Clinical Trial Evidence of Omega-3 Fatty Acids in ASCVD

Joseph Saseen, PharmD, BCPS, BCACP
Professor and Vice Chair

Skaggs School of Pharmacy and Pharmaceutical Sciences
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

1

Disclosure

Joseph J. Saseen

Reports no relevant financial relationships

2

Where are we with Lipid Lowering Therapy?

LDL-cholesterol

- Very strong direct association with ASCVD risk
  - Evidence from outcome trials
    - ASCVD event risk is reduced across a broad range of patients
    - New LDL-C lowering therapies and studies are forthcoming

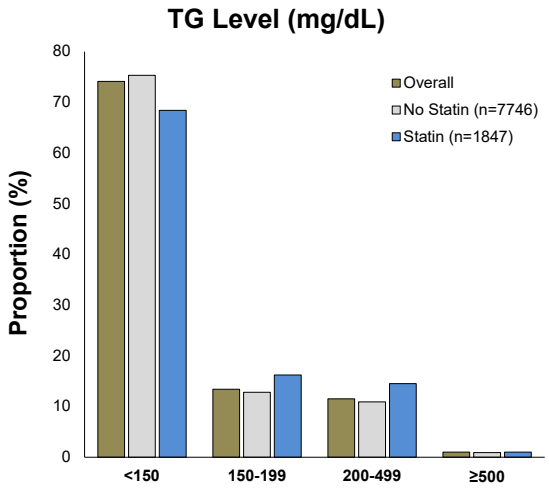
Elevated Triglycerides (TG)

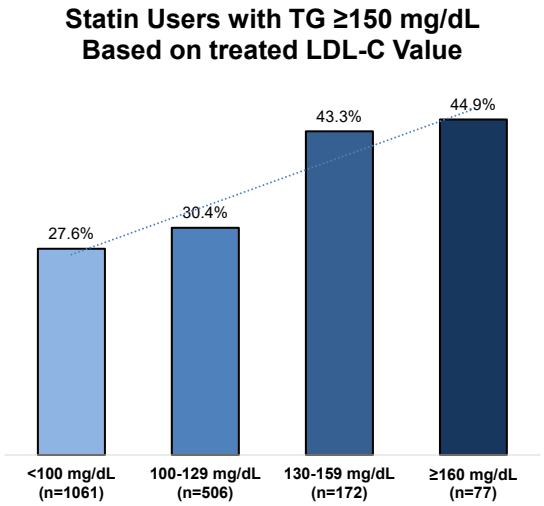
- Residual ASCVD risk in high-risk statin treated patients
  - Higher CV event risk and economic burden with TG 200-499 mg/dL versus <150 mg/dL
  - Evidence from outcome trials
    - Landmark trials with traditional triglyceride lowering medications have not clearly shown a benefit

Grundy SM, et al. Circulation 2019;139(25):e1082-e1143.
Toth PP, et al. J Am Heart Assoc. 2018;7(15):e008740.
Nichols GA, et al. J Clin Endocrinol Metab. 2018;103(8):3019-3027.

Hypertriglyceridemia in U.S. Adults: NHANES

9,593 adults with fasting TG values (2007-2014)





Fan W, et al. J Clin Lipidology 2019;13:100-108.

Drugs Affecting Lipoprotein Metabolism

	LDL-C ↓	HDL-C ↑	TG ↓
Statins	18-55%	5-15%	7-30%
Bile acid sequestrants	15-30%	3-5%	0-10%↑
Nicotinic acid	5-25%	15-35%	20-50%
Fibric acid derivatives	5%↓ to 20%↑	10-20%	20-50%
Ezetimibe	13-20%	3-5%	5-11%
Omega-3 fatty acids	6%↓ to 25%↑	5%↓ to 7%↑	19-44%
PCSK9 inhibitors	40-72%	0-10%	0-17%
Bempedoic acid	15-17%	6%↓	2%↓ to 6%↑

Primarily for LDL-C lowering

Primarily for TG lowering

Jacobson TA et al. J Clin Lipidol. 2014; 8:473-88.
Shimada YJ and Cannon CP. European Heart Journal doi:10.1093/eurheartj/ehv174
Nexletol (bempedoic acid) [package insert]. Ann Arbor,MI: Esperion Therapeutics, Inc.; 2020

5

Omega-3 Fatty Acid Use and CV Disease Risks

Meta-analysis of 10 placebo-controlled trials evaluating marine derived omega-3 fatty acids (mean 4.4 years)

Study, year	EPA/DHA (mg/day)	Prior CHD	Prior Stroke	Prior Diabetes	Statin use
DOIT, 2010 (n=563)	1176/840	23.6%	6.6%	8.2%	-
AREDS-2, 2014 (n=4203)	650/350	9.7%	5.0%	13.0%	44.4%
SU.DOL.OM3, 2010 (n=2501)	400/200	74.5%	25.5%	17.9%	83.1%
JELLIS, 2007 (n=18,645)	1800/none	n/a	n/a	16.3%	100%
Alpha Omega, 2010 (n=4837)	226/150	100%	7.2%	21.0%	85.2%
OMEGA, 2010 (n=3818)	460/380	22.5%	5.5%	27.0%	94.2%
R&P, 2013 (n=12,505)	850-1000 total	30.0%	4.8%	59.9%	100%
GISSI-HF, 2008 (n=6975)	394/472	51.8%	5.0%	28.3%	n/a
ORIGIN, 2012 (n=12,536)	465/375	64.6%	86.8%	88.4%	53.8%
GISSI-P, 1999 (n=11,334)	280/560	100%	n/a	18.9%	n/a

All EPA < 2 g/day

Aung T, et al. JAMA Cardiol. 2018;3(3):225-234.
GISSI-Prevenzione Investigators. Lancet. 1999;354:447–455.
GISSI-HF investigators. Lancet. 2008;372:1223–1230.
The Risk and Prevention Study Collaborative Group. N Engl J Med. 2013;368:1800–1808.
Einvik G, et al. Eur J Prev Cardiol. 2010;17:588–592.

6

Omega-3 Fatty Acid Use and CV Disease Risks

Outcome	10 trials Rate Ratio (95%CI)
Nonfatal MI	0.97 (0.87-1.08)
Total CHD	0.96 (0.90-1.01)
Total Stroke	1.03 (0.93-1.13)
CVD/CHD Death	0.93 (0.83-1.03)
Any Major Vascular Event	0.97 (0.93-1.01)

Aung T, et al. JAMA Cardiol. 2018;3(3):225-234.

7

Newer Trials with Omega−3 Fatty Acids

- The ASCEND Study
  - Randomized, double-blind trial in 15,480 primary prevention patients, age ≥40 yrs, with diabetes
  - EPA/DHA 460/380 mg/day vs. placebo (olive oil); mean 7.4 yrs
    - Serious vascular events: 8.9 vs 9.2% (RR 0.97 [0.87-1.08])
- The VITAL Study
  - Randomized, double-blind trial in 25,871 primary prevention patients, age ≥50 yrs (men) or ≥55 yrs (women)
  - EPA/DHA 465/375 mg/day vs. placebo; mean 5.3 yrs
    - Major CV events: 3.0 vs 3.2% (RR 0.92 [0.80-1.06])
    - Total MI: 1.1 vs 1.5% (RR 0.72 [0.59-0.90])

Bowman L, et al. N Engl J Med 2018; 379:1540-1550
Manson JE, et al. N Engl J Med 2019;380:23-32.

8

Omega-3 Fatty Acid Use and CV Disease Risks

Outcome	10 trials Rate Ratio (95%CI)	12 trials Rate Ratio (95%CI)
Nonfatal MI	0.97 (0.87-1.08)	**0.92** **(0.86-0.99)**
Total CHD	0.96 (0.90-1.01)	**0.95** **(0.91-0.99)**
Total Stroke	1.03 (0.93-1.13)	1.05 (0.98-1.14)
CVD/CHD Death	0.93 (0.83-1.03)	**0.93** **(0.88-0.99)**
Any Major Vascular Event	0.97 (0.93-1.01)	0.97 (0.94-1.00)

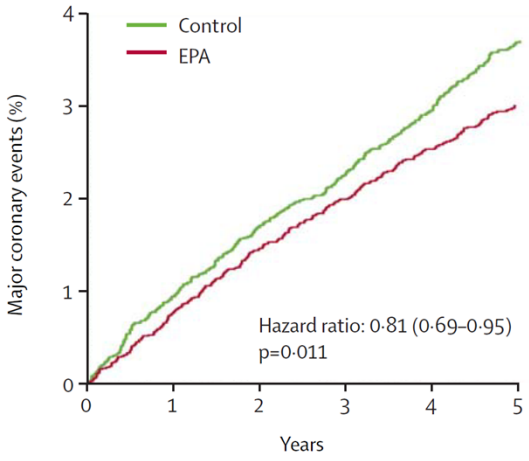
Hu Y, et al. J Am Heart Assoc. 2019;8:e013543.

9

EPA in Hypercholesterolaemic Patients (JELLIS)

- 18,645 Japanese patients, age 40-75 yrs (men) or postmenopausal to age 75 yrs (women)
- Primary and secondary prevention with total cholesterol >6.5 mmol/L
- All patients received low-intensity statin and randomly assigned, open-label:
  - EPA 1800 mg/day or placebo
  - 4.6 year mean duration

Primary Endpoint Results



Yokoyama M, et al. Lancet 2007;369:1090–98.

10

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

- Randomized, double-blind trial
- 8179 patients; age ≥45 yr with ASCVD, or age ≥50 yr with diabetes plus CV risk factors; on statin therapy with:
  - Fasting triglyceride 135-499 mg/dL (median 216 mg/dL)
  - LDL-C 41-100 mg/dL (median 75 mg/dL)
- Randomized to icosapent ethyl 4 g/day or placebo for 4.9 yr
- Primary Endpoint: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina

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

11

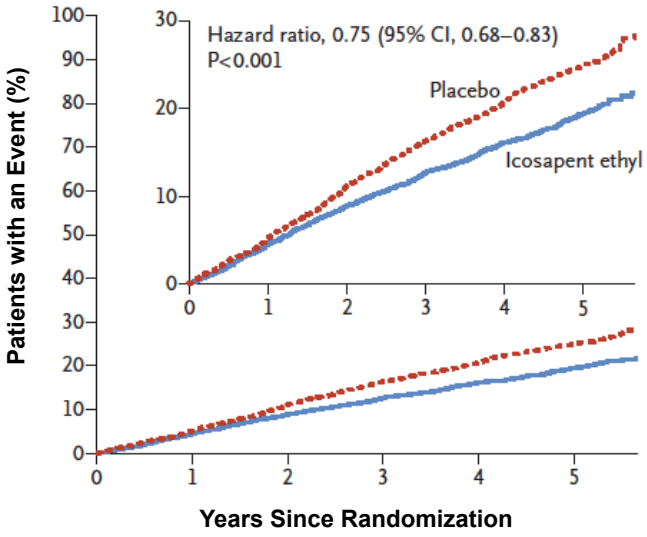
REDUCE-IT: Patient Characteristics

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age (yr)	64.0	64.0
Female, n (%)	1162 (28.4)	1195 (29.2)
Non-white, n (%)	398 (9.7)	401 (9.8)
CV Risk Category, n (%) • Secondary Prevention Cohort • Primary Prevention Cohort	 2892 (70.7) 1197 (29.3)	 2893 (70.7) 1197 (29.3)
Statin Intensity, Low/Moderate/High (%)	6.2/61.9/31.5	6.5/63.0/30.0
Median LDL-C, baseline/1-year (mg/dL)	74.0/77.0	76.0/84.0
Median Triglyceride, baseline/1-year (mg/dL)	216.5/175.0	216.0/221.0

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

12

REDUCE-IT: Primary Endpoint Results



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

13

REDUCE-IT: Adverse Effects

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Serious treatment-emergent adverse event, n (%)	1252 (30.6)	1254 (30.7)	0.98
Adverse event leading to withdrawal	321 (7.9)	335 (8.2)	0.6
Gastrointestinal Disorders: • Diarrhea • Constipation	1350 (33.0) 367 (9.0) 221 (5.4)	1437 (35.1) 453 (11.1) 149 (3.6)	0.04 0.002 <0.001
Peripheral edema	267 (6.5)	203 (5.0)	0.002
Atrial fibrillation	215 (5.3)	149 (3.9)	0.003
Anemia	191 (4.7)	236 (5.8)	0.03
Bleeding related disorders	111 (2.7)	85 (2.1)	0.06

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

14

Omega-3 Fatty Acid Use and CV Disease Risks

Outcome	10 trials Rate Ratio (95%CI)	12 trials Rate Ratio (95%CI)	13 trials Rate Ratio (95%CI)
Nonfatal MI	0.97 (0.87-1.08)	**0.92** **(0.86-0.99)**	**0.88** **(0.83-0.94)**
Total CHD	0.96 (0.90-1.01)	**0.95** **(0.91-0.99)**	**0.93** **(0.89-0.96)**
Total Stroke	1.03 (0.93-1.13)	1.05 (0.98-1.14)	1.02 (0.95-1.10)
CVD/CHD Death	0.93 (0.83-1.03)	**0.93** **(0.88-0.99)**	**0.92** **(0.88-0.97)**
Any Major Vascular Event	0.97 (0.93-1.01)	0.97 (0.94-1.00)	**0.95** **(0.93-0.98)**

Hu Y, et al. J Am Heart Assoc. 2019;8:e013543.

15

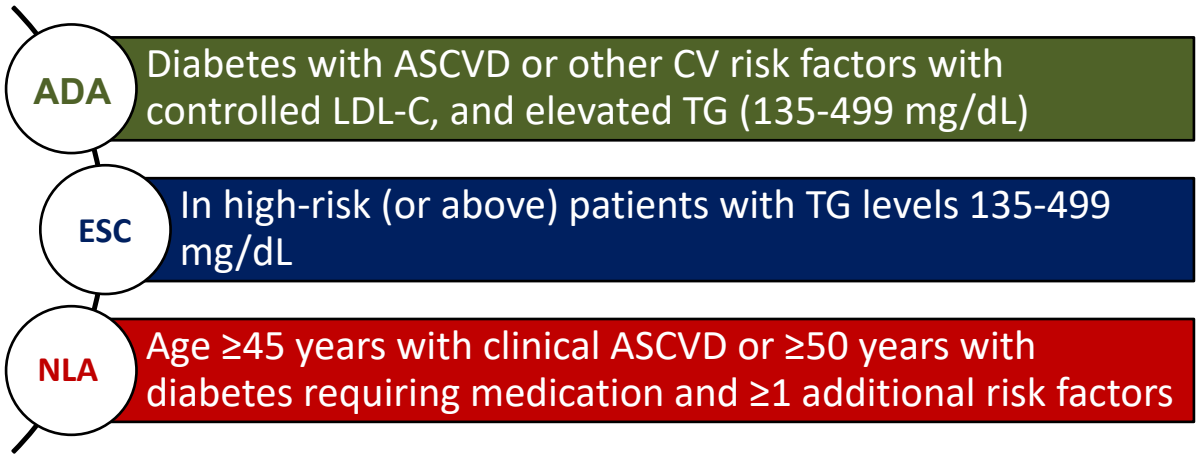
Food and Drug Administration

"The high-dose EPA product icosapent ethyl (*Vascepa*, Amarin) was today unanimously recommended by the FDA's Endocrinologic and Metabolic Drugs Advisory Committee for approval to reduce CV events as an adjunct to statin therapy in patients with elevated triglyceride levels."

FDA Panel Recommends High-Dose EPA for CV Event Reduction - Medscape - Nov 14, 2019.

16

Recommendations to Add Icosapent Ethyl to Statin Therapy



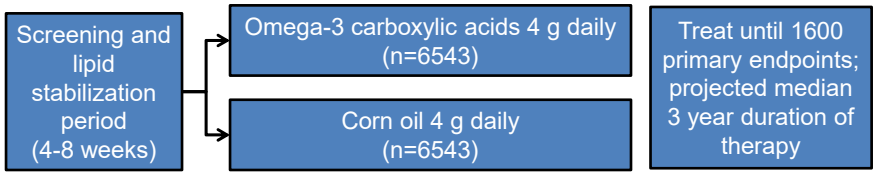
ADA = American Diabetes Association
ESC = European Society of Cardiology
NLA = National Lipid Association

American Diabetes Association. Diabetes Care. 2020;43(Suppl 1):S111-S134.
Mach F, et al. Eur Heart J 2020;41:111-88.
Orringer CE, et al. J Clin Lipidol. 2019;13:860-72.

17

STRENGTH Trial: Omega-3 Carboxylic Acids (EPA + DHA)

- High CV risk patients with:
  1) Established ASCVD, 2) Diabetes with an additional risk factor, or 3) High-risk primary prevention
- On optimal statin therapy
- Triglycerides 180-499 mg/dL and HDL-C <42 mg/dL (men), <47 mg/dL (women)



Primary Endpoint:
CV death, non-fatal MI, non-fatal stroke, coronary revascularization or hospitalization for unstable angina

- Study stopped due to its low likelihood of demonstrating benefit
- Full data to be presented at a forthcoming scientific meeting

Nicholls SJ, et al. Clin Cardiol. 2018;41:1281-8.
https://www.directorstalkinterviews.com/astrazeneca-to-close-phase-iii-strength-trial-for-epanova/412802518

18

Outcomes Data: Other TG Lowering Medications

Fibric Acid Derivatives

- CV event lowering with gemfibrozil vs placebo:
  - Helsinki Heart study (primary)
  - VA-HIT trial (secondary)
- No CV event lowering with fenofibrate vs placebo in type 2 diabetes
  - FIELD Trial
  - ACCORD (with simvastatin)

Niacin

- No CV event lowering with niacin vs placebo in ASCVD patients treated with simvastatin
  - AIM-HIGH
  - HPS2-Thirve

Frick MH, et al. *N Engl J Med*. 1987;317:1237-1245.
Rubins HB, et al. *N Engl J Med*. 1999;341:410-418.
Keech A, et al. *Lancet*. 2005;366:1849-1861.
ACCORD Study Group. *N Engl J Med*. 2010;362:1563-1574.

The HPS2-THRIVE Collaborative Group. N Engl J Med 2014;371:203-12.
Boden WE, et al. *N Engl J Med* 2011;365:2255-67.

19

Pemafibrate: Novel selective PPAR modulator

- Similar to other fibrates with higher receptor selectivity and possibly an improved safety, approved in Japan (2017)
- "Pemafibrate to Reduce CV Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT)"
  - 10,000 primary/secondary prevention patients with type 2 diabetes; TG 200-499 mg/dL, HDL-C ≤40 mg/dL
  - LDL-C ≤70 mg/dL if on statin; ≤100 mg/dL if statin intolerant
  - 5 year expected duration, but driven to 1092 primary events
  - Primary Endpoint:
    - CV death, MI, ischemic stroke, unstable angina requiring unplanned revascularization

https://clinicaltrials.gov/ct2/show/NCT03071692

20

Conclusions

- Large-scale clinical trials evaluating omega-3 fatty acids collectively have demonstrated a reduction in CV events
- Benefits seen in clinical trials are not homogenous
- Most robust results were demonstrated in the REDUCE-IT trial which used a unique EPA-only omega-3 fatty acid dosed 4 g/day

Comparison of Omega-3 Fatty Acid Products

Daniel E. Hilleman, PharmD, FCCP
Creighton University School of Pharmacy
and Health Professions
Omaha, NE

1

Disclosures - Daniel E. Hilleman, PharmD

- Consultant – Heron Therapeutics

2

Objectives

- Describe the differences between dietary supplement and prescription omega-3 fatty acids
- Identify the appropriate indications and doses of the available prescription omega-3 fatty acids
- Identify appropriate counseling for patients taking prescription omega-3 fatty acids

3

Omega-3 FA Products
Prescription

- Omega-3 *fatty acid ethyl esters*
  - Lovaza®, Omtryg®, generics
    - EPA 465 mg and DHA 375 mg per capsule
    - 2 g twice daily or 4 g once daily
    - Typically taken with food
- EPA *ethyl esters*
  - Vascepa®
    - EPA 1000 mg per capsule
    - 2 g twice daily with food (available as a 500mg or 1000mg capsule)
- Omega-3 *carboxylic acids* (free fatty acid form)
  - Epanova®
    - EPA 550 mg and DHA 200 mg per capsule
    - 2-4 g daily with/without food
    - Product not commercially available

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

4

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 Approval	Yes	No Proof of efficacy not required
Content and Purity	• Adhere to strict standards for content and purity • FDA Good manufacturing practice	• Products contain variable amounts of omega-3 FA • Most do not contain labelled content of omega-3 FA • Up to 36% fatty acid content is saturated fat • Oxidation • Potential contamination with harmful chemicals
Substitution	DHA/EPA combination products are not equivalent to EPA-only products	Dietary supplement fish oil products – not equivalent to and cannot be substituted for Rx OM3-FA products

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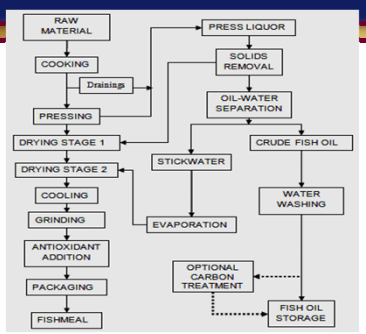
Dietary Supplement Fish Oils Are a By-product of Industrial Extraction Procedures



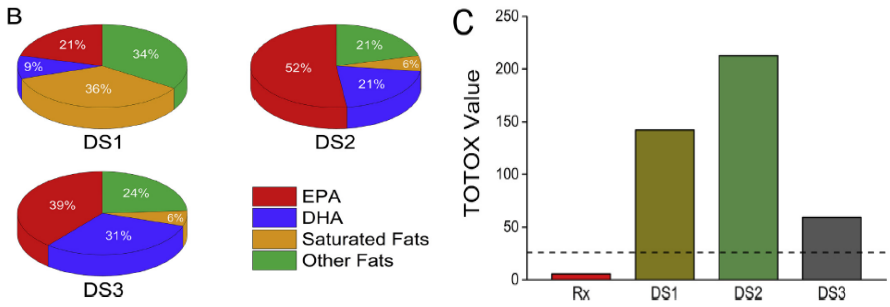
6

Omega-3 fatty acid fish oil dietary supplements contain saturated fats and oxidized lipids that may interfere with their intended biological benefits

R. Preston Mason [a, b, *], Samuel C.R. Sherratt [b]

[a] Department of Medicine, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, 02115-6110, USA
[b] Elucida Research LLC, Beverly, MA, 01915-0091, USA

Evaluated fatty acid content and oxidation in fish oil - 3 Dietary Supplements (DS)



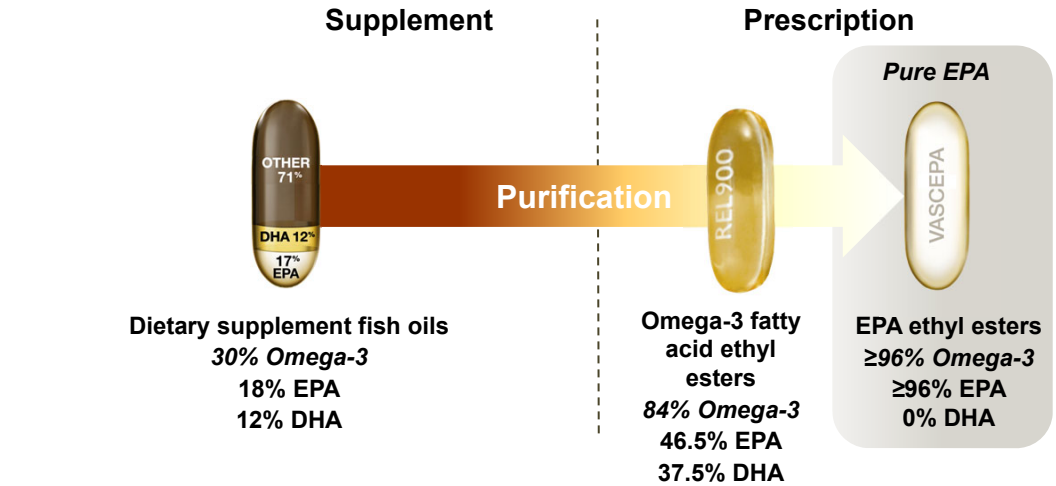
DS: fatty acid composition

DS and Rx: total oxidation

Biochemical and Biophysical Research Communications 483 (2017) 425–429

7

Dietary Supplement vs Prescription Fish Oil
Good Manufacturing Practices – FDA Regulations



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

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

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.

8

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]

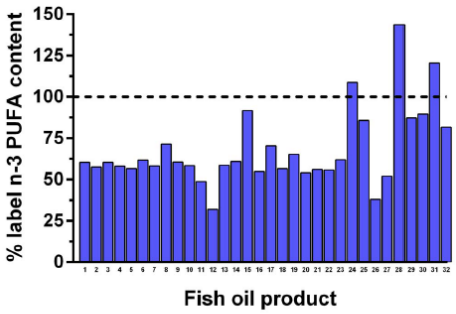


Figure 1 | The actual n-3 PUFA content (EPA + DHA) contained in individual retail fish oil products in relation to the claimed content (dotted line).

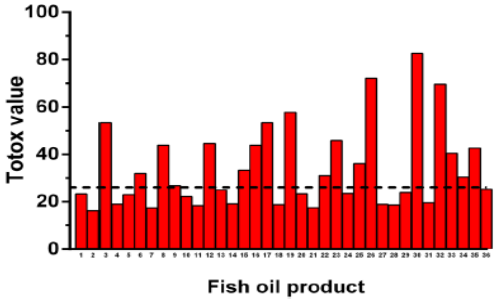


Figure 2 | The content of oxidation markers in retail fish oil tested in relation to recommended international thresholds (dotted lines).

9

METABOLIC SYNDROME AND RELATED DISORDERS
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Pp. 1–17
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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 median amount of EPA (460 mg) and DHA (400 mg) per serving in the liquid products was higher than 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."

10

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
- Common reasons for use – general health (34%), heart health (28%), MI/CAD (12%), arthritis (9%), lipid disorders (8%)
- 14% advised to take an OM-3 FA by a HCP
- 86% of patients were taking only 1 or 2 capsules per day
- 26% knew the active ingredient
- 81% purchased through a non-pharmacy retail outlet
- Approximately 4% had been given a prescription for an omega-3 fatty acid

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

11

Issues with Dietary Supplement Fish Oils

- Lack of potency
  - Most products do not contain substantial quantities of OM-3 FA
  - Greater number of daily doses to achieve 4 g/d of active ingredient
- Lack of purity
  - Most contain fats other than OM-3 FA
  - Many contain saturated fats
  - Most meet minimum standards for toxins (PCBs, mercury, arsenic, dioxin)
- Lack of documentation – labelled amount of active ingredient is not verified
- Fishing labelling
  - Pharmaceutical grade"
  - "Tested in FDA-approved laboratory"
  - Provide "Daily recommended intake for EPA and DHA"
- Variability – lot-lot and seasonal
- Adverse effects – GI (odor, taste, eructation) more common than with prescription products

12

Issues with Prescription OM-3 FA Products

- Purity, content, consistency – assured by GMP
- Value of prescription – evaluate adherence, counseling and monitoring
  - Negative patient perceptions about taking another prescription
  - Attitudes by patient and providers vary
- Cost
  - Insurance coverage
  - Co-pays
- FDA Indications
  - Severe hypertriglyceridemia – either prescription product
  - CV risk reduction – icosapent ethyl
- Guidelines – ADA, NLA and ESC/EAS have endorsed icosapent ethyl for CV risk reduction

13

Patient Counseling
Prescription Omega-3 Fatty Acids

- Dosing
  - Omega-3 fatty acid ethyl esters (EPA/DHA) 2 g twice daily or 4 g once daily with food
  - Icosapent ethyl 2 g (0.5 or 1.0 g/capsule) twice daily with food
  - Take capsules whole – do not chew, dissolve, or crush
  - Missing doses – take as soon as possible same day but do not double up on doses
- Adverse reactions/Precautions
  - Allergy to fish/shellfish – most tolerate fish oil supplement or RX EPA/DHA
  - Heart rhythm problems – atrial fibrillation
  - Bleeding – antiplatelet/anticoagulants
  - LDL-C levels – EPA/DHA combination acid ethyl esters may increase LDL-C levels
  - Liver disease - abnormal liver function tests
  - Side effects – muscle/joint pain; swelling of hands/feet/legs; GI complaints (constipation, dyspepsia, eructation, and taste perversion)

14

Summary

- Dietary supplements – no evidence of benefit for any medical indication
- Quality of dietary supplements is a concern
- No interchange of OM-3 FA products (RX or dietary supplement)
- Severe hypertriglyceridemia (≥ 500 mg/dl) – both RX products approved
- CV risk reduction – icosapent ethyl only
  - New FDA indication – established CV disease or diabetes mellitus with 2 or more additional risk factors (maximally tolerated statin and TG ≥ 150 mg/dl)
  - ADA, NLA, ESC/EAS – icosapent ethyl added to guidelines for CV risk reduction

15

Comparison of Omega-3 Fatty Acid Products

Thank You

16

VCU School of Pharmacy

Clinical Utility of Adjunct Therapies to Statins for ASCVD Event Reduction

Dave L. Dixon, PharmD, FACC, FCCP, FNLA, BCACP, CDES, CLS
Associate Professor & Vice-Chair for Clinical Services

1

Disclosures

- I have nothing to disclose related to the content of this presentation.

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2

Objectives

- At the conclusion of this activity, learners should be better able to:
  - Describe the spectrum of large-scale omega-3 fatty acids on ASCVD outcomes trials
  - Appreciate the difference between omega-3 fatty acids and their formulations to impact ASCVD events, including the negative role of dietary supplements
  - ***Use information on clinical utility of adjuncts to statin therapy to improve management of patients with or at high risk of ASCVD events***

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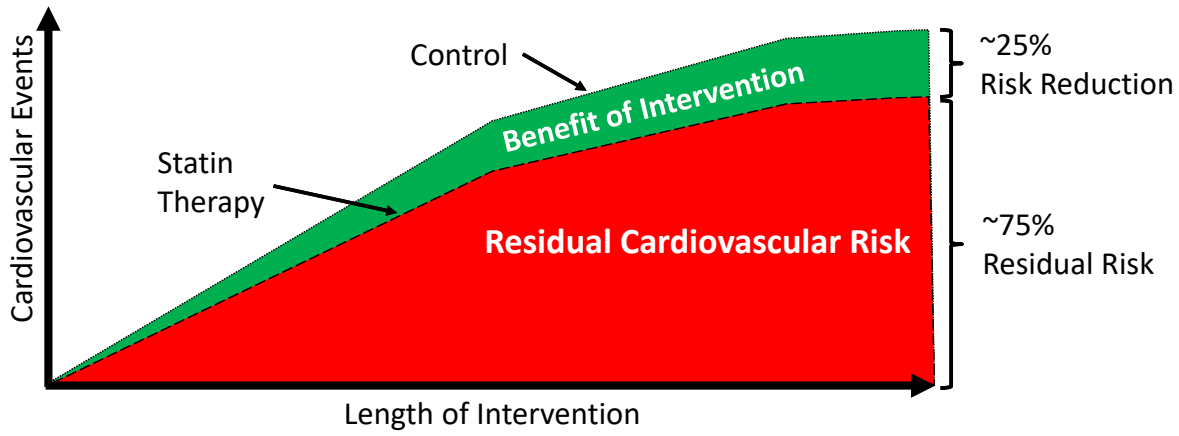
3

Statins and Residual Risk



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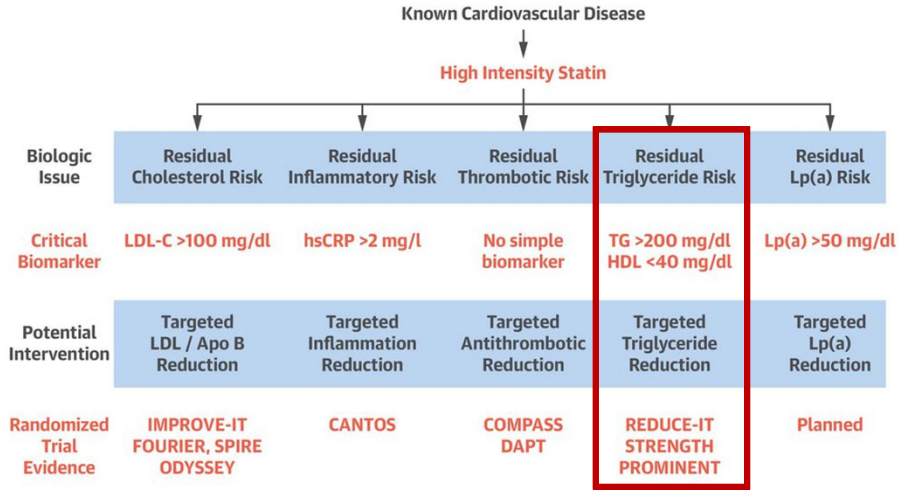
Silverman MG, et al. *JAMA.* 2016;316(12):1289-1297.

4

Personalized Approach to Residual Risk



Ridker PM, et al. *J Am Coll Cardiol*. 2018;72(25):3320-32.

5

Economic Burden of High TG Levels

Table 1 Projected number of US adults ≥ 45 y taking a statin and with ASCVD or diabetes, adjusted incremental total health care costs per capita, and projected total annual costs associated with triglycerides ≥150 mg/dL compared with <150 mg/dL overall and in subgroups

Group	Population sizes (95% CI), in millions from NHANES: Triglycerides < 150 mg/dL	Population sizes (95% CI), in millions from NHANES: Triglycerides ≥ 150 mg/dL	Adjusted incremental total health care costs per capita from Optum Research Database, USD: Triglycerides ≥ 150 mg/dL vs triglycerides < 150 mg/dL	Projected annual cost burden of triglycerides ≥150 mg/dL vs <150 mg/dL, billions of USD
Overall	12.0 (11.1-12.9)	6.2 (5.4-7.1)	$1730 ($1160-$2320)	$10.7 B ($6.8 B-$14.6 B)
Age, y				
45 to <55	1.8 (1.4-2.2)	1.2 (0.9-1.5)	$2300 ($1290-$3450)	$2.8 B ($1.3 B-$4.2 B)
55 to <65	2.7 (2.1-3.2)	1.8 (1.2-2.4)	$1500 ($650-$2390)	$2.7 B ($0.9 B-$4.5 B)
65+	7.5 (6.8-8.3)	3.2 (2.5-3.8)	$1390 ($550-$2350)	$4.5 B ($1.4 B-$7.5 B)
Sex				
Male	7.1 (6.4-7.8)	3.2 (2.5-3.9)	$1600 ($810-$2600)	$5.1 B ($2.0 B-$8.2 B)
Female	4.9 (4.3-5.6)	3.0 (2.3-3.6)	$1900 ($1200-$2540)	$5.7 B ($3.3 B-$8.1 B)
Diabetes				
Yes	7.3 (6.6-7.9)	4.8 (4.0-5.5)	$1850 ($1250-$2460)	$8.9 B ($5.7 B-$12.1 B)
No	4.7 (4.1-5.4)	1.4 (1.0-1.9)	$1190 ($-50-$2540)	$1.7 B ($-0.2 B-$3.6 B)
ASCVD				
Yes	7.3 (6.5-8.1)	3.2 (2.6-3.7)	$1740 ($610-$3030)	$5.4 B ($1.5 B-$9.3 B)
No	4.7 (4.2-5.2)	3.1 (2.6-3.7)	$1680 ($1080-$2300)	$5.2 B ($3.1 B-$7.3 B)

Overall costs of ↑ TG $10.7 billion per year

Highest among adults ≥65 years old and patients with diabetes

Case BC, et al. *J Clin Lipidol*. 2019;13:754-761.

6

Value in Healthcare

- **Clinical Value**
  - Number needed to treat (NNT)
  - Number of patients that would need to be treated for "x" years to avert one major cardiovascular event
- **Economic Value**
  - Cost of treatment must be balanced against NNT
  - Cost-effective: Use and benefits worth at least what is paid for them

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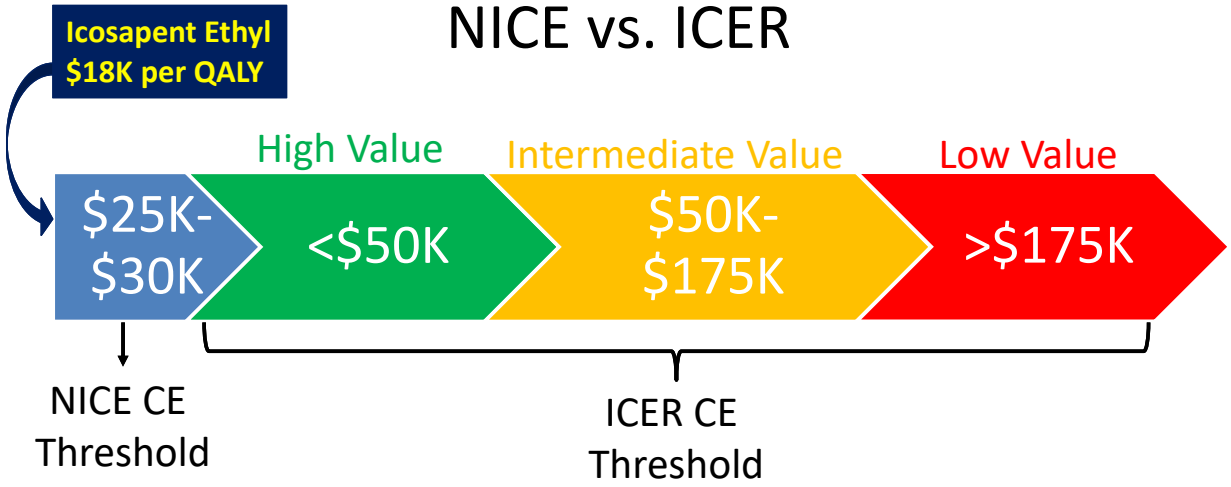
7

Cost-Effectiveness Thresholds

NICE vs. ICER



https://www.bhei.com/blog/fixed-cost-effectiveness-thresholds/. Accessed 2/10/20.

ICER: Institute for Clinical and Economic Review
NICE: The National Institute for Health and Clinical Excellence
QALY: Quality-Adjusted Life Year

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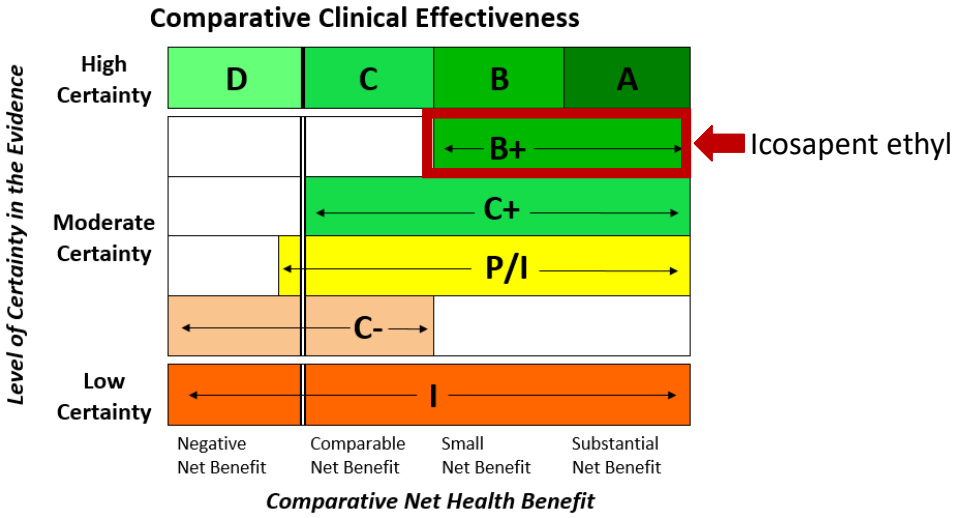
8

ICER Evidence Rating for Icosapent Ethyl



Ollendorf D, et al. Institute for Clinical and Economic Review, October 17, 2019. http://icer-review.org/material/cvd-final-evidence-report/

9

ICER Vote on Icosapent Ethyl

c) Is the evidence adequate to demonstrate that the net health benefit of icosapent ethyl added to optimal medical management (including statin therapy) is superior to that provided by optimal medical management (including statin therapy) alone?

Yes: 9 votes	No: 2 votes

A majority of the Council determined that the evidence was adequate to demonstrate a net health benefit of icosapent ethyl added to optimal medical management (including statin therapy).

The Council members who voted in the negative expressed concerns regarding the unexpected results in the REDUCE-IT trial compared to the many previous studies investigating fish oil that showed no benefit to cardiovascular health, and questioned whether these results could be replicated. One council member argued that the potential benefit of icosapent ethyl is relatively small when considering absolute effects. The other dissenting voter was concerned about the confounding factor of mineral oil being used in the placebo arm and potentially inflating the results. Council members did discuss the specific DHA and EPA composition of icosapent ethyl as it compares with other fish oil interventions currently on the market, as this composition may be responsible for the divergent results produced by the REDUCE-IT trial. However, they agreed that additional study is required to gain any certainty on this question.

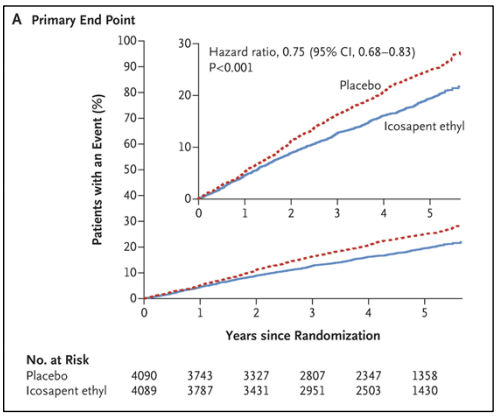
Ollendorf D, et al. Institute for Clinical and Economic Review, October 17, 2019. http://icer-review.org/material/cvd-final-evidence-report/

10

Cost-Effectiveness Analysis (CEA) of Icosapent Ethyl

Combined patient-level and simulation CEA

Costs for Icosapent Ethyl $4.16 per day



QALY (during trial period): 3.34

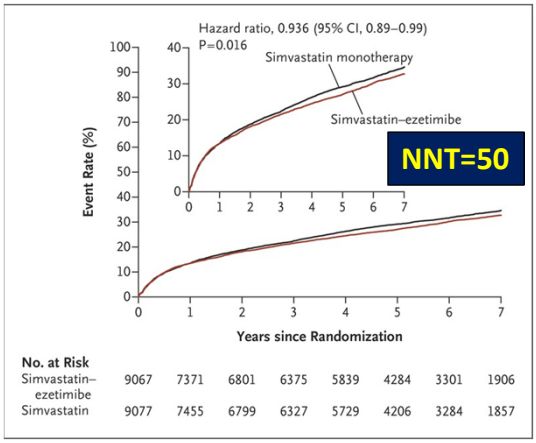
QALY (lifetime): 11.61

Icosapent ethyl was a *cost saving strategy* in 70% of simulations

Weintraub WS, et al. 2019 AHA Scientific Sessions.

11

Economic Evaluation of Ezetimibe Treatment



Ezetimibe + Statin	QALY
Lifetime ICER	$9,149
LDL-C ≥ 100 mg/dL	$839
LDL-C ≥ 70 mg/dL	$560

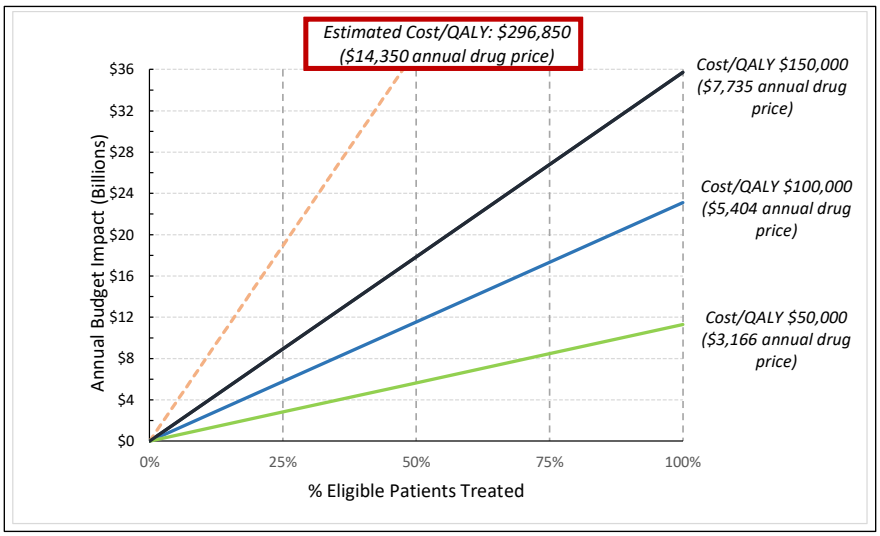
ICER: incremental cost-effectiveness ratio;
LDL: low-density lipoprotein cholesterol;
QALY: quality adjusted life year

***Based on assumed 90% price ↓ due to patent expiration**

Cannon CP, et al. *N Engl J Med* 2015;372:2387-2397.
Davies GM, et al. *Journal of Medical Economics.* 20:7;723-731.

12

ICER Value Graph for PCSK9 Inhibitors



Tice JA, et al. Institute for Clinical and Economic Review, November 24, 2015. https://icer-review.org/wp-content/uploads/2016/01/Final-Report-for-Posting-11-24-15-1.pdf

13

2018 ACC/AHA Multisociety Guidelines

Value Statement: Low Value (LOE: B-NR)	At mid-2018 list prices, PCSK9 inhibitors have a low cost value (>$150,000 per QALY) compared to good cost value (<$50,000 per QALY)
Value Statement: Uncertain Value (B-NR)	Among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 U.S. list prices.

NOTE: Based on initial wholesale acquisition price of $14K per year

Price was reduced by 60% in October 2018

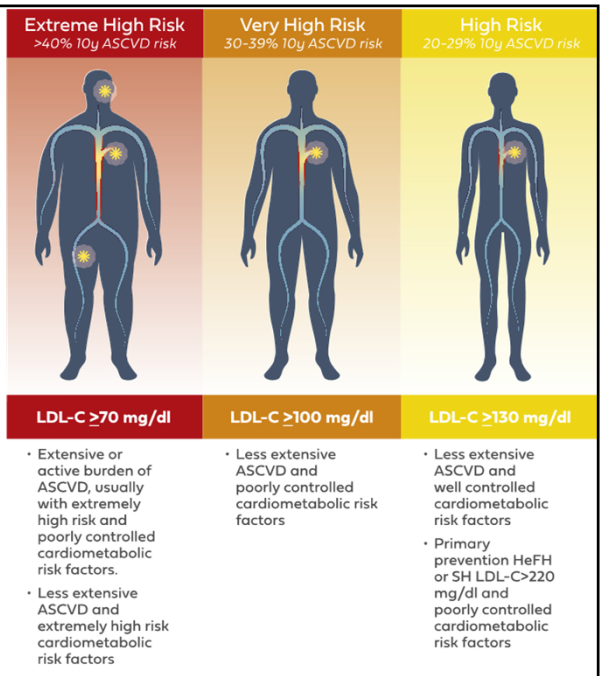
Grundy SM, et al. *Circulation*. 2019;139:e1082–e1143.

14

NLA Scientific Statement on Value of PCSK9 Inhibitors

Recommendations Based on:

- Maximally tolerated statin ± ezetimibe
- Wholesale acquisition price of $5400/yr
- A 65% LDL-C reduction with addition of a PCSK9 inhibitor
- Estimated 5-year NNT based on LDL-C reduction



Robinson JG, et al. *J Clin Lipidol*. 2019;13:525–537

15

Professional Society Recommendations Regarding Use of Icosapent Ethyl

- **March 2019 (reaffirmed in 2020)**: American Diabetes Association
  - Secondary prevention patients and patients with ASCVD risk factors with controlled LDL-C and TG levels of 135-499 mg/dL
  - Level A = "can be considered"
- **September 2019**: European Society of Cardiology/European Atherosclerosis Society
  - High-risk patients with TG levels of 135-499 mg/dL despite statins
  - Level B, Class IIa = "should be considered"
- **September 2019**: National Lipid Association
  - Recommended in the population studied in REDUCE-IT
  - Class I, Level B-R = "is recommended"

Diabetes Care. 2020; 43 (Suppl. 1): S111-S134.
European Heart Journal. 2020;41: 111-188.
J Clin Lipidol. 2019;13(6):860-872.

16

Icosapent Ethyl
NEW FDA Indication

- As an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated TG levels (**≥ 150 mg/dL**) and:
  - *Established cardiovascular disease OR*
  - *Diabetes mellitus and ≥2 additional risk factors for cardiovascular disease*

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Vascepa® Package Insert. December 2019.

17

Take Home Points

- Several new options available for reducing residual cardiovascular risk, but lack of clarity regarding which to use and when.
- Although ezetimibe is cost-effective, clinical benefit is modest compared to icosapent ethyl and PCSK9 inhibitors.
- Despite significant price reduction, cost-effectiveness of PCSK9 inhibitors remains limited to certain high-risk subgroups.
- Despite brand name medication costs, icosapent ethyl appears to be cost-effective and may be cost saving when compared to placebo.

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18

Audience Response Question

- Which of the following non-statin therapies is most likely to be *cost-saving* according to ICER?
  A. Ezetimibe
  B. Icosapent ethyl
  C. PCSK9 inhibitors
  D. None of the above

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