Hypertriglyceridemia: Causes Risks, and Treatment

Matthew Jay Budoff, MD, FACC, FAHA

Professor of Medicine

Endowed Chair of Preventive Cardiology

David Geffen School of Medicine at UCLA — Los Angeles, California

Disclosures

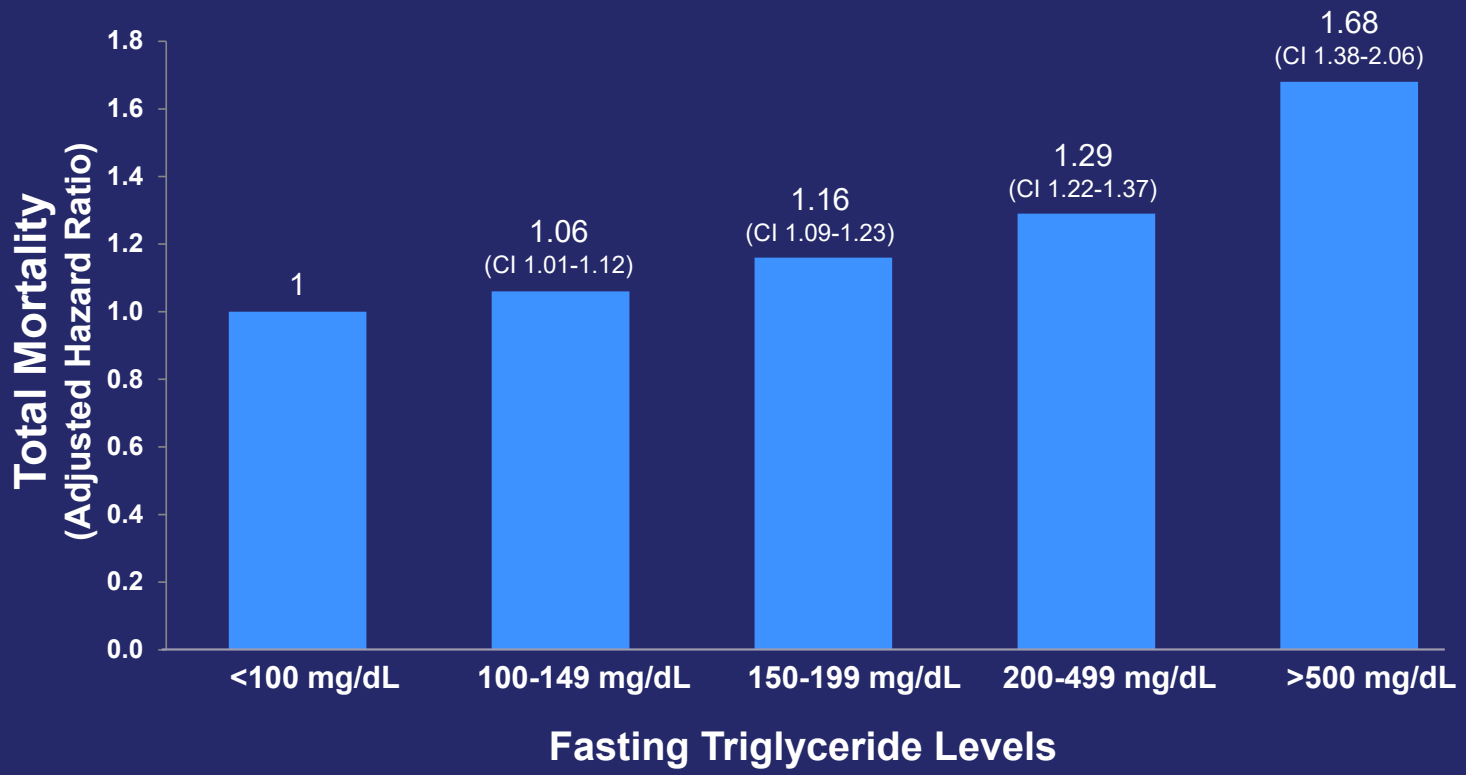
- **Commercial support disclosure slide:**
- This program has received no financial or in kind support from any commercial or other organization

Disclosures

Dr Budoff receives grant support and is on the speakers bureau for Amarin Pharma

All-cause Mortality Risk Increases as TG Levels Increase

15,355 patients who were screened for the Bezafibrate Infarction Prevention (BIP) trial. Twenty-two–year mortality data were obtained from the national registry.

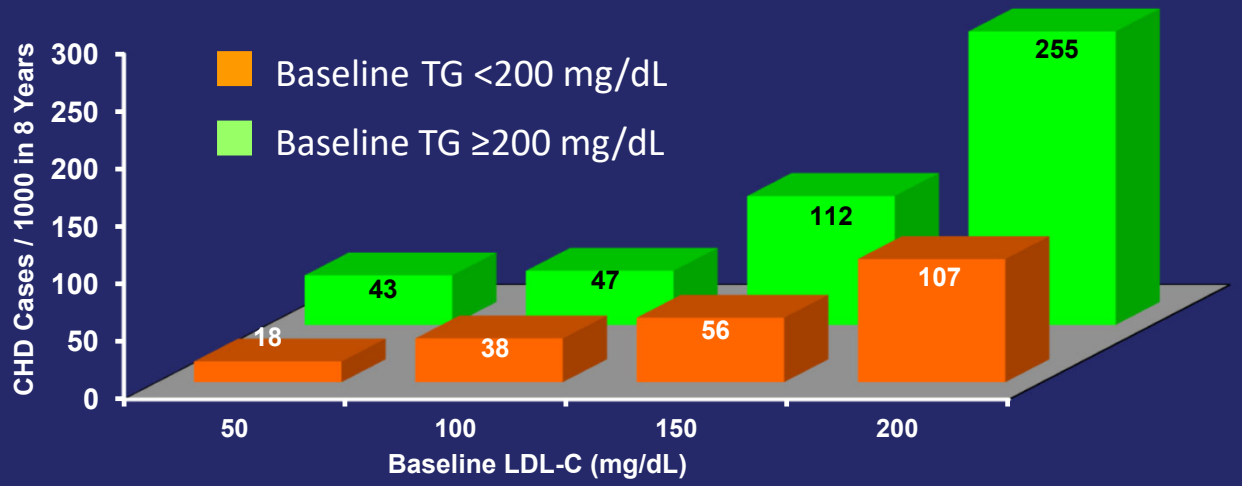


CI=confidence interval. Klempfner R et al. *Circ Cardiovasc Qual Outcomes*. 2016;9:100-8.

PROCAM:

High TG correlates with increased CHD risk at each LDL cutpoint

Incidence of CHD Events According to Serum LDL-C and TG Concentration*



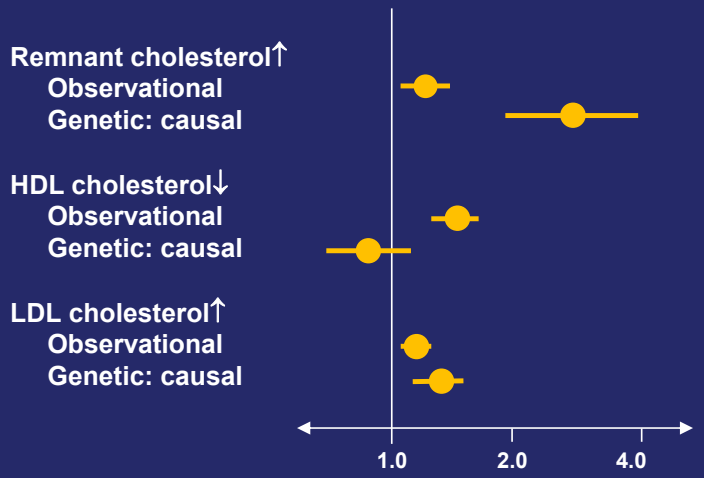
* Lipids from 4849 middle-aged men who were followed up for 8 years to record incidence of CHD. Study demonstrated that fasting levels of TGs were an independent risk factor for CHD events, irrespective of serum levels of LDL-C.

The effect of POM3 on the risk of pancreatitis in patients with very high TG levels has not been evaluated. The effect of POM3 on cardiovascular mortality and morbidity in patients with very high TG levels has not been determined.

Adapted from Assmann G, et al. *Eur Heart J.* 1998;19(suppl M):M8-M14.

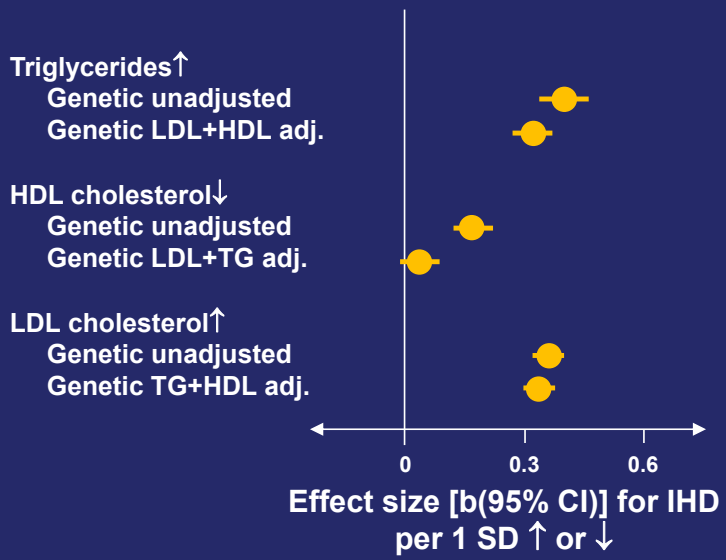
Genetic Epidemiology Evidence that Elevated Remnant-C Is Causally Linked to ASCVD

15 selected genetic variants



N=66,000 (12,000 IHD)
Varbo A et al. *J Am Coll Cardiol.* 2013;61:427-36.

Genome wide 185 SNPs



N=87,000 (22,000 IHD)
Do R et al. *Nat Genet.* 2013;45:1345-52.

IHD=ischemic heart disease; SNP=single nucleotide polymorphism.
Nordestgaard BG. *Circ Res*. 2016;118:547-63.

Mechanisms for High ASCVD Risk with HTG

ApoCIII Containing TG-rich Particles Promote Artery-Wall Inflammation

Apolipoprotein CIII

TG-rich particles

Cholesterol

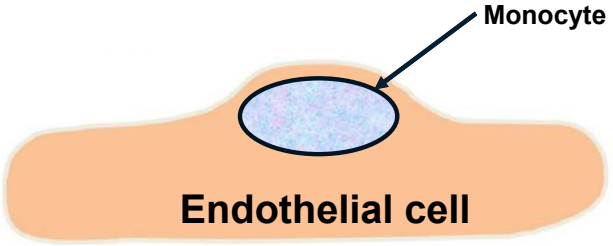
In HTG, TRP can deliver more cholesterol per particle to macrophages than LDL

Lipases → **Saturated Fatty Acids**

Foam cell formation

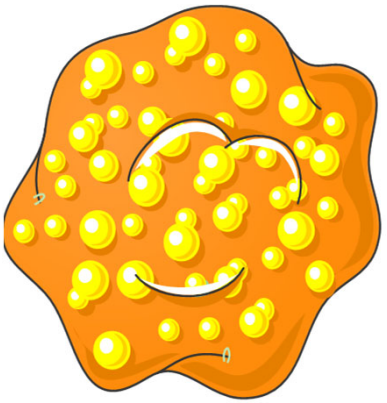
Putative transducers:
- •TLRs
- •PKC

Transcriptional Activators:
- •NFkB
- •p38 MAP kinase
- •Egr-1



Leukocyte recruitment

↑ Vascular cell adhesion molecule-1

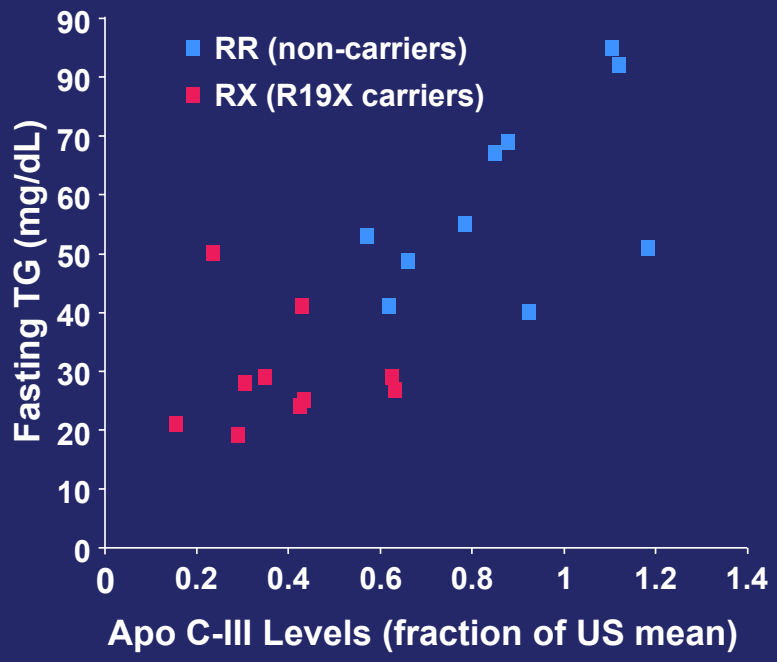


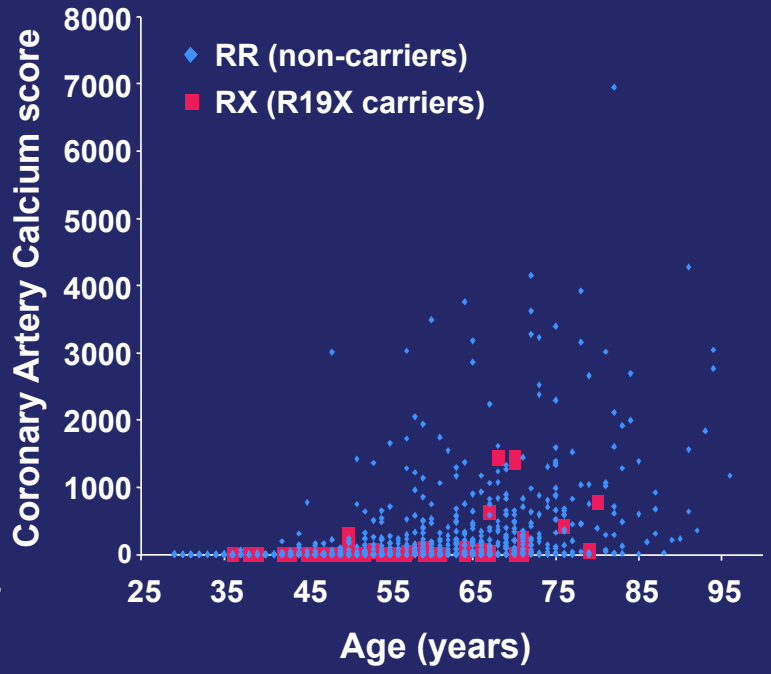
Inflammation

Production of:
- •MCP-1
- •IL-8
- •others

P. Libby 2019

An ApoC-III Loss-of-Function Mutation Causes Very Low TG Levels and Lower Coronary Calcium Scores

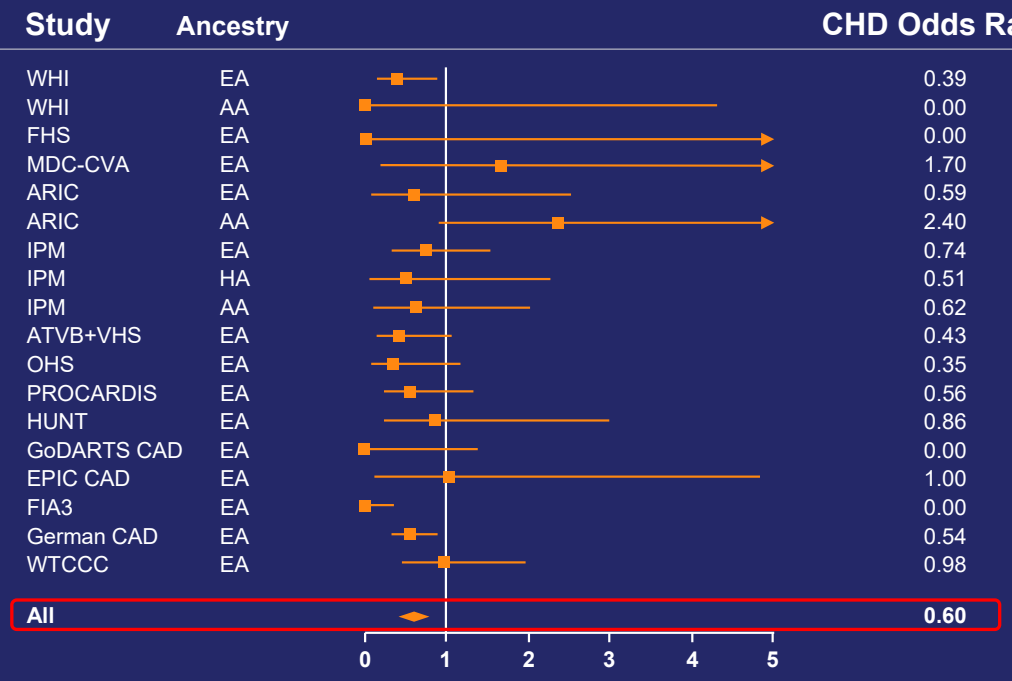




Apo C-III=gene encoding apolipoprotein (apo) C-III.
Data for R19x mutation in Amish population. Pollin TI et al. *Science.* 2008;322:1702-5.

Apo C-III Loss-of-function Mutations Reduce Apo C-III Levels *and* CHD Risk

Odds ratio of CHD of subjects with any of 4 Apo C-III loss-of-function mutations.
14 Studies; N= 110,970 participants (34,002 w/ CHD, 76,968 controls)

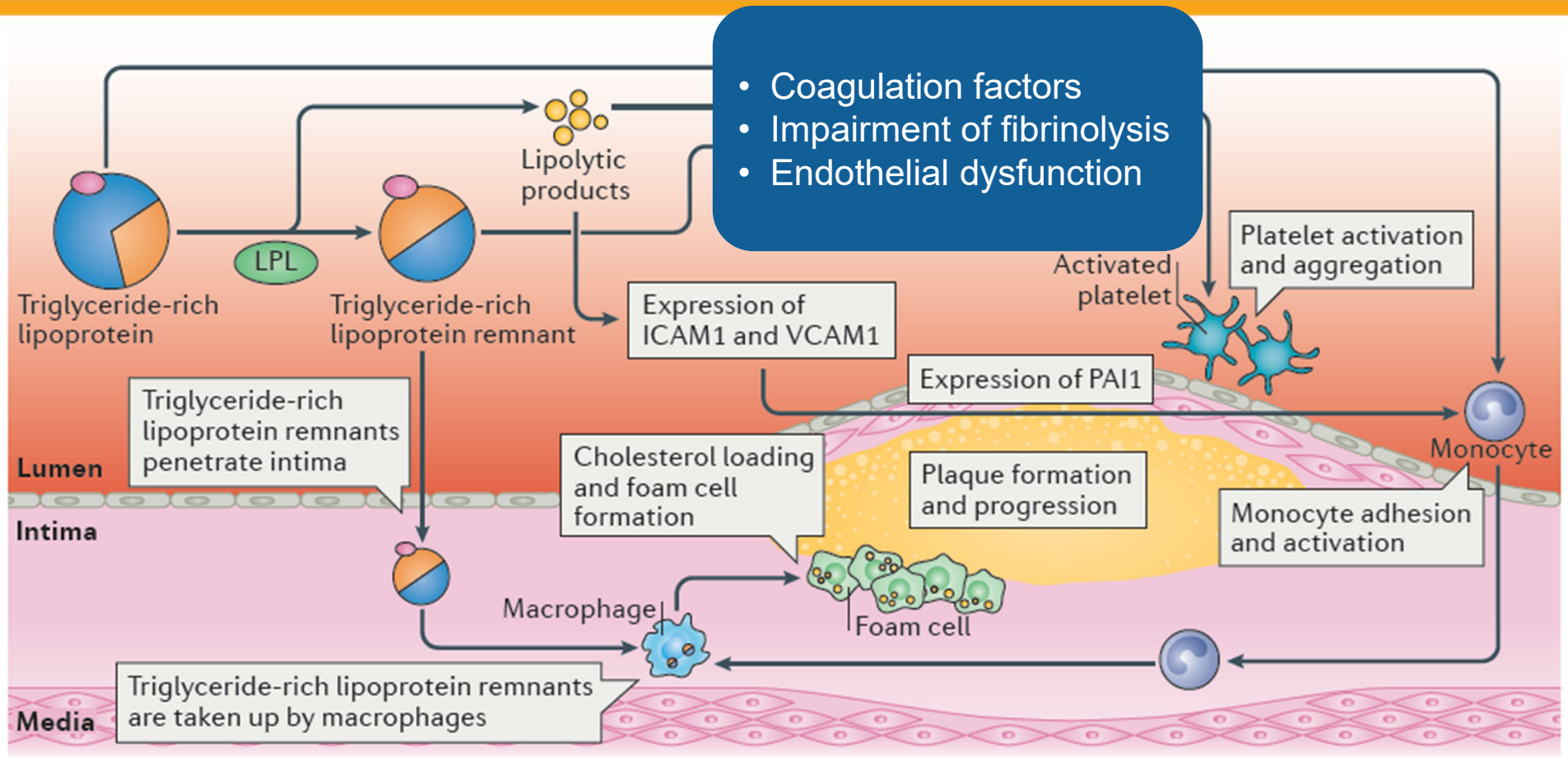


Apo C-III LoF mutations:

- **↓TG 39%**
- **↓CHD 40%**

The TG and HDL Working Group of the Exome Sequencing Project, NHLBI. *New Eng J Med*. 2014;371:22-31.

Elevated TG: Concurrent *Non-lipid* Factors That May Drive CVD Risk

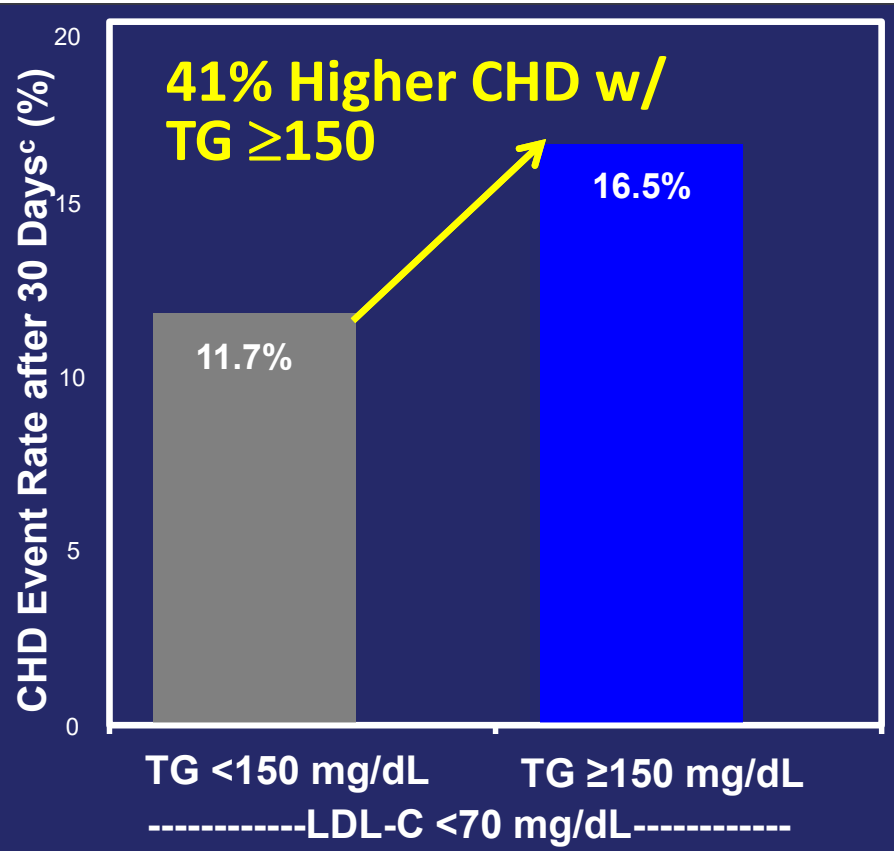


After Reiner Ž. *Nat Rev Cardiol.* 2017;14:401-11.

TG ≥150 mg/dL Predicts Higher CHD[a] Risk Despite *LDL-C <70 mg/dL* on *Statin Rx*

PROVE IT-TIMI 22 Trial[b]
(N=4162)

Referent Group
LDL-C ≥70 mg/dL
TG ≥150 mg/dL
Event Rate=17.9%

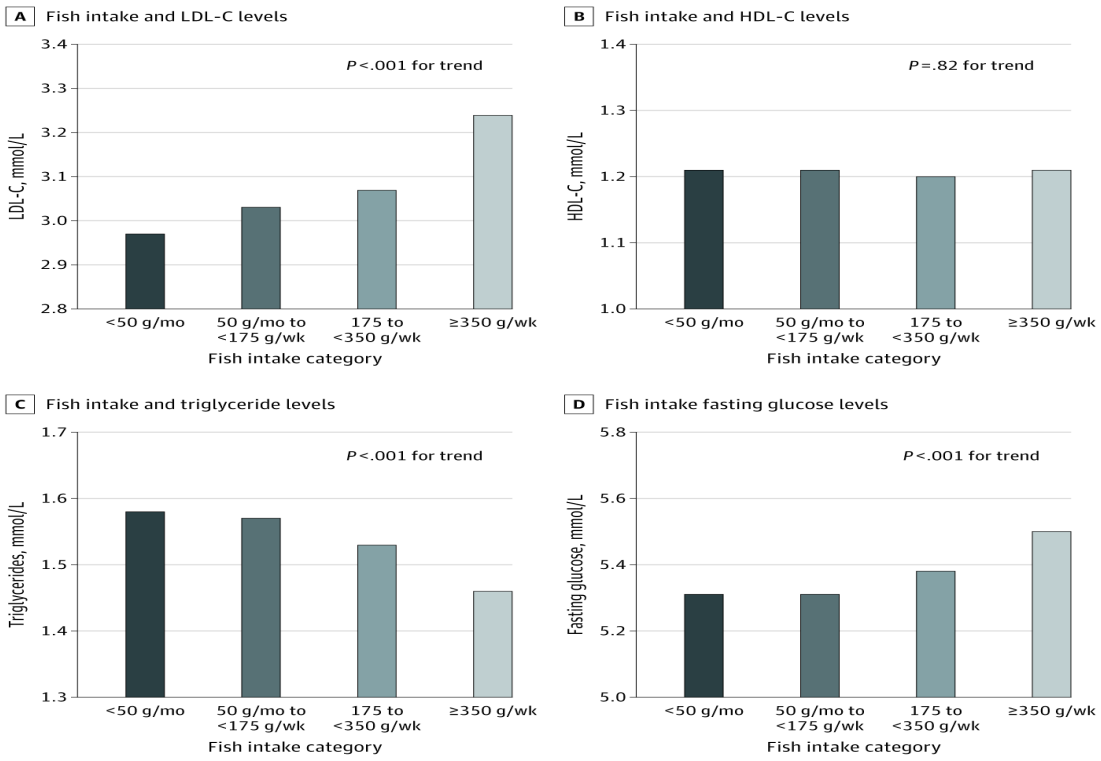


a. Death, MI, and recurrent ACS. b. ACS patients on atorvastatin 80 mg or pravastatin 40 mg. c. Adjusted for age, gender, low HDL-C, smoking, hypertension (HTN), obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment. CHD=coronary heart disease; HR=hazard ratio; PROVE IT-TIMI=Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis In Myocardial Infarction. Miller M et al. *J Am Coll Cardiol.* 2008;51:724-30.

JAMA Network™

From: **Associations of Fish Consumption With Risk of Cardiovascular Disease and Mortality Among Individuals With or Without Vascular Disease From 58 Countries**

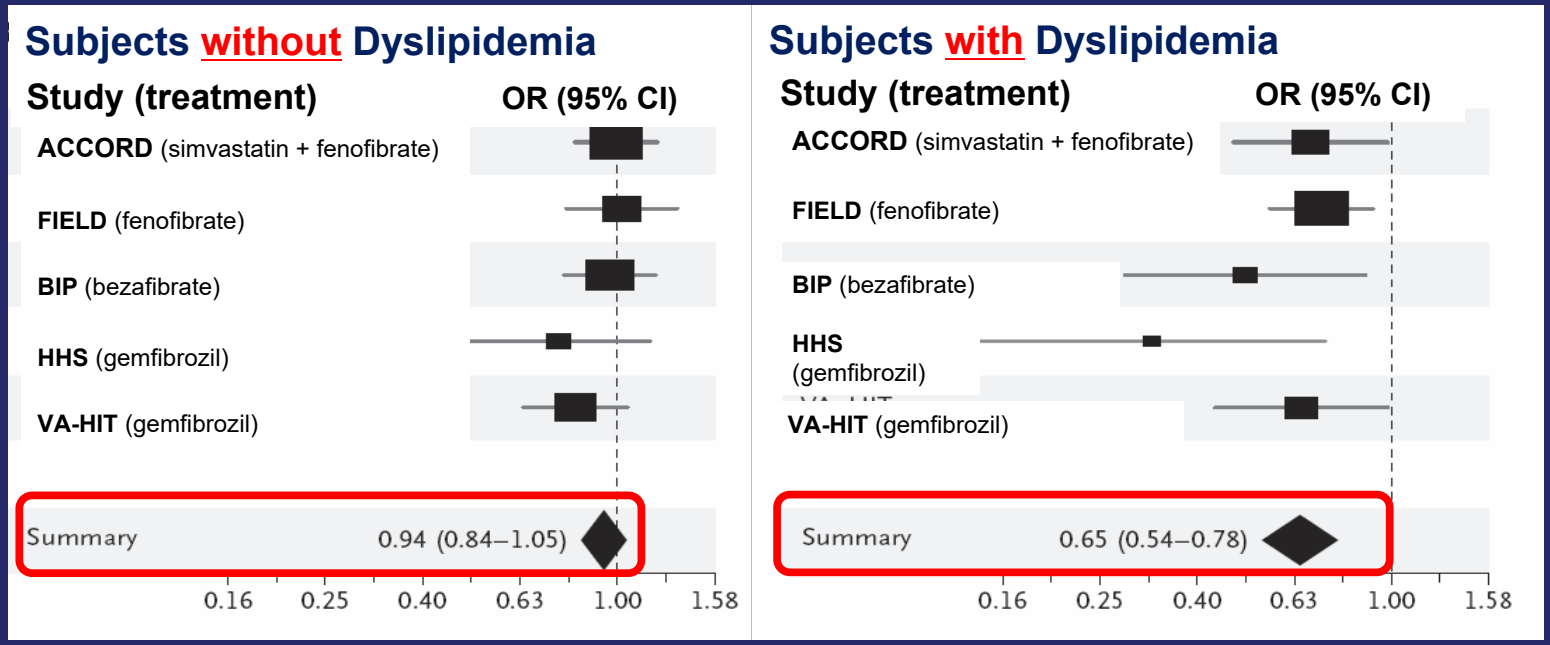
JAMA Intern Med. Published online March 08, 2021. doi:10.1001/jamainternmed.2021.0036



Mean Levels of Cardiovascular Risk Markers by Amount of Fish Intake in the Prospective Urban Rural Epidemiology (PURE) Trial (n = 147 541)Data adjusted for age, sex, study center (random effect), body mass index, educational level, smoking status, physical activity, alcohol intake, urban vs rural location, history of diabetes, cardiovascular disease, cancer, use of statin or antihypertension medication, and intake of fruit, vegetables, red meat, poultry, dairy, and total energy

Fibrates Reduce CHD Risk in Patients with HTG and Low HDL-C

A meta-analysis of randomized fibrate trials



TG ≥204 mg/dL, HDL-C ≤34mg/dL

Sacks FM et al. *N Engl J Med*. 2010;363:692-4.

CVOTs in Mild to Moderate Hypertriglyceridemia

	REDUCE-IT 2018	STRENGTH 2020	PROMINENT 2022
Agent	**EPA (EE); Vascepa**	**EPA+DHA (FFA); Epanova**	**SPPARMα - Pemafibrate**
Dose	**4 g/day**	**4 g/day**	**0.2 mg bid**
Population	International	International	International
N	8,179	13,078	10,514
Risk Profile	CVD (70%) or ↑CVD risk (30%)	CVD (50%) or ↑CVD risk (50%)	T2D Only CVD (2/3) or ↑CVD risk (1/3)
Follow-up	4.5 years	3.5 years	4 years (planned)
Statin Use	100% (at LDL-C goal)	100% (at LDL-C goal)	Moderate/High Intensity or LDL < 70 mg/dl
1° EP	Expanded MACE	Expanded MACE	Expanded MACE
Result	**Powered for 15% RRR**	**Powered for 15% RRR**	**Powered for 16.6% RRR**
Entry TG	**135 to 499 mg/dL**	**180 to 499 mg/dL**	**200 to 499 mg/dl**
Entry HDL	**NONE**	**< 42 mg/dl M, < 47 mg/dl W**	**≤ 40 mg/dl**
Average TG Lowering in Statin-Treated Patients with TG 200-499 mg/dl (2.26-5.63 mM)	- 18%	- 21%	- 40%

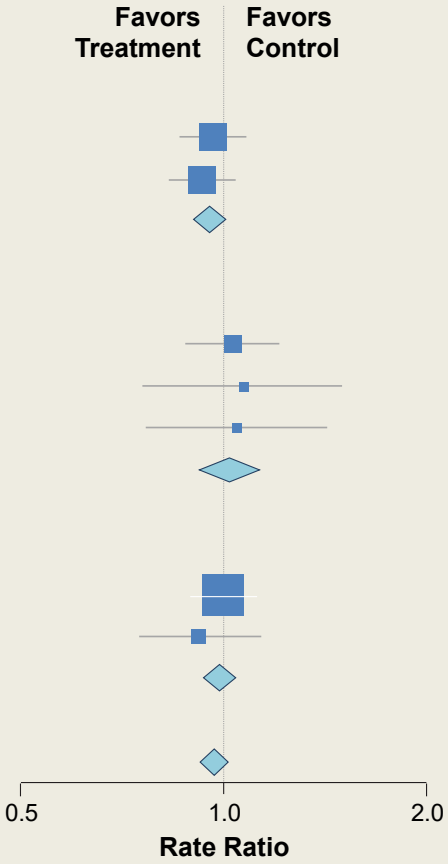
TG Level: *Is it a Biomarker, Risk Factor, or Treatment Target?*

- Elevated TG is a biomarker of CV risk
  - Supported by epidemiological, genetic, and clinical data
  - TG-rich lipoproteins (TRL) promote risk:
    - Remnant deposition and inflammation
    - Activation of platelets & thrombosis
- Is Elevated TG a Treatment Target?
    - REDUCE-IT patients benefited though CV benefit attributable to TG was small.
    - Await results of the PROMINENT trial

Miller M, Cannon CP, Murphy SA, et al. JACC 2008; 51: 724-730
Marston NA, Giugliano RP, Im K, et al. Circulation 2019;140:1308-1317
Miller M. Future Cardiol 2019;15:391-394;

Low Dose Omega-3 Mixtures Show No Significant CV Benefit

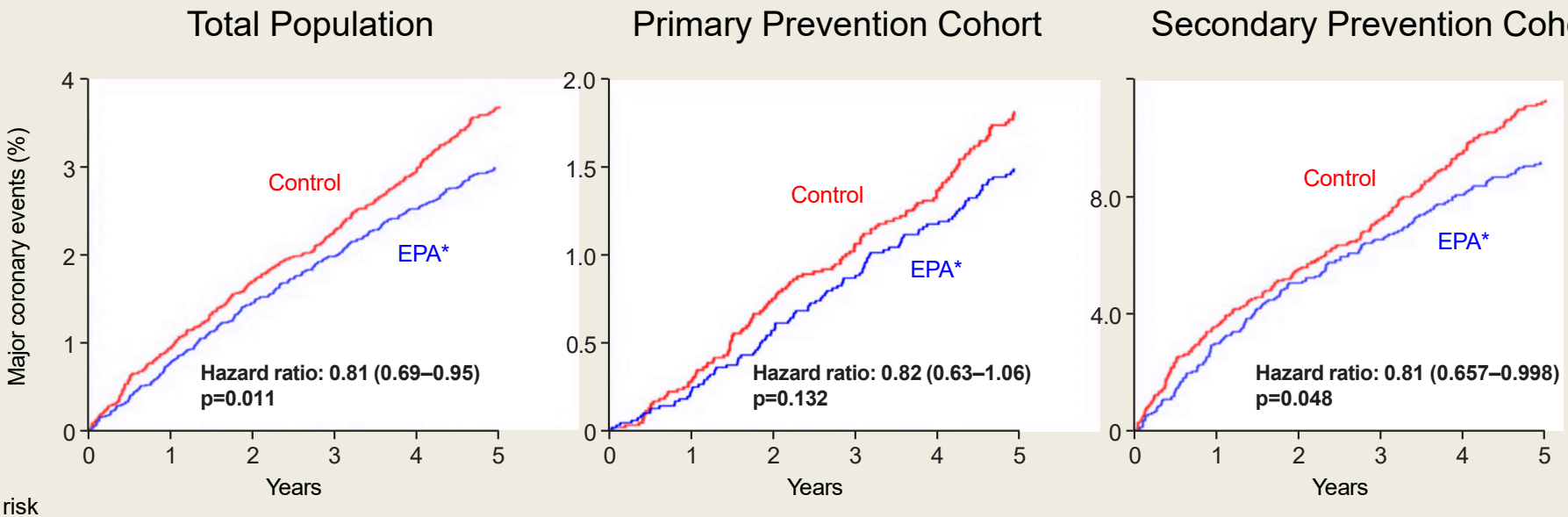
Source	No. of Events (%)		Rate Ratios (CI)
	Treatment	Control	
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87–1.08)
Coronary heart disease	1301 (3.3)	1394 (3.6)	0.93 (0.83–1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90–1.01)
			P=.12
Stroke			
Ischemic	574 (1.9)	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



Aung T, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77917 individuals. ***JAMA Cardiol.*** 2018;3:225-234.

JELIS: CV Risk Reduction with 1.8 g/d EPA in Japanese Hypercholesterolemic Patients

Kaplan-Meier Estimates of Incidence of Coronary Events

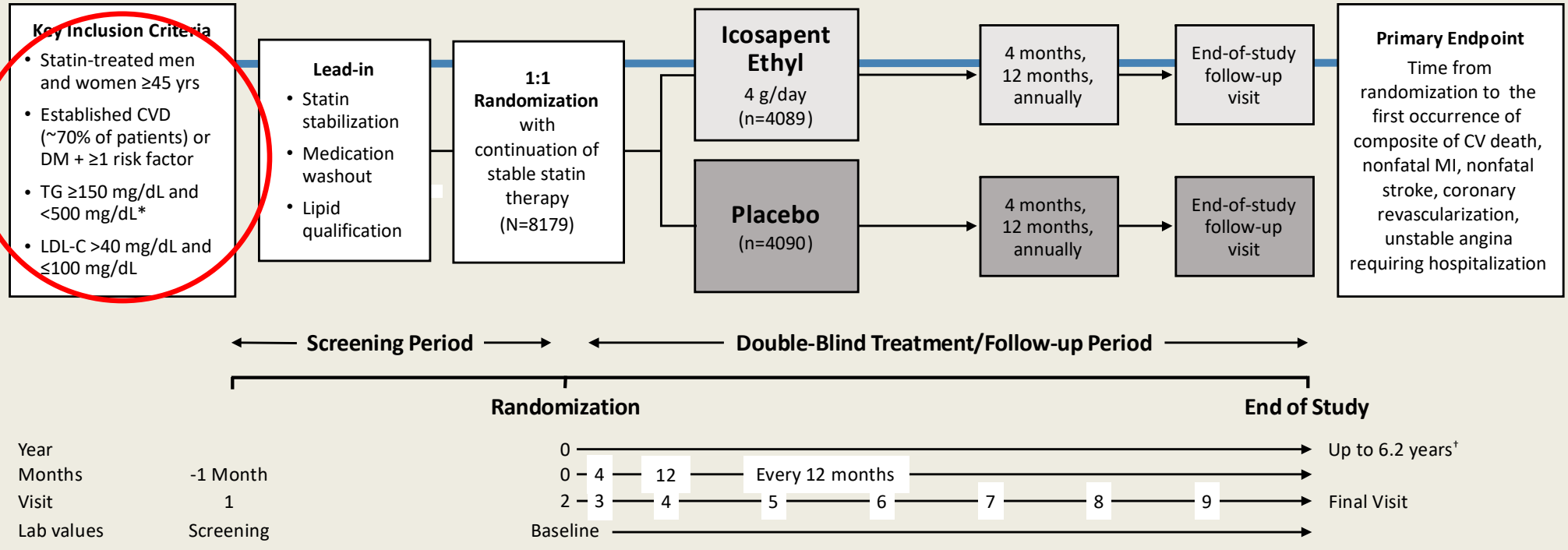


Numbers at risk																
Control group	9319	8931	8671	8433	8192	7958	7478	7204	7103	6841	6678	6508	1841	1727	1658	1592	1514	1450
Treatment group	9326	8929	8658	8389	8153	7924	7503	7210	7020	6823	6649	6482	1823	1719	1638	1566	1504	1442

*1.8 g/day

Adapted with permission from Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet.* 2007;369:1090-1098.

REDUCE-IT Design

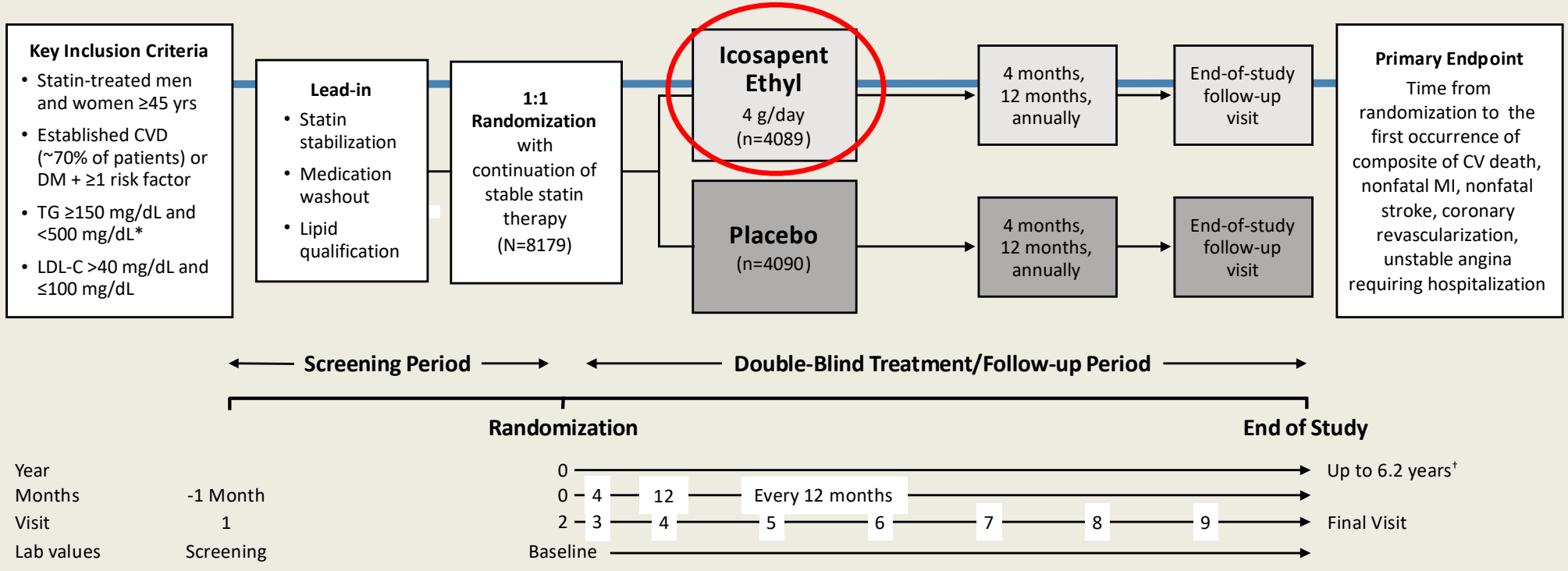


* Due to the variability of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

† Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).

Adapted with permission‡ from Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. *Clin Cardiol*. 2017;40:138-148. REDUCE-IT ClinicalTrials.gov number, NCT01492361. [‡https://creativecommons.org/licenses/by-nc/4.0/]

REDUCE-IT Design



* Due to the variability of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

† Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).

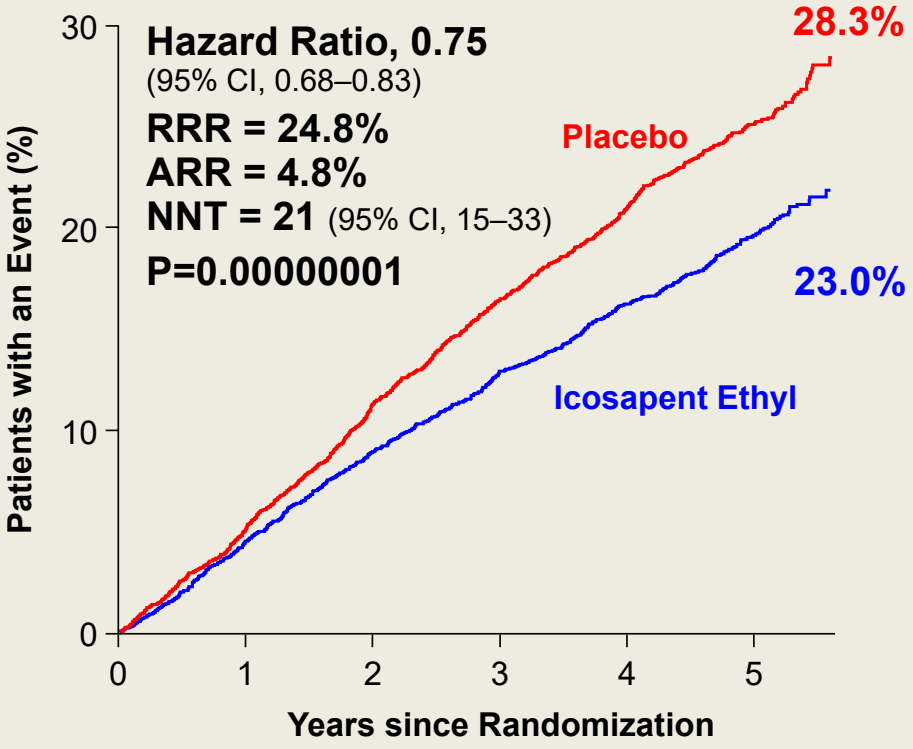
Adapted with permission‡ from Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. *Clin Cardiol*. 2017;40:138-148. REDUCE-IT ClinicalTrials.gov number, NCT01492361. [‡https://creativecommons.org/licenses/by-nc/4.0/]

REDUCE IT: CV risk reduction with 4 g purified EPA/d in statin-treated pts at high risk with elevated TGs

reduce-it

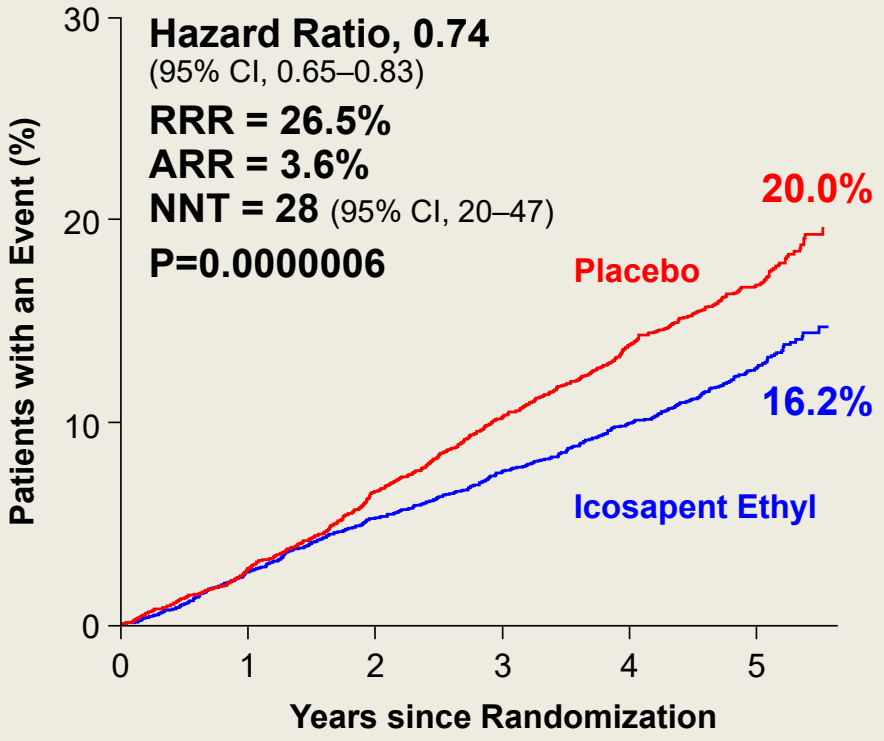
Primary Composite Endpoint:

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



Key Secondary Composite Endpoint:

CV Death, MI, Stroke



Bhatt DL, Steg PG, Miller M, et al. ***N Engl J Med.*** 2019

Effects on Biomarkers from Baseline to Year 1

reduce-it

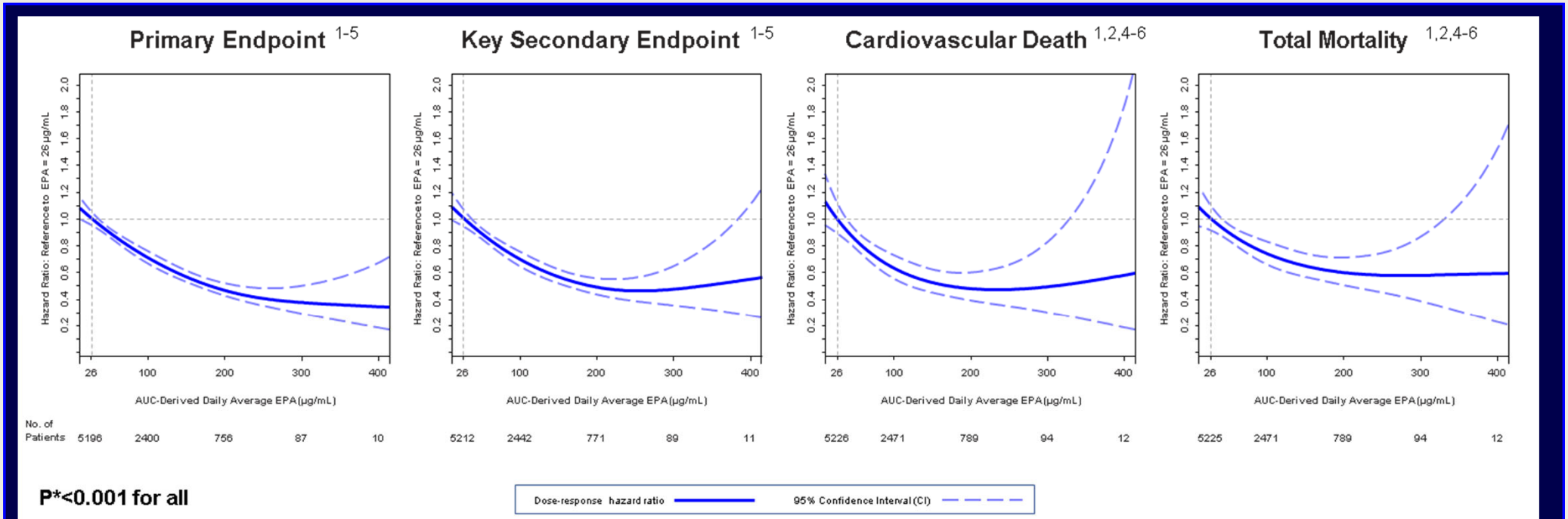
	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
Biomarker*	Baseline	Year 1	Baseline	Year 1	Absolute Change from Baseline	% Change from Baseline	% Change P-value
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.0	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
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<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.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

ODYSSEY OUTCOMES

Primary and key secondary composite endpoints, cardiovascular death, and total mortality by on-treatment serum EPA



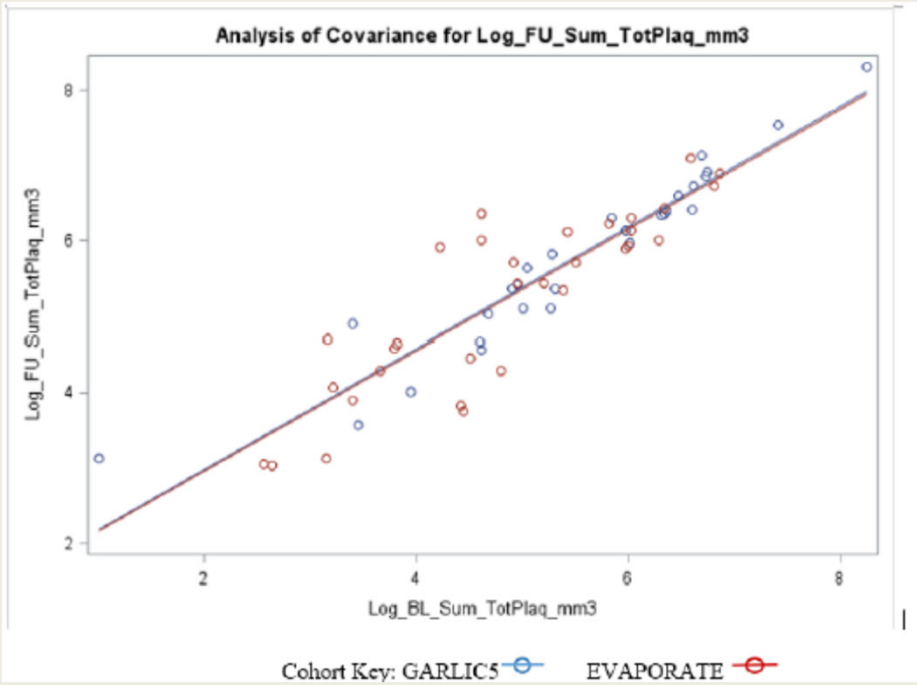
Note: Area under the curve (AUC)-derived daily average serum EPA (µg/mL) is the daily average of all available post baseline EPA measurements prior to the event. Dose-response hazard ratio (solid line) and 95% CI (dotted lines) are estimated from the Cox proportional hazard model with a spline term for EPA and adjustment for randomization factors and statin compliance[1], age[2], sex[3], baseline diabetes[4], hsCRP[5], treatment compliance[6].

***P value is <0.001 for both non-linear trend and for regression slope.**

Bhatt DL. ACC/WCC 2020, Chicago (virtual)

Placebo Rates of Progression : Mineral Versus Non-mineral Oils

Placebo progression rates using mineral oil is similar to non-mineral oil (cellulose) using same methodology, scanner and laboratory in a matched cohort.



Adjusted multivariate analysis of covariance tests did not show any significant difference in progression of TP volume (β: 0.04 ± 0.13 P = 0.7) or TNCP volume (β: 0.09 ± 0.17, P = 0.5) in the two groups.

Lakshmanan S, et al. ***Cardiovasc Res.*** 2020;116(3):479-482

JAMA Network™

QUESTION In statin-treated patients with high cardiovascular risk, high triglycerides, and low HDL cholesterol, does adding a carboxylic acid formulation of omega-3 fatty acids (EPA and DHA) to ongoing treatment improve cardiovascular outcomes?

CONCLUSION The findings from this randomized trial do not support use of this omega-3 fatty acid formulation to reduce major adverse cardiovascular events in patients at high cardiovascular risk.

POPULATION

8510 Men
4568 Women

Adults with high triglycerides and low HDL levels, treated with statins, and at high risk of adverse cardiovascular outcomes

Mean age: **62.5** years

LOCATIONS

675 Hospitals in **22** countries

INTERVENTION

13 078 Patients randomized

6539
Omega-3
4 g/d of omega-3 CA (carboxylic acid) capsules containing EPA and DHA for up to 5 years

6539
Corn oil
Comparator capsules for up to 5 years

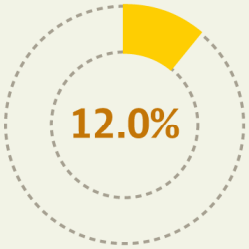
PRIMARY OUTCOME

Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization

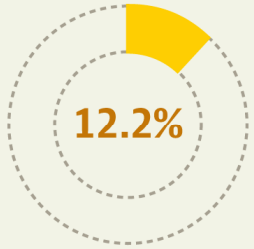
FINDINGS

Occurrence of composite outcome events

Omega-3
785 of 6539 patients



Corn oil
795 of 6539 patients



At early trial termination, there was no significant difference between groups in the primary outcome:

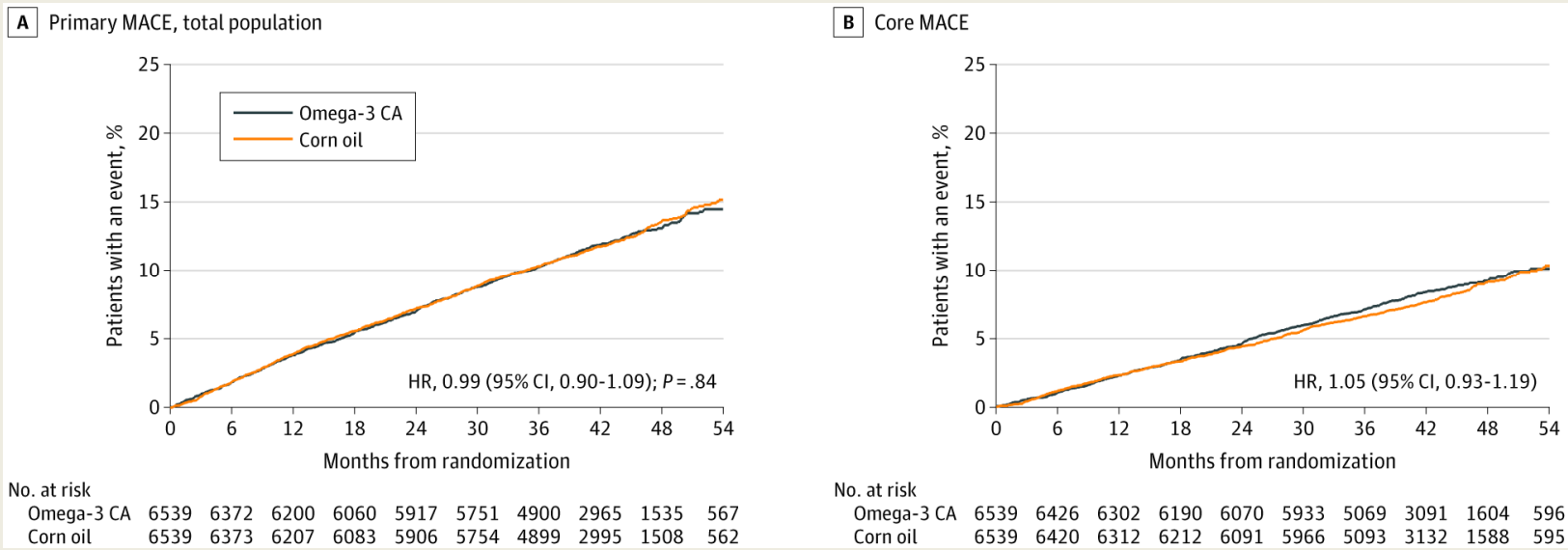
HR, **0.99** (95% CI, 0.90-1.09); *P* = .84

Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA*. Published online November 15, 2020. doi:10.1001/jama.2020.22258

Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial

CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for UA

CV death, nonfatal MI, nonfatal stroke



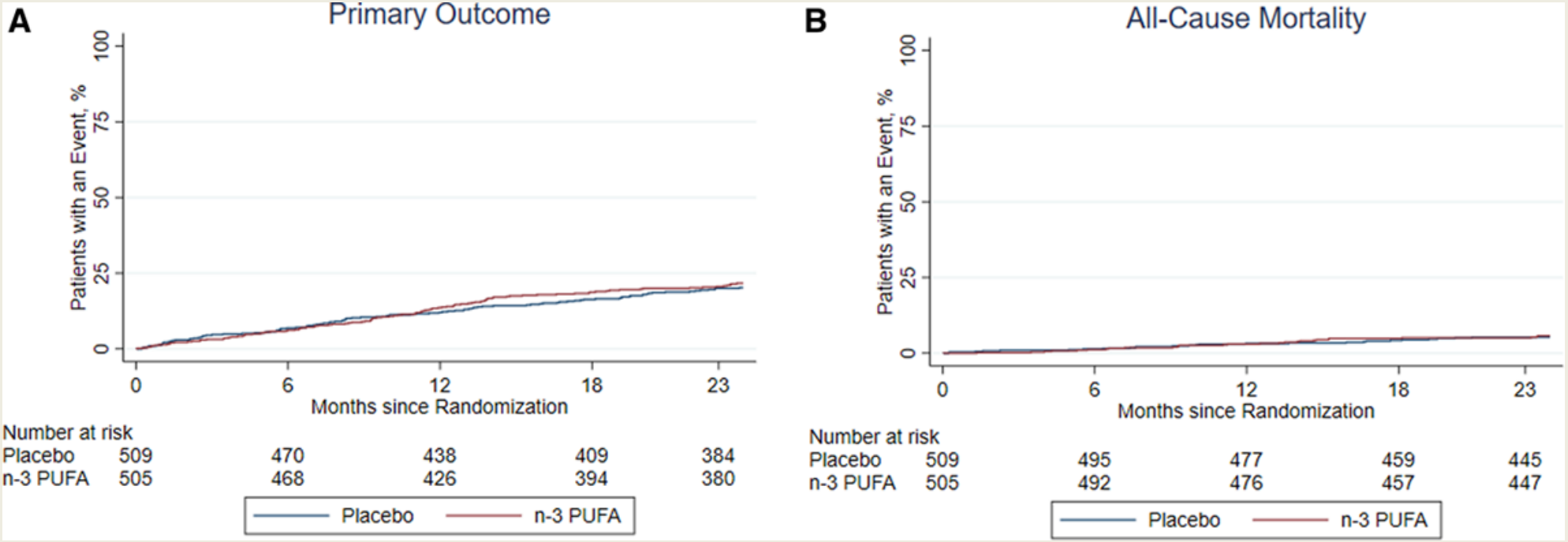
A, Median (Q1-Q3) observation time was 41.3 (36.0-47.5) months for patients receiving omega-3 CA and 41.4 (35.9-47.4) months for patients receiving corn oil.

B, Median (Q1-Q3) observation time of 41.5 (36.6-47.8) months for patients receiving omega-3 CA and 41.6 (36.8-47.4) months for patients receiving corn oil.

Nicholls SJ et al. ***JAMA***. 2020;324(22):2268-2280.

OMEMI

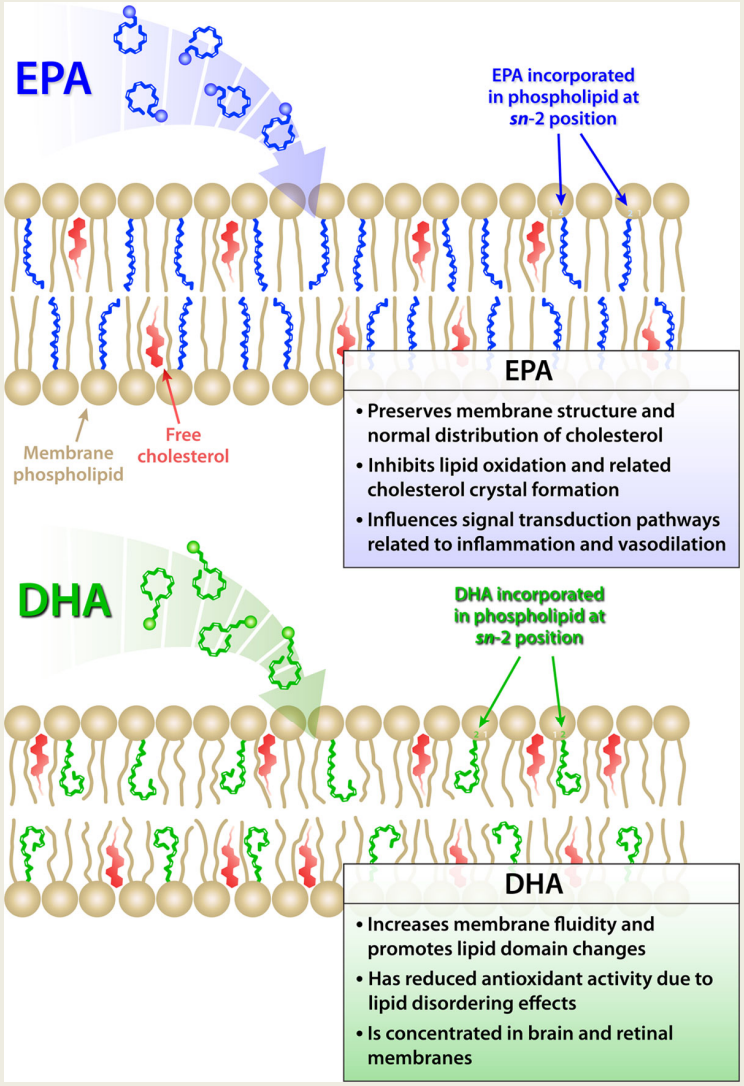
1027 pts with recent MI
1.8 g n-3 PUFA (930 mg eicosapentaenoic acid and 660 mg docosohexaenoic acid)



Kalstad et al. ***Circulation*** 2021;143:528–539

Molecular membrane interactions of omega-3 fatty acids

Proposed location and contrasting effects of EPA and DHA on membrane structure

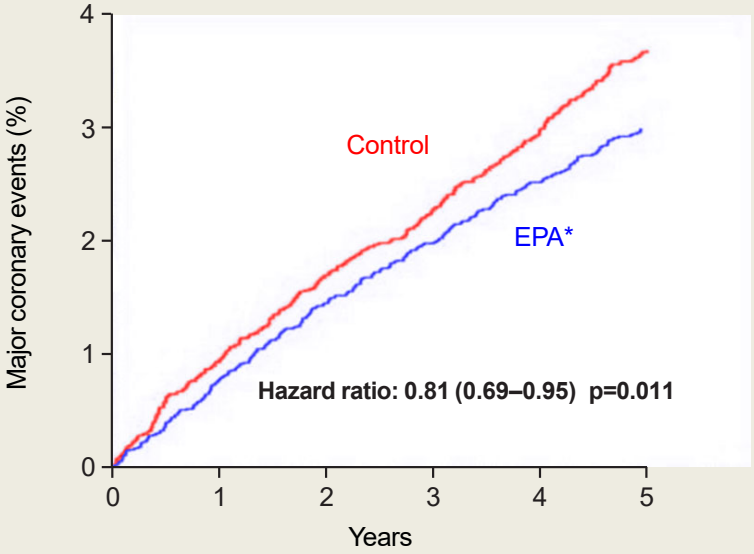


The insertion of EPA and DHA affect distinct regions of the membrane lipid bilayer due to differences in their hydrocarbon length and number of double bonds. The longer hydrocarbon length of DHA leads to more rapid isomerization and conformational changes that result in increased membrane fluidity and promotion of cholesterol domains. EPA has a more stable and extended structure that contributes to membrane stability as well as inhibition of lipid oxidation and cholesterol domain formation.

Mason P et al. ***ATVB*** 2020

Recent larger outcome trials using high dose O3FA

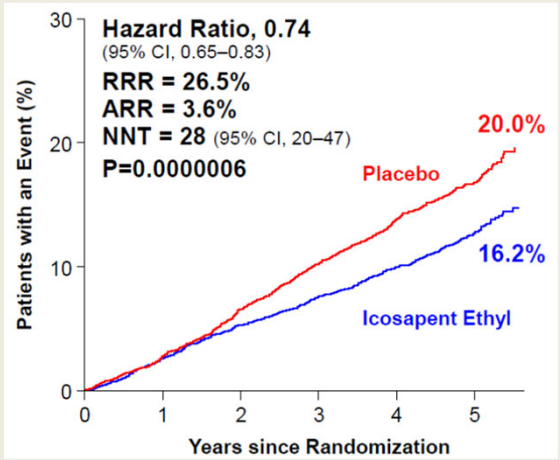
JELIS



1.8 g EPA
No placebo

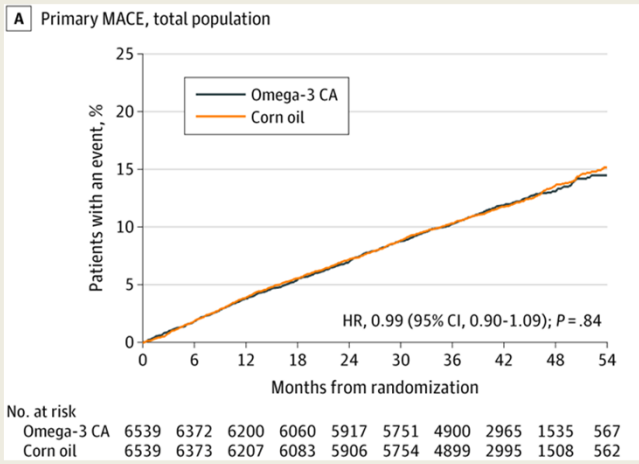
REDUCE IT

CV death/MI/Stroke



4 g EPA
Mineral oil placebo

STRENGTH



4 g EPA and DHA
Corn oil placebo

Conclusions

- Robust CV benefit of 4 g/day of icosapent ethyl [purified EPA, (EE)] in statin treated adults at high CV risk (secondary prevention or diabetics in primary prevention with one additional RF) and with elevated TGs

- Benefit of high dose EPA has been seen in JELIS (which used no placebo)

- Benefit was not seen with lower doses of O3FA, mixtures of O3FA or in other populations

Potential Benefits of EPA

Effects of EPA on Plaque Progression

	Endothelial Dysfunction/ Oxidative Stress	Inflammation/ Plaque Growth	Unstable Plaque
Increase	Endothelial function Nitric oxide bioavailablity	EPA/AA ratio IL-10	Fibrous cap thickness Lumen diameter Plaque stability
Decrease	Cholesterol crystalline domains Ox-LDL RLP-C Adhesion of monocytes Macrophages Foam cells	IL-6 ICAM-1 hsCRP Lp-PLA_2 MMPs	Plaque volume Arterial stiffness Plaque vulnerability Thrombosis Platelet activation

Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. *J Am Coll Cardiol*. 2018:72:330-343.

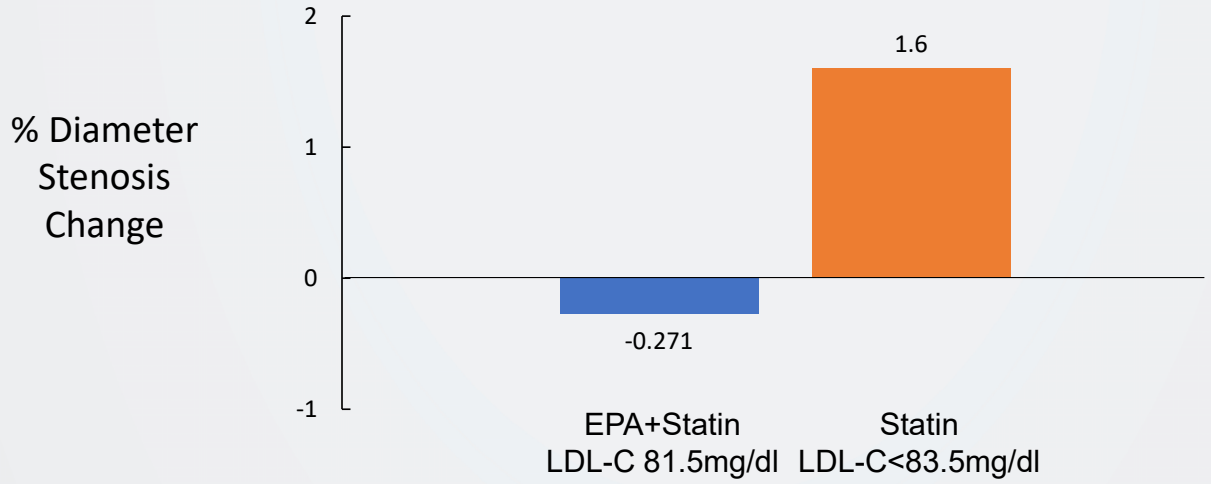
Potential Benefits of EPA

Effects of EPA on Plaque Progression

	Endothelial Dysfunction/ Oxidative Stress	Inflammation/ Plaque Growth	Unstable Plaque
Increase	Endothelial function Nitric oxide bioavailablity	EPA/AA ratio IL-10	Fibrous cap thickness Lumen diameter Plaque stability
Decrease	Cholesterol crystalline domains Ox-LDL RLP-C Adhesion of monocytes Macrophages Foam cells	IL-6 ICAM-1 hsCRP Lp-PLA_2 MMPs	Plaque volume Arterial stiffness Plaque vulnerability Thrombosis Platelet activation

Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. *J Am Coll Cardiol*. 2018:72:330-343.

Quantitative Coronary Angiography



- EPA/AA ratio had (-) relationship with progression of atherosclerosis (P for trend = 0.044)
- Highest quartile of EPA/AA ratio had a significantly higher risk of progression from lowest quartile (P<0.05)

Domei T, et al. *Eur Heart J.* 2013;34(Suppl 1):137.

CHERRY: IVUS STUDY

Randomized, Non-Blinded, Parallel-Group, Multicenter Study

Patient Population (N=193)
Adult Japanese CHD patients who underwent percutaneous
coronary intervention

Primary endpoint
Change in coronary plaque tissue characteristics as evaluated
by IB-IVUS

Secondary endpoints included
Changes in the volume of target coronary plaques, lipids and inflammatory markers, and major CV events

Pitavastatin 4 mg + EPA 1.8 g/day (n=97)

Pitavastatin 4 mg monotherapy (n=96)

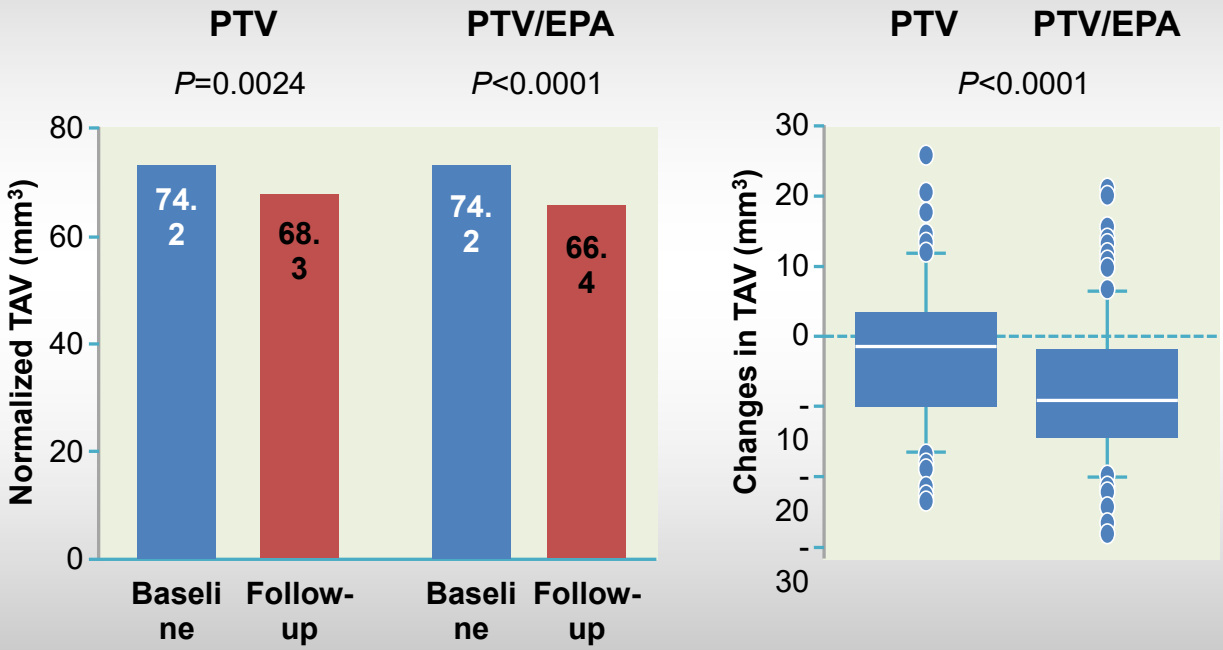
6-8 Months

- Mean baseline LDL-C levels for the statin and statin/EPA groups were 99 mg/dL and 107 mg/dL, respectively, and total cholesterol levels were 166 mg/dL and 175 mg/dL, respectively
- Median triglyceride levels were in the normal range at baseline in both arms (105 and 111 mg/dL)

IB-IVUS=integrated backscatter intravascular ultrasound.

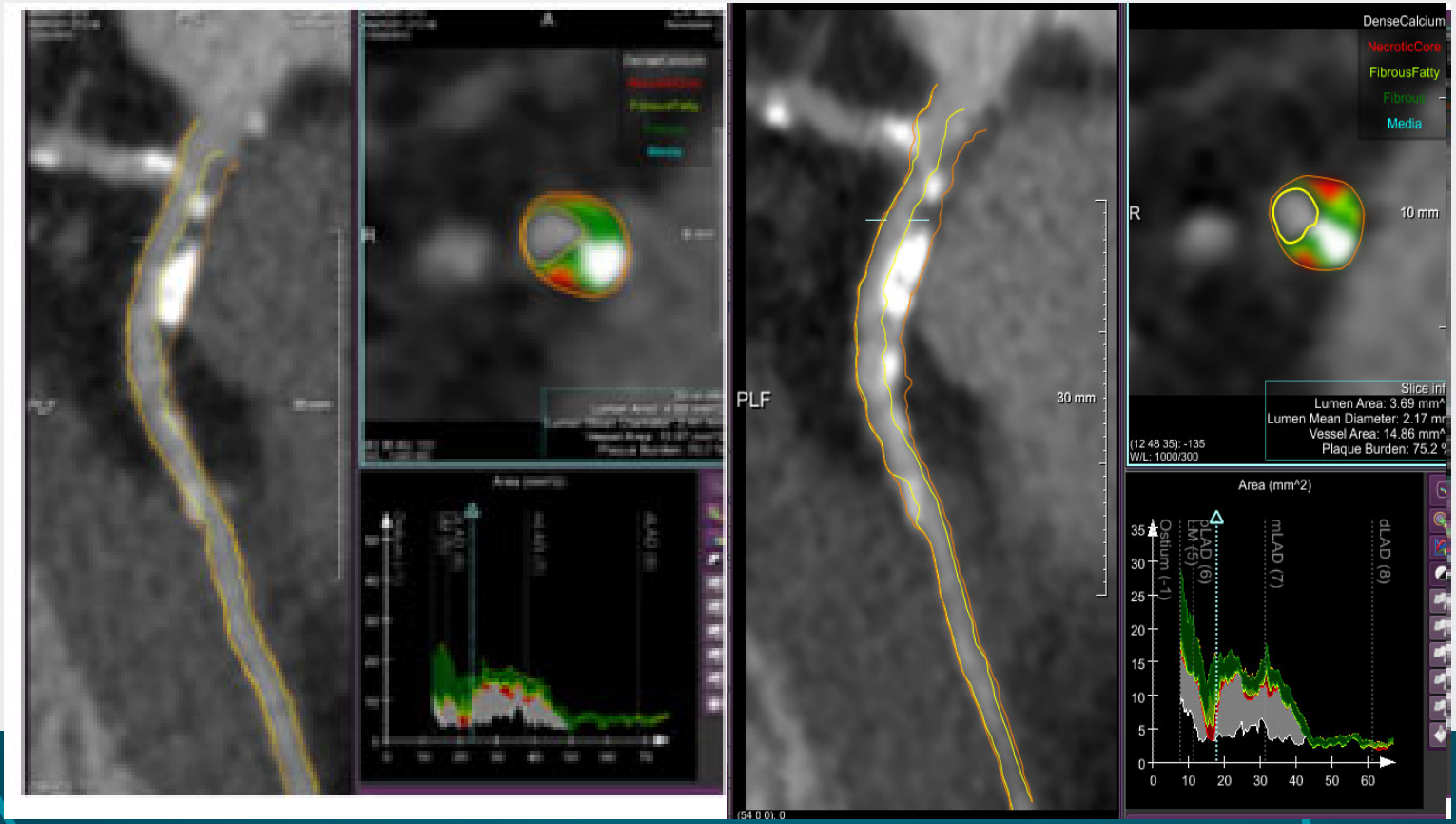
Watanabe T et al. *J Cardiol*. 2014;64(3):236-239.
Watanabe T et al. *J Cardiol*. 2017;70(6):537-544.

CHERRY: Change in Total Plaque Volume



PTV=pitavastatin; TAV=total atheroma volume.
Wilcoxon signed-rank test.
Watanabe T et al. *J Cardiol*. 2017;70(6):537-544.

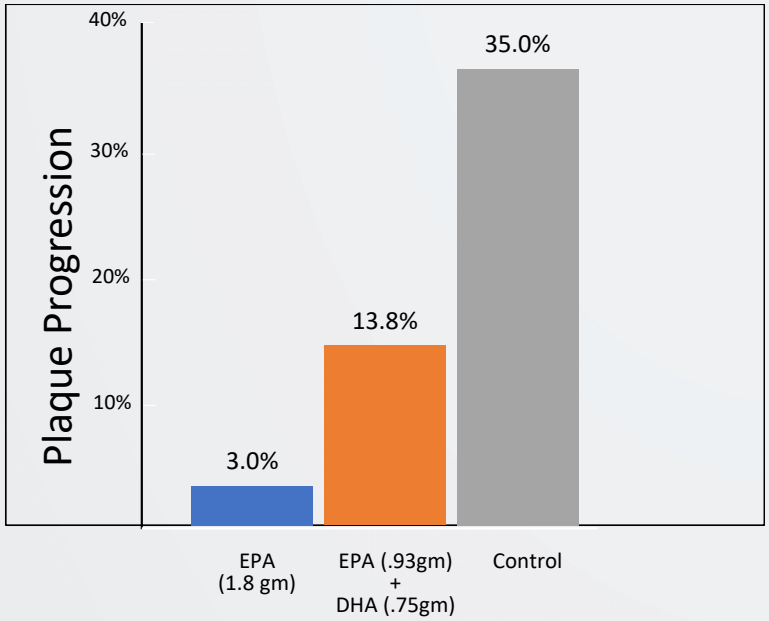
Serial CT Angiography to Assess Plaque Progression



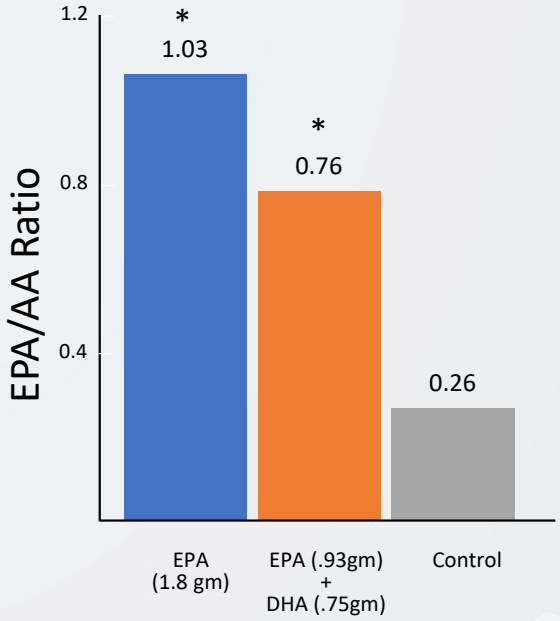
Clinical Effects of EPA/DHA on Atherosclerotic Plaques by Imaging Modality - Multi-detector Row Computed Tomography (MDCT)

82
Patients

1 Year
P<0.0061 between groups



1 Year
*P<0.0001 compared to control



Nagahana Y, et al. *Eur Heart J*. 2016;37(Suppl 1):1052.

Study Design

evaporate FINAL

Randomized, Double-Blind, Placebo-Controlled Trial

Patient Population (N=~80)

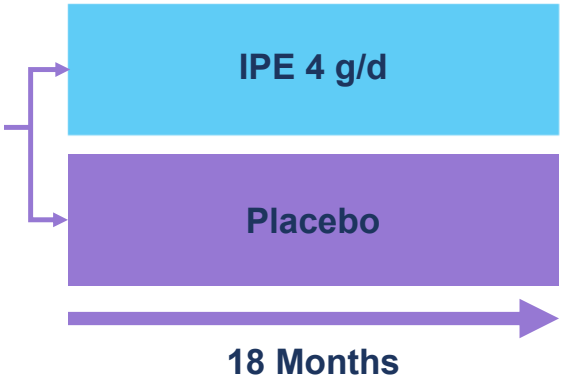
- 30–85 years of age
- TG: 135–499 mg/dL
- LDL-C >40 mg/dL and ≤115 mg/dL (on statin)
- ≥1 angiographic stenosis with ≥20% narrowing by CTA
- No history of MI, stroke, or life-threatening arrhythmia within the prior 6 months and no history of CABG

Primary endpoint

- Progression rates of low attenuation plaque

Secondary endpoints include

- Plaque morphology and composition
- (non-calcified, total, fibrous, fibrofatty, calcified)
- Markers of inflammation (Lp-PLA_2)
- LDL-C and HDL-C



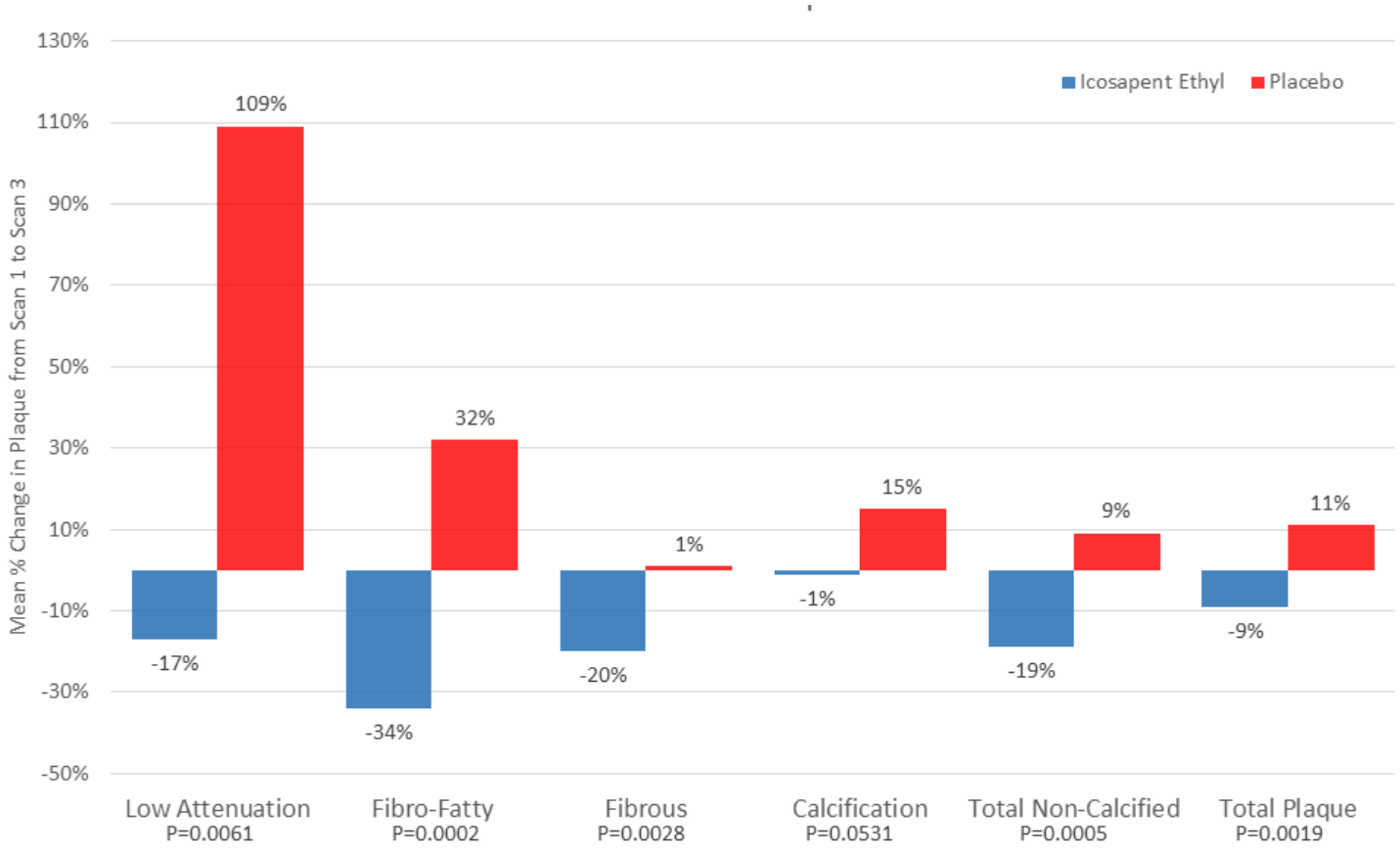
The EVAPORATE study sought to determine whether IPE will reduce plaque progression over 9 to 18 months compared to placebo in statin-treated patients

CABG=coronary artery bypass graft; CTA=computed tomography angiography.

EVAPORATE Clinical Trial. https://clinicaltrials.gov/ct2/show/NCT02926027.

BUDOFF et al. CLIN CARD 2017.

Change in Plaque Quantity Based on Treatment Group



ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Effect of Eicosapentaenoic and Docosahexaenoic Acids Added to Statin Therapy on Coronary Artery Plaque in Patients With Coronary Artery Disease: A Randomized Clinical Trial

Abdulhamied Alfaddagh, MD; Tarec K. Elajami, MD; Hasan Ashfaque, MD; Mohamad Saleh, MD; Bruce R. Bistrian, MD, PhD, MPH; Francine K. Welty, MD, PhD

- 285 subjects with stable coronary artery disease on statins were randomized to omega-3 ethylester
- (1.86 g of eicosapentaenoic acid and 1.5 g of docosahexaenoic acid daily) or no omega-3 (control) for 30 months
- Plaque volume was assessed by coronary computed tomographic angiography
- Noncalcified plaque volume was not different between groups

Slowing HEART diSease With Lifestyle and Omega-3 Fatty Acids (HEARTS)

Plaque Volume*	Controls		Omega-3 Ethyl-Ester		% Change From Baseline		
	Baseline Value Median [IQR]	30-Month Value Median [IQR]	Baseline Value Median [IQR]	30-Month Value Median [IQR]	Controls Median [IQR]	Omega-3 Ethyl-Ester Median [IQR]	*P* Value†
Intention-to-treat							
	(n=114)		(n=126)				
Fatty	8.6 [5.1, 14.0]	8.6 [5.3, 13.7]	9.4 [4.9, 14.7]	9.3 [5.5, 14.8]	2.9 [−9.8, 15.1]	0.8 [−10.4, 20.1]	0.94
Fibrous	15.1 [8.7, 23.0]	15.9 [9.2, 23.5]	17.5 [9.5, 25.5]	16.1 [9.7, 24.3]	4.6 [−8.0, 18.5]	0.1 [−12.2, 14.9]	0.063
Noncalcified	23.7 [14.3, 36.8]	24.7 [14.5, 36.6]	26.4 [14.3, 39.7]	25.7 [15.0, 39.9]	4.5 [−6.1, 15.8]	−2.4 [−9.8, 16.7]	0.14
Calcified	3.6 [1.3, 7.3]	6.2 [2.6, 10.3]	5.0 [2.4, 8.7]	6.4 [3.3, 10.3]	57.4 [4.3, 146.6]	39.1 [−5.2, 118.1]	0.18
Total	28.1 [16.6, 44.3]	33.8 [18.1, 46.5]	33.2 [17.9, 47.0]	33.4 [19.1, 50.5]	10.0 [−3.1, 25.9]	6.5 [−6.9, 19.2]	0.11

Alfaddagh et al. - JAHA 2017

ATHEROSCLEROSIS IMAGING AND OMEGA 3

- This data supports the elegant marriage of clinical trial results (**JELIS, REDUCE-IT**) and imaging (**NISHIO, CHERRY, EVAPORATE**), demonstrating consistent benefits of EPA on both outcomes and plaque reduction
- These data highlight the early and substantial impact of icosapent ethyl on the atherothrombotic burden in the at-risk population
- Conversely, combination EPA/DHA has no positive effects on outcomes (**STRENGTH**) or atherosclerosis (**HEARTS**)

CONCLUSIONS

- Triglycerides are a good marker of future CVD Risk
- Triglycerides are also associated with inflammation, endothelial dysfunction and increased risk of atherosclerosis (atherogenic)
- Treatment of triglycerides is typically – statin first, then icosapent ethyl
- Fibrates, dietary supplements of fish oils and niacin are NOT approved for treatment of triglycerides except in very high cases (TG > 500 mg/dl)

Thank you!

Budoff@UCLA.edu