Mechanistic clues to understanding the benefits of icosapent ethyl

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Icosapent Ethyl – Mechanistic Clues to Understanding the Benefits of Omega-3's

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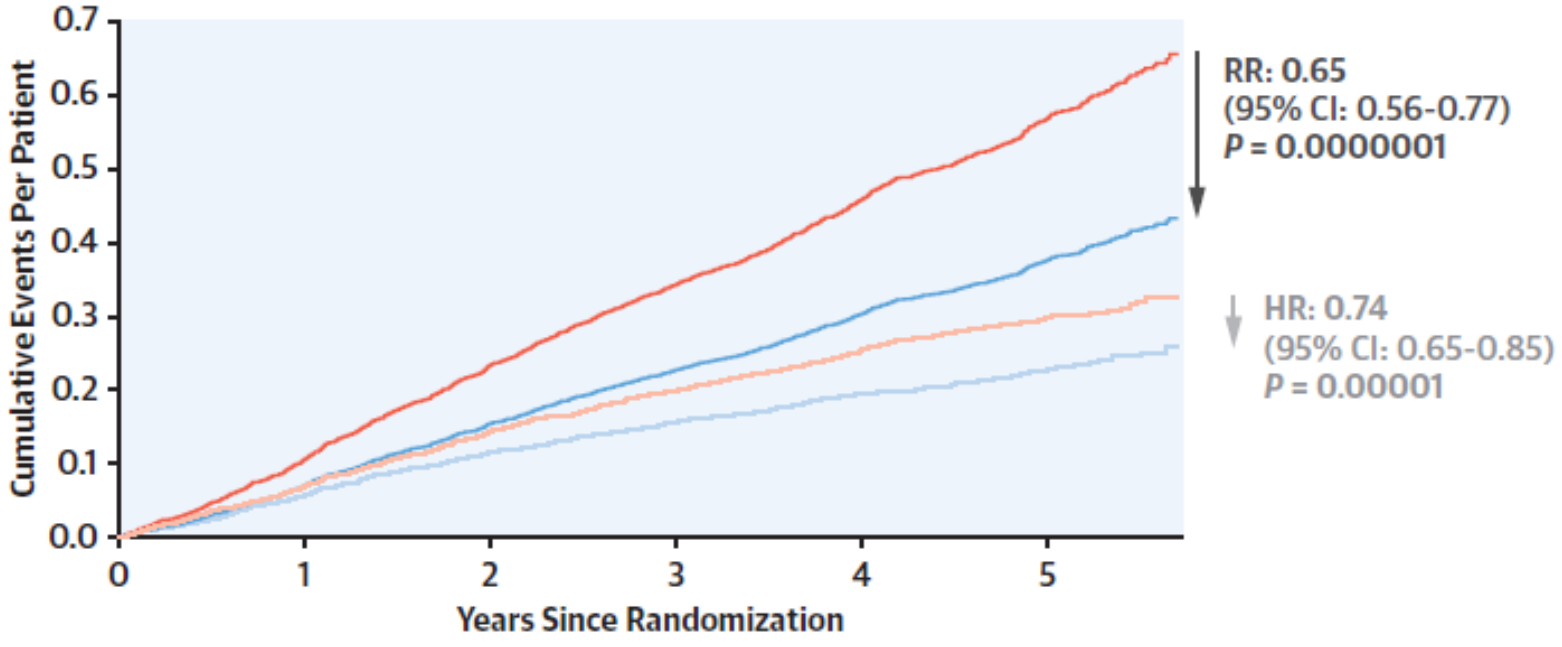
Disclosures

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

LATEST DATA FROM REDUCE-IT – Prior MI – JACC 2022

print & web 4 C/FP O

CENTRAL ILLUSTRATION Cumulative Incidence Curves of the Primary Composite Endpoint in Patients With Prior Myocardial Infarction

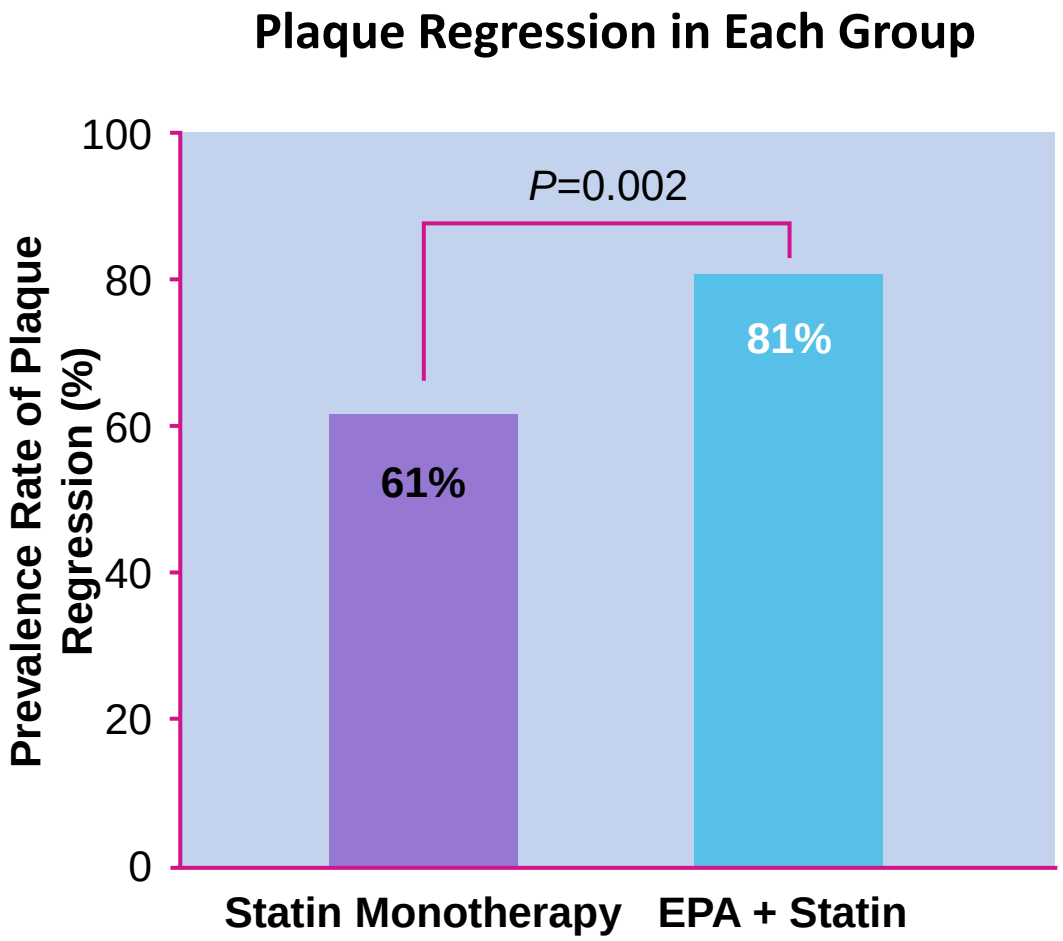


No. at Risk:						
Placebo	1,823	1,757	1,637	1,404	1,167	677
Icosapent Ethyl	1,870	1,812	1,691	1,440	1,237	698

Placebo: Total Events — Icosapent Ethyl: Total Events
Placebo: First Event — Icosapent Ethyl: First Event

Gaba P, et al. J Am Coll Cardiol. 2022;79(17):1660-1671.

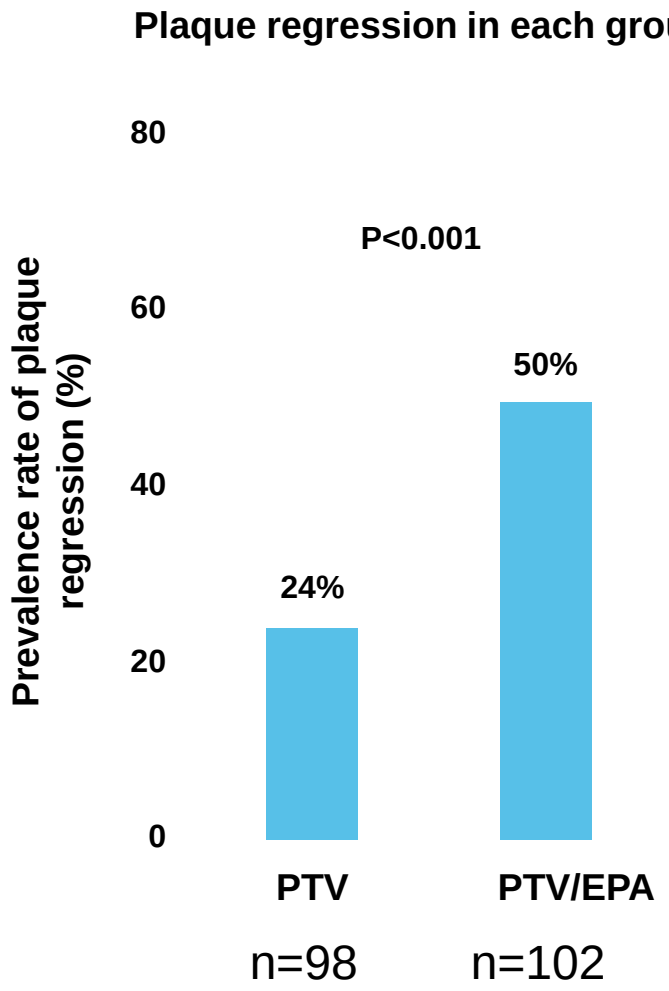
CHERRY: Plaque Regression Significantly Greater in the EPA + Statin Group Compared to Statin Monotherapy



Watanabe T et al. *J Cardiol*. 2017;70(6):537-544.

IVUS: EPA and Pitavastatin Significantly Increased Coronary Plaque Regression vs Pitavastatin Alone

- 200 CHD pts underwent PCI and were randomized to PTV 4 mg/d and PTV/EPA 4 mg/d + EPA 1800 mg/d
- Coronary plaque volume and composition in non-stented lesions were analyzed by integrated backscatter intravascular ultrasonography at baseline and 6-8 mo F/U

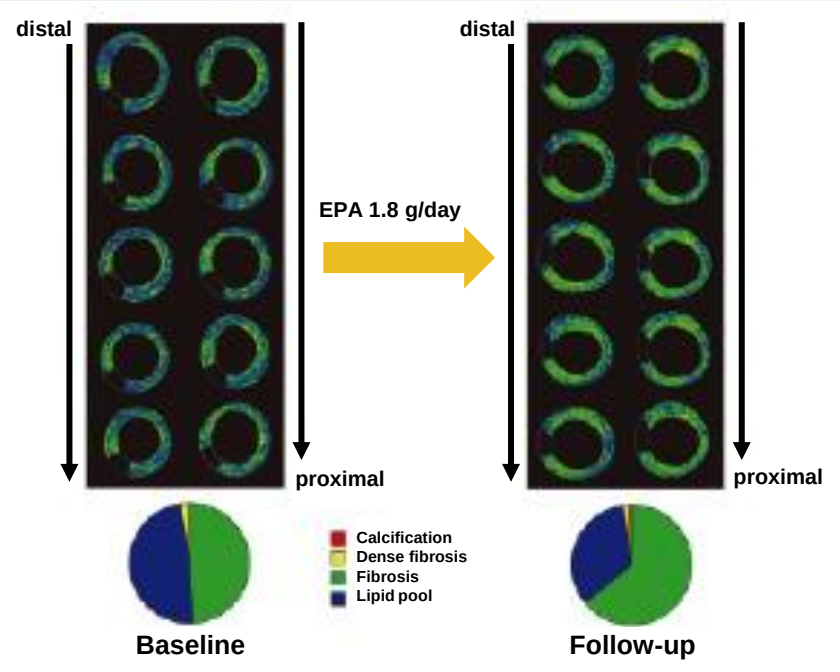


PTV=pitavastatin.

Ando K et al. *Circulation*. 2015;132:A12007.

EPA (1.8 g/day) Added to Statin Therapy Reduced Lipid Volume and Increased Fibrous Volume in Coronary Plaque

Color-coded maps of coronary arterial plaque using integrated backscatter intravascular ultrasound (IB-IVUS)



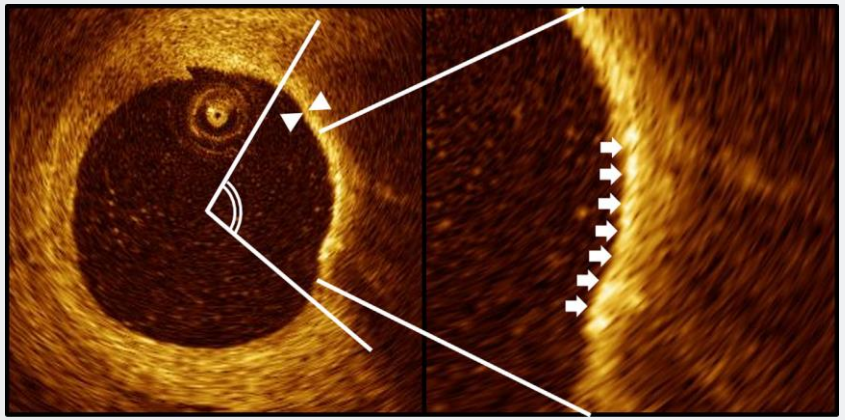
Percent Change	EPA	Control	*P*
Fibrous volume	11.7 ± 8.3	-9.2 ± 5.3	0.01
Lipid volume	-18.9 ± 9.2	8.4 ± 4.5	0.002
Dense fibrosis volume	20.0 ± 10.2	26.3 ± 13.2	0.62
Calcified volume	-8.9 ± 3.2	-27.3 ± 11.7	0.08

Percent volume of the fatty (lipid pool) and fibrous (fibrosis) components changed from 48.6% to 36.4% and from 49.1% to 61.3%, respectively.

N = 59 patients at baseline (peri-PCI) treated with statin (atorvastatin at 10 mg/day, n = 37; pitavastatin at 2 mg/day, n = 36; or rosuvastatin at 2.5 mg/day, n = 22) alone (n = 30) or statin + EPA 1.8 g (n = 29) for 6 months.

Niki T, et al. *Circ J*. 2016;80(2):450-460.

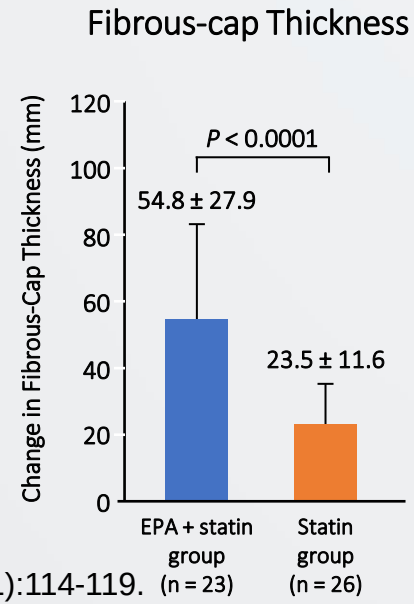
OCT: EPA + Statin Increases Fibrous Cap Thickness and Length

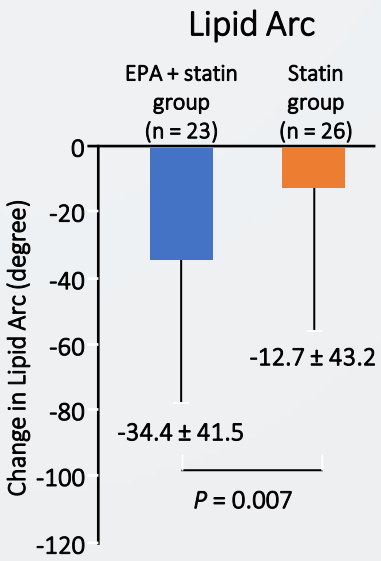


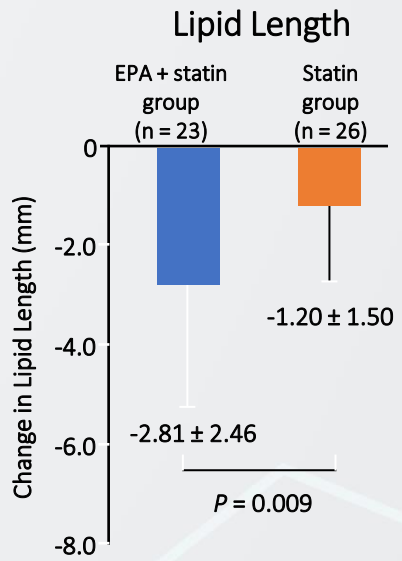
30 patients with untreated dyslipidemia were randomly assigned to EPA 1.8 g/day + rosuvastatin or rosuvastatin

49 non-culprit thin-cap fibroatheroma lesions were analyzed at baseline and after 9 months

Changes in optical coherence tomography parameters

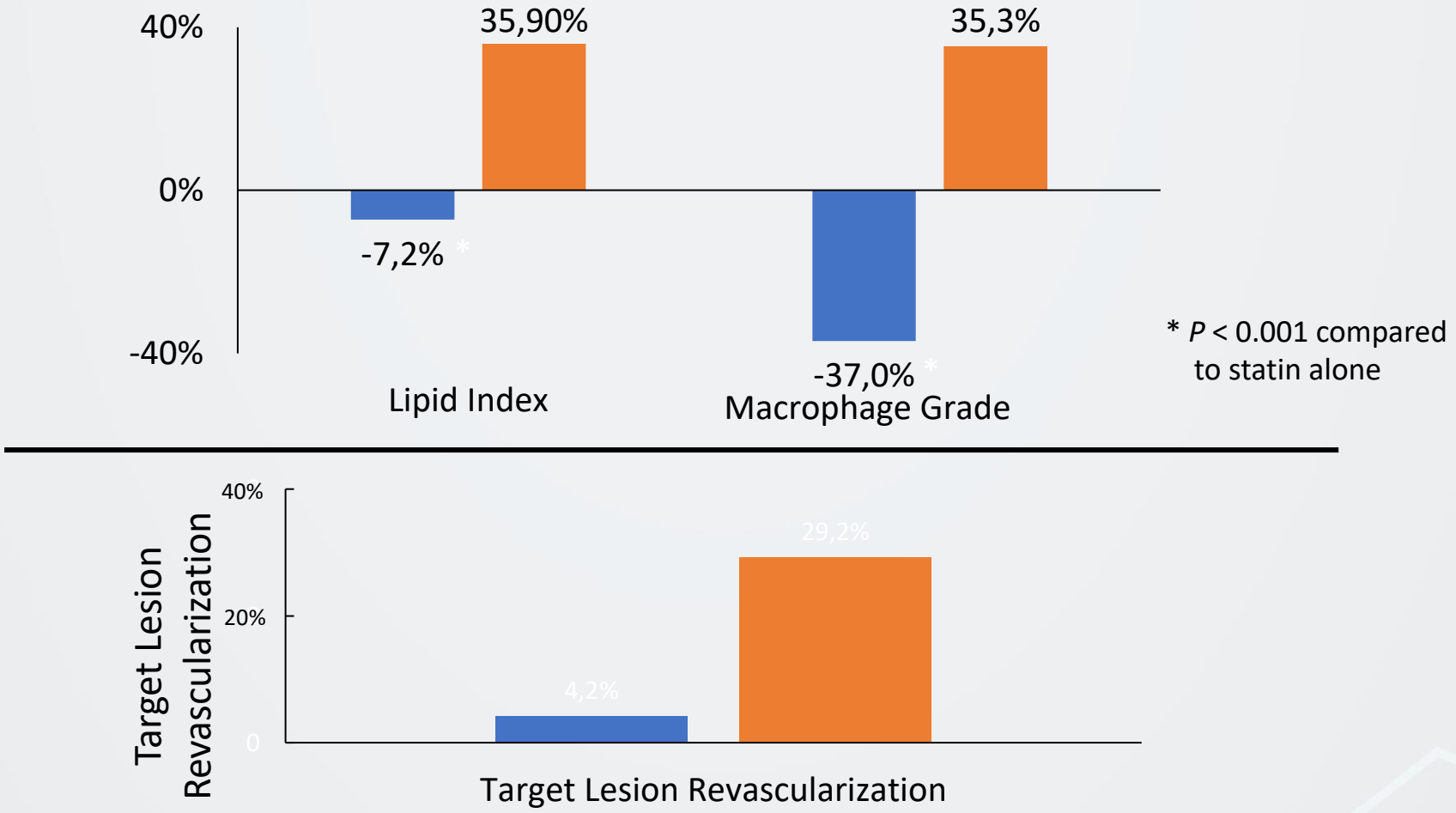






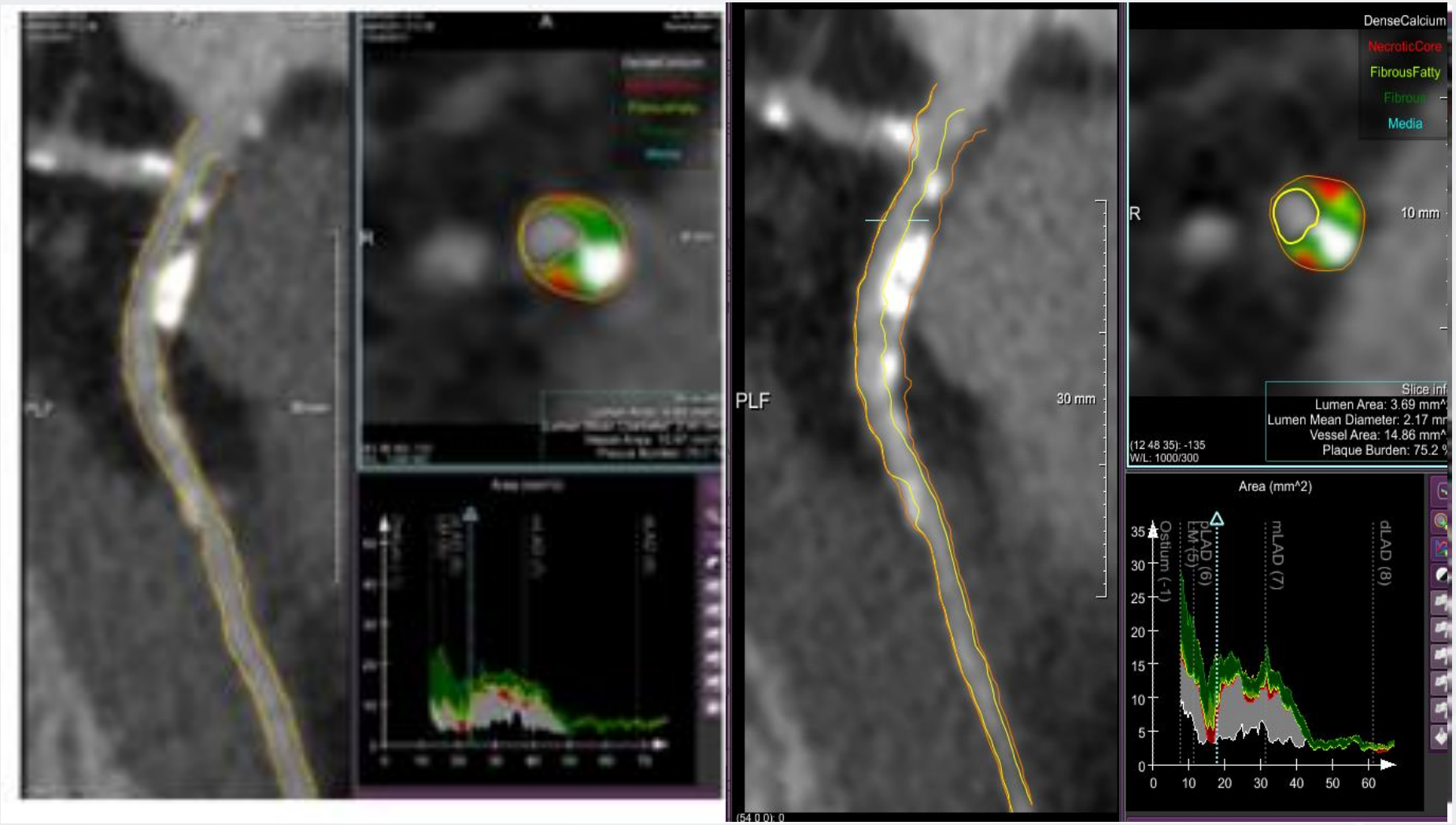
Nishio R, et al. *Atherosclerosis.* 2014;234(1):114-119.

Effect of Rosuvastatin and Eicosapentaenoic Acid on Neoatherosclerosis: The LINK-IT Trial



Kuroda K, et al. *EuroIntervention*. 2019;15(12): e1099-e1106.

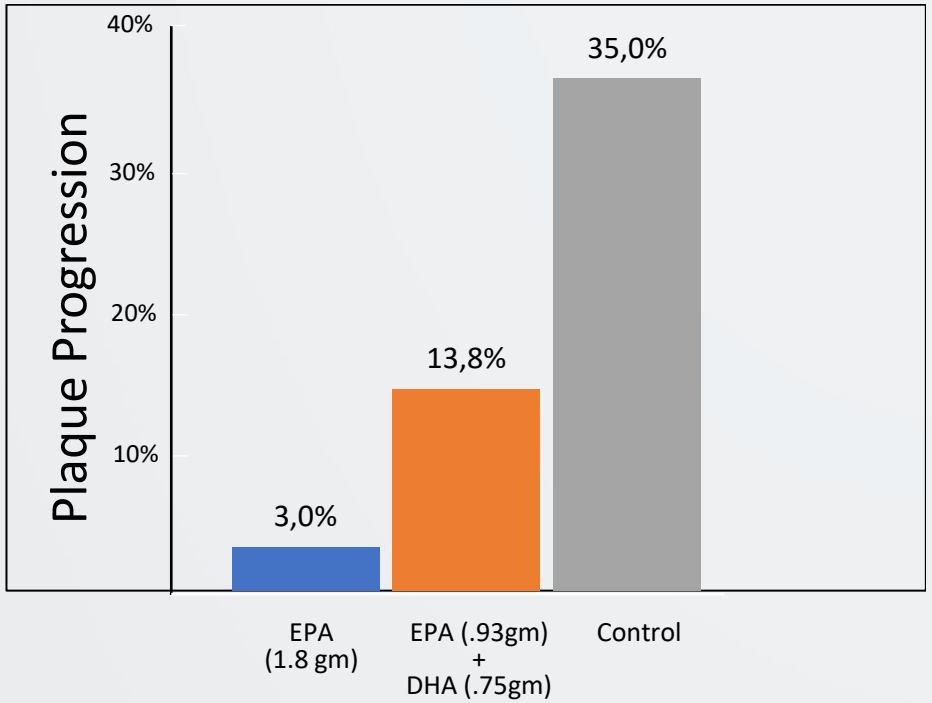
Serial CT Angiography to Assess Plaque Progression



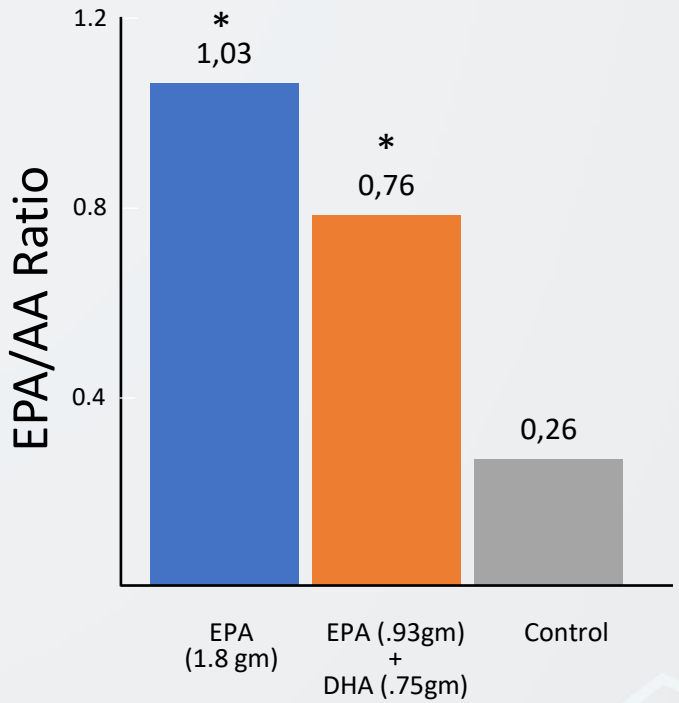
Clinical Effects of EPA/DHA on Atherosclerotic Plaques by Imaging Modality - Multi-detector Row Computed Tomography (MDCT)

82
Patients

1 Year
P<0.0061 between groups

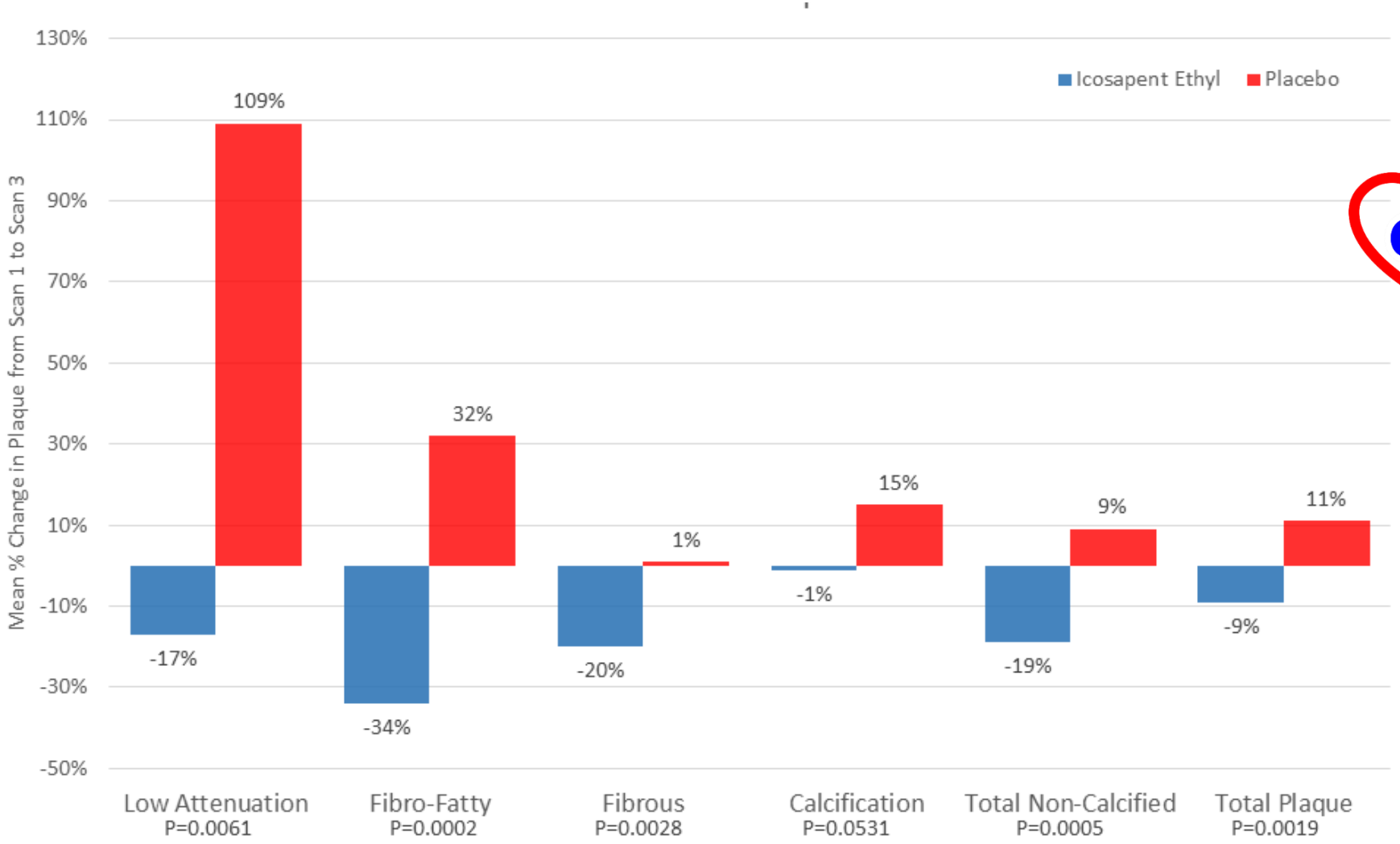


1 Year
*P<0.0001 compared to control



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

Change in Plaque Quantity Based on Treatment Group



evaporate FINAL

Budoff MJ, et al. *Eur Heart J*. 2020;41(40):3925-3932.

EVAPORATE AHA 2020

- To evaluate the effect of Icosapent ethyl (IPE) on vulnerable plaque features on serial CCTA at 9 months, using a novel software validated using histology, in patients enrolled in EVAPORATE trial

- Plaque characteristics including Lipid Rich Necrotic Core (LRNC), fibrous cap thickness, and intraplaque hemorrhage (IPH) were assessed using vascuCAP® (Elucid Bioimaging Inc., Boston, MA).

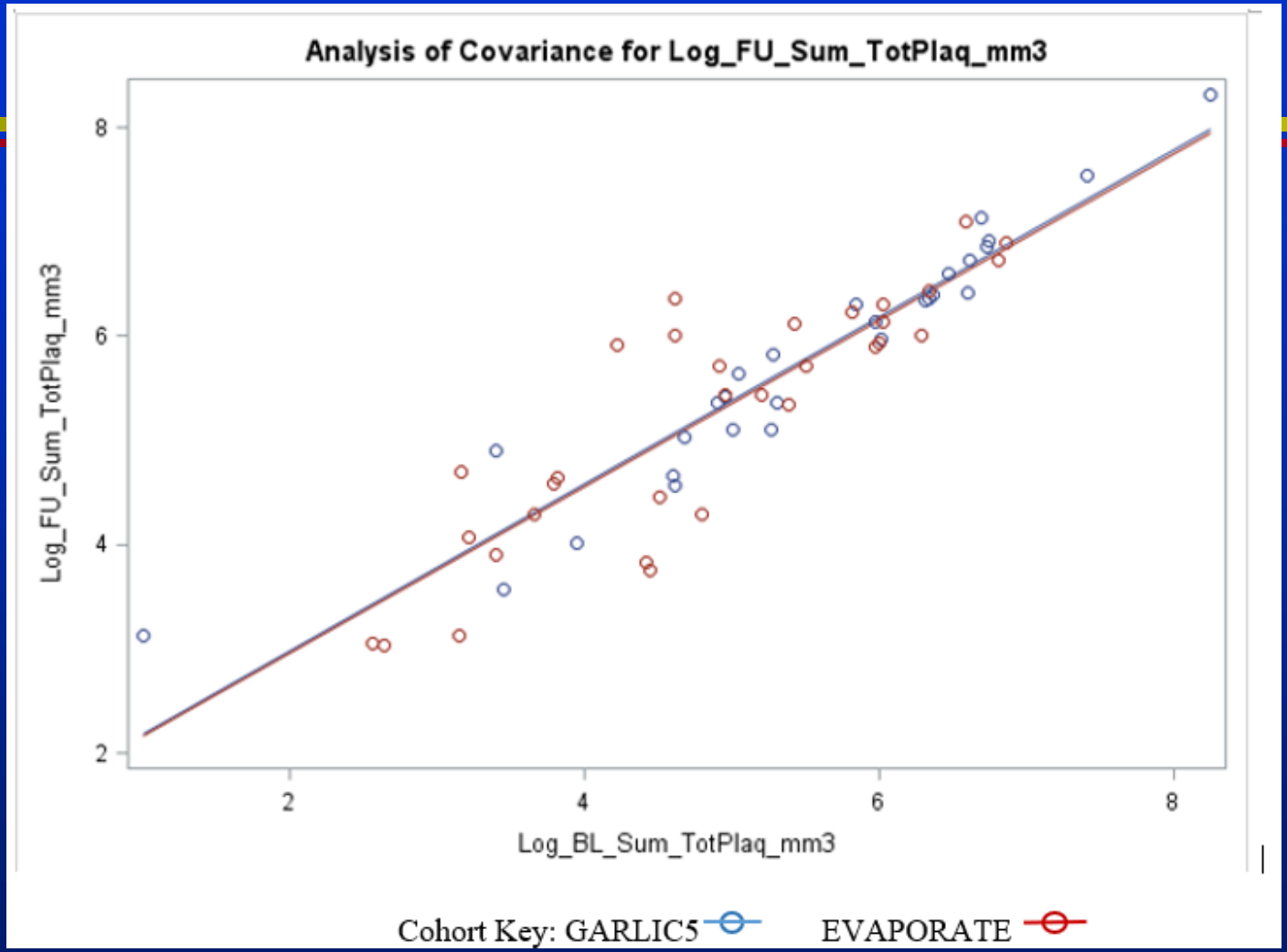
Results

- Relative to placebo, patients on IPE demonstrated:

  - **Decreased Lipid rich necrotic core (-1.4 vs. +9.7 mm3)**
  - **Reduced intra plaque hemorrhage (-0.02 vs. +0.3 mm3)**
  - **Increased cap thickness (+100 vs. -290 micron)**

- Indicating a migration of atherosclerotic plaque to a more stable phenotype.

MINERAL OIL VS CELLULOSE



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.

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

HEARTS

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 ethyl ester
- (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, NOSAKA**) and imaging (**NISHIO, CHERRY, EVAPORATE**), demonstrating consistent benefits of EPA on both outcomes and plaque reduction
- Compared with placebo, icosapent ethyl significantly reduced multiple plaque components, including vulnerable (low attenuation) plaque, lipid rich necrotic core, intra plaque hemorrhage and increased cap thickness
- Conversely, combination EPA/DHA has no positive effects on outcomes (**STRENGTH, OMEMI**) or atherosclerosis (**HEARTS, AQUAMARINE**)

Potential Benefits of EPA

	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, et al. *J Am Coll Cardiol*. 2018;72(3):330-343.

Thank you!

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