Adopting the New Therapeutic "Lineup" to Manage ASCVD

Central Symposium

Houston, TX

April 4, 2022
6:30 PM – 9:30 PM

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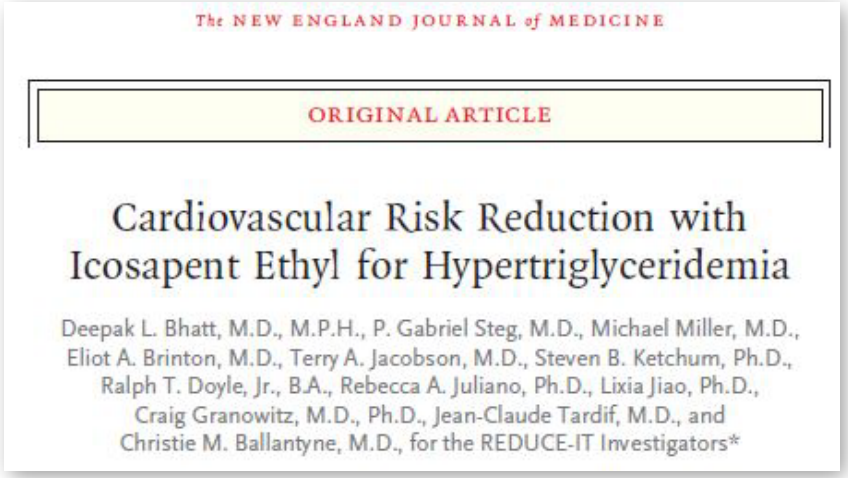
Welcome, Introductions, and Program Overview

Christie Ballantyne, MD, Program Chair

We Are in a New Era of ASCVD Prevention, Especially in Lipid Management!


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*


NLA Scientific Statement on the Use of Icosapent Ethyl in Statin-treated Patients with Elevated Triglycerides and High or Very High ASCVD Risk

Carl E. Orringer, MD, FNLA; Terry A. Jacobson, MD, FNLA; Kevin C. Maki, PhD, FNLA


2018 Guideline on the Management of Blood Cholesterol

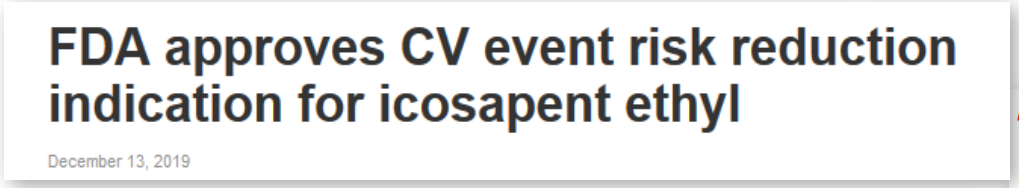

AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2020


NEWS

Year in Review: New Guidelines, Inclisiran, Dapagliflozin Impact CVD Prevention in 2019


FDA Approves Bempedoic Acid-Ezetimibe Combination for ASCVD, Heterozygous FH


FDA approves CV event risk reduction indication for icosapent ethyl

December 13, 2019


ORIGINAL ARTICLE

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

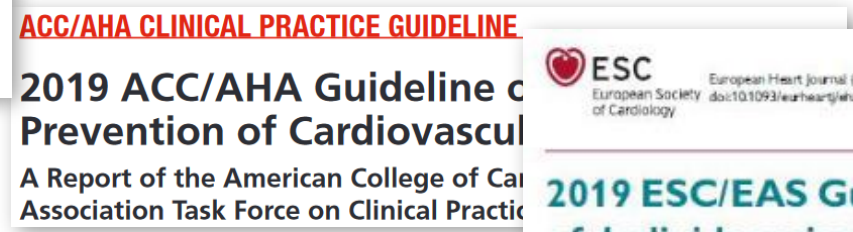
Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., et al., for the IMPROVE-IT Investigators*

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D. for the FOURIER Steering Committee and Investigators*

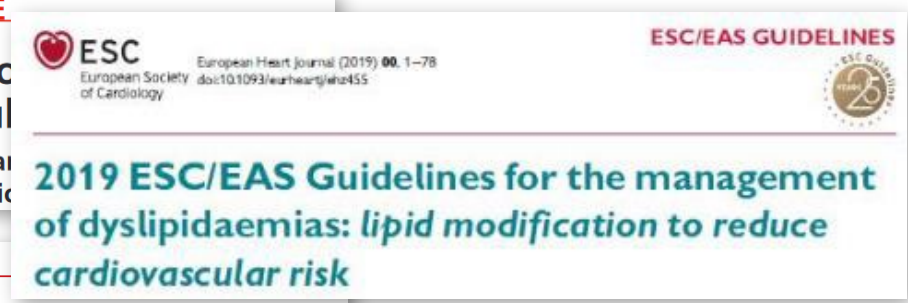
Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

Gregory G. Schwartz, M.D., Ph.D., P. Gabriel Steg, M.D., Michael Szarek, Ph.D., Deepak L. Bhatt, M.D., M.P.H., Vera A. Bittner, M.D., M.S.P.H., Rafael Diaz, M.D., Jay M. Edelberg, M.D., Ph.D., Shaun G. Goodman, M.D., Corinne Hanotin, M.D., Robert A. Harrington, M.D., J. Wouter Jukema, M.D., Ph.D., Guillaume Lecorps, M.Sc., et al., for the ODYSSEY OUTCOMES Committees and Investigators*


ACC/AHA CLINICAL PRACTICE GUIDELINE

2019 ACC/AHA Guideline on the Prevention of Cardiovascular

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice


ESC European Society of Cardiology

European Heart Journal (2019) 00, 1–78 doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*


AHA SCIENCE ADVISORY

Omega-3 Fatty Acids for the Management of Hypertriglyceridemia

A Science Advisory From the American Heart Association

Faculty

CHAIR

Christie M. Ballantyne, MD
Chief, Sections of Cardiology and Cardiovascular Research
Professor of Medicine
Department of Medicine
Baylor College of Medicine
Houston, TX

FACULTY

Gregory S. Pokrywka, MD, FACP, FNLA, FASCP, NCM
Director, Baltimore Lipid Center
Assistant Professor of Medicine
Johns Hopkins University School of Medicine
Towson, MD

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Professor, Department of Clinical Pharmacy
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FACULTY

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Professor of Medicine/Cardiology
Co-director, UCLA Program in Preventive Cardiology
Director, UCLA Barbra Streisand Women's
Heart Health Program
David Geffen School of Medicine at UCLA
Los Angeles, CA

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Learning Objectives

- Apply the key findings of large-scale omega-3 fatty acid clinical trials to clinical practice to reduce ASCVD events
- Apply recent clinical trial evidence of EPA to the care of patients with established CVD who are on statins and at risk of further CV events
- Identify barriers to the implementation of effective, long-term management of ASCVD

Agenda

- Burden of Heart Disease Today
- Atherogenic Dyslipidemia and New Approaches to Risk Assessment for ASCVD
- REDUCE-IT Clinical Trials and Omega-3 Fatty Acids for ASCVD Risk Reductions
- Recent Evidence from REDUCE-IT Sub-Studies
- Differential Biological Effects of Omega-3 Fatty Acids
- Role of the Pharmacist in Lipid Medication Access and Usage
- Clinical Approaches to Personalizing Medical Management of ASCVD Risk Factors: Case Discussions

Burden of Heart Disease Today

Christie Ballantyne, MD

Atherothrombosis: Clinical Manifestations

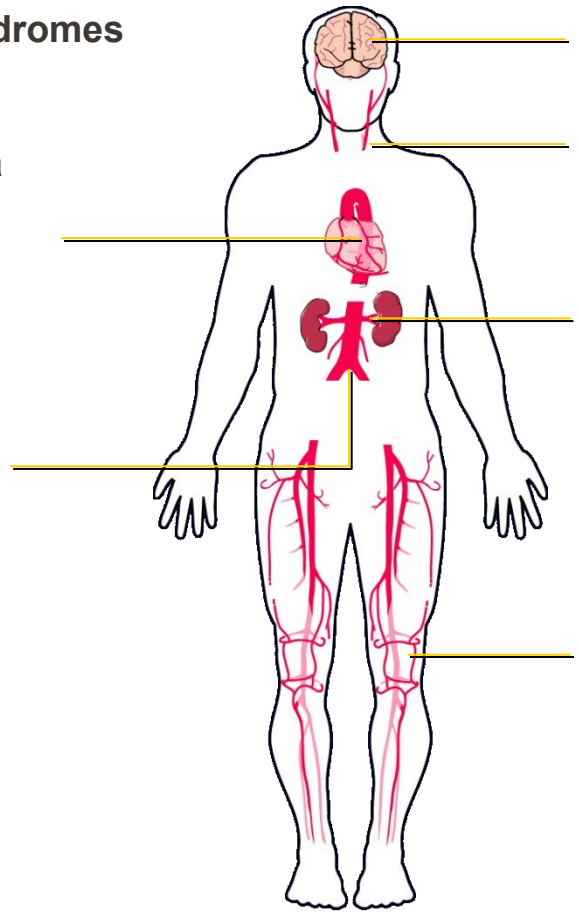
Acute coronary syndromes
- **STEMI**
- **NSTEMI**
- **Unstable angina**

Stable CAD

Atrial Fibrillation

Angioplasty
Bare metal stent
Drug-eluting stent
CABG

Abdominal aortic aneurysm (AAA)



Stroke
TIA
Intracranial stenosis

Carotid artery stenosis
CEA
Carotid stenting

Renal artery stenosis
Renal artery stenting

Peripheral arterial disease
Acute limb ischemia
Claudication
Amputation
Endovascular stenting
Peripheral bypass
Abnormal ABI

ABI, ankle brachial index; CAD, coronary artery disease; CEA, carotid endarterectomy; TIA, transient ischemic attack.

Meadows TA, Bhatt DL. *Circ Res.* 2007;100(9):1261-1275.

Coronary Heart Disease Prevalence in the US Is Massive!

Population Group	Prevalence, CHD, 2011–2014 Age ≥20 y	Prevalence, MI, 2011–2014 Age ≥20 y	New and Recurrent MI and Fatal CHD, Age ≥35 y	New and Recurrent MI, Age ≥35 y	Mortality,* CHD, 2015 All Ages	Mortality,* MI, 2015 All Ages	Hospital Discharges CHD, 2014 All Ages
Both sexes	16 500 000 (6.3%)	7 900 000 (3.0%)	1 055 000	805 000	366 801	114 023	1 021 000
Males	9 100 000 (7.4%)	4 700 000 (3.8%)	610 000	470 000	209 298 (57.1%)†	65 211 (57.2%)†	649 000
Females	7 400 000 (5.3%)	3 200 000 (2.3%)	445 000	335 000	157 503 (42.9%)†	48 812 (42.8%)†	372 000
NH white males	7.7%	4.0%	520 000‡	…	167 236	52 393	…
NH white females	5.3%	2.4%	370 000‡	…	124 614	38 407	…
NH black males	7.1%	3.3%	90 000‡	…	21 006	6400	…
NH black females	5.7%	2.2%	75 000‡	…	18 048	5723	…
Hispanic males	5.9%	2.9%	…	…	13 416	4246	…
Hispanic females	6.1%	2.1%	…	…	9639	3106	…
NH Asian males	5.0%	2.6%	…	…	5154	1516§	…
NH Asian females	2.6%	0.7%	…	…	3767	1167§	…
NH American Indian or Alaska Native	9.3%¶	…	…	…	2044	624	…

AHA Statistical Update. Heart disease and stroke statistics—2018 update. A report from the American Heart Association. *Circulation*. 2018;137(12):e67-e492.

Heart Disease Remains the #1 Cause of Death in the US. Stroke Is #5.

- **~720,000 Americans will have a new coronary event** (defined as first hospitalized MI or CHD death), and ~335,000 will have a recurrent event
- The estimated annual incidence of **MI is 605,000 new attacks and 200,000 recurrent attacks**
  - Average age at 1st MI is 65.6 years for males and 72.0 years for females
  - ~25% are silent

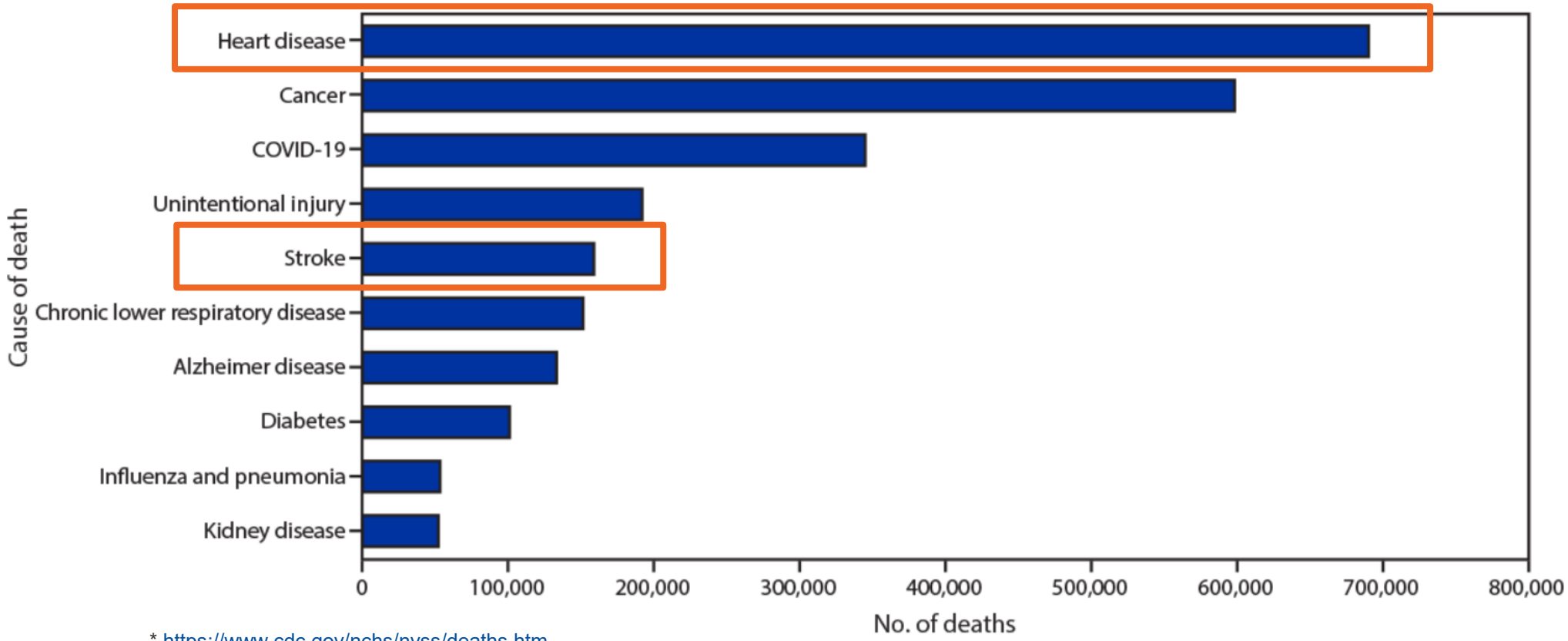
Population Group	Prevalence, CHD, **2011-2014 Age ≥20 y**	Prevalence, MI, **2011-2014 Age ≥20 y**	New and Recurrent **MI and Fatal CHD, Age ≥35 y**	New and Recurrent **MI, Age ≥35 y**	Mortality,* **CHD, 2015 All Ages**	Mortality,* MI, 2015 All Ages	Hospital Discharges CHD, 2014 All Ages
Both sexes	16,500,000 (6.3%)	7,900,000 (3.0%)	1,055,000	805,000	366,801	114,023	1,021,000
Males	9,100,000 (7.4%)	4,700,000 (3.8%)	610,000	470,000	209,298 (57.1%)†	65,211 (57.2%)†	649,000
Females	7,400,000 (5.3%)	3,200,000 (2.3%)	445,000	335,000	157,503 (42.9%)†	48,812 (42.8%)†	372,000

*Mortality for Hispanic, non-Hispanic (NH) American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses. †These percentages represent the portion of total CHD and MI mortality that is for males vs females.

CHD, coronary heart disease; MI, myocardial infarction. American Heart Association (AHA) Statistical Update. Benjamin EJ, et al. *Circulation.* 2018;137(12):e67-e492.

Despite COVID-19, Heart Disease Remains the #1 Cause of Death

FIGURE 2. Provisional* number of leading underlying causes of death† — National Vital Statistics System, United States, 2020



* https://www.cdc.gov/nchs/nvss/deaths.htm

† Based on death records received and processed as of March 21, 2021, for deaths occurring in the United States among US residents. Data included in this analysis include >99% of deaths that occurred in 2020. Ahmad FB, et al. *MMWR Morb Mortal Wkly Rep*. 2021;70(14):519-522.

Atherothrombosis – Global Perspective

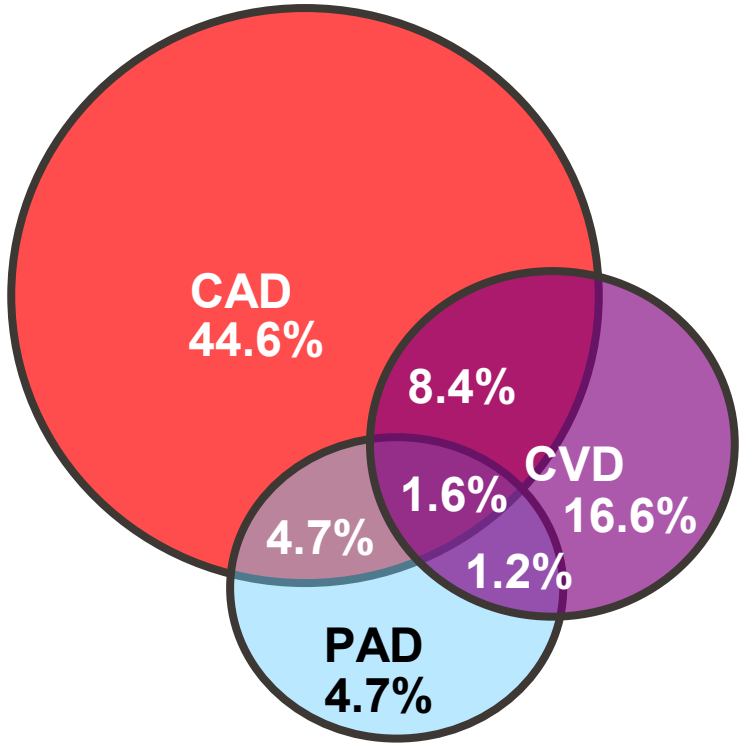
- Cardiovascular disease affects 4% of global population
  - (>500 million persons)[1]
- An estimated 17.9 million people died from CVDs in 2019 representing 32% of all global deaths[2]
  - Of these deaths, 85% were due to heart attack and stroke

1. Roth GA, Mensah GA, Johnson CO, et al. *J Am Coll Cardiol*. 2020;76(25):2982-3021; 2. World Health Organization. Cardiovascular Diseases Fact Sheet. 2022.

Prevalence of Atherothrombosis at Baseline

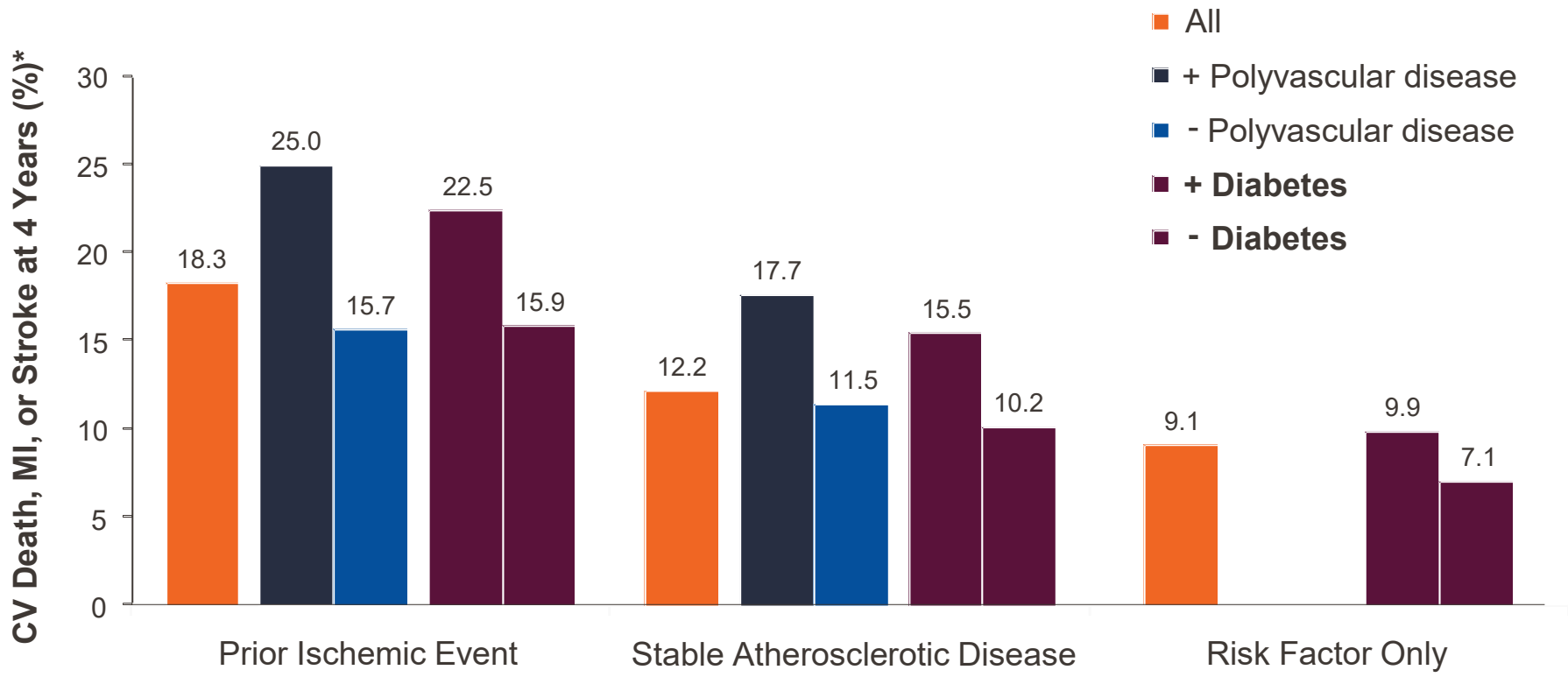
- Atherothrombotic status of international outpatient REACH Registry patients at baseline:
  - 18.2% Risk factors only (n = 12,389)
  - 59.3% CAD (n = 40,258)
  - 27.8% CVD (n = 18,843)
  - 12.2% PAD (n = 8,273)

  (single-bed disease and overlap in patients with polyvascular disease shown at right)
- Cardiovascular risk factor profiles were consistent across patient types and across all participating regions.



CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease; REACH, Reduction of Atherothrombosis for Continued Health.
Bhatt DL, et al. *JAMA.* 2006;295(2):180-189.

REACH Registry: CV Events at 4 Years

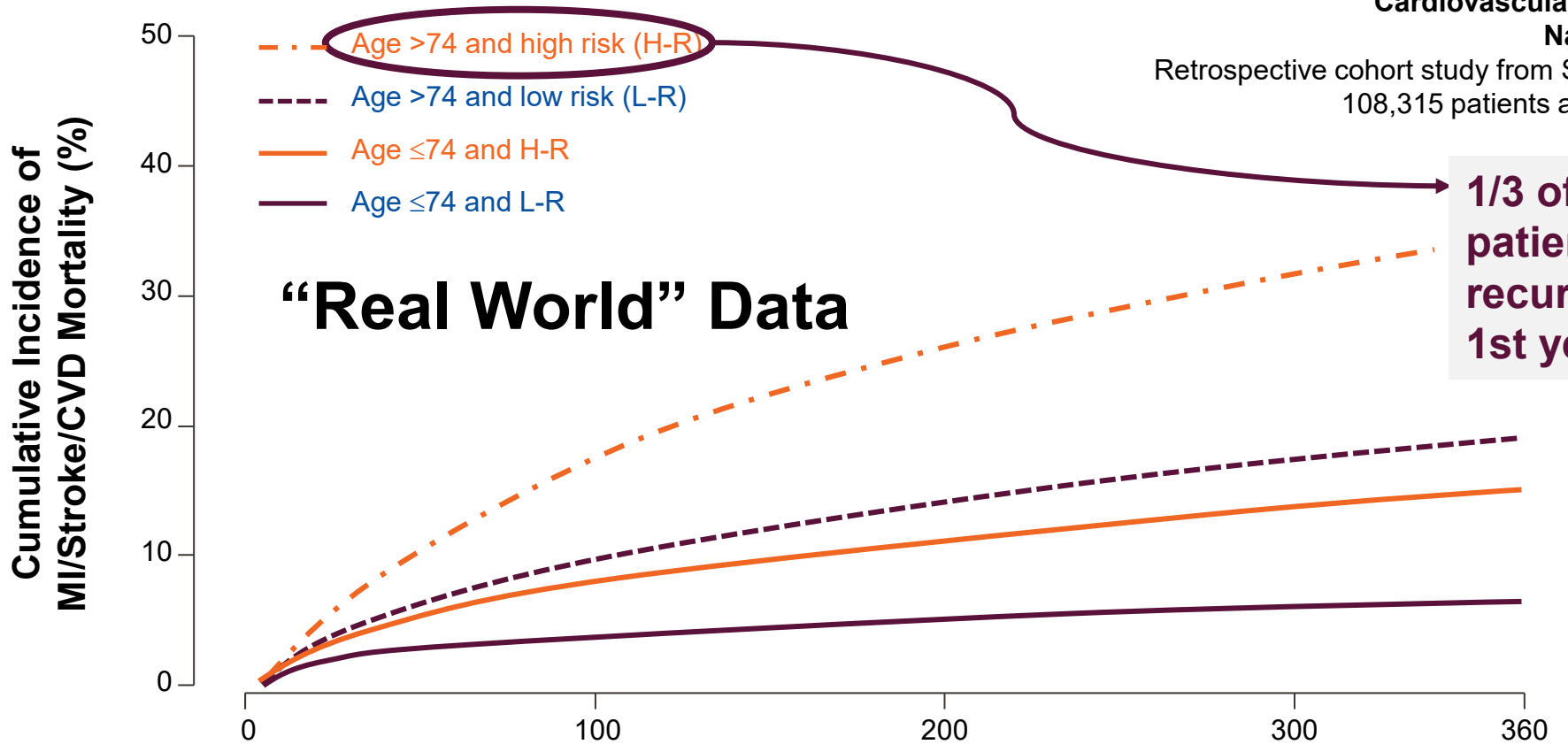


*All event rates adjusted for age and sex.

Bhatt DL, et al. *JAMA* 2010;304(12):1350-1357.

High Risk of MI, Ischemic Stroke, or CV Death During the 1st Year Following MI

Cardiovascular risk in post-MI patients: Nationwide real-world data
Retrospective cohort study from Swedish national registries: 108,315 patients admitted with MI 2006-2011



1/3 of elderly high-risk patients will have a recurrent event in the 1st year post-ACS

Number at Risk

≤74 + L-R	32,497	31,137	30,646	30,293	30,105
≤74 + H-R	17,850	16,291	15,562	15,016	14,744
>74 + L-R	20,165	17,977	16,859	16,026	15,588
>74 + H-R	26,742	21,415	18,659	16,875	15,930

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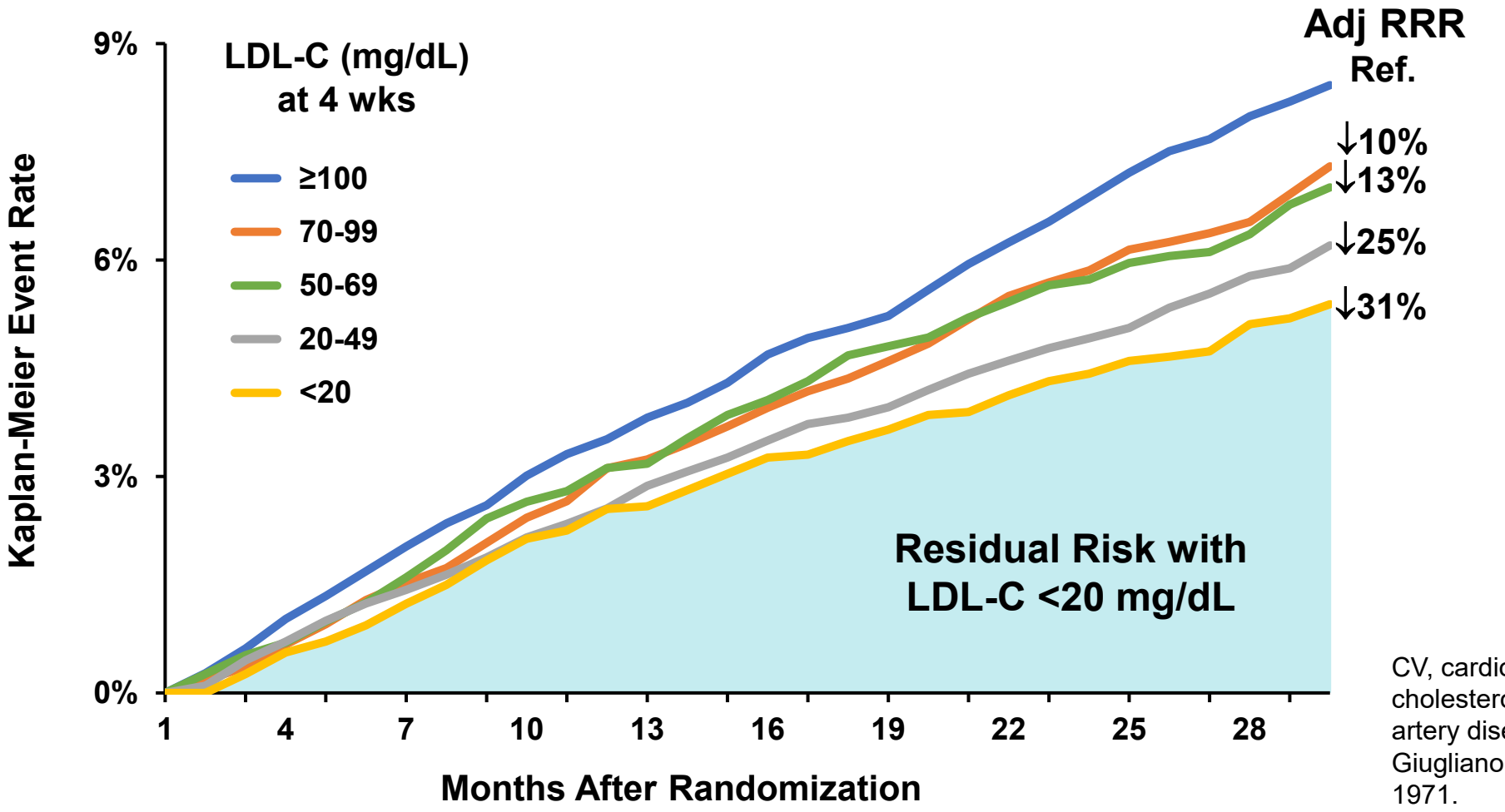
ACS, acute coronary syndrome; CV, cardiovascular; MI, myocardial infarction.
Jernberg T, et al. *Eur Heart J*. 2015;36(19):1163-1170.

Despite Low Achieved LDL-C at 1 Month, Risk of CV Death, MI, or Stroke Is Substantial



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25,982 high-risk, stable patients with established CV disease (prior MI or stroke, or symptomatic PAD) randomized to evolocumab or placebo

CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; RRR, relative risk ratio.

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

Think About Your Patients with Atherosclerotic Cardiovascular Disease (ASCVD)

- How many of your patients have ASCVD?
- How severe is the disease?
- How do your patients respond when you tell them they have ASCVD?
- How concerned are your patients about having a major ASCVD event?
- What level of difficulty do you have in managing these patients?
- What do you need to better manage them?

Atherogenic Dyslipidemia and New Approaches to Risk Assessment for ASCVD

Gregory Pokrywka, MD

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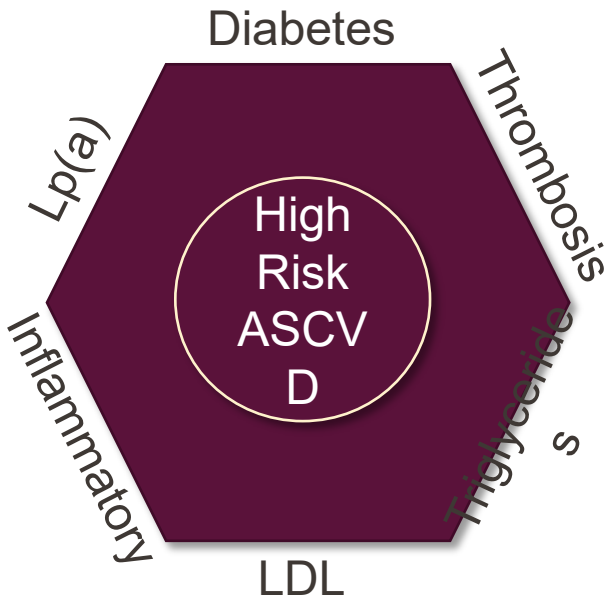
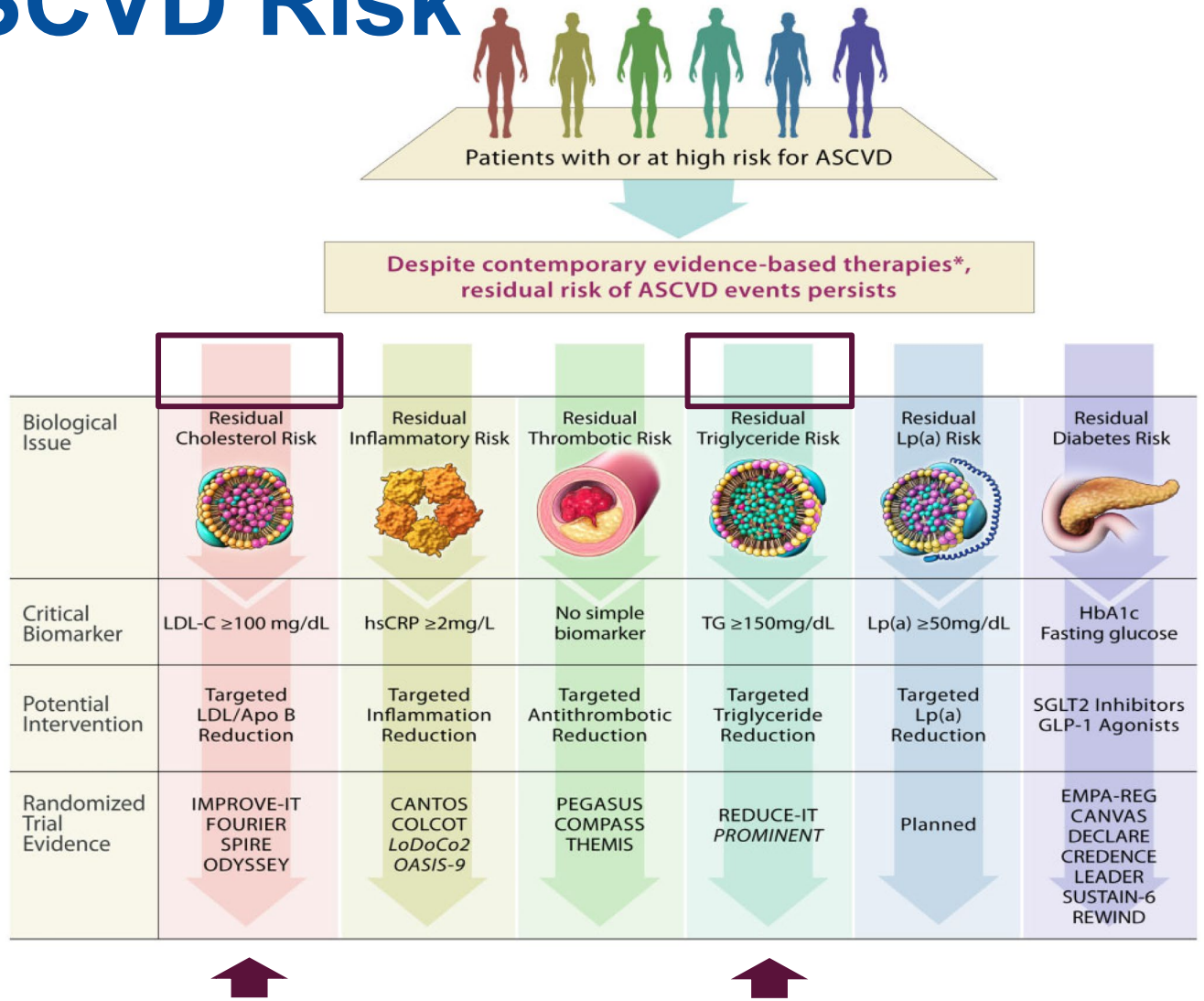
Risk Pathways in the Contemporary Management of ASCVD Risk





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

General Approach to CV Risk Assessment

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

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

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

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

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease.

Link to ASCVDplus: https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/

http://static.heart.org/riskcalc/app/index.html#!/baseline-risk

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

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

Introduced the Concept of Risk-Enhancing Factors

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

Risk-Enhancing Factors

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

5% to <7.5%
"Borderline Risk"

≥7.5% to <20%
"Intermediate Risk"

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

Additional Risk-Enhancing Factors

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

5% to <7.5%
"Borderline Risk"

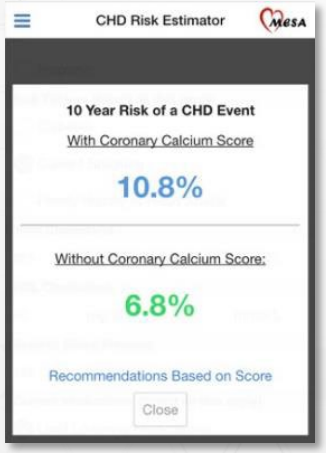
≥7.5% to <20%
"Intermediate Risk"

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

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

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

MESA Risk Score



CARDIA

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

≥7.5% to <20%
"Intermediate Risk"

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

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

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

High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL) despite maximally tolerated statin therapy and ezetimibe

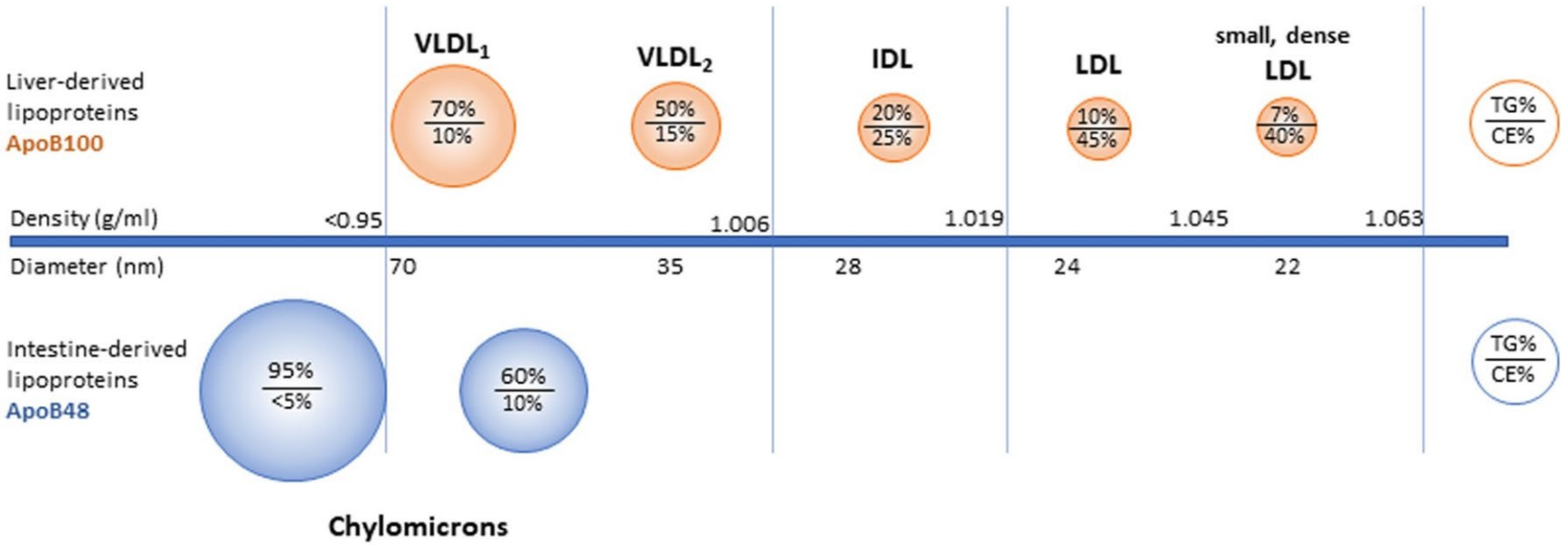
Very high risk = multiple major ASCVD events or 1 major ASCVD event + ≥2 high-risk conditions

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

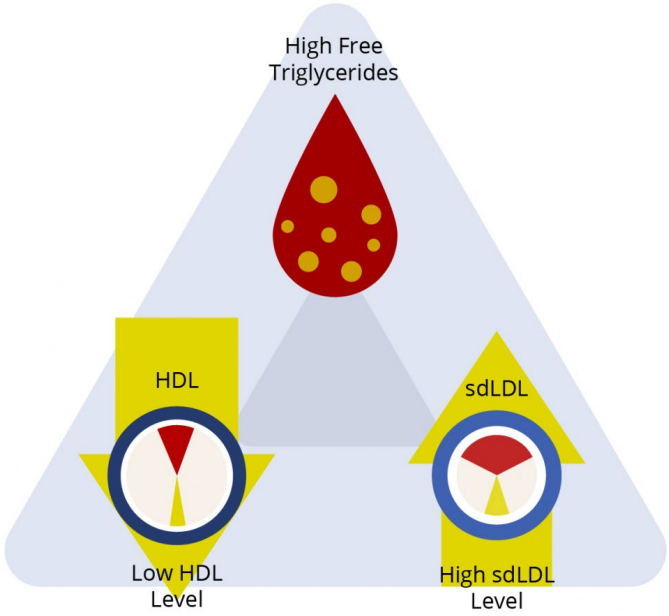
- *After* Grundy SM, et al. AHA/ACC/Multisociety 2018 Cholesterol Guidelines. *Circulation*. 2019;139(25):e1082-e1143.

Management Strategies that Focus on LDL Ignore Other Atherogenic Lipids

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

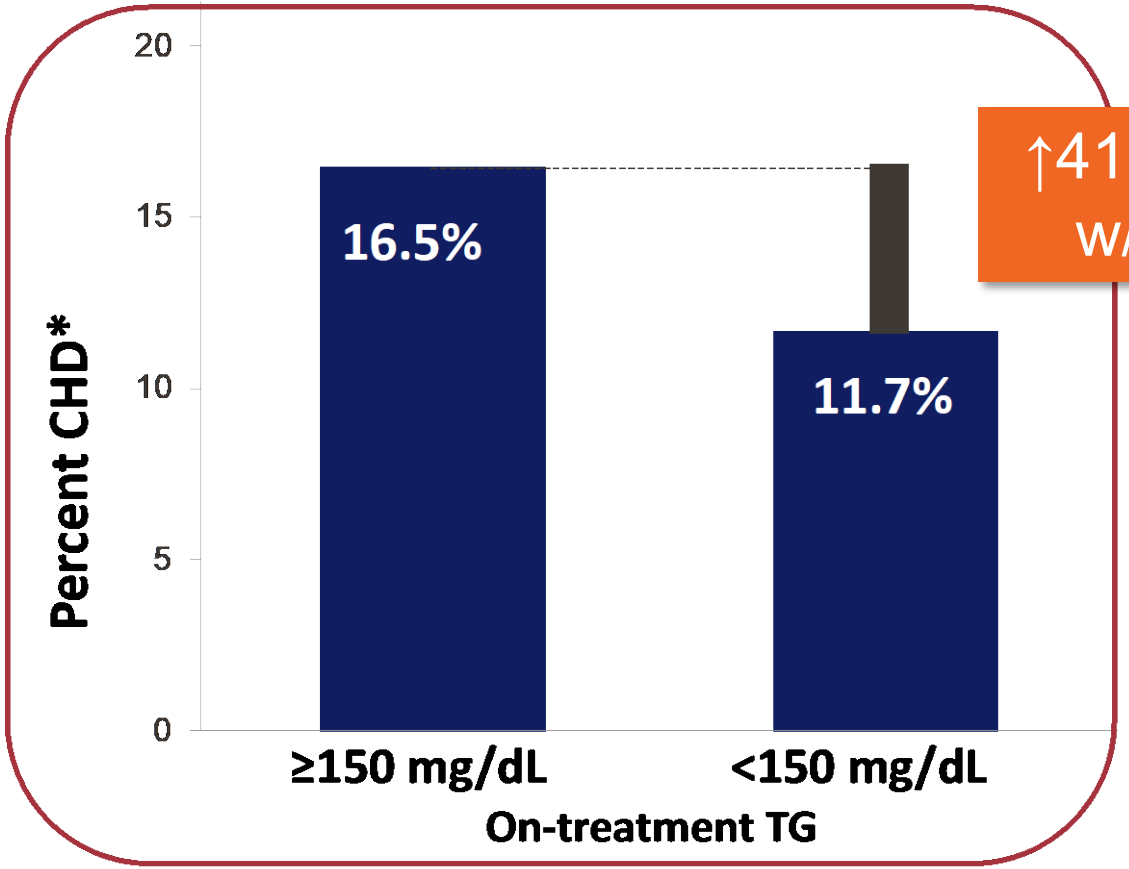


Atherogenic Dyslipidemia Triad
Clinical Markers



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

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

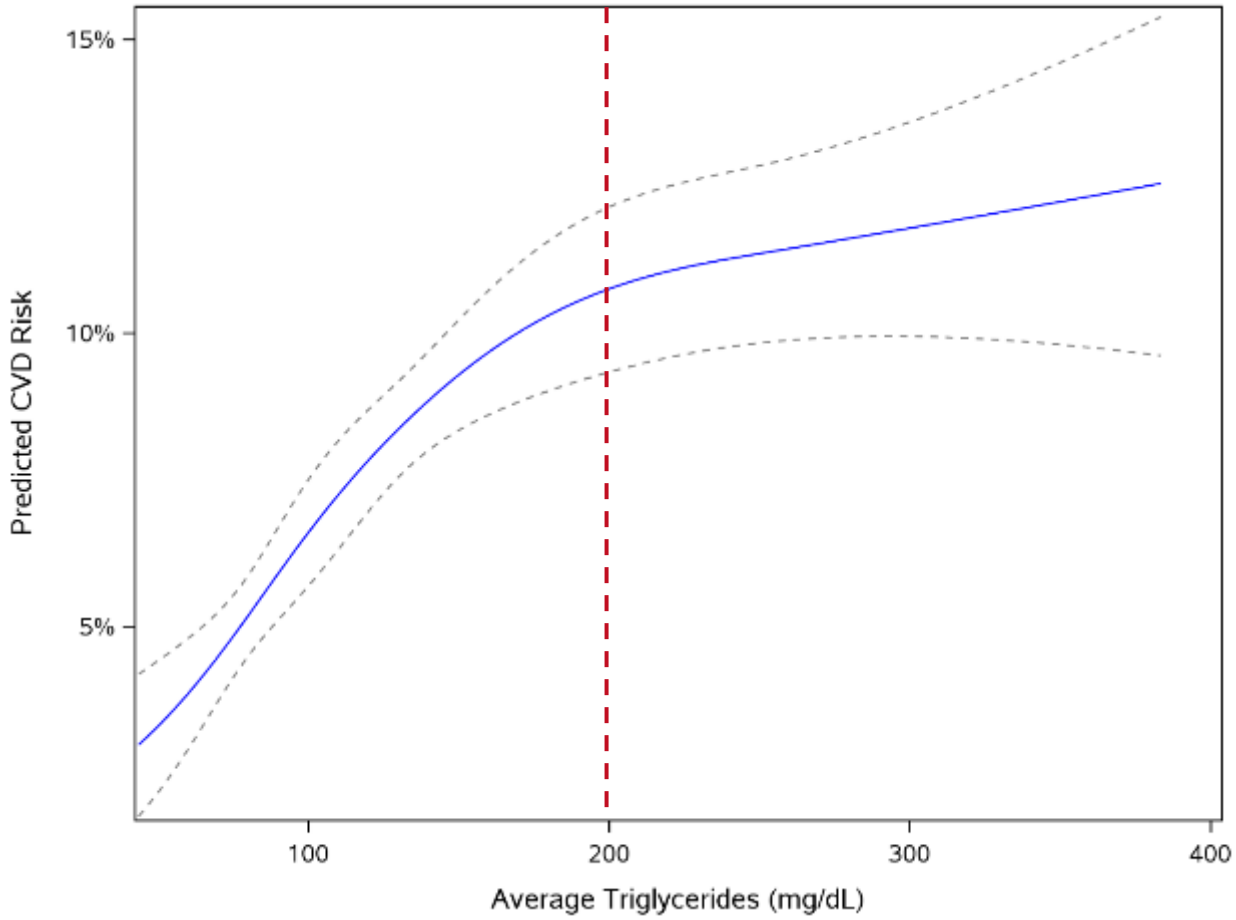


↑41% CVD Risk w/ mild HTG

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

*Death, myocardial infarction, or recurrent acute coronary syndrome. PROVE-IT-TIMI 22, Miller M, et al. *J Am Coll Cardiol*. 2008;51(7):724-730.

Lower Triglycerides Are Better: Direct Association Between Average Triglyceride



95% confidence intervals shown as dotted lines.

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

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

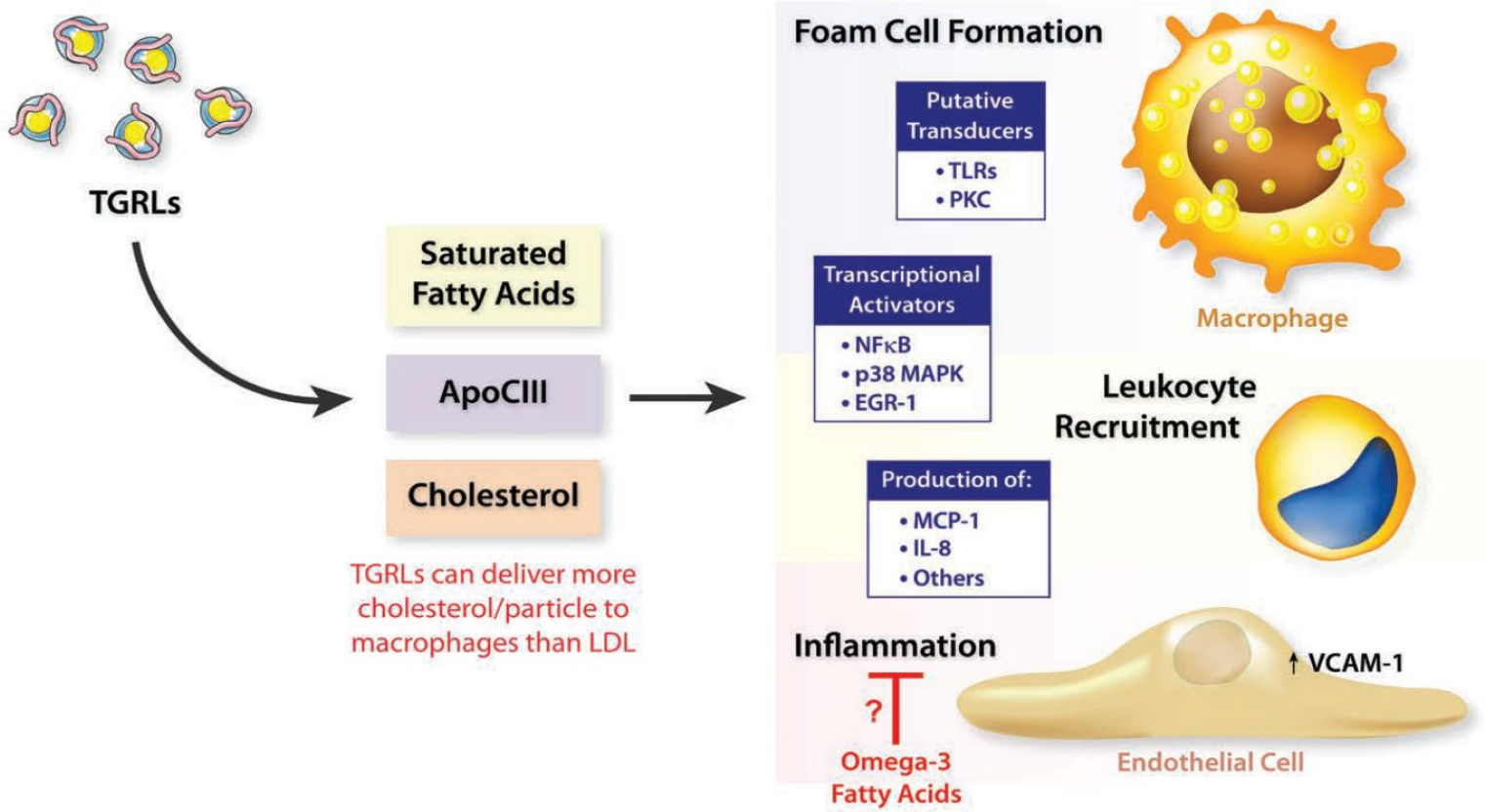
CVD events steeply increase across the entire range of TG levels to ~200 mg/dL, above which the relationship is less graded.

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

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

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

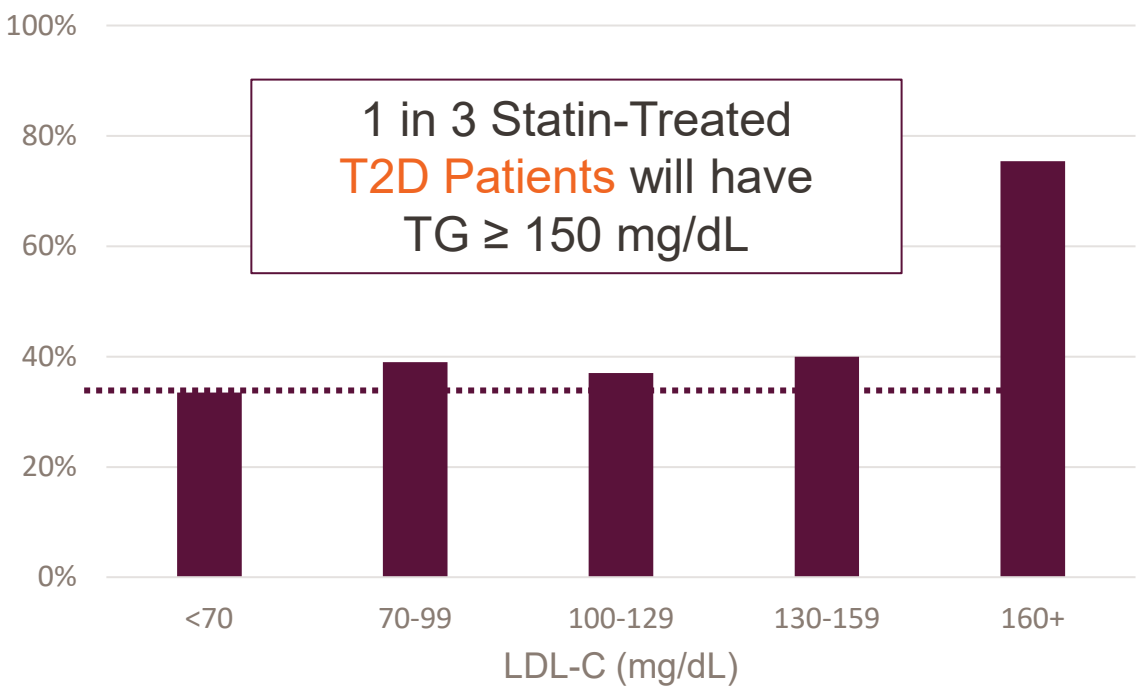
Atherogenic Pathways for Triglyceride-Rich Lipoproteins (TGRLs)



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

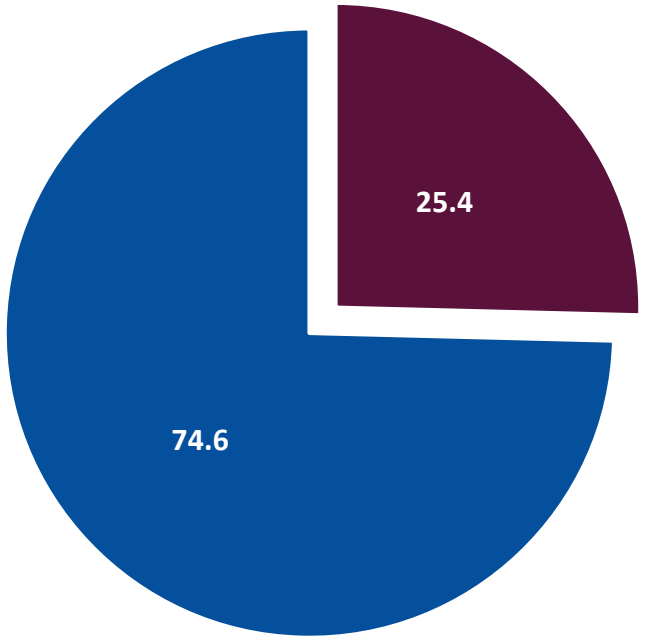
Contemporary Rates of HTG in Statin-Treated T2D or CVD

NHANES 2007-2014



W Fan, et al. *Diabetes Care.* 2019;42(12):2307-2314.

Ontario CVD Cohort (n=196,717)



1 in 4 CVD Patients
LDL < 100 mg/dL
TG ≥ 135 mg/dL

Lawler PR, et al. *Eur Heart J.* 2020;41(1):86-94.

What Does Expert Consensus Tell Us About Managing Triglycerides?

EXPERT CONSENSUS DECISION PATHWAY

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

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

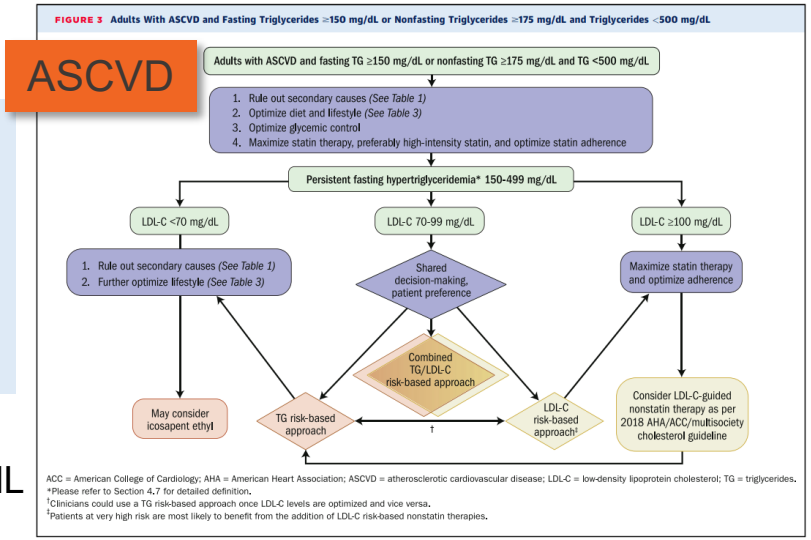
Endorsed by the National Lipid Association

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

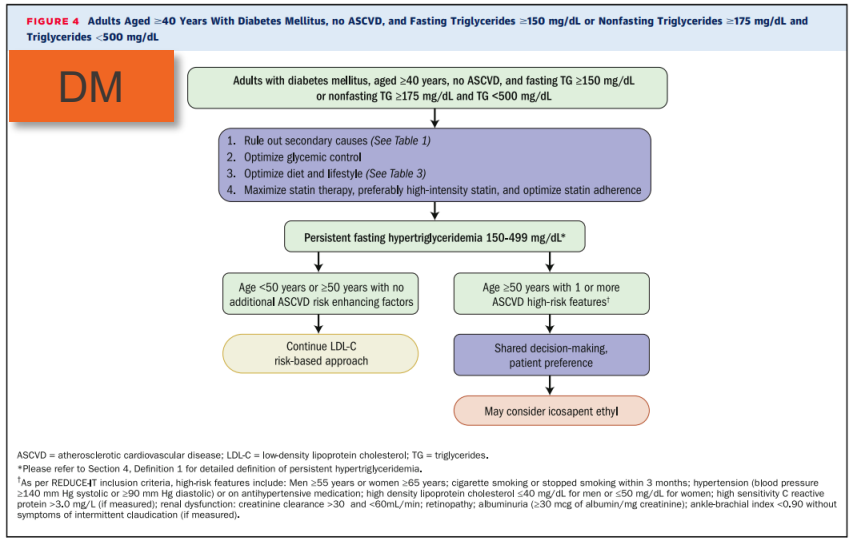
TG ≥ 500, "especially" ≥ 1000mg/dL

Medical Therapy
LDL-Lowering Pathway
TG-Lowering Pathway

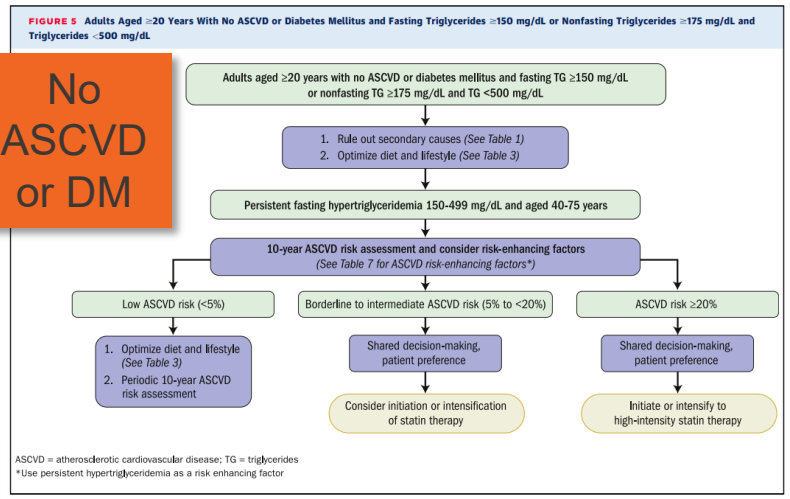
ASCVD



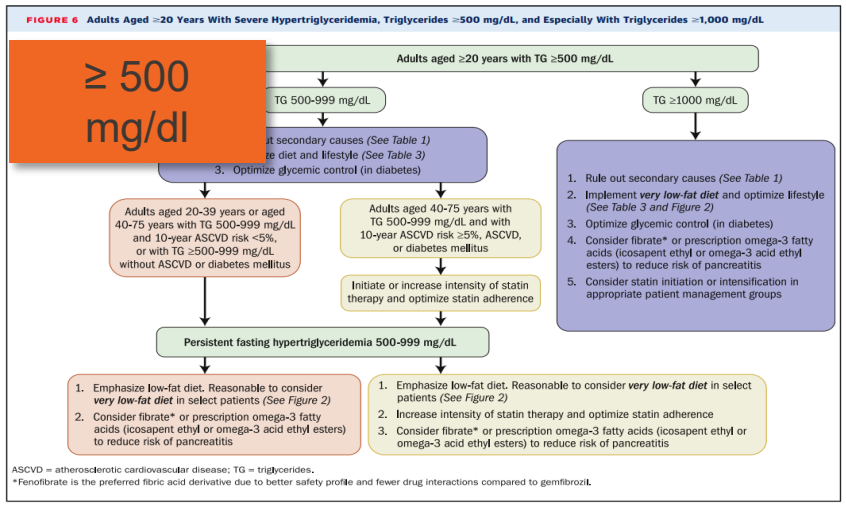
DM



No ASCVD or DM



≥ 500 mg/dl



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First, Rule Out Major Secondary Causes of Hypertriglyceridemia

Conditions

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

Medications

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

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

Second, Optimize Diet and Exercise

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

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

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

Virani S. 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients with Persistent Hypertriglyceridemia. JACC 2021;28(9)960-993

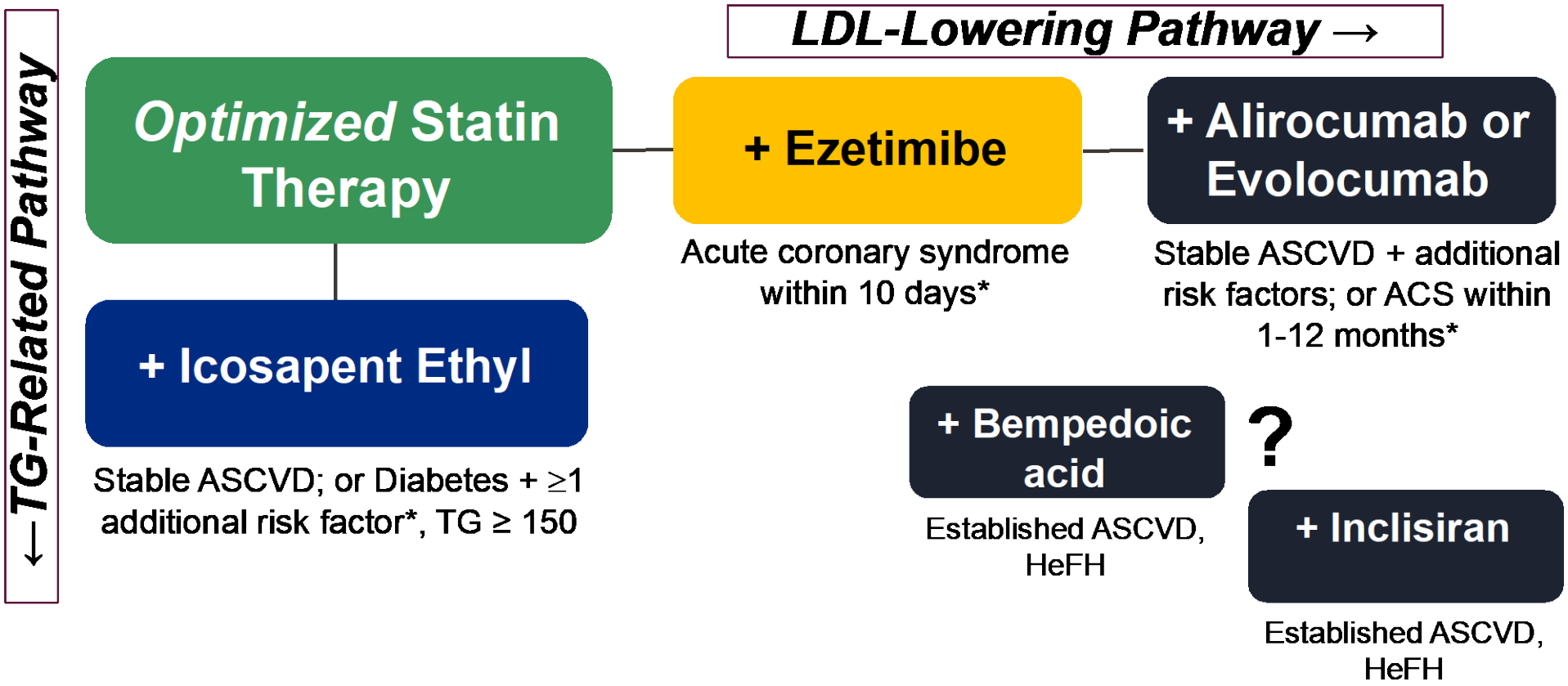
Key Prompts and Messaging Regarding Diet and Exercise

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

Be Specific
Be Numeric

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

Third, Medical Therapy



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

Our Patient - First Visit

- 60-year-old man
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, treated
- BMI 29 kg/m2
- Smoker

What is his yearly risk of ‘hard’ cardiovascular endpoints (heart attack, stroke, or death from cardiovascular disease)?

CVD Risk Scores in Secondary Prevention

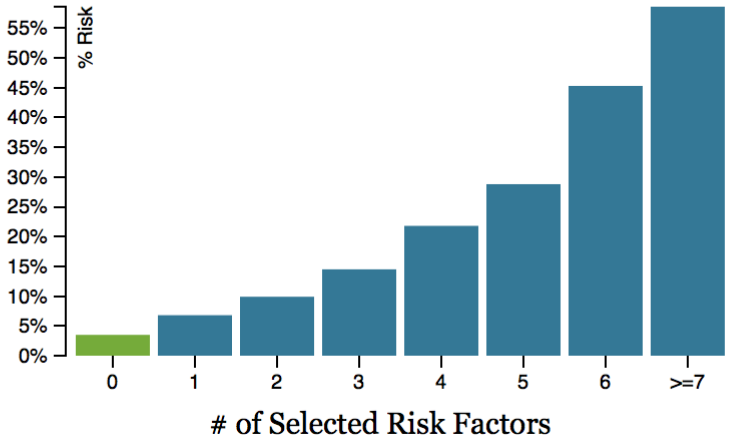
TIMI Risk Score for Secondary Prevention (TRS 2°P)

Risk in Patients with Known Atherosclerotic Vascular Disease

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

0 Risk Indicators Selected

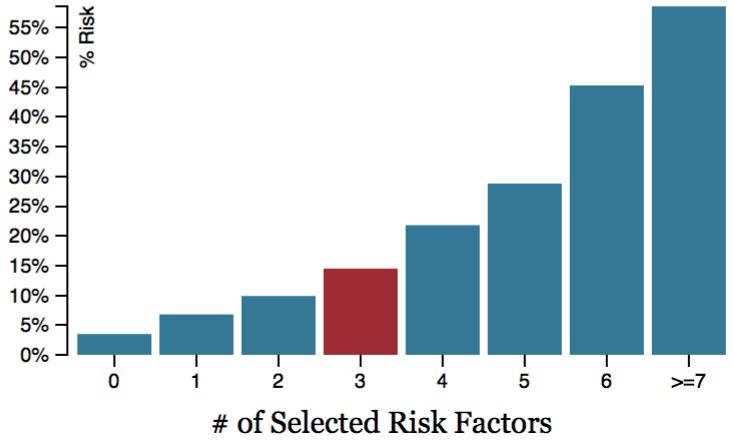
3.5% risk at 3 years of CV death, MI or Ischemic Stroke.



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

3 Risk Indicators Selected

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



Bohula EA, et al. Atherothrombotic Risk Stratification and the Efficacy and Safety of Vorapaxar in Patients with Stable Ischemic Heart Disease and Prior Myocardial Infarction. *Circulation* 2016;134 (4):304-13.

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

Our Patient - First Visit

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

- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension
- BMI 29 kg/m2

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

Summary

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

REDUCE-IT Clinical Trials and Omega-3 Fatty Acids for ASCVD Risk Reductions

Karol Watson, MD, PhD

medtelligence℠

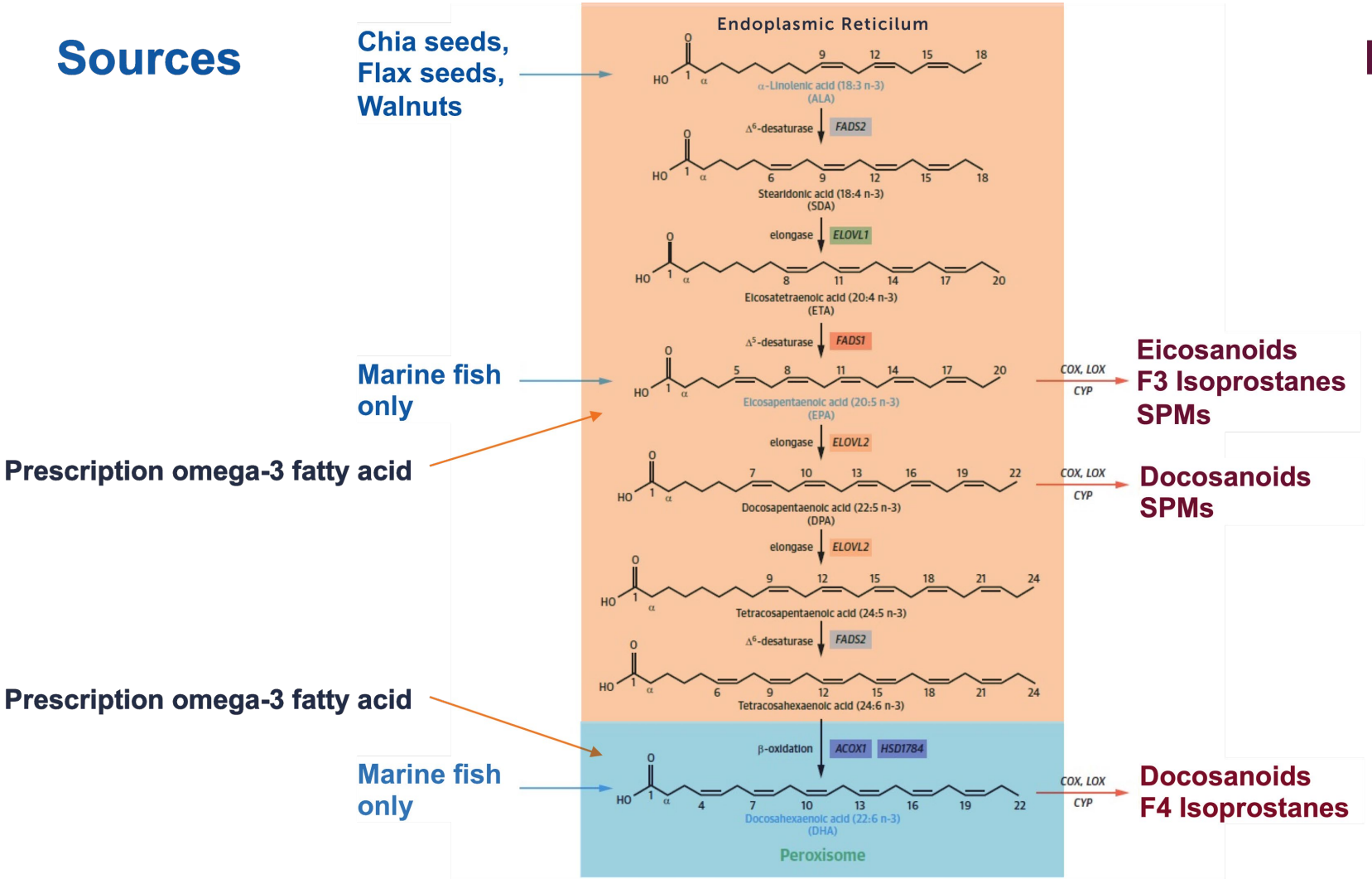
Large Clinical Trials of Statin Adjuncts Ezetimibe, PCSK9 Inhibitors, Fibrates, and Niacin

Positive Studies		Neutral Studies	
IMPROVE-IT Ezetimibe	HR = 0.936 (95% CI, 0.89-0.99) P = 0.016	ACCORD Fenofibrate	HR = 0.92 (95% CI, 0.79-1.08) P = 0.32
FOURIER Evolocumab	HR = 0.85 (95% CI, 0.79-0.92) P = 0.0001	FIELD Fenofibrate	HR = 0.89 (95% CI, 0.75-1.05) P = 0.16
ODYSSEY OUTCOMES Alirocumab	HR = 0.85 (95% CI, 0.78-0.93) P = 0.0001	AIM-HIGH Extended-release niacin	HR = 1.02 (95% CI, 0.87-1.21) Log-rank P = 0.79
		HPS2-THRIVE Extended-release niacin/laropiprant	HR = 0.96 (95% CI, 0.90-1.03) Log-rank P = 0.29

Cannon CP, et al. N Engl J Med. 2015;372(25):2387-2397. 2. Sabatine MS, et al. N Engl J Med. 2017;376(18):1713-1722. 3. Schwartz GG, et al. N Engl J Med. 2018;379(22):2097-2107.

ACCORD Study Group, et al. N Engl J Med. 2010;362(17):1563-1574. Keech A, et al. Lancet. 2005;366(9500):1849-1861. AIM-HIGH Investigators, et al. N Engl J Med. 2011;365(24):2255-2267. HPS2-THRIVE Collaborative Group, et al. N Engl J Med.

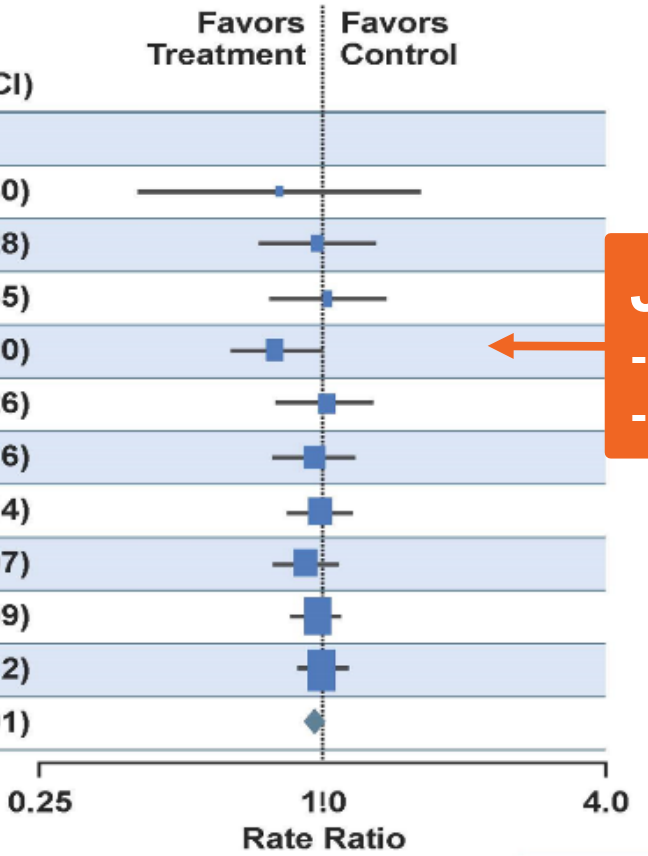
A Revolution in Omega-3 Fatty Acid Research



Reproduced with permission. Bhatt DL, Budoff MJ, Mason RP. *J Am Coll Cardiol*. 2020;76(18):2098-2101.

"TG-Lowering" Omega-3 CV Outcome Trials: *No* ↓*CVD* w/ Low-Dose EPA + DHA Mix (Diet-Sup or Rx)

Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Major Vascular Events			
DOIT	29 (10.3)	35 (12.5)	0.81 (0.41–1.60)
AREDS-2	213 (9.9)	208 (10.1)	0.98 (0.75–1.28)
SU.FOL.OM3	216 (17.2)	211 (16.9)	1.02 (0.78–1.35)
JELIS	262 (2.8)	324 (3.5)	0.80 (0.65–1.00)
Alpha Omega	332 (13.8)	331 (13.6)	1.02 (0.82–1.26)
OMEGA	534 (27.7)	541 (28.6)	0.96 (0.80–1.16)
R&P	733 (11.7)	745 (11.9)	0.99 (0.86–1.14)
GISSI-HF	783 (22.4)	831 (23.9)	0.92 (0.80–1.07)
ORIGIN	1276 (20.3)	1295 (20.7)	0.98 (0.87–1.09)
GISSI-P	1552 (27.4)	1550 (27.3)	1.00 (0.90–1.12)
All	5930 (15.2)	6071 (15.6)	0.97 (0.93–1.01)
			P=0.10



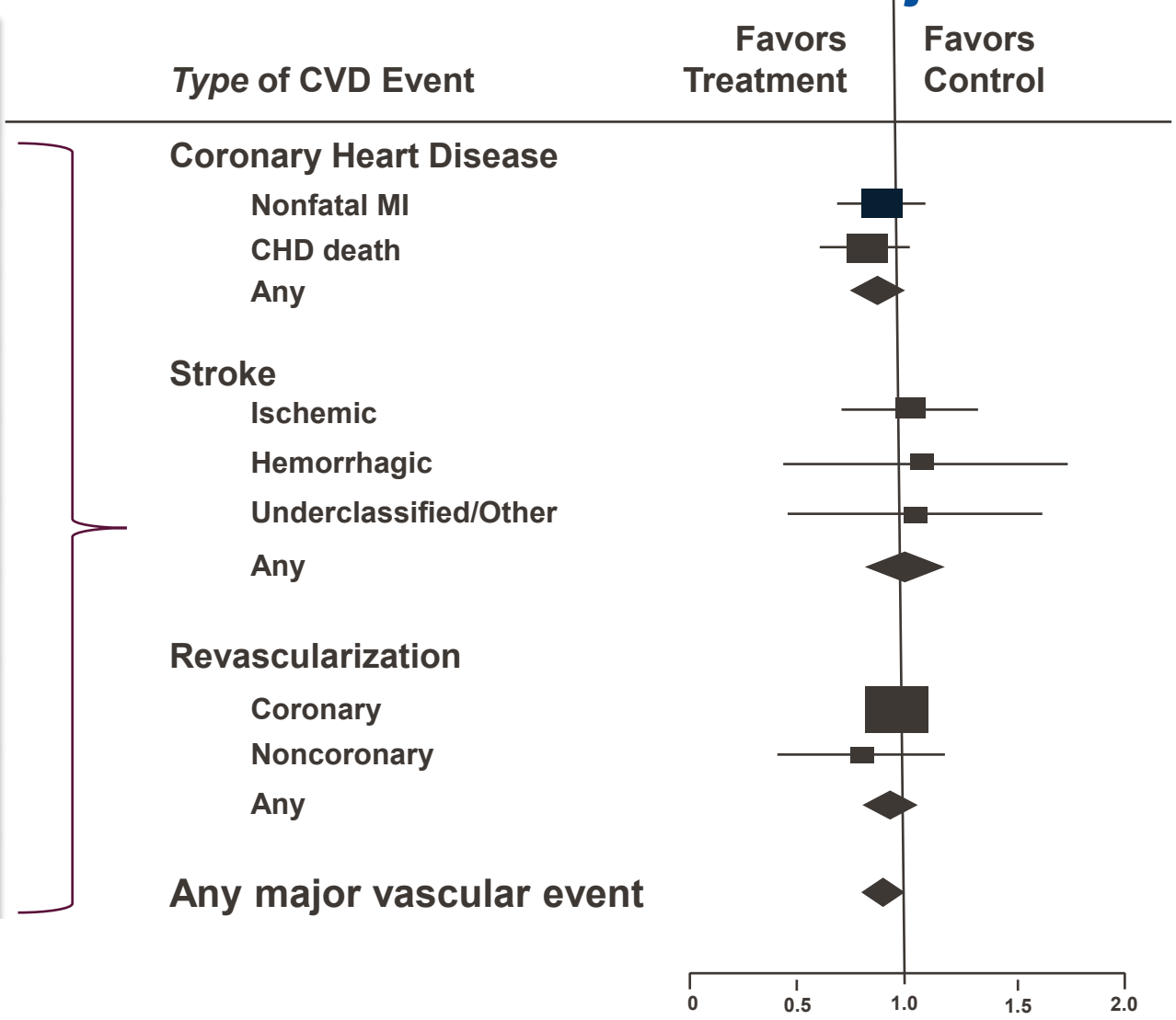
JELIS
--Only ***Positive*** Trial
--Only ***Pure EPA*** Trial

*Studies included: AREDS-2, Age-Related Eye Disease Study 2; DOIT, Diet and Omega-3 Intervention Trial; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure; GISSI-P, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione; JELIS, Japan Eicosapentaenoic Acid (EPA) Lipid Intervention Study; OMEGA, Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction; ORIGIN, Outcome Reduction With Initial Glargine Intervention; SU.FOL.OM3, Supplémentation en Folates et Omega-3; R&P, Risk and Prevention Study.

Aung T et al. *JAMA Cardiol.* 2018;3(3):225-234.

Lack of ↓CVD with Omega-3 FA: Due to Low Doses, Use of Dietary Supplements, Presence of DHA and/or Lack of Focus on HTG Subjects?

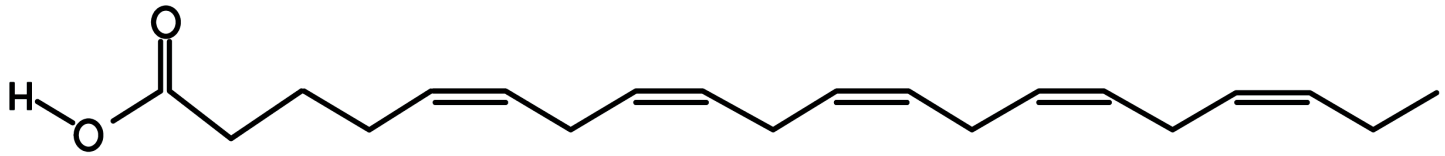
Study (Year)	EPA/DHA Dose (mg/d)	EPA / DHA Source
DOIT (2010)	1150 / 800	Dietary supplement
AREDS-2 (2014)	650 / 350	Dietary supplement
SU.FOL.OM3 (2010)	400 / 200	Dietary supplement
JELIS (2007)	1800 / 0	Pure EPA Rx
Alpha Omega (2010)	226 / 150	Margarine with dietary supplement
OMEGA (2010)	460 / 380	Rx EPA/DHA
R&P (2013)	500 / 500	Rx EPA/DHA
GISSI-HF (2008)	850 / 950	Rx EPA/DHA
ORIGIN (2012)	465 / 375	Rx EPA/DHA
GISSI-P (1999)	850 / 1700	Rx EPA/DHA

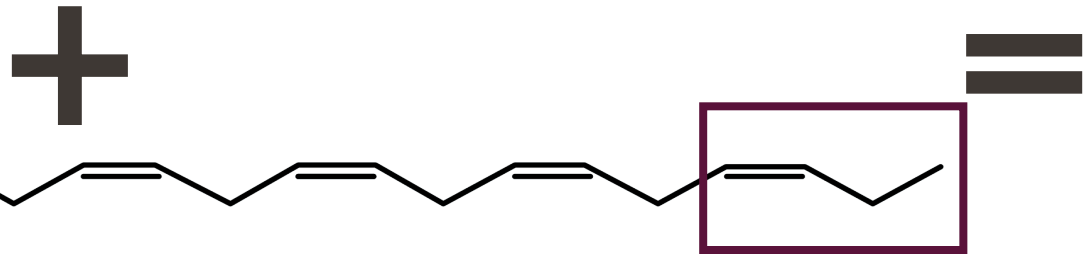


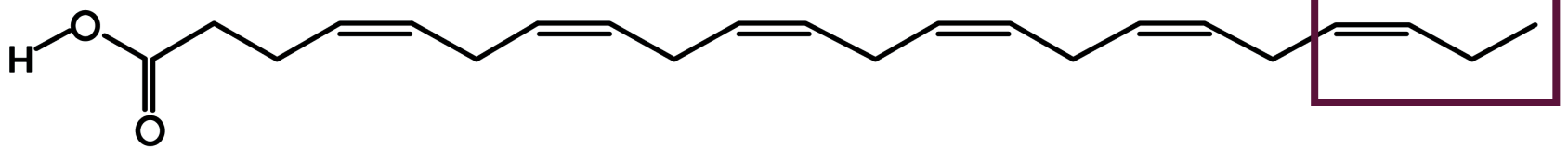
Aung T, et al. JAMA Cardiol. 2018;3(3):225-234.
Manson JE, et al. N Engl J Med. 2019;380(1):23-32.
wman L, et al. N Engl J Med. 2018;379(16):1540-1550.
Bhatt DL, et al. N Engl J Med. 2019;380(1):11-22.

EPA versus DHA: Look Similar but Are Apparently Different

Eicosapentaenoic acid (EPA) 20:5

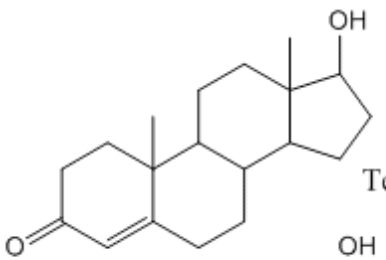




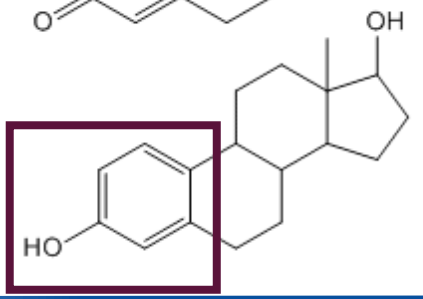


Docosahexaenoic acid (DHA) 22:6

Omega-3 PUFA



Testosterone

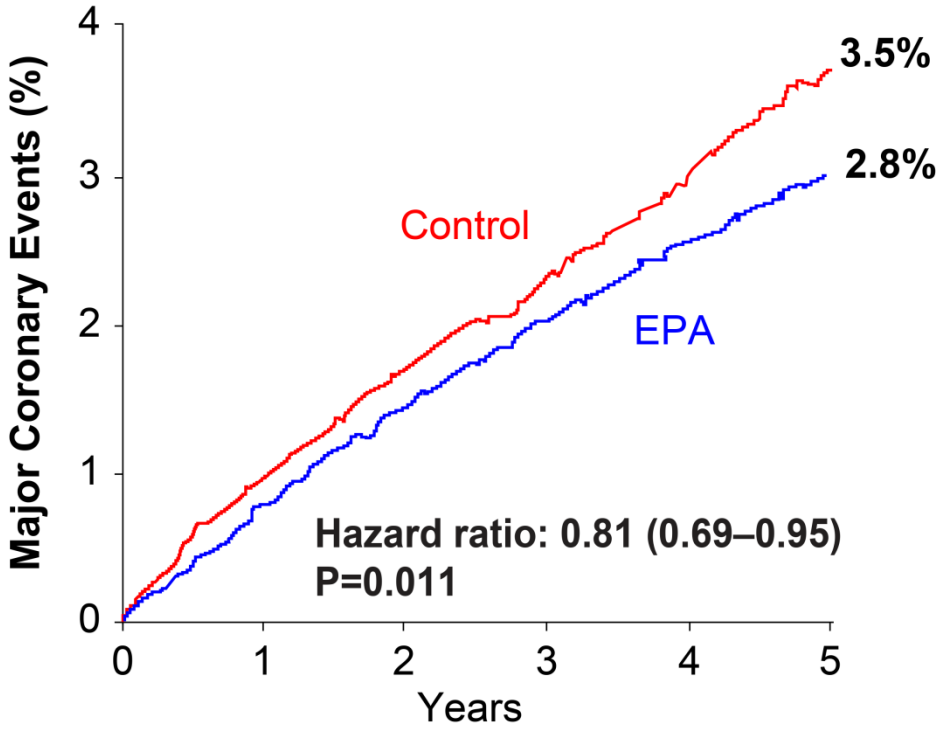


Estrogen

JELIS Showed CV Risk Reduction with Icosapent Ethyl (EPA)

Japanese patients with elevated TC randomized to statin alone or statin + ethyl-EPA (1.8 g/day Epadel) in PROBE study design (open-label, blinded endpoint adjudication)

Total Cohort (N = 18,645)
No prespecified minimum TG level



–19% RRR
(5% TG reduction)

- 80% primary prevention
- 69% women
- Median statin-naïve baseline TG ≈1.7 mmol/L (IQR 1.2-2.5)
- LDL-C ≈3.5 mmol/L with statin; managed per Japanese guidelines
- Stable form of EPA (protected from degradation)

P value adjusted for age, gender, smoking, diabetes, and hypertension.
PROBE, prospective, randomized, open-label, blinded endpoint; TC, total cholesterol; TG, triglycerides.

Yokoyama M, et al. Lancet. 2007;369(9567):1090-1098.

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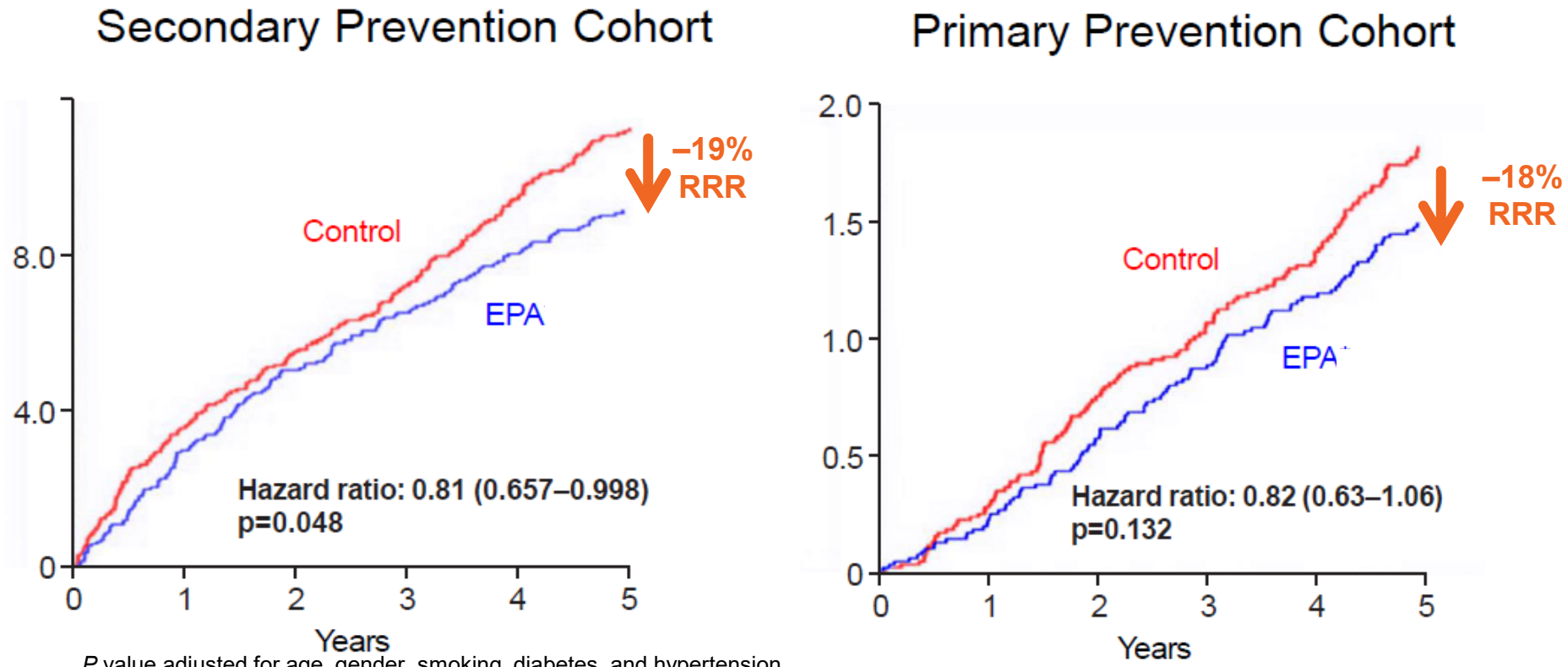

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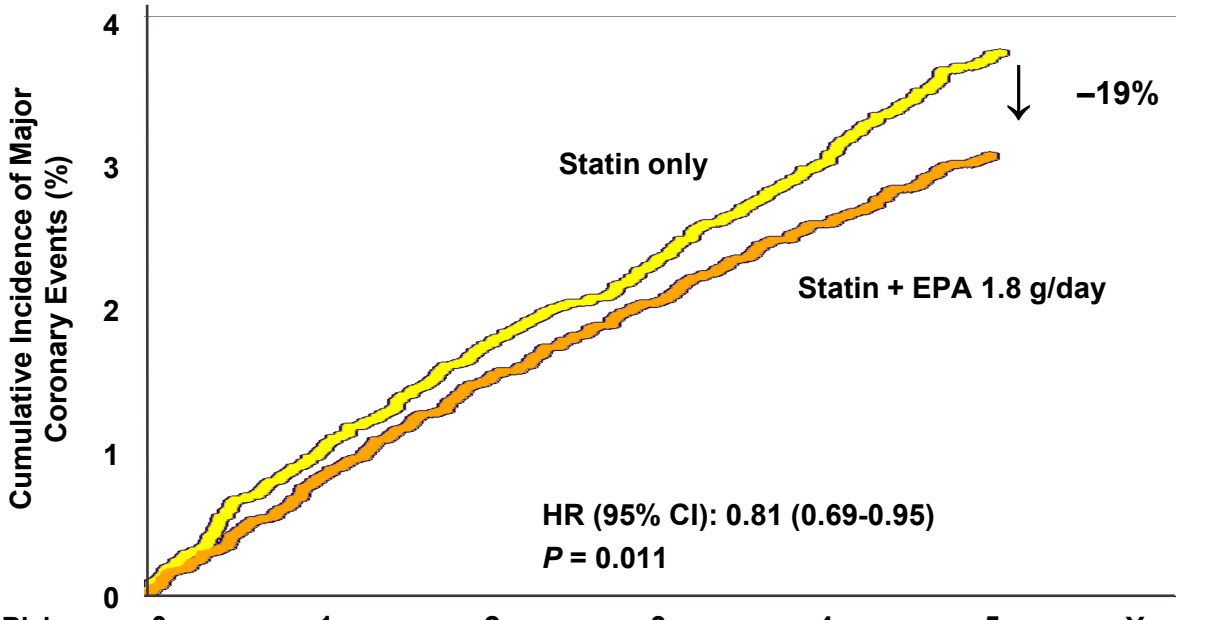
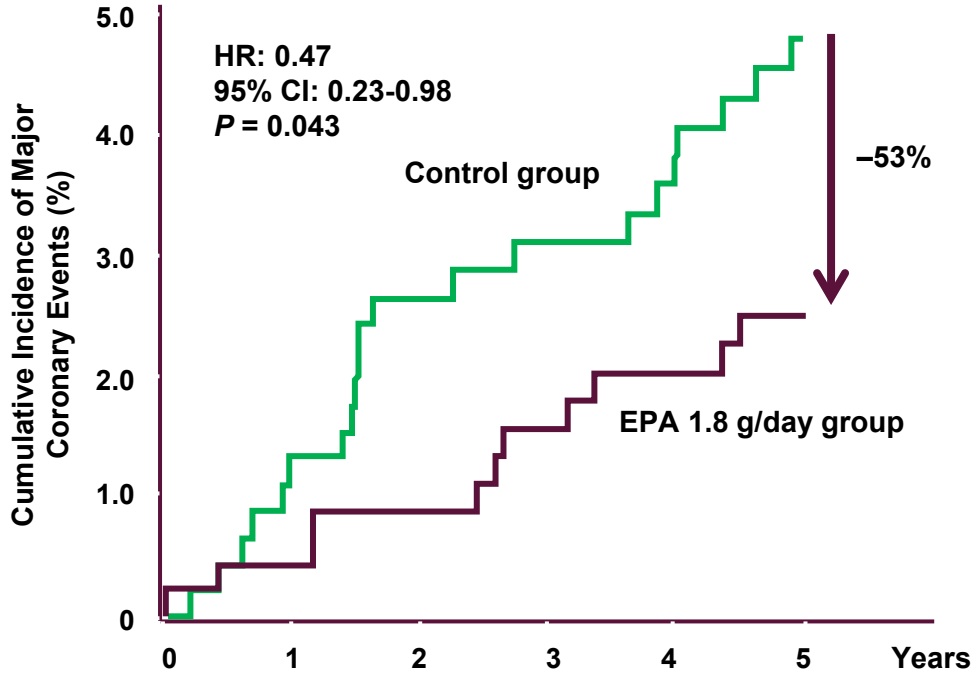
PROBE, prospective, randomized, open-label, blinded endpoint; TC, total cholesterol; TG, triglycerides.

Yokoyama M, et al. Lancet. 2007;369(9567):1090-1098.

JELIS: Rx Pure EPA + Statins Led to ↓Major Coronary Events* in Hypercholesterolemic Patients on Statins and in HTG Subgroup†



No. at Risk	0	1	2	3	4	5	Years
Control	9319	8931	8671	8433	8192	7958	
EPA	9326	8929	8658	8389	8153	7924	



No. of patients						
Control	475	444	432	414	400	392
EPA	482	455	443	427	413	403

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 nonfatal MI, unstable angina pectoris, angioplasty, stenting, or coronary artery bypass graft.

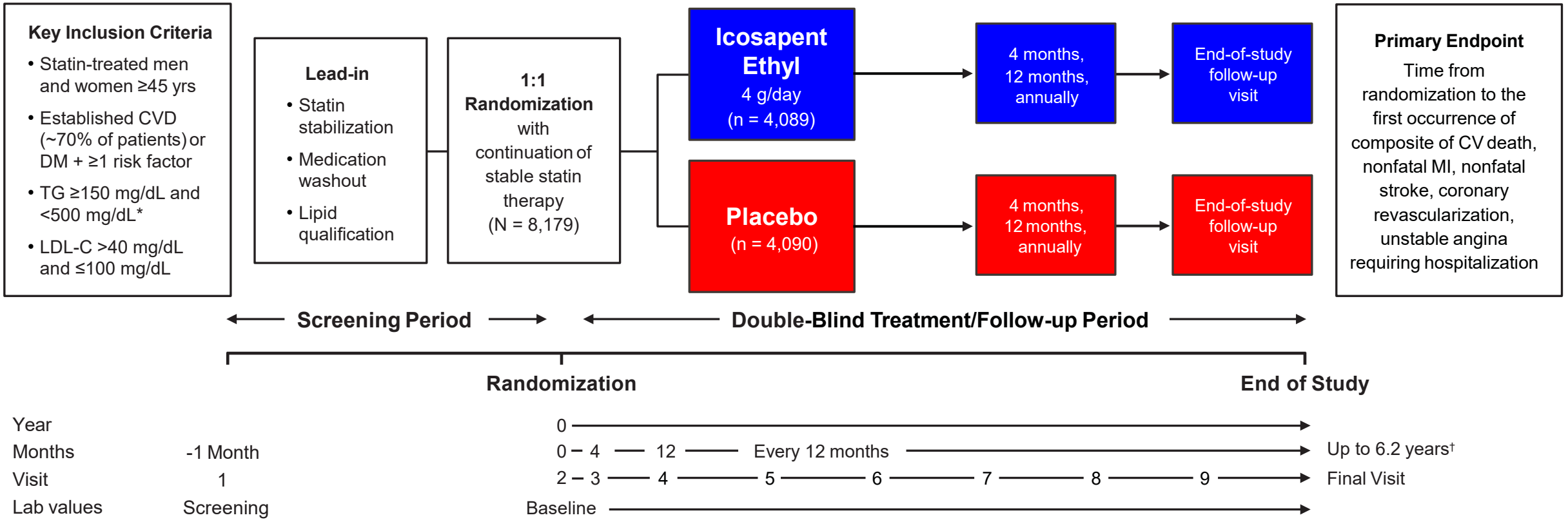
HR and *P* value adjusted for age, gender, smoking, diabetes, and HTN.

† Prespecified.

Yokoyama M, et al. *Lancet.* 2007;369(9567):1090-1098.

Saito Y, et al. *Atherosclerosis*. 2008;200(1):135-140.

REDUCE-IT Design

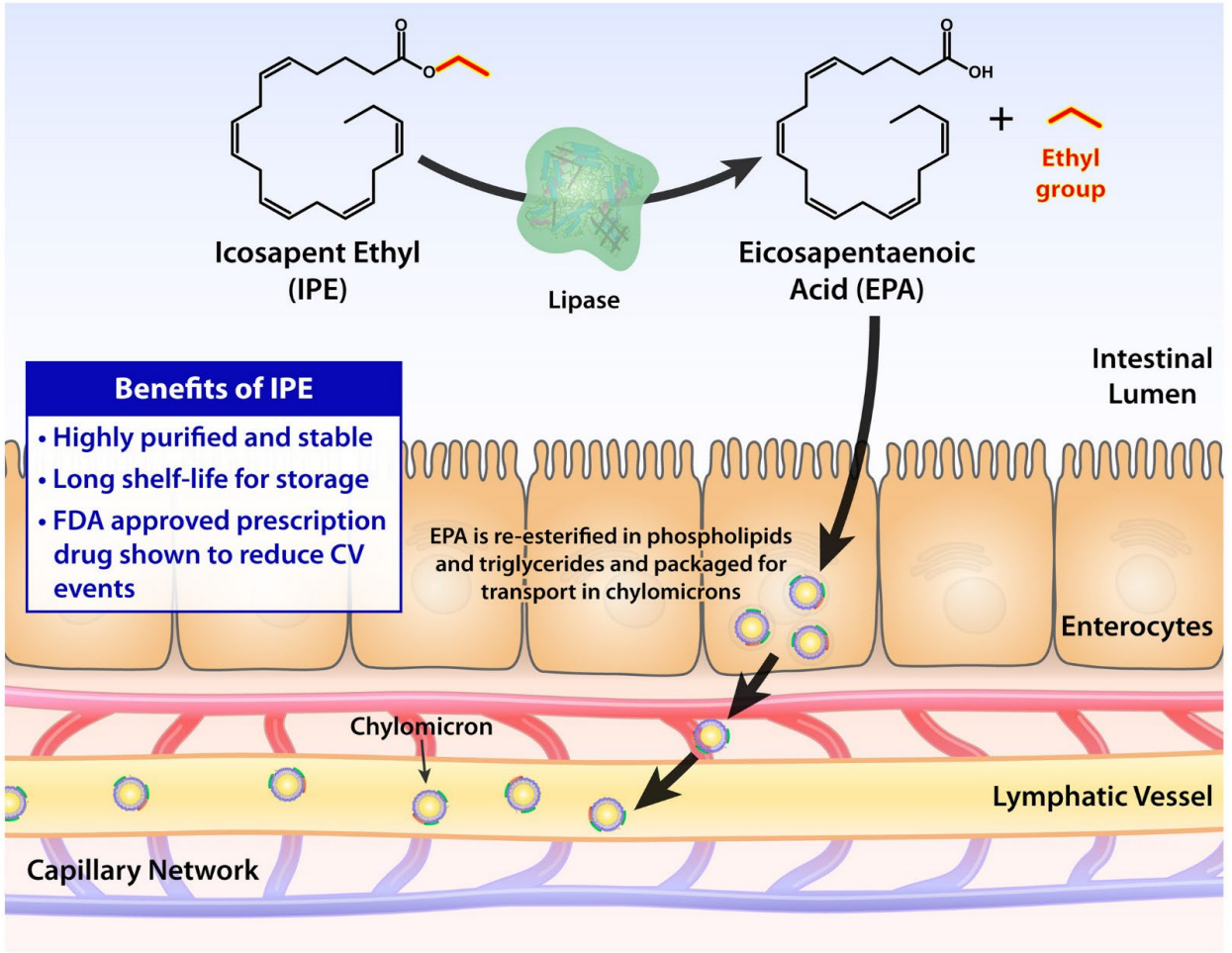


*Due to the variability of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability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

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

Bhatt DL, et al; REDUCE-IT Investigators. *Clin Cardiol.* 2017;40(3):138-148.
REDUCE-IT ClinicalTrials.gov identifier: NCT01492361.

Intestinal Processing and Absorption of Icosapent Ethyl (IPE)

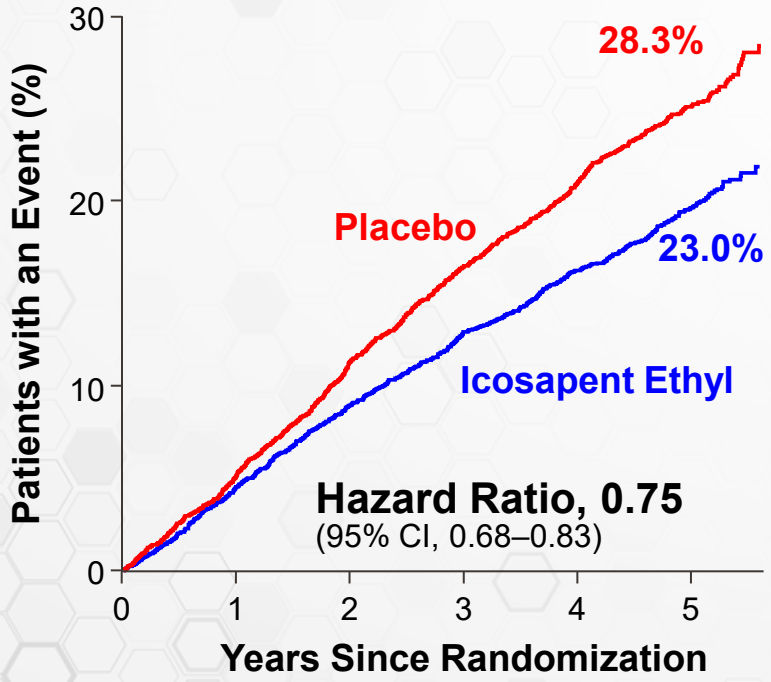


Wang X, Verma S, Mason RP, Bhatt DL. *Curr Diab Rep*. 2020;20(11):65.

REDUCE-IT Primary and Secondary Endpoints

Primary Composite Endpoint:

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



RRR = 24.8%

ARR = 4.8%

NNT = 21 (95% CI, 15–33)

***P* = 0.00000001**

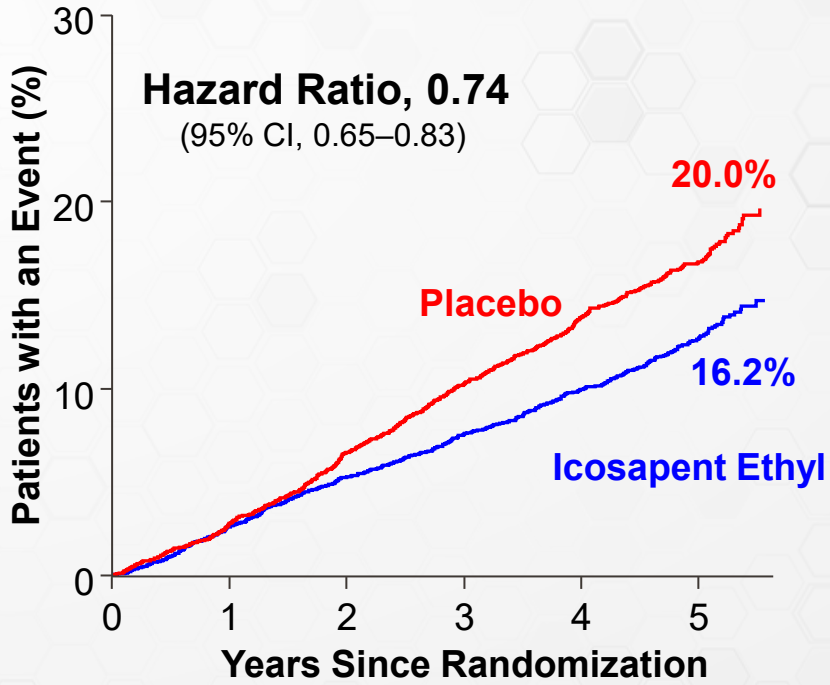
Bhatt DL, et al. *N Engl J Med*. 2019;380(1):11-22.

Key Inclusion Criteria

- Statin-treated men and women ≥45 yrs
- Established CVD (~70% of patients) or DM + ≥1 risk factor
- TG ≥ 150 mg/dL and <500 mg/dL
- LDL-C >40 mg/dL and ≤100 mg/dL

Key Secondary Composite Endpoint:

CV Death, MI, Stroke



RRR = 26.5%

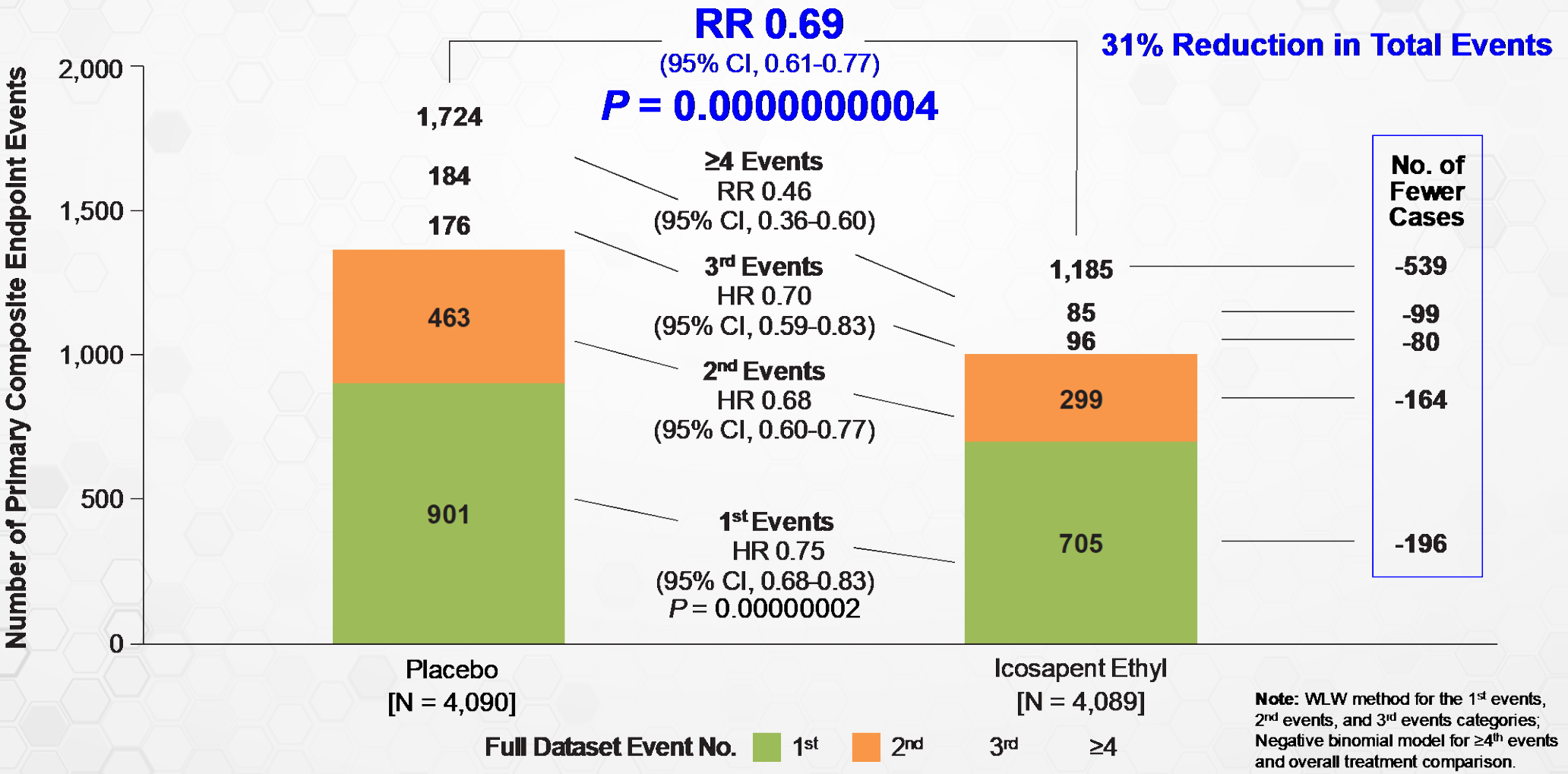
ARR = 3.6%

NNT = 28 (95% CI, 20–47)

***P* = 0.0000006**

First and Subsequent Events – Full Data

reduce-it 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, et al. *J Am Coll Cardiol*. 2019;73(22):2791-2802. Bhatt DL. ACC 2019; New Orleans.

Treatment-Emergent Adverse Events

No Overall Treatment Difference in Adverse Event Profiles

	Icosapent Ethyl (N = 4,089)	Placebo (N = 4,090)	P value*
Subjects with at least one TEAE, n (%)	3,343 (81.8%)	3,326 (81.3%)	0.63
Serious TEAE	1,252 (30.6%)	1,254 (30.7%)	0.98
TEAE leading to withdrawal of study drug	321 (7.9%)	335 (8.2%)	0.60
Serious TEAE leading to withdrawal of study drug	88 (2.2%)	88 (2.2%)	>0.99
Serious TEAE leading to death	94 (2.3%)	102 (2.5%)	0.61

TEAE event rates represent the enrolled high CV risk patients and the 4.9-year median study follow-up.
* From Fisher's exact test.

Bhatt DL, et al. *N Engl J Med.* 2019;380(1):11-22.

Treatment-Emergent Adverse Event of Interest: Bleeding

	Icosapent Ethyl (N = 4,089)	Placebo (N = 4,090)	*P* value*
All bleeding TEAEs	482 (11.8%)	404 (9.9%)	0.006
Bleeding SAEs	111 (2.7%)	85 (2.1%)	0.06
Gastrointestinal bleeding	62 (1.5%)	47 (1.1%)	0.15
Central nervous system bleeding	14 (0.3%)	10 (0.2%)	0.42
Other bleeding	41 (1.0%)	30 (0.7%)	0.19
Intracranial bleeding	0 (0.0%)	1 (0.0%)	>0.99
Hemorrhagic stroke	13 (0.3%)	10 (0.2%)	0.54

Note: Hemorrhagic stroke was an adjudicated endpoint; other bleeding events were included in safety analyses.
* From Fisher's exact test.

Bhatt DL, et al. *N Engl J Med.* 2019;380(1):11-22. FDA Advisory Committee, 2019.

Atrial Fibrillation or Flutter

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

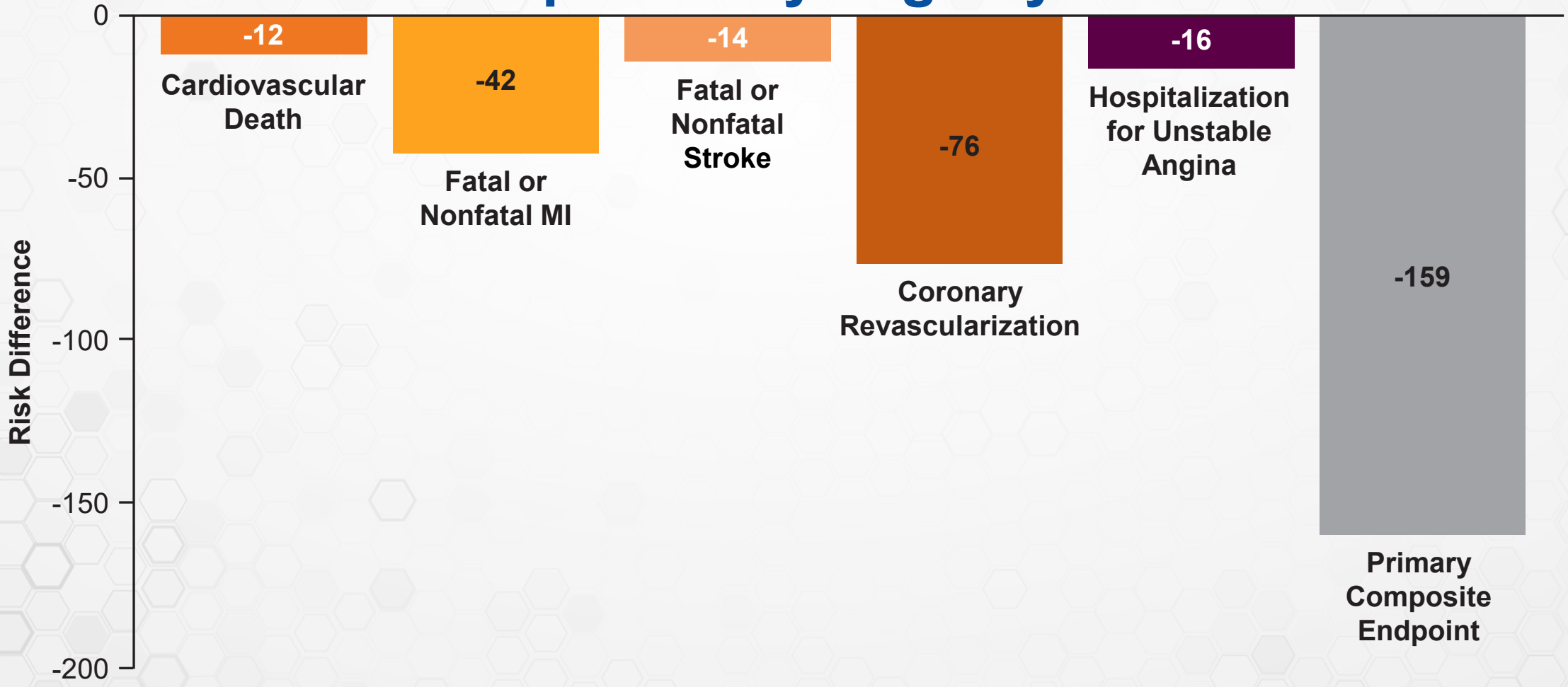
	Icosapent Ethyl (N = 4,089) n (%)	Placebo (N = 4,090) n (%)	*P* value*
Afib/Aflutter TEAEs and positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalization	321 (7.9)	248 (6.1)	0.002
Afib/Aflutter TEAEs[1]	236 (5.8)	183 (4.5)	0.008
Serious Afib/Aflutter TEAEs[2]	22 (0.5)	20 (0.5)	0.76
Positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalization[3]	127 (3.1)	84 (2.1)	0.004

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

* From Fisher's exact test.

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

REDUCE-IT: Decrease in Total Events for Every 1000 Patients on Icosapent Ethyl 4 g/day for 5 Years



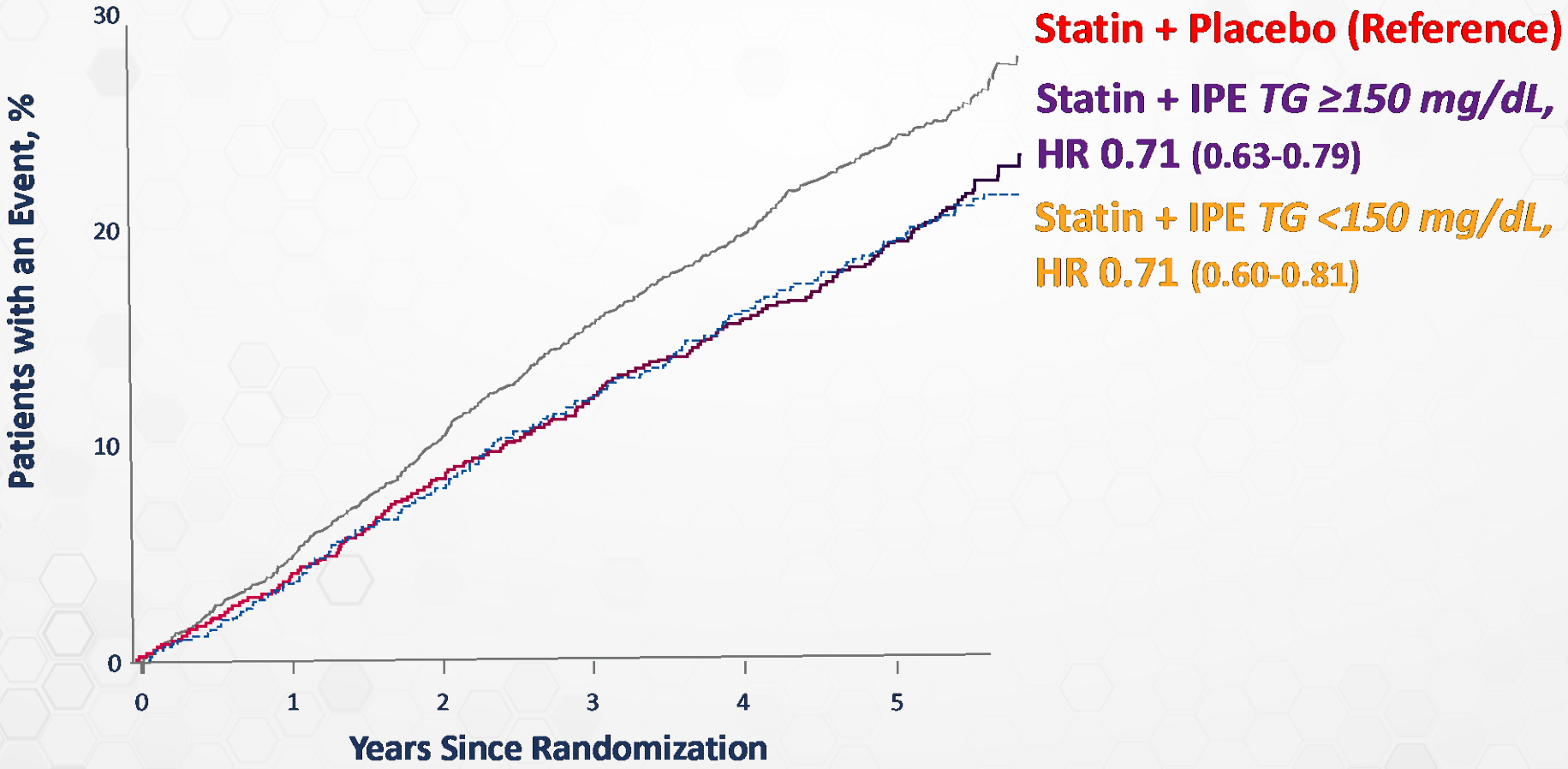
Bhatt DL, et al. *J Am Coll Cardiol*. 2019;73(22):2791-2802.

↓CVD with IPE Did *NOT* aVary by *Baseline* TG
(similar HR if TG ≥ or < 150 mg/dL)

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)	

Bhatt DL, et al. *N Engl J Med.* 2019;380(1):11-22.

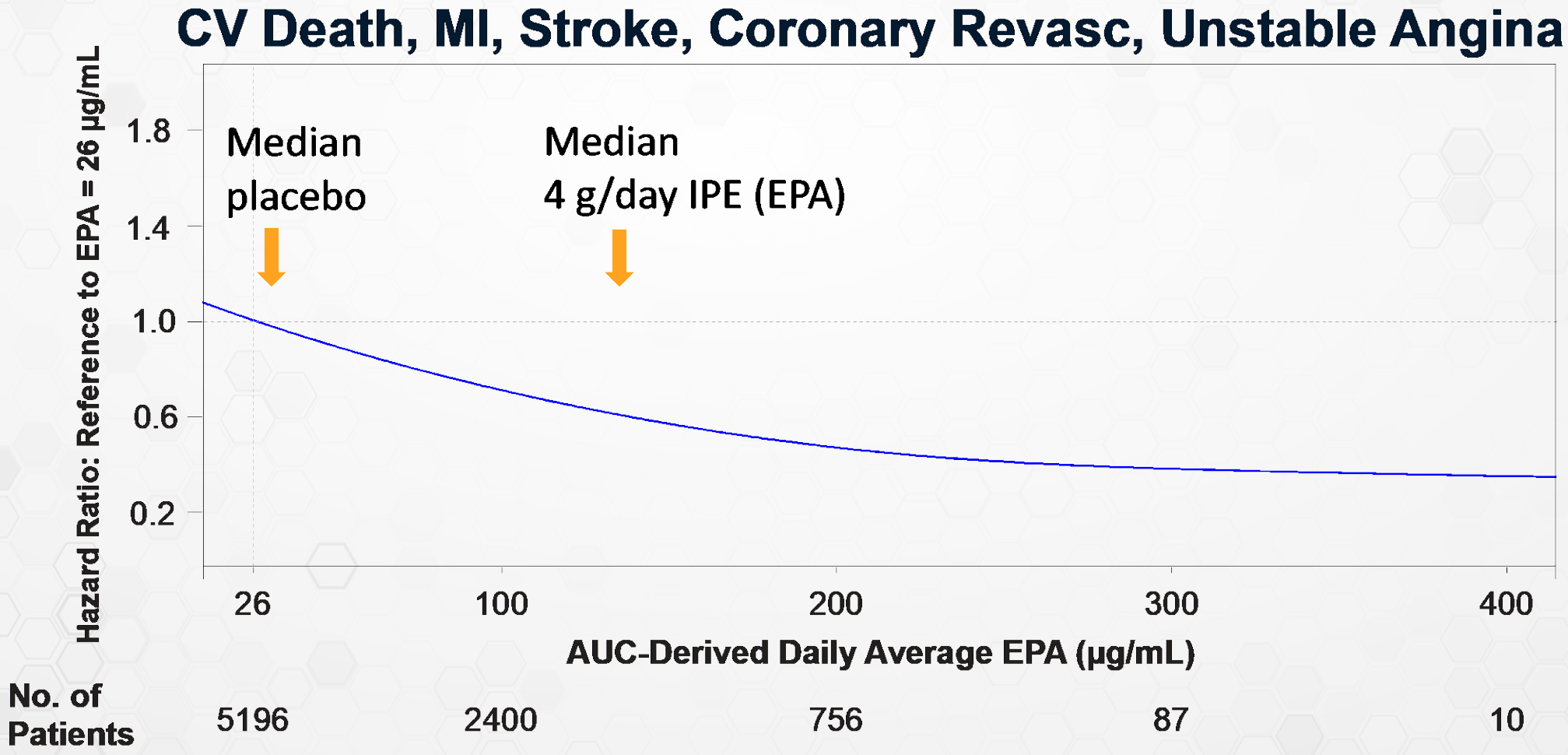
REDUCE-IT: On-Treatment TG (< or ≥ 150) Did Not Alter CVD Risk



First event composite: CV death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, hospitalization for unstable angina.

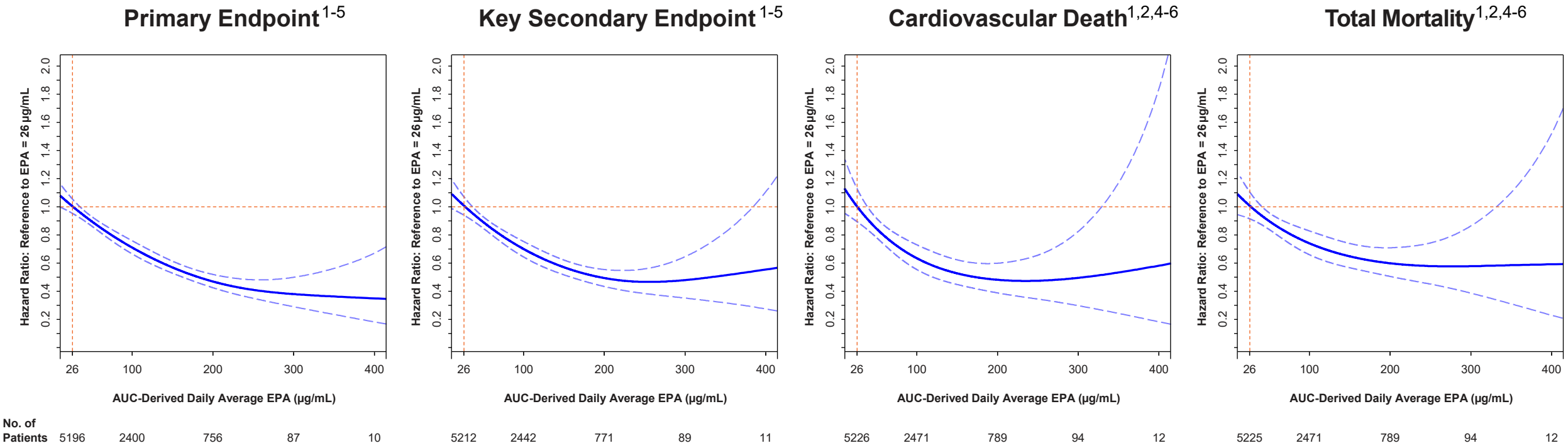
Bhatt DL, et al. *N Engl J Med.* 2019;380(1):11-22.

Primary Endpoint by On-Treatment Serum EPA



Adapted from Bhatt DL. Abstract presented at: ACC.20/WCC Virtual Meeting; March 30, 2020.

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



***P** < 0.001 for all**

Note: Area under the curve (AUC)-derived daily average serum EPA (µg/mL) is the daily average of all available post-baseline EPA measurements prior to the event. Dose-response hazard ratio (solid line) and 95% CI (dotted lines) are estimated from the Cox proportional hazard model with a spline term for EPA and adjustment for randomization factors and statin compliance[1], age[2], sex[3], baseline diabetes[4], hsCRP[5], treatment compliance.[6]

***P value is <0.001 for both nonlinear trend and for regression slope.**

Bhatt DL. ACC.20/WCC Virtual Meeting; March 30, 2020.a

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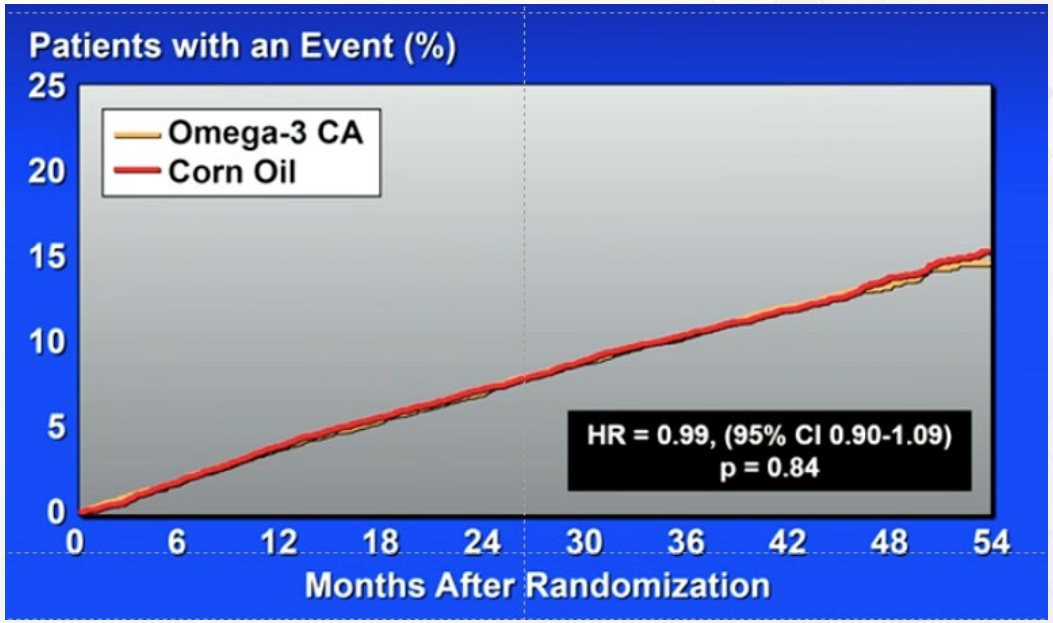
STRENGTH Trial Design, Details, and Primary Endpoint

- Randomized 13,078 patients Oct. 2014 – June 2017 (686 sites, 22 countries)
- Trial stopped by data monitoring board for “futility” January 8, 2020, after review of 1,384 MACE outcomes
- 1,580 MACE endpoints accrued by last patient visit May 14, 2020
- Median follow-up time 42.0 months and study drug 38.4 months

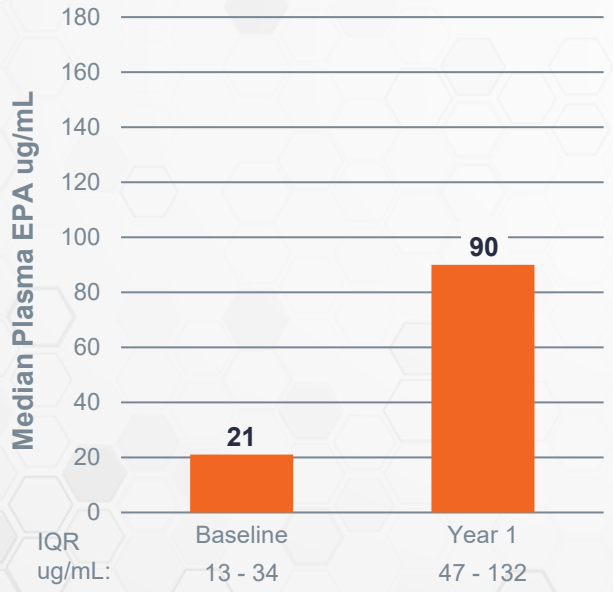
Primary Endpoint: MACE (CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina)



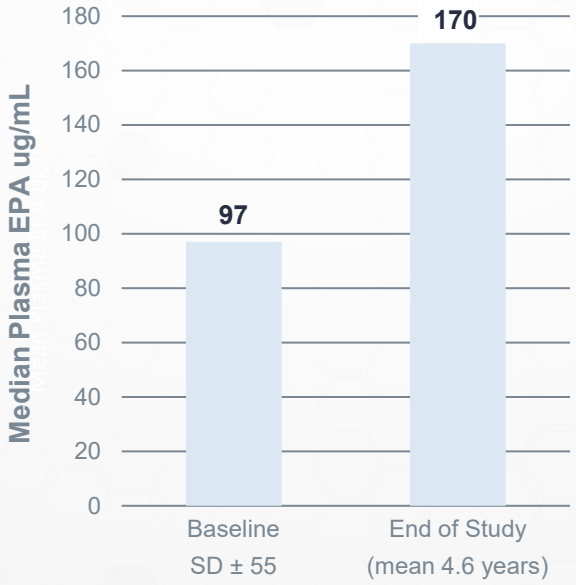
Lincoff AM. American Heart Association Virtual Scientific Sessions; November 15, 2020. Nicholls SJ, et al. *JAMA*. 2020;324(22):2268-2280.

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

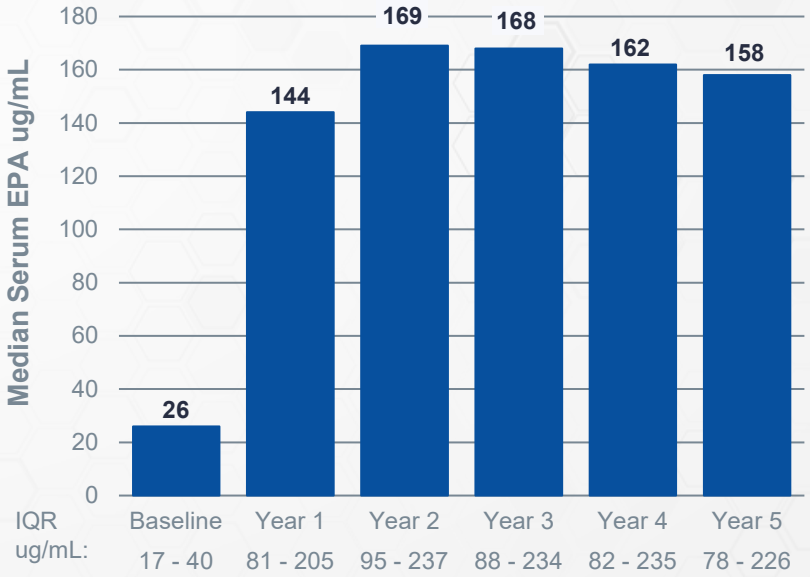
STRENGTH[1]
Plasma EPA



JELIS[2]
Plasma EPA



REDUCE-IT[3]
Serum EPA

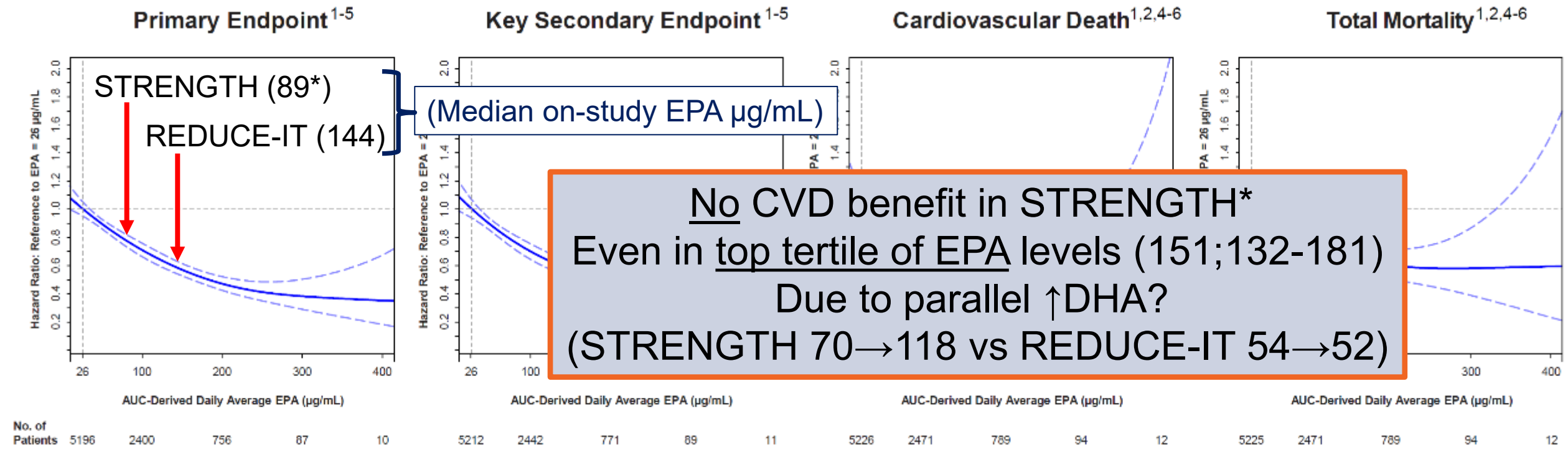


DRUG:	850 mg EPA/DHA carboxylic acid / 1-g capsule	300 mg capsules of >98% EPA ethyl esters	1 g icosapent ethyl (EPA ethyl ester) / 1-g capsule
DOSE:	4 g/d as 2 capsules 2x daily	1.8 g/d as 2 capsules 3x daily	4 g/d as 2 capsules 2x daily
POPULATION:	International	Japanese	International

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

1. Nicholls SJ, et al. *JAMA*. 2020;324(22):2268-2280. 2. Itakura H, et al. *J Atheroscler Thromb*. 2011;18(2):99-107. 3. Bhatt DL, et al. ACC 2020 Scientific Session (ACC.20)/World Congress of Cardiology (WCC); March 30, 2020. Abstract 20-LB-20501-ACC. 4. Dunbar RL, et al. Poster presented at the Gordon Conference on Atherosclerosis; Newry, Maine; June 16-21, 2019. 5. Dunbar RL, et al. Poster presented at NLA Scientific Sessions; December 9-12, 2020.

ASCVD Benefits Follow On-Study EPA Levels in REDUCE-IT (Pure EPA), but Not in STRENGTH (EPA+DHA)



P*<0.001 for all

Note: Area under the curve (AUC)-derived daily average serum EPA (µg/mL) is the daily average of all available post baseline EPA measurements prior to the event. Dose-response hazard ratio (solid line) and 95% CI (dotted lines) are estimated from the Cox proportional hazard model with a spline term for EPA and adjustment for randomization factors and statin compliance[1], age[2], sex[3], baseline diabetes[4], hsCRP[5], treatment compliance[6].

***P value is <0.001 for both non-linear trend and for regression slope.**

Bhatt DL. ACC/WCC 2020, Chicago (virtual).

Modified by Brinton EA, Apr 2021. *Nissen SE, et al. *JAMA Cardiol.* 2021;6(8):1-8.

Recent Cardiovascular Outcome Trials with Omega-3 Fatty Acids: Role of Formulation

	JELIS (18,645)	REDUCE-IT (8,179)	STRENGTH (13,078)
Population*	Hypercholesterolemic	High CV Risk, High TGs	High CV Risk, High TGs, low HDL
Formulation†	IPE (1.8 g/d EPA)	IPE (4 g/d EPA)	EPA/DHA carboxylic acids (4 g/d)
Baseline Median TG (mg/dL)	153	216	240
Baseline EPA (µg/mL)	97	26.1	21.0
Achieved EPA (µg/mL)	169	144	89.6
Increase in Achieved EPA Levels (%)	70	394	269
Triglyceride Lowering (%)	9	17	19
Primary Endpoint	Major coronary events	MACE	MACE
HR, 96% CI of Primary Endpoint	0.81, 0.69-0.95 (P = 0.011)	0.75, 0.68-0.93 (P < 0.001)	0.99, 0.90-1.09 (P = 0.84)

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

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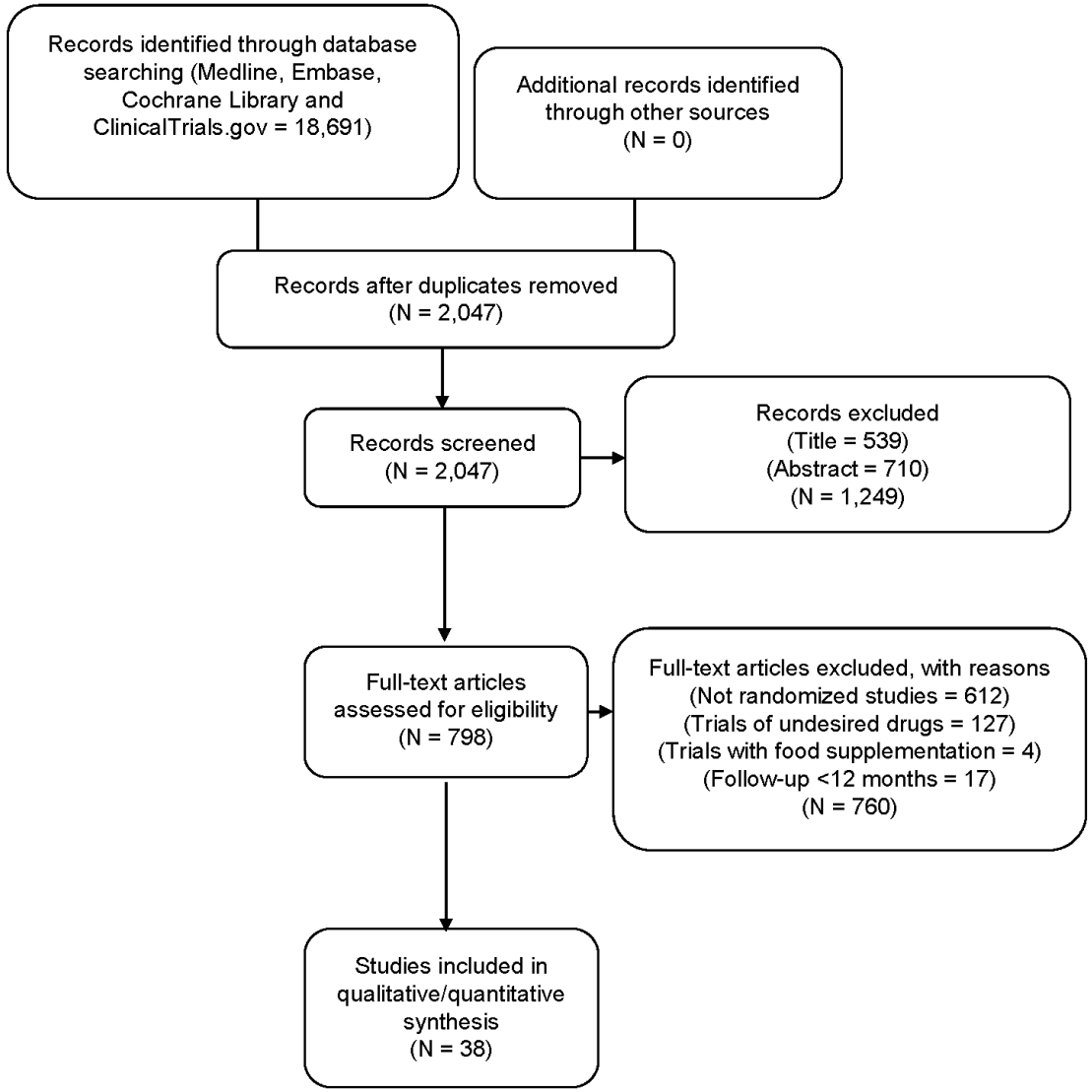
*Statin use was 100%
†IPE, icosapent ethyl.

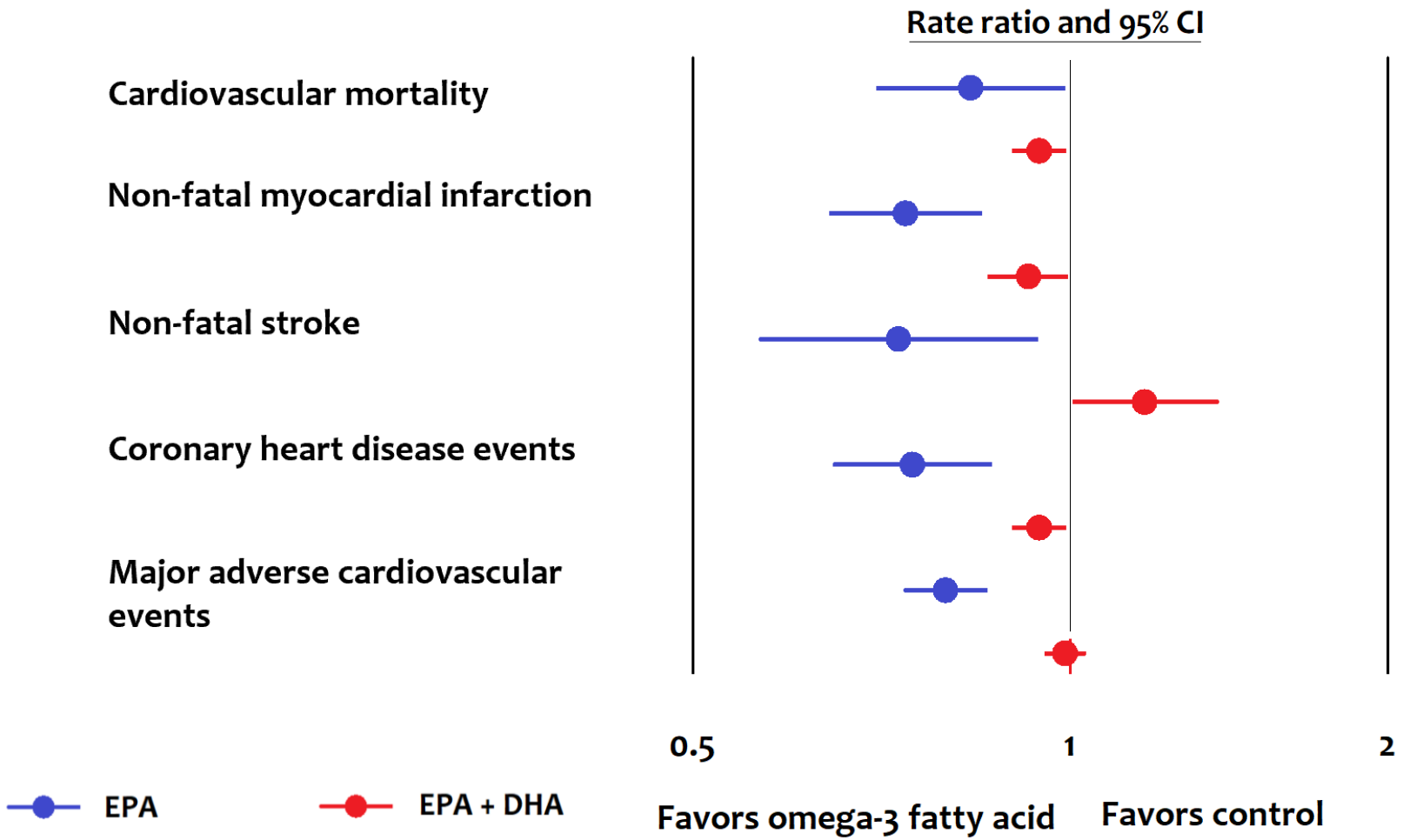
Meta-Analysis of OM3 Trials

- 38 trials
  - 4 compared EPA vs control
  - 34 compared EPA+DHA vs control
  - 22 studied primary prevention
- The dose of omega-3 FAs ranged from 0.4 g/day to 5.5 g/day. The EPA trials had dose ranges from 1.8 to 4.0 g/day and EPA+DHA from 0.4 to 5.5 g/day.
- The patients' mean age ranged from 39-78 years, and the proportion of enrolled women varied from 0% to 77.5%. Median follow-up across the trials was 2.0 years.



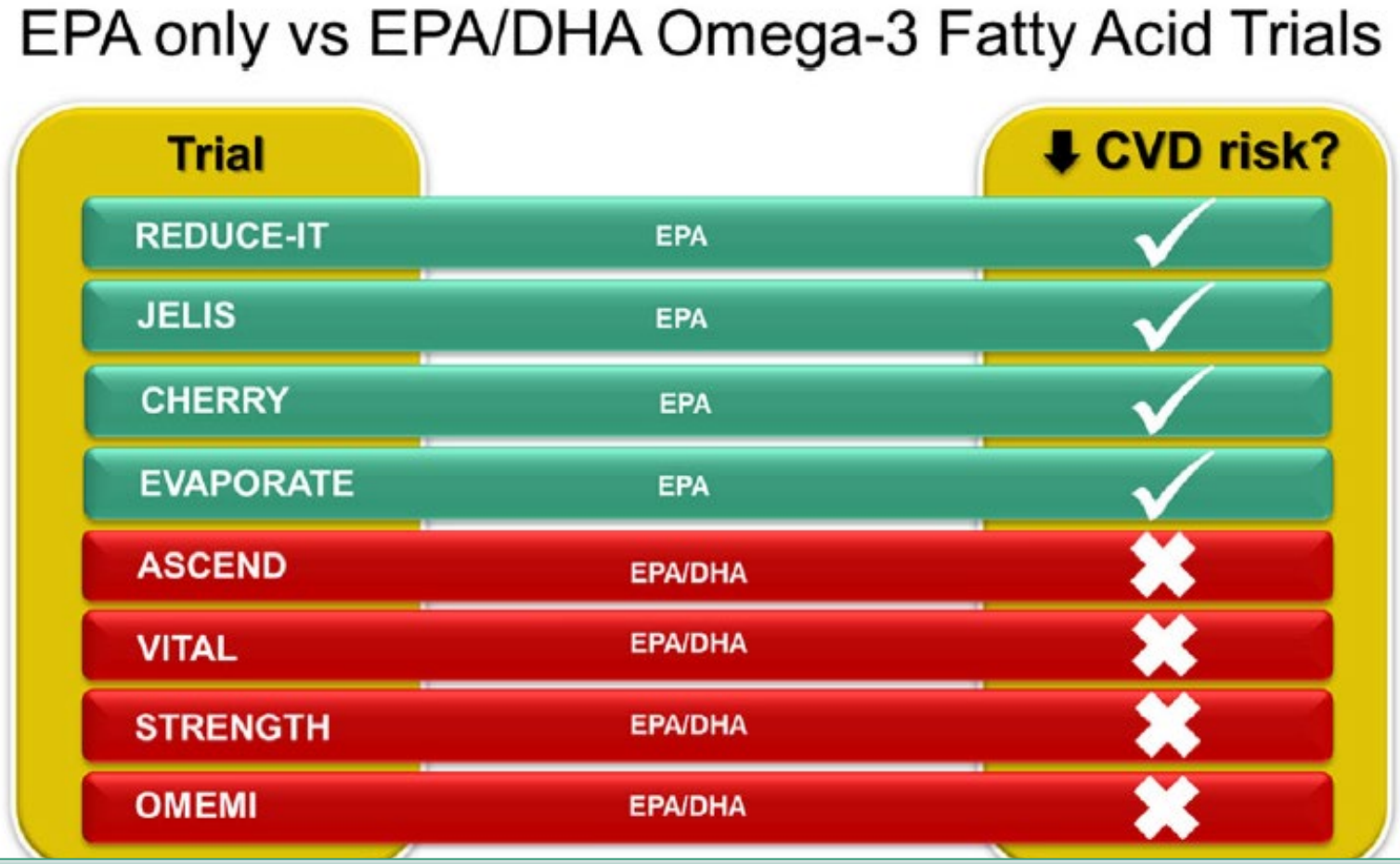
Khan SU, et al. EClinicalMedicine. 2021;38:100997.

Effect of Omega-3 Fatty Acids on CV Outcomes



Khan SU, et al. EClinicalMedicine. 2021;38:100997.

What Have We Learned From the Marine Omega-3 Fatty Acid Clinical Trials?

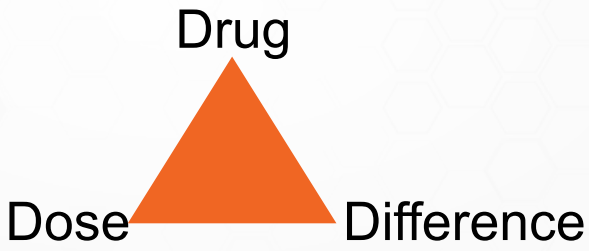


Studies demonstrate that EPA (without DHA) on top of standard of care consistently demonstrate greater reduction in atheromatous volume or CVD events than standard-of-care therapies alone.

Iqbal T, Miller M. *Curr Cardiol Rep*. 2021;23(8):111.

The Bottom Line for Patients with Elevated Triglycerides and High Risk of ASCVD

REDUCE-IT has shown that:



Icosapent ethyl at 4 g/day is indicated across a broad spectrum of ASCVD risk with HTG

Rx IPE has unique, well-documented MOA profile for benefit in ASCVD: atherogenic lipid-lowering, anti-inflammatory, anti-plaque effects, membrane stabilization, oxidation, endothelial dysfunction, etc.

Summary

- There remains substantial ASCVD risk despite low levels of LDL-C; elevated triglycerides and their remnants account for a portion of this residual risk
- Combination therapy of statins with fibrates or niacin have not shown effectiveness and are generally not recommended to reduce ASCVD event risk
- REDUCE-IT was a landmark trial showing that icosapent ethyl 4 g/day in addition to maximally tolerated statin therapy could reduce ASCVD events significantly, though its impact on triglycerides appears not to account for all of the substantial benefits of this therapy

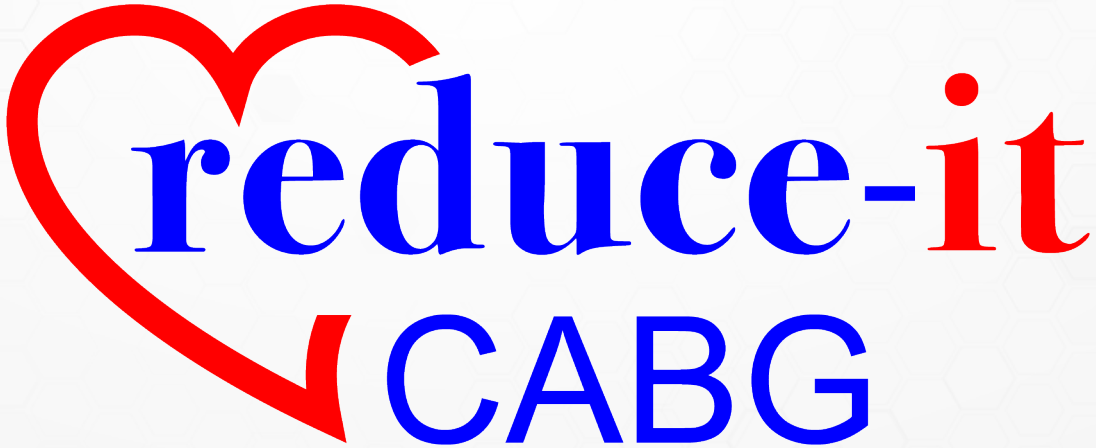
Panel Discussion

All faculty

Break

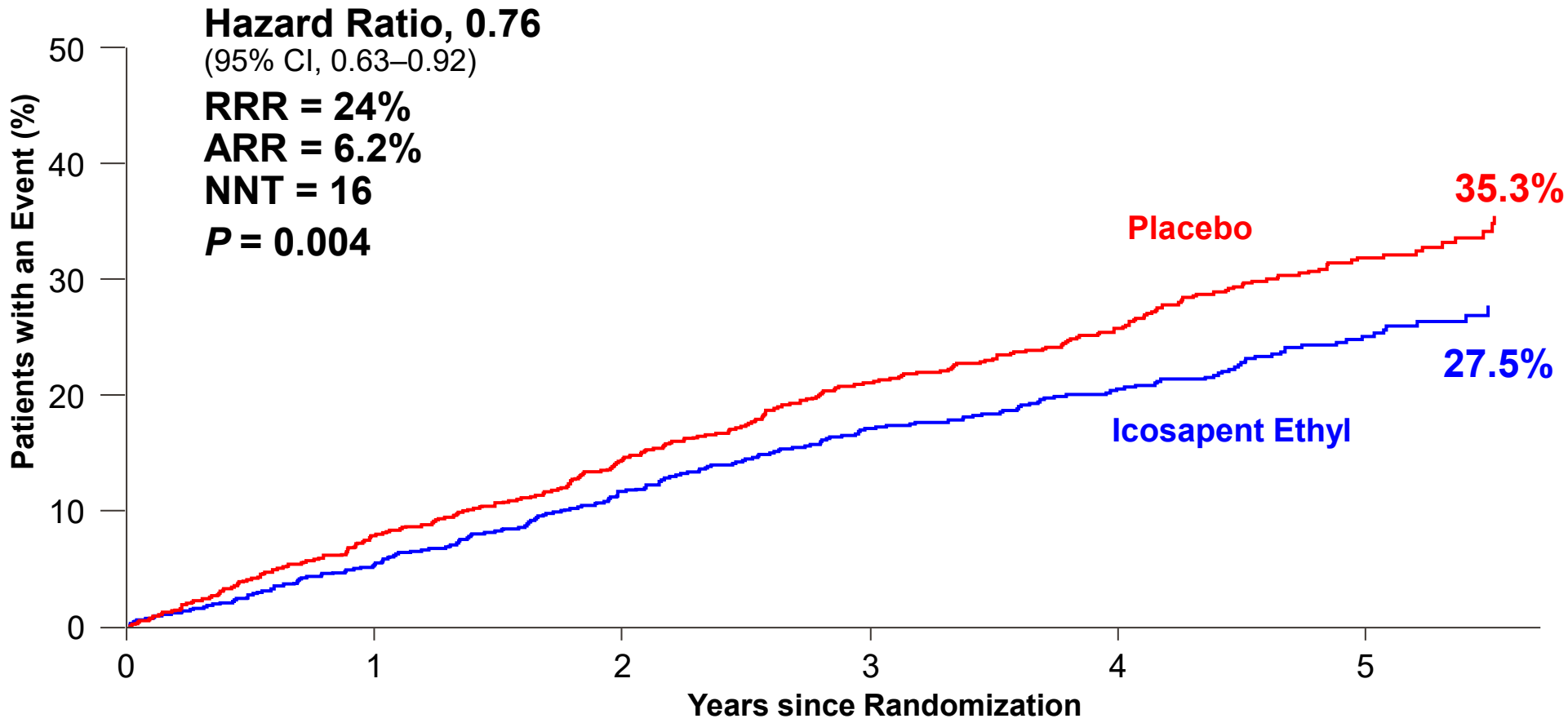
Recent Evidence from REDUCE-IT Sub-Studies

Karol Watson, MD, PhD


reduce-it
CABG

Primary Endpoint:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina:
Patients With a History of CABG; N = 1,837

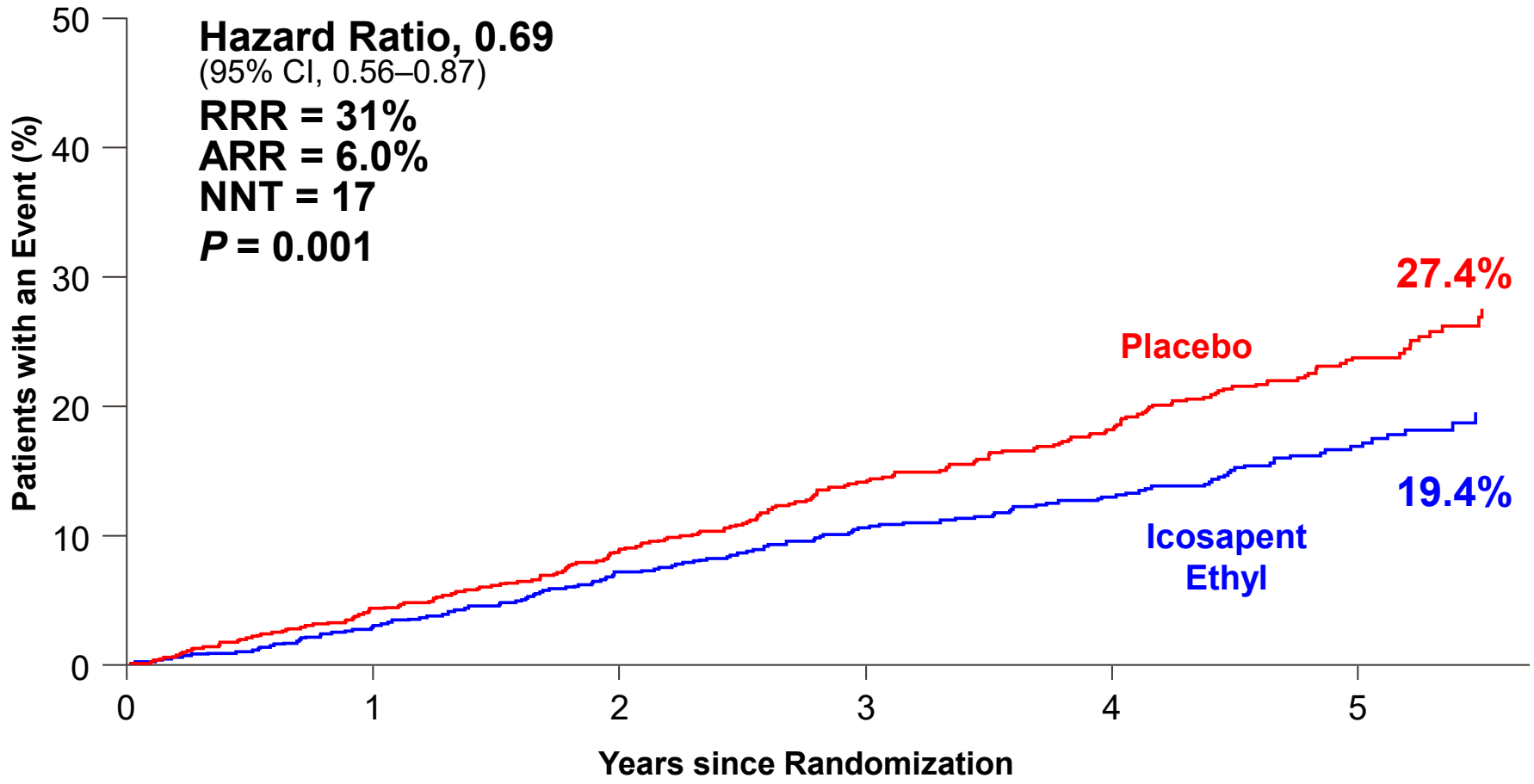
reduce-it CABG



Verma S, Bhatt DL, Steg PG, et al. AHA 2020, Virtual.

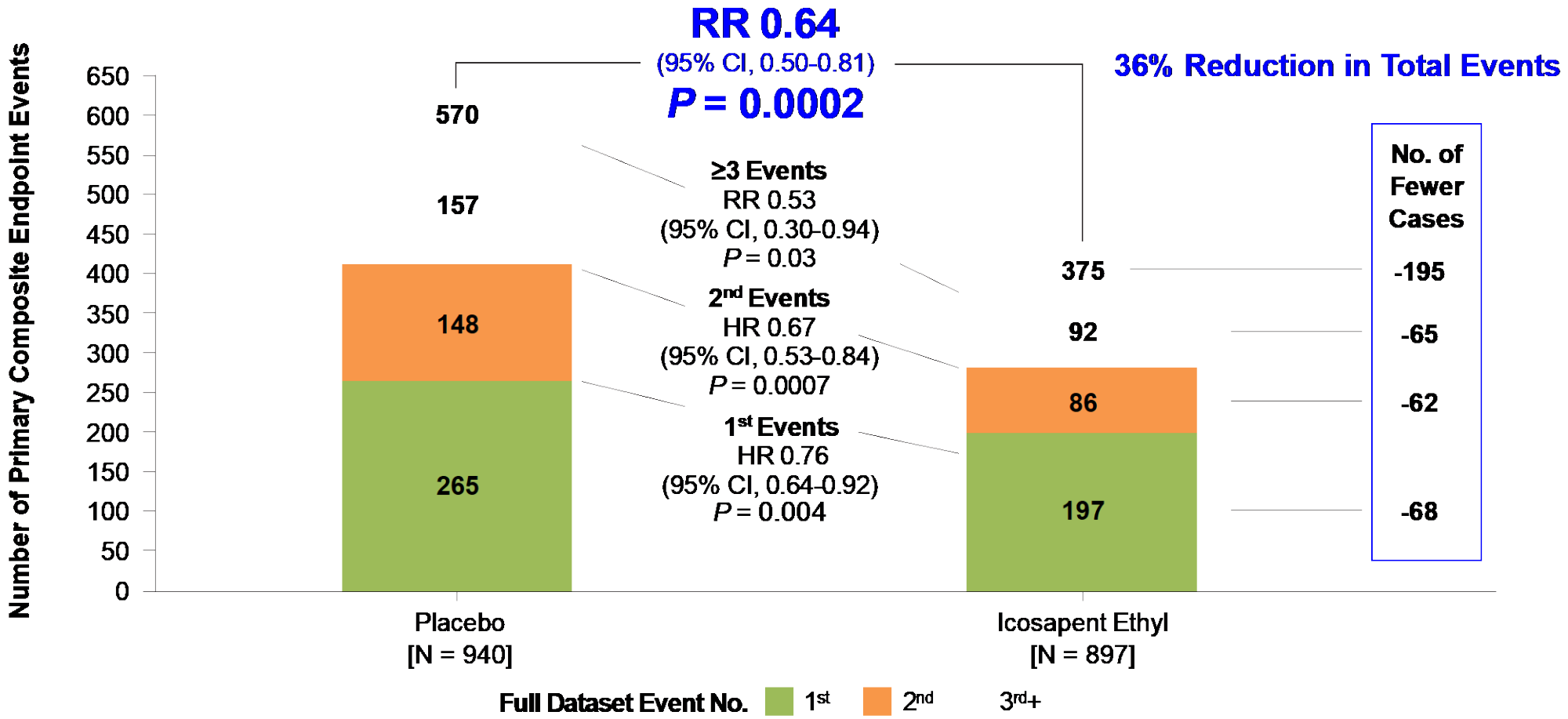
Key Secondary Endpoint: CV Death, MI, Stroke: Patients With a History of CABG; N = 1,837

reduce-it CABG



Verma S, Bhatt DL, Steg PG, et al. AHA 2020, Virtual.

First and Subsequent Events Full Dataset:
Patients with a History of CABG



Note: WLW method for the 1st events, 2nd events categories; Negative binomial model for ≥3 events and overall treatment comparison. This full dataset analysis does not exclude multiple endpoints occurring in a single calendar day.

Verma S, Bhatt DL, Steg PG, et al. AHA 2020, Virtual.

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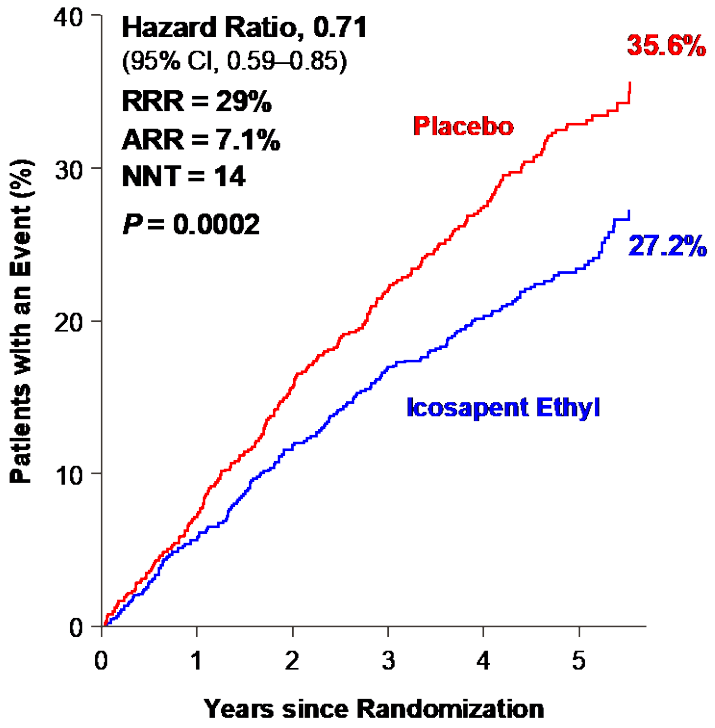
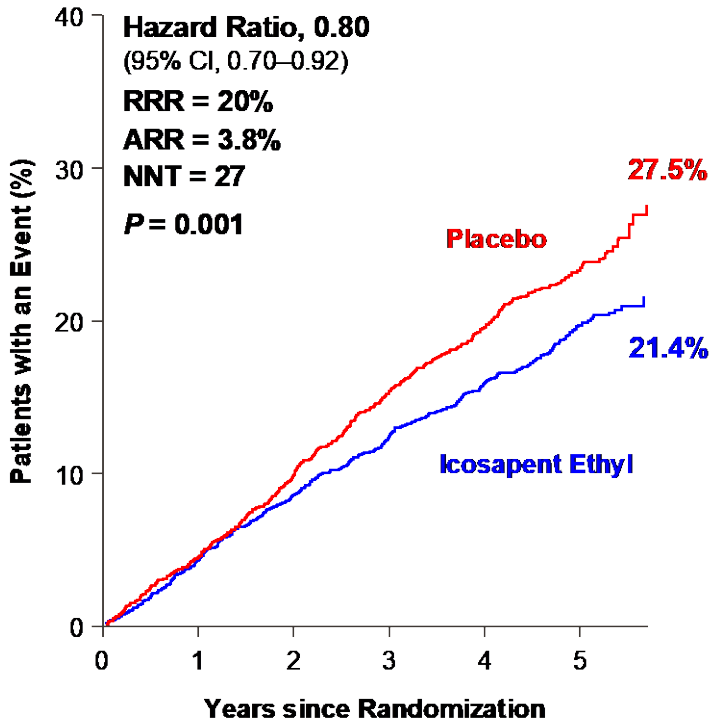
Primary Endpoint Events by eGFR at Baseline

reduce-it RENAL

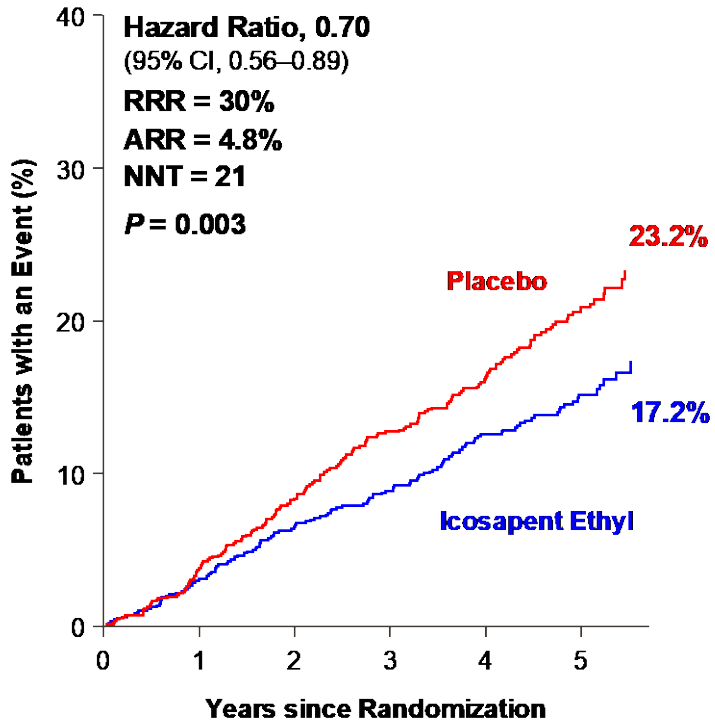
Patients with Baseline eGFR <60 mL/min/1.73 m²
N = 1,816



Patients with Baseline eGFR ≥60 to <90 mL/min/1.73 m²
N = 4,455



Patients with Baseline eGFR ≥90 mL/min/1.73 m²
N = 1,902

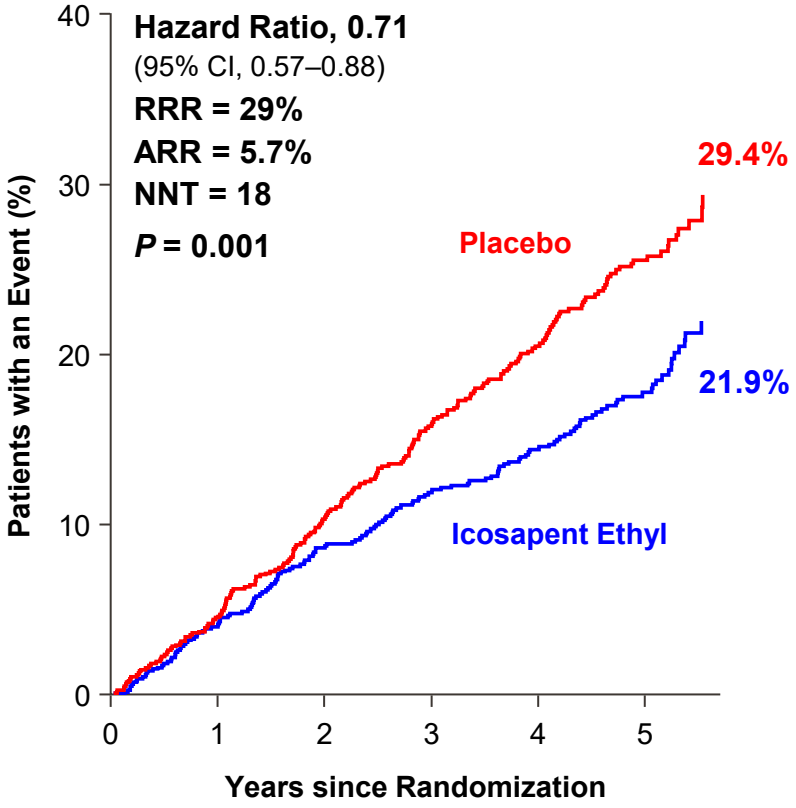


Majithia A, Bhatt DL, Friedman AN, et al. ASN 2020; Virtual.

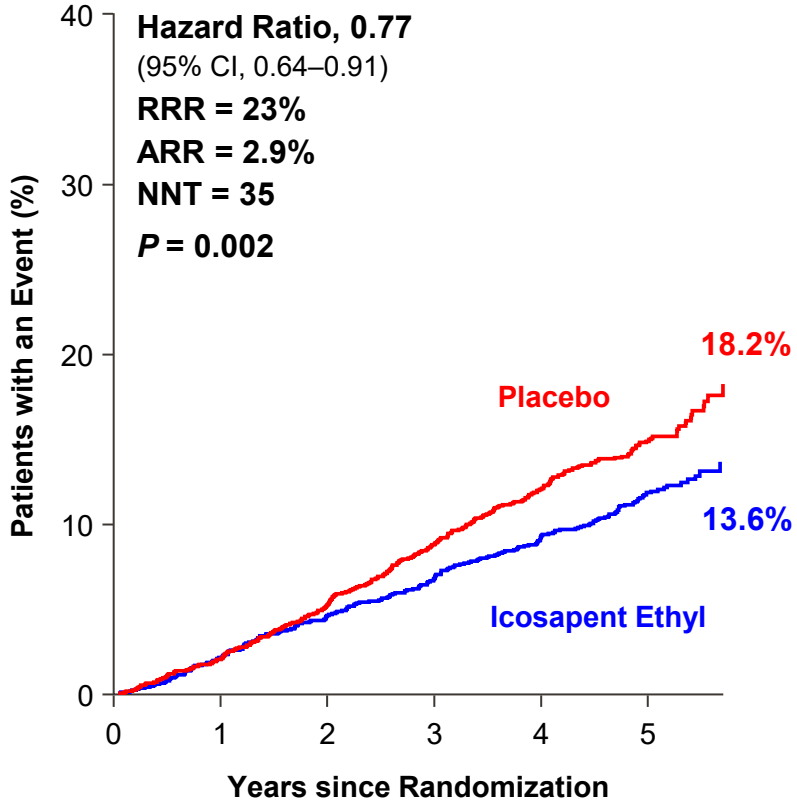
Key Secondary Endpoint Events by eGFR at Baseline

reduce-it RENAL

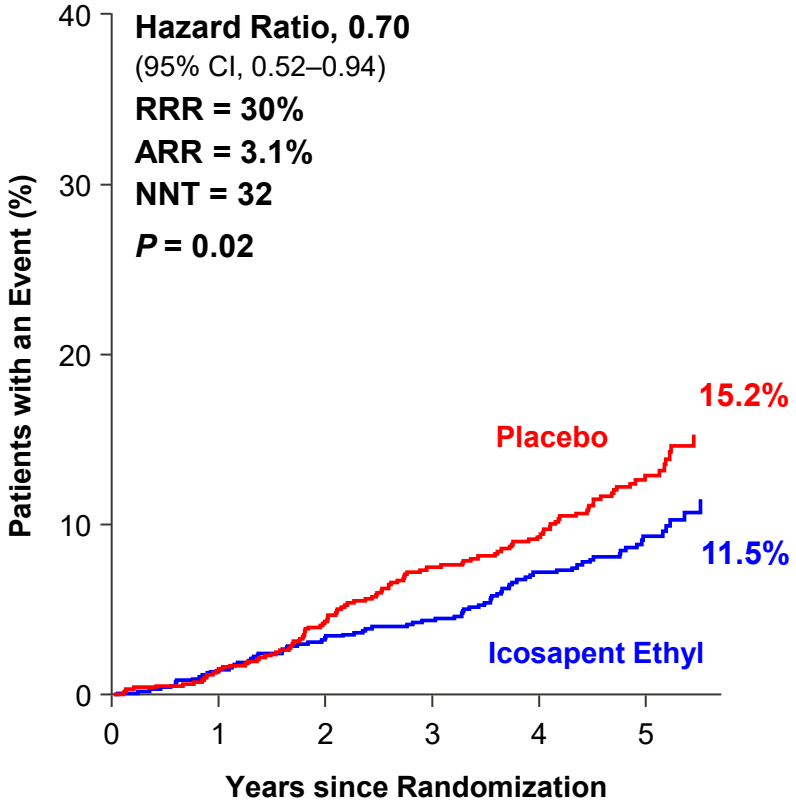
Patients with Baseline eGFR <60 mL/min/1.73 m²
N = 1,816



Patients with Baseline eGFR ≥60 to <90 mL/min/1.73 m²
N = 4,455



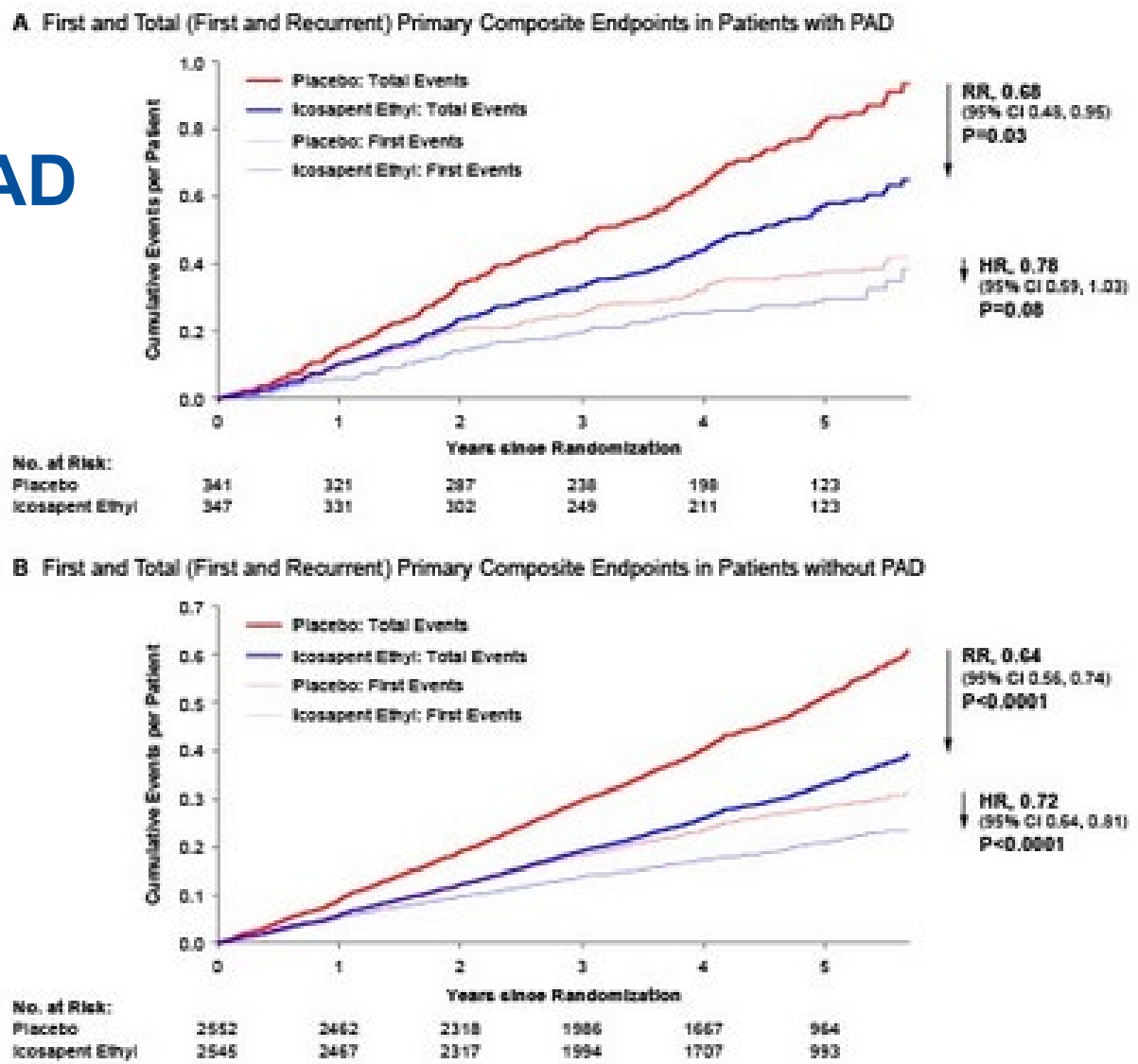
Patients with Baseline eGFR ≥90 mL/min/1.73 m²
N = 1,902



Majithia A, Bhatt DL, Friedman AN, et al. ASN 2020; Virtual.

Benefits of Icosapent Ethyl in Patients with Prior Peripheral Artery Disease: REDUCE-IT PAD

- 688 had PAD
- Primary endpoint event rate with PAD was 26.2% with IPE vs 32.8% with placebo.
- Total events were 112.8 per 1000 patient-years with IPE vs 162.3 with placebo.
- Safety did not differ substantially by PAD history and was generally consistent with the overall study.

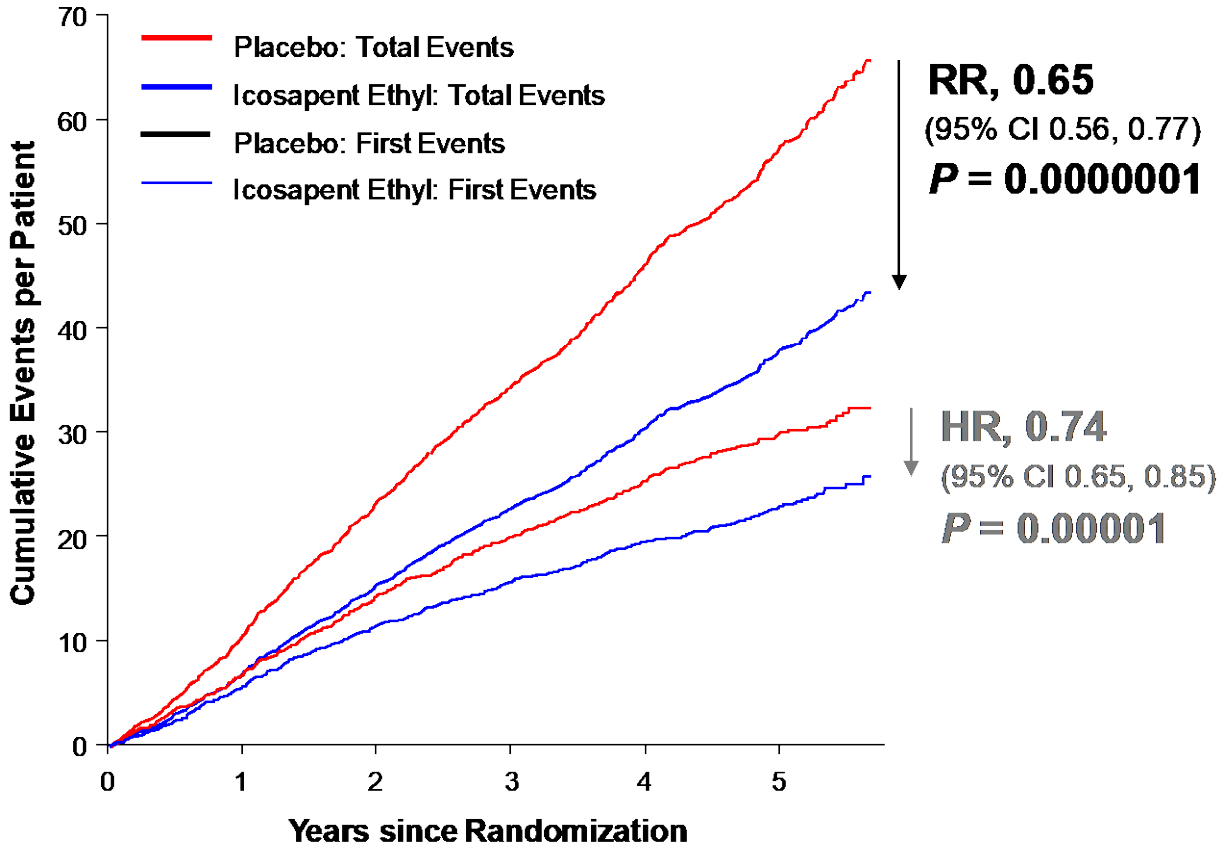


Bhatt DL, Steg PG, Miller M, et al. ESC 2021 (virtual).

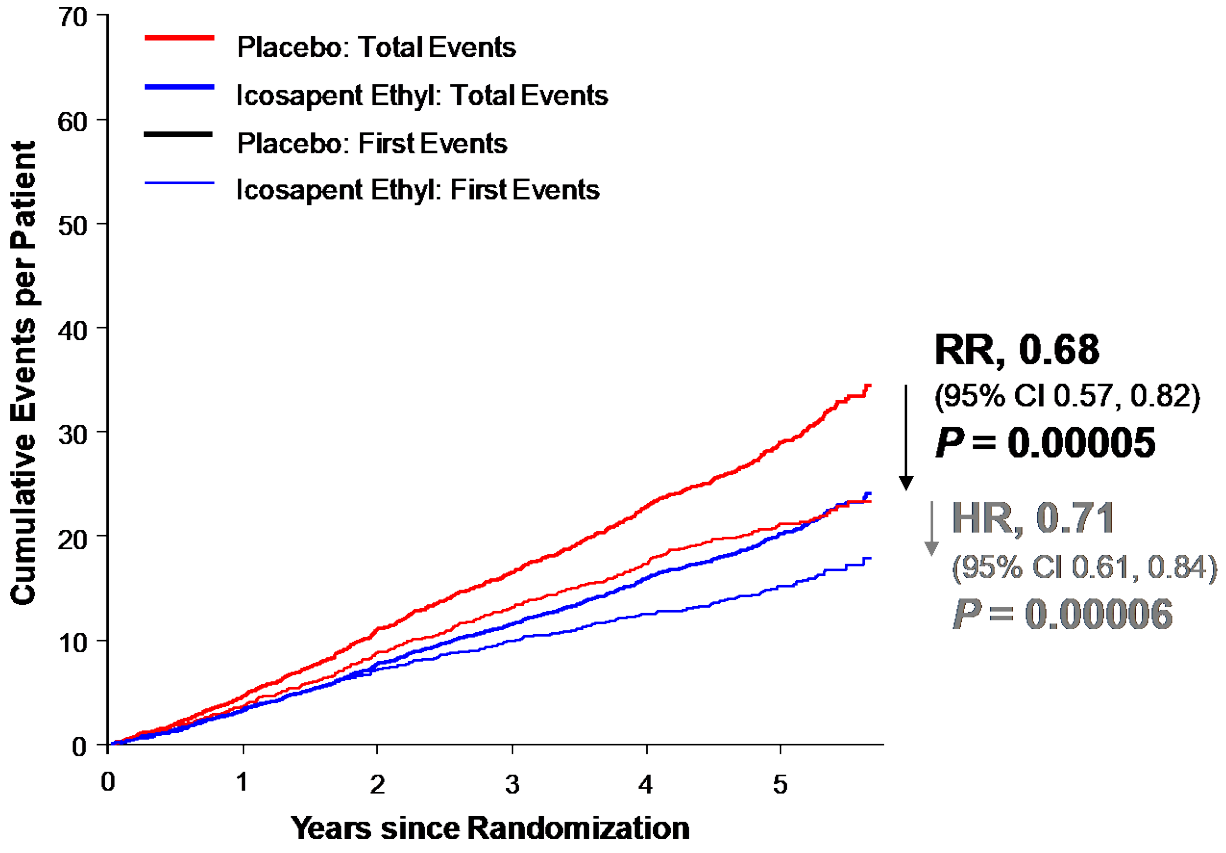

reduce-it
PRIOR MI

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

Primary Composite Endpoint



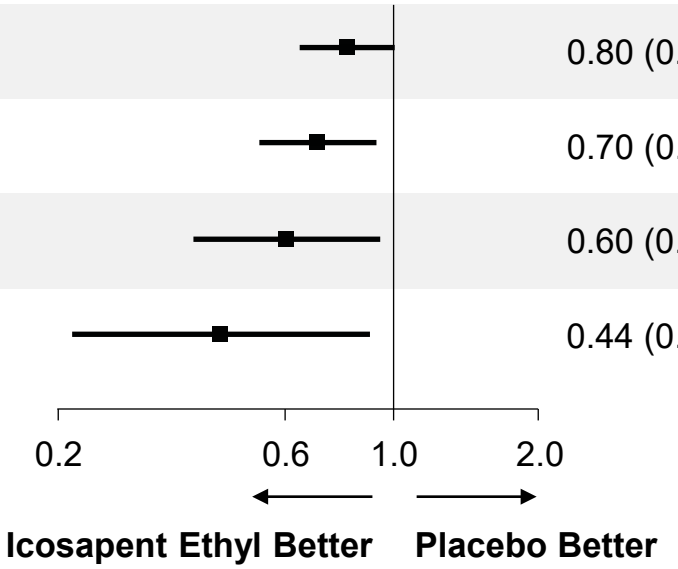
Key Secondary Composite Endpoint



Bhatt DL, Steg PG, Miller M, et al. ESC 2021 (virtual).

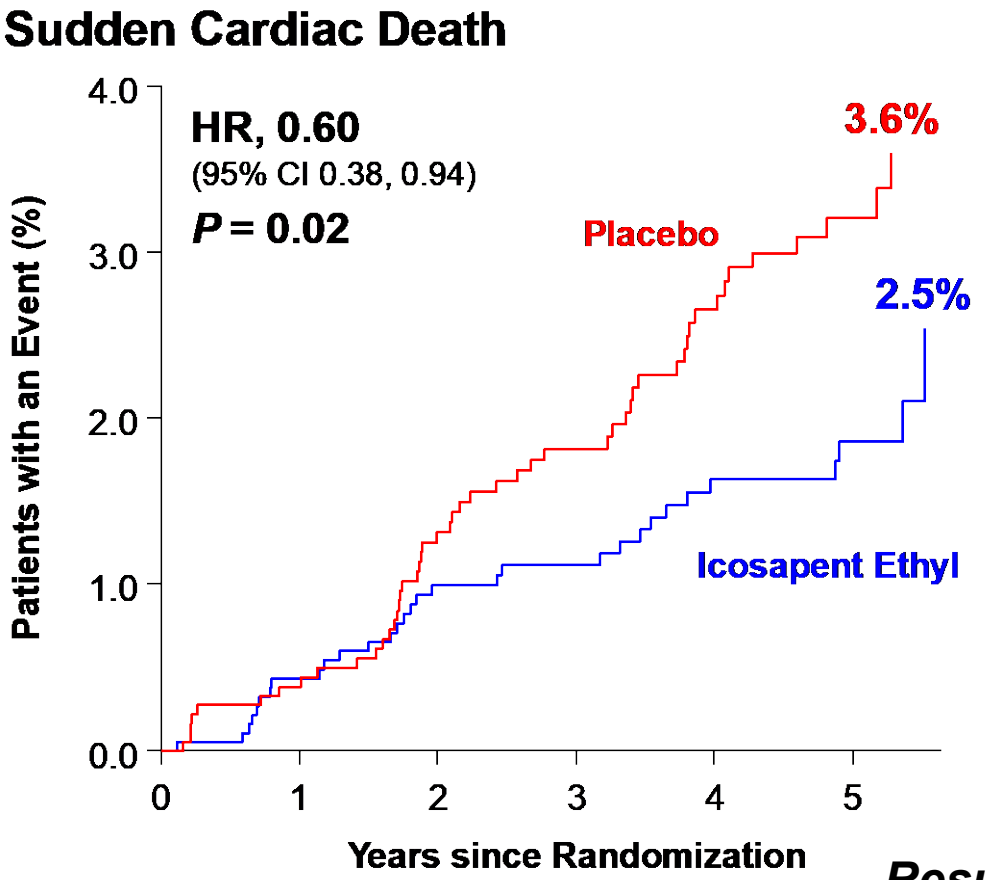
Cardiac Arrest and Sudden Cardiac Death in Patients with Prior MI

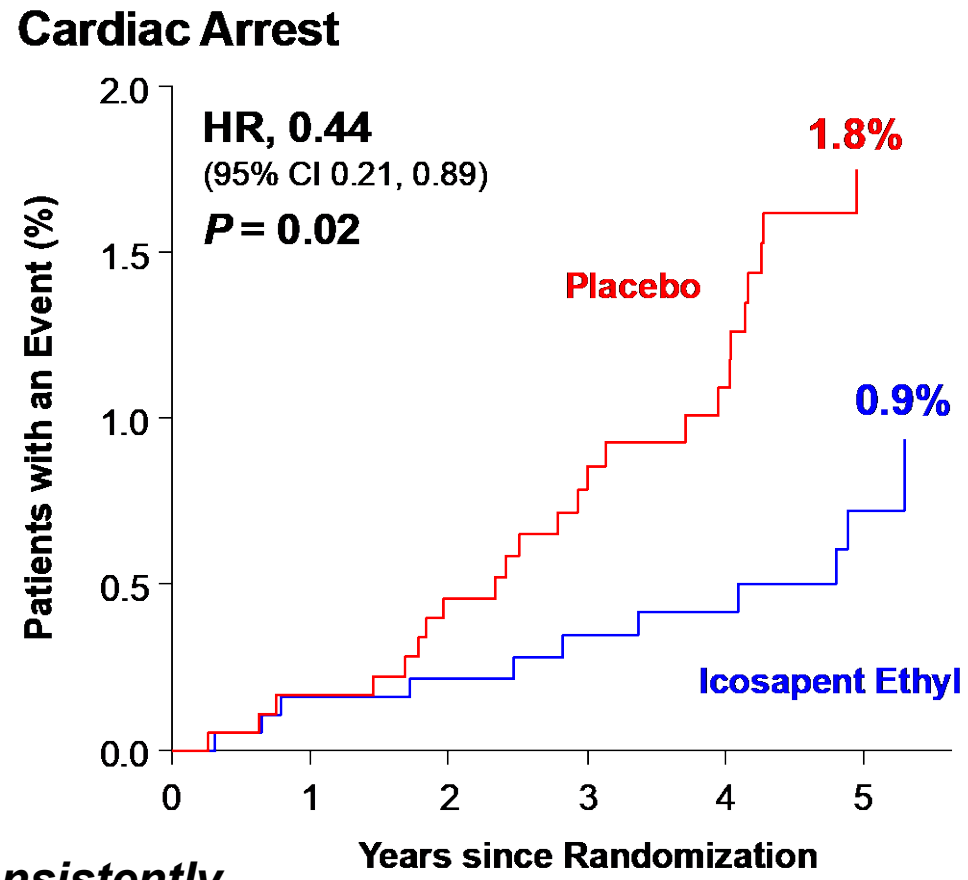
Endpoint	Icosapent Ethyl	Placebo	Icosapent Ethyl vs Placebo	*P* value
	n/N (%)	*n/N (%)*	*HR (95% CI)*	
Total Mortality	136/1870 (7.3)	163/1823 (8.9)	0.80 (0.64, 1.00)	0.05
Cardiovascular Death	84/1870 (4.5)	116/1823 (6.4)	0.70 (0.53, 0.92)	0.01
Sudden Cardiac Death	31/1870 (1.7)	50/1823 (2.7)	0.60 (0.38,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



Bhatt DL, Steg PG, Miller M, et al. ESC 2021 (virtual).
Steg PG, Miller M, et al. ESC 2021 (virtual).

Cardiac Arrest and Sudden Cardiac Death in Patients with Prior MI



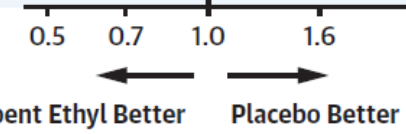


Results consistently statistically significant by ~4 years

Bhatt DL, Steg PG, Miller M, et al. ESC 2021 (virtual).

REDUCE-IT: Endpoints by Background Statin Agent and Statin Lipophilicity Category

Endpoint/Subgroup	Icosapent Ethyl	Placebo	Icosapent Ethyl vs Placebo	*P* Value	Interaction *P* Value
	n/N (%)	*n/N (%)*	*HR (95% CI)*		
Primary Endpoint	705/4,089 (17.2)	901/4,090 (22.0)	0.75 (0.68-0.83)	<0.0001	
Statin Agent					0.95
Atorvastatin	253/1,472 (17.2)	314/1,495 (21.0)	0.79 (0.67-0.93)	0.006	
Simvastatin	188/992 (19.0)	209/918 (22.8)	0.79 (0.65-0.96)	0.02	
Rosuvastatin	110/734 (15.0)	149/741 (20.1)	0.73 (0.57-0.94)	0.01	
Pravastatin	49/266 (18.4)	58/246 (23.6)	0.79 (0.54-1.16)	0.24	
Statin Category					0.67
Lipophilic	475/2,631 (18.1)	581/2,635 (22.0)	0.78 (0.69-0.88)	<0.0001	
Lipophobic	161/1,017 (15.8)	210/1,008 (20.8)	0.75 (0.61-0.93)	0.007	
Key Secondary Endpoint	459/4,089 (11.2)	606/4,090 (14.8)	0.74 (0.65-0.83)	<0.0001	
Statin Agent					0.68
Atorvastatin	168/1,462 (11.5)	225/1,487 (15.1)	0.73 (0.59-0.89)	0.002	
Simvastatin	132/972 (13.6)	134/888 (15.1)	0.86 (0.68-1.10)	0.24	
Rosuvastatin	67/730 (9.2)	94/725 (13.0)	0.71 (0.52-0.97)	0.03	
Pravastatin	35/261 (13.4)	41/238 (17.2)	0.78 (0.50-1.23)	0.29	
Statin Category					0.74
Lipophilic	318/2,618 (12.1)	400/2,618 (15.3)	0.76 (0.66-0.88)	0.0003	
Lipophobic	102/1,008 (10.1)	137/986 (13.9)	0.73 (0.57-0.95)	0.02	



Patients taking >1 statin before the onset of a primary or key secondary endpoint were excluded from statin agent analysis, and patients taking statins with different lipophilicity before the onset of an endpoint were excluded from statin category analysis.

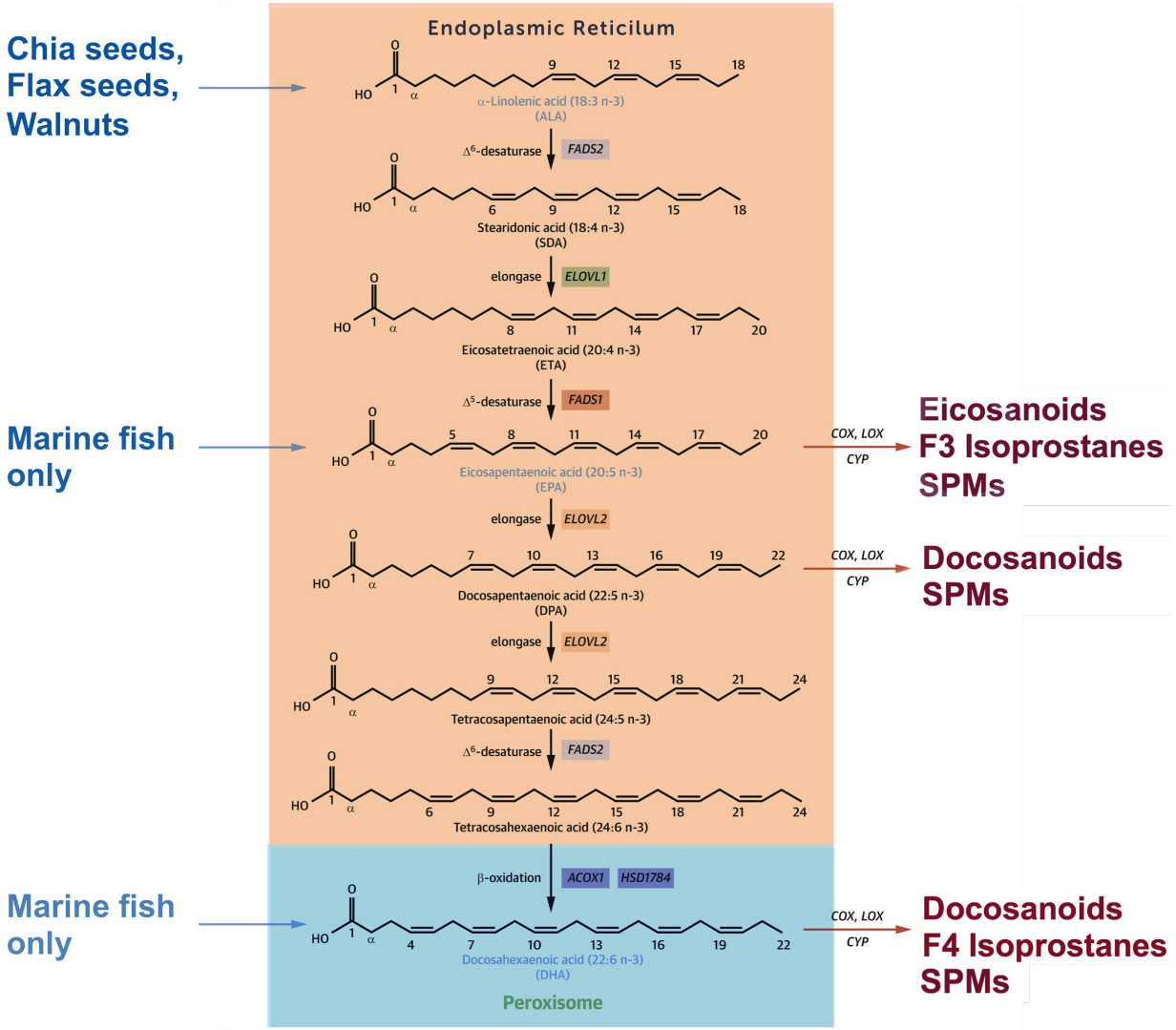
Singh N, et al. *J Am Coll Cardiol*. 2022;79(2):220-222.

Differential Biological Effects of Omega-3 Fatty Acids

Gregory Pokrywka, MD

medtelligence℠

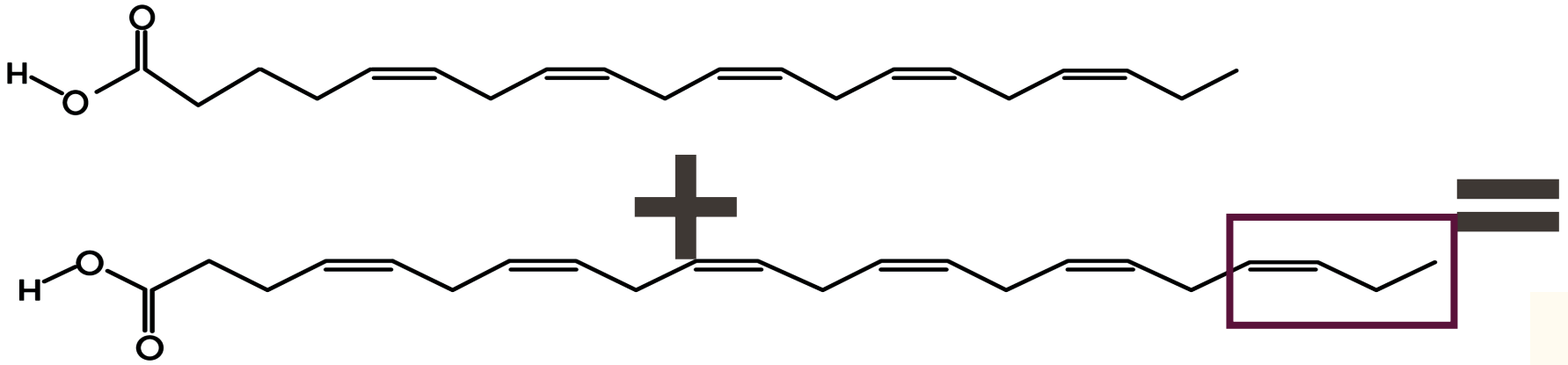
A Revolution in Omega-3 Fatty Acid Research



Reproduced with permission. Bhatt DL, Budoff MJ, Mason RP. *J Am Coll Cardiol*. 2020;76(18):2098-2101.

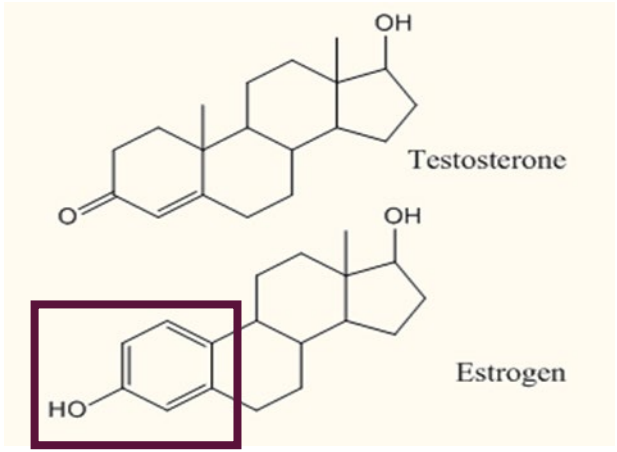
EPA Versus DHA: They Look Similar but Are Very Different!

Eicosapentaenoic acid (EPA) 20:5

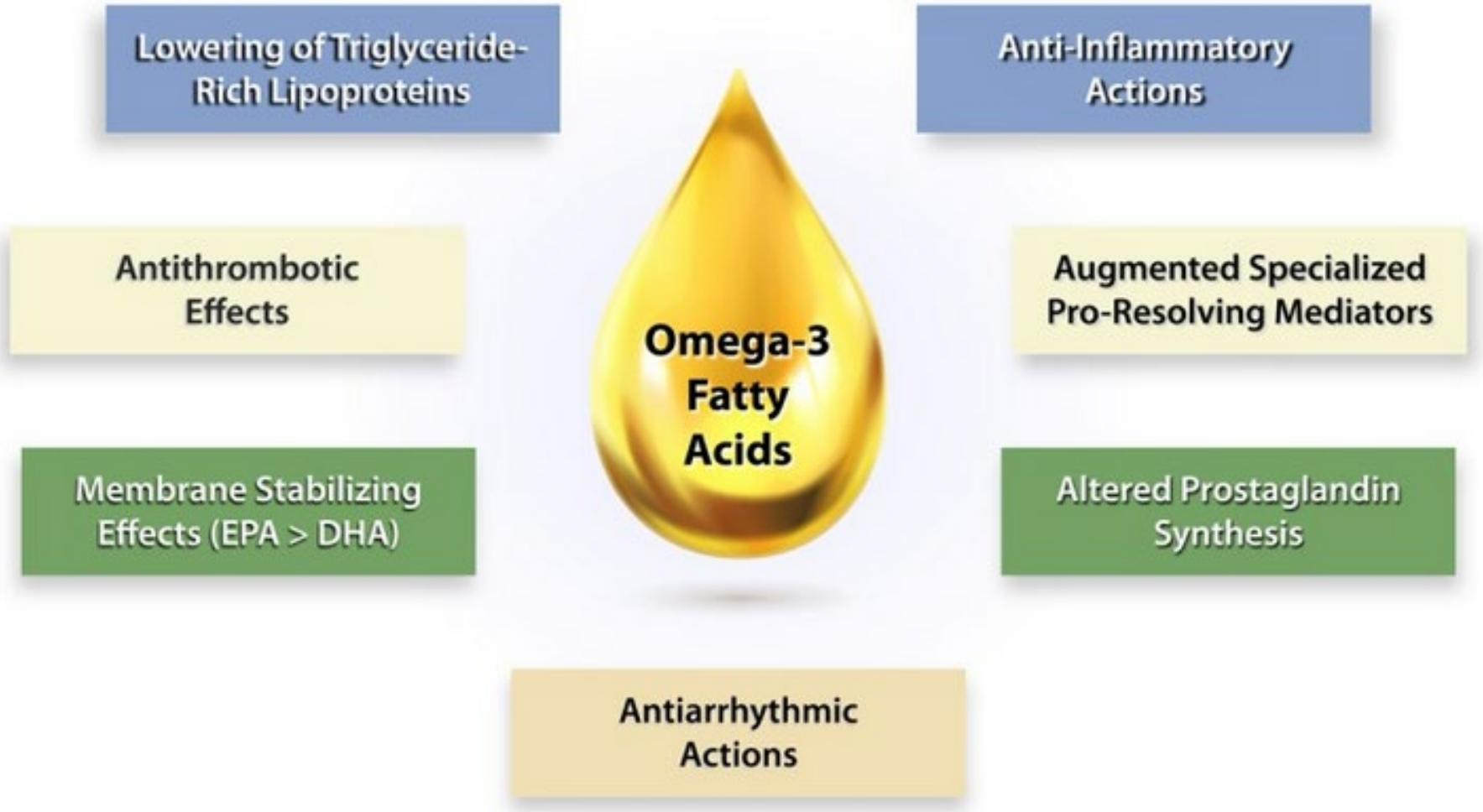


Docosahexaenoic acid (DHA) 22:6

Omega-3 PUFA

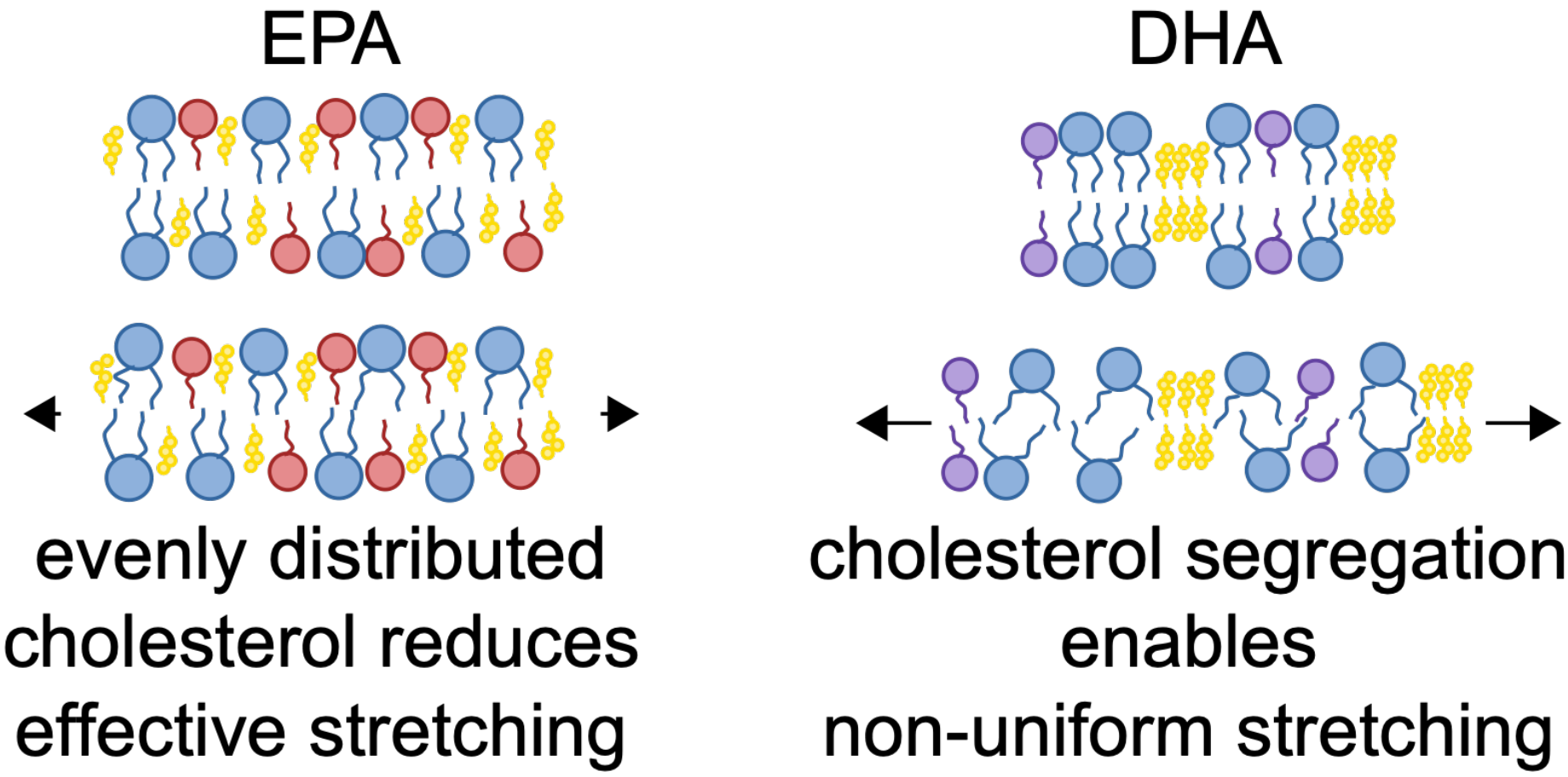


Potential Mechanisms of Cardioprotection for Omega-3 Fatty Acids



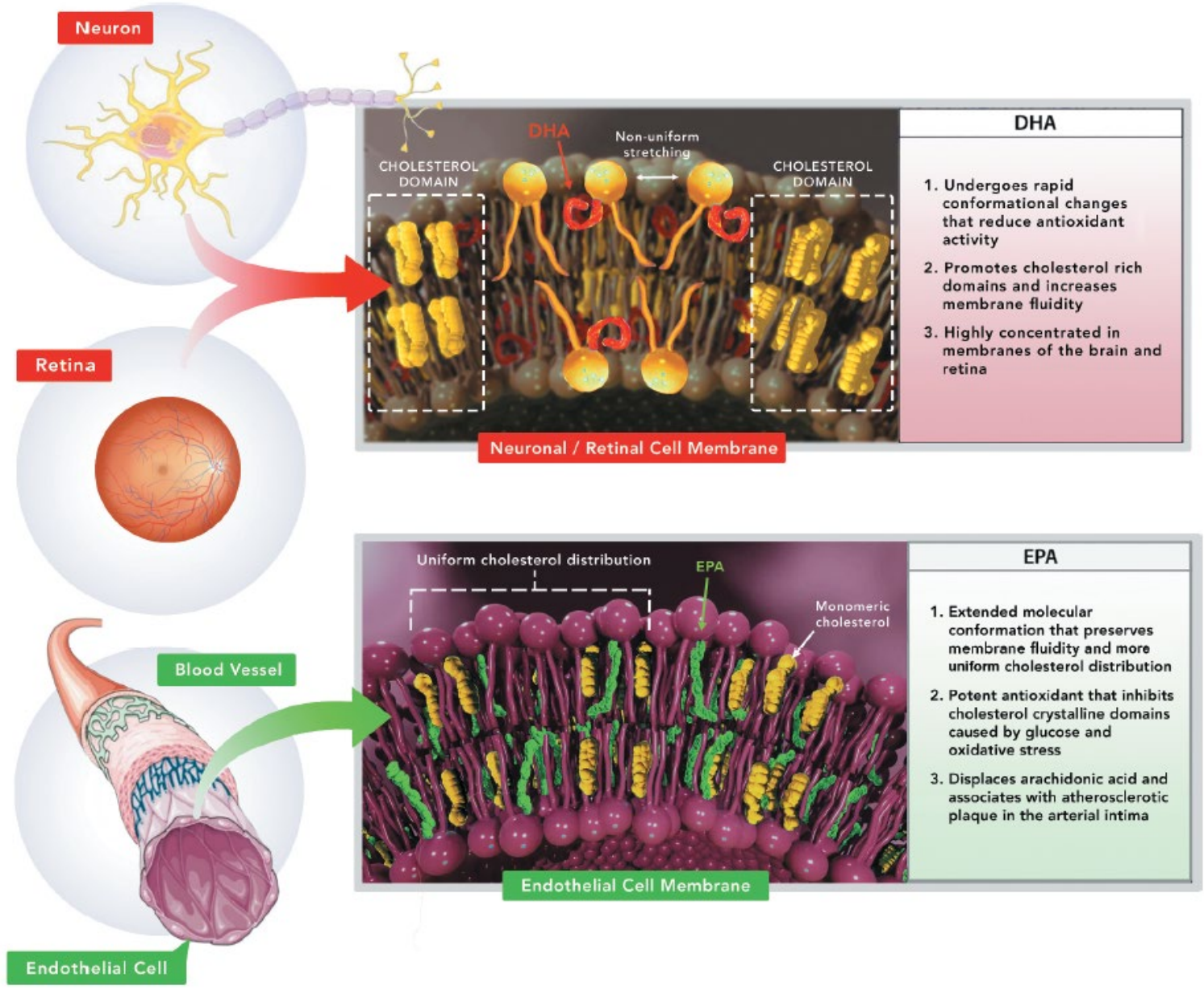
Reproduced with permission. Mason, RP, Libby P, Bhatt DL. *Arterioscler Thromb Vasc Biol*. 2020;40(5):1135-1147.

EPA and DHA Have Distinct Effects on Membrane Stability and Cholesterol Distribution



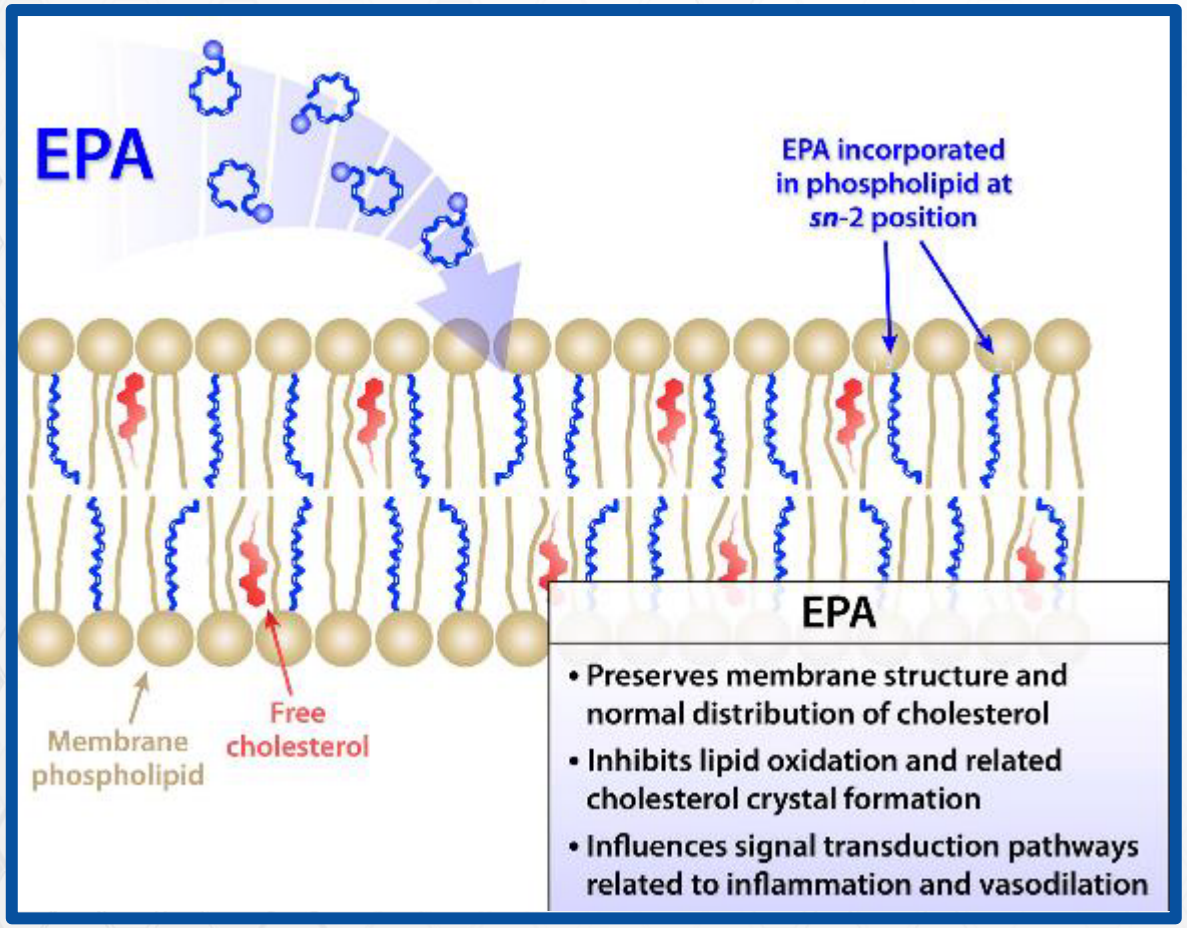
Jacobs ML, et al. *Biophys J.* 2021;120(11):2317-2329.

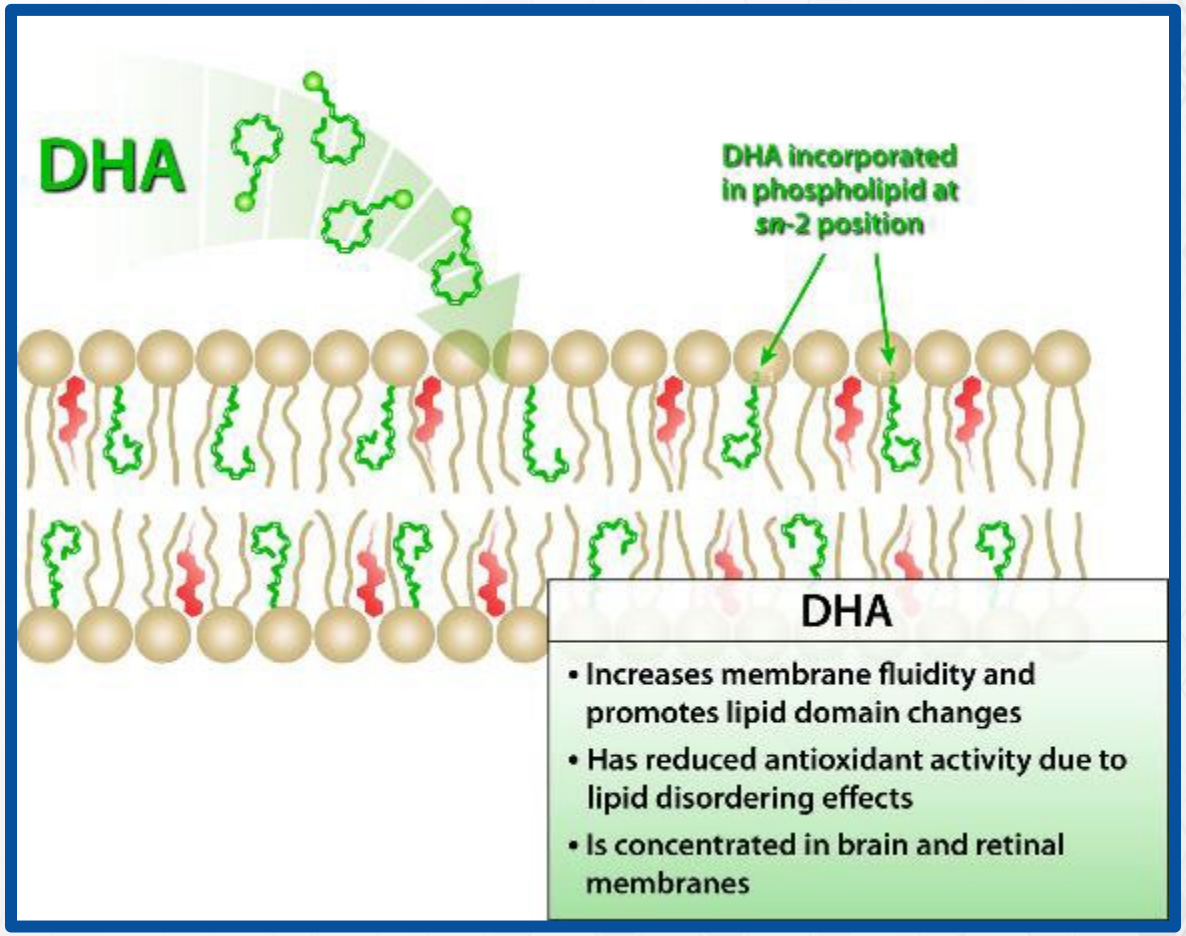
Distinct Membrane Interactions and Tissue Distributions of EPA and DHA



Pareek M, Mason RP, Bhatt DL. *Expert Opin Drug Saf*. 2022;21(1):31-42.

Contrasting Effects of EPA and DHA





Reproduced with permission. Mason RP, Libby P, Bhatt DL. *Arterioscler Thromb Vasc Biol*. 2020;40(5):1135-1147.

Distinct Differences Exist Between Marine Omega-3 Fatty Acids EPA and DHA

- Membrane stabilization and fluidity are very different
- Different resolvins are engaged
- Activity on oxidized LDL-C is different
- Different effects of anti-inflammatory biomarkers such as hsCRP

Mason RP, Libby P, Bhatt DL. *Arterioscler Thromb Vasc Biol*. 2020;40(5):1135-1147. Sherratt SCR, Mason RP. *Chem Phys Lipids*. 2018;212:73-79. Mason RP, et al. *J Cardiovasc Pharmacol*. 2016;68(1):33-40. Kohli P, Levy BD. *Br J Pharmacol*. 2009;158(4):960-971.

Comparative Effects of Omega-3 Fatty Acids and TG-Lowering Agents on Plaque Development

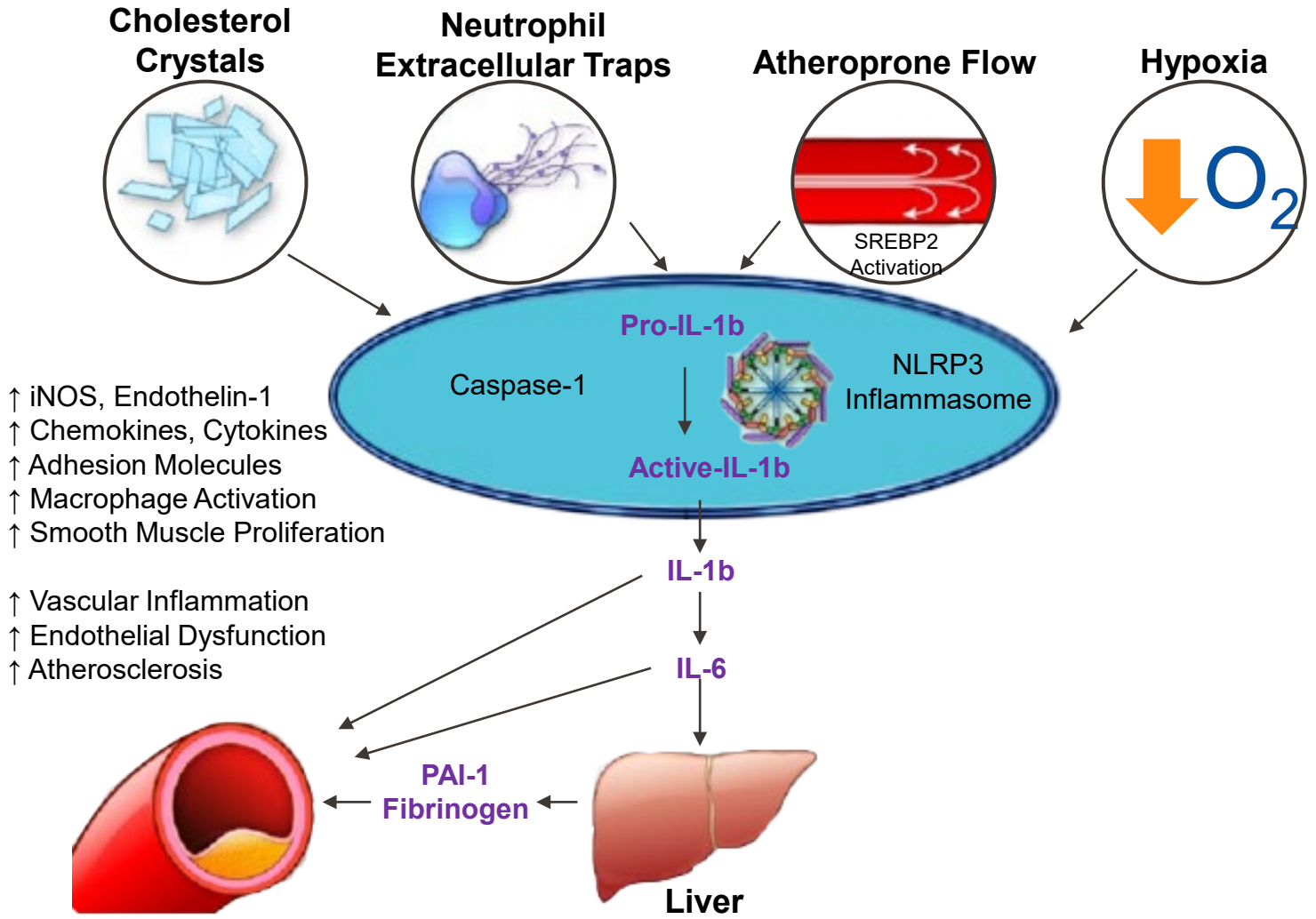
Mechanism of Action	EPA	DHA	Fibrates/Niacin
Does not raise LDL in pts with very high TGs[1,2,3]	+	–	–
Reduces hsCRP in patients with elevated TGs[4,5,6]	+	–	+
Maintains membrane cholesterol distribution[7]	+	–	–
Preserves membrane stability[7,8]	+	–	–
Inhibits cholesterol domains[9,10]	+	–	–
Enhances endothelial function with statin[11]	+	–	–
Inhibits sdLDL, LDL, VLDL, HDL oxidation[9,10,12,13]	+	–	–
Enhances ABCA-1 Cholesterol Efflux[14]	+	–	N/A

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

QUESTION 1

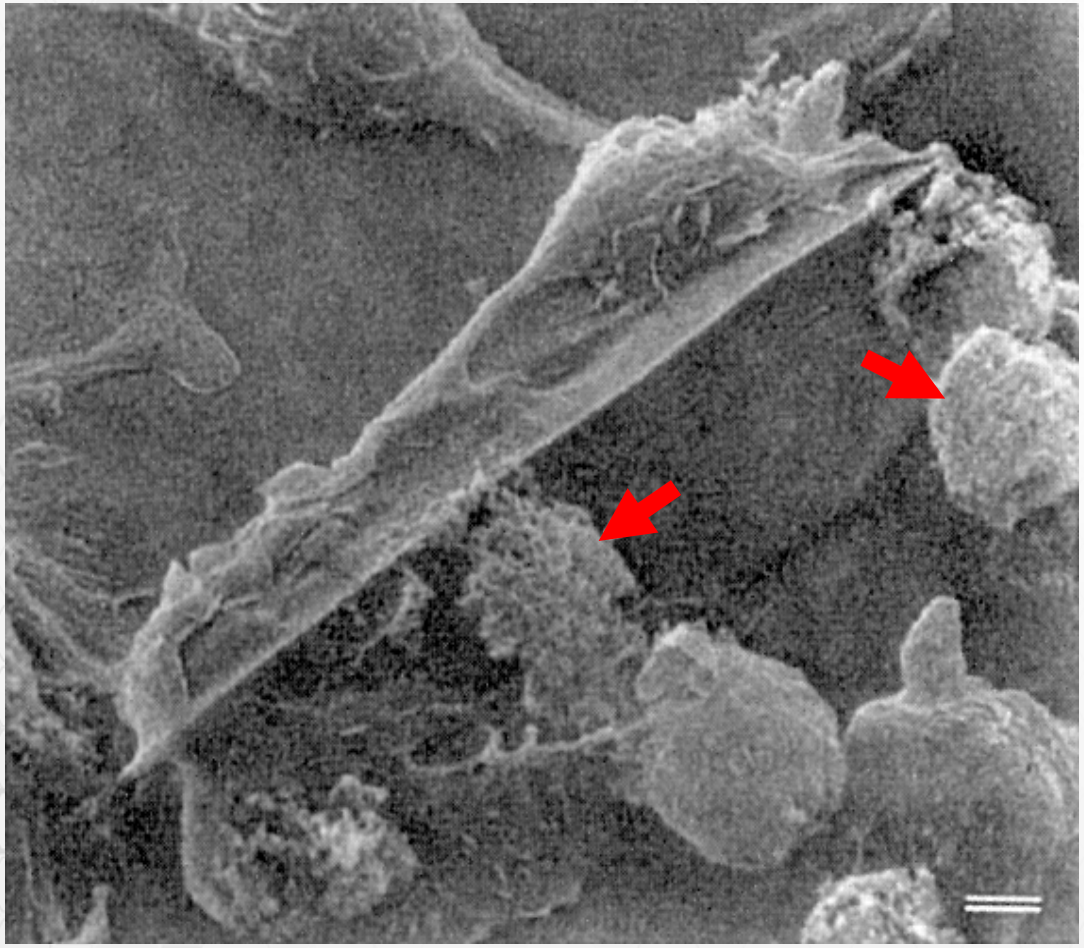
What effects do omega-3 FAs have on oxidation of the membrane, leading to cholesterol crystals?

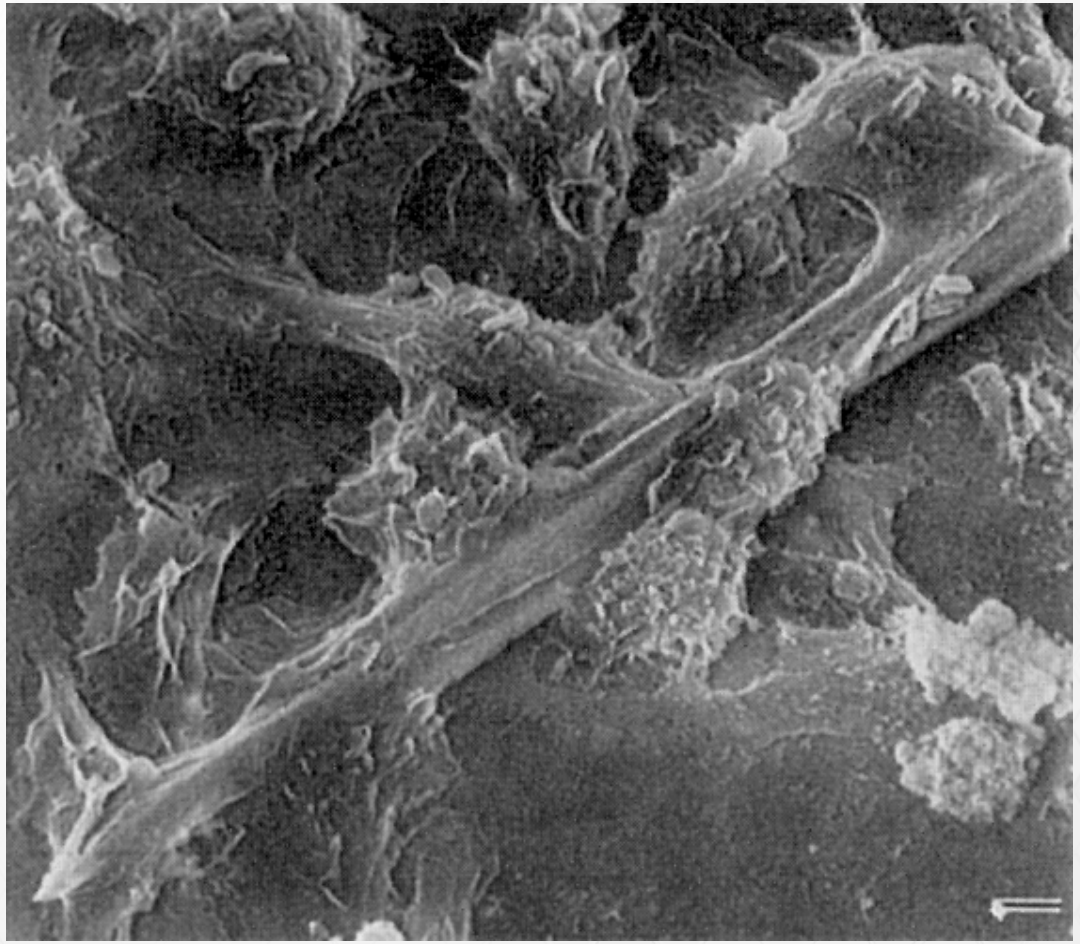
Cholesterol Crystals Trigger IL-1β Formation



Ridker PM. *Circ Res.* 2016;118(1):145-156.

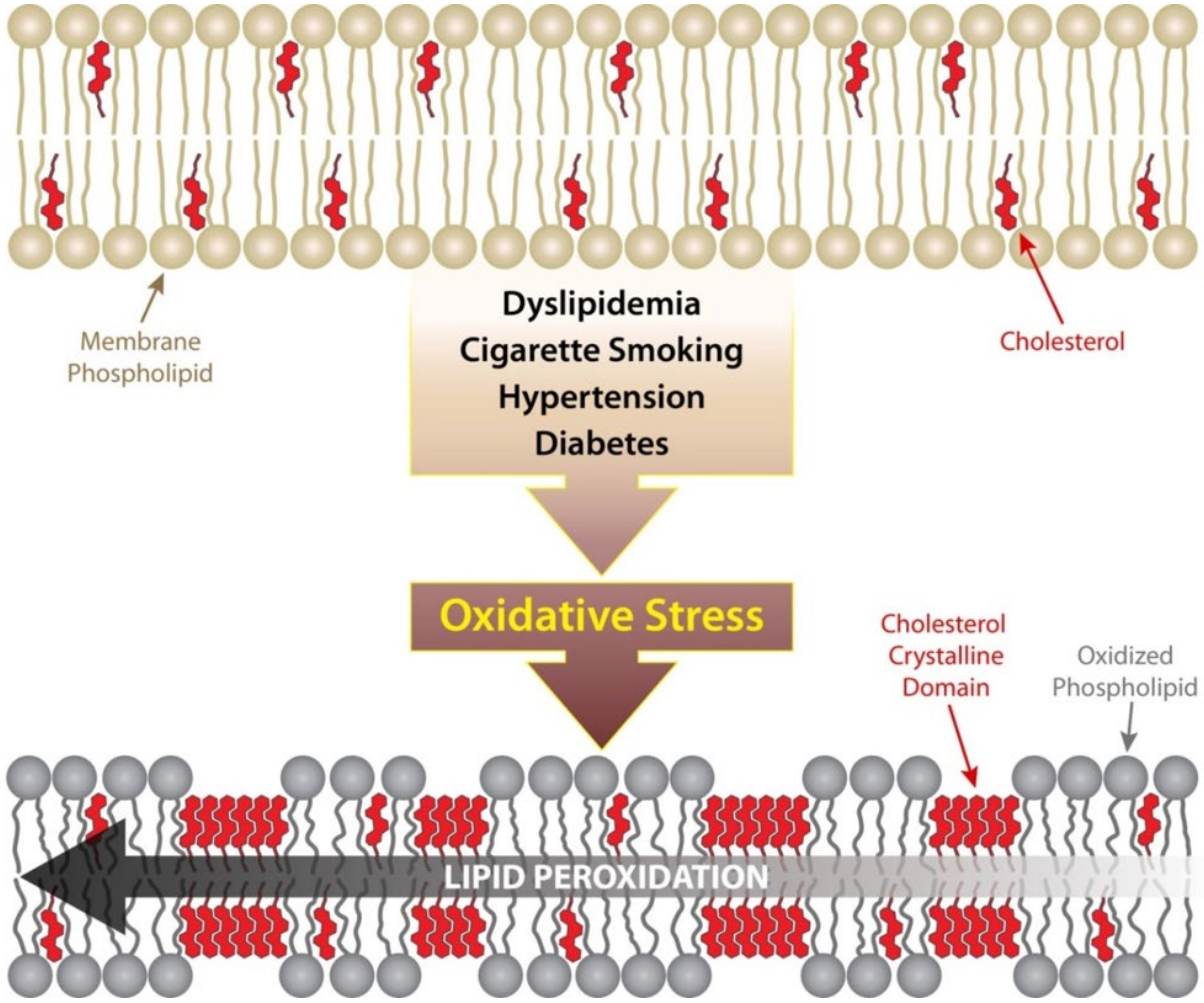
Cholesterol Crystals Associated with Atherosclerosis and Cell Death





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

CV Risk Factors Promote Oxidative Stress and Membrane Cholesterol Domain Formation

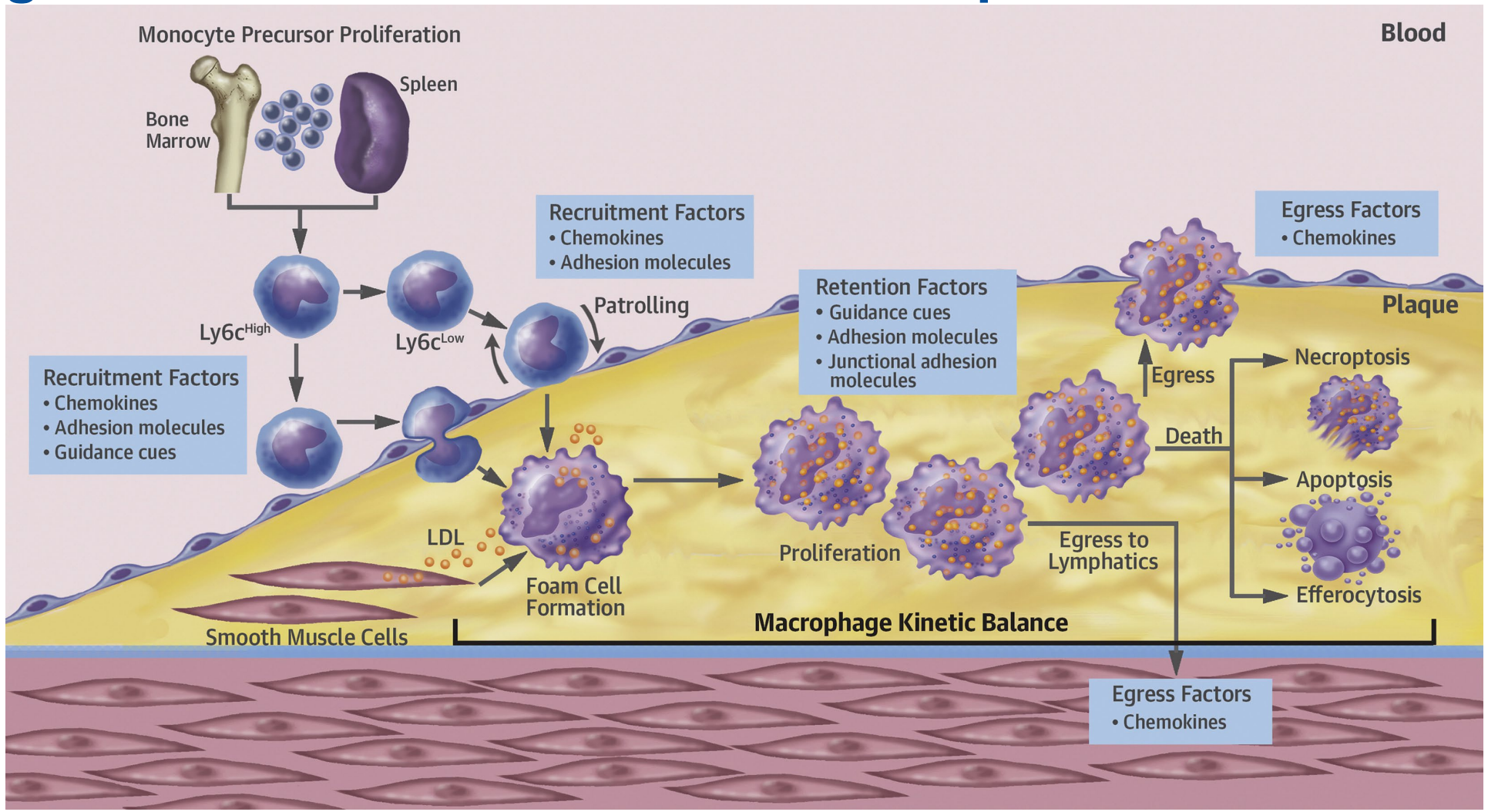


Adapted from Mason RP, Jacob RF. *Adv Exp Med Biol*. 2015;842:231-245.

QUESTION 2

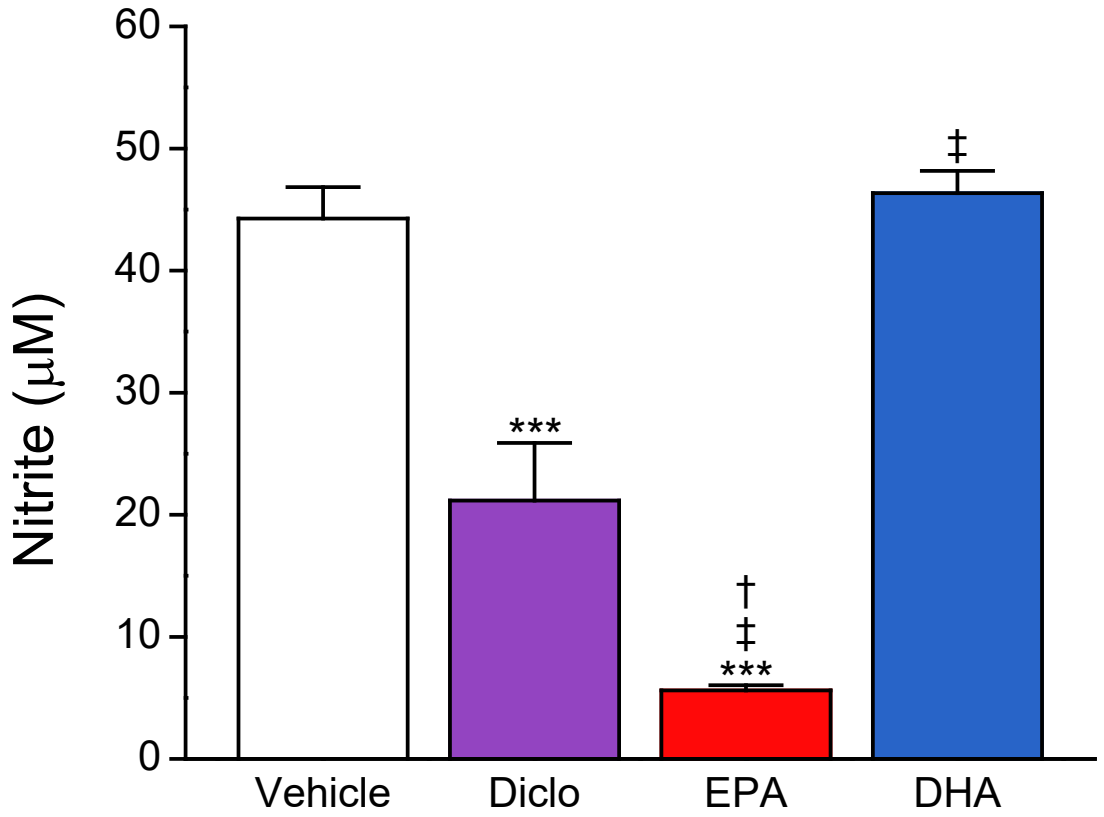
What effects do Omega-3 FAs have on macrophage activation?

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



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

EPA, but Not DHA, Reduces Macrophage Activation with LPS

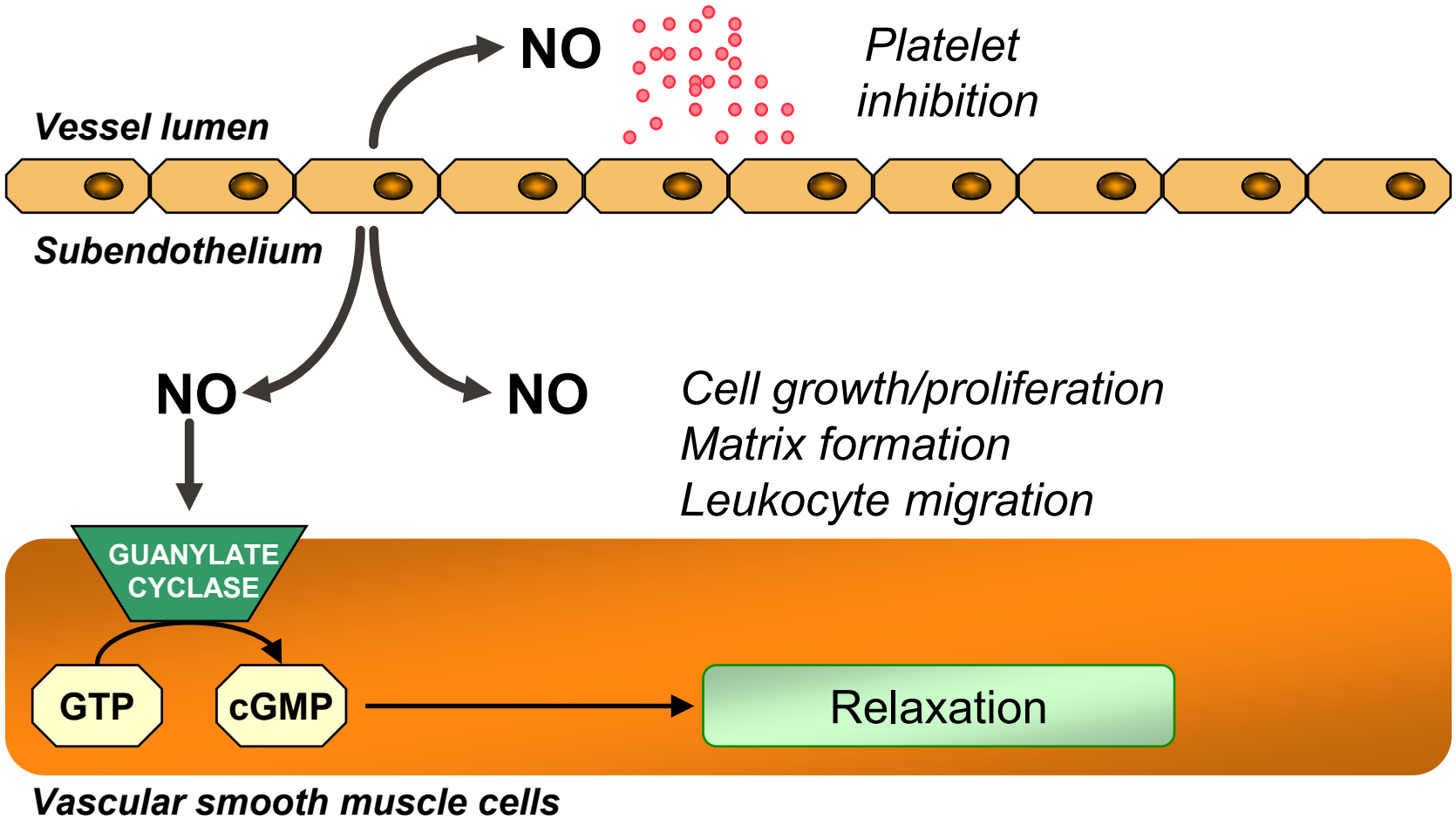


Diclo, Diclofenac; LPS, lipopolysaccharide.
LPS and diclofenac concentration = 1 µg/mL.
*** $P < 0.001$ versus vehicle; † $P < 0.001$ versus diclo; ‡ $P < 0.001$ versus DHA alone (Student-Newman-Keuls Multiple Comparisons Test; overall ANOVA: $P < 0.0001$, F = 140.94).
Values are mean ± SD (N = 3).
Al-Asfoor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

QUESTION 3

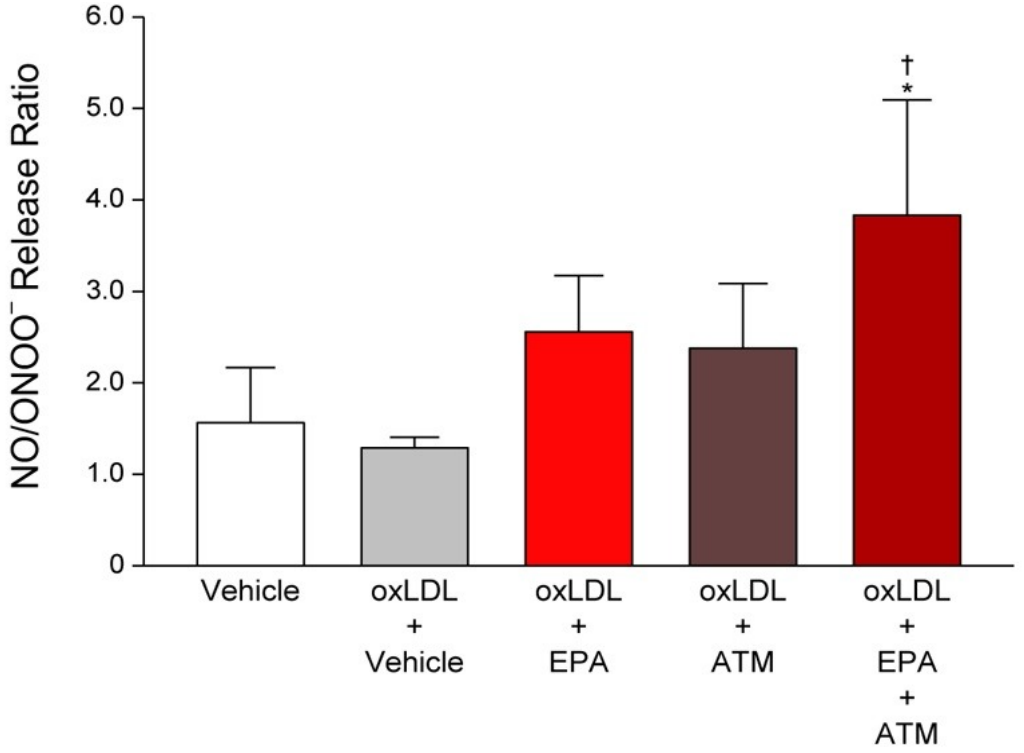
What effects do omega-3 FAs have on endothelial function and protein expression?

Endothelial Function and Role of Nitric Oxide



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

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

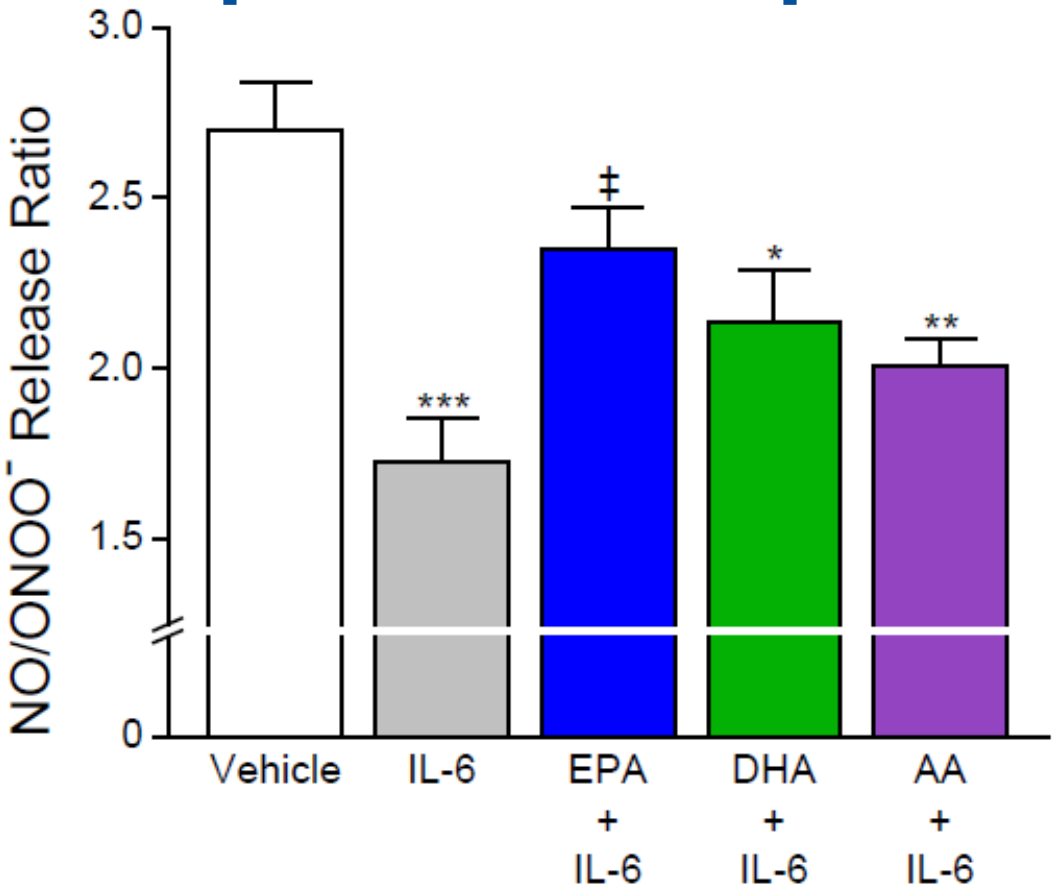


*p<0.01 versus vehicle alone (no oxLDL); †p<0.01 versus oxLDL+Vehicle (Student-Newman-Keuls multiple comparisons test; overall ANOVA: p=0.0030, F=6.768). Values are mean ± S.D. (N=3-7).

ATM, atorvastatin active metabolite.

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

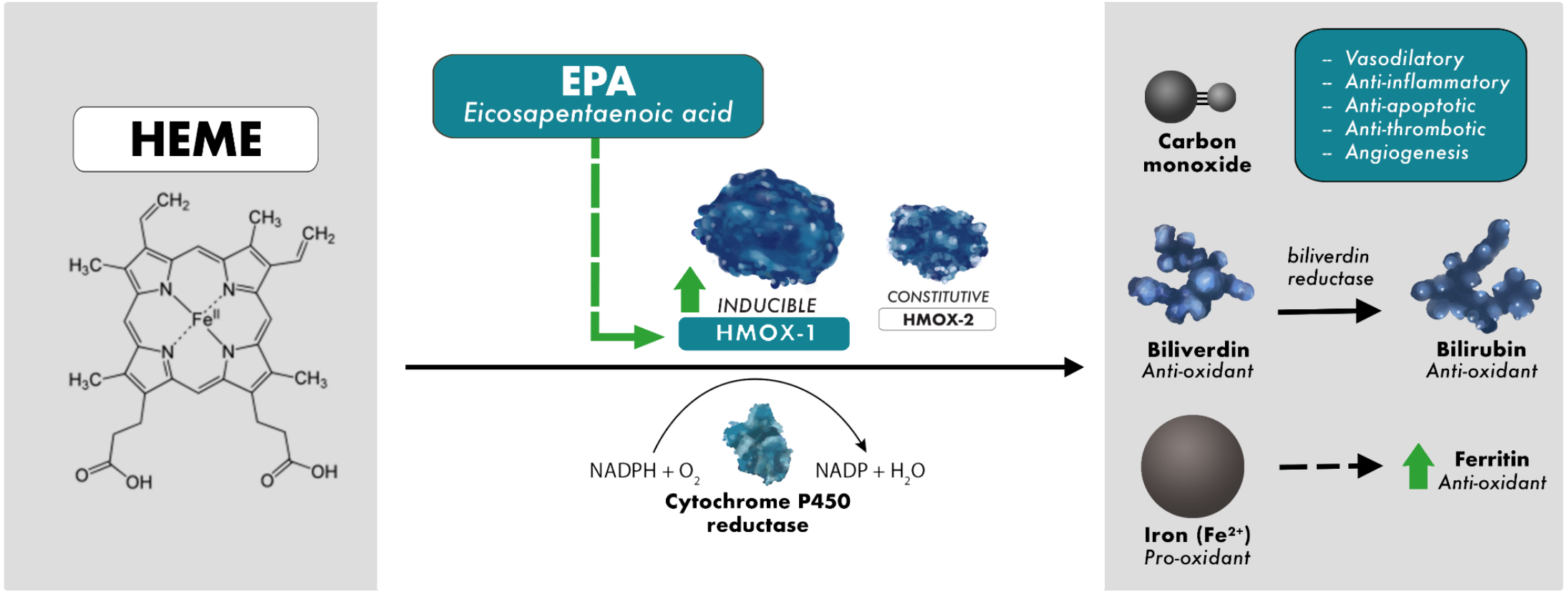
EPA Preserves Vascular Endothelial Function Following IL-6 Exposure Compared with DHA and AA



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

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

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



Sherratt SCR and Mason RP (2021). Created by Luke Groothoff (Elucida Research).

ESC European Society of Cardiology

European Heart Journal (2020) **00**, 1–8
doi:10.1093/eurheartj/ehaa652

FASTTRACK CONGRESS
Coronary artery disease

Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial

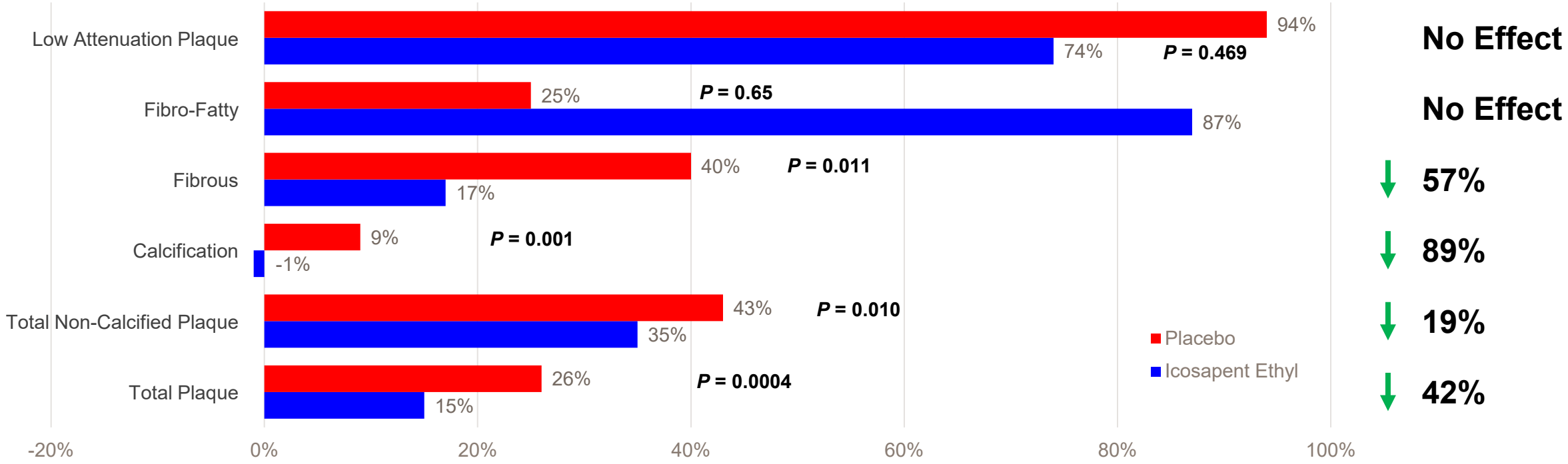
Matthew J. Budoff [1]*, Deepak L. Bhatt [2], April Kinninger [1], Suvasini Lakshmanan[1], Joseph B. Muhlestein[3], Viet T. Le [3,4], Heidi T. May [3], Kashif Shaikh[1], Chandana Shekar[1], Sion K. Roy[1], John Tayek[1], and John R. Nelson[5]

"The EVAPORATE trial sought to determine whether IPE 4 g/day, as an adjunct to diet and statin therapy, would result in a greater change from baseline in plaque volume, measured by serial multidetector computed tomography (MDCT), than placebo in statin-treated patients."

Interim EVAPORATE Results Show Substantial Early Effects of Icosapent Ethyl on Plaque Volume

- First study using MDCT to evaluate the effects of IPE 4 g/day vs placebo as an adjunct to statin on plaque volume/characteristics in a REDUCE-IT-like population
- Already demonstrated significant early changes in most plaque measurements by 9 months in a prespecified interim analysis

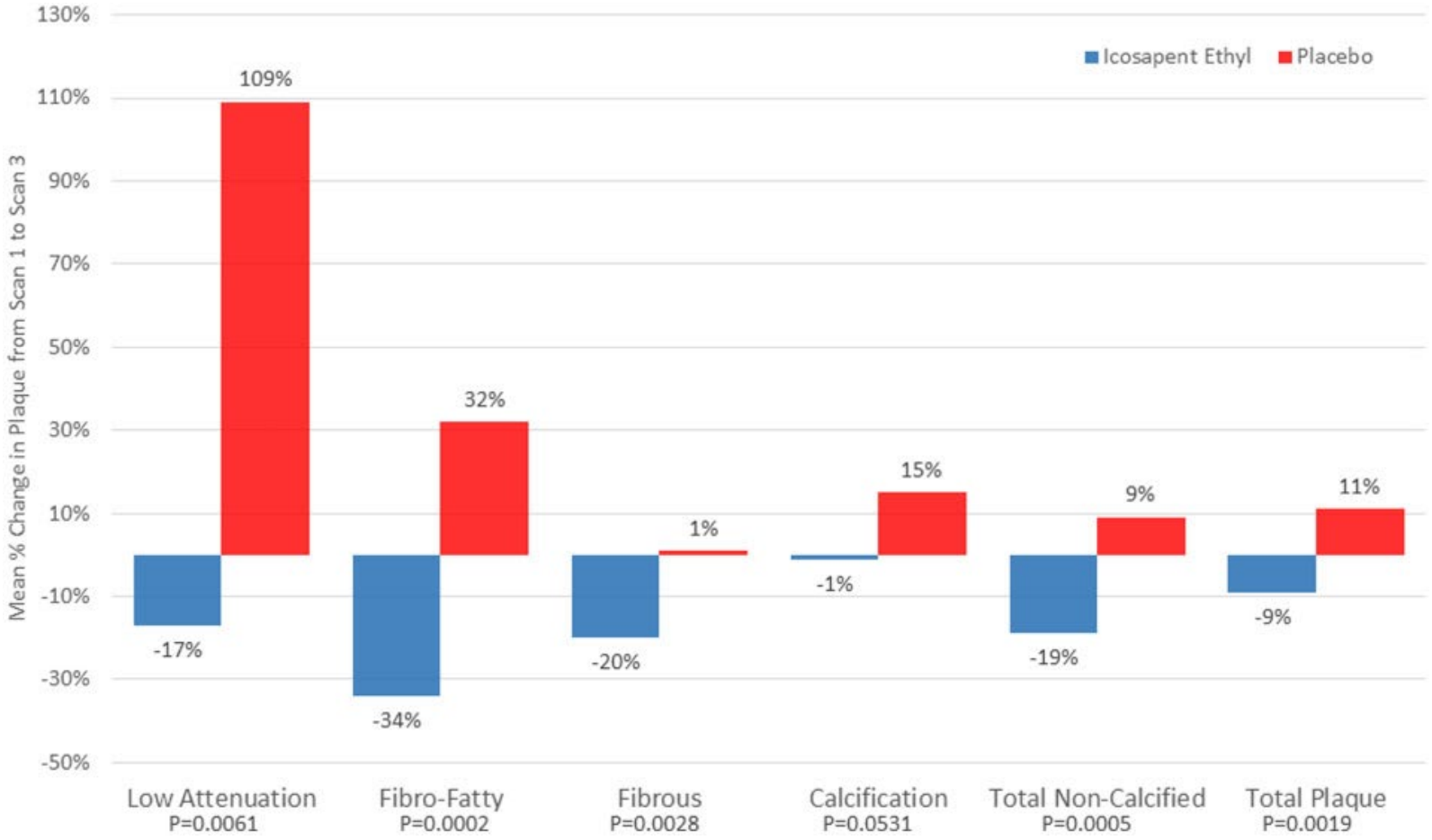
Fully adjusted median plaque progression at 9 months (median percent change in plaque volume)



Budoff M, et al. *Cardiovasc Res*. 2021;117(4):1070-1077.

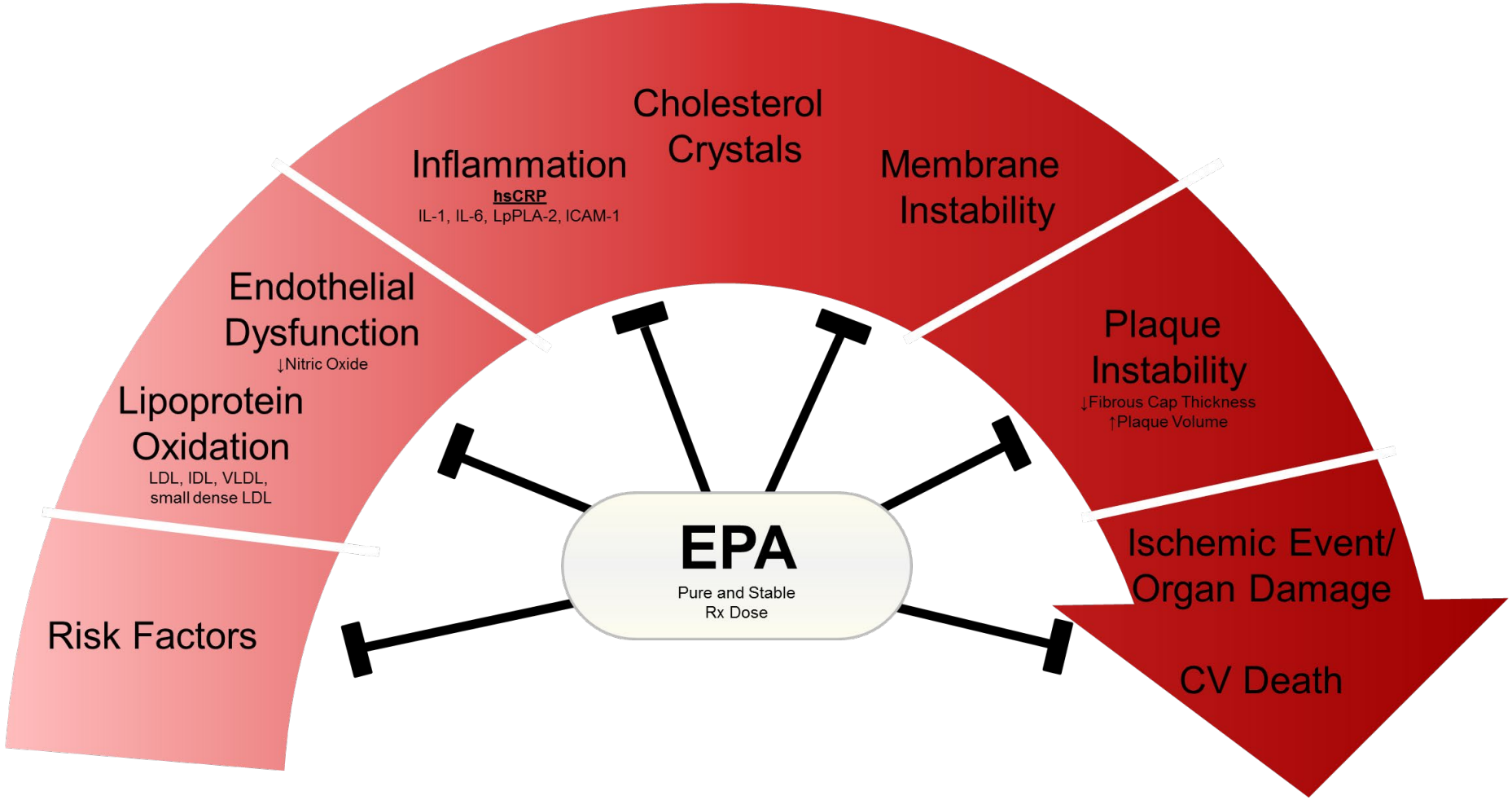
medtelligence℠

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



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

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



Bays HE, et al. *Am J Cardiovasc Drugs*. 2013;13:37-46; Borow KM, Nelson JR, Mason RP. *Atherosclerosis.* 2015;242:357-66; Bhatt DL, et al. *N Engl J Med.* 2019;380:11-22; Ganda OP, et al. *J Am Coll Cardiol*. 2018;72:330-343; Jia X, et al. *Curr Atheroscler Rep*. 2019;21:1; Mason RP, et al. *Biomed Pharmacother*. 2018;103:1231-1237; Ference BA, et al. *JAMA*. 2019;321:364-373.

Role of the Pharmacist in Lipid Medication Access and Usage

Joseph Saseen, PharmD, BCPS, CLS, FNLA
Professor and Associate Dean for Clinical Affairs
University of Colorado Anschutz Medical Campus
Aurora, CO

Role of the Clinical Pharmacist in CV Care

Patient-Specific Services

- Drug and Disease Management
- Collaborative Practice Agreements
- Patient Education
- Drug Interaction Screening, Drug Therapy Monitoring
- Pharmacogenetics, Pharmacokinetic/Pharmacodynamic Dosing
- Drug Information

Facility-Specific Services

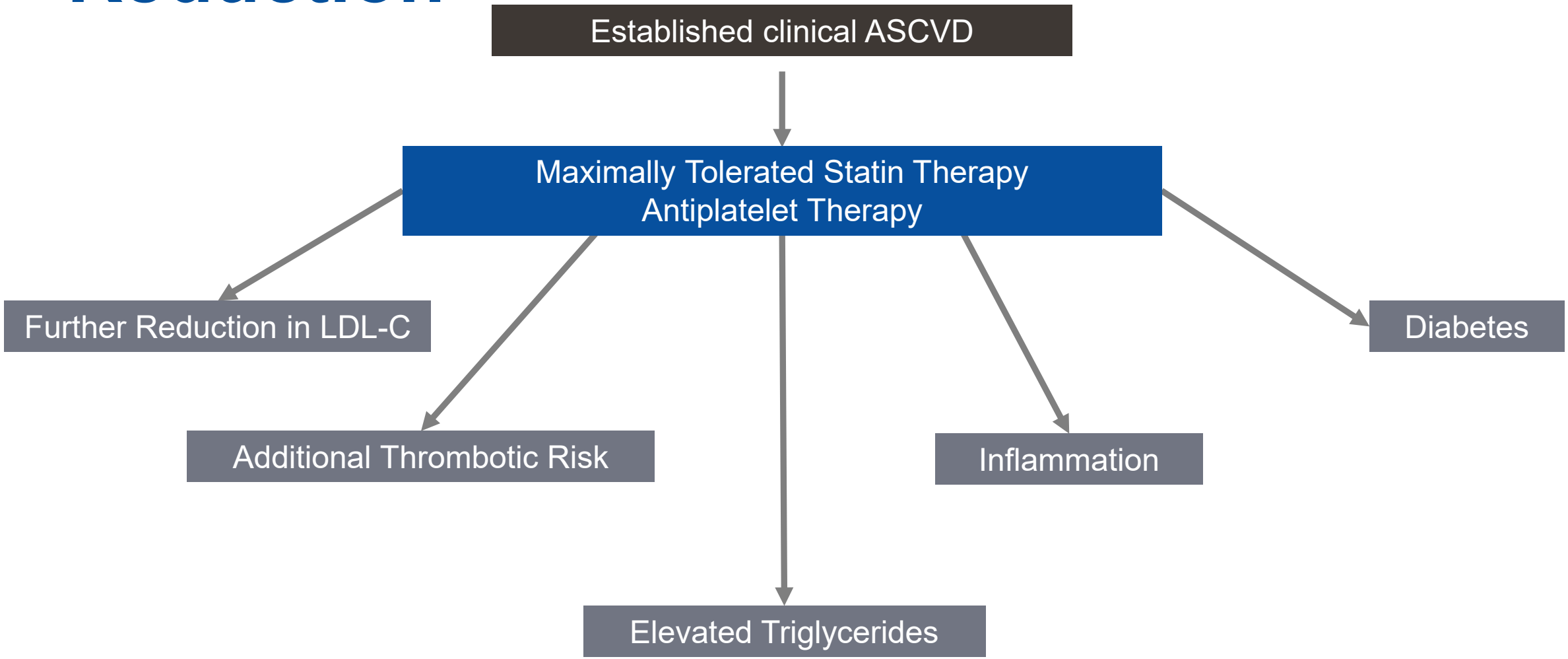
- Protocol, Guideline, and Policy Development and Review
- Research
- Core Measures and Quality Improvement Initiatives
- Medication Safety

Global Services

- Governmental and Societal Committee and Agencies
- Societal Guideline and Protocol Development
- Legal Consultation
- Public Health Initiatives

Dunn SP, et al. *J Am Coll Cardiol.* 2015;66(19):2129-2139.

Therapeutic Approaches to CV Risk Reduction

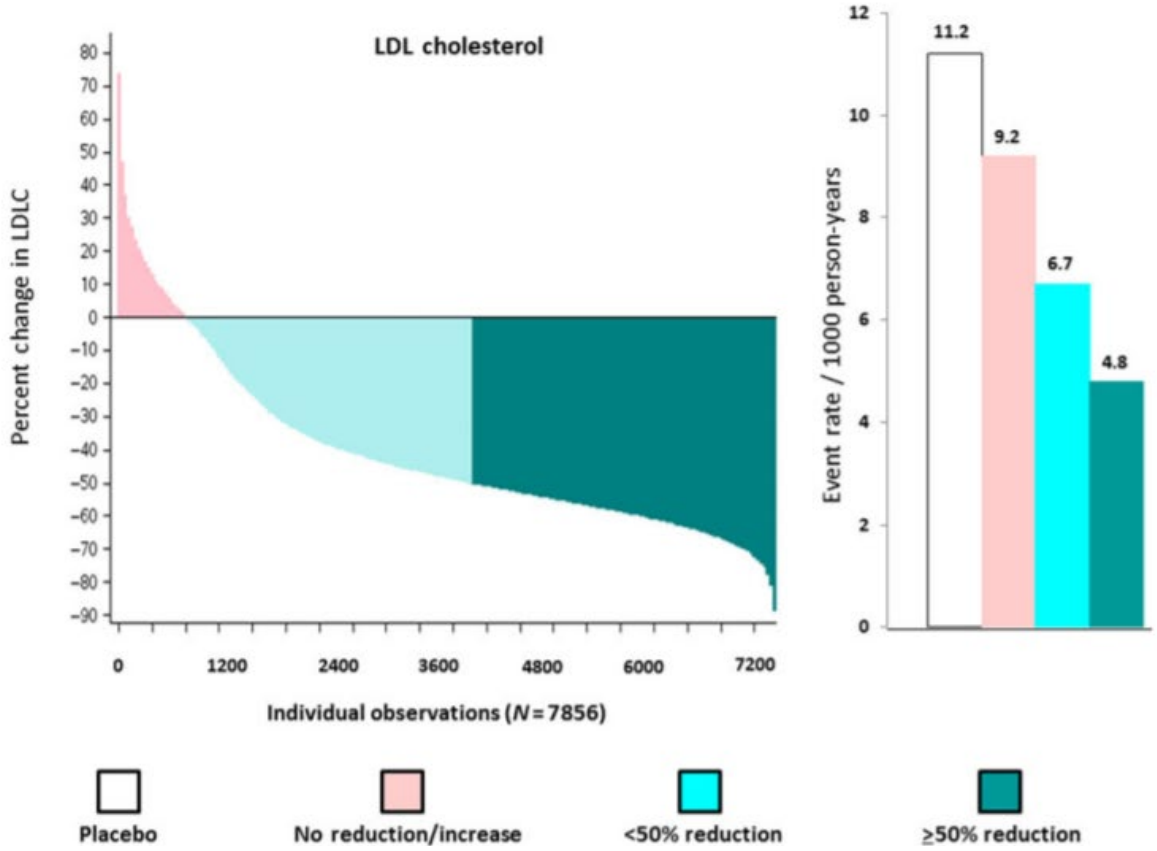


Intensity of Statin Therapy

	High Intensity	Moderate Intensity	Low Intensity
LDL-C* Lowering	≥50%	30 to 49%	<30%
	Atorvastatin (40 mg) 80 mg Rosuvastatin 20 mg (40 mg)	Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20-40 mg	Simvastatin 10 mg
		Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg twice daily Pitavastatin 1-4 mg	Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

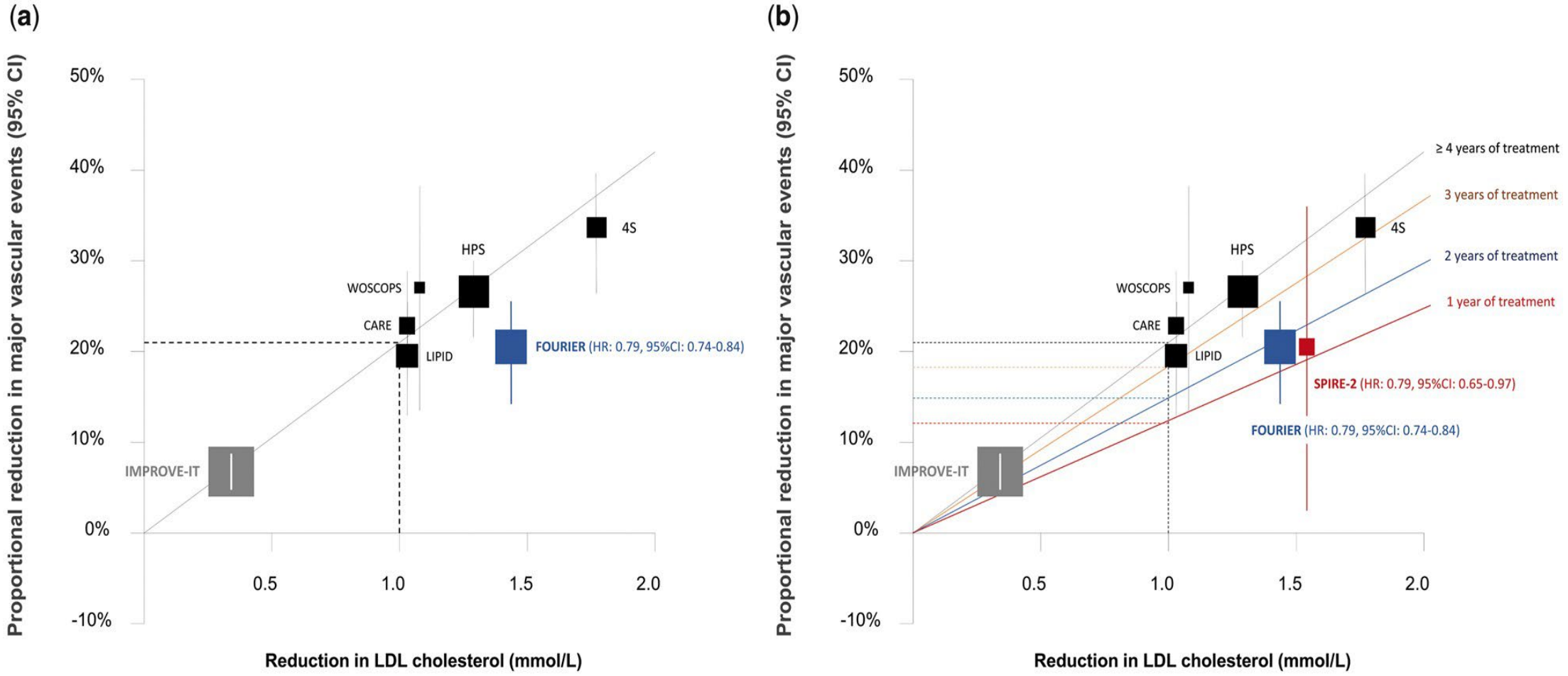
Stone NJ, et al. *Circulation*. 2014;129(25 Suppl 2):S1-S45.

Not All Patients Have the Same LDL-C Response. JUPITER: Variable Change in LDL-C on Rosuvastatin



Reproduced with permission. Ridker PM, et al. *Eur Heart J*. 2016;37(17):1373-1379.

Every 40 mg/dL Reduction in LDL ≈ 25% Reduction in Hard MACE (CV Death, MI, Stroke)



Ference, BA, et al. *Eur Heart J*. 2018;39(27):2540-2545.

Adherence to Statin Therapy Is Important

- Statins are generally well tolerated
  - >Three-quarters of the general population tolerate statin therapy, but
  - 10%-20% of patients prescribed a statin report statin intolerance
- Very effective in preventing clinical ASCVD across all LDL-C levels
- Rates of serious adverse events are very low
  - The risk of statin-induced serious muscle injury, including rhabdomyolysis, is <0.1%
  - The risk of statin-induced newly diagnosed diabetes mellitus is ≈0.2% per year of treatment

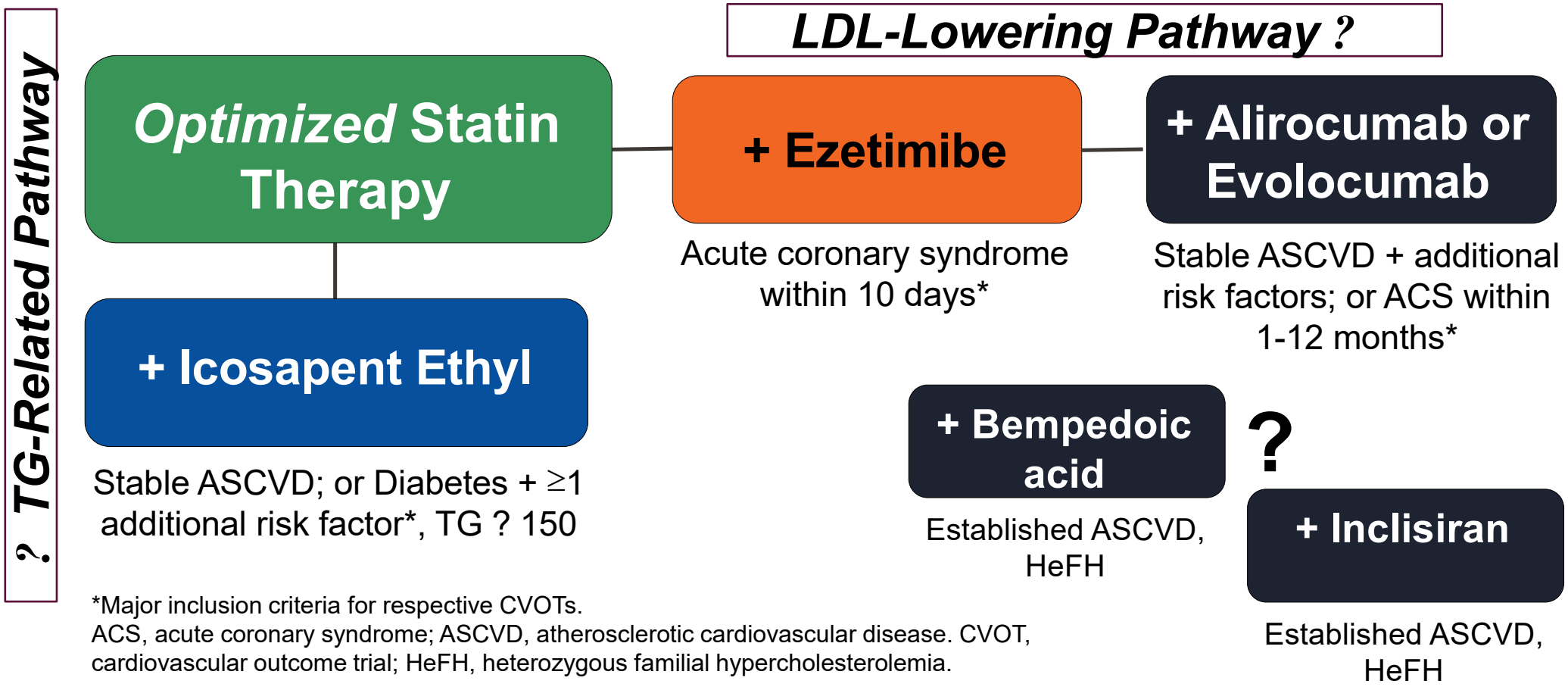
Toth PP, et al. *Am J Cardiovasc Drugs*. 2018;18(3):157-173.
Newman CB, et al. *Arterioscler Thromb Vasc Biol*. 2019;39(2):e38-e81.

Adherence to Statin Therapy Is Difficult

- A large proportion (40%-70%) of patients discontinue statin therapy within 1-2 years
  - Resulting in large increase in CVD events
- Perceived vs real effect may play a role as multiple studies show nocebo effect
  - Many patients can tolerate statins on rechallenge after reported statin intolerance

Toth PP, et al. Am J Cardiovasc Drugs. 2018;18(3):157-173.
Newman CB, et al. Arterioscler Thromb Vasc Biol. 2019;39(2):e38-e81.
Jacobson TA, et al. J Clin Lipidol. 2019;13(3):415-424.

Statin Therapy Adjuncts *Proven* to Reduce ASCVD



*Major inclusion criteria for respective CVOTs.
ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease. CVOT, cardiovascular outcome trial; HeFH, heterozygous familial hypercholesterolemia.

Orringer CE. *Trends Cardiovasc Med*. 2020;30(3):151-157.

Icosapent Ethyl (IPE) Now Indicated by the FDA for CVD Event Reduction

Original July 2012 (still indicated)

- As an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia
- Limitations of use: The effect of IPE on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined
- The daily dose is 4 g per day

New December 2019

- As an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥150 mg/dL) and
  - Established cardiovascular disease or
  - Diabetes mellitus and 2 or more additional risk factors for cardiovascular disease.

Released December 13, 2019. After https://www.vascepa.com/assets/pdf/Vascepa_PI.pdf

Icosapent Ethyl Is Now Included in the Treatment Guidelines or Recommended for Use by 19 Medical Associations Worldwide

- American College of Cardiology
- American Association of Clinical Endocrinology
- American Diabetes Association
- American Heart Association
- National Lipid Association
- Endocrine Society
- European Society of Cardiology
- European Atherosclerosis Society
- Chinese Society of Cardiology
- Japan Circulation Society
- Brazilian Society of Cardiology
- Thrombosis Canada

Virani SS, et al. *J Am Coll Cardiol*. 2021;78(9):960-993. Handelsman Y, et al. *Endocr Pract*. 2020;26(10):1196-1224. American Diabetes Association http://main.diabetes.org/dorg/bod/2019-2020/ADA-Strategic-Architecture.pdf. Kimura K, et al. *Circ J*. 2019;83(5):1085-1196. American Heart Association https://www.heart.org. European Society of Cardiology https://www.escardio.org/The-ESC/Who-we-are. European Atherosclerosis Society https://www.eas-society.org/page/about_eas. National Lipid Association https://www.lipid.org/about. American Association of Clinical Endocrinology https://www.aace.com/about/about-aace. Brazilian Society of Cardiology Cardiovascular Prevention Guideline Update http://publicacoes.cardiol.br/portal/abc/ingles/aop/2019/aop-diretriz-prevencao-cardiovascular-ingles.pdf. The Thrombosis Canada Clinical Guides. https://thrombosiscanada.ca/clinicalguides/#. Vargas-Uricoechea H, et al. *Revista ACE*. 2020;7(1):4-36, http://revistaendocrino.org/index.php/rcedm/article/view/573. Arnold SV, et al. *Circulation*. 2020; 141(19):e779-e806. Collet JP, et al. *Eur Heart J*. 2021;42(14):1289-1367. Newman C, et al. *J Clin Endocrinol Metab*. 2020; 105(12):dgaa674. Cardiology Committee of the National Medical Association, et al. *Chinese Journal of Cardiovascular Diseases*. 2020;48(12):1000-1038.

AHA Science Advisory: Safety and Tolerability of Prescription Omega-3 Fatty Acid Products

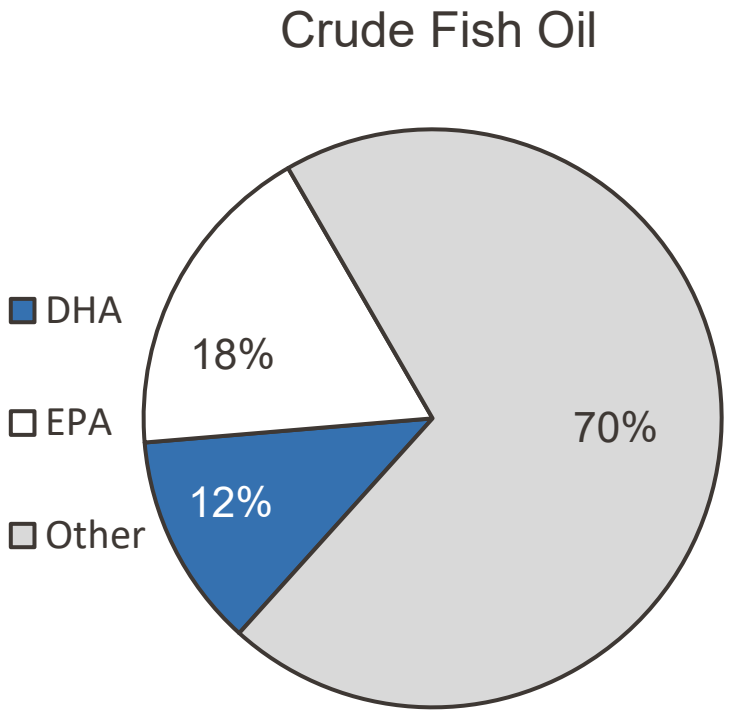
General	• All forms have a relatively benign adverse effect profile and are generally safe • Tolerability issues have been relatively minor; drug discontinuation rate is small (<5%)
Bleeding	• Known antiplatelet effects with all omega-3 fatty acid products • FDA suggests periodic monitoring if concurrent anticoagulant or antiplatelet use • Combinations have not been shown to increase significant bleeding
Gastrointestinal	• Adverse effects can include fishy taste, eructation, diarrhea, and nausea • Substantial difference in adverse effects among products (most with the carboxylic acid form)
Fish/seafood allergy	• Highly purified and do not appear to be allergenic • Patients with seafood allergy do not need to avoid use; FDA recommends to use with caution
Glycemic control	• Recent evidence shows that 4 grams/day does not adversely affect glucose metabolism

Skulas-Ray AC, et al. *Circulation*. 2019;140:e673-e691.

Fish Oil *Dietary Supplements*: Poorly Regulated but Widely Used

- There are *NO* over-the-counter omega-3 products (that would be FDA-regulated but non-prescription); *ONLY* dietary supplements (with minimal FDA oversight)
- Dietary supplements are *NOT* recommended to treat diseases, ***but***
- Benefits are claimed for heart, brain, weight, vision, inflammation, skin, liver fat, depression, age-related cognitive decline, allergies, bones, pregnancy/neonatal health, childhood behavior…
- Approximately 8% of US adults (19 million) take fish oil dietary supplements

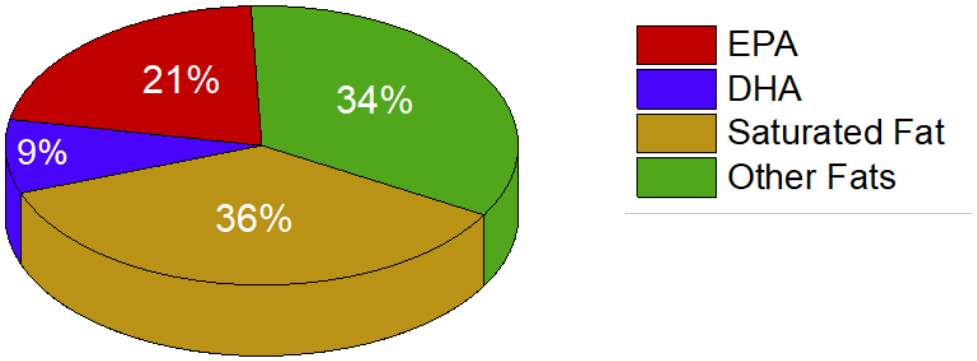
Critical Differences Between Dietary Supplement and Prescription Omega-3 Fatty Acids



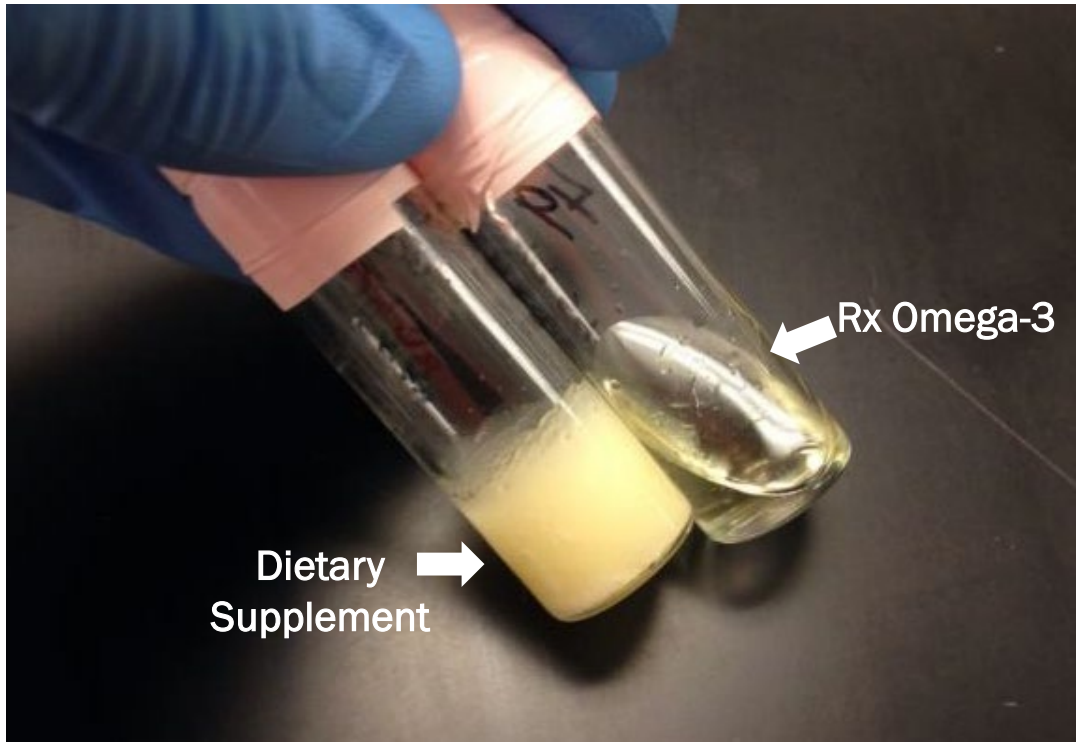
- OTC fish oil supplement
  - ≈20% DHA
  - ≈30% EPA
  - ≈50% other undisclosed oils (including saturated fat)
- Combination prescription omega-3 fatty acid
  - ≈42% DHA
  - ≈52% EPA
  - ≈6% Other undisclosed oils
- Prescription EPA-only
  - 100% IPE (ethyl ester of EPA)

Hilleman DE, et al. *Adv Ther*. 2020;37(2):656-670.

Dubious Content of *Leading* US Fish Oil Dietary Supplements



- Up to 36% of content may be saturated fat
- Omega-3 FA content often overstated
- Oxidation of omega-3 FA content can be high
  - even those meeting industry standards are more oxidized than Rx meds
- Contamination risk (pesticides, PCBs, etc.)
- Difficult to achieve EPA+DHA doses similar to Rx meds



High saturated fatty acid content of common fish oil dietary supplement makes it ***solid at room temperature*** (post-isolation)

Mason RP, Sherratt SCR. *Biochem Biophys Res Commun*. 2017;483(1):425-429. Hilleman D, Smer A. *Manag Care*. 2016;25(1):46-52. Albert BB, et al. *Sci Rep*. 2015;5:7928. Kleiner AC, et al. *J Sci Food Agric*. 2015;95(6):1260-1267. Ritter JC, et al. *J Sci Food Agric*. 2013:93(8):1935-1939. Jackowski SA, et al. *J Nutr Sci*. 2015;4:e30. Rundblad A, et al. *Br J Nutr*. 2017;117(9):1291-1298. European Medicines Agency, 2018: 712678.

Should You Use OTC Dietary Supplements for Your Patients with ASCVD?

FDA Product Classification	Food
Clinical Trials/FDA Pre-Approval	Not Required
Content and Purity	• Difficult to achieve AHA recommended OM-3 levels – 4 g EPA/day • 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

Sherratt SCR, et al. *Curr Opin Lipidol*. 2020;31(2):94-100.

Monitoring Response to Drug Therapy

- Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes and
  - Repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment
  - Repeat every 3 to 12 months as needed
- Responses to lifestyle and statin therapy are defined by percentage reductions in LDL-C levels compared with baseline
- Remind your patients how important it is for them to take their medications
  - Long-term benefits for them, their families, and community

Grundy SM, et al. *J Am Coll Cardiol.* 2019.25;73(24):e285-e350.

Counseling Tips

OTC ≠ Rx

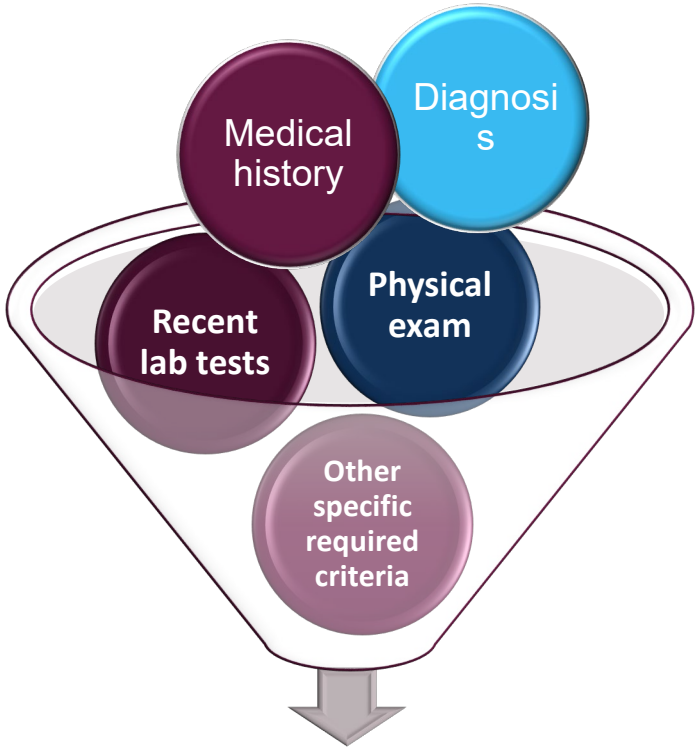
- OTC fish oil capsules are dietary supplements
  - They are NOT equal to prescription omega-3 fatty acids
- Prescription content to provide benefit is approximately 4 grams/day of omega-3 fatty acids; higher than the typical OTC dose
- OTC products contain much larger amounts of oxidized omega-3 acids than prescription products
- Fishy burp occurs primarily with the OTC products; prescription products are purified
- Yellow color common of OTC products indicates oxidation; prescription IPE is clear

Vascepa. Prescribing information. Amarin Pharma, Inc.; 2021; Lovaza. Drug label information. DailyMed. Woodward Pharma Services; 2021; Hilleman DE, et al. Adv Ther. 2020;37(2):656-670.

Getting Insurance Approval for ASCVD Medications

- Typically, at least 1 drug per class is on formulary
- Some hurdles for approval
- Two key actions:
  1. Make sure your patient information regarding indication criteria is clearly described
  2. Include guidelines recommendations and FDA indications citations and/or copies
- Don’t take NO! for an answer; try again until it gets approved
- Once you get the process down, it will be easier the next time

Clear and Comprehensive Documentation



Increased Likeliness of Approval

Panel Discussion

All faculty

Clinical Approaches to Personalizing Medical Management of ASCVD Risk Factors: Case Discussions

All Faculty

medtelligence℠

Our Patient – First Visit

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

CVD Risk Scores in Secondary Prevention

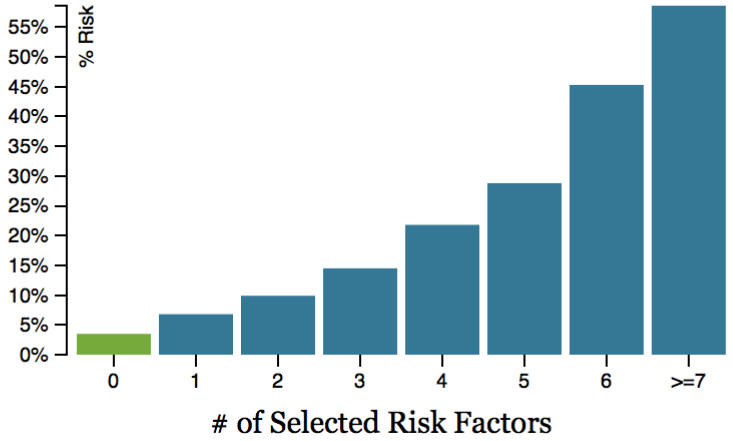
TIMI Risk Score for Secondary Prevention (TRS 2°P)

Risk in Patients with Known Atherosclerotic Vascular Disease

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

0 Risk Indicators Selected

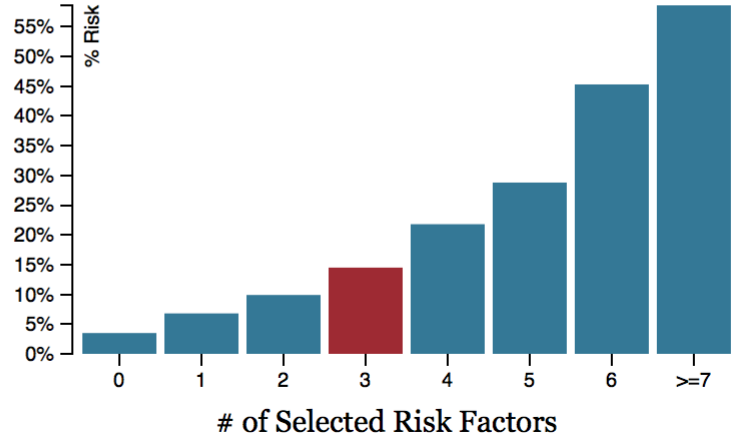
3.5% risk at 3 years of CV death, MI or Ischemic Stroke.



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

3 Risk Indicators Selected

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



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

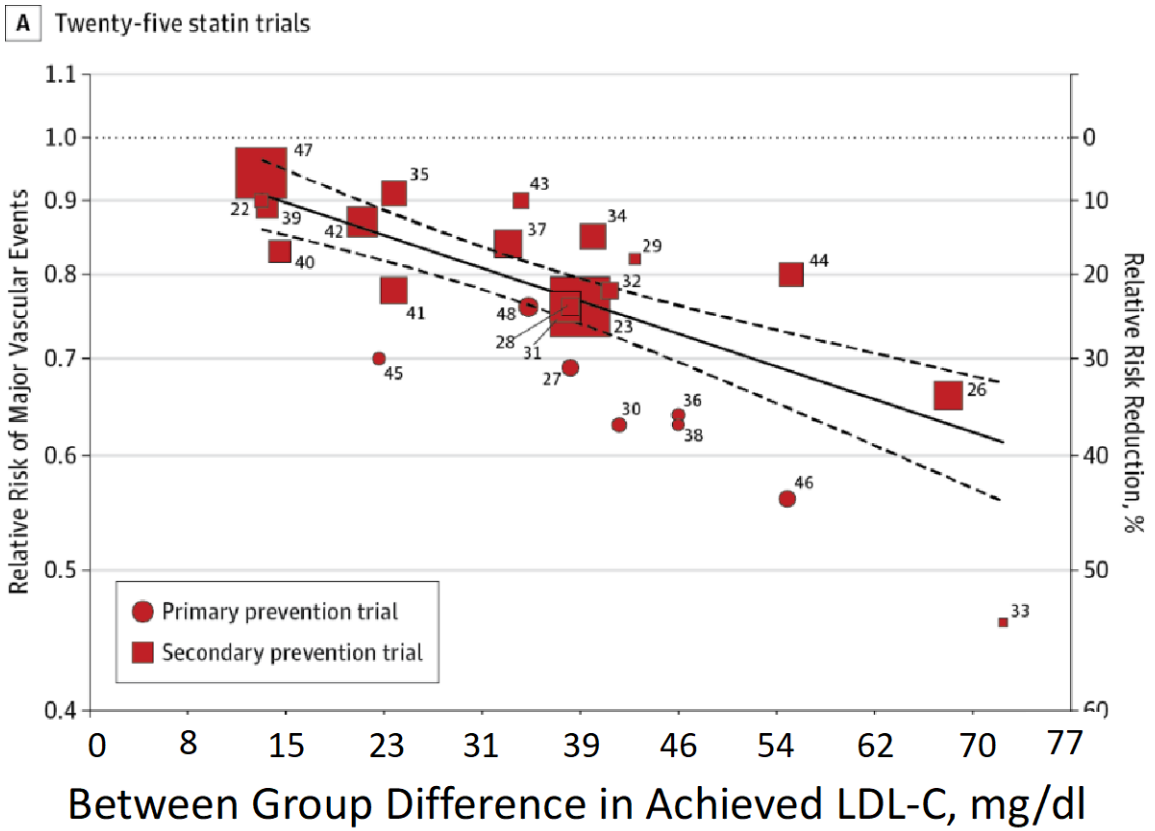
Validated in both trial and non-trial settings: www.timi.org

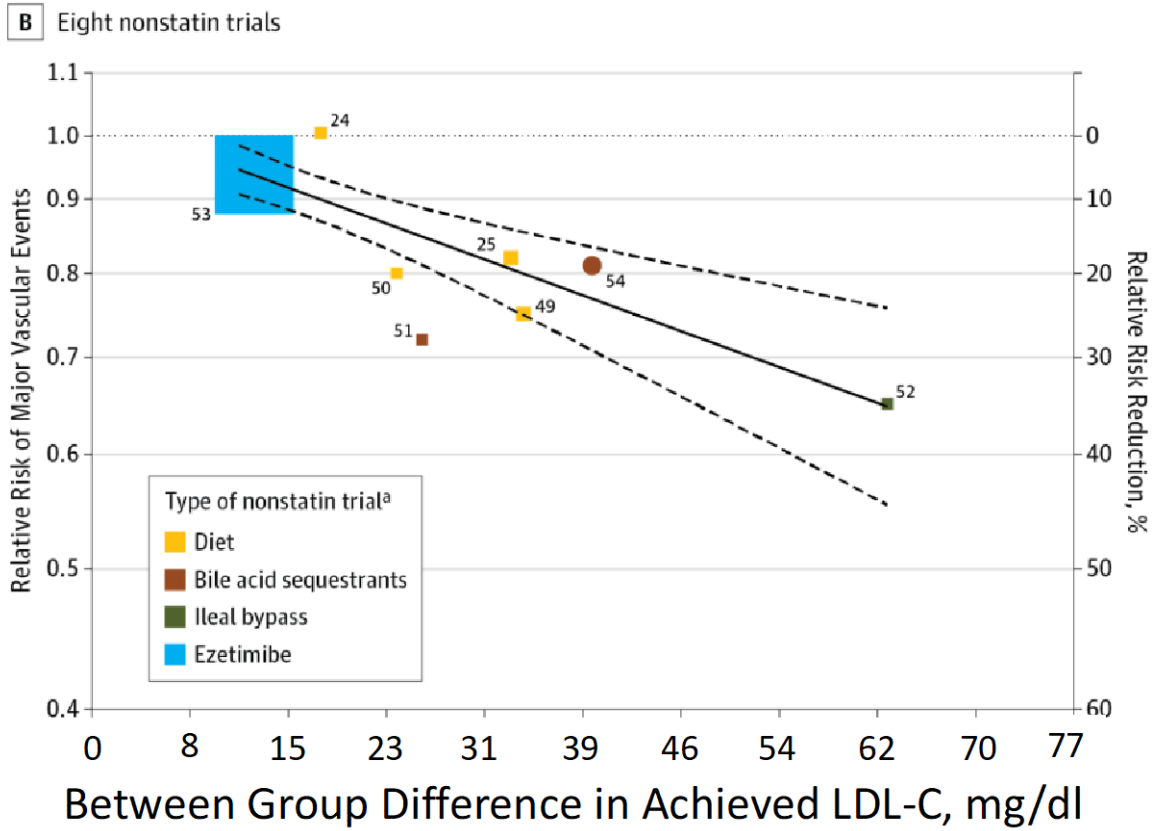
Our Patient – First Visit
Annual Risk of 3-Point MACE ~5% (TRS 2ºP)

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

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

Every 40 mg/dL Reduction in LDL ≈ 25% Reduction in Hard MACE





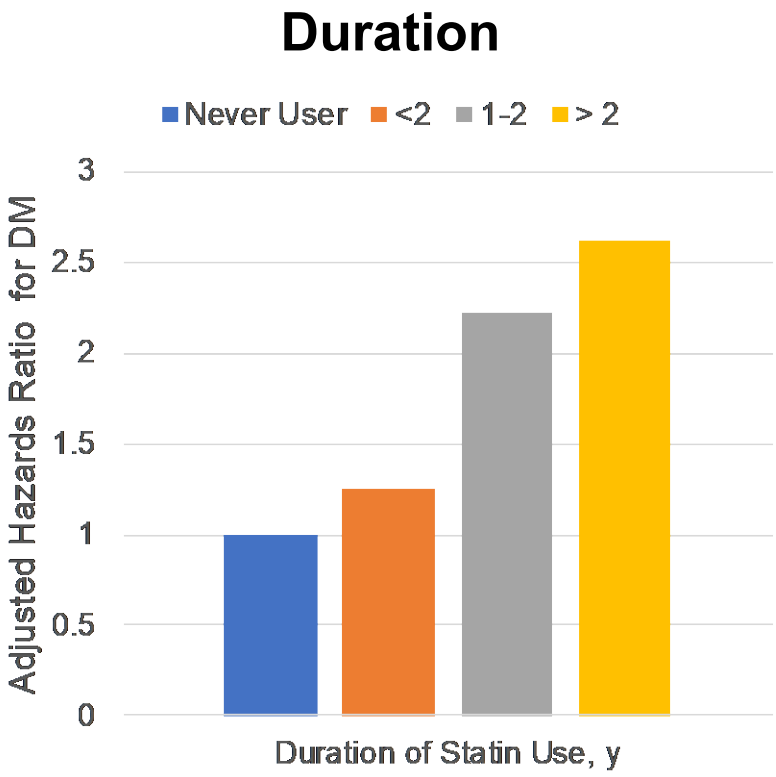
Silverman MG et al, JAMA. 2016;316(12):1289-1297. Association Between LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-Analysis

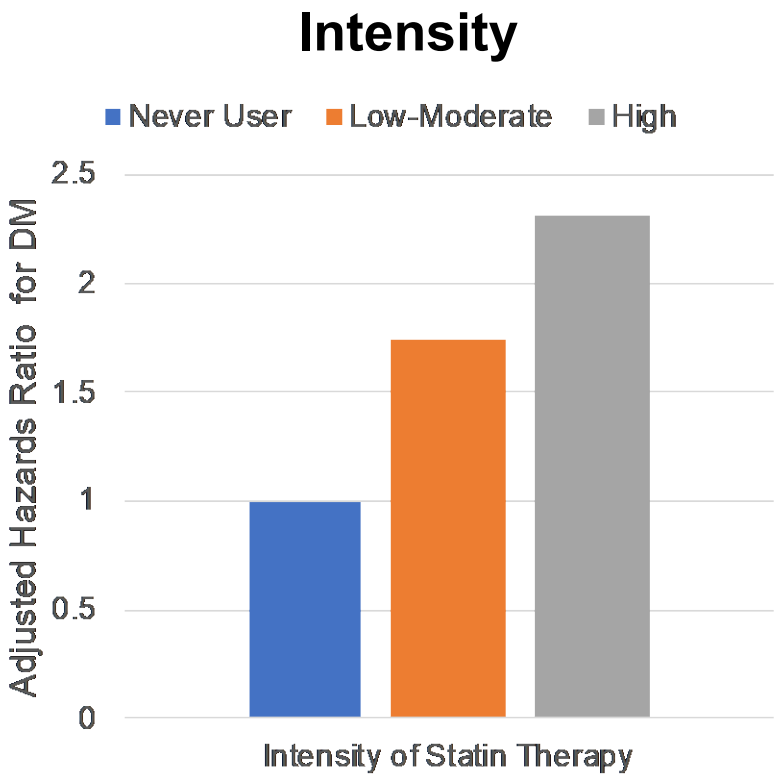
Intensity of Statin Therapy

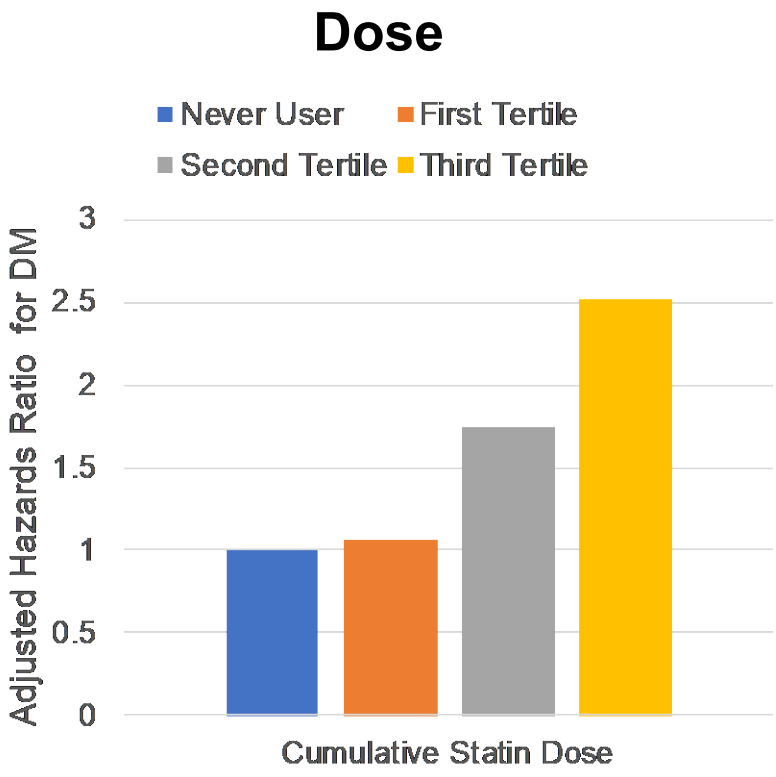
HIGH RISK PATIENT	MODERATE RISK PATIENT	LOW RISK PATIENT
High Intensity Statin	**Moderate Intensity Statin**	**Low Intensity Statin**
Daily dose lowers LDL-c ~50%	Daily dose lowers LDL-c ~30% -50%	Daily dose lowers LDL-c <30%
Atorvastatin (40†)-80 mg **Rosuvasatin 20 *(40)* mg**	Atorvastatin 10 *(20)* mg Rosuvastatin *(5)* 10 mg Simvastatin 20-40 mg‡ Pravstatin 40 *(80)* mg Lovastatin 40 mg *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 2-4 mg*	*Simvastatin 10 mg* Pravastatin 10-20 mg Lovastatin 20 mg *Fluvastatin 20-40 mg* *Pitavastatin 1 mg*

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL.
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.
Stone NJ, et al. *Circulation*. 2014;129(25 Suppl 2):S1-S45.

Risk of New-Onset Diabetes







Ko M et al, JAHA 2019;8:e011320. DOI: 10.1161/JAHA

Our Patient – After High-Intensity Statin
Annual Risk of 3-Point MACE ~3%

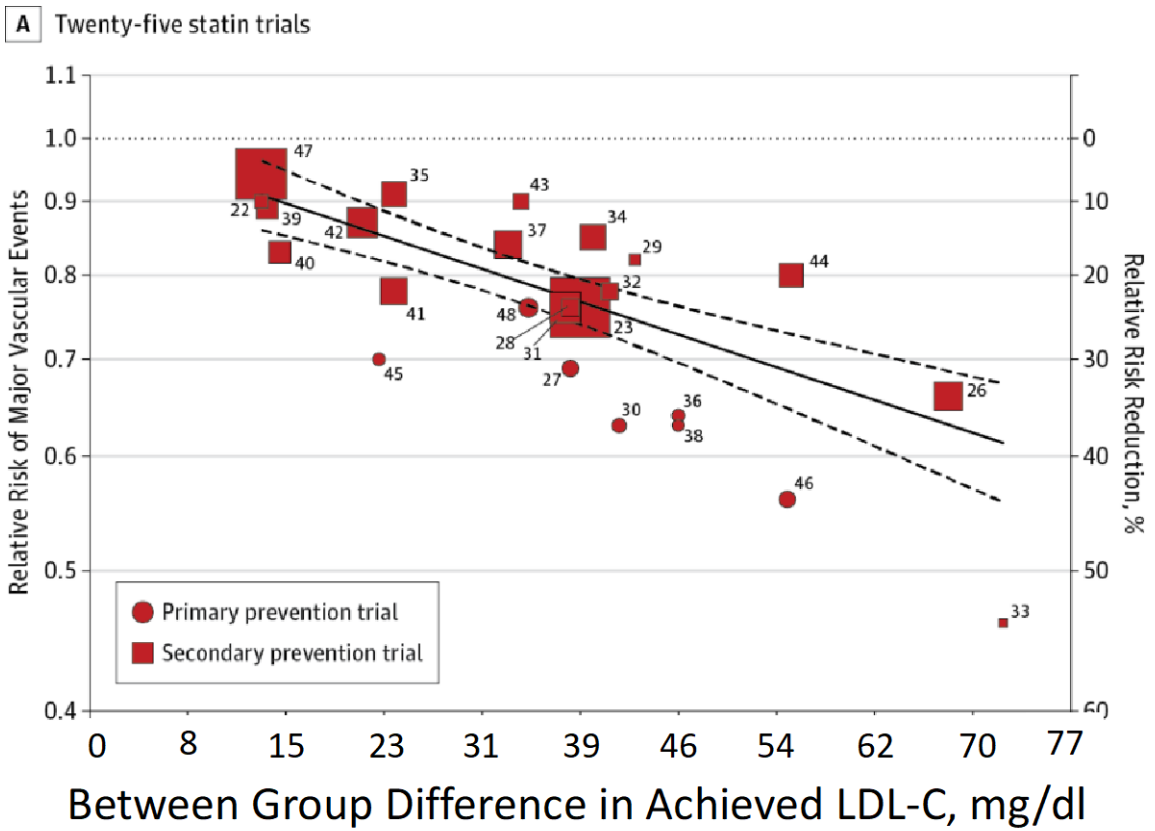
- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, treated
- BMI 29 kg/m^2

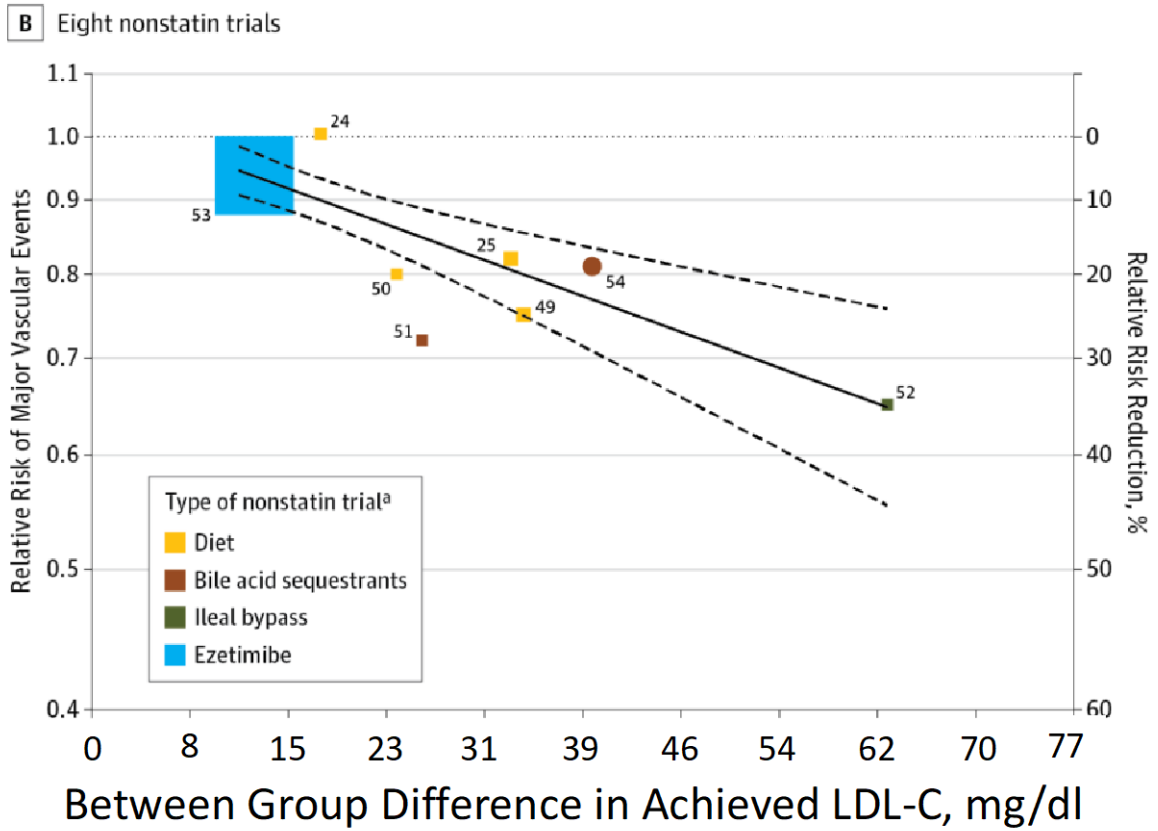
	Pre-Treatment	Post-Treatment
TC	260 mg/dL	168 mg/dL
LDL-C	170 mg/dL	85 mg/dL
TG	280 mg/dL	238 mg/dL
HDL-C	34 mg/dL	36 mg/dL
Non-HDL-C	226 mg/dL	133 mg/dL

- 85 mg/dL ~ -40% MACE
(7-30% ⇊ TG)

Do we need more LDL lowering?

Every 40 mg/dL Reduction in LDL ≈ 25% Reduction in Hard MACE





STEP 1

STEP 2

Silverman MG et al, JAMA. 2016;316(12):1289-1297. Association Between LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-Analysis

Our Patient – After HI Statin + Ezetimibe
Annual Risk of 3-Point MACE ~2.8%

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

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

-98 mg/dL ~ -43% MACE
(10-15% ⇊ TG)

Do we need more LDL lowering?

Our Patient – HI Statin + Ezetimibe + PCSK9i

Annual Risk of 3-Point MACE ~2.3%

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

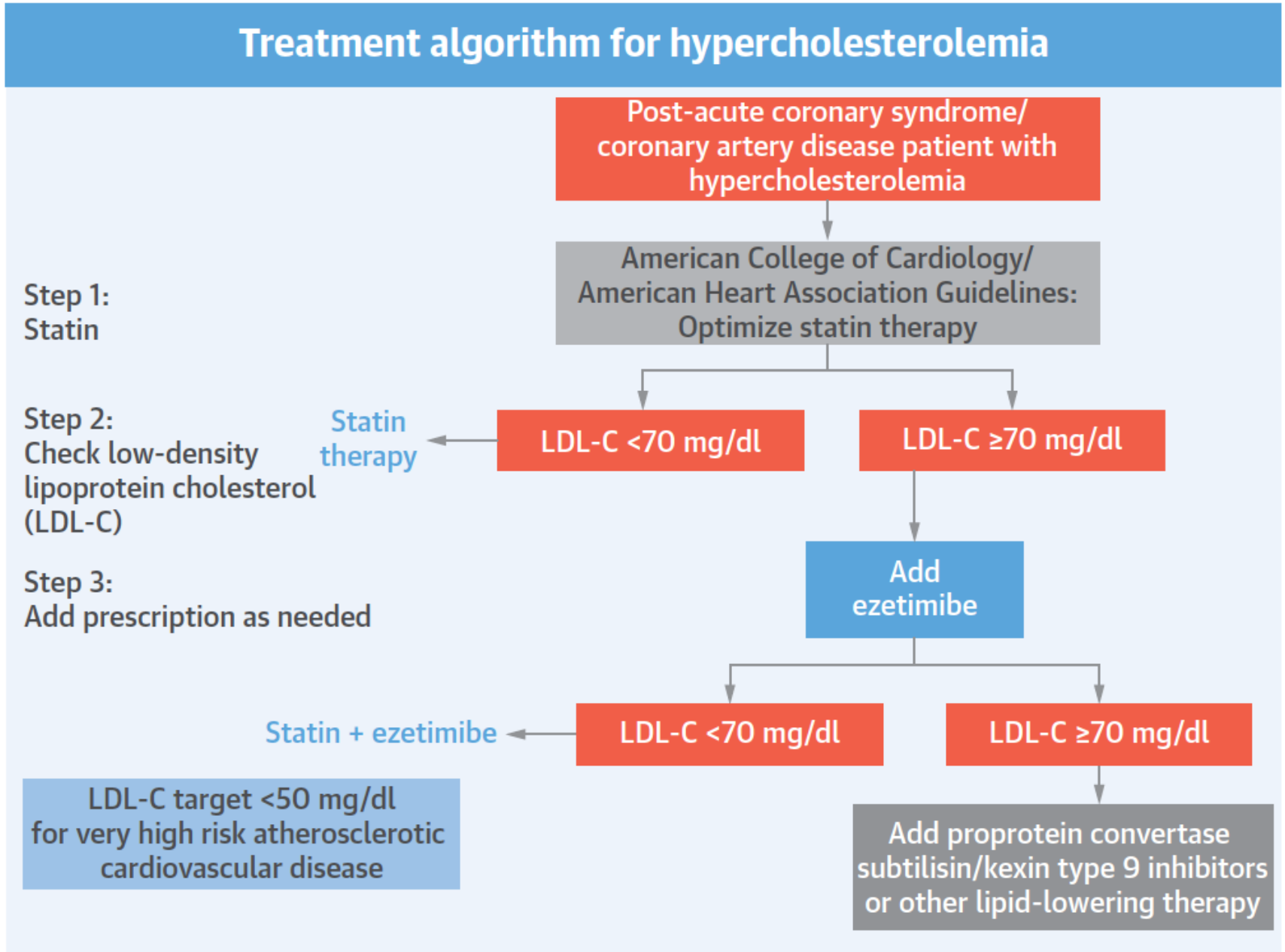
	Pre-Treatment	Post-Treatment
TC	152 mg/dL	104 mg/dL
LDL-C	72 mg/dL	29 mg/dL
TG	214 mg/dL	184 mg/dL
HDL-C	37 mg/dL	38 mg/dL
Non-HDL-C	115 mg/dL	66 mg/dL

-141 mg/dL ~ -54% MACE

(5-25% ⇊ TG)

Other Choices?

So far, we've played by this rulebook…



Rosenson, R.S. et al. J Am Coll Cardiol. 2018;72(3):314–29.

In Patients with Hypertriglyceridemia, We Have Another Option

- Prior to REDUCE-IT, no randomized clinical trials have demonstrated benefit in patients specifically enrolled based on hypertriglyceridemia
- Because of the data we've shown you, icosapent ethyl is another option in this high-risk patient

Our Patient – Statin + Ezetimibe + EPA (IPE)

Annual Risk of 3-Point MACE ~2.1% (Versus 2.3% with PCSK9i)

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

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

- 26% in 3-pt MACE with enhanced efficacy in Patients with Mixed Dyslipidemia

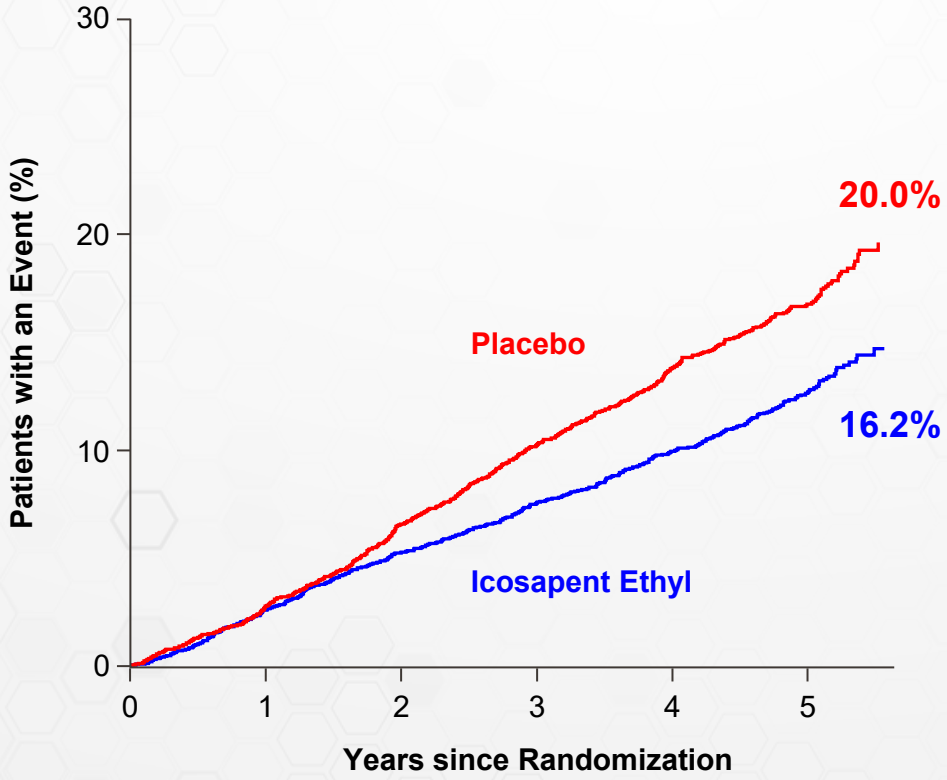
Addition of EPA (IPE)

When to Add Icosapent Ethyl in Secondary Prevention

- The bifurcation is at near goal LDL in the patient with residual hypertriglyceridemia
- Achieve similar risk reduction from baseline versus addition of PCSK9i
- Possibly add earlier in treatment plan when LDL-C <100 mg/dL (CV mortality benefit), but many statin and non-statin LDL-lowering therapies will have some (modest) effects on TGs

Remember That the Treatment Benefit Emerges After 1.5 Years

Composite: CV death, nonfatal MI, nonfatal stroke



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

RRR = 26.5%

ARR = 3.6%

NNT = 28 (95% CI, 20–47)

***P* = 0.0000006**

Bhatt DL, et al. *N Engl J Med*. 2019;380(1):11-22.

Case #1: Ms. P

- 61-year-old woman s/p IWMI 9 months ago
- Smokes 1 PPD for 30 years, hypertension, on ARB, minimal exercise
- BP 126/78, BMI 31, HbA1c 6.3%
- At time of MI, was not on statin; LDLc 144 mg/dL, HDLc 39 mg/dL, TG 167 mg/dL, Tchol 217 mg/dL
- Started on atorvastatin 80 mg but stopped due to severe bilateral thigh pain after one month; subsequently tried and failed rosuvastatin 10 mg once a day and once a week and pravastatin 40 mg every other day
- Counseled on heart-healthy diet and exercise program and started a smoking cessation program
- Able to tolerate ezetimibe 10 mg/dL

Case #1: Ms. P (continued)

- Repeat LDLc on ezetimibe 10 mg/dL (was 120 mg/dL)
- Started on evolocumab 140 mg sq/wks
- Lost 8 lbs and stopped smoking; walking 5 times a week
- Repeat labs: LDLc 73 mg/dL, HDLc 43 mg/dL, TG 151 mg/dL, total cholesterol 146 mg/dL

- Next step ??

Meet Catherine

History

- 61-year-old female with a history of CABG x 4 in 2003, dyslipidemia, hypertension, type 2 diabetes, and obesity
- Presented in 2014 with abnormal coronary CT angiogram
- More recent left superficial femoral artery angioplasty and stent placement with good pedal pulse (7/2018)
- She is here for the results of her nuclear stress test on 12/29/18 (she was experiencing reoccurring angina with exertion)

Meet Catherine (continued)

Medications

- Olmesartan/Chlorthalidone 40/25 mg daily
- Amlodipine 10 mg at night
- Carvedilol CR 40 mg daily
- Rosuvastatin 20 mg daily
- Ezetimibe 10 mg daily
- Clopidogrel 75 mg daily
- Metformin 2000 mg daily
- Semaglutide 0.5 mg once weekly

Labs (mg/dL)

- Total Cholesterol 184
- HDL-C 50
- LDL-C 82
- TRG 227
- Non-HDL-C 134
- Lp(a) 118

Vitals

- BP 134/77 mm Hg
- HR 86 bpm
- BMI 37

Meet Catherine (continued)

- We properly document that she is taking rosuvastatin 20 mg daily and ezetimibe 10 mg daily
- Add evolocumab 140 mg subcutaneous every 14 days

Catherine's angina is improving, but we are still concerned about her triglyceride levels.

Meet Catherine (continued)

Catherine had an excellent response to the addition of icosapent ethyl 2 g BID.

Medications

- Olmesartan/Chlorthalidone 40/25 mg daily
- Amlodipine 10 mg at night
- Carvedilol CR 40 mg daily
- **Rosuvastatin 20 mg daily**
- **Ezetimibe 10 mg daily**
- **Icosapent ethyl 2 g BID**
- Clopidogrel 75 mg daily
- Metformin 2000 mg daily
- Semaglutide 0.5 mg once weekly

Labs (mg/dL)

- Total Cholesterol 125
- HDL-C 52
- LDL-C 51
- TRG 112
- Non-HDL-C 73
- Lp(a) 85

Vitals

- BP 128/76 mm Hg
- HR 76 bpm
- BMI 36

Closing Comments

Christie Ballantyne, MD