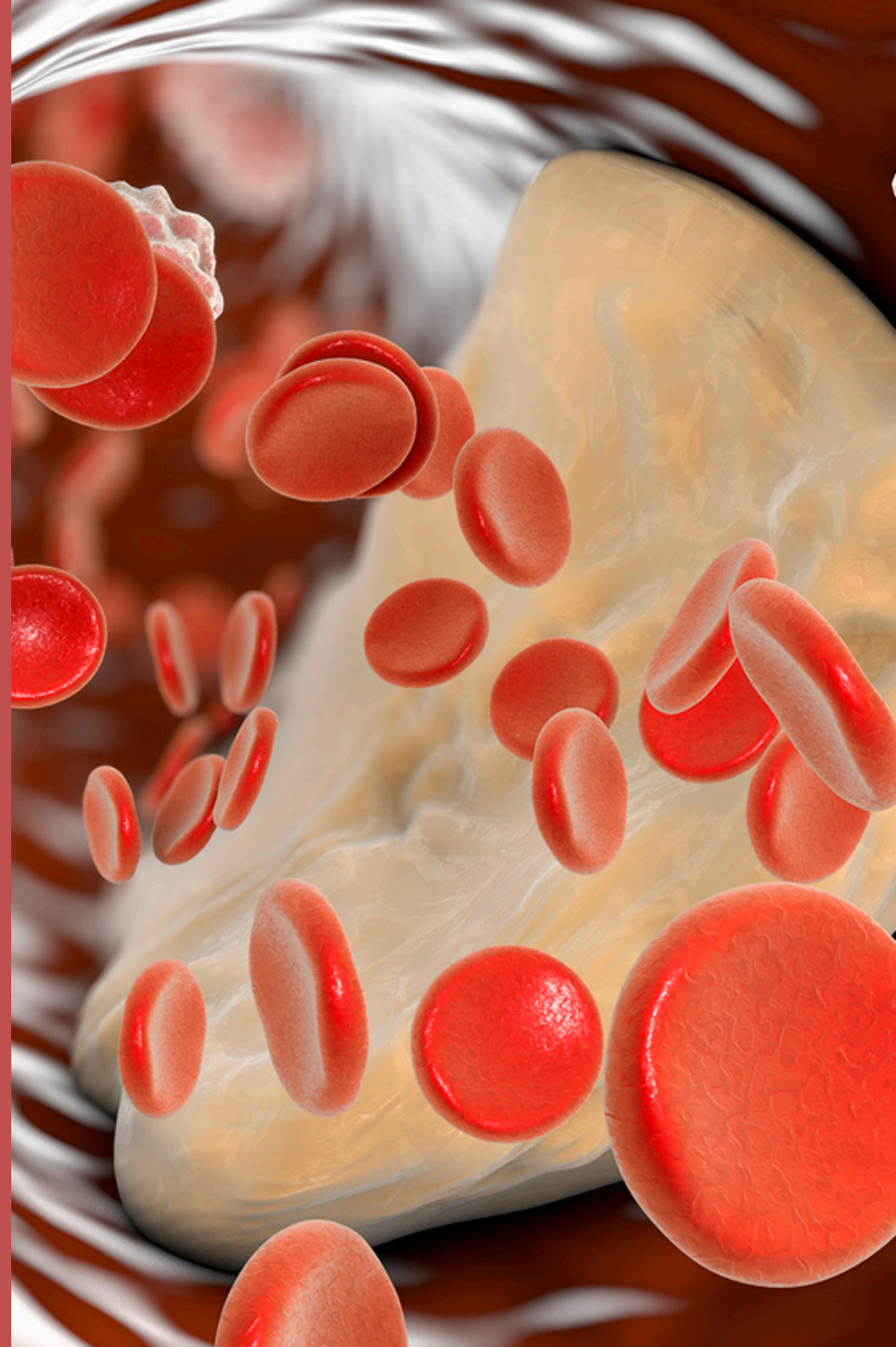
Biology of Omega-3 Fatty Acids in Cardiovascular Disease:

What Do We Know

Jorge Plutzky, MD
Director, Preventive Cardiology
Cardiovascular Division
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

Harvard Medical School

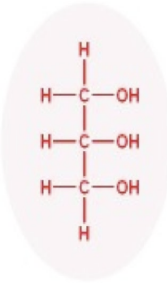
BRIGHAM AND WOMEN'S HOSPITAL



■ BENCH TO BEDSIDE VOLUME 15 | NUMBER 6 | JUNE 2009 NATURE MEDICINE

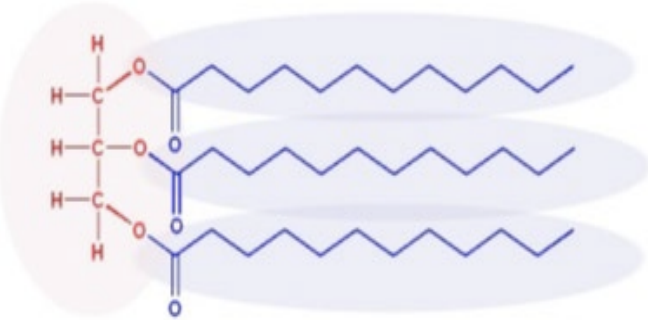
The mighty, mighty fatty acid

Aliphatic, anhydrous carboxylic acids



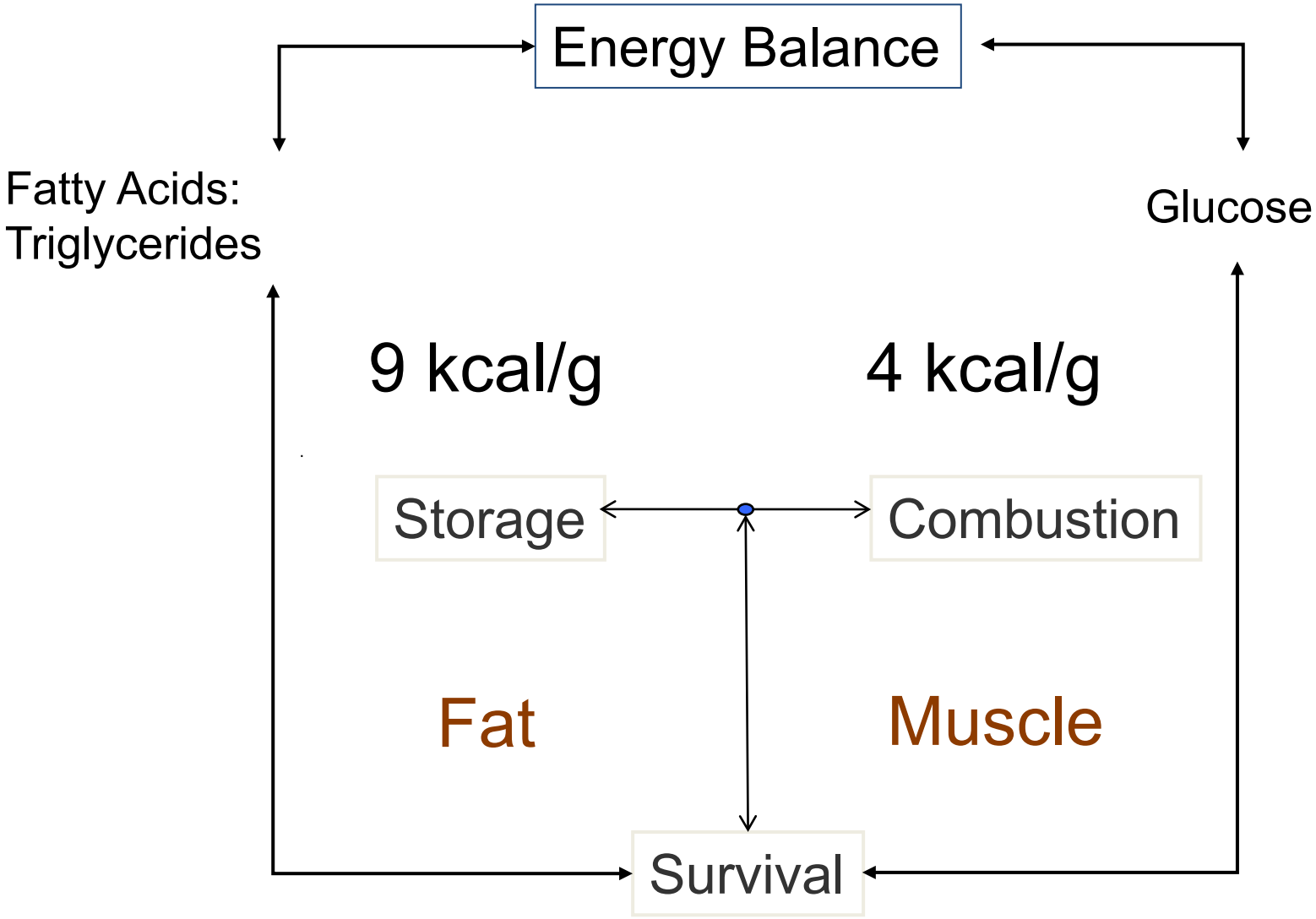
Glycerol

- Highest energy yield
- Pack more tightly than glucose/glycogen
- Minimal water required for storage
  - Glycogen: highly hydrate polymer
  - Triglyceride: anhydrous
- Lighter, more portable

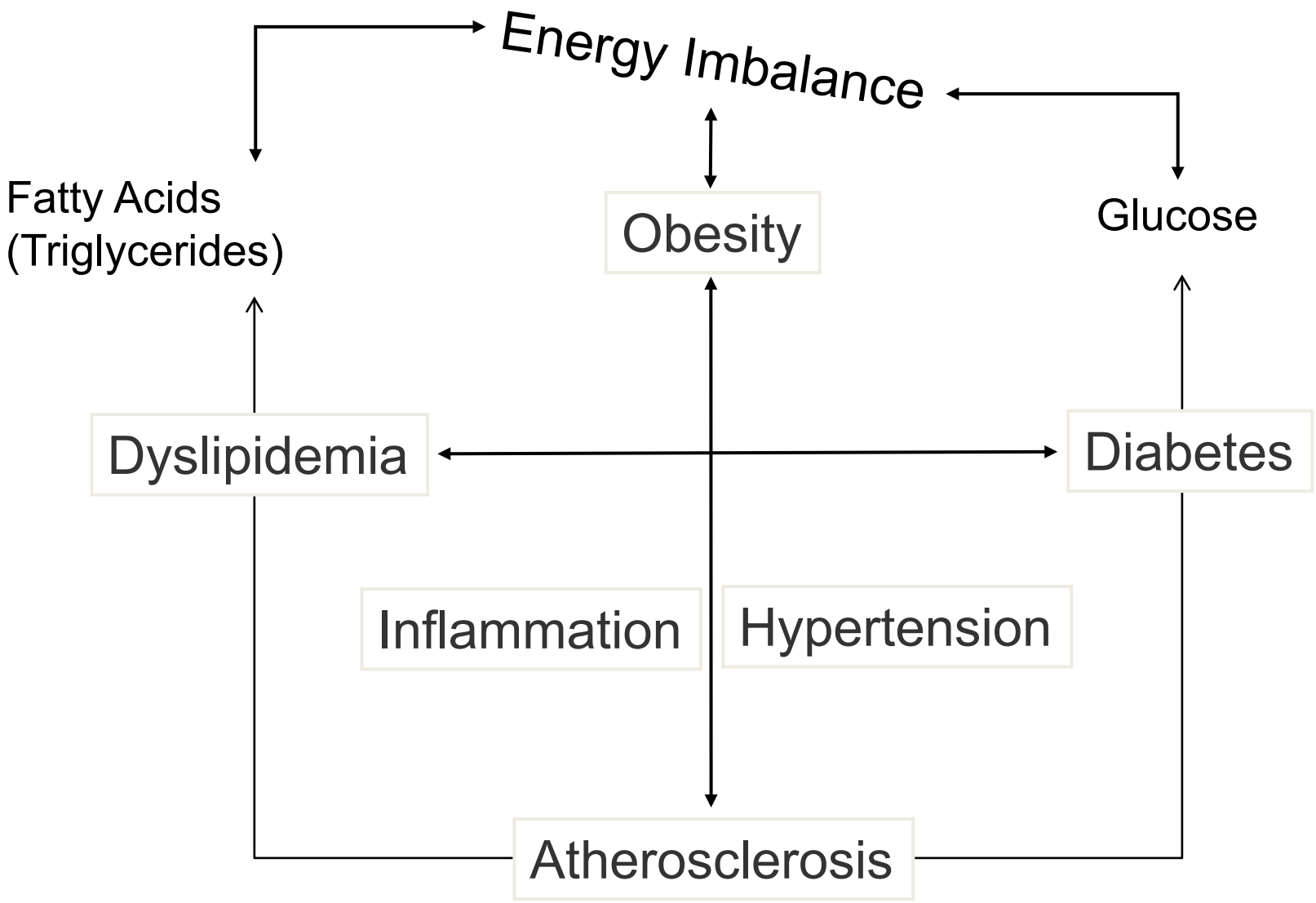


Tri - Acyl - Glycerol

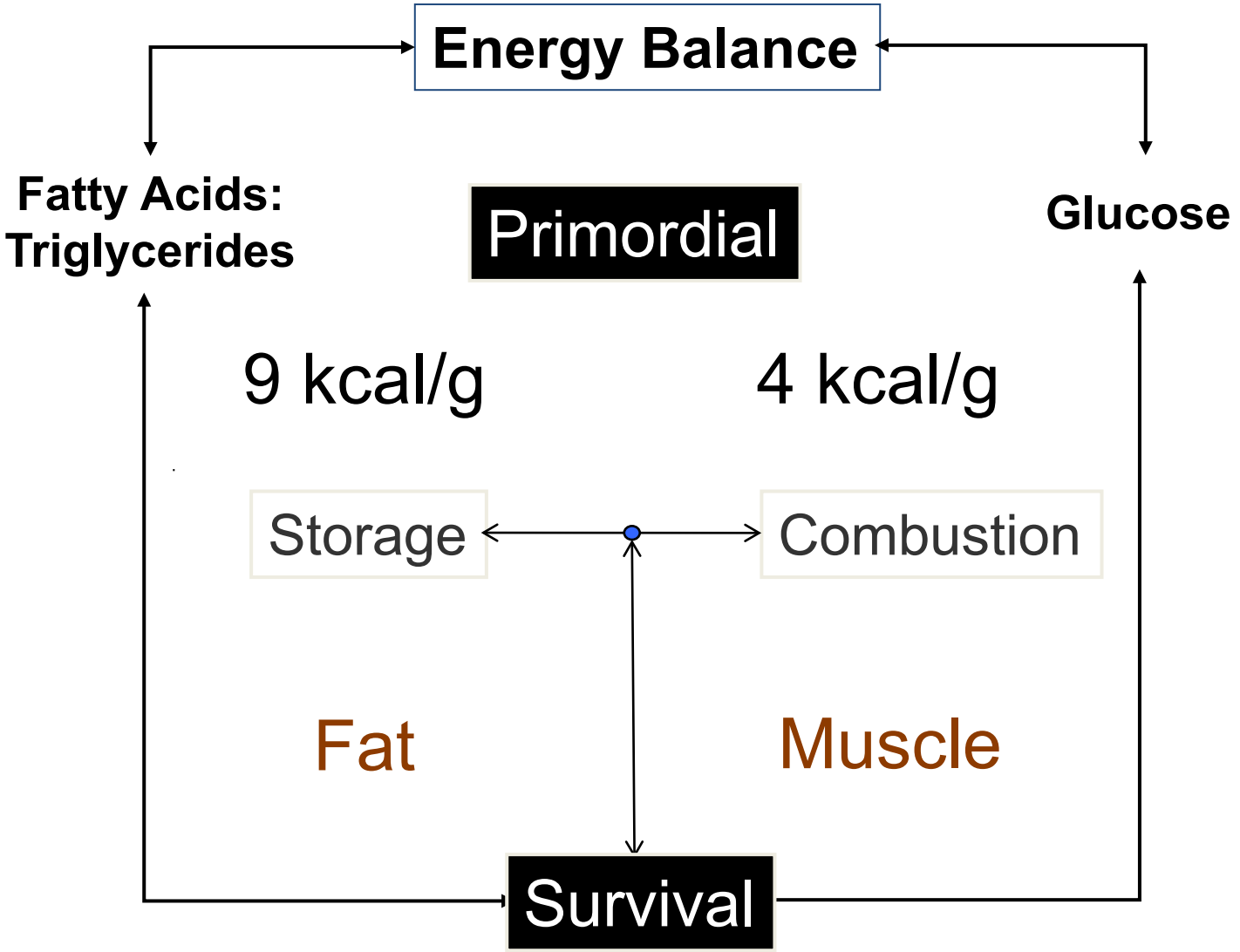
Plutzy J, Nature Medicine 2009



Plutzky, Nat Med 2009, Circ Res 2011

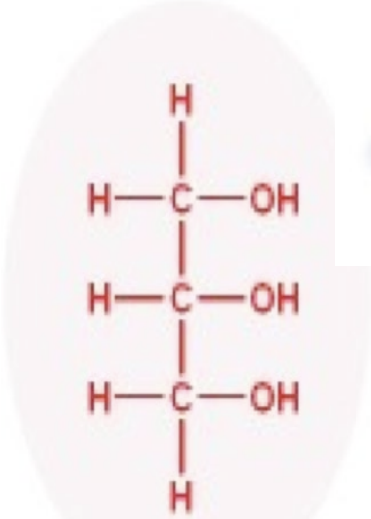


Plutzky, Nat Med 2009, Circ Res 2011



Fatty acid handling: complex, highly regulated, carefully controlled
Fatty acids as biologic active signaling molecules

Glycerol



Fatty Acid

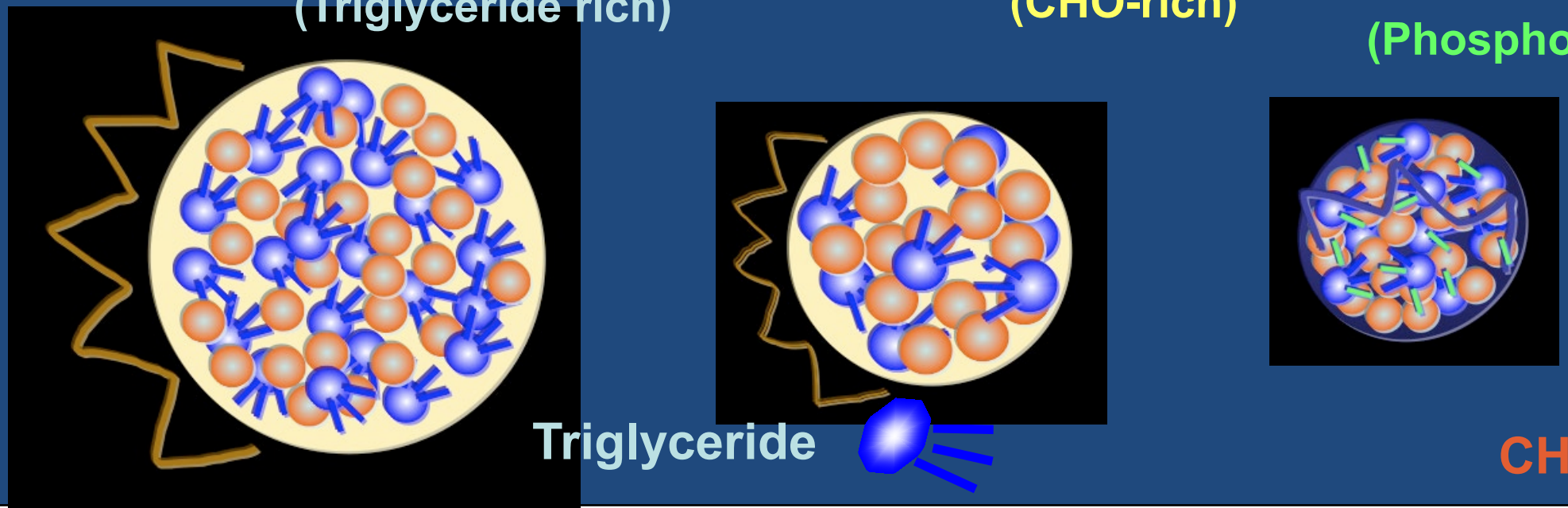
Tri - Acyl - Glycerol

Free

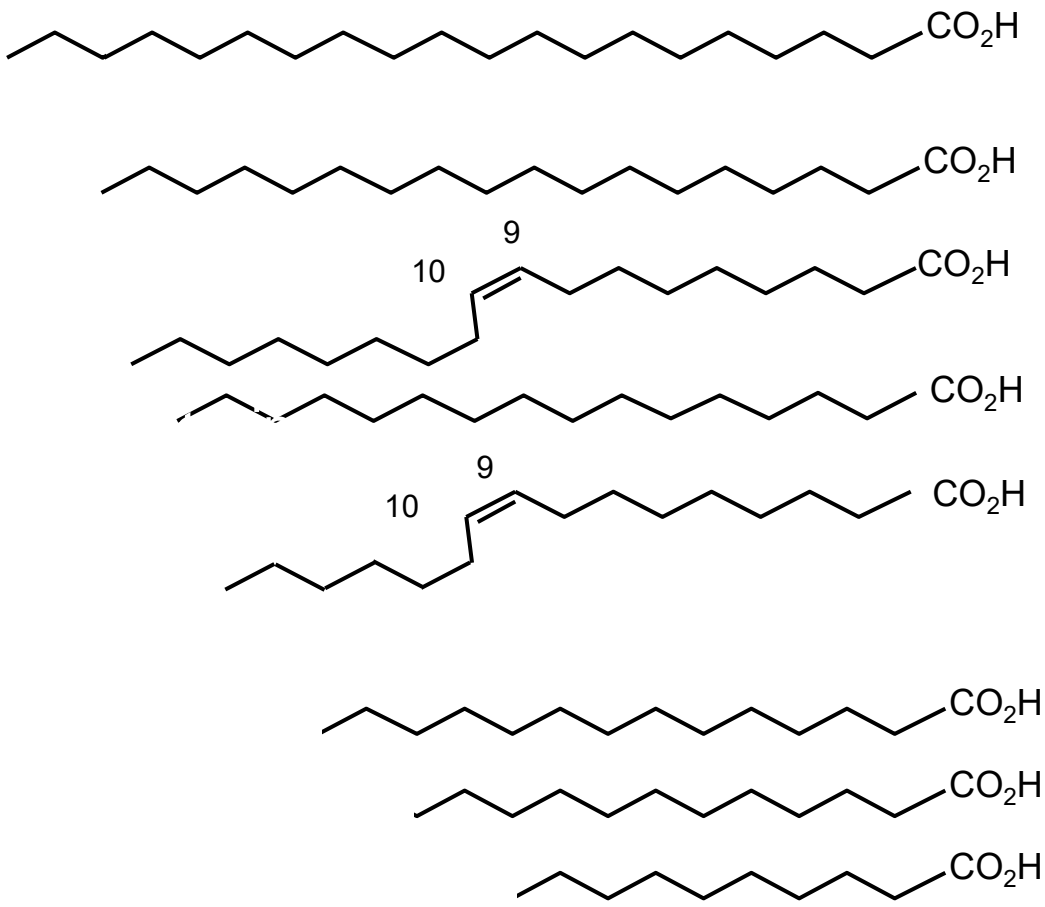
VLDL (Triglyceride rich)

LDL (CHO-rich)

HDL (Phospholipid)



Diversity Among Fatty Acids: Structural and Beyond



eicosanoic acid	C20:0
stearic acid	C18:0
oleic acid	C18:0(Δ^9)
palmitic acid	C16:0
palmitoleic acid	C16:0(Δ^9)
myristic acid	C14:0
lauric acid	C12:0
capric acid	C10:0

- Chain length
- Saturation
- Oxidation

Biological + chemical properties

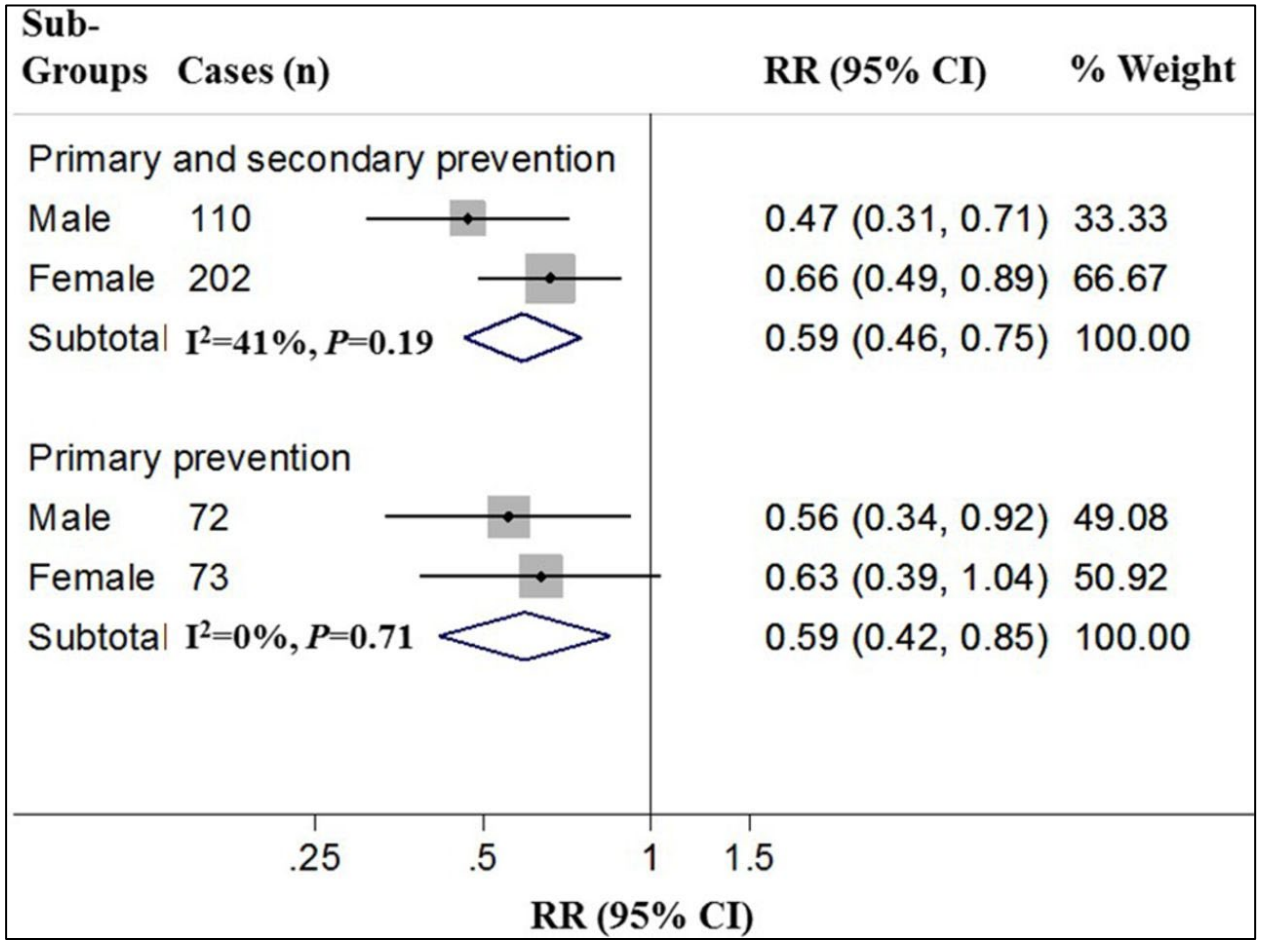
Longstanding Clues: Dietary Intake of Different Fatty Acids May Impact CV Risk

Dietary Prevention of Coronary Heart Disease: The Finnish Mental Hospital Study

OSMO TURPEINEN, MARTTI J, MAIJA PEKKARINEN, MATTI MIETTINEN, REINO ELOSUO, ERKKI PAAVILAINEN

International Journal of Epidemiology, Volume 8, Issue 2, June 1979, Pages 99–118,

- Prospect swap of saturated fat for polyunsaturated fat (or vice a versa) at 2 psychiatric hospitals, 1222 patients; primary and secondary CHD.
- 6 years follow-up.



Annals of Internal Medicine®

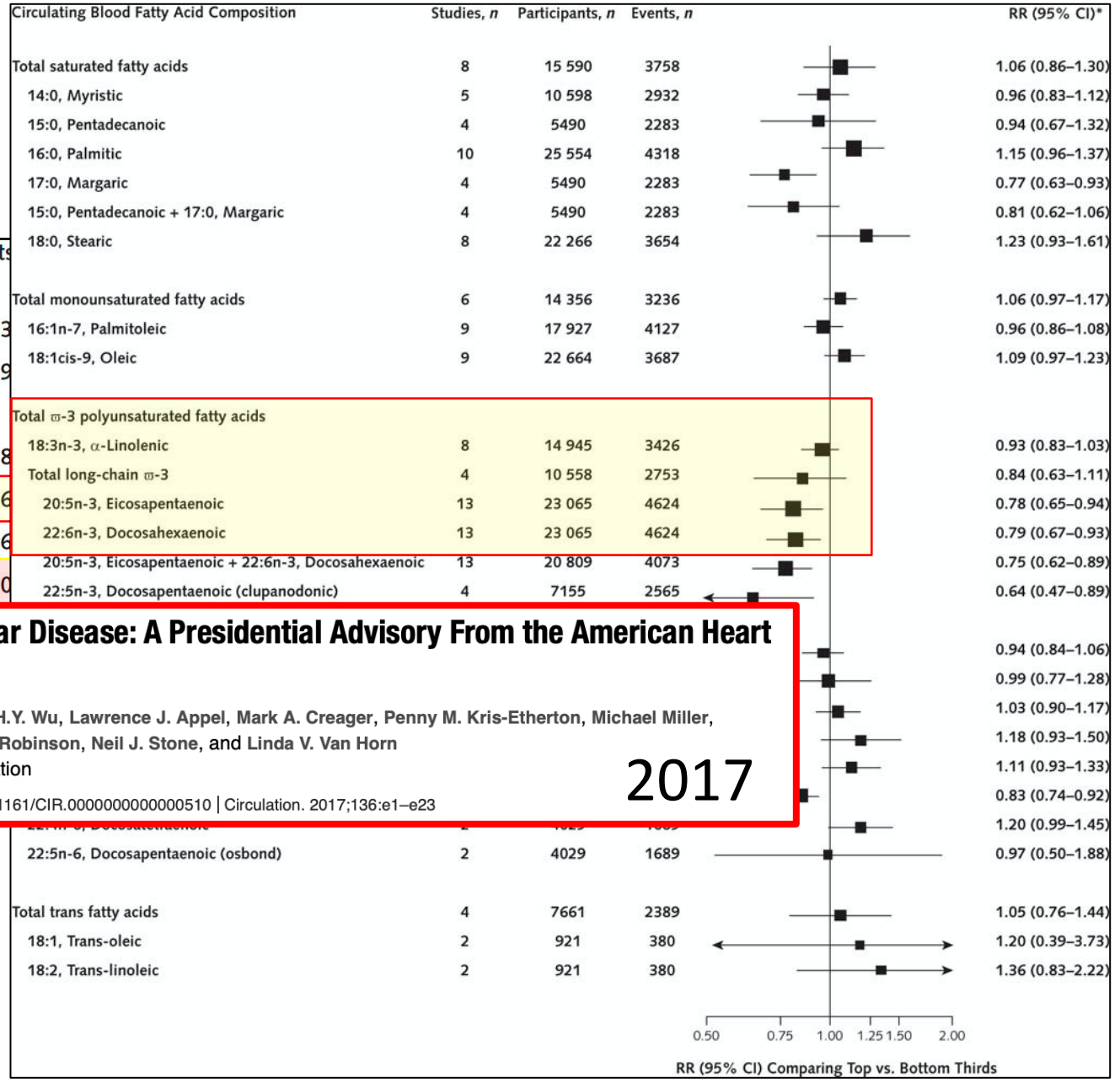
Reviews | 18 March 2014

Association of Dietary, Circulating, and Supplement Fatty Acids With Coronary Risk

A Systematic Review and Meta-analysis

Rajiv Chowdhury, MD, PhD, Samantha Warnakula, MPhil, Setor Kunutsor, MD, MSt, ... View all authors

Fatty Acid Intake	Studies, *n*	Participants
Total saturated fatty acids	20	276 763
Total monounsaturated fatty acids	9	144 219
Total ω-3 fatty acids		
α-Linolenic	7	157 258
Total long-chain ω-3	16	422 786
Total ω-6 fatty acids	8	206 376
Total trans fatty acids	5	155 270



Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association

Frank M. Sacks, Alice H. Lichtenstein, Jason H.Y. Wu, Lawrence J. Appel, Mark A. Creager, Penny M. Kris-Etherton, Michael Miller, Eric B. Rimm, Lawrence L. Rudel, Jennifer G. Robinson, Neil J. Stone, and Linda V. Van Horn
and On behalf of the American Heart Association

Originally published 15 Jun 2017 | https://doi.org/10.1161/CIR.0000000000000510 | Circulation. 2017;136:e1–e23

2017

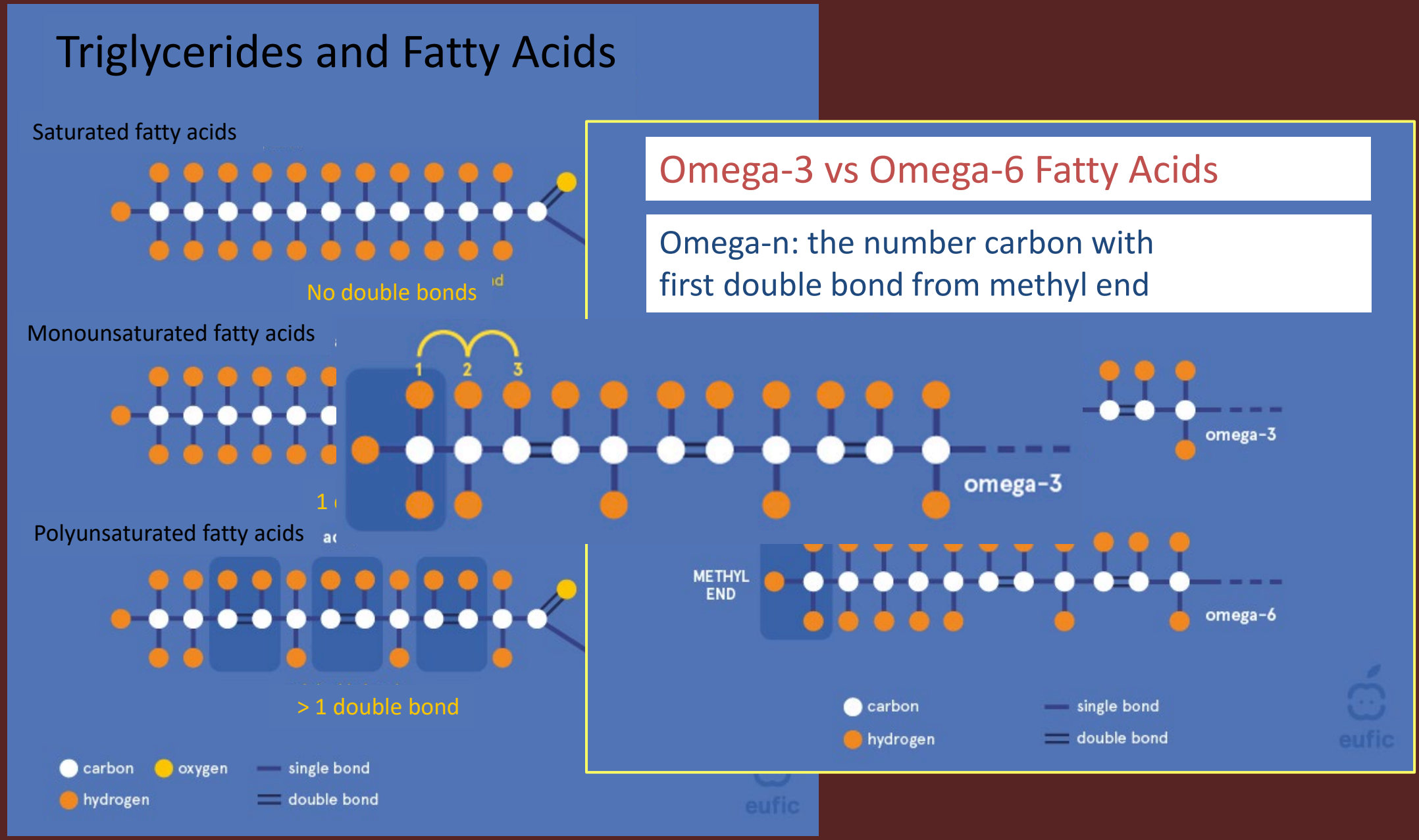
JAMA Intern Med. 2016 August 01; 176(8): 1155–1166. doi:10.1001/jamainternmed.2016.2925.

ω-3 Polyunsaturated Fatty Acid Biomarkers and Coronary Heart Disease:

Pooling Project of 19 Cohort Studies

Liana C. Del Gobbo, PhD, Fumiaki Imamura, PhD, Stella Aslibekyan, PhD, Matti Marklund, PhD, Jyrki K. Virtanen, PhD, Maria Wennberg, PhD, Mohammad Y. Yakoob, PhD, Stephanie E. Chiuve,

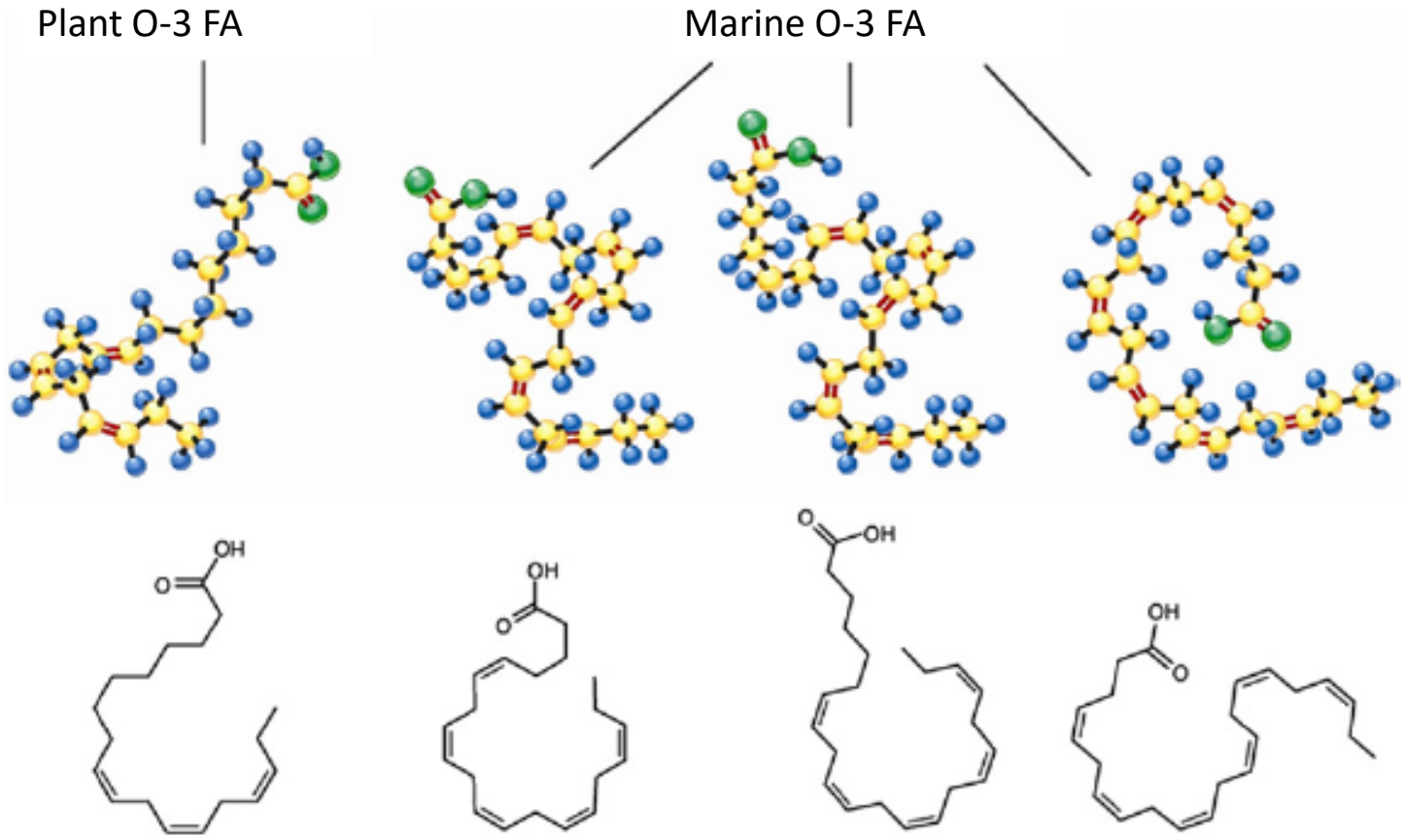
Triglycerides and Fatty Acids



https://www.eufic.org European Food Information Council

OMEGA-3 FATTY ACIDS

Diet Only



Alpha-Linolenic Acid: ALA	EicosapentaenoicAcid: EPA	Docosapentaenoic Acid: DPA	Docosahexaenoic Acid: DHA

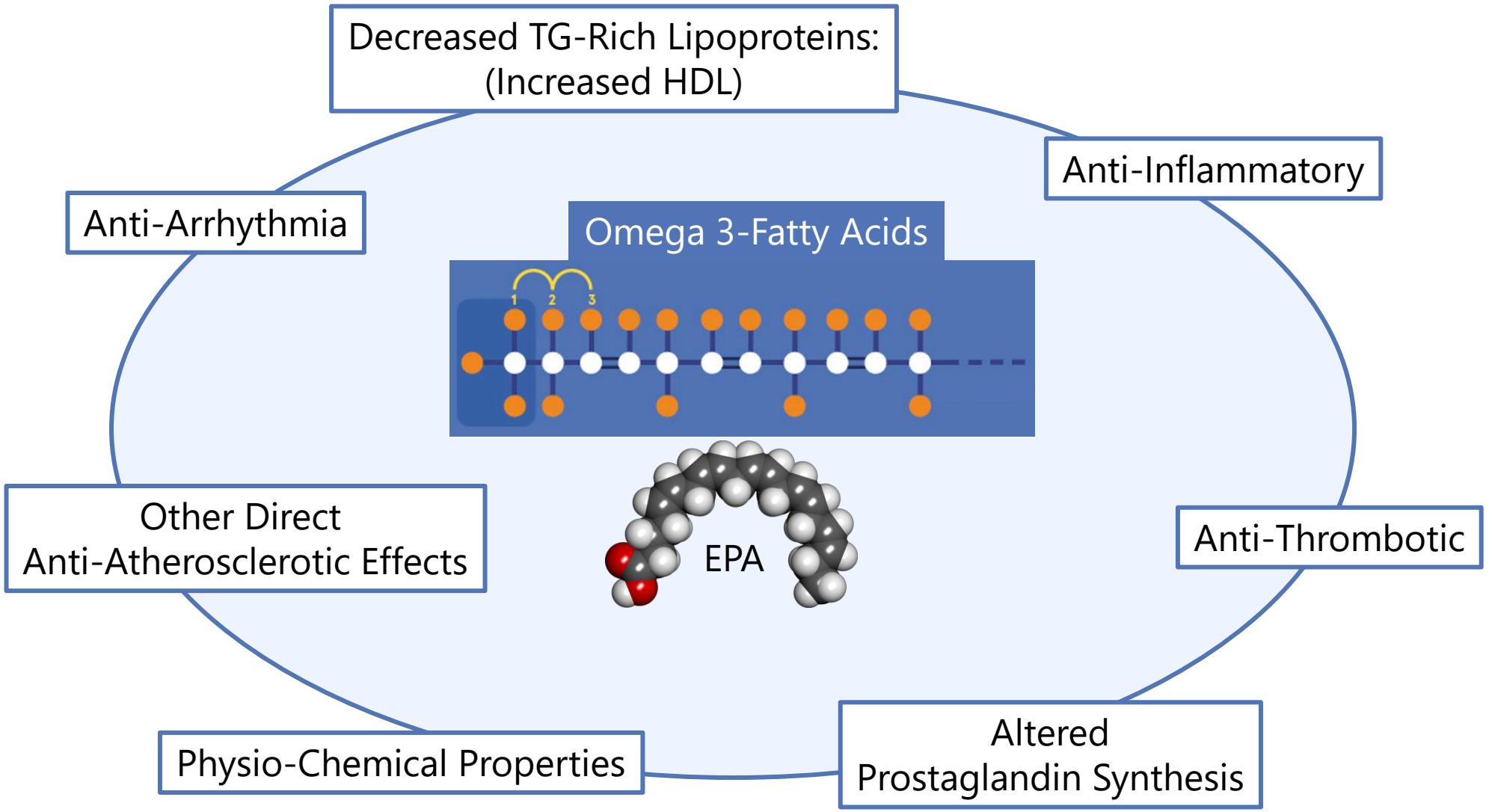
Mozaffarian D, Lu J, *JACC*. 2011;58:2047-67.

FDA-Approved Prescription Omega-3 FAs

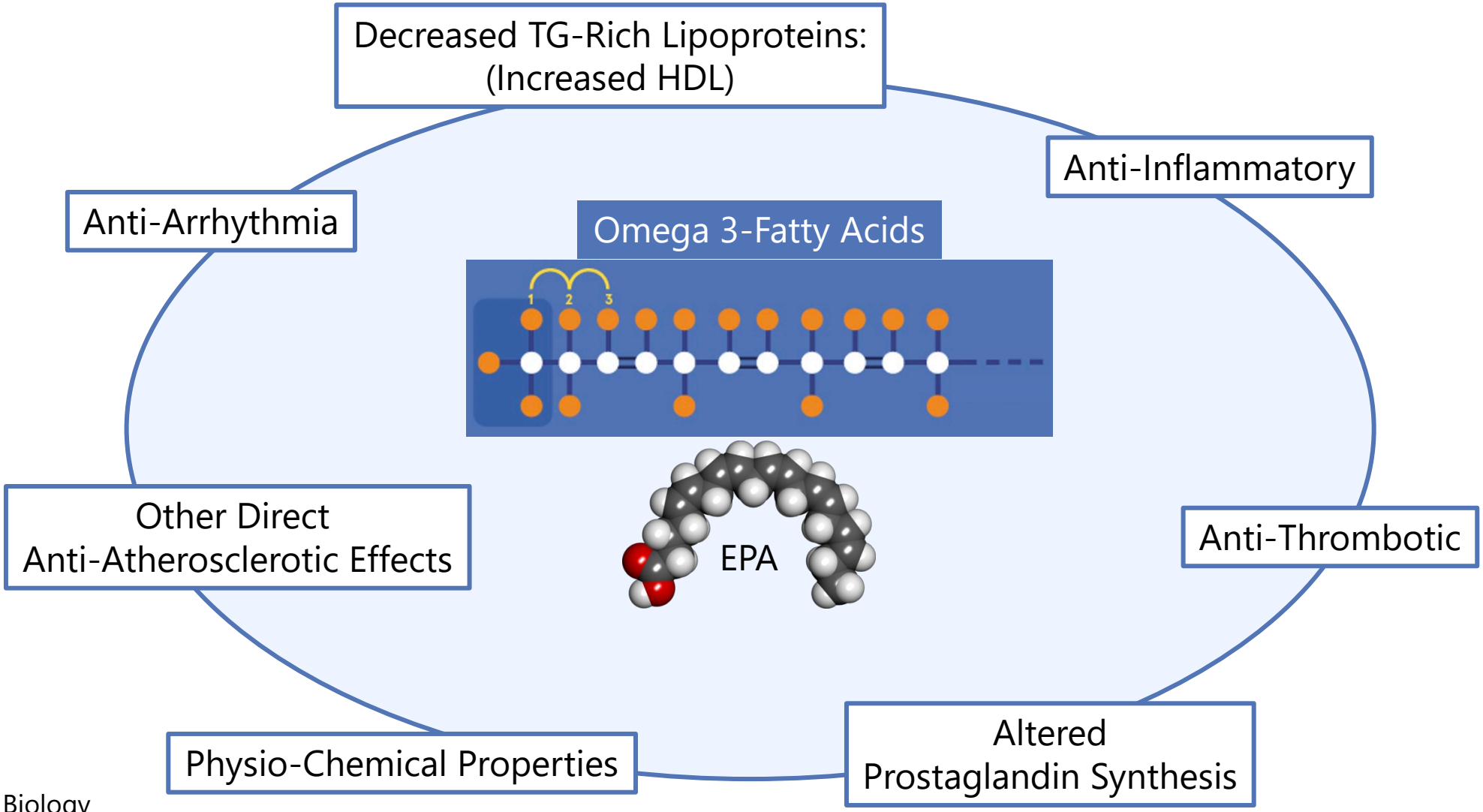
	EPA+DHA EE[1,2]	EPA only EE[3]	EPA+DHA FFA[4]
Brand Name	Lovaza, Omtryg	Vascepa	Epanova
Generic available?	Yes	No	No
EPA/DHA Ratio	55/45	100/0	73/27
Regimen, capsules	2 BID w/ meals or 4 QD w/ meals[2]	2 BID w/ meals	2 or 4 QD, meal independent
Clinical Trial Population		REDUCE-IT: ↑CVD risk (30%) or +CVD (70%):	STRENGTH: ↑CVD risk (50%) or +CVD (50%):
Outcome		**Positive**	**Negative**

[1]Lovaza prescribing information, generics available. [2] Omtryg prescribing information [3]Vascepa prescribing information.
[4]Epanova prescribing information. EE: Ethyl Ester; FFA: Free Fatty Acid

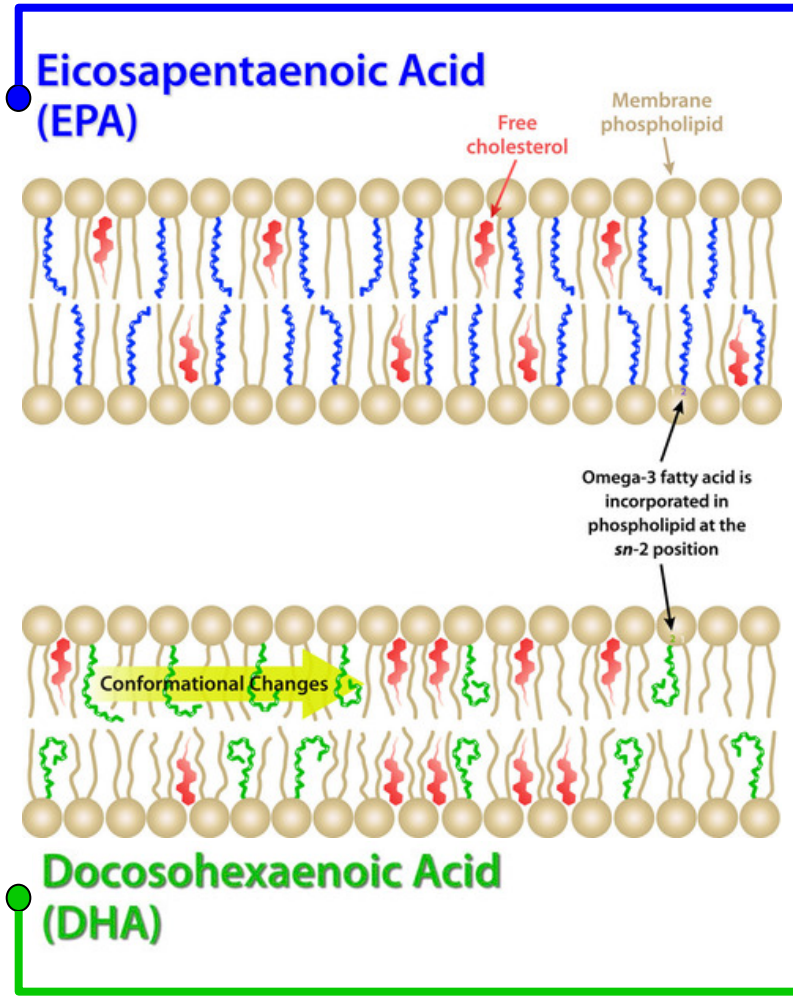
Omega 3-Fatty Acids: Multiple Pleiotropic Mechanisms Underlying Clinical Effects?



Omega 3-Fatty Acids: Multiple Pleiotropic Mechanisms Underlying Clinical Effects?



EPA Incorporation Favorably Alters Membrane Properties



- Membrane stabilizing
- Physiologic holesterol distribution
- Decreased lipid oxidation
- Decreased cholesterol crystal formation
- Modulation of signal pathways
  - Inflammation
  - Vasoreactivity

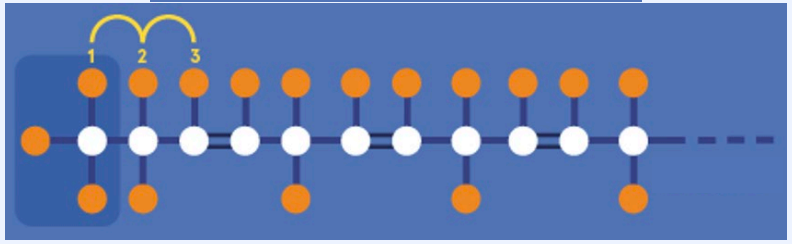
- Increased membrane fluidity
- Increased concentratio0n in brain, eye
- Altered lipid domains
- Decreased anti-oxidant properties
- Decreased cholesterol crystal formation

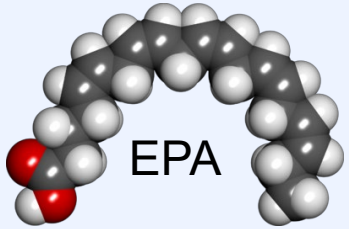
Mason, et al. ATVB. 40: 1135-1147

Anti-Arrhythmia

Atrial Fibrillation
Ventricular Fib/Tachycardia

Omega 3-Fatty Acids





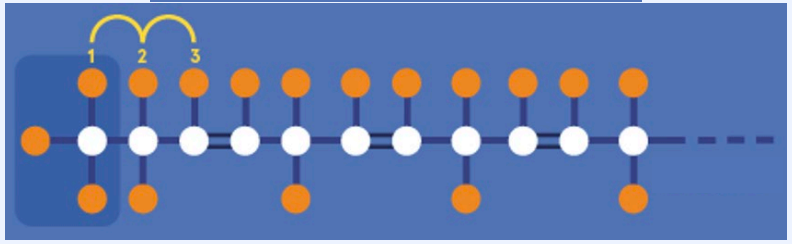
Physio-Chemical Properties

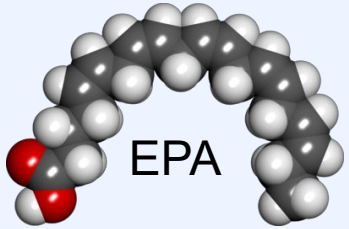
Membrane Biology and Stabilization

Anti-Arrhythmia

Atrial Fibrillation
Ventricular Fib/Tachycardia

Omega 3-Fatty Acids





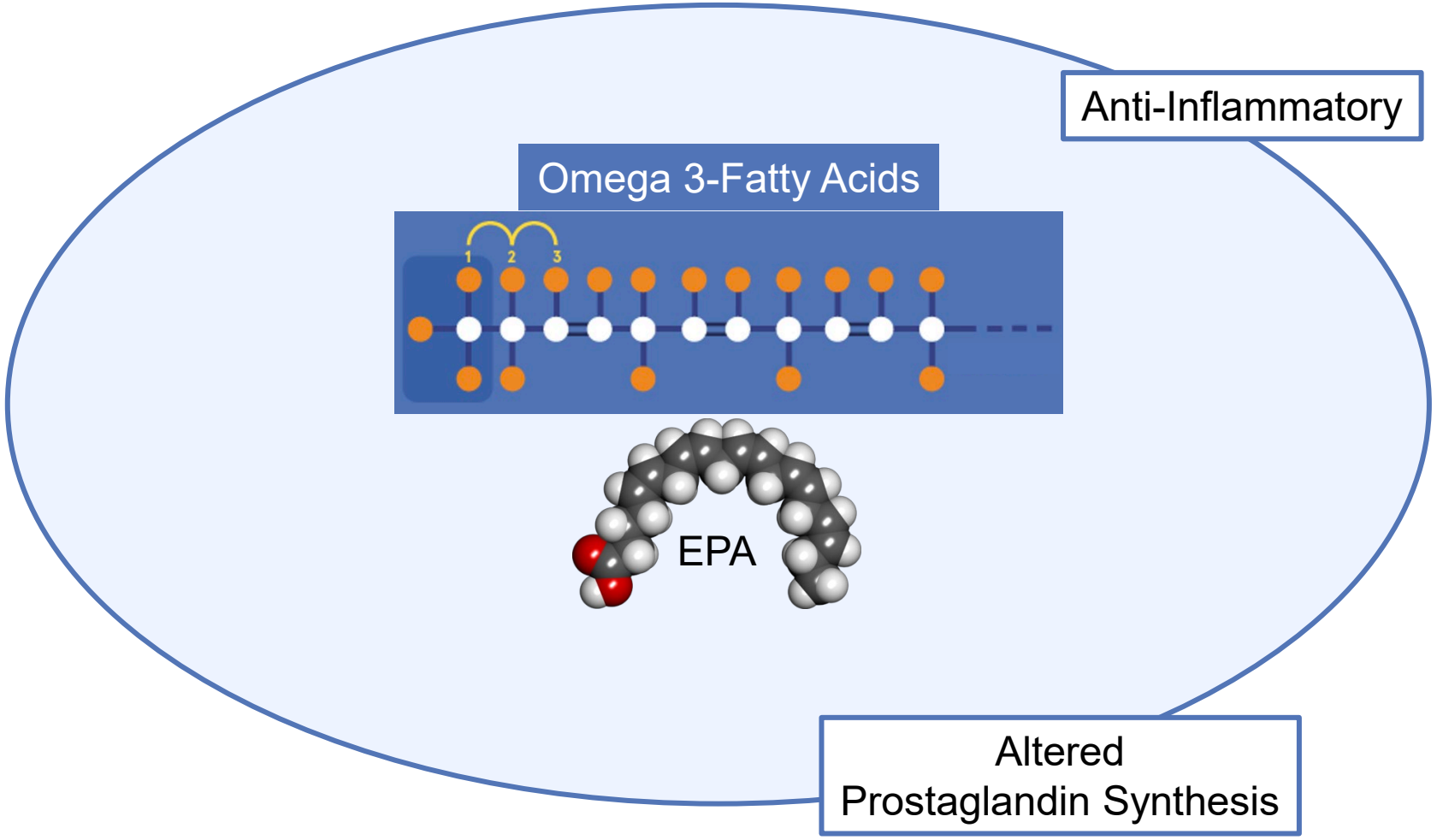
Anti-Thrombotic

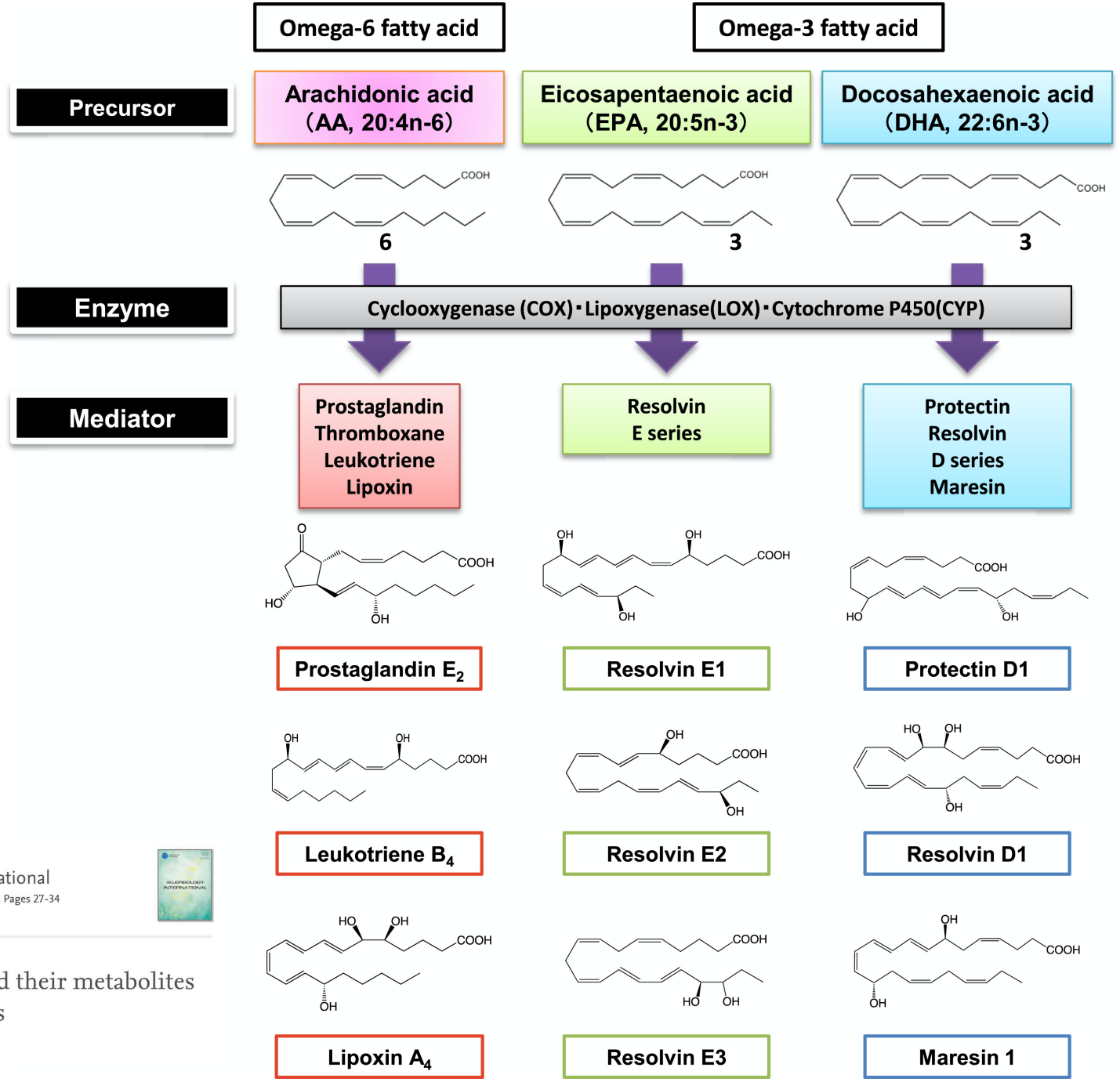
Platelets
Platelet Reactivity
Coagulant balance

Physio-Chemical Properties

Membrane Biology and Stabilization

Inflammation Resolution:
Increased Resolvin Mediators:





Allergology International
Volume 64, Issue 1, January 2015, Pages 27-34

Invited review article

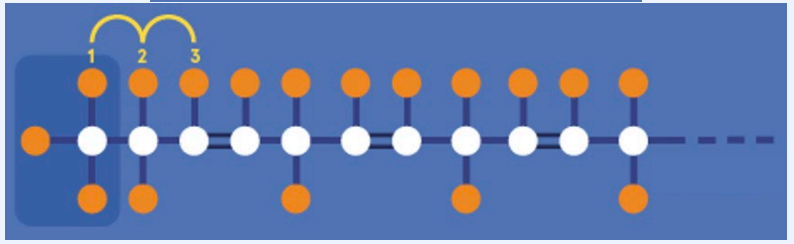
Role of omega-3 fatty acids and their metabolites in asthma and allergic diseases

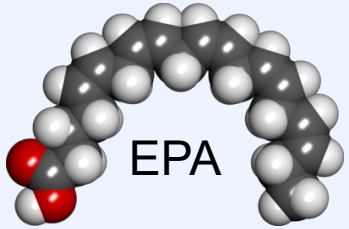
Jun Miyata [a], Makoto Arita [a, b]

Inflammation Resolution:
Increased Resolvin Mediators:

Anti-Inflammatory

Omega 3-Fatty Acids

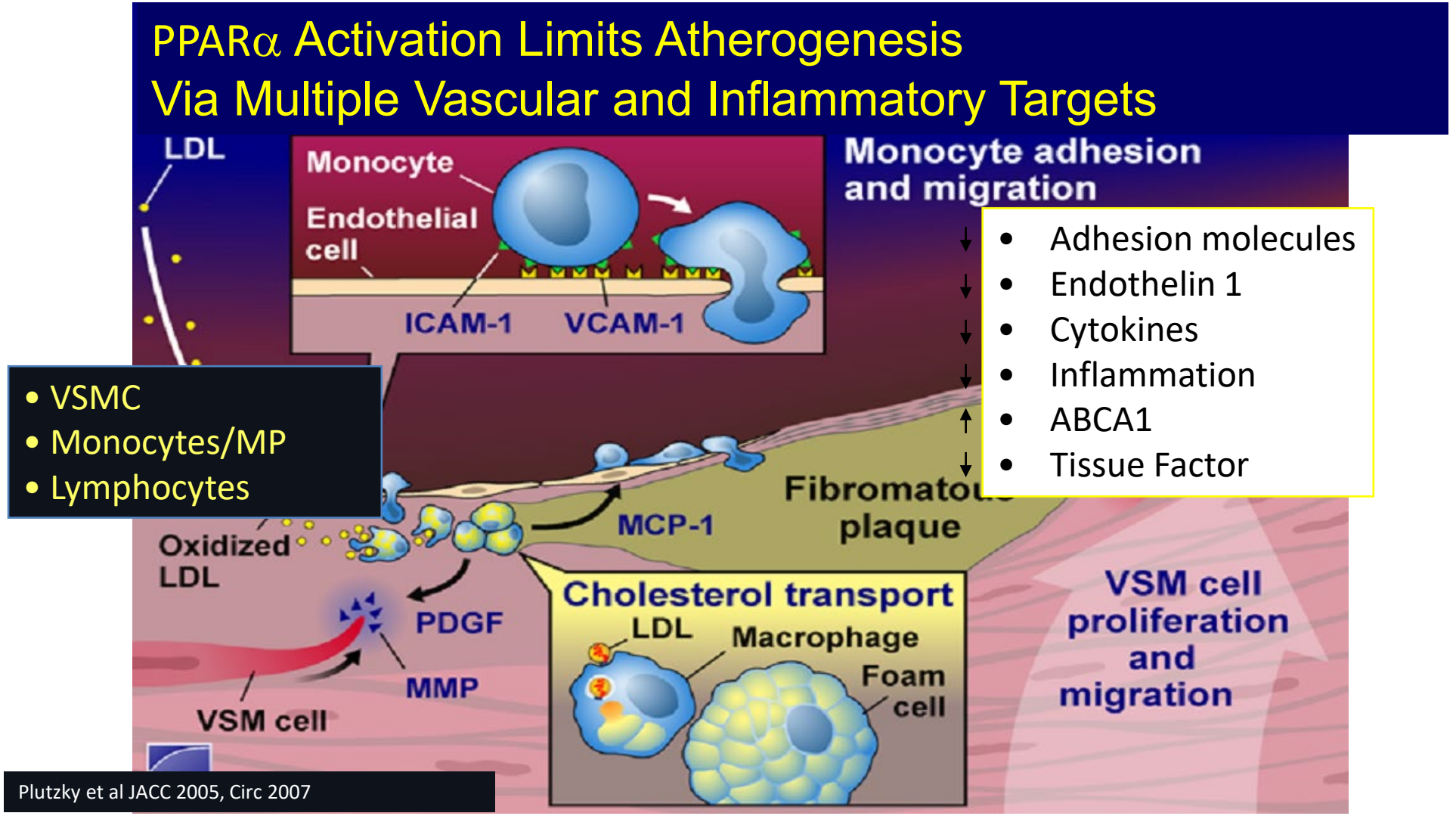




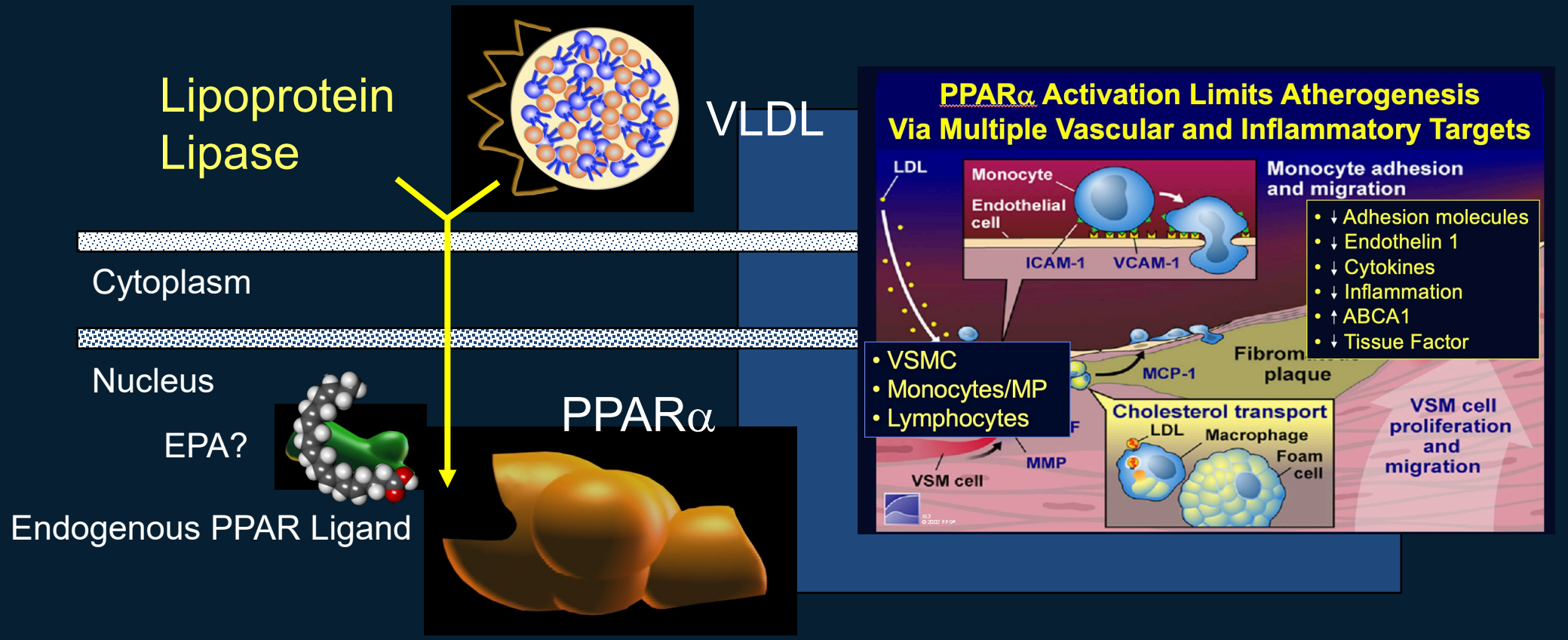
Endogenous
PPARα
Activation

Altered
Prostaglandin Synthesis

PPARα Exerts Antiatherogenic Effects via Multiple Vascular Targets



Plutzky et al JACC 2005, Circ 2007



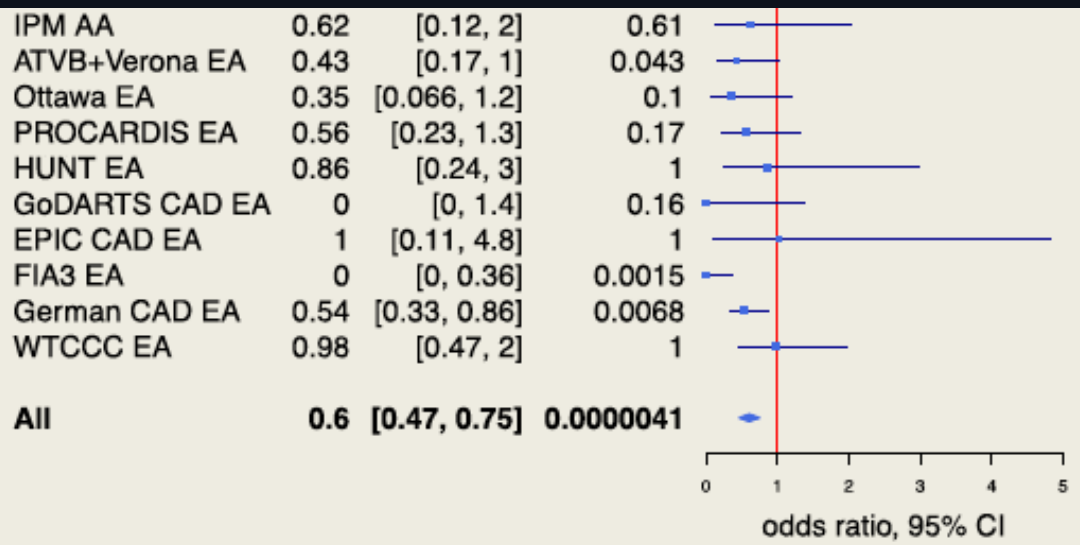
PPAR gene regulation differs in response to distinct ligands

- VLDL hydrolysis by LPL releases specific fatty acids.
- PPARα activation by LPL/VLDL differs from fibrates.
- Mechanism for TG genetic athero-protection:
  LPL gain of function, ApoC3 loss of function.
- Mechanism for EPA vascular + inflammatory effects?

PNAS 2003
JBC 2004
ATVB 2006
Circ Res 2006

APOC3 mutation carriers have 40% LOWER risk for CHD

ApoC3: Endogenous LPL Inhibitor
Consistent with:
- Increased LPL action
- Increased ENDOGENOUS PPARα ligand generation

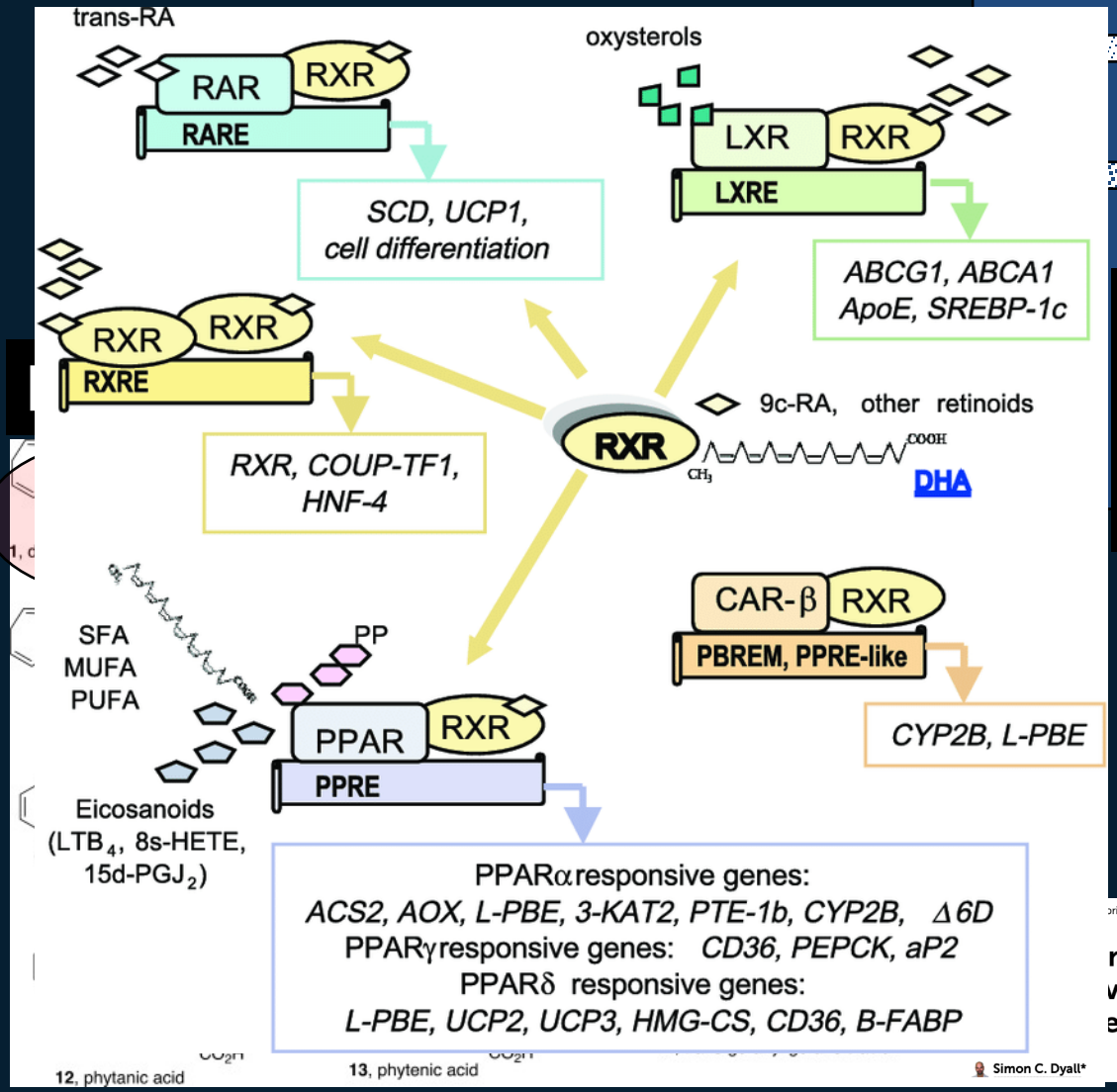


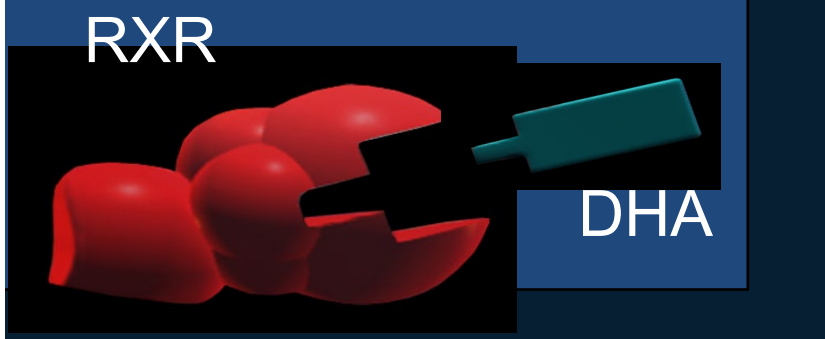
TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. N Engl J Med 2014;371:22-31.

Do CV Benefits of EPA Alone Derive from the Absence of DHA?

DHA vs EPA: Differing Nuclear Receptor Activation

DHA is an RXR Ligand; Untoward Effects of RXR Activation?





RXR: Partner for many nuclear receptors.

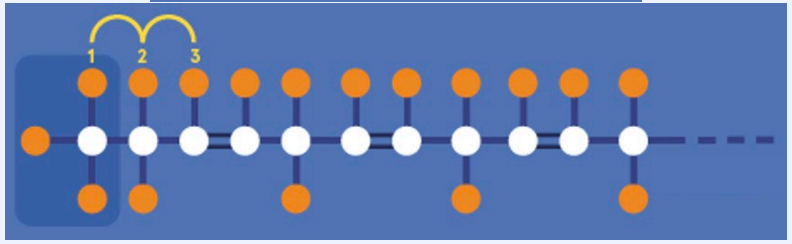
ril 2015 | https://doi.org/10.3389/fnagi.2015.00052

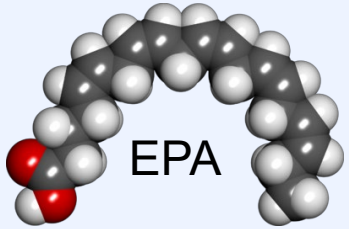
n omega-3 fatty acids and the
view of the independent and
ects of EPA, DPA and DHA

Perlmann et al Science 2000

Decreased TG-Rich Lipoproteins:
(Increased HDL)

Omega 3-Fatty Acids

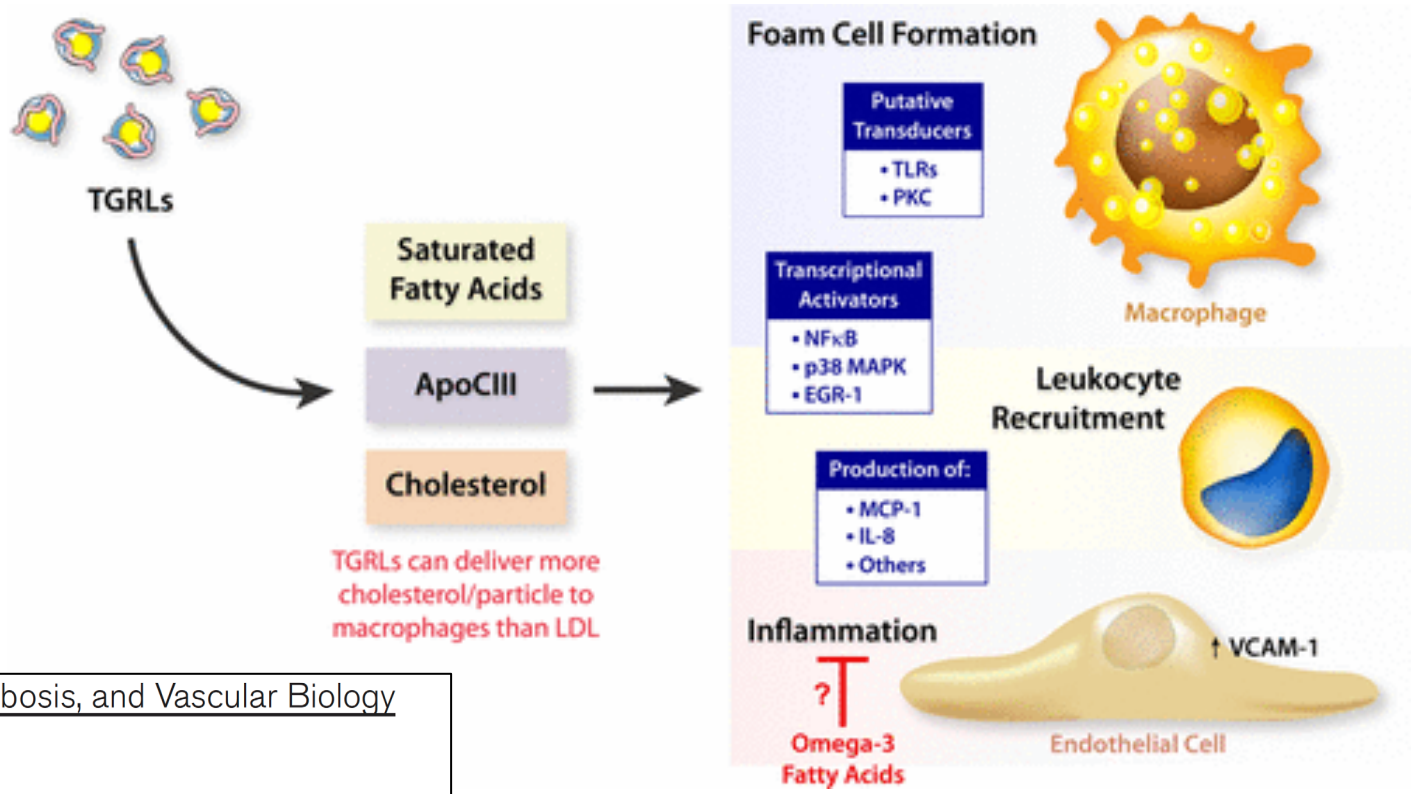




EPA

Direct
Anti-Atherosclerotic Effects

Triglyceride-Rich Lipoproteins Increase Cholesterol Delivery to Macrophages and the Arterial Wall



Arteriosclerosis, Thrombosis, and Vascular Biology

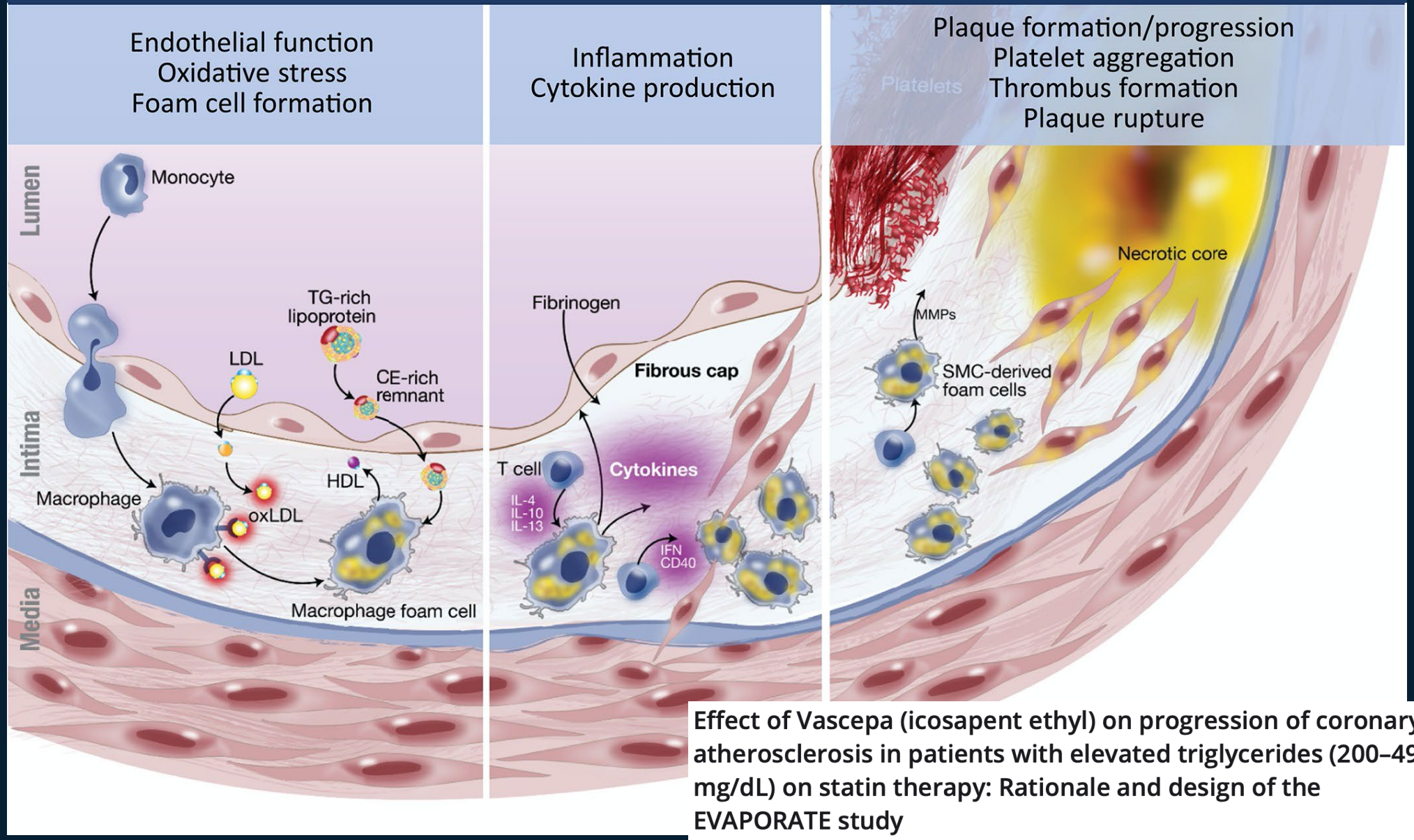
BRIEF REVIEW

Emerging Mechanisms of Cardiovascular Protection for the Omega-3 Fatty Acid Eicosapentaenoic Acid

R. Preston Mason, Peter Libby, Deepak L. Bhatt

Mason, et al. ATVB. 40: 1135-1147, 2020

EPA: Potential Direct Effects On Atherosclerosis



Effect of Vascepa (icosapent ethyl) on progression of coronary atherosclerosis in patients with elevated triglycerides (200–499 mg/dL) on statin therapy: Rationale and design of the EVAPORATE study

Matthew Budoff, J. Brent Muhlestein, Viet T. Le, Heidi T. May, Sion Roy, John R. Nelson

Clinical Card 41, 2018, 13-19

Biology of Omega-3 Fatty Acids in Cardiovascular Disease: What We Know

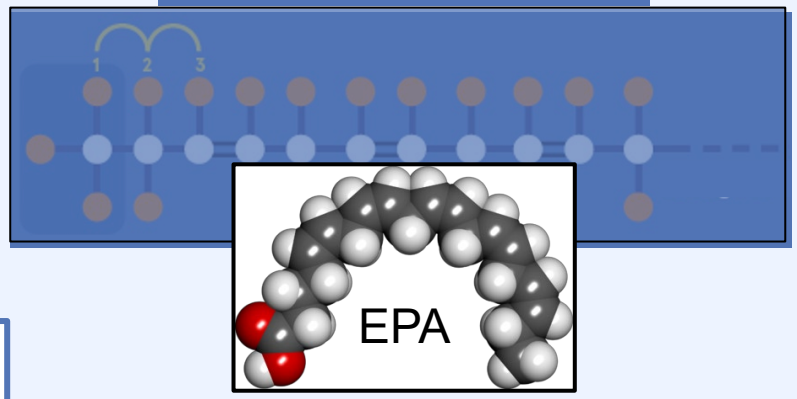
Decreased TG-Rich Lipoproteins: (Increased HDL)

Inflammation Resolution: Increased Resolvin Mediators

Anti-Inflammatory

Omega 3-Fatty Acids

Anti-Arrhythmia



Endogenous PPARα Activation

Other Direct Anti-Atherosclerotic Effects

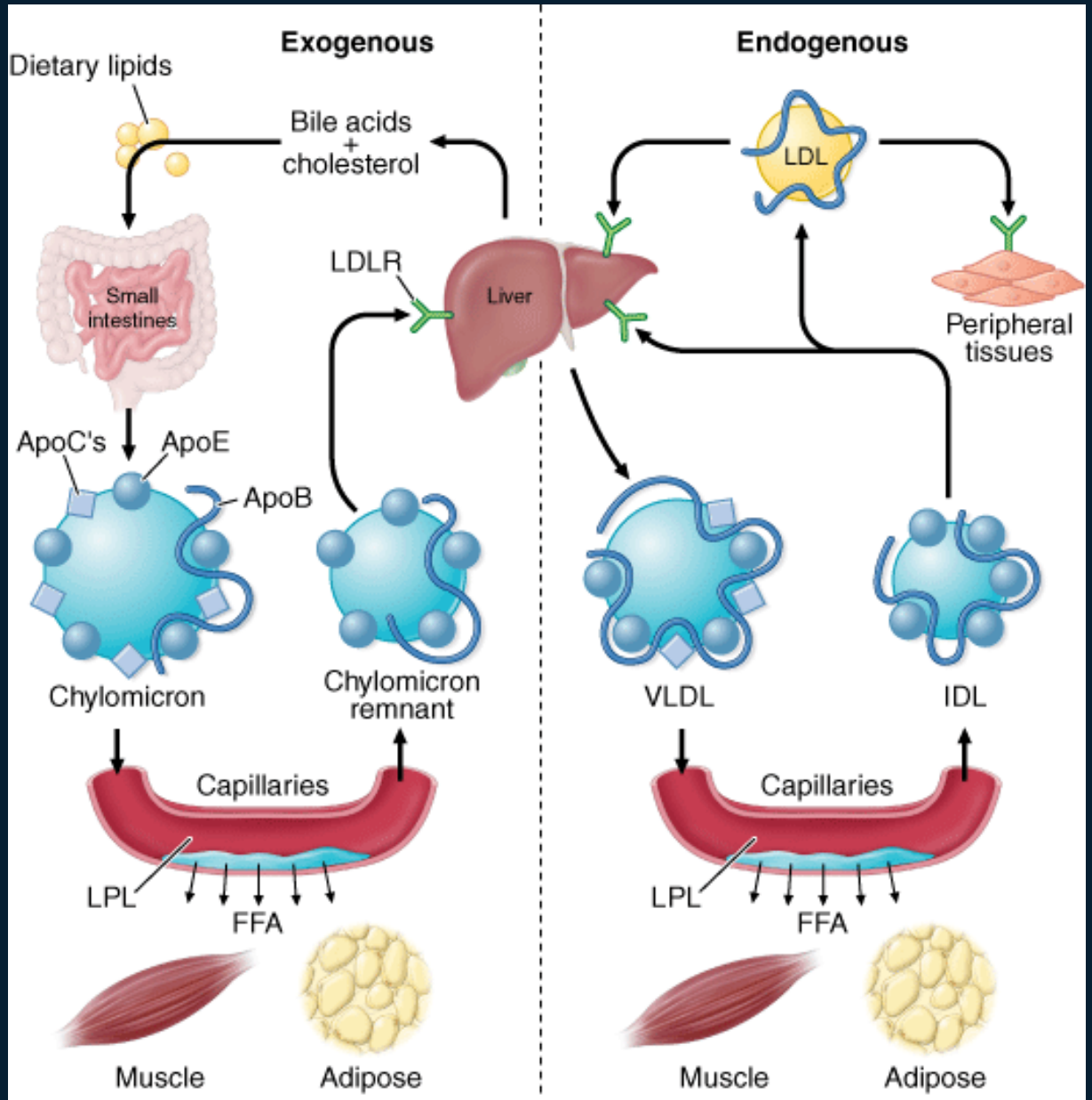
Anti-Thrombotic

What We Need to Find Out

Physio-Chemical Properties

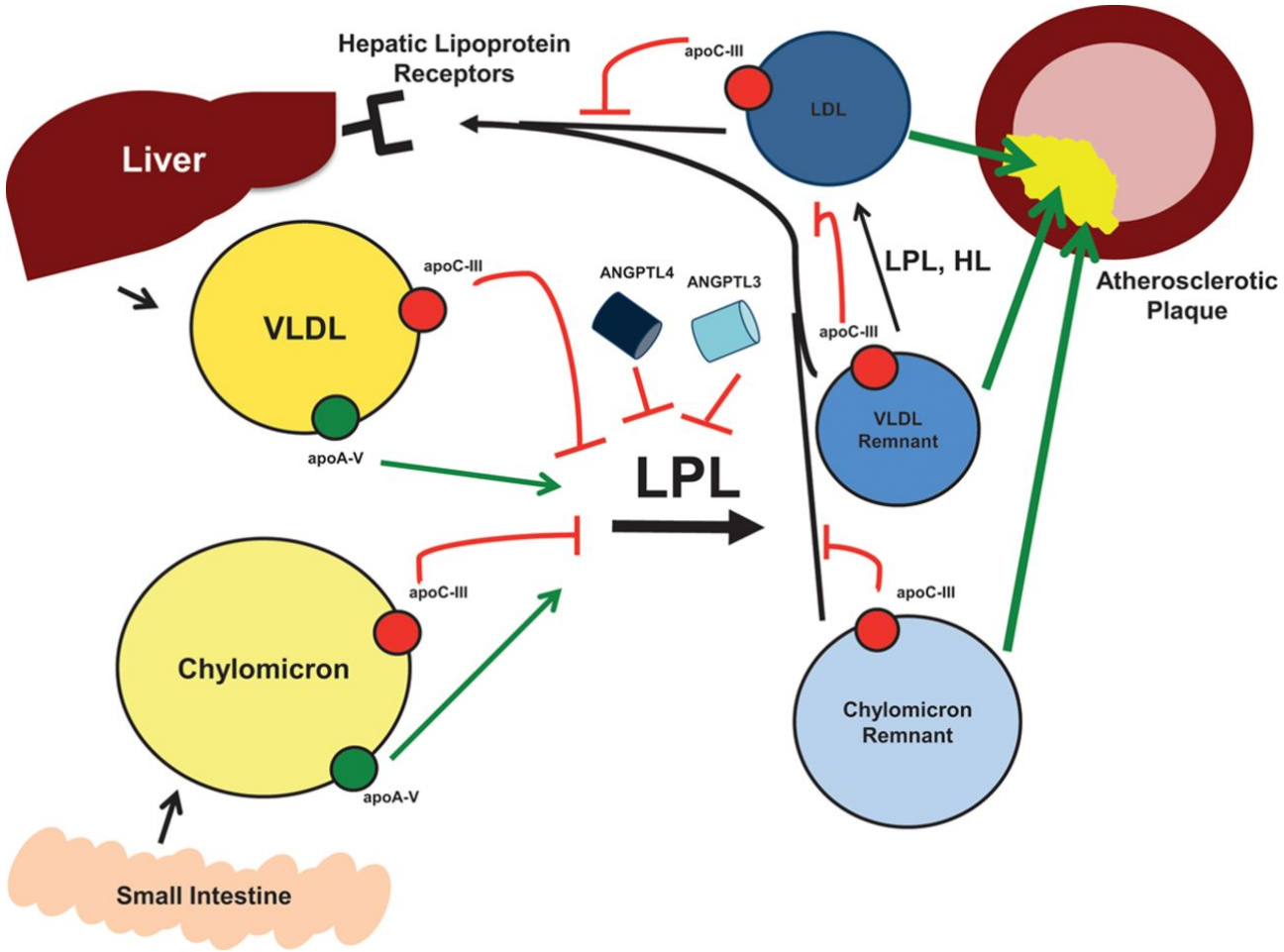
Altered Prostaglandin Synthesis

New Era of Lipid Biology and CV Risk Reduction



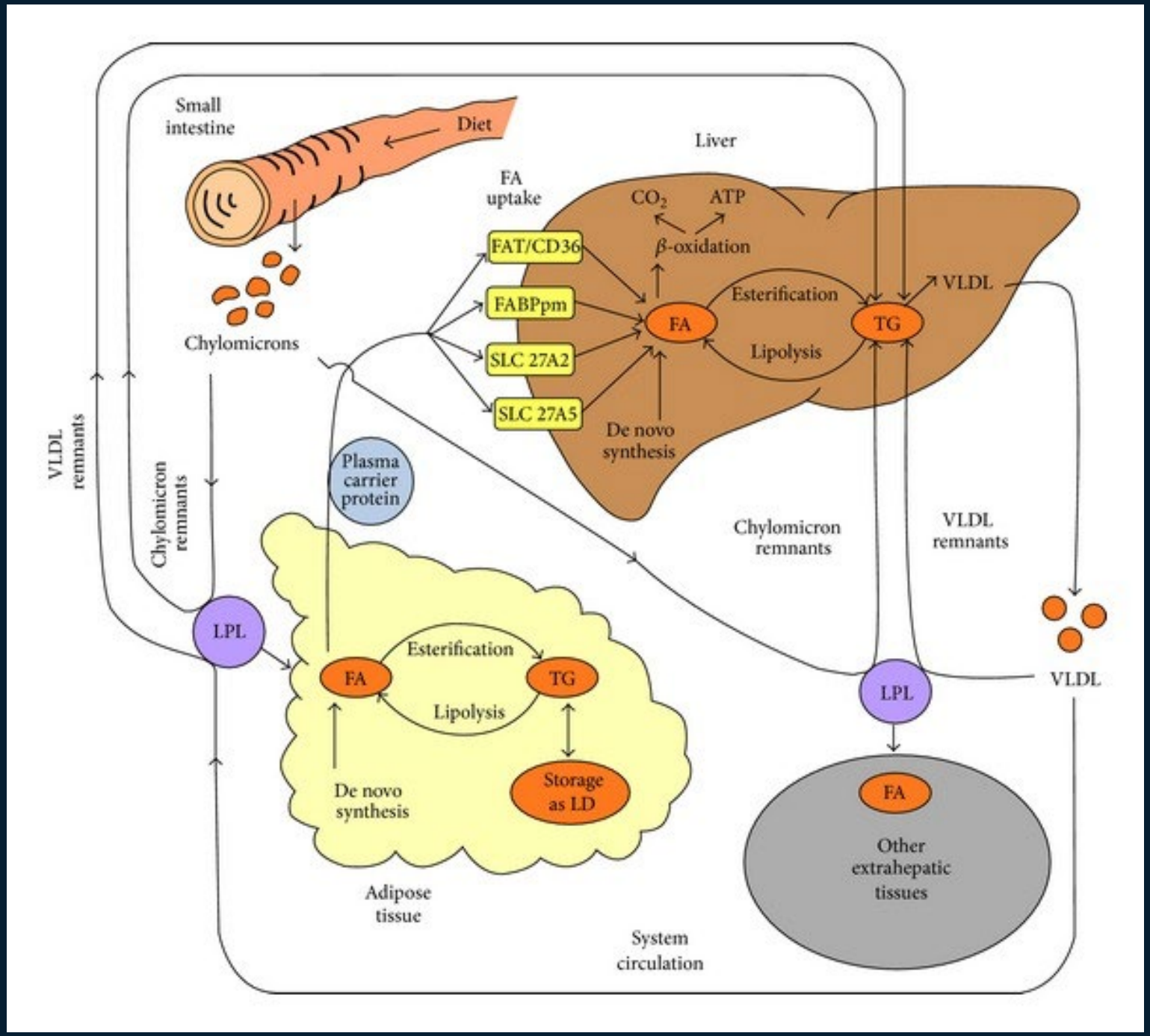
Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

ApoC-III and ApoA-V in Plasma Triglyceride Metabolism



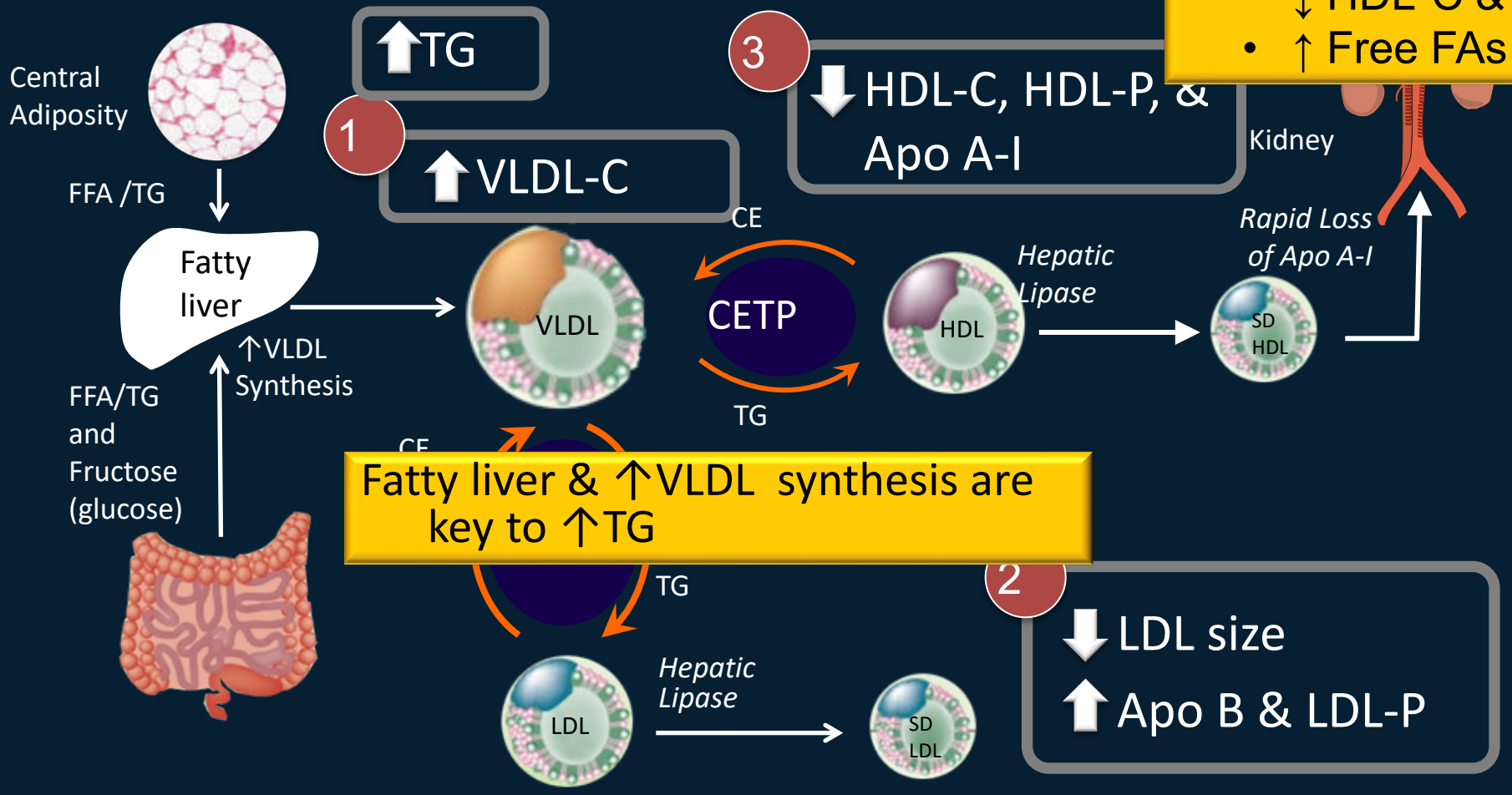
Khetarpal, Rader ATVB 2015;35:e3-e9

Fatty Acid Transport



PPAR Res 2014:432647

Hypertriglyceridemia and low HDL

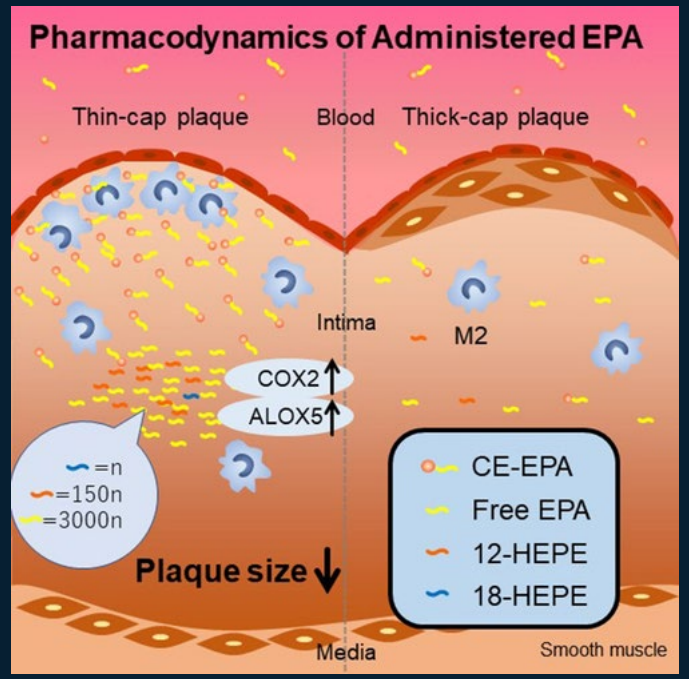


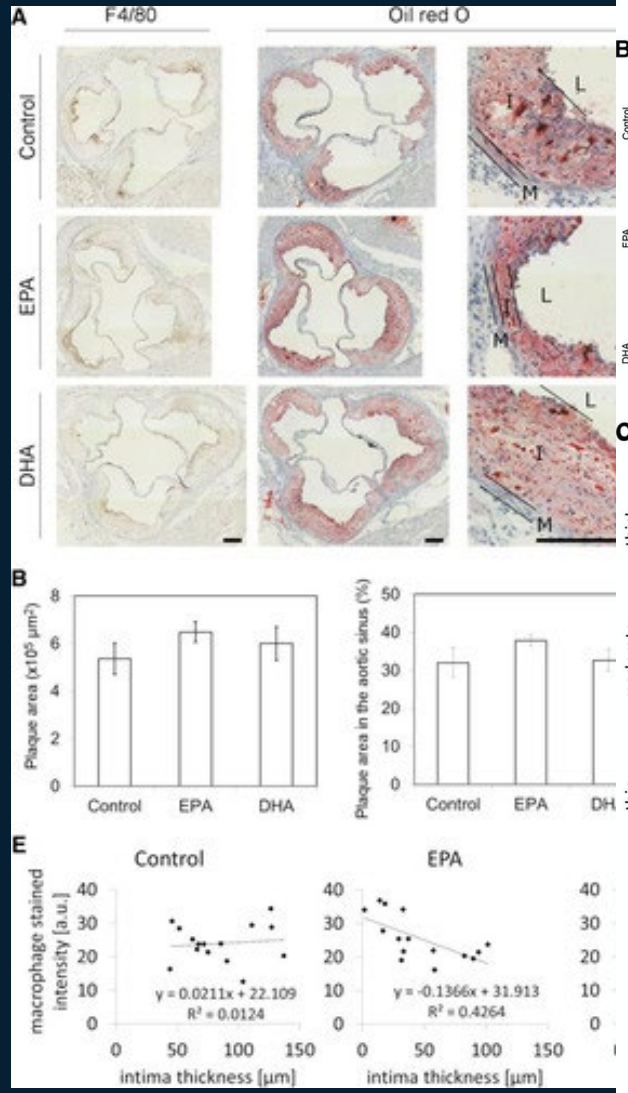
Apo=apolipoprotein; CETP=CE transfer protein; FFA=free fatty acid; HDL=high-density lipoprotein; HDL-C=HDL cholesterol; HDL-P=HDL particle; LDL=low-density lipoprotein; LDL-P=LDL particle; SD=small dense; VLDL=very-low-density lipoprotein; VLDL-C=VLDL cholesterol.

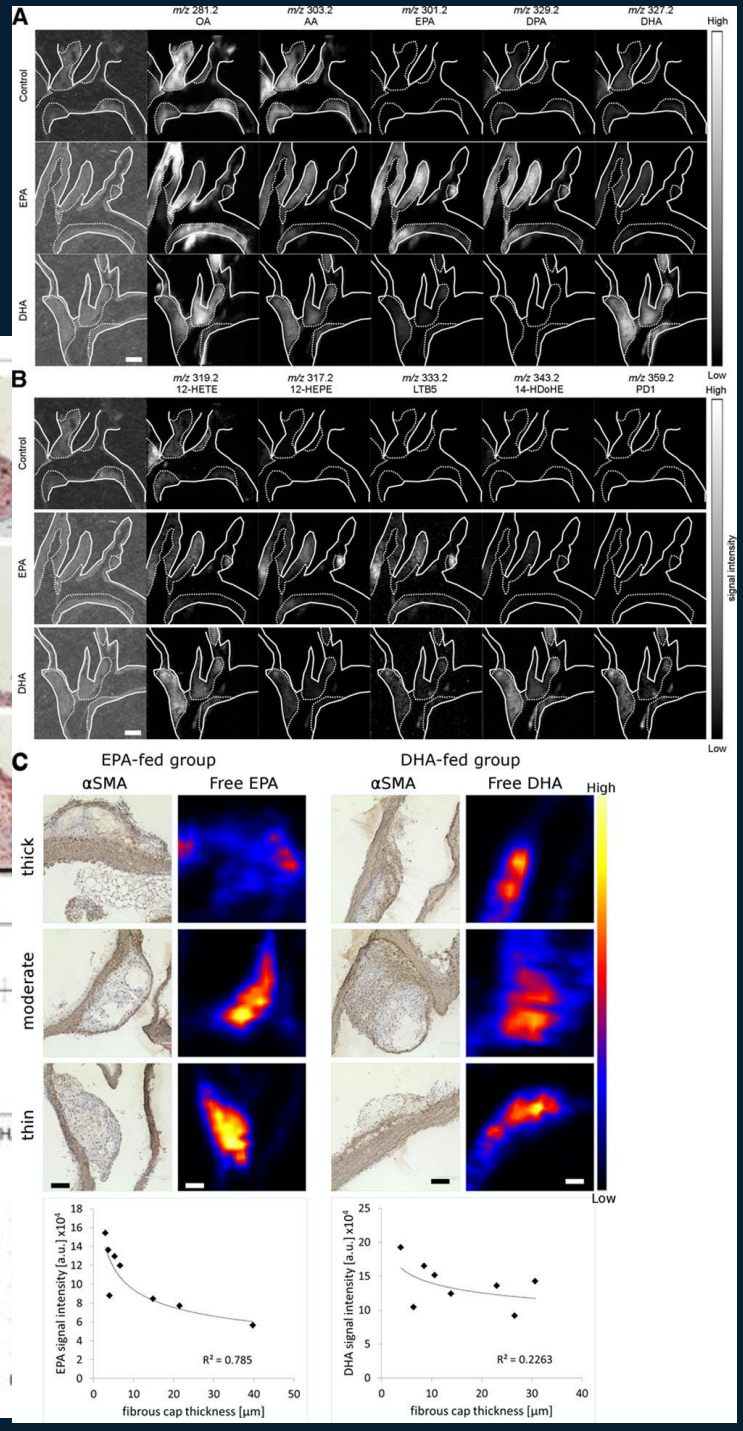
Preferential Incorporation of Administered Eicosapentaenoic Acid Into Thin-Cap Atherosclerotic Plaques

Tomohito Sato, Makoto Horikawa, Shiro Takei, Fumiyoshi Yamazaki, Takashi K. Ito, Takeshi Kondo, Takanobu Sakurai, Tomoaki Kahyo, Koji Ikegami, Shumpei Sato, Ryota Sato, Yasutaka Jinno, Hiroyuki Kawano, Satoko Naoe, Makoto Arita, Yukiyasu Kashiwagi, Mitsutoshi Setou

Originally published 1 Aug 2019 | https://doi.org/10.1161/ATVBAHA.119.313093 | Arteriosclerosis, Thrombosis, and Vascular Biology. 2019;39:1802–1816







Use of Omega-3 Fatty Acids in Patients with Diabetes

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

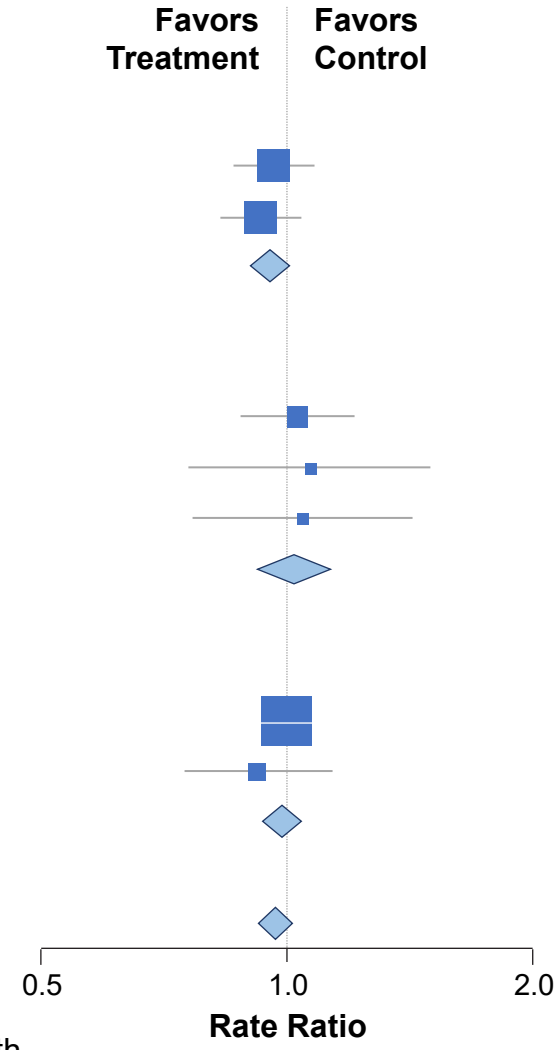
Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, LevelEx, Medscape Cardiology, PhaseBio, PLx Pharma, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); **Research Funding**: Abbott, Afimmune, **Amarin**, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, Takeda.

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

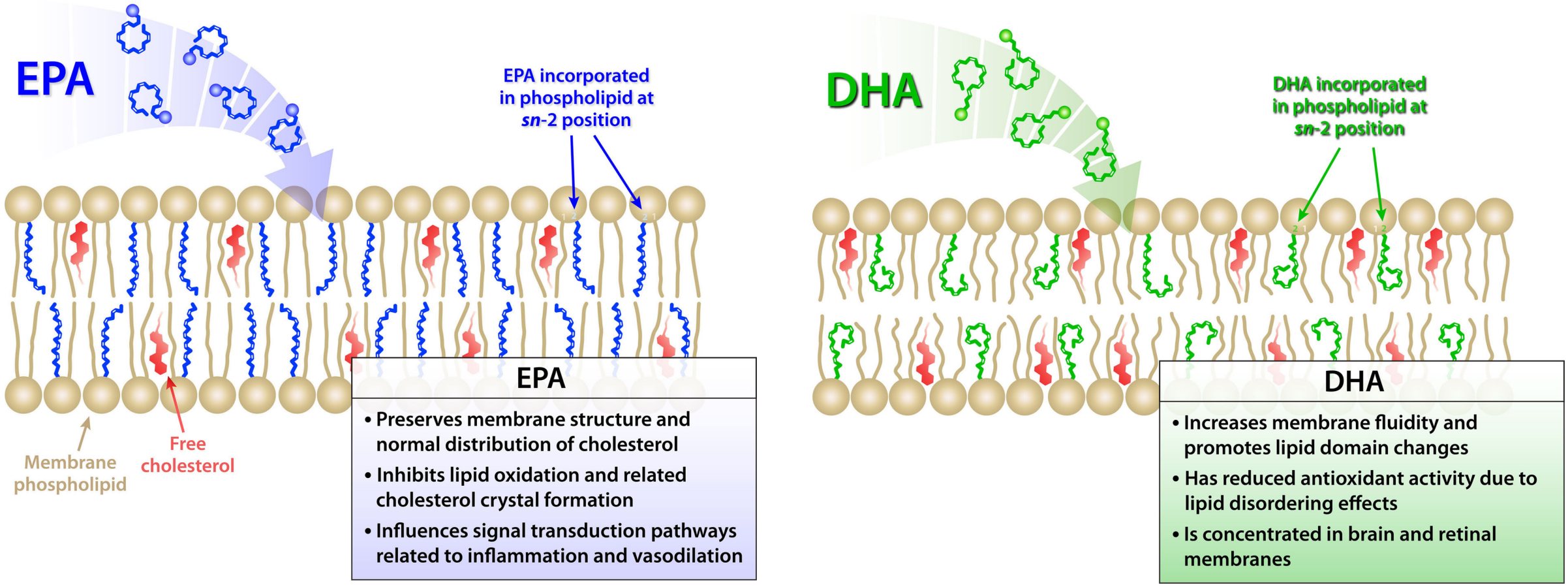
Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

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



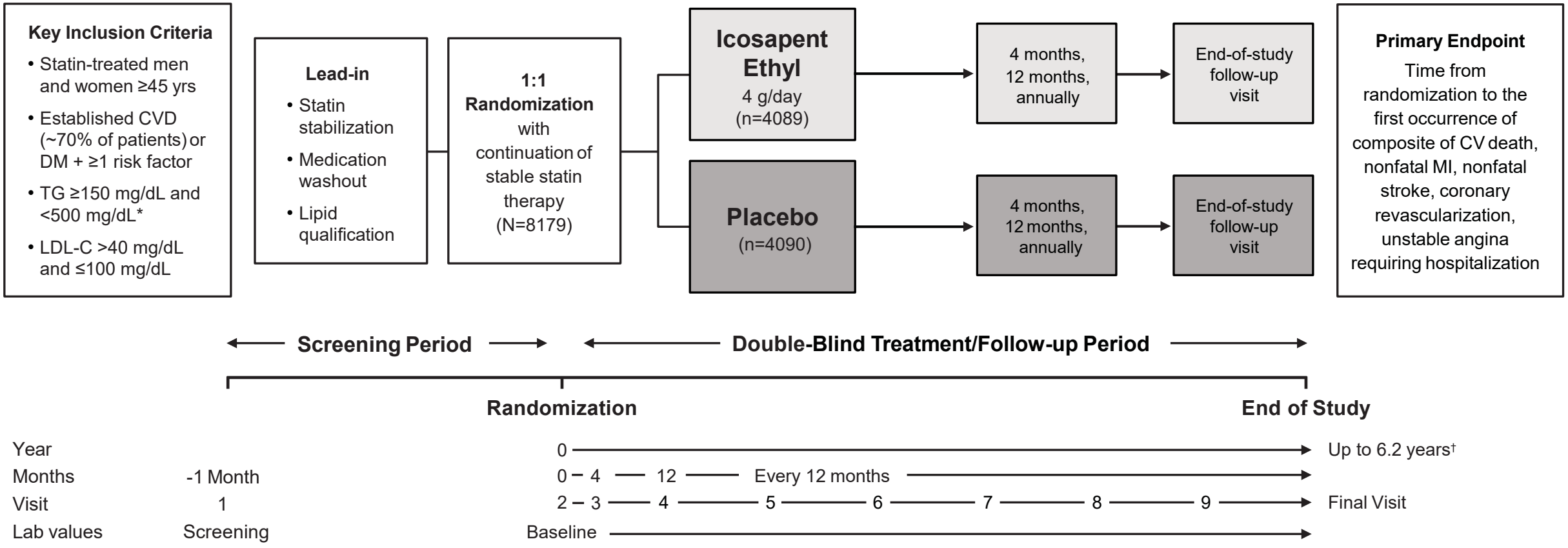
Adapted with permission* from Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77917 individuals. *JAMA Cardiol.* 2018;3:225-234. [*https://creativecommons.org/licenses.org/by-nc/4.0/]

Contrasting Effects of EPA and DHA



Mason RP, Libby P, Bhatt DL. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2020.

REDUCE-IT Design



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

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

Adapted with permission‡ from Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. 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.

Primary and Key Secondary Composite Endpoints

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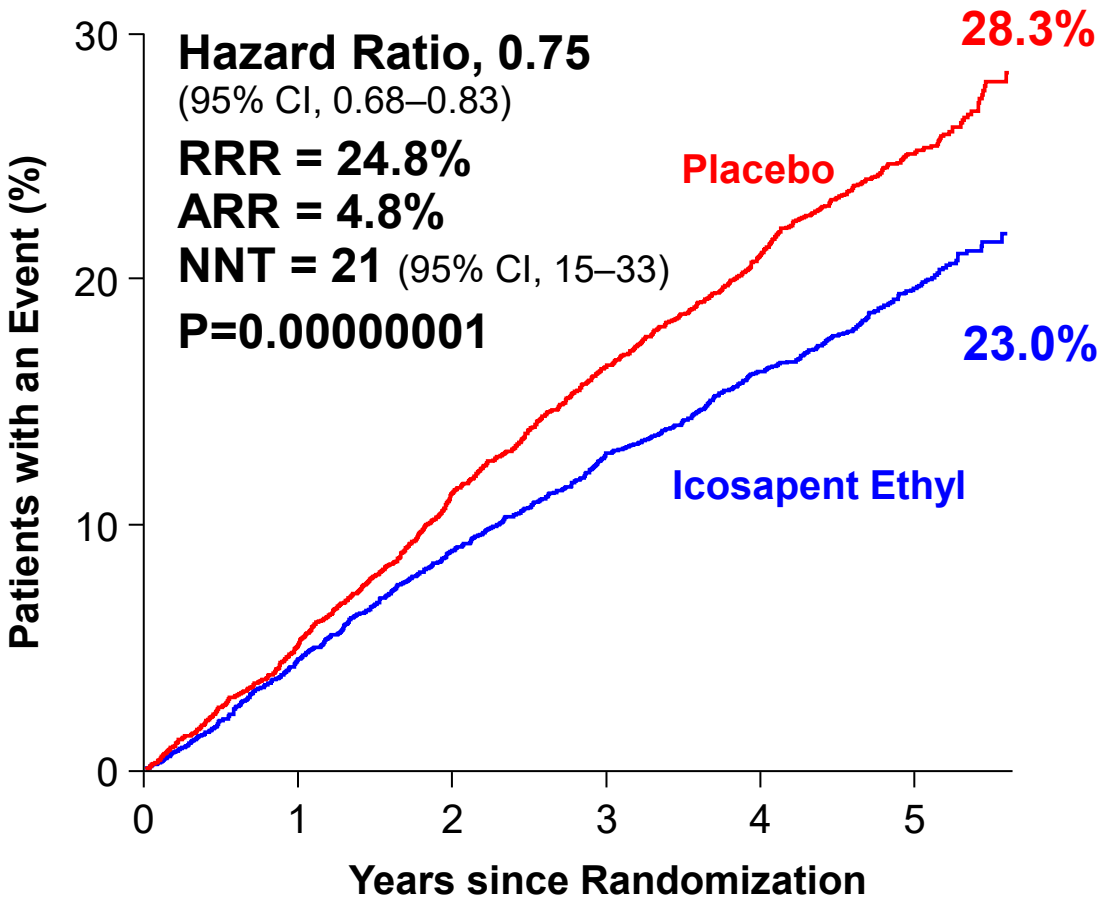
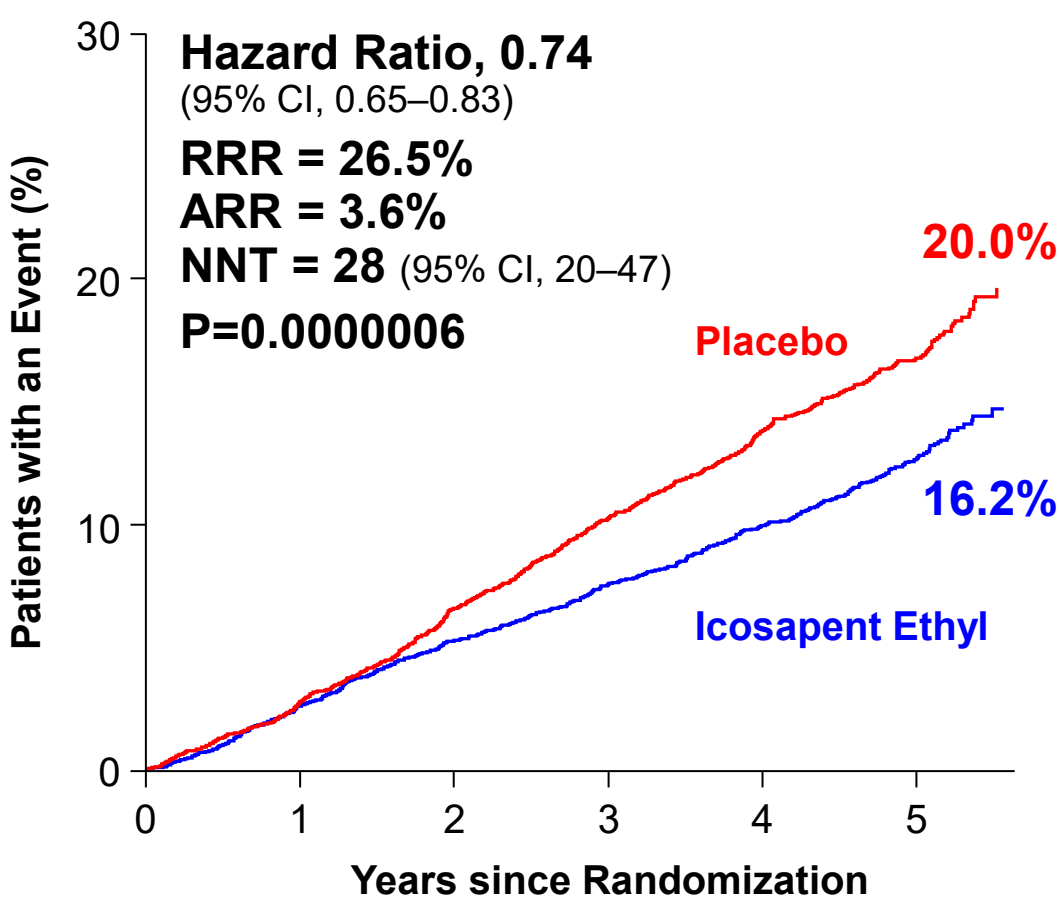
Primary Composite Endpoint:

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



Key Secondary Composite Endpoint:

CV Death, MI, Stroke



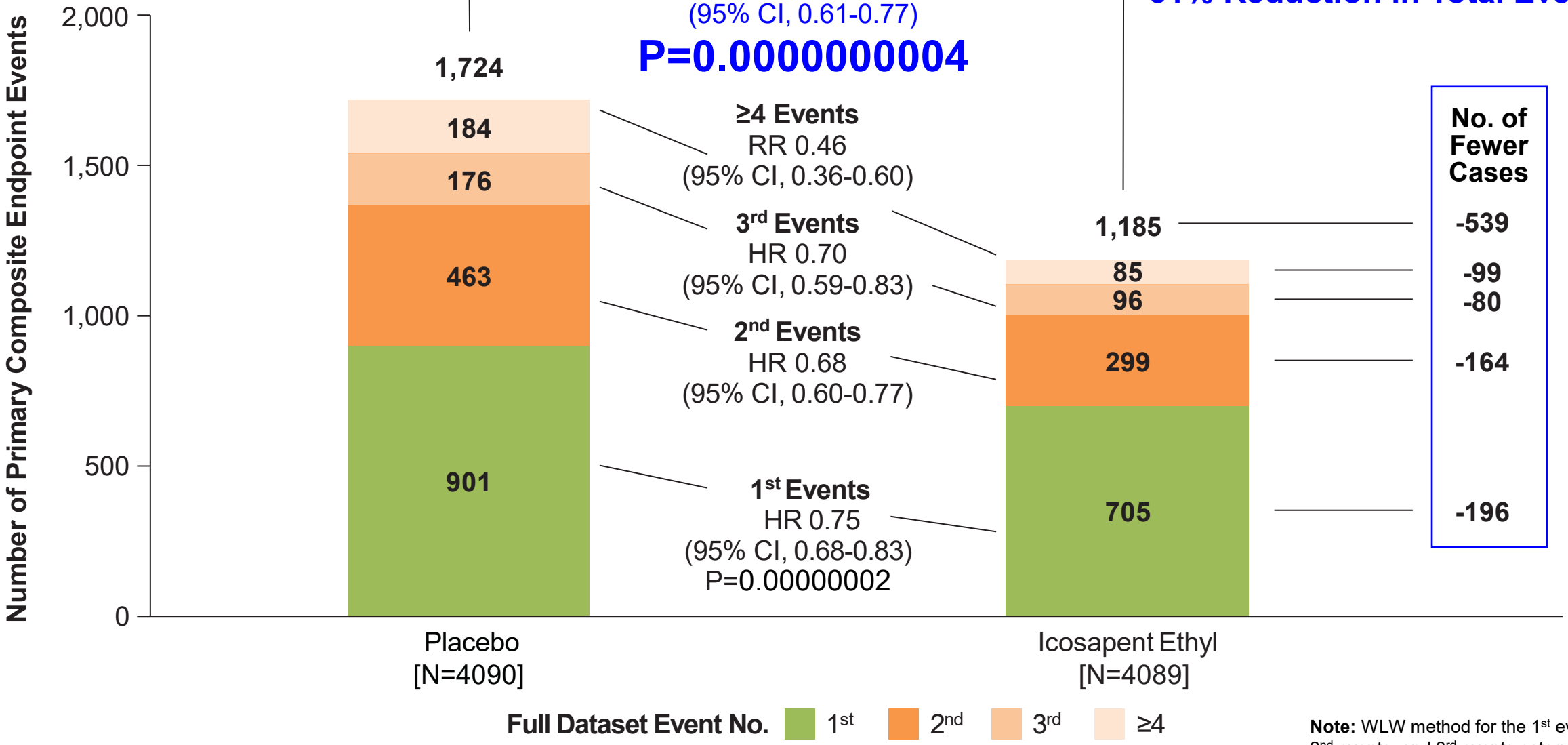
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

First and Subsequent Events – Full Data

reduce-it TOTAL EVENTS

RR 0.69
(95% CI, 0.61-0.77)
P=0.0000000004

31% Reduction in Total Events



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.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DIABETES

Number of Baseline Anti-Diabetes Medications: Diabetes Subgroup

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Anti-Diabetes Medications Taken at Baseline, n (%)	Icosapent Ethyl (N=2394)	Placebo (N=2393)	Overall (N=4787)
No Anti-Diabetes Medications	221 (9.2)	208 (8.7)	429 (9.0)
Anti-Diabetes Medications	2173 (90.8)	2185 (91.3)	4358 (91.0)
One Anti-Diabetes Medication	951 (39.7)	1038 (43.4)	1989 (41.6)
Two Anti-Diabetes Medication	806 (33.7)	792 (33.1)	1598 (33.4)
Three Anti-Diabetes Medication	347 (14.5)	288 (12.0)	635 (13.3)
Four or more Anti-Diabetes Medications	69 (2.9)	67 (2.8)	136 (2.8)

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population with diabetes at baseline (N).

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

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

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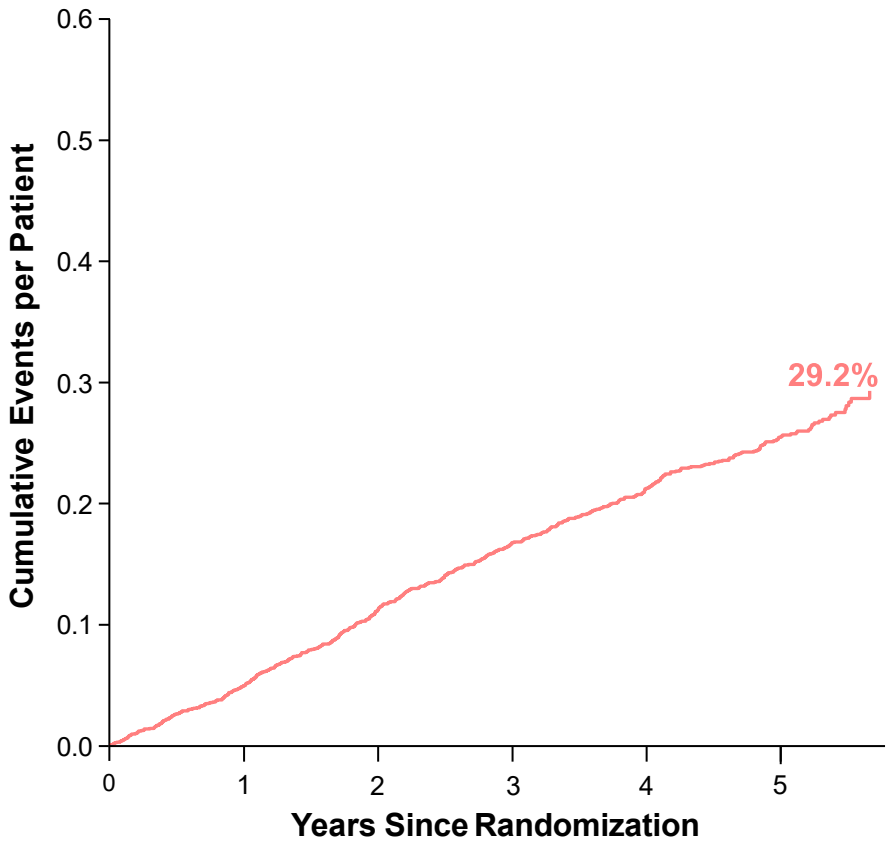
Primary Composite Endpoint



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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.

Time to First and Total Primary and Key Secondary Endpoint Events:
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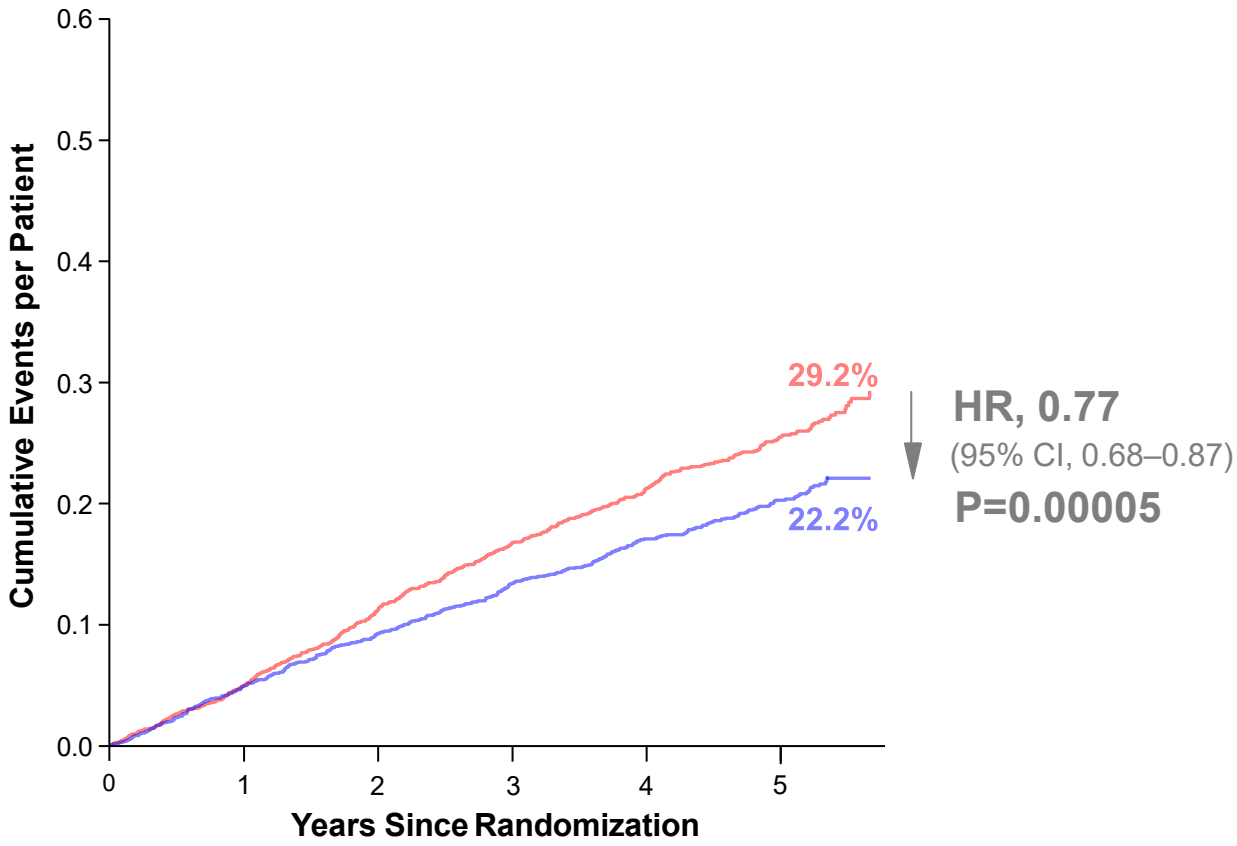

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reduce-it DIABETES

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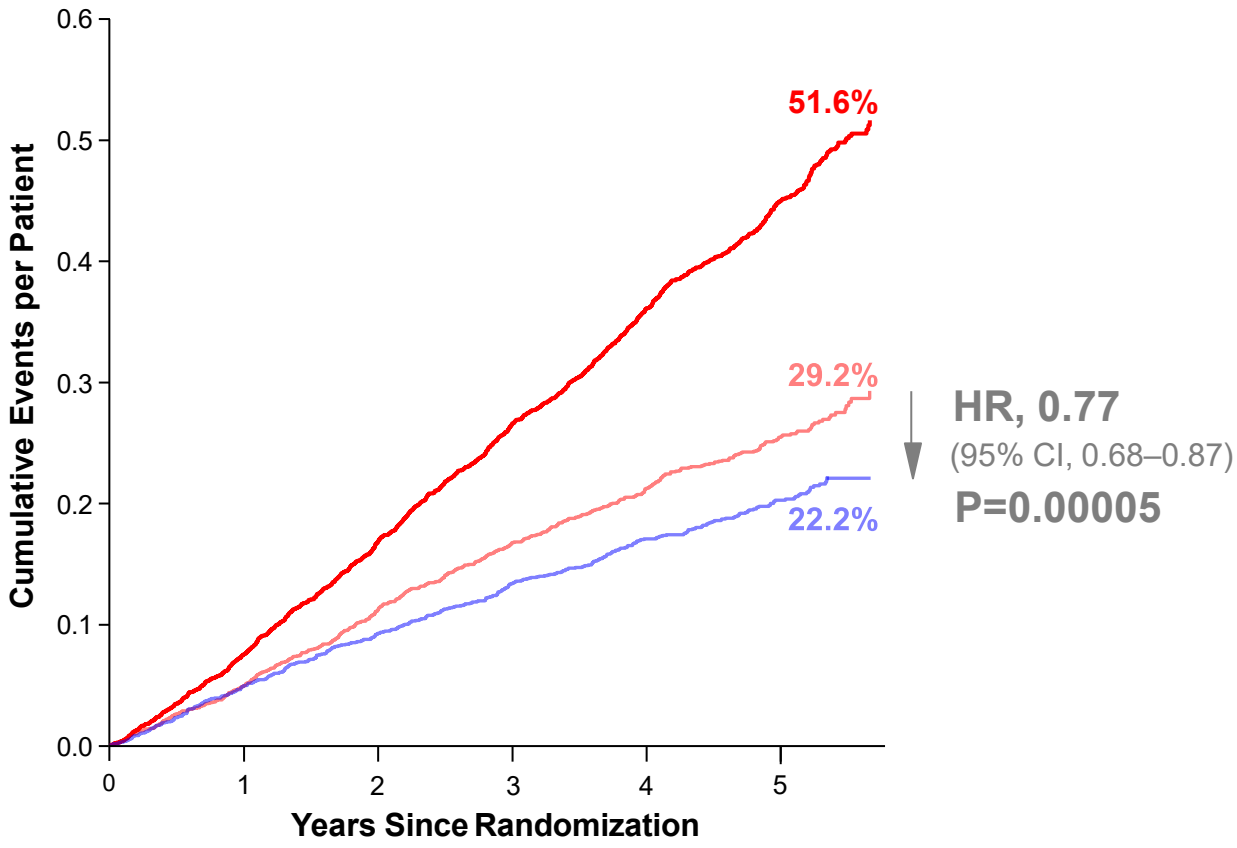

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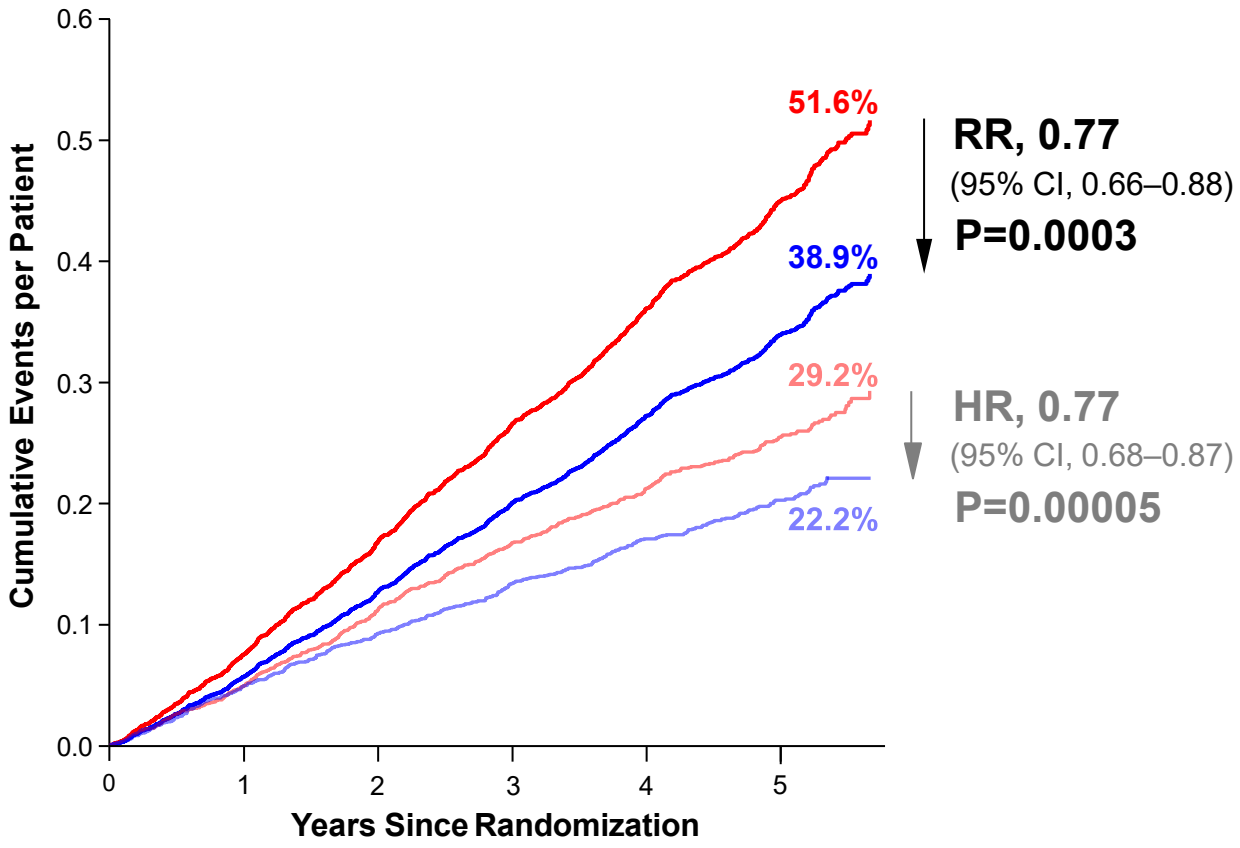

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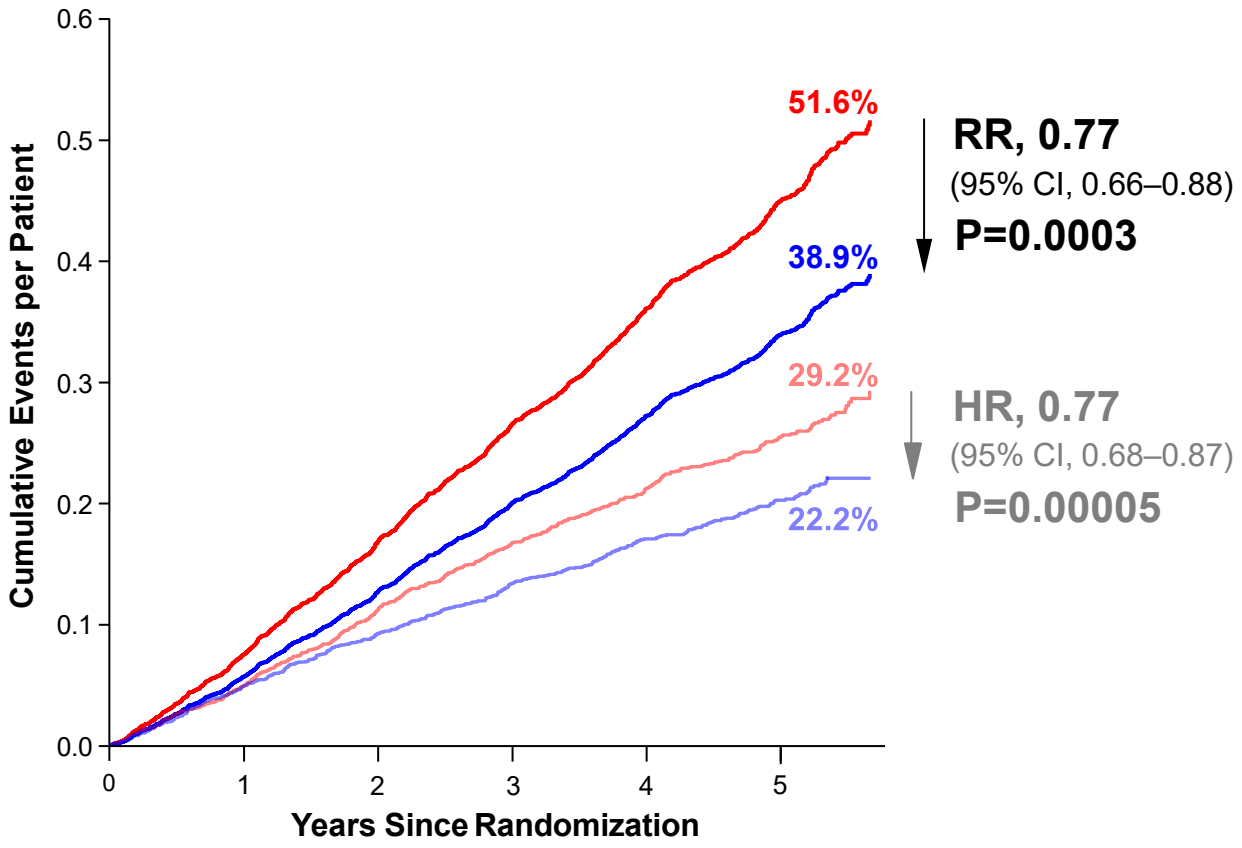
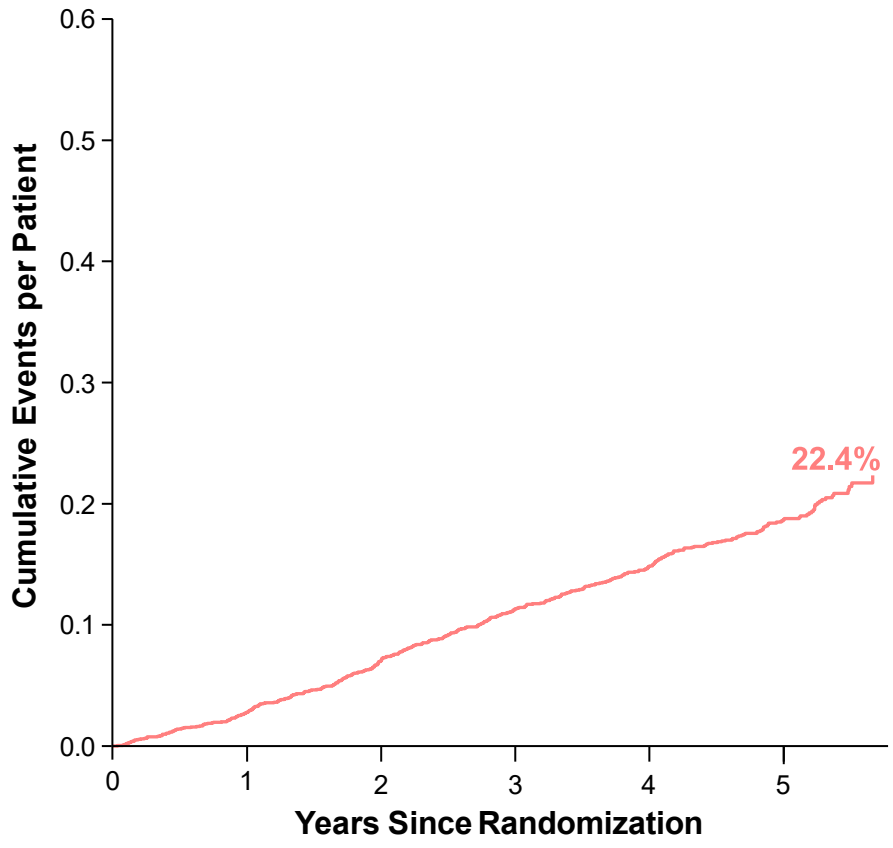


Key Secondary Composite Endpoint



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

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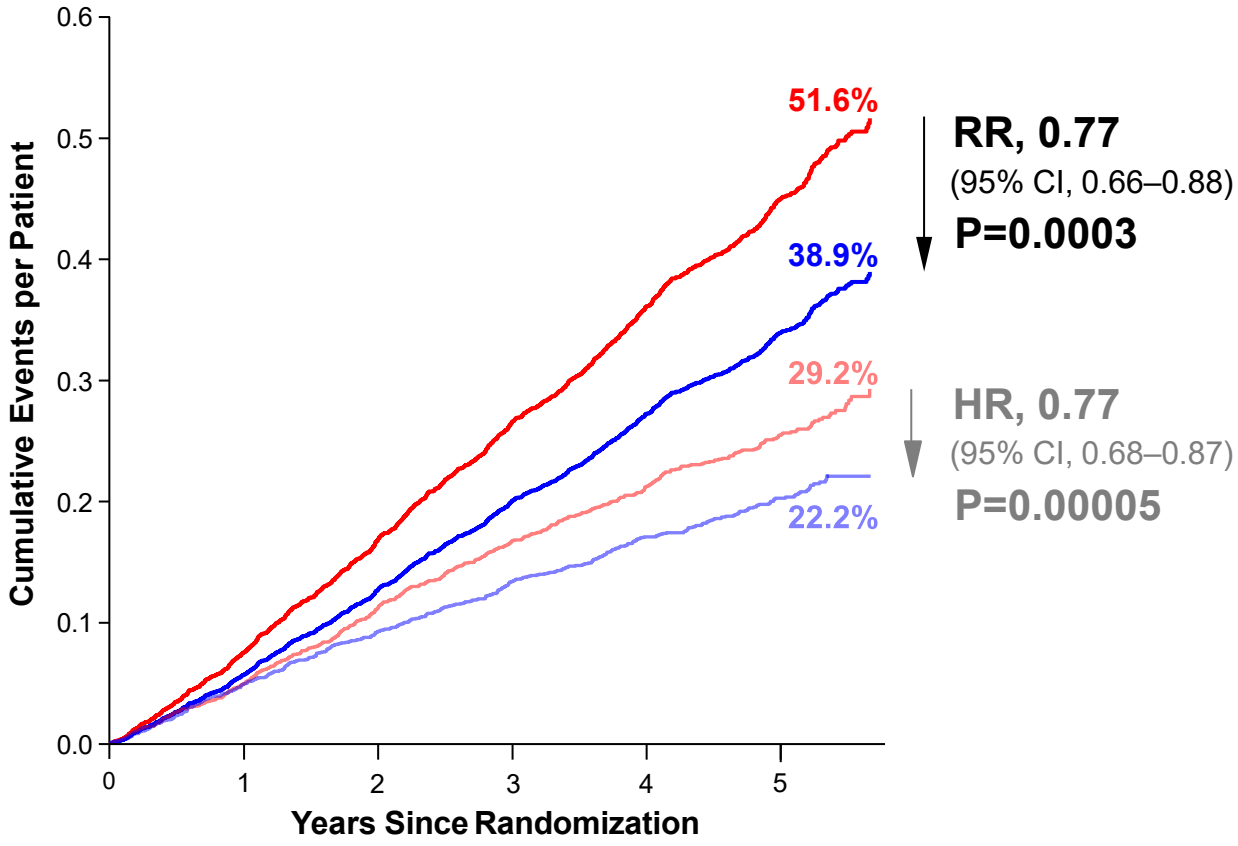
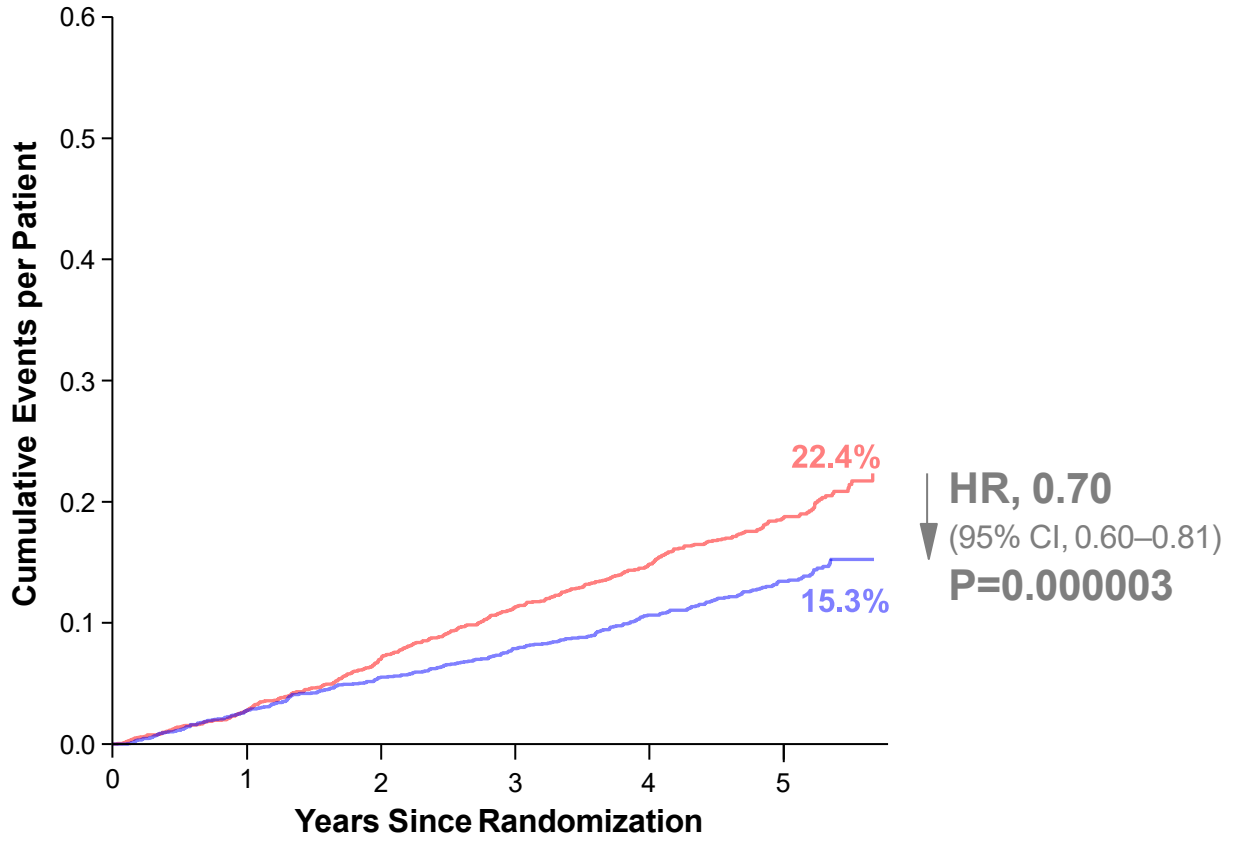


Key Secondary Composite Endpoint



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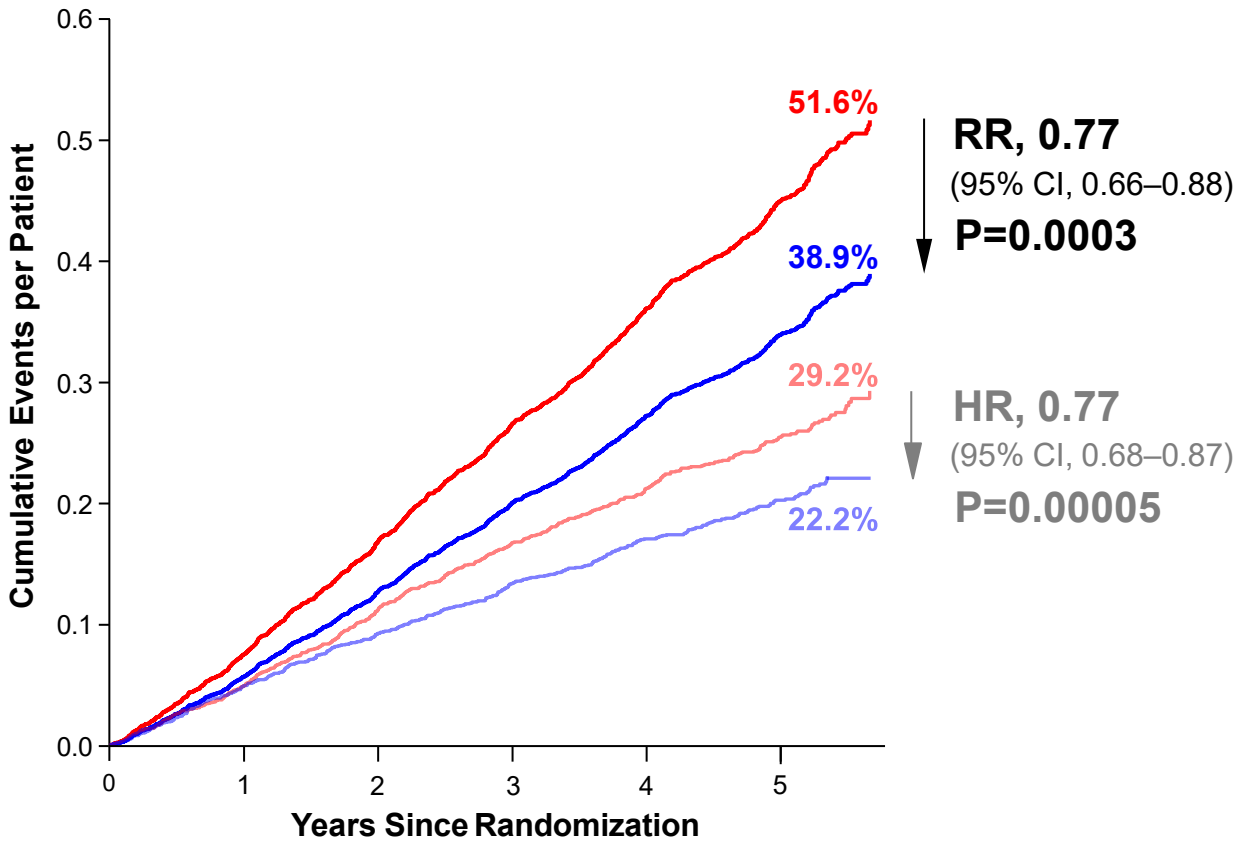
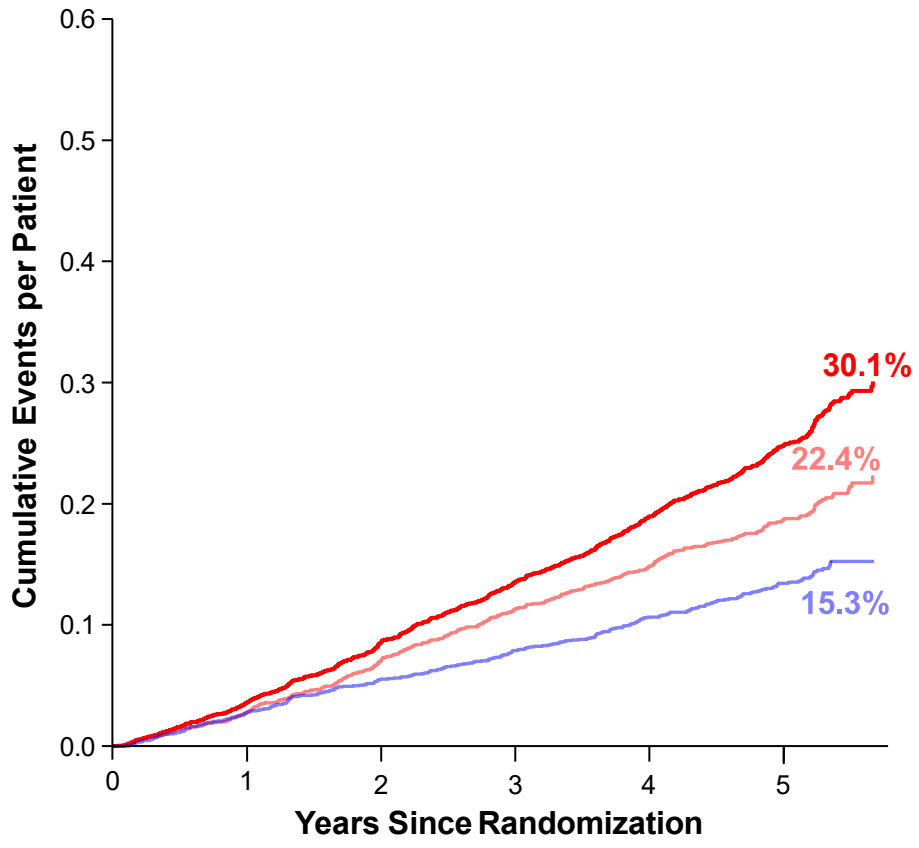


Key Secondary Composite Endpoint



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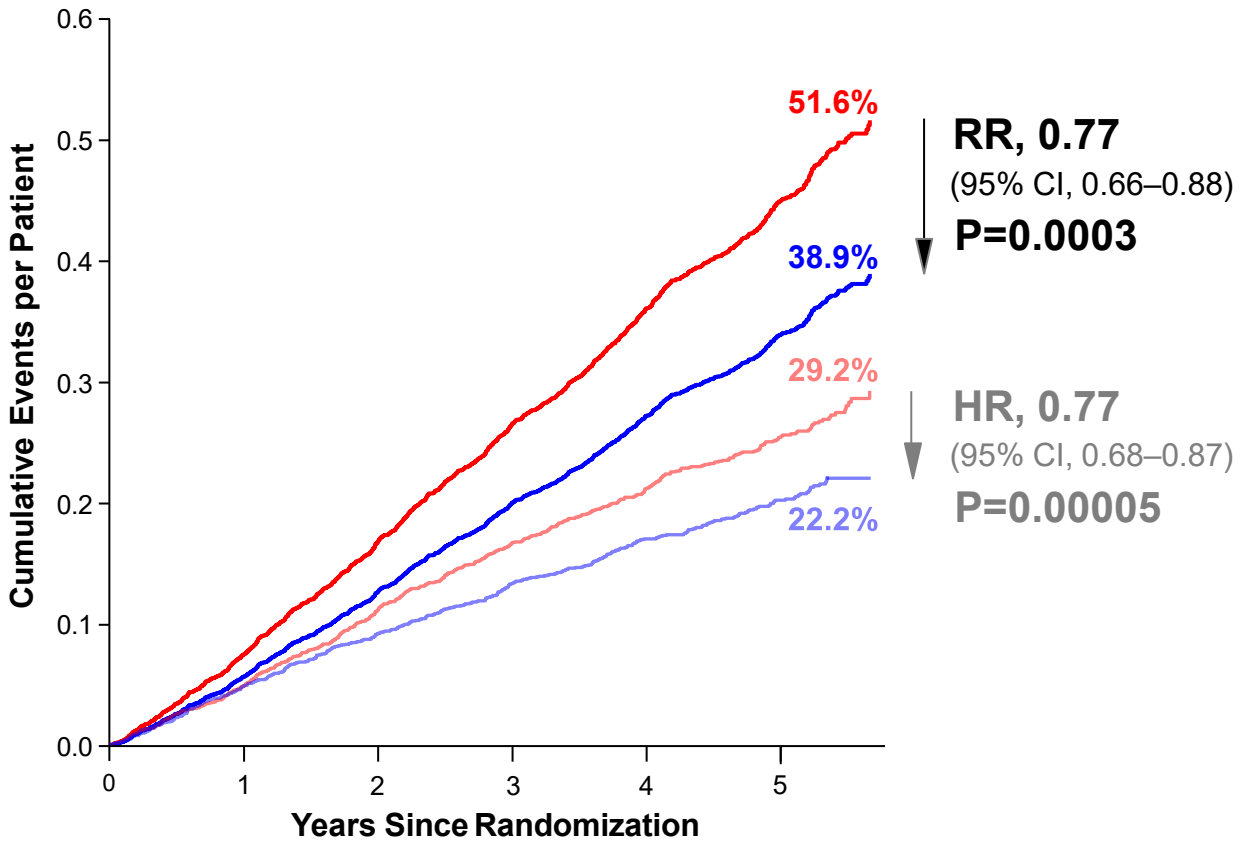

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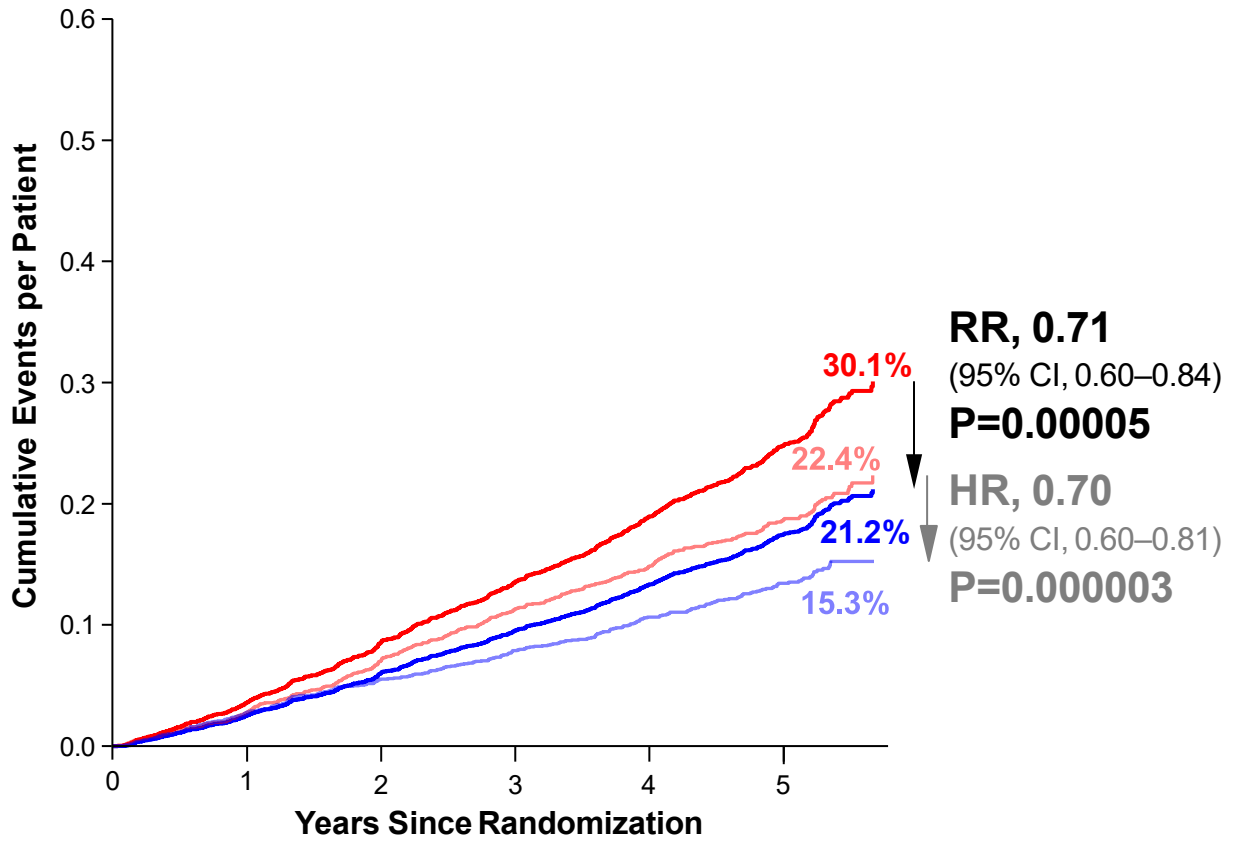

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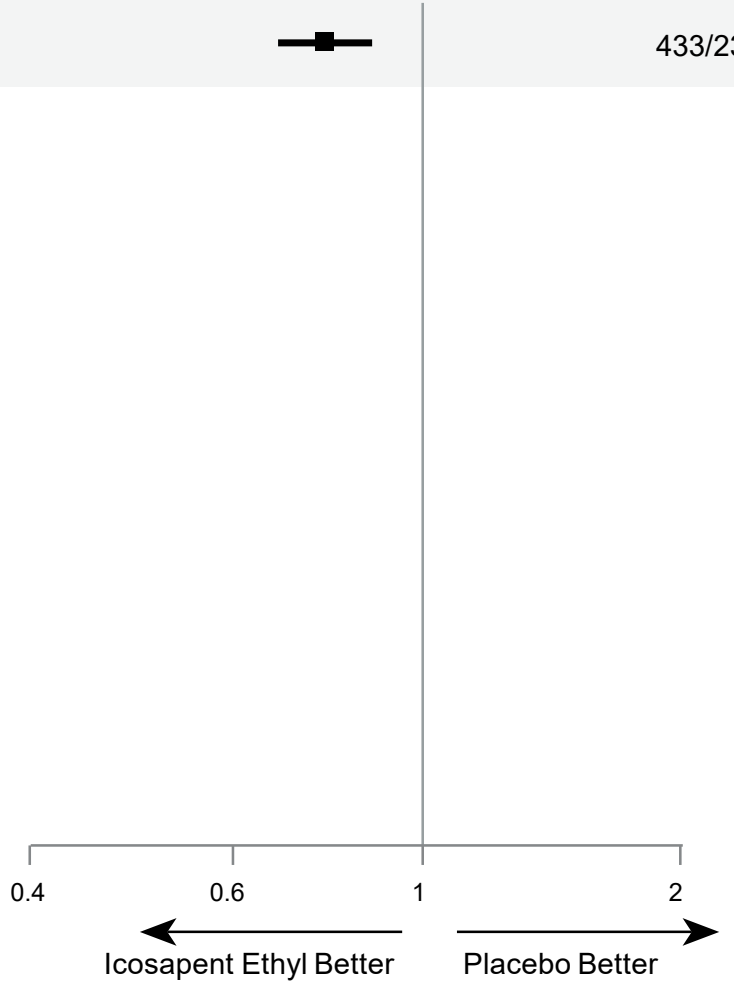
Prespecified Hierarchical Testing:
Diabetes Subgroup

Endpoint	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	Relative Risk Reduction	P-value
Primary Composite Endpoint		433/2394 (18.1%)	536/2393 (22.4%)	0.77 (0.68–0.87)	23%	<0.0001



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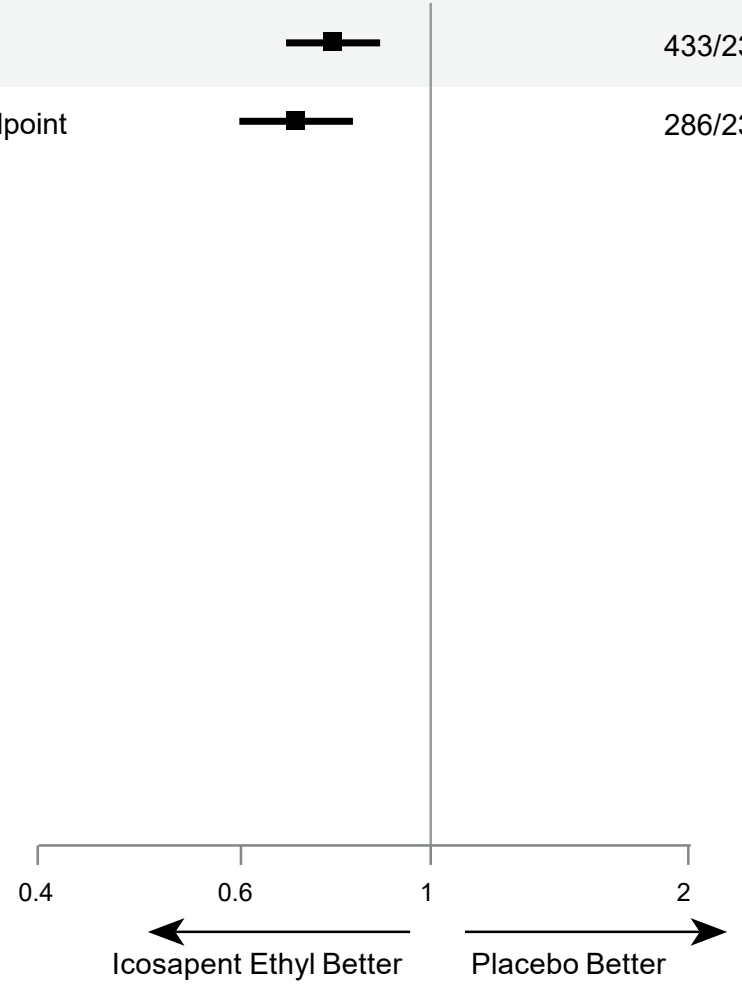

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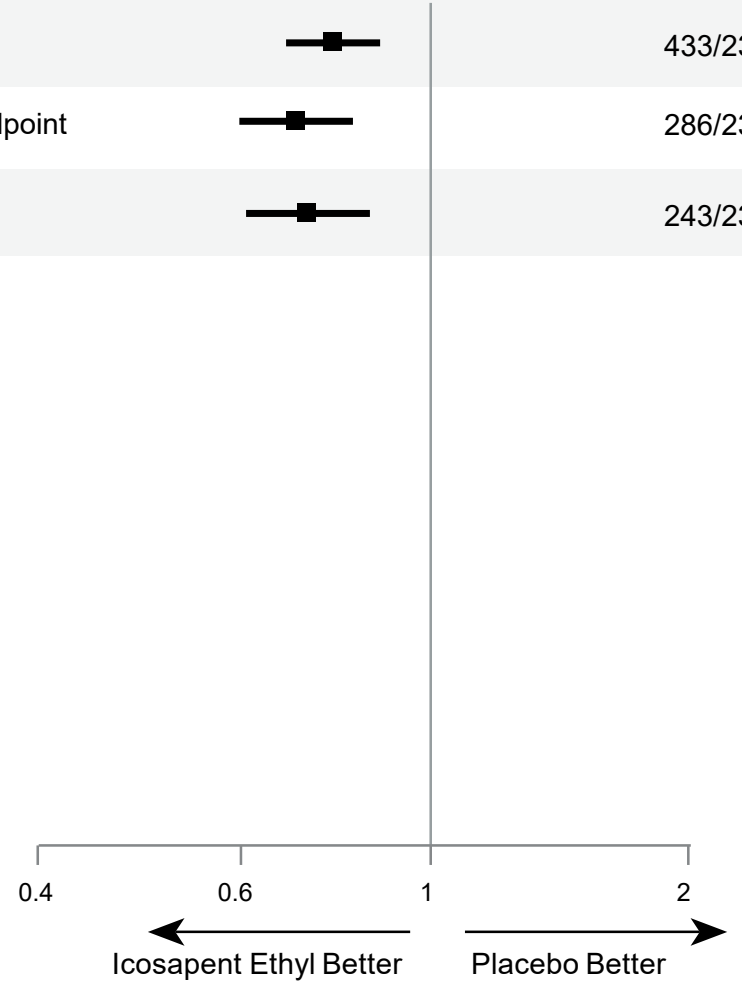

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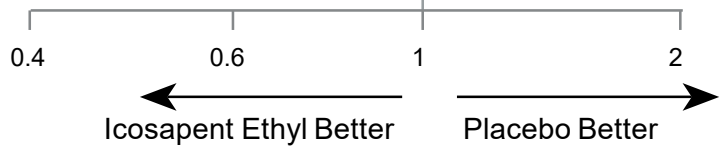

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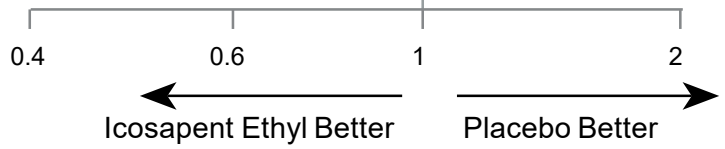
Urgent or Emergent Revascularization		136/2394 (5.7%)	173/2393 (7.2%)	0.76 (0.61–0.95)	24%	0.02



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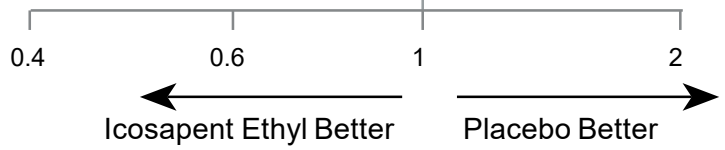

Bhatt DL, Brinton EA, Miller M, et al. ADA 2020, Chicago (virtual).

Prespecified Hierarchical Testing:
Diabetes Subgroup

reduce-it DIABETES

Endpoint	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	Relative Risk Reduction	P-value
Primary Composite Endpoint		433/2394 (18.1%)	536/2393 (22.4%)	0.77 (0.68–0.87)	23%	<0.0001
Key Secondary Composite Endpoint		286/2394 (11.9%)	391/2393 (16.3%)	0.70 (0.60–0.81)	30%	<0.0001
Cardiovascular Death or Nonfatal Myocardial Infarction		243/2394 (10.2%)	324/2393 (13.5%)	0.72 (0.61–0.85)	28%	<0.0001
Fatal or Nonfatal Myocardial Infarction		147/2394 (6.1%)	212/2393 (8.9%)	0.67 (0.54–0.83)	33%	0.0002
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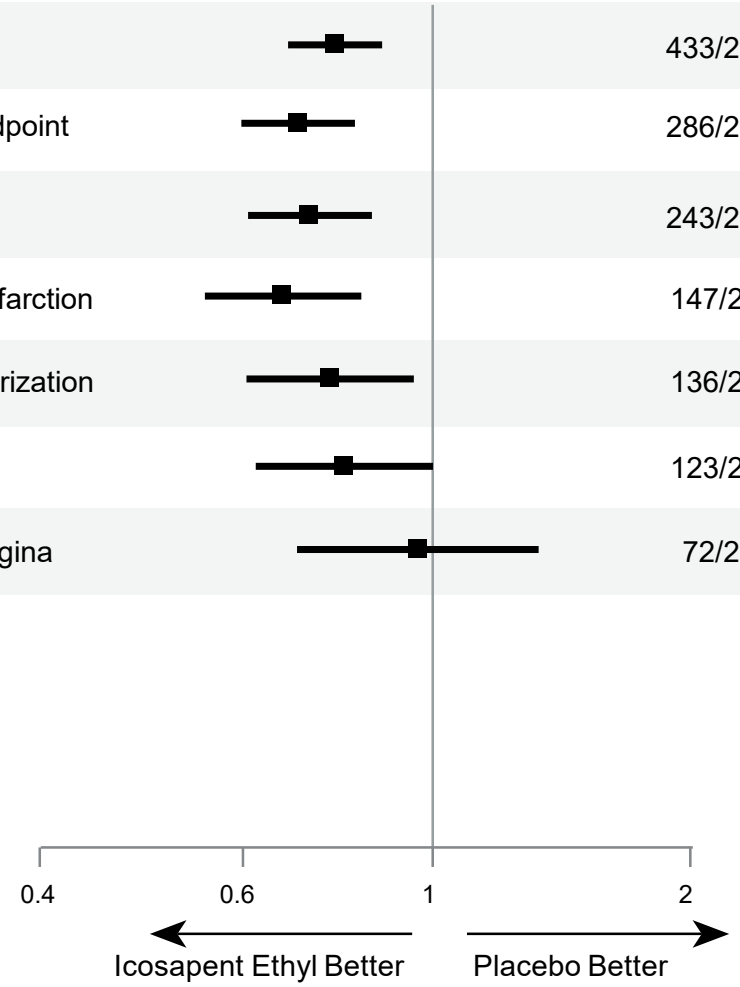
Hospitalization for Unstable Angina		72/2394 (3.0%)	74/2393 (3.1%)	0.96 (0.69–1.33)	4%	0.81



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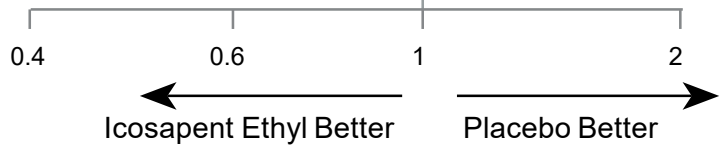
Fatal or Non-Fatal Stroke		62/2394 (2.6%)	92/2393 (3.8%)	0.65 (0.47–0.90)	35%	0.009



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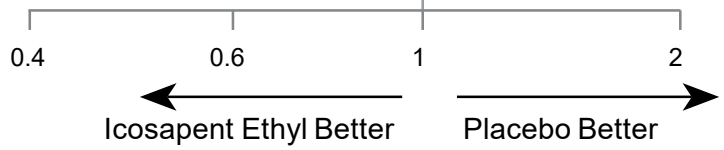
Total Mortality/Nonfatal Myocardial Infarction, or Nonfatal Stroke		335/2394 (14.0%)	435/2393 (18.2%)	0.73 (0.64–0.84)	27%	<0.0001



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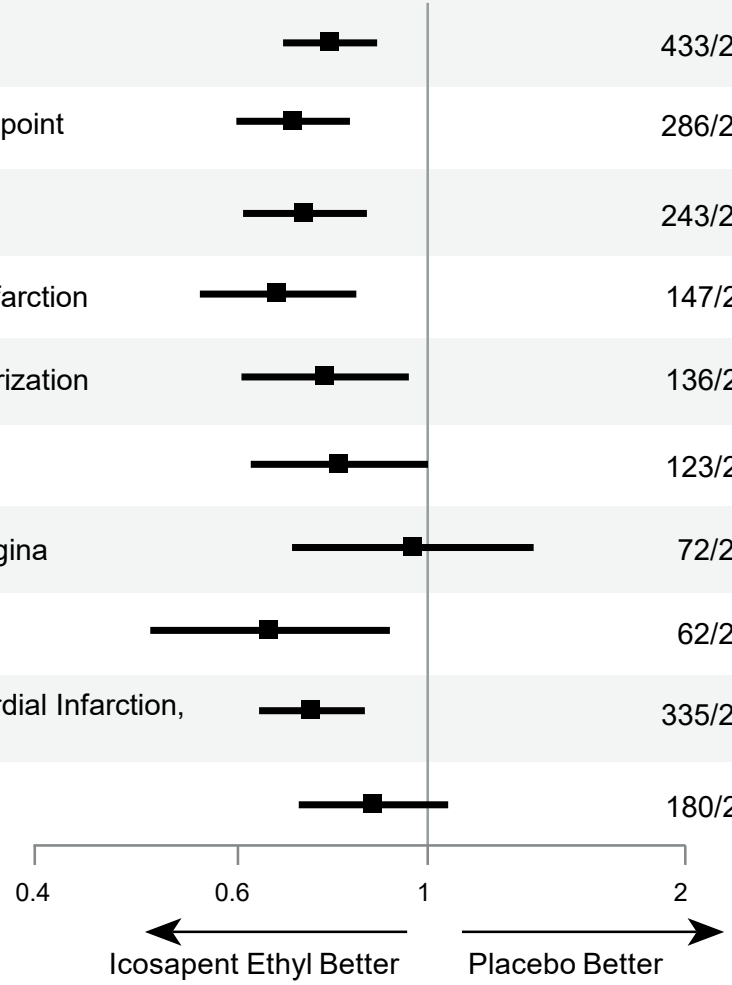
Total Mortality/Nonfatal Myocardial Infarction, or Nonfatal Stroke		335/2394 (14.0%)	435/2393 (18.2%)	0.73 (0.64–0.84)	27%	<0.0001
Total Mortality		180/2394 (7.5%)	202/2393 (8.4%)	0.86 (0.71–1.06)	14%	0.15



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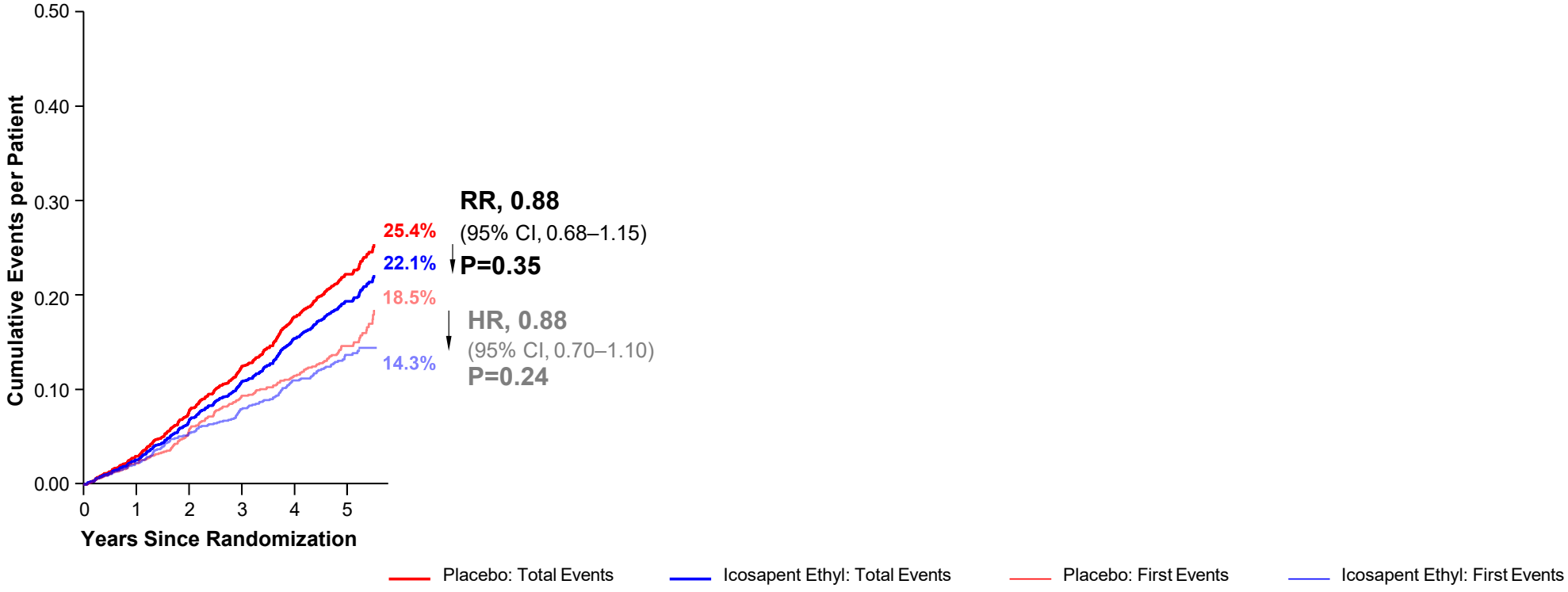
Time to First and Total Primary Endpoint Events by CV Risk Category and Diabetes Status at Baseline

Patients without Established CVD
With Diabetes and Other Risk Factors



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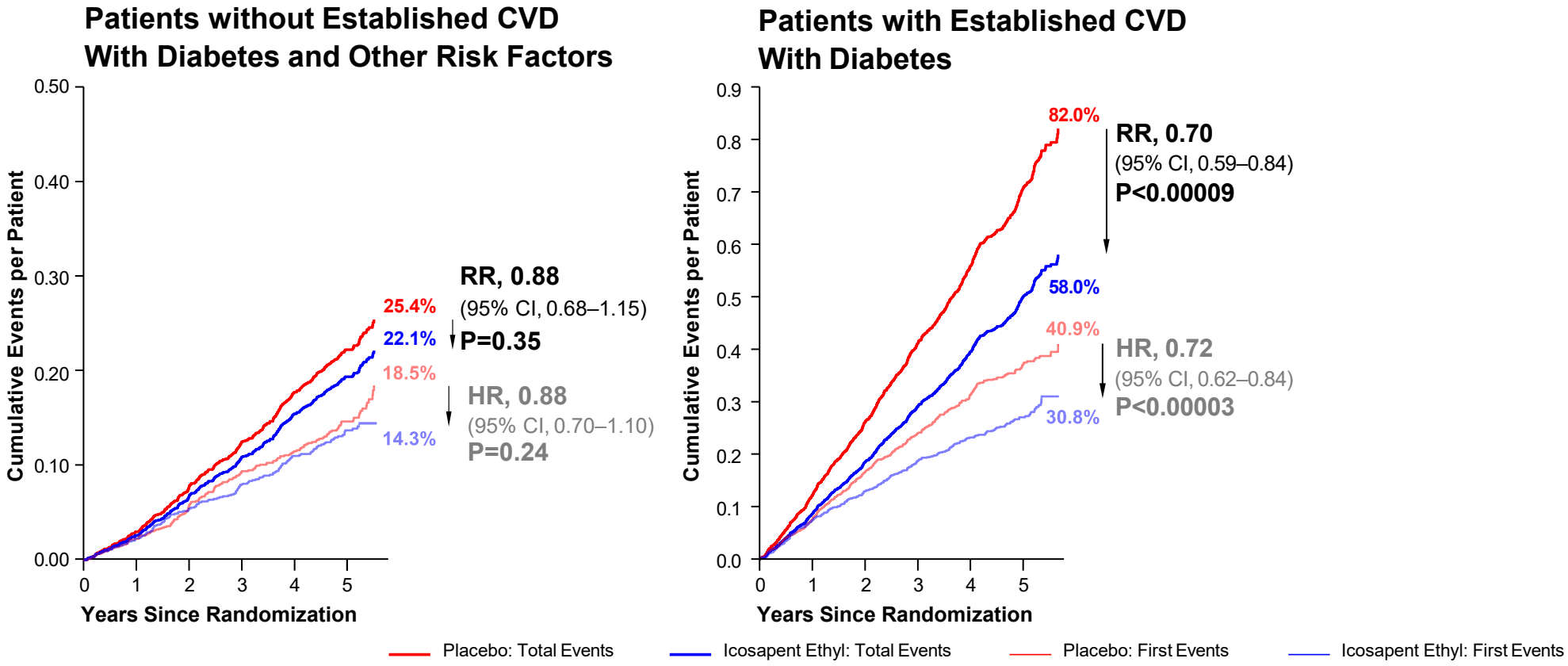

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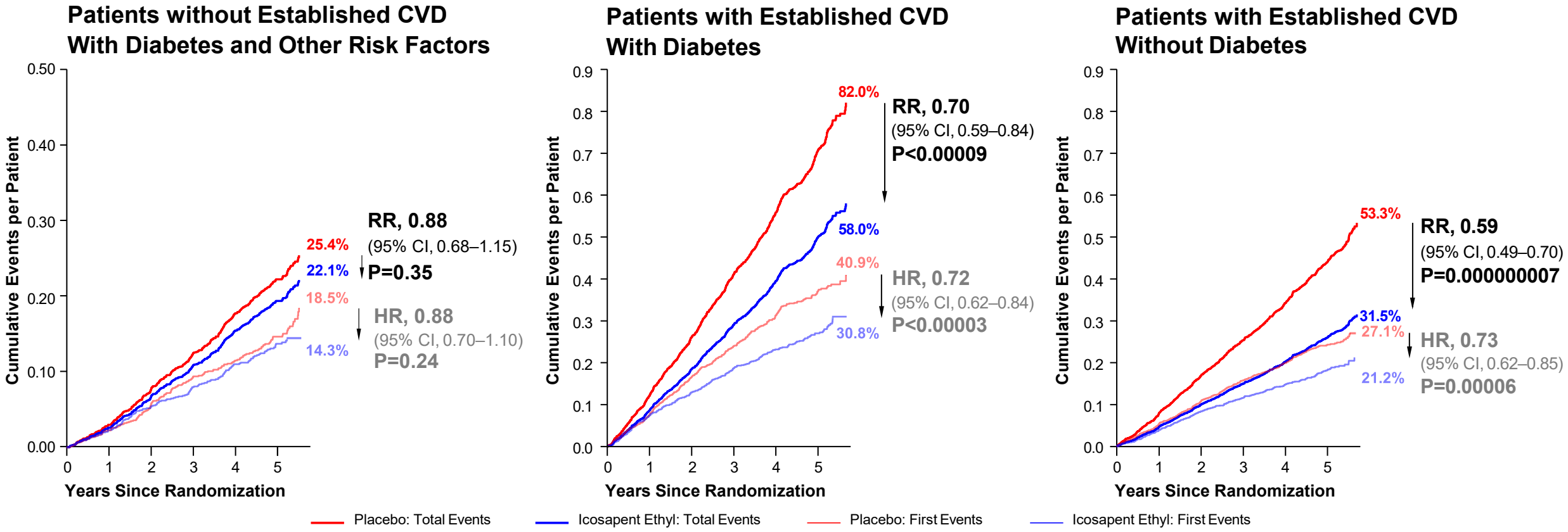

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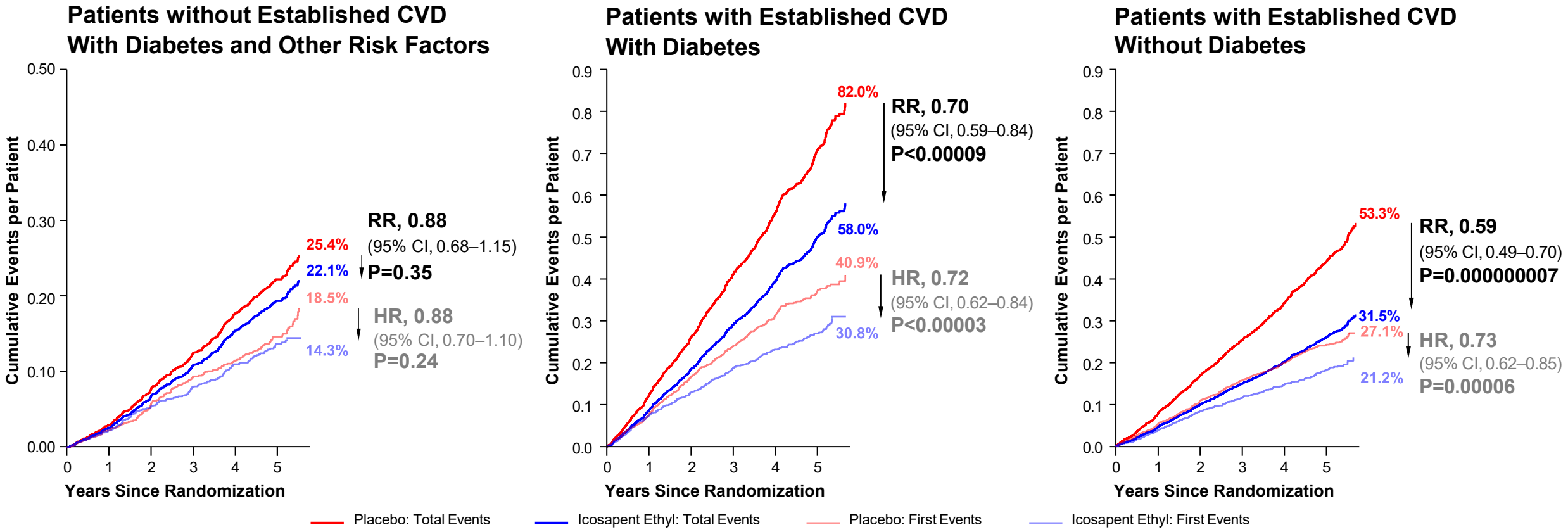

Interaction P-value between patients with established CVD with diabetes and patients with established CVD without diabetes = 0.98
Interaction P-value between patients with diabetes and other risk factors, patients with established CVD with diabetes, and patients with established CVD without diabetes = 0.32

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Safety: Diabetes Subgroup

Safety was generally consistent with the full study, including increases in atrial fibrillation/flutter (3.5% vs 2.2%; p=0.13) and bleeding (13.1% vs 10.9%; p=0.02).

Serious bleeding was not significantly different (3.2% vs 2.5%; p=0.19).

There were no meaningful between-group differences in HbA1c or glucose control across study visits, including placebo-corrected median changes from baseline to year 1 for HbA1c (0%, p=0.19) and glucose (-0.06 mmol/L, p=0.34).

Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced both first and total primary endpoint events in patients with diabetes at baseline by **23%** and **24%**, respectively.

For the key secondary endpoint of hard MACE, reductions for first and total events were **30%** and **29%**, respectively.

Reductions were consistent and robust across the prespecified hierarchy of endpoints, among patients with diabetes with or without cardiovascular disease, as well as those with established CVD and no diabetes at baseline.

These data highlight the substantial impact of icosapent ethyl on the underlying atherothrombotic burden in the at-risk **REDUCE-IT** population, both in those with but also in those without diabetes mellitus.

BRIGHAM AND WOMEN'S HOSPITAL

Heart & Vascular Center

Thank You!

Deepak L. Bhatt, MD, MPH
Executive Director,
Interventional Cardiovascular Programs,
BWH Heart & Vascular Center;
Professor of Medicine,
Harvard Medical School
Email: DLBhattMD@post.harvard.edu
Twitter: @DLBhattMD

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