The benefits of icosapent ethyl in addressing residual risk: What is the evidence?

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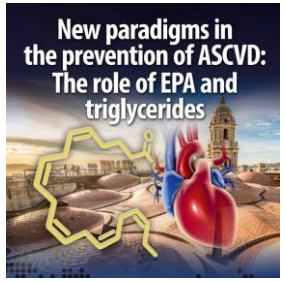


Potential Mechanisms of Cardioprotection For Omega-3 Fatty Acids

Lowering of Triglyceride Rich Lipoproteins

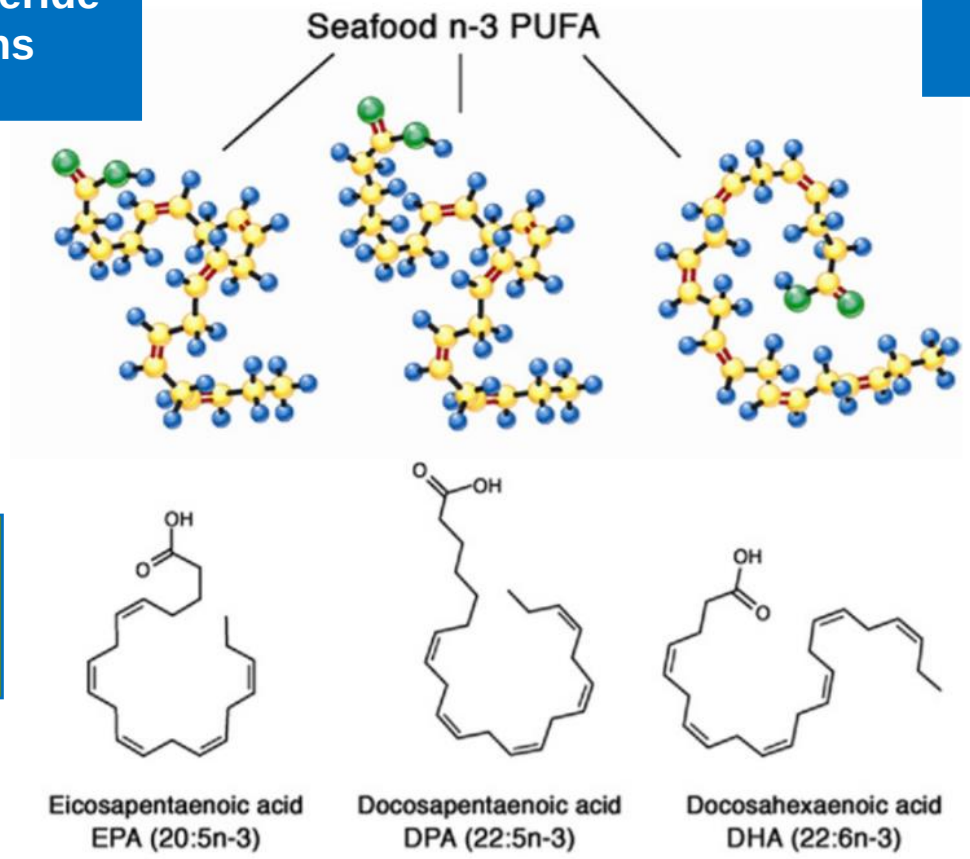
Anti-Inflammatory Actions

Antithrombotic Effects

Augmented Specialized Pro-resolving Mediators

Membrane Stabilizing Effects (EPA>DHA)

Altered Prostaglandin Synthesis



Icosapent ethyl is a stable, highly purified ethyl ester of eicosapentaenoic acid

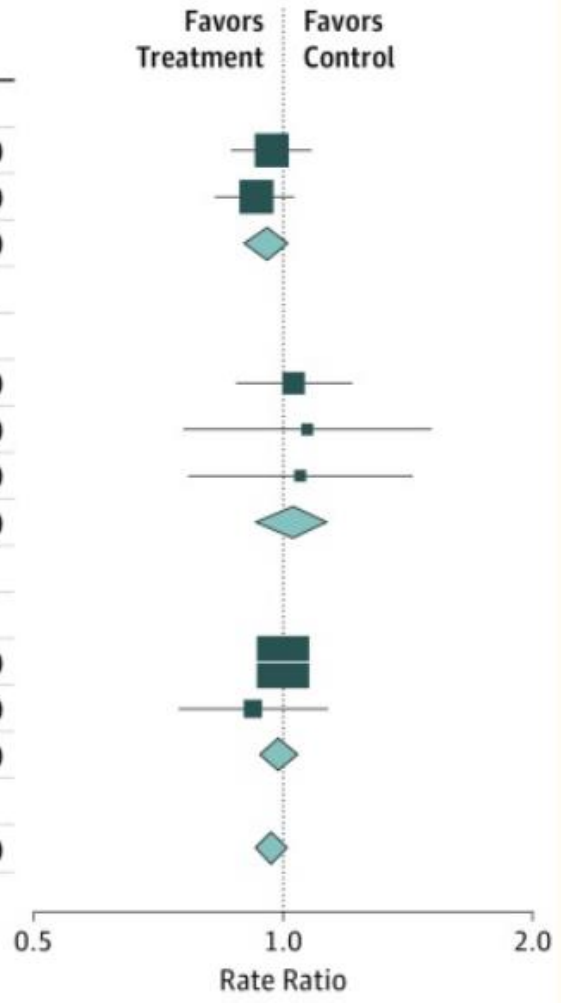
Arterioscler Thromb Vasc Biol. 2020;40:1135-1147.
J Am Coll Cardiol. 2011;58:2047-67.

Low Dose Omega-3 Fatty Acids do not offer cardioprotection

Meta-Analysis of 10 trials n=78000

Associations of Low Dose Omega-3 Fatty Acids With Major Vascular Events*

Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87-1.08)
Coronary heart disease death	1301 (3.3)	1394 (3.6)	0.93 (0.83-1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90-1.01)
			P = .12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88-1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76-1.51)
Unclassified/other	142 (0.4)	135 (0.3)	1.05 (0.77-1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93-1.13)
			P = .60
Revascularization			
Coronary	3044 (9.3)	3040 (9.3)	1.00 (0.93-1.07)
Noncoronary	305 (2.7)	330 (2.9)	0.92 (0.75-1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94-1.04)
			P = .60
Any major vascular event	5930 (15.2)	6071 (15.6)	0.97 (0.93-1.01)
			P = .10



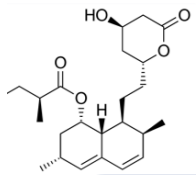
No significant association with:

- fatal or nonfatal CHD
- any major vascular events

*Meta-analysis of 10 trials (N = 77917).

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

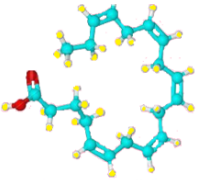
Effects of EPA on plaque:



STATINS:

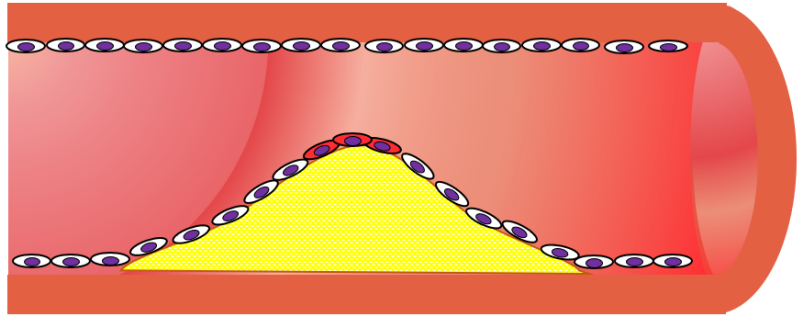
- Calcification increased
- Inflammation: decreased by lowering LDL-C
- LDL-C: Lowered significantly
- PAR-1 expression increased

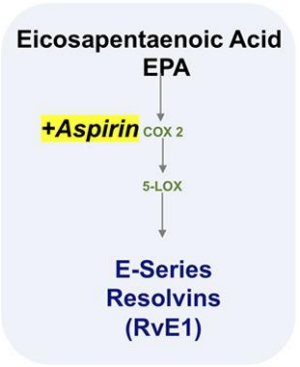
EPA:

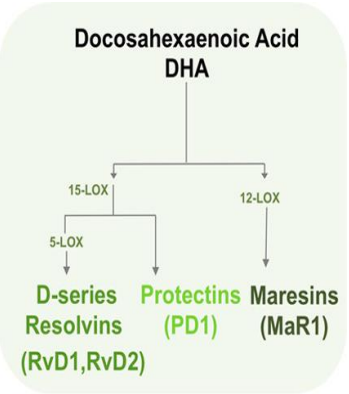


- Calcification: No effect
- Inflammation: decreased by modulating WBC accumulation
- LDL-C: No significant effect
- Platelet reactivity modulated
- Resolvins increased

- Improved endothelial function
- Necrotic core decreased
- Adhesion molecules decreased
- Fibrous cap increased
- Plaque atheroma volume decreased



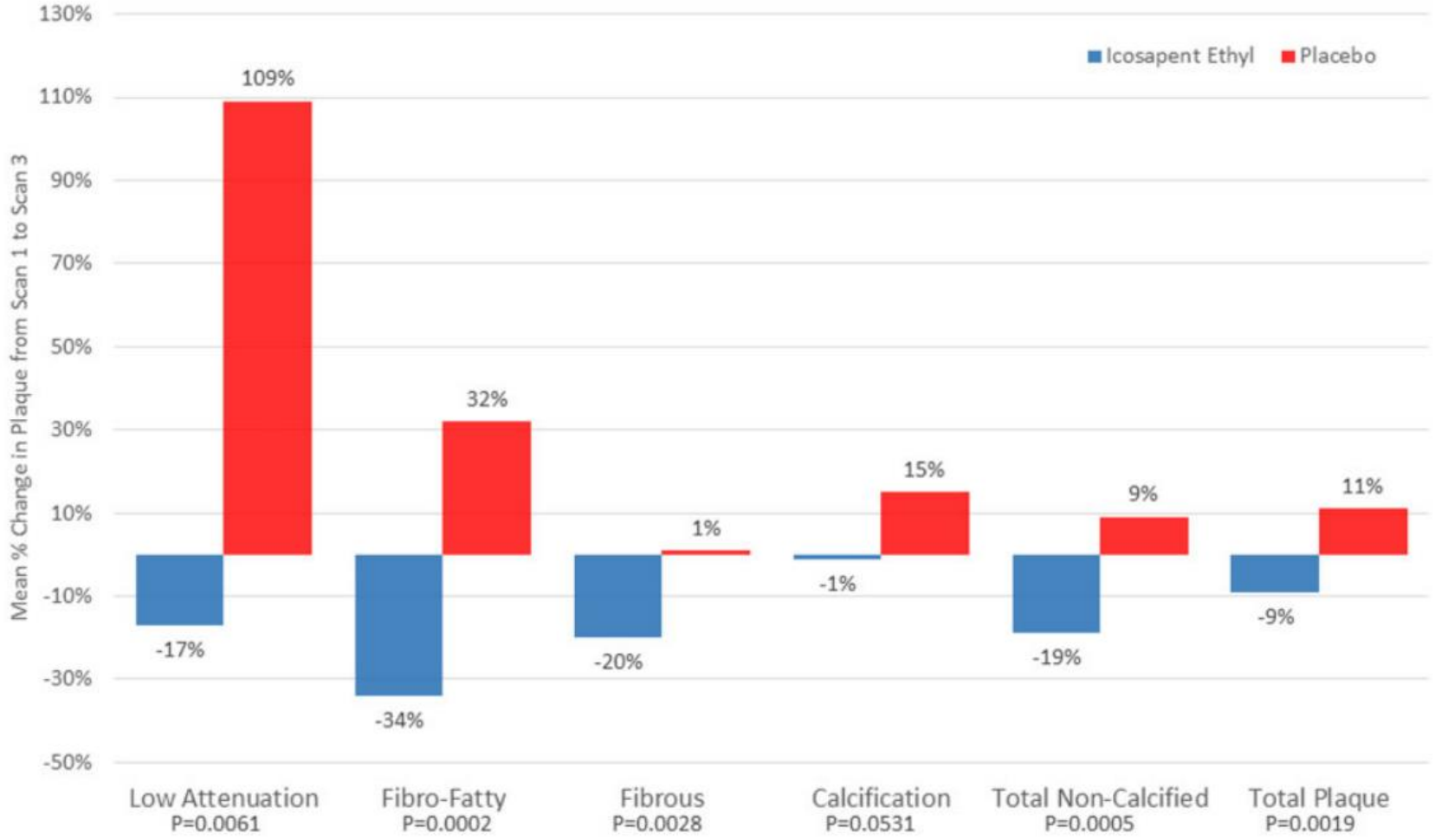




Resolvin E1 has antiplatelet functions and a protective role in animal models of atherosclerosis

Tokgözoğlu, Eur Heart J 2020.
Circulation Research. Next-Gen Inflammation Resolution, Volume: 126: 91-93.

Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy

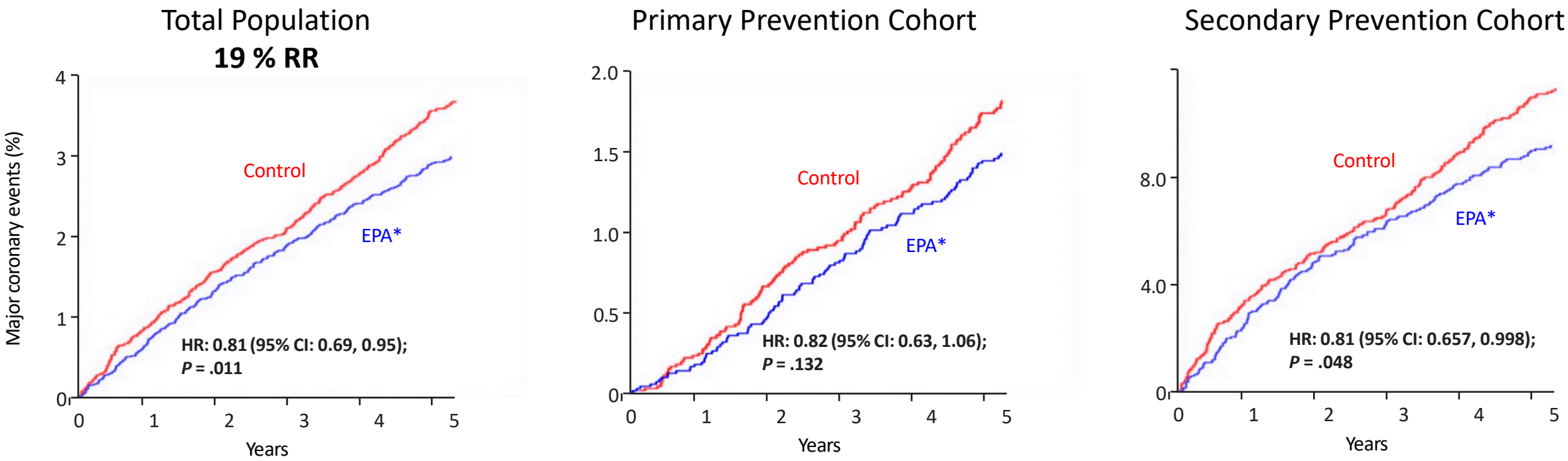


Eur Heart J. 2020;41:3925-3932.

JELIS Study: First to show efficacy of high dose EPA

18,645 Japanese pts with TC above 250 mg/dL. 1.8 g EPA supplementation was tested, FU 6.4 y

Kaplan-Meier Estimates of Incidence of Coronary Events



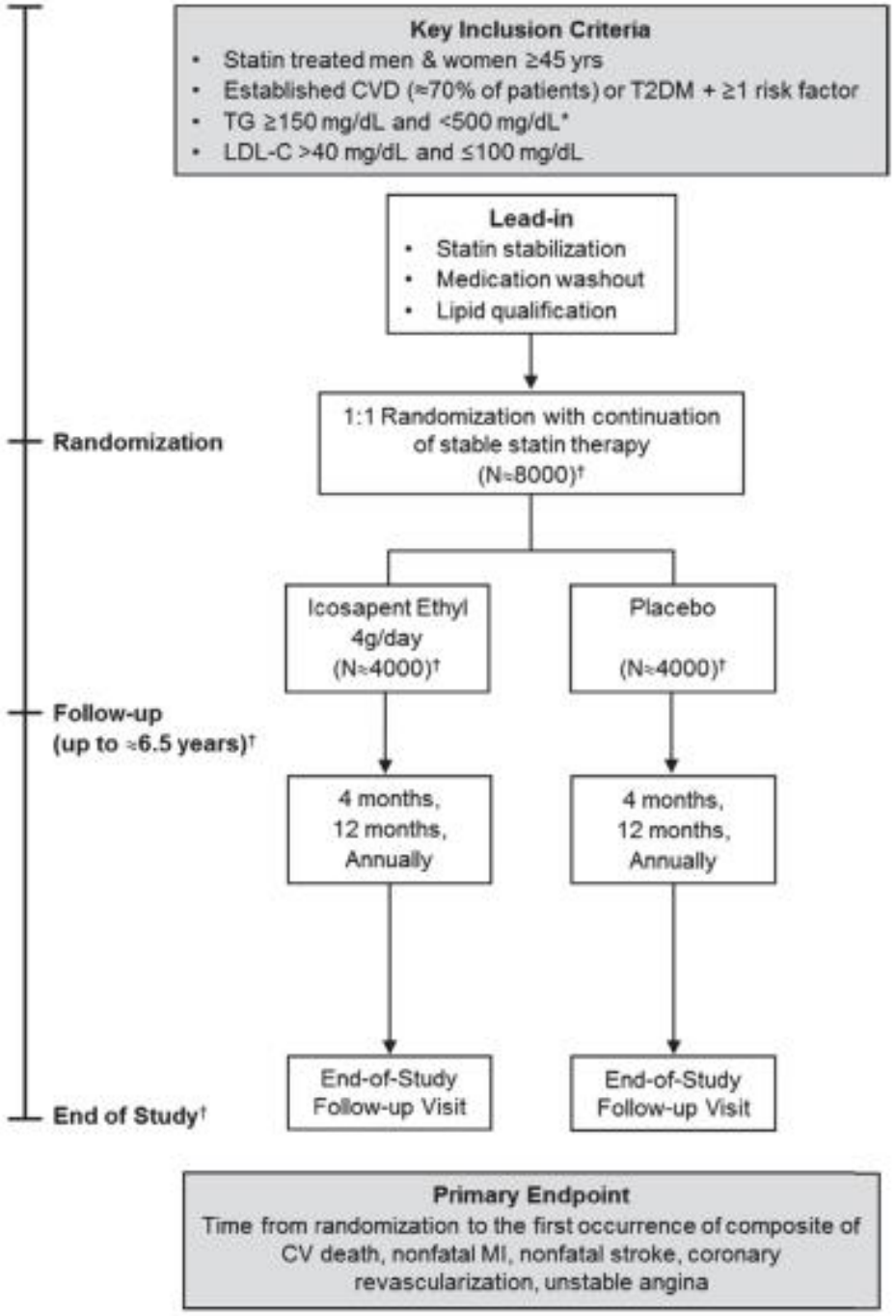
*1800 mg/d

Significant decrease in CV events mostly driven by secondary prevention group in subgroup of high TG, low HDL decrease was 53%

Yokoyama M, et al. Lancet. 2007;369:1090-1098.

REDUCE-IT

- 8179 patients were randomly assigned to receive 2 g of icosapent ethyl twice daily or placebo.
- The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina.
- 4.9 y FU



N Engl J Med. 2019;380:11-22.

REDUCE-IT: Effects on Biomarkers

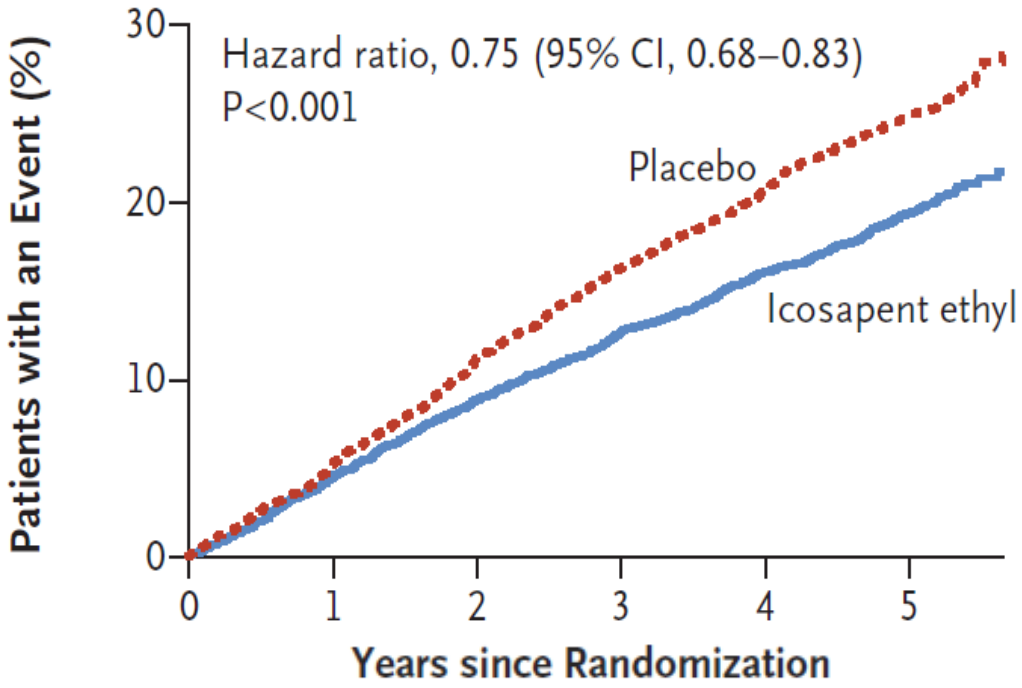
	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
Biomarker*	**Baseline**	**Year 1**	**Baseline**	**Year 1**	**Absolute Change from Baseline**	**% Change from Baseline**	**% Change P-value**
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.5	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

*Apo B and hsCRP were measured at Year 2.

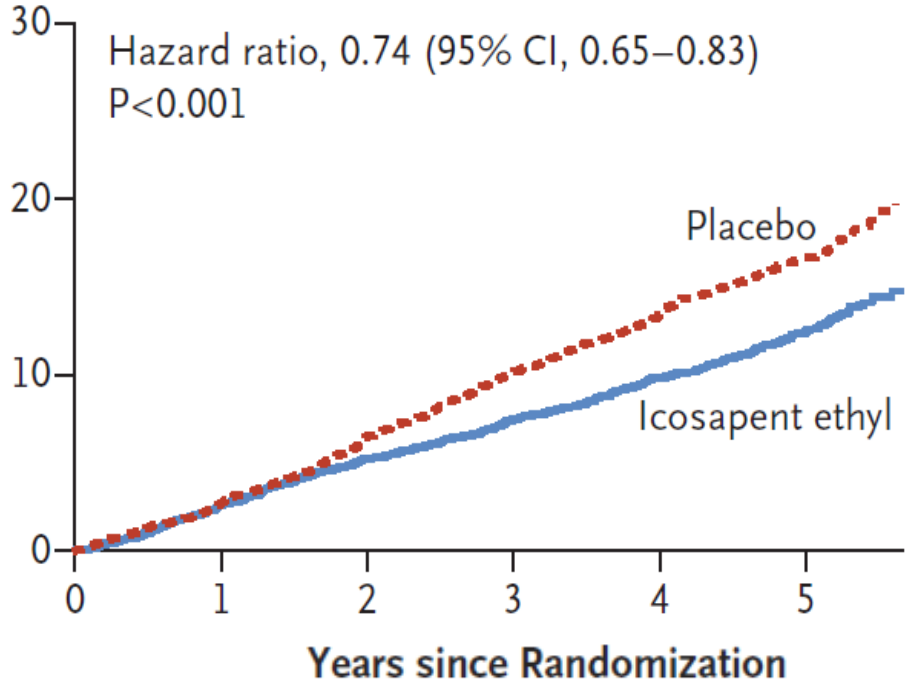
N Engl J Med. 2019;380:11-22.

Icosapent Ethyl (EPA) vs Placebo (Mineral Oil)
REDUCE-IT

Primary Endpoint: 5-Point MACE



Secondary Endpoint†



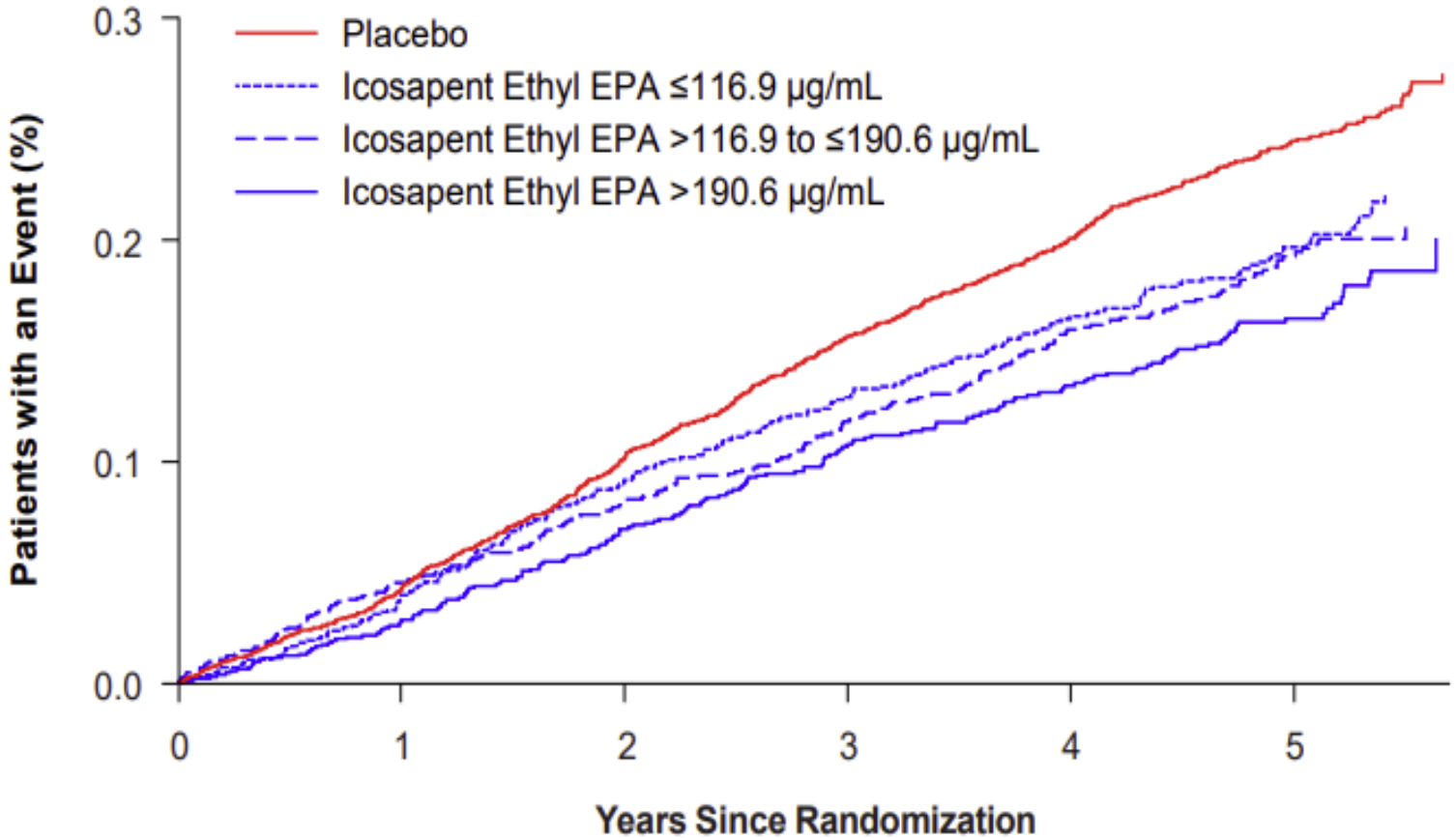
*†Composite of CV death, nonfatal MI, or nonfatal stroke.
MACE, major adverse cardiac event

Benefit of IPE was consistent regardless of baseline LDL-C or TGs

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

Primary End Point by Average of EPA Level at Years 1, 2, 3 and End of Study

	Hazard Ratio (95% CI):
Icosapent Ethyl EPA ≤116.9 µg/mL vs Placebo	0.85 (073–0.99)
Icosapent Ethyl EPA >116.9 to ≤190.6 µg/mL vs Placebo	0.74 (0.63–0.86)
Icosapent Ethyl EPA >190.6 µg/mL vs Placebo	0.63 (0.54–0.74)

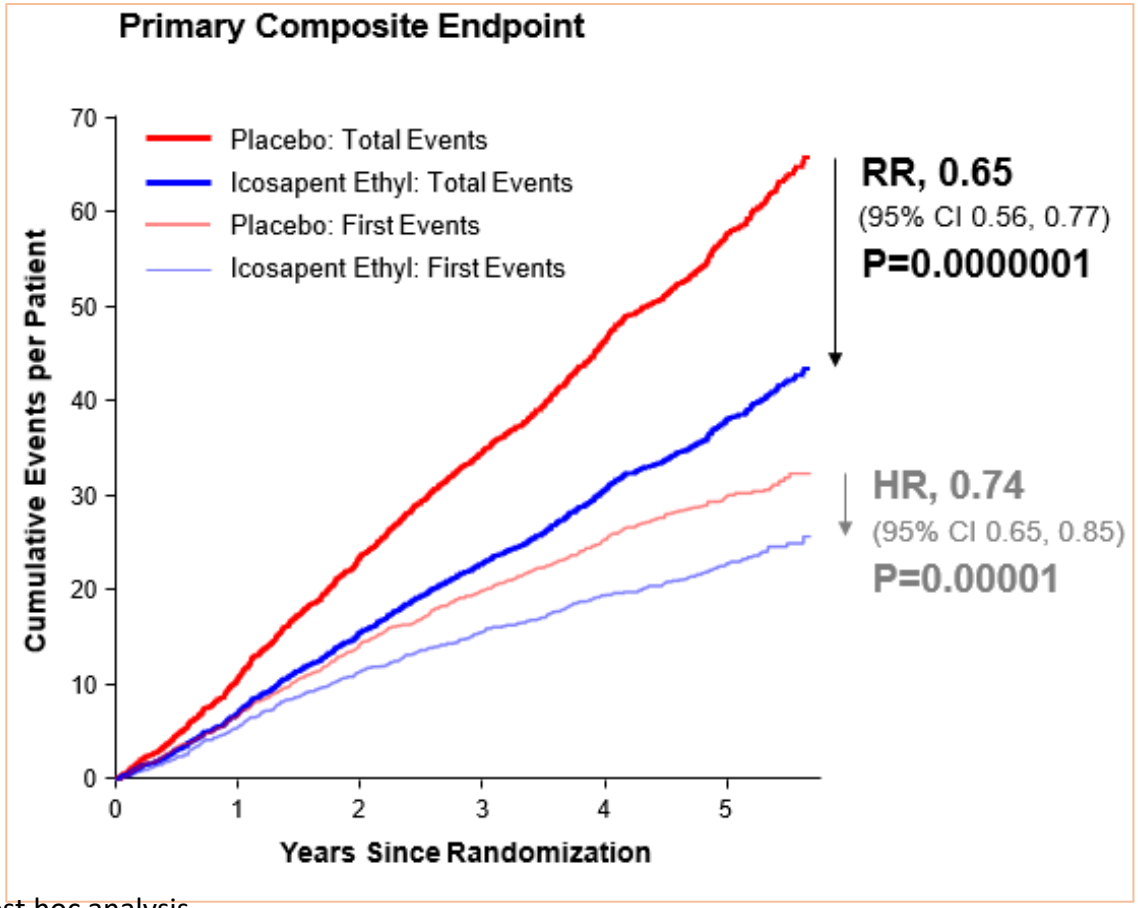


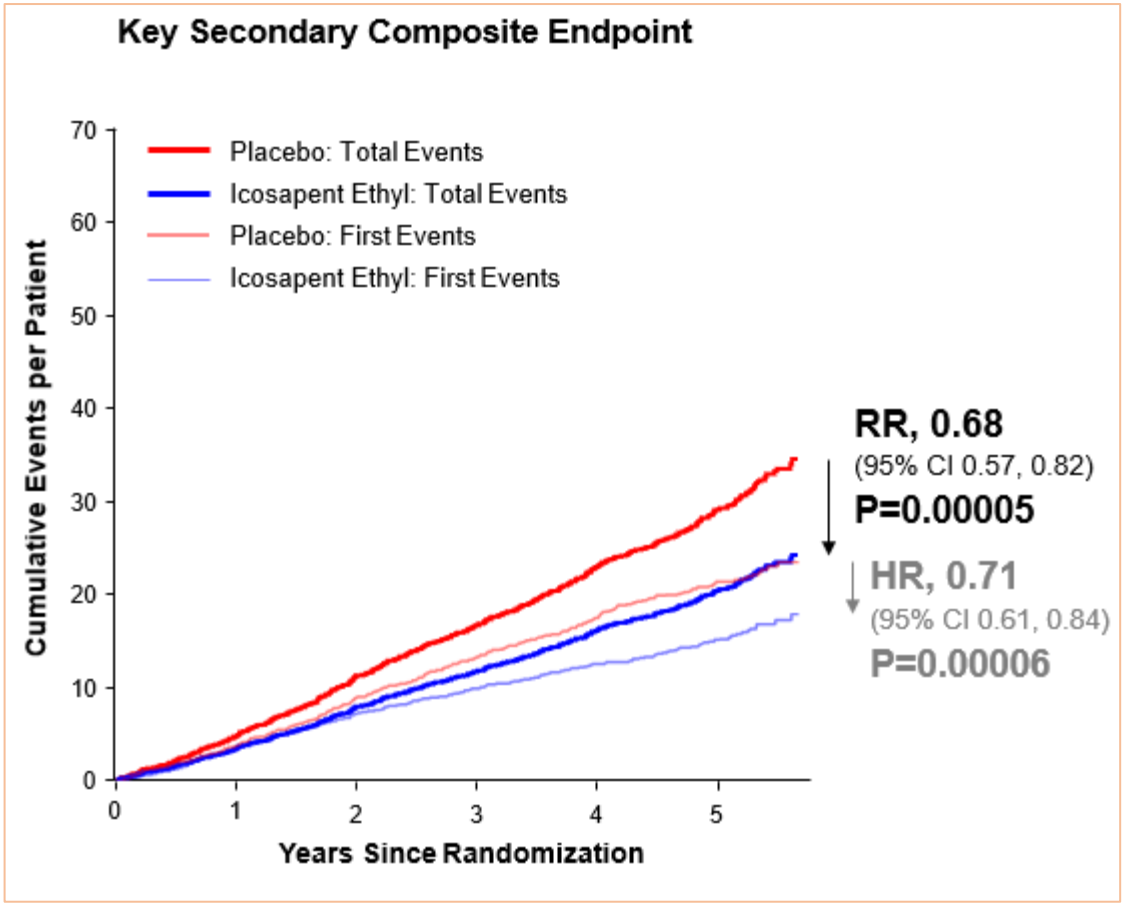
Abstract 20-LB-20501-ACC. Presented March 30, 2020.

Subgroup analyses from REDUCE-IT

Patients with Prior MI* (N= 3693):

Icosapent ethyl reduced First and Total Primary and Secondary Endpoints

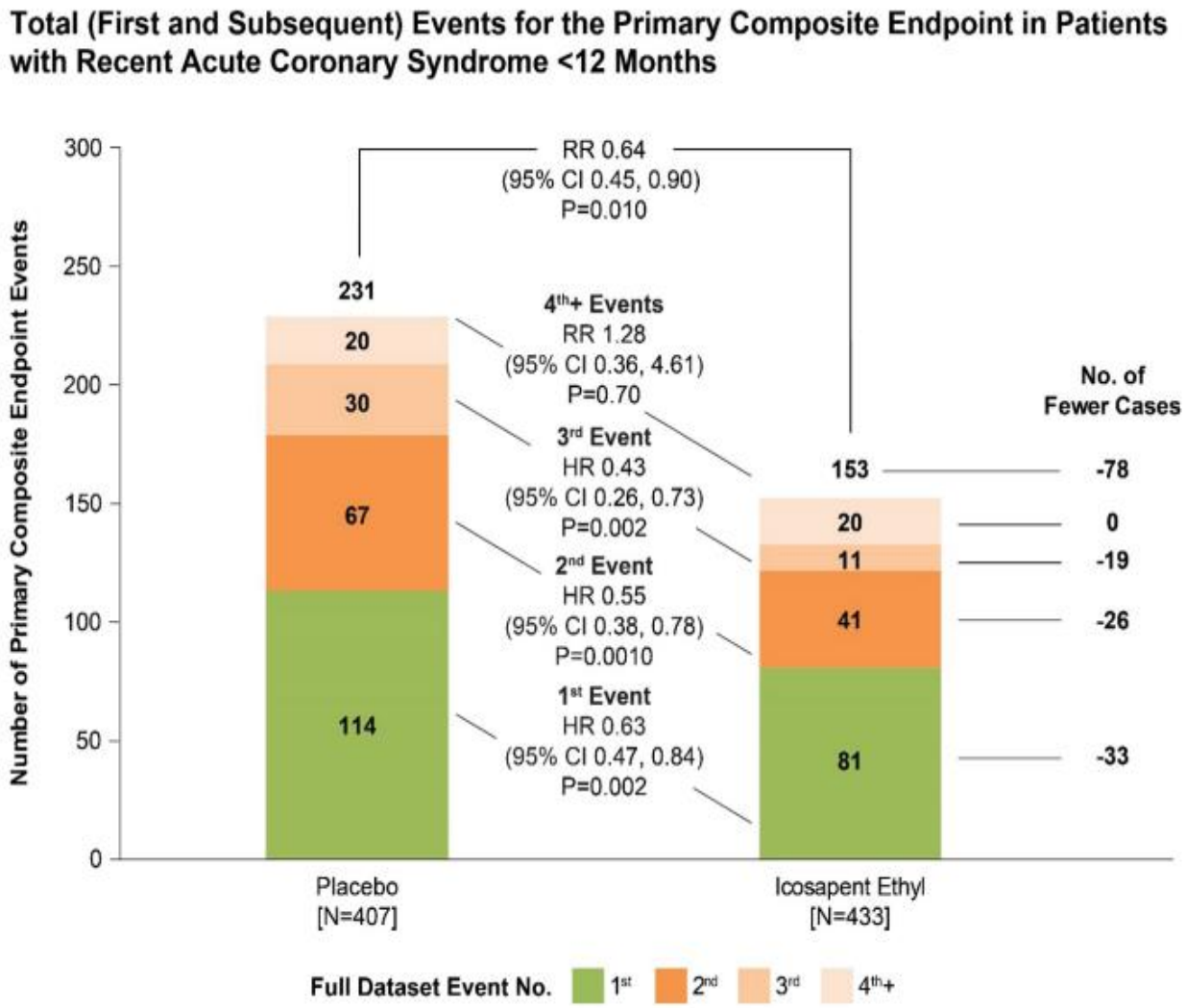




* Post hoc analysis

Gaba P et al., JACC 2022;79.

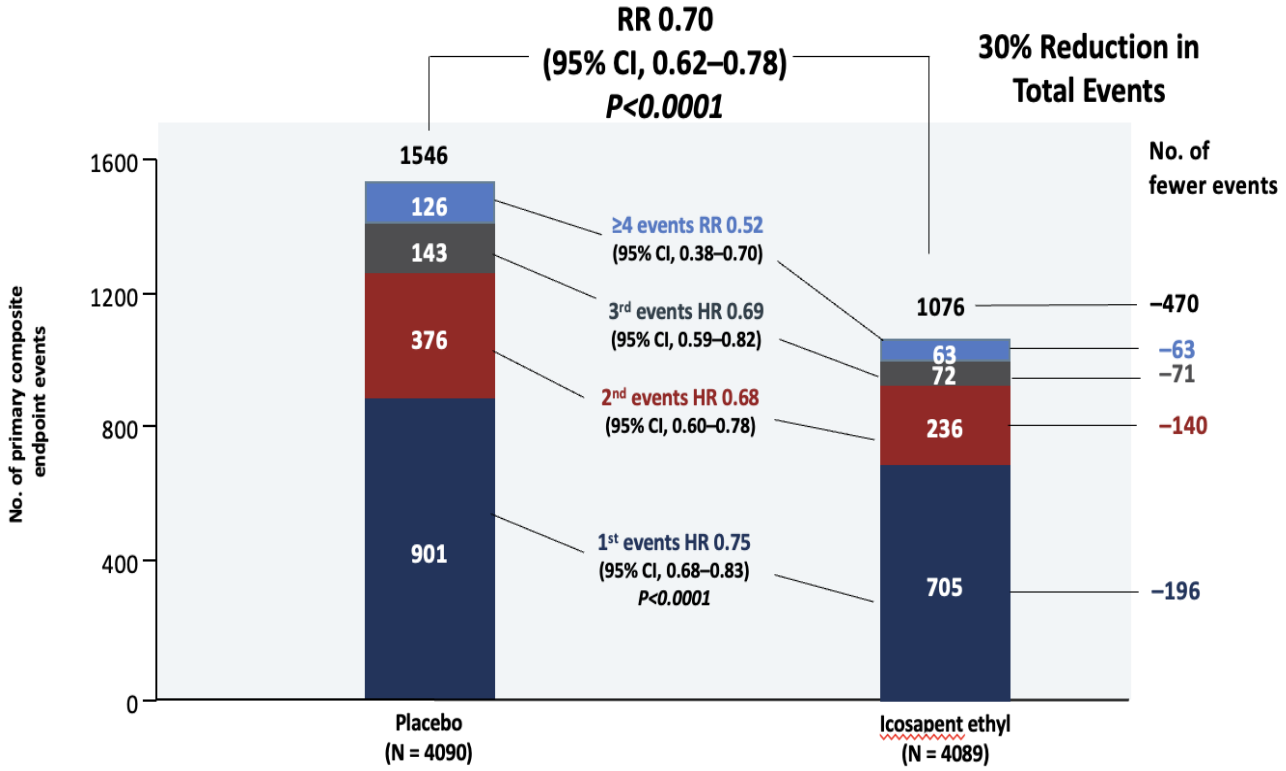
Subgroup analyses from REDUCE-IT



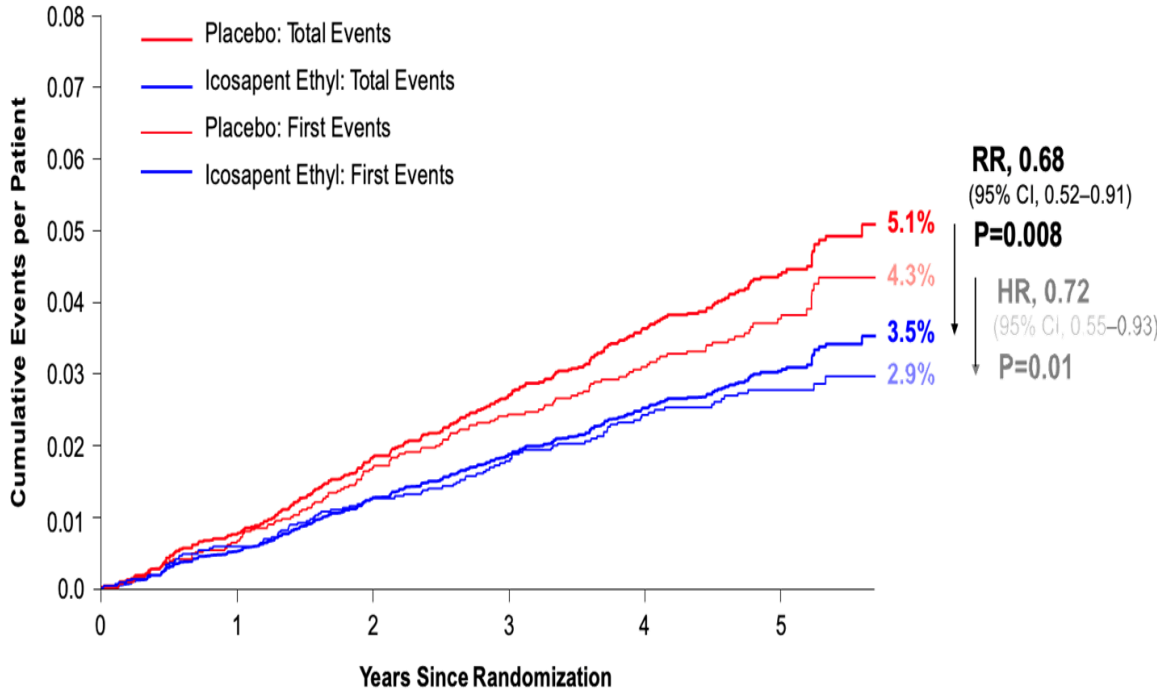
JACC 2023 Mar, 81 (8_Supplement) 1113

Subgroup analyses from REDUCE-IT

Icosapent ethyl substantially reduced the burden of first, subsequent and total ischaemic events



Icosapent ethyl Reduced First and Total Strokes

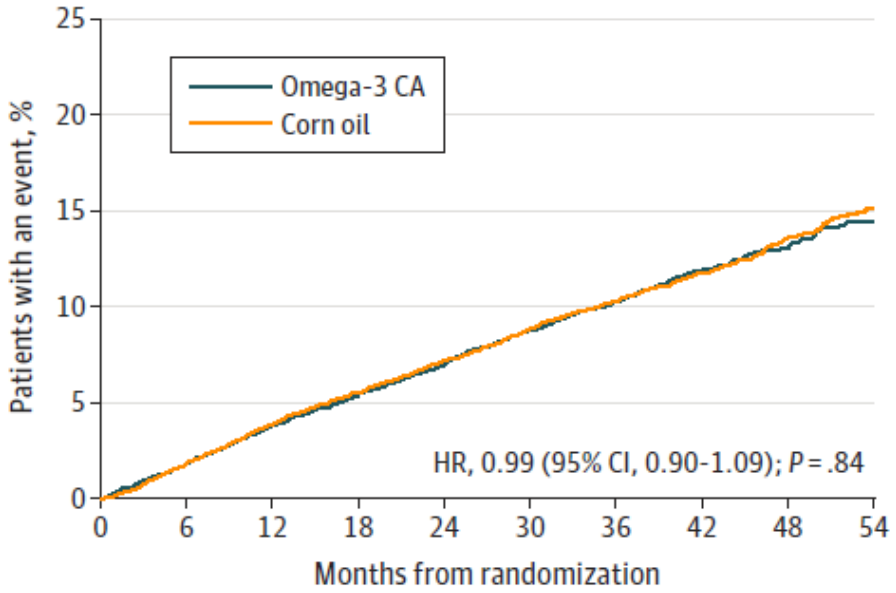


Bhatt DL, et al. J Am Coll Cardiol. 2019;73.
Bhatt DL. ISC 2021 (congress presentation).

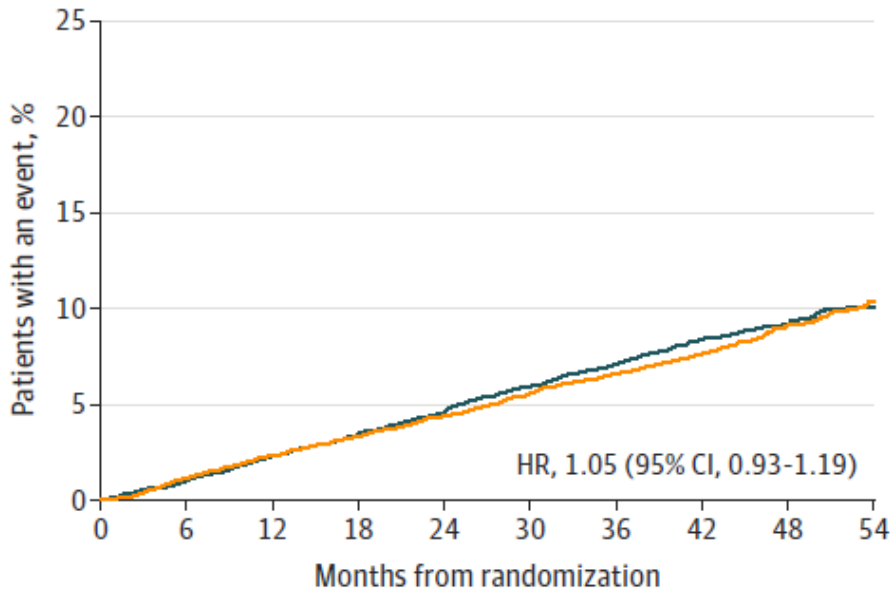
STRENGTH Trial

13,078 statin-treated patients with high CV risk, hypertriglyceridemia, and low HDL-C
Randomized to EPA + DHA 4 g/d

Primary MACE, total population *



Core MACE *



*Primary MACE consisted of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina. Core MACE included CV death, nonfatal MI, and nonfatal stroke.

Trial stopped by Data Monitoring Board for “futility” after review of 1,384 MACE outcome

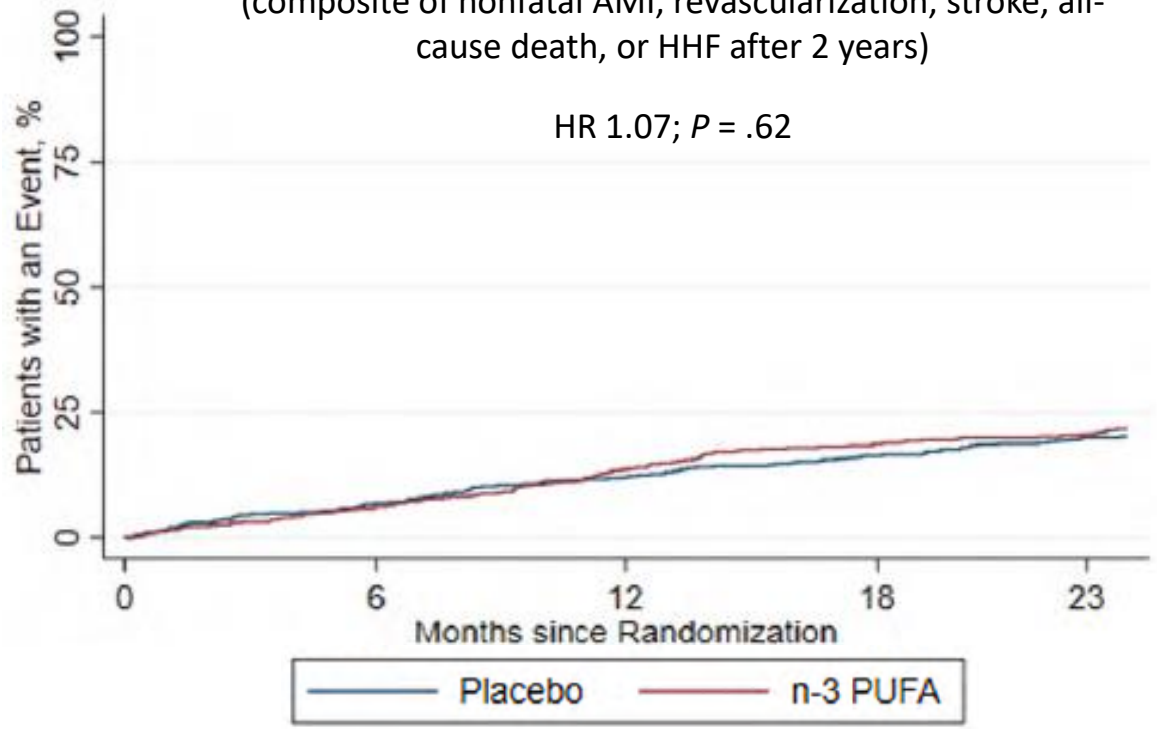
Nicholls SJ, et al. JAMA. 2020;324:2268-2280.

OMEMI Trial: Effects of n-3 PUFA in Older Patients

1.8 g n-3 PUFA (930 mg EPA and 660 mg DHA) vs placebo (corn oil) daily to standard of care in patients aged 70 to 82 years with recent (2 to 8 weeks) AMI (N = 1027)

Primary outcome
(composite of nonfatal AMI, revascularization, stroke, all-cause death, or HHF after 2 years)

HR 1.07; *P* = .62



- No difference in all-cause mortality
- New-onset AF: n-3 PUFA (7.2%) vs placebo (4.0%); *P* < .06
- Major bleeding (BARC ≥ 2): n-3 PUFA (10.7%) vs placebo (11.0%); *P* < .87

AF, atrial fibrillation; AMI, acute myocardial infarction; BARC, Bleeding Academic Research Consortium; HHF, hospitalization for heart failure; HR, hazard ratio.

Kalstad AA, et al. Circulation. 2021;143:528-539.

Risks Associated With Omega-3 FAs

REDUCE-IT	EPA (n = 4089)	Placebo (n = 4090)	P Value
Atrial fibrillation	5.3%	3.9%	.003
Bleeding-related disorders	2.7%	2.1%	.06
GI bleeding	1.5%	1.1%	.15
CNS bleeding	0.3%	0.2%	.42
Other bleeding	1.0%	0.7%	.19

Significant reduction in stroke despite higher rate of AF in REDUCE-IT

STRENGTH	EPA + DHA (n = 6532)	Placebo (n = 6535)	P Value
Atrial fibrillation	2.2%	1.3%	< .001
Any bleeding event	4.9%	4.9%	NA
TIMI criteria major bleeding event	0.8%	0.7%	NA

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

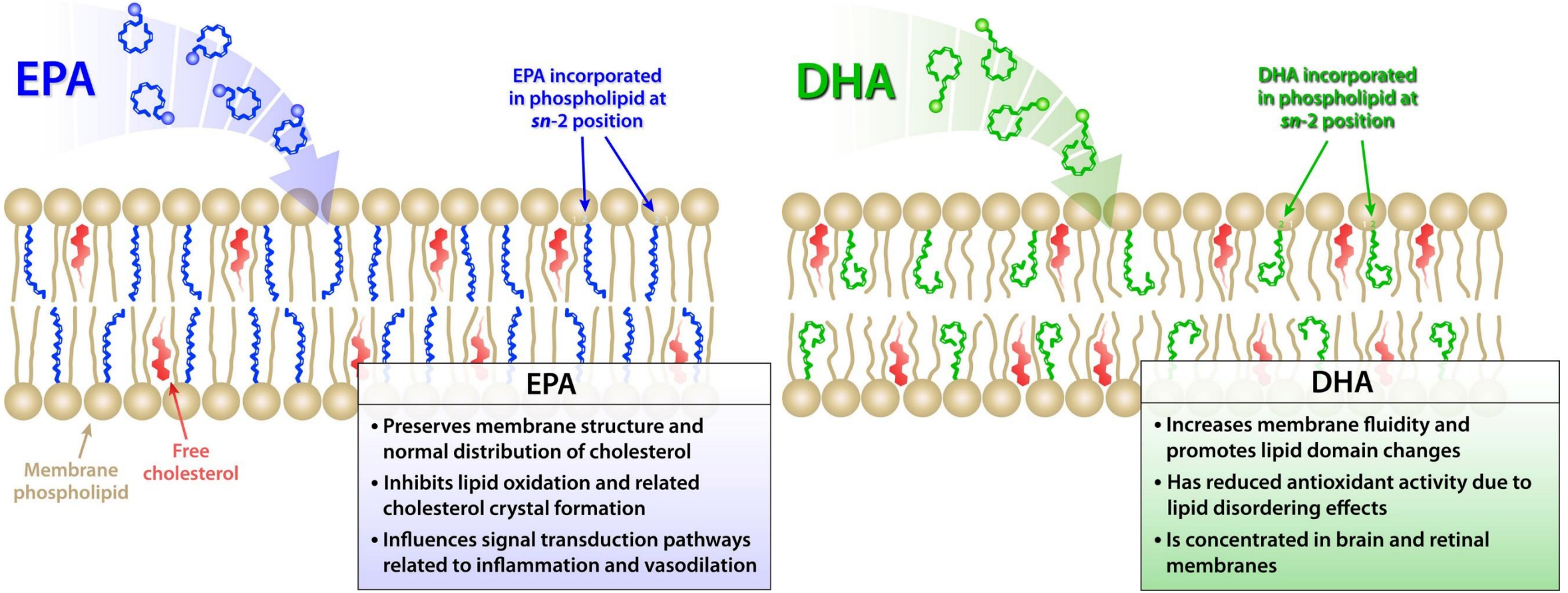
REDUCE-IT and STRENGTH Differences

	REDUCE-IT	STRENGTH
Active Treatment	Icosapent ethyl 2 g twice daily (EPA only)	Omega-3 carboxylic acid 4 g daily (~ 2.3 g EPA + 0.8 gDHA)
High risk ASCVD	70,7	56
High intensity statin use	31	50
Follow-up (years)	4,9	3,5 (stopped early)
LDL-C	6.6% less than placebo	+1.2% more than placebo
% EPA level change	+393.5	+268.8
Placebo	Mineral oil	Corn oil

EMA concluded a putative negative effect of mineral oil should not account for more than 0.3-3% of MACE events

Bhatt DL, et al. N Engl J Med. 2019;380:11-22
Nicholls SJ, et al. JAMA. 2020;324:2268-2280.
Eur H J Pharmacother. 2021,7:e7-e8.

EPA and DHA have contrasting Effects on cell membranes

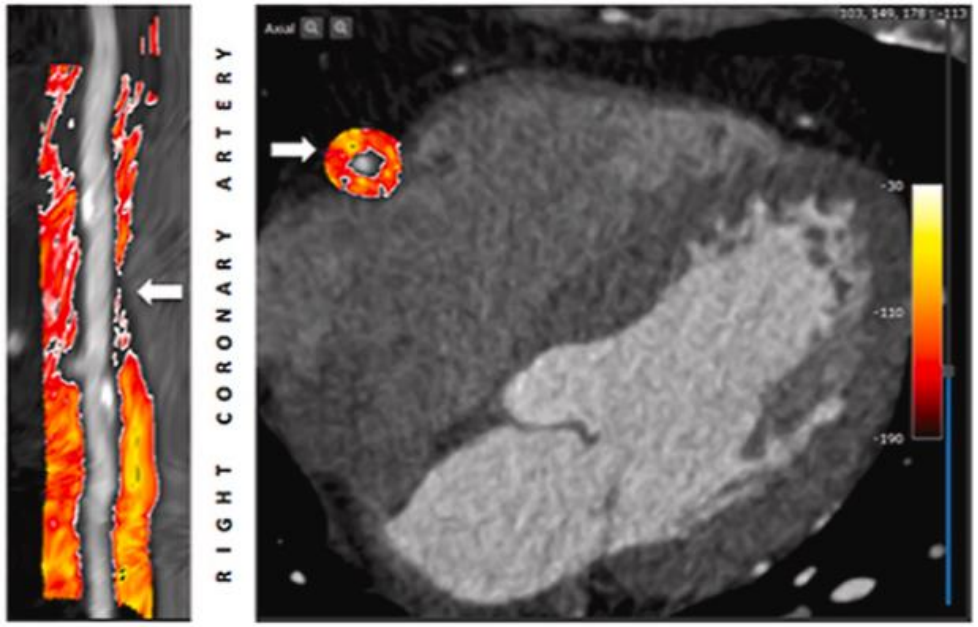


Arteriosclerosis, Thrombosis, and Vascular Biology 2020
JCI 2002;110:905

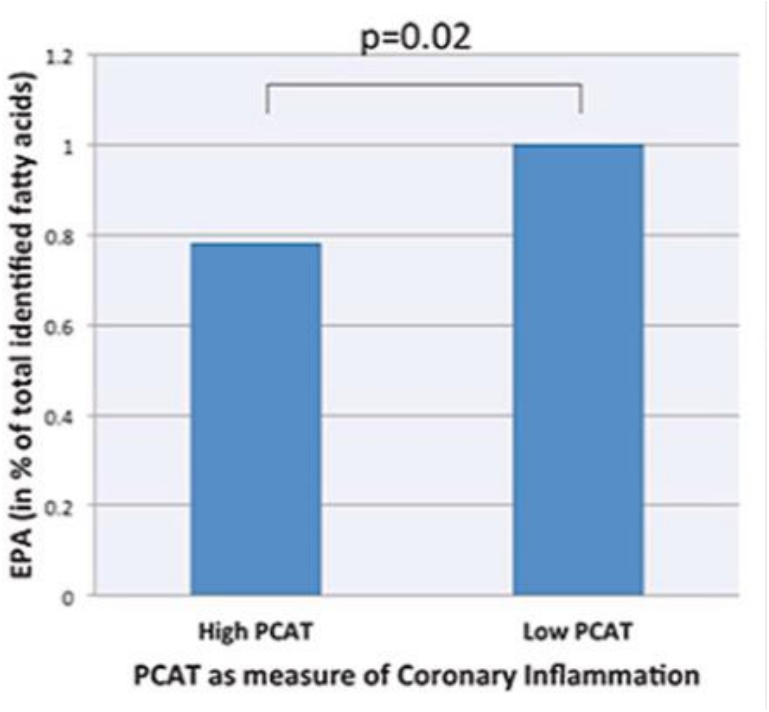
Macrophage transition from foam cell to necrotic/inflammatory is membrane cholesterol load dependent

High pericoronary adipose tissue attenuation is a marker of inflammation on CT

High plasma levels of EPA but not DHA were associated with
lower pericoronary adipose tissue attenuation on CTA in 64 symptomatic patients



Pericoronary Adipose Tissue (PCAT) Attenuation Analysis

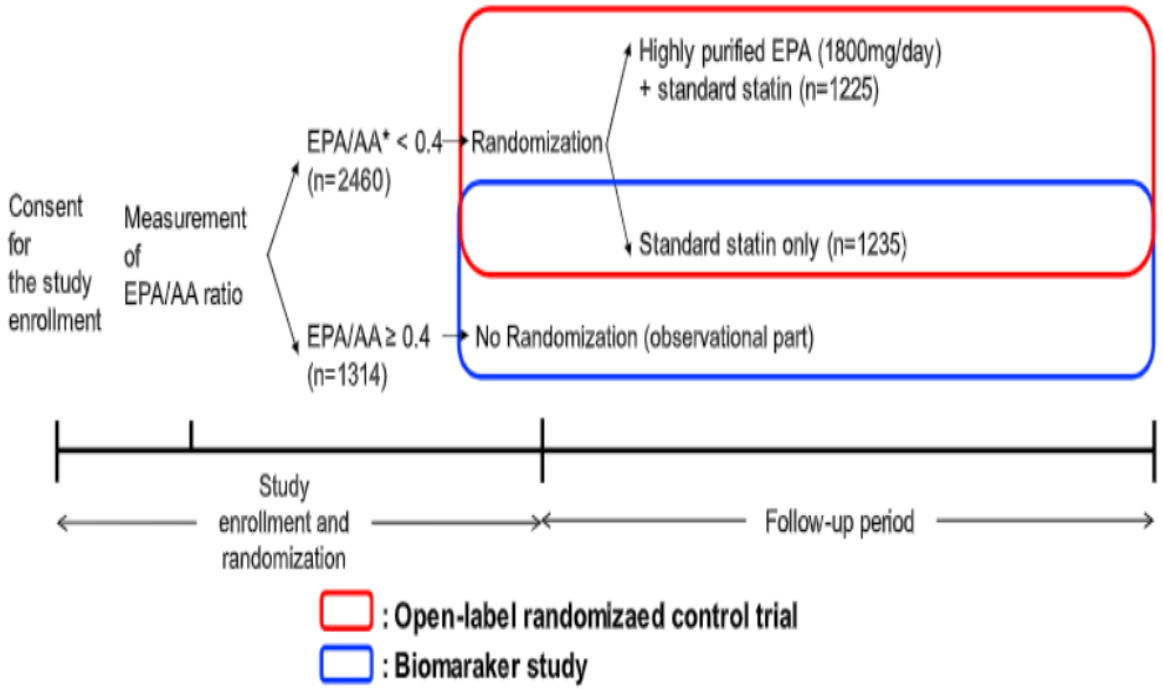


PCAT as measure of Coronary Inflammation

- Significantly higher values of EPA but not DHA were seen in patients with lower PCAT attenuation with significant negative correlation between PCAT attenuation and EPA (*P* = 0.002)

Atherosclerosis. 2021;316:73-78.

RESPECT-EPA Trial:



- Open-label randomized controlled trial 2,460 Japanese patients with CAD on statin with low EPA/AA ratio (0.4 or less)
- Icosapent ethyl 1800 mg (n = 1,249) vs. control (n = 1,257).
- Primary end point CV death, MI, stroke, UNSA, revasc 10.9% vs 14.9% (p = 0.055).
- No placebo control, underpowered.
- AF and GIS side effects more in IPA group.

AHA 2022.

Interventions to Reduce TGRL to Decrease CV Risk

Lifestyle, managing other RF's

LDL reduction with high intensity statin

TGRL lowering therapies

Icosapent ethyl
(ACC consensus, European Guidelines)

Fibrates
(European Guidelines)

New therapies?
ApoC3 inhibitor
ANGPTL3 inhibitor

2021 ESC Guidelines on CV Prevention

Recommendations for drug treatments of patients with hypertriglyceridaemia

Recommendations	Class	Level
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia (triglycerides >2.3 mmol/L [200 mg/dL]).	I	A
In patients taking statins who are at LDL-C goal with triglycerides >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered.	IIb	B
In high-risk (or above) patients with triglycerides >1.5 mmol/L (135 mg/dL) despite statin treatment and lifestyle measures, n-3 PUFAs (icosapent ethyl 2 x 2 g/day) may be considered in combination with a statin.	IIb	B

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)