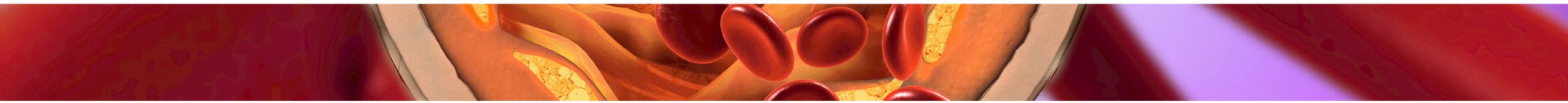
Tailoring Prevention in Reducing ASCVD Risk: Who, What, How, and Why?

2022 ACP Internal Medicine Annual Scientific Sessions

Chicago, IL

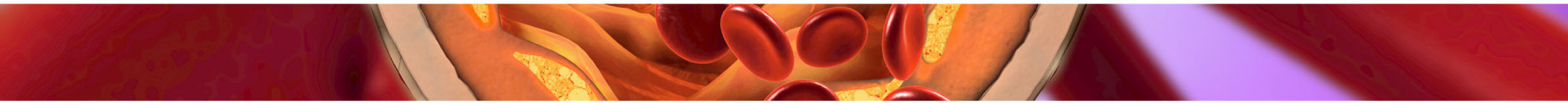
April 28, 2022

6:30-8:30 PM



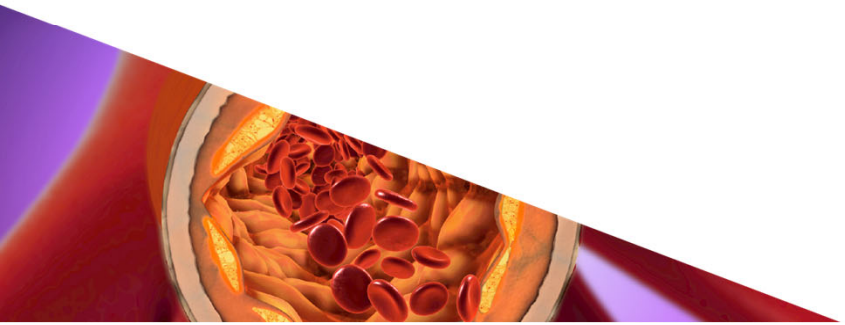
Welcome, Introductions, and Program Overview

Eliot Brinton, MD, Program Chair



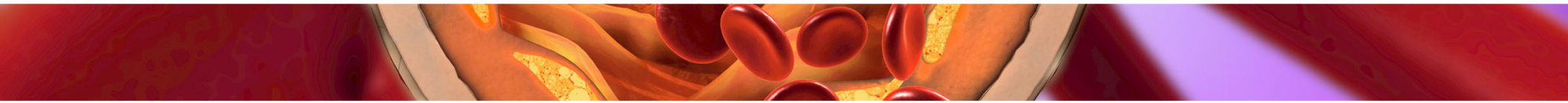
Learning Objectives

- Exhibit greater competence in stratifying patients at risk of future ASCVD events
- Differentiate various omega-3 formulations in clinical practice based on the evidence of impact on ASCVD risk in the most recent clinical trials



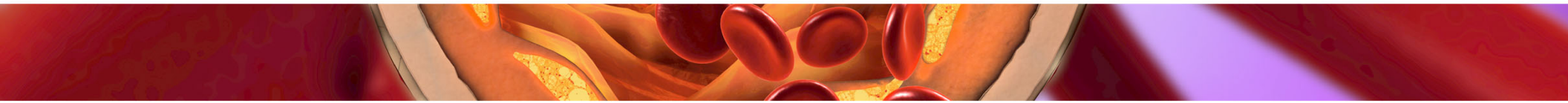
Agenda

- Update on Determining Risk Status in ASCVD
- Recent Evidence from REDUCE-IT: Latest Clinical Trials
- Differential Biological Effects of Omega-3 Fatty Acids
- Practical Considerations to Manage Residual Risk



Update on Determining Risk Status in ASCVD

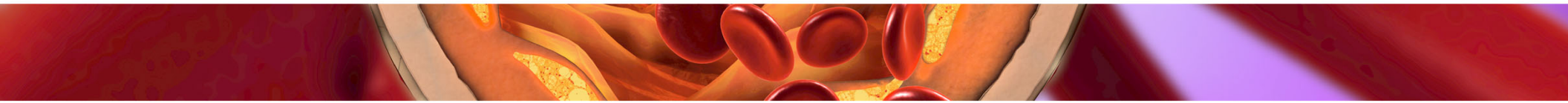
James Underberg, MD



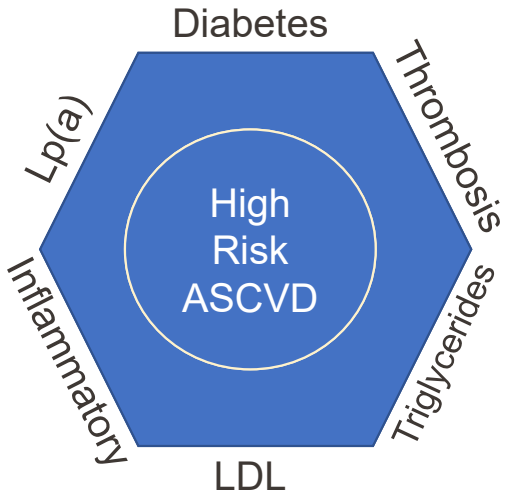
Polling Question

After an ASC event, what percent of your patients have optimized lipid management after one year?

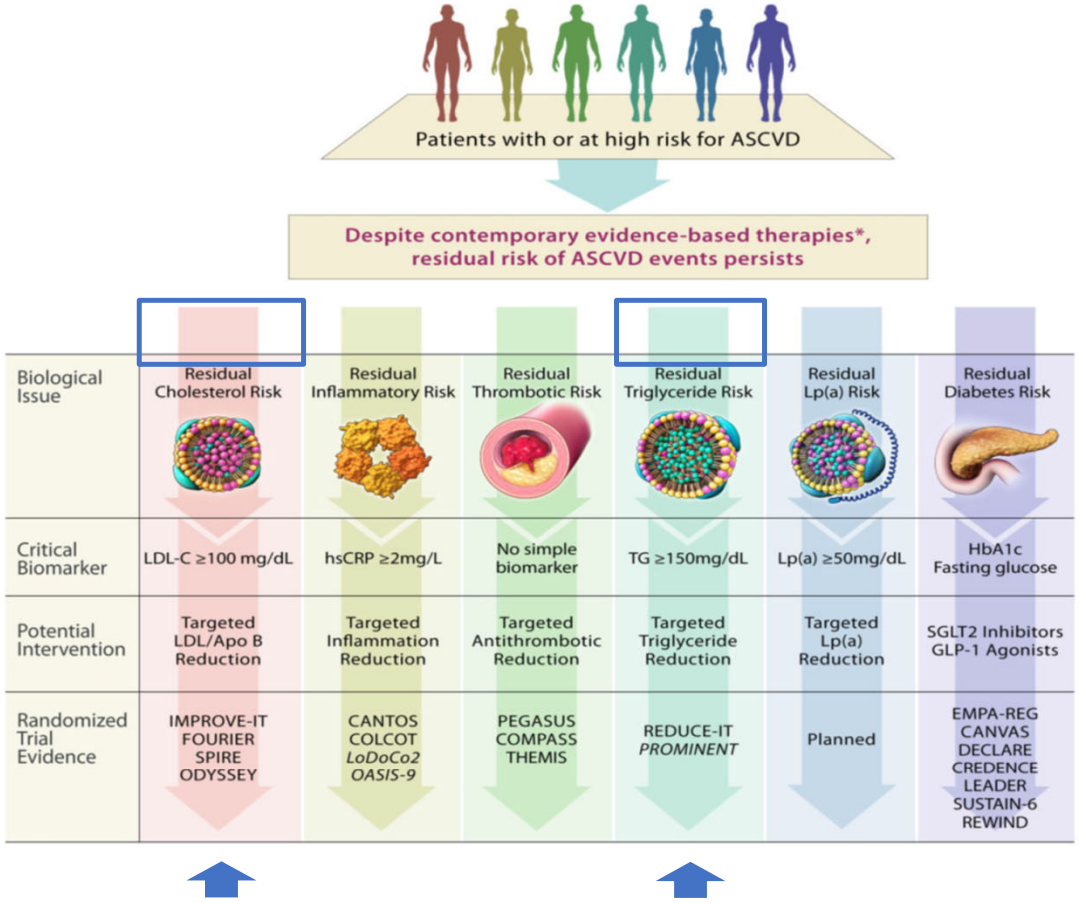
10%
30%
50%
80%
100%

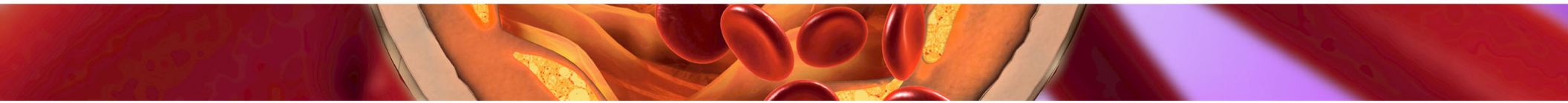


Risk Pathways in the Contemporary Management of ASCVD Risk



Lawler PR, et al. *Eur Heart J.* 2021;42(1):113-131.





General Approach to CV Risk Assessment

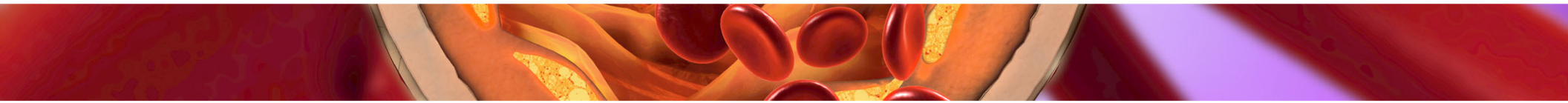
1. Use the ASCVDPlus to Assess Risk Category (q 5-6y for those without ASCVD)

<5% "Low Risk"	5% to <7.5% "Borderline Risk"	≥7.5% to <20% "Intermediate Risk"	≥20% "High Risk"

- Estimates 10-year hard ASCVD (nonfatal MI, CHD death, stroke) for ages 40-79 and lifetime risk for ages 20-59
- Intended to promote patient-provider risk discussion and best strategies to reduce risk
- ≥7.5% widely accepted threshold for initiating statin therapy, not a mandatory prescription for a statin

2. Then use the ACC/AHA Prevention guideline algorithms to guide management

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease.
Link to ASCVDplus: https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/
http://static.heart.org/riskcalc/app/index.html#!/baseline-risk

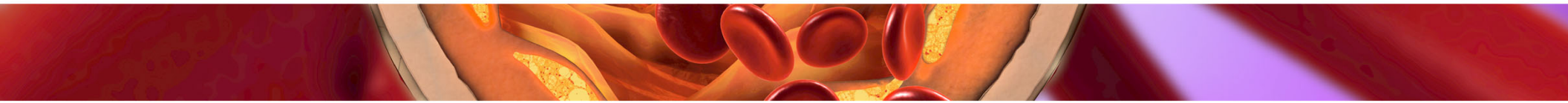


2018 Multisociety Cholesterol Guidelines and 2019 ACC/AHA Guidelines on Primary Prevention

- **Statin therapy is first-line treatment for prevention of ASCVD in patients with:**
  - Clinical ASCVD ✓
  - Elevated LDL-C levels (≥190 mg/dL) ✓
  - Diabetes mellitus who are age 40 to 75 years (LDL ≥70 mg/dL) ✓
  - Age 40-75 without above, but determined to be at sufficient ASCVD risk after a clinician–patient risk discussion

Introduced the Concept of Risk-Enhancing Factors

Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143. Arnett DK, et al. *Circulation*. 2019;140(11):e596-e646.



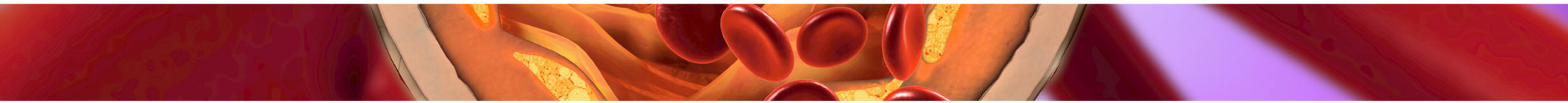
Risk-Enhancing Factors

- Family history of premature ASCVD (men <55 y; women <65 y)
- Primary hypercholesterolemia
- Metabolic syndrome (≥ 3 of: increased WC, increased TGs, increased BP, increased glucose, and decreased HDL-C)
- Chronic kidney disease
- Chronic inflammatory conditions (eg, psoriasis, RA, HIV/AIDS)

5% to <7.5%
"Borderline Risk"

≥7.5% to <20%
"Intermediate Risk"

Grundy SM, et al. Circulation. 2019;139(25):e1082-e1143.



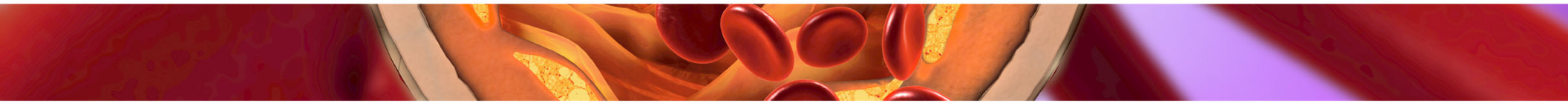
Additional Risk-Enhancing Factors

- History of premature menopause (before age 40 y) or pregnancy-associated conditions that ↑ASCVD risk (eg, preeclampsia)
- High-risk race/ethnicity (eg, South Asian ancestry)
- Persistent primary HTG (≥ 175 mg/dL), optimally 3 determinations
- If measured:
  - High-sensitivity C-reactive protein (≥ 2 mg/L)
  - Lipoprotein(a) (≥ 50 mg/dL or 125 nmol/L)
  - Apolipoprotein B (≥130 mg/dL)
  - Ankle-brachial index (< 0.9)

After Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143.

5% to <7.5%
"Borderline Risk"

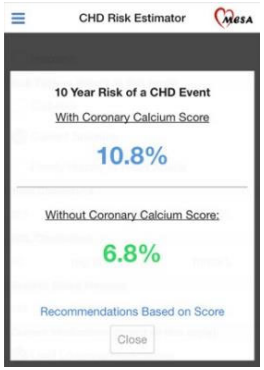
≥7.5% to <20%
"Intermediate Risk"



Selective Use of CAC Score to Guide Statin Therapy in Borderline and Intermediate-Risk Patients

- A CAC score predicts ASCVD events in a graded fashion
  - 0 statin therapy may be withheld or postponed unless higher-risk conditions are present
  - 1-99 favors statin therapy
  - 100+ initiate statin therapy

MESA Risk Score

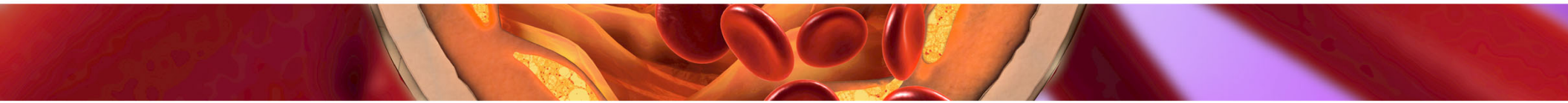


CARDIA

FRAMINGHAM HEART STUDY
Three Generations of Dedication
1948
1971
2002
A Project of the National Heart, Lung, and Blood Institute and Boston University

≥7.5% to <20%
"Intermediate Risk"

Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143. Authors/Task Force Members, et al. *Atherosclerosis.* 2019;290:140-205.



Very High-Risk ASCVD (Subgroup of Patients with ASCVD)

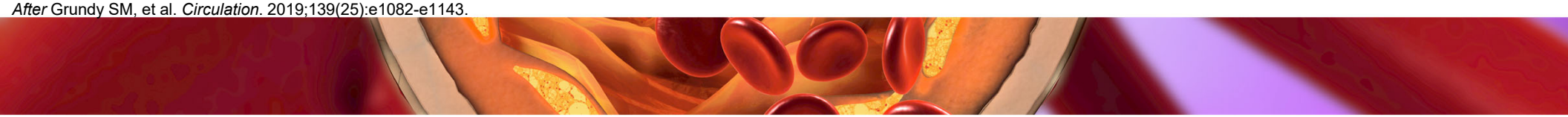
Major ASCVD Events
Recent ACS
History of MI
History of ischemic stroke
Symptomatic peripheral arterial disease

High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD
ated statin therapy and ezetimibe

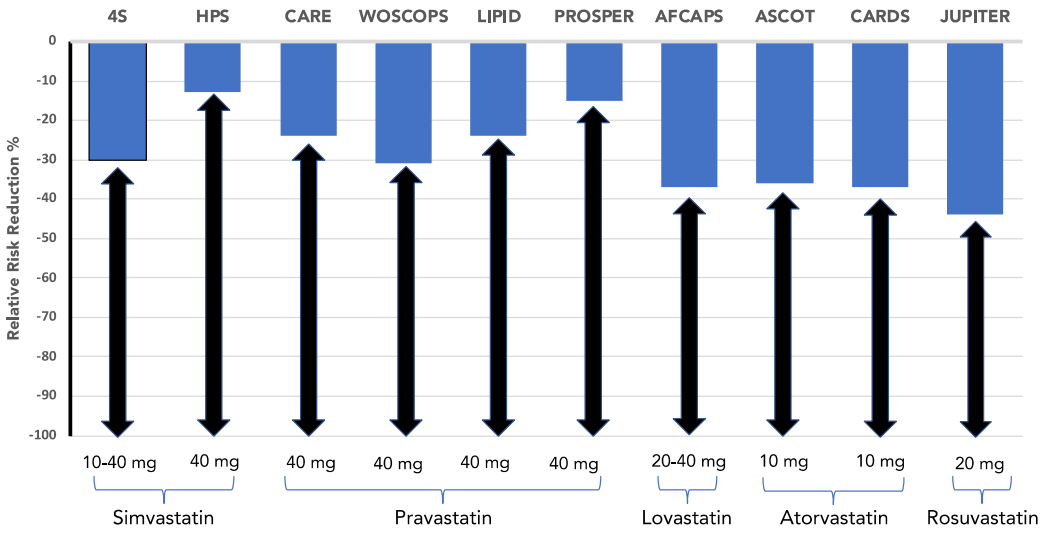
Very high risk = multiple major ASCVD events or 1 major ASCVD event + ≥2 high-risk conditions

→ Statins + ezetimibe + PCSK9i until LDL ≤ 70 mg/dL

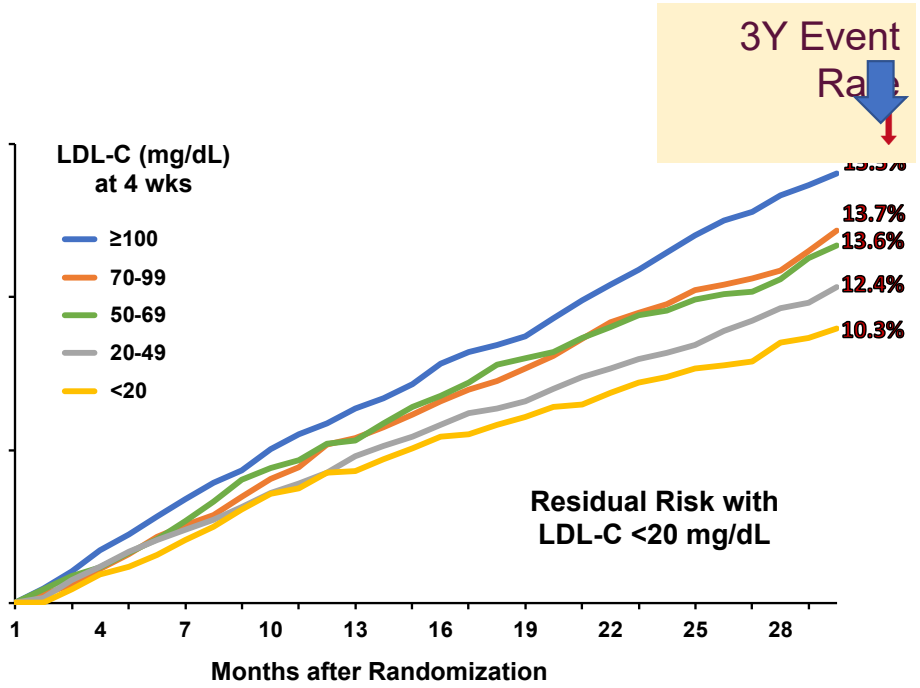
After Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143.



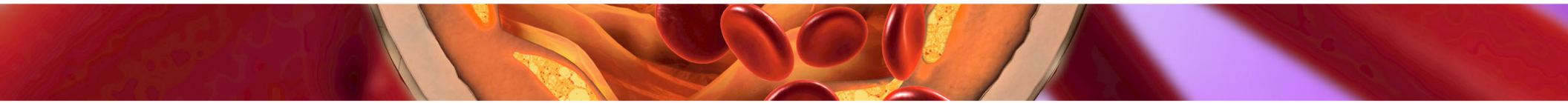
Despite ↓ASCVD with Statin Monotherapy or in Combination with PCSK9i, Substantial CV Risk Remains



Adapted from Chapman MJ, et al. *Pharmacol Ther*. 2010;126(3):314-345.

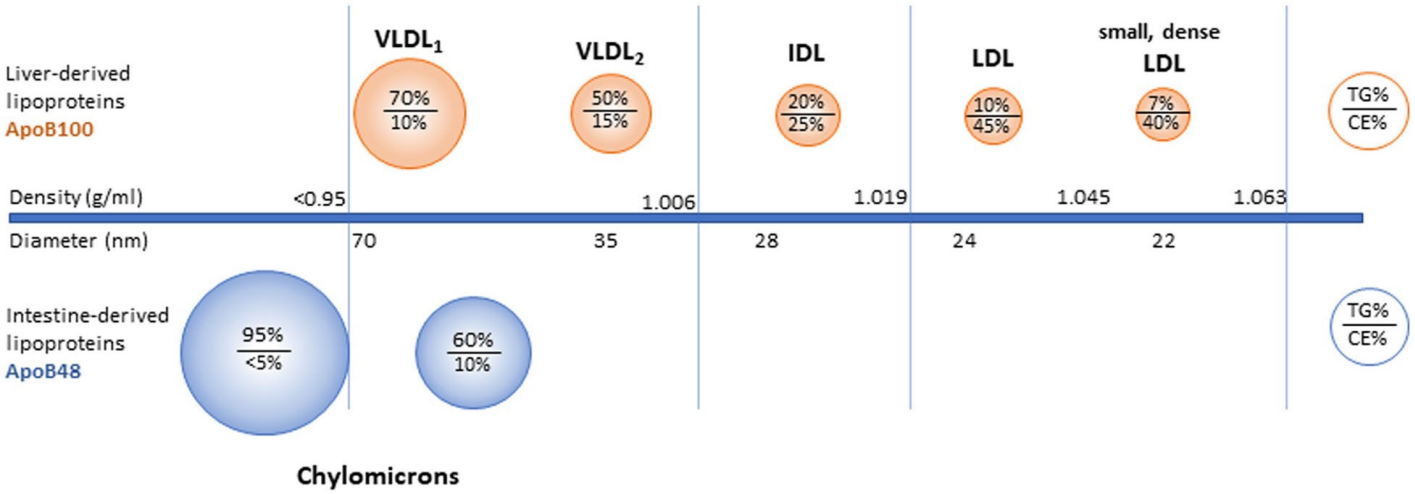


Giugliano RP, et al. *Lancet.* 2017;390(10106):1962-1971.

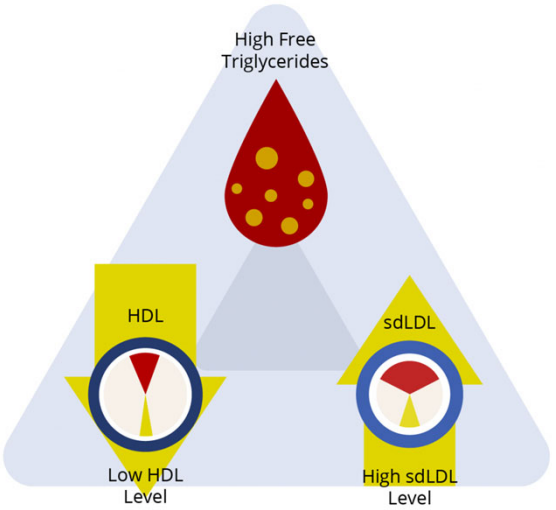


Management Strategies that Focus on LDL Ignore Other Atherogenic Lipids

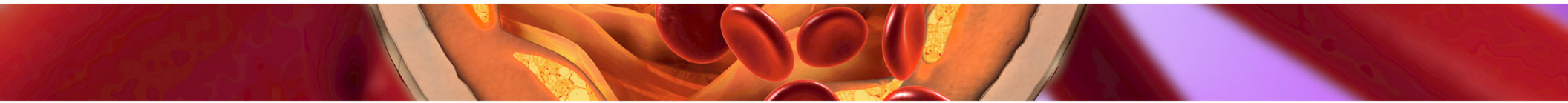
Atherogenic lipids (apo B containing lipid particles) include a range of particles



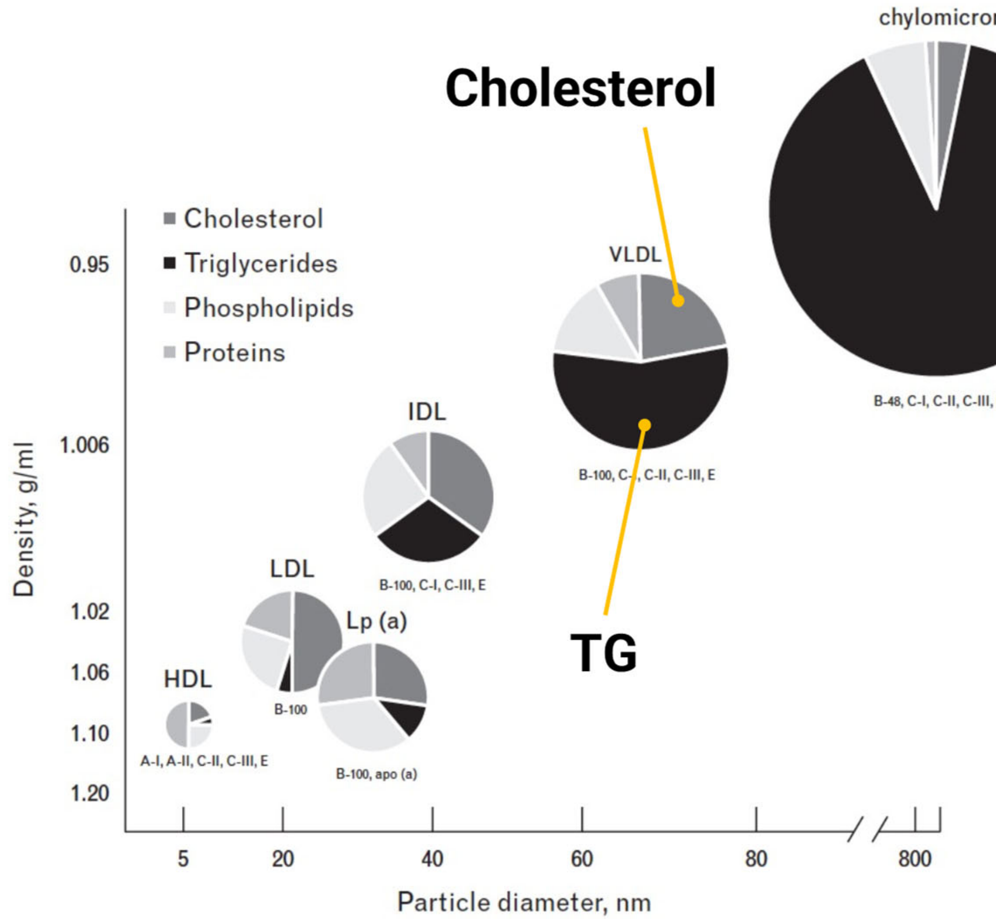
Atherogenic Dyslipidemia Triad
Clinical Markers



Ginsberg HN, et al. *Eur Heart J*. 2021;42(47):4791-4806,



Plasma TG estimates total TG <u>not</u> TG distribution or cholesterol content of TRLs: One-Third of Total Cholesterol



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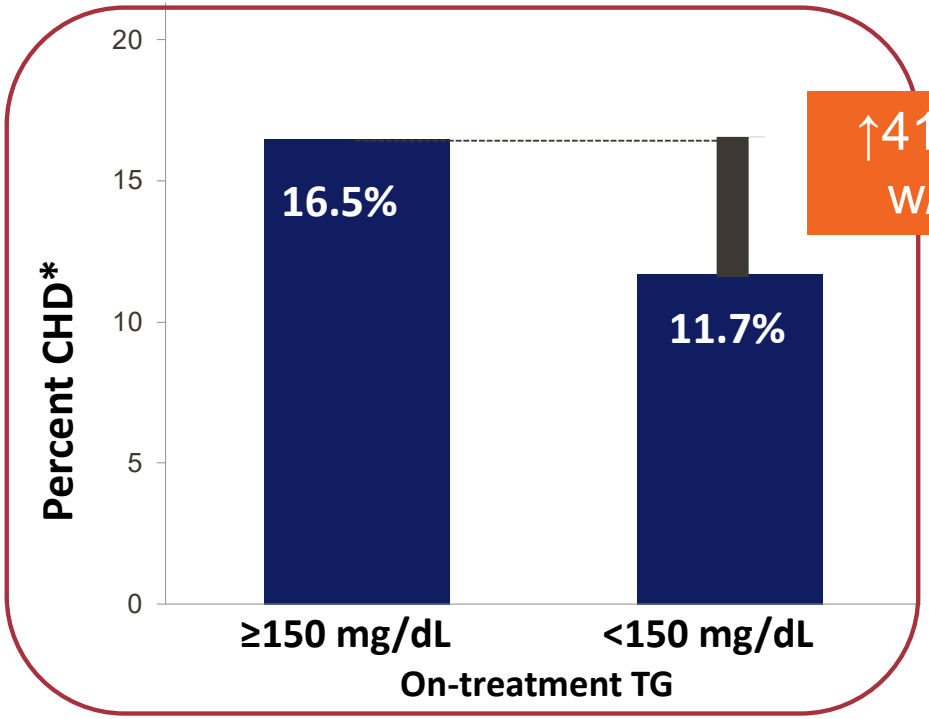
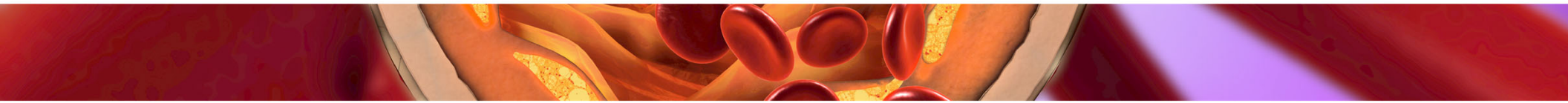
Residual HTG Predicted Residual ASCVD Risk Despite *LDL-C at Goal* on High-Intensity Statin Monotherapy

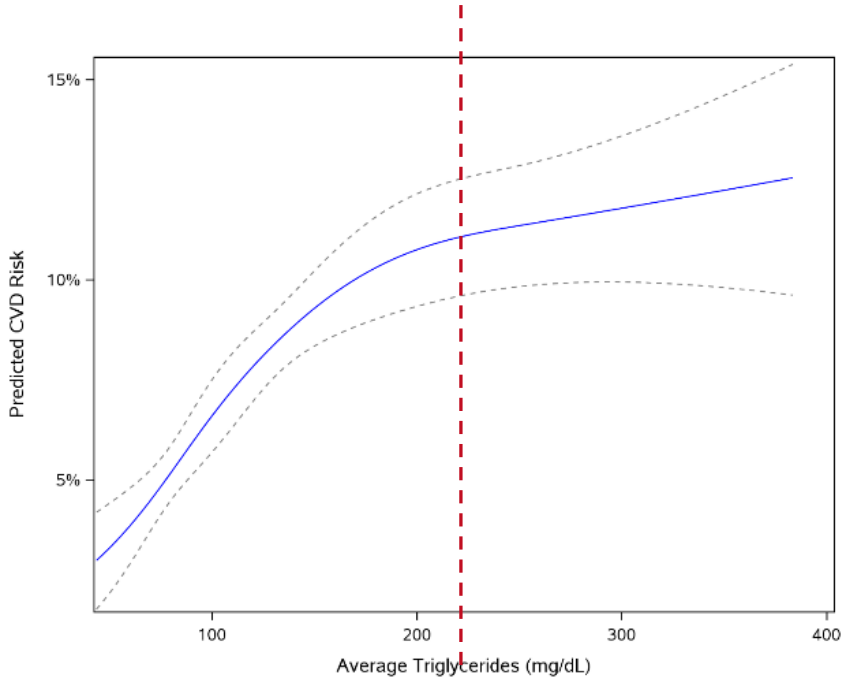


↑41% CVD risk w/ mild HTG

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



Lower Triglycerides Are Better: Direct Association Between Average Triglyceride Level and CVD

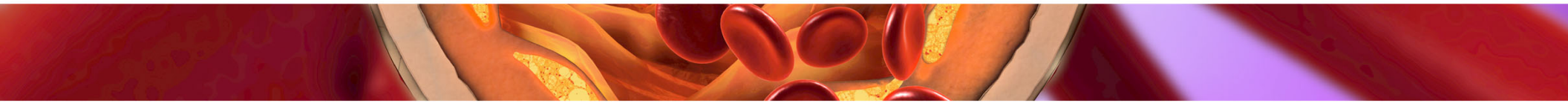


95% confidence intervals shown as dotted lines.

Aberra T, et al. J Clin Lipidol. 2020; 14(4):438-447.e3.

- Data from 8,068 primary prevention patients in Atherosclerosis Risk in Communities Study (ARIC) and Framingham Offspring Study
- Baseline characteristics:
  - 40 to 65 years old
  - No CVD
- ≥2 TG measurements on record
- Endpoint: Time to MI, stroke, or CV death
- Follow-up for up to 10 years to first event

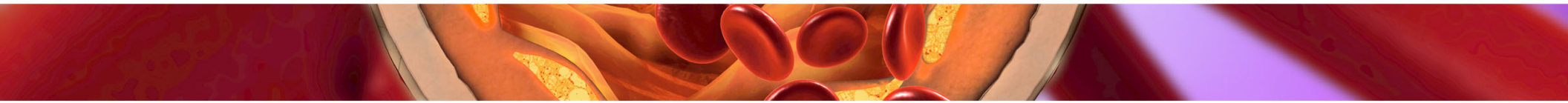
CVD events steeply increase across the entire range of TG levels to ~200 mg/dL, above which the relationship is less graded.



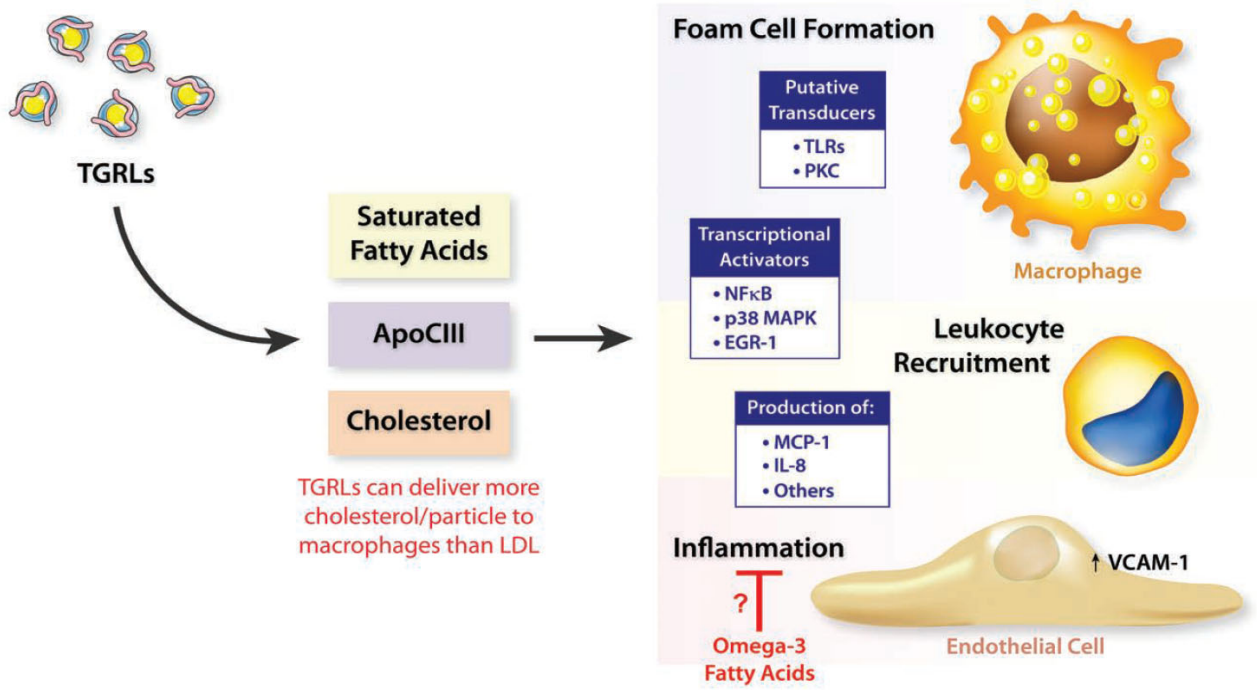
Why Triglyceride-Rich Lipoproteins and Their Remnants Are *Causally* Related to ASCVD

- Observational studies: mild-moderate HTG is a strong and independent predictor of ASCVD and all-cause mortality[1]
- Mendelian randomization (genetic) studies: factors related to TG metabolism support *causality* in ↑CV risk[2]
  - Apo A-5
  - Apo C-3
  - ANGPTL4
  - ANGPTL3
  - Lipoprotein lipase
- TG-rich lipoproteins promote inflammation much *more* than does LDL[3]
- Remnant lipoproteins accumulate in arterial intima macrophage foam cells *more readily* than does LDL[1]

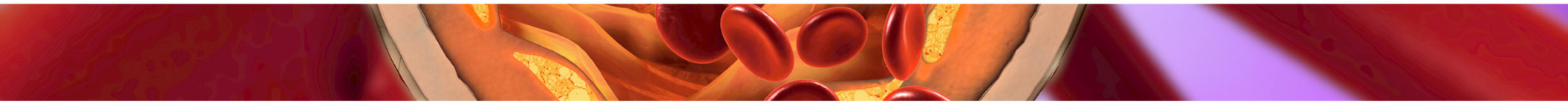
[1]Nordestgaard B. *Circ Res*. 2016;118(4):547-563. [2]Rip J, et al. *Arterioscler Thromb Vasc Biol*. 2006;26(6):1236-1245; [3]Hansen SEJ, et al. *Clin Chem*. 2019;65(2):321-332. Plutzky PNAS 2006. Johansen, et al. *J Lipid Res*. 2011;52(2):189-206. Voight BF, et al. *Lancet*. 2012;380(9841):572-580. Nordestgaard BG, Varbo A. *Lancet*. 2014;384(9943):626-635. TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. *N Engl J Med*. 2014;371(1):22-31. Wang J, et al. *Nat Clin Pract Cardiovasc Med*. 2008;5(11):730-737.



Atherogenic Pathways for Triglyceride-Rich Lipoproteins (TGRLs)



EGR-1, early growth response protein 1; LDL, low-density lipoprotein; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor-κB; PKC, protein kinase C; TLR, toll-like receptors; VCAM-1, vascular cell adhesion molecule 1.



What Does Expert Consensus Tell Us About Managing Triglycerides?

EXPERT CONSENSUS DECISION PATHWAY

2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia

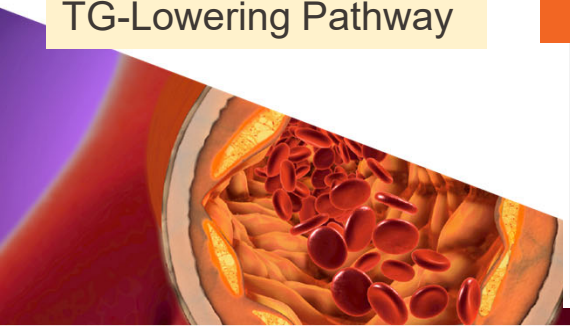
A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the National Lipid Association

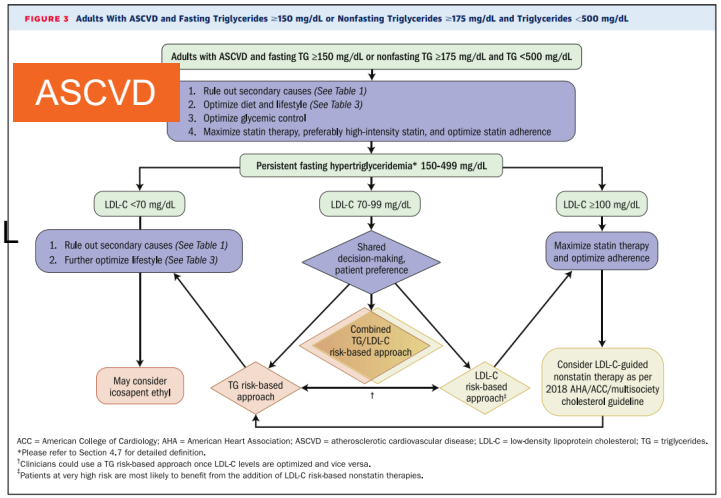
F TG ≥150 or NF ≥175 and <500 mg/dL
- ASCVD
- Age ≥ 40 with DM but no ASCVD
- Age ≥ 20 without ASCVD or DM

TG ≥ 500, "especially" ≥ 1000 mg/dL

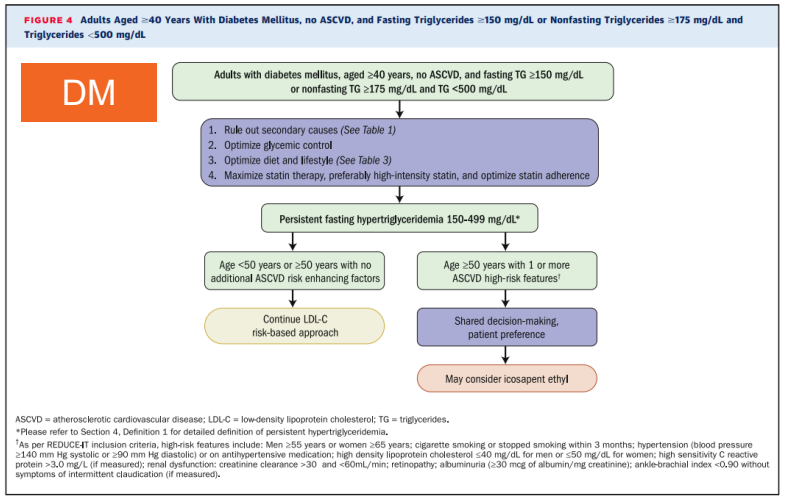
Medical Therapy
LDL-Lowering Pathway
TG-Lowering Pathway



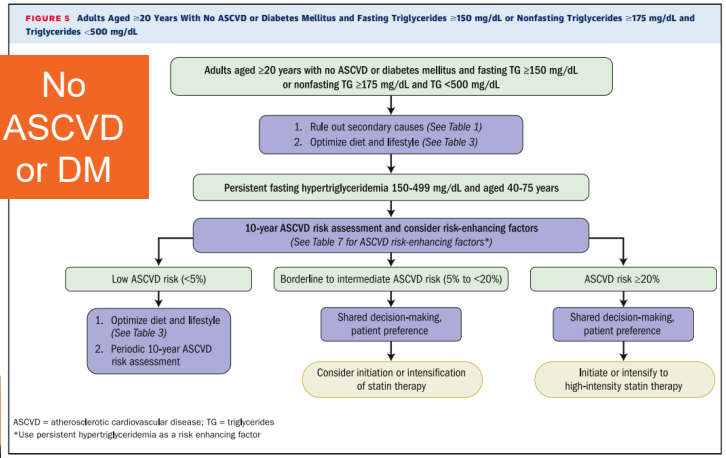
ASCVD



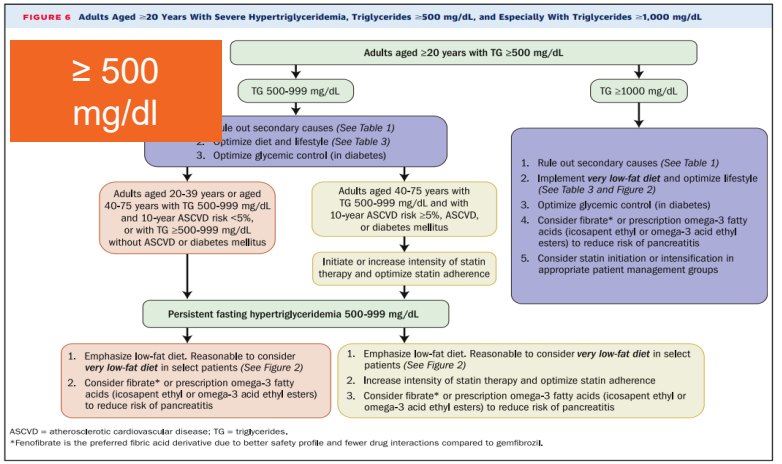
DM



No ASCVD or DM



≥ 500 mg/dl



First, Rule Out Major Secondary Causes of Hypertriglyceridemia

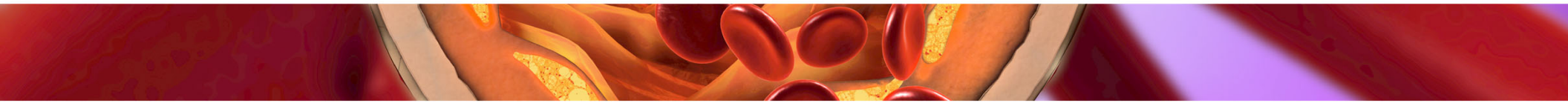
Conditions

- Diabetes mellitus, insulin resistance
- Obesity
- Alcohol
- Chronic kidney disease
- Nephrotic syndrome
- Hypothyroidism
- HIV
- Hepatocellular disease
- Inflammatory diseases

Medications

- Oral estrogens
- Bile acid sequestrants
- Antiretroviral regimens
  - especially for HIV disease
- Phenothiazines – 2nd generation
- Nonselective beta-blockers
- Diuretics
- Glucocorticoids
- Immunosuppressants
- Tamoxifen
- Isotretinoin

Bays HE. In: Kwiterovich PO Jr, ed. *The Johns Hopkins Textbook of Dyslipidemia*. 1st ed. Lippincott Williams & Wilkins;2010:245-257.



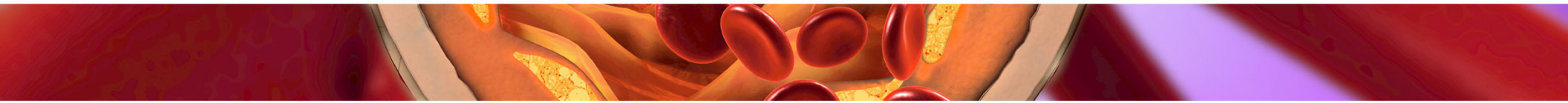
Second, Optimize Diet and Exercise

- Most important is what the patient can do, and do lifelong.
- Need consistent, relentless messaging from medical professionals

Lifestyle Intervention	Reduction in Triglycerides (%)	Qualifier
Weight loss (54-56)	Up to 70%	Although most patients will likely experience reductions in triglyceride levels of 10%-20% with weight loss, evidence suggests that in some patients, a reduction in triglyceride levels of up to 70% may be achieved
Dietary modifications (including alcohol—restrict or abstain completely) (57)	>70%	Response may vary depending on the baseline triglyceride level and how strictly dietary recommendations are followed
Physical activity and exercise (58-62)	Up to 30%	Response may vary depending on the type, duration, and intensity of activity

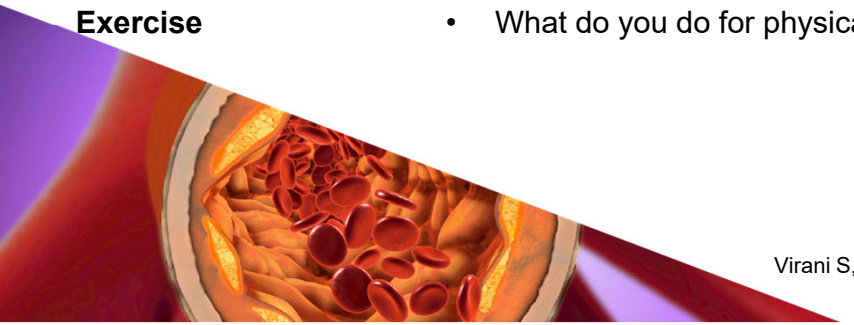
- Access and ability to pay for fresh fruits, vegetables, lean meat
- Processed foods require no preparation time
- In many places, unhealthy calories are simply the most affordable option
- But with exercise (cheap), a good rule of thumb is every 5% to 10% decrease in weight gets about 20% lower triglycerides

Virani S, et al. *J Am Coll Cardiol*. 2021;78(9):960-993.



Key Prompts and Messaging Regarding Diet and Exercise

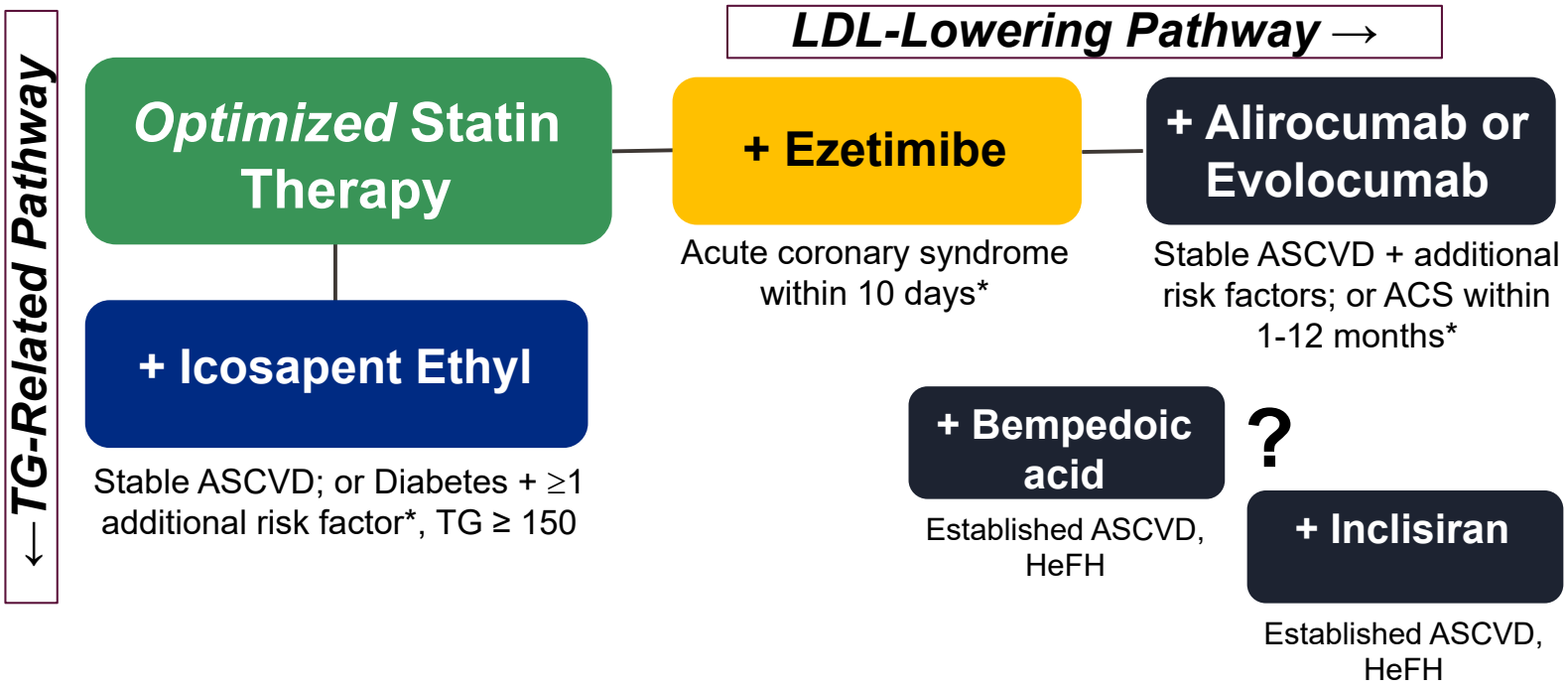
Component	Ask Your Patients	Clinical Message
Sugar-Sweetened Beverages	• How often do you drink sugar-sweetened beverages (soft drinks, fruit drinks, or sports/energy drinks)?	• Instead, try no-calorie sparkling water with lemon slice
Sweets	• How often do you eat sweets (pastries, desserts, or candy)?	• Instead, try fresh fruit or a small piece of dark chocolate
Alcohol	• How often do you drink alcoholic beverages (beer, wine, or spirits)?	• If you drink alcohol, have 1 beer or glass of wine instead of a mixed drink (high in alcohol, sugar, and calories)
Saturated Fats	• How often do you eat foods that are deep fried or high in saturated fats (butter, coconut oil, full-fat dairy, fatty red meat)?	• Try lean meats (chicken). Switch to liquid oils (canola or olive) instead of butter or tropical oils. Try switching to low-fat dairy.
Weight	• Have you gained any weight in the past year?	• If you are ready to lose weight, follow a healthy weight loss diet that achieves slow, steady (and sustained) weight loss instead of a fad diet
Exercise	• What do you do for physical activity? How often?	• Incorporate walks with small weights • Park farther away, take stairs, stand more



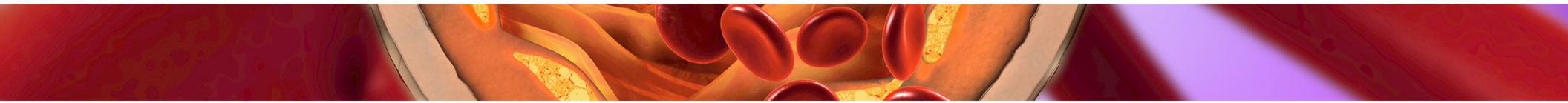
Be Specific
Be Numeric

Virani S, et al. *J Am Coll Cardiol*. 2021;78(9):960-993

Third, Medical Therapy

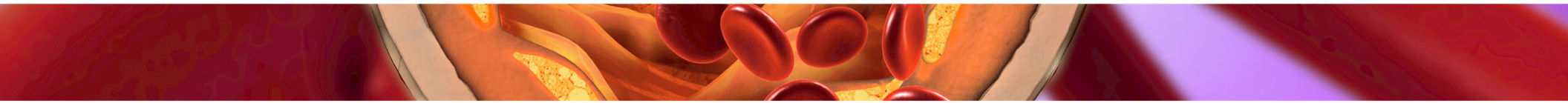


*Major inclusion criteria for respective CVOTs.
ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia.
After Orringer CE. *Trends in Cardiovasc Med*. 2019;30(3):151-157.



Our Patient – First Visit

- 60-year-old man
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, treated
- BMI 29 kg/m^2
- Smoker
- **What is his yearly risk of 'hard' cardiovascular endpoints (heart attack, stroke, or death from cardiovascular disease)?**



CVD Risk Scores in Secondary Prevention

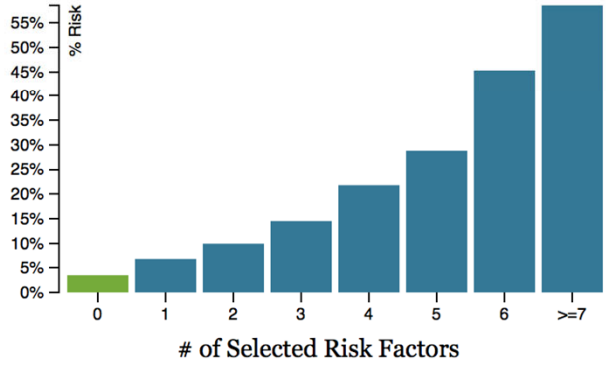
TIMI Risk Score for Secondary Prevention (TRS 2°P)

Risk in Patients with Known Atherosclerotic Vascular Disease

CHF
HTN
Age >= 75
DM
Prior Stroke
Prior CABG
PAD
eGFR < 60
Current Smoking

0 Risk Indicators Selected

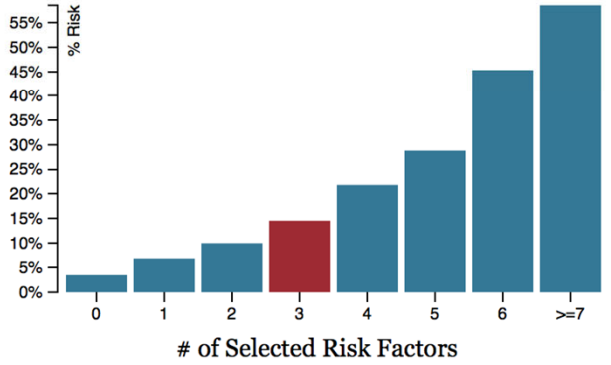
3.5% risk at 3 years of CV death, MI or Ischemic Stroke.



CHF
HTN
Age >= 75
DM
Prior Stroke
Prior CABG
PAD
eGFR < 60
Current Smoking

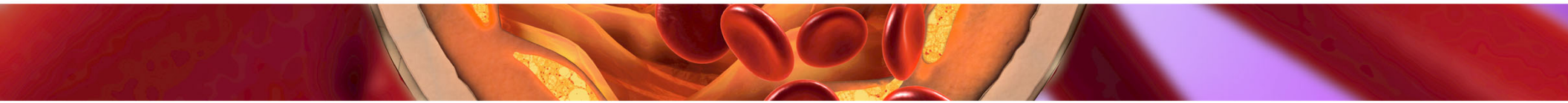
3 Risk Indicators Selected

14.5% risk at 3 years of CV death, MI or Ischemic Stroke.



Bohula EA, et al. Circulation 2016;134(4):304-313.

Validated in both trial and non-trial settings: www.timi.org

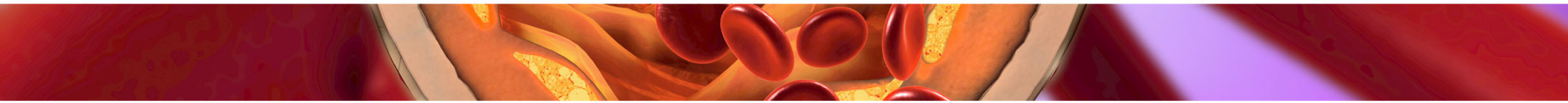


Our Patient – First Visit

Annual Risk of 3-Point MACE ~5% (TRS 2ºP)

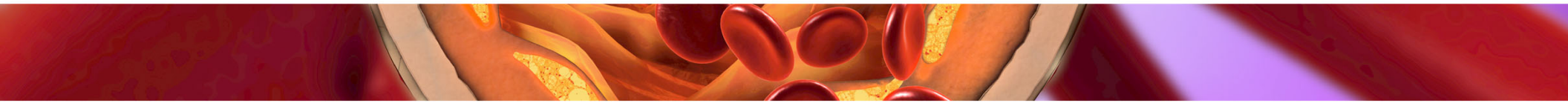
- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension
- BMI 29 kg/m^2

	Pre-Treatment
TC	260 mg/dL
LDL-C	170 mg/dL
TG	280 mg/dL
HDL-C	34 mg/dL
Non-HDL-C	226 mg/dL



Summary

- Assessment of ASCVD risk includes use of: the ASCVD risk calculator, CAC testing, identification of risk enhancing factors, and very high-risk groups **(LDL first)**
- Elevations in TG demonstrate increased risk in ASCVD events beyond monotherapy with statins **(residual TG risk)**
- TGs and their remnants, TGRLs, are atherogenic **(biology)**
- Elevated TG levels are pervasive in the US **(burden)**
- Guidelines are evolving to reflect these shifts **(treatment)**



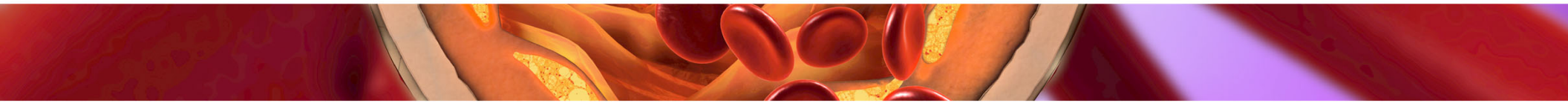
Recent Evidence from REDUCE-IT

Deepak L. Bhatt, MD, MPH

Executive Director of Interventional Cardiovascular Programs,
Brigham and Women's Hospital Heart and Vascular Center
Professor of Medicine, Harvard Medical School

BWH BRIGHAM AND WOMEN'S HOSPITAL
| Heart & Vascular Center |

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL



Disclosures

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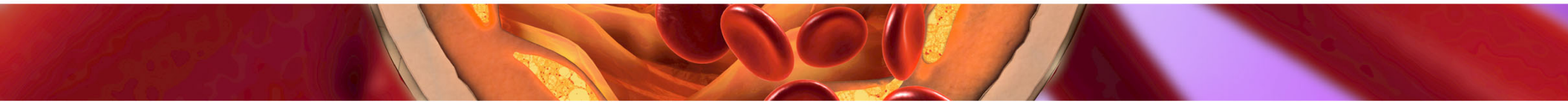
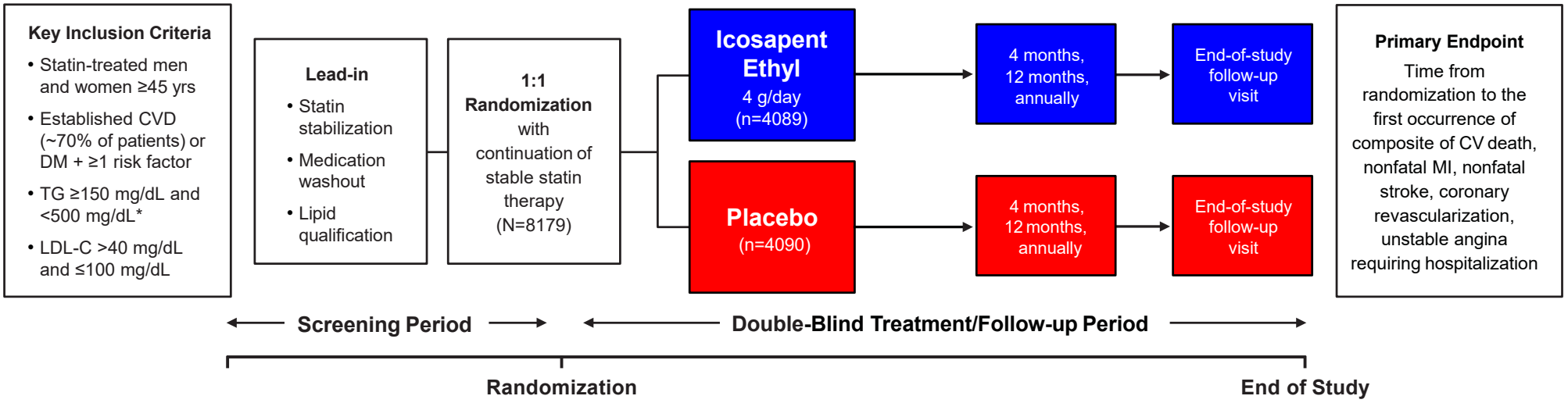
REDUCE-IT was sponsored by Amarin Pharma, Inc. This presentation may include off-label and/or investigational uses of drugs.



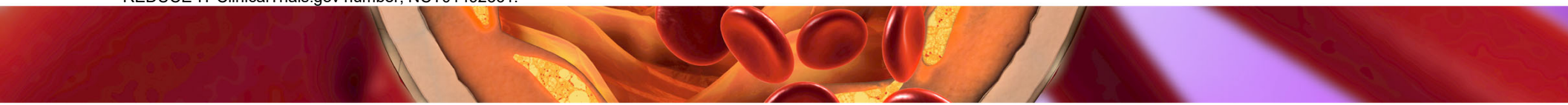
REDUCE-IT Design



*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).

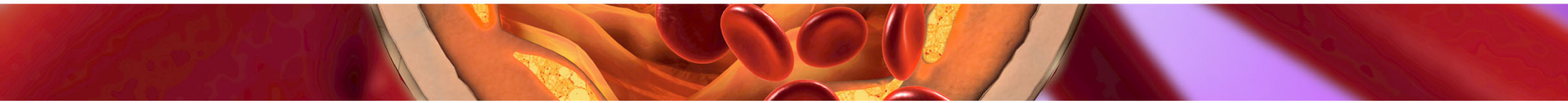
Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol.* 2017;40:138-148.
REDUCE-IT ClinicalTrials.gov number, NCT01492361.



Key Baseline Medical Therapy

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Antiplatelet	3257 (79.7%)	3236 (79.1%)
One Antiplatelet	2416 (59.1%)	2408 (58.9%)
Two or More Antiplatelets	841 (20.6%)	828 (20.2%)
Anticoagulant	385 (9.4%)	390 (9.5%)
ACEi or ARB	3164 (77.4%)	3176 (77.7%)
Beta Blocker	2902 (71.0%)	2880 (70.4%)
Statin	4077 (99.7%)	4068 (99.5%)

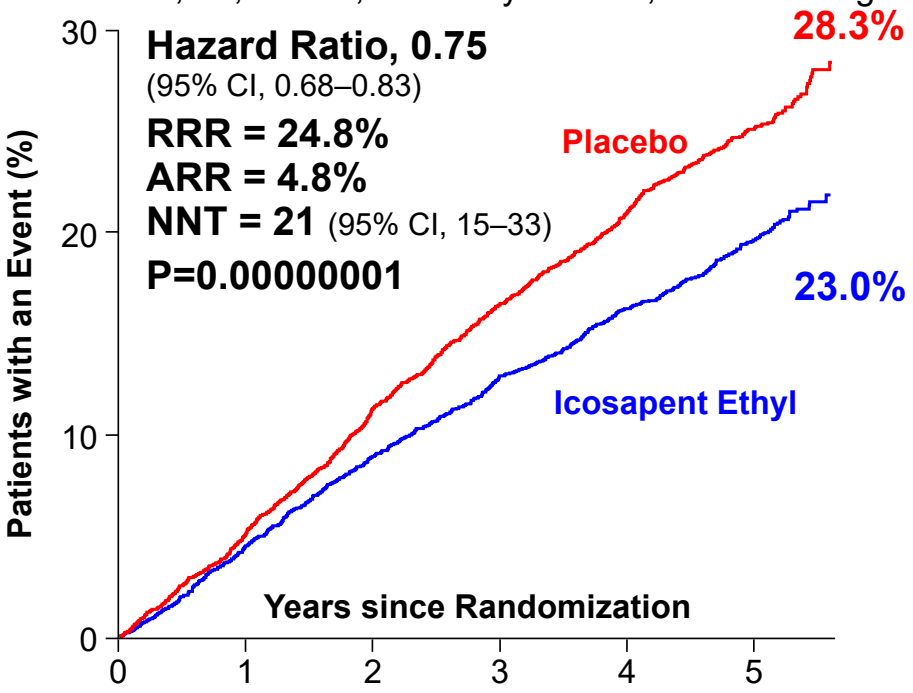
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802.



Primary and Key Secondary Composite Endpoints

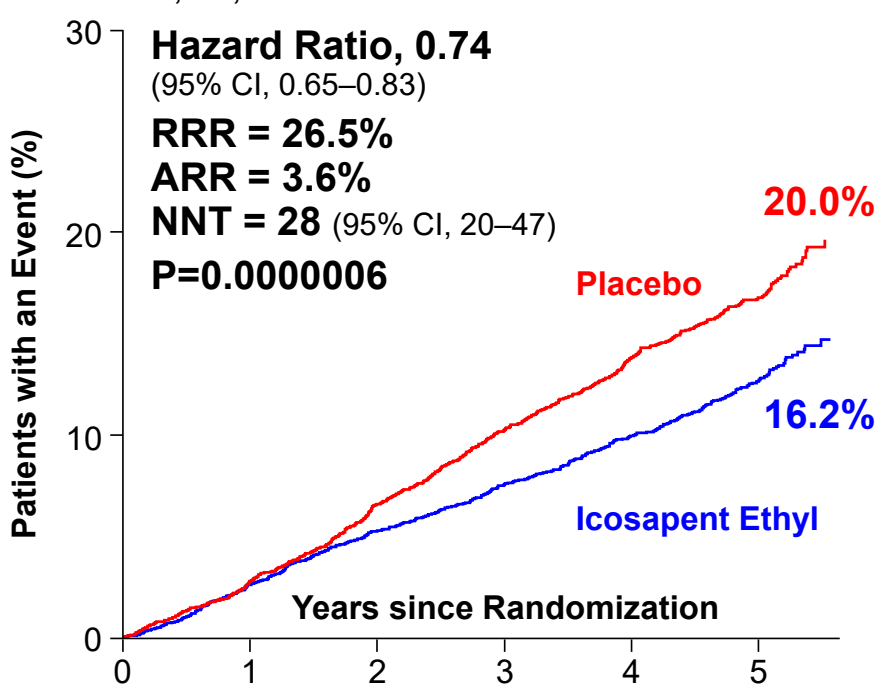
Primary Composite Endpoint:

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

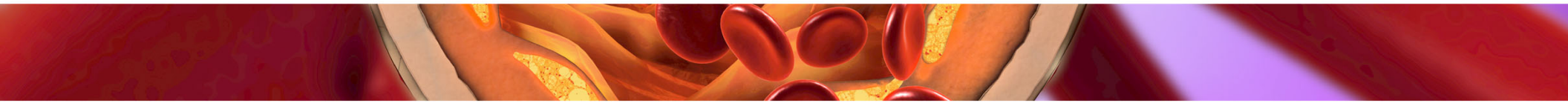


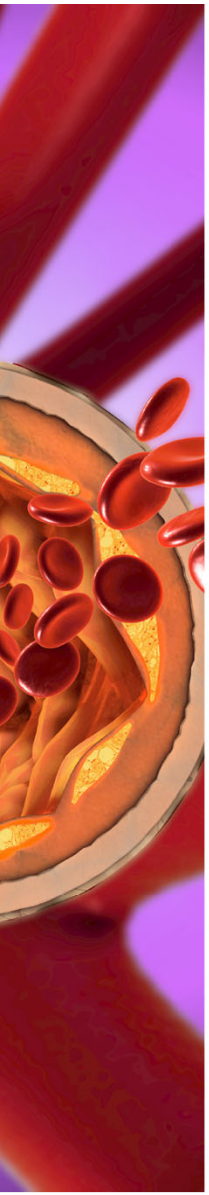
Key Secondary Composite Endpoint:

CV Death, MI, Stroke

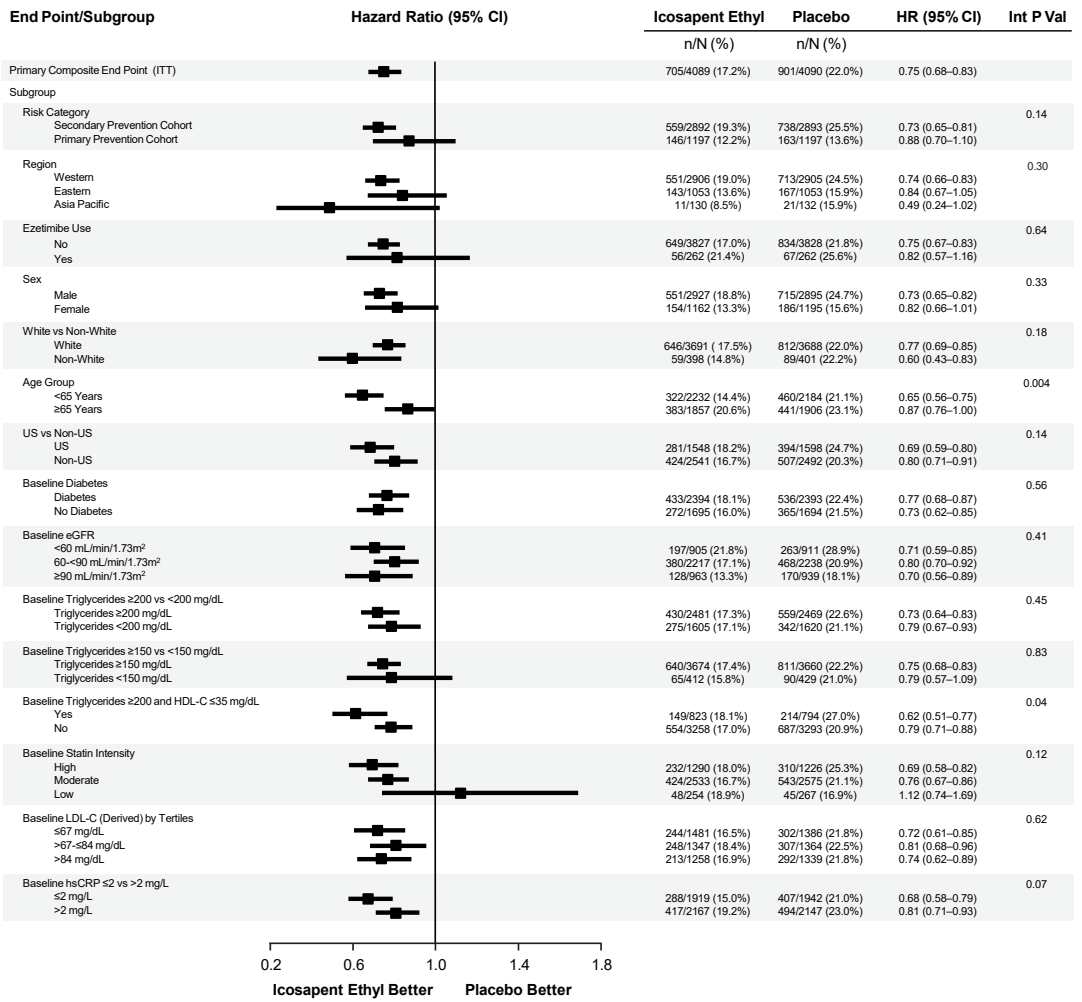


Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

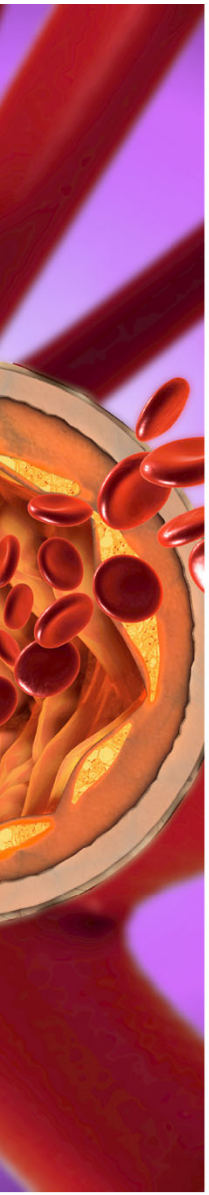




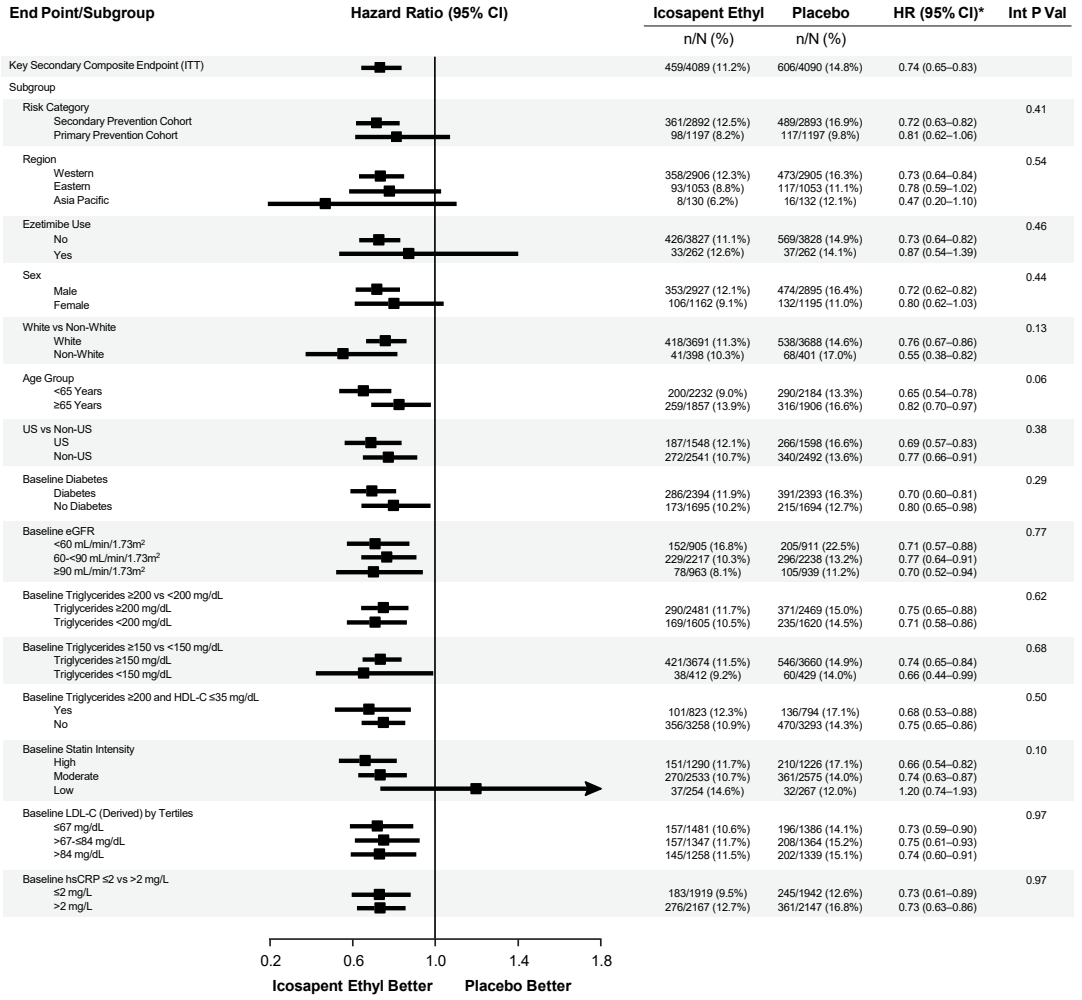
Primary End Point in Subgroups



Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22.



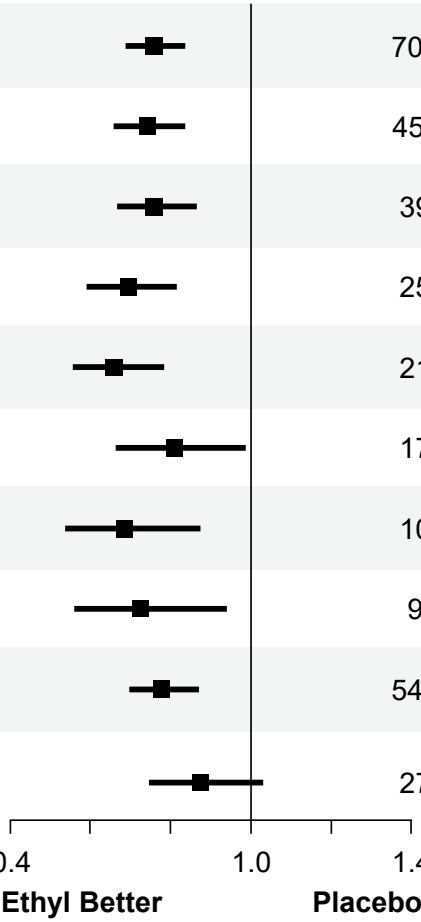
Key Secondary End Point in Subgroups



Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22.

Prespecified Hierarchical Testing

Endpoint	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 Emergent 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

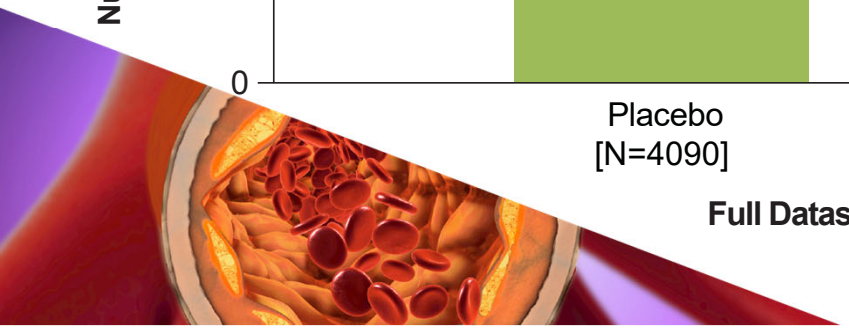


RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

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

First and Subsequent Events – Full Data



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

Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802. Bhatt DL. ACC 2019, New Orleans.

Treatment-Emergent Adverse Events

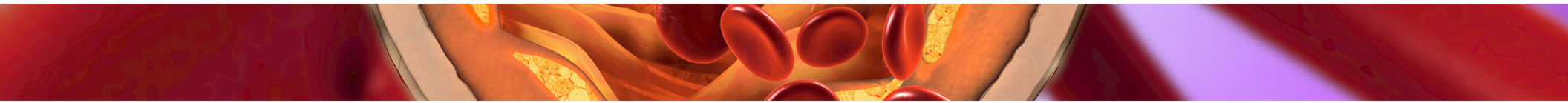
No Overall Treatment Difference in Adverse Event Profiles

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value*
Subjects with at Least One TEAE, n (%)	3343 (81.8%)	3326 (81.3%)	0.63
Serious TEAE	1252 (30.6%)	1254 (30.7%)	0.98
TEAE Leading to Withdrawal of Study Drug	321 (7.9%)	335 (8.2%)	0.60
Serious TEAE Leading to Withdrawal of Study Drug	88 (2.2%)	88 (2.2%)	>0.99
Serious TEAE Leading to Death	94 (2.3%)	102 (2.5%)	0.61

TEAE event rates represent the enrolled high CV risk patients and the 4.9-year median study follow-up.

* From Fisher's exact test.

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



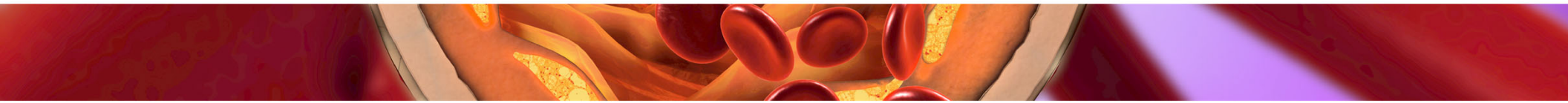
Treatment-Emergent Adverse Event of Interest: Bleeding

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value*
All Bleeding TEAEs	482 (11.8%)	404 (9.9%)	0.006
Bleeding SAEs	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
Intracranial Bleeding	0 (0.0%)	1(0.0%)	>0.99
Hemorrhagic Stroke	13 (0.3%)	10 (0.2%)	0.54

Note: Hemorrhagic stroke was an adjudicated endpoint; other bleeding events were included in safety analyses

* From Fisher's exact test.

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22. FDA Advisory Committee, 2019.



Atrial Fibrillation or Flutter

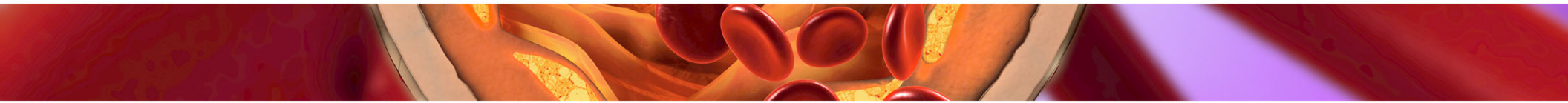
- Atrial fibrillation/flutter requiring hospitalization ≥24 hours was an adjudicated efficacy endpoint
- All other atrial fibrillation/flutter events reside in the safety database

	Icosapent Ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	P-value*
Afib/Aflutter TEAEs and positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalization	321 (7.9)	248 (6.1)	0.002
Afib/Aflutter TEAEs[1]	236 (5.8)	183 (4.5)	0.008
Serious Afib/Aflutter TEAEs[2]	22 (0.5)	20 (0.5)	0.76
Positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalization[3]	127 (3.1)	84 (2.1)	0.004

Note: Clinical consequences, including stroke, MI, cardiac arrest, and sudden cardiac death were reduced in the overall ITT population, with consistent results in those with a history of atrial fibrillation at baseline.

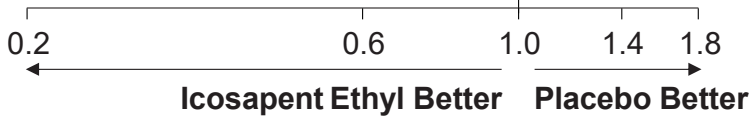
* From Fisher's exact test.

1. Includes atrial fibrillation/flutter TEAEs. 2. Includes a subset of atrial fibrillation/flutter AEs meeting seriousness criteria. 3. Includes positively adjudicated atrial fibrillation/flutter requiring ≥24 hours hospitalization clinical events by the Clinical Endpoint Committee.



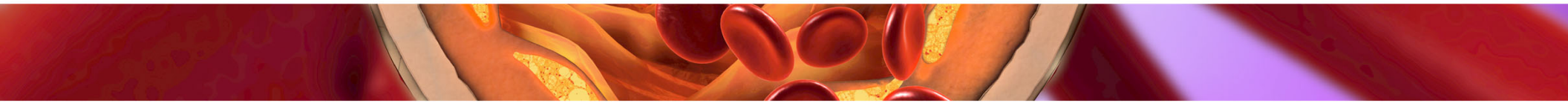
Primary Composite Endpoint: Total Events by Baseline TG Tertiles

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*				
≥0.9 to ≤2.1 mmol/L	56.4	74.5	0.74 (0.61–0.90)	0.0025
>2.1 to ≤2.8 mmol/L	63.2	86.8	0.77 (0.63–0.95)	0.0120
>2.8 to ≤15.8 mmol/L	64.4	107.4	0.60 (0.50–0.73)	<0.0001



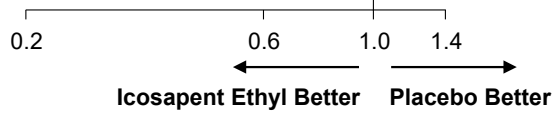
***P (interaction) = 0.17**

Bhatt DL, Steg PG, Miller M, et al. J Am Coll Cardiol. 2019; 74:1159-61.



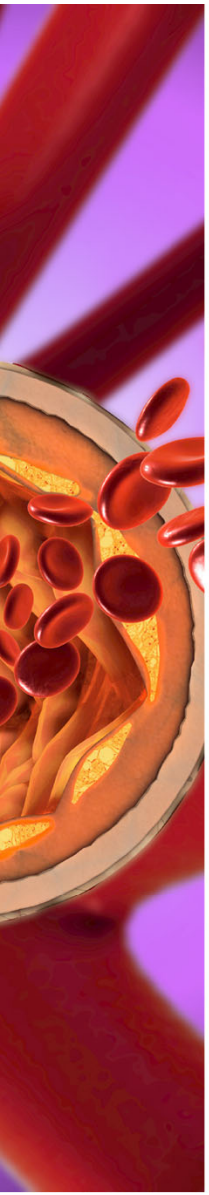
Total Key Secondary Endpoint Events: Biomarkers

Endpoint/Subgroup	N	Icosapent Ethyl, Rate per 1000 Patient Years	Placebo, Rate per 1000 Patient Years	ARD, Events per 1000 Patient Years	Rate Ratio (95% CI)	P value for Interaction
Overall Primary Endpoint	8179	31.7	44.1	-12.4	0.72 (0.63–0.82)	
Biomarkers						
Baseline triglycerides (200)						0.89
≥200 mg/dL (2.3 mmol/L)	4950	33.9	47.7	-13.8	0.71 (0.60–0.84)	
<200 mg/dL (2.3 mmol/L)	3225	28.6	39.2	-10.6	0.72 (0.58–0.90)	
Baseline triglycerides ≥200 mg/dL (2.3 mmol/L and HDL-C <35 mg/dL (0.9 mmol/L)						0.37
Yes	1617	35.9	57.7	-21.8	0.63 (0.48–0.83)	
No	6511	30.6	41.1	-10.6	0.74 (0.63–0.86)	
Baseline LDL cholesterol tertiles						0.77
≤67 mg/dL (1.7 mmol/L)	2867	30.4	45.0	-14.5	0.67 (0.53–0.85)	
>67-84 mg/dL (1.7-2.2 mmol/L)	2711	31.7	45.1	-13.4	0.72 (0.57–0.90)	
>84 mg/dL (2.2 mmol/L	2597	33.1	42.2	-9.0	0.76 (0.61–0.96)	
Baseline high-sensitivity CRP						0.42
≤2 mg/L	3861	24.6	36.1	-11.5	0.67 (0.55–0.82)	
>2 mg/L	4314	38.2	51.6	-13.4	0.75 (0.63–0.89)	



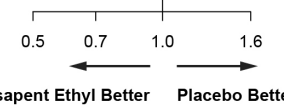
ARD = Absolute Risk Difference

Bhatt DL, Steg PG, Miller, M et al., ESC 2020, Amsterdam (virtual)



Primary and Key Secondary Endpoints: By Statin and Lipophilicity

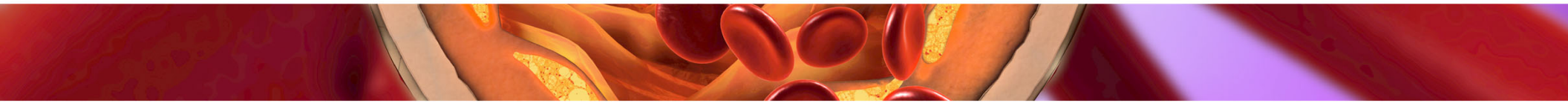
Endpoint/Subgroup	Icosapent Ethyl	Placebo	Icosapent Ethyl vs. Placebo	P-value	Interaction P-value
	n/N (%)	*n/N (%)*	*HR (95% CI)*		
Primary Endpoint	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68, 0.83)	<0.0001	
Statin Agent					0.95
Atorvastatin	253/1472 (17.2)	314/1495 (21.0)	0.79 (0.67, 0.93)	0.006	
Simvastatin	188/992 (19.0)	209/918 (22.8)	0.79 (0.65, 0.96)	0.02	
Rosuvastatin	110/734 (15.0)	149/741 (20.1)	0.73 (0.57, 0.94)	0.01	
Pravastatin	49/266 (18.4)	58/246 (23.6)	0.79 (0.54, 1.16)	0.24	
Statin Category					0.67
Lipophilic	475/2631 (18.1)	581/2635 (22.0)	0.78 (0.69, 0.88)	<0.0001	
Lipophobic	161/1017 (15.8)	210/1008 (20.8)	0.75 (0.61, 0.93)	0.007	
Key Secondary Endpoint	459/4089 (11.2)	606/4090 (14.8)	0.74 (0.65, 0.83)	<0.0001	
Statin Agent					0.68
Atorvastatin	168/1462 (11.5)	225/1487 (15.1)	0.73 (0.59, 0.89)	0.002	
Simvastatin	132/972 (13.6)	134/888 (15.1)	0.86 (0.68, 1.10)	0.24	
Rosuvastatin	67/730 (9.2)	94/725 (13.0)	0.71 (0.52, 0.97)	0.03	
Pravastatin	35/261 (13.4)	41/238 (17.2)	0.78 (0.50, 1.23)	0.29	
Statin Category					0.74
Lipophilic	318/2618 (12.1)	400/2618 (15.3)	0.76 (0.66, 0.88)	0.0003	
Lipophobic	102/1008 (10.1)	137/986 (13.9)	0.73 (0.57, 0.95)	0.02	



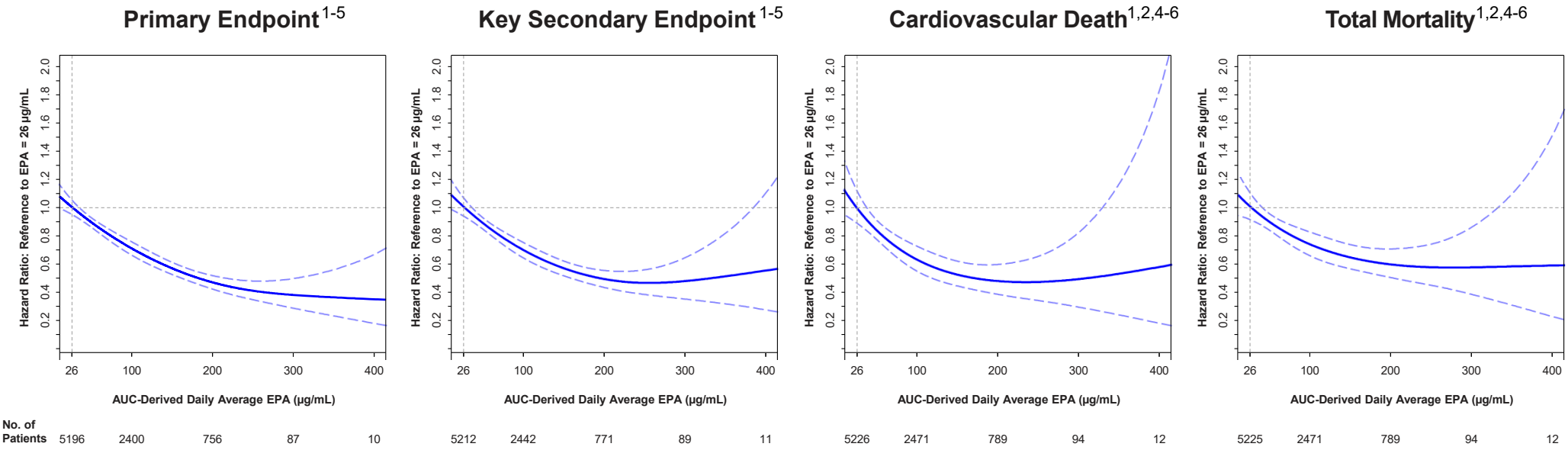
Patients taking more than one statin before the onset of a primary or key secondary endpoint were excluded from Statin Agent analysis, and patients taking statins with different lipophilicity before the onset of an endpoint were excluded from Statin Category analysis.

Singh N, Bhatt DL, Miller, M et al. *J Am Coll Cardiol*. 2022; 79:220-222.

reduce-it EPA



Primary and Key Secondary Composite Endpoints, Cardiovascular Death, and Total Mortality by On-Treatment Serum EPA

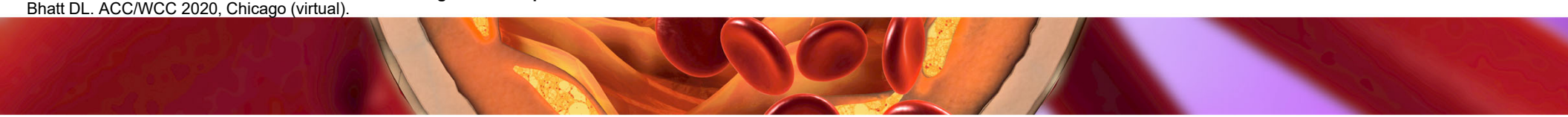


P*<0.001 for all

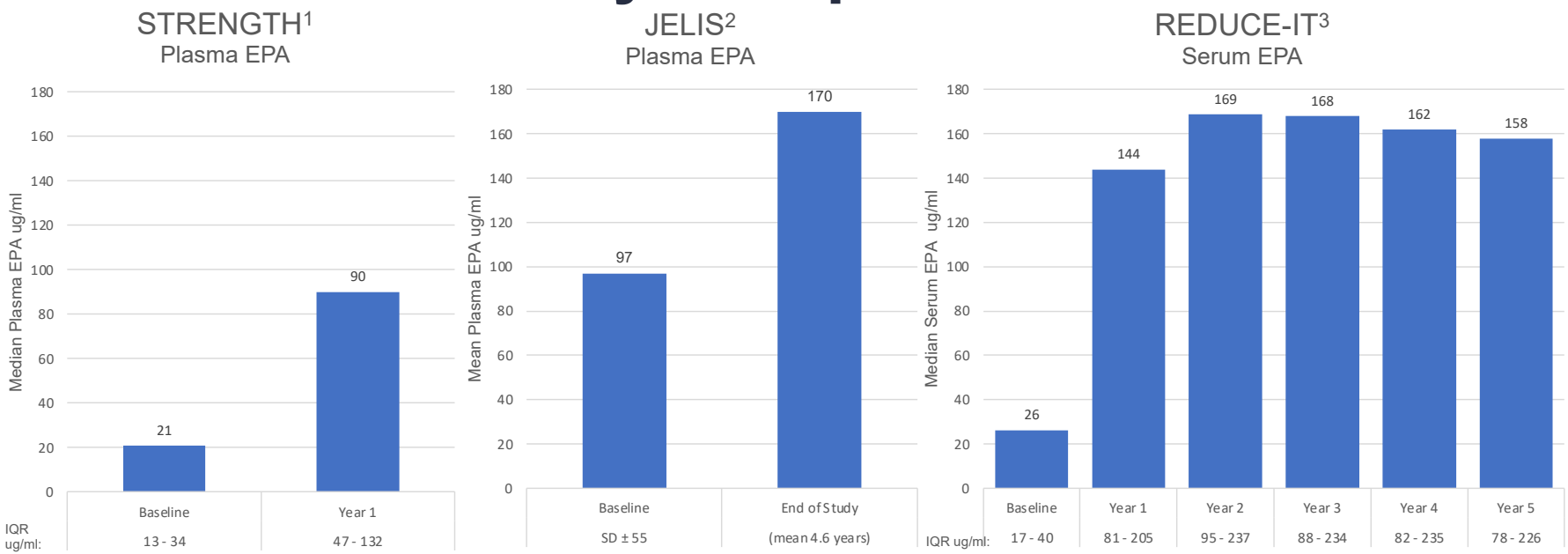
Note: Area under the curve (AUC)-derived daily average serum EPA (µg/mL) is the daily average of all available post baseline EPA measurements prior to the event. Dose-response hazard ratio (solid line) and 95% CI (dotted lines) are estimated from the Cox proportional hazard model with a spline term for 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).



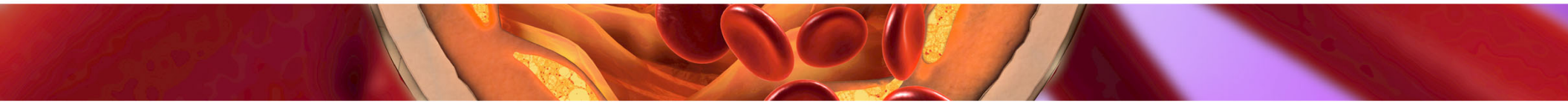
Baseline and Achieved EPA Levels in Omega-3 CVOTs Cross-study Comparison



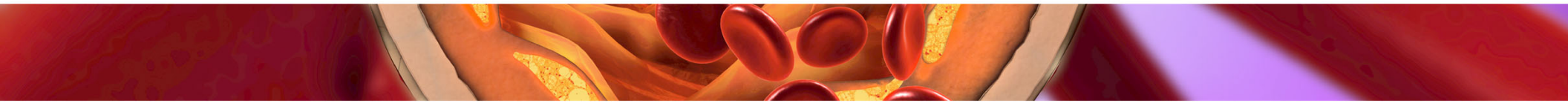
Drug:	850 mg mixed omega-3 carboxylic acid / 1g capsule	>980 mg EPA ethyl ester / 1g capsule	1g icosapent ethyl (EPA ethyl ester) / 1g capsule
Dose		1.8 g/d	4 g/d
Population:	International	Japanese	International

Plasma and serum EPA levels have been strongly correlated, with plasma levels being slightly higher than serum levels[4,5]

1. Nicholls SJ, et al. *JAMA*. 2020 Nov 15:e2022258 2. Itakura H, et al. *J Atheroscler Thromb*. 2011;18:99–107. 3. Bhatt DL, et al. ACC 2020 Scientific Session (ACC.20)/World Congress of Cardiology (WCC): Abstract 20-LB-20501-ACC. Presented March 30, 2020. 4. Dunbar RL, et al. Poster presented at the Gordon Conference on Atherosclerosis, June 16-21, 2019, Newry, Maine. 5. Dunbar, RL, et al. poster presented at NLA Scientific Sessions, Dec 9-12, 2020.



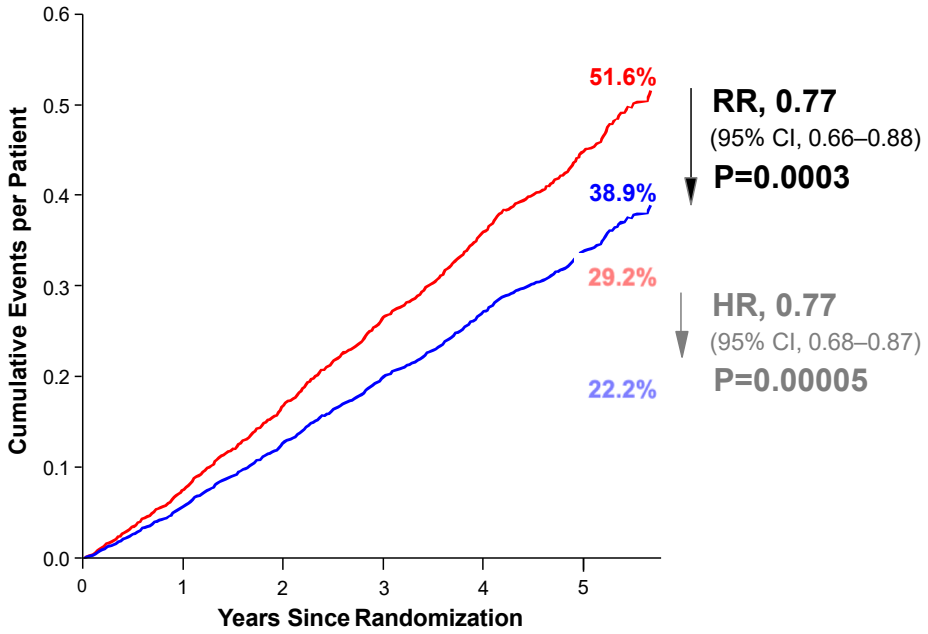
reduce-it DIABETES



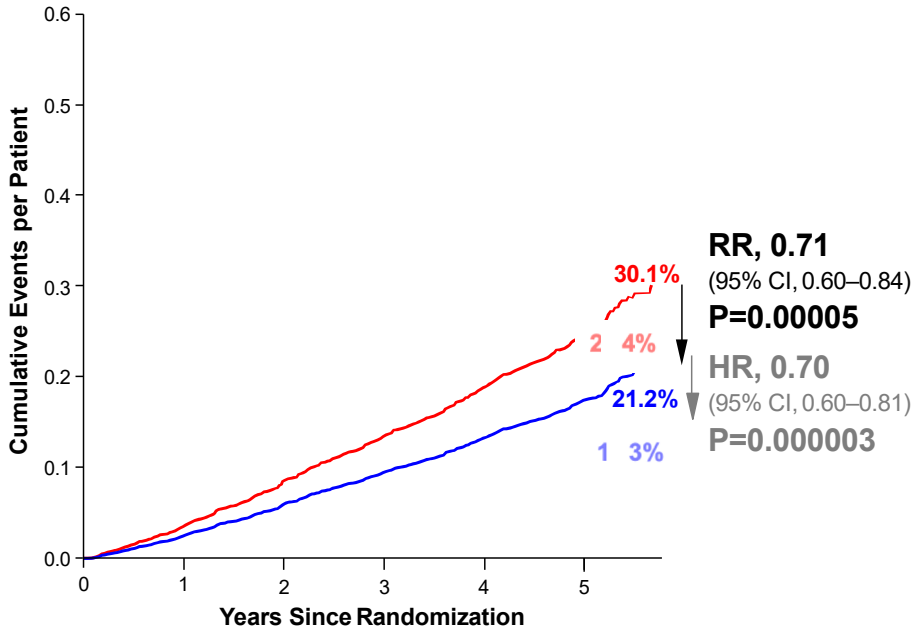
Time to First and Total Primary and Key Secondary Endpoint Events:
Diabetes Subgroup: N=4787

reduce-it DIABETES

Primary Composite Endpoint



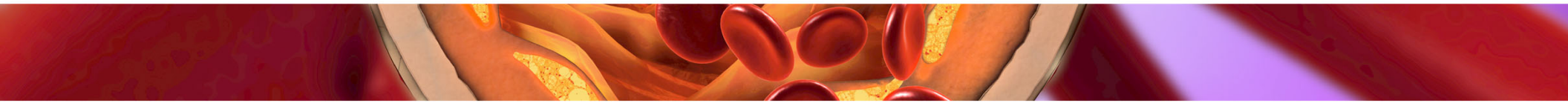
Key Secondary Composite Endpoint



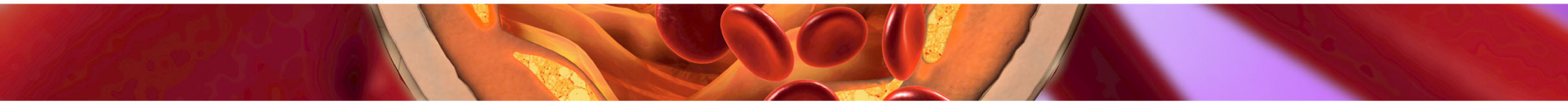
Placebo: Total Events — Icosapent Ethyl: Total Events — Placebo: First Events — Icosapent Ethyl: First Events

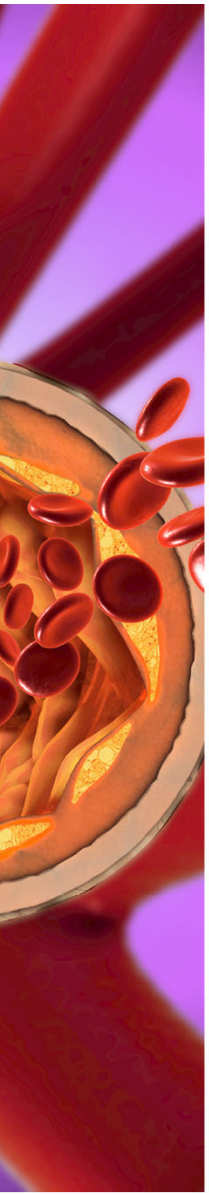
Bhatt DL, Brinton EA, Miller M, et al. ADA 2020, Chicago (virtual).

Total events analyses are based on reduced dataset accounting for statistical handling of multiple endpoints occurring in a single calendar day by counting as a single event.

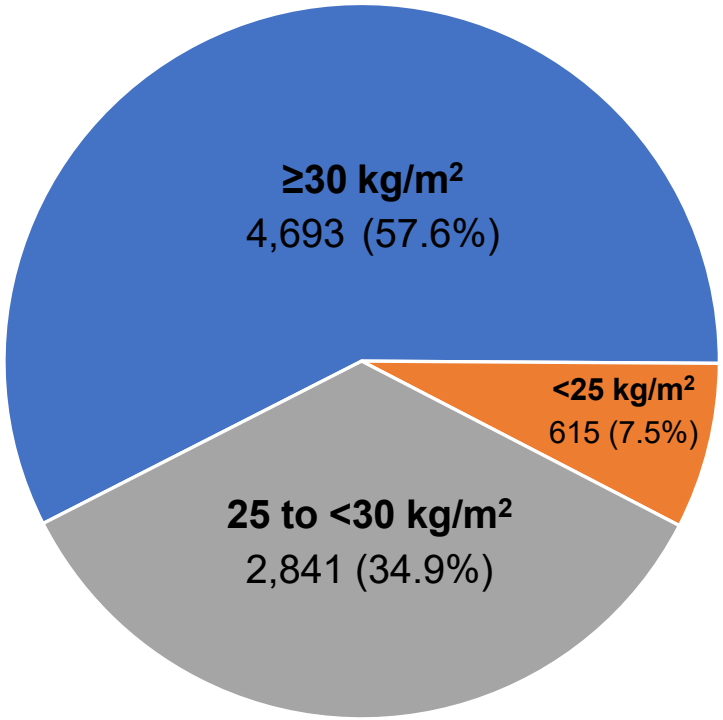


reduce-it BMI





Summary of Baseline BMI (kg/m²) by Category in REDUCE-IT



	≥30 kg/m²	<25 kg/m²	25 to <30 kg/m²
Median (Q1, Q3):	33.9 (31.7, 37.1))	23.8 (22.9, 24.5)	27.8 (26.6, 28.9)
Min, Max:	30.0, 65.0	16.4, 24.9	25.0, 29.9

Overall
8149
Median (Q1, Q3):
30.8 (27.8, 34.6)
Min, Max:
16.4, 65.0

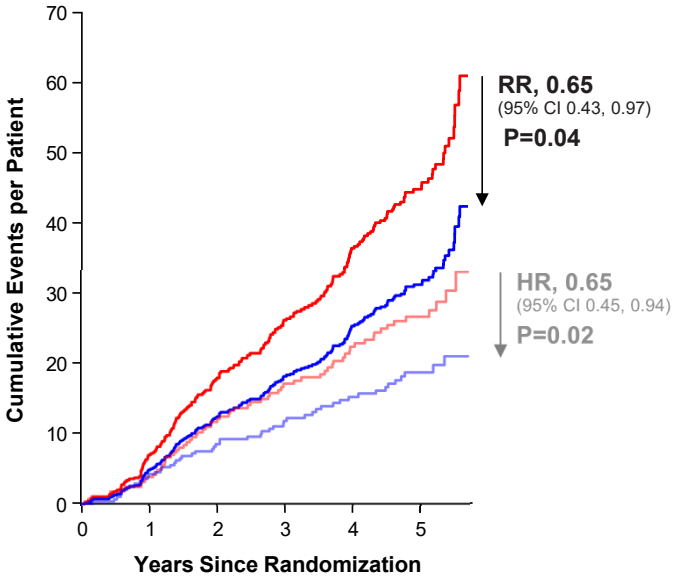
BMI (kg/m²)	Median Weight	
	kg	*lb*
Overall	91.1	200.8
<25	69.1	152.3
25 to <30	82.3	181.4
≥30	100.7	222.0

Bhatt DL, Brinton EA, Steg PG, et al. ADA 2021 (virtual).

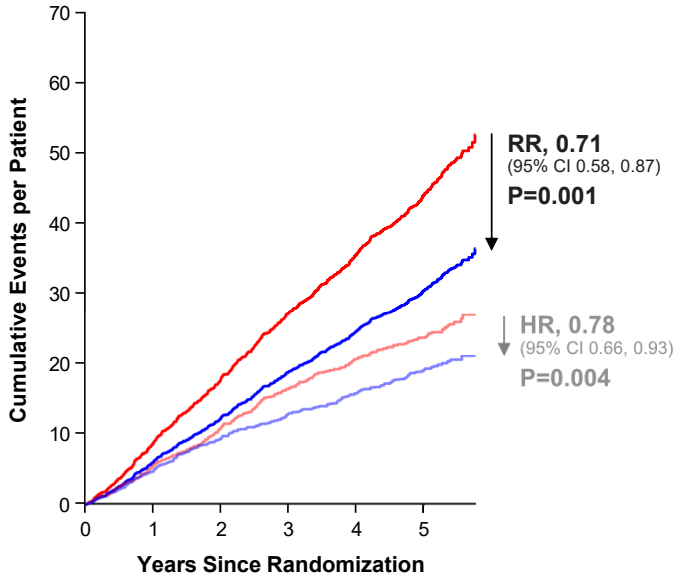
Time to First and Total Primary Endpoints by BMI

reduce-it BMI

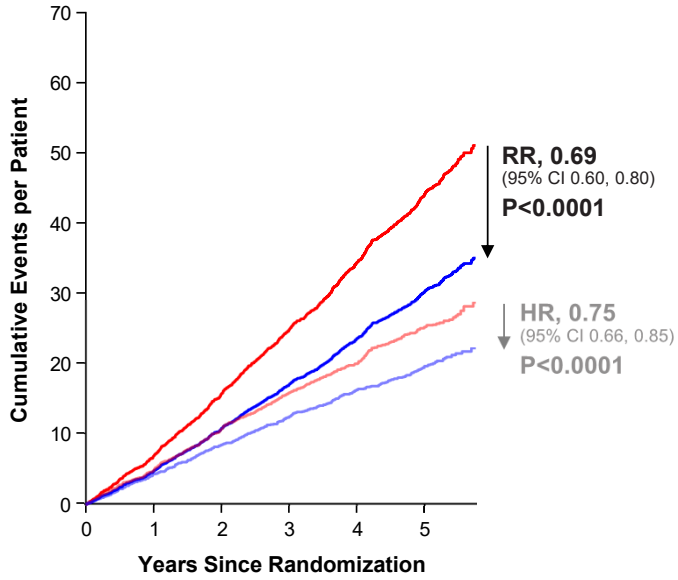
Total (First and Subsequent) and Time to the First Primary Composite Endpoint Events
ITT Population + BMI <25 kg/m² at Baseline



Total (First and Subsequent) and Time to the First Primary Composite Endpoint Events
ITT Population + BMI 25 to <30 kg/m² at Baseline



Total (First and Subsequent) and Time to the First Primary Composite Endpoint Events
ITT Population + BMI ≥30 kg/m² at Baseline



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

Bhatt DL, Brinton EA, Steg PG, et al. ADA 2021 (virtual).

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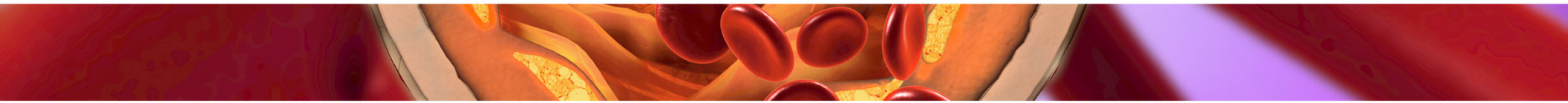
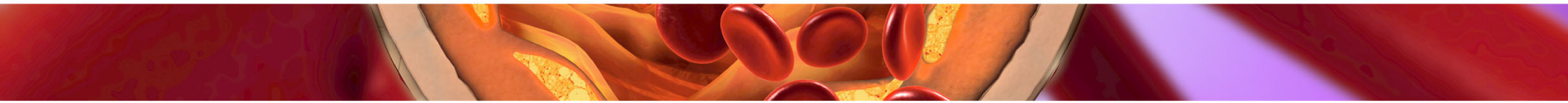
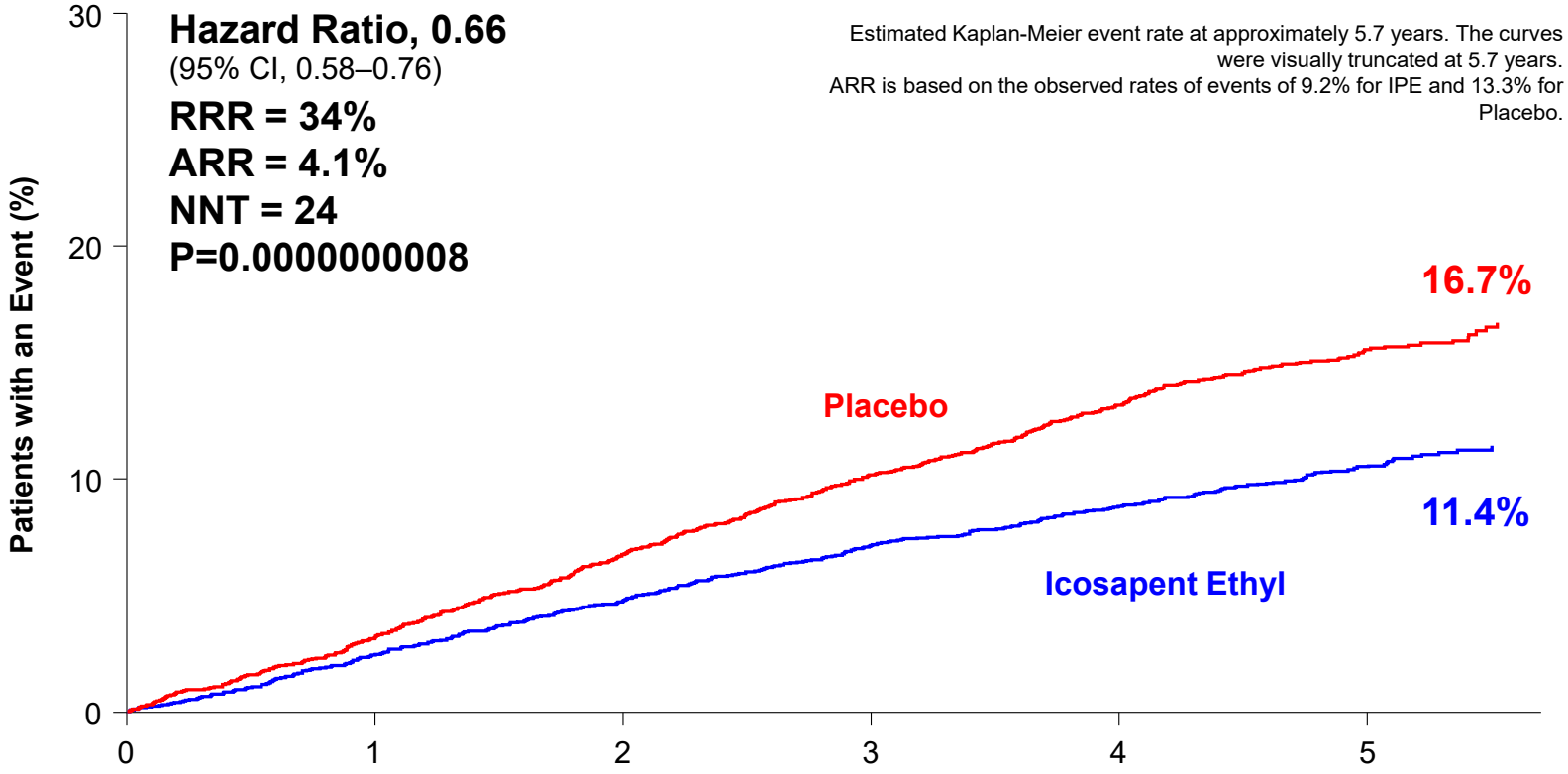


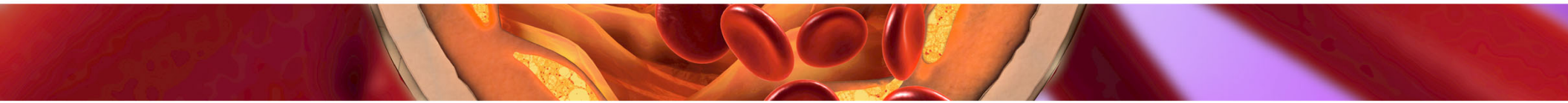
reduce-it REVASC



Time to Coronary Revascularization

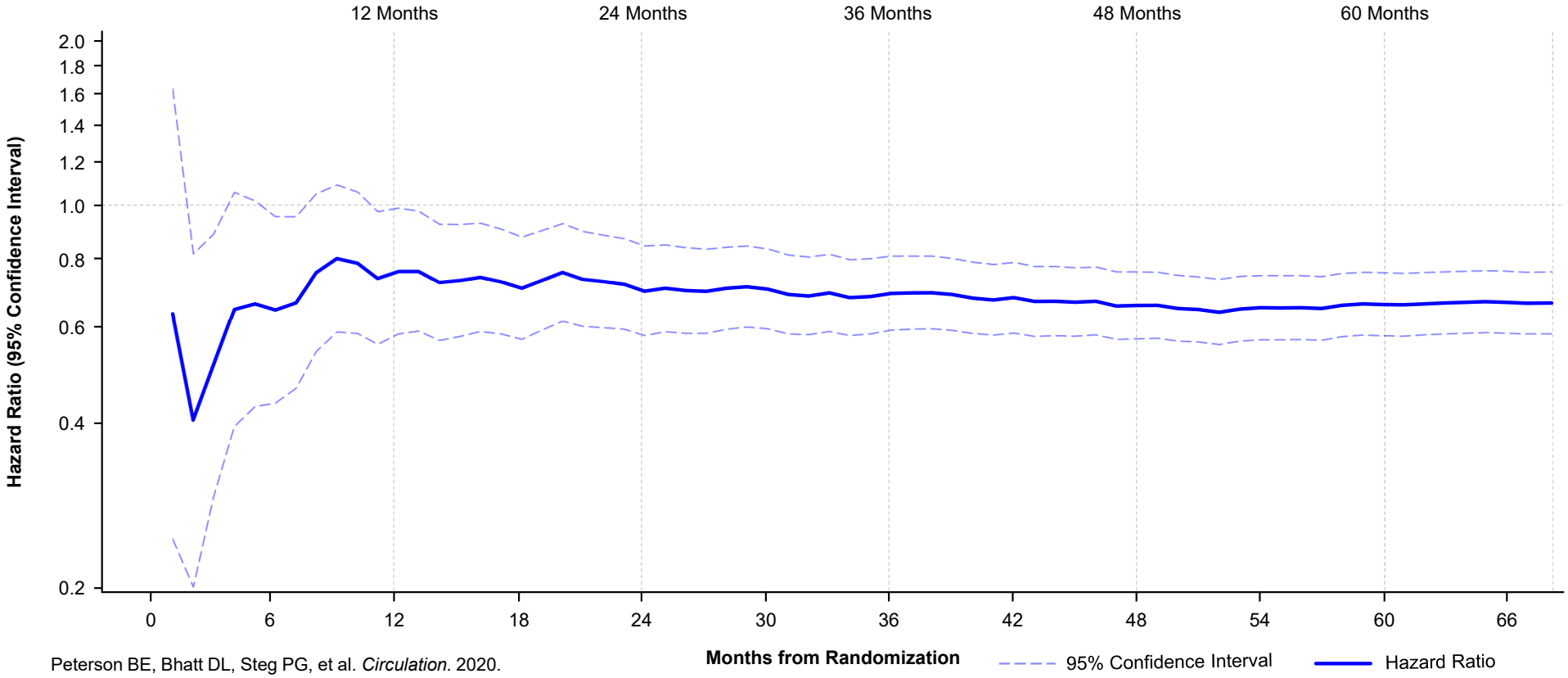


Peterson BE, Bhatt DL, Steg PG, et al. *Circulation.* 2020.

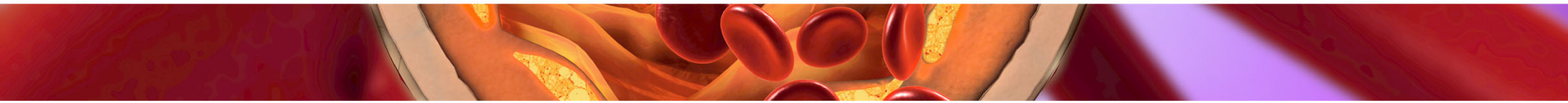


Time to Coronary Revascularization Benefit

Very early benefit demonstrated

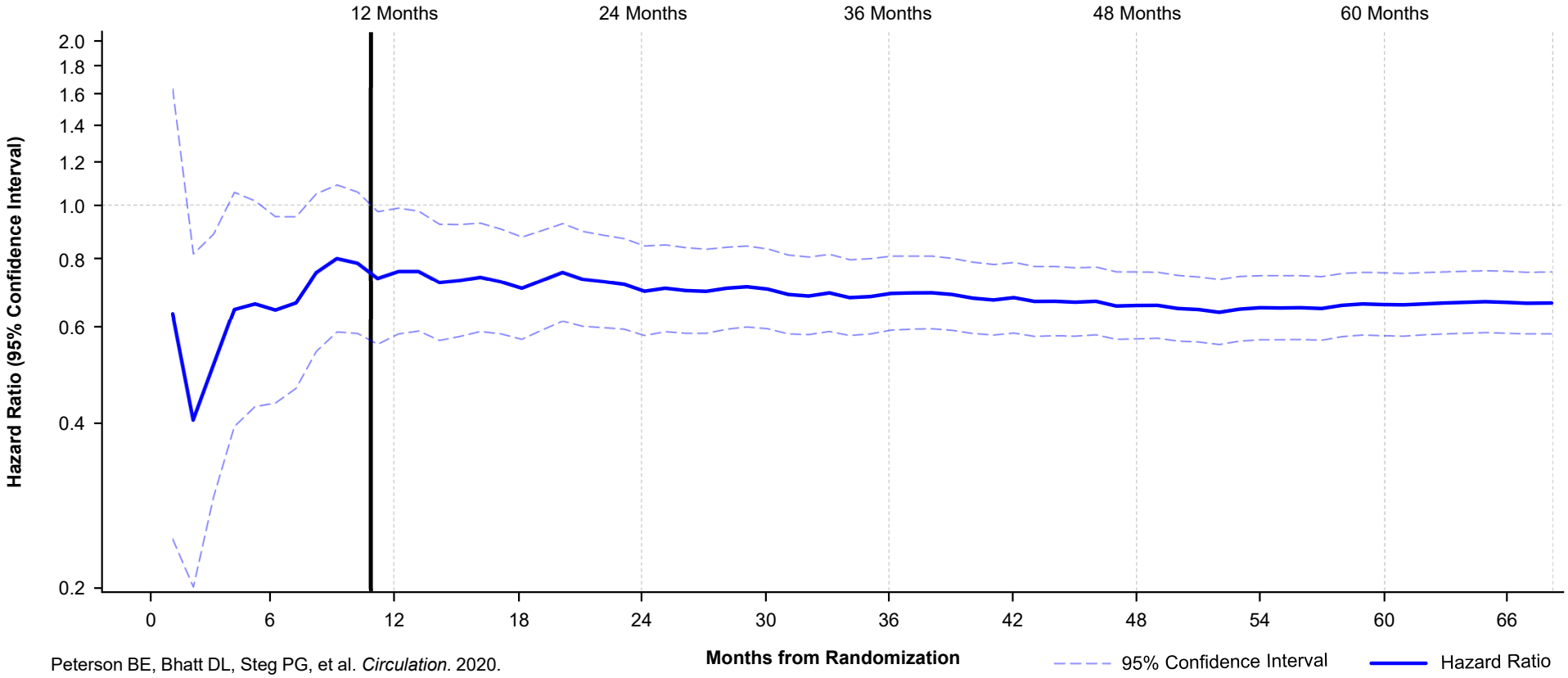


Peterson BE, Bhatt DL, Steg PG, et al. *Circulation.* 2020.

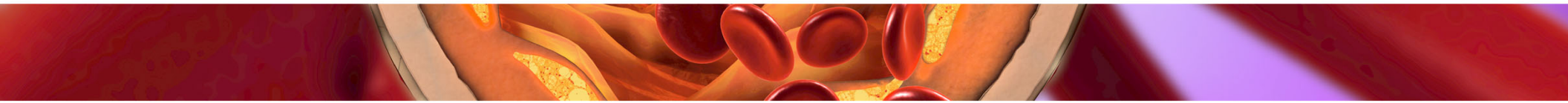


Time to Coronary Revascularization Benefit

Very early benefit demonstrated, with consistent statistical significance obtained by only 11 months

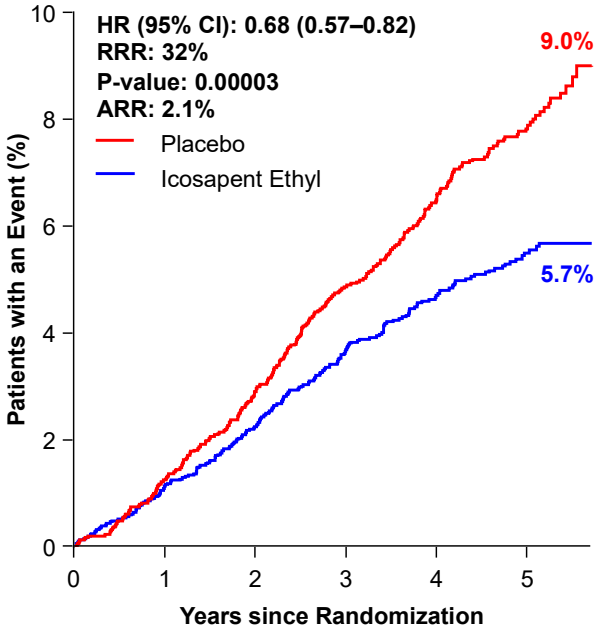


Peterson BE, Bhatt DL, Steg PG, et al. *Circulation.* 2020.

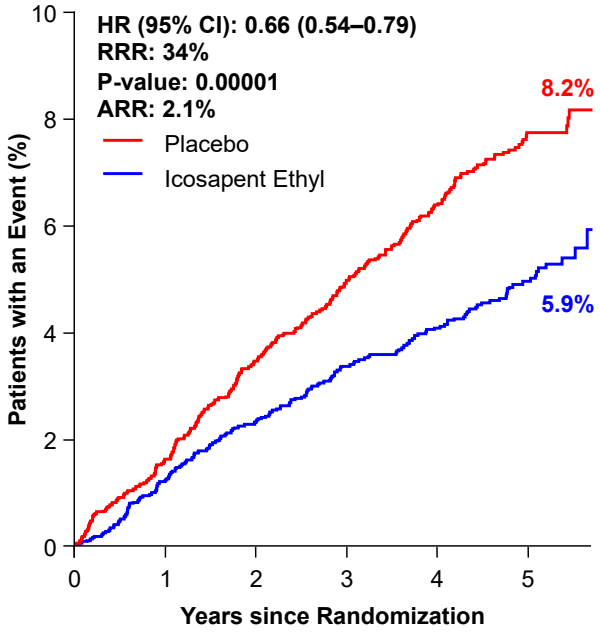


Time to Elective, Urgent, and Emergent Revascularization Events

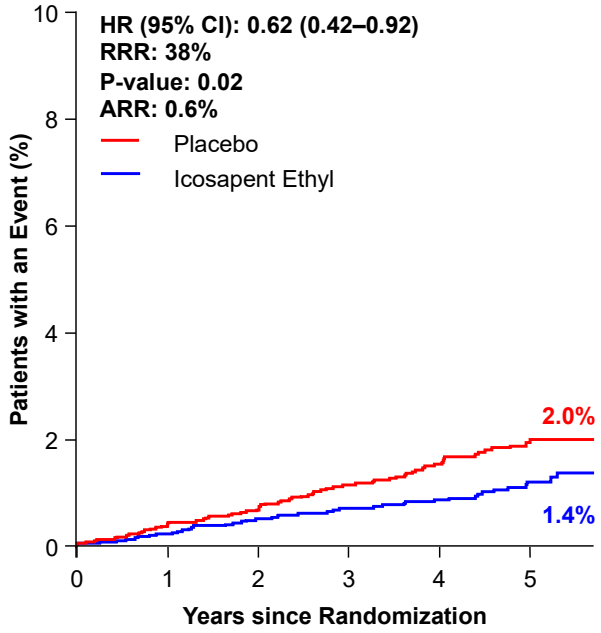
Time to Elective Coronary Revascularization



Time to Urgent Coronary Revascularization

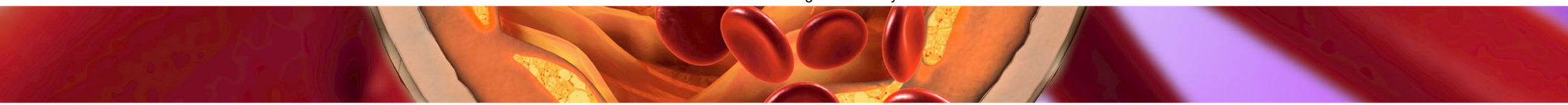


Time to Emergent Coronary Revascularization



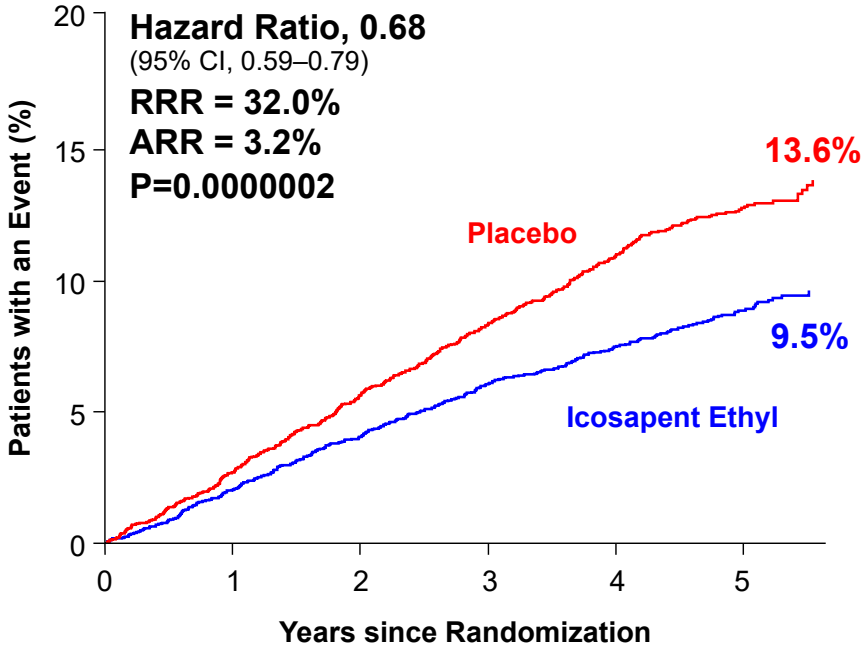
Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years.
Time to Elective Revascularization ARR is based on the observed event rates of 4.7% for IPE and 6.8% for Placebo.
Time to Urgent Coronary Revascularization ARR is based on the observed event rates of 4.4% for IPE and 6.6% for Placebo.
Time to Emergent Coronary Revascularization ARR is based on the observed event rates of 1.0% for IPE and 1.6% for Placebo.

Peterson BE, Bhatt DL, Steg PG, et al. Circulation. 2020.

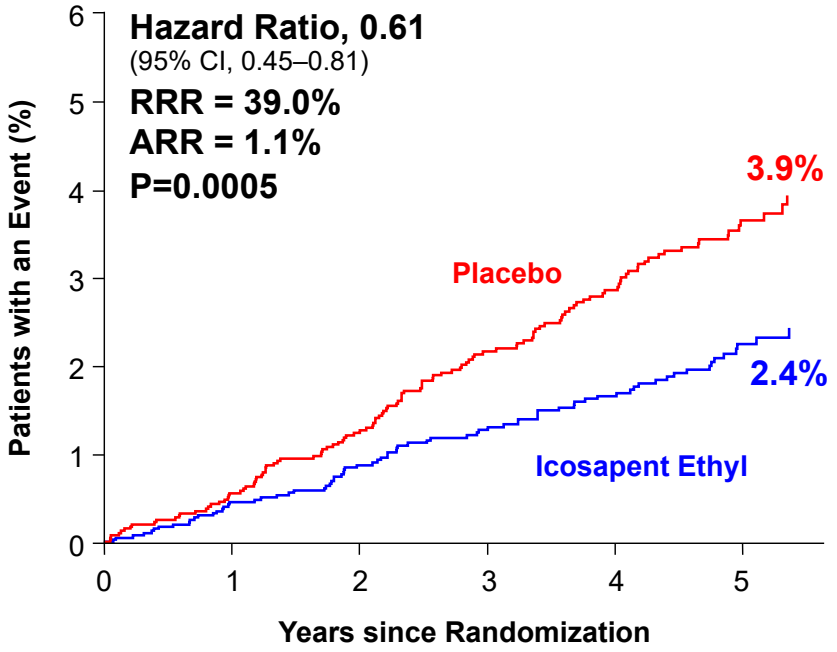


Time to PCI and CABG

Time to Percutaneous Coronary Intervention

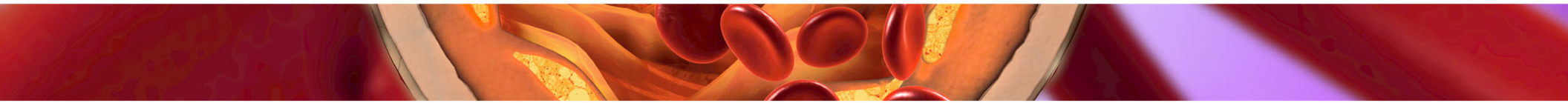


Time to Coronary Artery Bypass Graft

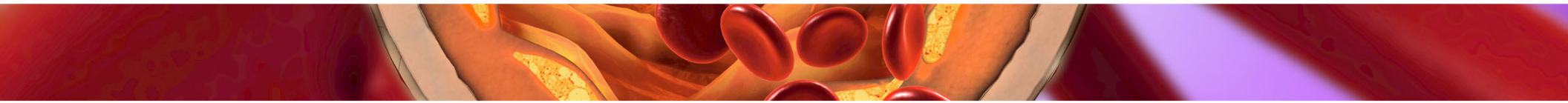


Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years.
Time to PCI ARR is based on the observed event rates of 7.7% for IPE and 10.9% for Placebo.
Time to CABG ARR is based on the observed event rates of 2.9% for IPE and 3.0% for Placebo.

Peterson BE, Bhatt DL, Steg PG, et al. *Circulation.* 2020.

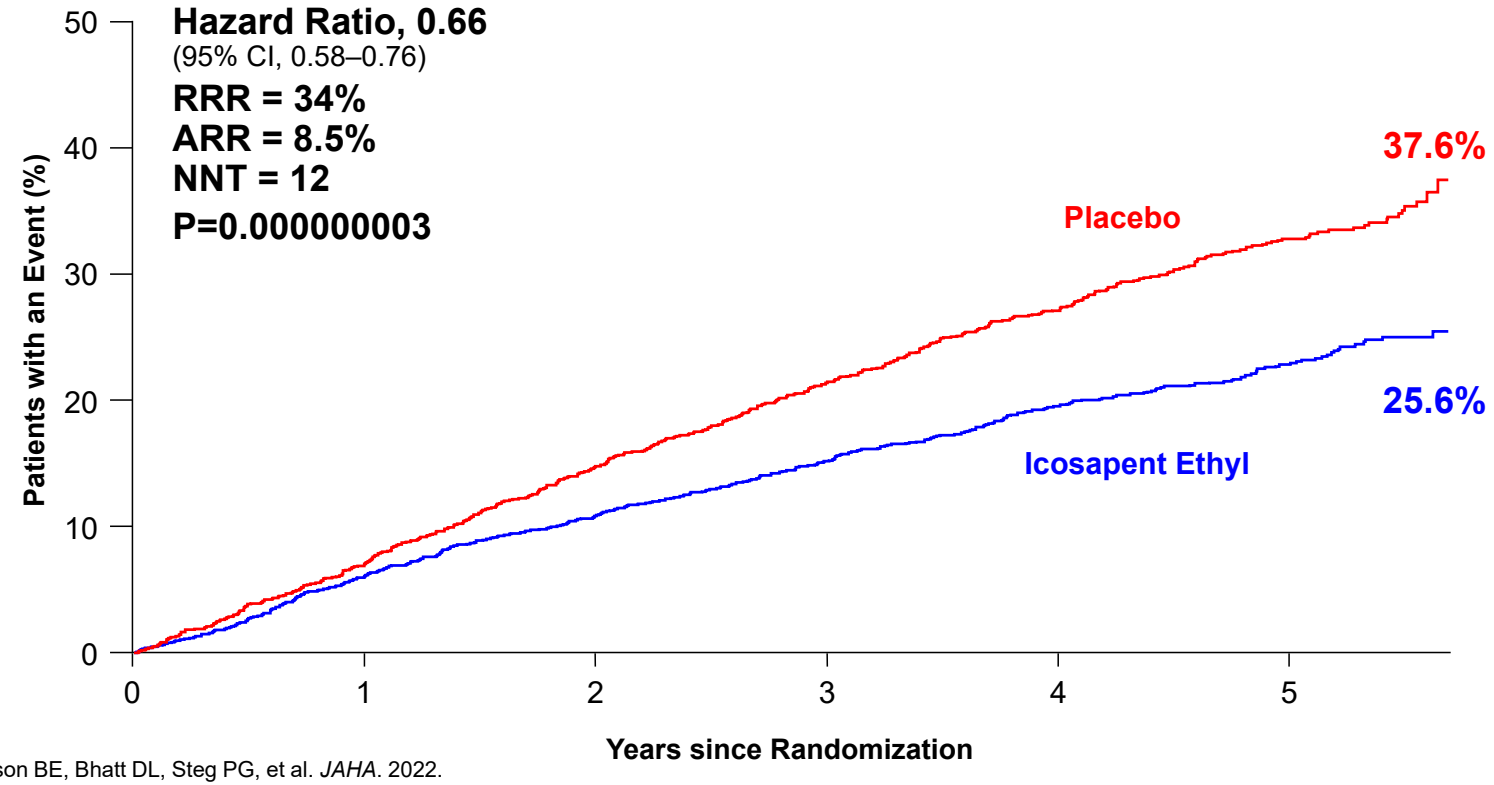


reduce-it PCI



Primary Endpoint:

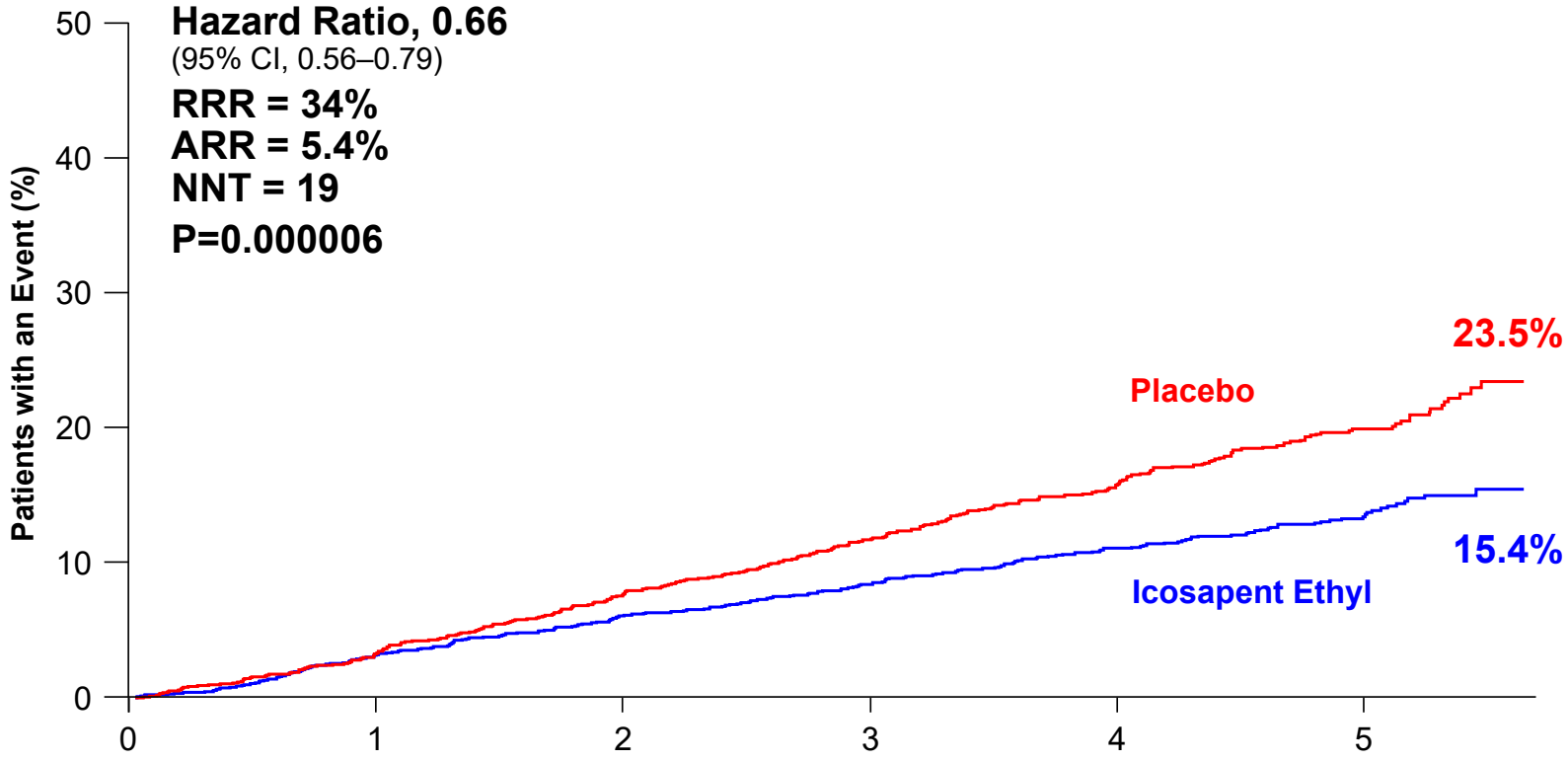
CV Death, Nonfatal MI, Nonfatal Stroke, Coronary Revasc, Unstable Angina: Patients With a History of PCI (N=3408)



Peterson BE, Bhatt DL, Steg PG, et al. *JAHA*. 2022.

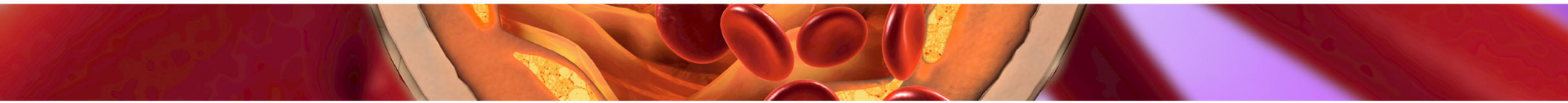
Key Secondary Endpoint:

CV Death, MI, Stroke:Patients With a History of PCI (N=3408)



Peterson BE, Bhatt DL, Steg PG, et al. *JAHA*. 2022.

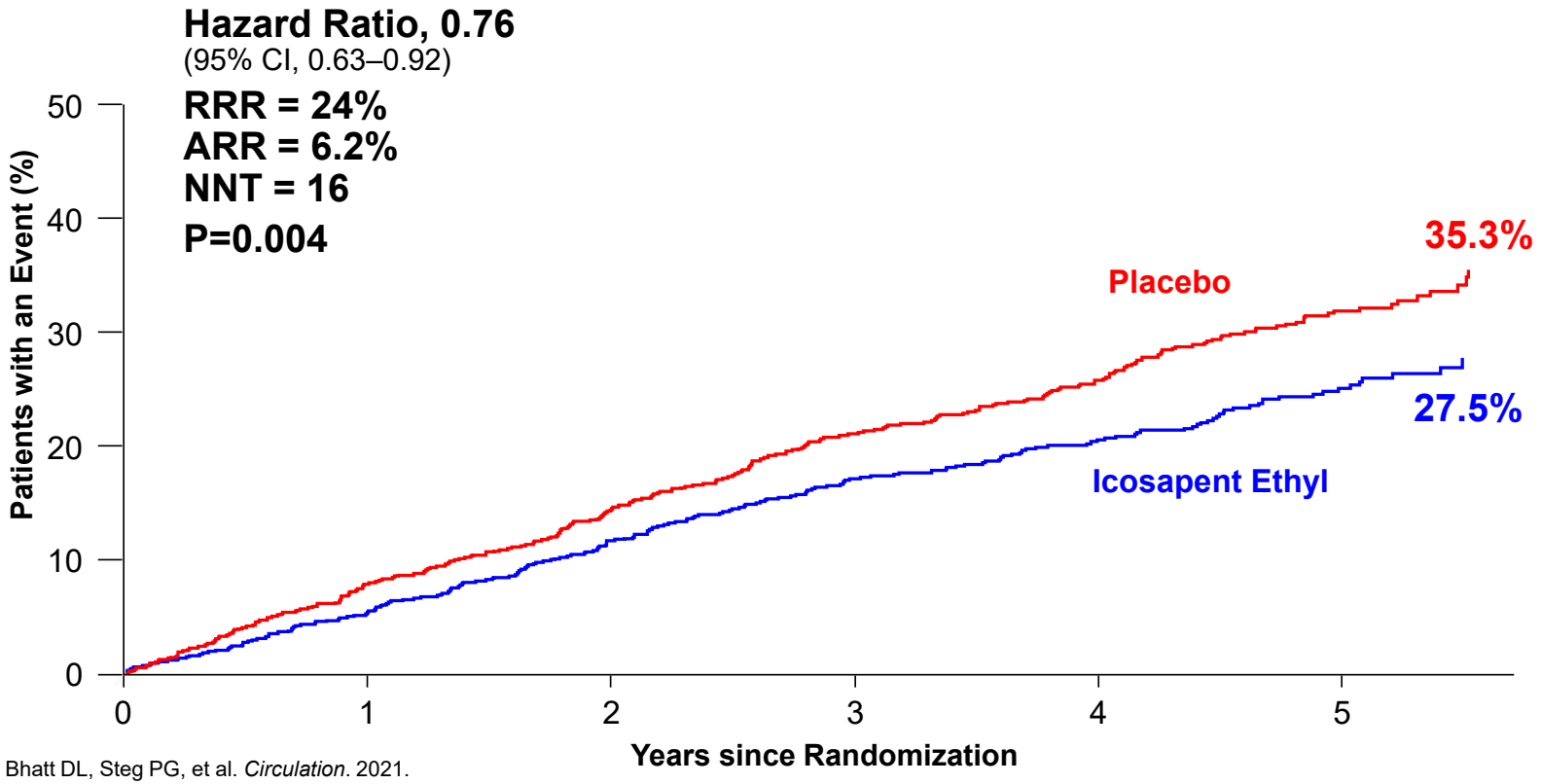
reduce-it CABG



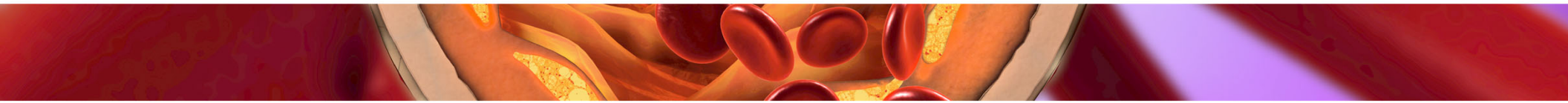
Primary Endpoint:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina: Patients With a History of CABG; N=1837

reduce-it CABG



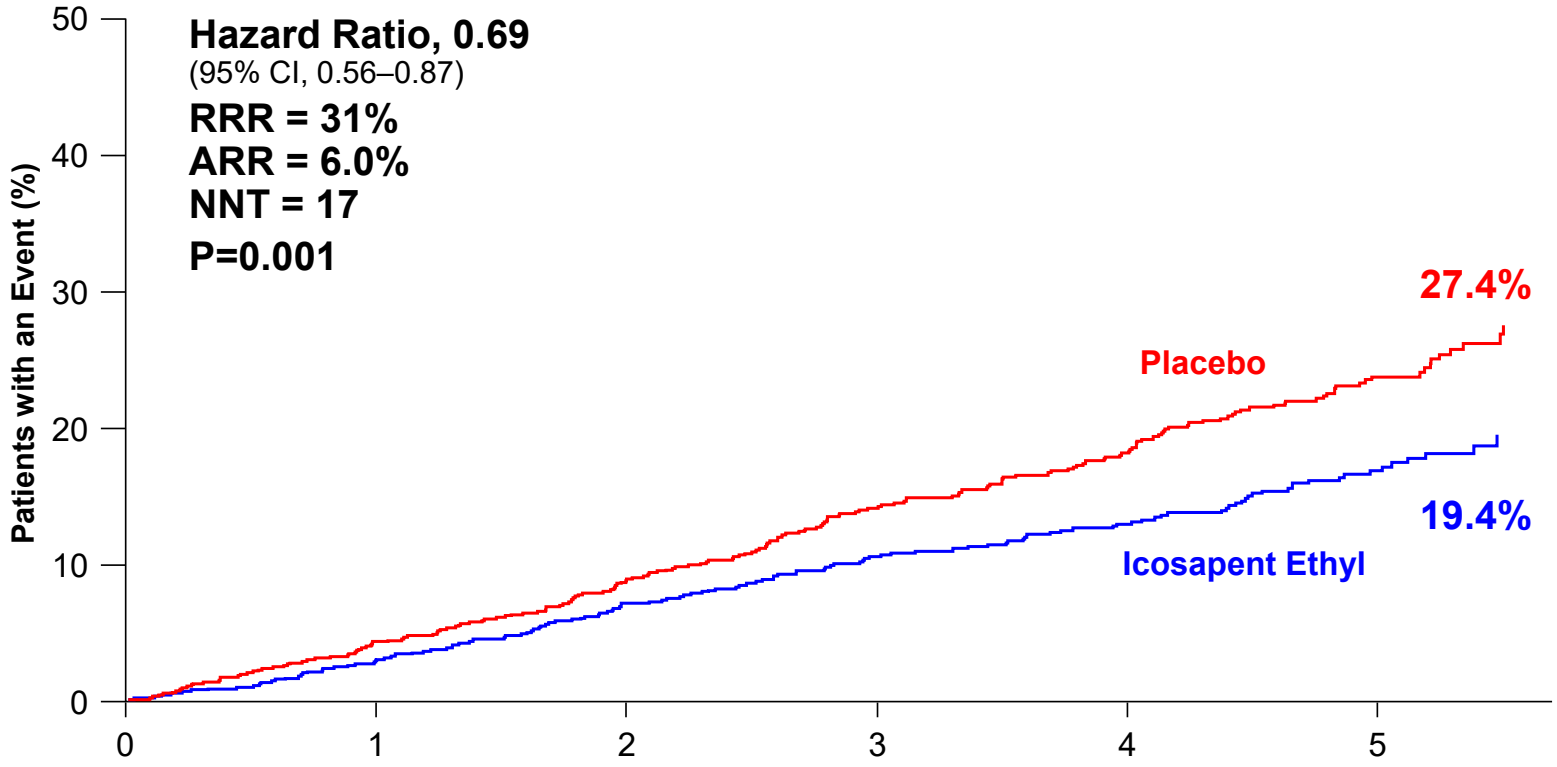
Verma S, Bhatt DL, Steg PG, et al. *Circulation*. 2021.



Key Secondary Endpoint:

CV Death, MI, Stroke: Patients With a History of CABG; N=1837

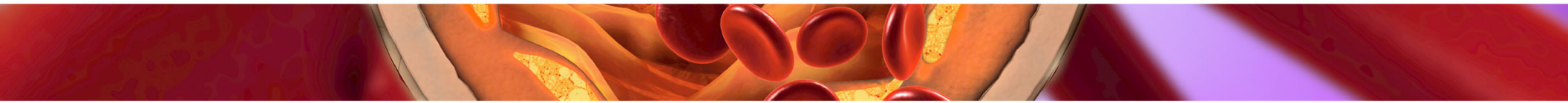
reduce-it CABG



Verma S, Bhatt DL, Steg PG, et al. *Circulation*. 2021.

reduce-it

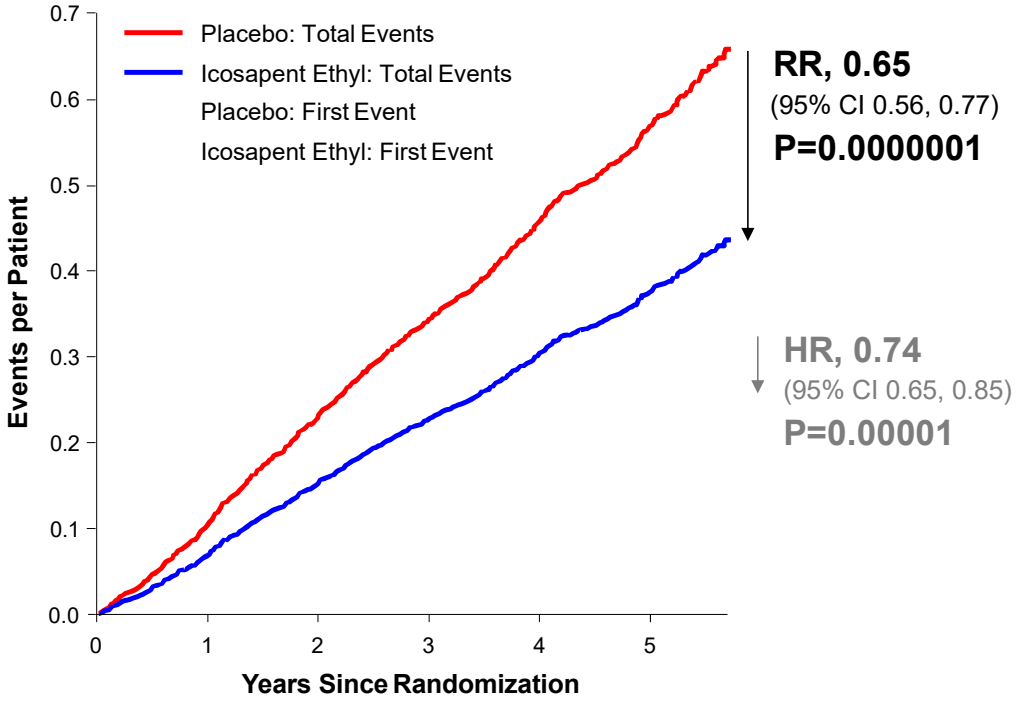
PRIOR MI



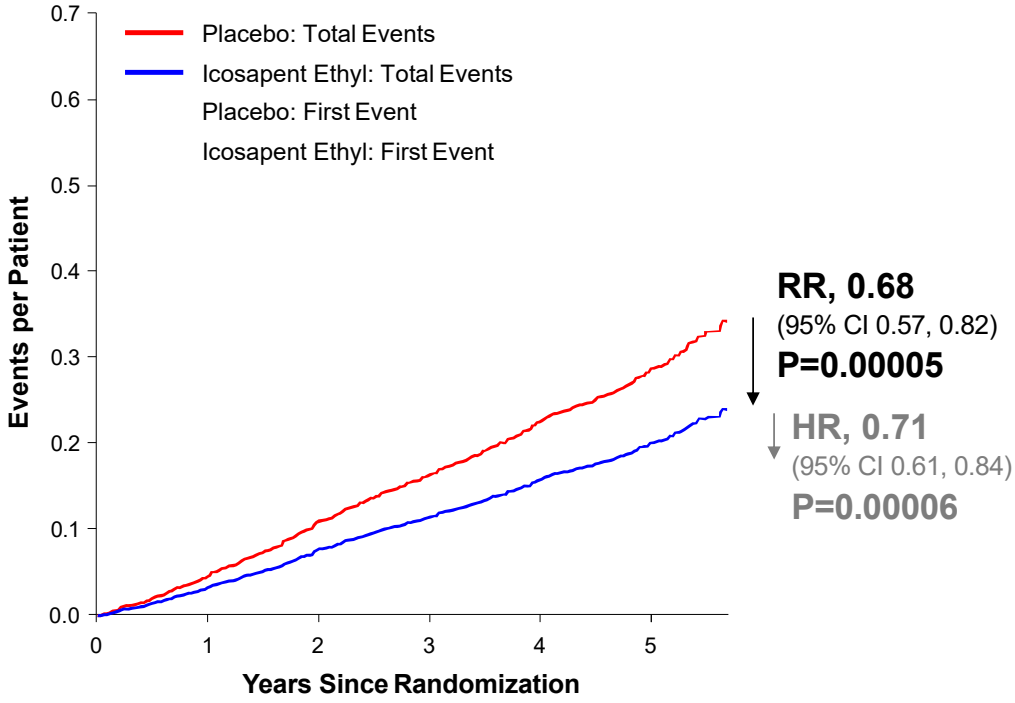
First and Total Primary and Key Secondary Endpoints in Patients with Prior MI

reduce-it PRIOR MI

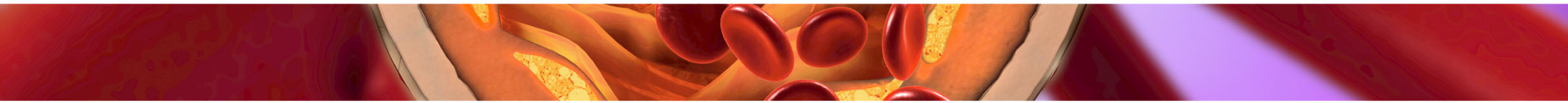
Primary Composite Endpoint



Key Secondary Composite Endpoint

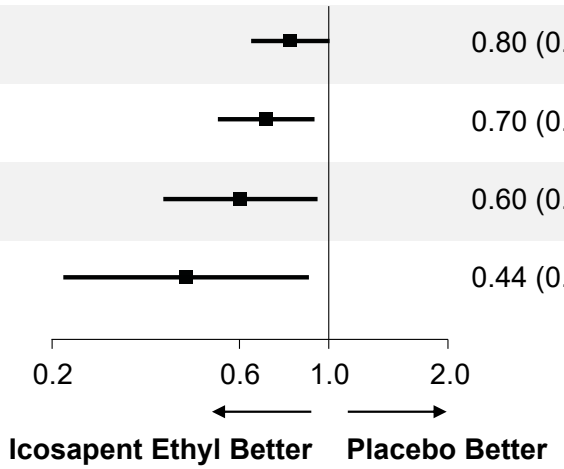


Gaba P, Bhatt DL, Steg PG, et al. *JACC* 2022.

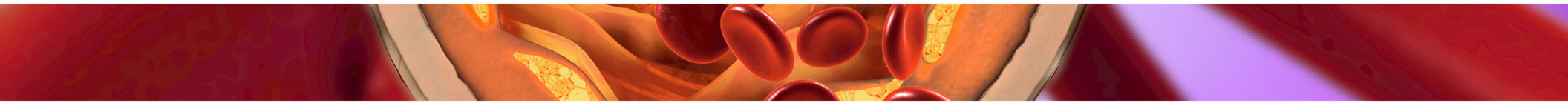


Cardiac Arrest and Sudden Cardiac Death in Patients with Prior MI

Endpoint	Icosapent Ethyl	Placebo	Icosapent Ethyl vs. Placebo	P-value
	n/N (%)	*n/N (%)*	*HR (95% CI)*	
Total Mortality	136/1870 (7.3)	163/1823 (8.9)	0.80 (0.64, 1.00)	0.05
Cardiovascular Death	84/1870 (4.5)	116/1823 (6.4)	0.70 (0.53, 0.92)	0.01
Sudden Cardiac Death	31/1870 (1.7)	50/1823 (2.7)	0.60 (0.38, 0.94)	0.02
Cardiac Arrest	11/1870 (0.6)	24/1823 (1.3)	0.44 (0.21, 0.89)	0.02



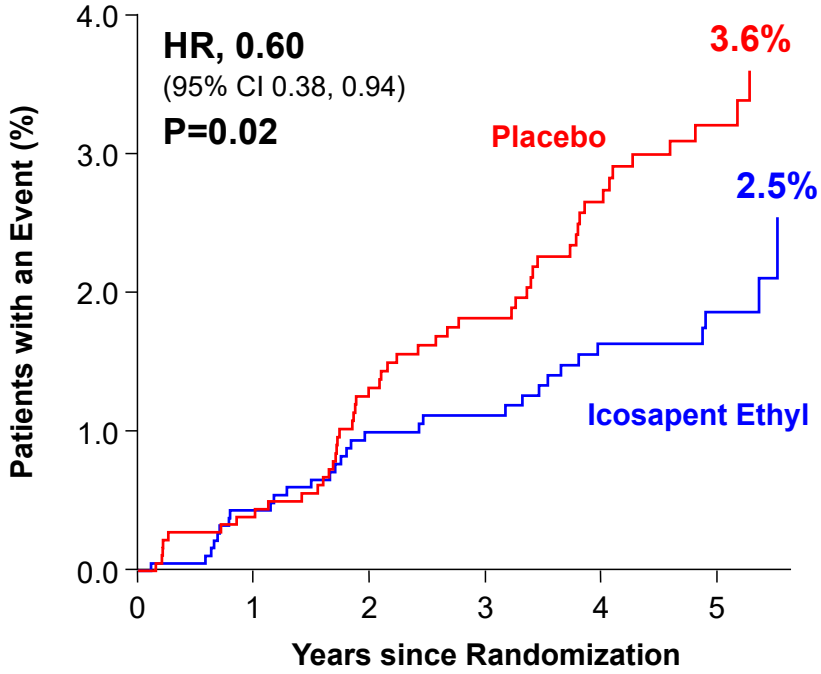
Gaba P, Bhatt DL, Steg PG, et al. *JACC* 2022.



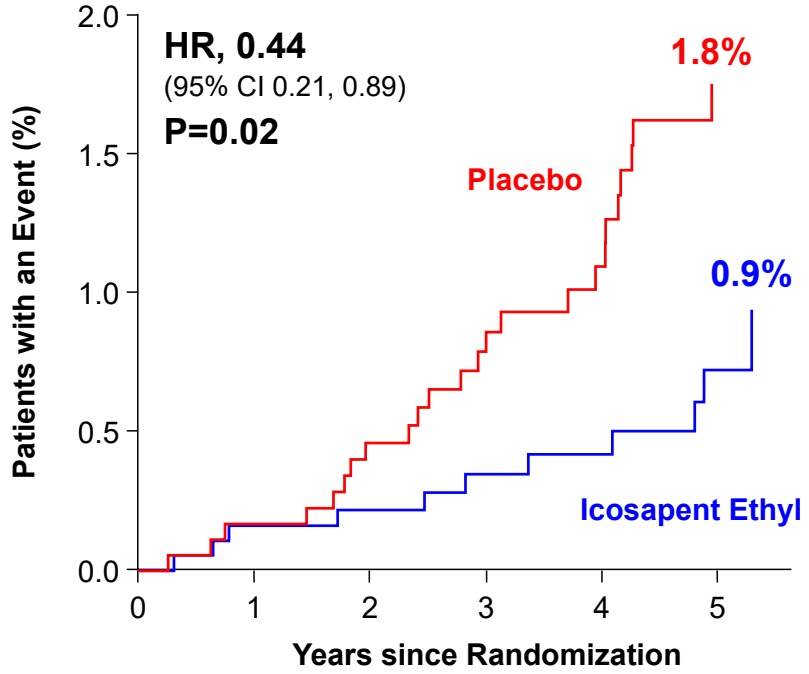
Cardiac Arrest and Sudden Cardiac Death in Patients with Prior MI

reduce-it PRIOR MI

Sudden Cardiac Death

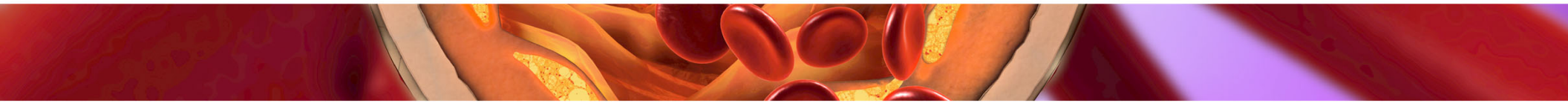


Cardiac Arrest



Results consistently statistically significant by ~ 4 years

Gaba P, Bhatt DL, Steg PG, et al. *JACC* 2022.



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Heart & Vascular Center

Thank You!

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HARVARD MEDICAL SCHOOL
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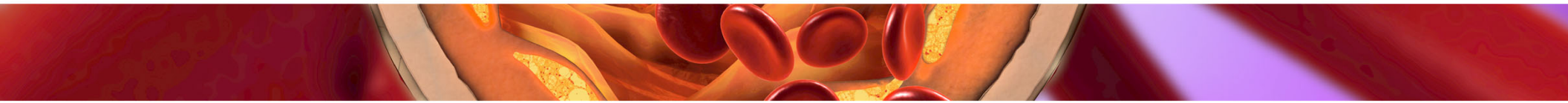
Differential Biological Effects of Omega-3 Fatty Acids

American College of Physicians
Annual Scientific Sessions
April 28,2022; Chicago, IL

Eliot A. Brinton, MD, FAHA, FNLA
Past-President, American Board of Clinical Lipidology
President, Utah Lipid Center
Salt Lake City, UT, USA
eliot.brinton@utah.edu

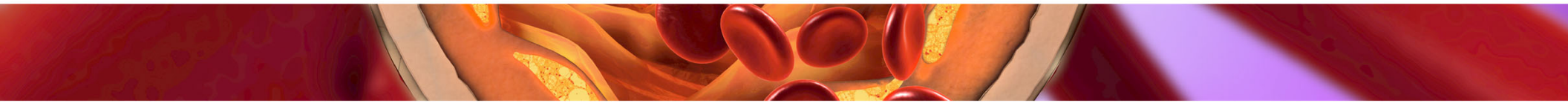
UTAH LIPID CENTER



Duality of Interest

Dr. Brinton has received:

- Research support from Regeneron
- Honoraria as a consultant/advisor: 89bio, Amarin, Amgen, Amryt, Dalcor, Esperion, Immunovant, Kowa, Merck, Novartis, Pfizer
- Honoraria as a speaker: Amarin, Amgen, Amryt, Esperion



Polling Question

What percent of patients seen by you for the first time will state they are taking “fish oil” when asked about medication history?

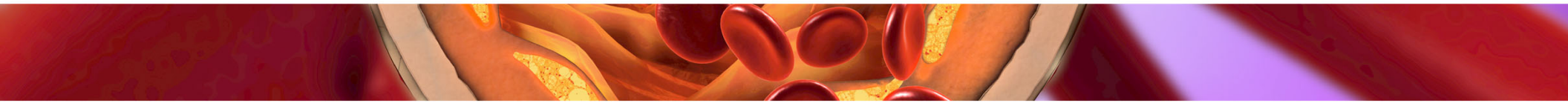
10%

30%

50%

80%

100%



Polling Question

What percent of your patients taking any type of omega-3 fatty acid preparation are taking a prescription grade version?

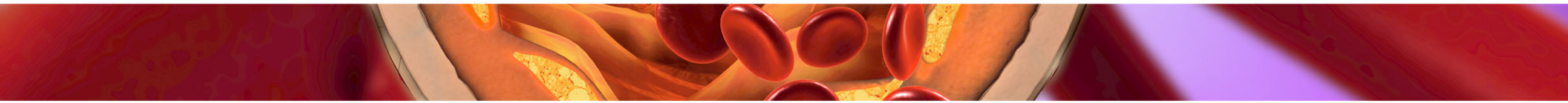
10%

30%

50%

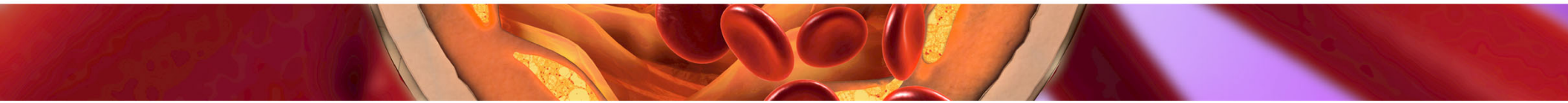
80%

100%



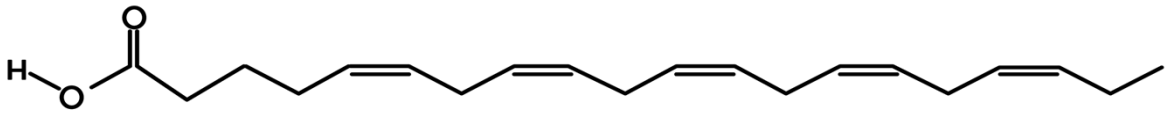
Comparing/Contrasting EPA vs DHA Mechanisms Relevant to Atherosclerosis

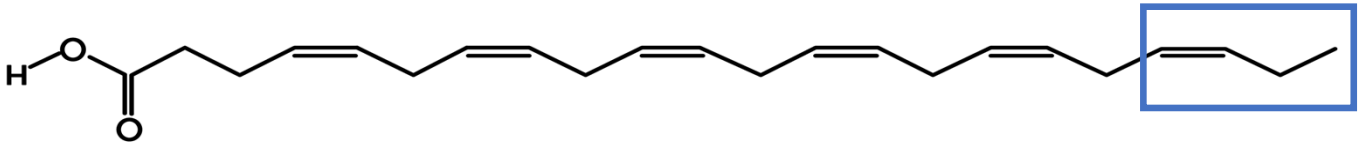
- Oxidation
- Inflammation
- Cholesterol domain and crystal formation
- Cholesterol efflux, etc.
- Plaque progression/regression



EPA Versus DHA: Structurally Similar but Functionally Different!

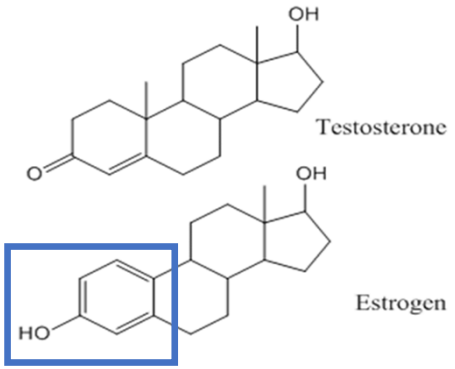
Eicosapentaenoic acid (EPA) 20:5

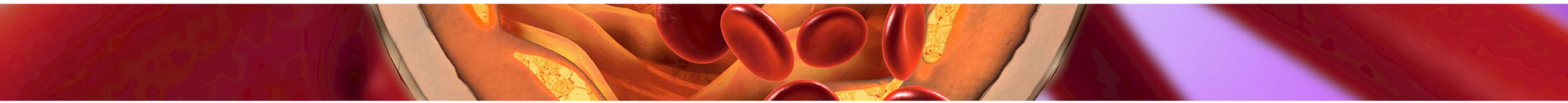




Docosahexaenoic acid (DHA) 22:6

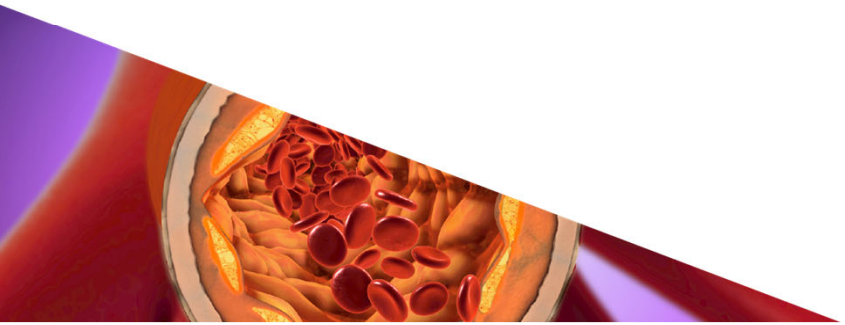
Omega-3 PUFA



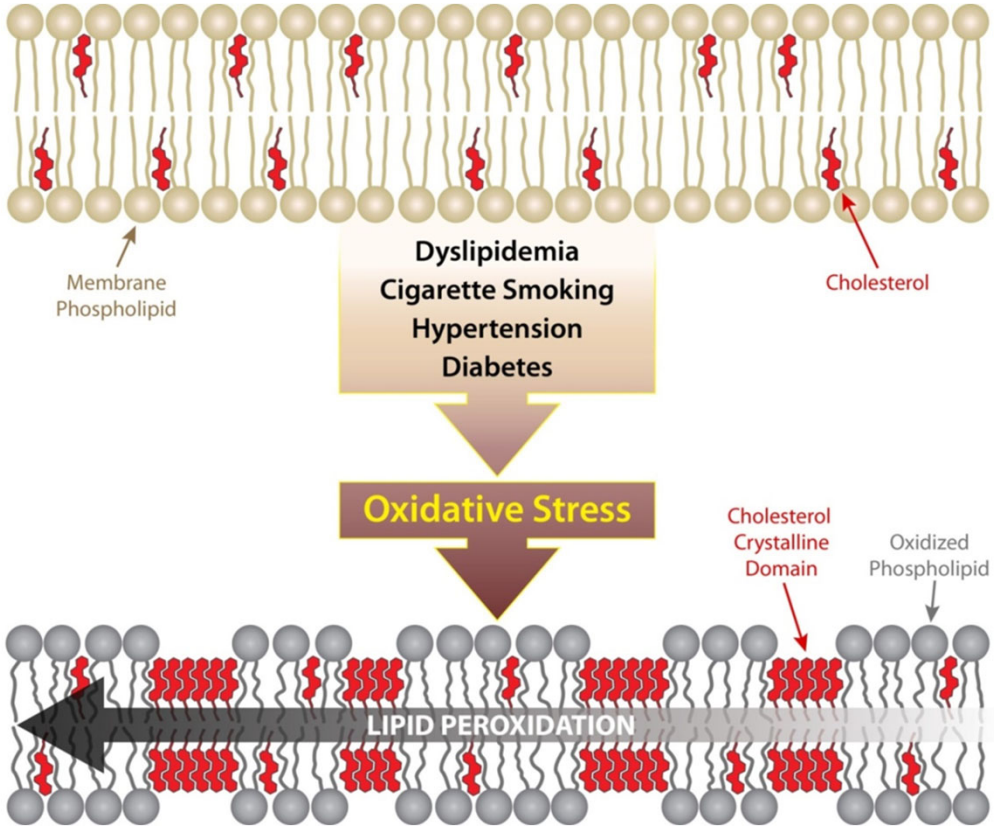


QUESTION 1

What is the role of *oxidation* in atherogenesis, and how are EPA and DHA *antioxidants*?

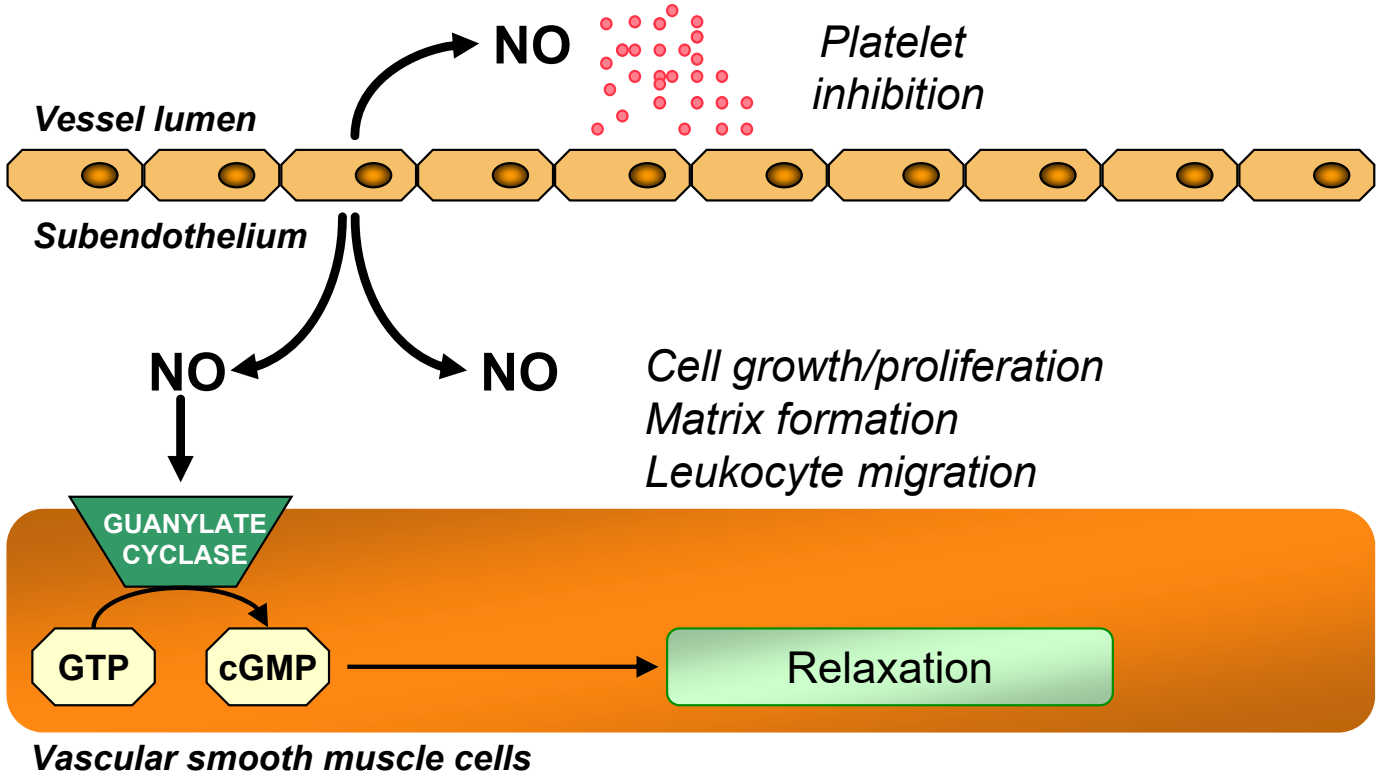


CV Risk Factors Promote Oxidative Stress and Membrane Cholesterol Domain Formation

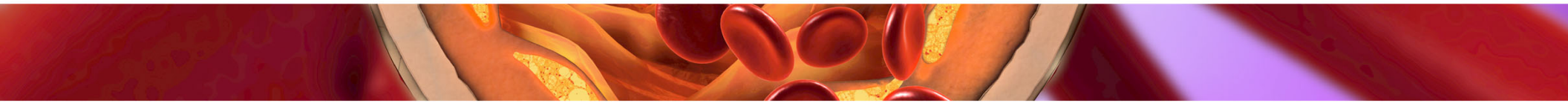


Adapted from Mason RP, Jacob RF. *Ad*

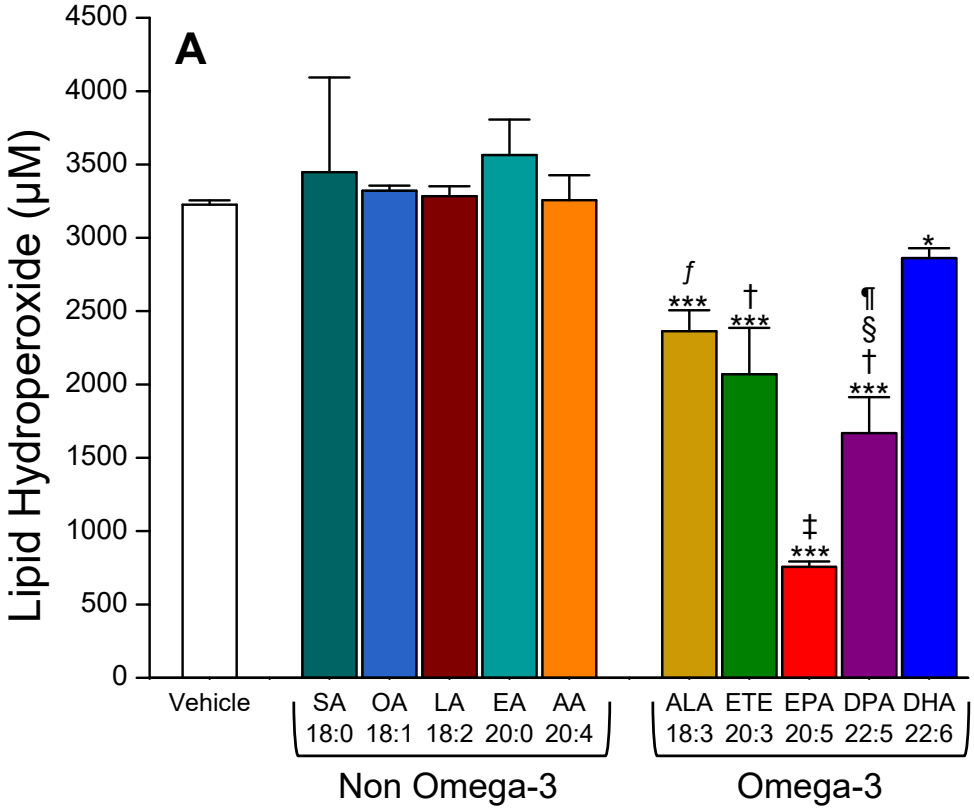
Endothelial Function and Role of Nitric Oxide

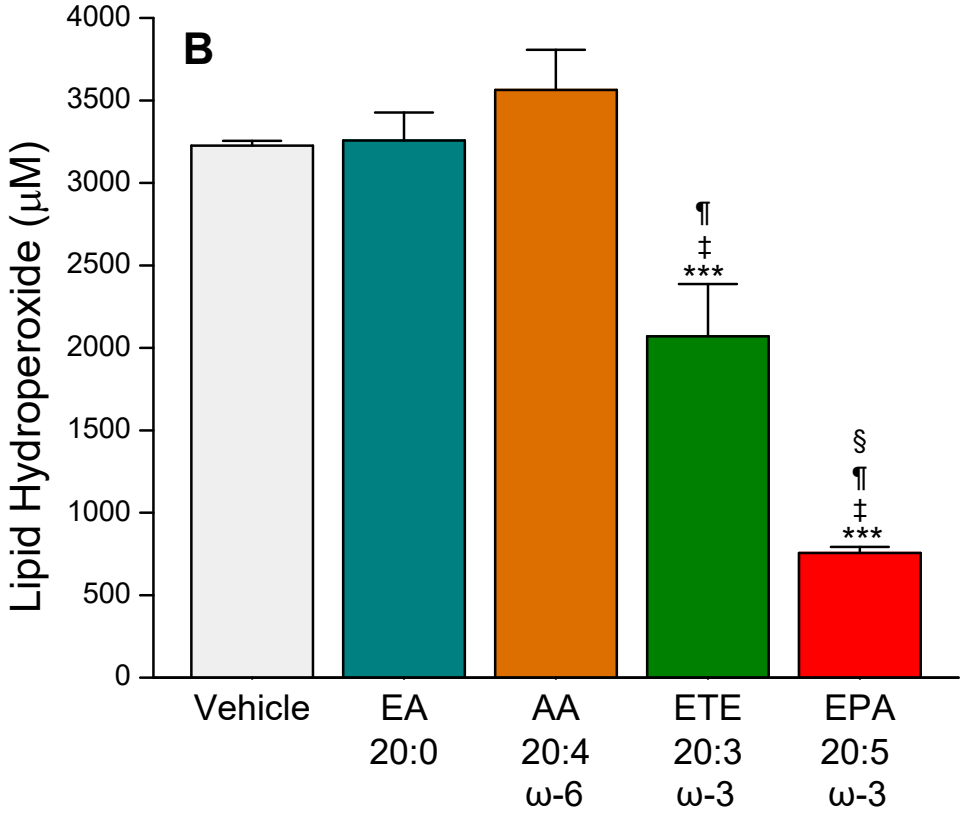


Behrendt D, Ganz P. *Am J Cardiol*. 2002;90(10C):40L-48L; Vita JA. *J Card Fail*. 2003;9(5 Suppl Nitric Oxide):S199-S204.

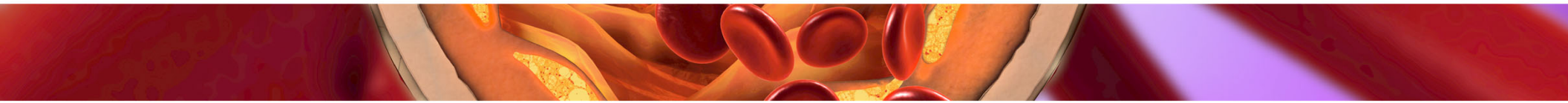


Comparative Effects of Long Chain FAs on Oxidation of Membranes

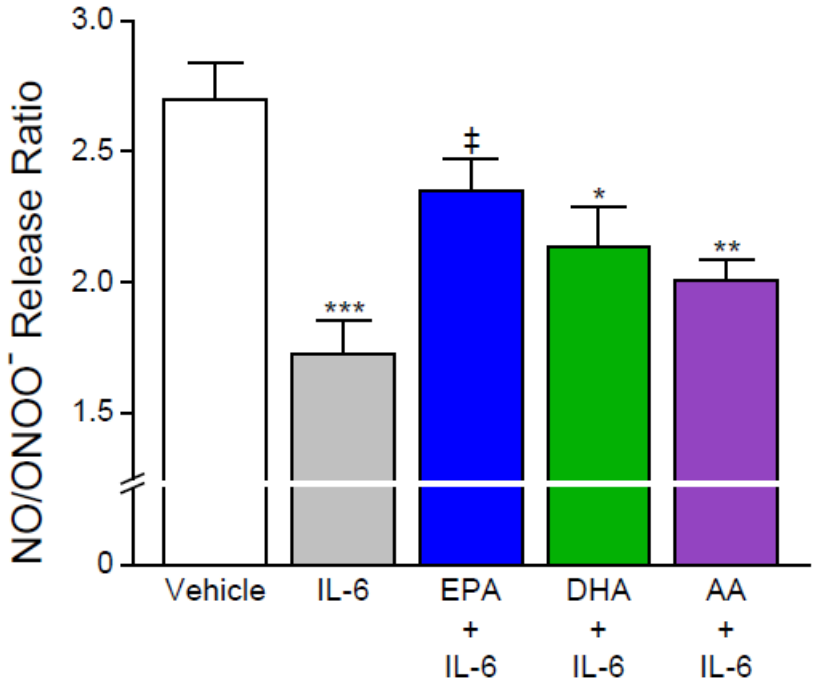




Sherratt SCR, et al. *Biochim Biophys Acta Biomembr*. 2020;1862(7):183254.

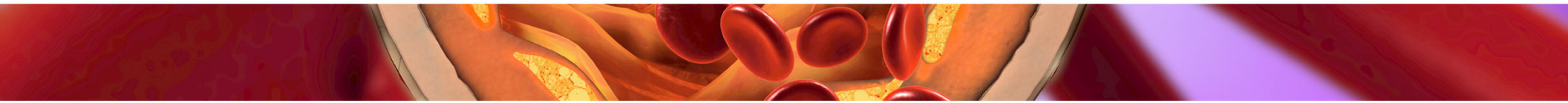


EPA Preserves Vascular Endothelial Function Following IL-6 Exposure Compared with DHA and AA

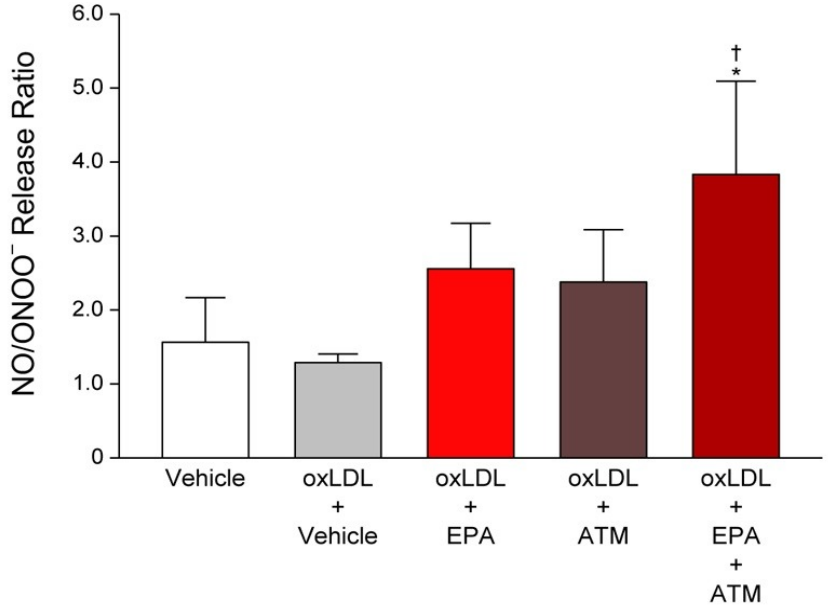


Statistical indicators: ***p<0.001 versus vehicle; **p<0.01 versus vehicle; *p<0.05 versus vehicle; ‡p<0.05 versus IL-6 alone (Student-Newman-Keuls Multiple Comparisons Test; overall ANOVA: p = 0.0007, F = 8.488). Values are mean ± SEM (N = 4-5).

Presented at NLA 2020 (*Abstract #: 244*). Mason RP, Dawoud H, Sherratt SCR, Libby P, Bhatt DL, Malinski T.

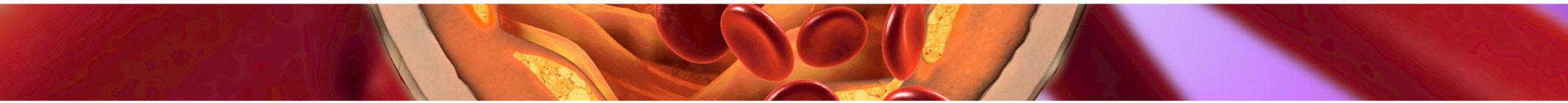


Combined Effects of EPA and Statin on Endothelial Function and eNOS Coupling

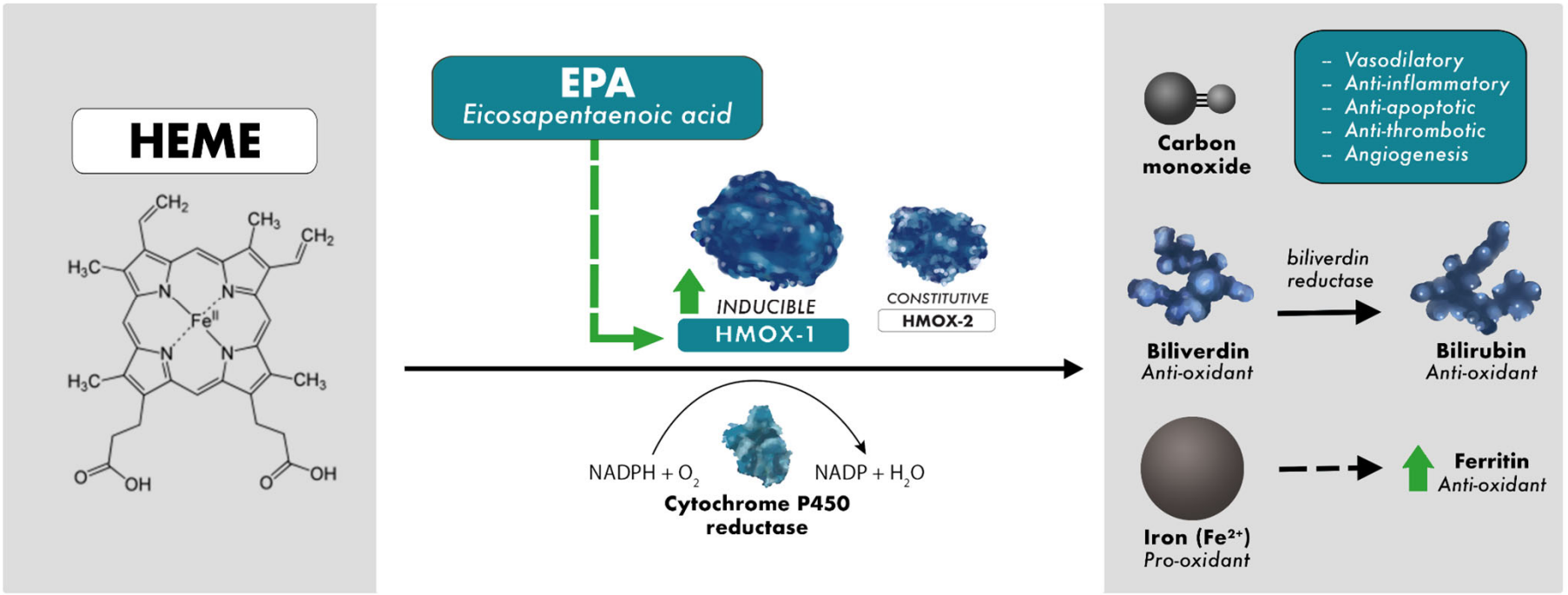


*p<0.01 versus vehicle alone (no oxLDL); †p<0.01 versus oxLDL+Vehicle (Student-Newman-Keuls multiple comparisons test; overall ANOVA: p=0.0030, F=6.768). Values are mean ± S.D. (N=3-7).

ATM, atorvastatin active metabolite.
Mason RP, et al. *Biomed Pharmacother.* 2018;103:1231-1237.

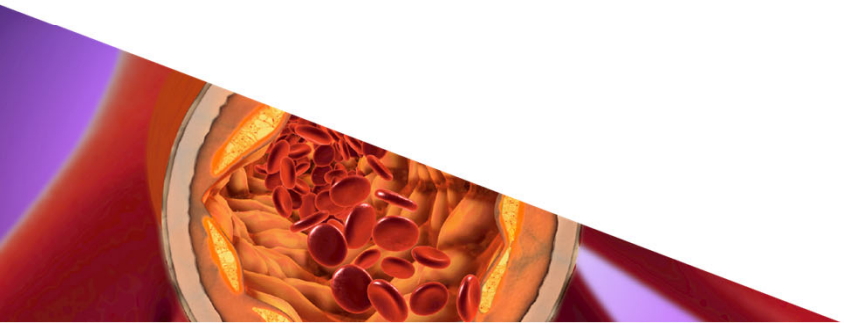


EPA Increases Heme Oxygenase-1 Expression, Thereby Potentially Increasing Downstream Cytoprotective Effects

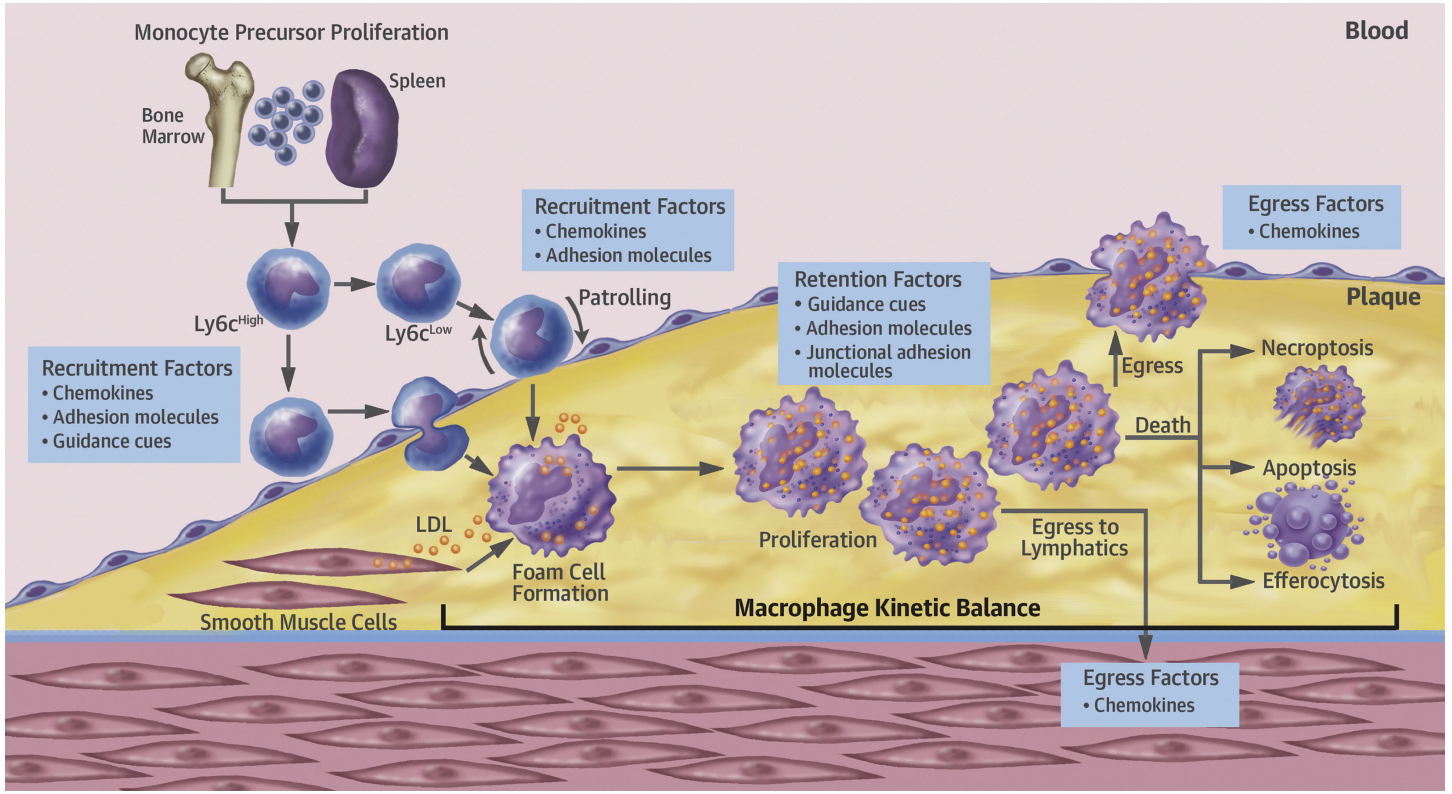


QUESTION 2

What is the role of *inflammation* in atherogenesis, and how are EPA and DHA *anti-inflammatory*?

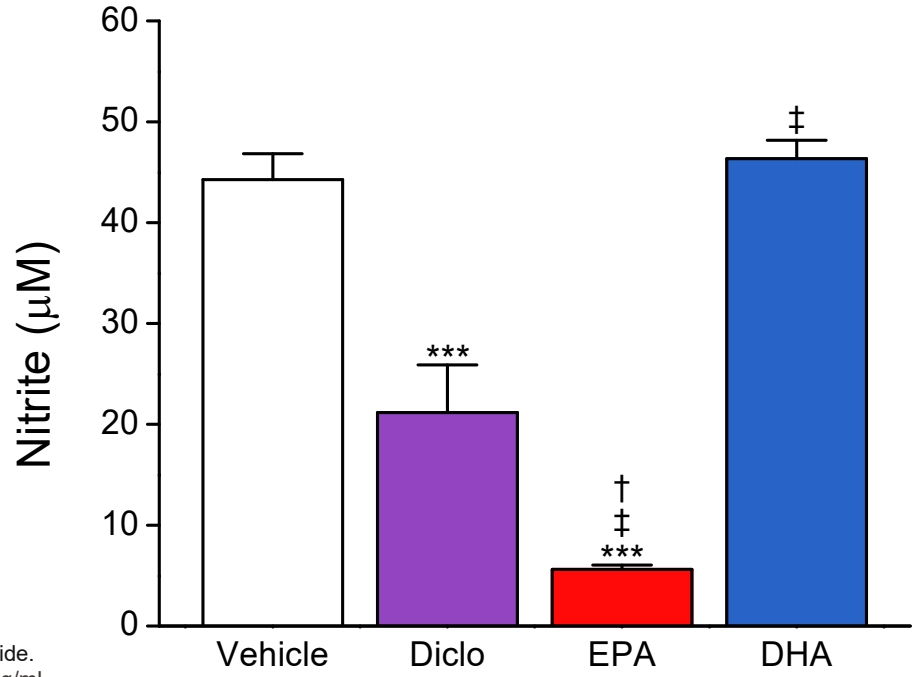


Macrophages Play a Key Role in the Initiation and Progression of the Atherosclerotic Plaque

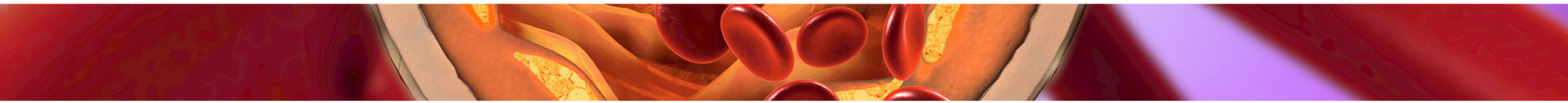


Moore KJ, et al. *J Am Coll Cardiol*. 2018;72(18):2181-2197.

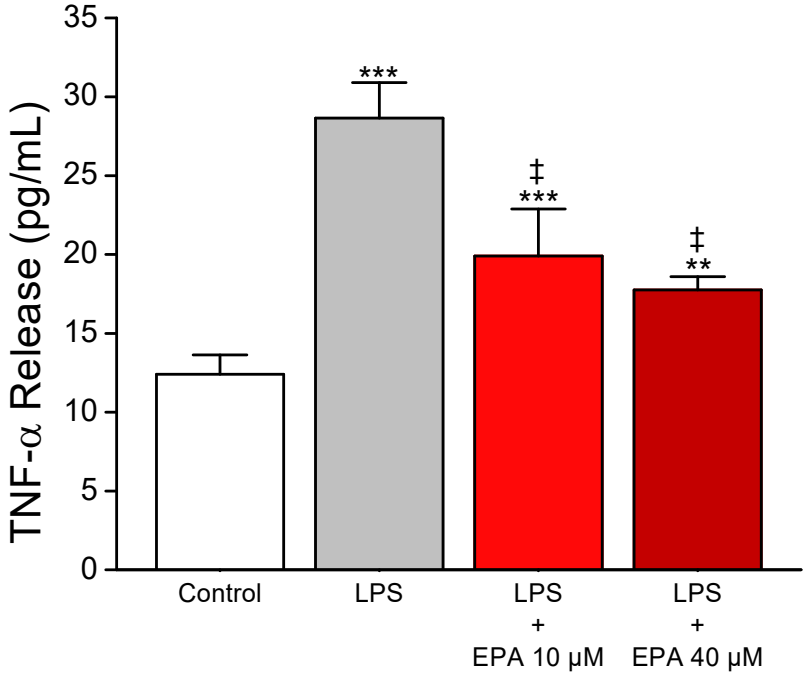
EPA, but Not DHA, Reduces Macrophage Activation with LPS



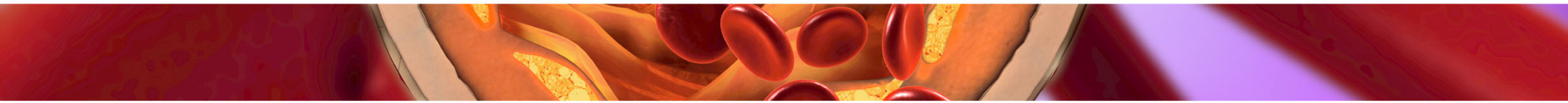
Diclo, Diclofenac; LPS, lipopolysaccharide.
LPS and diclofenac concentration = 1 μg/mL.
*** $P < 0.001$ versus vehicle; † $P < 0.001$ versus diclo; ‡ $P < 0.001$ versus DHA alone (Student-Newman-Keuls Multiple Comparisons Test; overall ANOVA: $P < 0.0001$,
F = 140.94).
Values are mean ± SD (N = 3).
Al-Asfoor S, et al. EAS 2021.



EPA Reduces TNF-α Release from LPS-Challenged Macrophages in a Dose-Dependent Manner



LPS, lipopolysaccharide.
LPS concentration = 1 µg/mL.
*** $P < 0.001$ versus control; ** $P < 0.01$ versus control; ‡ $P < 0.001$ versus LPS (Student-Newman-Keuls Multiple Comparisons Test; overall ANOVA: $P < 0.0001$, F = 44.888).
Values are mean ± SD (N = 4).

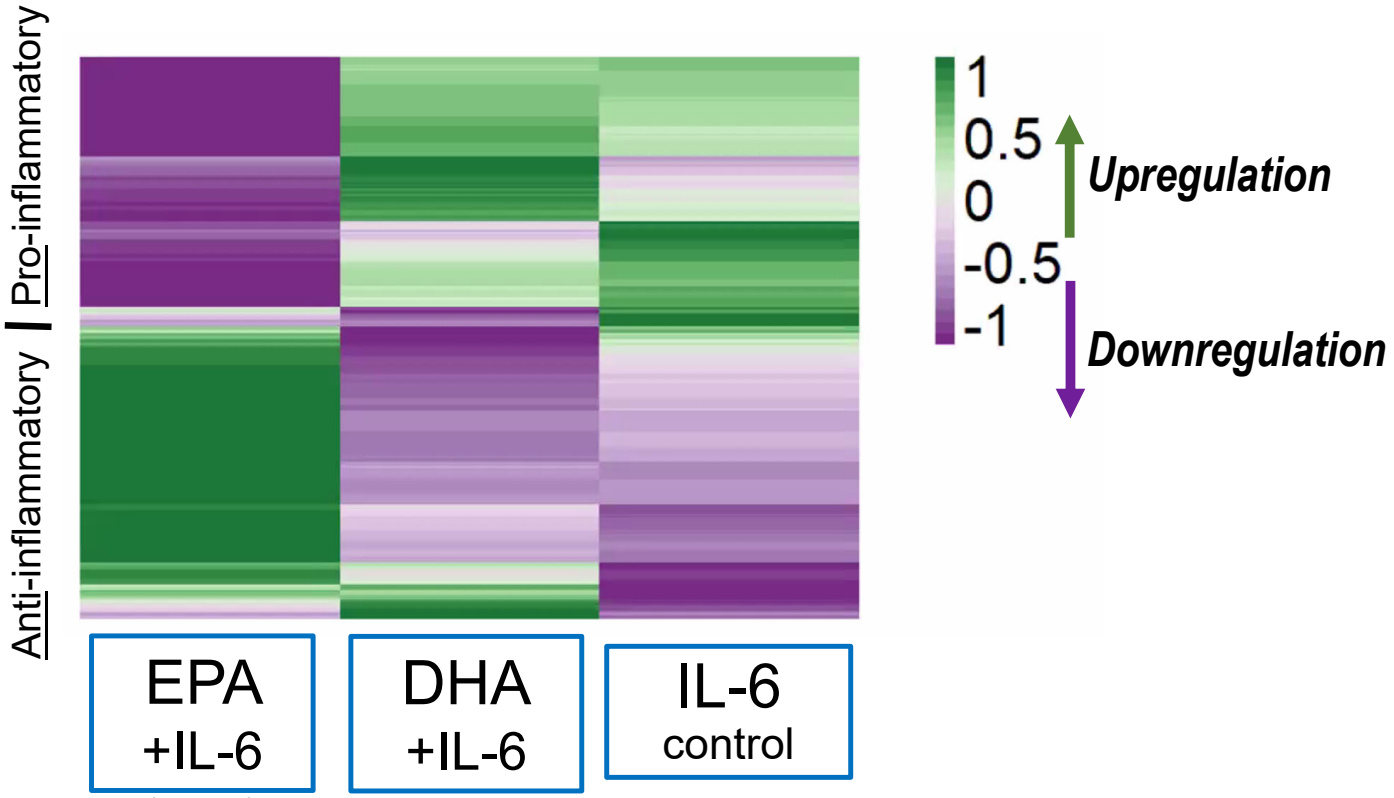


EPA Reverses Pro-Inflammatory Proteomics of IL-6 vs Little Effect from DHA

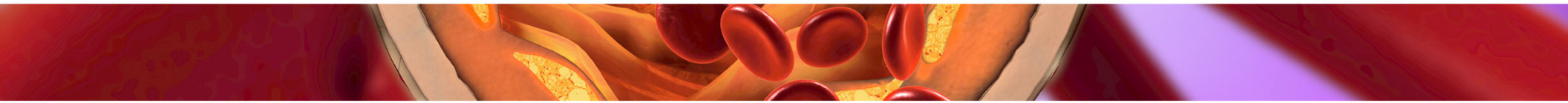
Proteomic analyses show that EPA:

- Downregulates pro-inflammatory proteins (purple)
- Upregulates anti-inflammatory proteins (green)

But DHA does the opposite (like the pro-inflammatory IL-6 control)

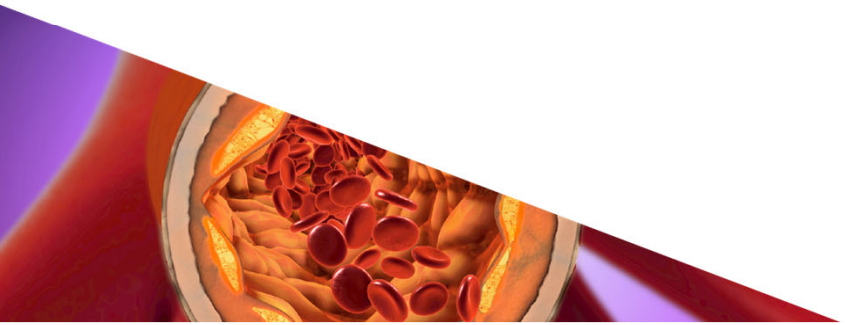


Unpublished data. R. Preston Mason, Elucida Research and Harvard/Brigham & Women's Hospital

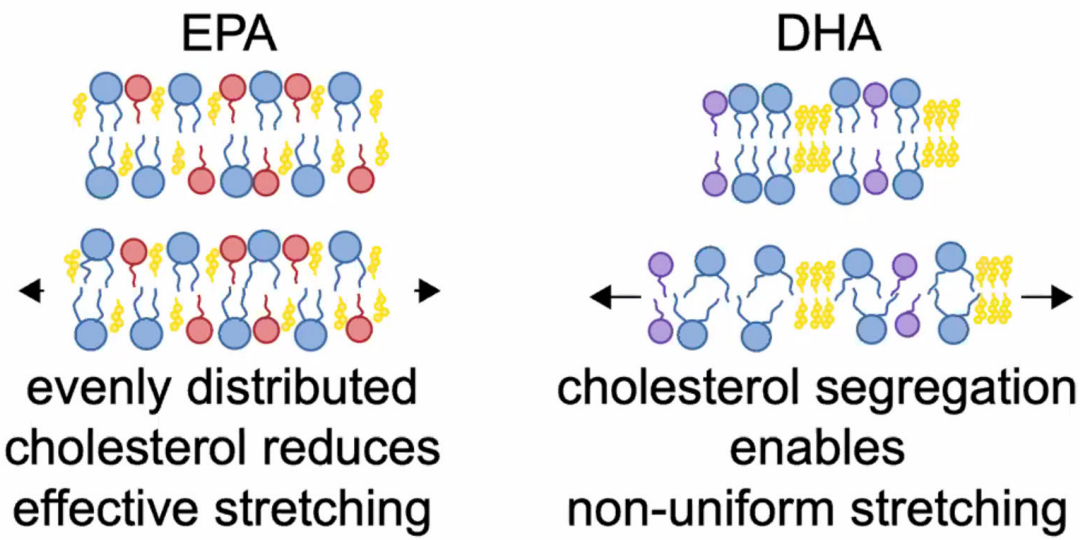


QUESTION 3

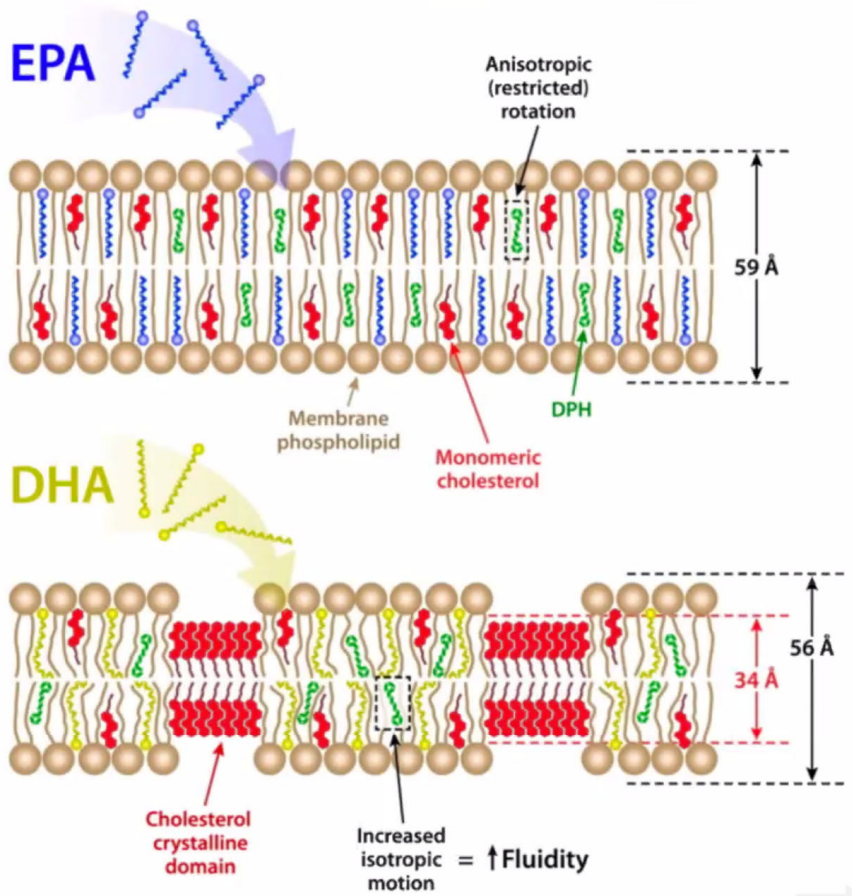
What are the roles of *cholesterol domains* and *crystals* in atherogenesis, and how do EPA and DHA affect their progression?



Multiple Labs Indicate EPA and DHA have Distinct Effects on Membranes and Cholesterol Distribution

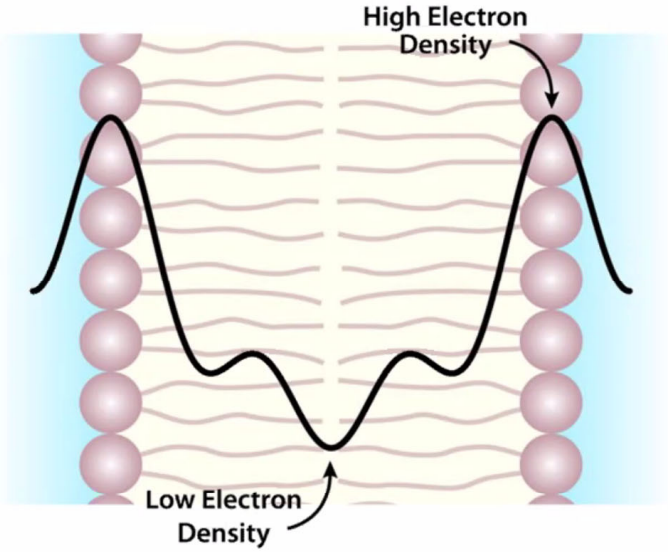


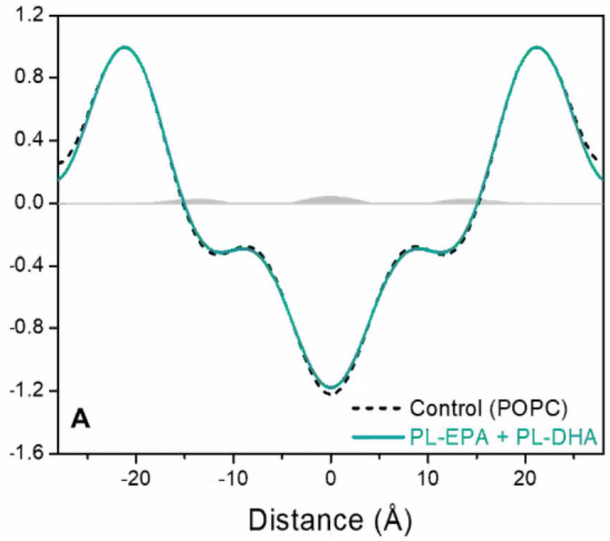
Jacobs et al. *Biophysical Journal* 2021;120:2317-2329

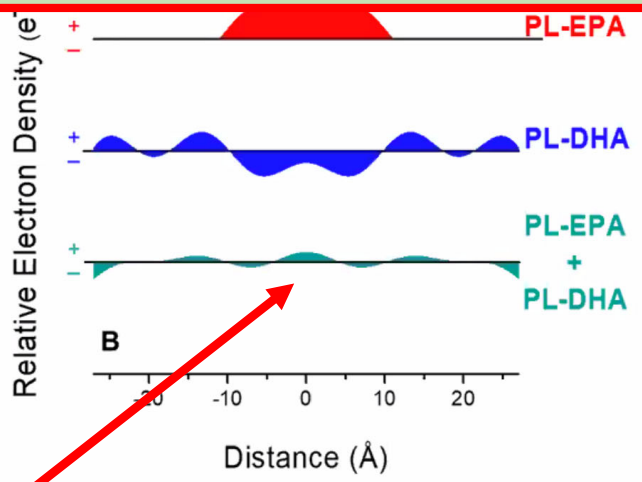


Mason RP et al. *Biochim Biophys Acta*. 2016;1858:3131-3140.

EPA and DHA Differentially Influence Membrane Structure and Electron Density





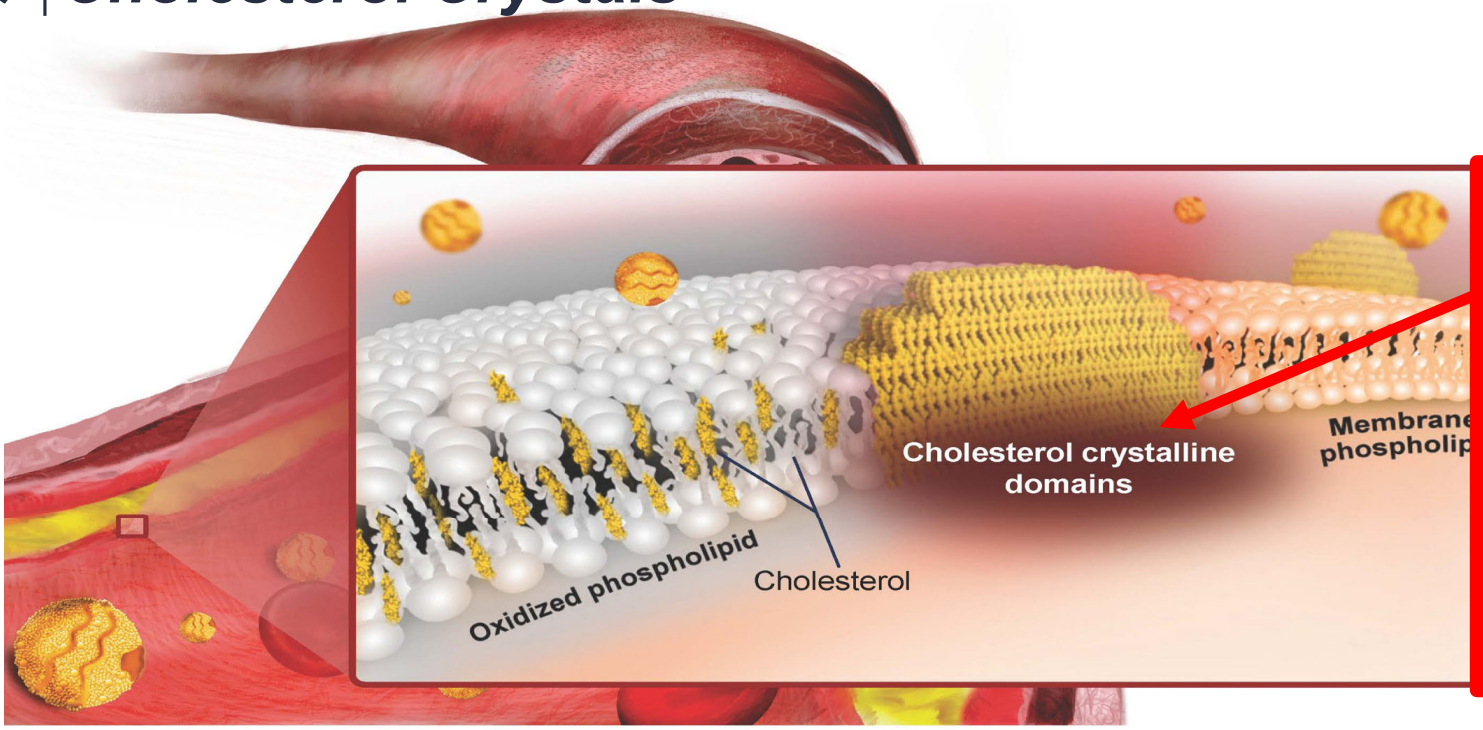


Pure EPA Stabilizes Cell Membranes

Addition of DHA to pure EPA Negates the EPA Benefit

Sherratt SCR et al. *Journal of Lipid Research*. 2021;62:100106.

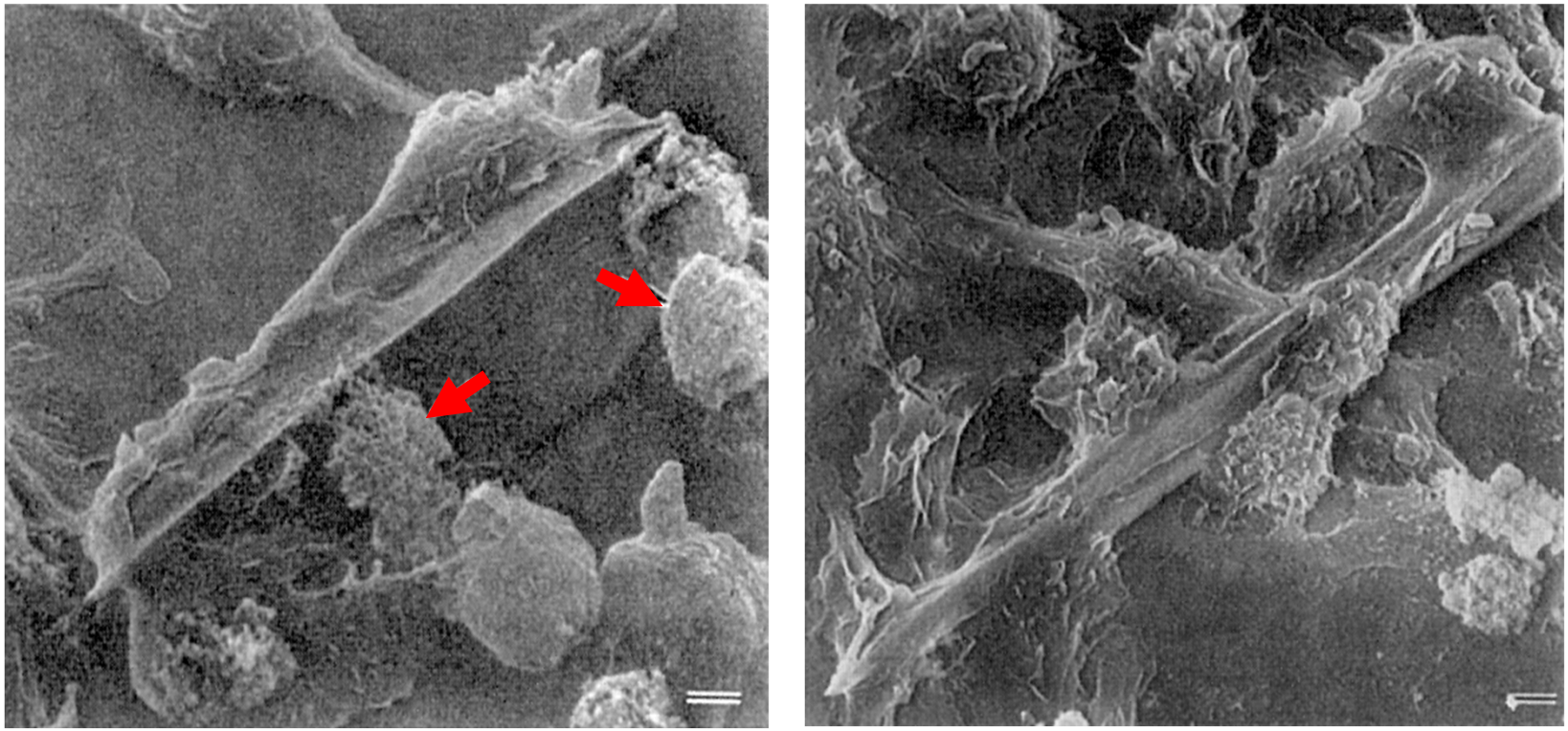
DHA *Increases* Membrane *Fluidity*, and Is a Less-Effective Antioxidant, Leading to ↑Cholesterol Crystalline *Domains* & ↑*Cholesterol Crystals*



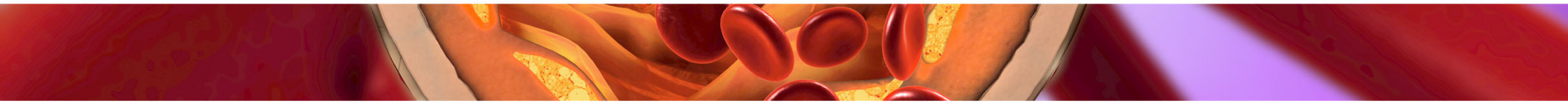
DHA ***promotes*** formation of ***cholesterol crystalline domains*** which may lead to ***cholesterol crystals***

Mason RP, Jacob RF. *Biochim Biophys Acta*. 2015;1848(2):502-509.

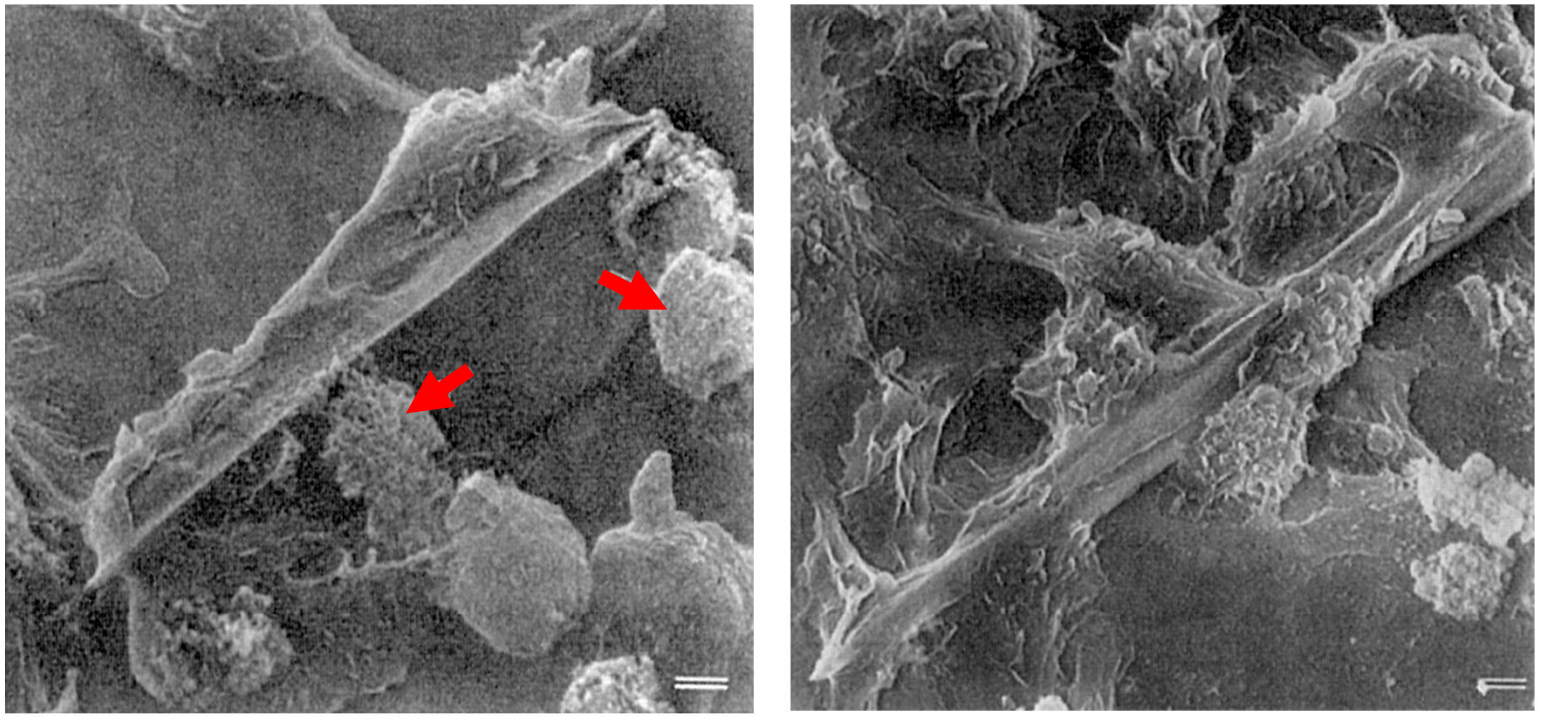
Cholesterol Crystals Associated with Atherosclerosis and Cell Death



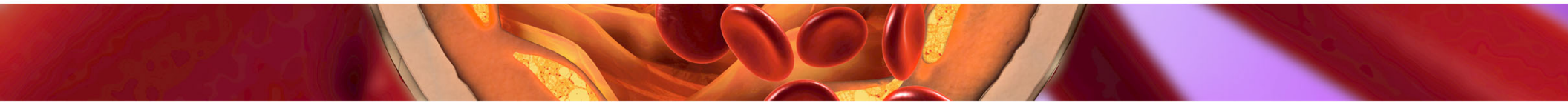
Kellner-Weibel G, et al. *Arterioscler Thromb Vasc Biol*. 1999;19(8):1891-1898.



Cholesterol Crystals Evolve from Excess *Cholesterol Domain* Formation and Can Cause Macrophage *Death* and Plaque *Rupture*

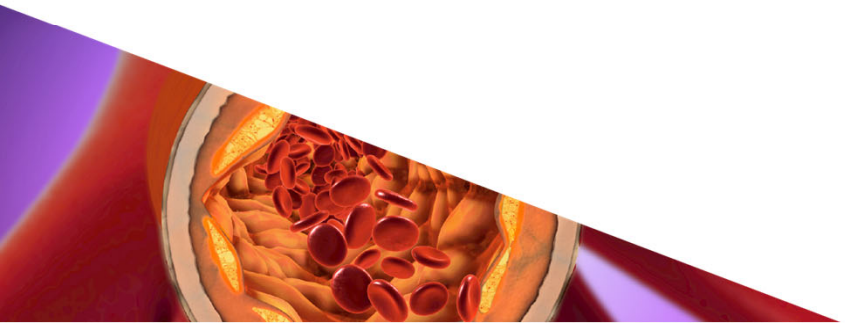


Kellner-Weibel G, et al. *Arterioscler Thromb Vasc Biol*. 1999;19(8):1891-1898.

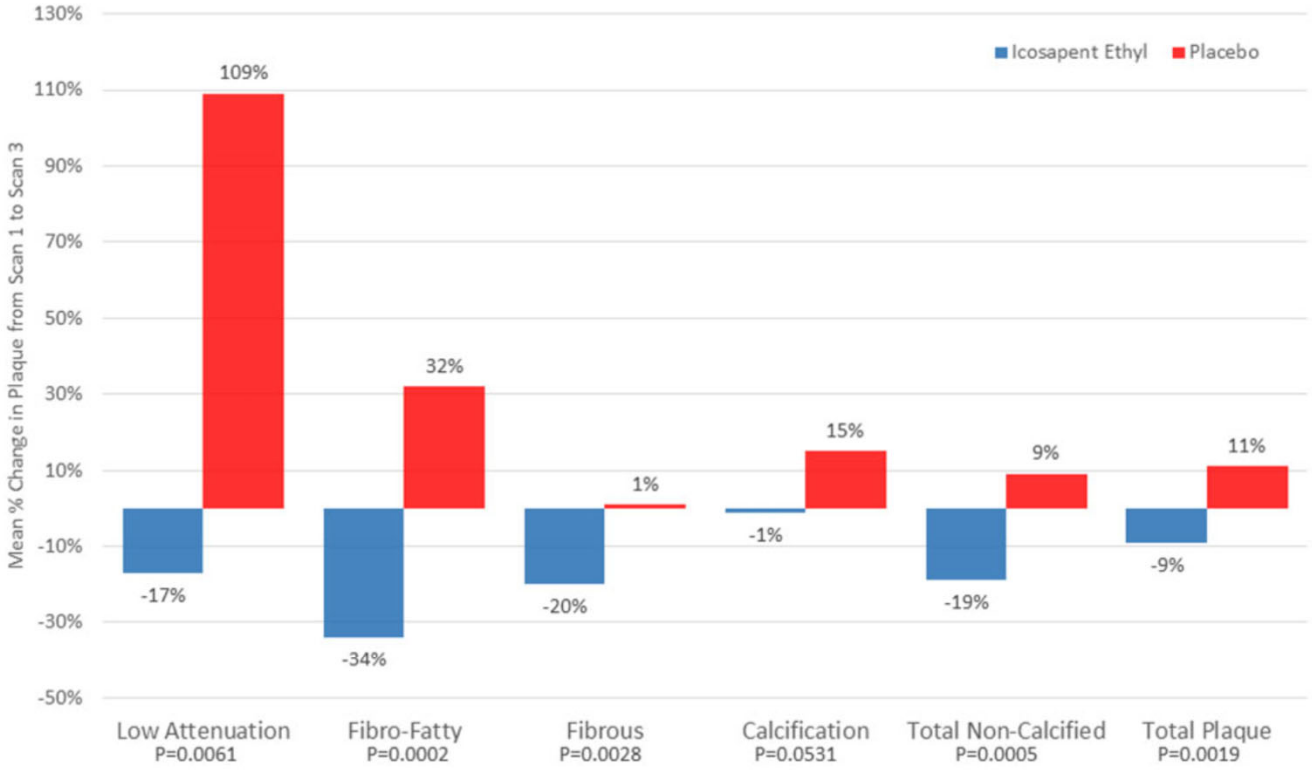


QUESTION 4

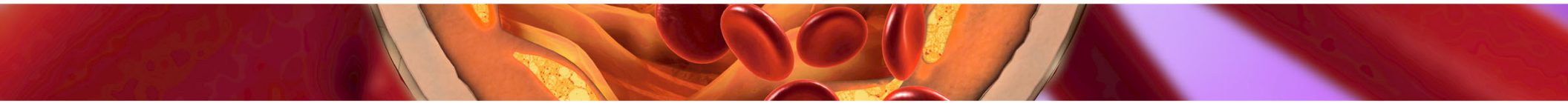
How do EPA and DHA affect coronary artery plaques in human subjects?



Final EVAPORATE Results Show Effects of Icosapent Ethyl on Plaque Volume and Composition



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

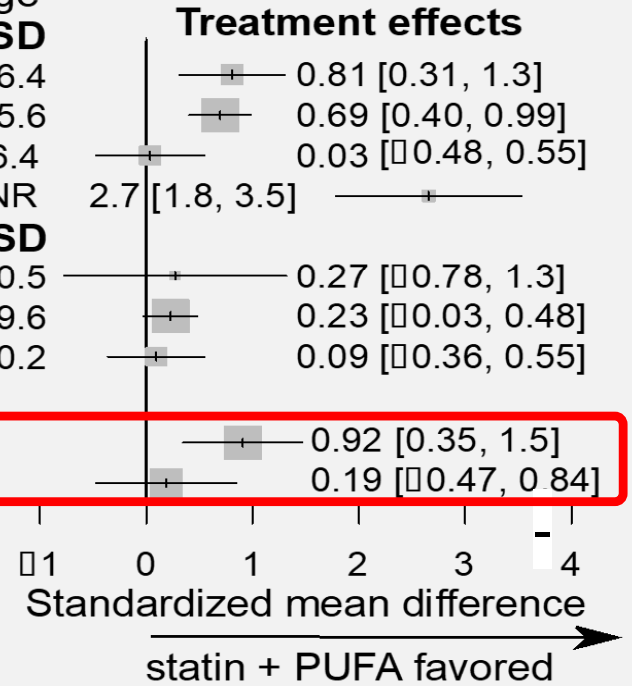


EPA *Reduces* Coronary Atherosclerosis, but EPA/DHA Does *Not*

*Subgroup analysis

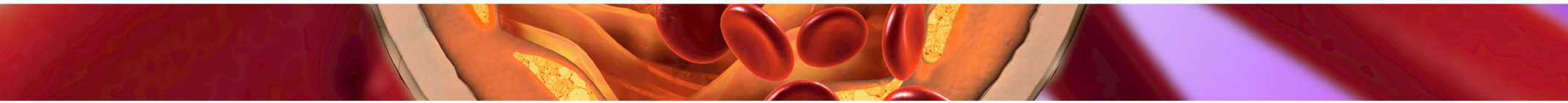
Total plaque volume (by CT Angiogram)

	statin			statin + PUFA		
	% vol change			% vol change		
EPA studies	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Budoff 2020 (EVAPORATE)	37	11.0	29.6	31	−9.0	16.4
Watanabe 2017 (CHERRY)	96	−2.1	11.8	97	−11.7	15.6
Niki 2016	30	−1.1	8.3	29	−1.4	6.4
Wakita 2011	20	−1.5	NR	20	−21.9	NR
EPA/DHA studies	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Takeuchi 2020 (AQUAMARINE*)	5	−2.2	16.0	12	−5.6	10.5
Alfaddagh 2017 (HEARTS)	114	11.0	21.8	126	6.3	19.6
Ahn 2016	36	−8.5	55.5	38	−12.7	30.2
Pooled estimates		**Total N**			**Total N**	
statin + EPA		**183**			**177**	
statin + EPA/DHA		**155**			**176**	



A Systematic Review and Meta-Analysis of Randomized Prospective Trials

Sheppard, JP. AHA Ann Sci Sessions; November 2021. Abstract P2037.

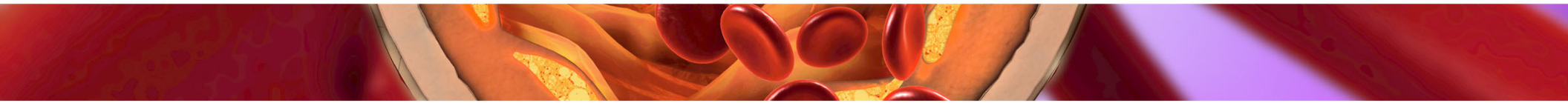


EPA + DHA Mix of FFA in STRENGTH *Failed* to Reduce ASCVD, Even at 4 g/d: ***WHY?***

(Rx Om-3 carboxylic acid—Epanova)

- Trial very similar to REDUCE-IT, but used EPA+DHA mix instead of pure EPA
- But ***no CVD benefit*** (vs 25% ASCVD in REDUCE-IT)
- Why so different (negative/neutral)??
- Likely due to addition of DHA to EPA
- **DHA** is weakly anti-atherogenic to neutral to even ***pro-*** **atherogenic!**

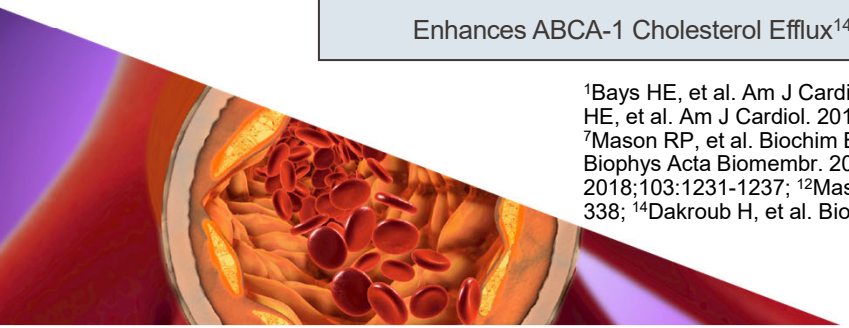
STRENGTH: Long-Term Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia. Nicholls SJ, et al. *JAMA*. 2020;324(22);2268-2280



EPA Has More Anti-Atherosclerotic Mechanisms than either DHA or Fibrates and Niacin

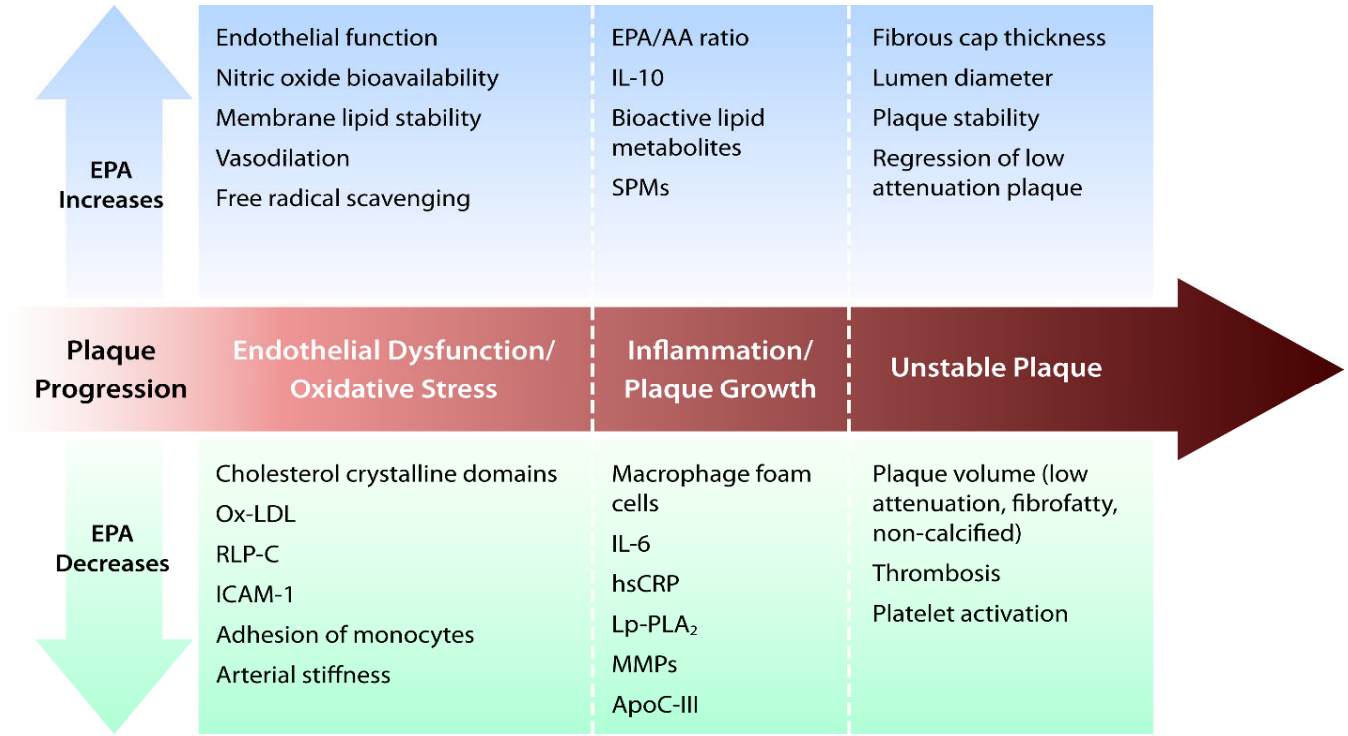
Mechanism of Action	EPA	DHA	Fibrates/Niacin
Does not raise LDL in pts with very high TGs[1,2,3]	+	–	–
Reduces hsCRP in patients with elevated TGs[4,5,6]	+	–	+
		–	–
		–	–
		–	–
		–	–
Inhibits sdLDL, LDL, VLDL, HDL oxidation[9,10,12,13]	+	–	–
Enhances ABCA-1 Cholesterol Efflux[14]	+	–	+

PROMINENT Tested CV Outcomes in Patients with HTG/low HDL-C and Diabetes (similar to REDUCE-IT and STRENGTH) on Pemafibrate vs Placebo
but it was Stopped Early for Futility (4/8/22)—further evidence that fibrates don't prevent CVD when added to a statin



[1]Bays HE, et al. Am J Cardiol. 2011;108:682-690; [2]Jacobson TA, et al. J Clin Lipidol. 2012;6:5-18; [3]Goldberg AC, et al. Clin Ther. 1989;11(1):69-83; [4]Bays HE, et al. Am J Cardiol. 2013;13:37-46; [5]Dunbar RL, et al. Lipids Health Dis. 2015;14:98; [6]Belfort R, et al. J Clin Endocrin Metabol. 2010;95:829-836; [7]Mason RP, et al. Biochim Biophys Acta. 2016;1858:3131-3140; [8]Sherratt SC, RP Mason. Chem Phys Lipid. 2018;212:73-79; [9]Sherratt SC, et al. Biochim Biophys Acta Biomembr. 2020;1862:183254; [10]Mason RP, RF Jacob. Biochim Biophys Acta. 2015;1848:502-509; [11]Mason RP, et al. Biomed Pharmacother. 2018;103:1231-1237; [12]Mason RP, et al. J Cardiovasc Pharmacol. 2016;68:33-40; [13]Sherratt SC, Mason RP. Biochem Biophys Res Comm. 2018;496:335-338; [14]Dakroub H, et al. Biochim Biophys Acta Mol Cell Biol Lipids. 2021;1866:159016.

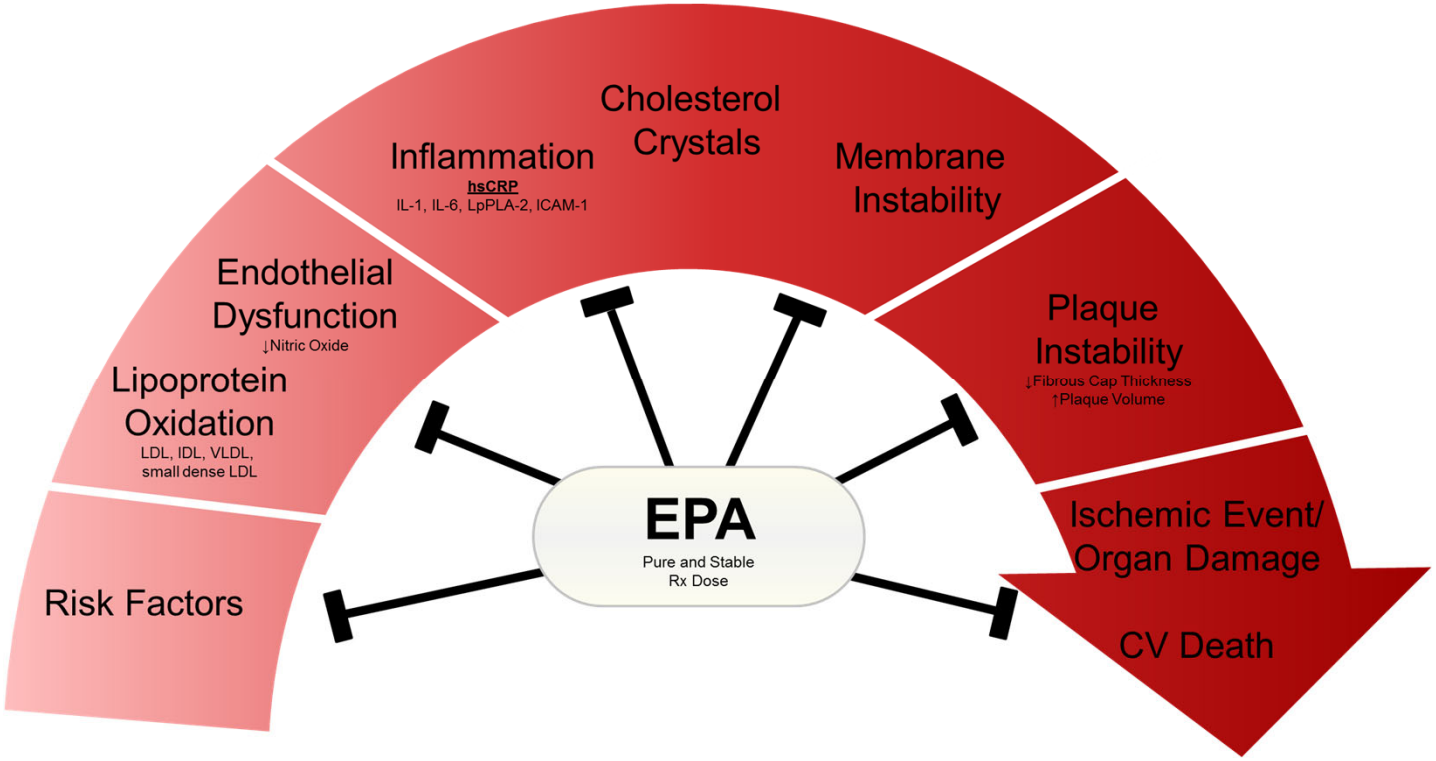
EPA and Atherosclerosis



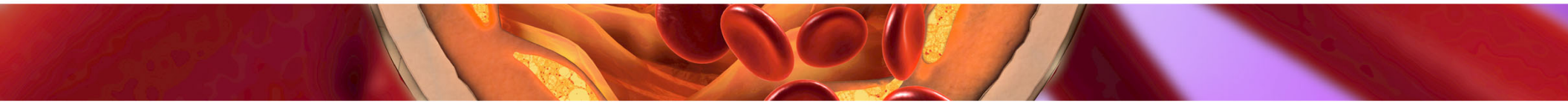
AA, arachidonic acid; hsCRP, high-sensitivity C-reactive protein; ICAM, intercellular adhesion molecule; IL, interleukin; Lp-PLA2, lipoprotein-associated phospholipase A2; MMPs, matrix metalloproteinases; Ox-LDL, oxidized low-density lipoprotein; RLP-C, remnant-like lipoprotein particle cholesterol.

Mason RP, Eckel RH. *Am J Med*. 2021;134(9):1085-1090.

EPA Interferes with the CV Disease Continuum at Multiple Points to Reduce 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;72:330-343; Jia X, et al. *Curr Atheroscler Rep*. 2019;21:1; Mason RP, et al. *Biomed Pharmacother*. 2018;103:1231-1237; Ference BA, et al. *JAMA*. 2019;321:364-373.

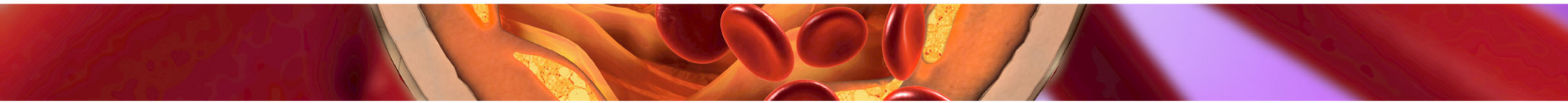


Practical Considerations to Manage Residual Risk

Eliot Brinton, MD

and

James Underberg, MD

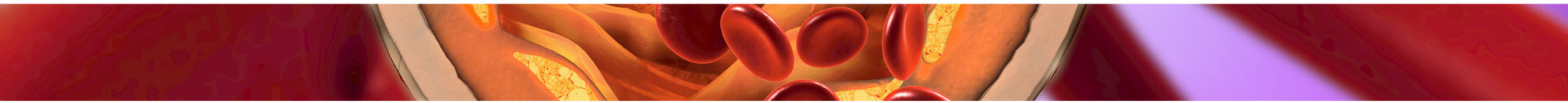


Our Patient – First Visit

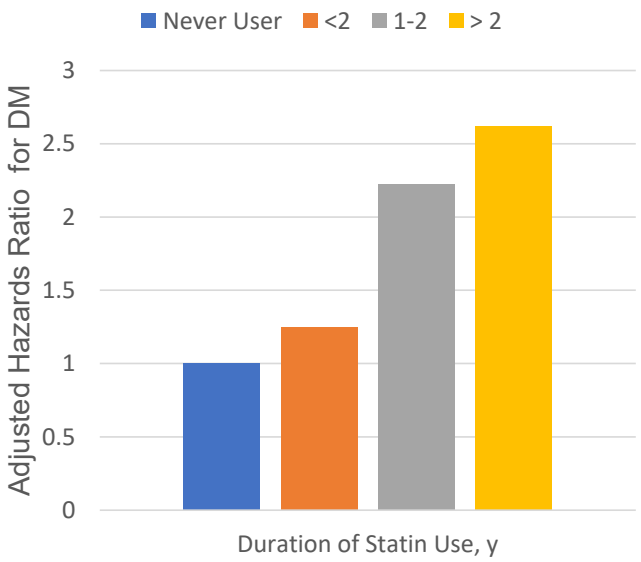
Annual Risk of 3-Point MACE ~5% (TRS 2ºP)

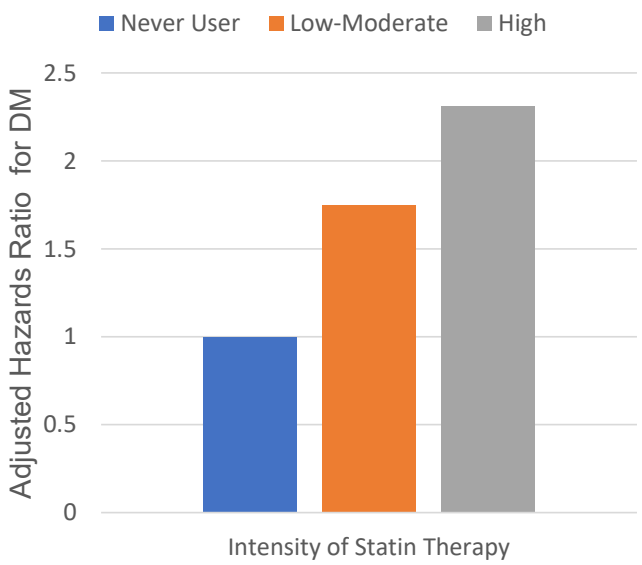
- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, controlled on ARB
- BMI 29 kg/m^2, waist 40”, A1c 6.0, metabolic syndrome

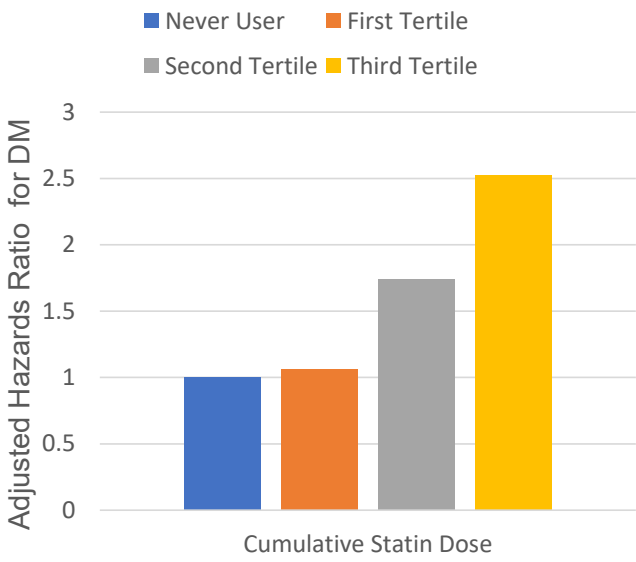
	Pre-Treatment
TC	260 mg/dL
LDL-C	170 mg/dL
TG	280 mg/dL
HDL-C	34 mg/dL
Non-HDL-C	226 mg/dL



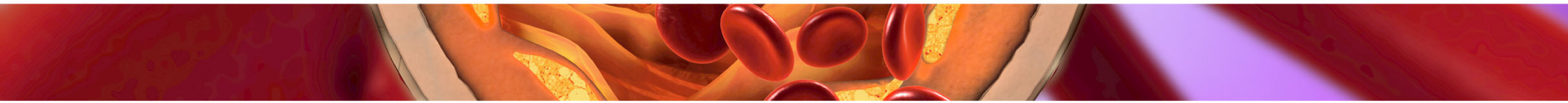
Risk of New-Onset Diabetes







Ko MJ, et al. *J Am Heart Assoc*. 2019;8(8):e011320.



Our Patient – On Atorvastatin 80 mg/d

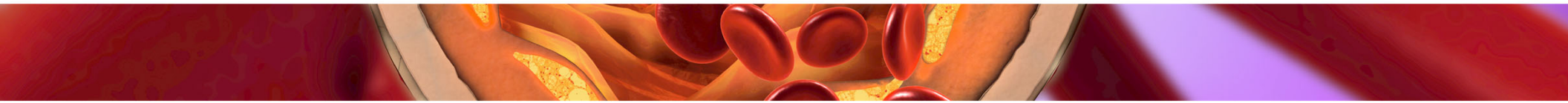
Annual Risk of 3-Point MACE ~3%

- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, controlled on ARB
- BMI 29 kg/m^2, waist 40”, A1c 6.0, metabolic syndrome

	Pre-Treatment	Post-Treatment
TC	260 mg/dL	168 mg/dL
LDL-C	170 mg/dL	85 mg/dL
TG	280 mg/dL	238 mg/dL
HDL-C	34 mg/dL	36 mg/dL
Non-HDL-C	226 mg/dL	133 mg/dL

- 85 mg/dL ~ -40% MACE

(7-30% ⇊ TG)



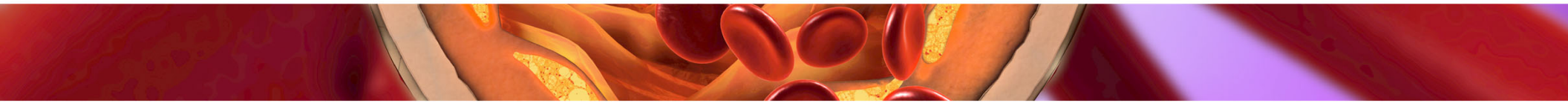
Our Patient – On Atorvastatin 80 mg/d

Annual Risk of 3-Point MACE ~3%

- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, controlled on ARB
- BMI 29 kg/m^2, waist 40”, A1c 6.0, metabolic syndrome

	Pre-Treatment	Post-Treatment
TC	260 mg/dL	168 mg/dL
LDL-C	170 mg/dL	85 mg/dL
TG	280 mg/dL	238 mg/dL
HDL-C	34 mg/dL	36 mg/dL
Non-HDL-C	226 mg/dL	133 mg/dL

Does he need more LDL lowering?



Our Patient – On Atorva 80 + *Ezetimibe*

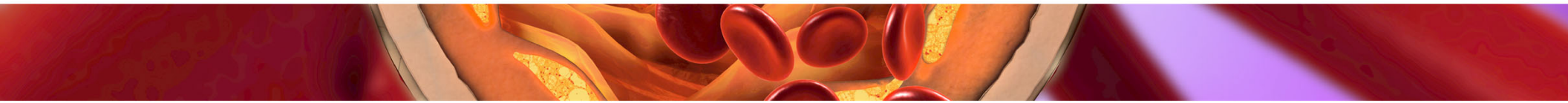
Annual Risk of 3-Point MACE ~2.8%

- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, controlled on ARB
- BMI 29 kg/m^2, waist 40”, A1c 6.0, metabolic syndrome

	Pre-Treatment	Post-Treatment
TC	168 mg/dL	152 mg/dL
LDL-C	85 mg/dL	72 mg/dL
TG	238 mg/dL	214 mg/dL
HDL	36 mg/dL	37 mg/dL
Non-HDL-C	133 mg/dL	115 mg/dL

-98 mg/dL ~ -43% MACE

(10-15% ⇊ TG)



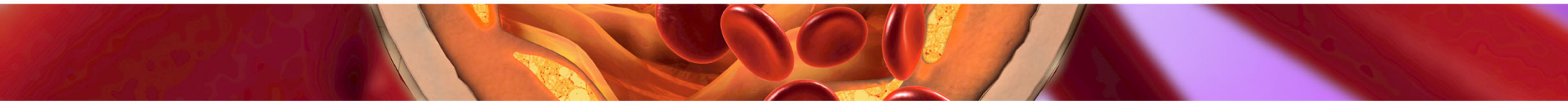
Our Patient – On Atorva 80 + *Ezetimibe*

Annual Risk of 3-Point MACE ~2.8%

- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, controlled on ARB
- BMI 29 kg/m^2, waist 40”, A1c 6.0, metabolic syndrome

What next? No changes? *More LDL*↓? Other?

	Pre-Treatment	Post-Treatment
TC	168 mg/dL	152 mg/dL
LDL-C	85 mg/dL	72 mg/dL
TG	238 mg/dL	214 mg/dL
HDL-C	36 mg/dL	37 mg/dL
Non-HDL-C	133 mg/dL	115 mg/dL



Our Patient – Atorva 80 + Ezetimibe + *PCSK9i*

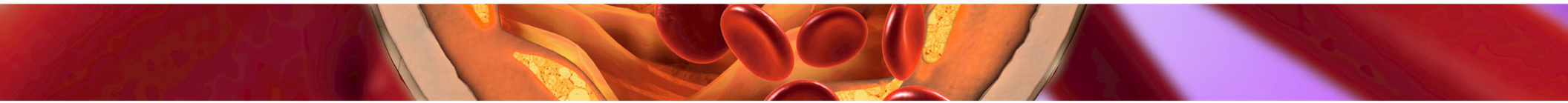
↓ASCVD risk by *15%*

- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, controlled on ARB
- BMI 29 kg/m^2, waist 40”, A1c 6.0, metabolic syndrome

	Pre-Treatment	Post-Treatment
TC	152 mg/dL	104 mg/dL
LDL-C	72 mg/dL	29 mg/dL
TG	214 mg/dL	184 mg/dL
HDL-C	37 mg/dL	38 mg/dL
Non-HDL-C	115 mg/dL	66 mg/dL

-141 mg/dL ~ -54% MACE

(5-25% ⇊ TG)



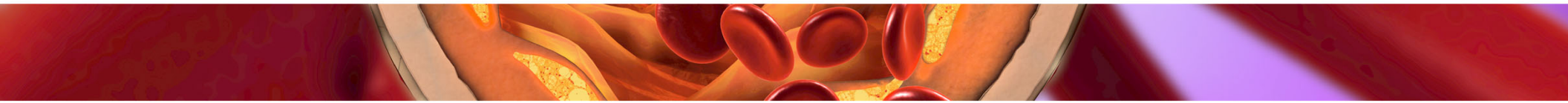
Our Patient – On Atorva 80 + *Ezetimibe*

Annual Risk of 3-Point MACE ~2.8%

- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, controlled on ARB
- BMI 29 kg/m^2, waist 40”, A1c 6.0, metabolic syndrome

What next? No changes? More LDL↓? *Other*?

	Pre-Treatment	Post-Treatment
TC	168 mg/dL	152 mg/dL
LDL-C	85 mg/dL	72 mg/dL
TG	238 mg/dL	214 mg/dL
HDL-C	36 mg/dL	37 mg/dL
Non-HDL-C	133 mg/dL	115 mg/dL



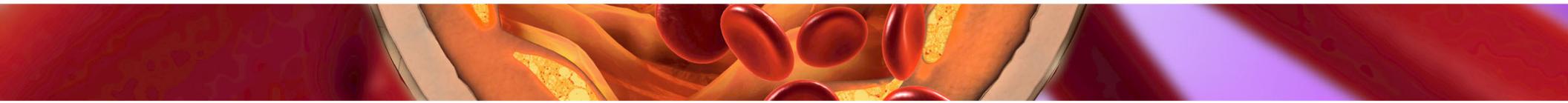
Our Patient – Atorva + Ezetimibe + *IPE*

↓ASCVD risk by *25%* (vs ↓*15%* w/ PCSK9i)

- 60-year-old man, smoker
- Post-MI, 1 year ago; PAD, s/p R fem-pop bypass
- Hypertension, treated
- BMI 29 kg/m^2

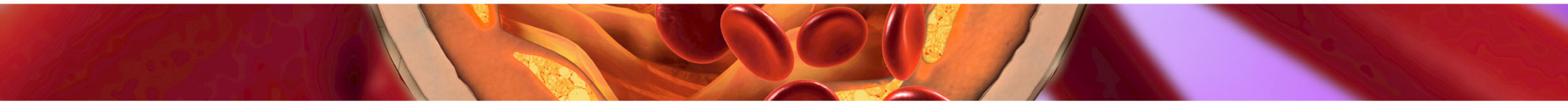
	Pre-Treatment	Post-Treatment
TC	152 mg/dL	145 mg/dL
LDL-C	72 mg/dL	72 mg/dL
TG	214 mg/dL	176 mg/dL
HDL-C	37 mg/dL	38 mg/dL
Non-HDL-C	115 mg/dL	107 mg/dL

- 26% in 3-pt MACE with Mortality Benefit and enhanced efficacy in patients with Mixed Dyslipidemia: TG ≥ 200 and HDL ≤ 35



Q&A

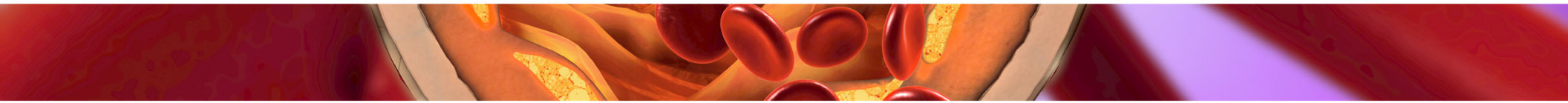
James Underberg, MD, Deepak Bhatt, MD, and Eliot Brinton, MD



Learning Assessment 1

According to the ACC Expert Consensus to Reduce ASCVD Risk, what treatment should be considered for an adult with ASCVD, fasting TG 150-499 mg/dL and LDL-C <70 mg/dL after optimizing lifestyle and ruling out secondary causes?

A. Ezetimibe
B. Niacin
C. Fibrates
D. Icosapent Ethyl



Learning Assessment 2

Which of the following statements about the biologic activity of EPA and DHA is ***TRUE***?

A. Both have similar activity on membrane stabilization
B. DHA has more potent antioxidant activity than EPA
C. EPA has more potent anti-inflammatory effects than DHA
D. Research shows that both EPA and DHA have similar effects, so their activity is considered a class effect