AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS | AMERICAN COLLEGE OF ENDOCRINOLOGY

Omega-3 Fatty Acids

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Introduction

- What are omega-3 fatty acids/fish oil and how do they fit into treatment for dyslipidemia?
- What are the recommendations and considerations for treatment with omega-3 fatty acids/fish oil?

Supplemental Omega-3 Fish Oil

- Evidence indicates that the consumption of fish oil 2 to 4 g daily can reduce TG by ≥25%, while producing only slight increases in LDL-C levels.
- Because of the demonstrated TG benefits associated with omega-3 fatty acids (EPA and DHA), the AHA supports 2 servings of fatty fish per week for the general population
- Individuals with ASCVD should consume 1 g of EPA and DHA daily through fatty fish (preferably) or high-quality dietary supplements.

AHA, American Heart Association; ASCVD: atherosclerotic cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

Prescription Omega-3 Fish Oil

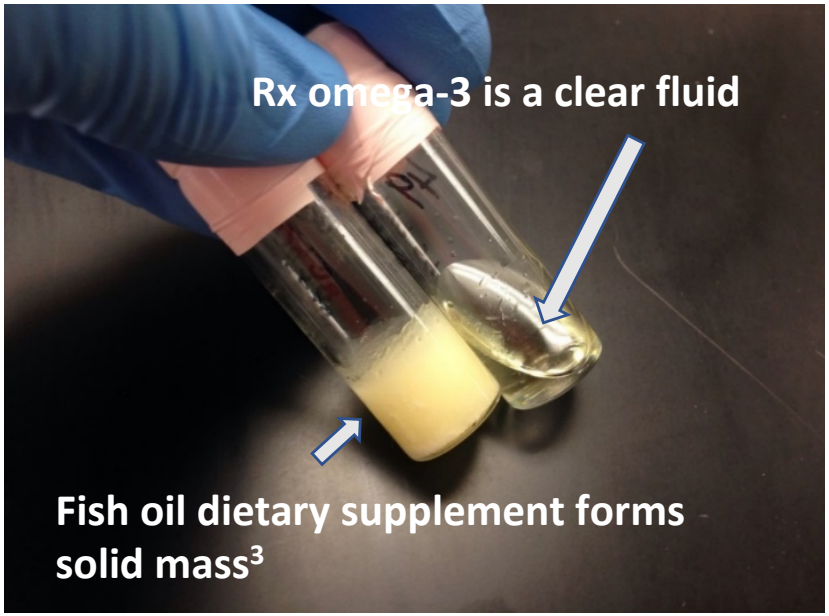
- Although the benefit of reducing TG levels is uncertain, several studies suggest that TG reduction is associated with a significant decrease in non-fatal MI, with a trend toward reduced ASCVD events.
- OTC omega-3 supplements are not FDA-regulated
  - May not have the quantity of omega-3 listed on the label
  - May contain other ingredients or contaminants
  - May cause mild side effects such as fish burps and upset stomach
- AACE recommends:
  - Prescription omega-3 oil 2 to 4 g daily to treat severe hypertriglyceridemia (TG >500 mg/dL).
  - Dietary supplements are not FDA-approved for treatment of hypertriglyceridemia and generally are not recommended for this purpose.

AACE, American Association of Clinical Endocrinologists; ASCVD: atherosclerotic cardiovascular disease; FDA, U.S. Food and Drug Administration; OTC, over-the-counter; TG, triglycerides.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497; WebMD. Omega-3 fish oil supplements and prescriptions.

Omega-3 Fatty Acid Dietary Supplements

- Fish oil: Among the most commonly used dietary supplements by U.S. adults[1]
  - Global sales may reach $3.3 billion by 2020
  - 19 million (8%) took fish oil dietary supplement in previous 30 days[2]
- There are no omega-3 OTC products in U.S. (only prescriptions and dietary supplements)
- Dietary supplements are not FDA-regulated; their content and efficacy often remain unverified.[3]



FDA, U.S. Food and Drug Administration; OTC, over-the-counter.

1. Barnes PM et al. National Health Statistics Reports. 2008;12:1-24.
2. NIH NCCIH. Available at: https://nccih.nih.gov/health/omega3/introduction.htm
3. Mason RP, Sherratt SC. *Biochem Biophys Res Commun*. 2017;483:425-9.

Prescription vs Dietary Supplement Omega-3 FA

	Prescriptions		Dietary Supplements
	EPA	EPA +DHA	
FDA classification	Drug	Drug	Food
FDA approval	Yes	Yes	No
Ingredients	EPA	EPA + DHA	Variable EPA + DHA (vs few pure EPA) + other PUFAs and saturated FA
Omega-3 per capsule	0.98 g	0.84 g	Usually 0.2–0.4 g EPA; 0.1–0.3 g DHA
Capsules/day to provide 4 g omega-3	4	~4	Usually 10–20
Purity/efficacy and safety tested	Yes	Yes	Not required (usually not done)

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FDA, U.S. Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; PUFA, polyunsaturated fatty acids.

Prescription Omega-3 Fatty Acid Formulations

	EPA+DHA EE[1,2]	EPA only EE[3]	EPA+DHA FFA[4]
Brand Name	*Lovaza*	*Vascepa*	*Epanova (not yet available)*
Generic Available?	Yes[5]	No	No
Indication	Adjunct to diet to ↓TG levels in adult patients with severe hypertriglyceridemia (≥500 mg/dL)		
Omega-3 content	• EPA: 0.465 g • DHA: 0.375 g • EPA/DHA: 55%/45%	• EPA: 1 g • EPA/DHA: 100%/0%	• EPA: 0.55 g • DHA: 0.2 g • EPA/DHA: 73%/27%
Regimen, capsules	• 2 BID w/ food or • 4 QD w/ food[2]	• 2 BID w/ food	• 2 or 4 QD, meal independent

BID, twice daily; DHA, docosahexaenoic acid; EE, ethyl ester; EPA, eicosapentaenoic acid; FFA, free fatty acid; QD, once daily.

1. Lovaza PI, generics available. 2. Omtryg PI. 3. Vascepa PI. 4. Epanova PI. 5. Generic and Lovaza cost the same. EE=ethyl ester; FFA=free FA; PI=prescribing information.
Sperling LS, Nelson JR. *Curr Med Res Opin*. 2016;32:301-11.

Similarities and Differences of Prescription Omega-3 Fatty Acid Formulations

	EPA+DHA EE[1,2]	EPA only EE[3]
Brand Name	Lovaza	Vascepa
Lowers TG	Yes	Yes
Lowers non-HDL-C	Yes	Yes
Raises LDL-C	Yes	No

DHA, docosahexaenoic acid; EE, ethyl ester; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

1. Lovaza prescribing information, generics available. 2. Omtryg prescribing information. 3. Vascepa prescribing information. 4. Epanova prescribing information. Sperling LS, Nelson JR. *Curr Med Res Opin*. 2016;32:301-11.

AHRQ Evidence for Clinical Benefit of Omega-3 Fish Oil

- According to a recent U.S. AHRQ technical review:
  - Fish oil supplementation raises HDL-C and LDL-C by ≤2 mg/dL while lowering TG
  - Individuals with high baseline TG levels experience greater benefit than those with lower levels
  - Moderate-to-high evidence exists to indicate that fish oil intake does not affect major CV events, all-cause death, total CHD, sudden cardiac death, coronary revascularization, atrial fibrillation, or blood pressure
  - While randomized controlled trials have not shown improved CV outcomes with fish oil supplementation, observational studies have showed possible benefit

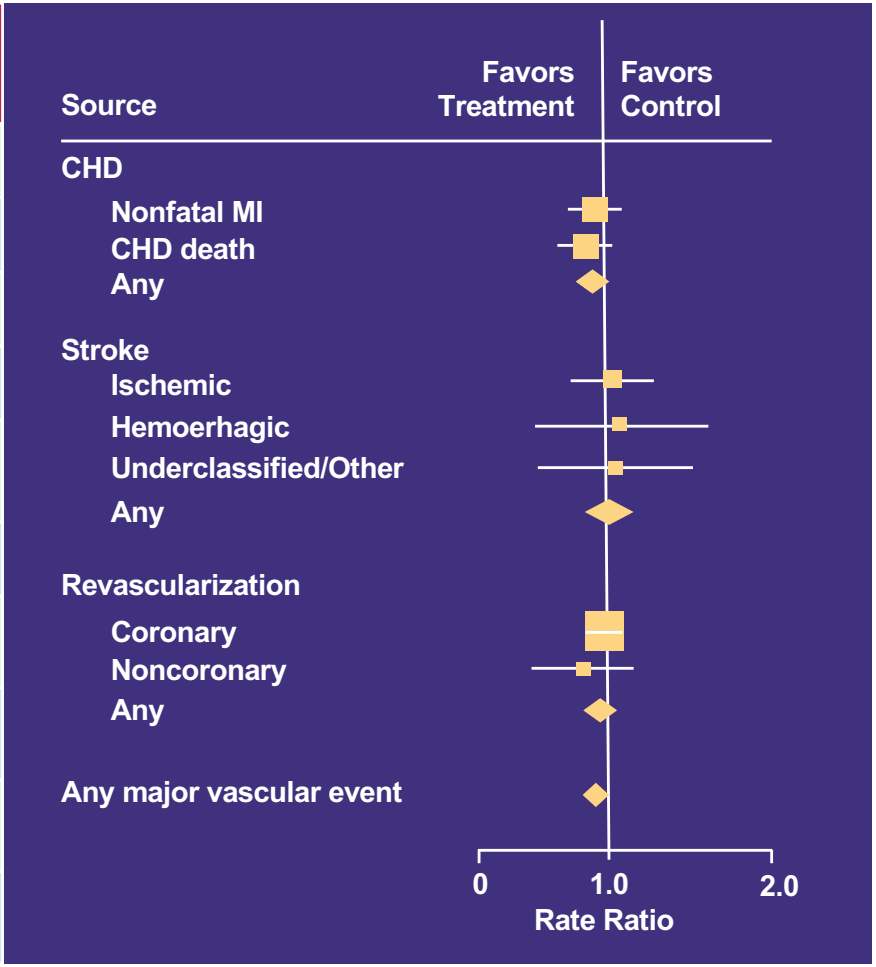
AHRQ, Agency for Healthcare Research and Quality; CHD, coronary heart disease; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Balk, et al. AHRQ Evidence Report/Technology Assessment No. 223 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."

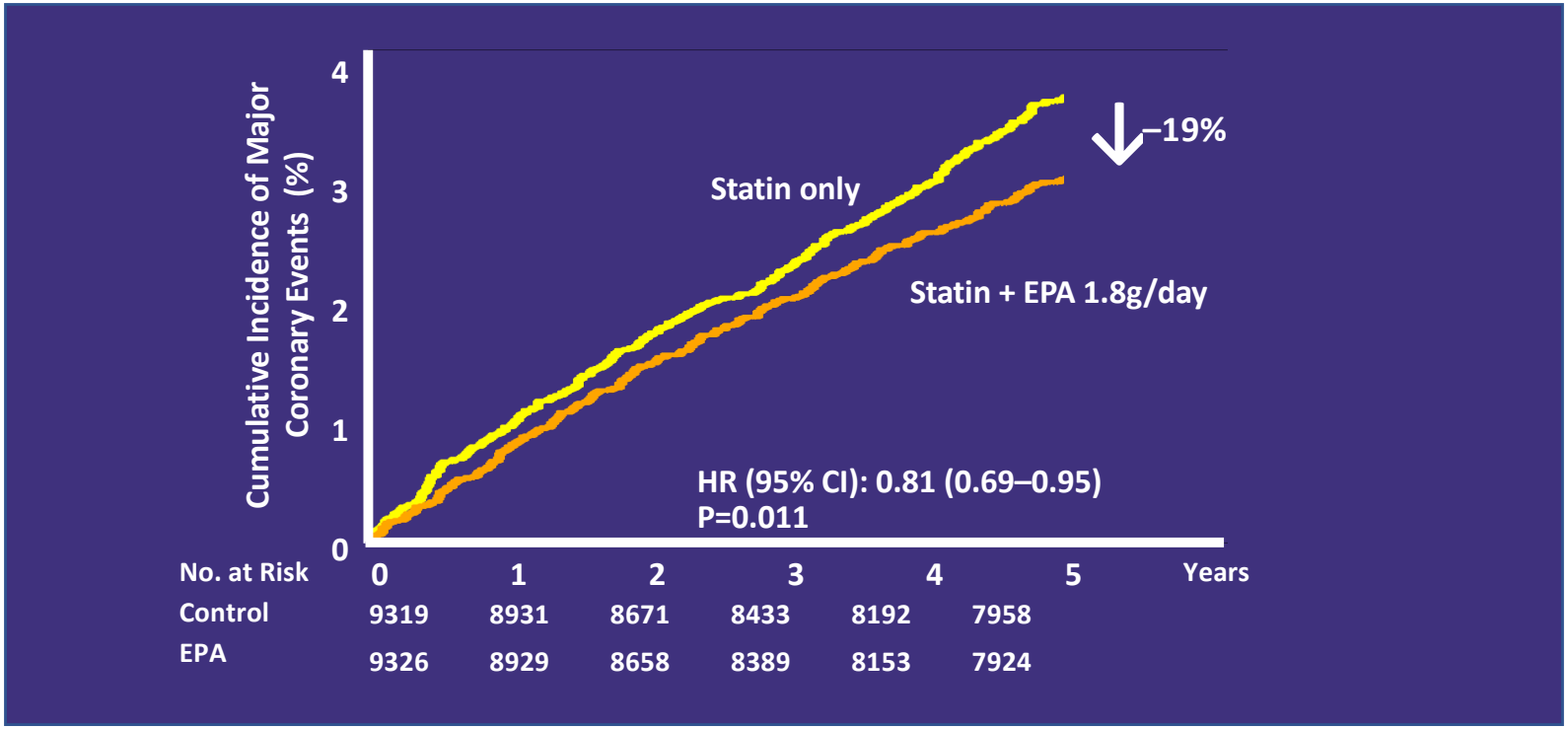
Study (Year)	EPA/DHA Dose (mg/d)	EPA / DHA Source
DOIT (2010)	1150 / 800	Dietary supplement
AREDS-2 (2014)	650 / 350	Dietary supplement
SU.FOL.OM3 (2010)	400 / 200	Dietary supplement
JELIS (2007)	1800 / NA	Pure EPA Rx
Alpha Omega (2010)	226 / 150	Margarine with dietary supplement
OMEGA (2010)	460 / 380	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



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

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

JELIS: EPA Reduced Major Coronary Events* in Hypercholesterolemic Patients on Statins



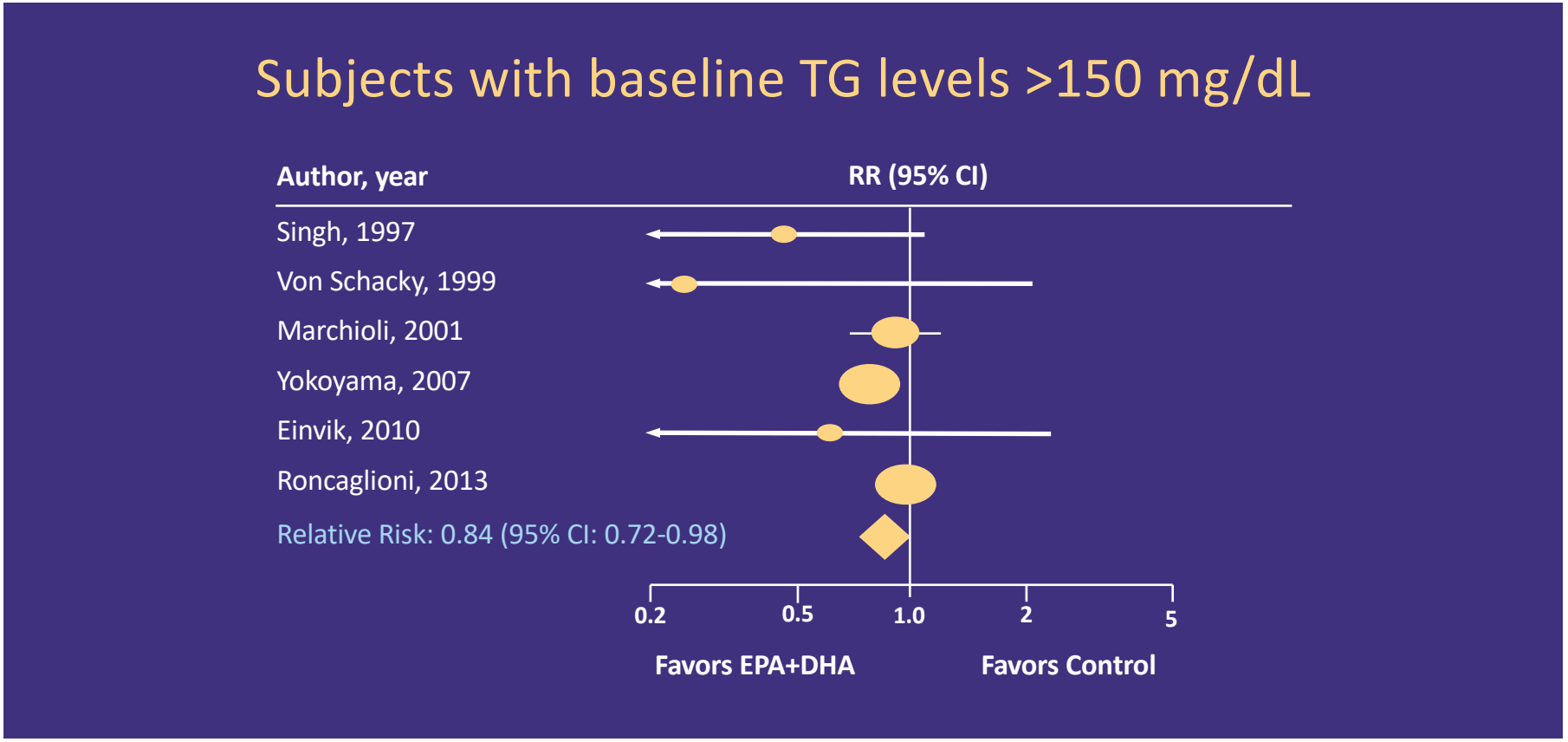
N=18,645 Japanese pts with TC ≥251 mg/dL prior to baseline statin treatment. Baseline TG=153 mg/dL. Statin up-titrated to 20 mg pravastatin or 10 mg simvastatin for LDL-C control.

*Primary endpoint: sudden cardiac death, fatal and non-fatal MI, unstable angina pectoris, angioplasty, stenting, or coronary artery bypass graft.

Yokoyama M et al. *Lancet.* 2007;369:1090-8.

CI, confidence interval; EPA, eicosapentaenoic acid; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TC, total cholesterol; TG, triglycerides.

Randomized Controlled Trials and Prospective Cohort Studies of EPA+DHA and CHD Risk



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

Alexander DD et al. *Mayo Clin Proc*. 2017;92:15-29.

Ongoing Omega-3 Cardiovascular Outcomes Trials

	REDUCE-IT	STRENGTH
Agent Dose	EPA (EE) 4 g/d	EPA+DHA (FFA) 4 g/d
Population	International	International
N	~8000	Estimated 13,000
Age	≥45 years	≥18 years
Risk profile	CVD (70%) or ↑CVD risk (30%)	CVD (50%) or ↑CVD risk (50%)
Follow-up	4–6 years (planned)	3–5 years (planned)
Statin use	100% (at LDL-C goal)	100% (at LDL-C goal)
Primary outcome	Expanded MACE	Expanded MACE
Result	Powered for 15% RRR	Powered for 15% RRR
Entry TG Entry HDL-C	200 to 499 mg/dL NONE	200 to 499 mg/dL <40 mg/dL M, <45 mg/dL W

CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; M, men; MACE, major adverse cardiovascular event; RRR, relative risk reduction; T2D, type 2 diabetes; TG, triglycerides; W, women.

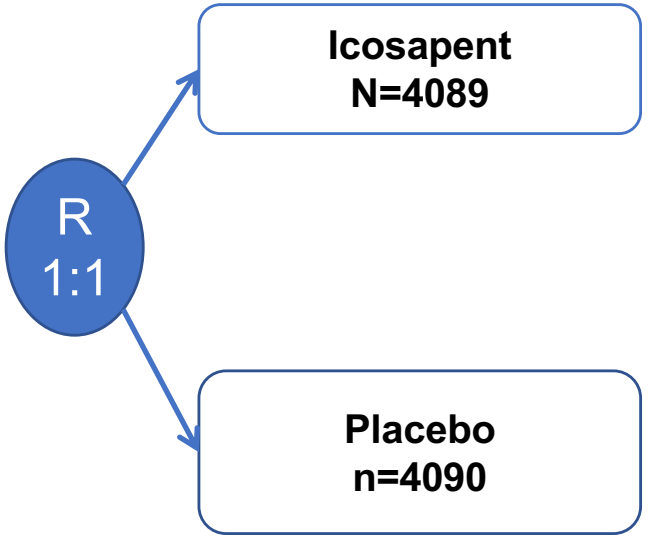
http://www.clinicaltrials.gov. PROMINENT: NCT03071692; REDUCE-IT: NCT01492361; Bhatt DL, et al. *Clin Cardiol.* 2017 Mar;40(3):138-148

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

REDUCE-IT Study Design and Objectives

Eligibility criteria:

- Age ≥45 years with CVD, or ≥50 years with diabetes with ≥1 additional risk factor for CVD
- Fasting TG levels ≥150mg/dL* and <500 mg/dL
- LDL-C >40mg/dL and ≤100mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to randomization



Primary outcome:
Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina

Key secondary outcome:
Composite of CV death, nonfatal MI, or nonfatal stroke

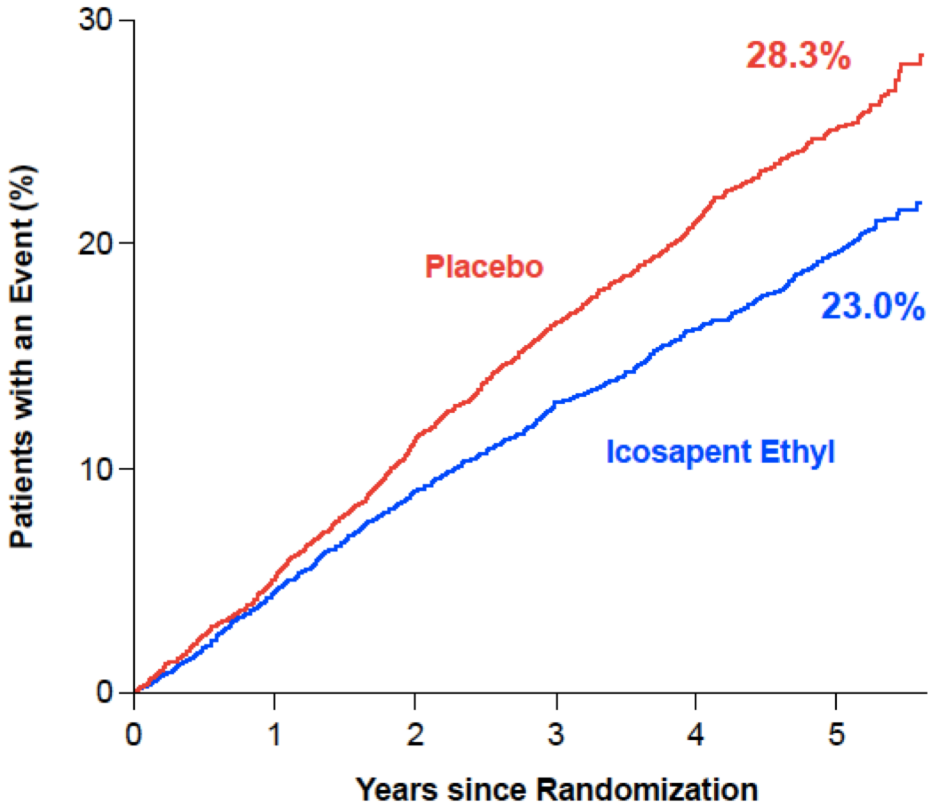
- **Study design:** Phase 3B, multi-center, randomized, double-blind, placebo-controlled trial with long-term follow-up at 470 centers, worldwide
- **Primary objective:** To assess whether treatment with icosapent ethyl reduces ischemic events in statin-treated patients with high TG at elevated CV risk

*Due to the variability of TGs, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying TG ≥135 mg/dL.

CV, cardiovascular; CVD, cardiovascular disease, LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TG, triglycerides.

Bhatt DL, et al. *Clin Cardiol*. 2017;40(3)138-148. (Epub prior to print).

REDUCE-IT: Key Primary Endpoint (CV Death, MI, Stroke, Coronary Revascularization, Unstable Angina)

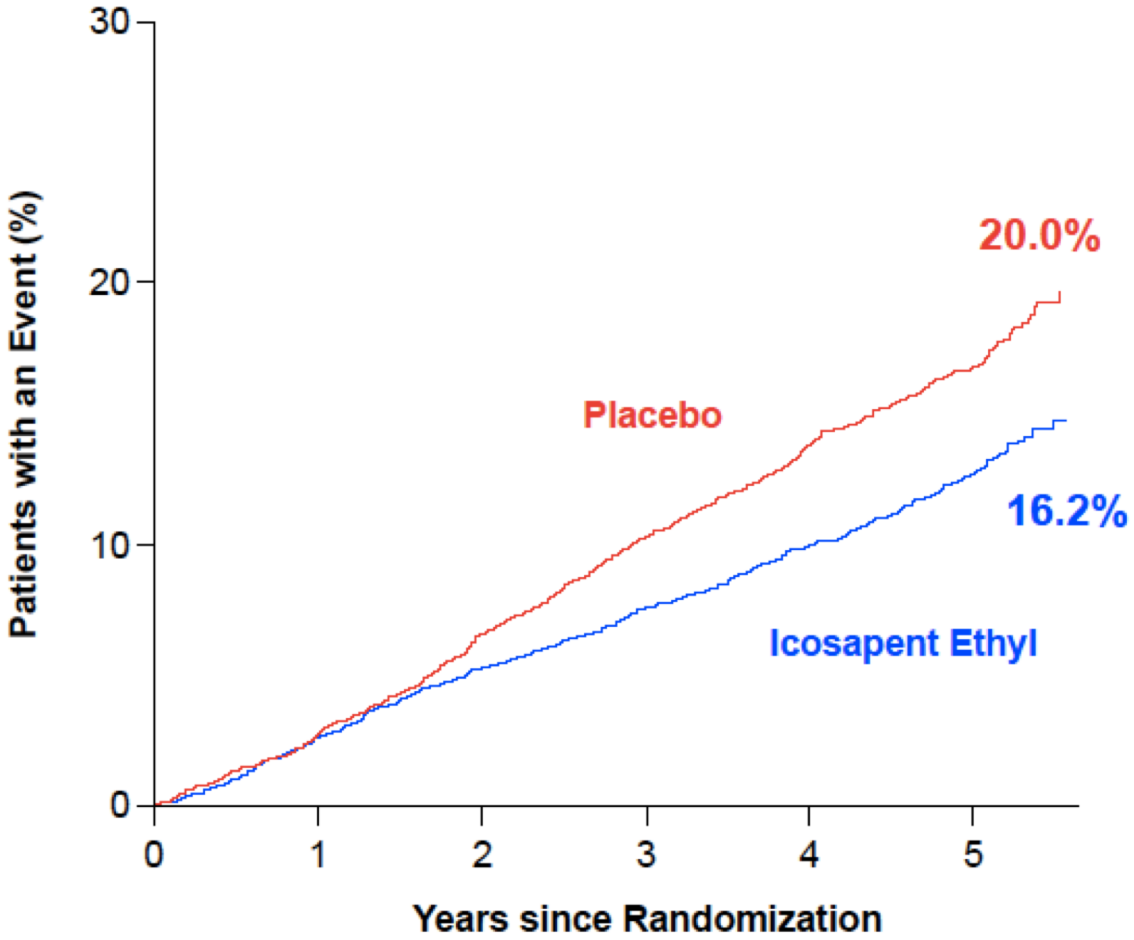


Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

ARR, absolute risk reduction; CV, cardiovascular; MI, myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction.

Bhatt DL, et al. *Clin Cardiol*. 2017;40(3)138-148. (Epub prior to print).

REDUCE-IT: 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

ARR, absolute risk reduction; CV, cardiovascular; MI, myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction.

FDA-approved Pharmacologic Therapy for Very High TG and Fredrickson Types III & IV

Drug Class	Very High TG Indications*			Notable Adverse Effects
	TG >500 mg/dL	Type III Hyper-lipidemia	Type IV Hyper-lipidemia	
Omega-3 FA (EPA/DHA)[a]	√			Eructation, dyspepsia, taste perversion
Omega-3 FA (EPA only)[a]	√			Arthralgia
Fenofibrate[b]	√			Abnormal liver function test, myalgia, increased creatinine, nausea
Extended-release niacin[c]	√			Flushing, nausea, diarrhea, vomiting, cough
Statins[d]	√	√	√	Myalgia, new-onset T2D, hyperglycemia

*Data from individual product labeling for each drug in patients with very high TG. †AEs: Incidence >Placebo and: ≥3% for ω-3/EPA/DHA; ≥2% for ω-3/EPA, fenofibrate, statins; ≥5% for niacin. [a]4 g per day. [b]145 mg per day. [c]2 g per day. [d]Atorvastatin, rosuvastatin, simvastatin.

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acids; T2D, type 2 diabetes; TG, triglycerides.

Miller M et al. *Circulation*. 2011;123:2292-333. Fredrickson DS, Lees RS. C*irculation*. 1965;31:321-7.
Lewis B. *Proc R Soc Med*. 1971;64:905-8.

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.

Nelson JR et al. *Vascul Pharmacol.* 2017;91:1-9. *After* Bays HE. Chapter 21. *The John Hopkins Textbook of Dyslipidemia*, by Peter O Kwiterovich, 2010; 245-57.

Fenofibrate vs Omega-3 vs Niacin for Hypertriglyceridemia: Summary

	Fenofibrate	Rx Omega-3	Niacin
Δ TG	↓↓↓	↓↓↓	↓↓
Δ LDL-C	↑↑↑ to →	↑↑↑ to → to ↓	↓ to ↓↓
Δ Non-HDL-C	→ to ↓	→ to ↓	↓ to ↓↓
Δ HDL-C	→ to ↑	→ to ↑	↑ to ↑↑
↓ CVD Efficacy	0 to +	0 to +++	0 to +
↓ Mortality	0	++	+
Non-CVD Benefits	0 to ++	0 to ++?	0
Safety	+ to –	+++	– – – to 0
"Natural"	0	++	+
Access (cost/generic)	+ to ++	– to ++	++ to +++
Tolerability	++ to –	++ to –	– – –
Ease of use	+++	+++	– –

CVD=cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Starting Dosages and Dose Ranges

Omega-3 Fatty Acids

Agent	Usual recommended starting daily dosage	Dose range	Method of administration
Omega-3-acid ethyl esters (Lovaza)	4 g per day	4 g per day (1 or 2 doses)	Oral
Icosapent ethyl (Vascepa)	4 g per day	4 g per day (2 doses)	Oral

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497; Lovaza (omega-3-acid ethyl esters) [PI]; 2015; Vascepa (icosapent ethyl) [PI]; 2016.

Metabolic Effects

Omega-3 Fatty Acids

- Icosapent ethyl ↓ LDL-C 5%, whereas omega-3-acid ethyl esters ↑ LDL-C 45%
- In individuals with severe hypertriglyceridemia, reduces TG 27%-45%, TC 7%-10%, VLDL-C 20%-42%, apolipoprotein B 4%, and non-HDL-C 8%-14%
  - Most likely by reducing hepatic VLDL-TG synthesis and/or secretion and enhancing TG clearance from circulating VLDL particles.
- Other potential mechanisms of action include:
  - Increased ß-oxidation
  - Inhibition of acyl-CoA
  - 1,2-diacylglyceral acyltransferase
  - Decreased hepatic lipogenesis
  - Increased plasma lipoprotein activity

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497; Lovaza (omega-3-acid ethyl esters) [PI]; 2015; Vascepa (icosapent ethyl) [PI]; 2016.

Omega-3 Fatty Acids: Treatment and Monitoring Considerations

- Assess TG levels prior to initiating and periodically during therapy
- Omega-3-acid ethyl esters can increase LDL-C levels; monitor LDL-C levels during treatment
- Omega-3s may prolong bleeding time; monitor coagulation status periodically in patients receiving treatment with omega-3 fatty acids and other drugs affecting coagulation
- Monitor ALT and AST levels periodically during treatment in patients with hepatic impairment; some patients may experience increases in ALT levels only.
- Exercise caution when treating patients with a known hypersensitivity to fish and/or shellfish

AF, atrial fibrillation; ALT, alanine transaminase; AST, aspartate aminotransferase; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.; Lovaza (omega-3-acid ethyl esters) [PI]; 2015; Vascepa (icosapent ethyl) [PI]; 2016.

Omega-3 Fatty Acids: Safety Considerations

The effect of omega-3 fatty acids on CV morbidity and mortality and the risk of pancreatitis has not been determined in patients with severe hypertriglyceridemia

In patients with paroxysmal or persistent AF, therapy with omega-3-acid ethyl esters may be associated with increased frequency of symptomatic AF or flutter, especially within the first 2 to 3 months after initiation

Most common adverse events include arthralgia (2.3%), eructation (4%), dyspepsia (3%), and taste perversion (4%); may also experience constipation, gastrointestinal disorders, vomiting, rash, or pruritus

Omega-3s should be used with caution in nursing mothers and only be used in pregnant women if the benefits of treatment outweigh the potential risk of fetal harm

AF, atrial fibrillation; CV, cardiovascular.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

Conclusion

- Omega-3 fatty acid/fish oil supplementation is highly effective at treating hypertriglyceridemia
- AACE recommends 2g to 4g per day of prescription omega-3 oil in patients with TG >500 mg/dL
- Omega-3 fatty acid/fish oil supplementation may also moderately increase HDL-C and LDL-C
  - LDL-C levels should be monitored
- Evidence suggests that fish oil supplementation does not affect CV events

AACE, American Association of Clinical Endocrinologists; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.