Clinicians Live: New Opportunities to Reduce Residual Risk Beyond Statin Therapy

MAY 16, 2019 | Turnberry Isle Miami | Aventura, FL

AGENDA

6:45 PM	Registration and Buffet Dinner
7:00 PM	Program Overview *Sergio Fazio, MD, PhD, Chair*
7:10 PM	REDUCE-IT and Other Omega-3 Trials *Michael Miller, MD*
7:25 PM	Biologic Basis for EPA Modulation in Reducing ASCVD Events Seen in REDUCE-IT *R. Preston Mason, PhD*
7:40 PM	Clinician Live Discussion *All Faculty*
7:55 PM	Q&A with the Audience *Faculty and Participants*
8:10 PM	Challenging Cases for Discussion *Faculty and Participants*
8:25 PM	Closing Comments *Sergio Fazio, MD, PhD, Chair*
8:30 PM	Adjourn

Faculty slides are available online: medtelligence.net/may16

Scroll to the "Related" section and click on "Syllabus"

OBJECTIVES & ACCREDITATION

PROGRAM OVERVIEW

This innovative and engaging symposium will provide in-depth coverage of key issues and guidelines surrounding the management of CV risk beyond statin therapy. Prominent, internationally known faculty will highlight relevant clinical pearls to improve patient management and clinical outcomes.

ACTIVITY TYPE

Live

TARGET AUDIENCE

This activity is designed to meet the needs of lipidologist, internists, endocrinologists, physician assistants, pharmacists, registered nurses, nurse practitioners, advance practice registered nurses and registered dietitians with an interest in lipid management.

LEARNING OBJECTIVES

At the Conclusion of this activity, participants should be able to:

- Discuss the results and importance of REDUCE-IT and other recent cardiovascular outcomes trials that reduce ASCVD events beyond statin therapy.
- Describe the potential biologic basis for the reductions in ASCVD events observed in REDUCE-IT.
- Apply evidence-based trial evidence and guidelines to lifestyle and therapeutic approaches for managing patients with or at high risk of ASCVD events.
- Discuss strategies to improve the knowledge, skills or performance of the healthcare team.

CRITERIA FOR SUCCESS

Statements of credit will be awarded based on the participant's attendance and submission of the activity evaluation form. Partial credit may be awarded for ACPE credit. A statement of credit will be available upon completion of an online evaluation/claimed credit form at www.lipid.org/cme. The deadline to claim credit is **June 14, 2019**.

For Pharmacists: Upon receipt of the completed activity evaluation form, transcript information will be available at www.mycpemonitor.net within 4 weeks.

COMMERCIAL SUPPORT

This educational activity is supported by educational grants from Amarin Pharma Inc.

CREDIT DESIGNATION

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

CME credit provided by the National Lipid Association

In support of improving patient care, this activity has been planned and implemented by The National Lipid Association and Medtelligence. The National Lipid Association is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physician Credit Designation Statement

The National Lipid Association designates this live activity for a maximum of 1.50 *AMA PRA Category 1 Credits™*. Physicians should claim only credit commensurate with the extent of their participation in this activity.

Physician Assistants

NCCPA accepts *AMA PRA Category I Credit™* from organizations accredited by ACCME.

Dietitians

The National Lipid Association is a Continuing Professional Education (CPE) Accredited Provider with the Commission on Dietetic Registration (CDR). Registered dietitians (RDs) and dietetic technicians, registered (DTRs) will receive 1.50 continuing professional education units (CPEUs) for completion of this program/ materials. CDR Accredited Provider #NL002.

Pharmacist Accreditation Statement

Universal Activity Number – JA0007192-9999-19-011-L01-P (Application)
This Activity has been approved for 1.50 contact hour(s) (.150 CEUs) of the Accreditation Council for Pharmacy Education.

Nursing

The maximum number of hours awarded for this CE activity is 1.5 contact hours.

Pharmacotherapy contact hours for Advance Practice Registered Nurses to be determined on participant certificate.

CHAIR

Sergio Fazio, MD, PhD
William and Sonja Connor Chair of Preventive Cardiology
Professor of Medicine, Physiology & Pharmacology
Director, Center for Preventive Cardiology
Knight Cardiovascular Institute
Oregon Health & Science University
Portland, OR

FACULTY

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Beverly, MA

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Cardiology Nurse Practitioner
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Immediate Past- President, National Lipid Association
New York, NY

DISCLOSURE OF UNLABELED USE AND INVESTIGATIONAL PRODUCTS
This educational activity may include discussion of uses of agents that are investigational and/or unapproved by the FDA. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

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It is the policy of NLA to ensure independence, balance, objectivity, scientific rigor, and integrity in all of its continuing education activities. Planners, faculty, reviewers, and staff have disclosed any financial relationships with commercial interests as defined by the ACCME**.**

DISCLAIMER
This course is designed solely to provide the healthcare professional with information to assist in his/her practice and professional development and is not to be considered a diagnostic tool to replace professional advice or treatment. The course serves as a general guide to the healthcare professional, and therefore, cannot be considered as giving legal, nursing, medical, or other professional advice in specific cases. The NLA specifically disclaims responsibility for any adverse consequences resulting directly or indirectly from information in the course, for undetected error, or through reader's misunderstanding of content.

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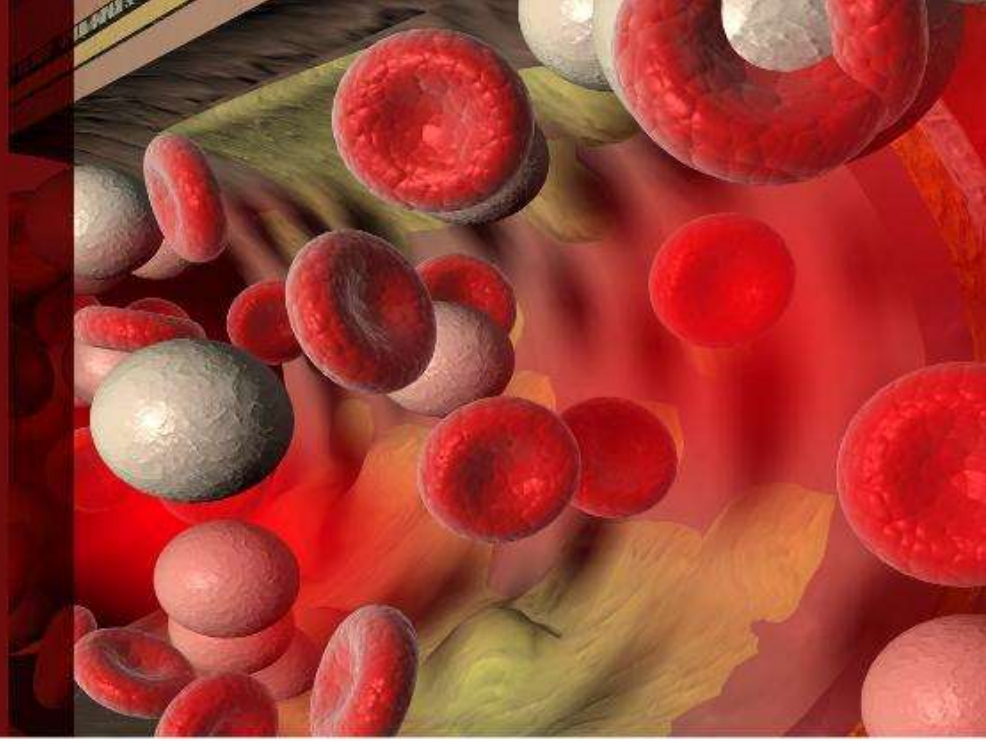
FACULTY/PLANNER FINANCIAL DISCLOSURES

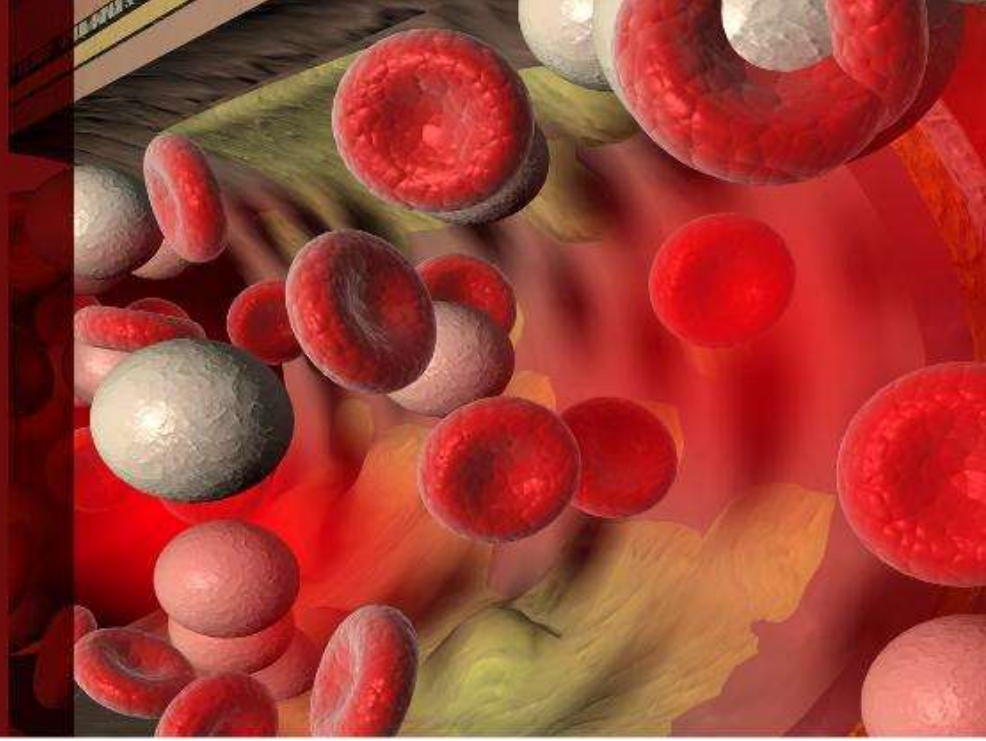
Name	Relationship	Company
Fazio, Sergio	Consultant	Amarin, Amgen, AstraZeneca, Esperion, Novartis
Mason, R. Preston	Contracted Research	Amarin, Amgen, ARCA Biopharma, Daiichi Sankyo, Pfizer
Miller, Michael	Consultant	Amarin
Minissian, Margo	Consultant	Amgen
Underberg, James	Advisory Board	Akcea, Alexion, Akcea, Ambry, Amgen, Regeneron, Sanofi
	Consultant	Amgen
	Contracted Research	Aegerion, Pfizer
	Speakers Bureau	Aegerion, Akcea, Alexion, Amarin, Amgen, Regeneron, Sanofi
STAFF/ REVIEWER DISCLOSURES		
NLA	N/A	NLA staff has nothing to disclose.
Medtelligence	N/A	Medtelligence staff has nothing to disclose.
Hemphill, Linda	Contracted Research	Akcea/Ionis, The Medicines Company, Regeneron
	Consultant	Akcea

This syllabus is not intended to be an exact representation of the faculty presentations.



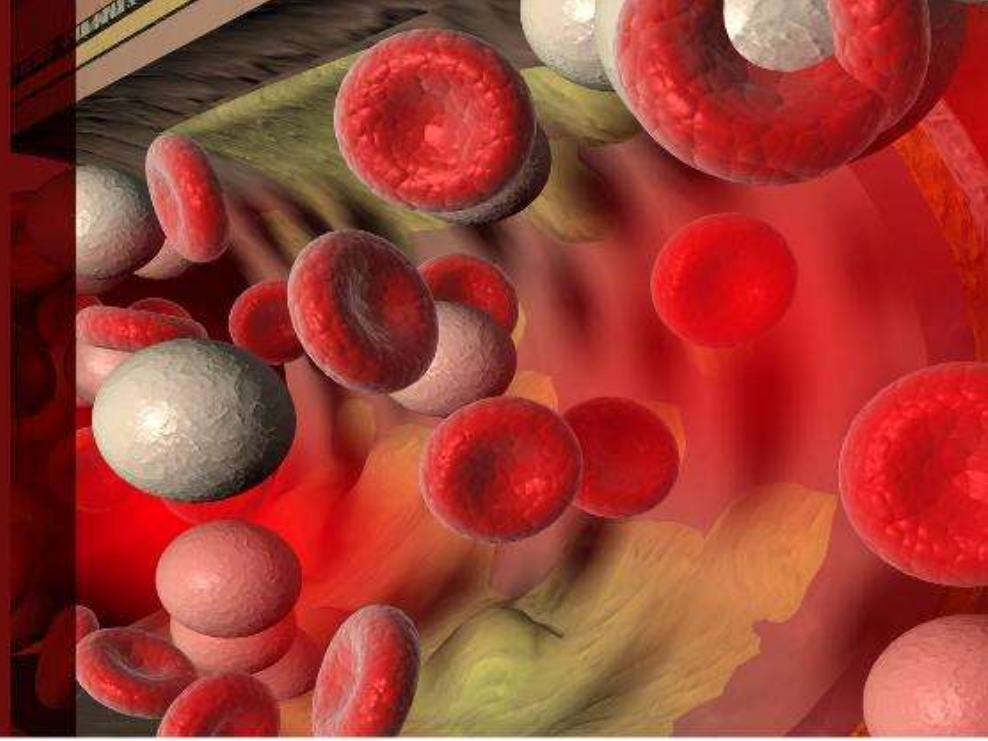
It is being provided as a useful reference that we encourage you to use during and after the activity.

Clinicians Live: New Opportunities to Reduce Residual Risk Beyond Statin Therapy



May 16, 2019

Opening Remarks

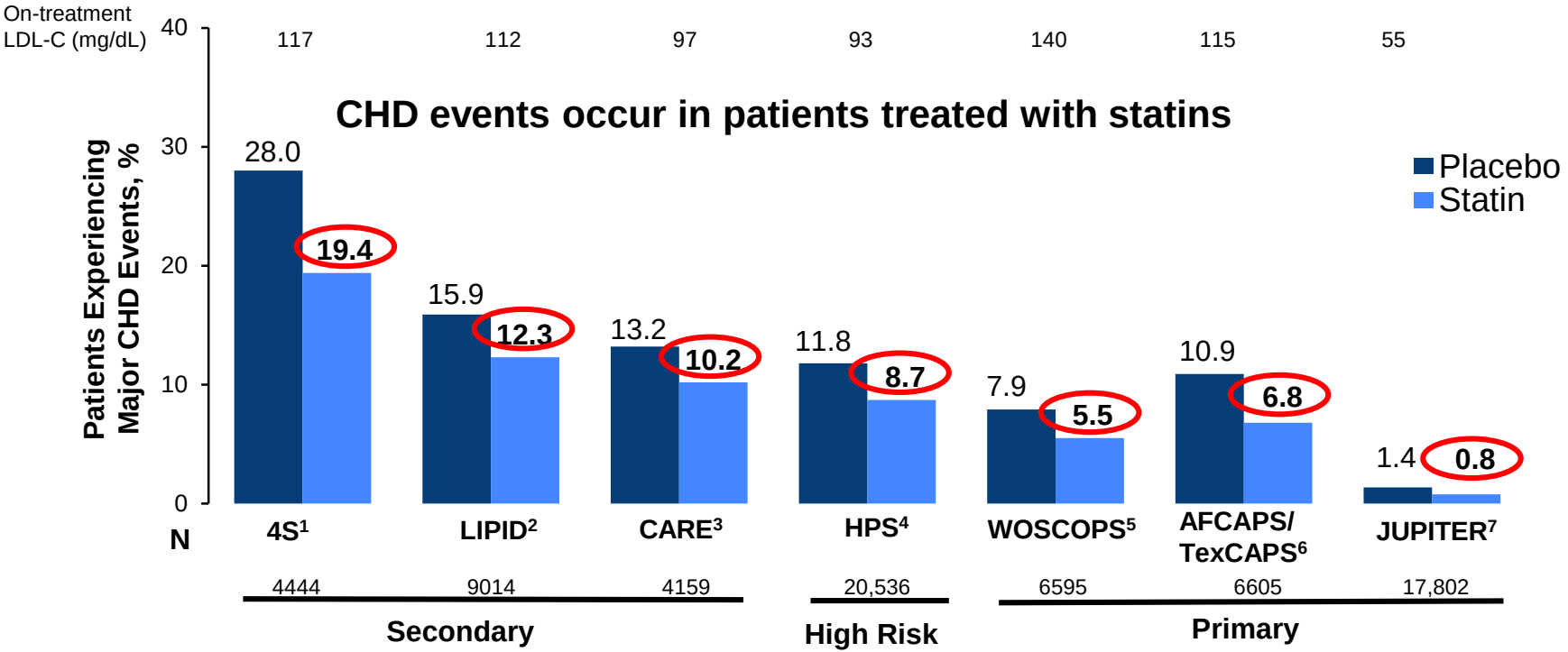


Sergio Fazio, MD, PhD
William and Sonja Connor Professor of Medicine
Director, Center for Preventive Cardiology
Knight Cardiovascular Institute
Oregon Health & Science University
Portland, OR

A 68-year-old gentleman with 30 years of continuous exposure to statin therapy and recent finding of calcified coronaries (Agatston 2450)

“I thought the statin was supposed to protect me”

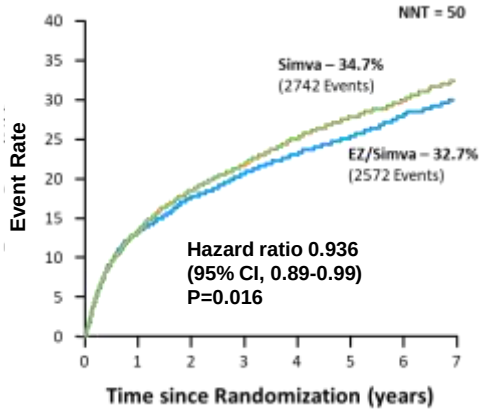
Despite ASCVD Benefit with Statin Monotherapy, Substantial Residual CV Risk Remains



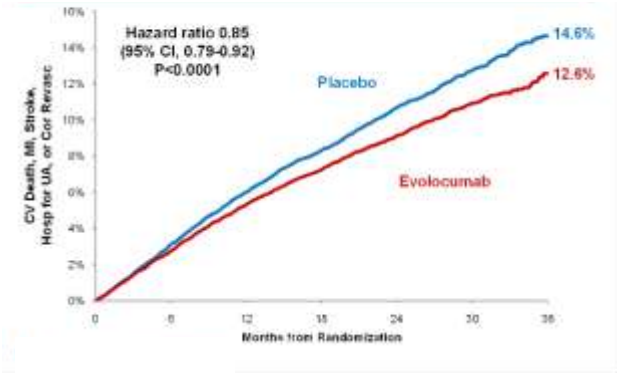
Residual CV risk may be due not only to other lipid measures that may not be controlled, but other risk factors at suboptimal control such as hypertension, diabetes, or smoking.

[1]4S Group. *Lancet.* 1994;344:1383-9. [2]LIPID Study Group. *N Engl J Med.* 1998;339:1349-57. [3]Sacks FM et al. *N Engl J Med.* 1996;335:1001-9. [4]HPS Collaborative Group. *Lancet.* 2002;360:7-22. [5]Shepherd J et al. *N Engl J Med.* 1995;333:1301-7. [6]Downs JR et al. *JAMA.* 1998;279:1615-22. [7]Ridker PM et al. *N Engl J Med.* 2008;359:2195-207.

LDL-C Lowering with Statin Adjuncts Further Reduce MACE



IMPROVE-IT[1]



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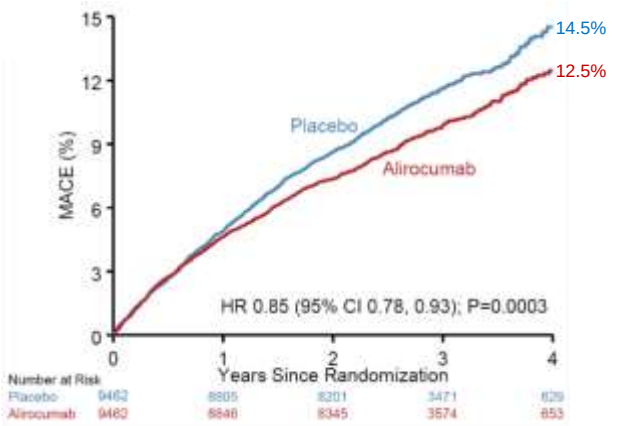
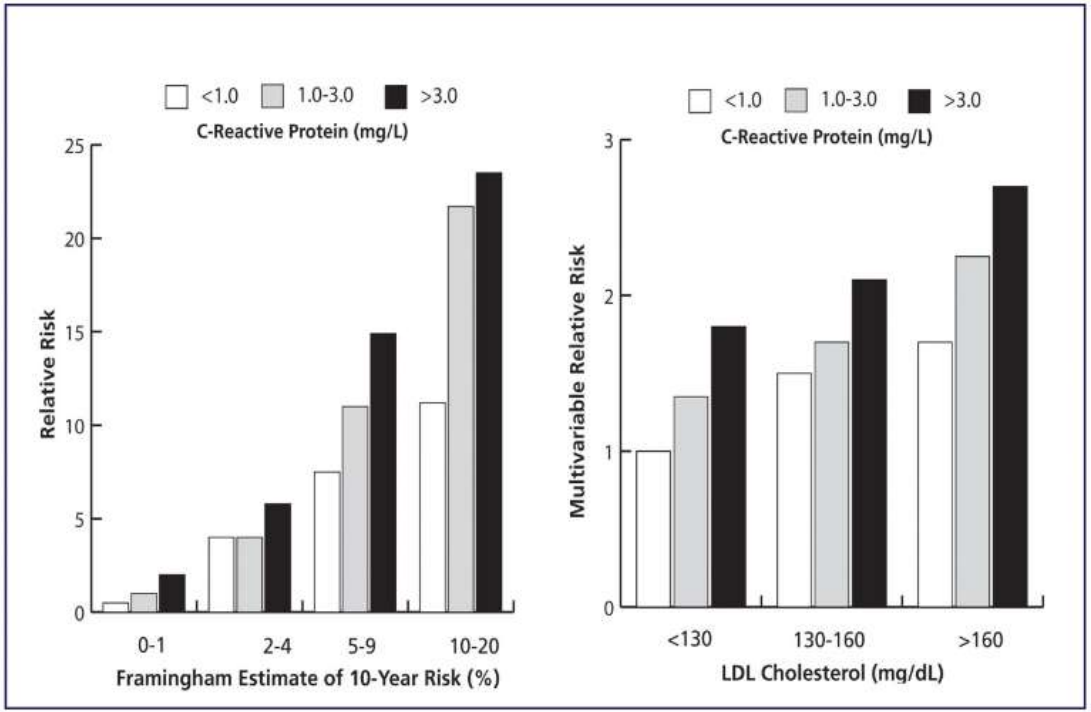


ODYSSEY Outcomes[3]

CI=confidence interval; Cor Revasc=coronary revascularization; EZ=ezetimibe; HR=hazard ratio; MACE=major adverse cardiovascular events; MI=myocardial infarction; NNT=number needed to treat; Simva=simvastatin; UA=unstable angina.

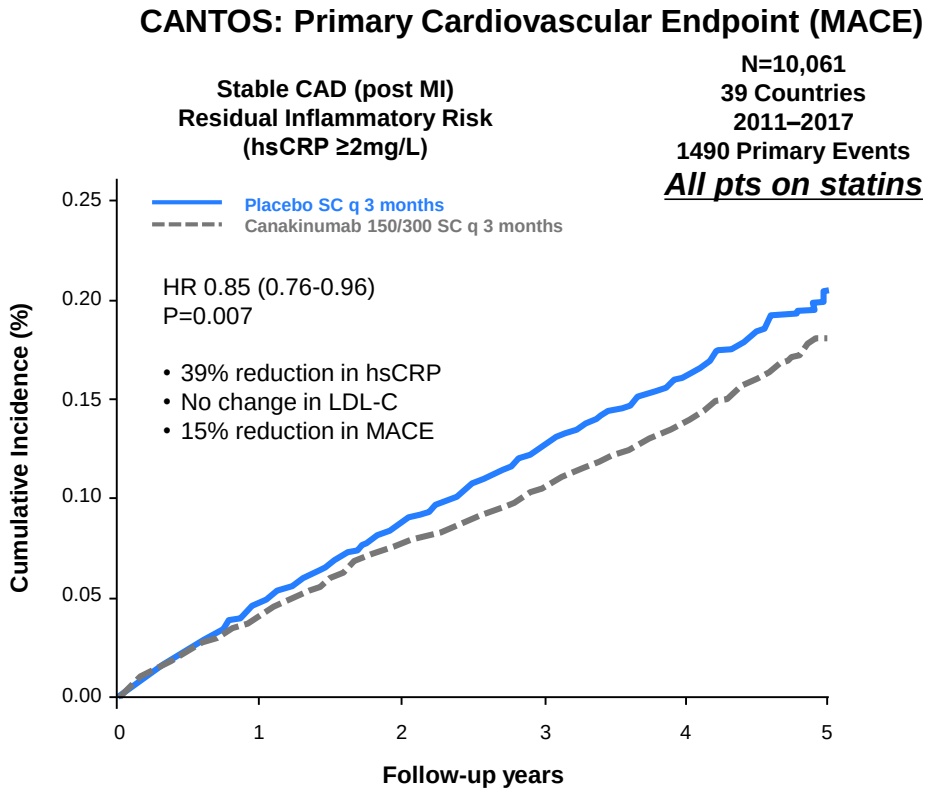
1. Cannon CP et al. *N Engl J Med*. 2015;372:2387-97. 2. Sabatine MS et al. *N Engl J Med.* 2017;376:1713-22. 3. Schwartz GG et al. *N Engl J Med*. 2018;379:2097-107.

High Sensitivity C-Reactive Protein Adds to CVD Risk Prediction



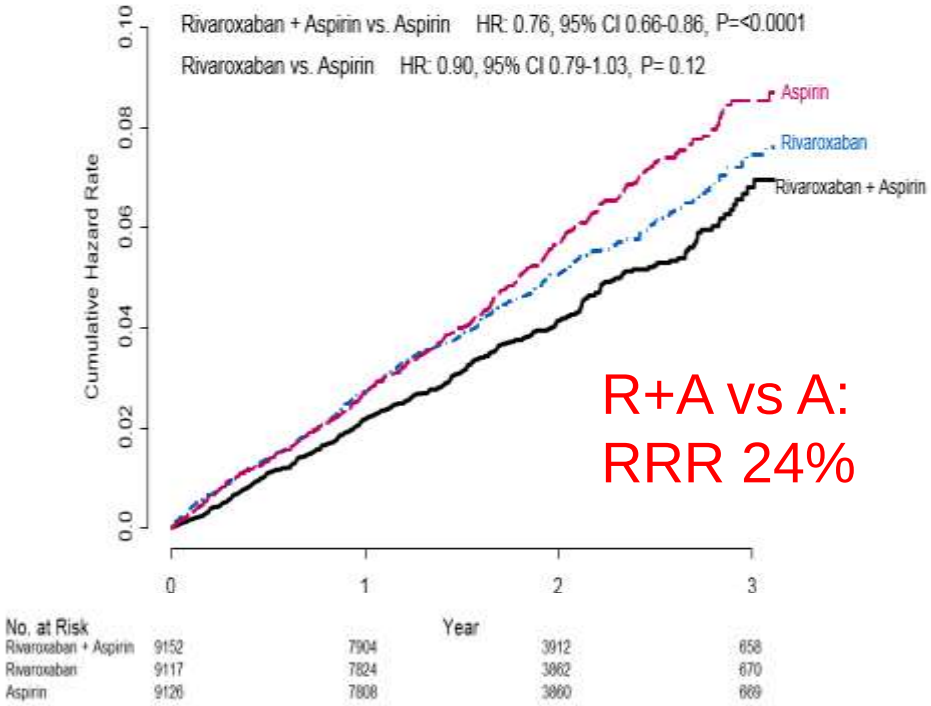
Ridker P et al. *Circulation*. 2003;108:2292-7.

CANTOS: Reducing Inflammation “Alone” (Anti IL1-beta mAb, marker hsCRP) Reduces CV Events



COMPASS: Primary Endpoint: CV Death, Stroke, MI

Documented CAD or PAD;
N=27,402



R+A vs A:
RRR 24%

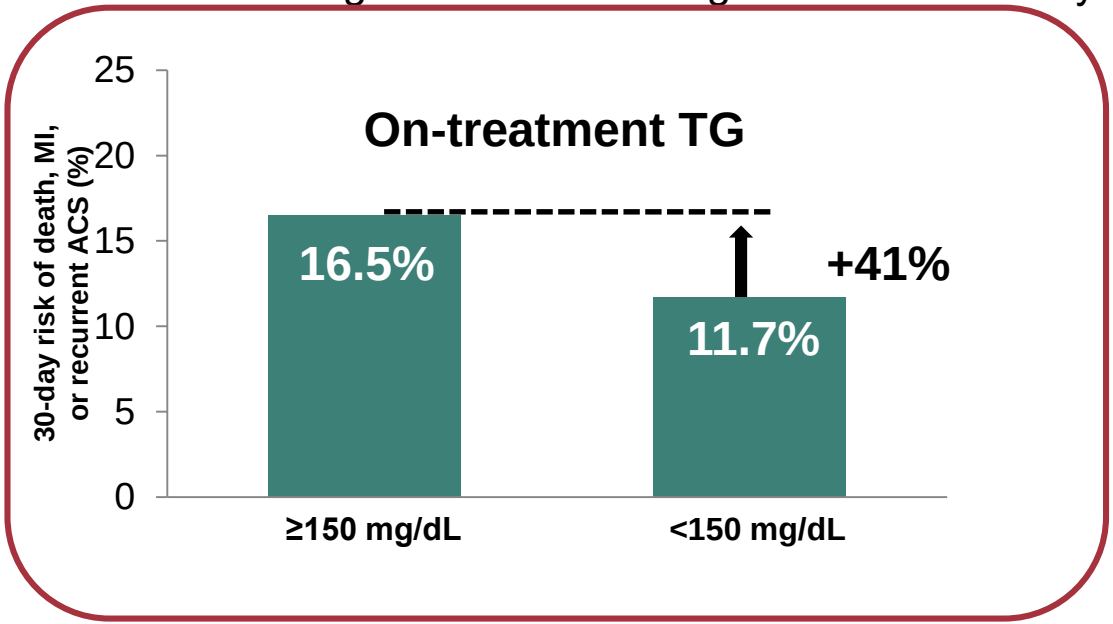
Risk Reduction of R+A vs A Rivaroxaban plus aspirin (R+A) vs aspirin (A)			
	Absolute RR	Relative RR	P
Primary outcome	↓1.3%	↓24%	<0.0001
All-cause death	↓0.7%	↓18%	0.01
Bleeding	↑1.2%	↑70%	0.01

Primary Endpoint Components				
	R + A N=9152	**A** N=9126	**Rivaroxaban + Aspirin vs Aspirin**	
Outcome	**N (%)**	**N (%)**	**HR (95% CI)**	**P**
CV death	160 (1.7%)	203 (2.2%)	0.78 (0.64-0.96)	0.02
Stroke	83 (0.9%)	142 (1.6%)	0.58 (0.44-0.76)	<0.001
MI	178 (1.9%)	205 (2.2%)	0.86 (0.70-1.05)	0.14

Eikelboom JW et al. *N Eng J Med*. 2017;377:1319-30.

Residual HTG Predicts Residual ASCVD Risk Despite *LDL-C at Goal* on Statin Monotherapy

Despite achieving LDL-C <70 mg/dL with a high-dose statin,
patients with TG ≥150 mg/dL have a 41% higher risk of coronary events*



*Death, myocardial infarction, or recurrent acute coronary syndrome; PROVE IT-TIMI 22.
Miller M et al. *J Am Coll Cardiol*. 2008;51:724-30.

Fenofibrate Outcome Studies

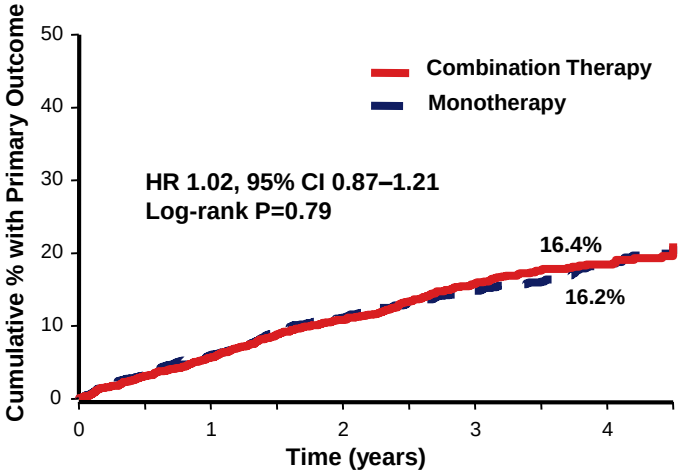
Study	CV Risk Profile	Statin Use	Daily Inter-vention	Median Baseline TG Level	Effect on TG Level	Primary Outcome	Primary Outcome Results
ACCORD (N=5518)	• T2DM • 40-79 yrs w/CVD ***or*** • 55-79 yrs w/ ≥2 CV risk factors	All pts: Open-label simvastatin (mean dose: 22 mg/d)	Fenofibrate	162 mg/dL	–26%	• Nonfatal MI or • Stroke or • CV death (Mean f/u: 4.7 yrs)	• HR=0.92* (95% CI, 0.79-1.08) • P=0.32
FIELD (N=9795**)**	• T2DM • 50-75 yrs	Added during study in 2547 pts (26%)	Fenofibrate	154 mg/dL	–30% (at 1 yr)	• Nonfatal MI or • CHD death Median f/u: 5 yrs	• HR=0.89* (95% CI, 0.75-1.05) • P=0.16

***Note that *post hoc* analysis for both studies found statistically significant benefit in the subgroup of patients with TG≥204 mg/dL & HDL-C ≤34 md/dL (Sacks FM et al. *N Engl J Med*. 2010;363:692-4).**

ACCORD Study Group et al. *N Engl J Med*. 2010;362:1563-74. Keech A et al. *Lancet*. 2005;366:1849-61.

Niacin Outcome Studies

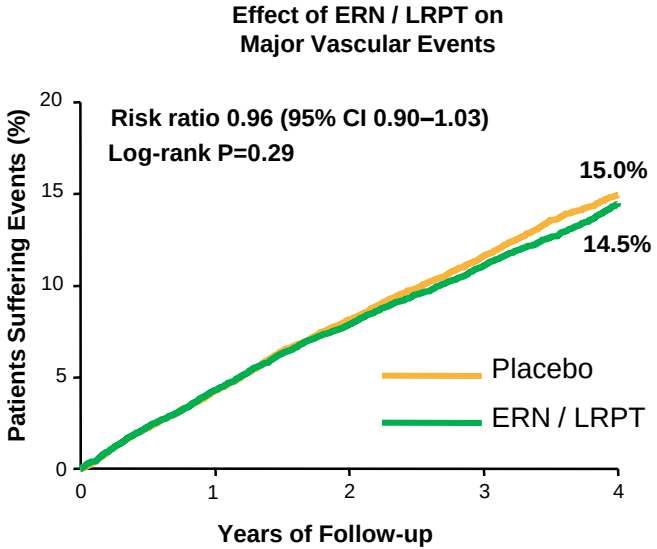
AIM-HIGH *(–29% TG)*



N at risk					
Monotherapy	1696	1581	1381	910	436
Combination Therapy	1718	1606	1366	903	428

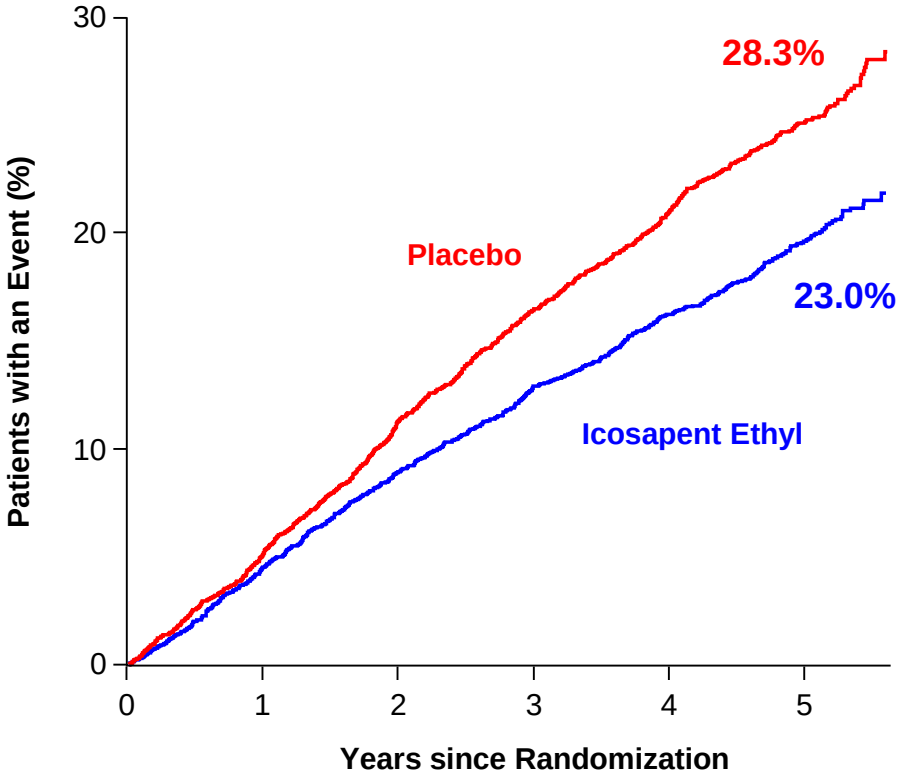
Boden WE et al. *N Engl J Med.* 2011;365:2255-67

HPS2-THRIVE *(–26% TG)*



HPS2-THRIVE Collaborative Group. *N Engl J Med*. 2014;371:203-12.

REDUCE-IT Study of EPA: Effect on the Primary Endpoint
(CV Death, MI, Stroke, Coronary Revasc, 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; CI=confidence interval; Revasc=revascularization; RRR=relative risk reduction.

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

CVOTs in Diabetes

Study (N)	Drug (Class)	Primary endpoint	Hazard ratio
EMPA-REG[1] 7,020	Empagliflozin SGLT-2	CV death, non-fatal myocardial infarction, or non-fatal stroke	0.86, (95% CI, 0.74, 0.99) P=0.0382
LEADER[2] 9,340	Liraglutide GLP-1 RA		0.87, (95% CI, 0.78-0.97) P=0.001 for non-inferiority P=0.01 for superiority
SUSTAIN-6[3] 3,297	Semaglutide GLP-1 RA		0.74, (95% CI, 0.58–0.95) P<0.001 for noninferiority P=0.02 for superiority
CANVAS[4] 10,134	Canagliflozin SGLT-2		0.86, (95% CI, 0.75-0.97) P<0.0001 for noninferiority P=0.0158 for superiority
HARMONY[5] 10,793	Albiglutide GLP-1 RA		0.78, (95% CI, 0.68–0.90) P<0.0001 for non-inferiority P=0.0006 for superiority
DECLARE TIMI-58[6] 17,160	Dapagliflozin SGLT-2	CV death, non-fatal myocardial infarction, or ischemic stroke	0.93, (95% CI, 0.84-1.03) P<0.001 for noninferiority P=0.17 for superiority

[1]Zinman B et al. *N Engl J Med.* 2015;373:2117-28. [2]Marso SP et al. *N Engl J Med.* 2016;375:311-22. [3]Marso SP et al. *N Engl J Med.* 2016;375:1834-44. [4]Neal B et al. *N Engl J Med.* 2017;377:644-57. [5] Hernandez AF et al. *Lancet.* 2018;392;1519-29. [6]Wiviott SD et al. *N Engl J Med.* 2019;380:347-57.

Mechanism-Based Statin-Adjunct Therapy for ASCVD Prevention

Prior ASCVD Event or High-Risk 1º Prevention: On Aggressive Statin MonoRx

Residual Risk Factors

↑Pro-atherogenic factor	Cholesterol	Inflammation	Thrombosis	Triglycerides	Lp(a)
Biomarker	LDL-C >100 mg/dL	hsCRP >2 mg/L	No established Biomarker	TG >135 mg/dL (HDL <40 mg/dL)	Lp(a) >50 mg/dL
Intervention	Ezetimibe or PCSK9i	Anti-Inflammatory (IL-inhibition)	Anti-coagulant or Anti-platelet	RX Omega-3 EPA (EPA+DHA, pemafibrate?)	Lp(a) ASO
Randomized Trial Evidence	IMPROVE-IT FOURIER SPIRE ODYSSEY	CANTOS (CIRT *negative*)	COMPASS PEGASUS	REDUCE-IT	Planned

REDUCE-IT?

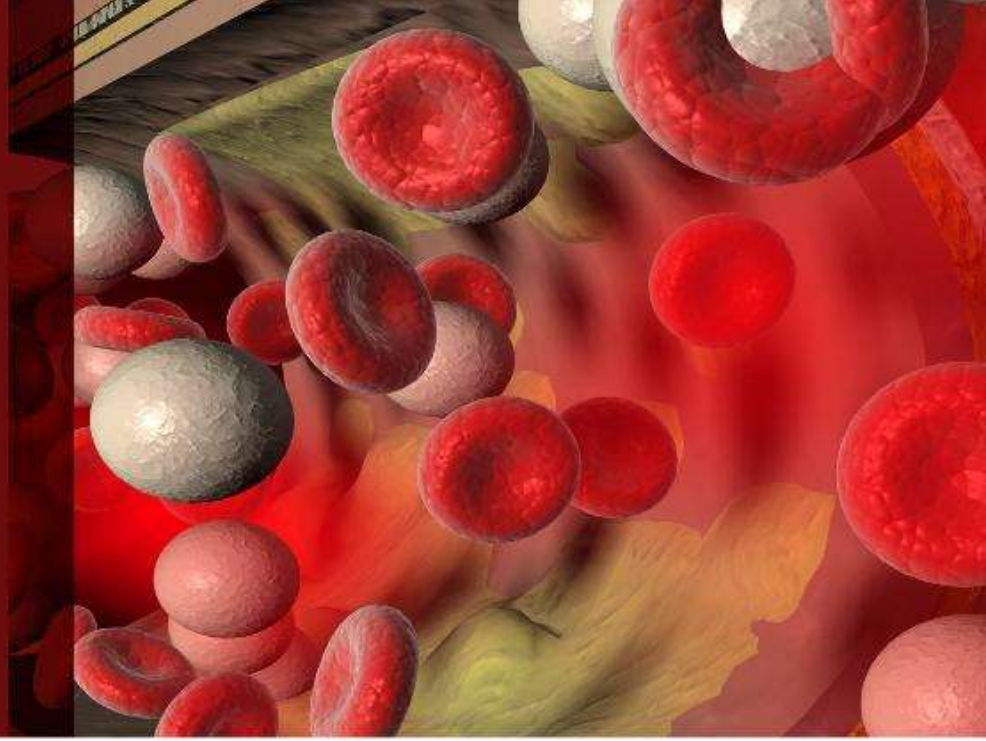
ASO=antisense oligonucleotide.

After Ridker PM. *J Am Coll Cardiol*. 2018;72:3320-31.

This evening we will…..

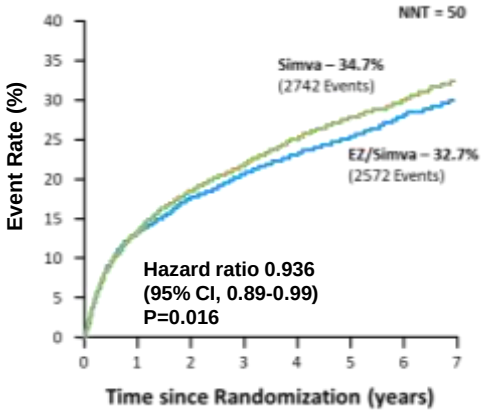
- Discuss different approaches leading to additional CVD risk reduction in statin takers
- Evaluate the mechanisms by which EPA reduces CVD risk in high TG patients
- Compare EPA to other TG-lowering agents for CVD risk reduction
- Determine the value of additional LDL lowering vs use of EPA in patients with elevated residual risk
- Position the role of inflammation in CVD risk assessment and management

REDUCE-IT and Omega-3 Trials

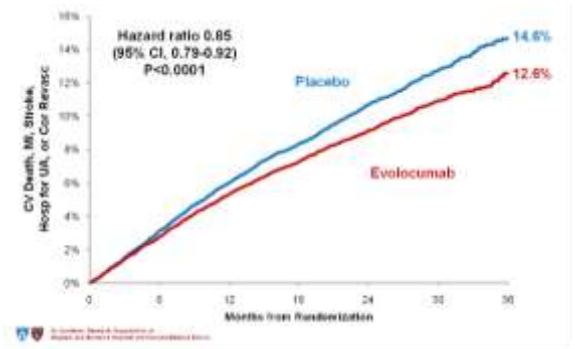


Michael Miller, MD, FACC, FAHA
Professor of Cardiovascular Medicine
University of Maryland School of Medicine
Baltimore, MD

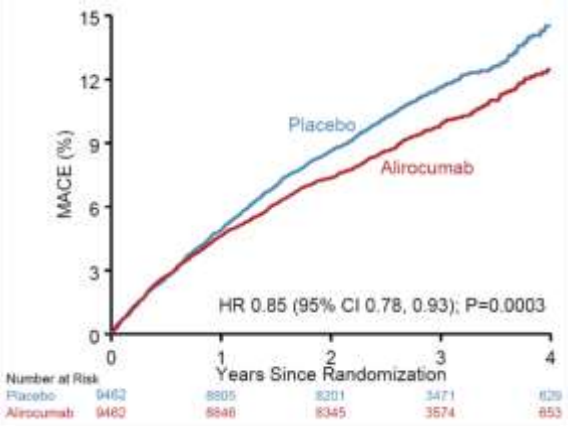
Successful Statin Add-on Trials (5–15% RRR)



IMPROVE-IT[1]



FOURIER[2]

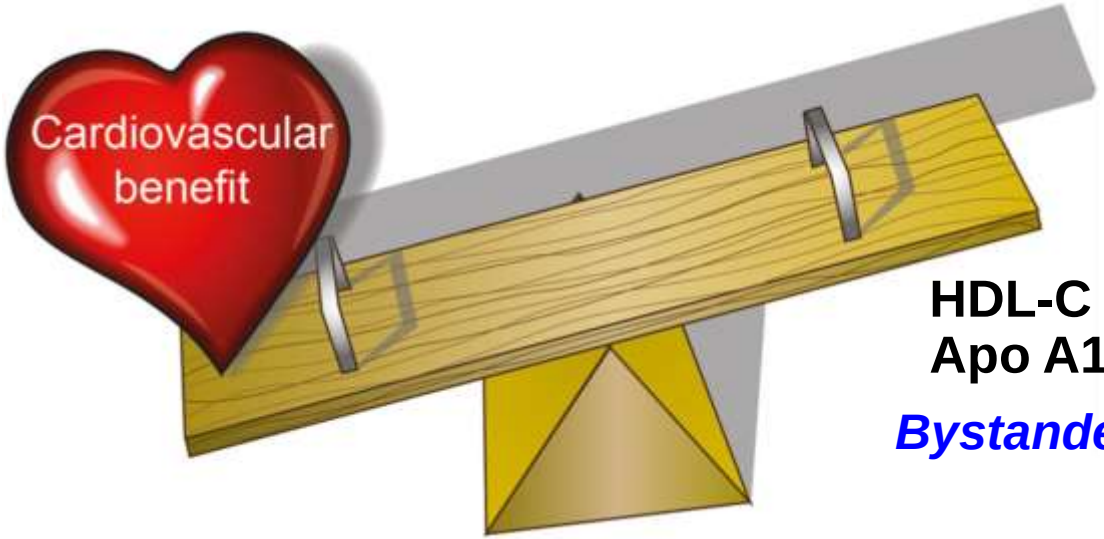


ODYSSEY Outcomes[3]

CI=confidence interval; Cor Revasc=coronary revascularization; EZ=ezetimibe; HR=hazard ratio; MACE=major adverse cardiovascular events; MI =myocardial infarction; NNT=number needed to treat; Simva=simvastatin; UA unstable angina.

1. Cannon CP et al. *N Engl J Med*. 2015;372:2387-97.
2. Sabatine MS et al. *N Engl J Med.* 2017;376:1713-22.
3. Steg PG. Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab - ODYSSEY OUTCOMES. March 10, 2018. http://www.acc.org/latest-in-cardiology/clinical-trials/2018/03/09/08/02/odyssey-outcomes.

Triglycerides as a Causal Risk Factor?



HDL-C
Apo A1

Bystanders?

Triglyceride-rich lipoproteins
Apo C3, Apo A5, AngPTL4

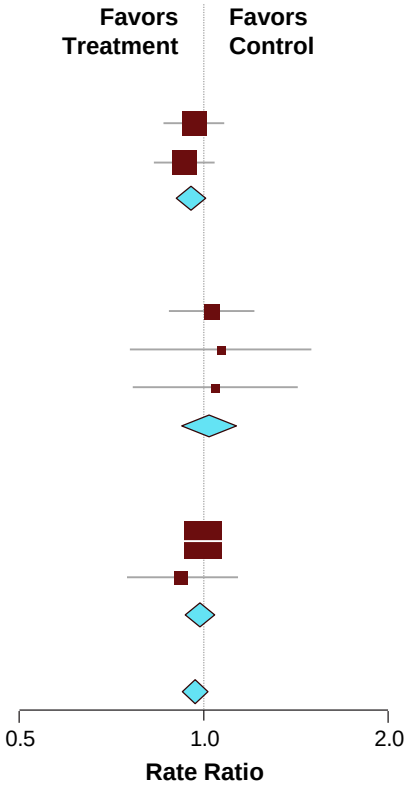
Causal risk factors?

Adapted from Libby P. *Eur Heart J*. 2015;36:774-6.

European Heart Journal

Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

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=0.12
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=0.60
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=0.60
Any major vascular event	5930 (15.2)	6071 (15.6)	0.97 (0.93–1.01)
			P=0.10



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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*

ASCEND: A randomized trial of omega-3 fatty acids (fish oil) versus placebo for primary cardiovascular prevention in 15,480 patients with diabetes

Jane Armitage and Louise Bowman

on behalf of the ASCEND Study Collaborative Group

Funded by British Heart Foundation, UK Medical Research Council
and support from Abbott, Bayer, Mylan and Solvay
Designed, conducted and analysed independently of the funders
University of Oxford is the trial sponsor

ESC Congress
Munich 2018

British Heart Foundation

MRC Population Health Research Unit

University of Oxford

ASCEND Trial Design

Eligibility: Age ≥40 years; any DIABETES; no prior CV disease

Participants: 15,480 UK patients

Randomization: Omega-3 fatty acids 1 g capsule/day vs placebo
(and aspirin 100 mg daily vs placebo)

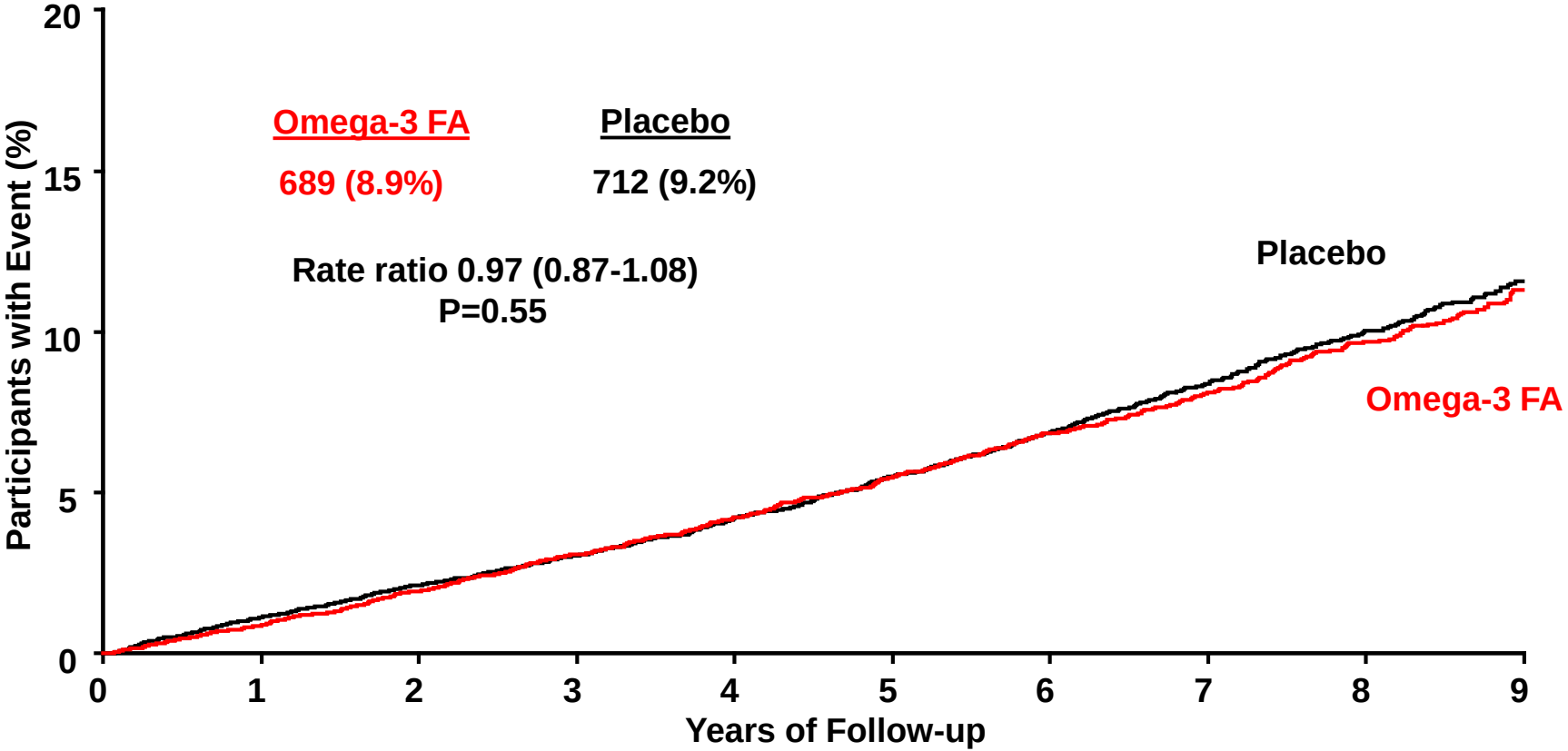
Follow-up: Mean 7.4 years; >99% complete for morbidity & mortality

Adherence: Average adherence to omega-3 capsules 77%

Streamlined methods: mail-based (questionnaires & study treatment);
no study clinics; 2x2 factorial design; highly cost-effective

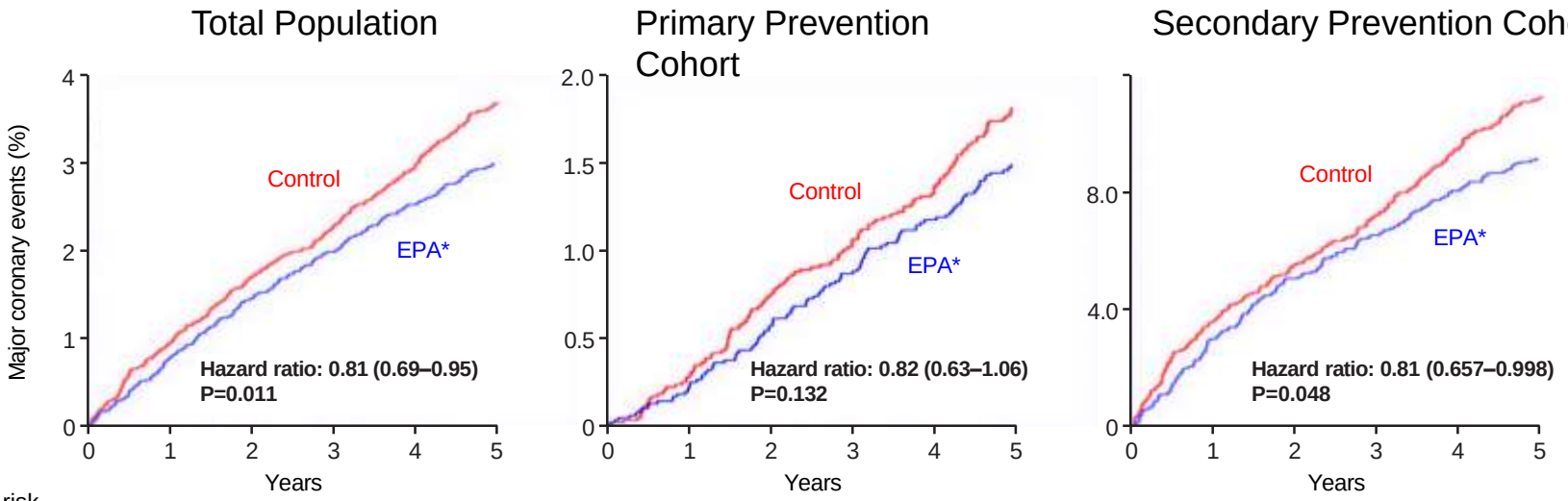
ASCEND Study Collaborative Group. *Trials*. 2016;17:286 / *Am Heart J*. 2018;198:135-44.

Effect of Omega-3 FA Supplements on Serious Vascular Events



JELIS Suggests CV Risk Reduction with EPA in Japanese Hypercholesterolemic Patients

Kaplan-Meier Estimates of Incidence of Coronary Events



Numbers at risk						
Control group	9319	8931	8671	8433	8192	7958
Treatment group	9326	8929	8658	8389	8153	7924

7478	7204	7103	6841	6678	6508
7503	7210	7020	6823	6649	6482

1841	1727	1658	1592	1514	1450
1823	1719	1638	1566	1504	1442

*1.8 g/day

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

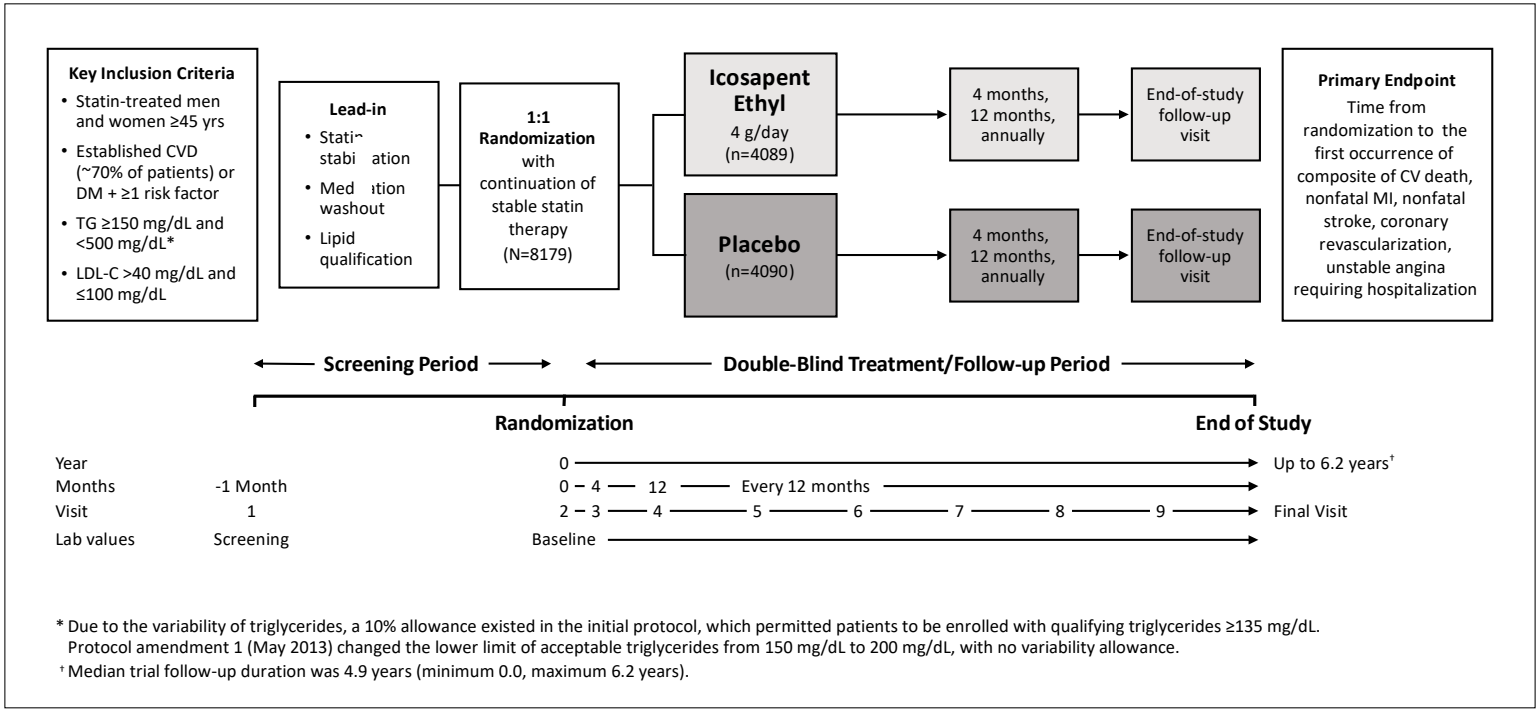
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 3, 2019 VOL. 380 NO. 1

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

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 from Bhatt DL et al. *Clin Cardiol*. 2017;40:138-48. REDUCE-IT ClinicalTrials.gov number, NCT01492361.

Key Inclusion Criteria – REDUCE-IT

1. Age ≥45 years with established CVD (Secondary Prevention Cohort) *or* ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)

2. Fasting TG levels ≥150 mg/dL and <500 mg/dL*

3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

*Due to the variability of triglycerides, a 10% allowance existing 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.

Adapted from Bhatt DL et al. *Clin Cardiol*. 2017;40:138-48.

Key Exclusion Criteria

1. Severe (NYHA class IV) heart failure
2. Severe liver disease
3. History of pancreatitis
4. Hypersensitivity to fish and/or shellfish

Adapted from Bhatt DL et al. *Clin Cardiol*. 2017;40:138-48.

Key Baseline Characteristics

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age (years), Median (Q1-Q3)	64.0 (57.0 - 69.0)	64.0 (57.0 - 69.0)
Female, n (%)	1162 (28.4%)	1195 (29.2%)
Non-White, n (%)	398 (9.7%)	401 (9.8%)
Westernized Region, n (%)	2906 (71.1%)	2905 (71.0%)
CV Risk Category, n (%)		
Secondary Prevention Cohort	2892 (70.7%)	2893 (70.7%)
Primary Prevention Cohort	1197 (29.3%)	1197 (29.3%)
Ezetimibe Use, n (%)	262 (6.4%)	262 (6.4%)
Statin Intensity, n (%)		
Low	254 (6.2%)	267 (6.5%)
Moderate	2533 (61.9%)	2575 (63.0%)
High	1290 (31.5%)	1226 (30.0%)
Type 2 Diabetes, n (%)	2367 (57.9%)	2363 (57.8%)
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5 - 46.0)	40.0 (35.0 - 46.0)
LDL-C (mg/dL), Median (Q1-Q3)	74.0 (61.5 - 88.0)	76.0 (63.0 - 89.0)
Triglycerides Category		
<150 mg/dL	412 (10.1%)	429 (10.5%)
150 to <200 mg/dL	1193 (29.2%)	1191 (29.1%)
≥200 mg/dL	2481 (60.7%)	2469 (60.4%)

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

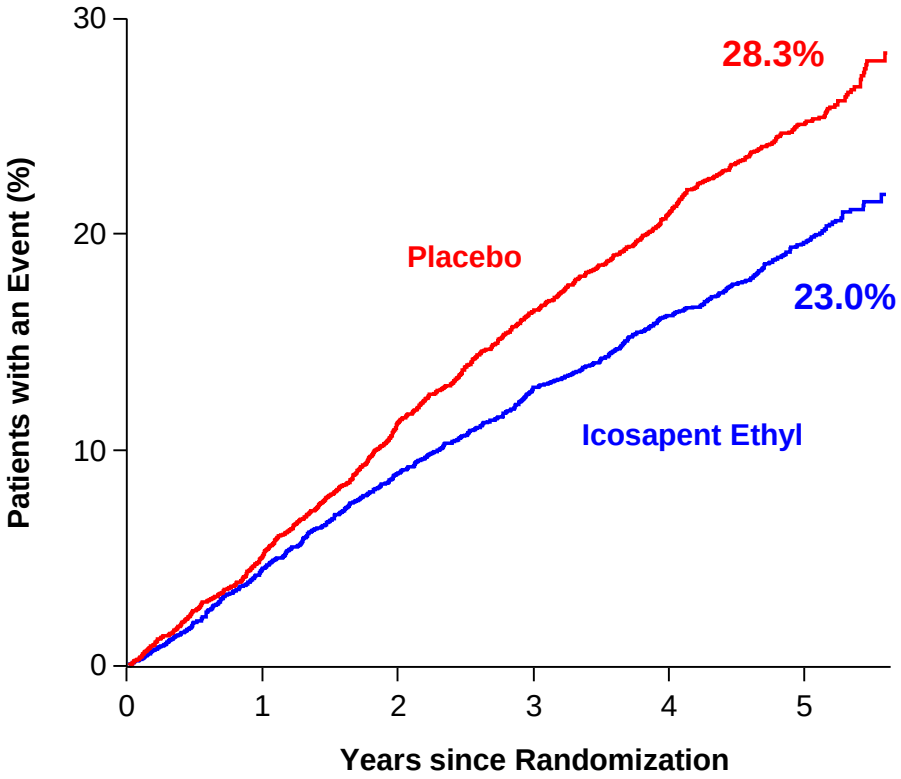
Effects on Biomarkers from Baseline to Year 1

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

Primary Endpoint:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75

(95% CI, 0.68–0.83)

RRR = 24.8%

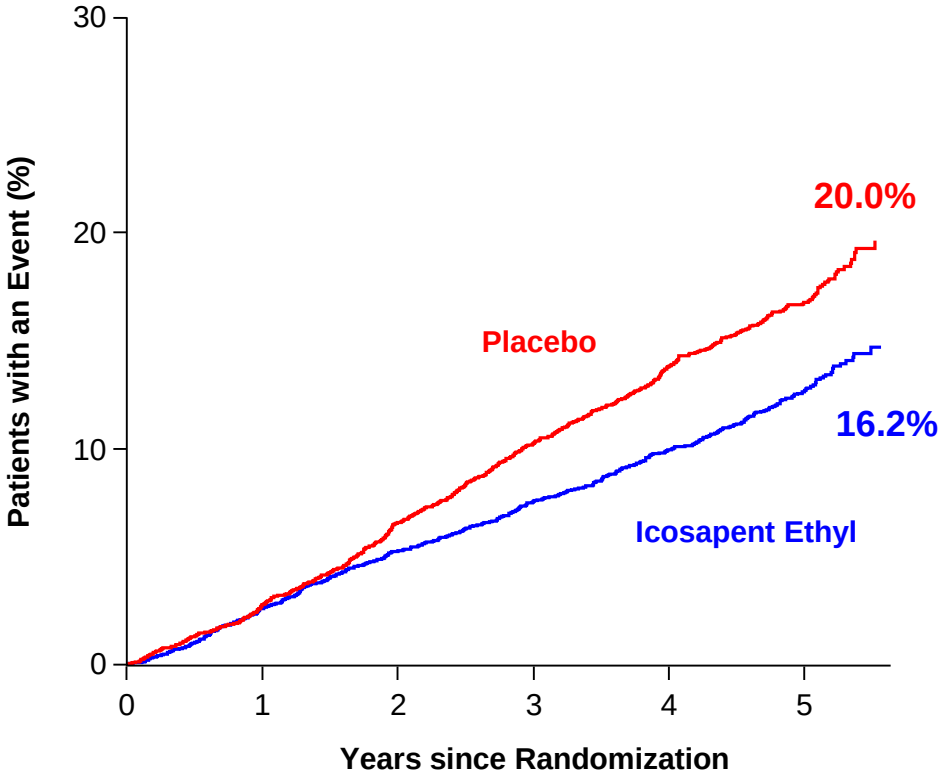
ARR = 4.8%

NNT = 21 (95% CI, 15–33)

P=0.00000001

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

Key Secondary Endpoint:
CV Death, MI, Stroke



Hazard Ratio, 0.74

(95% CI, 0.65–0.83)

RRR = 26.5%

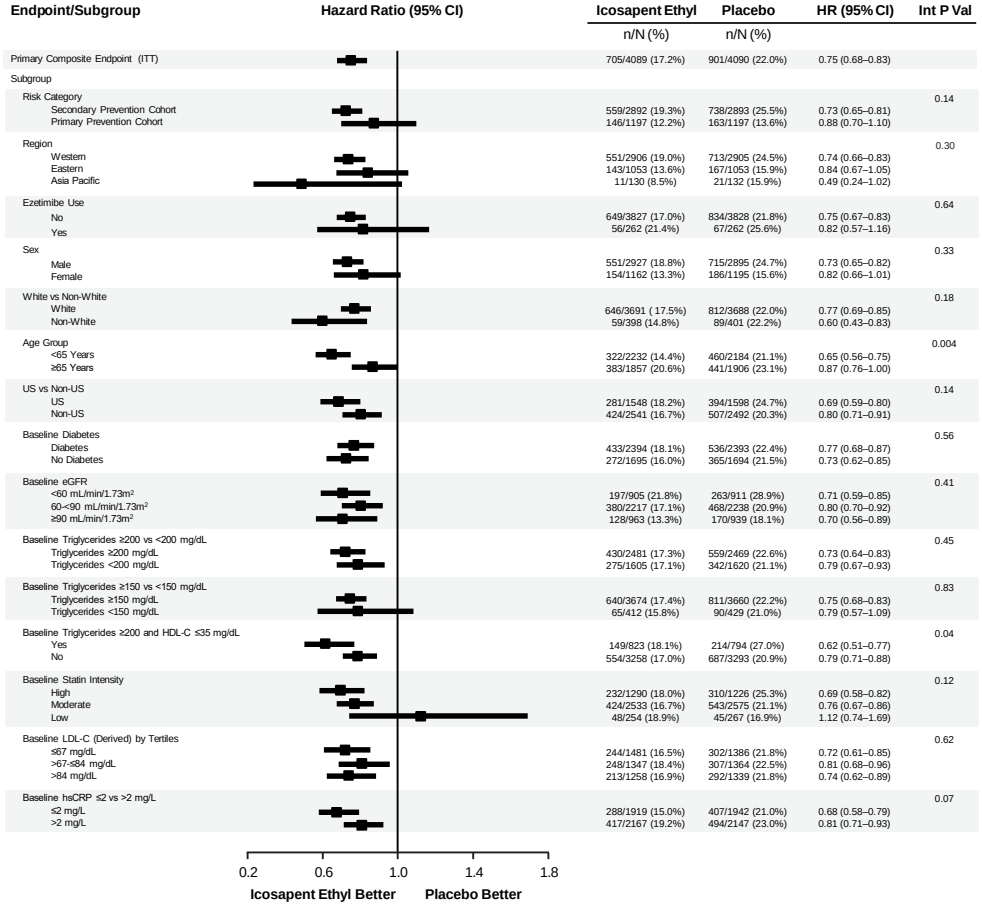
ARR = 3.6%

NNT = 28 (95% CI, 20–47)

P=0.0000006

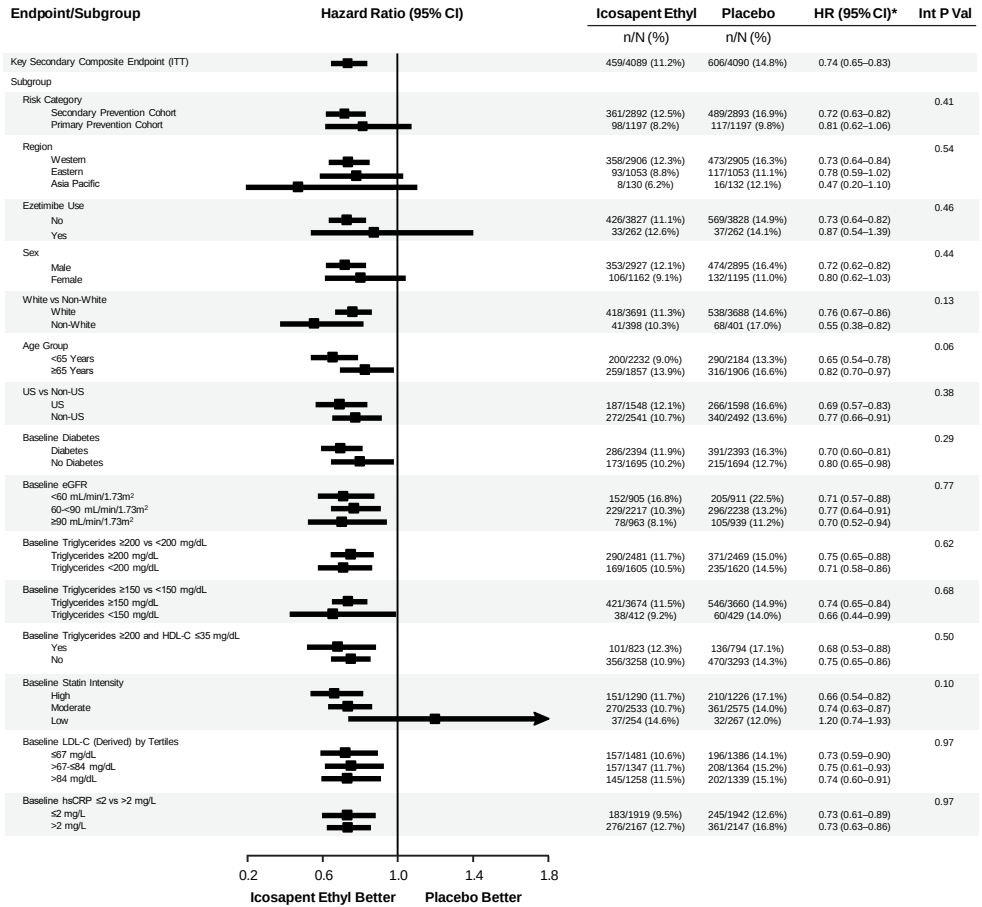
Bhatt DL et al. *N Engl J Med*. 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

Primary Endpoint in Subgroups



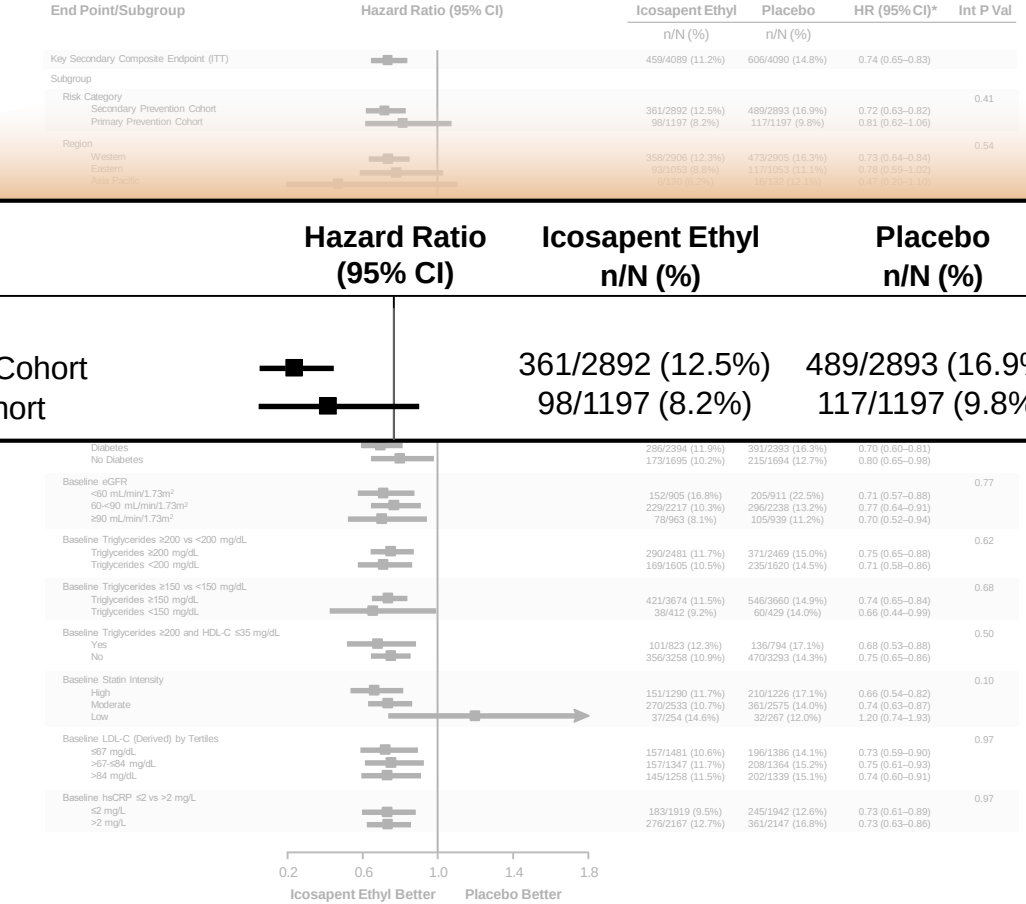
Bhatt DL et al. *N Engl J Med*. 2019; 380:11-22.

Key Secondary Endpoint in Subgroups



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

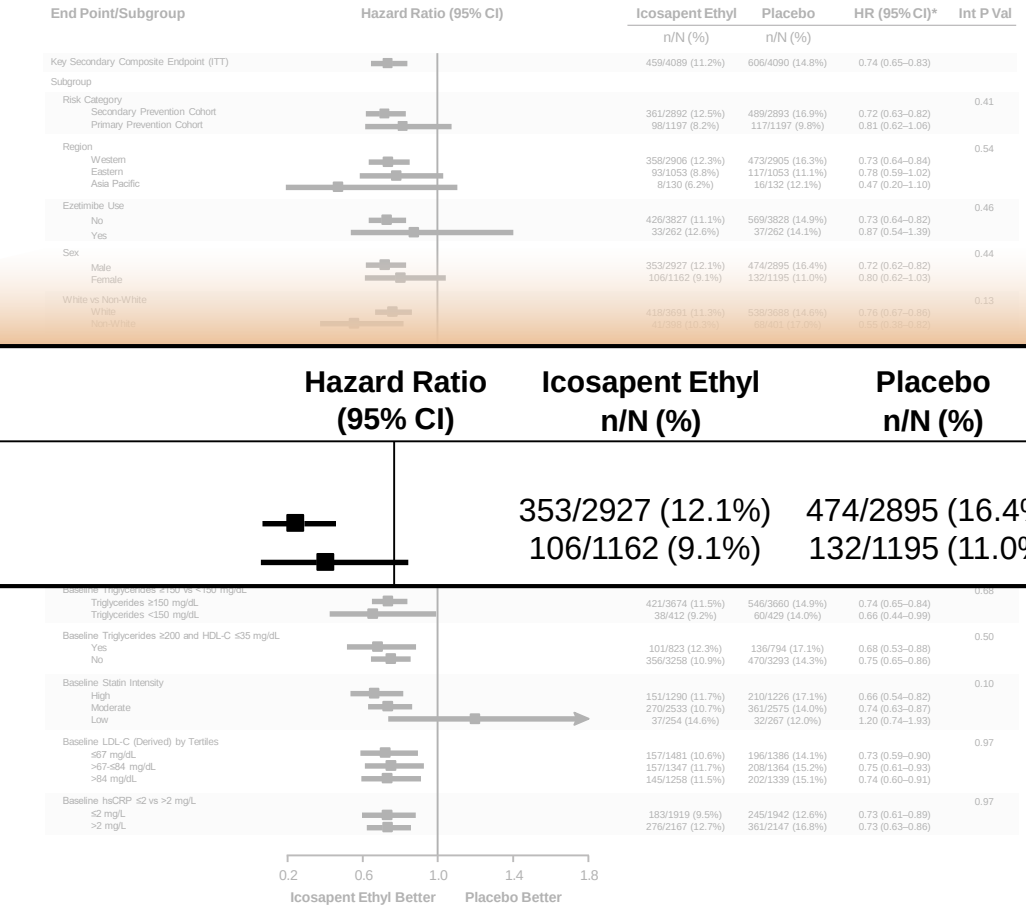
Key Secondary Endpoint in Subgroups



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Risk Category					0.41
Secondary Prevention Cohort		361/2892 (12.5%)	489/2893 (16.9%)	0.72 (0.63–0.82)	
Primary Prevention Cohort		98/1197 (8.2%)	117/1197 (9.8%)	0.81 (0.62–1.06)	

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

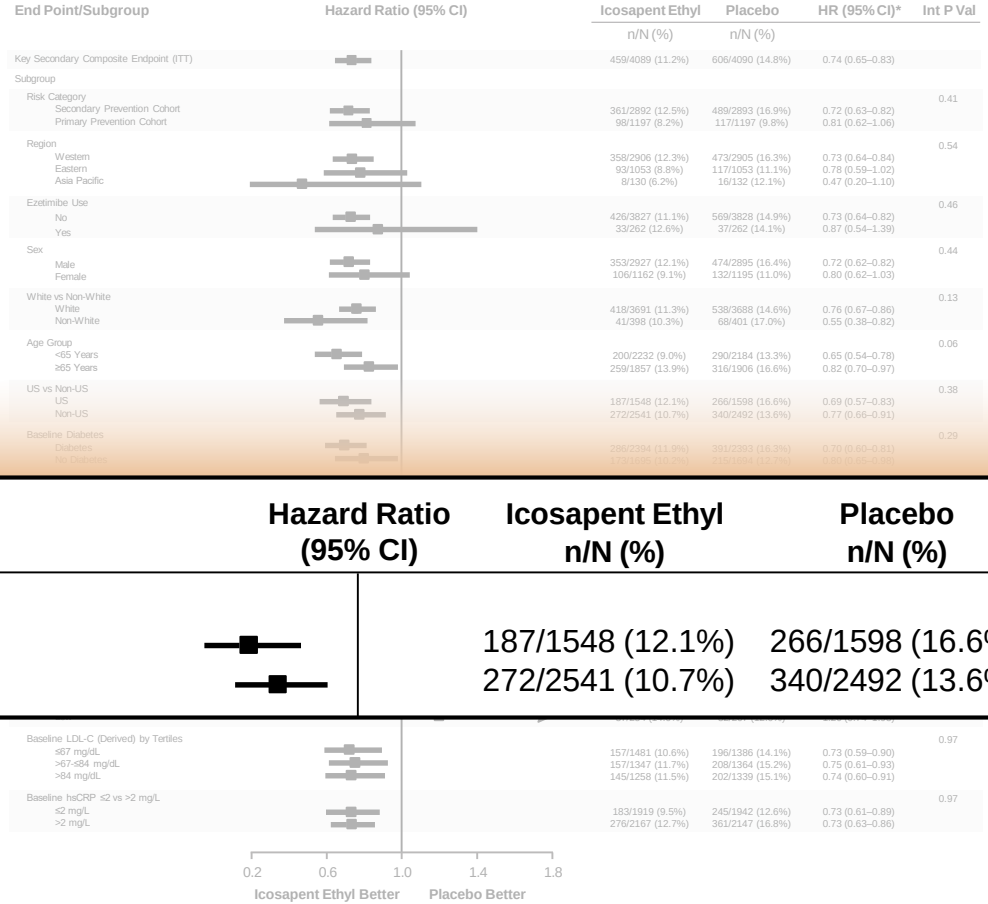
Key Secondary Endpoint in Subgroups



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Sex					0.44
Male		353/2927 (12.1%)	474/2895 (16.4%)	0.72 (0.62–0.82)	
Female		106/1162 (9.1%)	132/1195 (11.0%)	0.80 (0.62–1.03)	

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

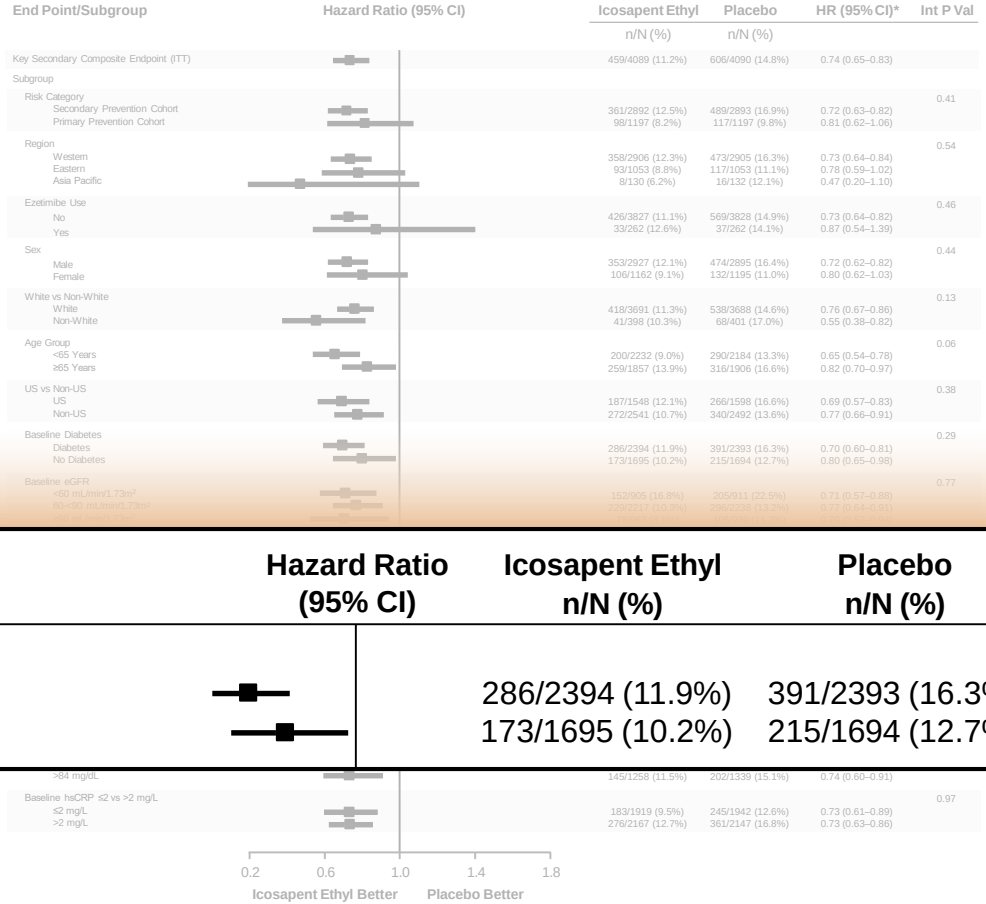
Key Secondary Endpoint in Subgroups



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
US vs Non-US					0.38
US		187/1548 (12.1%)	266/1598 (16.6%)	0.69 (0.57–0.83)	
Non-US		272/2541 (10.7%)	340/2492 (13.6%)	0.77 (0.66–0.91)	

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

Key Secondary Endpoint in Subgroups



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Diabetes					0.29
Diabetes		286/2394 (11.9%)	391/2393 (16.3%)	0.70 (0.60–0.81)	
No Diabetes		173/1695 (10.2%)	215/1694 (12.7%)	0.80 (0.65–0.98)	

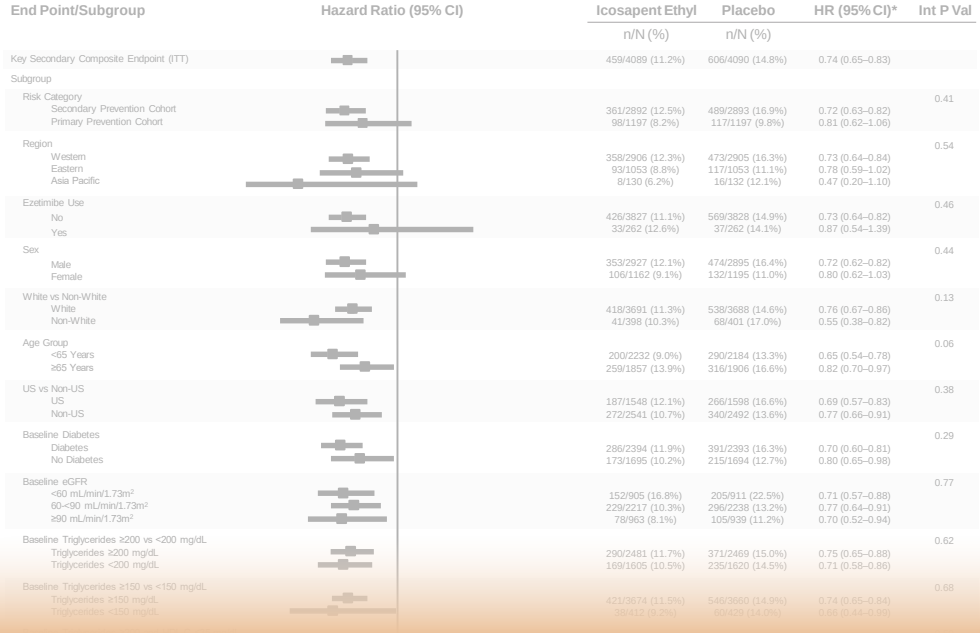
Bhatt DL et al. *N Engl J Med*. 2019; 380:11-22.

Key Secondary Endpoint in Subgroups

Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Triglycerides ≥200 vs <200 mg/dL					0.62
Triglycerides ≥200 mg/dL		290/2481 (11.7%)	371/2469 (15.0%)	0.75 (0.65–0.88)	
Triglycerides <200 mg/dL		169/1605 (10.5%)	235/1620 (14.5%)	0.71 (0.58–0.86)	

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

Key Secondary Endpoint in Subgroups

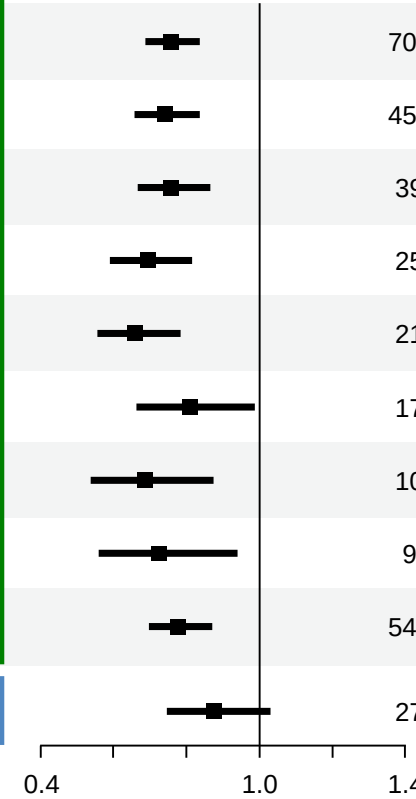


Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Triglycerides ≥150 vs <150 mg/dL					0.68
Triglycerides ≥150 mg/dL		421/3674 (11.5%)	546/3660 (14.9%)	0.74 (0.65–0.84)	
Triglycerides <150 mg/dL		38/412 (9.2%)	60/429 (14.0%)	0.66 (0.44–0.99)	

Icosapent Ethyl Better Placebo Better

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

Prespecified Hierarchical Testing



Endpoint	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)		705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%	<0.001
Key Secondary Composite (ITT)		459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction		392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%	<0.001
Fatal or Nonfatal Myocardial Infarction		250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%	<0.001
Urgent or Emergency Revascularization		216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%	<0.001
Cardiovascular Death		174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%	0.03
Hospitalization for Unstable Angina		108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%	0.002
Fatal or Nonfatal Stroke		98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke		549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%	<0.001
Total Mortality		274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%	0.09

RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

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

REDUCE-IT Tertiary Endpoints:
Cardiac Arrest, Sudden Cardiac Death, Arrhythmias

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)
Cardiac Arrest	**22/4089 (0.5%)**	**42/4090 (1.0%)**	**0.52 (0.31, 0.86)**
Sudden Cardiac Death	**61/4089 (1.5%)**	**87/4090 (2.1%)**	**0.69 (0.50, 0.96)**
Cardiac Arrhythmias Requiring Hospitalization of ≥ 24 Hours	188/4089 (4.6%)	154/4090 (3.8%)	1.21 (0.97, 1.49)

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

REDUCE-IT Tertiary Endpoints: Revascularization

Revascularization Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)
Coronary	**376/4089 (9.2%)**	**544/4090 (13.3%)**	**0.66 (0.58, 0.76)**
Emergency	**41/4089 (1.0%)**	**65/4090 (1.6%)**	**0.62 (0.42, 0.92)**
Urgent	**181/4089 (4.4%)**	**268/4090 (6.6%)**	**0.66 (0.54, 0.79)**
Elective	**194/4089 (4.7%)**	**278/4090 (6.8%)**	**0.68 (0.57, 0.82)**
Carotid Revascularization	31/4089 (0.8%)	26/4090 (0.6%)	1.18 (0.70, 1.98)
Salvage Revascularization	0/4089 (0.0%)	2/4090 (0.0%)	0.00 (0.00, -)

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

Treatment-emergent Adverse Event of Interest: Serious Bleeding

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Bleeding related disorders	111 (2.7%)	85 (2.1%)	0.06
Gastrointestinal bleeding	62 (1.5%)	47 (1.1%)	0.15
Central nervous system bleeding	14 (0.3%)	10 (0.2%)	0.42
Other bleeding	41 (1.0%)	30 (0.7%)	0.19

- No fatal bleeding events in either group
- Adjudicated hemorrhagic stroke - no significant difference between treatments (13 icosapent ethyl vs 10 placebo; P=0.55)

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

Adjudicated Events: Hospitalization for Atrial Fibrillation or Atrial Flutter

Primary System Organ Class Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Positively Adjudicated Atrial Fibrillation/Flutter[1]	127 (3.1%)	84 (2.1%)	0.004

Note: Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N).
All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
[1] Includes positively adjudicated Atrial Fibrillation/Flutter clinical events by the Clinical Endpoint Committee (CEC). P value was based on stratified log-rank test.

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

Conclusions

Compared with placebo, icosapent ethyl 4 g/day significantly reduced important CV events by **25%**, including:

- **20%** reduction in death due to cardiovascular causes
- **31%** reduction in heart attack
- **28%** reduction in stroke

Low rate of adverse effects, including:

- Small but significant increase in atrial fibrillation/flutter
- Non-statistically significant increase in serious bleeding

Consistent efficacy across multiple subgroups

- Including baseline triglycerides from 135-500 mg/dL
- Including secondary and primary prevention cohorts

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

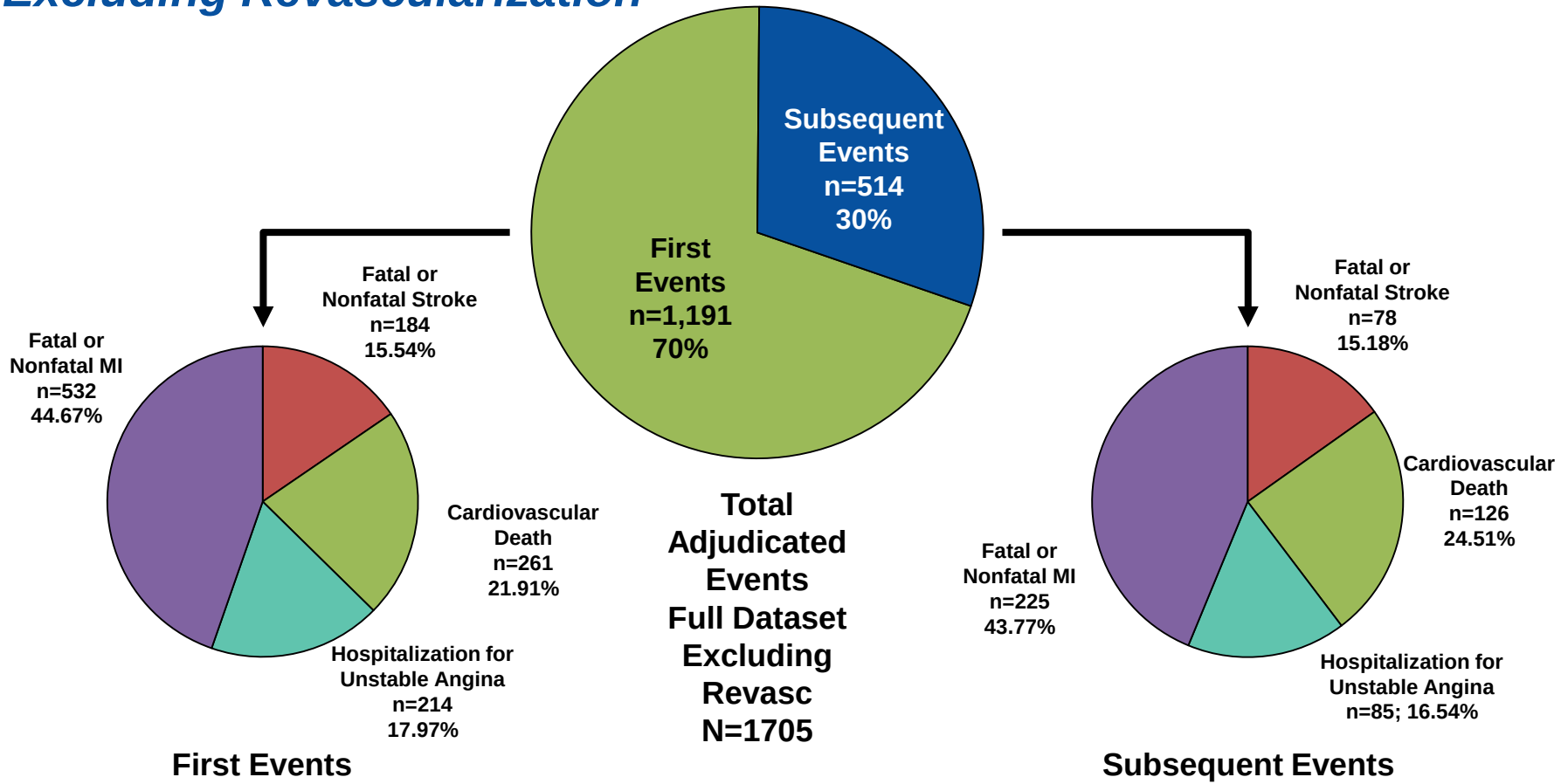
Effects of Icosapent Ethyl on Total Ischemic Events: From REDUCE-IT

Deepak L. Bhatt, MD, MPH,[a] Ph. Gabriel Steg, MD,[b,c] Michael Miller, MD,[d] Eliot A. Brinton, MD,[e] Terry A. Jacobson, MD,[f] Steven B. Ketchum, PhD,[g] Ralph T. Doyle, Jr, BA,[g] Rebecca A. Juliano, PhD,[g] Lixia Jiao, PhD,[g] Craig Granowitz, MD, PhD,[g] Jean-Claude Tardif, MD,[h] John Gregson, PhD,[i] Stuart J. Pocock, PhD,[i] Christie M. Ballantyne, MD,[j] on Behalf of the REDUCE-IT Investigators*

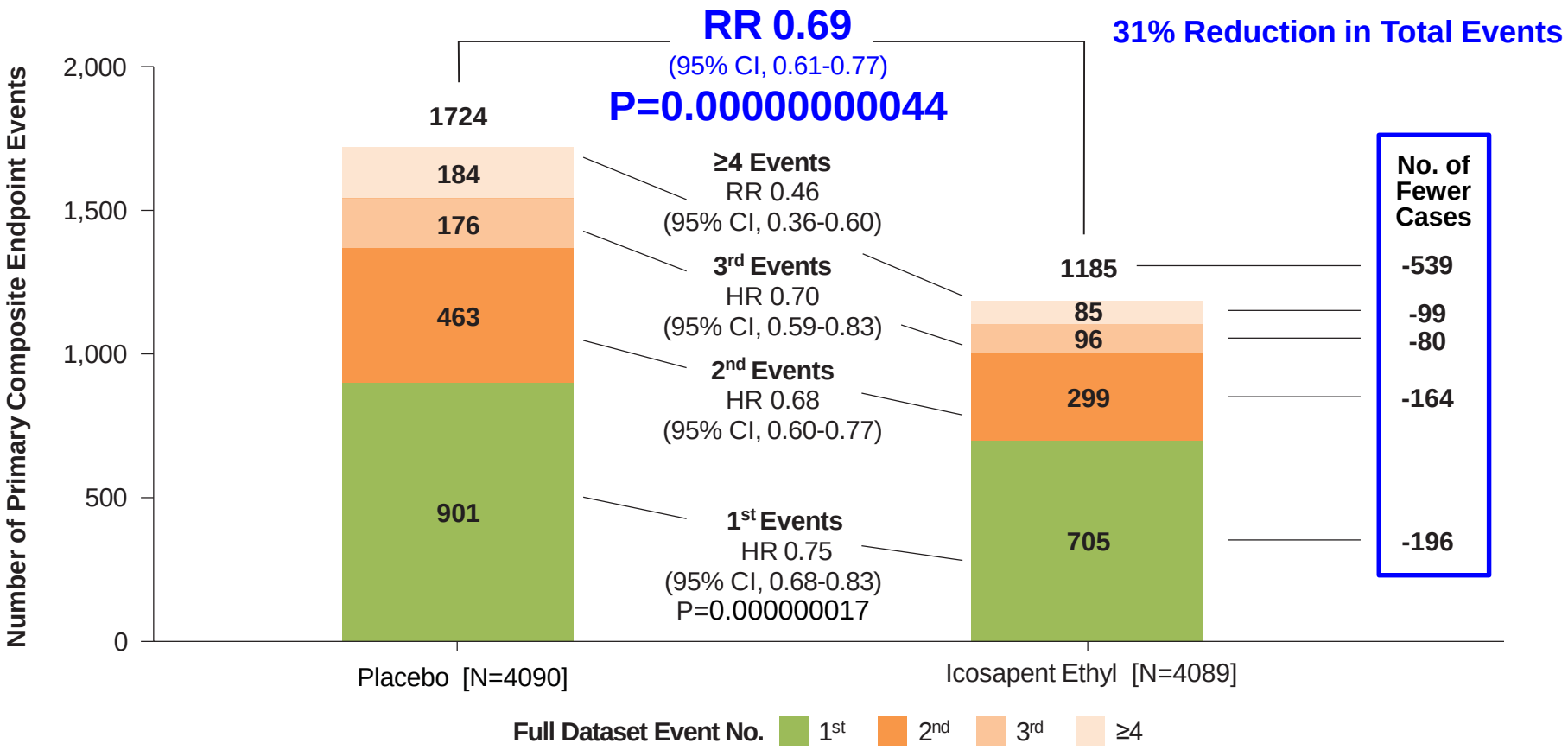
Article available at http://www.onlinejacc.org/content/early/2019/03/01/j.jacc.2019.02.032
Slides available for download at https://www.ACC.org

Proportions of First and Subsequent Events

Excluding Revascularization



First and Subsequent Events – Full Data



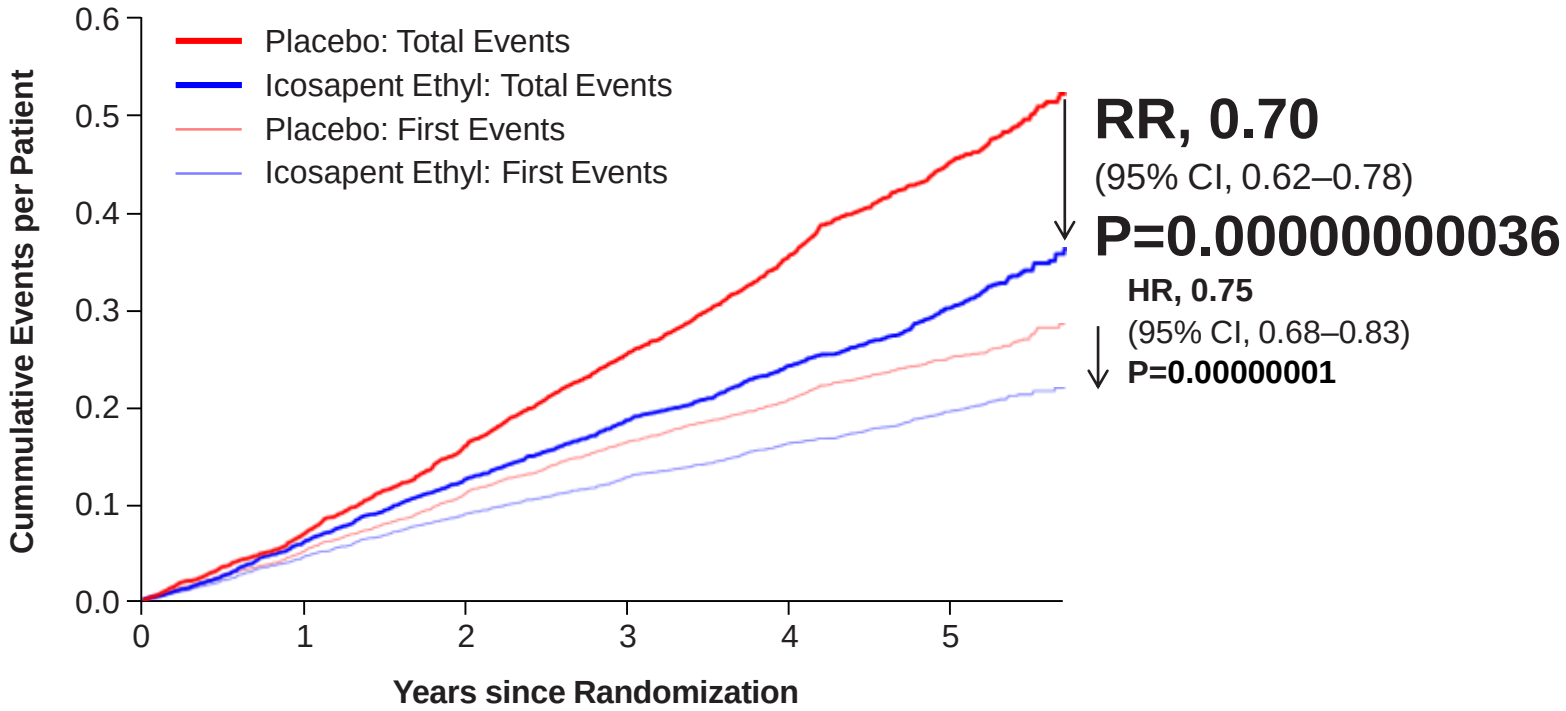
Bhatt DL et al. *J Am Coll Cardiol*. 2019;Mar 18(Epub ahead of print).

Note: WLW method for the 1st events, 2nd events, and 3rd events categories; Negative binomial model for ≥4th events and overall treatment comparison.

Total (First and Subsequent) Events

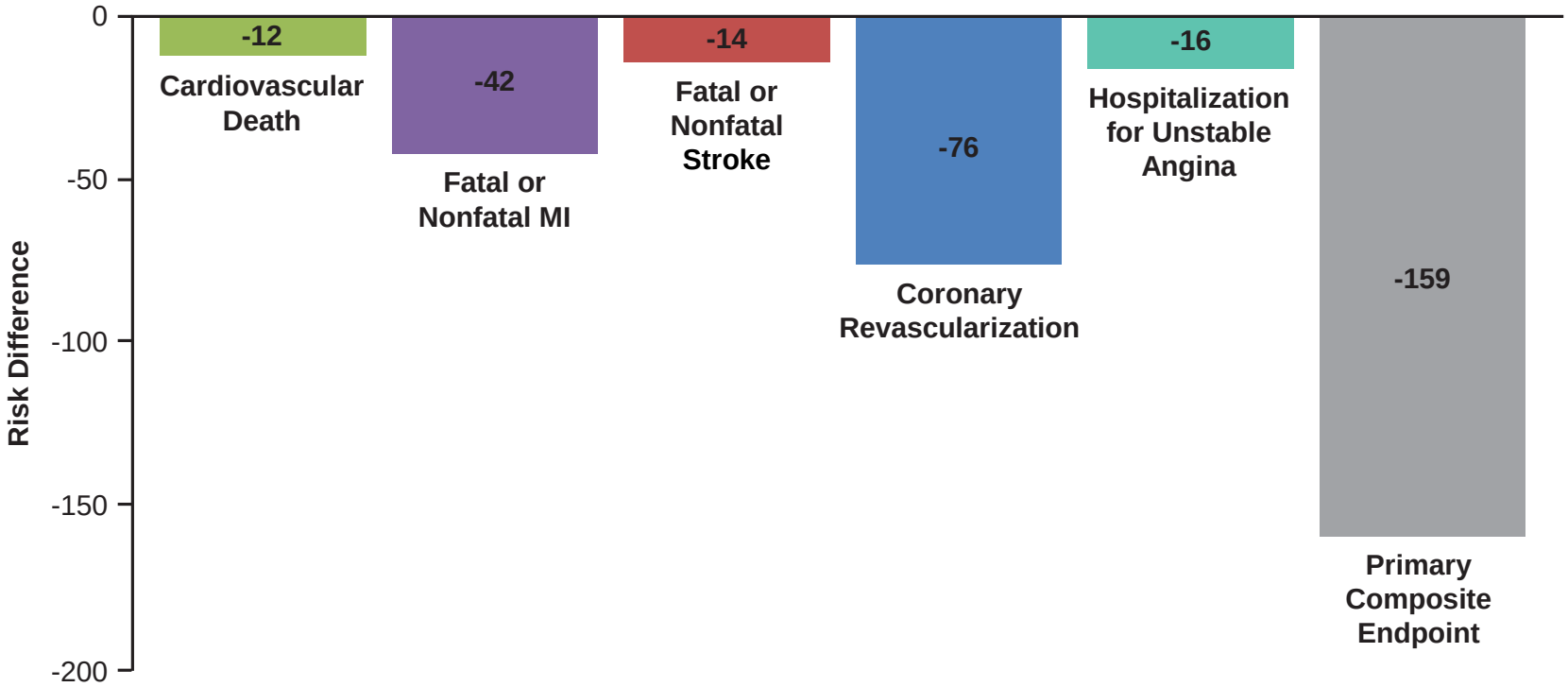
Primary: CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

Primary Composite Endpoint



Bhatt DL et al. *J Am Coll Cardiol*. 2019;Mar 18(Epub ahead of print).

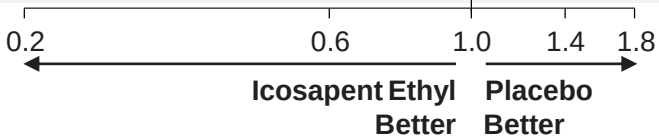
For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:



Bhatt DL et al. *J Am Coll Cardiol*. 2019;Mar 18(Epub ahead of print).

Primary Composite Endpoint: Total Endpoint Events by Baseline TG Tertiles

TOTAL EVENTS – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	RR (95% CI)	P-value
	Rate per 1000 Patient Years	Rate per 1000 Patient Years		
Primary Composite Endpoint (ITT)	61.1	88.8	0.70 (0.62–0.78)	<0.0001
Baseline Triglycerides by Tertiles*				
≥81 to ≤190 mg/dL	56.4	74.5	0.74 (0.61–0.90)	0.0025
>190 to ≤250 mg/dL	63.2	86.8	0.77 (0.63–0.95)	0.0120
>250 to ≤1401 mg/dL	64.4	107.4	0.60 (0.50–0.73)	<0.0001



***P (interaction) = 0.17**

Bhatt DL. ACC 2019, New Orleans.

Conclusions

Compared with placebo, icosapent ethyl 4 g/day significantly reduced total cardiovascular events by **30%**, including:

- **25%** reduction in first cardiovascular events
- **32%** reduction in second cardiovascular events
- **31%** reduction in third cardiovascular events
- **48%** reduction in fourth or more cardiovascular events

Analysis of first, recurrent, and total events demonstrates the large burden of ischemic events in statin-treated patients with baseline triglycerides > ~100 mg/dL and the potential role of icosapent ethyl in reducing this residual risk

Bhatt DL et al. *J Am Coll Cardiol*. 2019;Mar 18(Epub ahead of print). Bhatt DL. ACC 2019, New Orleans.

Update to ADA Standards of Medical Care in Diabetes–2019.
Annotation published March 27, 2019.

Treatment of Other Lipoprotein Fractions or Targets:

In patients with ASCVD or other cardiac risk factors on a statin with controlled LDL-C, but elevated triglycerides (135-499), the addition of icosapent ethyl should be considered to reduce cardiovascular risk. A

“It should be noted that data are lacking with other omega-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products."

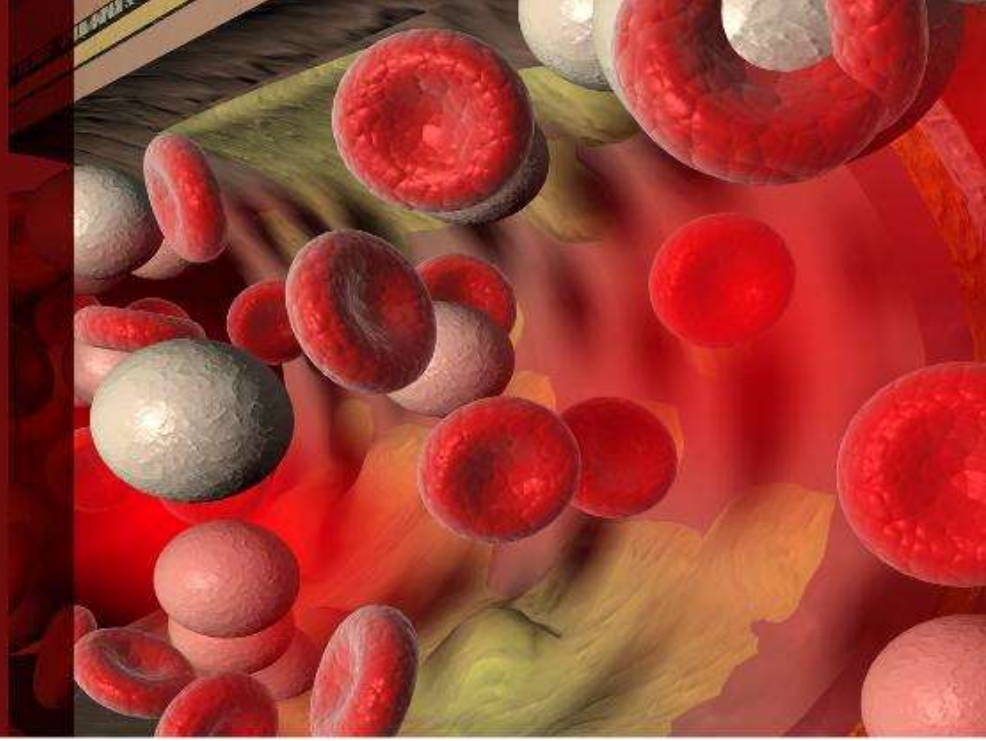
American Diabetes Association. 10. Cardiovascular disease and risk management: *Standards of Medical Care in Diabetes—2019* [web annotation]. *Diabetes Care.* 2019;42(Suppl. 1):S103–S123. Retrieved from https://hyp.is/JHhz_ICrEembFJ9LIVBZIw

CV Outcomes Trials in Patients with HTG

	Reported	Ongoing	
	REDUCE-IT*	**STRENGTH***	**PROMINENT***
Agent **Dose**	EPA (EE) 4 g/d	EPA+DHA (FFA) 4 g/d	SPPARMα – Pemafibrate 0.2 mg bid
N	8179	Estimated 13,000	Estimated 10,000
Age	≥45 years	≥18 years	≥18 years
Risk Profile	CVD (70%) or ↑CVD risk (30%)	CVD (50%) or ↑CVD risk (50%)	T2DM only CVD (2/3) or ↑CVD risk (1/3)
Follow-up	4–6 years (planned)	3–5 years (planned)	5 years (planned)
Statin Use	100% (at LDL-C goal)	100% (at LDL-C goal)	Moderate- / high-intensity or LDL <70 mg/dL
Primary Endpoint	Expanded MACE	Expanded MACE	Expanded MACE
Entry TG **Entry HDL-C**	135–499 mg/dL N/A	200–499 mg/dL <40 mg/dL M, <45 mg/dL W	200–499 mg/dL ≤40 mg/dL

*Locations: International sites; Statistics: Powered for 15% RRR.
REDUCE-IT: Bhatt DL et al. *N Engl J Med.* 2019;380:11-22. STRENGTH: NCT02104817. PROMINENT: NCT03071692.

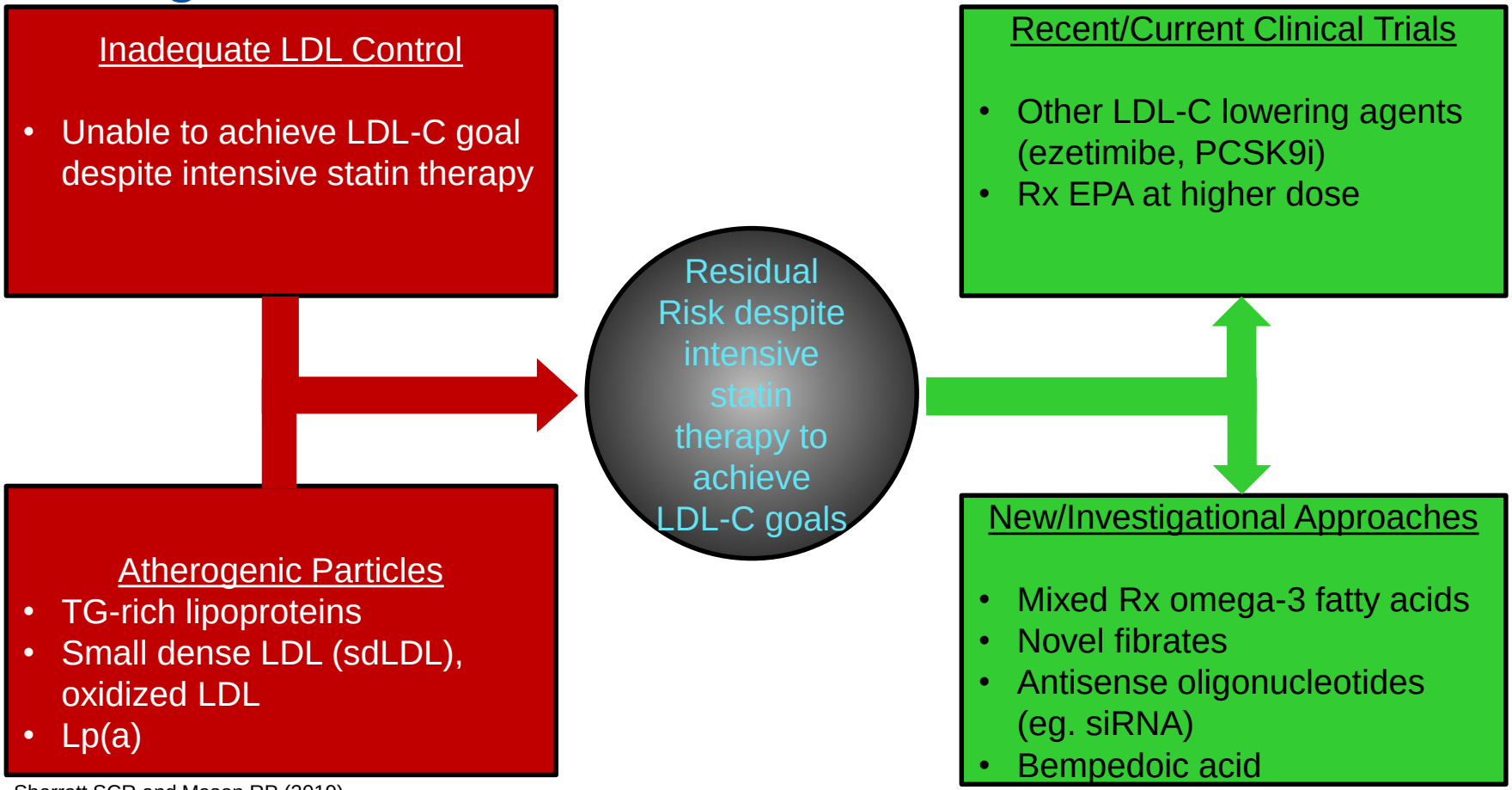
Biologic Basis for EPA Modulation in Reducing ASCVD Events Seen in REDUCE-IT



ELUCIDA RESEARCH

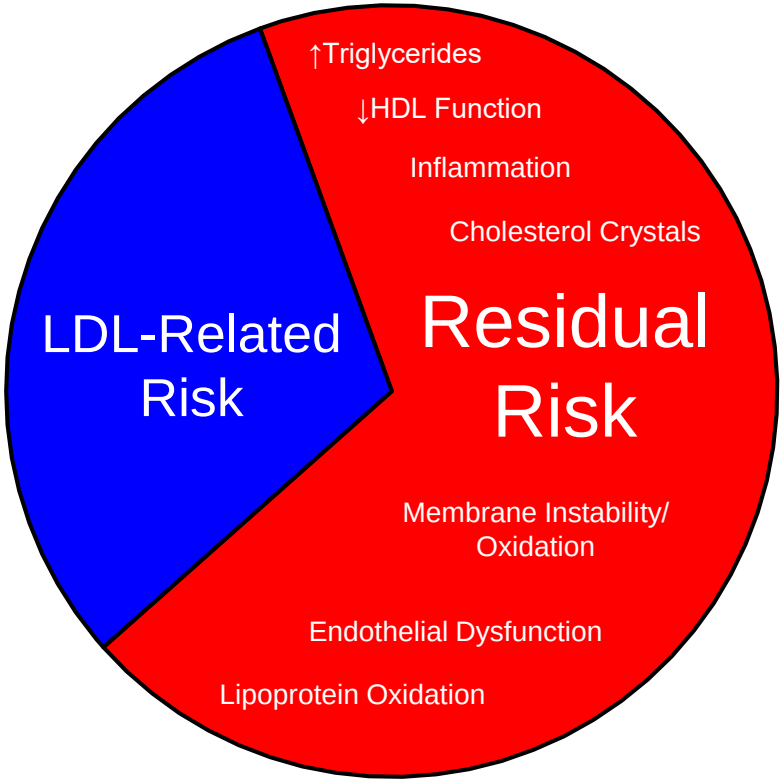
R. Preston Mason, PhD

Factors Leading to Residual Risk and New Treatment Strategies



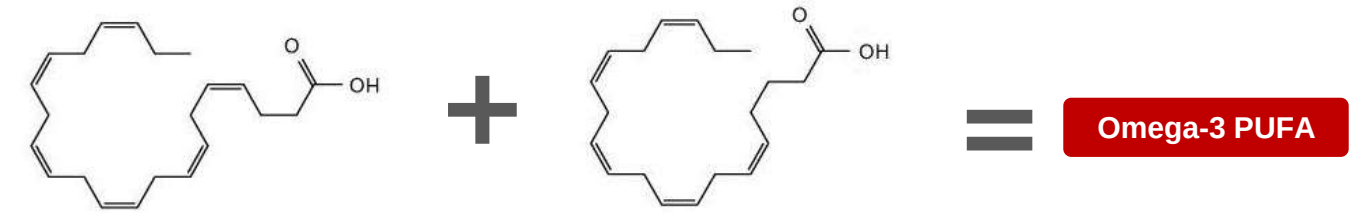
Sherratt SCR and Mason RP (2019).

The Challenge of Dyslipidemic Residual Risk Beyond LDL



Sherratt SCR and Mason RP (2019).

Omega-3 Polyunsaturated Fatty Acids (PUFAs) Are Another Management Option Studied for CV Risk Reduction

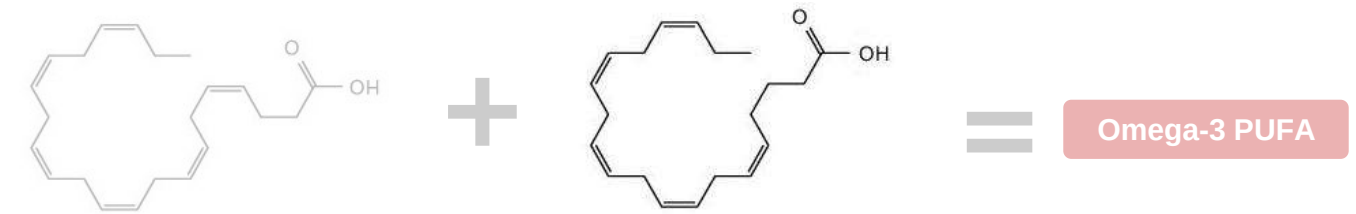


Docosahexaenoic acid (DHA)
22 Carbon, 6 Double bonds

Eicosapentaenoic acid (EPA)
20 Carbon, 5 Double bonds

Libby P. Triglycerides on the rise: should we swap seats on the seesaw? *Eur Heart J*. 2015;36:774-6.
Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol*. 2018;72:330-43.
Ference BA, Kastelein JJP, Ray KK, et al. Association of triglyceride-lowering LPL variants and LDL-C–lowering LDLR variants with risk of coronary heart disease. *JAMA*. 2019;321:364-73.
Borow KM, Nelson JR, Mason RP. *Atherosclerosis*. 2015;242:357-66.

Omega-3 Polyunsaturated Fatty Acids (PUFAs) Are Another Management Option Studied for CV Risk Reduction



Docosahexaenoic acid (DHA)

22 Carbon, 6 Double bonds

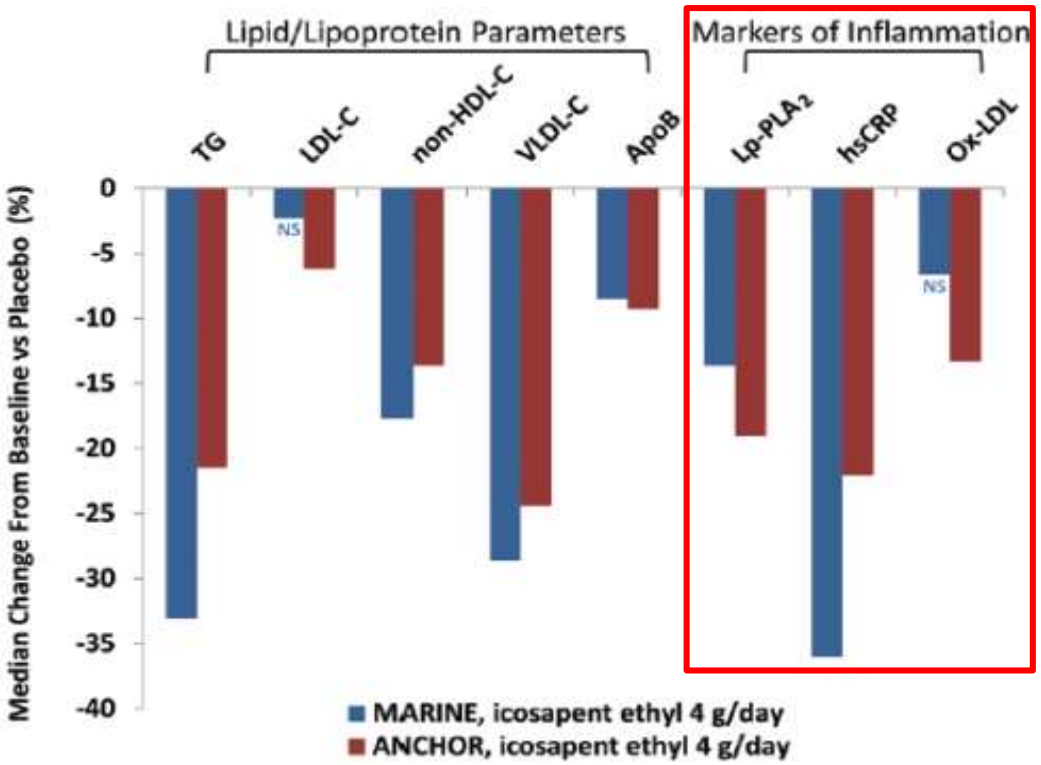
Eicosapentaenoic acid (EPA)

20 Carbon, 5 Double bonds

However, recent studies have assessed the mechanism of action of a pure, prescription dose of EPA and subsequent impact CV risk reduction.

Libby P. Triglycerides on the rise: should we swap seats on the seesaw? *Eur Heart J*. 2015;36:774-6.
Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol*. 2018;72:330-43.
Ference BA, Kastelein JJP, Ray KK, et al. Association of triglyceride-lowering LPL variants and LDL-C–lowering LDLR variants with risk of coronary heart disease. *JAMA*. 2019;321:364-73.
Borow KM, Nelson JR, Mason RP. *Atherosclerosis*. 2015;242:357-66.

Effects of EPA on non-HDL-C and Inflammatory Markers in Patients with Elevated TGs



Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46.

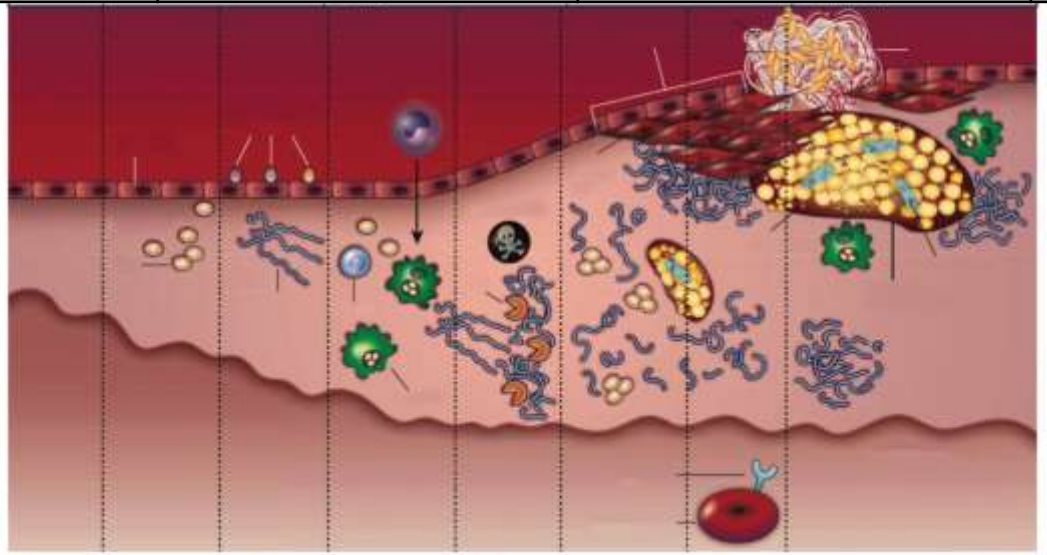
Lipid Therapies Have Different Effects on hsCRP

Lipid Therapy	hsCRP Levels
Statins	↓
EPA (4 g)	↓
EPA (4 g) + Statin	↓↓
EPA/DHA (4 g)	⇔
Ezetimibe	⇔
Ezetimibe + Statin	↓
PCSK9i + Statin	⇔

Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46. Dunbar RL et al. *Lipids Health Dis.* 2015:14:98. Ridker PM et al. *N Engl J Med.* 2008;359:2195-207. Bohula EA et al. *Circulation*. 2015;132:1224-33. Pradhan AD et al. *Circulation*. 2018;138:141-9.

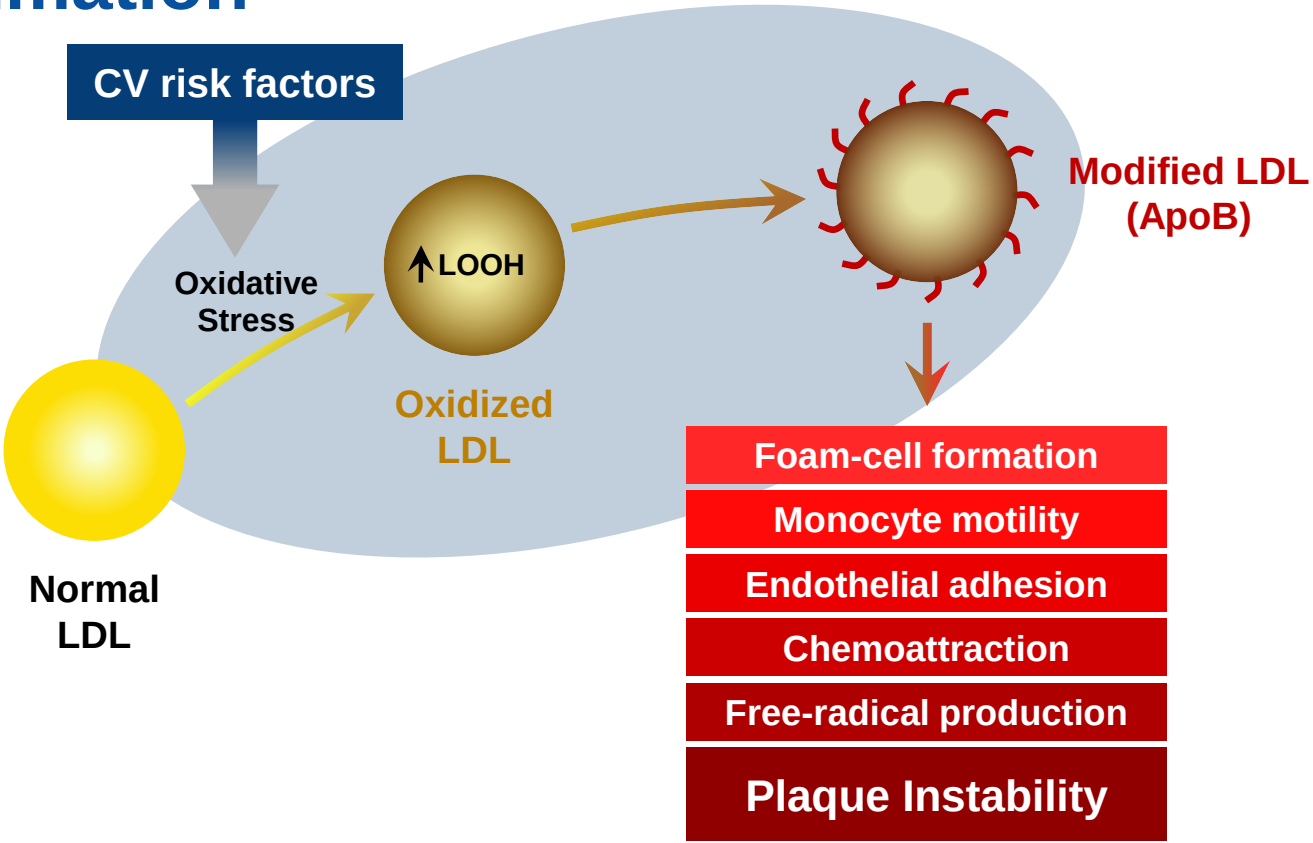
Potential Effects of Omega-3 on Plaque

Pathological Parameters and Processes in Atherosclerosis				
Circulating parameters	Endothelial cell dysfunction & activation	Inflammation, monocyte recruitment, & proteolysis	Lipid core and fibrous cap formation with ongoing inflammation	Plaque formation, progression, & thrombosis
Beneficial Effects of EPA				
↓TG ↓Non-HDL-C ↓ApoB ↓VLDL-C	↑Antioxidant effects ↑Endothelial function ↓Cholesterol crystalline domains ↓RLP-C	↑EPA/AA ratio ↑Resolvins, protectins & IL-10 ↓Inflammation: Ox-LDL, IL-6, hsCRP, $LpPLA_2$, & ICAM-1 ↓Monocyte adhesion ↓MMPs	↑Fibrous cap thickness ↑Lumen diameter ↓Macrophages ↓Foam cell formation ↓Ongoing inflammation	↑Plaque stability ↓Plaque formation & progression ↓Plaque volume & vulnerability ↓Arterial stiffness ↓Platelet response ↓Thrombosis



Borow KM, Nelson JR, Mason RP. *Atherosclerosis.* 2015;242:357-66. Nemiroff RL. Supplement to *Contemporary OB/GYN.* 2016.

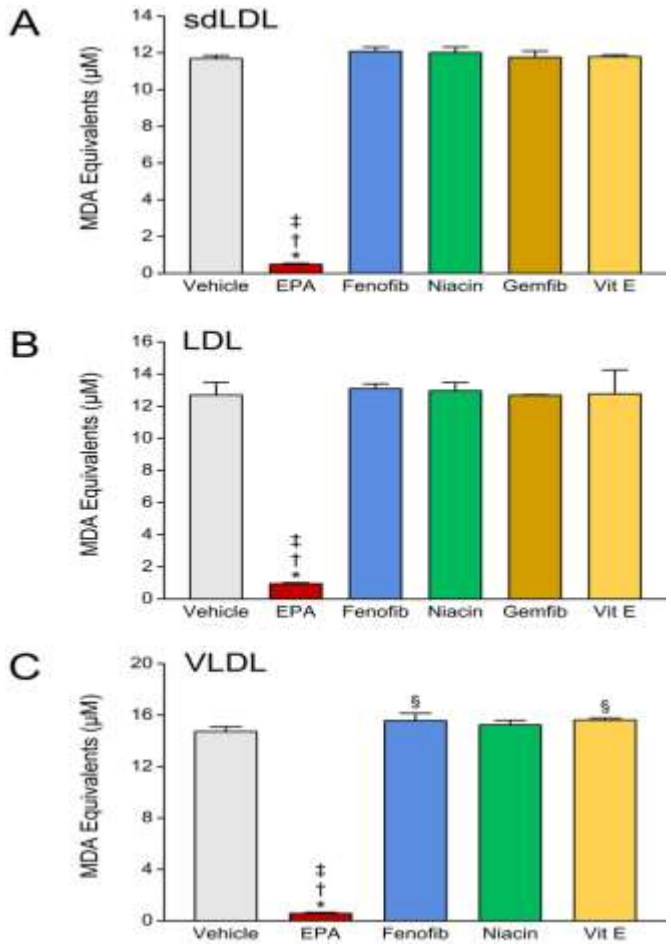
LDL Oxidation Triggers Vascular Injury and Inflammation



Jacob RF and Mason RP (2018).

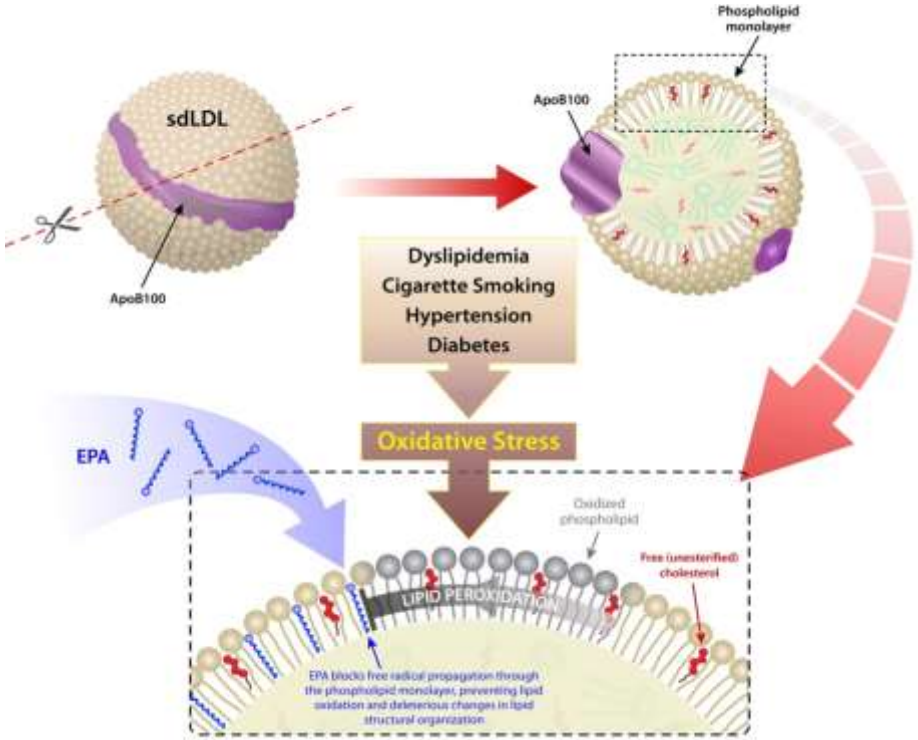
Comparative Effects of TG-lowering Agents on Lipoprotein Oxidation

Each agent was tested at 10 μM



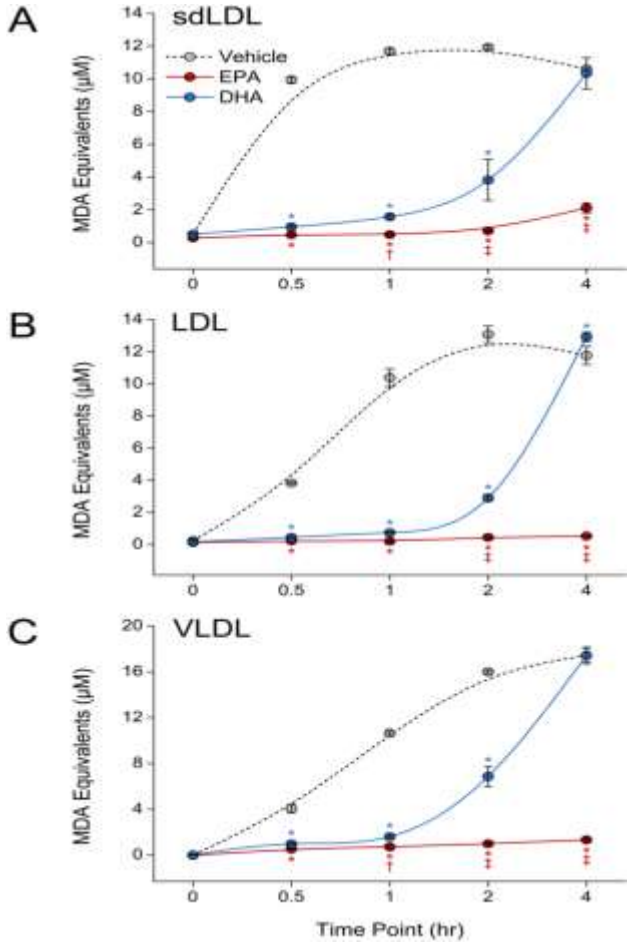
Mason RP et al. *J Cardiovasc Pharmacol* 2016;68:33-40.

Schematic Illustration of the Protective Effects of EPA on sdLDL Lipid Oxidation



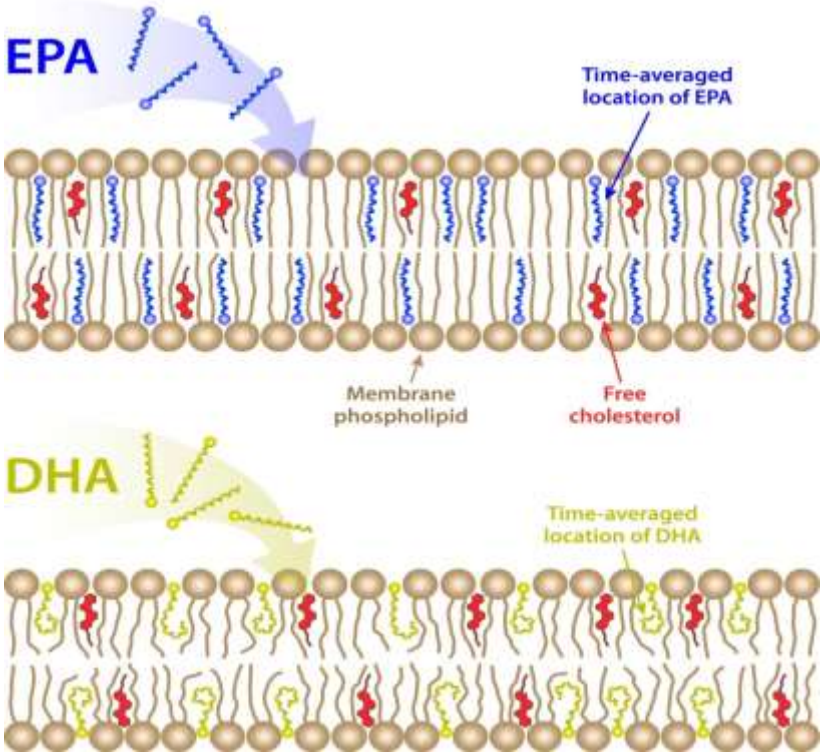
Adapted from: Mason RP, Jacob RF. *Diabetes.* 2015;64(Suppl 1):A178-A179.

Comparative Effects of EPA and DHA on Oxidation in Different ApoB Particles



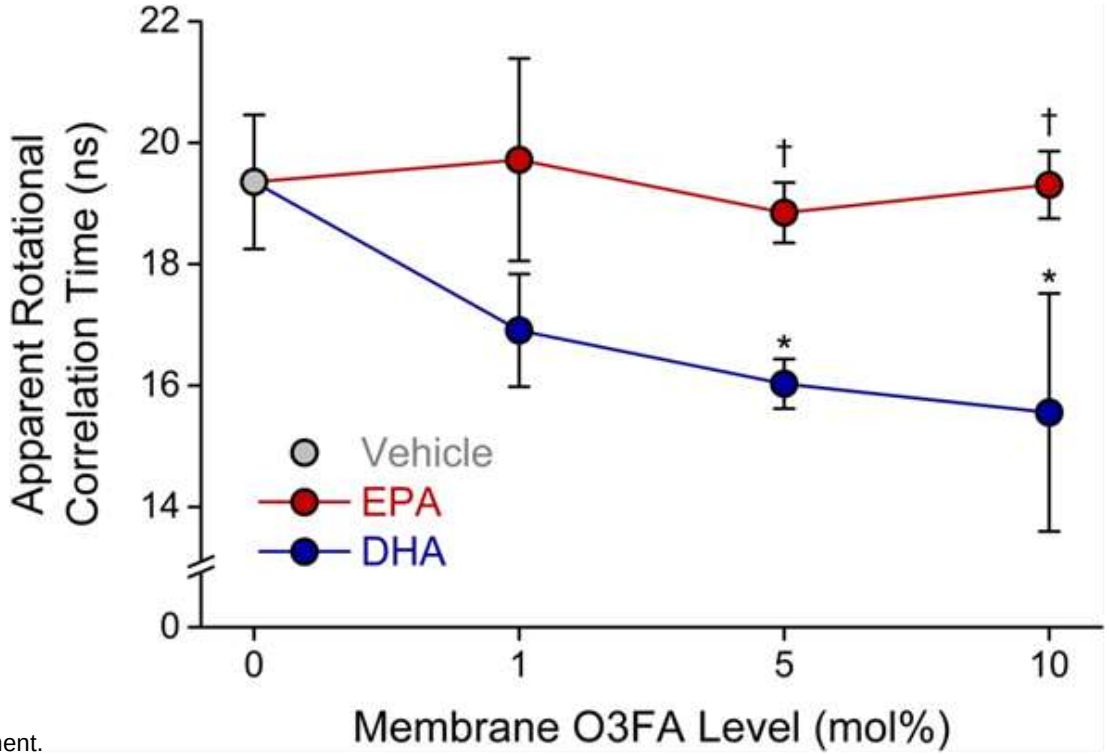
Mason RP et al. *J Cardiovasc Pharmacol* 2016;68:33-40.

Biophysical Analysis: EPA has Stable Extended Conformation in the Membrane while DHA has Disordering Effect



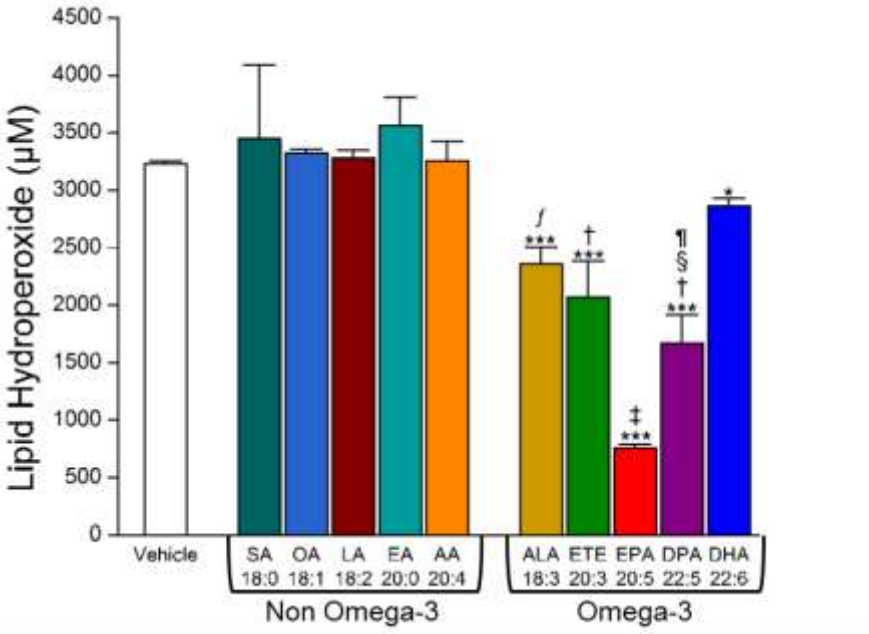
Sherratt SCR, Mason RP. *Chem Phys Lipids* 2018;212:73-9.

DHA Disorders the Membrane Environment while EPA has no Effect on Membrane Fluidity



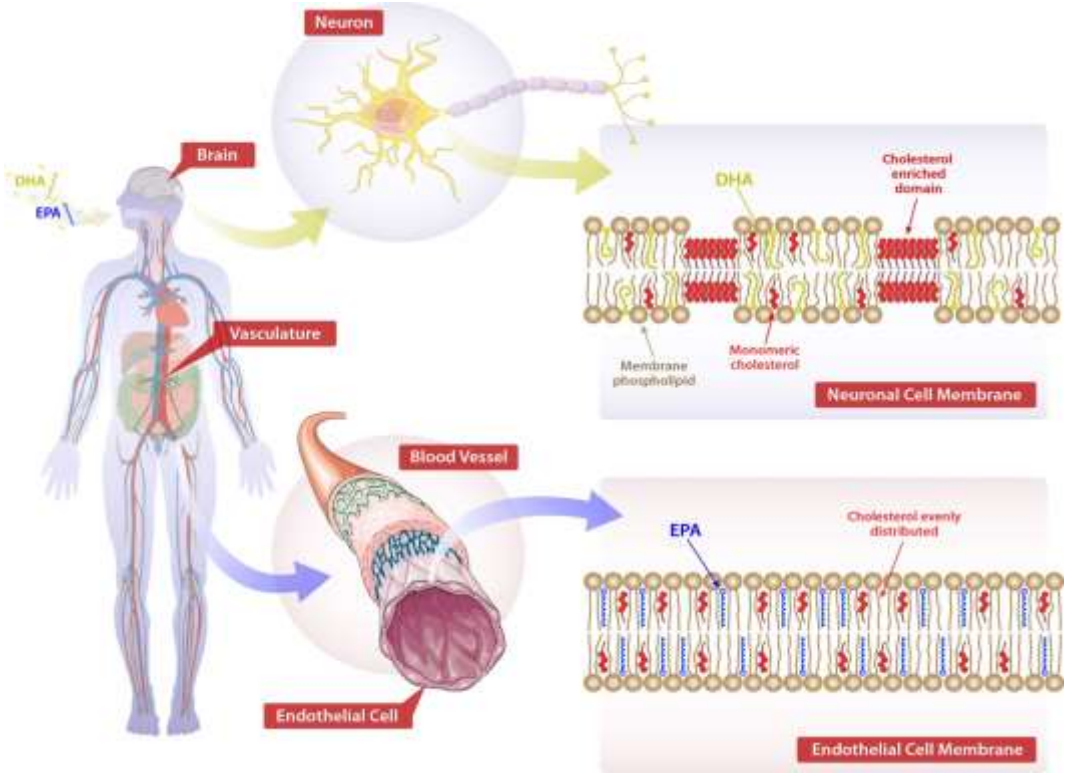
*P<0.05 vs control (vehicle) treatment.
†P<0.05 vs cognate (equimolar) DHA treatment.
Mason RP et al. *Biochim Biophys Acta.* 2016;1858:3131-40.

Comparative Effects of Long Chain Fatty Acids on Lipid Oxidation in Model Membrane Bilayers



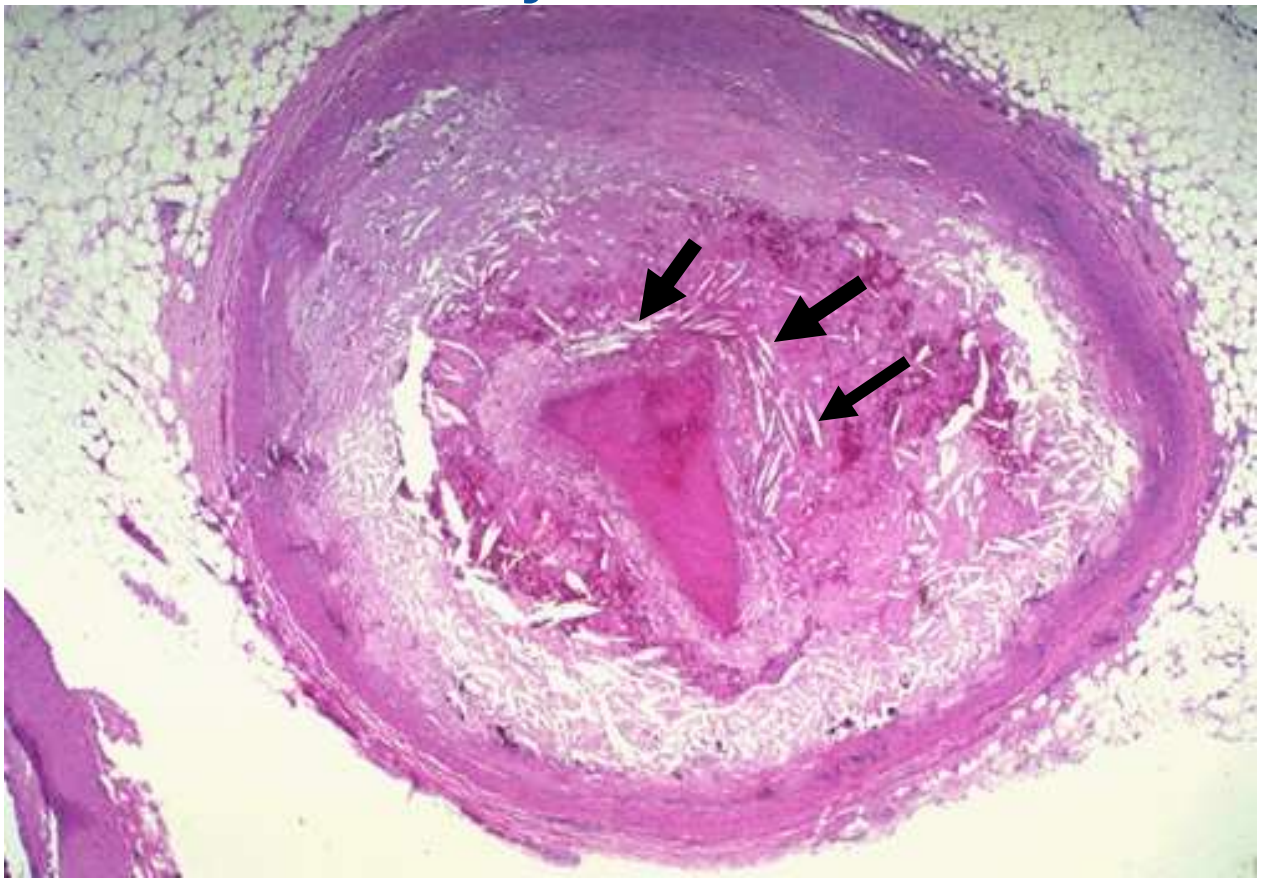
Statistical indicators: ***P<0.001 vs vehicle. *P<0.05 vs vehicle. ‡P<0.001 vs all treatments. †P<0.001 vs DHA. §P<0.01 vs ALA. ¶P<0.05 vs ETE. ʃP<0.01 vs DHA. (Student-Newman-Keuls Multiple Comparisons Test; overall ANOVA: P<0.0001, F = 74.054). Values are mean ± SD (N = 3). Data were analyzed by group (all OM-3 FA and vehicle, all non-OM-3 FA and vehicle).
Sherratt SCR, Mason RP. *WCIRDC* (2018).

EPA and DHA have Distinct Roles in Human Physiology Mediated by Membrane Interactions



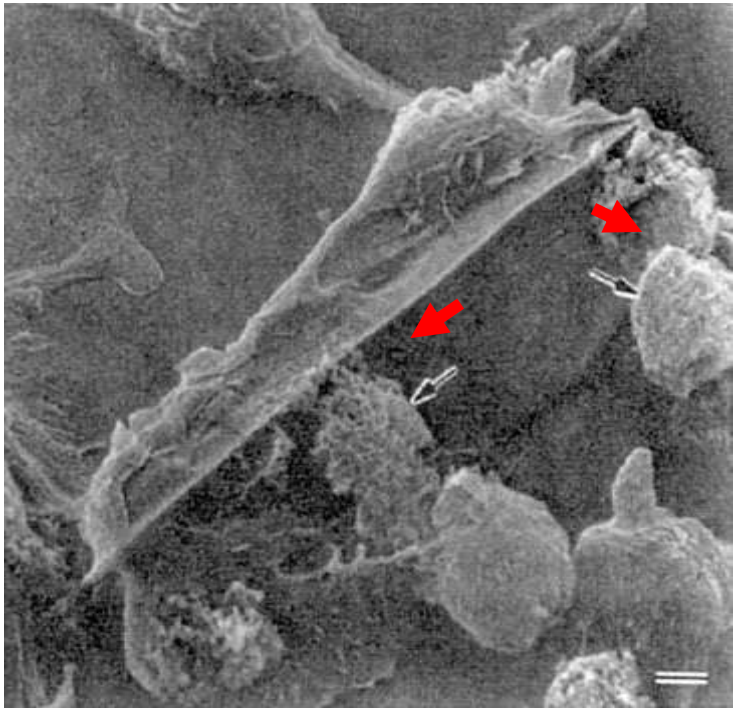
Mason RP. *Curr Atheroscler Rep.* 2019;21:2-11.

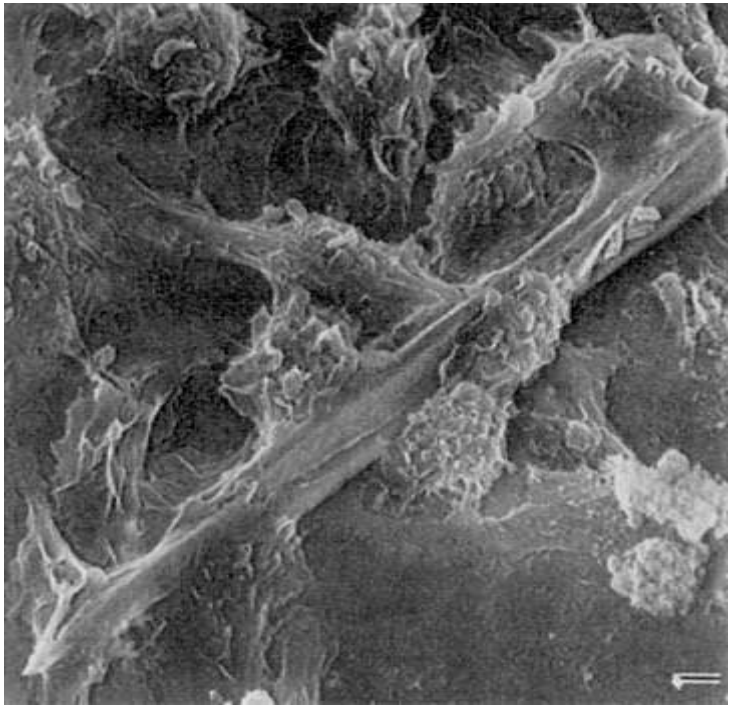
Atherothrombotic Lesions are Characterized by Abundant Cholesterol Crystals



WebPath. https://webpath.med.utah.edu/ATHHTML/ATH010.html

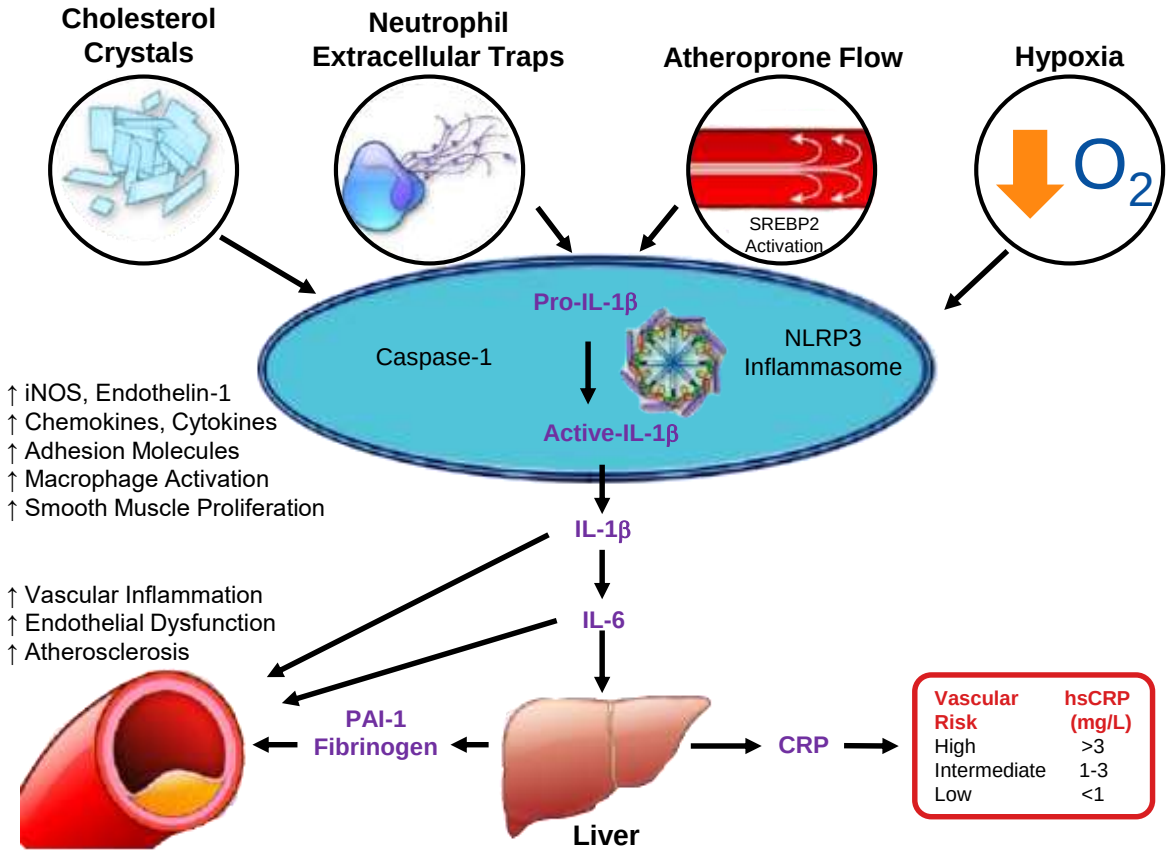
Cholesterol Crystals Associated with Atherosclerosis and Cell Death





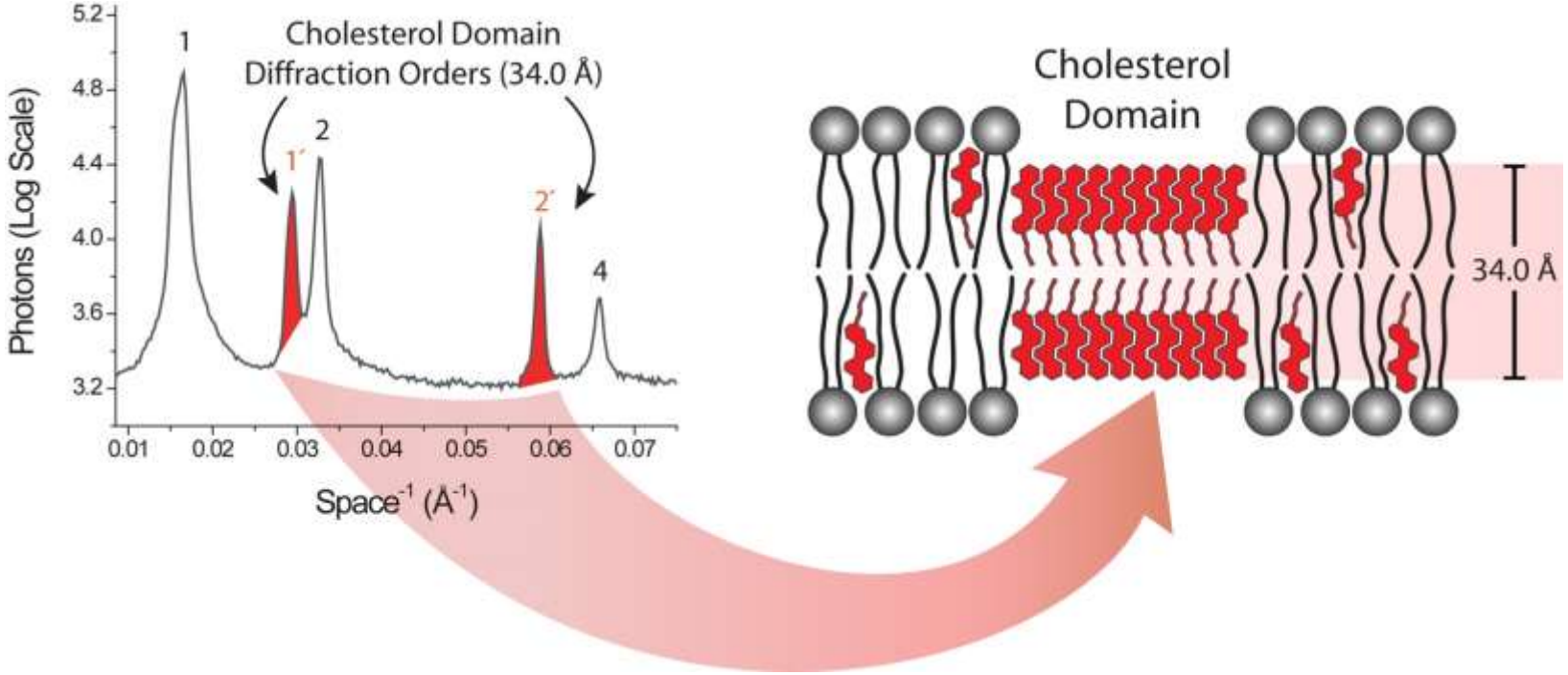
Kellner-Weibel G, Mason RP, et al. *Arterioscler Thromb Vasc Biol.* 1999;19:1891-8.

Cholesterol Crystals Trigger IL-1β Formation



Ridker PM. *Circ Res* 2016;118:145-56.

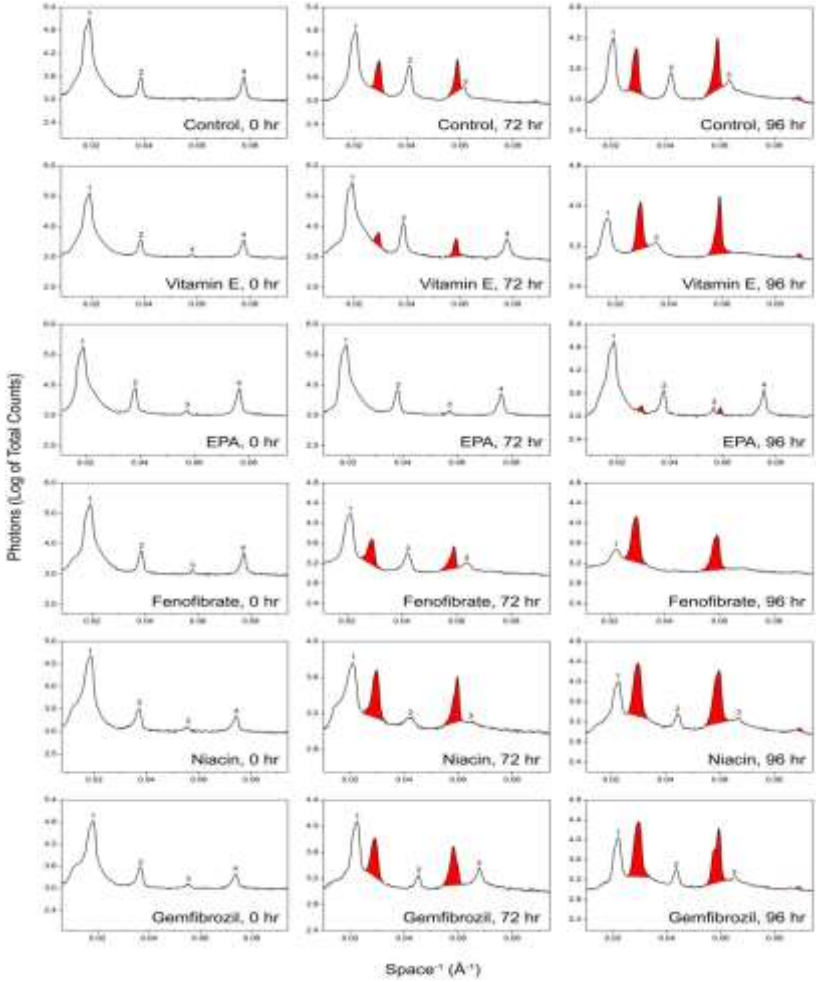
Characterizing Membrane Cholesterol Crystalline Domains by X-ray Diffraction



Mason RP et al. *J Biol Chem.* 2006;281:9337-45.

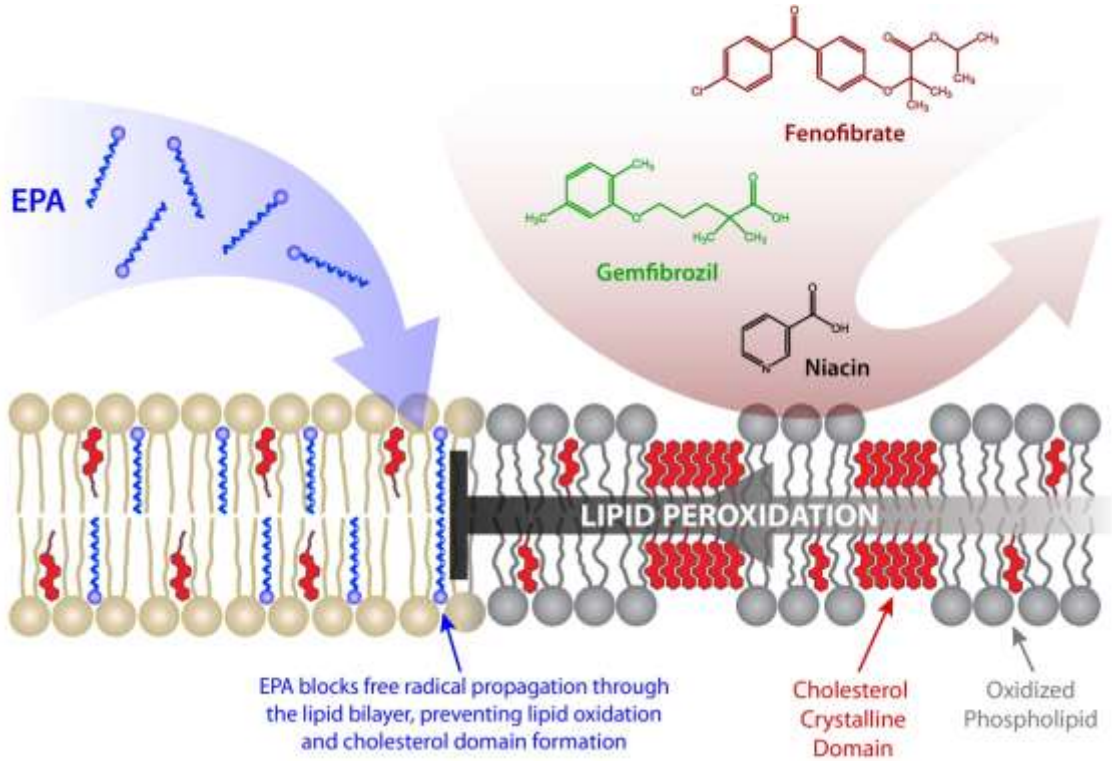
Effects of TG-lowering Agent on Cholesterol Crystalline Domains

- Comparison of Vitamin E, EPA, Fenofibrate, Niacin, and Gemfibrozil



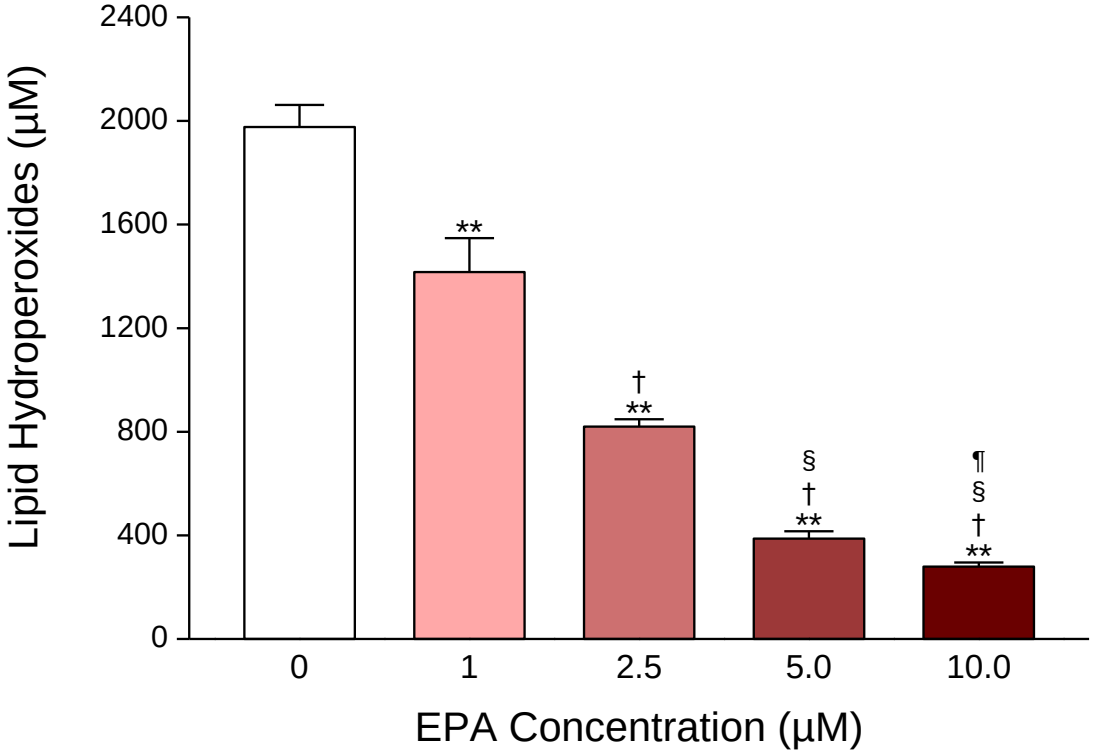
Mason RP, Jacob RF. *Biochim Biophys Acta* 2015;1848:502-9.

EPA, But Not Other TG-lowering Agents, Inhibits Lipid Oxidation & Cholesterol Domain Formation



Adapted from Mason RP, Jacob RF. *Biochim Biophys Acta*. 2015;1848:502-9.

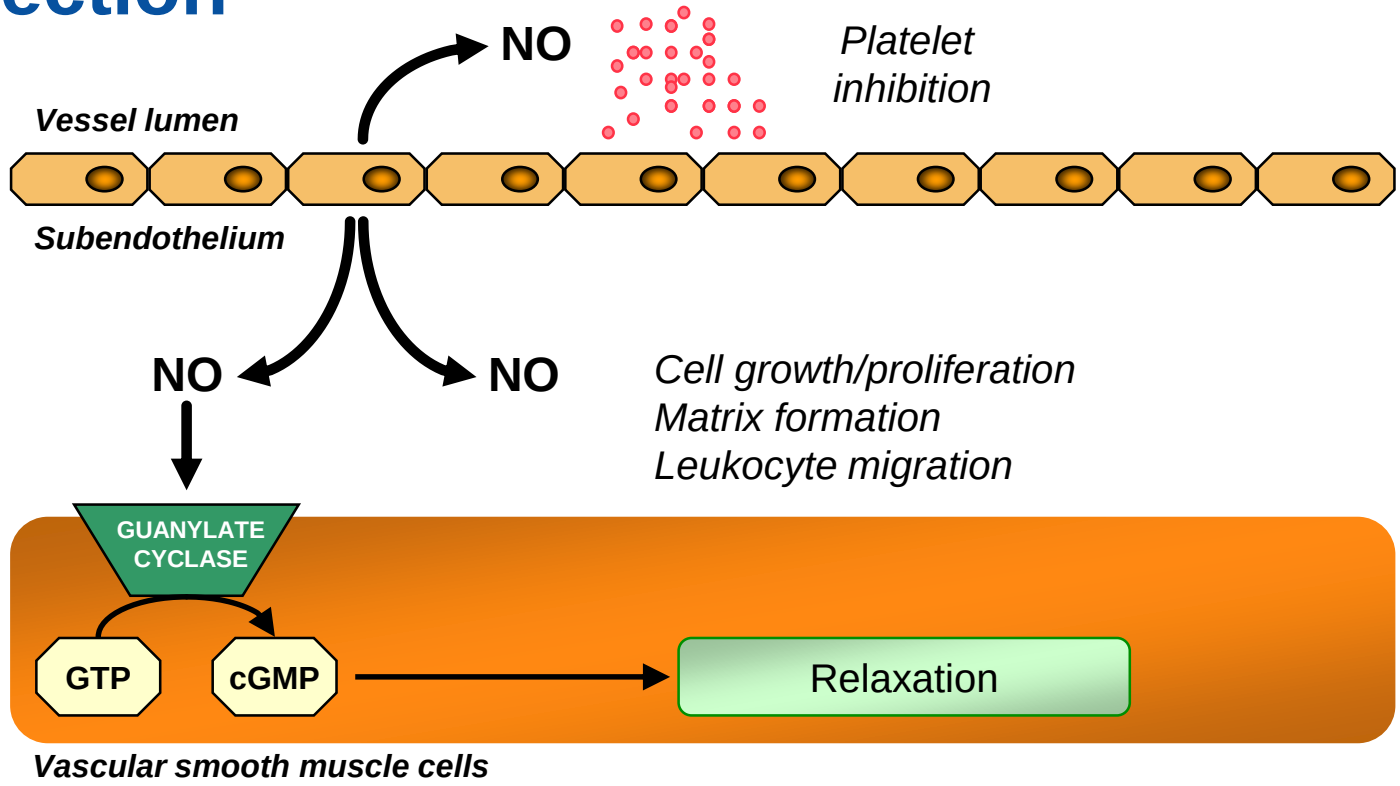
EPA Inhibits Membrane Lipid Peroxidation in a Dose-dependent Fashion



**P<0.001 vs vehicle-treated control. †P<0.001 vs 1.0 µM EPA. §P<0.001 vs 2.5 µM EPA. §P<0.05 vs 5.0 µM EPA. (Student-Newman-Keuls multiple comparisons test; overall ANOVA: P<0.0001, F=561.62). Values are mean ± SD (N=6).

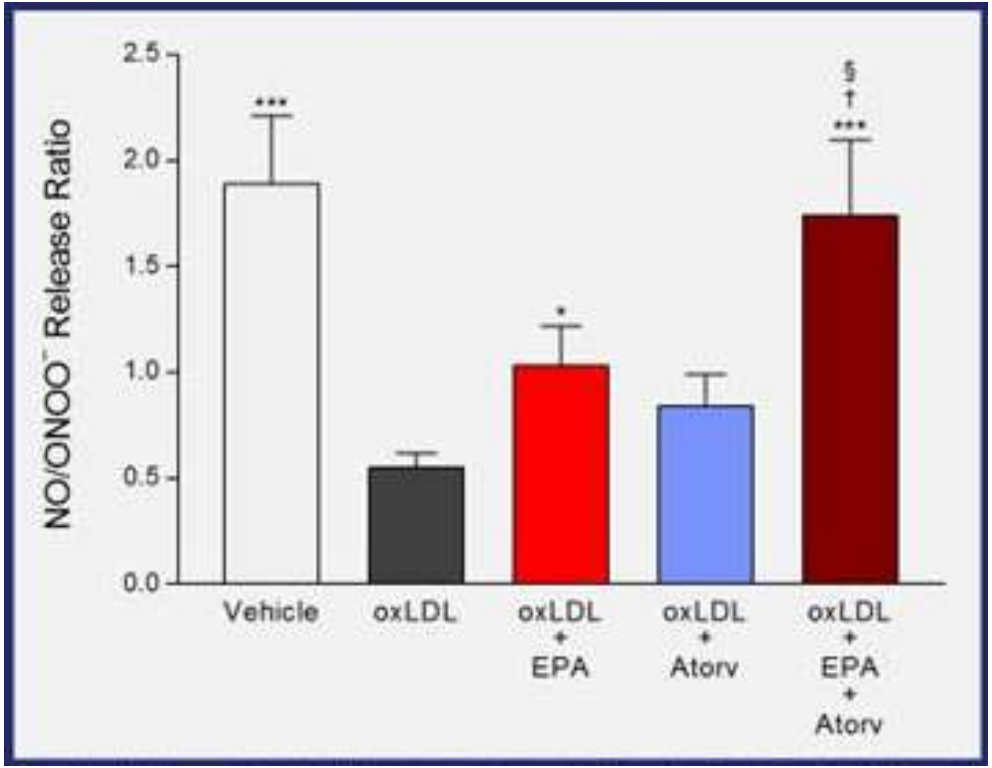
Mason RP, Jacob RF. *Biochim Biophys Acta*. 2015;1848:502-9.

Nitric Oxide Is a Key Mediator of Vascular Protection



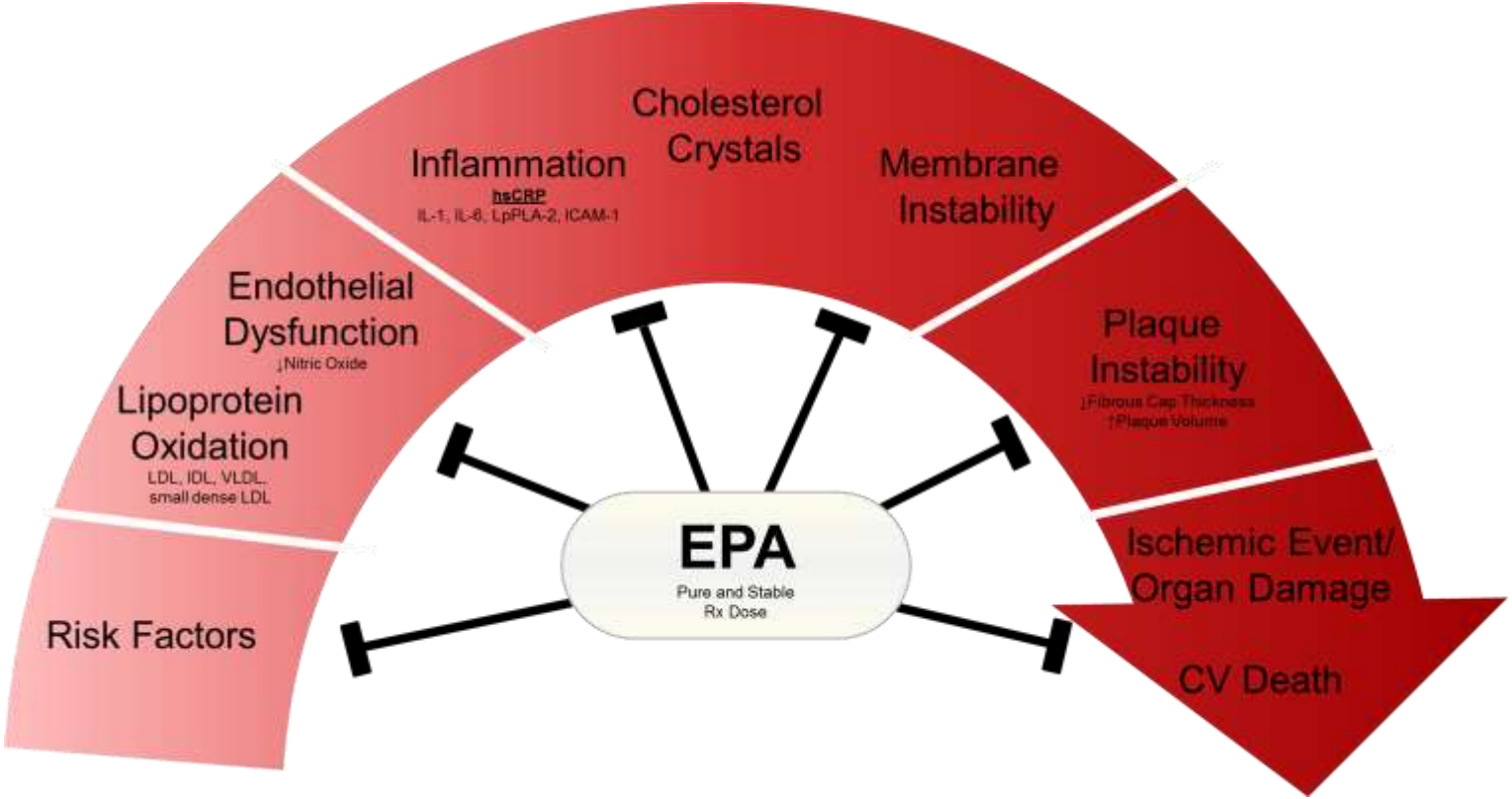
Behrendt D, Ganz P. *Am J Cardiol*. 2002;90(10C):40L-48L.
Vita JA. *J Card Fail*. 2003;9(5 Suppl Nitric Oxide):S199-S204.

Combined Effects of EPA and Atorvastatin on Human Endothelial Function after Treatment with Oxidized LDL



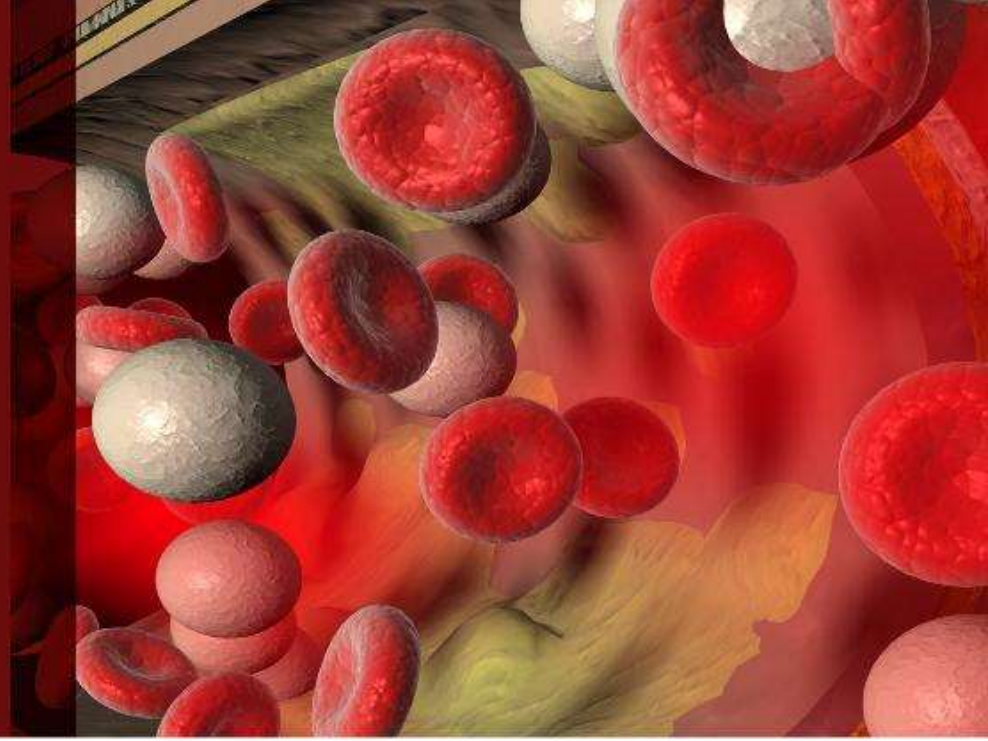
Atorvastatin active metabolite was used in this study. Values are mean ± SD (N=3-6).
*P<0.05 and ***P<0.001 vs oxLDL. †P<0.01 vs oxLDL + EPA. §P<0.001 vs oxLDL + Atorv.
Mason RP et al. *Biomed Pharmacother*. 2018;103:1231-7.

EPA Interferes with the Cardiovascular Disease Continuum at Multiple Points to Reduce CV Events

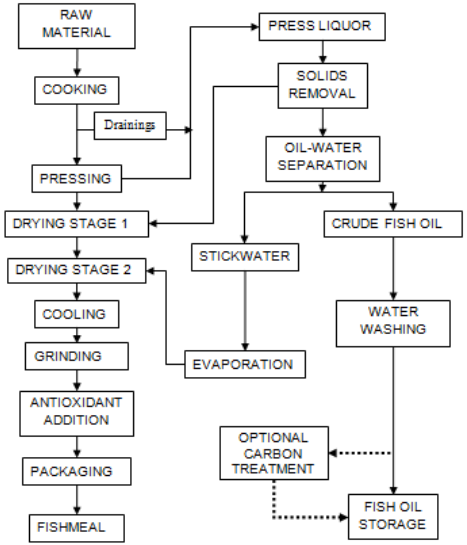


Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46; Borow KM, Nelson JR, Mason RP. *Atherosclerosis.* 2015;242:357-66; Bhatt DL et al. *N Engl J Med.* 2019;380:11-22; Ganda OP et al. *J Am Coll Cardiol*. 2018;72:330-43; Jia X et al. *Curr Atheroscler Rep*. 2019;21:1; Mason RP et al. *Biomed Pharmacother*. 2018;103:1231-7; Ference BA et al. *JAMA*. 2019;321:364-73.
Sherratt SCR and Mason RP (2019).

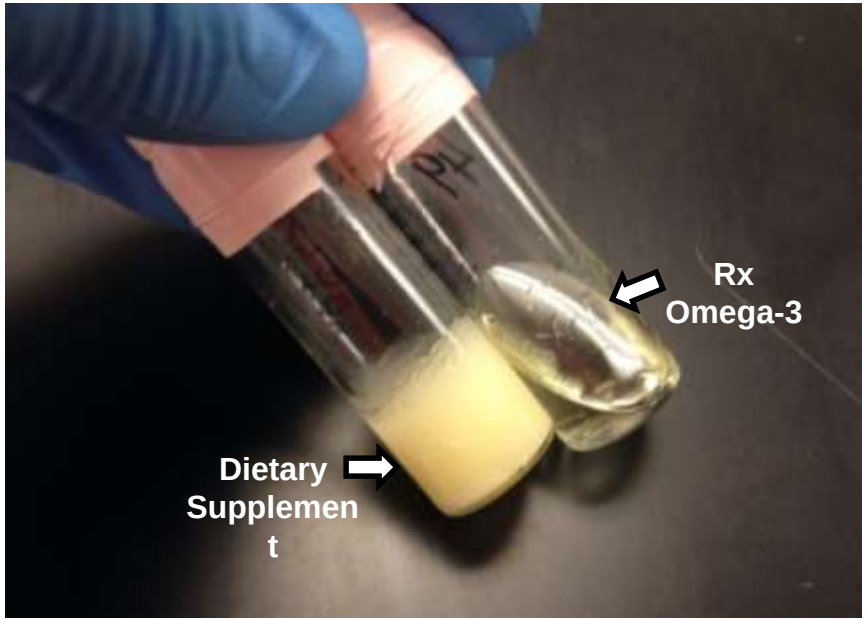
Are Fish Oil Dietary Supplements Appropriate for CV Patients?



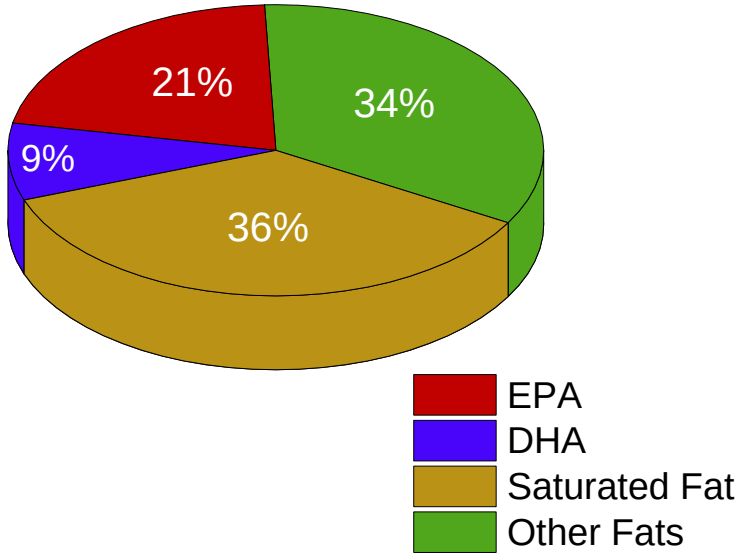
Dietary FO Supplements Are a By-product of Industrial Extraction Procedures



Fatty Acid Content of Leading U.S. Fish Oil Supplement



Saturated fatty acid content in fish oil supplement results in solid mass following isolation



Mason RP, Sherratt SCR. *Biochem Biophys Res Commun.* 2017;483:425-9.

Achieving a Recommended 4 g Daily Dose of Omega-3 with Common Fish Oil Supplements

Icosapent ethyl

EPA Dietary Supplement from label

Krill oil from label

Fish Oil Dietary Supplements: Right for CV Patients?

FDA Product Classification[1] → Food

Clinical Trials/FDA Pre-Approval[1] → Not Required

Content & Purity[2-9] →
- Difficult to achieve AHA recommended OM-3 levels
- Contain high levels of saturated fats
- Advertised omega-3 content overstated
- Contain oxidized lipids leading to dyslipidemia and increased CV risk
- Contain PCBs and dioxins at levels known to be harmful for humans

1. US Food and Drug Administration. www.fda.gov/Food/DietarySupplements/default.htm. Updated April 4, 2016. Accessed May 13, 2019. 2. Hilleman D, Smer A. *Manag Care*. 2016;25:46-52. 3. Mason RP, Sherratt SCR. *Biochem Biophys Res Commun.* 2017;483:425-9. 4. Albert BB et al. *Sci Rep*. 2015;5:7928. 5. Kleiner AC et al. *J Sci Food Agric*. 2015;95:1260-7. 6. Ritter JC et al. *J Sci Food Agric*. 2013:93:1935-9. 7. Jackowski SA et al. *J Nutr Sci*. 2015;4:e30. 8. Rundblad A et al. *Br J Nutr*. 2017;117:1291-8. 9. European Medicines Agency, 2018: 712678.

Conclusion

- Inflammation, oxidative stress and endothelial dysfunction are causally related to atherosclerosis;

- Omega-3 FA (EPA) interferes with mechanisms of atherosclerosis at therapeutic concentrations as compared to other TG-lowering agents or omega-3 FA formulations. This may contribute to clinical benefits as seen in REDUCE-IT;

- Dietary supplements are not an appropriate substitute for FDA-approved and tested omega-3 fatty acids in patients.

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