New Options to Reduce Cardiovascular Events in ASCVD

Online CME Activity

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Michael Miller, MD
Professor of Cardiovascular Medicine, Epidemiology & Public Health
University of Maryland School of Medicine
Director, Center for Preventive Cardiology
University of Maryland Medical Center
Baltimore, MD

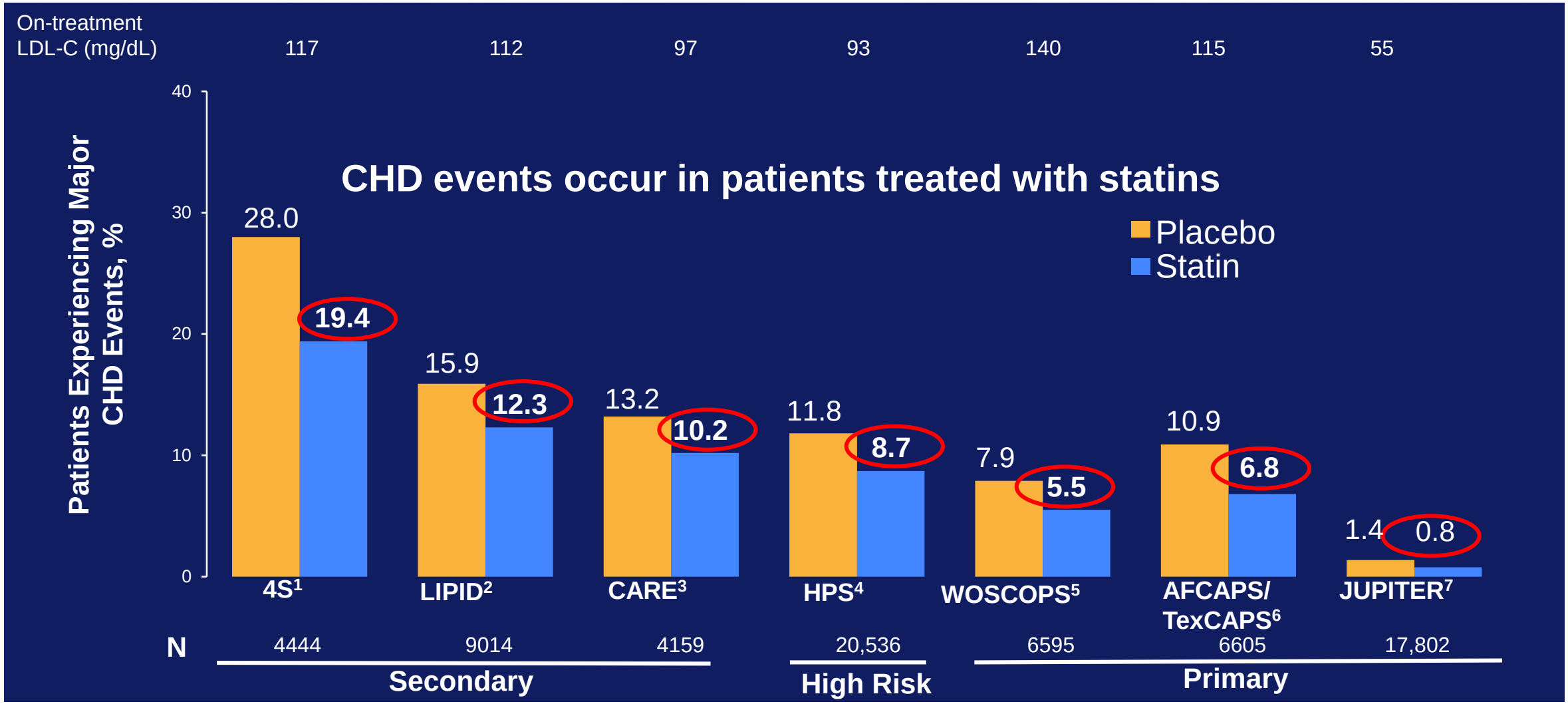
Introduction

AHA Scientific Statement: Prevalence of Elevated TG

20+ yrs	>150 mg/dL	>200 mg/dL	>500 mg/dL
Overall	31%	16%	1.1%
Men	35%	20%	1.8%
Women	27%	13%	0.5%
Heritage			
Mexican	35%	20%	1.4%
African	16%	8%	0.4%
European	33%	18%	1.1%

Miller M et al. *Circulation.* 2011;123:2292-333.

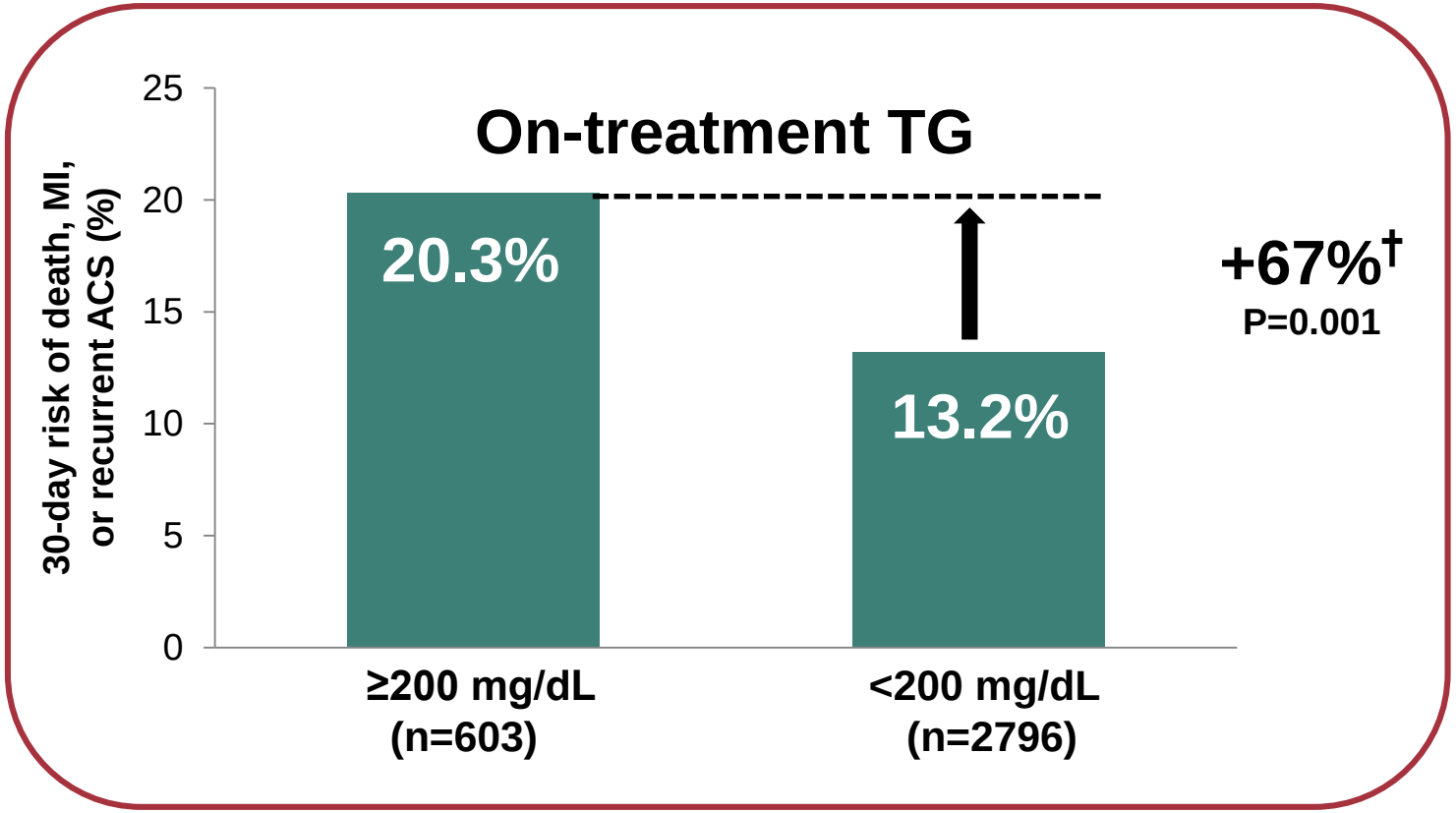
Major Statin Trials: Despite Benefit, Substantial Residual CV Risk Remains



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

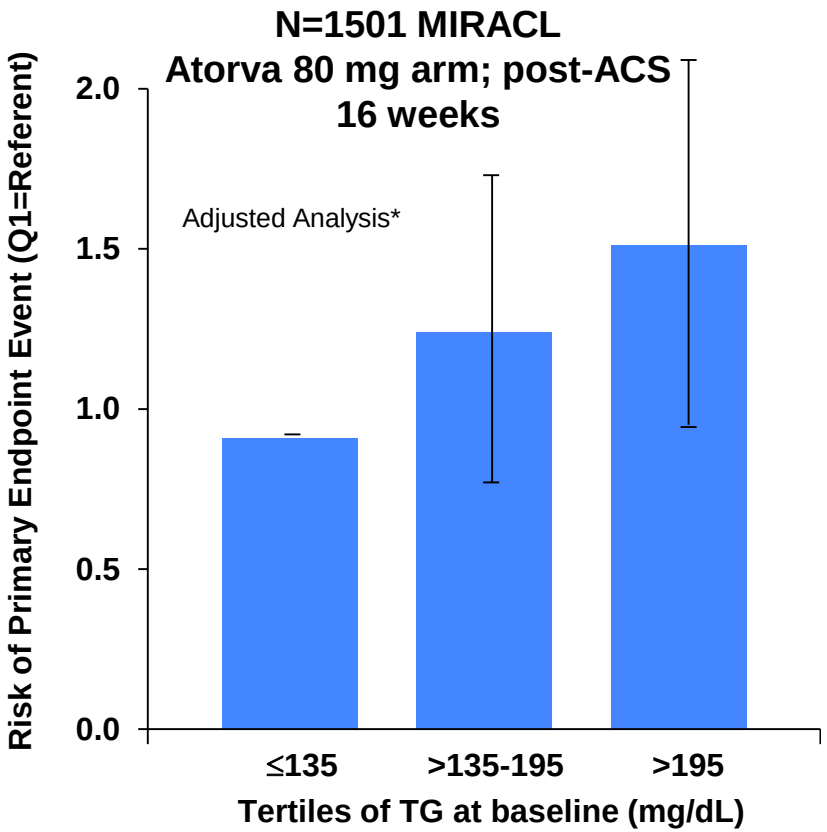
PROVE IT-TIMI 22: Elevated TG Levels Increase Risk of a Coronary Event, Despite LDL-C at Goal

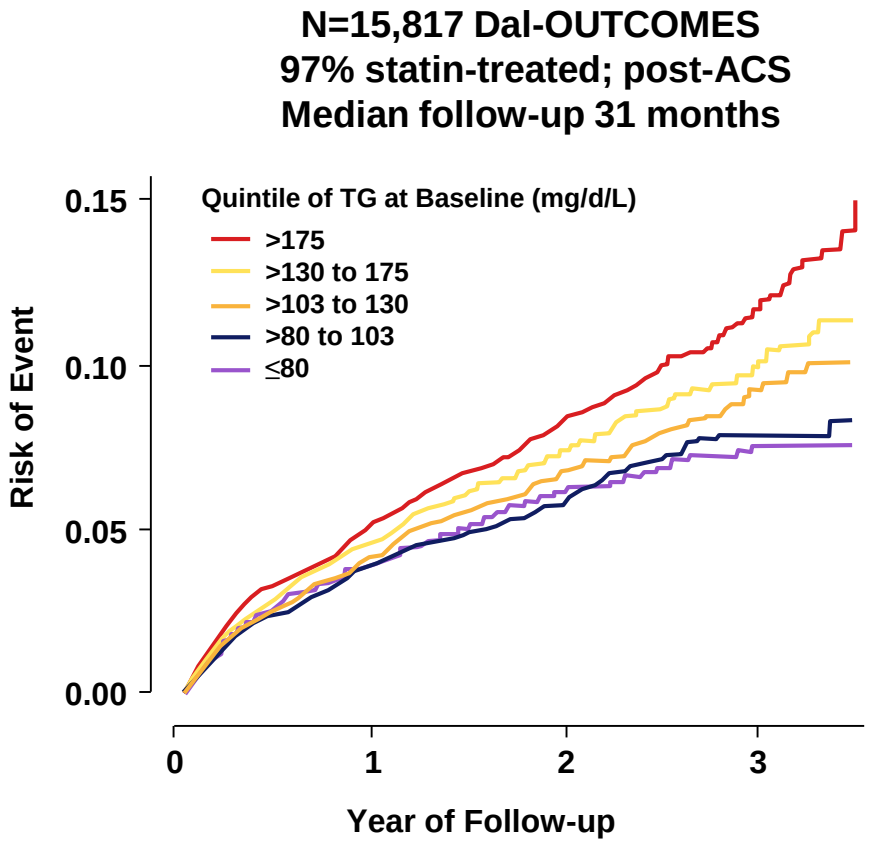
Despite achieving LDL-C <70 mg/dL with a high-dose statin, patients with TG ≥200 mg/dL have a 67% higher risk of coronary events*



*Death, myocardial infarction, or recurrent acute coronary syndrome
†Calculated from adjusted hazard ratio of TG <200 mg/dL (95% CI) = 0.60 (0.45-0.81)
Miller M et al. *J Am Coll Cardiol*. 2008;51:724-30.

On Statin Rx, TG Levels Associate with Short- and Long-term CV Risk





Fasting TG levels are strongly linked to both short-term and long-term major CV event risk on background statin therapy, independent of LDL-C

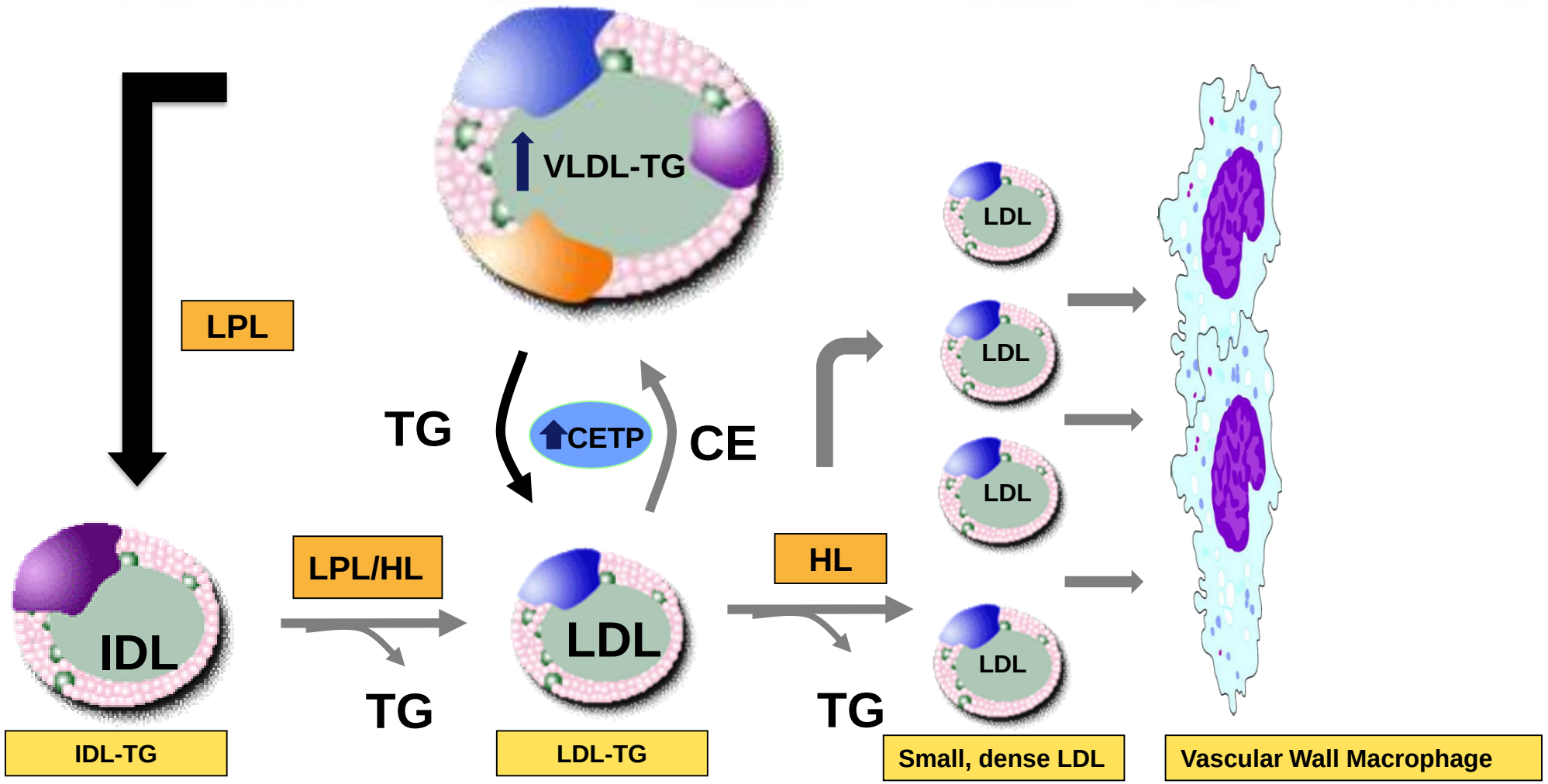
*P for trend=0.03.

ACS=acute coronary syndrome; HTG=hypertriglyceridemia. Schwartz GG et al. *J Am Coll Cardiol*. 2015;65:2267-75.

Elevated TG (TRL): Drivers of CVD Risk

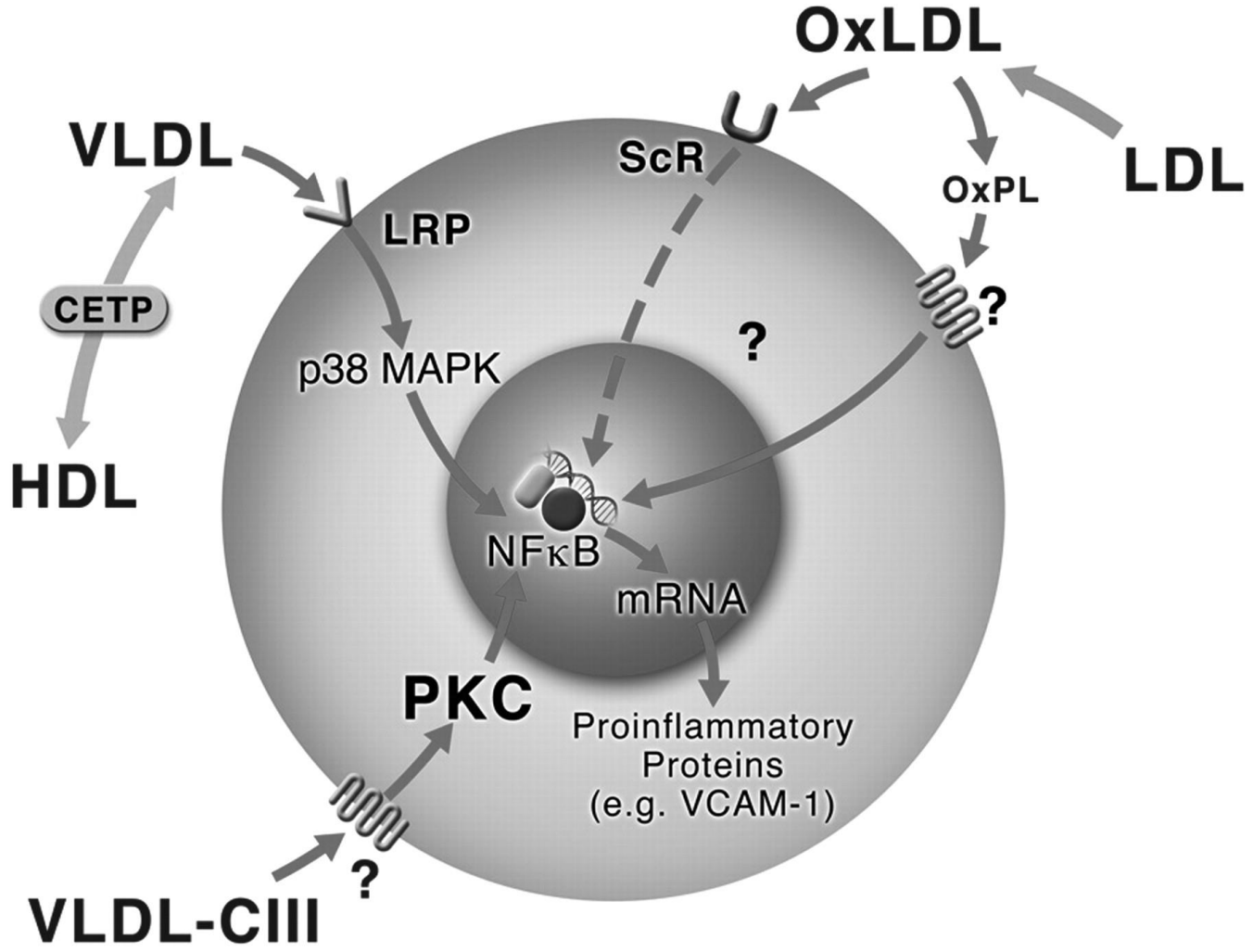
Lipid Based
Non-lipid Based

Elevated TG: ↑LDL-TG Partially Drives CVD Risk



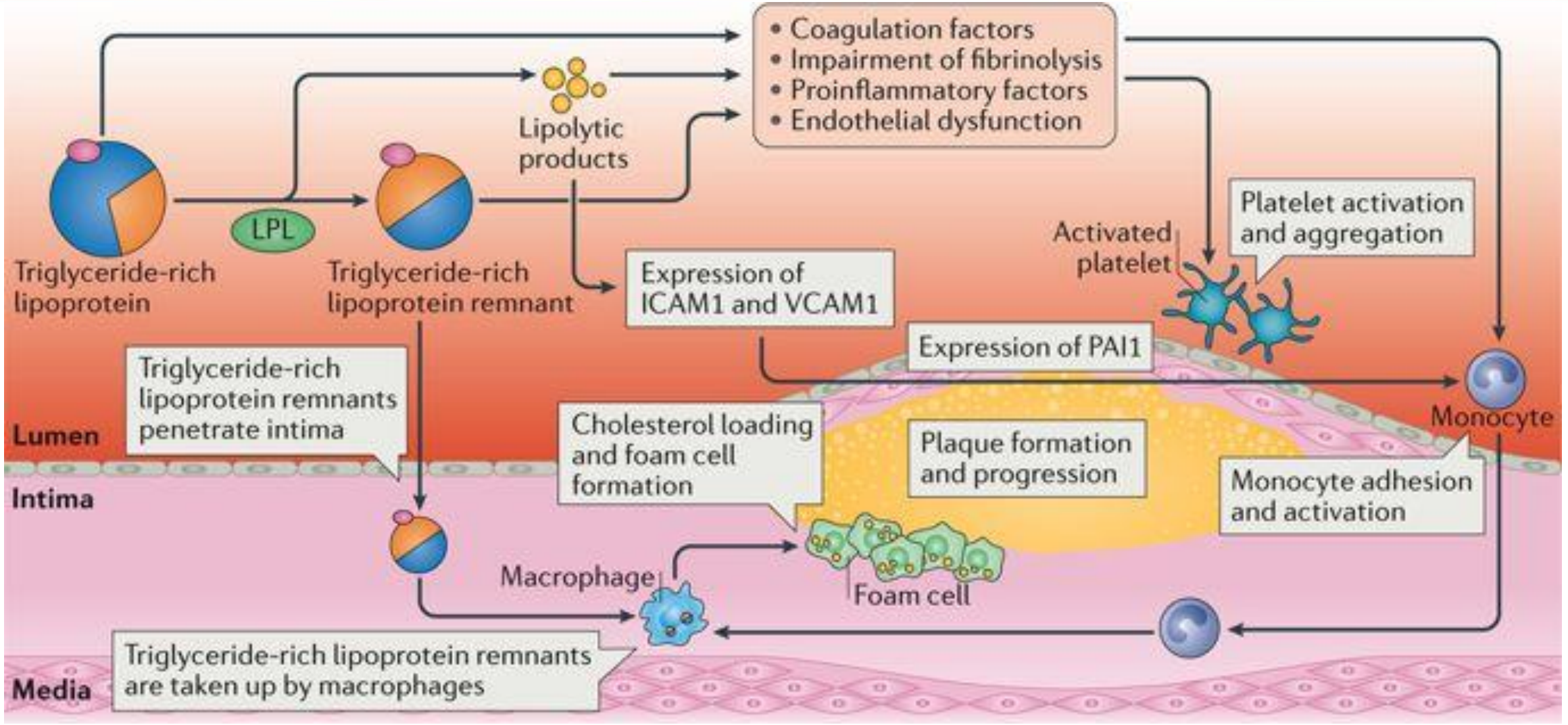
Saeed A et al. *J Am Coll Cardiol*. 2018;72:156-69. Miller M. *J Am Coll Cardiol*. 2018;72:170-2.

Elevated TG: Remnants & APOC3 Partially Drives CVD Risk



Libby P. *Circ Res*. 2007;100:299-301.

Elevated TG: Non-Lipid Factors Driving CVD Risk



Reiner, Ž. *Nat. Rev. Cardiol. 2017;*14:401-411.

Unsuccessful Fibrate Outcome Studies with Statin Use

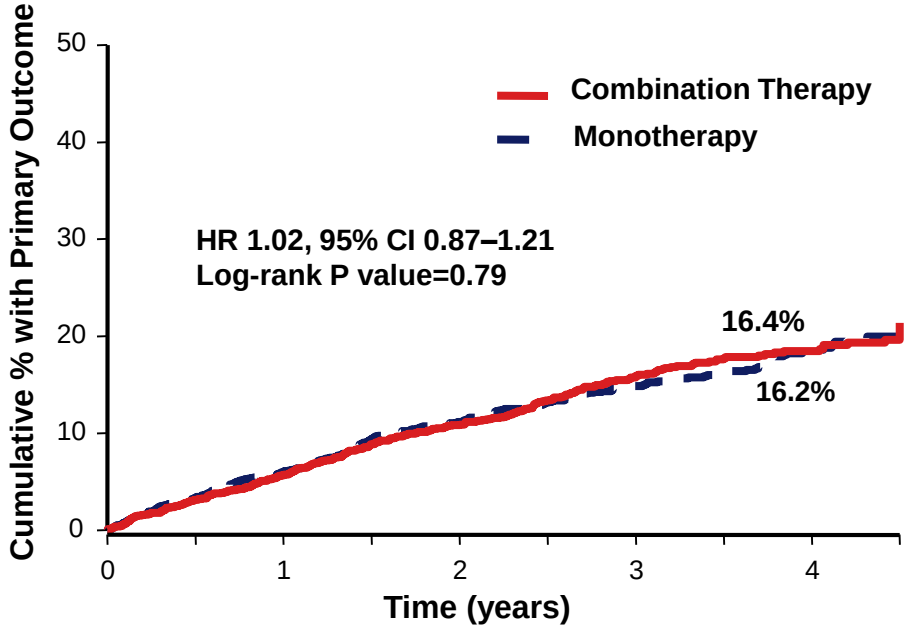
Study	CV Risk Profile	N	Daily Inter-vention	Statin Use	Baseline TG Level	Effect on TG Level	Primary Outcome	Primary Outcome Results
ACCORD	• T2DM • Age 40-79 yrs w/ CVD or • Age 55-79 yrs w/ ≥2 CV risk factors	5518	Fenofibrate	Open-label simvastatin (mean dose: 22 mg)	162 mg/dL (median)	–26%	• Nonfatal MI or • Stroke or • CV death Mean f/u: 4.7 yrs	• HR=0.92 (95% CI, 0.79-1.08) • P=0.32 • ARR=NC (2.2% w/ fenofibrate vs 2.4% w/ placebo)
FIELD	• Age 50-75 yrs • T2DM	9795	Micronized fenofibrate 200 mg QD	Added during study in 2547 pts	154 mg/dL (median)	–30% at 1 year	• Nonfatal MI or • CHD death Median f/u: 5 yrs	• HR=0.89 (95% CI, 0.75-1.05) • P=0.16 • ARR=1.4%

ARR=absolute risk reduction; NC=not calculated.

Adapted from Handelsman Y, Shapiro MD. *Endocr Pract*. 2017;23:100-12. Sacks FM et al. *N Engl J Med.* 2010;363:692-4.

Unsuccessful Niacin Outcome Studies with Statin Use

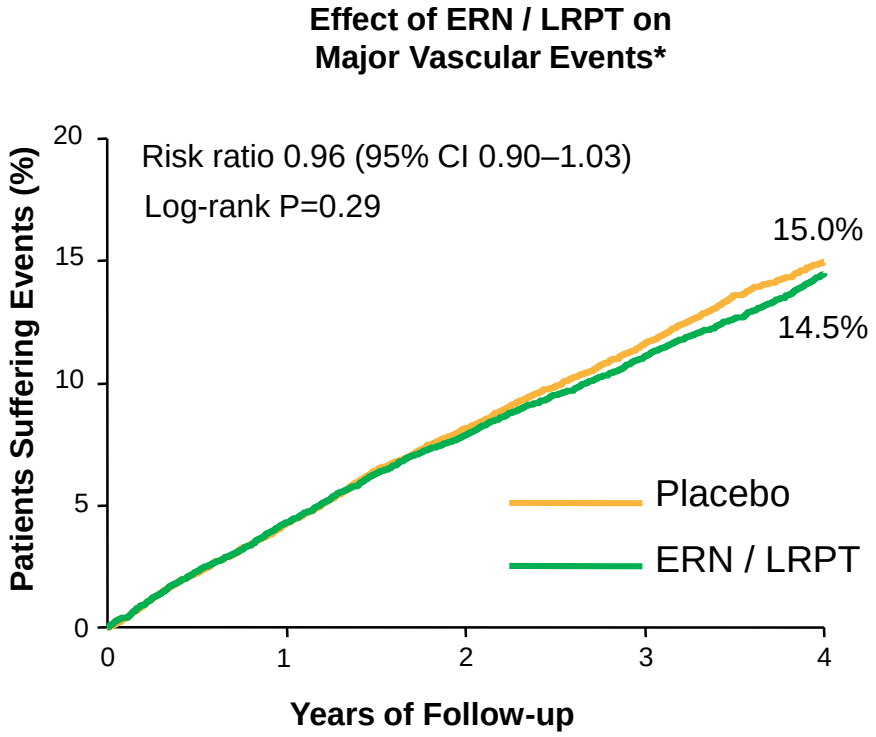
AIM-HIGH *(–29% TG)*



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

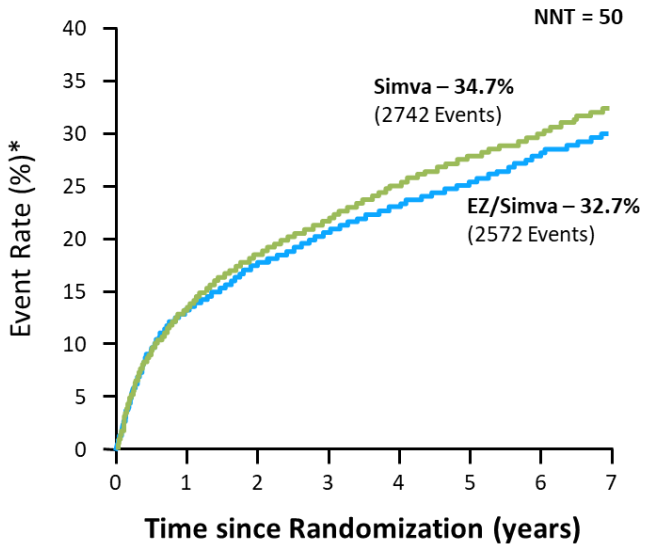
Boden WE et al. *N Engl J Med.* 2011;365:2255-67

HPS2-THRIVE *(–26% TG)*

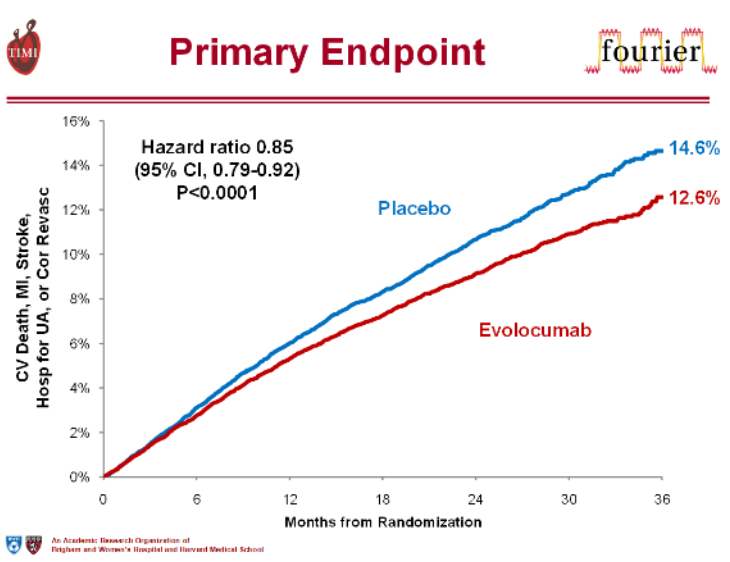


HPS2-THRIVE Collaborative Group. *N Engl J Med*. 2014;371:203-12.

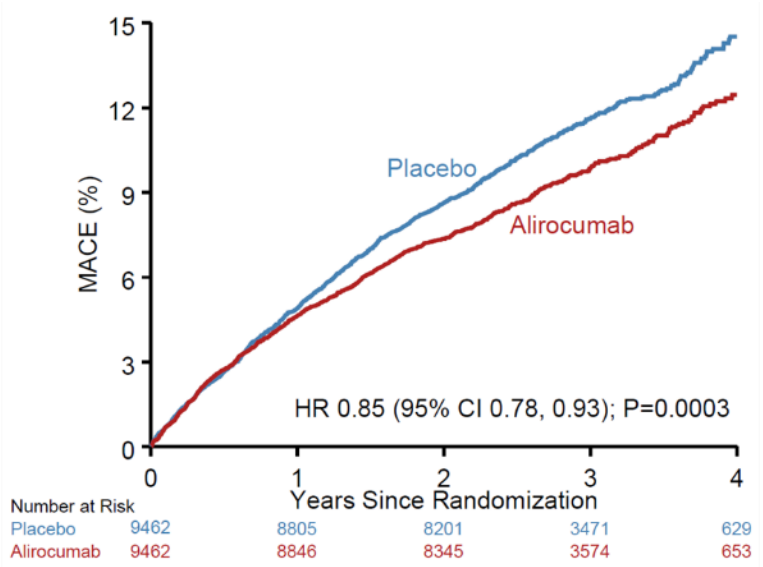
Successful Outcome Studies with Statin Use (5-15% RRR)



IMPROVE-IT[1]



FOURIER[2]

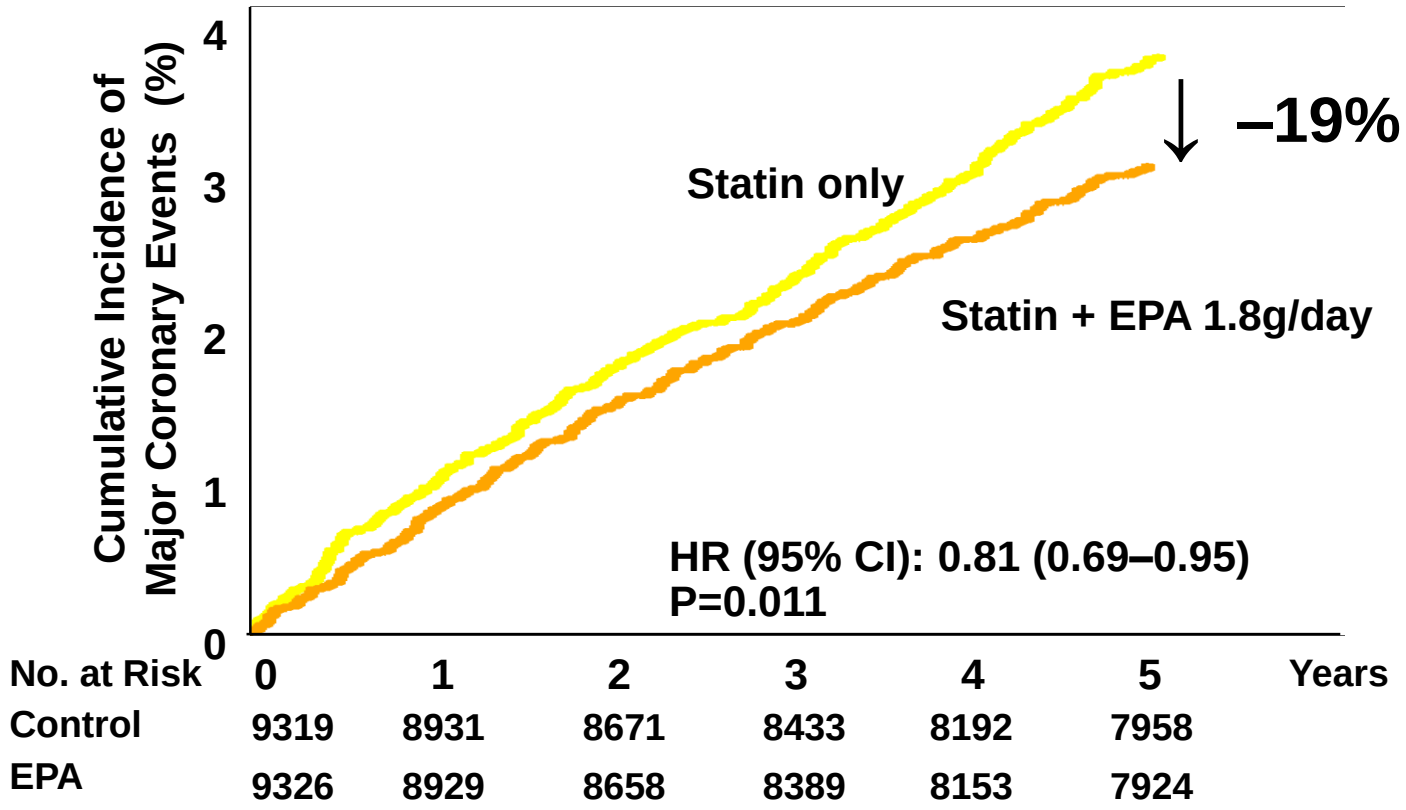


ODYSSEY Outcomes[3]

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

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

JELIS: Successful Outcome Study with Statin Use (19%)

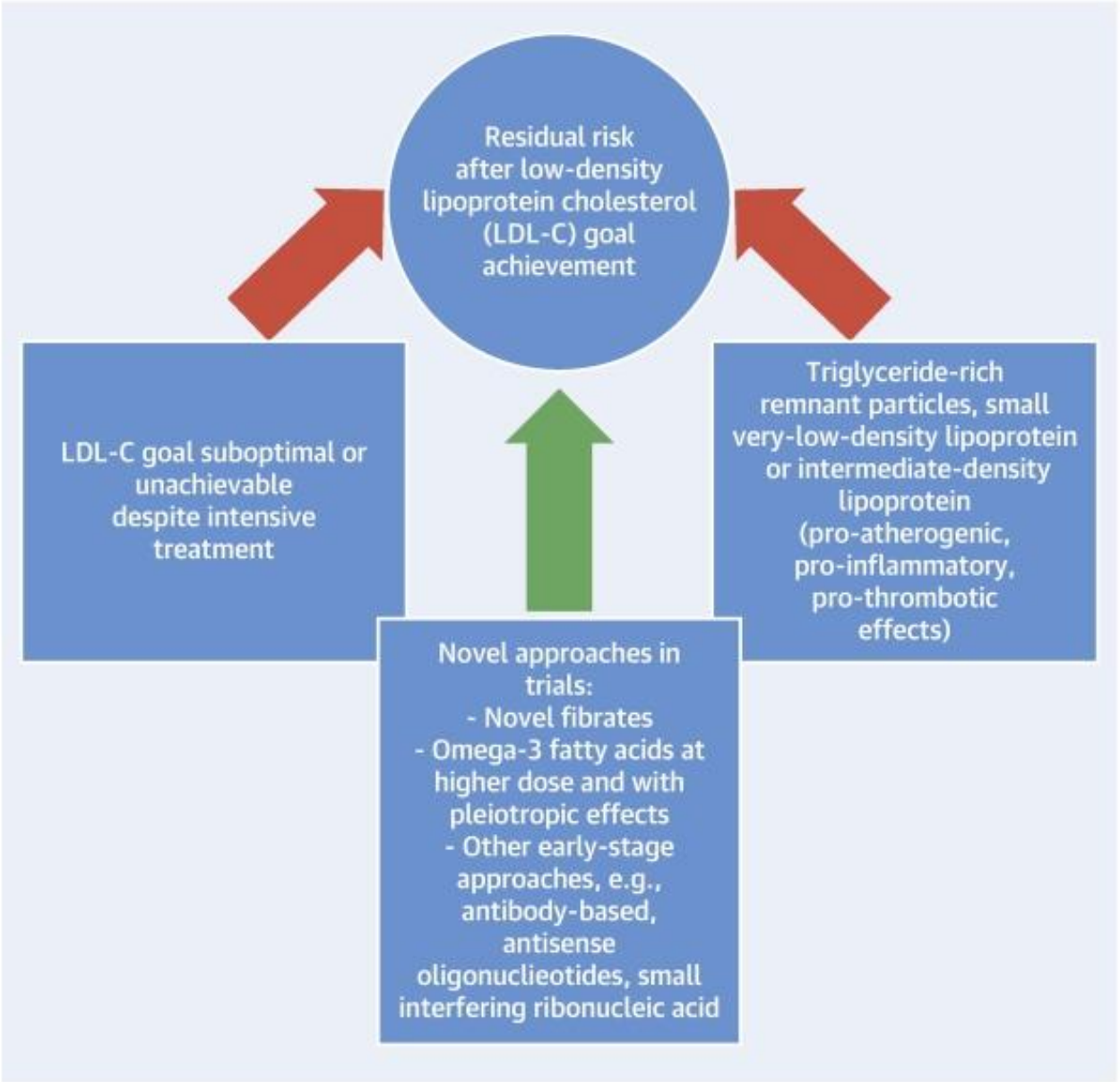


N=18,645 Japanese pts with TC ≥251 mg/dL prior to baseline statin Rx. Baseline TG=153 mg/dL.
Statin up-titrated to 20 mg pravastatin or 10 mg simvastatin for LDL-C control.

*Primary endpoint: Sudden cardiac death, fatal and non-fatal MI, unstable angina pectoris, angioplasty, stenting, or coronary artery bypass graft.

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

CENTRAL ILLUSTRATION: Promising Therapies for Hypertriglyceridemia



Ganda, O.P. et al. J Am Coll Cardiol. 2018;72(3):330–43.

University of Copenhagen & Copenhagen University Hospital

Central Role of Triglyceride-rich Lipoproteins in CVD Residual Risk Beyond Statin Therapy

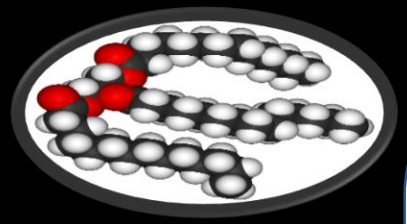
Børge G Nordestgaard

Professor, Chief Physician, MD, DMSc

Conflict of Interest Disclosure: the Danish tax payer

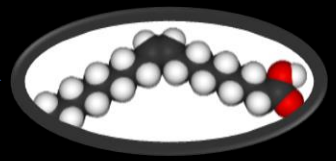
Consultancies or talks sponsored by AstraZeneca, Sanofi, Regeneron, Ionis, Akcea, Amgen, Kowa, Denka Seiken, Amarin

From triglyceride-rich lipoproteins to disease



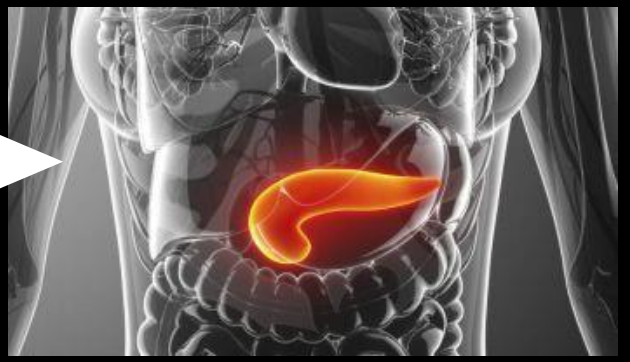
Triglycerides

Lipoprotein lipase



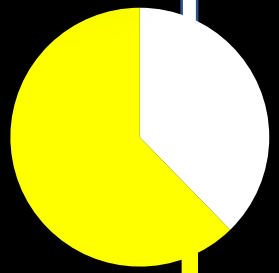
Free fatty acids

Inflammation

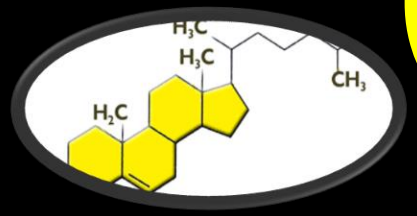


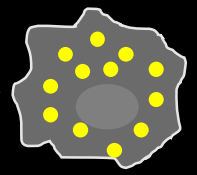
Acute pancreatis

Remnant

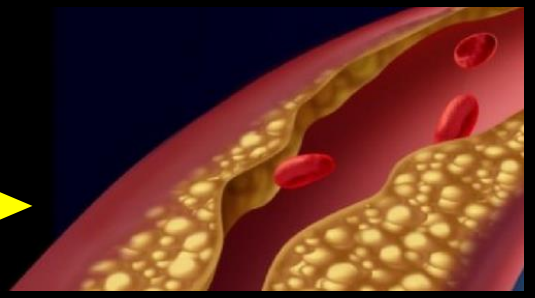


Cholesterol





Foam cell

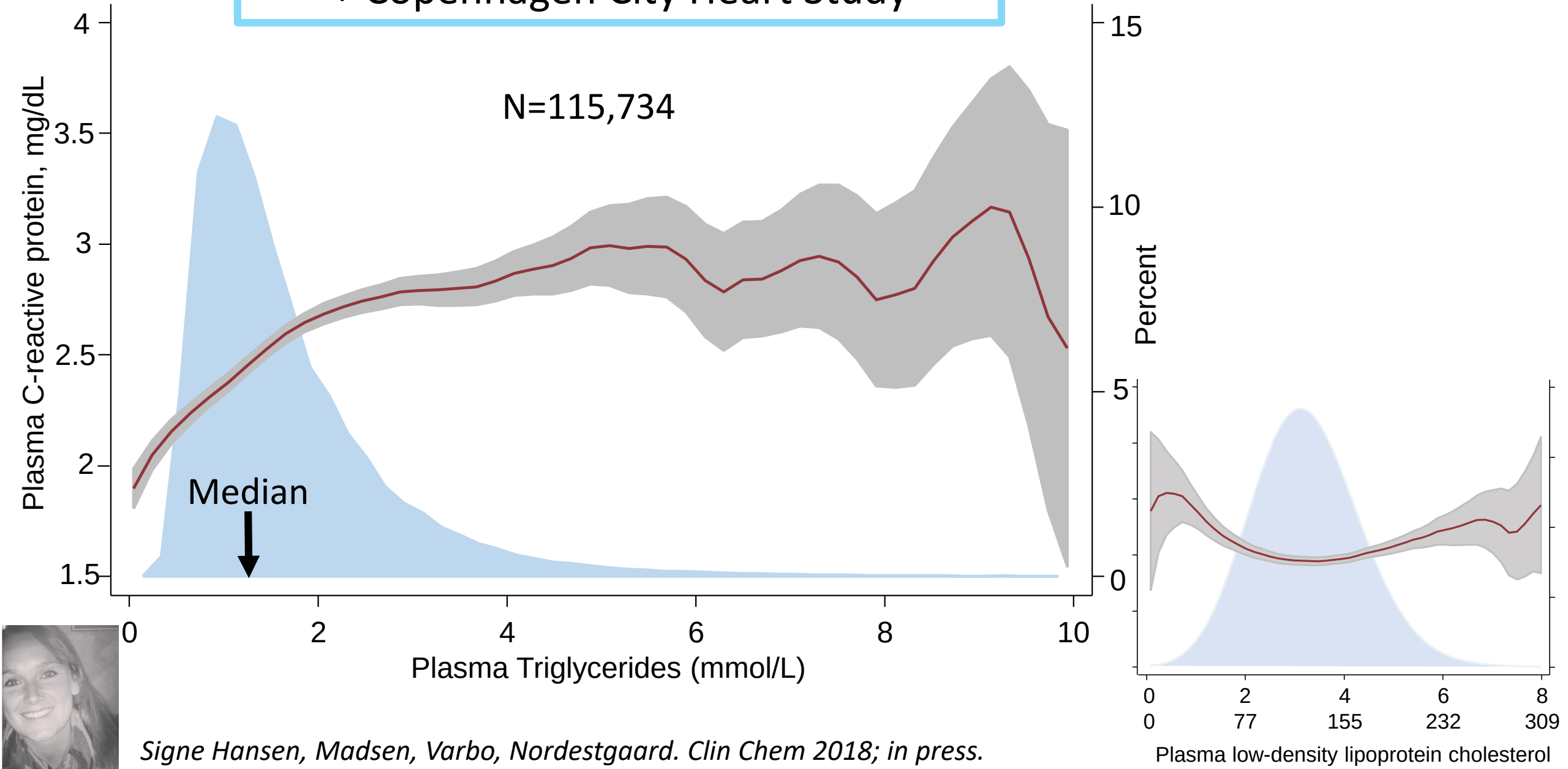


Atherosclerosis

Myocardial infarction

Nordestgaard 2018

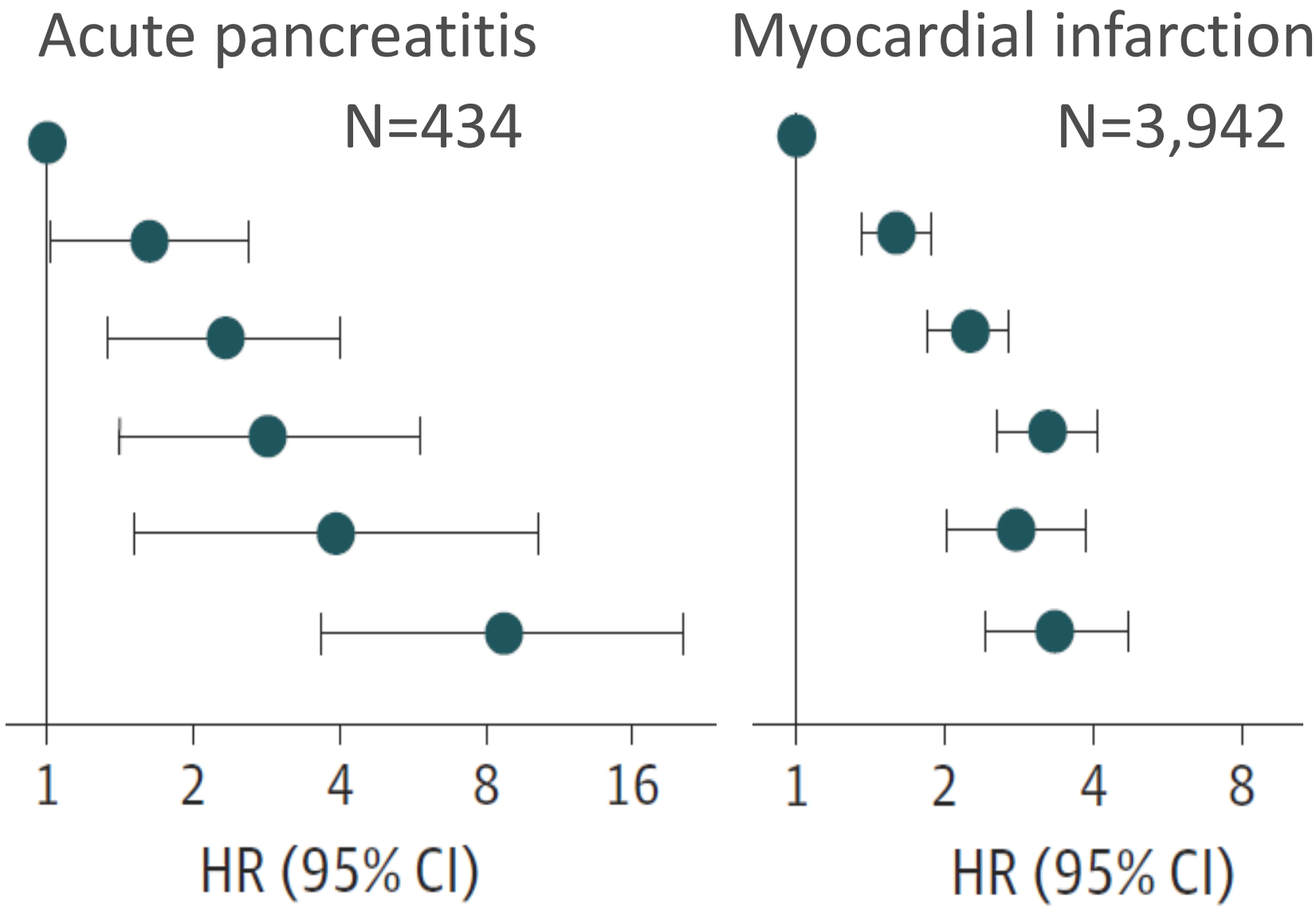
Copenhagen General Population Study + Copenhagen City Heart Study



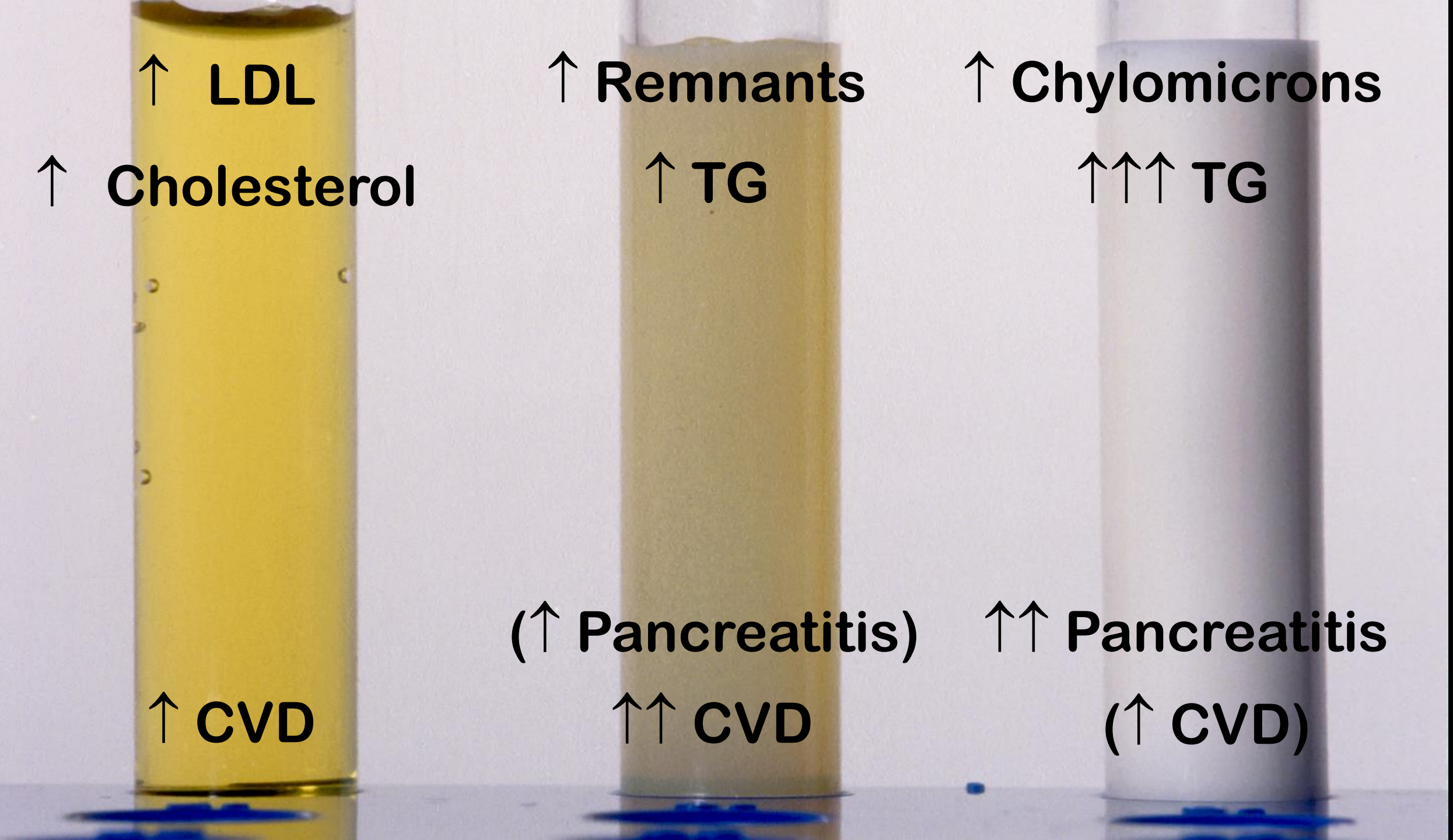
Signe Hansen, Madsen, Varbo, Nordestgaard. Clin Chem 2018; in press.

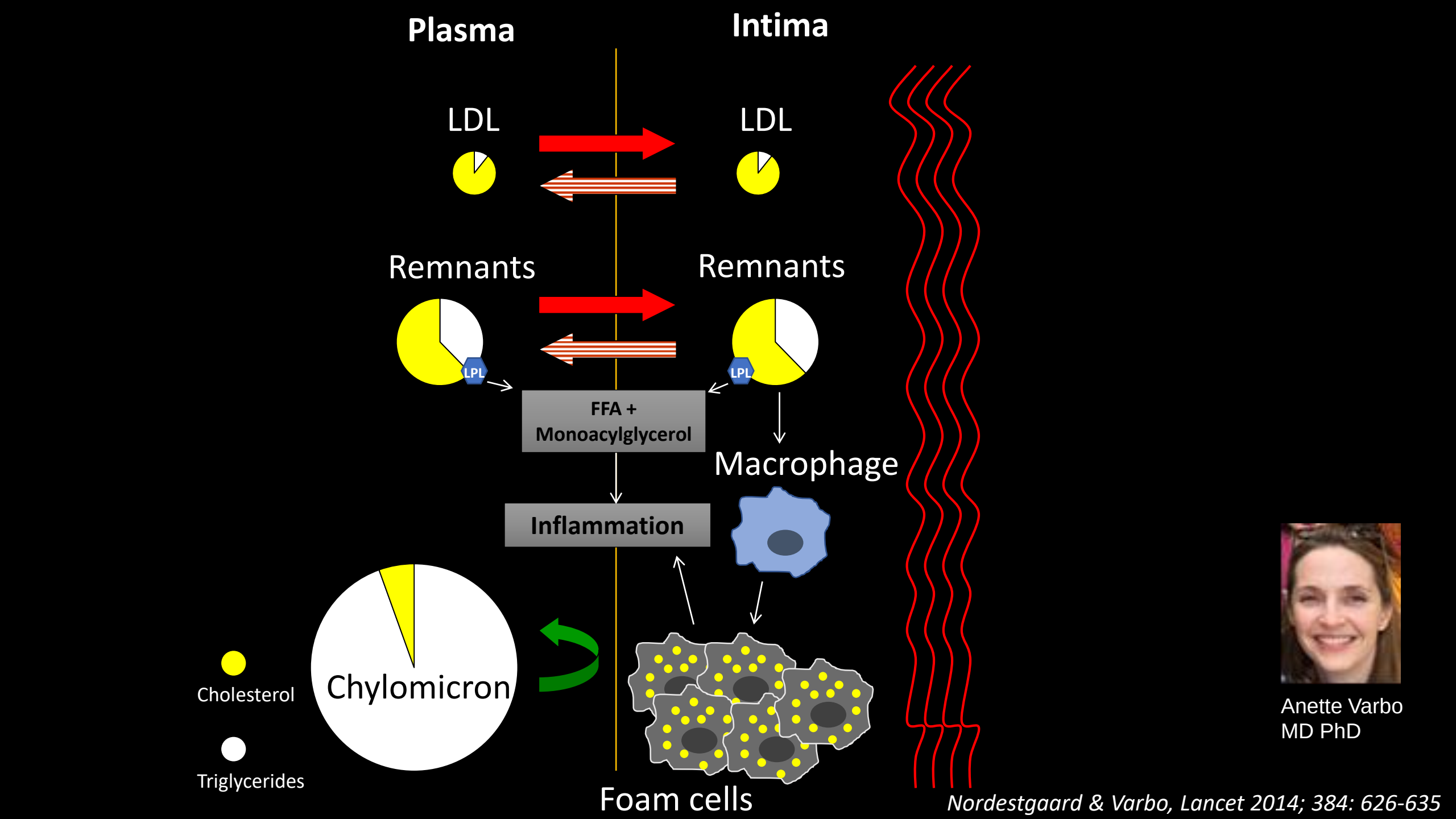
116,550 individuals from the Copenhagen General Population Study

Triglycerides, mg/dL (mmol/L)
<89 (<1.00)
89-176 (1.00-1.99)
177-265 (2.00-2.99)
266-353 (3.00-3.99)
354-442 (4.00-4.99)
≥443 (≥5.00)



Pedersen, Langsted, Nordestgaard JAMA Intern Med 2016; 176: 1834-1842


↑ LDL
↑ Cholesterol
↑ CVD
↑ Remnants
↑ TG
(↑ Pancreatitis)
↑↑ CVD
↑ Chylomicrons
↑↑↑ TG
↑↑ Pancreatitis
(↑ CVD)
Nordestgaard 2015



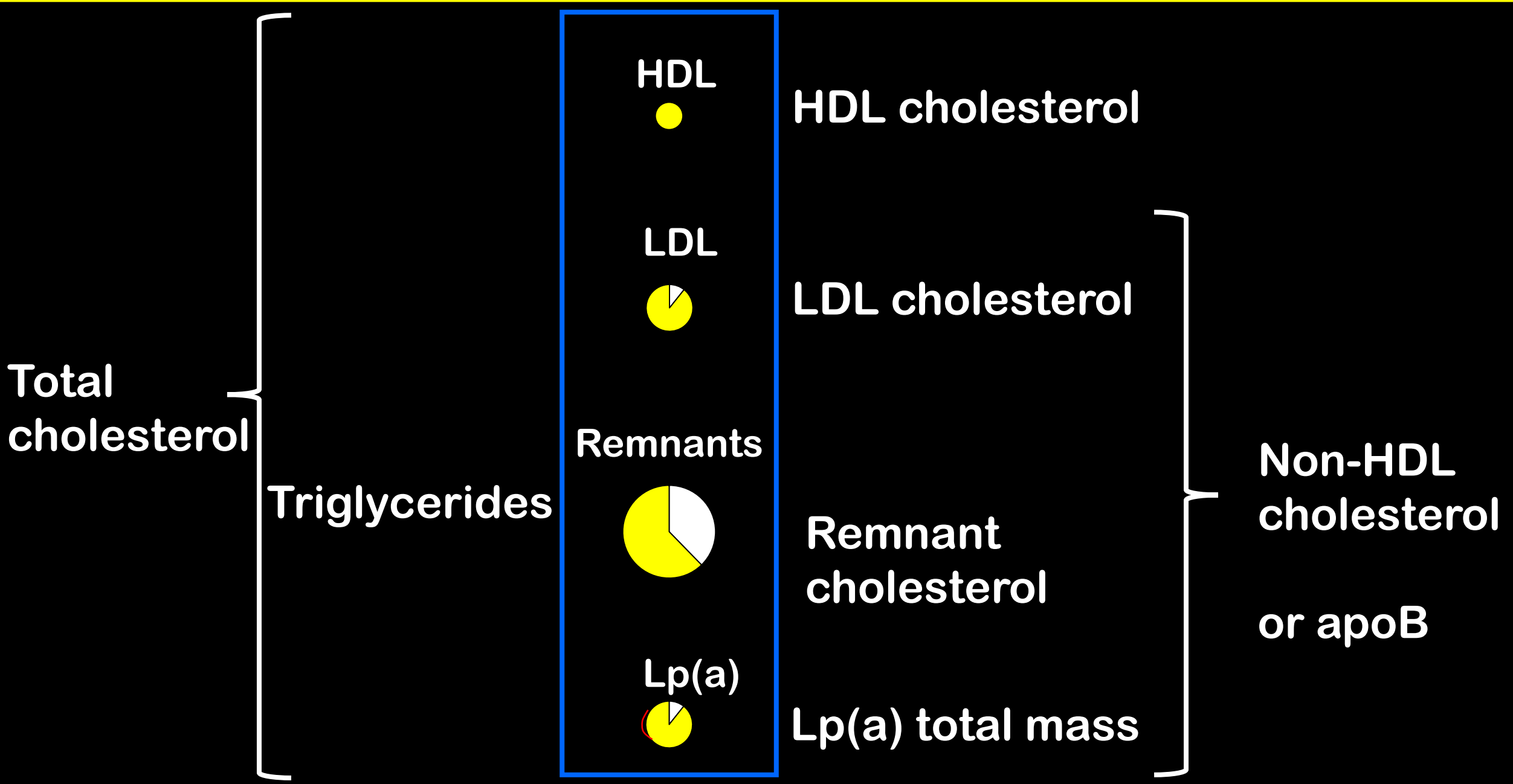
Anette Varbo
MD PhD

Nordestgaard & Varbo, Lancet 2014; 384: 626-635

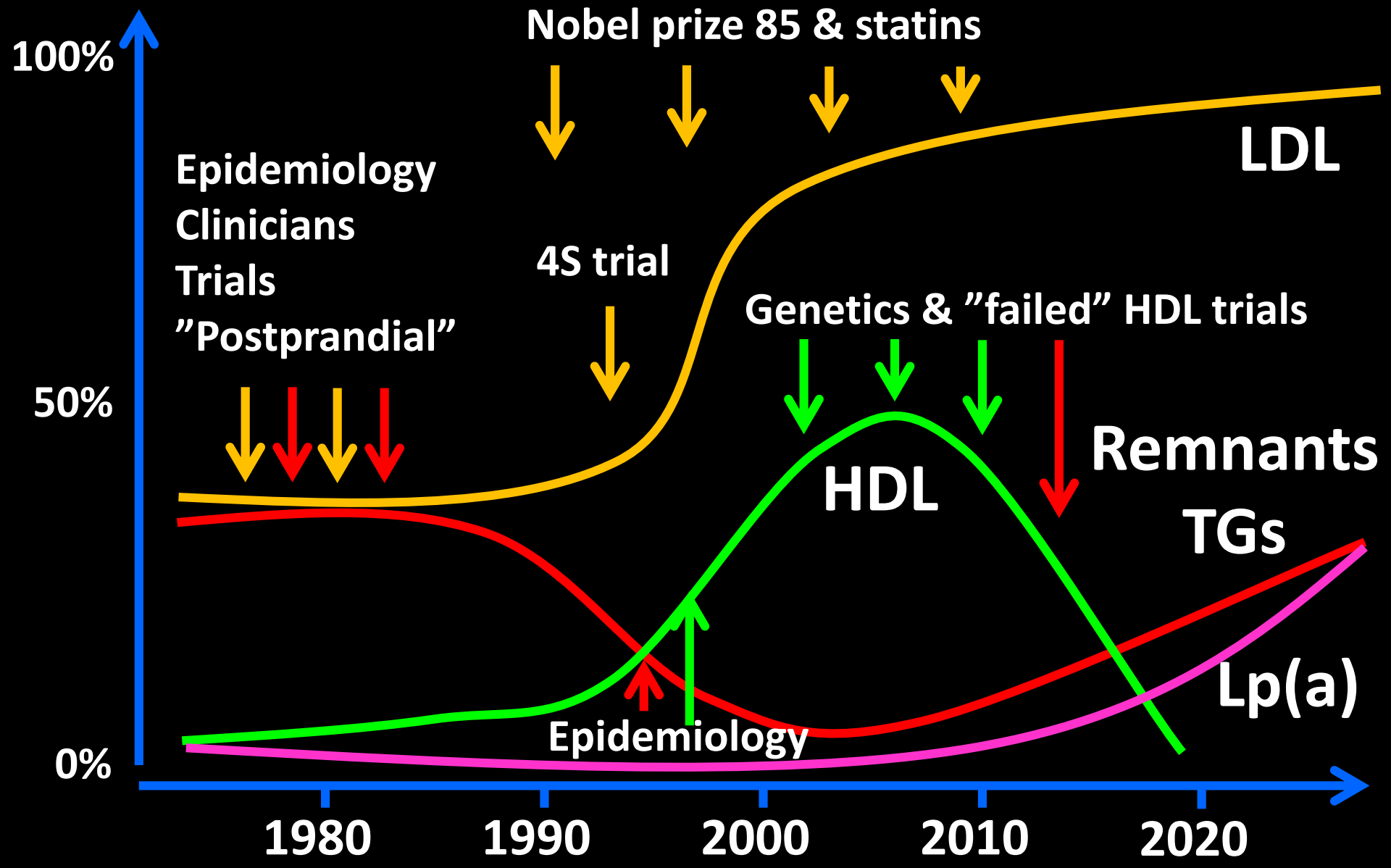
Lipids

Lipoproteins

Nordestgaard Eur Heart J 2016; 37: 1944-1958 modified

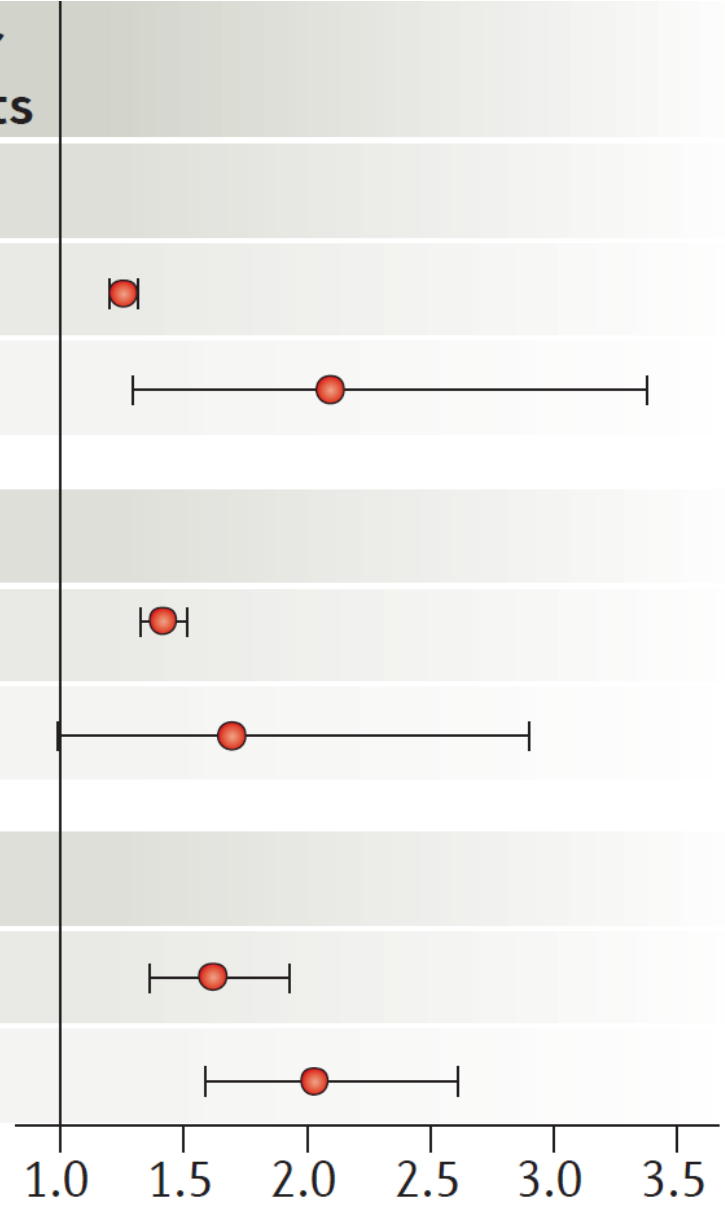


Clinical focus on lipoproteins for CVD prevention



Nordestgaard Circ Res 2016; 118: 547-563 modified

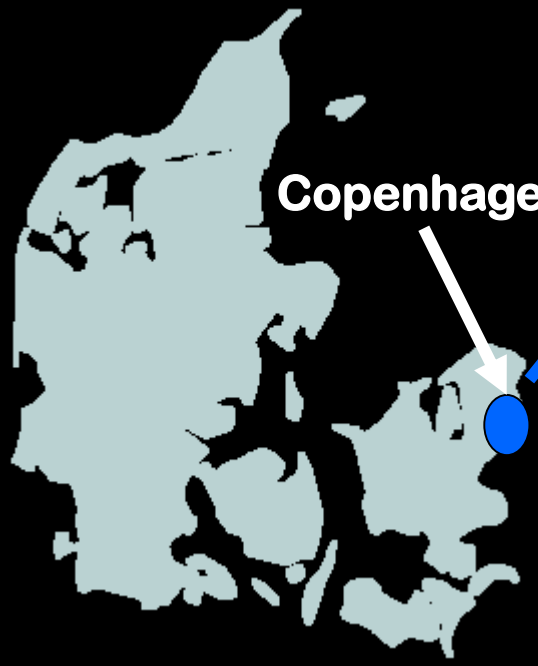
	n	Number of events
LDL cholesterol: increase of 39 mg/dl (1 mmol/l)		
Observational	108,554	2,210
Genetic (*APOB, HMGCR, LDLR, PCSK9*)	95,908	4,155
Remnant cholesterol: increase of 39 mg/dl (1 mmol/l)		
Observational	108,508	2,219
Genetic (*APOA5, GCKR, LPL, TRIB1*)	97,745	4,199
Lipoprotein(a) cholesterol: increase of 39 mg/dl (1 mmol/l)		
Observational	108,550	2,210
Genetic (*LPA*)	103,715	4,425



Copenhagen General Population Study

Nordestgaard, Nicholls, Langsted, Ray & Tybjærg-Hansen. Nat Rev Cardiol 2018; 15: 261-272

Copenhagen City Heart Study (CCHS)



N=15,000

41 yrs follow-up

No losses to follow-up
1977-2018

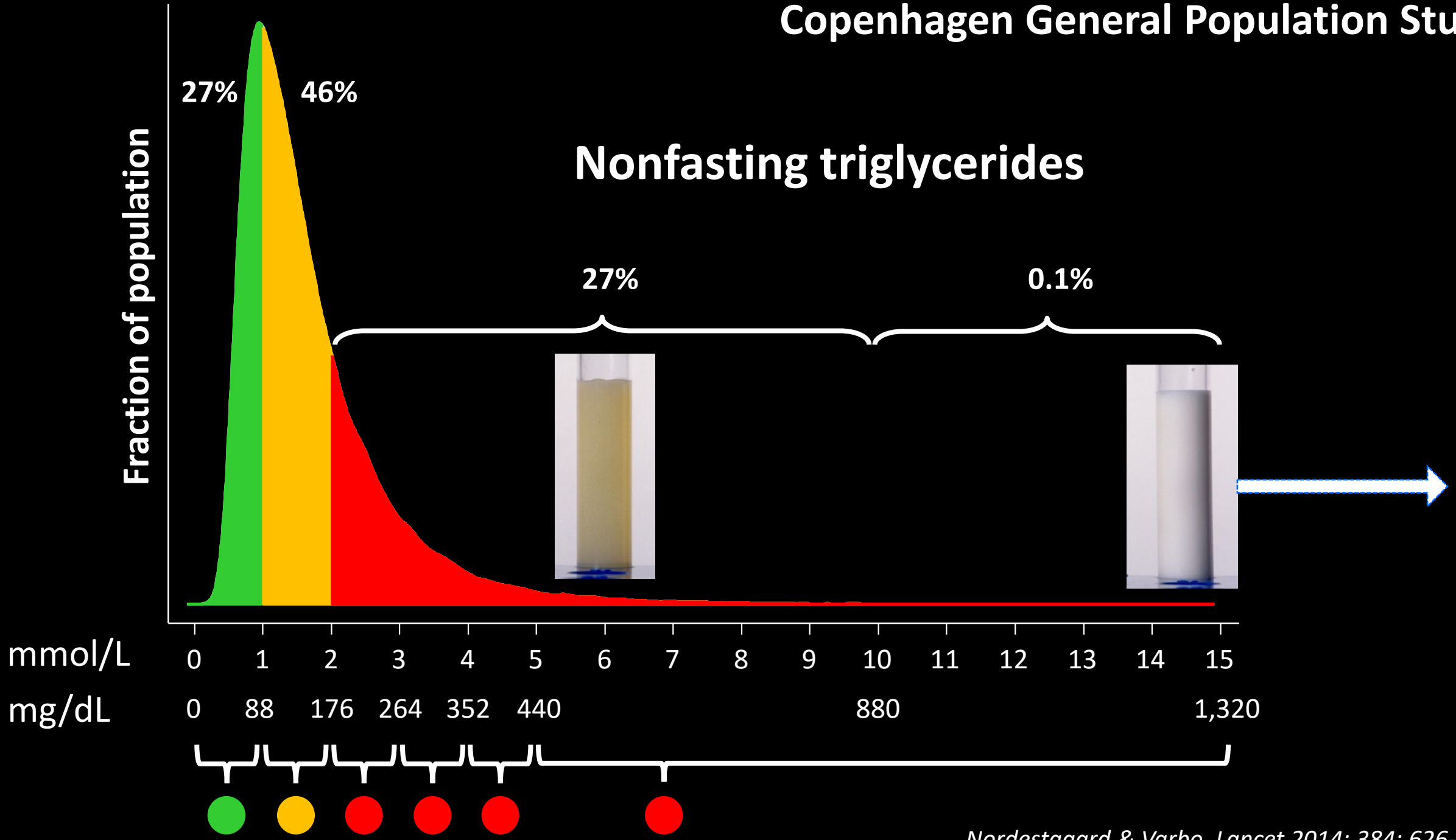
N=110,000+

15 yrs follow-up

Copenhagen General Population Study (CGPS)

Nordestgaard 2018

Copenhagen General Population Study

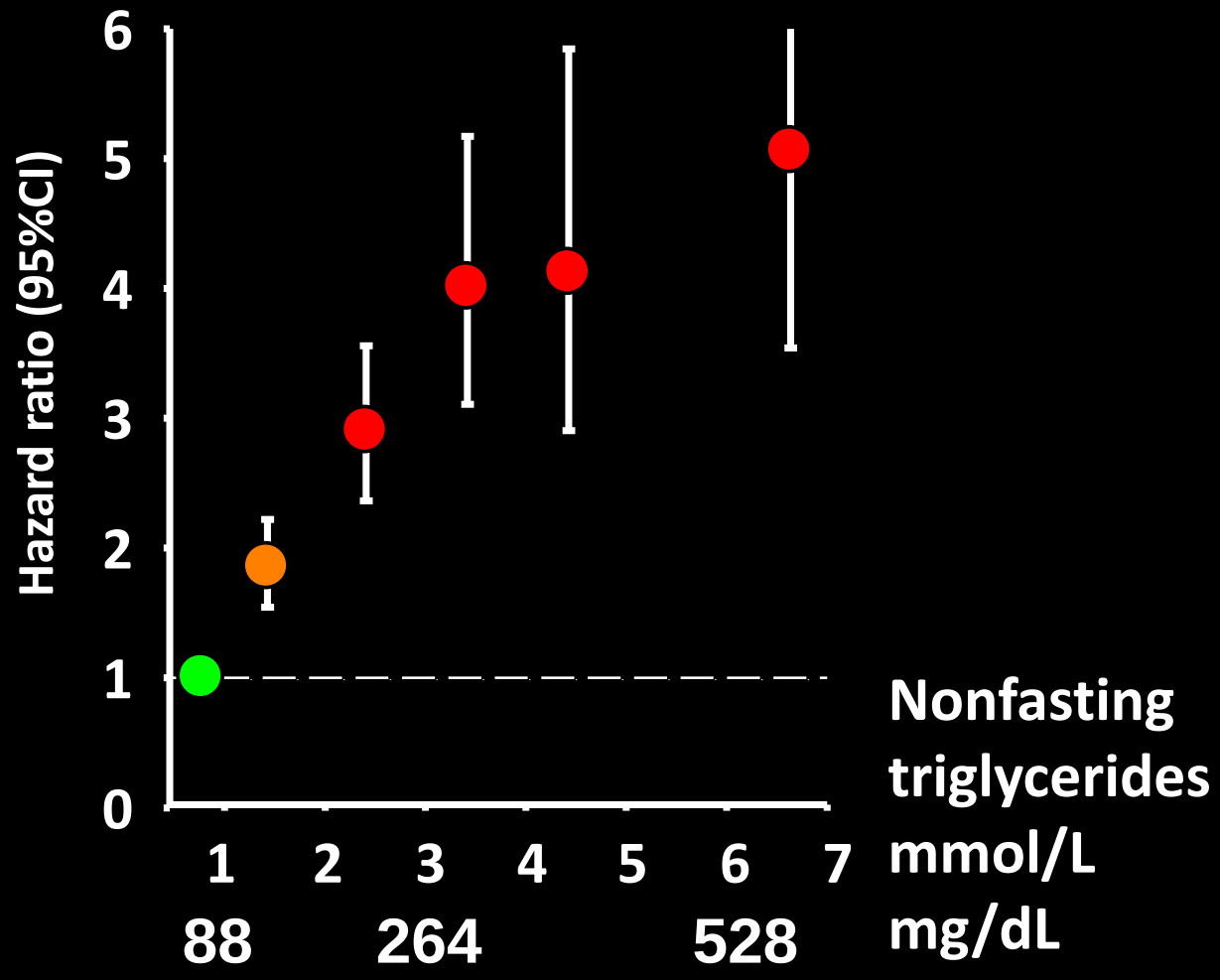


Nordestgaard & Varbo, Lancet 2014; 384: 626-635

Copenhagen City Heart Study and Copenhagen General Population Study

Myocardial infarction

N=96,394 (Events = 3,287)

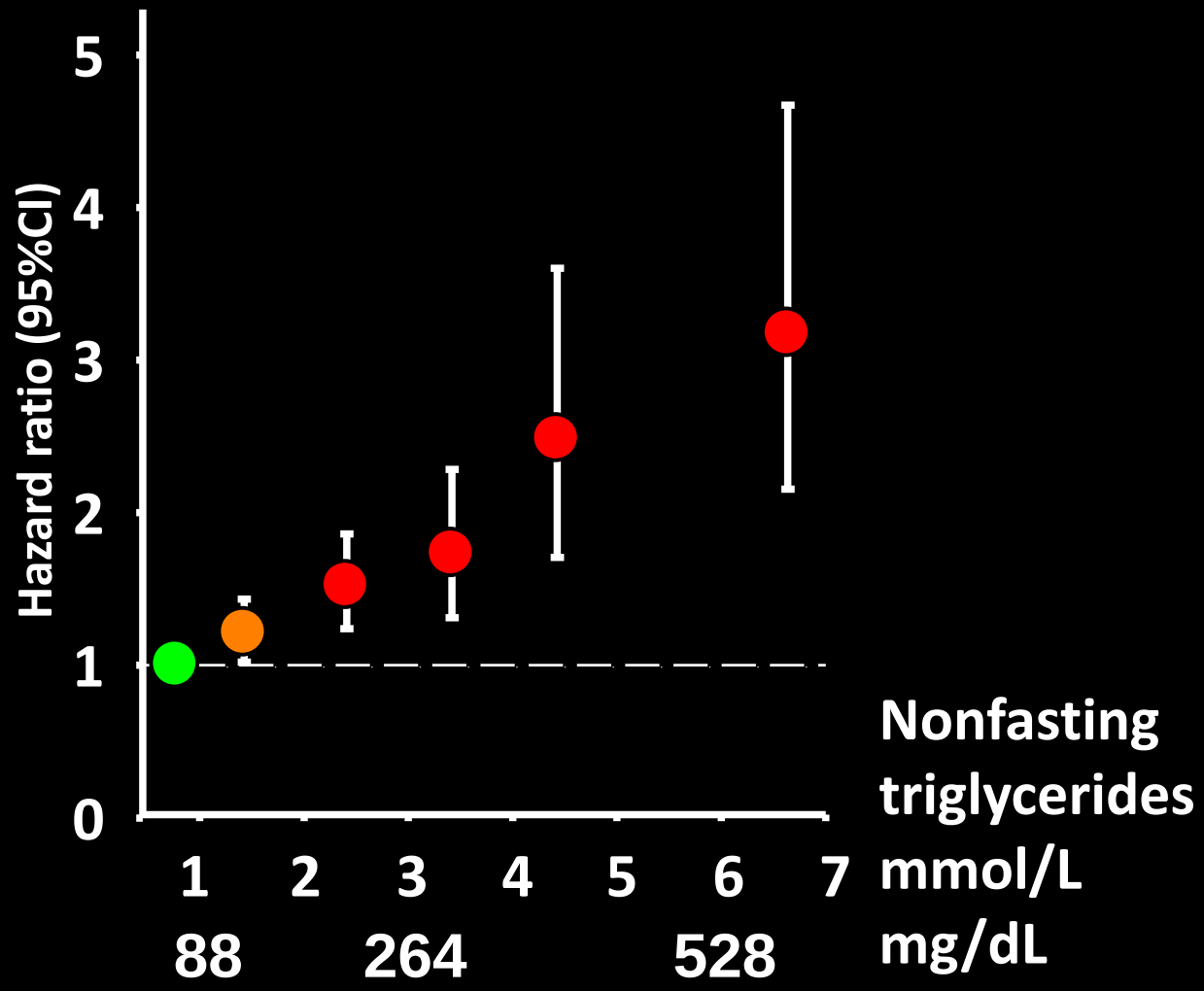


Nordestgaard & Varbo, Lancet 2014; 384: 626-635

Copenhagen City Heart Study and Copenhagen General Population Study

Ischemic stroke

N=97,442 (Events = 2,994)

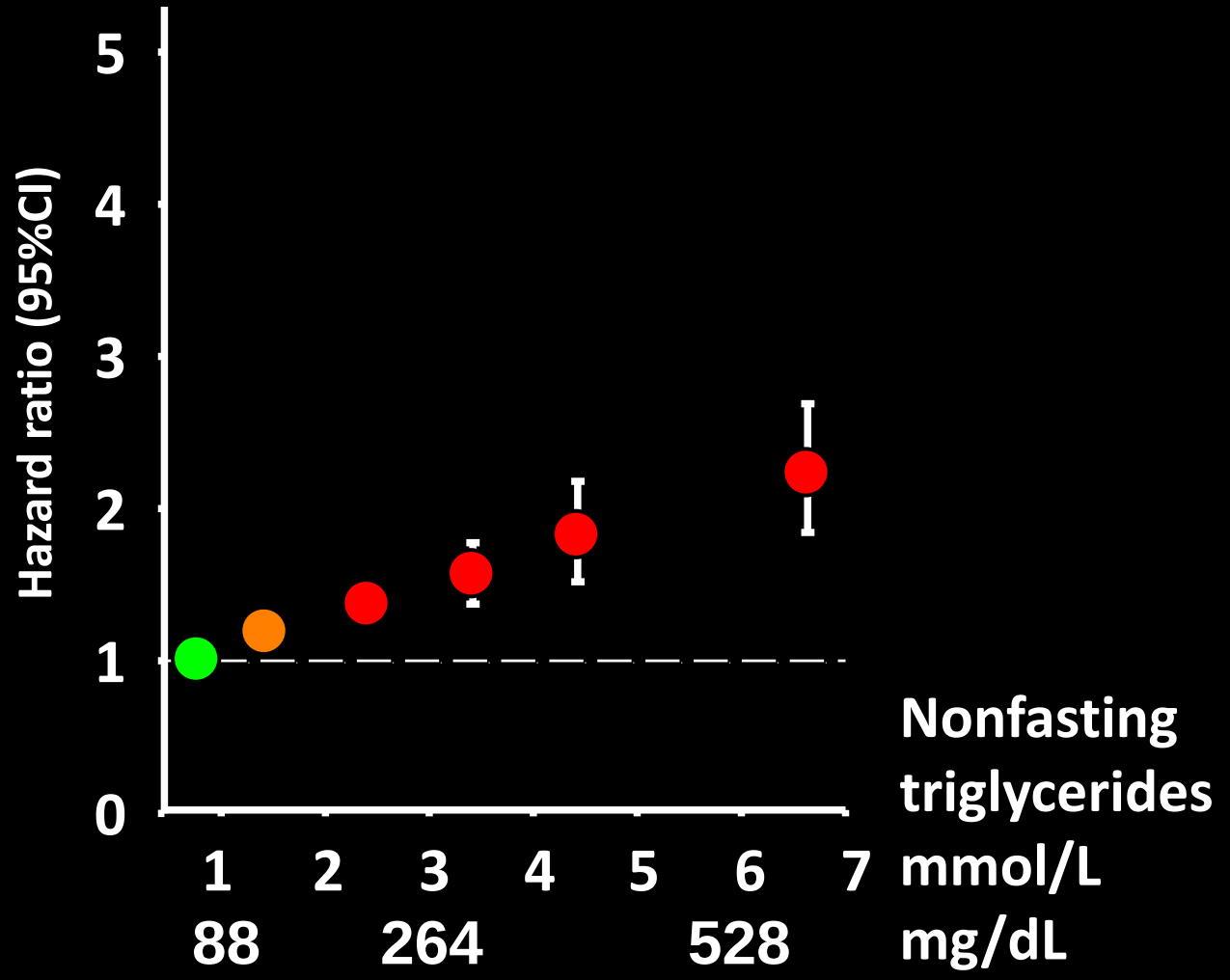


Nordestgaard & Varbo, Lancet 2014; 384: 626-635

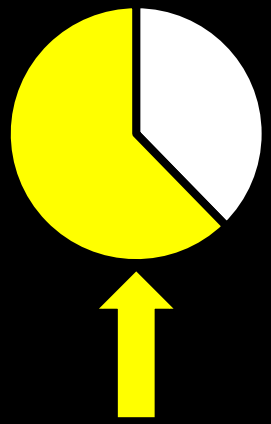
Copenhagen City Heart Study and Copenhagen General Population Study

All-cause mortality

N=98,515 (Events = 14,547)



Nordestgaard & Varbo, Lancet 2014; 384: 626-635



Remnant cholesterol

(= cholesterol content of triglyceride-rich lipoproteins)

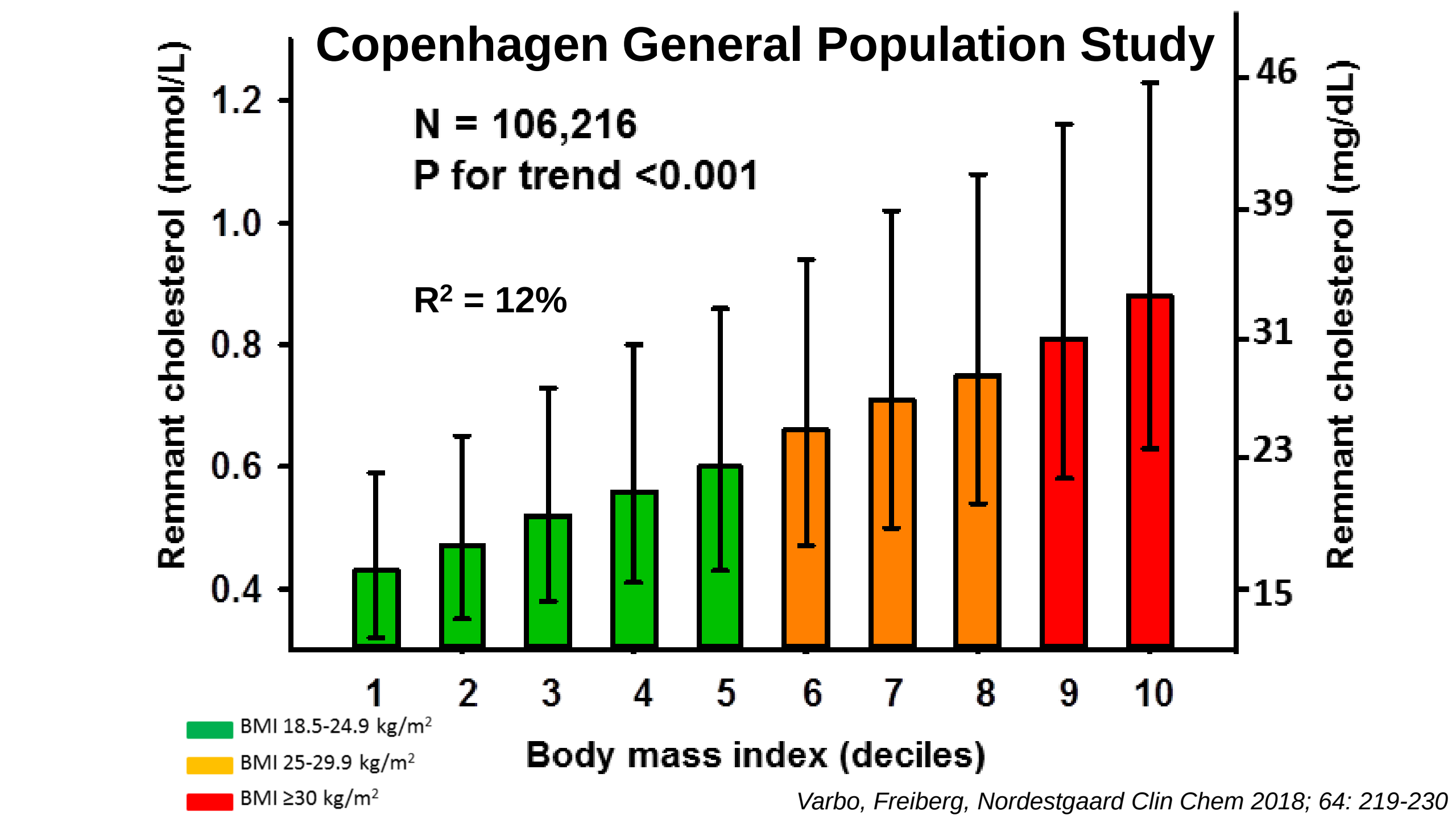
Calculated: total cholesterol minus LDL-C minus HDL-C

Measured: direct automated assay available

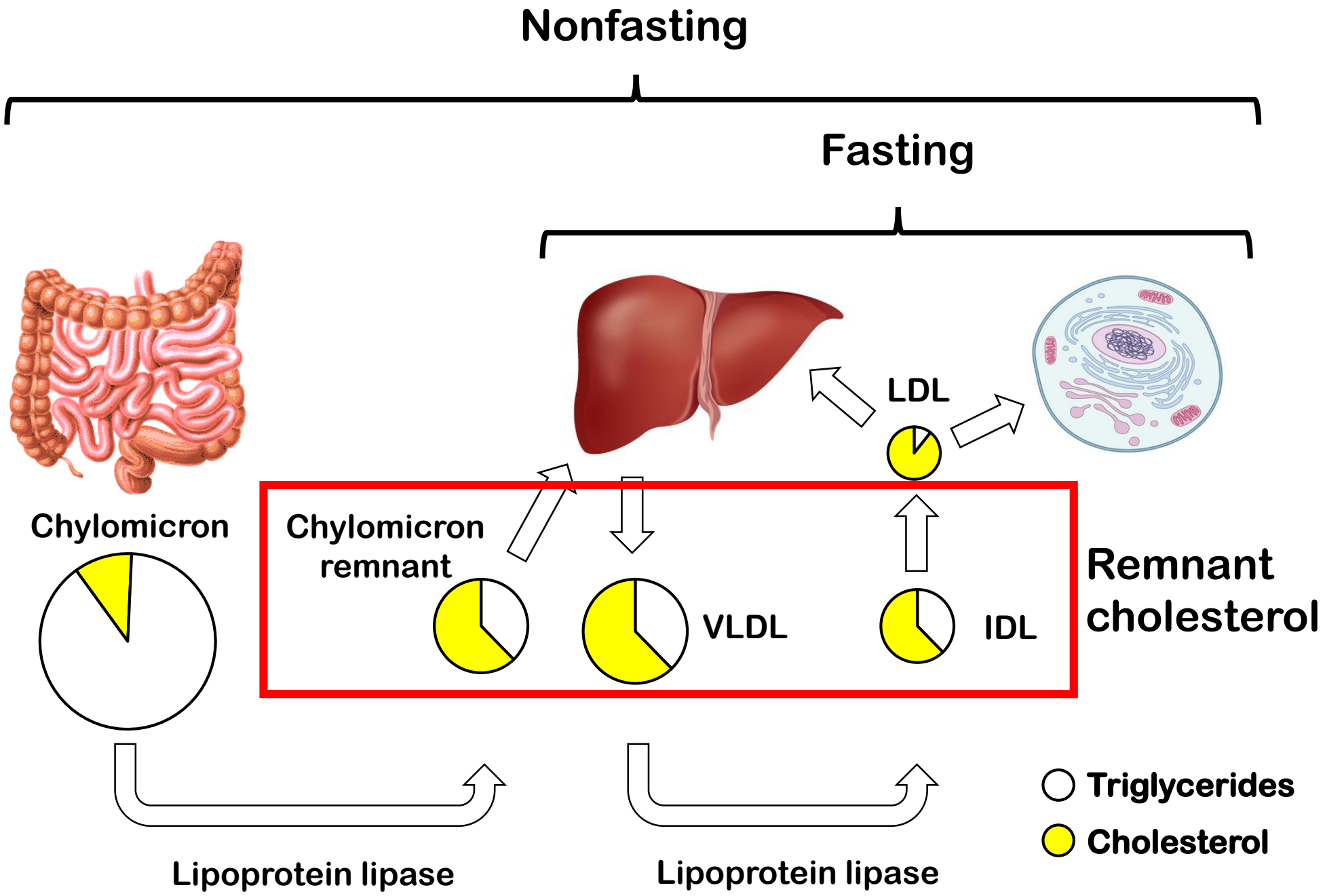
Nordestgaard 2018

Nordestgaard 2018

Obesity ↔ diabetes ↔ metabolic syndrome ↔ remnant lipoproteins



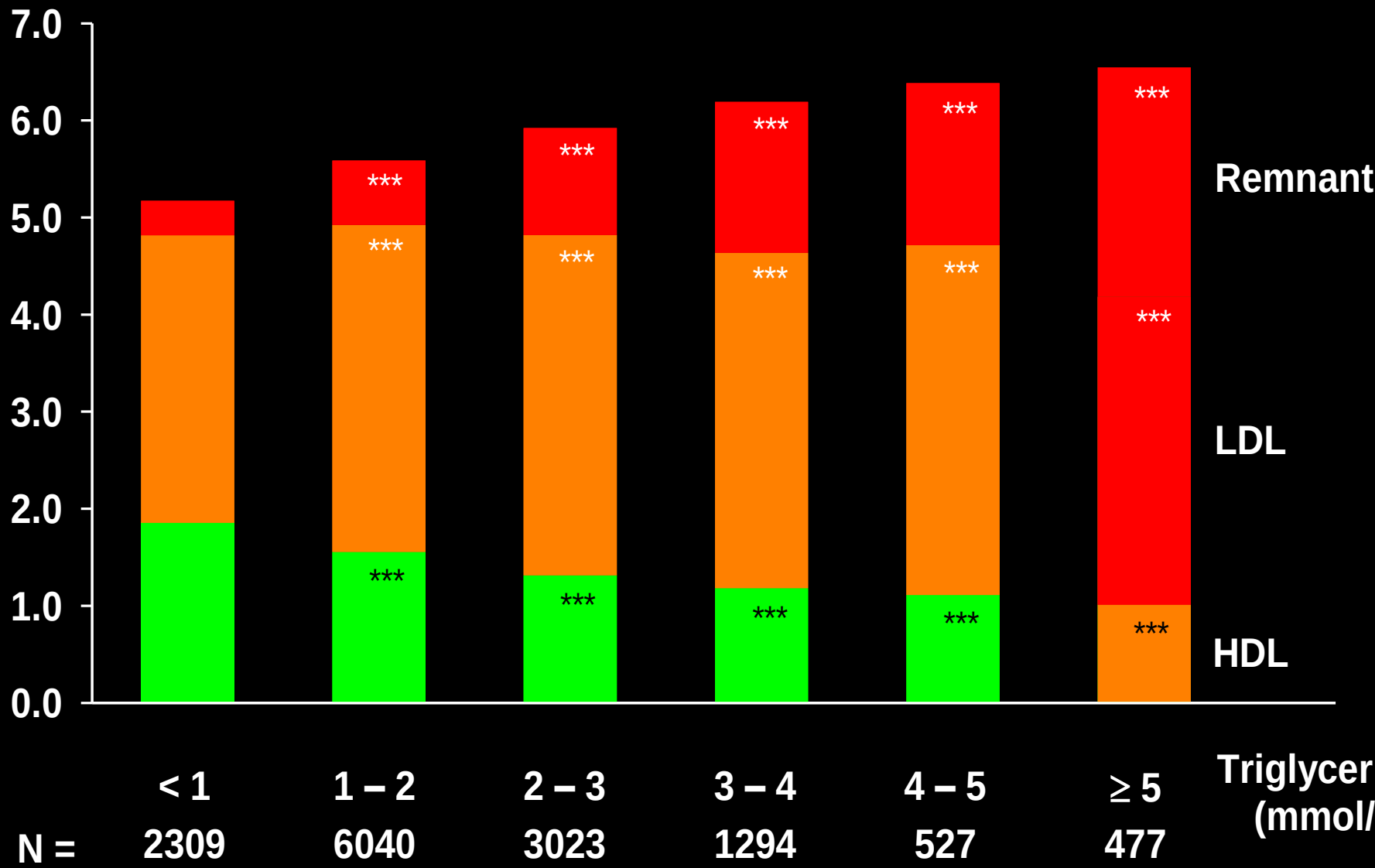
Varbo, Freiberg, Nordestgaard Clin Chem 2018; 64: 219-230



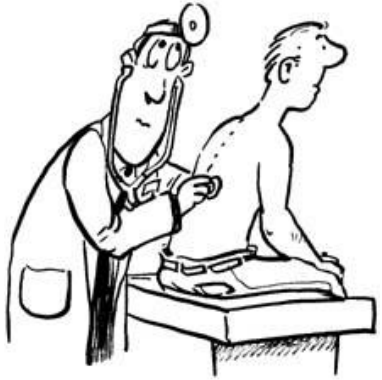
Nordestgaard JACC 2017; 70: 1637-46

Lipoprotein cholesterol, mmol/ L

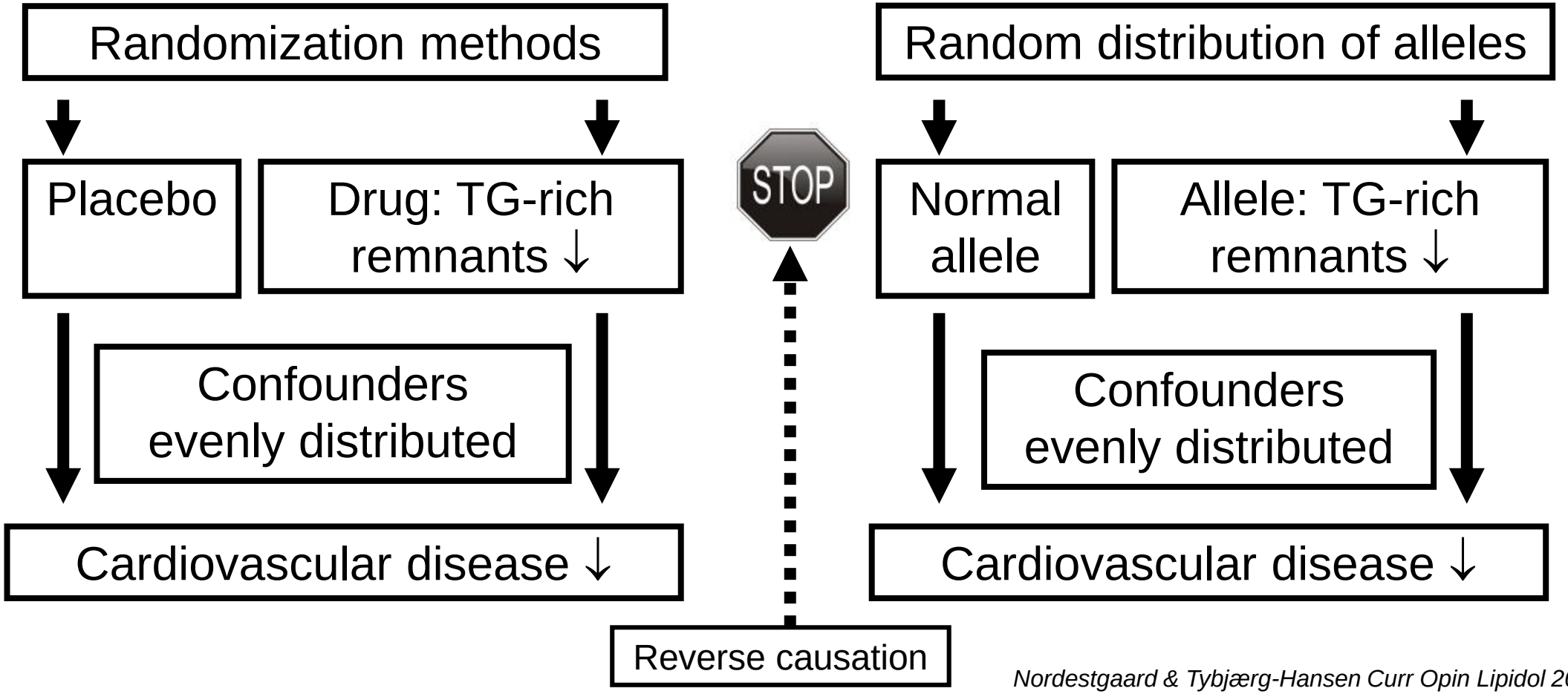
Copenhagen General Population Study



Freiberg, Nordestgaard 2011



Randomized trial vs. Mendelian randomization



Nordestgaard & Tybjærg-Hansen Curr Opin Lipidol 2011;22:113-22

Remnant cholesterol

mg/dL	mmol/L
<15	<0.4
15-23	0.4-0.6
23-27	0.6-0.7
27-42	0.7-1.1
>42	>1.1

HDL cholesterol

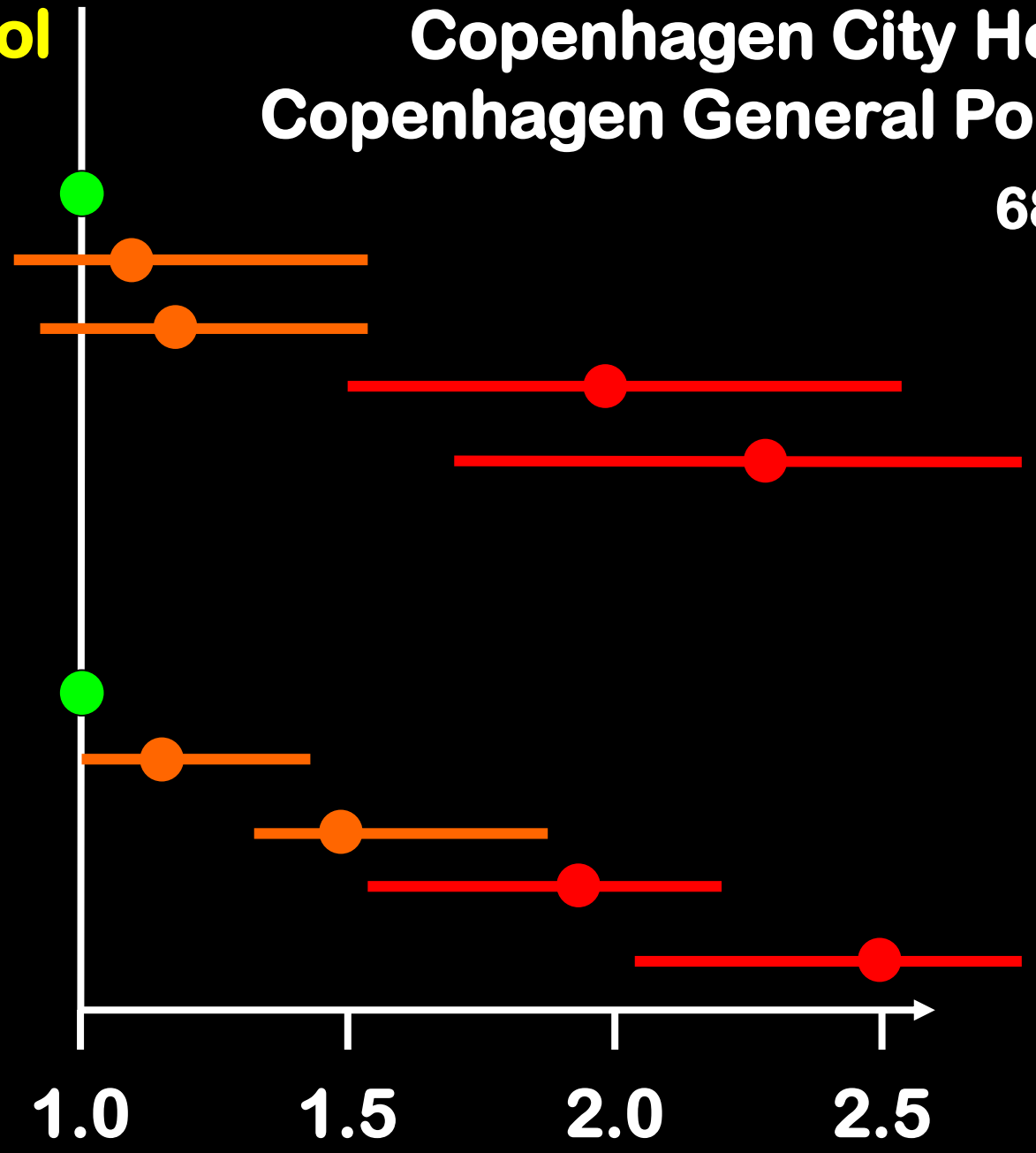
mg/dL	mmol/L
>77	>2.0
66-77	1.7-2.0
54-66	1.4-1.7
46-54	1.2-1.4
<46	<1.2

Quintiles

Copenhagen City Heart Study and
Copenhagen General Population Study

68,000 Individuals

12,000 IHD



Varbo et al. JACC 2013;61:427-436

Copenhagen City Heart Study and
Copenhagen General Population Study

68,000 Individuals

12,000 IHD

Remnant cholesterol↑

Plasma: observational

Genetic: causal

Remnant↑ / HDL-C↓

Plasma

Genetic

HDL cholesterol↓

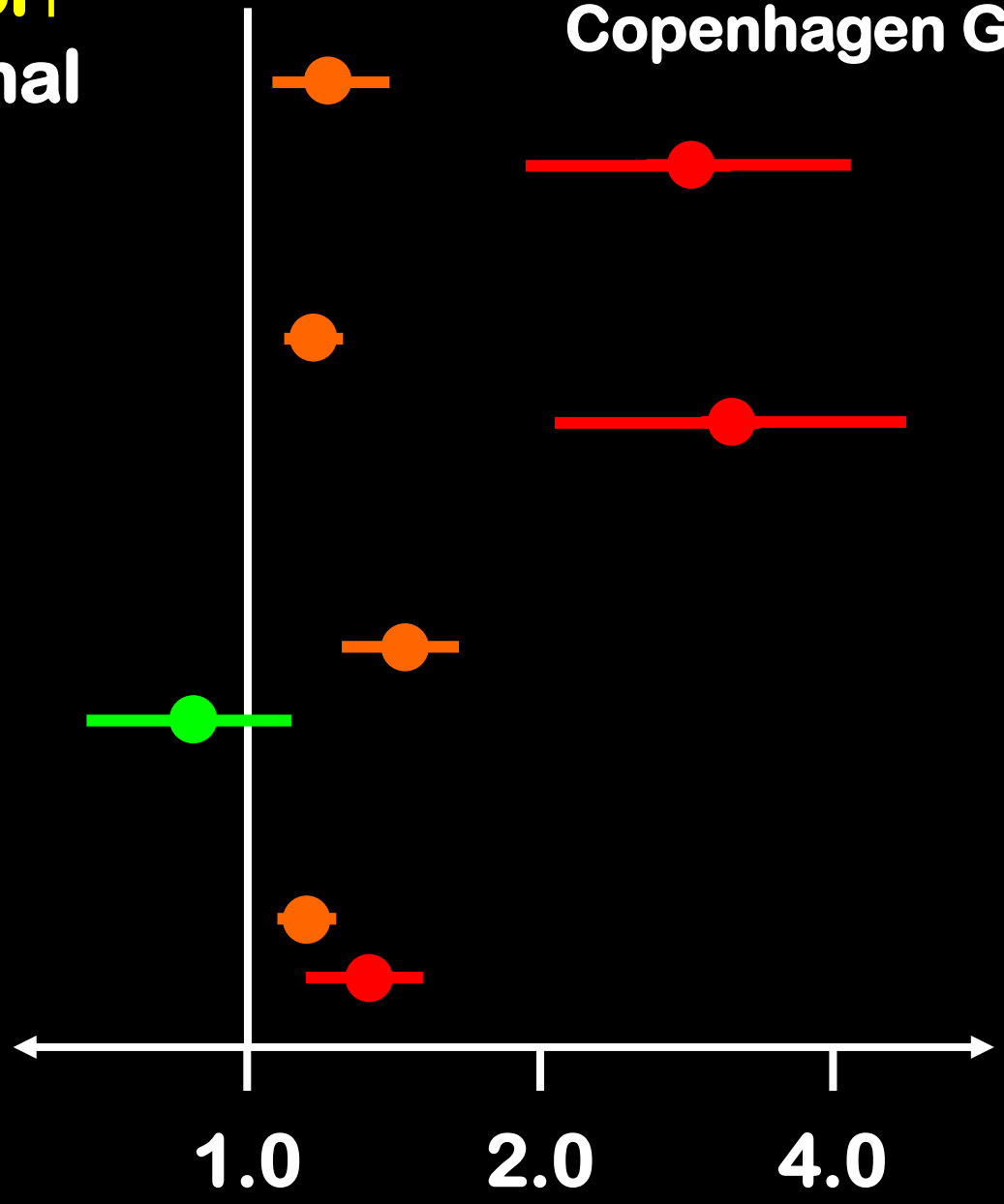
Plasma

Genetic

LDL cholesterol↑

Plasma

Genetic



Selected genetic variants without pleotropic effects

Varbo et al. JACC 2013;61:427-436

Hazard ratio for ischemic heart disease per 39 mg/dL = 1 mmol/L change

Common variants associated with plasma triglycerides and risk for coronary artery disease

NATURE GENETICS VOLUME 45 | NUMBER 11 | NOVEMBER 2013

Elevated Remnant Cholesterol Causes Both Low-Grade Inflammation and Ischemic Heart Disease, Whereas Elevated Low-Density Lipoprotein Cholesterol Causes Ischemic Heart Disease Without Inflammation *Circulation.* 2013

Anette Varbo, Marianne Benn, Anne Tybjærg-Hansen and Børge G. Nordestgaard

Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction

European Heart Journal (2013)

Anders Berg Jørgensen[1], Ruth Frikke-Schmidt[1,2], Anders Sode West[1], Peer Grande[3], Børge G. Nordestgaard[2,4,5], and Anne Tybjærg-Hansen[1,2,5*]

NEJM 2014 ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3* and Risk of Ischemic Vascular Disease

Anders Berg Jørgensen, M.D., Ph.D., Ruth Frikke-Schmidt, M.D., D.M.Sc., Børge G. Nordestgaard, M.D., D.M.Sc., and Anne Tybjærg-Hansen, M.D., D.M.Sc.

NEJM 2016 ORIGINAL ARTICLE

Coding Variation in *ANGPTL4*, *LPL*, and *SVEP1* and the Risk of Coronary Disease

Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators*

Variants with large effects on blood lipids and the role of cholesterol and triglycerides in coronary disease

Anna Helgadottir[1,2], Solveig Gretarsdottir[1], Gudmar Thorleifsson[1], Eirikur Hjartarson[1], Asgeir Sigurdsson[1],

NATURE GENETICS VOLUME 48 | NUMBER 6 | JUNE 2016

JAMA | Original Investigation

Association of Rare and Common Variation in the Lipoprotein Lipase Gene With Coronary Artery Disease

Amit V. Khera, MD; Hong-Hee Won, PhD; Gina M. Peloso, PhD; Colm O'Dushlaine, PhD; Dajiang Liu, PhD;

2017

Other genetic studies with same conclusion:

TG-rich remnants cause cardiovascular disease

- independent of LDL-C and HDL-C

NEJM 2014 ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3*, Triglycerides, and Coronary Disease

The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute*

NEJM 2016 ORIGINAL ARTICLE

Inactivating Variants in *ANGPTL4* and Risk of Coronary Artery Disease

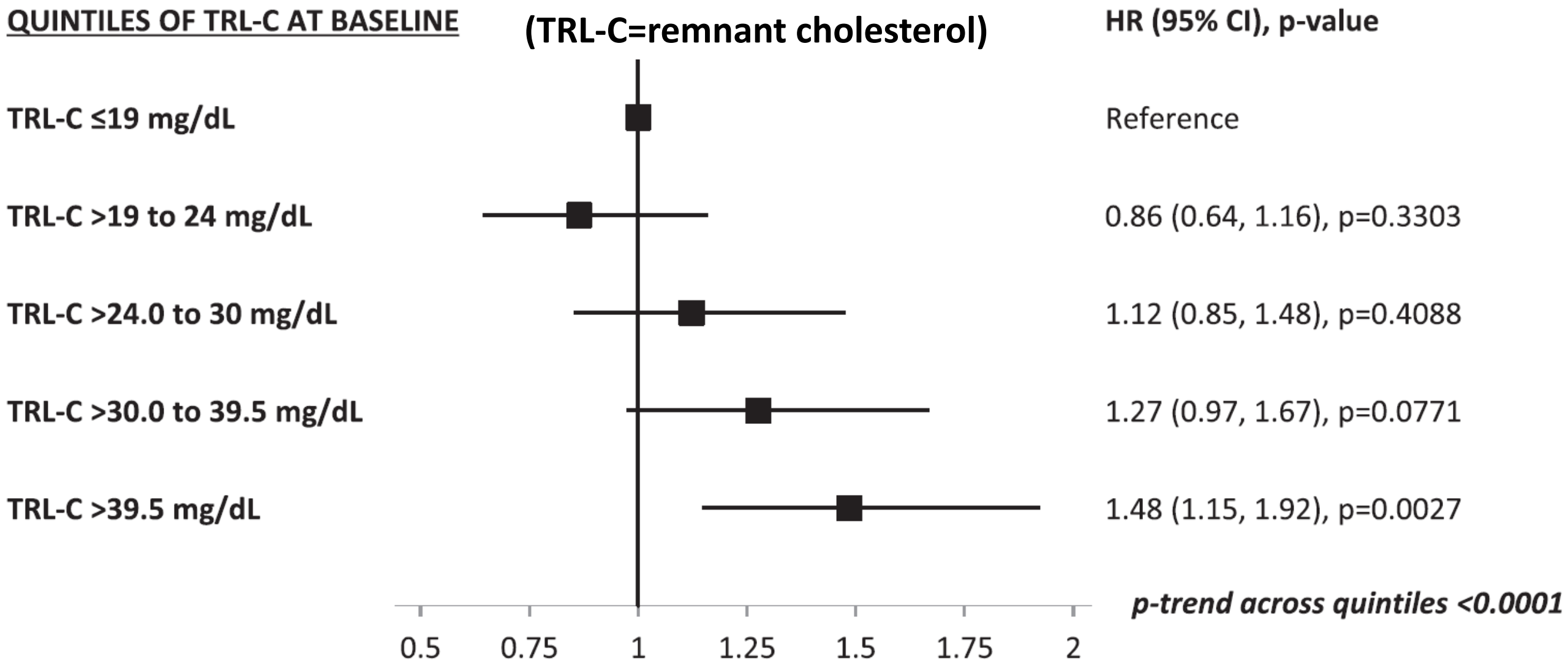
Frederick E. Dewey, M.D., Viktoria Gusarova, Ph.D., Colm O'Dushlaine, Ph.D., Omri Gottesman, M.D., Jesus Trejos, M.S., Charleen Hunt, Ph.D.,

NEJM 2017 ORIGINAL ARTICLE

Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease

F.E. Dewey, V. Gusarova, R.L. Dunbar, C. O'Dushlaine, C. Schurmann, O. Gottesman, S. McCarthy, C.V. Van Hout, S. Bruse, H.M. Dansky, J.B. Leader,

TNT trial (Treating to New Targets)



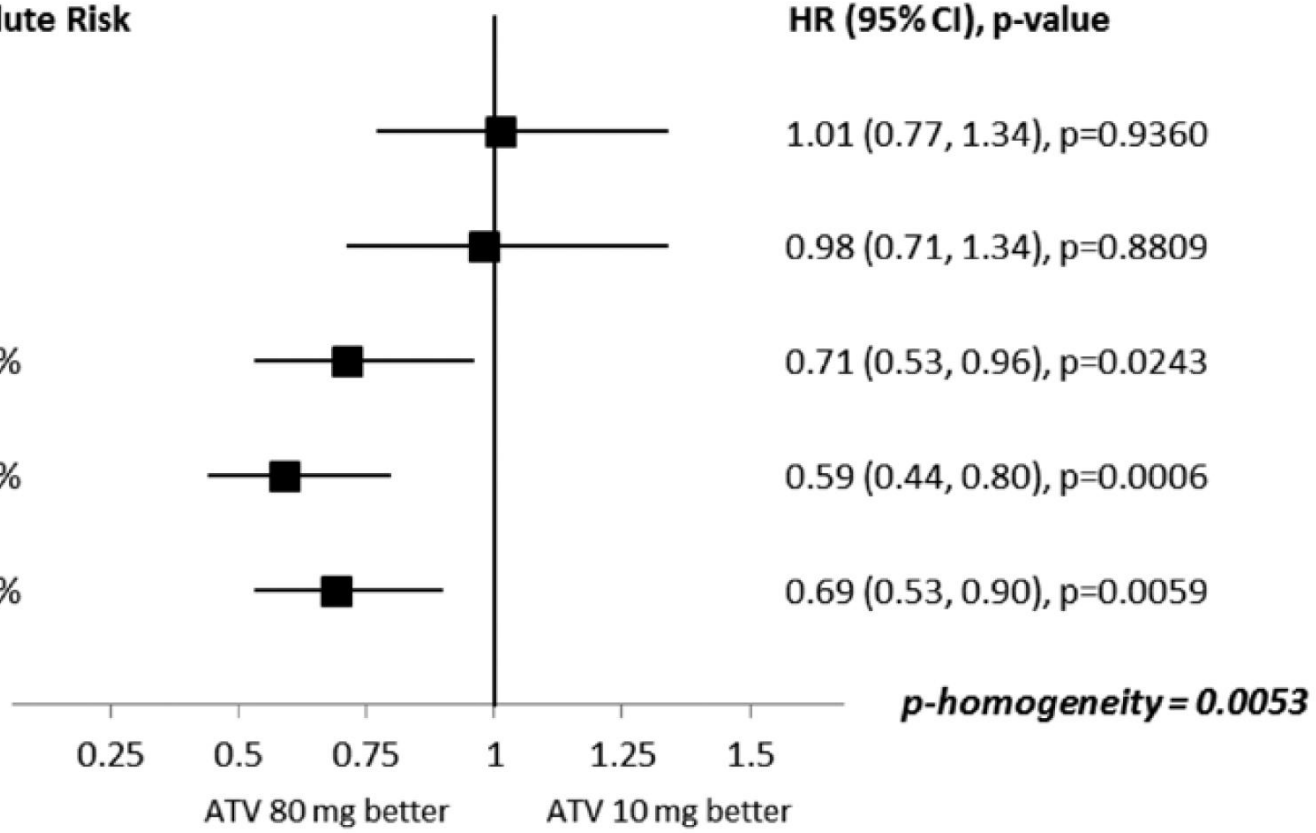
Risk of major cardiovascular events among patients receiving atorvastatin 10 mg

Vallejo-Vaz AJ…..Ray KK. Circulation 2018;138:770-781

TNT trial (Treating to New Targets)

(TRL-C=remnant cholesterol)

QUINTILES OF TRL-C AT BASELINE	5-year Event Rate (%) ATV 80mg	ATV 10mg	Absolute Risk	HR (95% CI), p-value
TRL-C ≤19 mg/dL	9.76%	9.72%		1.01 (0.77, 1.34), p=0.9360
TRL-C >19 to 24 mg/dL	8.20%	8.62%		0.98 (0.71, 1.34), p=0.8809
TRL-C >24.0 to 30 mg/dL	8.21%	10.58%	-2.38%	0.71 (0.53, 0.96), p=0.0243
TRL-C >30.0 to 39.5 mg/dL	7.36%	12.07%	-4.71%	0.59 (0.44, 0.80), p=0.0006
TRL-C >39.5 mg/dL	9.84%	13.77%	-3.92%	0.69 (0.53, 0.90), p=0.0059



Effect of atorvastatin 80 mg versus atorvastatin 10 mg on the risk of major cardiovascular events

Vallejo-Vaz AJ…..Ray KK. Circulation 2018;138:770-781

Lipids, Apolipoproteins, and Their Ratios in Relation to Cardiovascular Events With Statin Treatment

John J.P. Kastelein, MD, PhD; Wim A. van der Steeg, MD; Ingar Holme, PhD;

Circulation. 2008;117:3002-3009.

Impact of Triglyceride Levels Beyond Low-Density Lipoprotein Cholesterol After Acute Coronary Syndrome in the PROVE IT-TIMI 22 Trial

J Am Coll Cardiol 2008;51:724–30

Michael Miller, MD, FACC,* Christopher P. Cannon, MD, FACC,† Sabina A. Murphy, MPH,† Jie Qin, MS,† Kausik K. Ray, MD, MRCP,‡ Eugene Braunwald, MD, MACC,† for the PROVE IT-TIMI 22 Investigators

Plasma Triglycerides and Cardiovascular Events in the Treating to New Targets and Incremental Decrease in End-Points Through Aggressive Lipid Lowering Trials of Statins in Patients With Coronary Artery Disease

Ole Faergeman, MD, DMSc[a,*], Ingar Holme, PhD[b], Rana Fayyad, PhD[c], Sonal Bhatia, MD[c],

Am J Cardiol 2009;104:459–463

Increased Remnant Cholesterol Explains Part of Residual Risk of All-Cause Mortality in 5414 Patients with Ischemic Heart Disease

Anne-Marie K. Jepsen,[1,2] Anne Langsted,[1,2] Anette Varbo,[1,2] Lia E. Bang,[2,3] Pia R. Kamstrup,[1,2] and Børge G. Nordestgaard[1,2*]

Clinical Chemistry 62:4 593-604 (2016)

Elevated Triglyceride Level Is Independently Associated With Increased All-Cause Mortality in Patients With Established Coronary Heart Disease

Twenty-Two–Year Follow-Up of the Bezafibrate Infarction Prevention Study and Registry

Robert Klempfner, MD; Aharon Erez, MD; Ben-Zekry Sagit, MD; Ilan Goldenberg, MD; Enrique Fisman, MD; Eran Kopel, MD; Nir Shlomo, MA; Ariel Israel, MD; Alexander Tenenbaum, MD, PhD

Circ Cardiovasc Qual Outcomes. 2016;9:100-108

Other clinical studies with similar data / conclusion:

TG-rich remnants explain CV & mortality residual risk beyond statin therapy

- independent of LDL-C and HDL-C

Association of LDL Cholesterol, Non–HDL Cholesterol, and Apolipoprotein B Levels With Risk of Cardiovascular Events Among Patients Treated With Statins

A Meta-analysis

S. Matthijs Boekholdt, MD, PhD

JAMA. 2012;307(12):1302-1309

Fasting Triglycerides Predict Recurrent Ischemic Events in Patients With Acute Coronary Syndrome Treated With Statins

Gregory G. Schwartz, MD, PhD,* Markus Abt, PhD,† Weihang Bao, PhD,‡ David DeMicco, PharmD,‡ David Kallend, MD,† Michael Miller, MD,§ Hardi Mundl, MD,† Anders G. Olsson, MD, PhD||¶

J Am Coll Cardiol 2015;65:2267–75

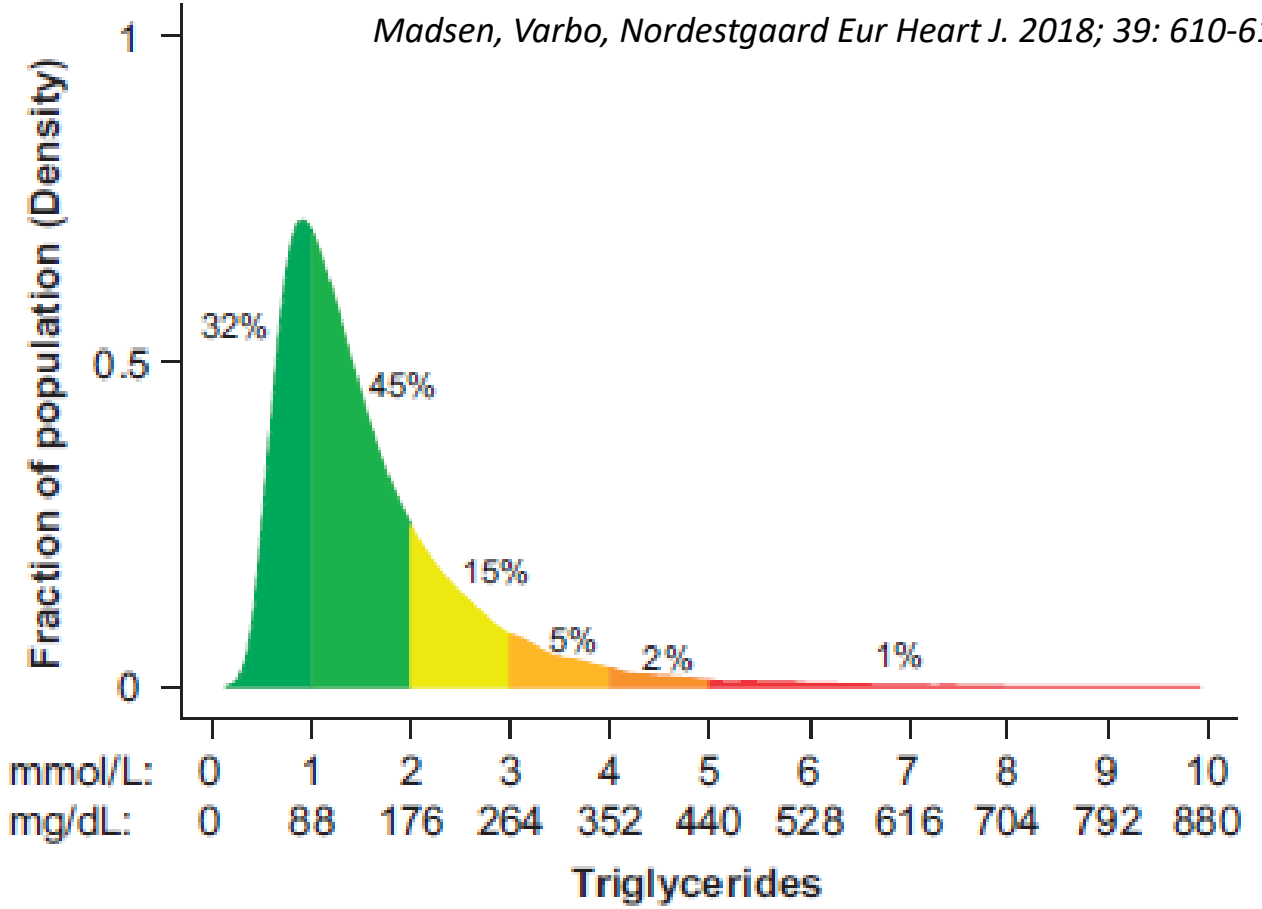
Residual Risk of Atherosclerotic Cardiovascular Events in Relation to Reductions in Very-Low-Density Lipoproteins

Patrick R. Lawler, MD, MPH; Akintunde O. Akinkuolie, MBBS, MPH; Paulo Harada, MD, PhD, MPH; Robert J. Glynn, ScD; Daniel I. Chasman, PhD; Paul M Ridker, MD, MPH; Samia Mora, MD, MHS

Lawler PR et al. J Am Heart Assoc. 2017 6 e007402

Unmet need for primary prevention in individuals with hypertriglyceridaemia not eligible for statin therapy according to European Society of Cardiology/European Atherosclerosis Society guidelines: a contemporary population-based study

Madsen, Varbo, Nordestgaard Eur Heart J. 2018; 39: 610-619



The Copenhagen General Population Study 2003-2015
58,547 individuals aged 40 to 65
All free of ASCVD, diabetes and statin use at baseline

Definite statin eligible according to ESC/EAS guidelines

No
86%
N=50,455

Yes
14%
N=8,092

Triglycerides, mmol/L (mg/dL)

<3 (264)
79%
N=46,360

≥3 (264)
7%
N=4,095

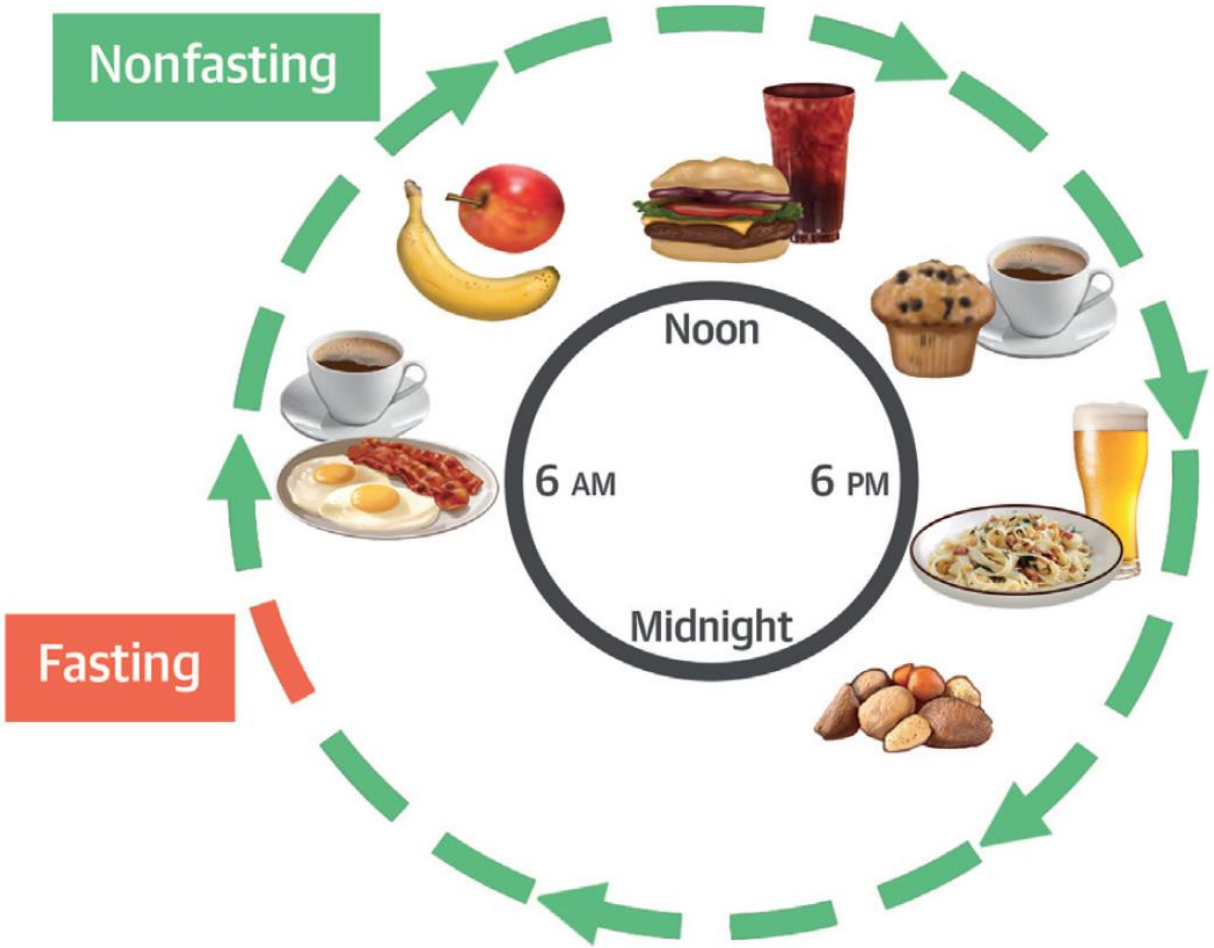
Cumulative incidence of MACE at age 70, % (95% CI)

8.1 (7.3-8.9)	14.6 (12.6-16.8)	16.5 (14.0-19.3)

Estimated 10-year risk of MACE, % (95% CI)

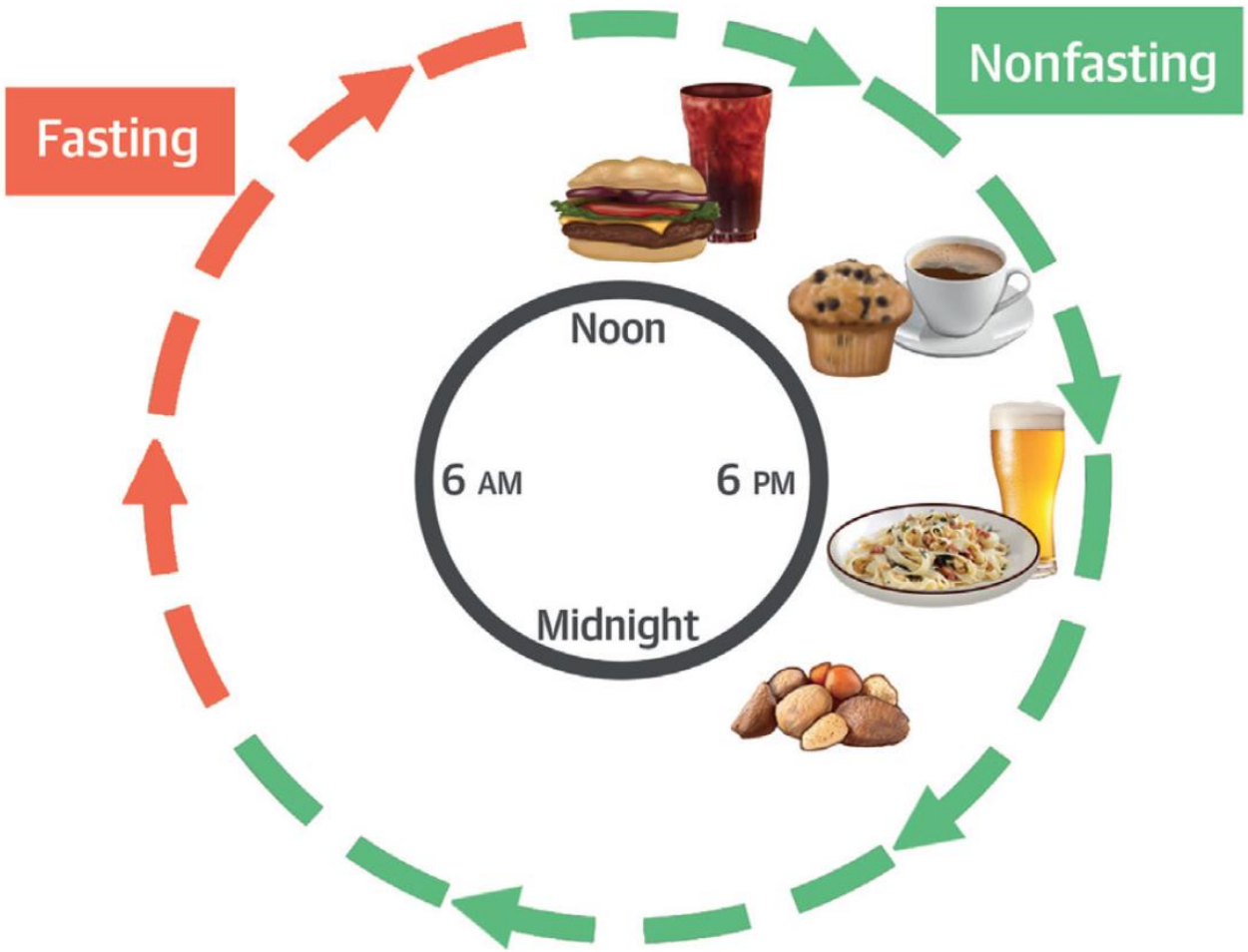
2.8 (2.6-3.0)	5.7 (4.9-6.6)	7.6 (6.9-8.3)
51 years	51 years	60 years

Nonfasting Lipid Profiles



Evidence-Driven

Fasting Lipid Profiles

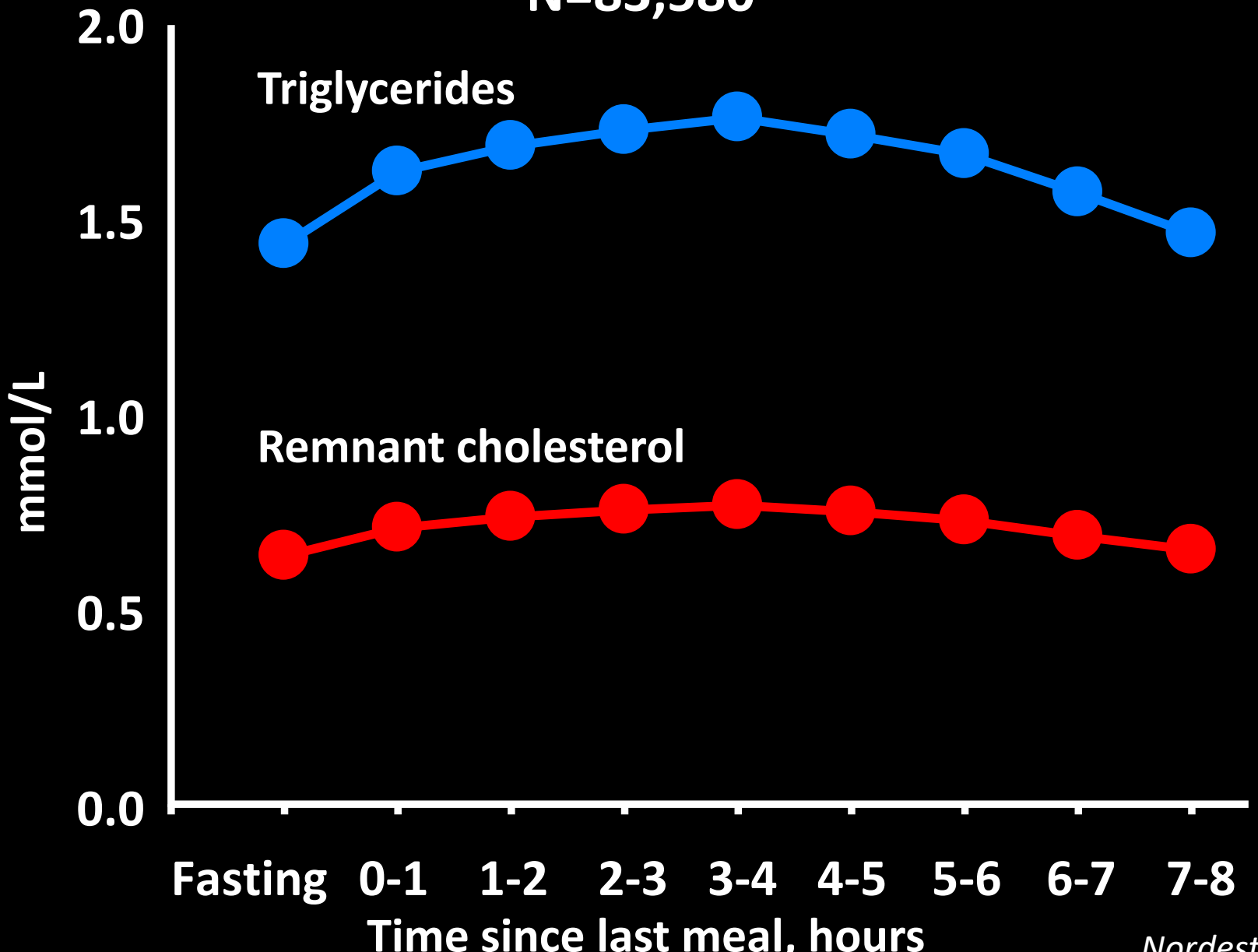


Belief-Driven

Nordestgaard JACC 2017; 70: 1637-46

Copenhagen General Population Study

N=83,580



Nordestgaard JACC 2017; 70: 1637-46

Endorsement of nonfasting lipid profiles by societies, guidelines, & statements

Year	Region	Society/guideline/statement
2017	US	AACE/ACE: American Association of Clinical Endocrinologists & American College of Endocrinology
2016	Brazil	Consensus of five medical societies
2016	Europe	ESC/EAS: European Society of Cardiology & European Atherosclerosis Society
2016	Canada	CCS: Canadian Cardiovascular Society
2016	Canada	CHEP: Canadian Hypertension Education Program
2016	Europe	EAS/EFLM: European Atherosclerosis Society & European Federation of Clinical Chemistry and Laboratory Medicine
2014	US	VA/DoD: Veterans Affairs & US Department of Defense
2014	UK	NICE: National Institute for Health and Care Excellence
2011	US	AHA: American Heart Association
2009	Denmark	DSKB: Danish Society for Clinical Biochemistry

Before 2009 essentially all societies, guidelines, and statements either required fasting before lipid profile measurement or did not mention requirements

Nordestgaard JACC 2017; 70: 1637-46

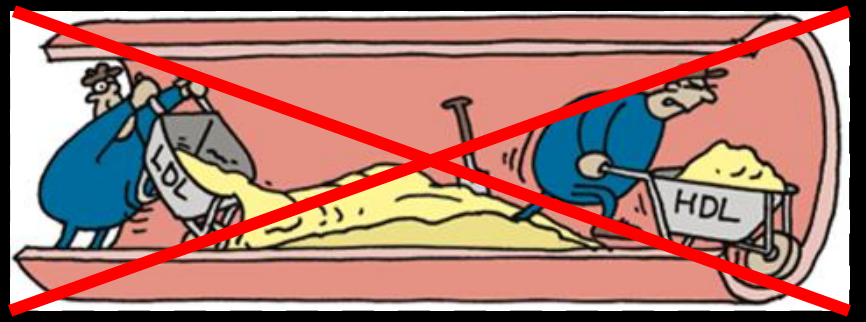
ApoB containing lipoproteins

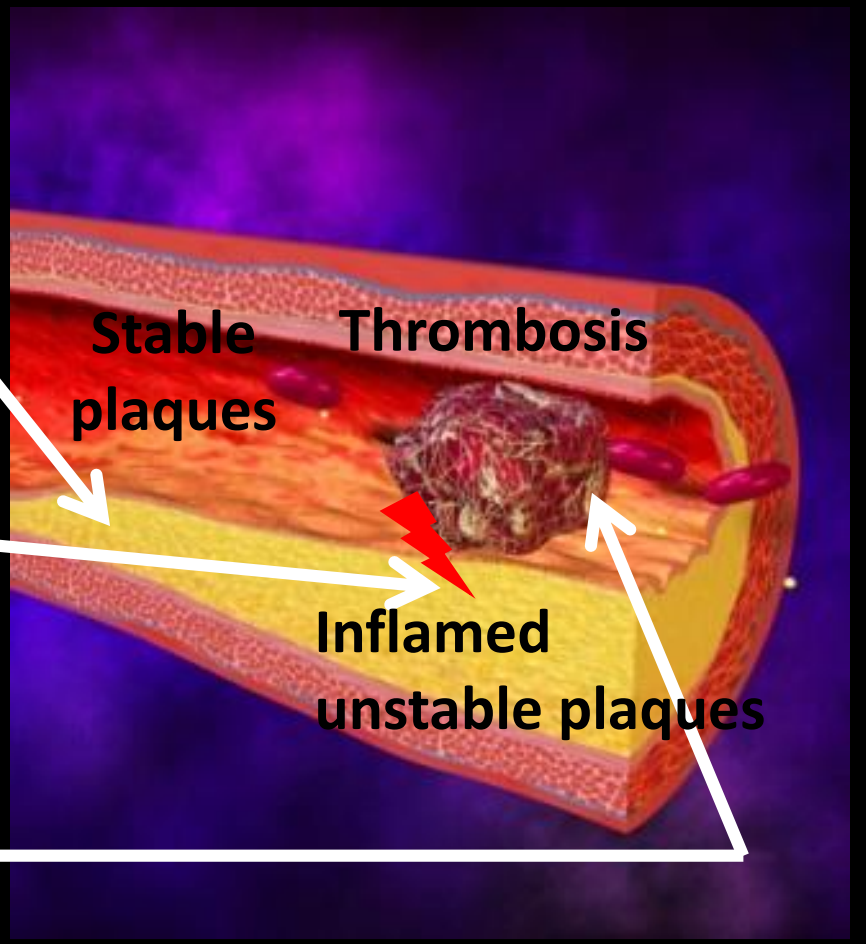
HDL

LDL

Remnants

Lp(a)



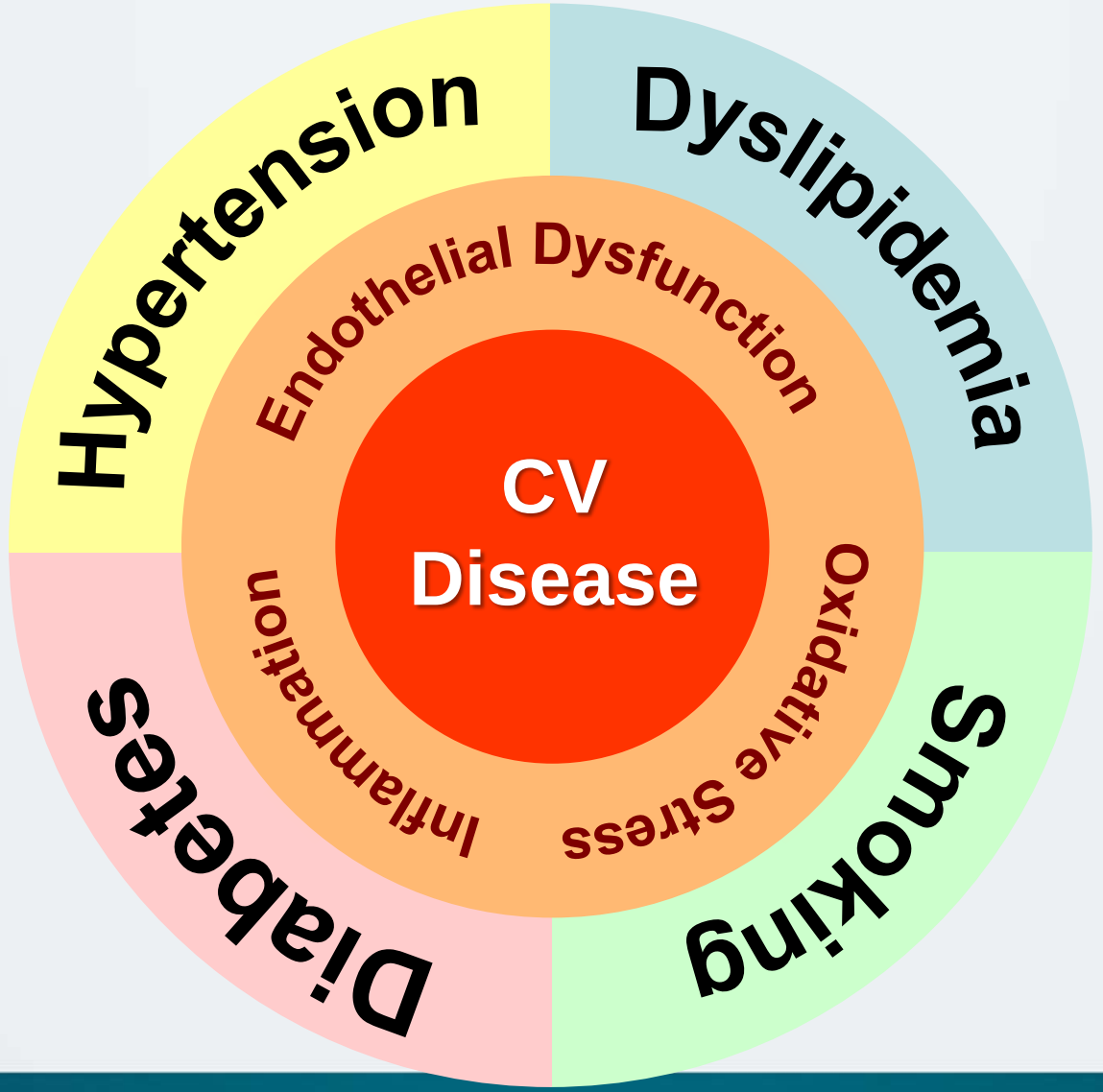


Nordestgaard 2018

Biologic Basis for TGRL Modulation in Reducing Atherosclerosis

R. Preston Mason, PhD

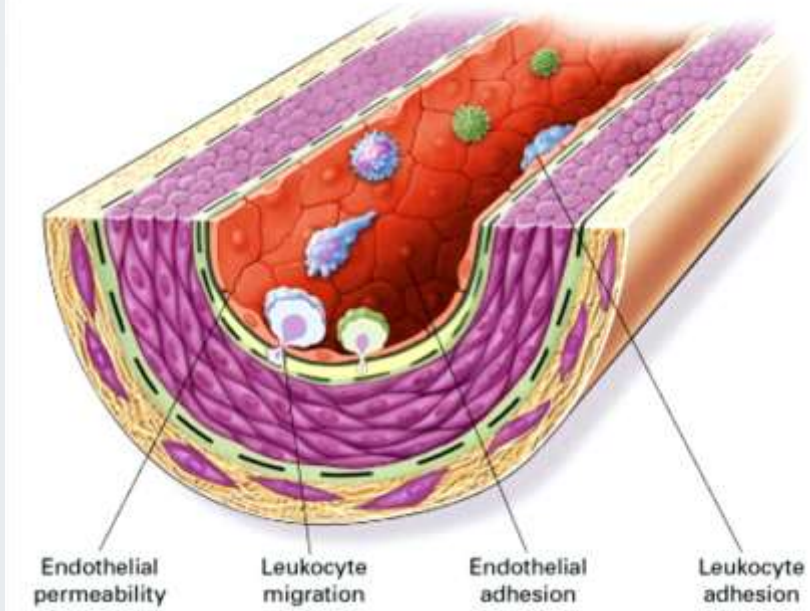
CV Risk Factors and Common Pathophysiologic Processes



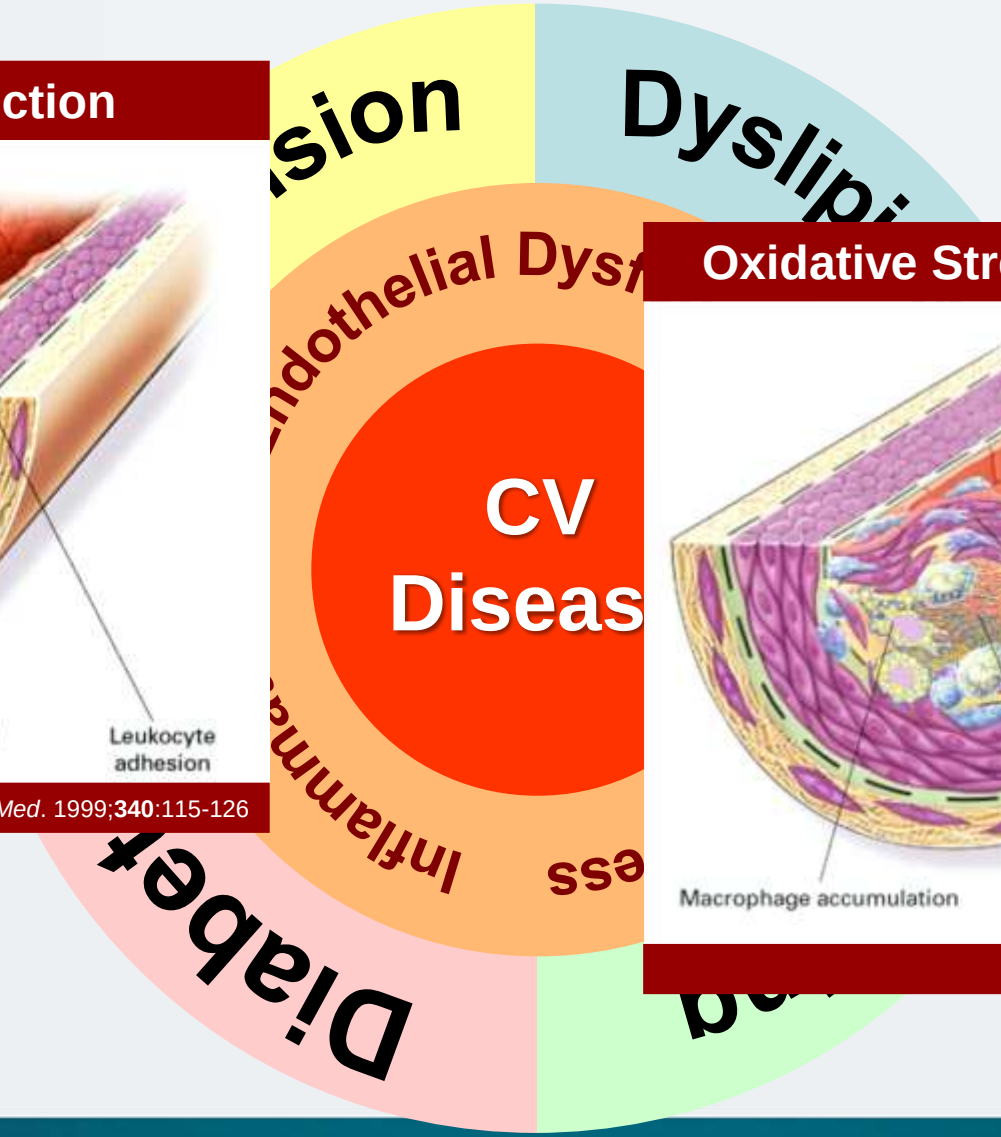
Jacob RF and Mason RP (2018)

CV Risk Factors and Common Pathophysiologic Processes

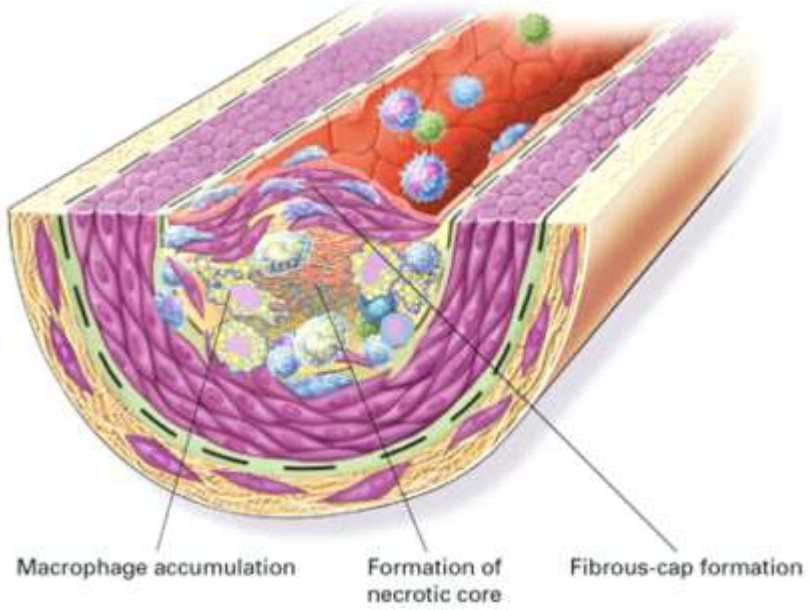
Endothelial Dysfunction



Ross R. *N Engl J Med*. 1999;**340**:115-126



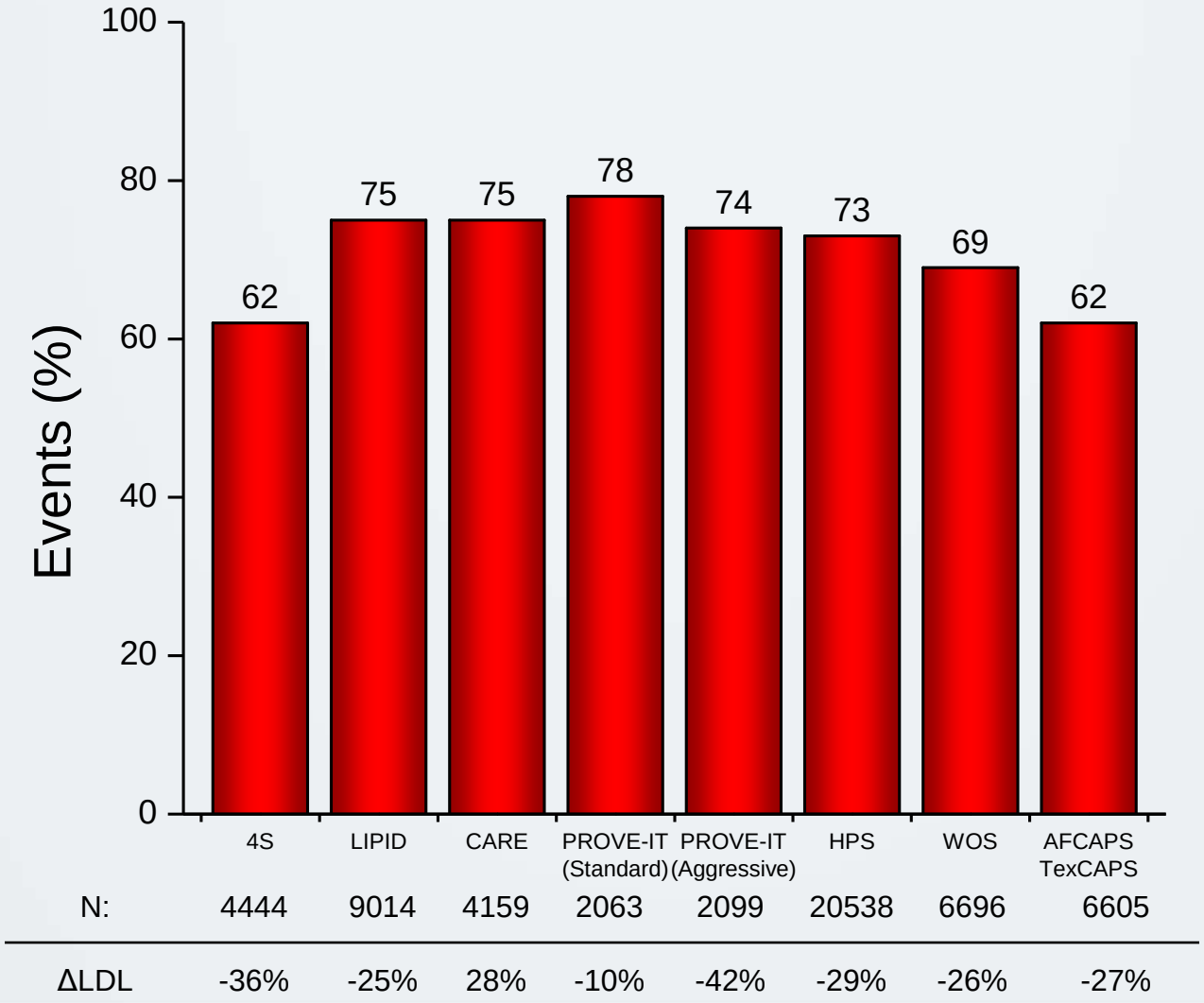
Oxidative Stress & Inflammation



Ross R. *N Engl J Med.* 1999;**340**:115-126

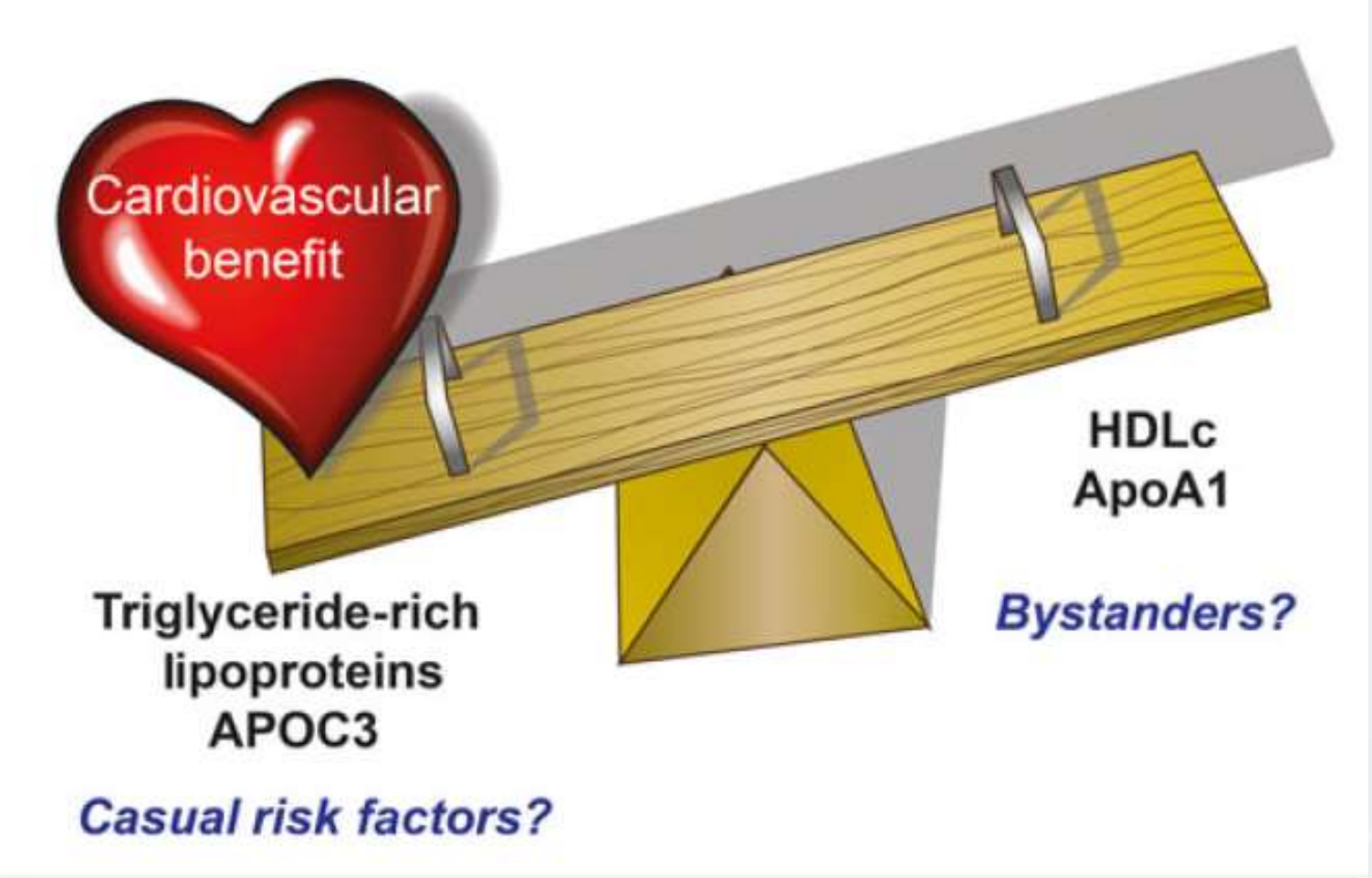
Jacob RF and Mason RP (2018)

The Forgotten Majority: Residual Burden of Events in the Statin "Megatrials"



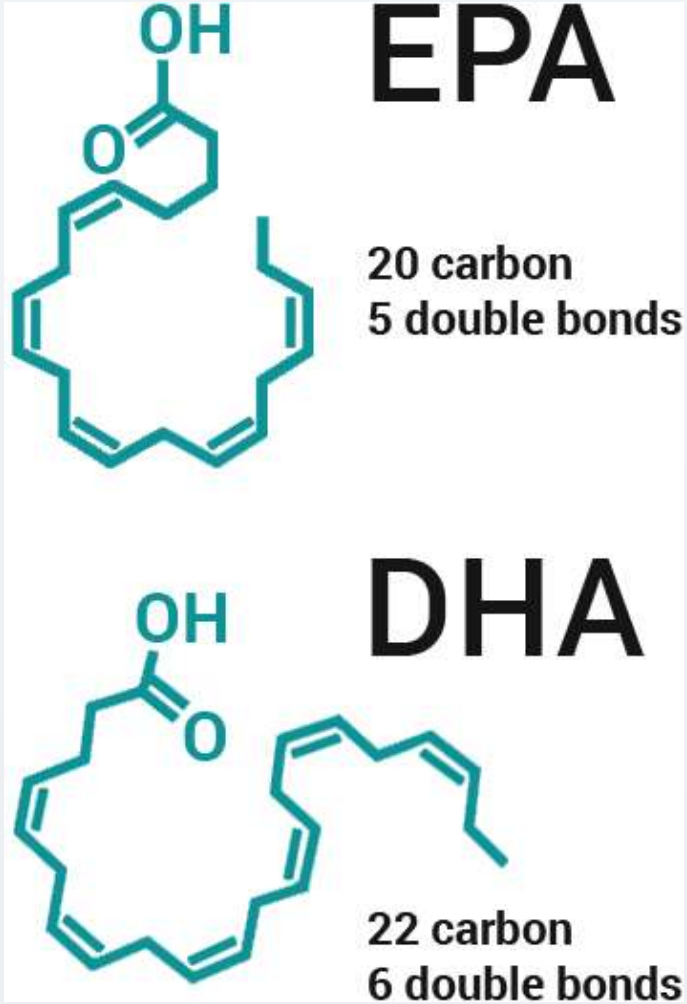
Libby P. *J Am Coll Cardiol.* 2005;46:1225-8.

“Triglycerides on the Rise: Should we Swap Seats on the Seesaw?”

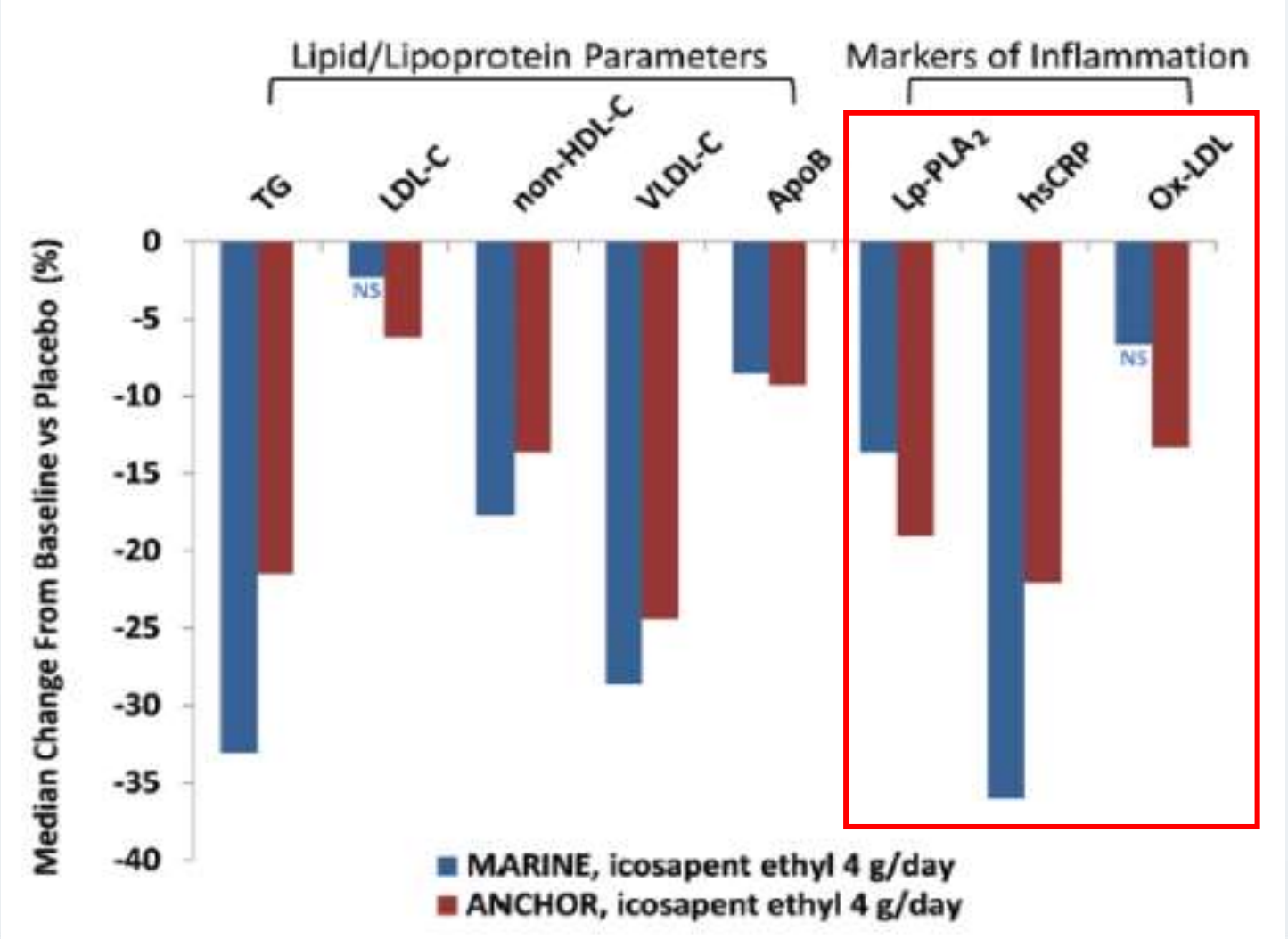


Libby P. *Eur Heart J*. 2015;36:774-6.

Could Therapeutic Levels of Omega-3 EPA Slow Atherosclerotic Disease?

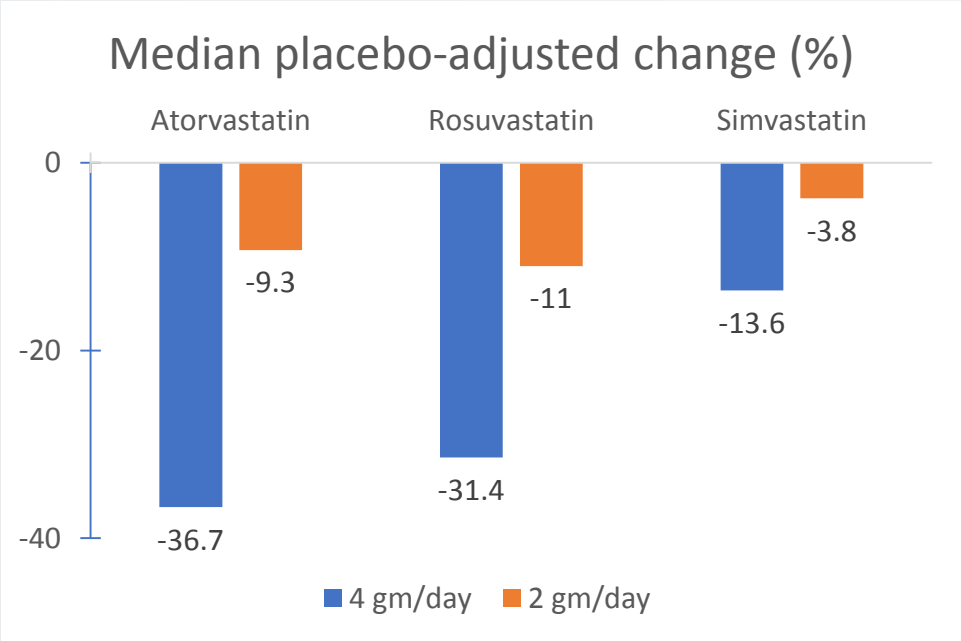


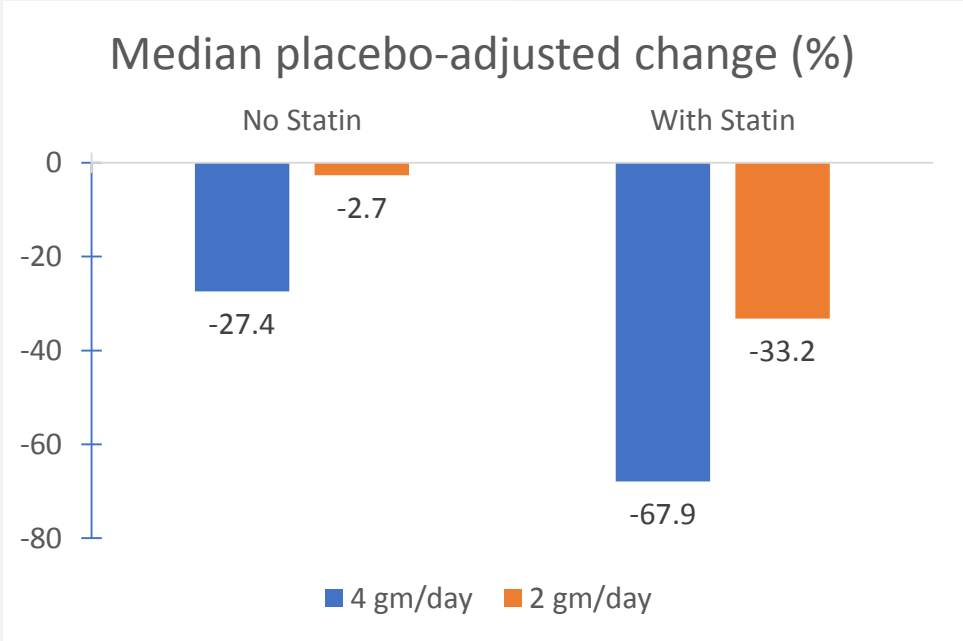
Effects of EPA on non-HDL-C and Inflammatory Markers in Patients with Elevated TGs



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

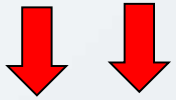
Reductions in hsCRP with EPA Enhanced with Intensive Statin Use





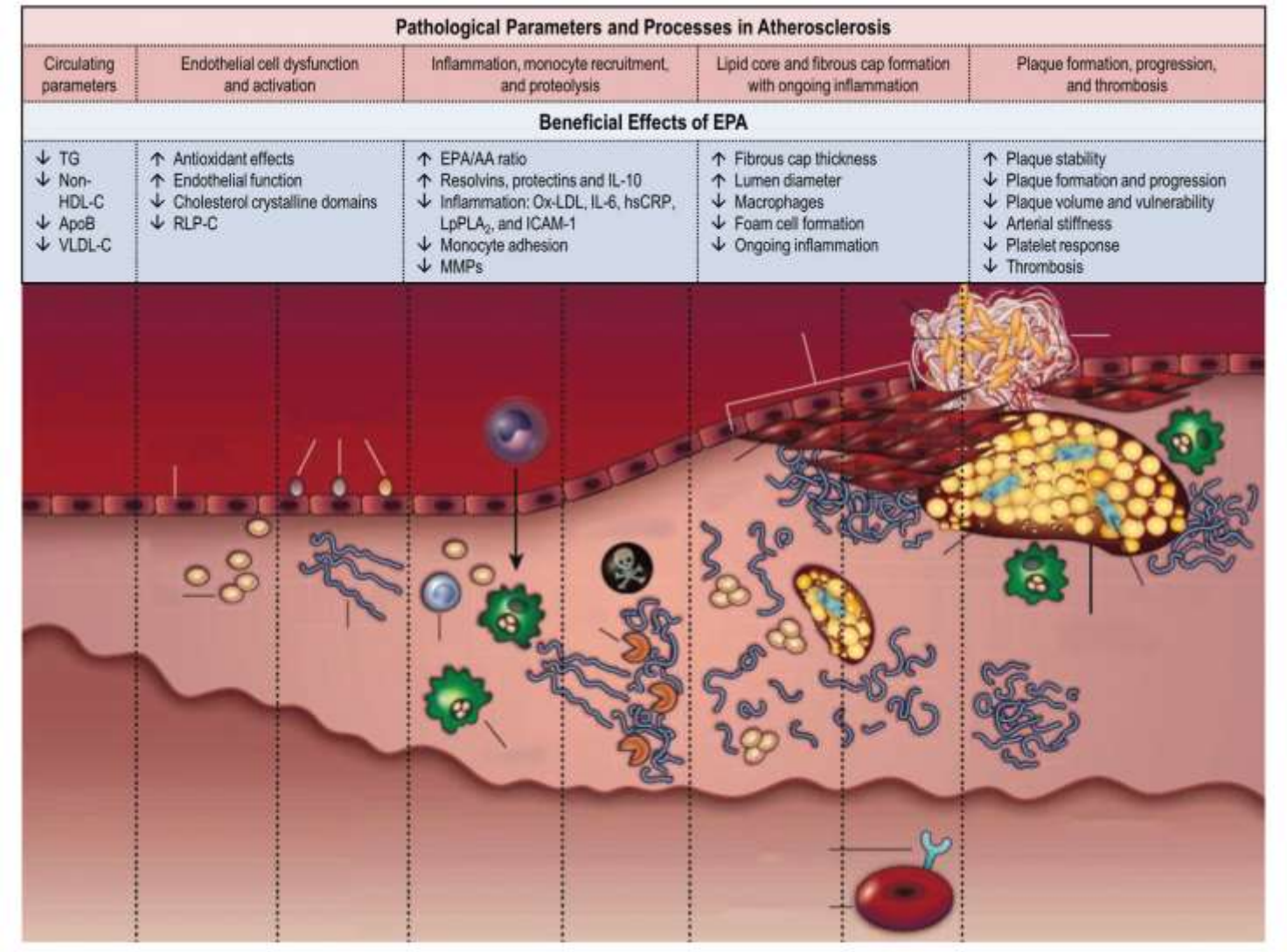
Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46.

Lipid Therapy has Different Effects on hsCRP

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

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

Potential Effects of Omega-3 on Plaque Development



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

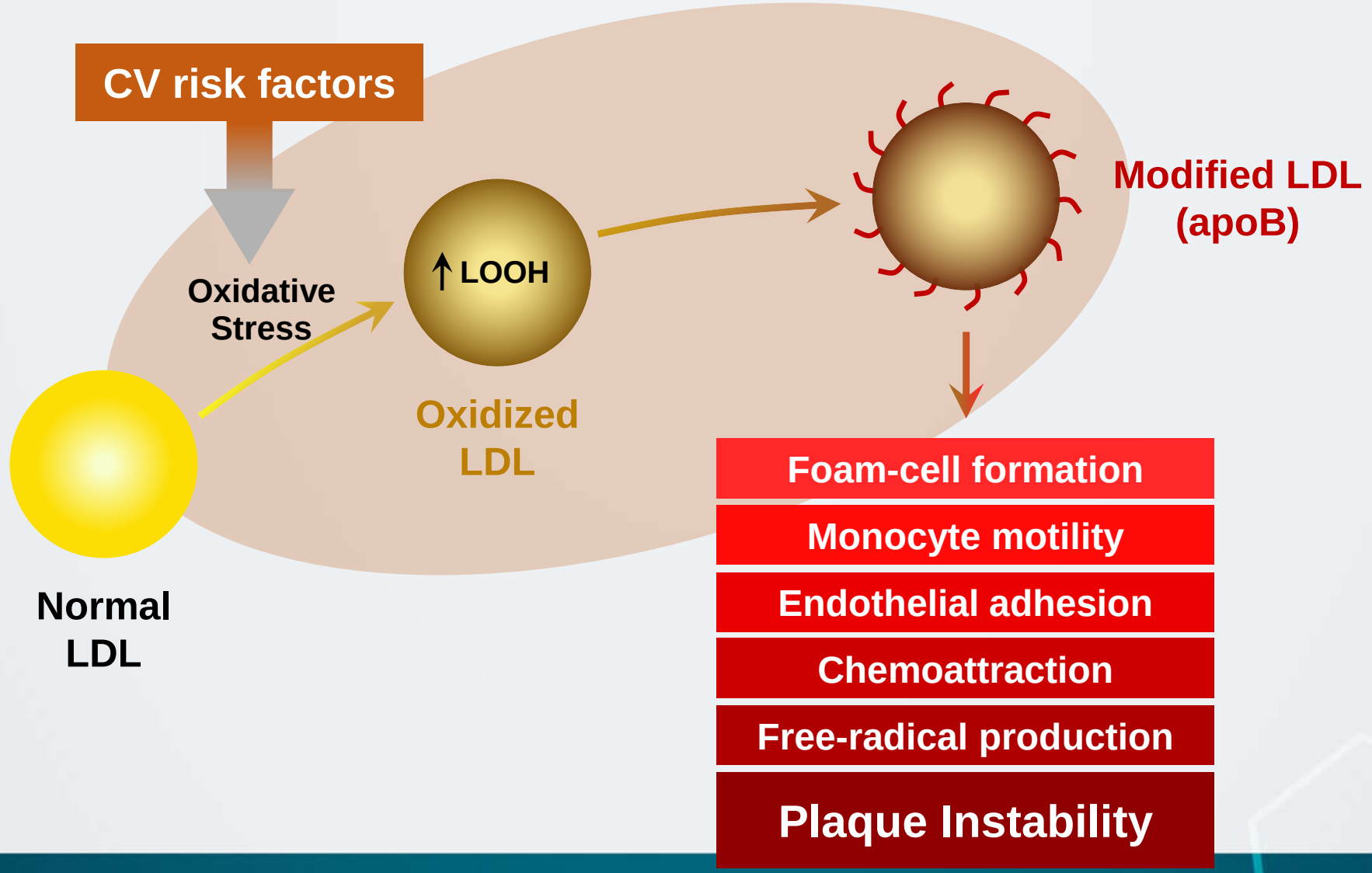
Questions

1. *Do Omega-3 FAs (EPA, EPA/DHA) have effects on atherosclerosis beyond TG reduction?*
2. *Are these effects of Omega-3 FAs different from other TG-lowering agents?*
3. *Are these effects of Omega-3 FAs enhanced with a statin?*

Question 1

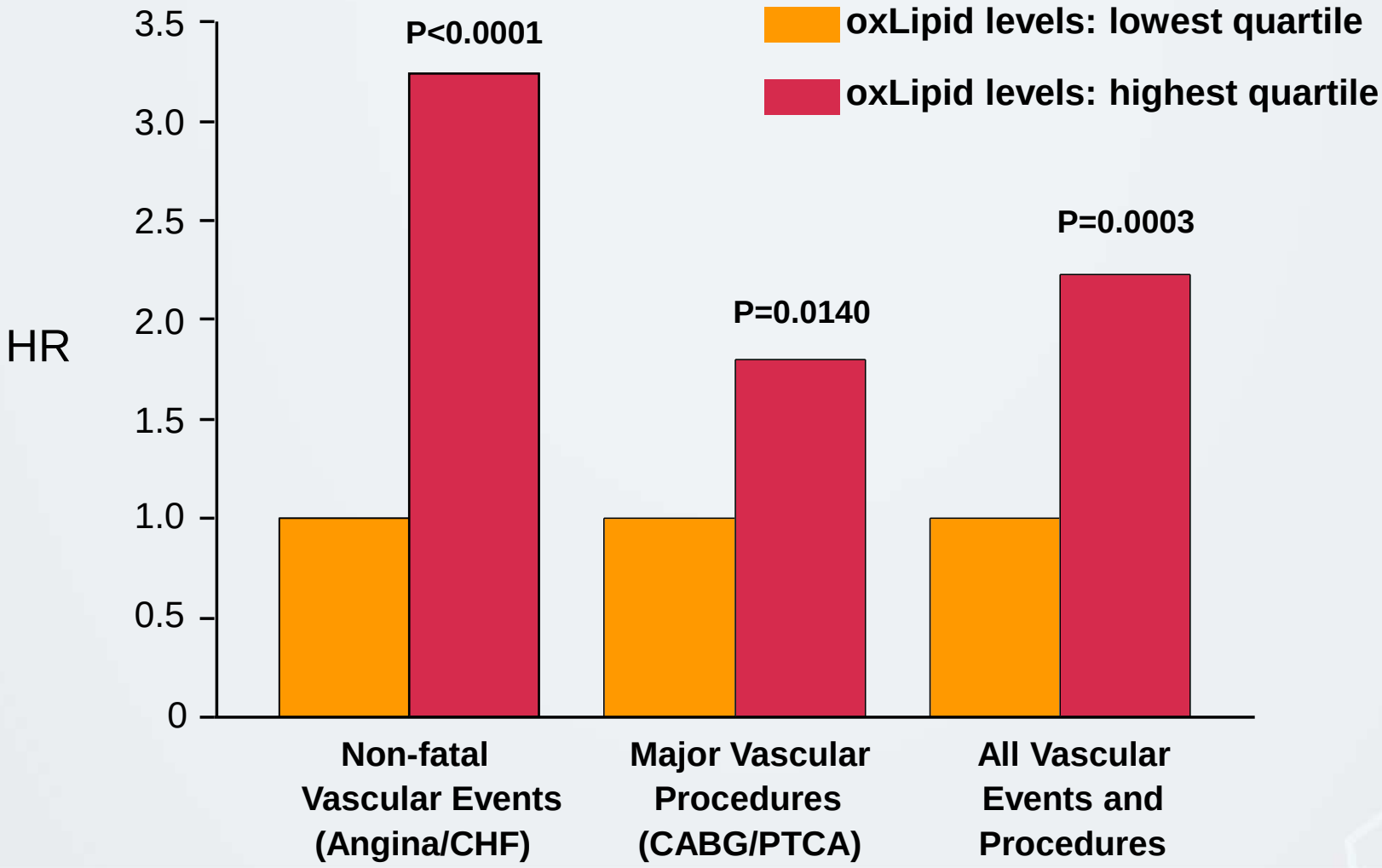
*What effects do Omega-3 Fatty Acids and other TG-lowering agents have on **oxidation** of Apo-B containing particles (LDL, VLDL, sdLDL)?*

LDL Oxidation Triggers Vascular Injury and Inflammation



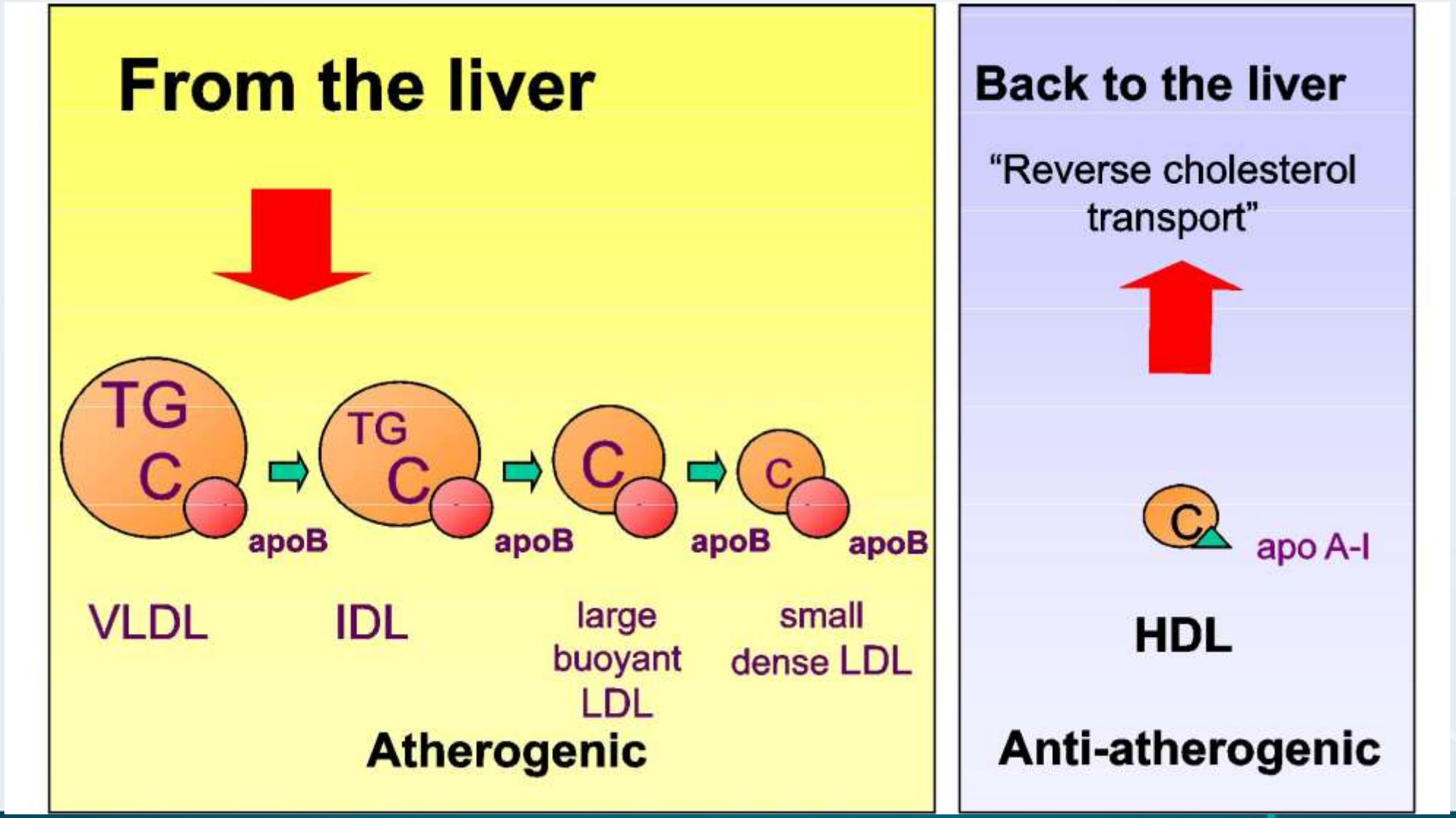
Jacob RF and Mason RP (2018)

Lipid Oxidation Levels Predict CV Events in 634 Patients with CAD



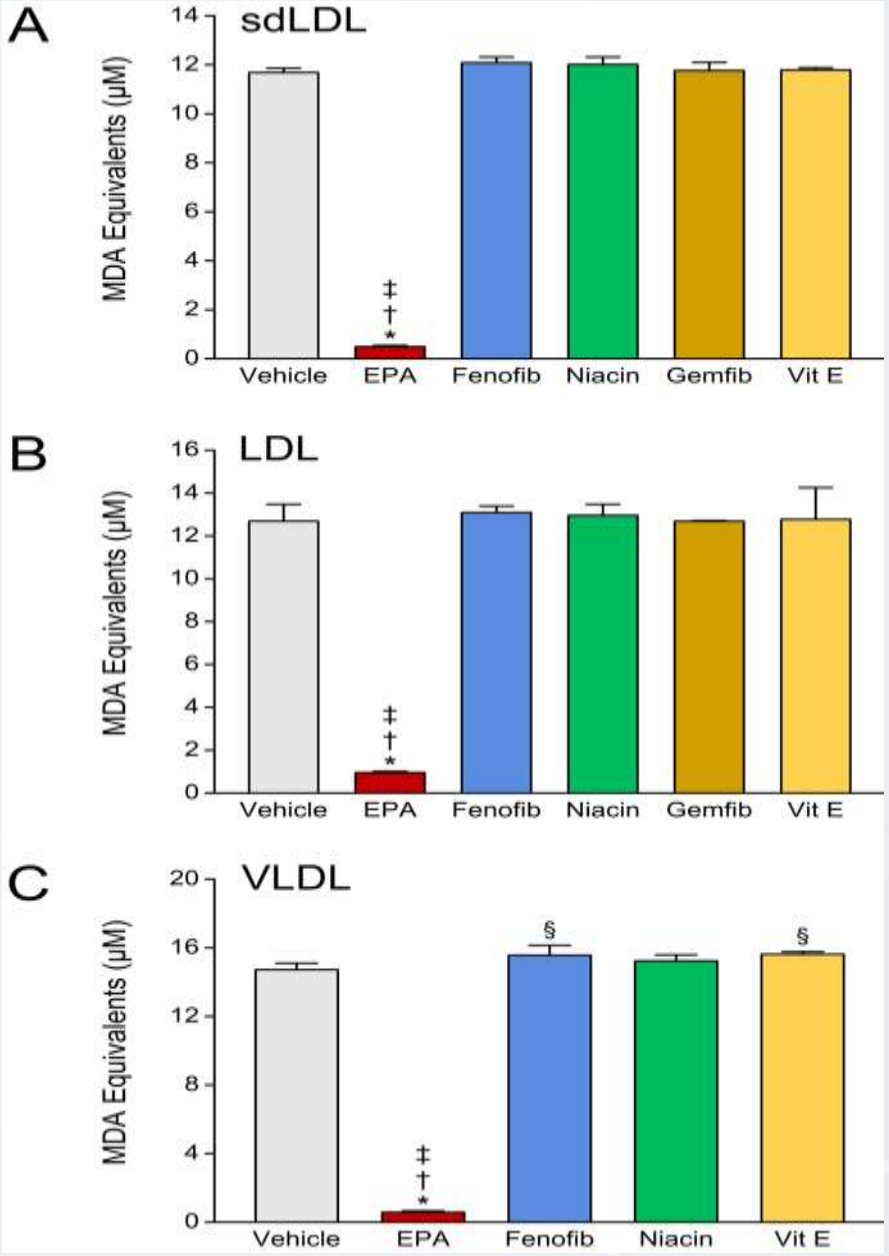
Walter MF, Mason RP, et al. *J Am Coll Cardiol*. 2008;51:1196-202.

ApoB Containing Particles are Atherogenic



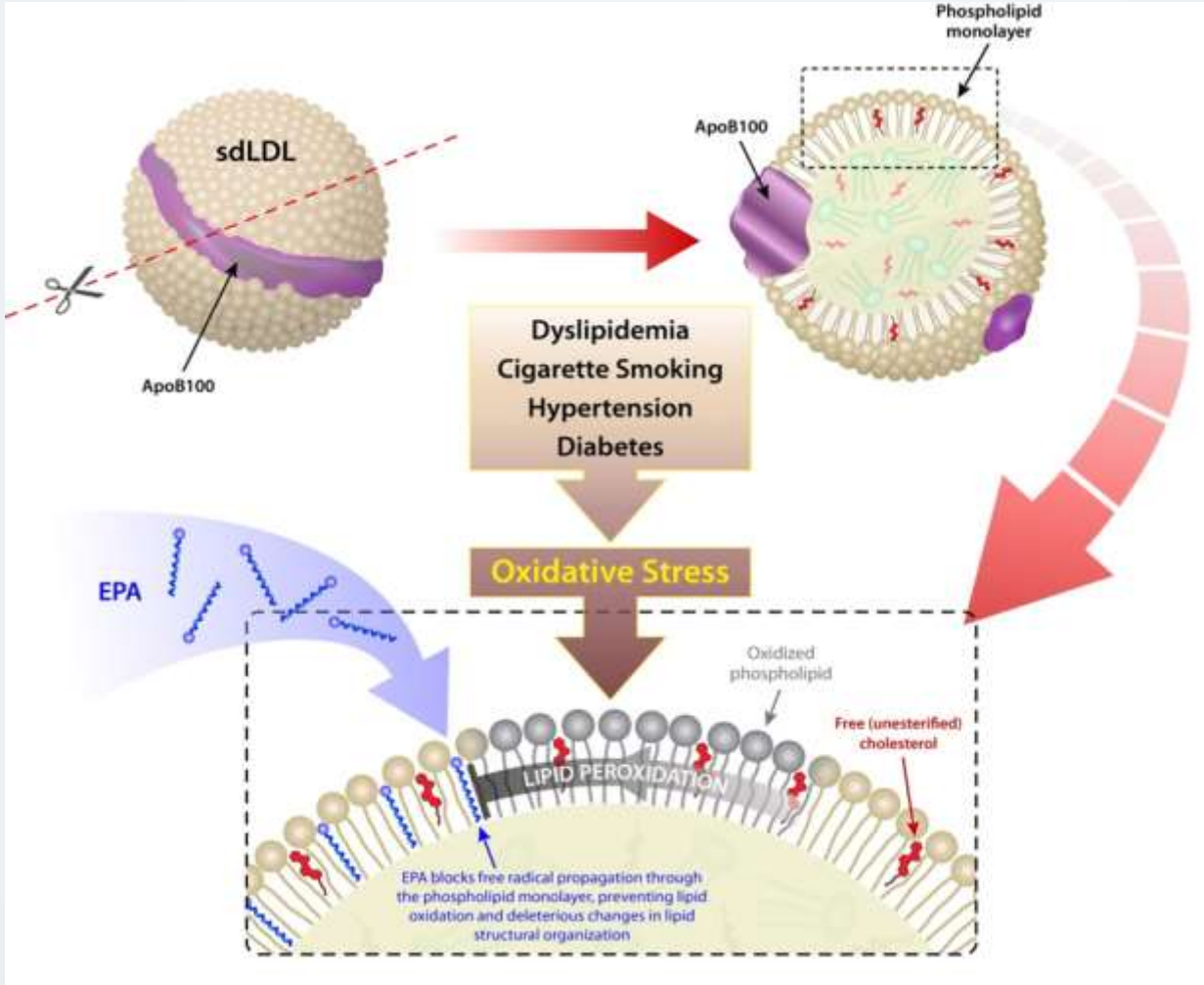
Comparative Effects of TG-lowering Agents on Lipoprotein Oxidation:

Each agent was tested at 10 μM



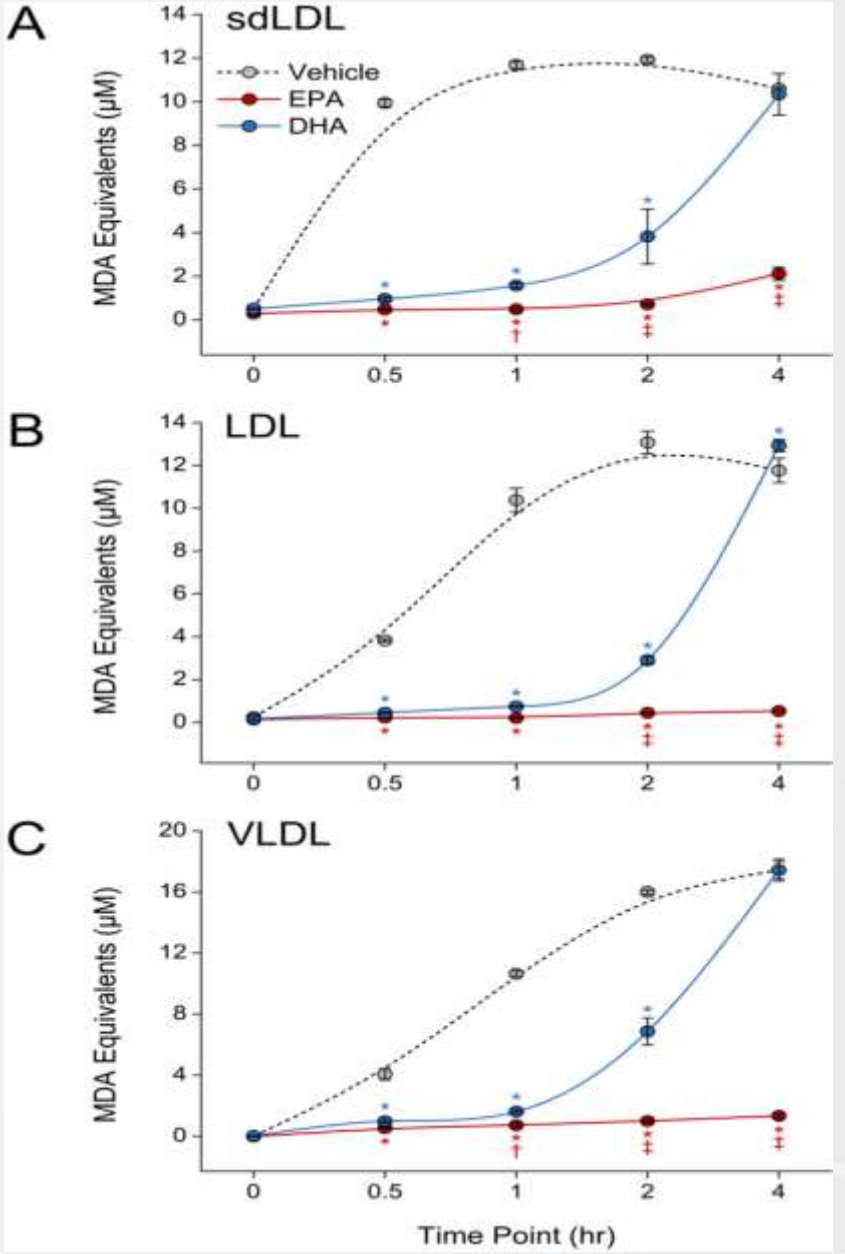
Mason RP et al. *J Cardiovasc Pharmacol.* 2016;68:33-40.

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



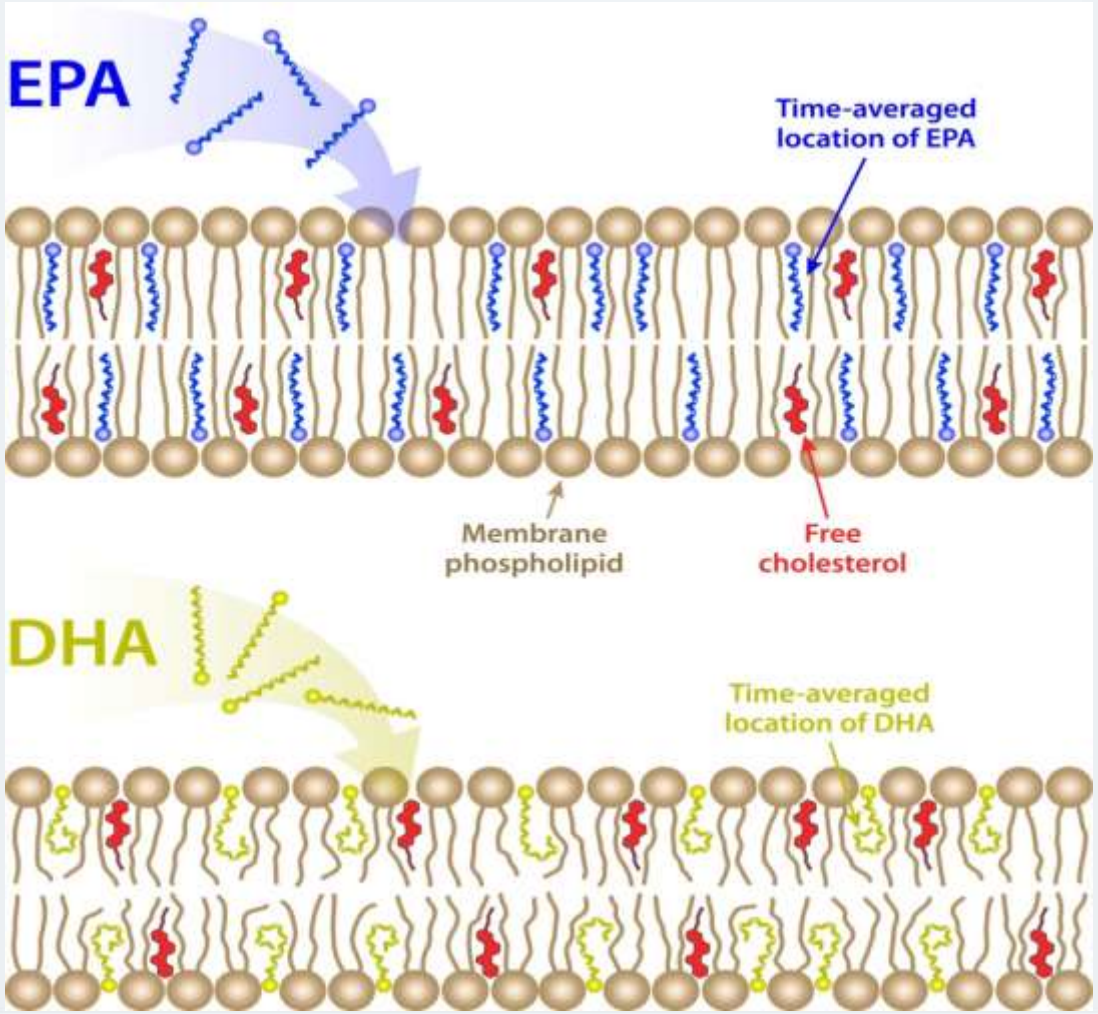
Adapted from: Mason RP and Jacob RF. *Diabetes.* 2015;64(Suppl 1):A178-A179.

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



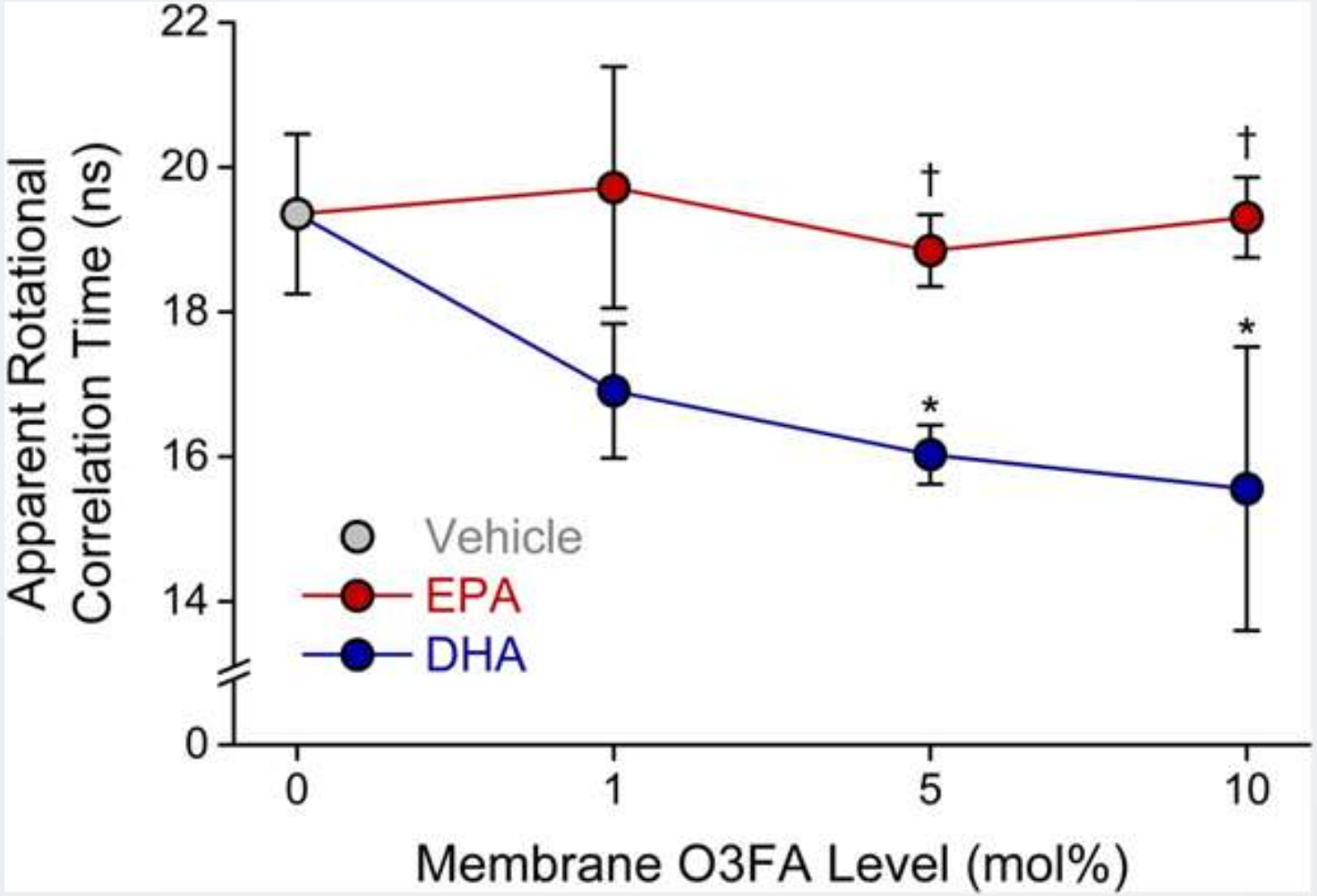
Mason RP et al. *J Cardiovasc Pharmacol.* 2016;68:33-40.

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



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

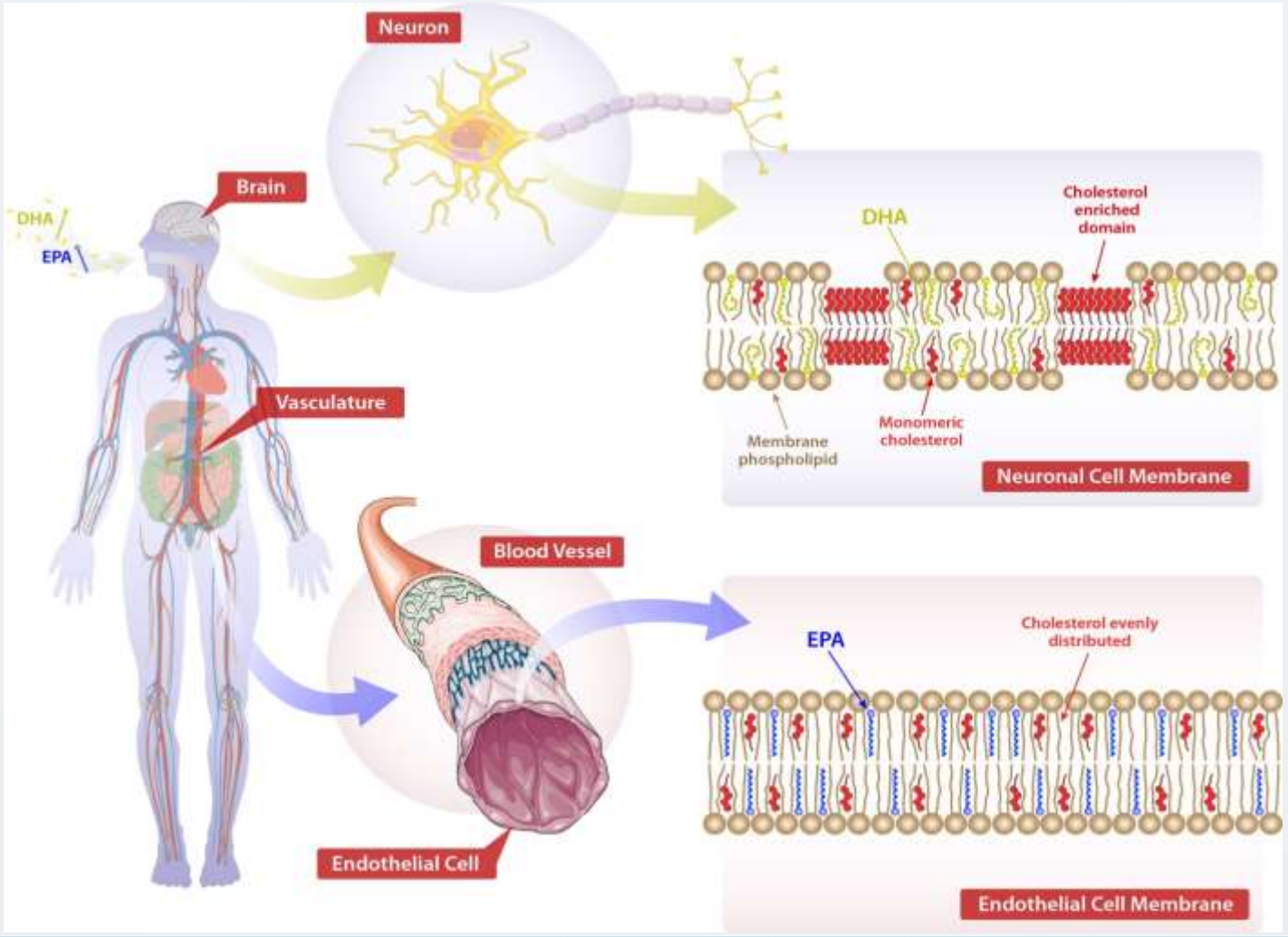
DHA Disorders the Membrane Environment while EPA has no Effect on Membrane Fluidity



*P<0.05 vs control (vehicle) treatment. †P<0.05 vs cognate (equimolar) DHA treatment.

Mason et al. *Biochim Biophys Acta.* 2016;1858:3131-40.

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

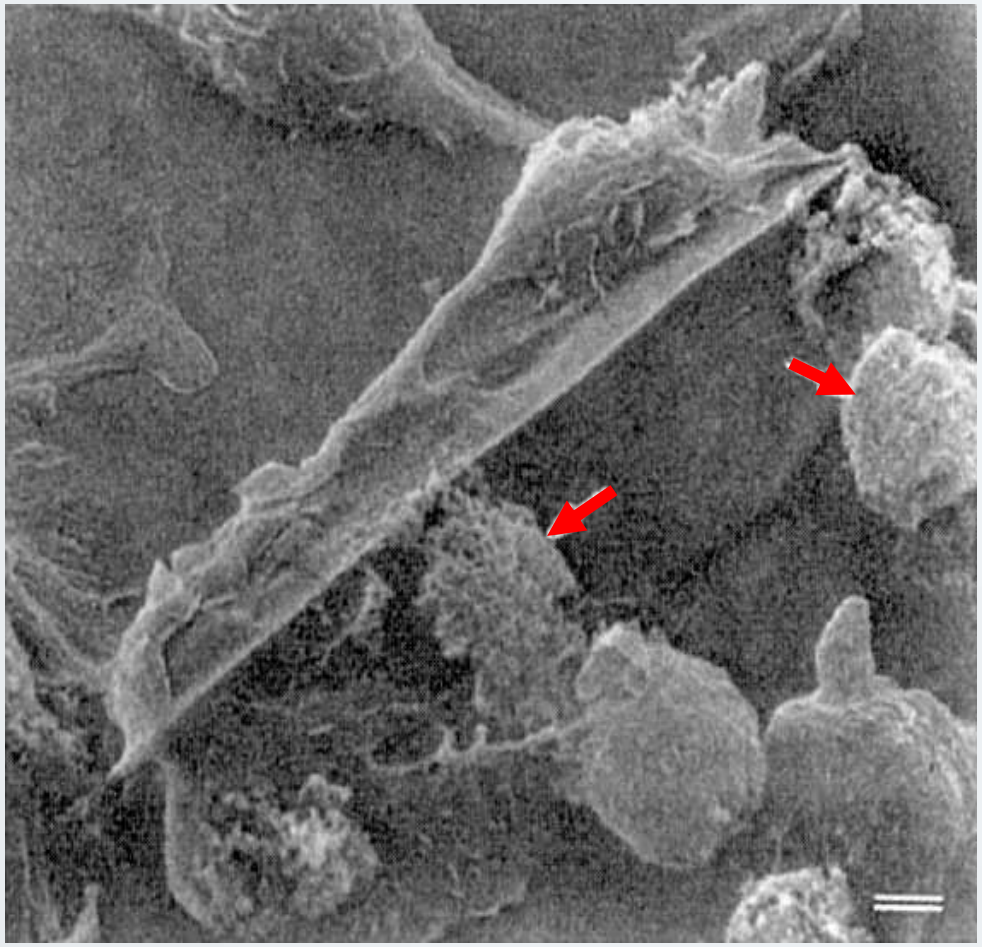


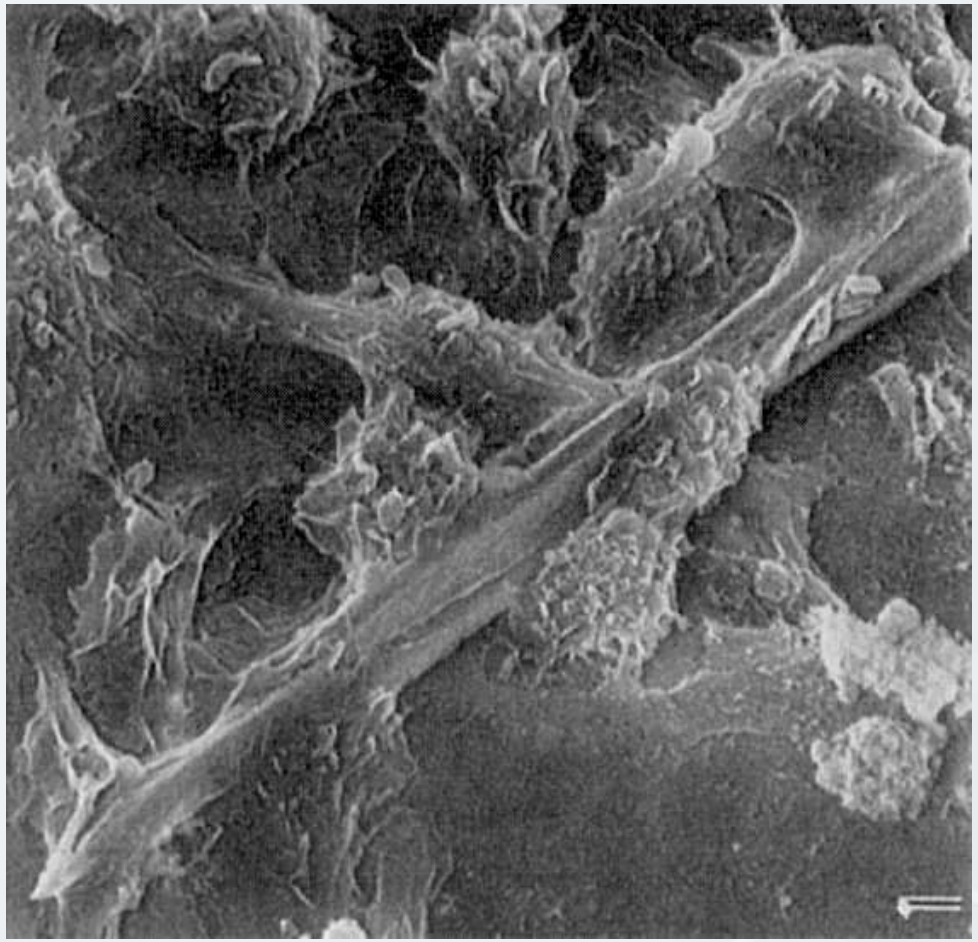
Jacob RF and Mason RP (2018)

Question 2

What effects do Omega-3 FAs and other TG-lowering agents have on oxidation of the membrane, leading to cholesterol crystals?

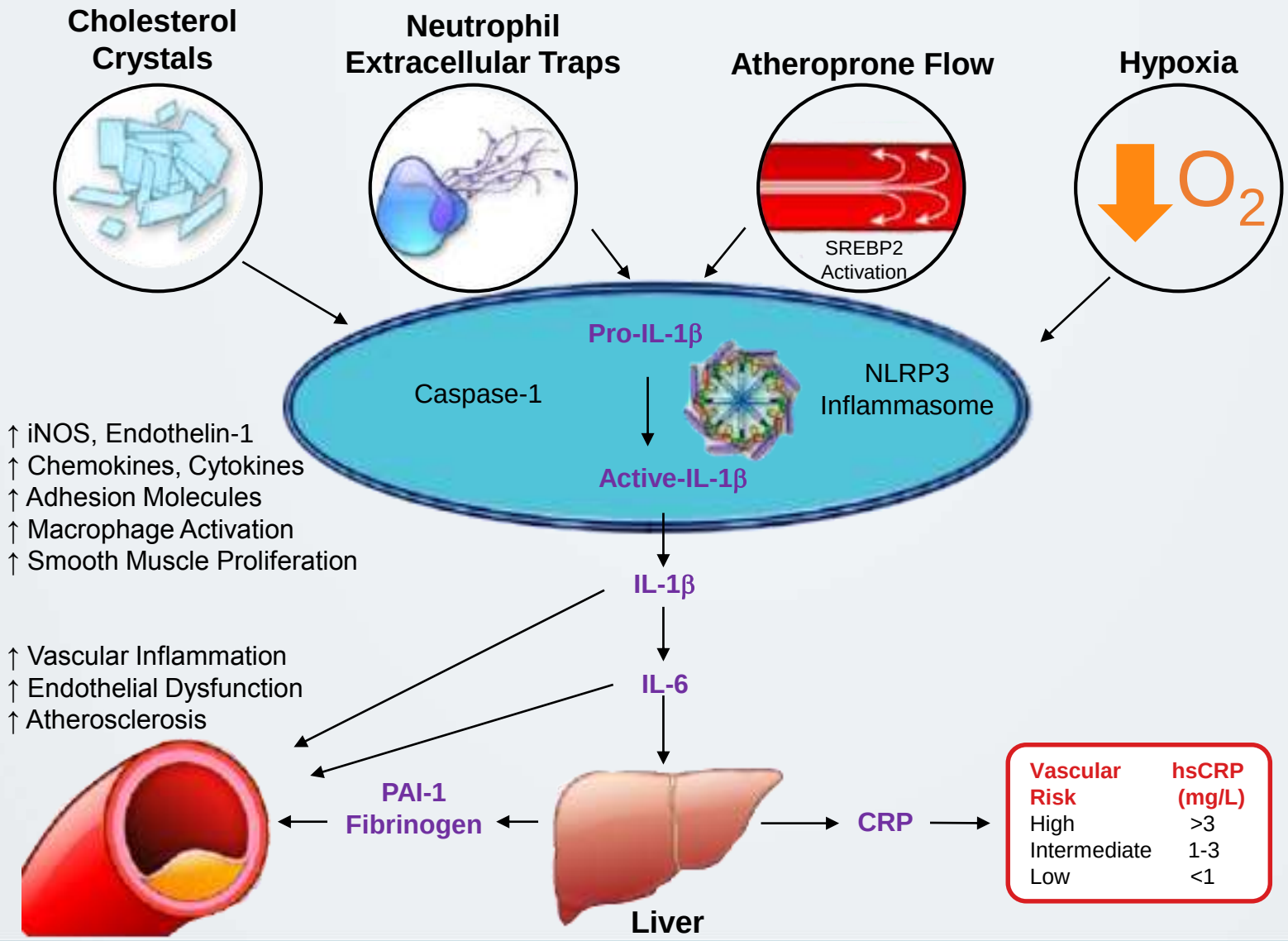
Cholesterol Crystals Associated with Atherosclerosis and Cell Death



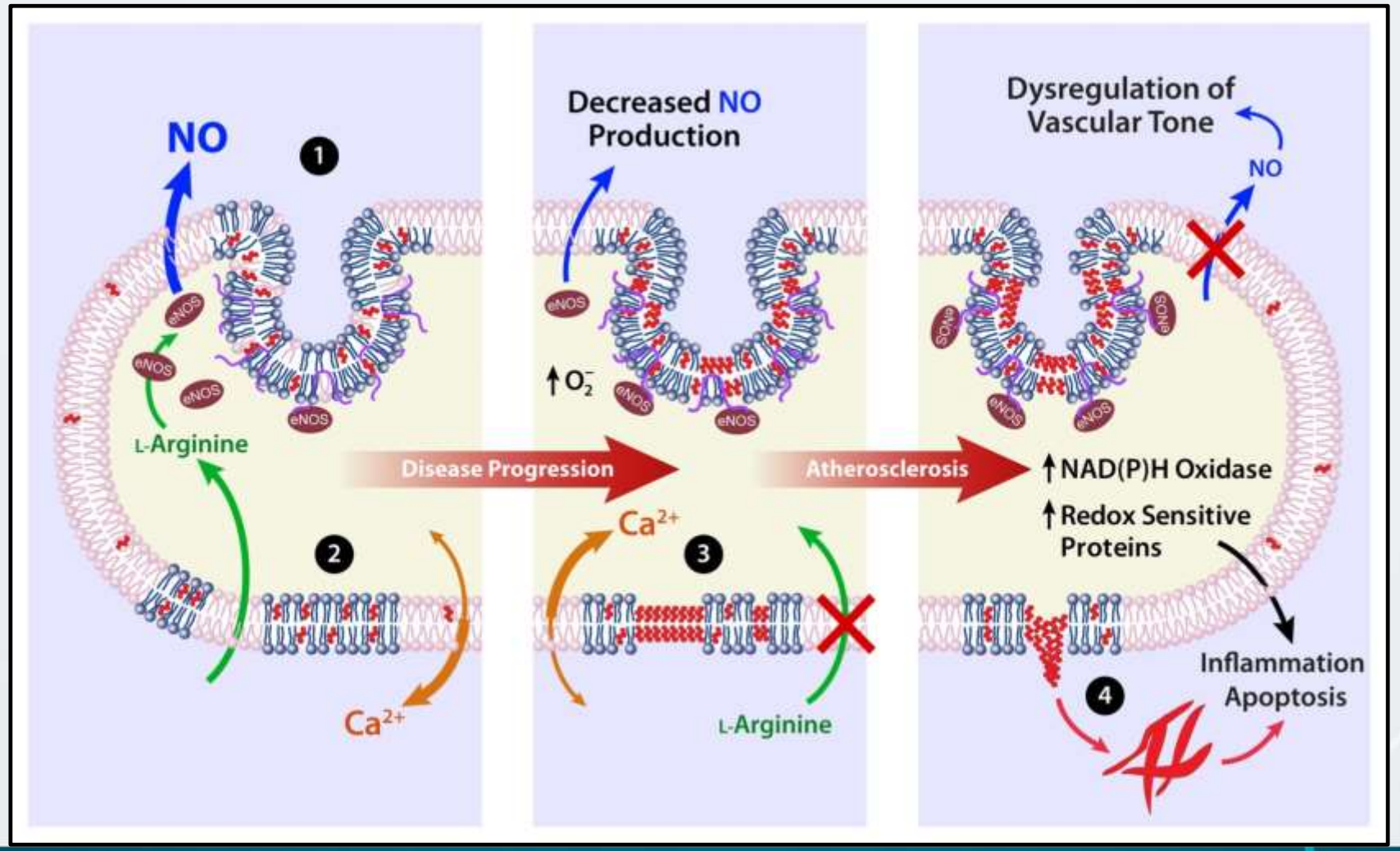


Kellner-Weibel G, Mason RP, et al. *Arterioscler Thromb Vasc Biol.* 1999;19:1891-8.

Cholesterol Crystals Trigger IL-1β Formation

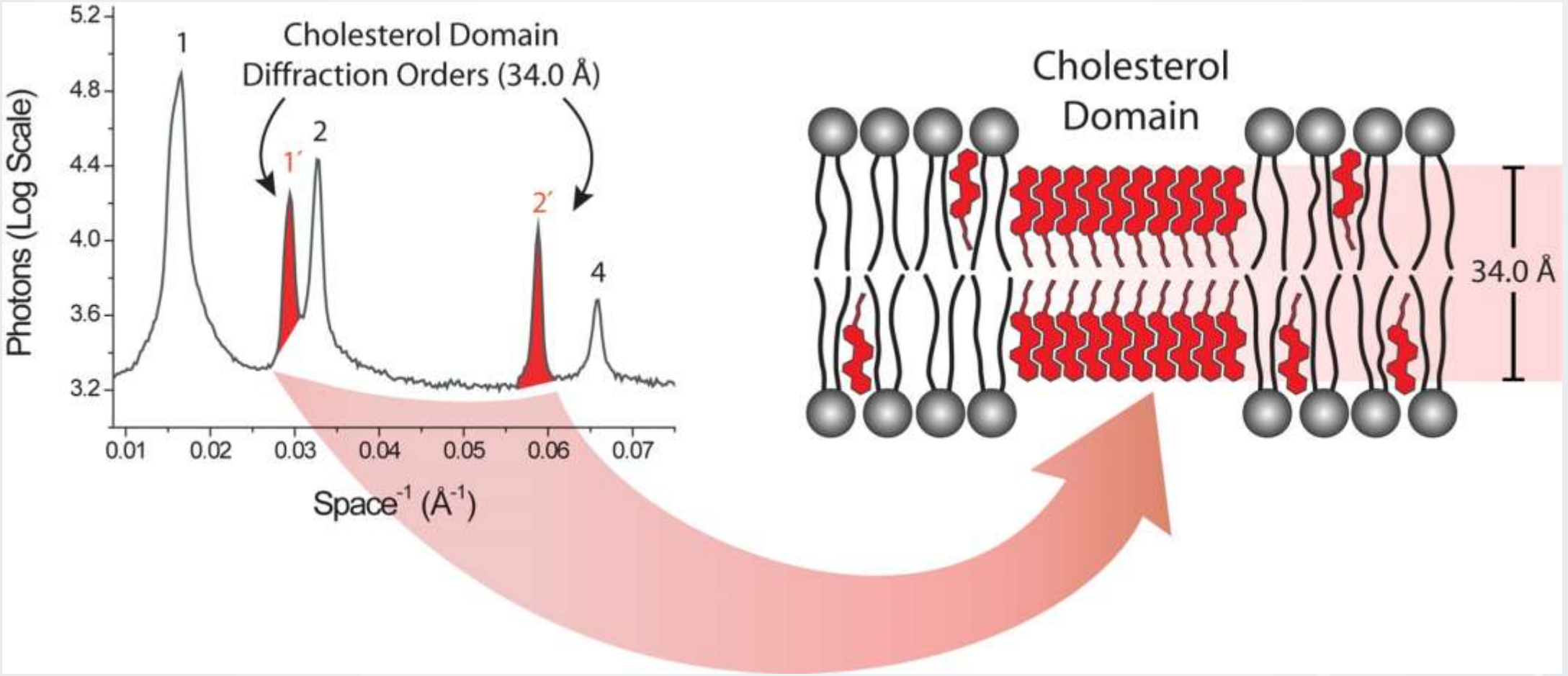


Membrane Lipid Oxidation and Cholesterol Domains with Atherosclerosis



Mason RP and Jacob RF. *Circulation.* 2003;107:2270-3.

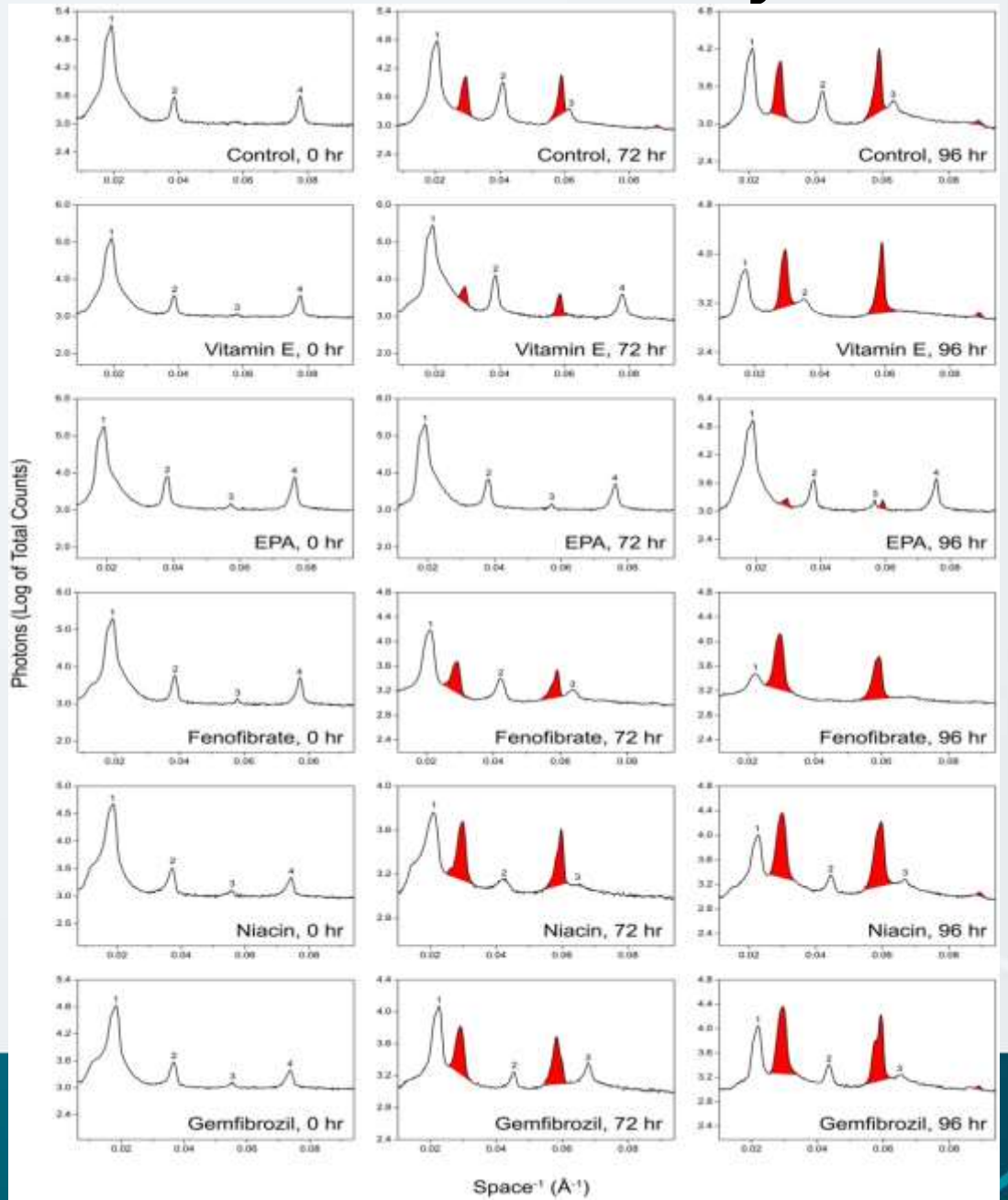
Characterizing Membrane Cholesterol Crystalline Domains by X-ray Diffraction



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

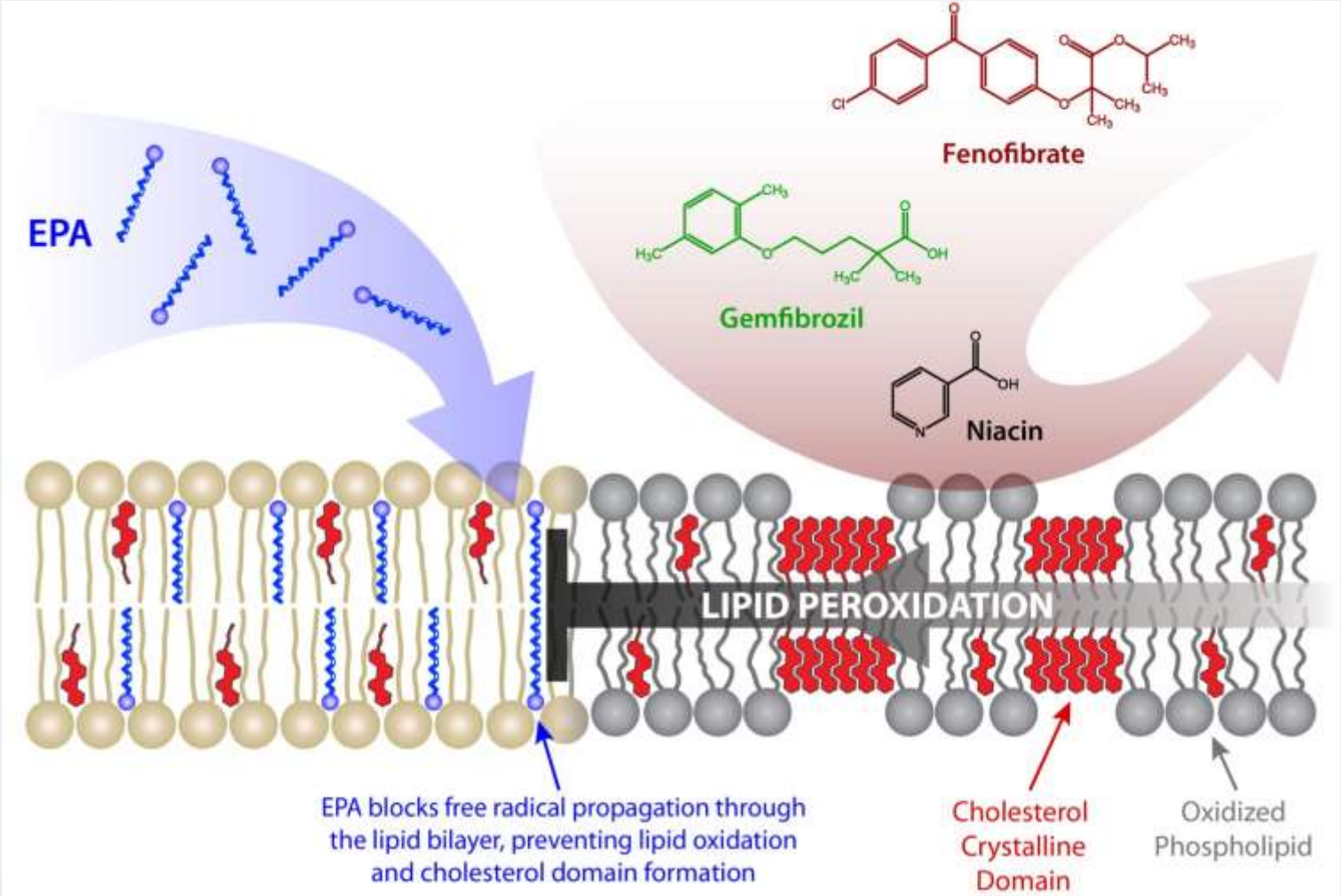
Effects of TG-lowering Agent on Cholesterol Crystalline Domains

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



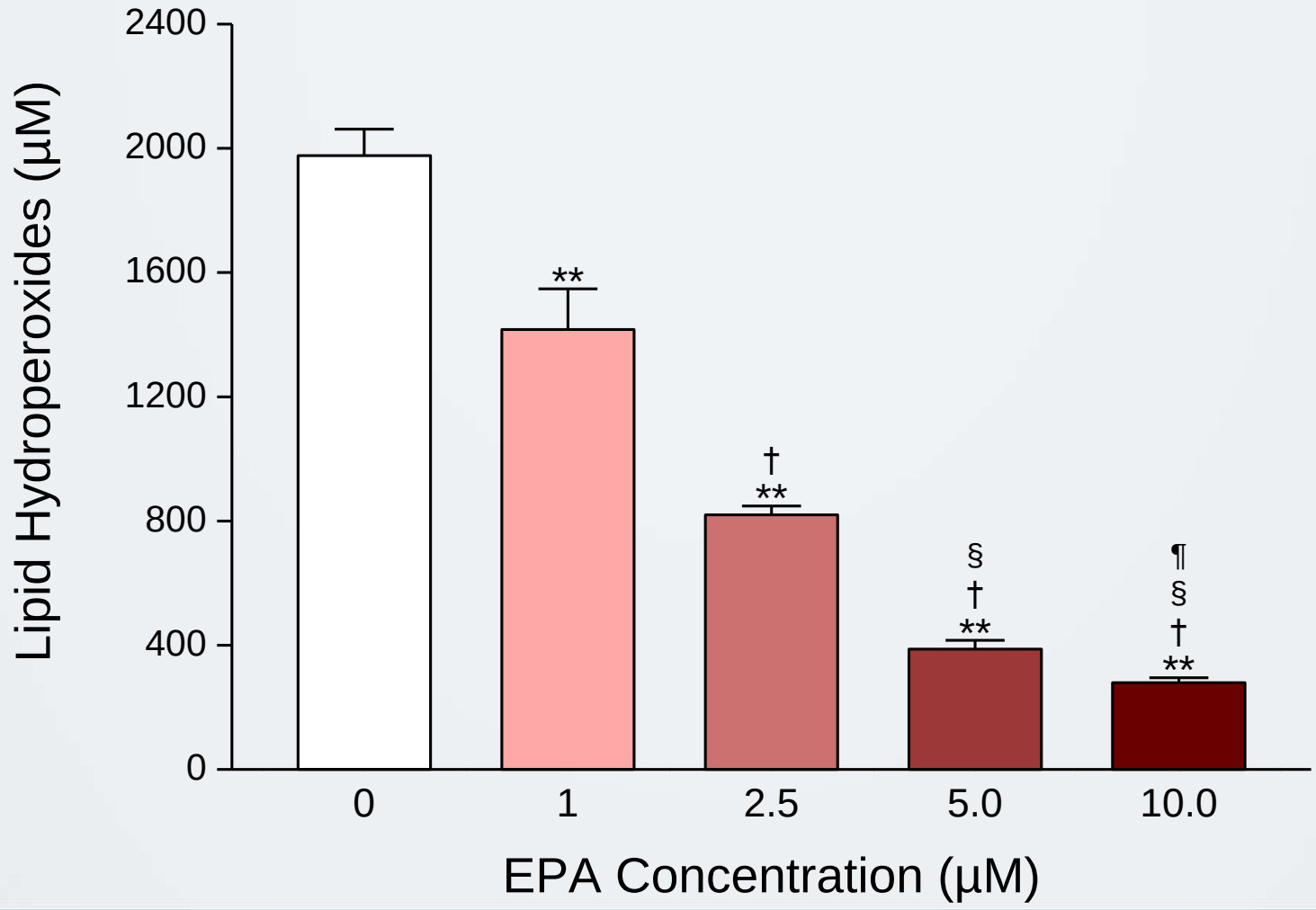
Mason RP and Jacob RF. *Biochim Biophys Acta.* 2015;1848:502-9.

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



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

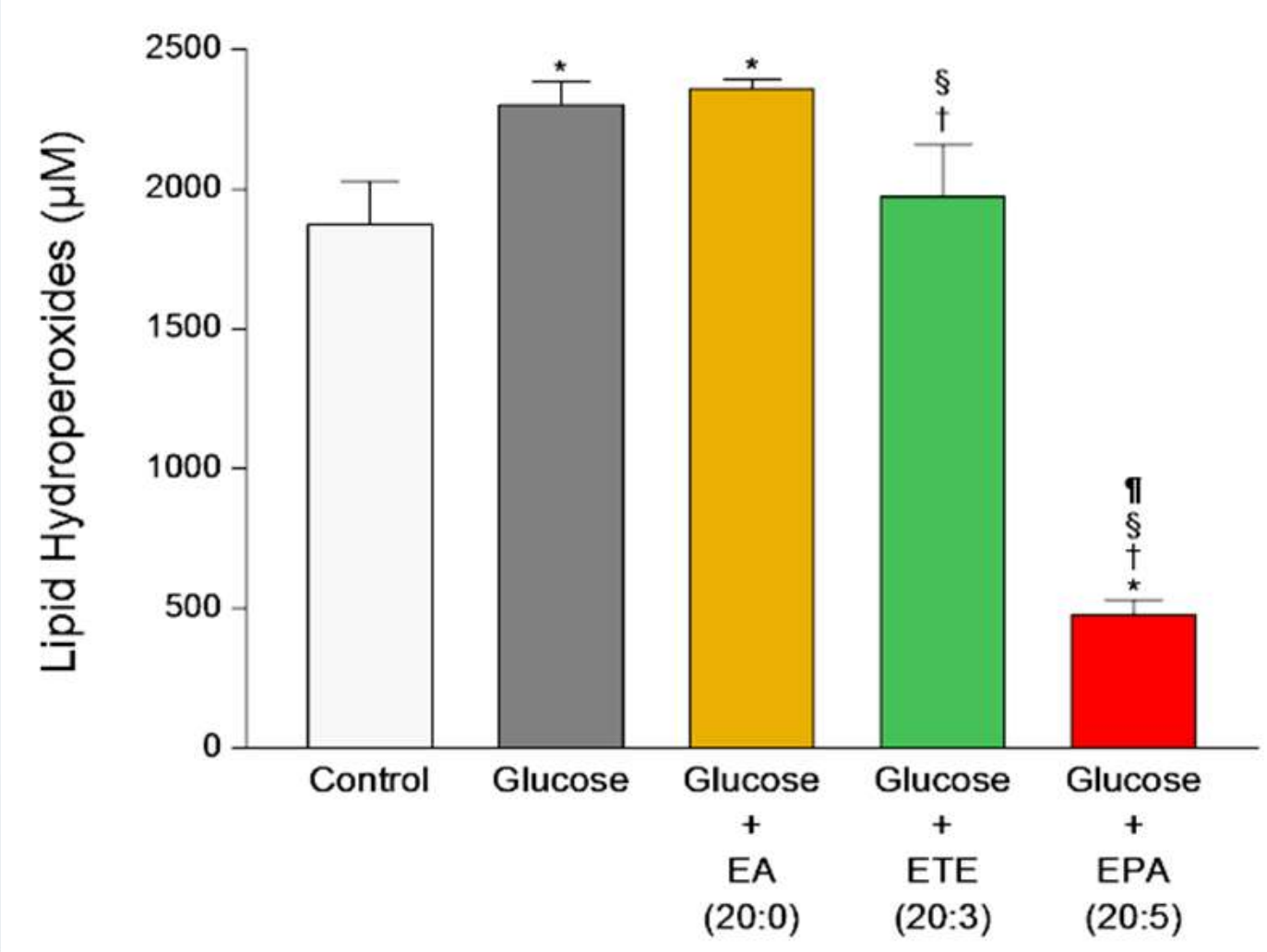
EPA Inhibits Membrane Lipid Peroxidation in a Dose-dependent Fashion



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

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

Effect of Structure on Antioxidant Activity of EPA in Membranes

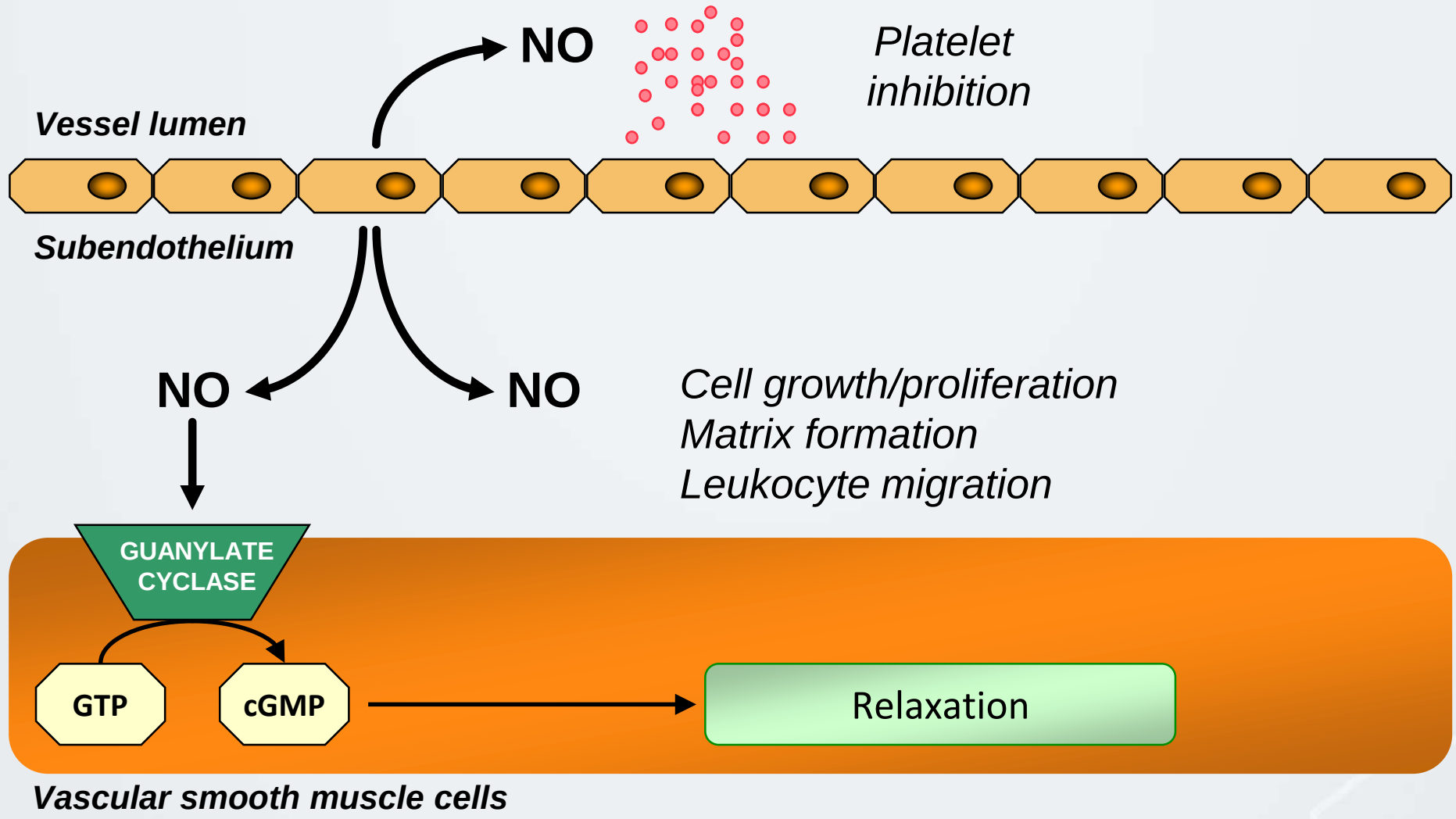


*P<0.001 vs vehicle-treated control. †P<0.001 vs glucose-treated control. §P<0.001 vs EA. ¶P<0.001 vs ETE.
(Student-Newman-Keuls multiple comparisons test; overall ANOVA: P<0.0001, F=248.73). Values are mean ± SD (N=6).

Question 3

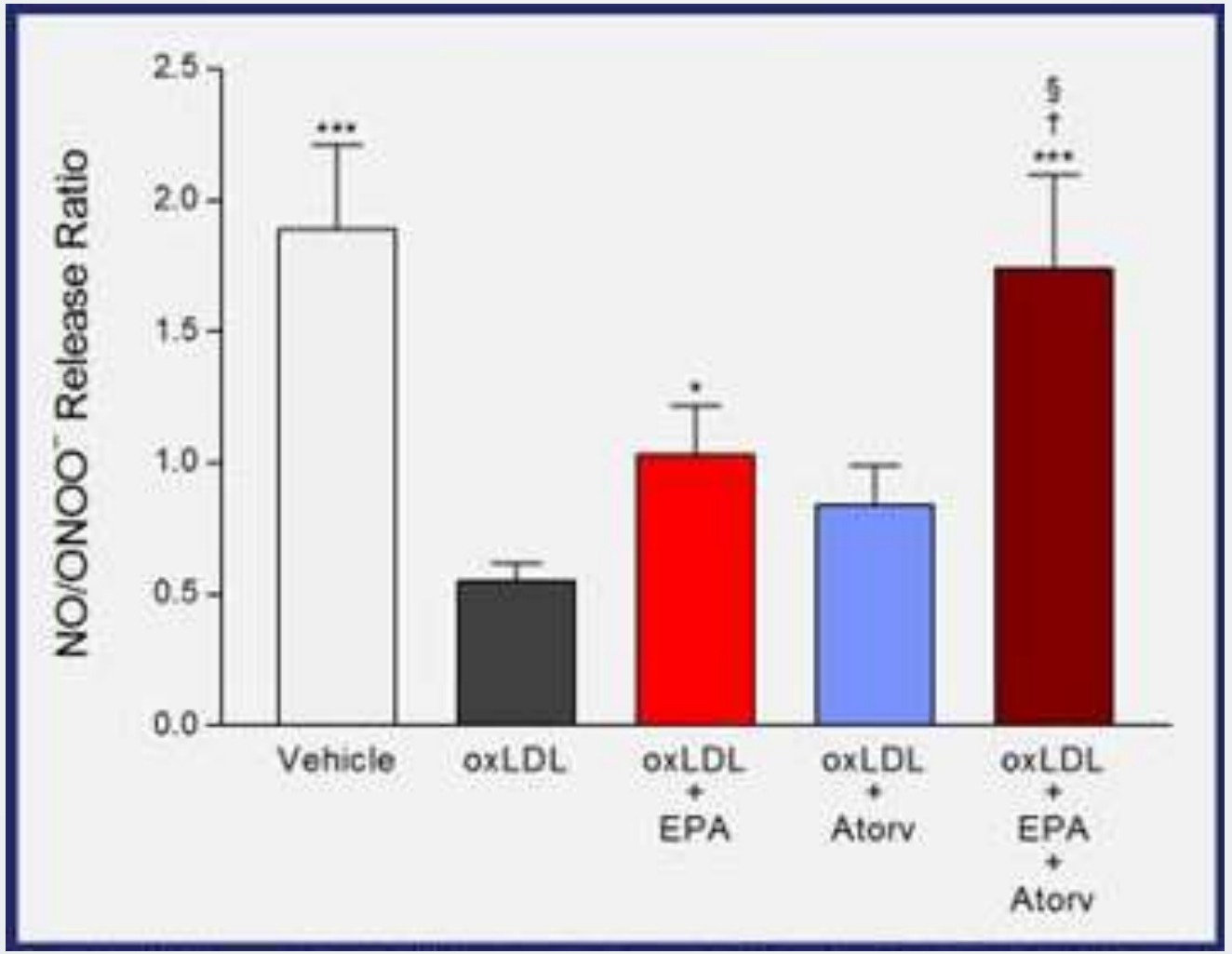
What effects do Omega-3 Fatty Acids and statins have on endothelial dysfunction?

Nitric Oxide Is a Key Mediator of Vascular Protection



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

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

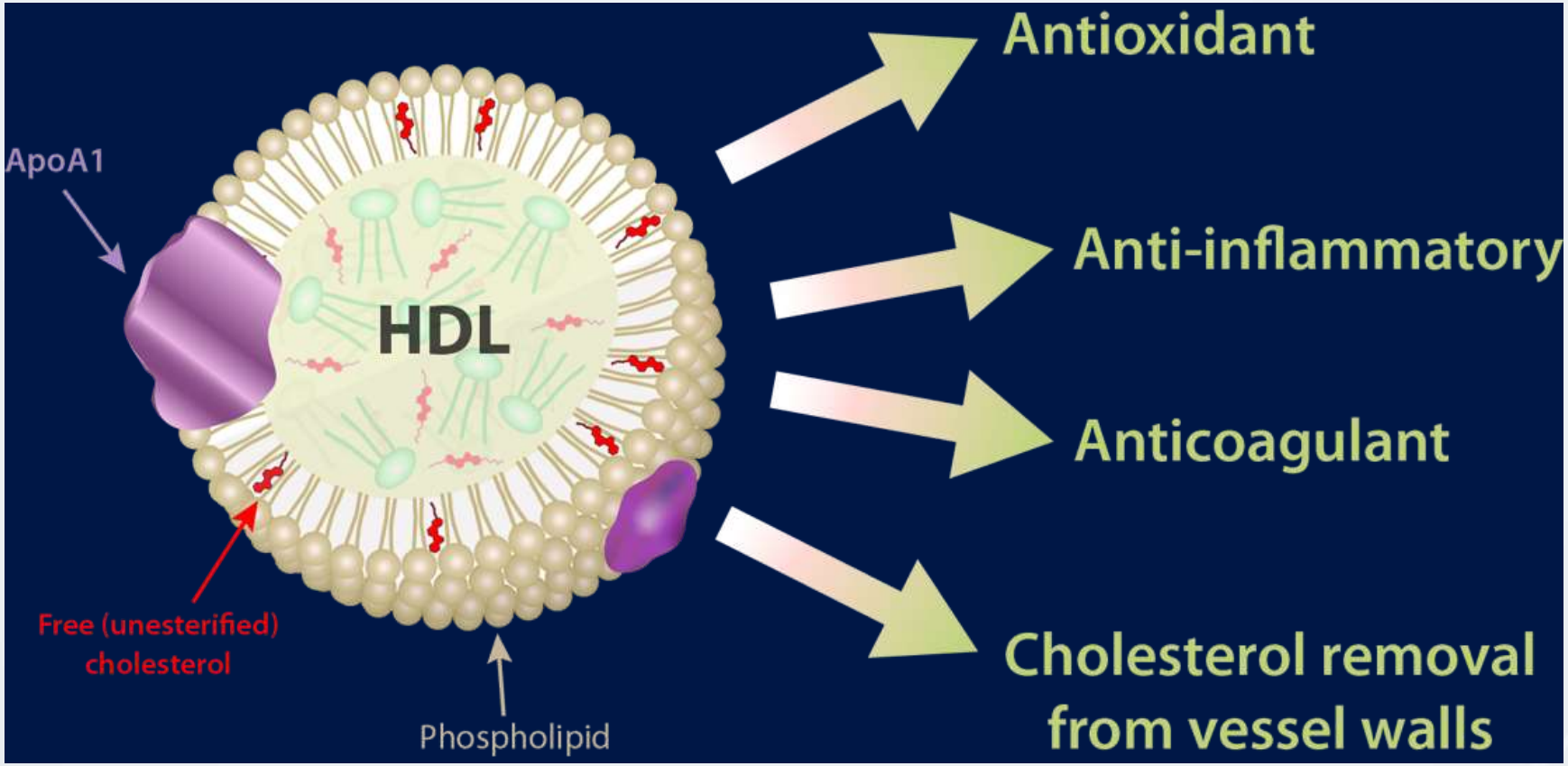


Atorvastatin active metabolite was used in this study. Values are mean ± SD (N=3-6).
*P<0.05 and ***P<0.001 vs oxLDL. †P<0.01 vs oxLDL + EPA. §P<0.001 vs oxLDL + Atorv.
Mason RP et al. *Biomed Pharmacother*. 2018;203:1231-7.

Question 4

*What effects do Omega-3 Fatty Acids and other TG-lowering agents have on **HDL function**?*

Structure and Benefits of HDL



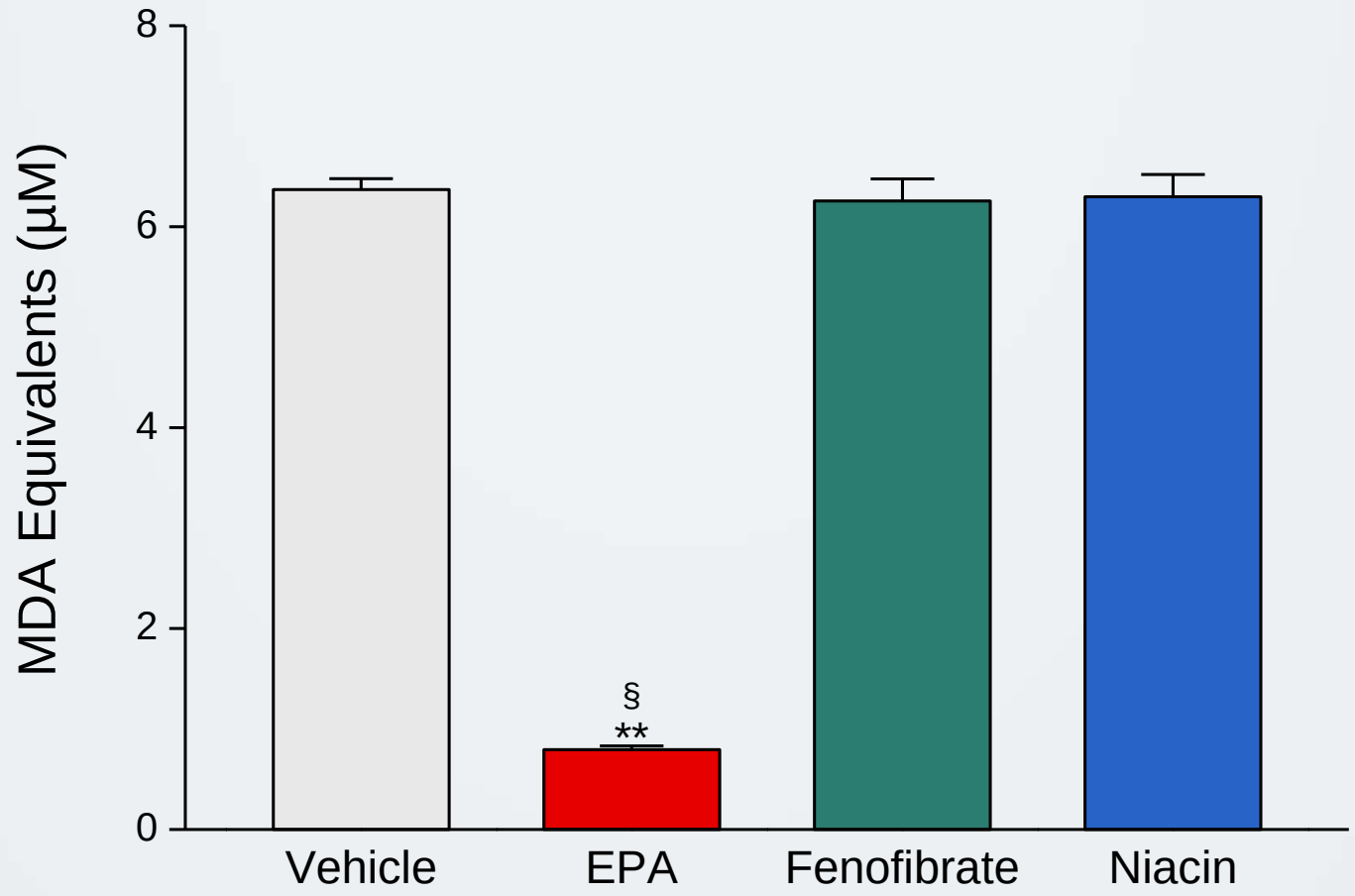
Mason RP and Sherratt SCR. *WCIRDC* Poster Presentation. Burbank, CA. 2018.

Effects of EPA on HDL Function

- Increased HDL-associated PON1 activity
- Enhanced cholesterol efflux capacity in macrophages
- Reduced VCAM-1 expression in endothelial cells
- Increases resolvin E3 production in endothelial cells

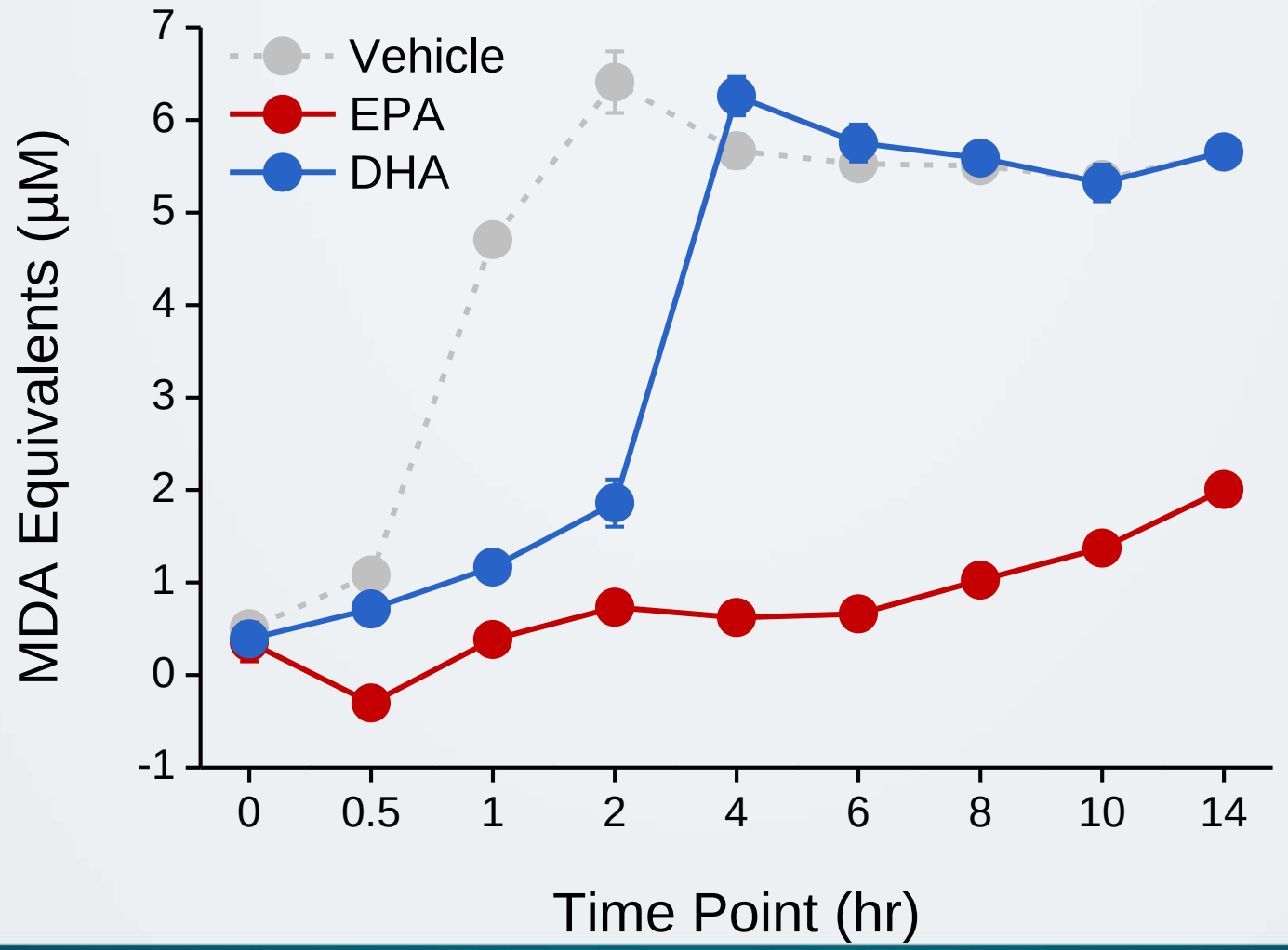
Tanaka N et al. *Atherosclerosis*. 2014;237:577-83.
Tanaka N et al. *Circ J*. 2018;82:596-601.
Sherratt SCR and Mason RP. *Biochem Biophys Res Comm*. 2018;496:335-8.

EPA Inhibits HDL Oxidation as Compared to Fenofibrate or Niacin



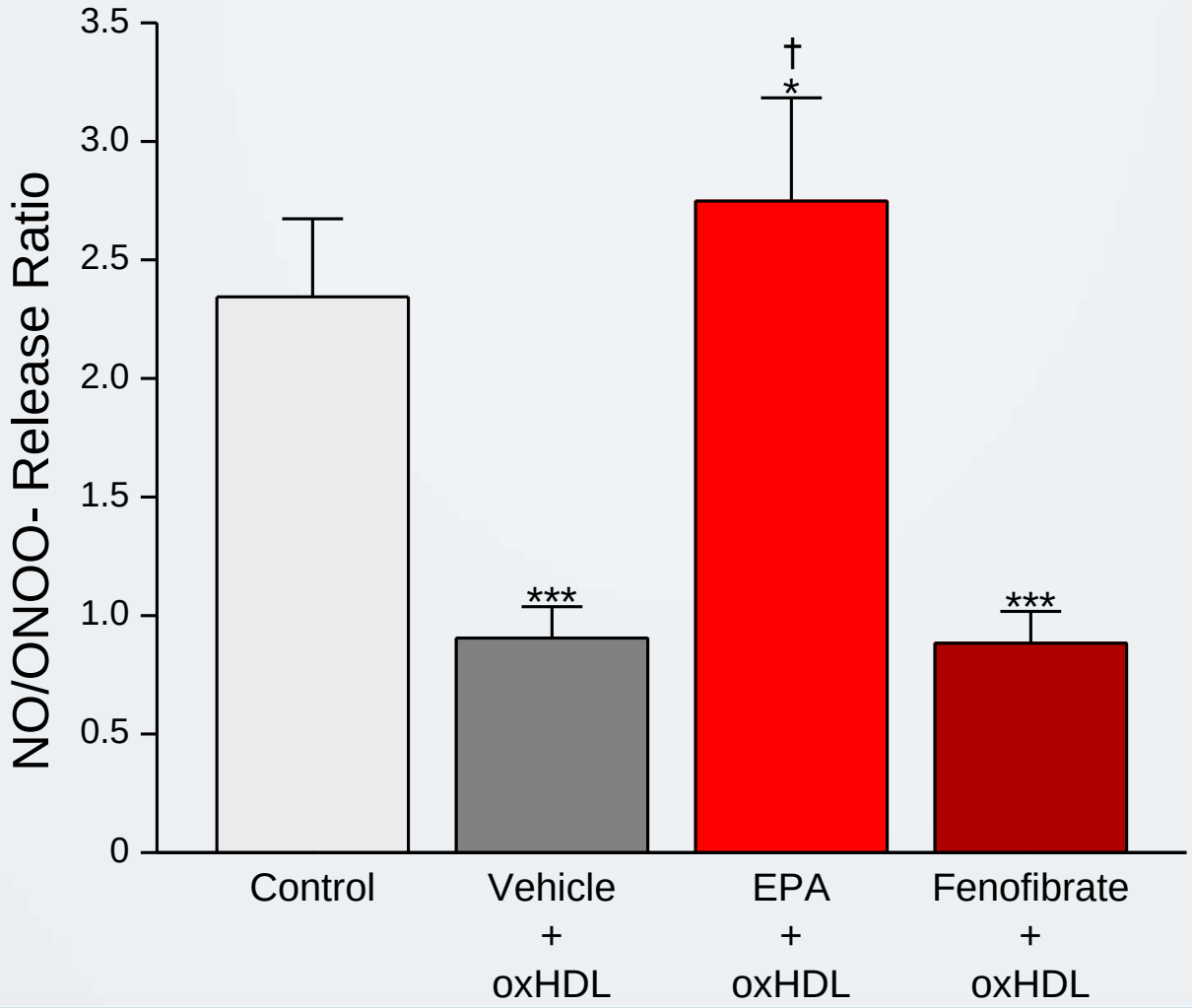
**P<0.001 vs vehicle. §P<0.001 vs Fenofibrate or Niacin. (Student-Newman-Keuls multiple comparisons test; overall ANOVA: P<0.0001, F=833.86).
Values are mean ± SD (N=3).
Mason RP et al. European Atherosclerosis Society. 2018.

Effects of EPA and DHA on Oxidation of HDL



Sherratt SCR and Mason RP. *Biochem Biophys Res Comm*. 2018;496:335-8.

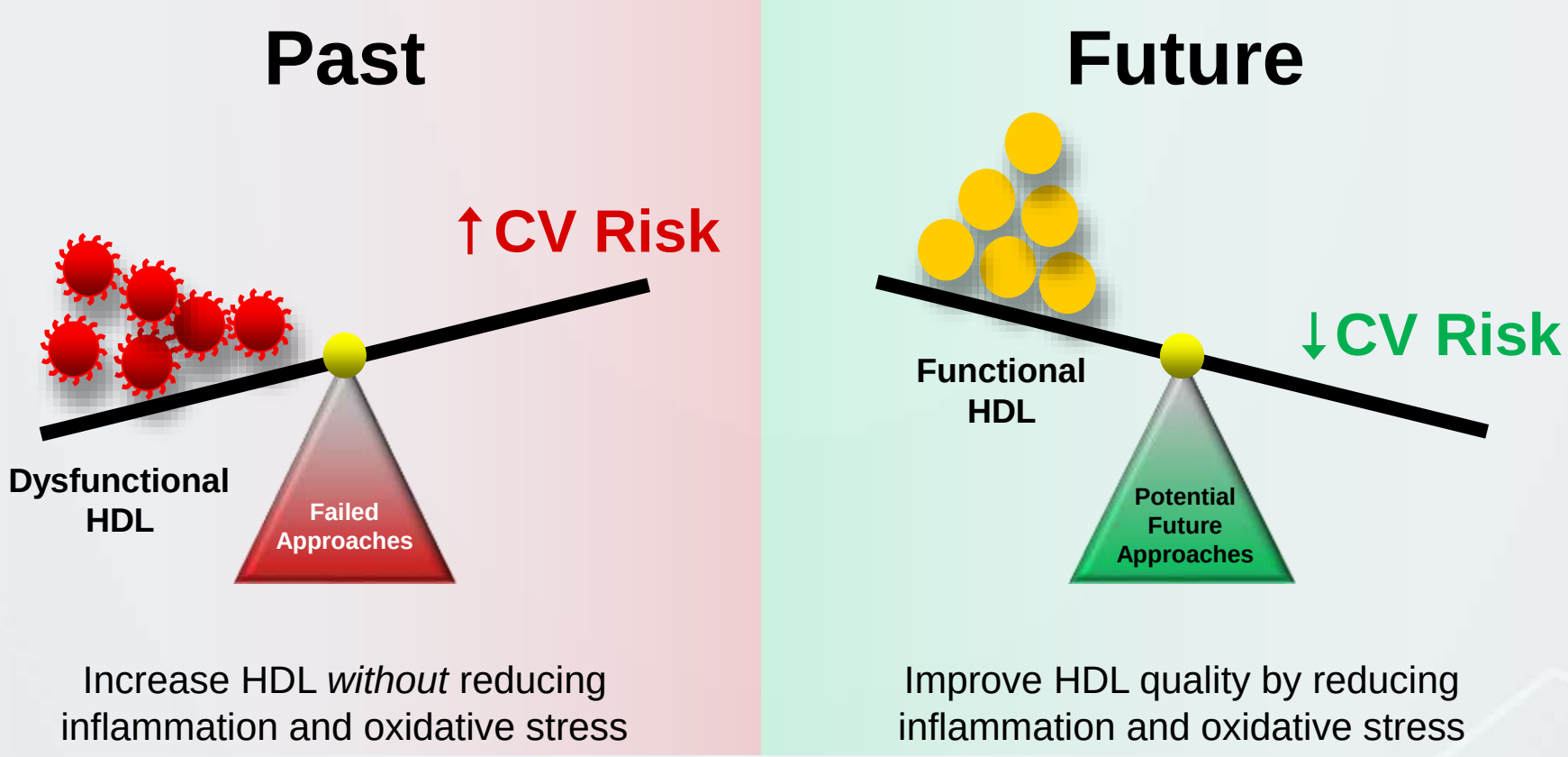
Effect of TG-lowering Agents on HDL Mediated Endothelial Function Following Oxidation



*P<0.05 and ***P<0.001 vs control. †P<0.001 vs vehicle + oxHDL or Fenofibrate + oxHDL.
(Student-Newman-Keuls multiple comparisons test; overall ANOVA: P<0.0001, F=61.063); values are mean ± SD (N=4-6).

Mason RP et al. European Atherosclerosis Society. 2018.

HDL-C as a CV Therapy?



Increase HDL *without* reducing inflammation and oxidative stress

Improve HDL quality by reducing inflammation and oxidative stress

Mason RP et al. European Atherosclerosis Society. 2018.

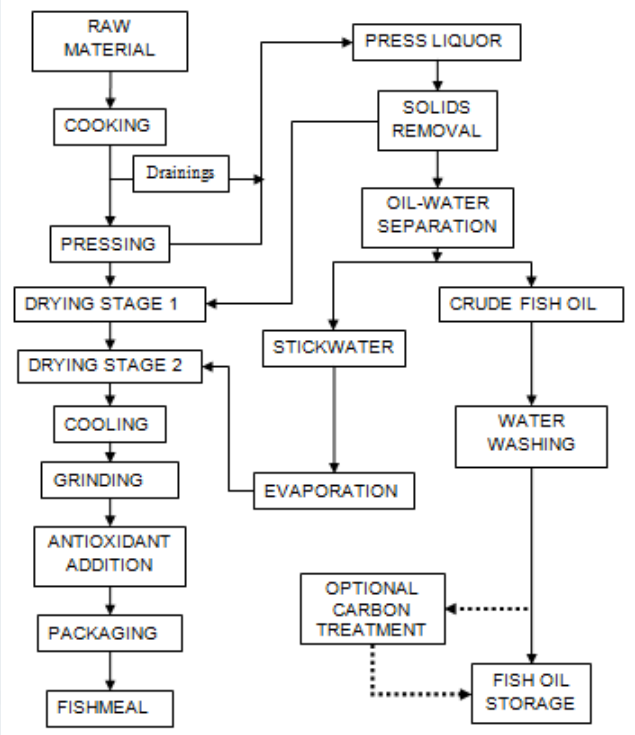
Are Fish Oil Dietary Supplements Appropriate for CV Patients?

Fish Oil Dietary Supplements

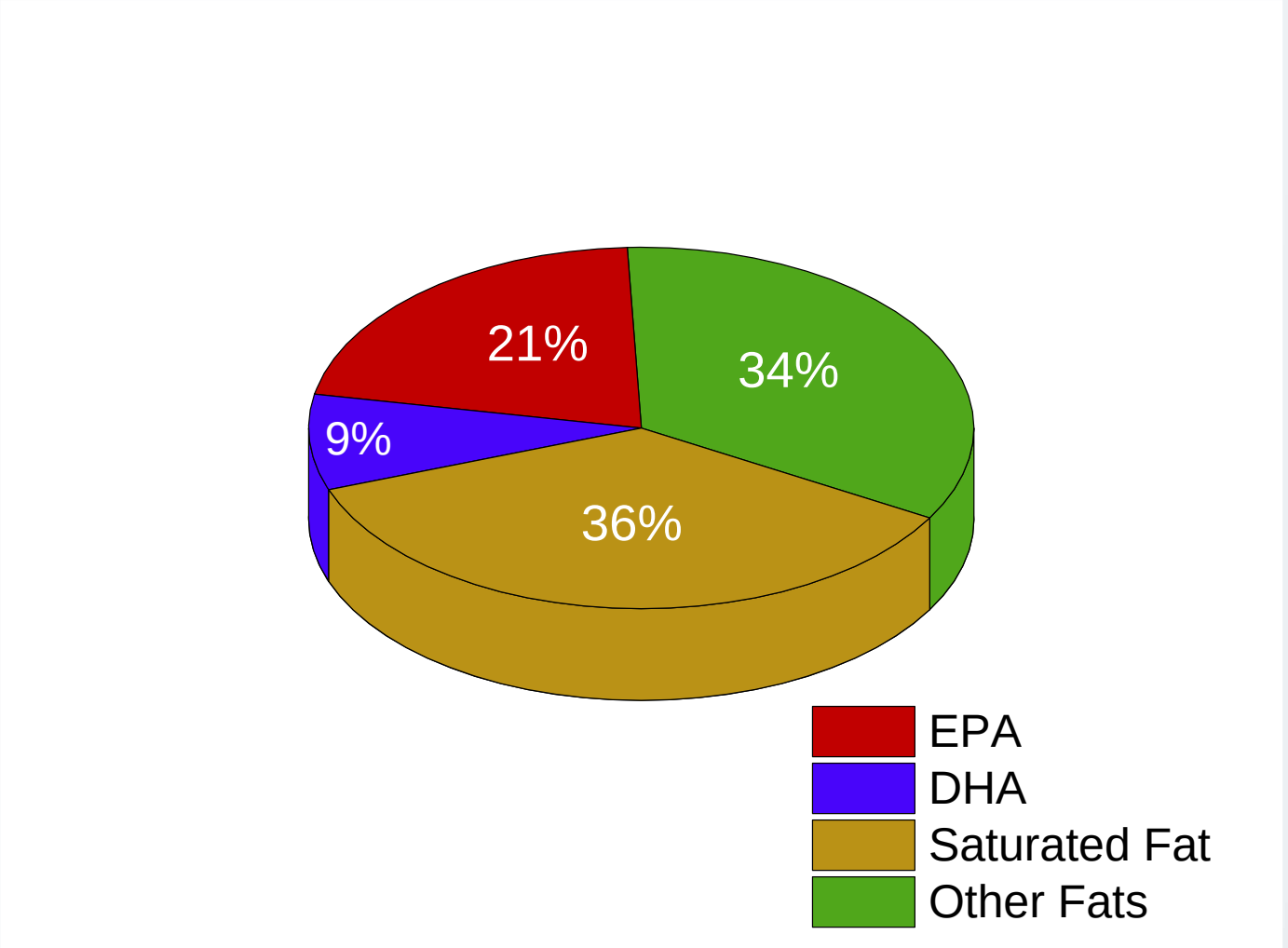
- Leading DS taken by US adults is fish oil[1]
  - 19 million fish oil DS consumed each month[1]
- ~80% of PharmDs and MDs who recommend fish oil supplements think, mistakenly, that they are FDA-approved OTC[2]
  - 30% of PharmDs and 22% of MDs believe Rx and DS are similar in strength and content[2]

1. "Omega-3 Supplements: In Depth". NCCIH. N.p., 2009. Web. 7 Apr. 2016.
2. Fairleigh Dickinson University's Public Mind™ Poll, Omega-3 Physician/Pharmacist Study, March 2013.

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

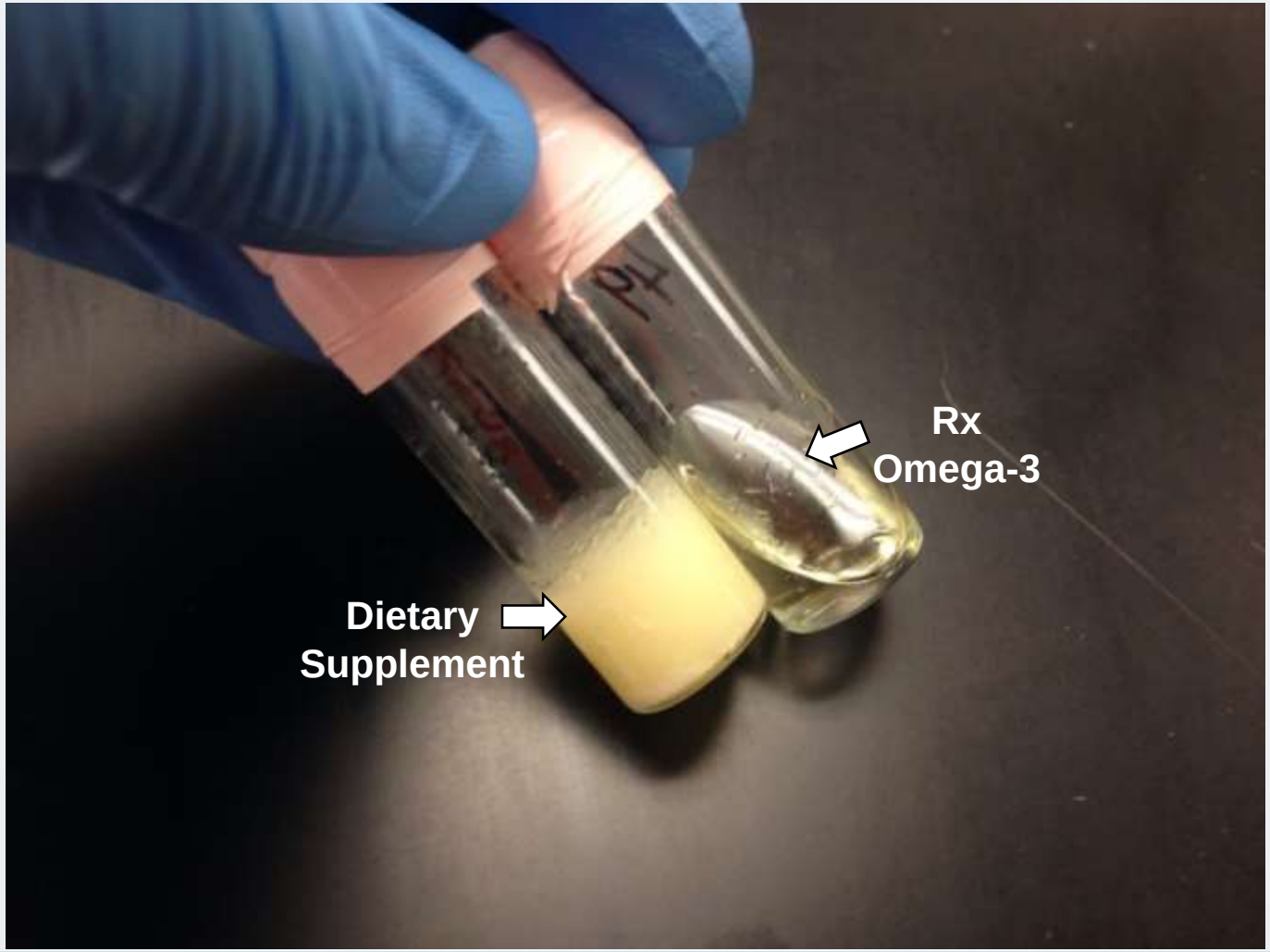


Fatty Acid Content of Leading US Fish Oil Supplement

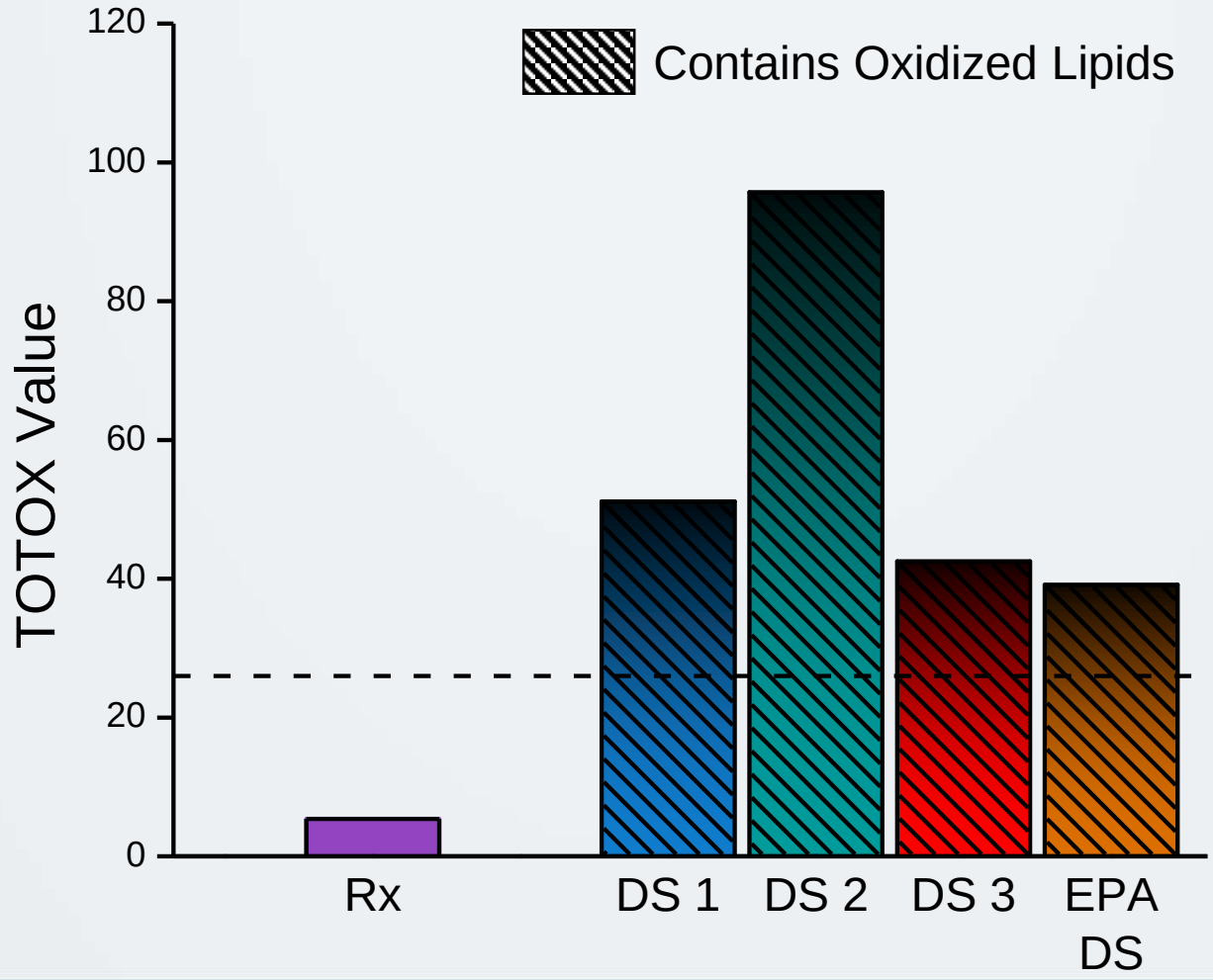


Mason RP and Sherratt SCR. *Biochem Biophys Res Commun.* 2017;483:425-9.

Saturated Fatty Acid Content in Fish Oil Supplement Results in Solid Mass following Isolation



Supplement Total Oxidation Values Exceed International Thresholds

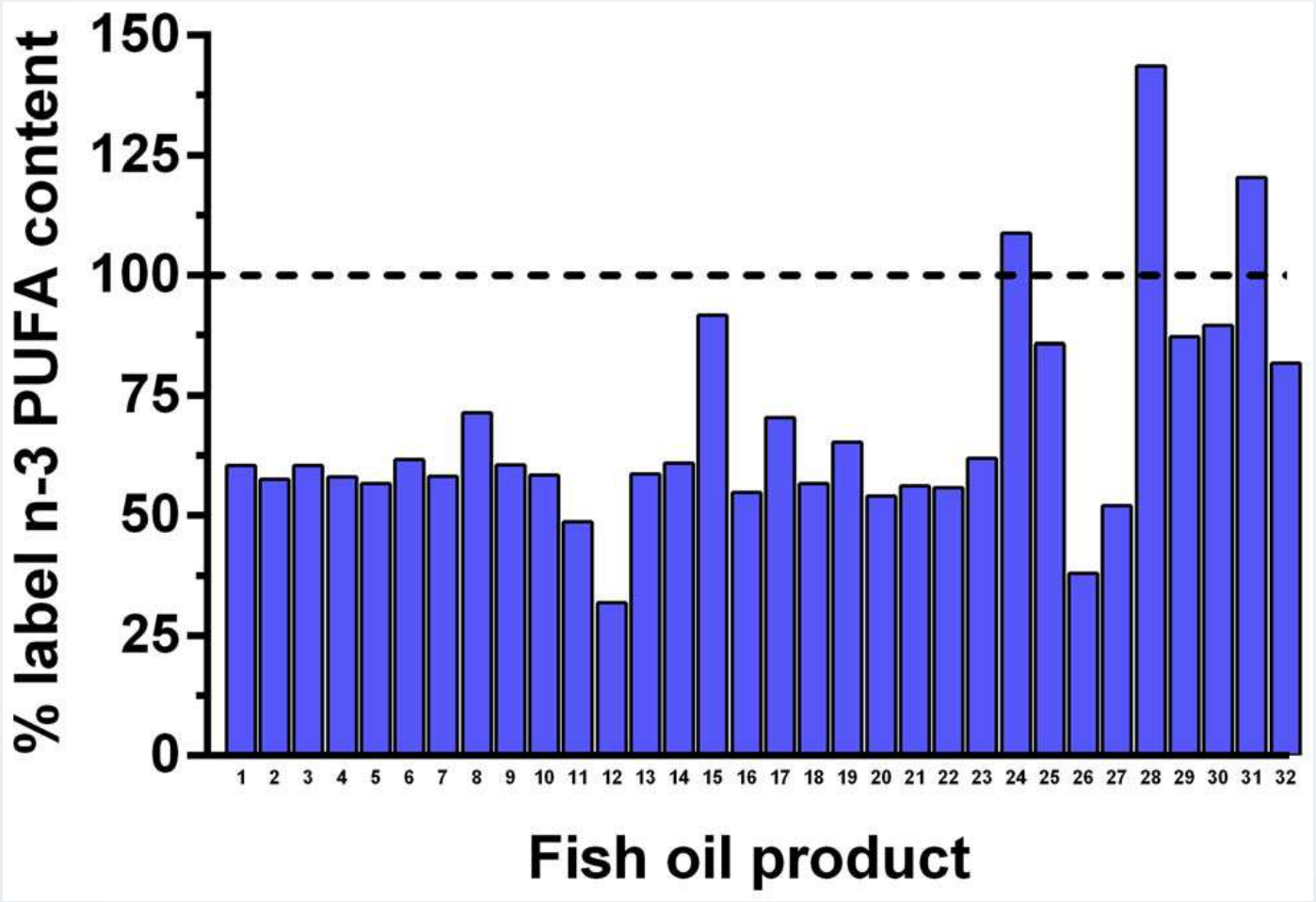


International threshold for oxidation (US Council for Responsible Nutrition. Voluntary Monograph: Omega-3 DHA, Omega-3 EPA, Omega-3 DHA & EPA (2006). Available at: http://www.crnusa.org/pdfs/O3FINALMONOGRAPHdoc.pdf. [Date of access: 09/04/2015].

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

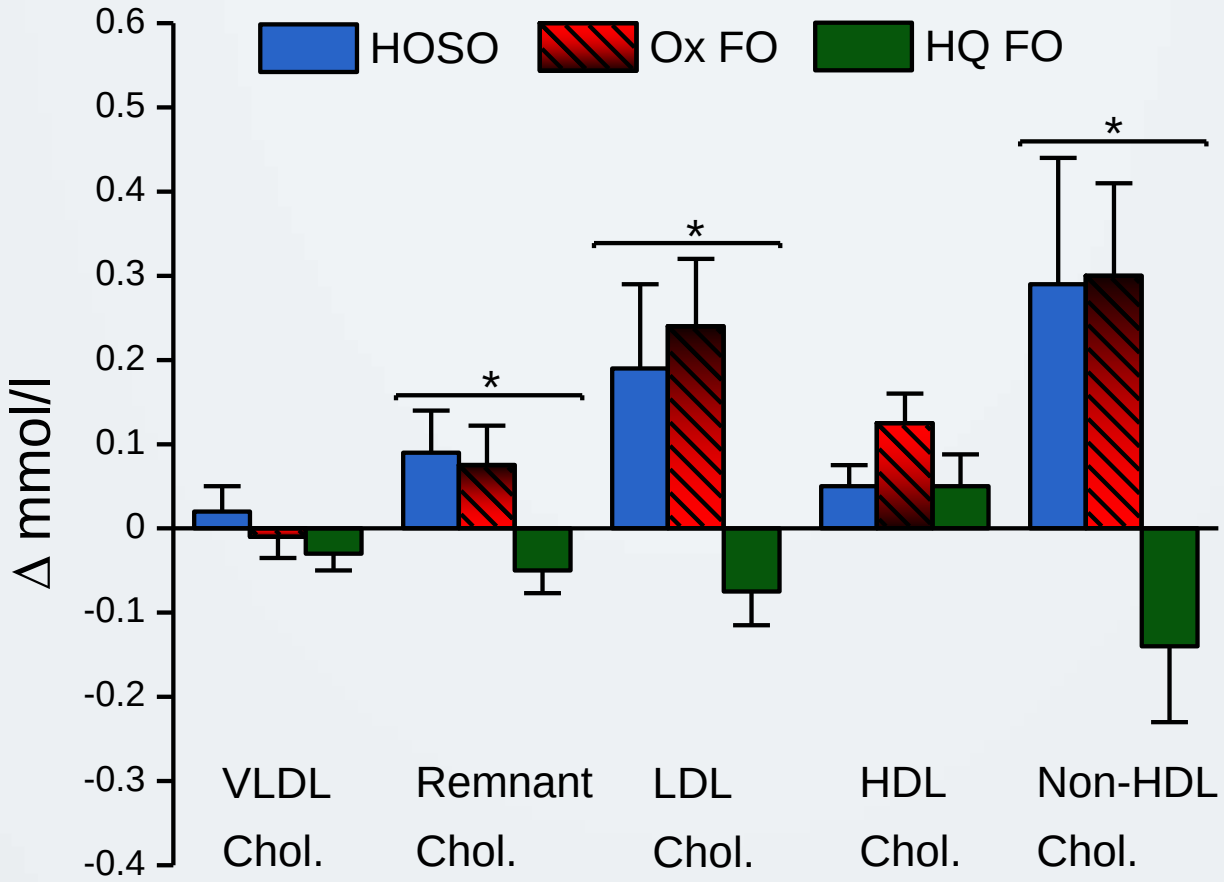
Achieving a Recommended 4 g Daily Dose of Omega-3 with Common Fish Oil Supplements

Fish Oil Supplement Claims Are Inaccurate and Overstate Actual Content



Albert BB et al. *Sci Rep*. 2015;5:7928.

Oxidized Fish Oil Negatively Impacts Key Lipid Factors



PV of 18 mEq/kg and TOTOX 45.Statistical Indicator: *P<0.05. (Values are mean ± SD.)
Source: Rundblad A et al. *Br J Nutr*. 2017;117:1291-8.

Environmental and Processing Contaminants Found in Supplements Are Harmful to Humans

- Heavy metals
  - –Mercury, Lead
- Dioxins, dibenzofurans, dioxin-like polychlorinated biphenyls (PCBs)

"Fish oils extracted from captured marine fish species did not meet the requirements for human consumption…regarding the sum of dioxin and dl-PCB."[1]

[1]Merkle S et al. *Food Control.* 2017;73(Part B):1379-87.

Summary of Fish Oil Dietary Supplements: Right for CV Patients?

FDA Product Classification[1] → Food

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

Content & Purity[2-8] →
- Difficult to achieve AHA recommended OM-3 levels
- Contain high levels of saturated fats
- Advertised omega-3 content overstated
- Contain oxidized lipids leading to dyslipidemia and increased CV risk
- Contain PCBs and dioxins at levels known to be harmful for humans

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

Conclusion

- Inflammation, oxidative stress, and endothelial dysfunction are causally related to atherosclerosis;
- Omega-3 FA (EPA) interferes with mechanisms of atherosclerosis at therapeutic concentrations as compared to other TG-lowering agents or omega-3 FA formulations. This may contribute to clinical benefits as seen in REDUCE-IT;
- Dietary supplements are not an appropriate substitute for FDA-approved and tested omega-3 fatty acids in patients.

BRIGHAM AND WOMEN'S HOSPITAL

ELUCIDA RESEARCH

Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

Deepak L Bhatt, MD, MPH, Ph. Gabriel Steg, MD, Michael Miller, MD,

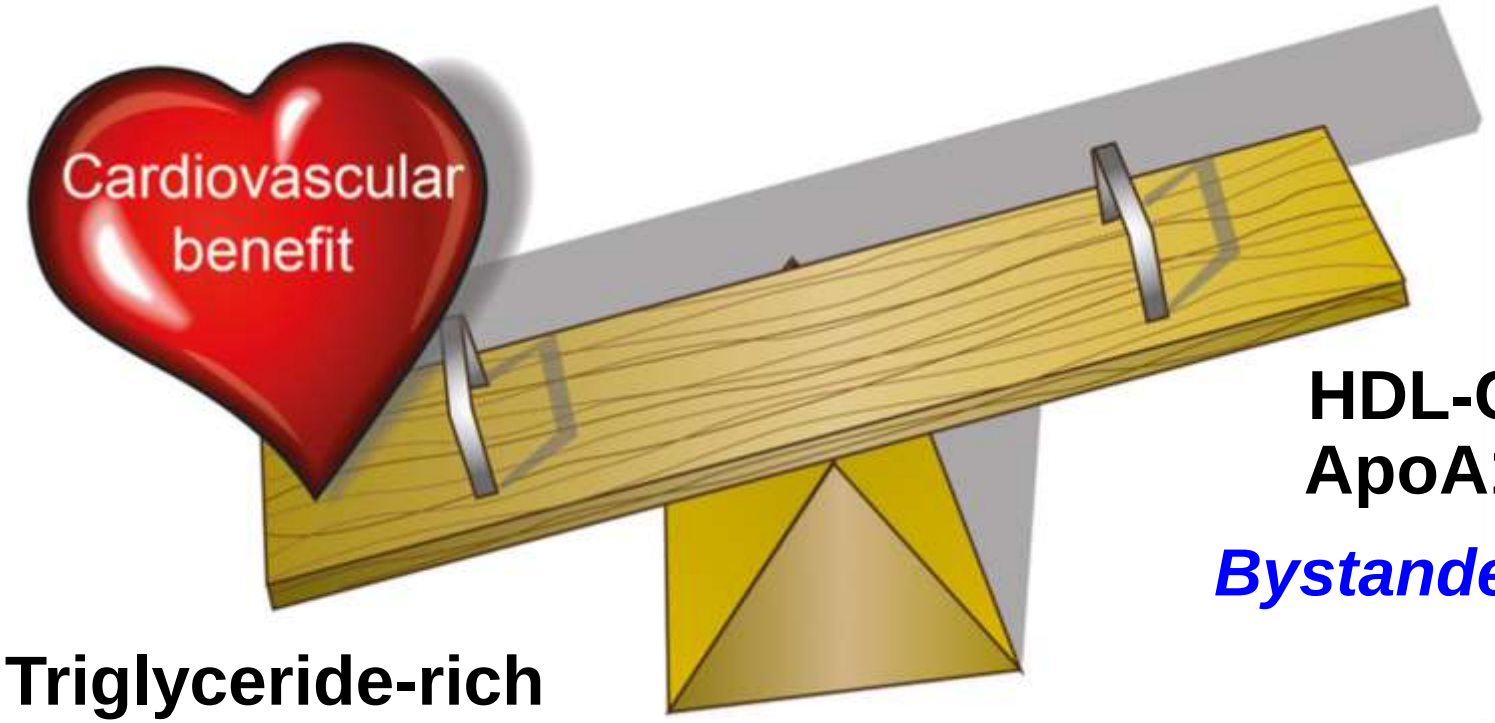
Eliot A. Brinton, MD, Terry A. Jacobson, MD, Steven B. Ketchum, PhD,

Ralph T. Doyle, Jr., BA, Rebecca A. Juliano, PhD, Lixia Jiao, PhD,

Craig Granowitz, MD, PhD, Jean-Claude Tardif, MD, Christie M. Ballantyne, MD,

on Behalf of the REDUCE-IT Investigators

Triglycerides a Causal Risk Factor?



Triglyceride-rich lipoproteins
ApoC3

Causal risk factors?

HDL-C
ApoA1

Bystanders?

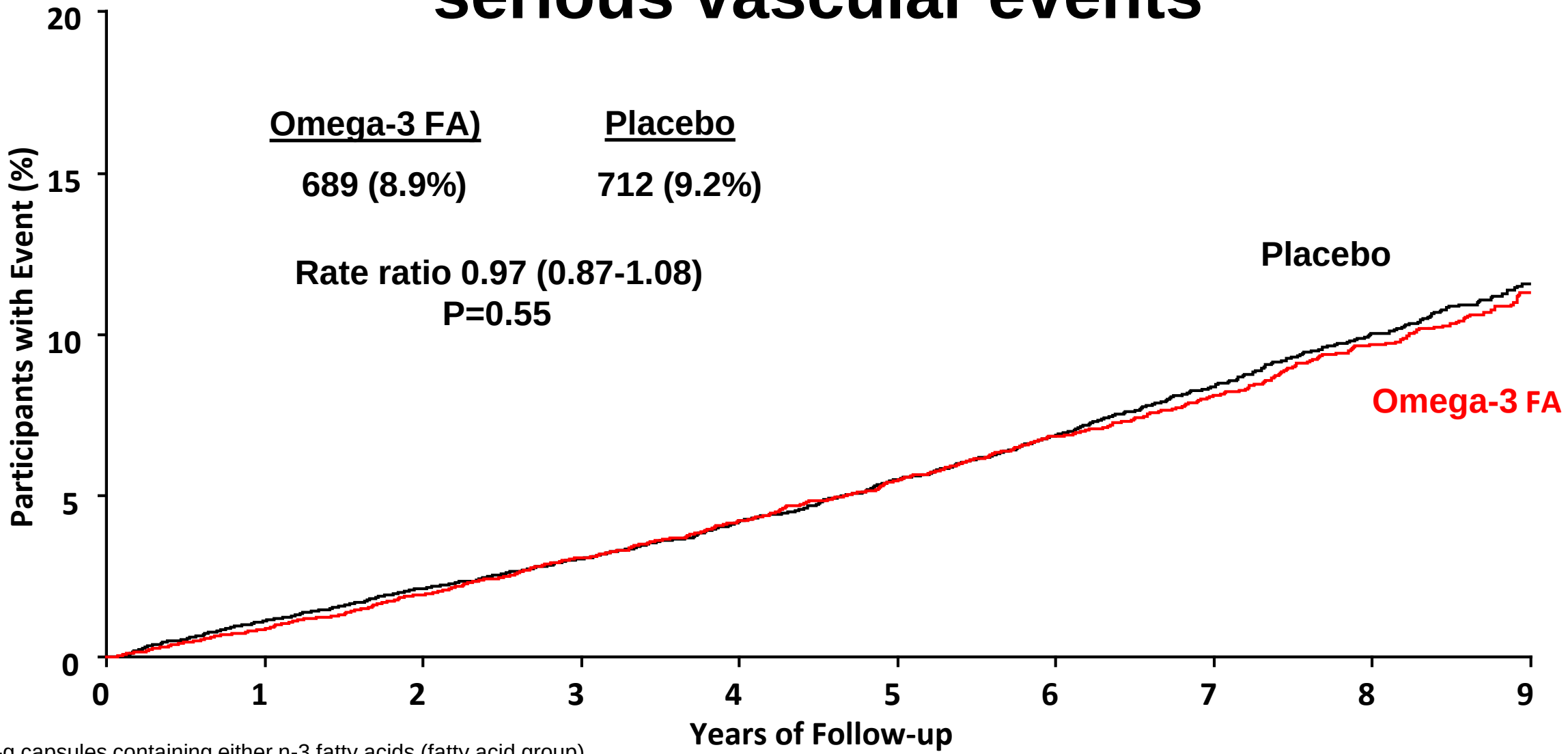
Adapted with permission from Libby P. Triglycerides on the rise: should we swap seats on the seesaw? *Eur Heart J*. 2015;36:774-776.

ASCEND trial design

Eligibility:	Age ≥ 40 years; any DIABETES; no prior cardiovascular disease
Participants:	15,480 UK patients
Randomization:	Omega-3 fatty acids 1 g capsule/day vs placebo (and aspirin 100 mg daily vs placebo)
Follow-up:	Mean 7.4 years; >99% complete for morbidity & mortality
Adherence:	Average adherence to omega-3 capsules 77%

ASCEND Study Collaborative Group. Trials 2016;17:286 / Am Heart J 2018;198:135-144

Effect of omega-3 FA supplements on serious vascular events



1-g capsules containing either n-3 fatty acids (fatty acid group)

ASCEND Study Collaborative Group, et al. *N Engl J Med*. 2018;379(16):1540-1550.

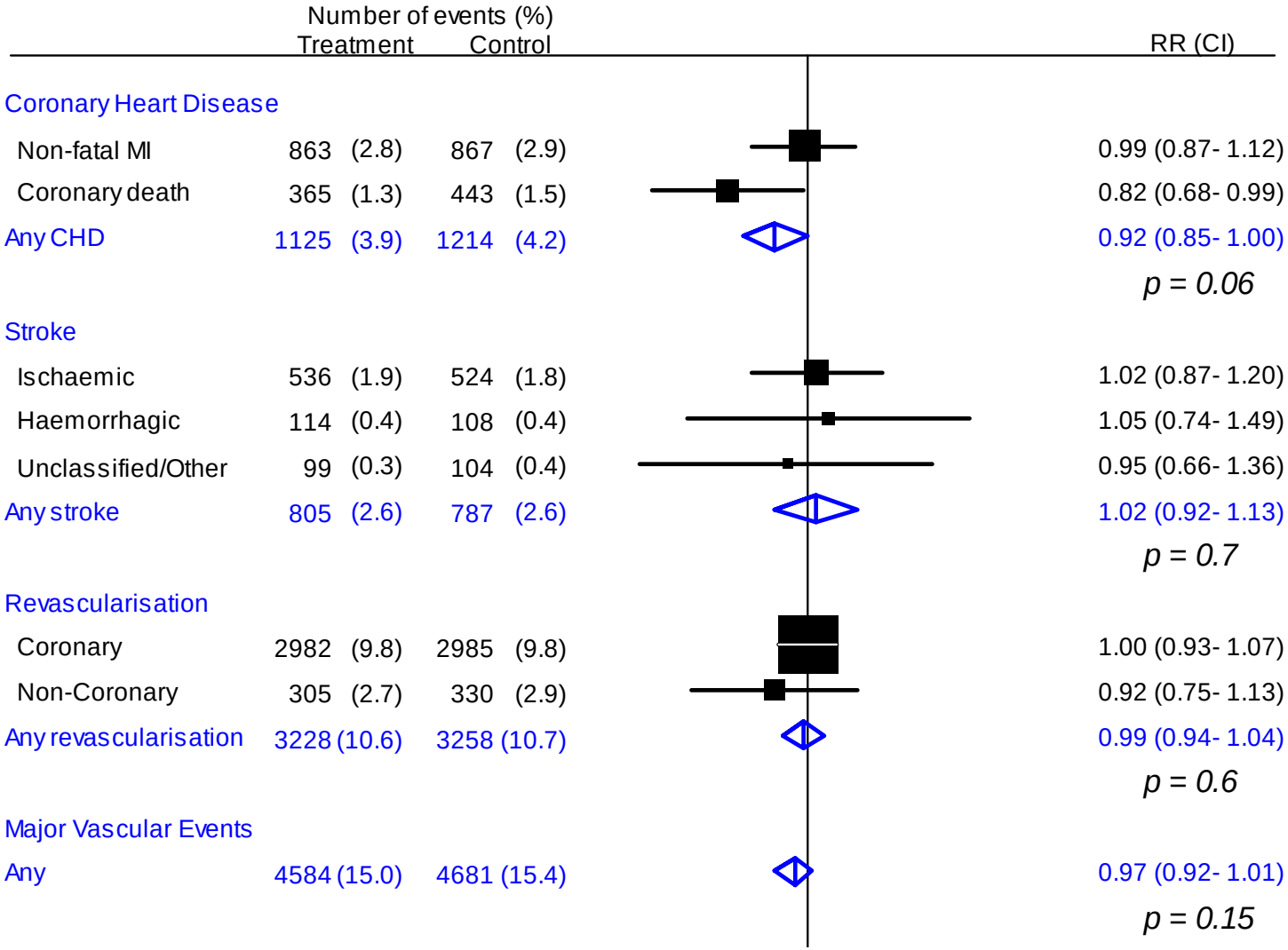
Effect of omega-3 FA supplements

Tabular meta-analysis of large randomized trials
(>500 participants for at least 1 year)

10 trials including 77,917 participants
28,722 (37% with diabetes)

Mean follow-up 4.4 years

ASCEND: 15,480 participants with DM
7.4 years mean follow-up



Fish oil supplements are widely used

- Estimated global market for omega-3 products was $31 billion in 2015
- In a large UK prospective study, 31% of adults reported taking fish oils
- Estimates suggest 7.8% of US population (19 million people) take fish oil supplements
- Benefits claimed on the: heart, brain, weight, vision, inflammation, skin, pregnancy and early life, liver fat, depression, childhood behaviour, mental decline, allergies, bones…

Summary: Omega-3 FA supplementation in diabetes

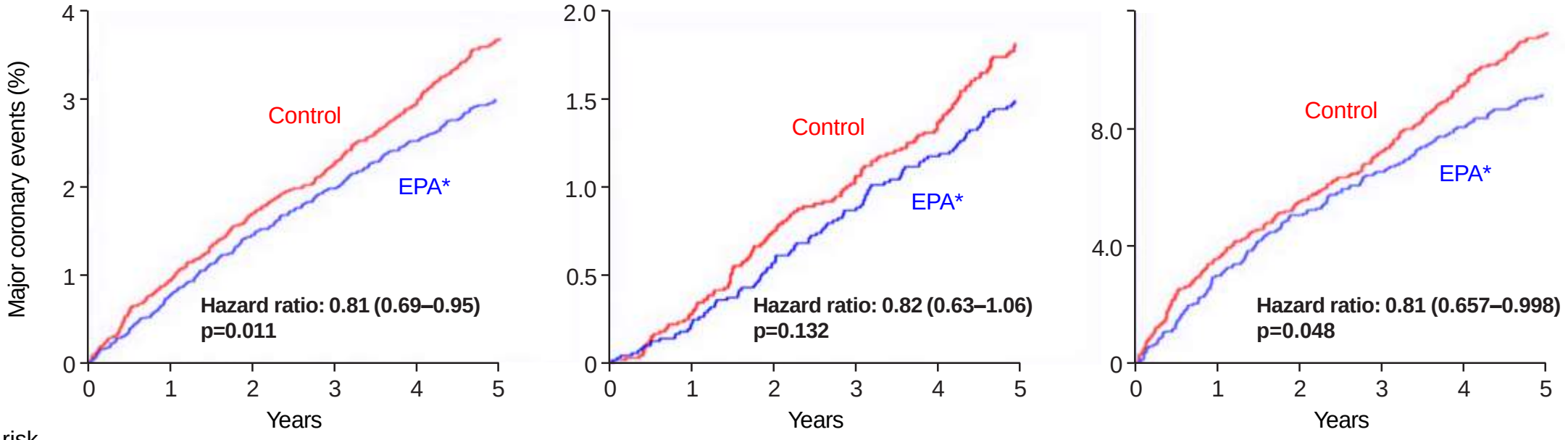
- ASCEND is the largest and longest duration placebo-controlled randomized trial of omega-3 FA supplementation
- No effect on primary outcome of serious vascular events
- No effect on cancer, total or cause-specific mortality
- No safety concerns
- Guideline recommendations should be reconsidered

The VITamin D and OmegA-3 TriaL (VITAL): Principal Results for Vitamin D and Omega-3 Fatty Acid Supplementation in the Primary Prevention of Cardiovascular Disease and Cancer

- 25,871 participants (primary prevention)
- Median follow-up of 5.3 years
- Major cardiovascular event occurred in 386 participants in the n−3 group and in 419 in the placebo group
  - **hazard ratio, 0.92; P=0.24**

JELIS Suggests CV Risk Reduction with EPA in Japanese Hypercholesterolemic Patients

Kaplan-Meier Estimates of Incidence of Coronary Events



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

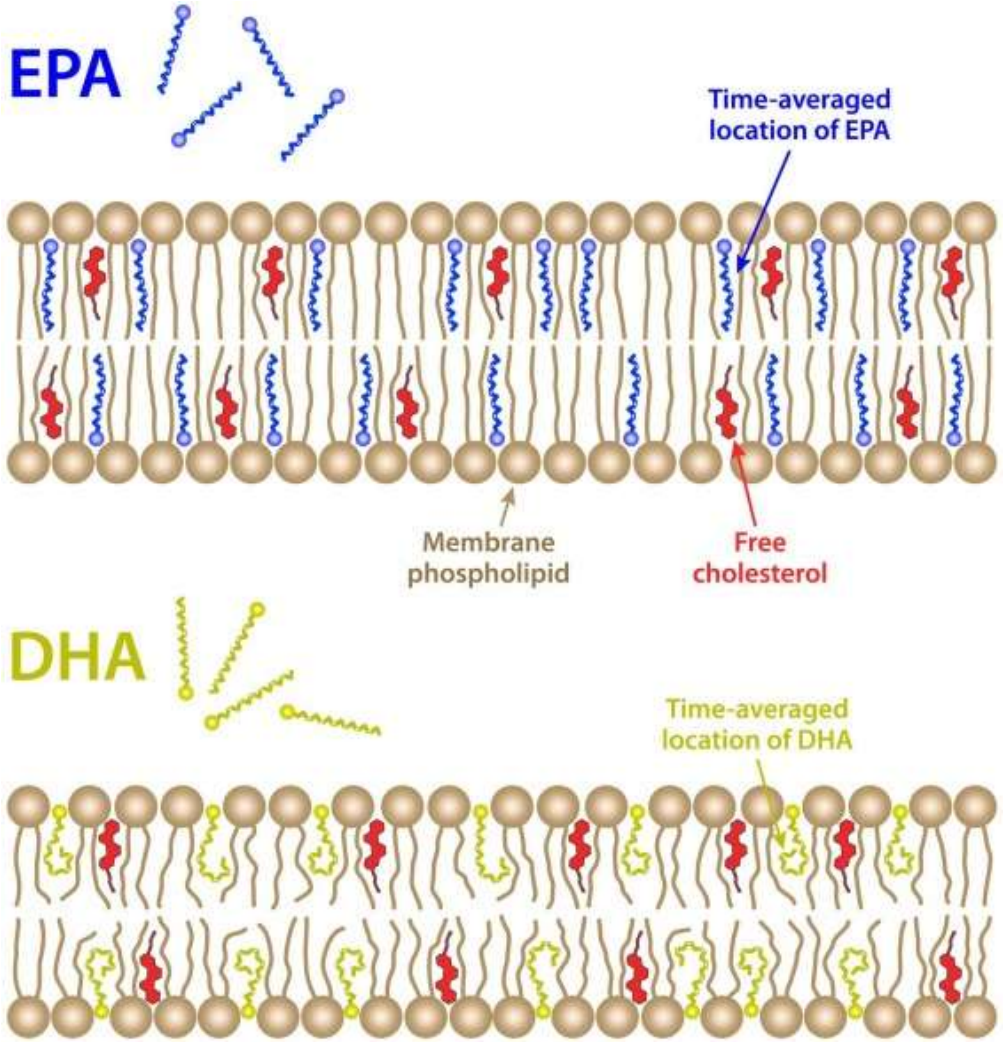
7478	7204	7103	6841	6678	6508
7503	7210	7020	6823	6649	6482

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

*1.8 g/day

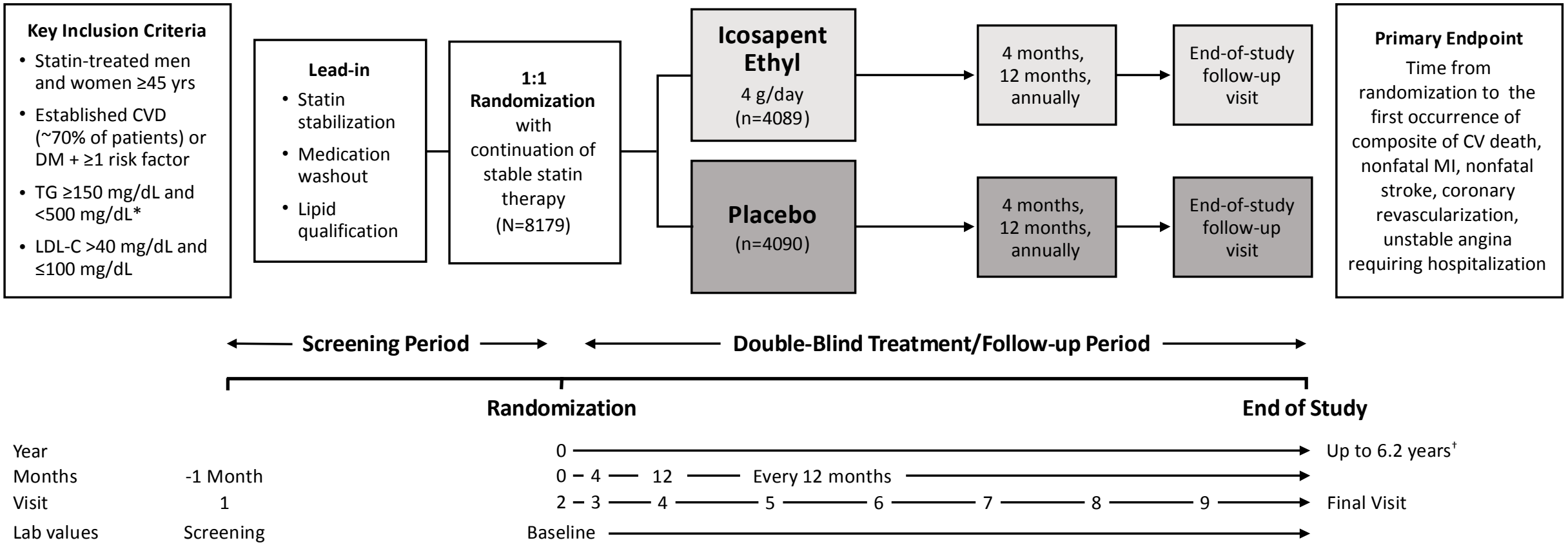
Adapted with permission from Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet.* 2007;369:1090-1098.

EPA and DHA Have Differing Effects on Cellular Membranes



Reprinted with permission* from Sherratt SCR, Mason RP. Eicosapentaenoic acid and docosahexaenoic acid have distinct membrane locations and lipid interactions as determined by X-ray diffraction. *Chem Phys Lipids*. 2018;212:73-79. [*https://creativecommons.org/licenses.org/by-nc/4.0/]

REDUCE-IT Design



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

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

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

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

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

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

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

Inclusion Criteria for Secondary Prevention Cohort

One or more of the following:

1. Documented coronary artery disease
   - Multi vessel CAD (≥50% stenosis in ≥2 major epicardial coronary arteries – with or without antecedent revascularization
   - Prior MI
   - Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome with ST-segment deviation or biomarker positivity
2. Documented cerebrovascular or carotid disease
   - Prior ischemic stroke
   - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis
   - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis
   - History of carotid revascularization
3. Documented peripheral artery disease
   - Ankle-brachial index <0.9 with symptoms of intermittent claudication
   - History of aorto-iliac or peripheral artery intervention

Inclusion Criteria for Primary Prevention Cohort

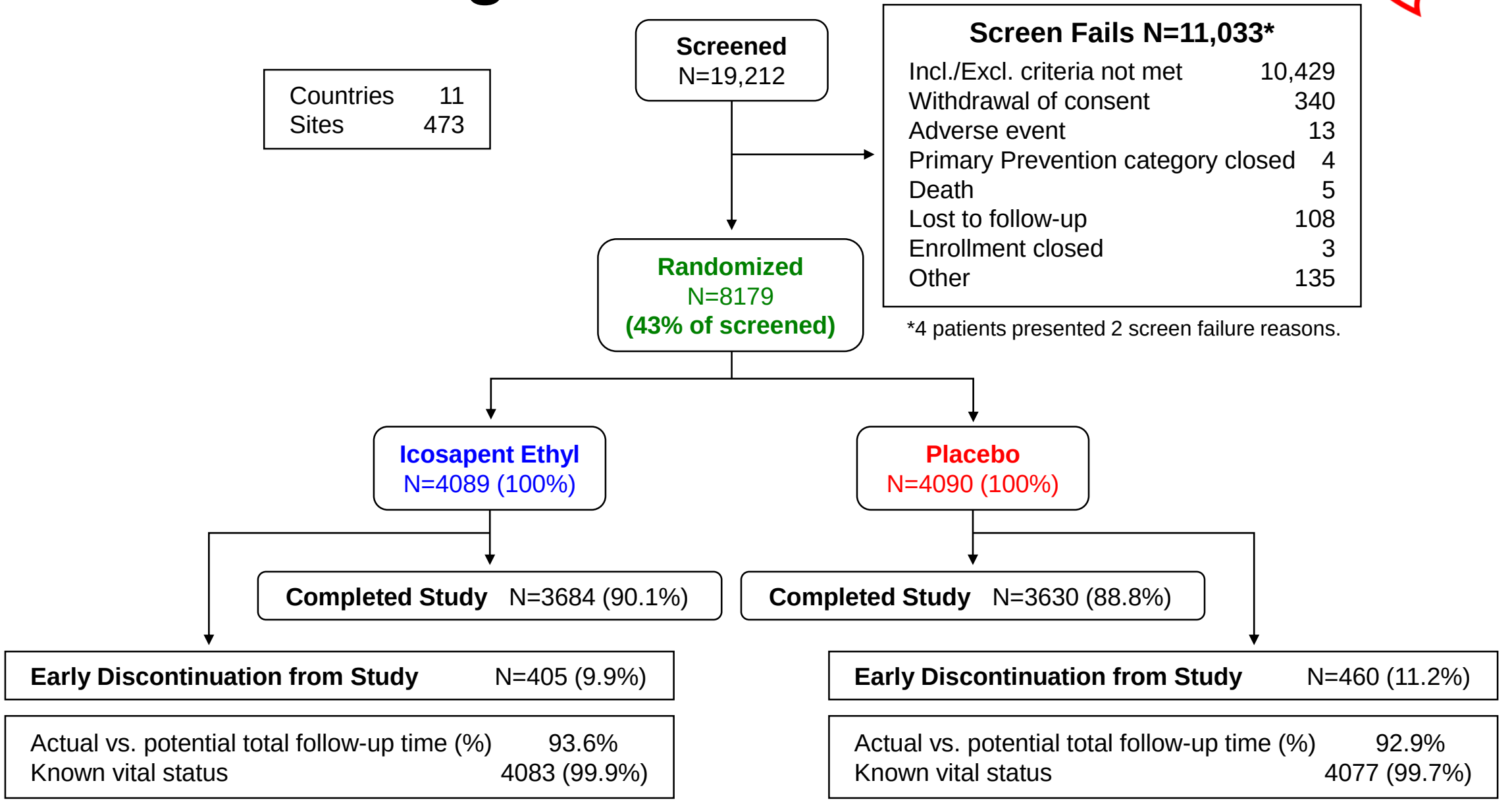
1. Diabetes mellitus requiring medication AND
2. ≥50 years of age AND
3. ≥1 additional risk factor for CVD
   - Men ≥55 years and women ≥65 years
   - Cigarette smoker or stopped smoking within 3 months
   - Hypertension (≥140 mmHg systolic OR ≥90 mmHg diastolic) or on antihypertensive medication;
   - HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women
   - hsCRP >3.0 mg/L
   - Renal dysfunction: Creatinine clearance >30 and <60 mL/min
   - Retinopathy
   - Micro- or macroalbuminuria
   - ABI <0.9 without symptoms of intermittent claudication

Patients with diabetes and CVD are counted under Secondary Prevention Cohort

Key Exclusion Criteria

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

CONSORT Diagram



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

Median trial follow up duration was 4.9 years.

REDUCE-IT Study PI and Committees

Global Principal Investigator and Steering Committee Chair

Deepak L. Bhatt MD, MPH, Professor of Medicine at Harvard Medical School, Executive Director of Interventional Cardiovascular Programs at Brigham and Women's Hospital Heart & Vascular Center, and the Global Principal Investigator and Steering Committee Chair of REDUCE-IT

Steering Committee

Deepak L. Bhatt MD, MPH (Chair and Global Principal Investigator), Christie M. Ballantyne MD, Eliot A. Brinton MD, Terry A. Jacobson MD, Michael Miller MD, Ph. Gabriel Steg MD, Jean-Claude Tardif MD

Data Monitoring Committee

Brian Olshansky MD (Chair), Mina Chung MD, Al Hallstrom PhD, Lesly A. Pearce MS (non-voting independent statistician)
Independent Statistical Center Support for Data Monitoring Committee: Cyrus Mehta PhD, Rajat Mukherjee PhD

Clinical Endpoint Committee

C. Michael Gibson MD, MS (Chair), Anjan K. Chakrabarti MD, MPH, Eli V. Gelfand MD, Robert P. Giugliano MD, SM, Megan Carroll Leary MD, Duane S. Pinto MD, MPH, Yuri B. Pride MD

Key Baseline Characteristics

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

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

Effects on Biomarkers from Baseline to Year 1

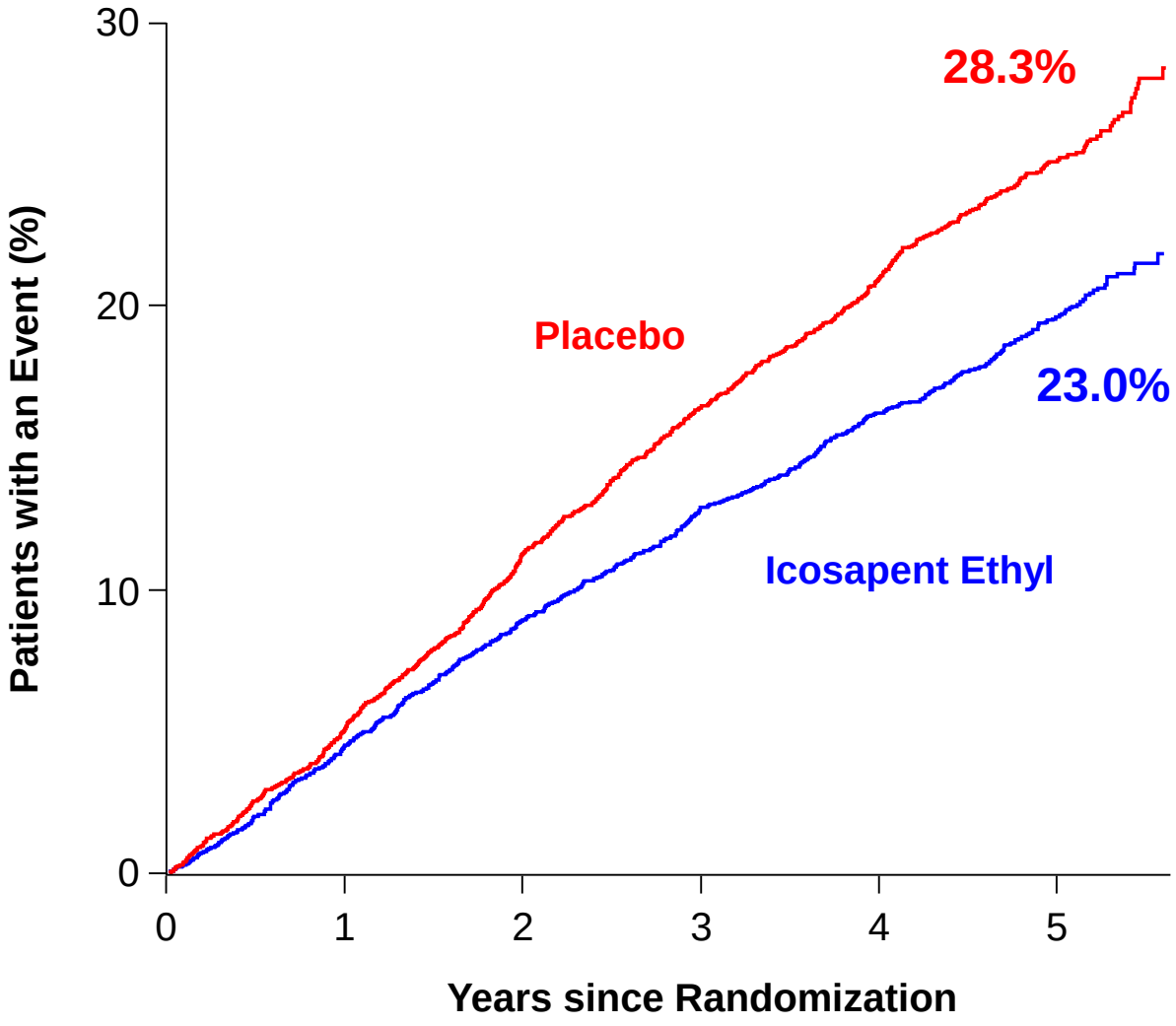
	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
Biomarker*	**Baseline**	**Year 1**	**Baseline**	**Year 1**	**Absolute Change from Baseline**	**% Change from Baseline**	**% Change P-value**
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

*Apo B and hsCRP were measured at Year 2.

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

Primary End Point:

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



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

RRR = 24.8%

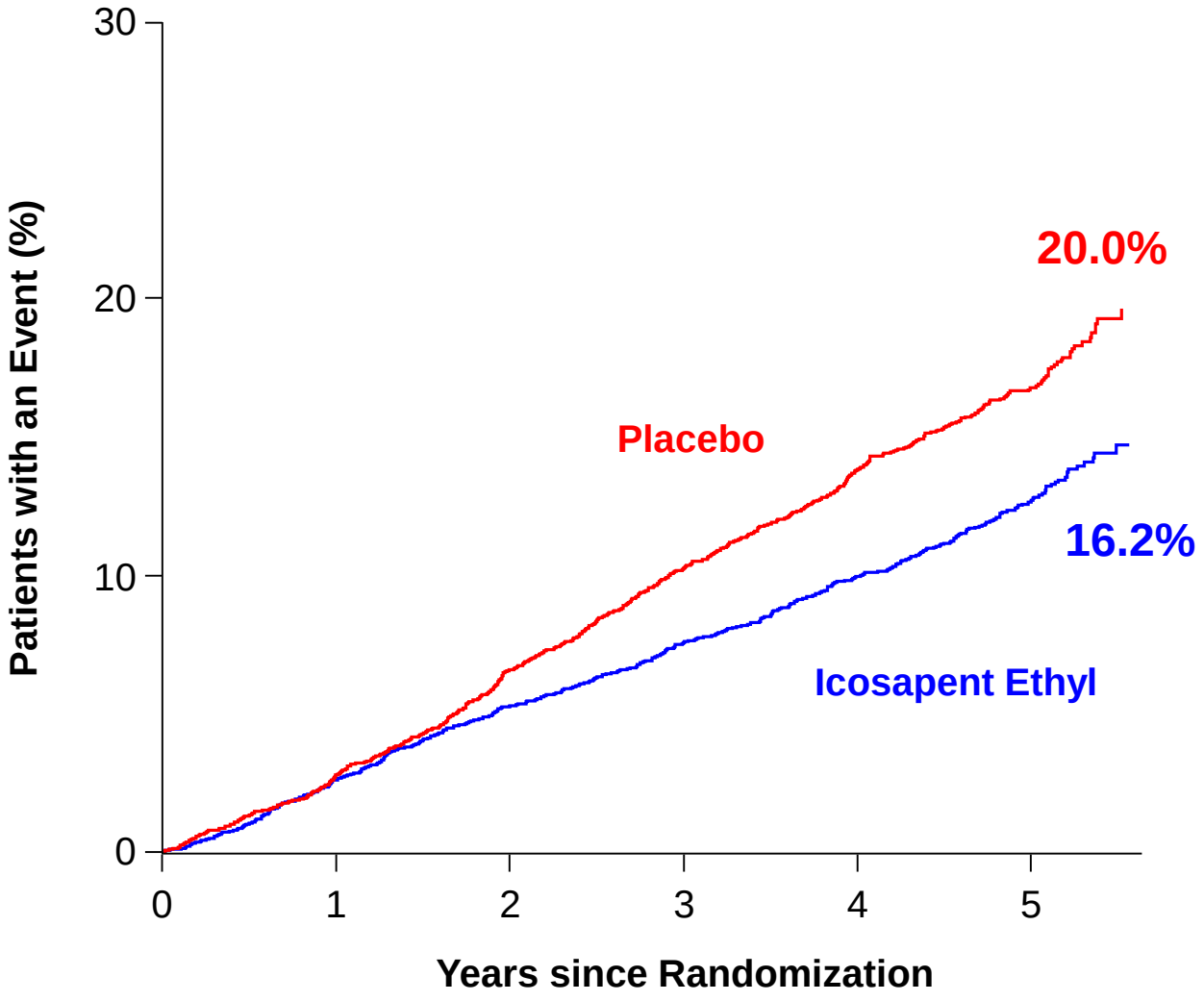
ARR = 4.8%

NNT = 21 (95% CI, 15–33)

P=0.00000001

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

Key Secondary End Point:
CV Death, MI, Stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)

RRR = 26.5%

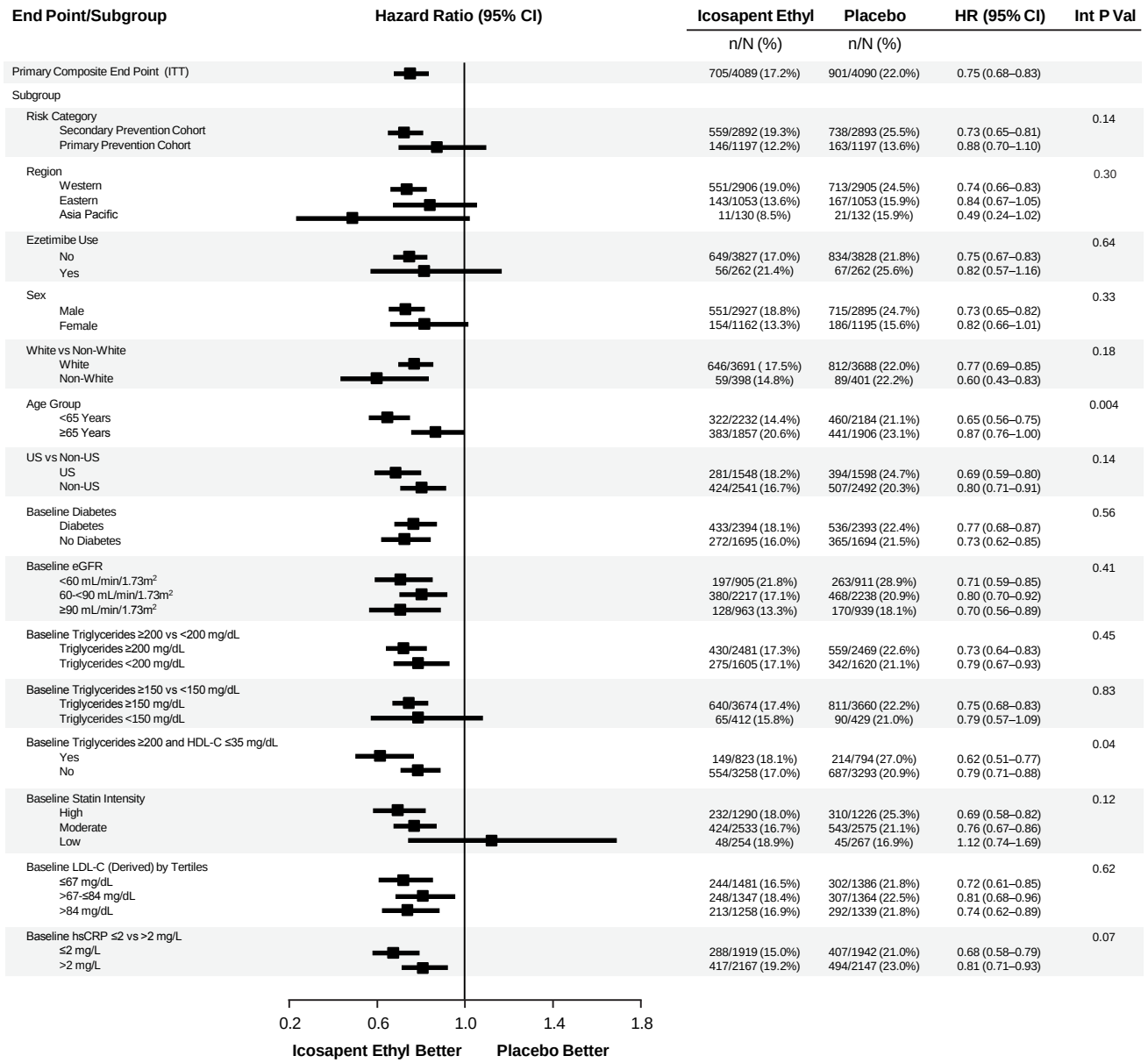
ARR = 3.6%

NNT = 28 (95% CI, 20–47)

P=0.0000006

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

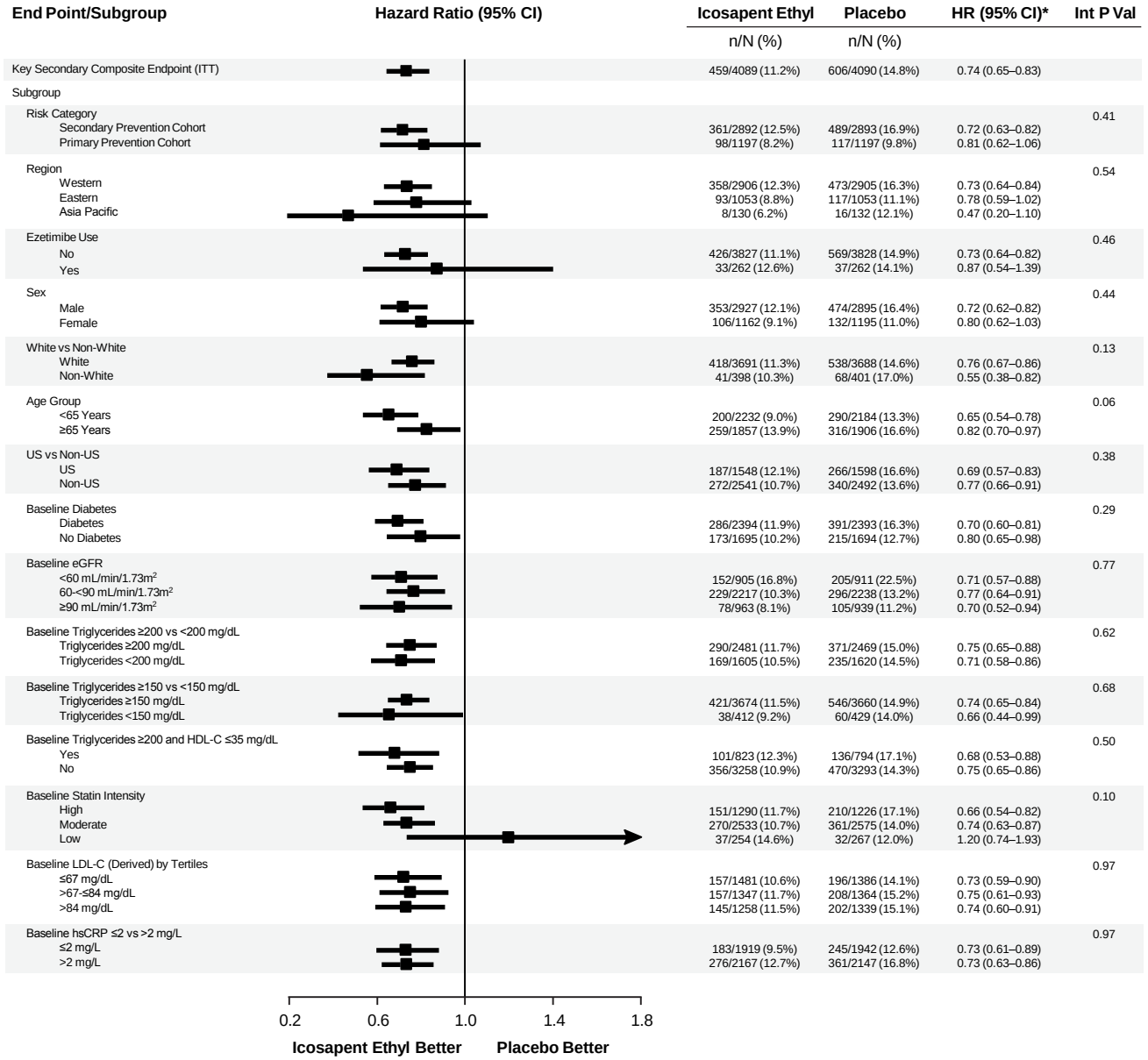
Primary End Point in Subgroups



End Point/Subgroup	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Primary Composite End Point (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	
Subgroup				
Risk Category				0.14
Secondary Prevention Cohort	559/2892 (19.3%)	738/2893 (25.5%)	0.73 (0.65–0.81)	
Primary Prevention Cohort	146/1197 (12.2%)	163/1197 (13.6%)	0.88 (0.70–1.10)	
Region				0.30
Western	551/2906 (19.0%)	713/2905 (24.5%)	0.74 (0.66–0.83)	
Eastern	143/1053 (13.6%)	167/1053 (15.9%)	0.84 (0.67–1.05)	
Asia Pacific	11/130 (8.5%)	21/132 (15.9%)	0.49 (0.24–1.02)	
Ezetimibe Use				0.64
No	649/3827 (17.0%)	834/3828 (21.8%)	0.75 (0.67–0.83)	
Yes	56/262 (21.4%)	67/262 (25.6%)	0.82 (0.57–1.16)	
Sex				0.33
Male	551/2927 (18.8%)	715/2895 (24.7%)	0.73 (0.65–0.82)	
Female	154/1162 (13.3%)	186/1195 (15.6%)	0.82 (0.66–1.01)	
White vs Non-White				0.18
White	646/3691 (17.5%)	812/3688 (22.0%)	0.77 (0.69–0.85)	
Non-White	59/398 (14.8%)	89/401 (22.2%)	0.60 (0.43–0.83)	
Age Group				0.004
<65 Years	322/2232 (14.4%)	460/2184 (21.1%)	0.65 (0.56–0.75)	
≥65 Years	383/1857 (20.6%)	441/1906 (23.1%)	0.87 (0.76–1.00)	
US vs Non-US				0.14
US	281/1548 (18.2%)	394/1598 (24.7%)	0.69 (0.59–0.80)	
Non-US	424/2541 (16.7%)	507/2492 (20.3%)	0.80 (0.71–0.91)	
Baseline Diabetes				0.56
Diabetes	433/2394 (18.1%)	536/2393 (22.4%)	0.77 (0.68–0.87)	
No Diabetes	272/1695 (16.0%)	365/1694 (21.5%)	0.73 (0.62–0.85)	
Baseline eGFR				0.41
<60 mL/min/1.73m^2	197/905 (21.8%)	263/911 (28.9%)	0.71 (0.59–0.85)	
60-<90 mL/min/1.73m^2	380/2217 (17.1%)	468/2238 (20.9%)	0.80 (0.70–0.92)	
≥90 mL/min/1.73m^2	128/963 (13.3%)	170/939 (18.1%)	0.70 (0.56–0.89)	
Baseline Triglycerides ≥200 vs <200 mg/dL				0.45
Triglycerides ≥200 mg/dL	430/2481 (17.3%)	559/2469 (22.6%)	0.73 (0.64–0.83)	
Triglycerides <200 mg/dL	275/1605 (17.1%)	342/1620 (21.1%)	0.79 (0.67–0.93)	
Baseline Triglycerides ≥150 vs <150 mg/dL				0.83
Triglycerides ≥150 mg/dL	640/3674 (17.4%)	811/3660 (22.2%)	0.75 (0.68–0.83)	
Triglycerides <150 mg/dL	65/412 (15.8%)	90/429 (21.0%)	0.79 (0.57–1.09)	
Baseline Triglycerides ≥200 and HDL-C ≤35 mg/dL				0.04
Yes	149/823 (18.1%)	214/794 (27.0%)	0.62 (0.51–0.77)	
No	554/3258 (17.0%)	687/3293 (20.9%)	0.79 (0.71–0.88)	
Baseline Statin Intensity				0.12
High	232/1290 (18.0%)	310/1226 (25.3%)	0.69 (0.58–0.82)	
Moderate	424/2533 (16.7%)	543/2575 (21.1%)	0.76 (0.67–0.86)	
Low	48/254 (18.9%)	45/267 (16.9%)	1.12 (0.74–1.69)	
Baseline LDL-C (Derived) by Tertiles				0.62
≤67 mg/dL	244/1481 (16.5%)	302/1386 (21.8%)	0.72 (0.61–0.85)	
>67-≤84 mg/dL	248/1347 (18.4%)	307/1364 (22.5%)	0.81 (0.68–0.96)	
>84 mg/dL	213/1258 (16.9%)	292/1339 (21.8%)	0.74 (0.62–0.89)	
Baseline hsCRP ≤2 vs >2 mg/L				0.07
≤2 mg/L	288/1919 (15.0%)	407/1942 (21.0%)	0.68 (0.58–0.79)	
>2 mg/L	417/2167 (19.2%)	494/2147 (23.0%)	0.81 (0.71–0.93)	

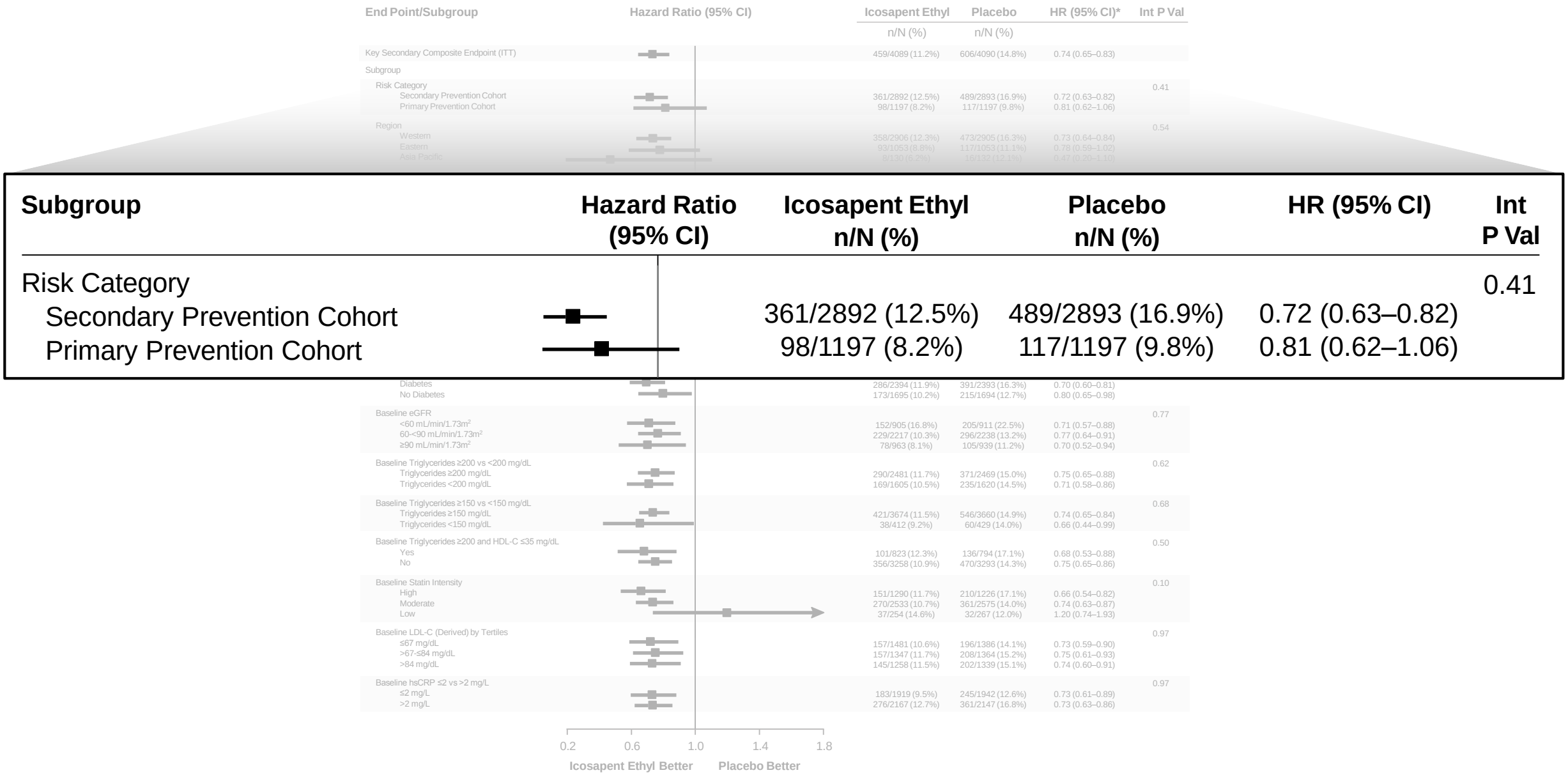
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Key Secondary End Point in Subgroups



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

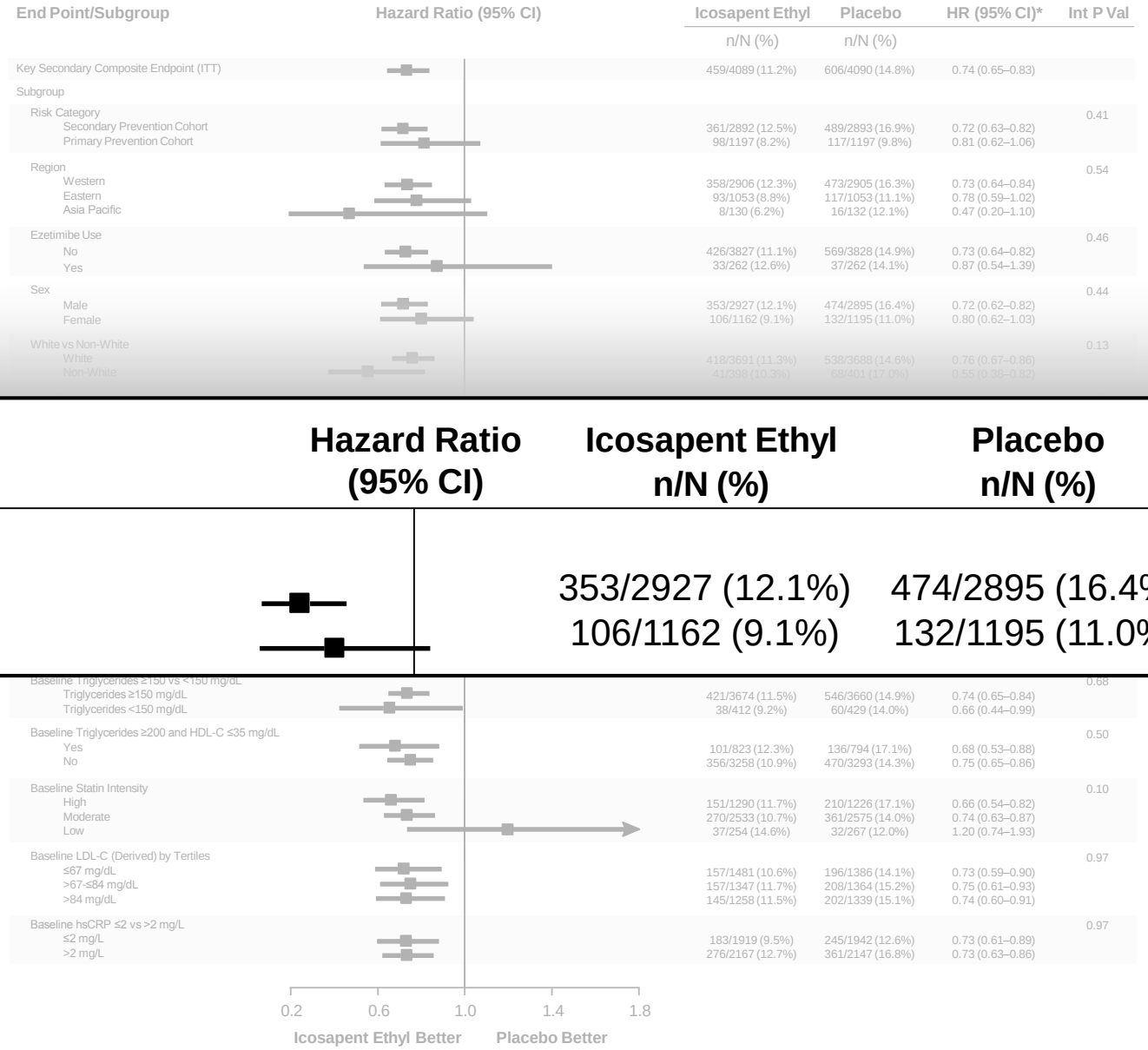
Key Secondary End Point in Subgroups



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

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

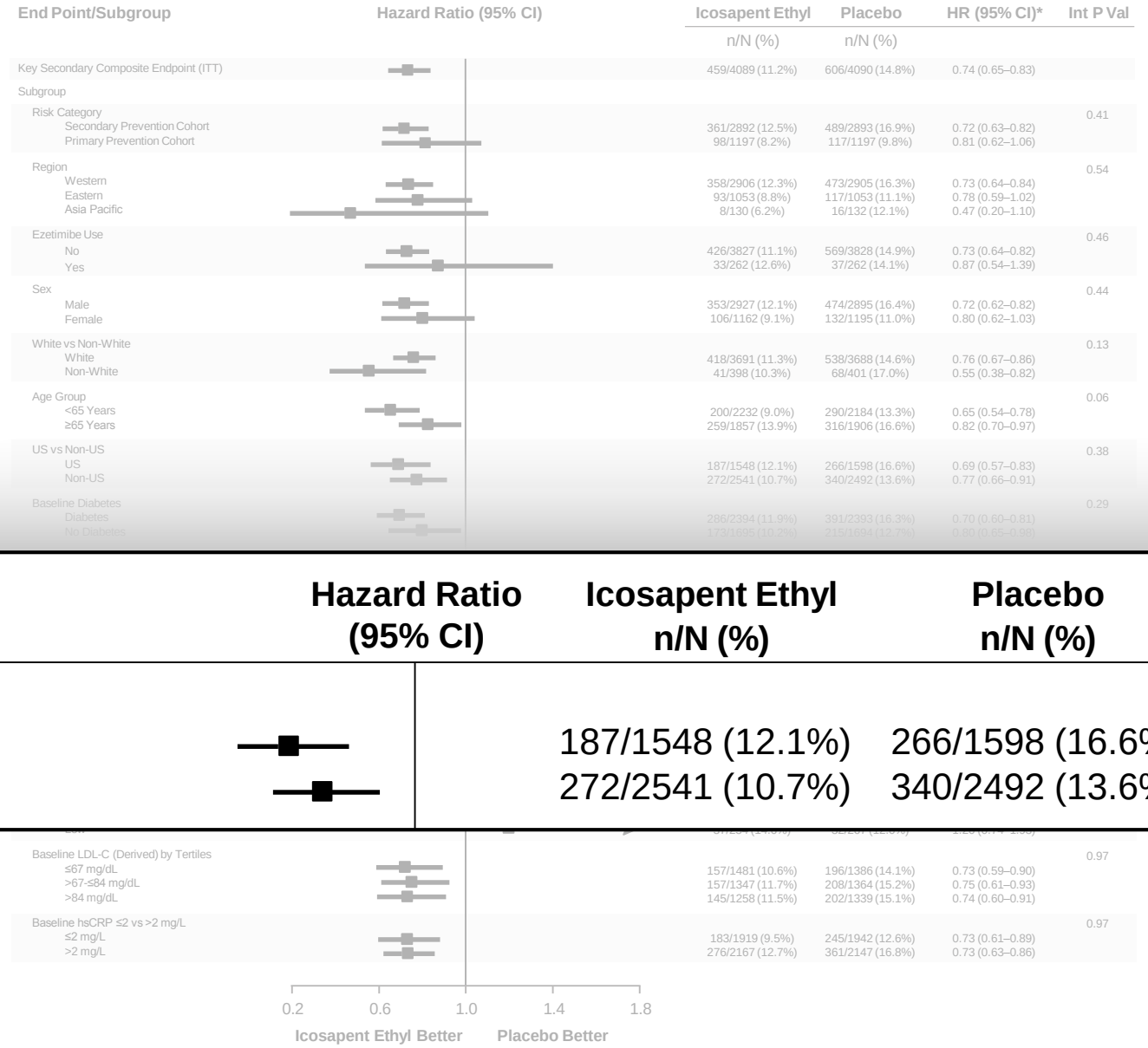
Key Secondary End Point in Subgroups



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

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

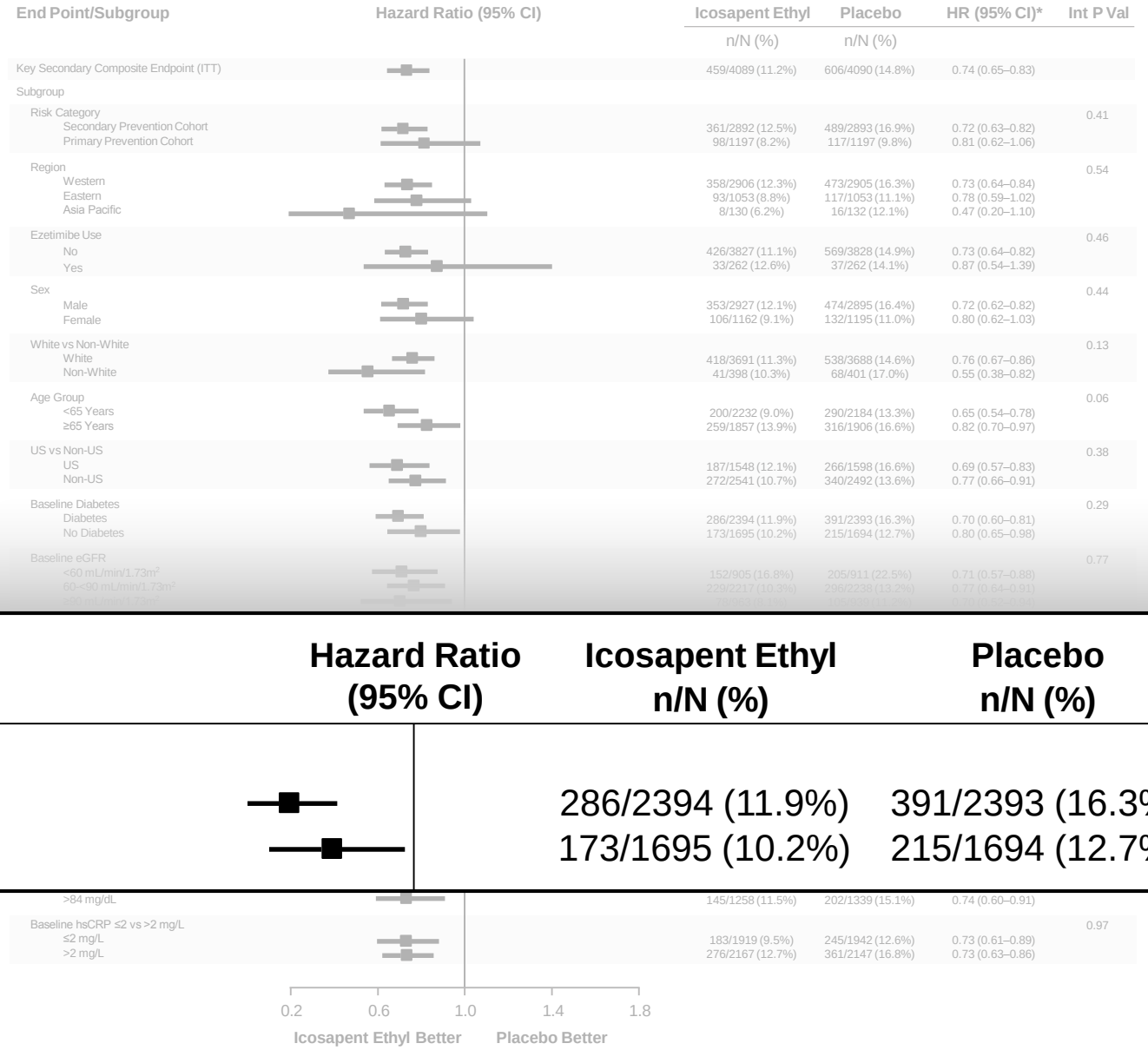
Key Secondary End Point in Subgroups



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

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

Key Secondary End Point in Subgroups



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

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

Key Secondary End Point in Subgroups

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

0.2 0.6 1.0 1.4 1.8

Icosapent Ethyl Better Placebo Better

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

Key Secondary End Point in Subgroups

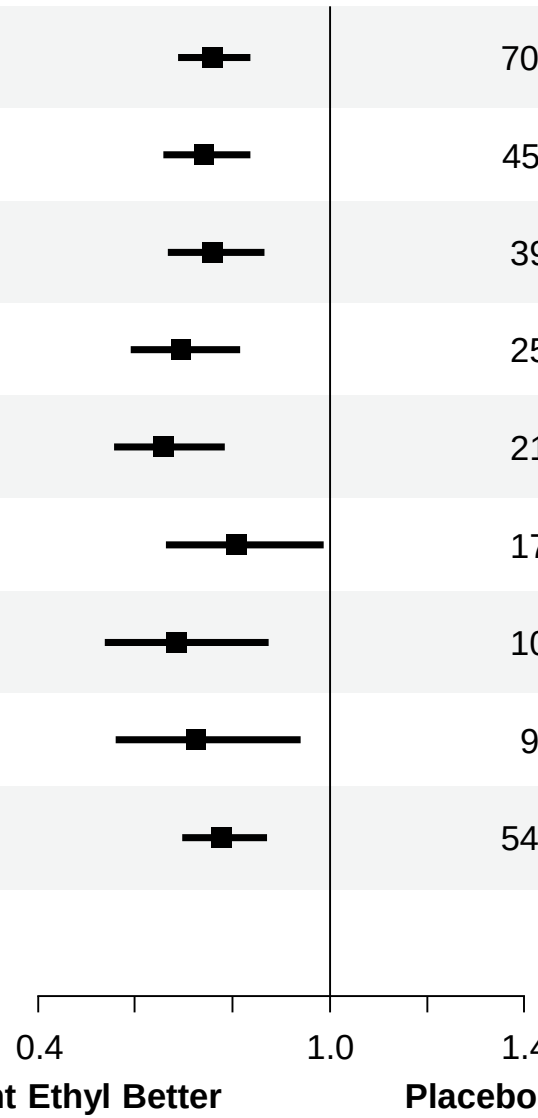
Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Triglycerides ≥150 vs <150 mg/dL					0.68
Triglycerides ≥150 mg/dL		421/3674 (11.5%)	546/3660 (14.9%)	0.74 (0.65–0.84)	
Triglycerides <150 mg/dL		38/412 (9.2%)	60/429 (14.0%)	0.66 (0.44–0.99)	

Icosapent Ethyl Better Placebo Better

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

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

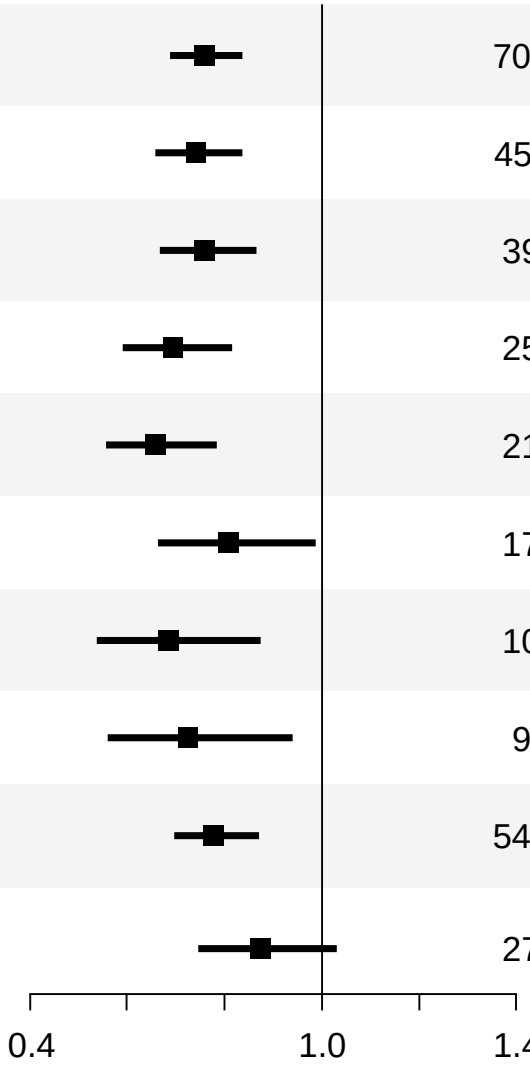


RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

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

Prespecified Hierarchical Testing



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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.* 2018.

REDUCE-IT Tertiary Revasc Endpoints

Revascularization Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)
Coronary	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58, 0.76)
Emergent	41/4089 (1.0%)	65/4090 (1.6%)	0.62 (0.42, 0.92)
Urgent	181/4089 (4.4%)	268/4090 (6.6%)	0.66 (0.54, 0.79)
Elective	194/4089 (4.7%)	278/4090 (6.8%)	0.68 (0.57, 0.82)

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

REDUCE-IT Tertiary Endpoints: Cardiac Arrest, SCD

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)
Cardiac Arrest	22/4089 (0.5%)	42/4090 (1.0%)	0.52 (0.31, 0.86)
Sudden Cardiac Death	61/4089 (1.5%)	87/4090 (2.1%)	0.69 (0.50, 0.96)

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

Treatment-Emergent Adverse Events

	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%)	1.00
Serious TEAE Leading to Death	94 (2.3%)	102 (2.5%)	0.61

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

Treatment-Emergent Adverse Event of Interest: Serious Bleeding

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

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

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

Most Frequent Treatment-Emergent Adverse Events: ≥5% in Either Treatment Group and Significantly Different

Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Diarrhea	367 (9.0%)	453 (11.1%)	0.002
Peripheral edema	267 (6.5%)	203 (5.0%)	0.002
Constipation	221 (5.4%)	149 (3.6%)	<0.001
Atrial fibrillation	215 (5.3%)	159 (3.9%)	0.003
Anemia	191 (4.7%)	236 (5.8%)	0.03

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

Adjudicated Events: Hospitalization for Atrial Fibrillation or Atrial Flutter

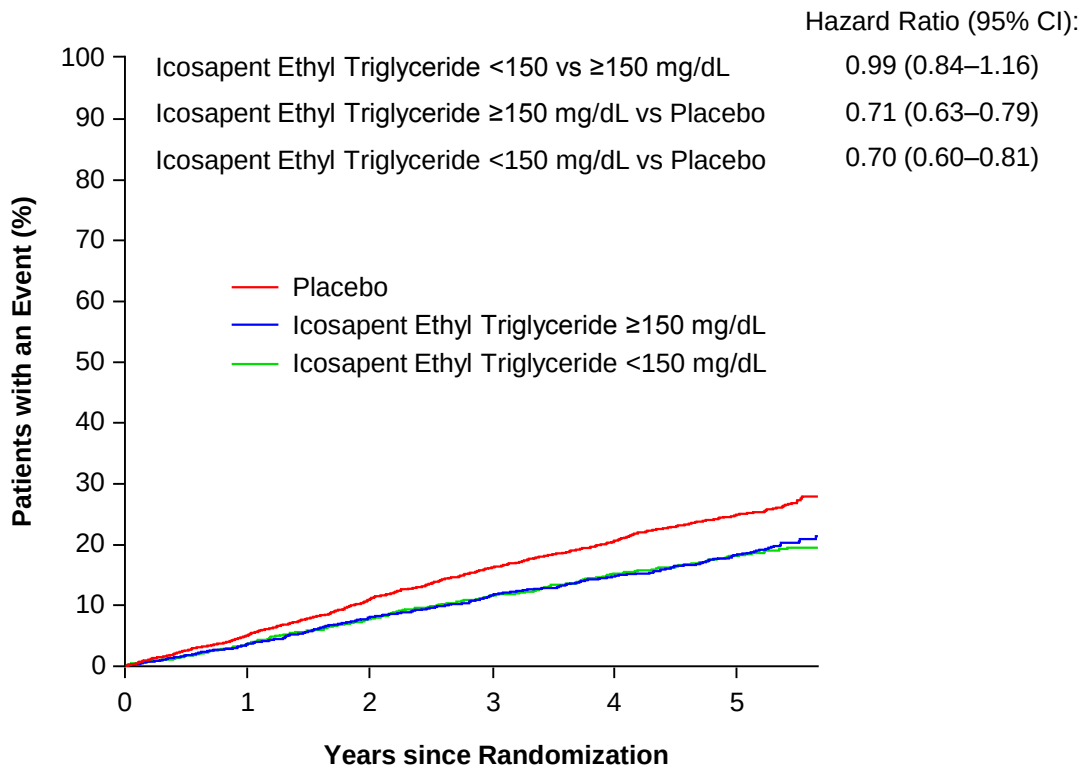
Primary System Organ Class Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Positively Adjudicated Atrial Fibrillation/Flutter[1]	127 (3.1%)	84 (2.1%)	0.004

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

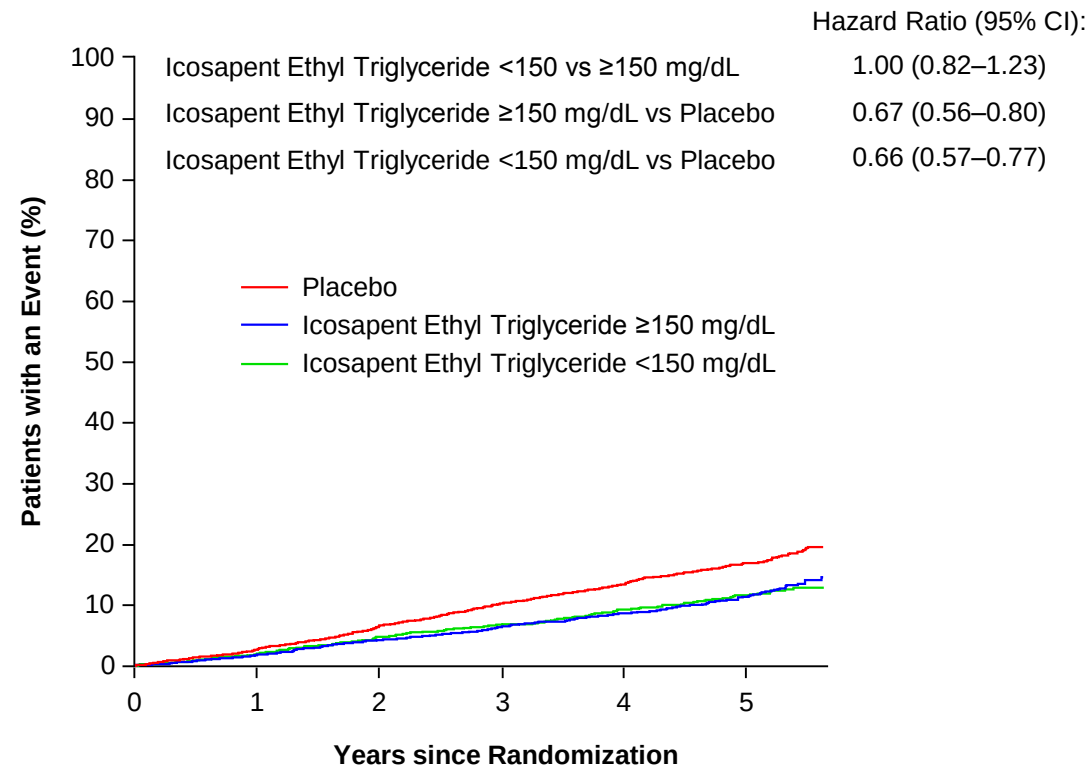
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Achieved Triglyceride Levels: <150 mg/dL and ≥150 mg/dL

A Primary End Point by Achieved Triglyceride Level at 1 Year



B Key Secondary End Point by Achieved Triglyceride Level at 1 Year



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

Limitations

Few patients on ezetimibe

- Though data appeared consistent in that subgroup

Concomitant PCSK9 inhibitors prohibited

- Though no reason to think they are not additive

Small difference (5 mg/dL) in LDL-C between groups

- Cannot tell from this study if due to drug or placebo
- Would not account for 25% RRR
- JELIS saw 19% RRR in open label design, no placebo
- Consistent benefit in patients with LDL-C ↑ vs no LDL-C ↑

Pending Questions

Cannot comment on mechanisms of benefit from this study

- Consistent reduction across triglyceride range (135-500)
- Similar benefit by 1-year triglycerides < or > 150 mg/dL
- Detailed biomarker and genetic analyses are planned

Cannot comment on cost-effectiveness

- Though with NNT of 21, likely cost-effective
- Formal cost-effectiveness analyses planned
- Full benefits not captured with only first events, await recurrent and total events analyses

Conclusions

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

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

Low rate of adverse effects, including:

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

Consistent efficacy across multiple subgroups

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

We thank the investigators, the study coordinators, and especially the 8,179 patients in REDUCE-IT!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

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

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