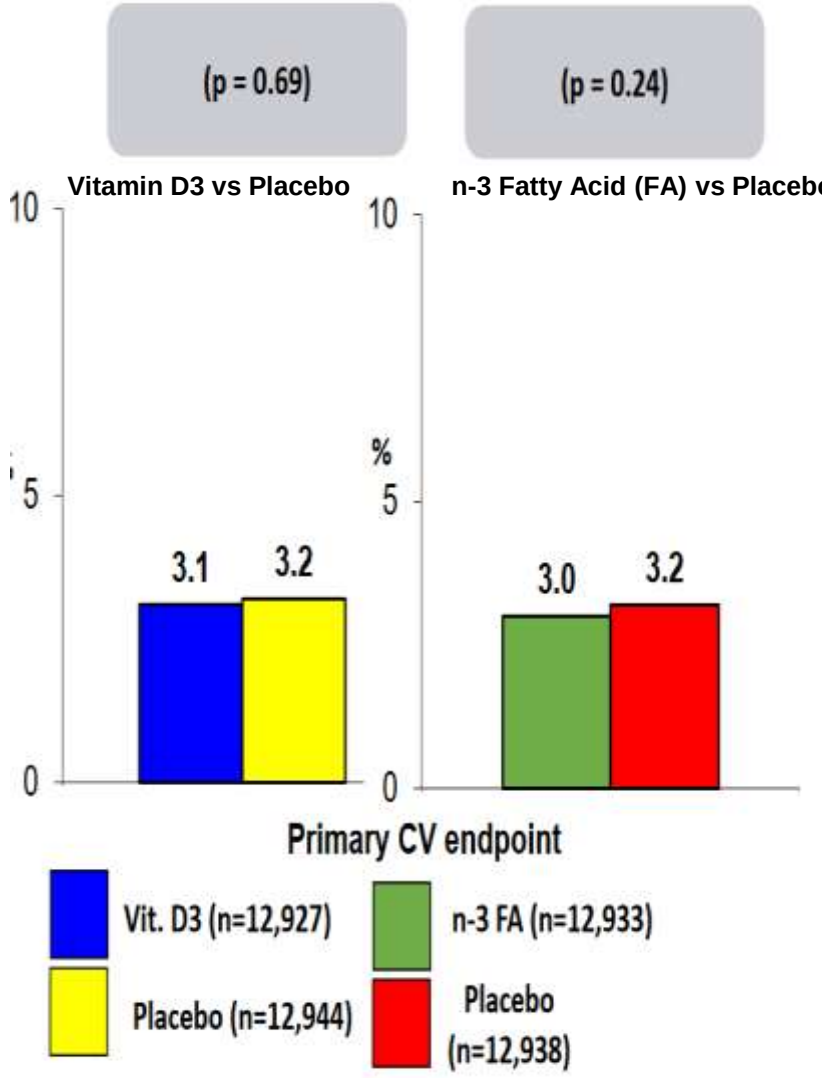


*1-g capsules containing either n-3 fatty acids (fatty acid group) matching placebo (olive oil) daily.

ASCEND Study Collaborative Group et al. *N Engl J Med*. 2018;379:1540-50.

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

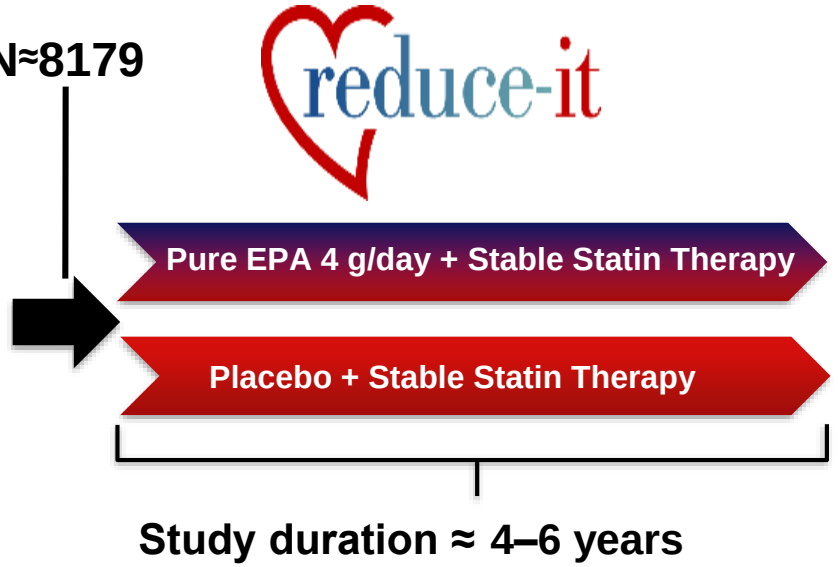


Manson JE et al. *N Engl J Med.* 2019;380:23-32, 33-44.

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



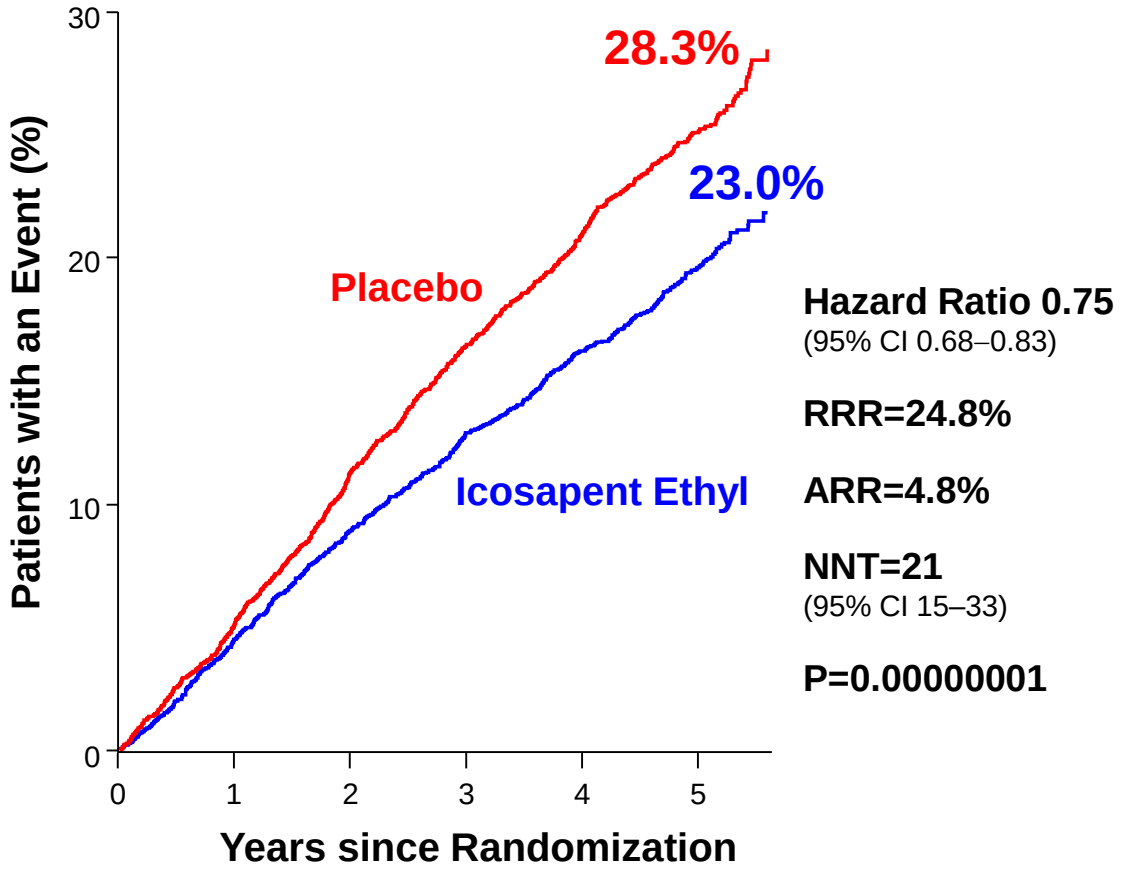
Primary Endpoint
1st major CV event

- CV death
- Nonfatal MI
- Nonfatal stroke
- Coronary revascularization
- Unstable angina requiring hospitalization

Bhatt DL et al. *N Engl J Med.* 2019;380:11-22.

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

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



Hazard Ratio 0.75
(95% CI 0.68–0.83)

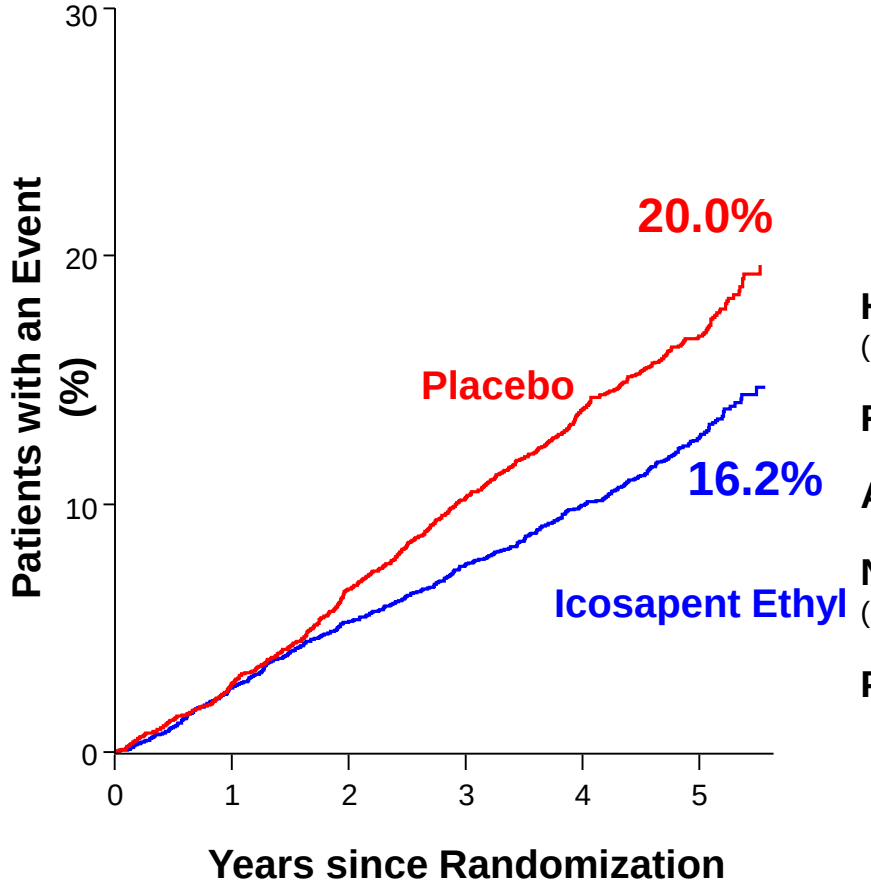
RRR=24.8%

ARR=4.8%

NNT=21
(95% CI 15–33)

P=0.00000001

Key Secondary Endpoint
CV Death, MI, Stroke



Hazard Ratio 0.74
(95% CI 0.65–0.83)

RRR=26.5%

ARR=3.6%

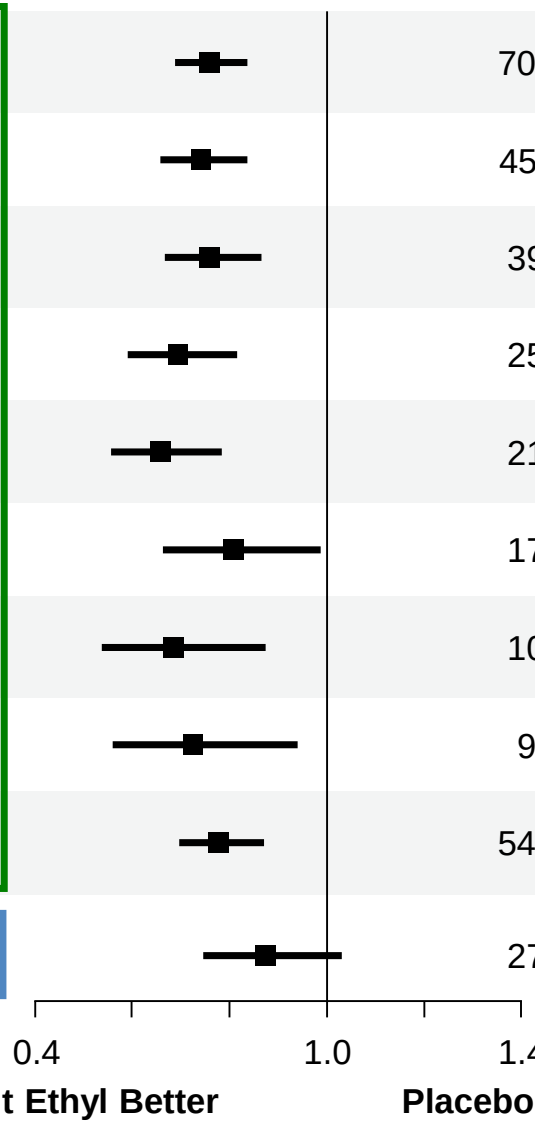
NNT=28
(95% CI 20–47)

P=0.0000006

Bhatt DL et al. *N Engl J Med.* 2019;380:11-22. Bhatt DL. AHA 2018, Chicago.

REDUCE-IT: Prespecified Hierarchical Testing

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergency Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09



RRR=relative risk reduction

Bhatt DL. AHA 2018, Chicago.

Bhatt DL et al. *N Engl J Med.* 2019;380:11-22.

REDUCE-IT: Treatment Emergent Adverse Events

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

Bhatt DL et al. *N Engl J Med.* 2019;380:11-22.

REDUCE-IT: Adverse Events of Interest
Serious Bleeding and AF

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

- 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	**127 (3.1%)**	**84 (2.1%)**	**0.004**

Bhatt DL et al. *N Engl J Med.* 2019;380:11-22.

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

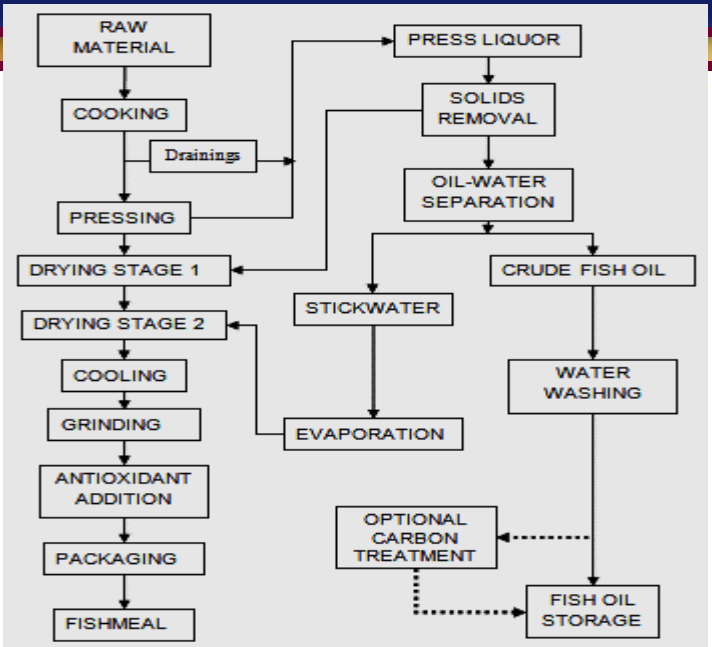
- Omega-3 *fatty acid ethyl esters*
  - Lovaza® + generics
    - 2 g BID with food or 4 g Qday with food
- EPA *ethyl esters*
  - Vascepa®
    - 2 g BID with food
- Omega-3 *carboxylic acids* (free fatty acid form)
  - Epanova®
    - 2-4 g daily with/without food
    - Product currently not available commercially

Backes J et al. *Lipids Health Dis*. 2016;15:118.

Dietary Supplements vs Rx Fish Oil

	Prescription	Dietary Supplements
FDA Product Classification	**Drug**	**Food**
Clinical Trials Required Pre-approval	**Yes**	**Not required** **FDA has to prove that a supplement is not safe to restrict use or remove from the market**
FDA Pre-approval	**Yes**	**No** **Proof of efficacy not required**
Content and Purity	• **Adhere to strict standards for content and purity** • **Digested content is pure**	• **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**
Substitution	**DHA/EPA combination products are not equivalent to EPA-only products**	**OM3-FA dietary supplements are not equivalent to and should not be substituted for Rx OM3-FA products**

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

Purification

Omega-3 fatty acid ethyl esters

84% Omega-3

46.5% EPA

37.5% DHA

Pure EPA

EPA ethyl esters

≥96% Omega-3

≥96% EPA

0% DHA

1. VASCEPA [package insert]. Bedminster, NJ: Amarin Pharma, Inc; 2016.
2. Lovaza [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2015.

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

Benjamin B. Albert[1], José G. B. Derraik[1], David Cameron-Smith[1], Paul L. Hofman[1], Sergey Tumanov[2], Silas G. Villas-Boas[2], Manohar L. Garg[3] & Wayne S. Cutfield[1]

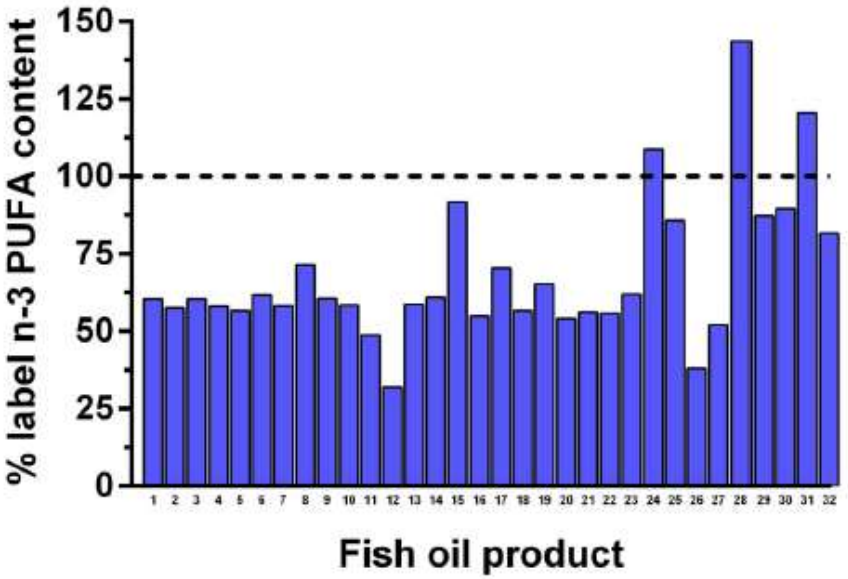


Figure 1 | The actual n-3 PUFA content (EPA + DHA) contained in individual retail fish oil products in relation to the claimed content (dotted line).

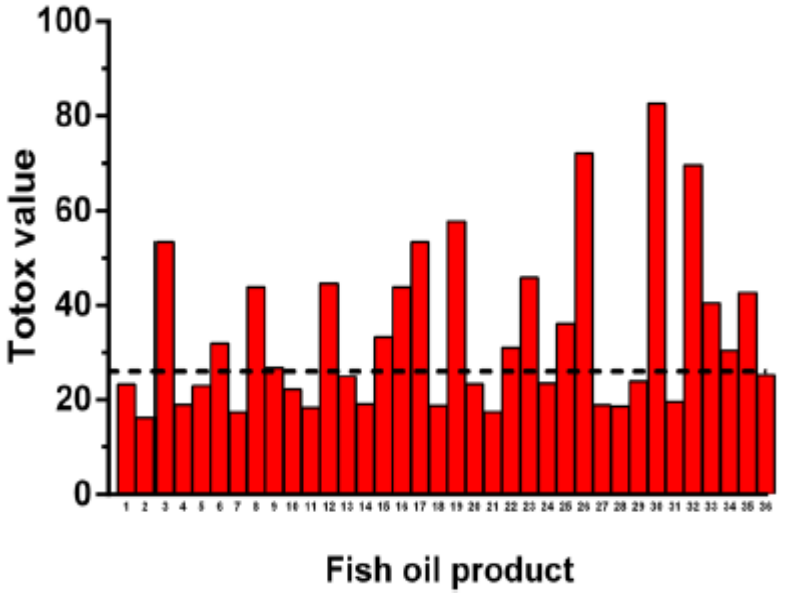


Figure 2 | The content of oxidation markers in retail fish oil tested in relation to recommended international thresholds (dotted lines).

SCIENTIFIC REPORTS | 5 : 7928 | DOI: 10.1038/srep07928

Published
21 January 2015

METABOLIC SYNDROME AND RELATED DISORDERS
Volume X, Number X, 2011

Pp. 1–17
DOI: 10.1089/met.2011.0004

ORIGINAL ARTICLE

Long Chain Omega-3 Dietary Supplements: A Review of the National Library of Medicine Herbal Supplement Database

Atanaz Zargar, Pharm.D., and Matthew K. Ito, Pharm.D., FCCP, FNLA, CLS

Abstract

Background: Dietary fish oil supplements are increasingly used as an alternative to prescription-grade omega-3 fatty acids (P-OM3) for the treatment of hypertriglyceridemia. The content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in these supplement products varies widely and may result in a suboptimal response. The aim of this study was to review marketed fish oil supplements and to develop a reference for clinicians to compare products.

Methods: The National Library of Medicine Herbal Supplement Database was systematically searched using fish oil, EPA, DHA, and omega-3 fatty acid as search terms. Daily doses needed to achieve the Food and Drug Administration (FDA)-approved dose (RxDose) (3,360 mg of combined EPA and DHA) were calculated from the milligrams of EPA and DHA per serving, and suggested retail prices were used to calculate monthly cost of each product. A "usage criteria" was set to highlight products at the RxDose with a monthly cost of <$50, daily servings <8, daily amount of vitamins A and D less than or equal to the U.S. Dietary Reference Intake upper limit defined as 10,000 and 4,000 IU, respectively, and if the product was U.S. Pharmacopeia verified.

Results: A total of 163 products were identified, and 102 nonliquid and liquid products met our entry criteria. The median amount of EPA and DHA per serving in the nonliquid products was 216 mg and 200 mg, respectively, and the median number of servings at the RxDose was 11.2 at a median monthly cost of $63.49. The

- 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

Hilleman D et al. *J Pharm Pract.* 2019; DOI: 10.117/0897190018824485

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

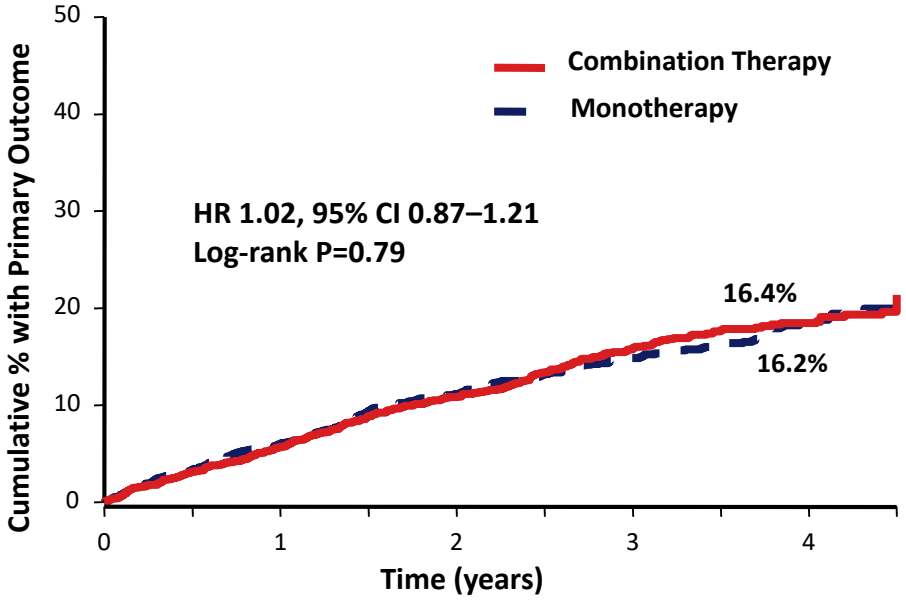
- Pros
  - Pure
  - Consistent
  - Value of prescription
    - Counseling
    - Monitoring
  - Greater adherence
  - Adverse effects
- Cons
  - Cost
    - High copay
    - Formulary coverage
  - Insurance changes
  - Patient perception
  - Expanded indication for EPA-only product
  - Guideline recommendation for EPA-only product

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

Michael B. Bottorff, PharmD, *Chair*
Professor and Chair
Department of Pharmacy Practice
Manchester College of Pharmacy
Ft. Wayne, IN

Negative Niacin Outcome Studies (Added to Statin Therapy)

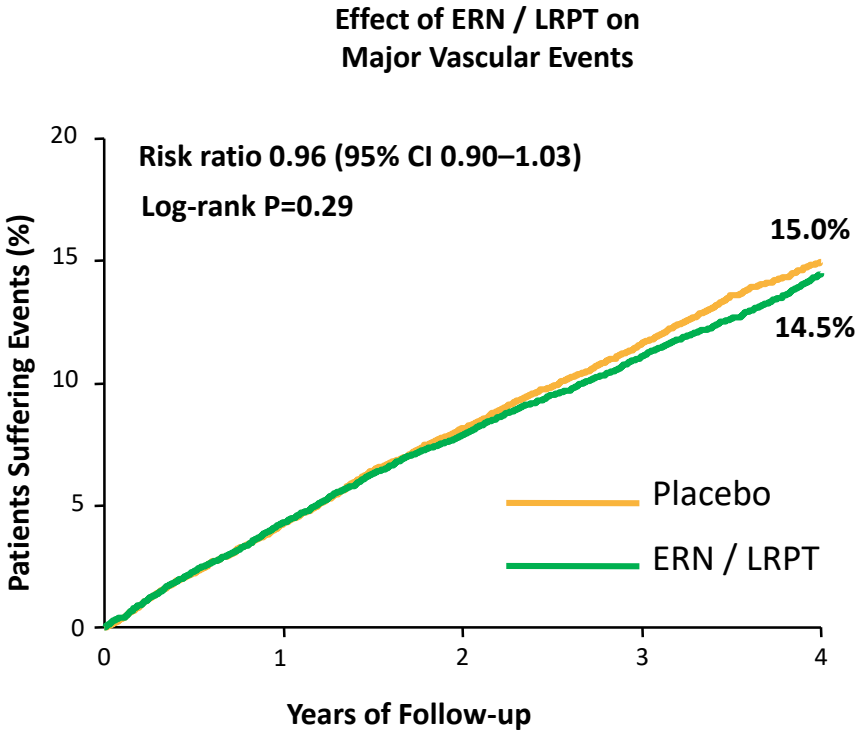
AIM-HIGH *(–29% TG)*



N at risk					
Monotherapy	1696	1581	1381	910	436
Combination Therapy	1718	1606	1366	903	428

Boden WE et al. *N Engl J Med.* 2011;365:2255-67

HPS2-THRIVE *(–26% TG)*



HPS2-THRIVE Collaborative Group. *N Engl J Med*. 2014;371:203-12.

Negative* Fenofibrate CVOTs *(As Statin Adjunct)*

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

***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).**

ACCORD Study Group et al. *N Engl J Med*. 2010;362:1563-74. Keech A et al. *Lancet*. 2005;366:1849-61.