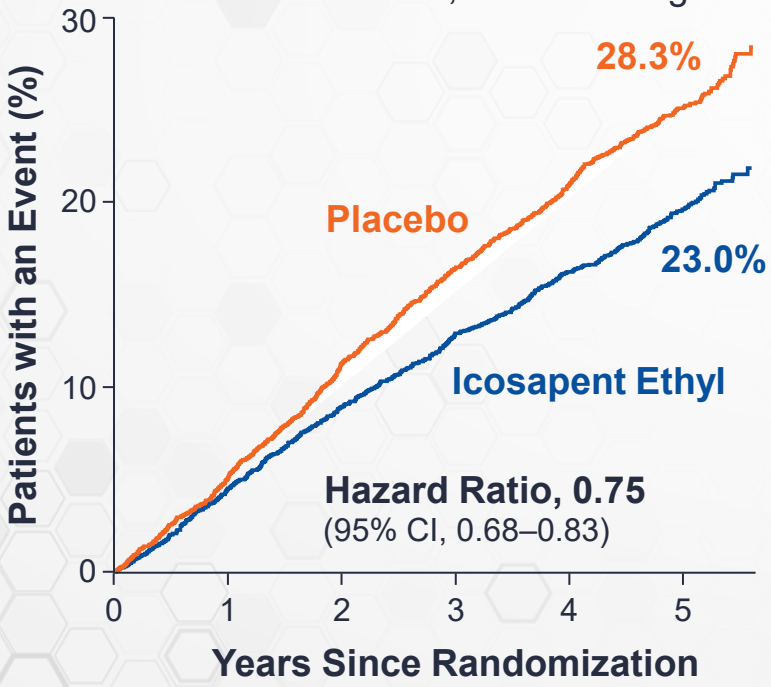
Variable Effects of Omega-3 Fatty Acids for ASCVD Event Reduction: Why?

These slides are meant to be used as an accompaniment to the presentation for note taking purposes. They are not intended as a standalone reference.

REDUCE-IT Primary and Secondary Endpoints

Primary Endpoint

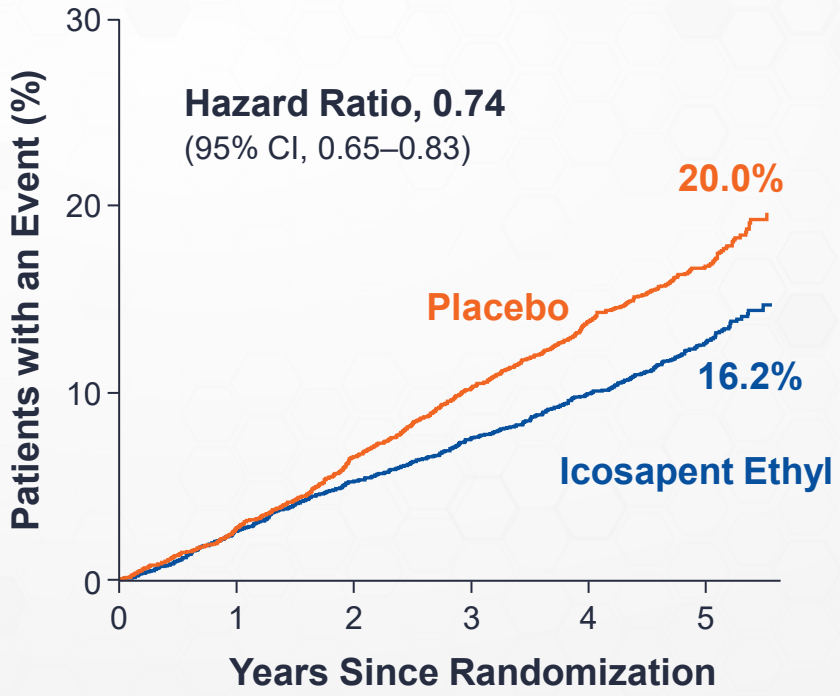
CV Death, MI, Stroke, Coronary Revascularization, Unstable Angina



RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
***P* = 0.00000001**

Key Secondary Endpoint

CV Death, MI, Stroke



RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
***P* = 0.0000006**

Key Inclusion Criteria (n = 8,179)

- Statin-treated men and women ≥45 yrs
- Established CVD (~70% of patients) or DM + ≥1 risk factor
- TG ≥150 mg/dL and <500 mg/dL
- LDL-C >40 mg/dL and ≤100 mg/dL

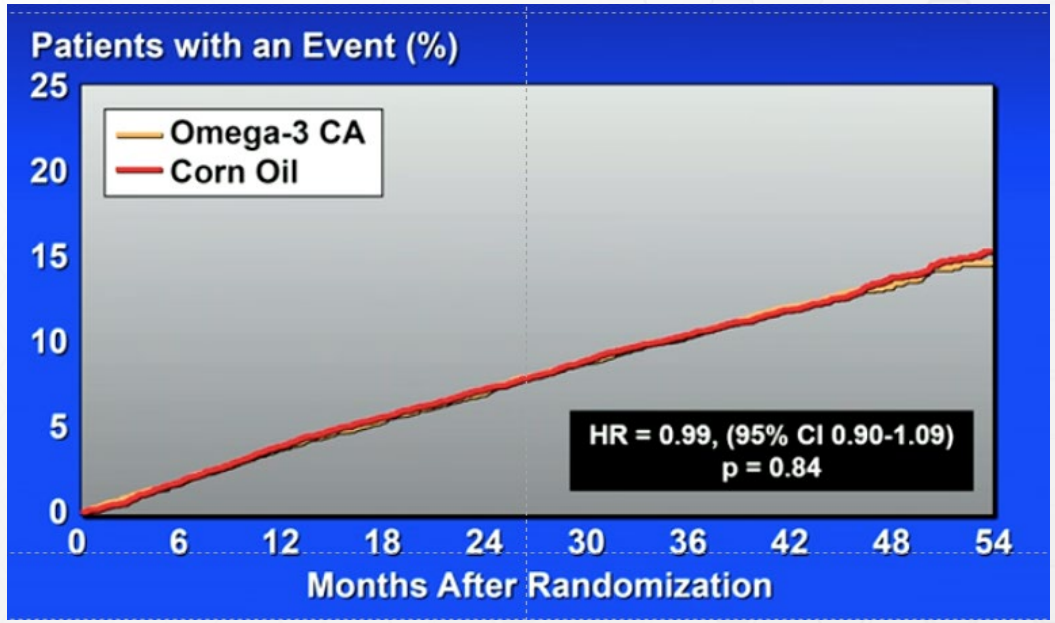
Bhatt DL, et al. *N Engl J Med*. 2019;380(1):11-22. Bhatt DL. AHA 2018, Chicago.

STRENGTH Trial Design, Details, and Primary Endpoint

- Randomized 13,078 patients Oct 2014 – June 2017 (675 sites, 22 countries)
- Statin-treated adult patients (≥18 years) were included who had triglyceride 180-499 mg/dL, and HDL-C <42 mg/dL for men or <47 mg/dL for women
  - Presence of established ASCVD
  - Type 1 or 2 diabetes ≥ 40 years for men and ≥50 years for women with at least 1 additional risk factor
  - High-risk primary prevention patients aged ≥50 years for men or ≥60 years for women with at least 1 additional risk factor
- Trial stopped by data monitoring board for "futility" Jan 8, 2020, after review of 1,384 MACE outcomes
- 1,580 MACE endpoints accrued by last patient visit May 14, 2020
- Median follow-up time 42.0 months, and study drug 38.2 months

Primary endpoint:

MACE (CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina)



Lincoff AM. American Heart Association Virtual Scientific Sessions; November 15, 2020. Nicholls SJ, et al. *JAMA*. 2020;324(22):2268-2280.

Comparison Between REDUCE-IT and STRENGTH

Trial (% of patients with known cardiovascular disease at baseline)	Groups	Patients with event/total patients, n/N (%) Omega-3	Patients with event/total patients, n/N (%) Placebo	Hazard ratio (95% CI)
REDUCE-IT (70.7%)		**Icosapent ethyl**	**Mineral oil**	
	All participants	705/4089 (17.2%)	901/4090 (22%)	0.75 (0.68–0.83)*
	Primary prevention	146/1197 (12.2%)	163/1197 (13.6%)	0.88 (0.70–1.10)
	Secondary prevention	559/2982 (19.3%)	738/2893 (25.5%)	0.73 (0.65–0.81)
STRENGTH (56%)		**Eicosapentaenoic acid + Docosahexaenoic acid**	**Corn oil**	
	All participants	785/6539 (12%)	795/6539 (12.2%)	0.99 (0.90–1.09)
	Primary prevention	216/2901 (7.4%)	185/2861 (6.5%)	1.16 (0.95–1.41)
	Secondary prevention	569/3638 (15.6%)	610/3678 (16.6%)	0.94 (0.84–1.05)

REDUCE-IT indicates Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial; and STRENGTH, Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia. *P<0.001.

Pirillo A and Catapano AL. *Circulation*. 2021;144:183–185. DOI: 10.1161/CIRCULATIONAHA.121.053144.

Controversy About STRENGTH and REDUCE-IT

- STRENGTH had a triglyceride range of 180-499 mg/dL
- REDUCE-IT had a triglyceride range of 150-499 mg/dL
- REDUCE-IT used mineral oil as the placebo that was endorsed by the FDA
- Some raised concern that mineral oil may have a negative effect on CV health
- Mineral oil has been used as a lubricant laxative for years

Nicholls SJ, et al. *JAMA*. 2020;324(22):2268-2280. Bhatt DL, et al. *N Engl J Med*. 2019;380(1):11-22.

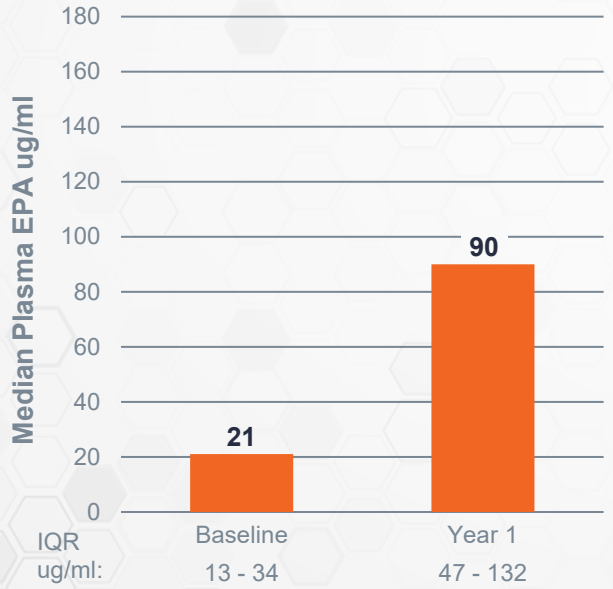
Controversy About STRENGTH and REDUCE-IT

- Review of 80 clinical studies that used some form of mineral oil as a placebo[1]
  - Lack of absorption interference
  - Lack of effects on:
    - Blood lipids
    - Inflammatory markers
    - Blood pressure
- STRENGTH used corn oil as the placebo
- Mineral oil was reviewed extensively by the FDA, Health Canada, and the European Medicines Agency

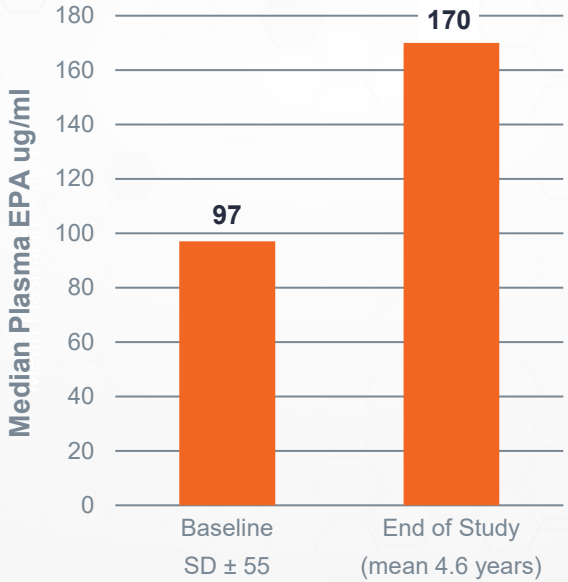
[1]Olshansky B, et al. Eur Heart J Suppl. 2020;22(Supplement J):J34-J48.

Baseline and Achieved EPA Levels in Omega-3 CVOTs: Cross-Study Comparison

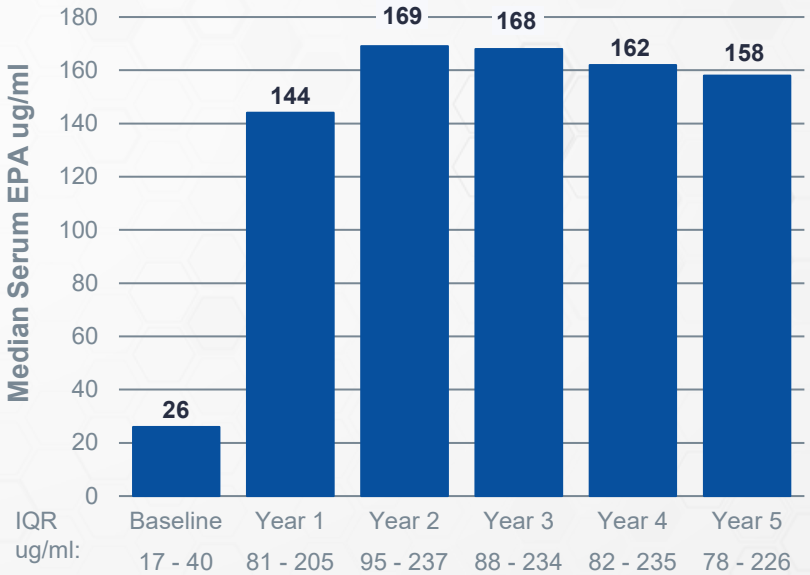
STRENGTH[1]
Plasma EPA



JELIS[2]
Plasma EPA



REDUCE-IT[3]
Serum EPA

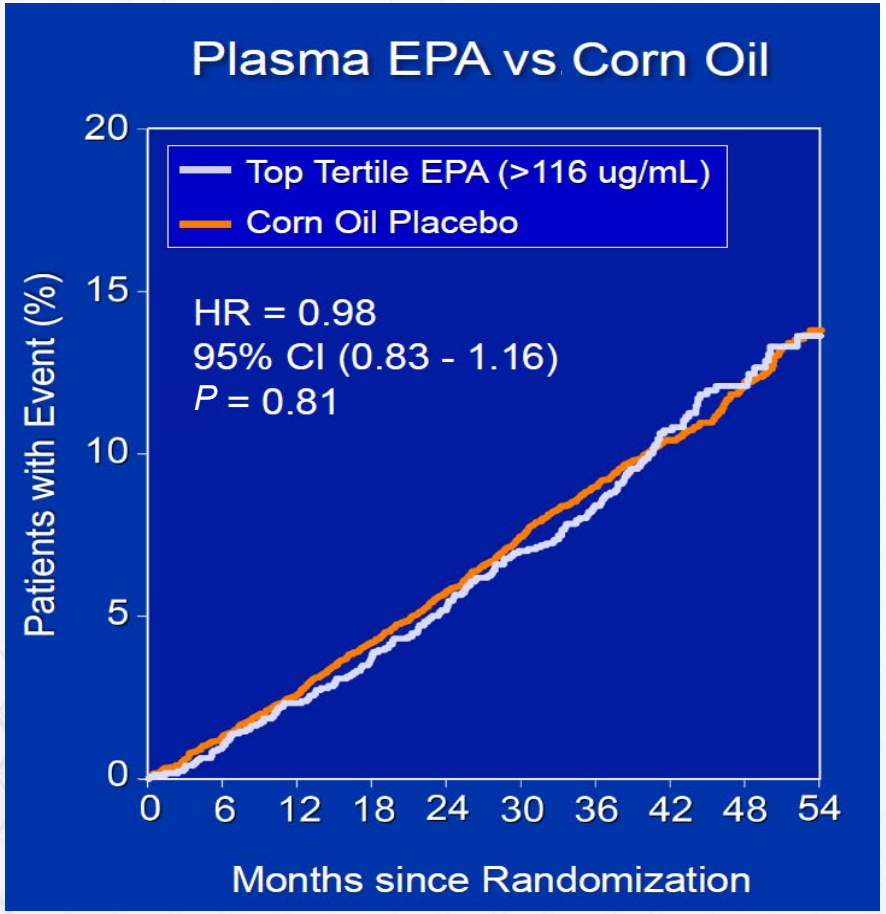


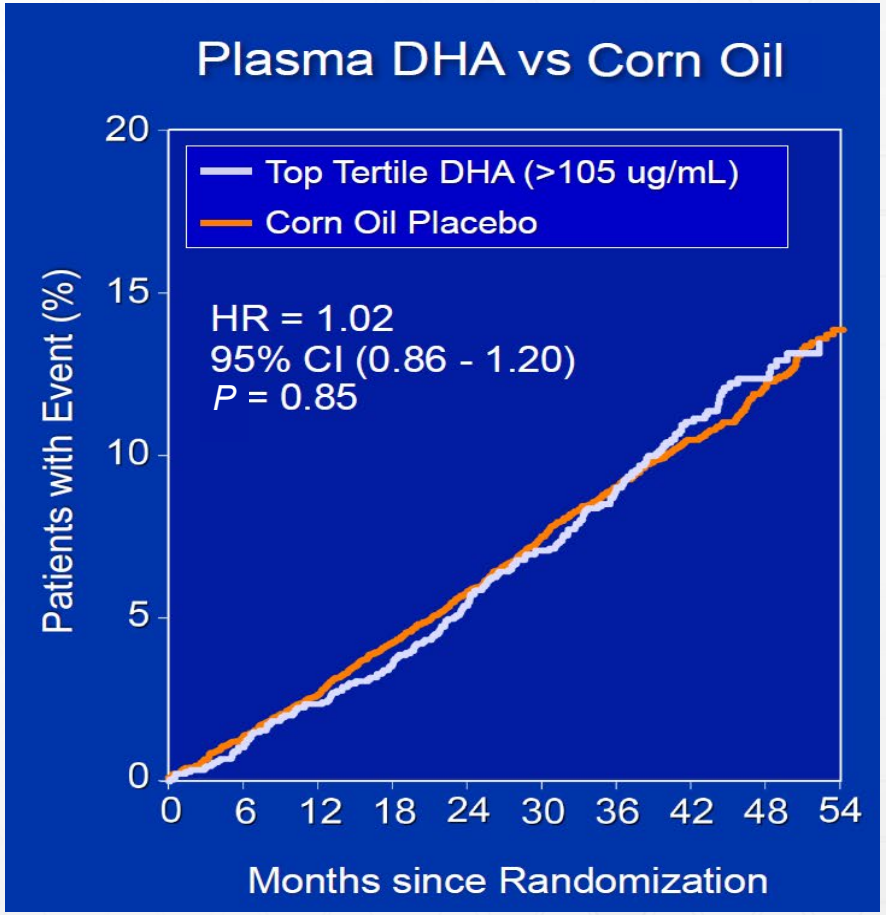
Drug:	850 mg EPA/DHA carboxylic acid/ 1g capsule	300 mg capsules of >98% EPA ethyl esters	1g icosapent ethyl (EPA ethyl ester)/ 1g capsule
Dose:	4 g/d as 2 capsules 2x daily	1.8 g/d as 2 capsules 3x daily	4 g/d as 2 capsules 2x daily
Population:	International	Japanese	International

Plasma and serum EPA levels have been strongly correlated, with plasma levels being slightly higher than serum levels[4,5]

1. Nicholls SJ, et al. *JAMA*. 2020;324(22):2268-2280. 2. Itakura H, et al. *J Atheroscler Thromb*. 2011;18(2):99-107. 3. Bhatt DL, et al. ACC 2020 Scientific Session (ACC.20)/World Congress of Cardiology (WCC); March 30, 2020. Abstract 20-LB-20501-ACC. 4. Dunbar RL, et al. Poster presented at the Gordon Conference on Atherosclerosis; Newry, Maine; June 16-21, 2019. 5. Dunbar RL, et al. Poster presented at NLA Scientific Sessions; December 9-12, 2020.

MACE: Top Tertile of Achieved EPA and DHA





Nissen S. ACC Virtual 2021.

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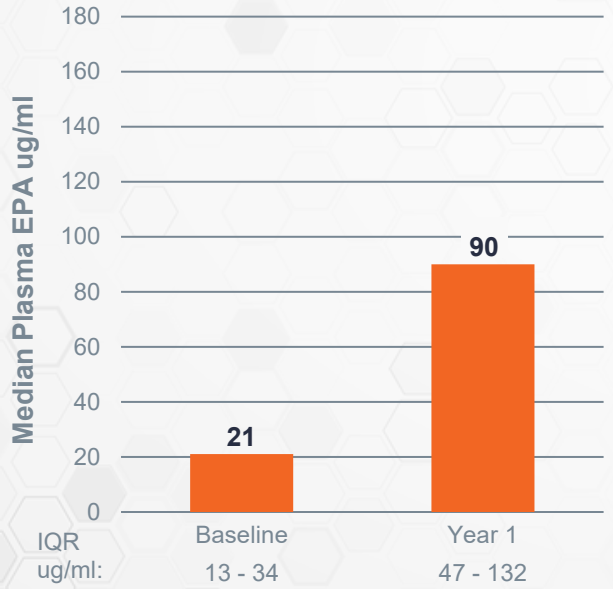
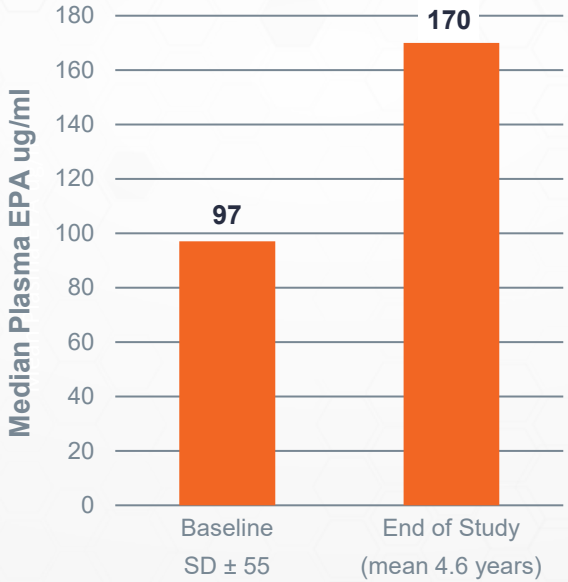
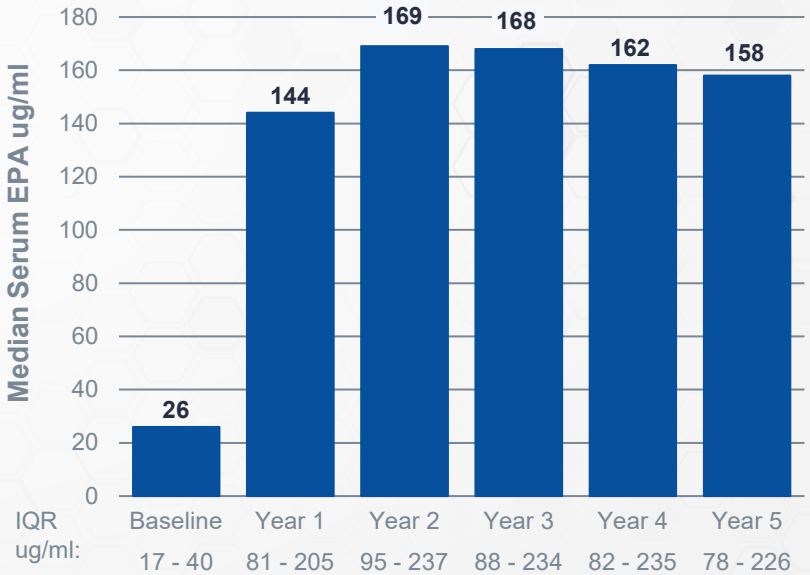


JELIS[2]
Plasma EPA



REDUCE-IT[3]
Serum EPA



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STRENGTH (median patient follow-up was 42.0 months)

	Omega-3 CA (N = 6,532)	Placebo (N = 6,535)
Gastrointestinal disorders	1616 (24.7%)	959 (14.7%)
Diarrhea	780 (11.9%)	323 (4.9%)
Dyspepsia	90 (1.4%)	42 (0.6%)
Nausea	207 (3.2%)	113 (1.7%)
Abdominal discomfort	87 (1.3%)	36 (0.6%)
Bleeding-related disorders	322 (4.9%)	322 (4.9%)
TEAE leading to withdrawal of study drug	708 (10.8%)	525 (8.0%)
Atrial fibrillation	144 (2.2%)	86 (1.3%)

REDUCE-IT (median patient follow-up was 58.8 months)

	Icosapent Ethyl (N = 4,089)	Placebo (N = 4,090)
Gastrointestinal disorders	1350 (33.0%)	1437 (35.1%)
Diarrhea	367 (9.0%)	453 (11.1%)
Constipation	221 (5.4%)	149 (3.6%)
Nausea	190 (4.6%)	197 (4.8%)
Gastroesophageal reflux disease	124 (3.0%)	118 (2.9%)
Bleeding-related disorders	111 (2.7%)	85 (2.1%)
TEAE leading to withdrawal of study drug	321 (7.9%)	335 (8.2%)
Atrial fibrillation	215 (5.3%)	159 (3.9%)

CA, carboxylic acid; TEAE, treatment-emergent adverse events. Nicholls SJ, et al. *JAMA*. 2020;324(22):2268-2280. Bhatt DL, et al. *N Engl J Med*. 2019;380(1):11-22.

What Have We Learned From the Marine Omega-3 Fatty Acid Clinical Trials?

Supplements/low-dose EPA/DHA:	***Does Not*** Reduce CVD Risk
Intermediate-dose EPA/DHA:	***Does Not*** Reduce CVD Risk
High-dose EPA/DHA:	***Does Not*** Reduce CVD Risk
Intermediate-dose EPA only:	**Reduces** CVD Risk
High-dose EPA only:	**Reduces** CVD Risk

Counseling Tips

- Dietary supplements ARE NOT EQUAL to prescription omega-3

Dietary supplements ≠ Rx

- All Rx is not equal (omega-3 acid ethyl esters are DHA/EPA while icosapent ethyl is EPA only
- MUST take 2g BID
- Decrease fishy burp concerns by **storing in refrigerator**
- Talk about safety concerns with the patient, then the provider

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