New Opportunities to Improve Management of Patients with or at High Risk of ASCVD Events

APRIL 11, 2019 | Philadelphia 201 Hotel | Philadelphia, PA

AGENDA

6:30 PM	**Registration and Buffet Dinner**
7:00	**Program Overview** *Deepak L. Bhatt, MD, MPH, Chair*
7:10	**Update on Determining Risk Status in ASCVD** *Sergio Fazio, MD, PhD*
7:25	**Discussion and Q&A** *Faculty and Participants*
7:30	**New Approaches to the Management of Patients at High Risk of CVD Events** *Michael Miller, MD*
7:45	**Discussion and Q&A** *Faculty and Participants*
7:50	**Managing Residual Risk Beyond LDL-C Lowering Therapy** *Deepak L. Bhatt, MD, MPH, Chair*
8:15	**Discussion and Q&A** *Faculty and Participants*
8:20	**Practical Considerations to Manage Residual Risk** *Sergio Fazio, MD, PhD*
8:35	**Discussion and Q&A** *Faculty and Participants*
8:40	**Case Simulations on Primary and Secondary Prevention of ASCVD Events** *All Faculty*
8:50	**Closing Comments** *Deepak L. Bhatt, MD, MPH, Chair*
9:00 PM	**Adjourn**

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

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

Update on Determining Risk Status in ASCVD

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Disclosures: Sergio Fazio, MD, PhD

- Consulting Fees: Amarin, Amgen, AstraZeneca, Esperion, Novartis

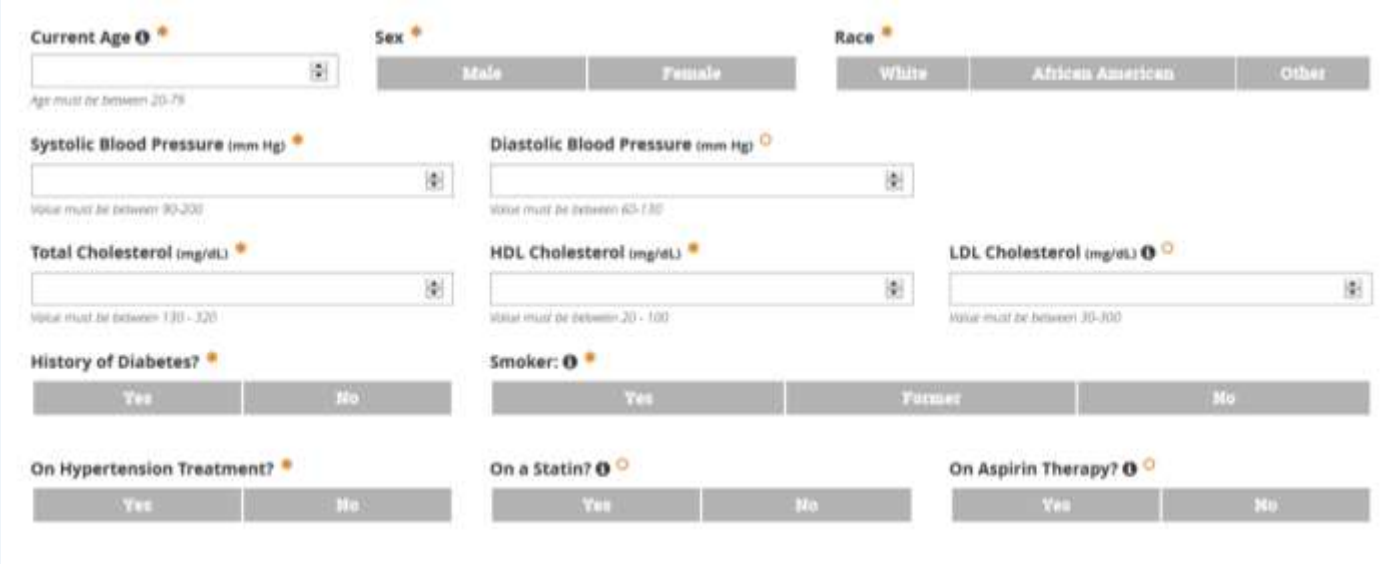
ACC Risk Calculator Plus to Assess Risk Category

tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate

1. Use the calculator to Assess Risk Category

<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% identifies statin eligibility, not a mandatory prescription for a statin



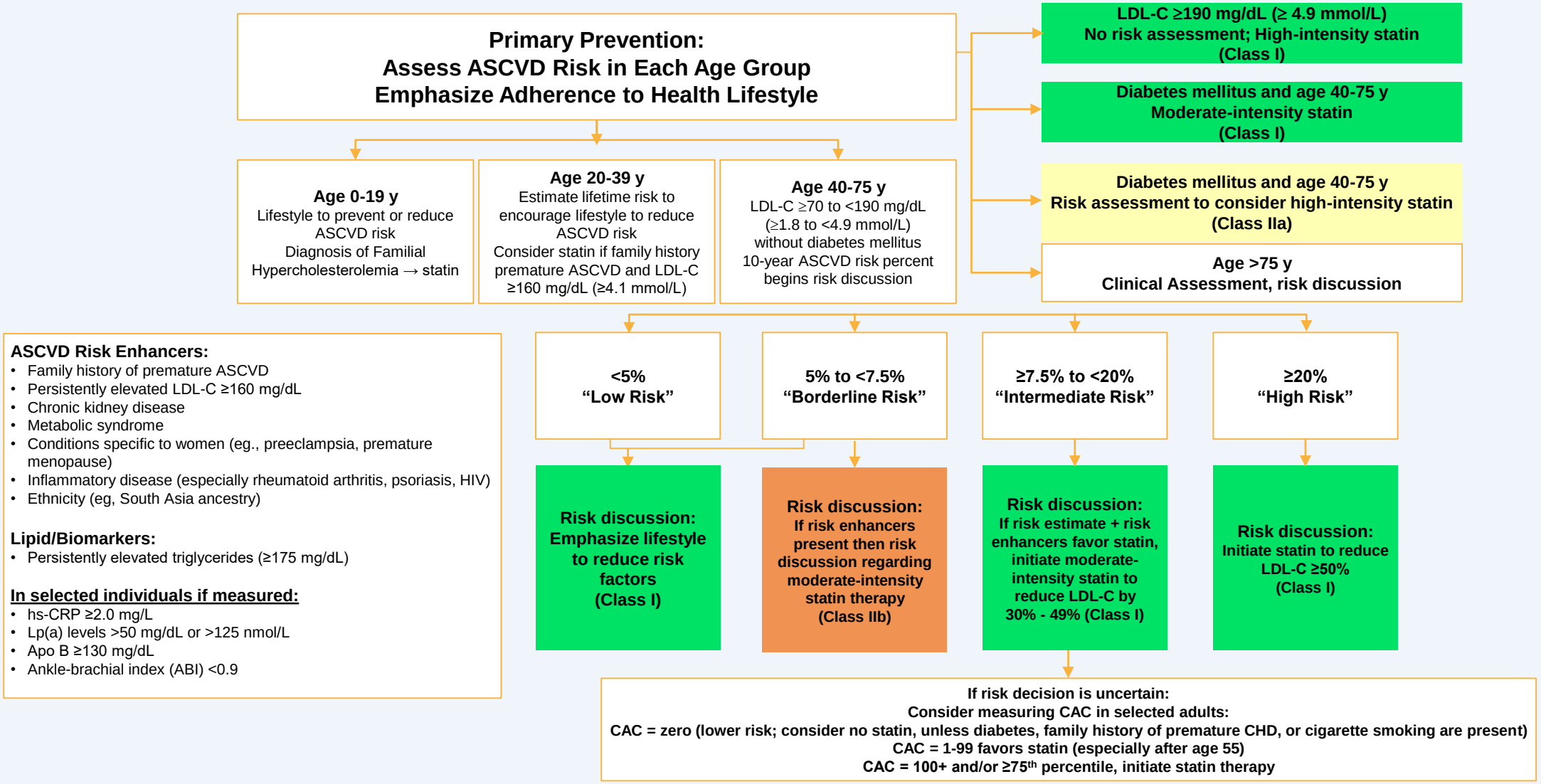
2. Then use the new ACC/AHA Cholesterol guideline algorithms to guide management

3. Also available: MESA 10-Year CHD Risk with Coronary Artery Calcification*

-iPhone and Android app

*mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Primary Prevention



Grundy SM et al. *Circulation*. 2018;Nov. 10 [Epub ahead of print]. Although high TG was noted as a CVD risk factor, treatment of HTG was covered only briefly and prescription omega-3 was not mentioned. (Published simultaneously with REDUCE-IT)

ASCVD Risk Stratification: From High to Extremely High

AACE Lipid Guidelines

Risk Category (10-year ASCVD risk)	
Very High (20-30%)	**Extreme[1] (>30%)**
ASCVD	ASCVD progressive despite LDL-C <70
DM ***OR*** CKD (3-4)[2] **+** other risk factor	ASCVD ***plus*** • DM • CKD ***OR*** • FH
FH[3]	Premature ASCVD

1. LDL-C goal <55 mg/dL.
2. Mild to moderately CKD, eGFR 15-60.
3. FH=Familial Hypercholesterolemia (heterozygous).

After Jellinger PS et al. *Endocrine Pract*. 2017;23:479-97.

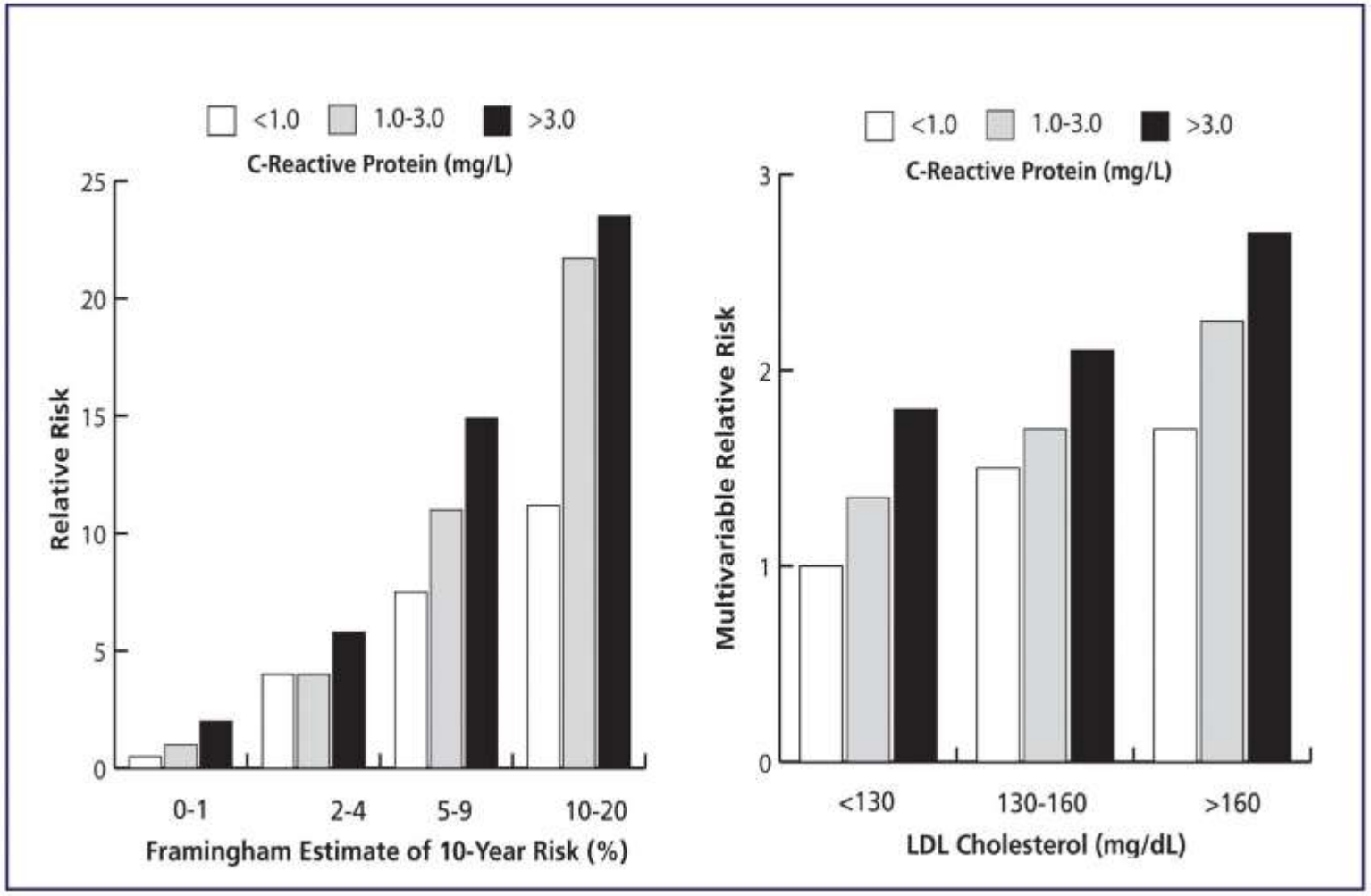
Robinson et al.

Risk Category (10-year ASCVD risk)		
High (20-30%)	**Very High (30-40%)**	**Extremely High[4] (>40%)**
ASCVD Event ***w/o*** MetSynd[5]	Prior ASCVD ***plus*** MetSynd	Severe ASCVD: • Multi-system ***OR*** • Recurrent (***plus*** MetSynd)
FH[3] ***w/o*** ASCVD		

4. Higher Risk = Lower NNT = More cost-effective.
5. Termed “poorly controlled cardiometabolic milieu”, similar to the conventional definition of the Metabolic Syndrome (abbr. “MetSynd”):
↑TG, ↓HDL-C, DM2, central obesity, ↑glucose/insulin, etc.

After Robinson JG, Watson KE. *Rev Cardiovasc Med*. 2018;19(S1):S1-S8.

Elevated hsCRP Levels Add to CVD Risk Predicted by Elevated LDL-C or by the Framingham Risk Score



hsCRP=High-sensitivity C-reactive protein. Ridker P et al. *Circulation*. 2003;108:2292-7.

Classification of Fasting TG Levels (2011 AHA/2014 NLA)

Fasting Triglycerides (mg/dL)	
<100	Optimal
<150	Normal
150–199	Borderline high
200–499	High
≥500	Very high

Jacobson TA et al. *J Clin Lipi*dol. 2014;8:473-88.
AHA Scientific Statement. Miller M et al. *Circulation*. 2011;123:2292-333.

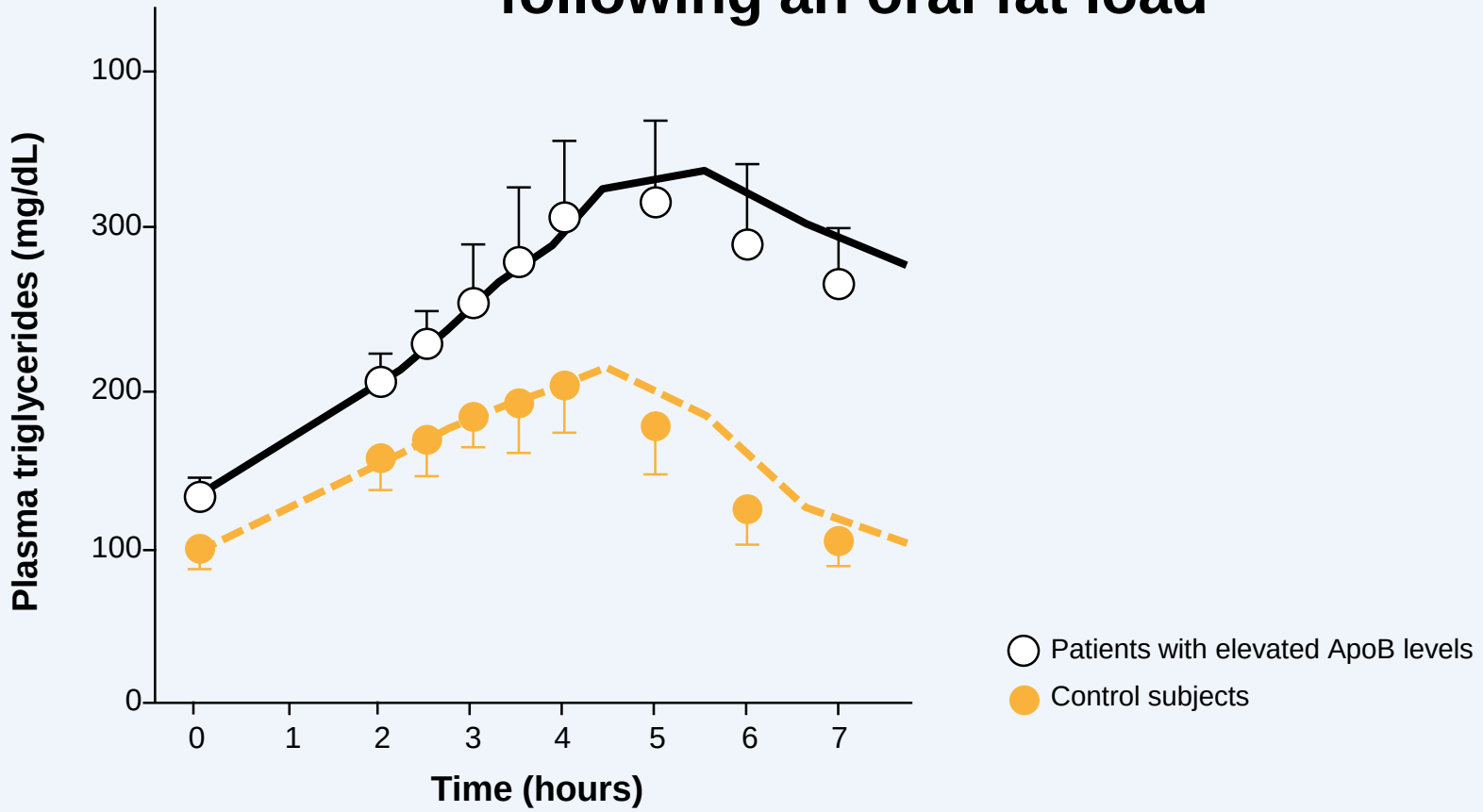
Fasting and Non-fasting TG and Non-HDL-C

- Fasting TG is used to categorize TG elevation
- Studies show that non-fasting TG are a superior predictor of incident CVD vs fasting TG
- Non-fasting TG approximate fasting levels after a low-fat meal (eg, <15g fat), but are **at least 50% higher** after a high-fat meal (eg, >50g fat)
- When non-fasting TG is ≥200 mg/dL, a fasting lipid panel is recommended within 4 weeks
- Non-HDL-C is accurate fasting or nonfasting, and is the best predictor of CVD risk in patients w/ HTG*

*NLA Recommendations. Jacobson TA et al. *J Clin Lipi*dol. 2014;8:473-88.
AHA Scientific Statement. Miller M et al. *Circulation*. 2011;123:2292-333.

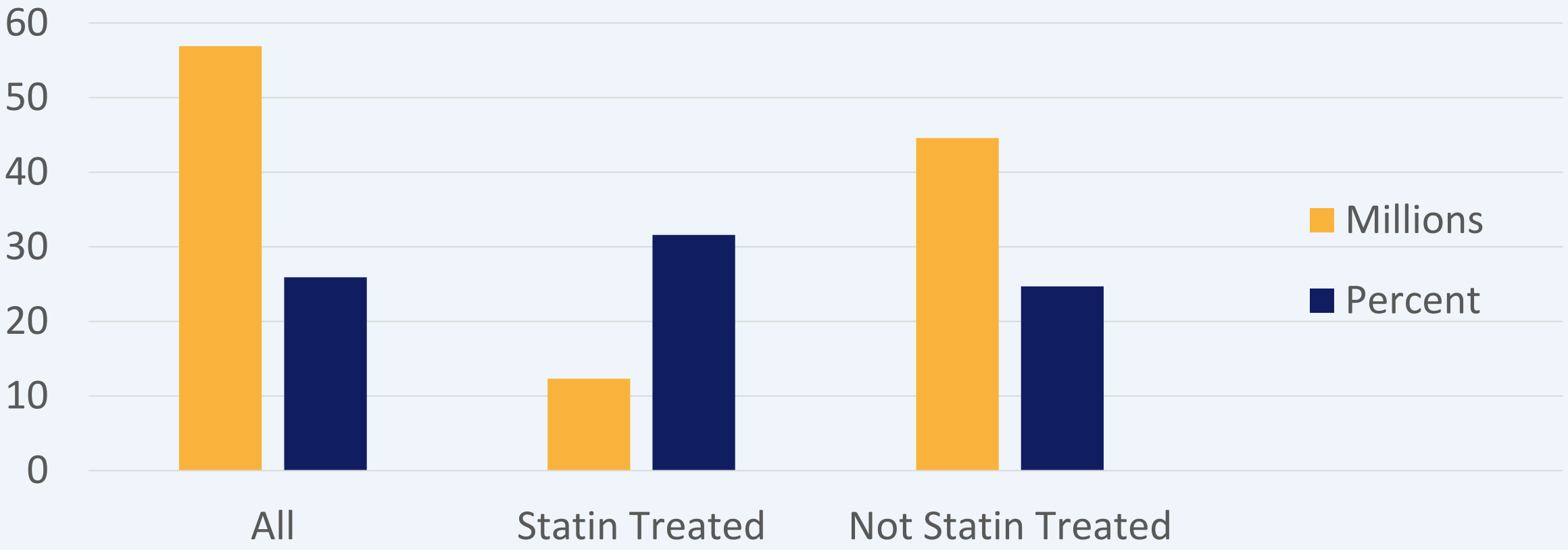
Fasting Levels of Triglycerides Do Not Reflect True Exposure

Serial changes and plasma triglycerides following an oral fat load



Genest J et al. *Arteriosclerosis*. 1986;6:297-304.

Prevalence of Hypertriglyceridemia (Triglycerides ≥150 mg/dL) in the U.S.



9593 US adults aged >20 years (219.9 million projected) in the US National Health and Nutrition Examination Surveys 2007-2014 were studied.

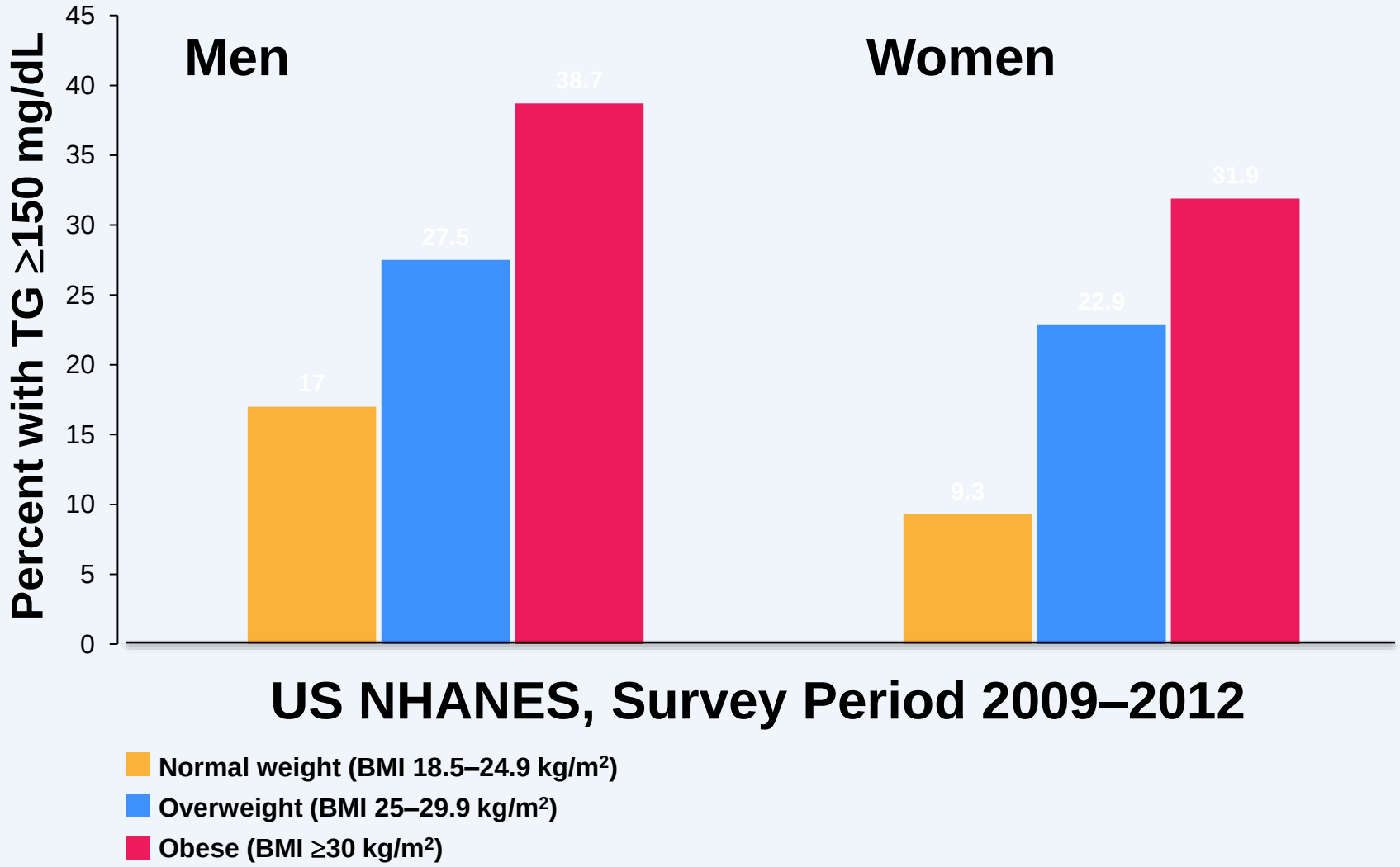
Fan W et al. *J Clin Lipidol*. *J Clin Lipidol*. 2019;13:100-108.

Most Forms of Hypertriglyceridemia Are Acquired

Cause	Clinically useful details
Dietary factors	↑Saturated fat and ↑glycemic index
	↑Simple sugars and ↓dietary fiber Alcohol, Sedentary lifestyle
Adiposopathy	↑Visceral adiposity
Diabetes mellitus	With poorly controlled glucose homeostasis
Hypothyroidism	If not adequately controlled
Nephrotic syndrome	
Medications	Antiretrovirals; Some phenothiazines and 2nd-generation antipsychotics; Nonselective beta-blockers; Thiazide diuretics; Oral estrogen; Tamoxifen; Glucocorticoids; Isotretinoin
Systemic Diseases	SLE, RA, Sjögren's syndrome

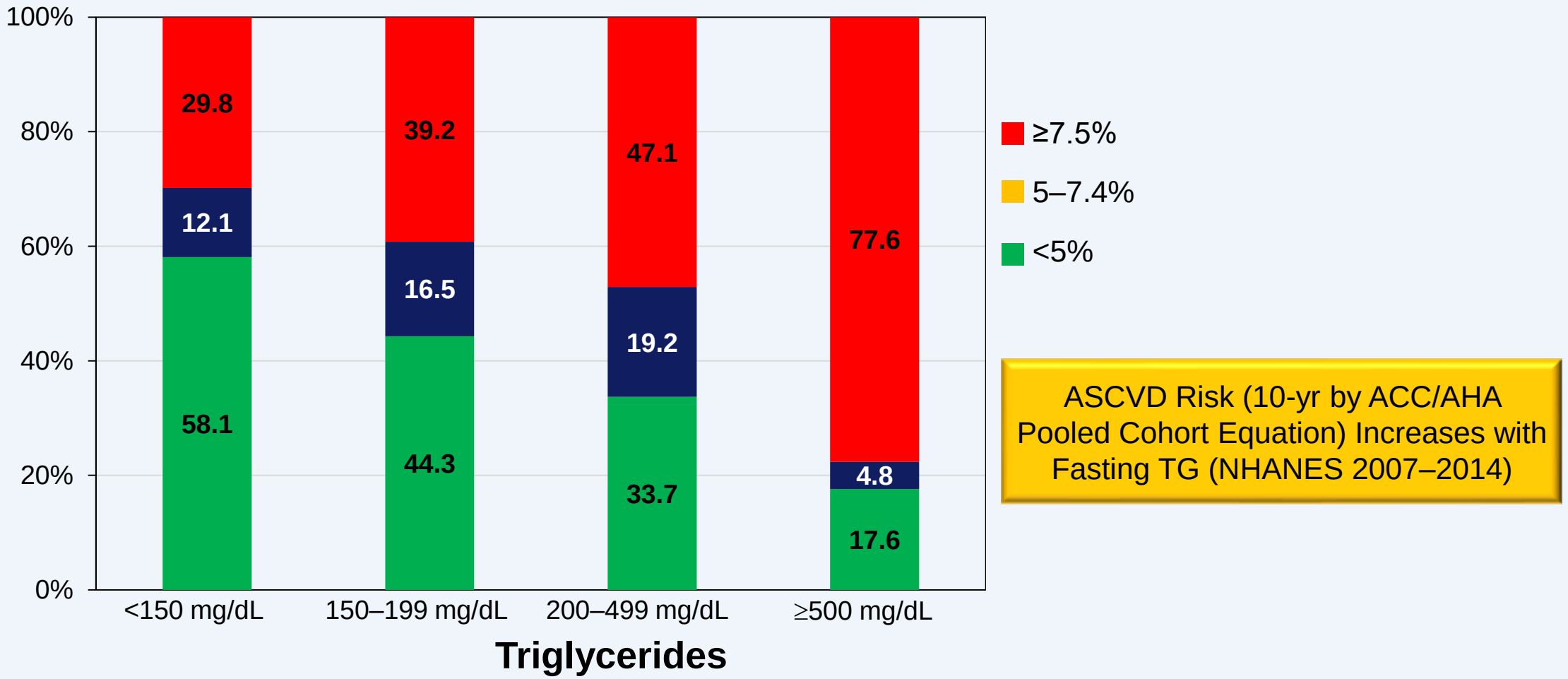
Bays HE. In: Kwiterovich PO Jr, ed. *The Johns Hopkins Textbook of Dyslipidemia*. 1st ed. Lippincott Williams & Wilkins;2010:245-57.

Obesity As Strong Predictor of Fasting TG ≥150 mg/dL



BMI=body mass index. Carroll MD et al. NCHS Data Brief, No 198. National Center for Health Statistics. 2015.

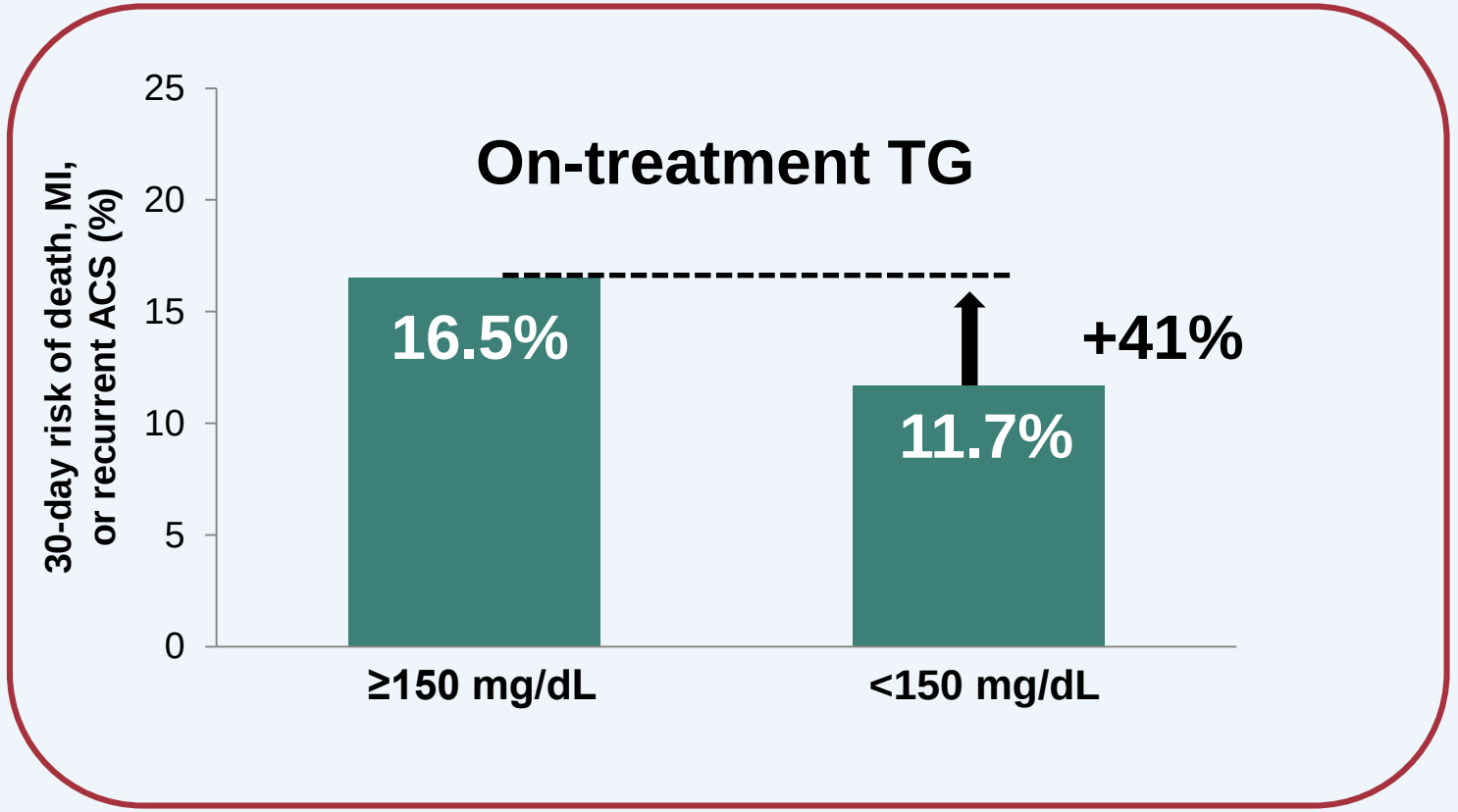
Elevated CVD Risk in Subjects with Hypertriglyceridemia



P<0.0001 (weighted) for comparing proportion of ACC/AHA Pooled Cohort 10-year ASCVD risk score categories among triglyceride levels.

Fan W et al. *J Clin Lipidol*. 2019;13:100-108.

HTG Predicts Residual ASCVD Risk in Subjects with LDL-C at Goal on Statin Monotherapy



*Death, myocardial infarction, or recurrent acute coronary syndrome, PROVE-IT-TIMI 22

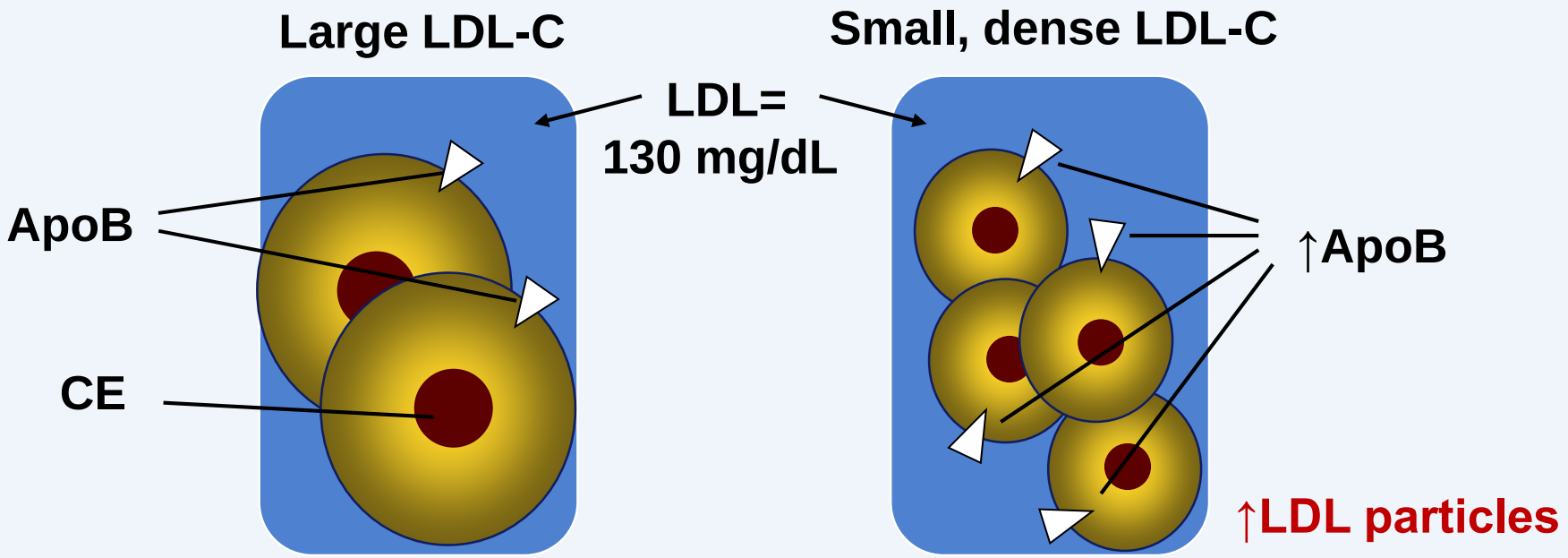
Miller M et al. *J Am Coll Cardiol*. 2008;51:724-30.

Diagnosing and Treating Secondary Causes of HTG

- Take a Hx of diet (calories, fat, sugar, alcohol, body weight, weight changes) and physical activity (frequency, type, intensity)
- Measure BMI, waist, TSH, fasting glucose, A1c, urinary protein
- Recommend low-calorie, low-sugar, low-to-no alcohol, low-fat, high-fiber diet
- Recommend appropriate physical activity plan
- Treat underlying diseases causing HTG (eg, ↑A1c, ↓thyroid function)
- Consider changing TG-raising medications
- Use TG-lowering medications

Bays HE. In: Kwiterovich PO Jr, ed. *The Johns Hopkins Textbook of Dyslipidemia*. 1st ed. Lippincott Williams & Wilkins;2010:245-57.

LDL-C Measurement May Underestimate CVD Risk In HTG Subjects



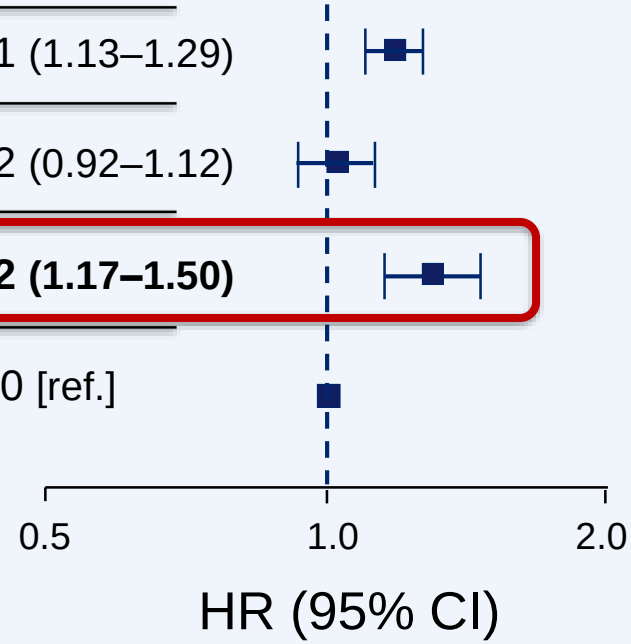
Fasting Lipid Panel:		Fasting Lipid Panel:		
TC	198 mg/dL	TC	210 mg/dL	
LDL-C	130 mg/dL ⟷	LDL-C	130 mg/dL	
TG	90 mg/dL	TG	250 mg/dL	
HDL-C	50 mg/dL	HDL-C	30 mg/dL	↓HDL-C
Non-HDL-C	148 mg/dL	Non-HDL-C	180 mg/dL	↑Non-HDL-C

Otvos JD et al. *Am J Cardiol*. 2002;90:22i-29i.

Non-HDL-C: A Better ASCVD Risk Predictor than LDL-C

N=62,154

Target Level		Major CV Events (n)	Subjects (n)	HR (95% CI)
LDL-C (mg/dL)	Non-HDL-C (mg/dL)			
≥100	≥130	1877	10,419	1.21 (1.13–1.29)
≥100	<130	467	2873	1.02 (0.92–1.12)
<100	**≥130**	**283**	**1435**	**1.32 (1.17–1.50)**
<100	<130	2760	23,426	1.00 [ref.]



Meta-analysis data at baseline and at 1-year follow-up; 8 randomized controlled statin trials published 1994-2008.
Boekholdt M et al. *JAMA*. 2012;307:1302-9.

Conclusions

- CVD risk stratification is based on the layering of evidence from medical and family history, physical examination, biomarkers, genetic testing, and cardiovascular imaging
- Elevated TG are linked to formation of small dense LDL
- Elevated TG levels are associated with elevated hsCRP levels
- Moderate hypertriglyceridemia increases CVD risk in subjects with statin-controlled LDL-C
- Management of elevated TG may reduce CVD risk

New Approaches to Management of Patients at High-Risk of CVD Events

Michael Miller, MD

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University of Maryland School of Medicine
Baltimore, MD

Disclosures

- *Consulting Fee:* Amarin (Steering Committee: REDUCE-IT trial)
- *Contracted Research (paid to institution):* Akcea, Dalgene, NIH, Kowa, Novartis, Novo-Nordisk, Regeneron

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Secondary Prevention

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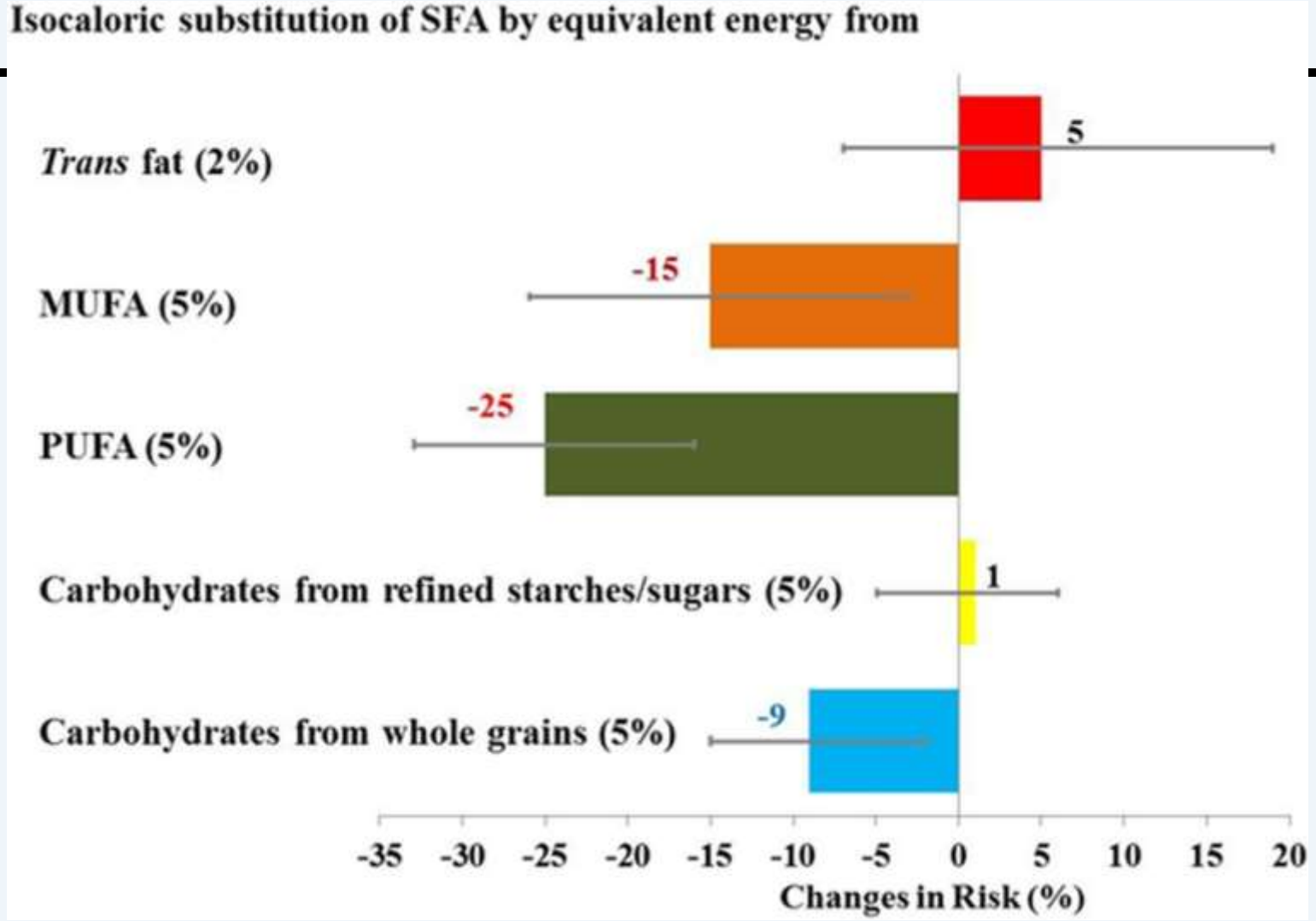


Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association
Volume: 136, Issue: 3, Pages: e1-e23, DOI: (10.1161/CIR.0000000000000510)

CENTRAL ILLUSTRATION: Evidence for Cardiovascular Health Impact of Foods Reviewed

Summary of heart-harmful and heart-healthy foods/diets

Evidence of harm; limit or avoid

Coconut oil and **palm oil** are high in saturated fatty acids and raise cholesterol

Eggs have a serum cholesterol-raising effect

Juicing of fruits/vegetables with pulp removal increases caloric concentration*

Southern diets (added fats and oils, fried foods, eggs, organ and processed meats, sugar-sweetened drinks)

Inconclusive evidence; for harm or benefit

Sunflower oil and other liquid vegetable oils

High-dose antioxidant **supplements**

Juicing of fruits/vegetables without pulp removal*

Gluten-containing foods (for people without gluten-related disease)

Evidence of benefit; recommended

Extra-virgin olive oil reduces some CVD outcomes when consumed in moderate quantities

Blueberries and **strawberries** (>3 servings/week) induce protective antioxidants

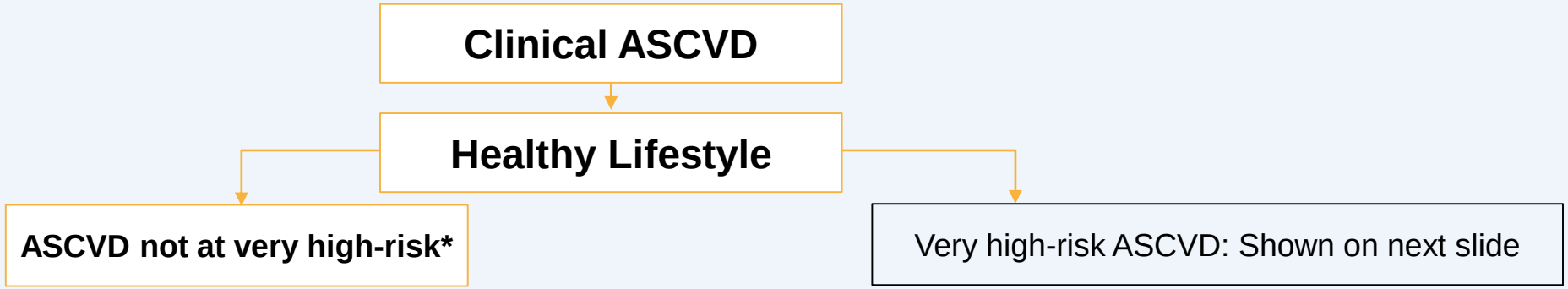
30 g serving of **nuts**/day. Portion control is necessary to avoid weight gain.†

Green leafy vegetables have significant cardio-protective properties when consumed daily

Plant-based proteins are significantly more heart-healthy compared to animal proteins

Freeman, A.M. et al. J Am Coll Cardiol. 2017;69(9):1172–87.

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Secondary Prevention



*ACS, hx of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin.

- Class I (Strong). Benefit >>> Risk.
- Class IIa (Moderate). Benefit >> Risk.
- Class IIb (Weak). Benefit ≥ Risk.

Grundy SM et al. *Circulation*. 2018;Nov. 10 [Epub ahead of print].

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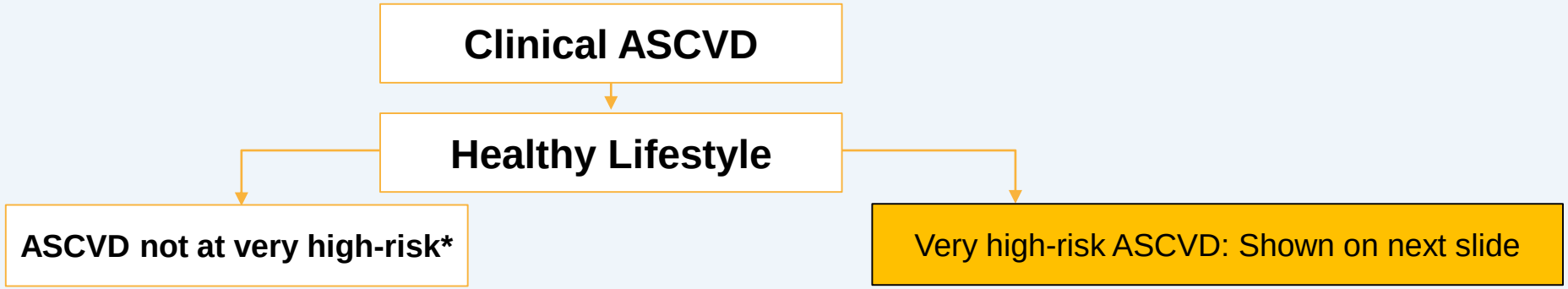

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Very High Risk of Future CVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation (S4.1-39))
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 (eGFR 15-59 mL/min/1.73 m^2) (S4.1-15, S4.1-17)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

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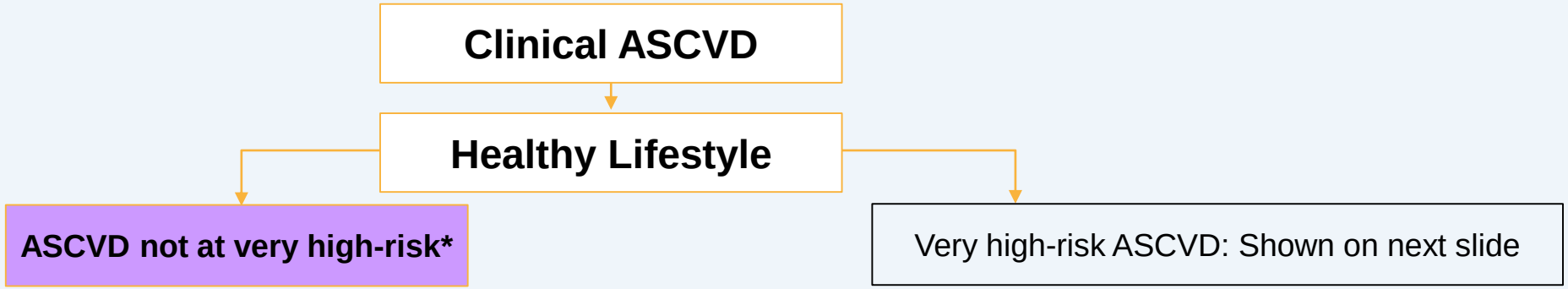

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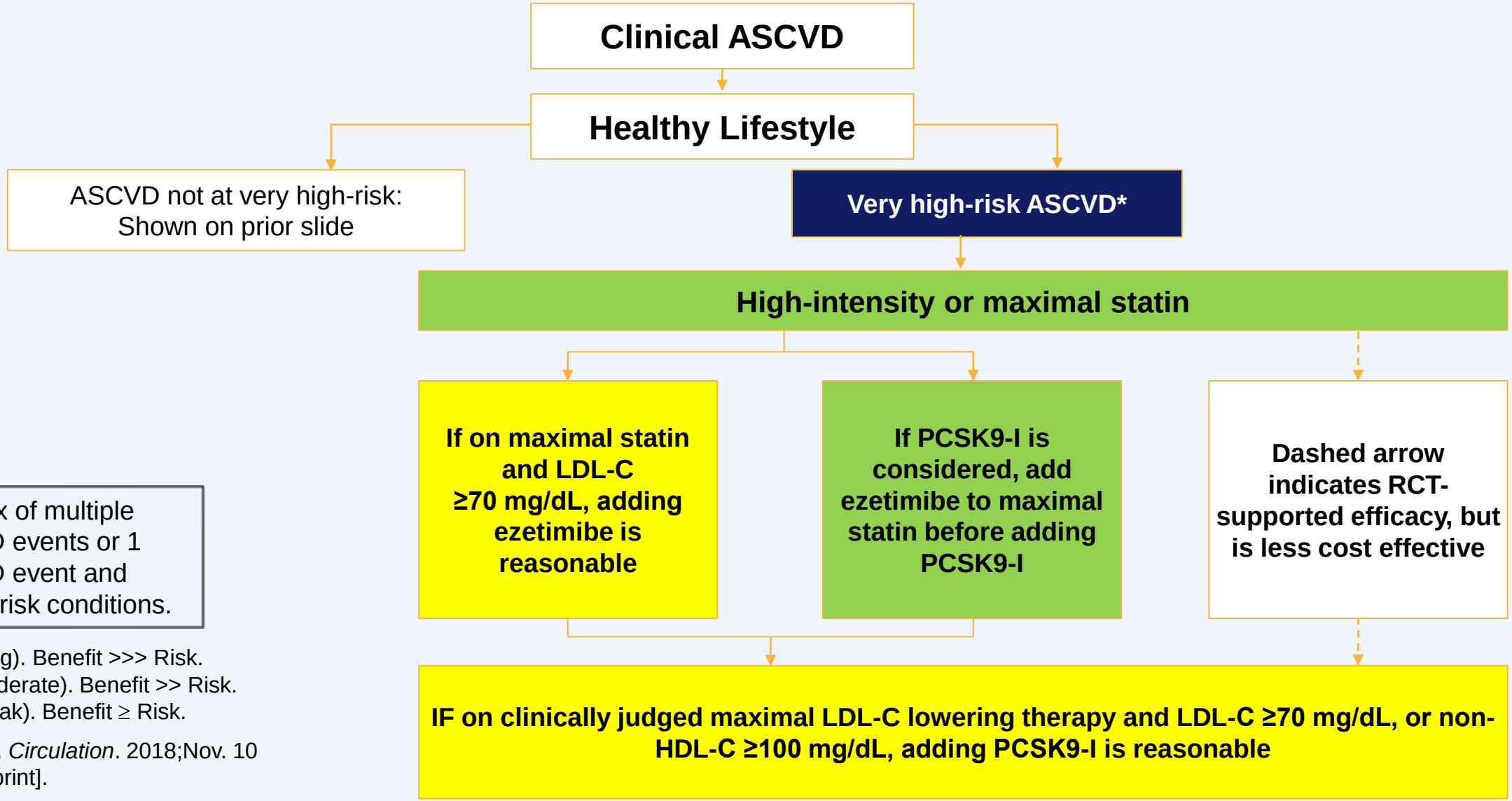

*Includes a hx of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

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ACC/AHA Cholesterol Guidelines: Intensity of Statin Therapy

High-, Moderate-, and Low-intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-intensity Statin Therapy	Moderate-intensity Statin Therapy	Low-intensity Statin Therapy
Daily dose lowers LDL-C on average, by approximately ≥50%	Daily dose lowers LDL-C on average, by approximately 30% to <50%	Daily dose lowers LDL-C on average, by <30%
Atorvastatin (40†)-80 mg **Rosuvastatin 20 (40) mg**	**Atorvastatin 10 (20) mg** **Rosuvastatin (5) 10 mg** **Simvastatin 20-40 mg‡** **Pravastatin 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*

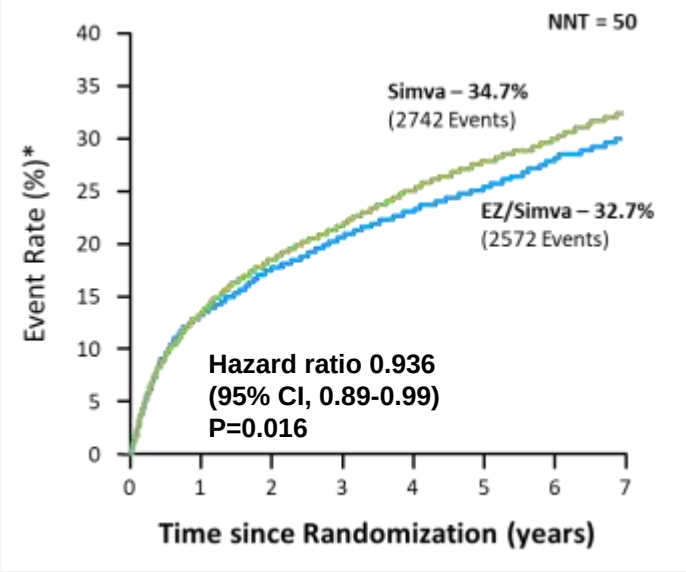
*Individual responses to statin therapy varied in the randomized controlled trials (RCTs) and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.

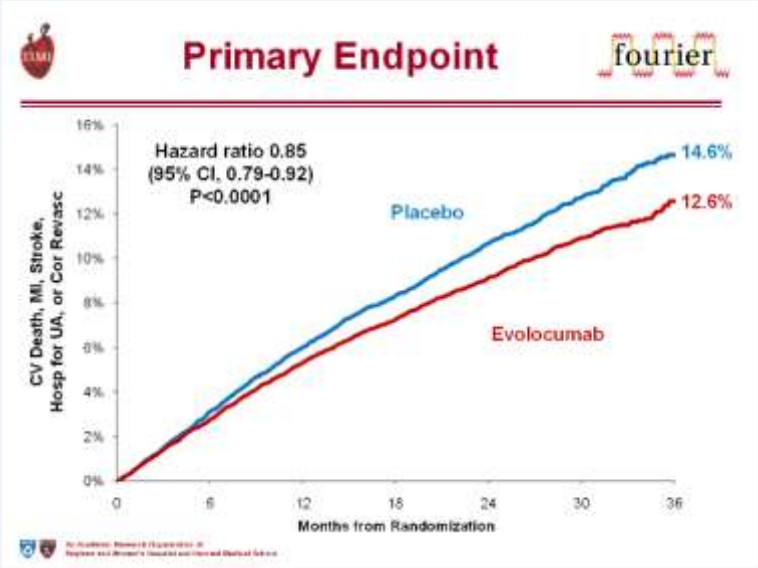
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).

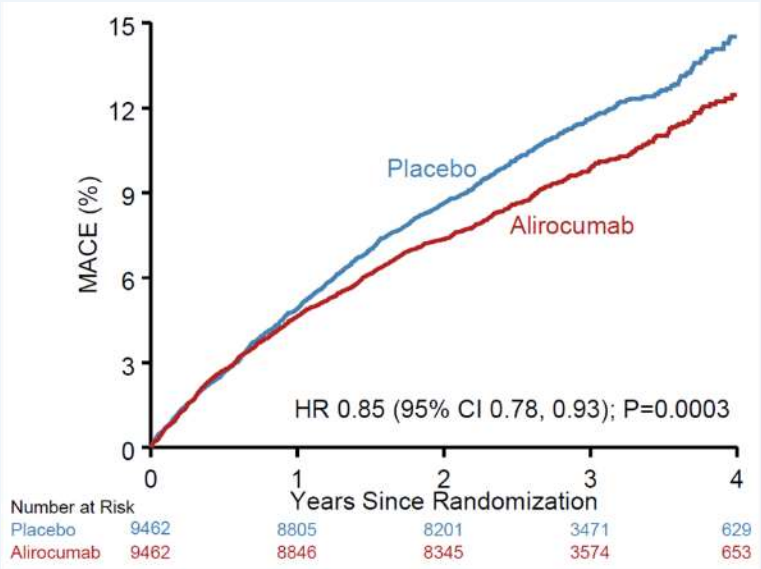
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the US Food and Drug Administration due to the increased risk of myopathy, including rhabdomyolysis.

Stone NJ et al. *J Am Coll Cardiol.* 2014;63(25 Pt B):2889-934.

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







IMPROVE-IT[1] **FOURIER[2]** **ODYSSEY Outcomes[3]**

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

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

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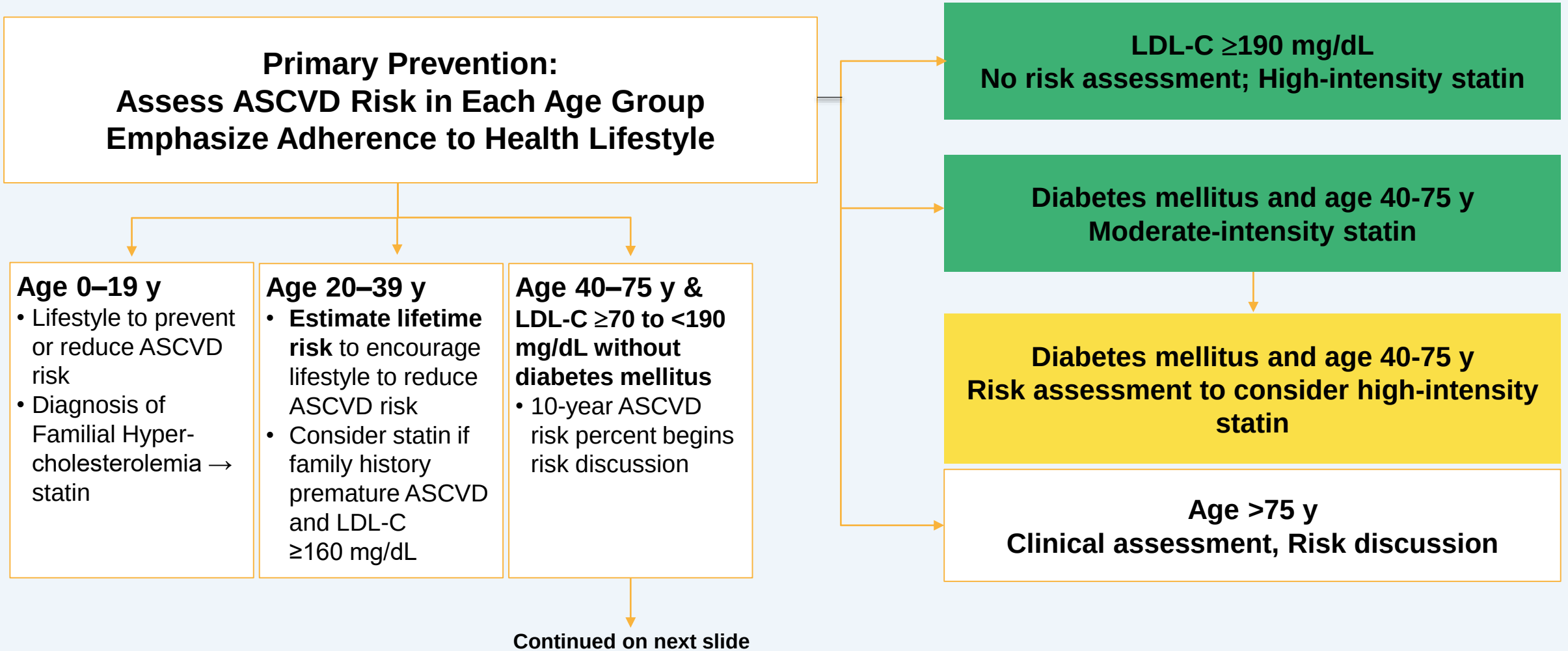

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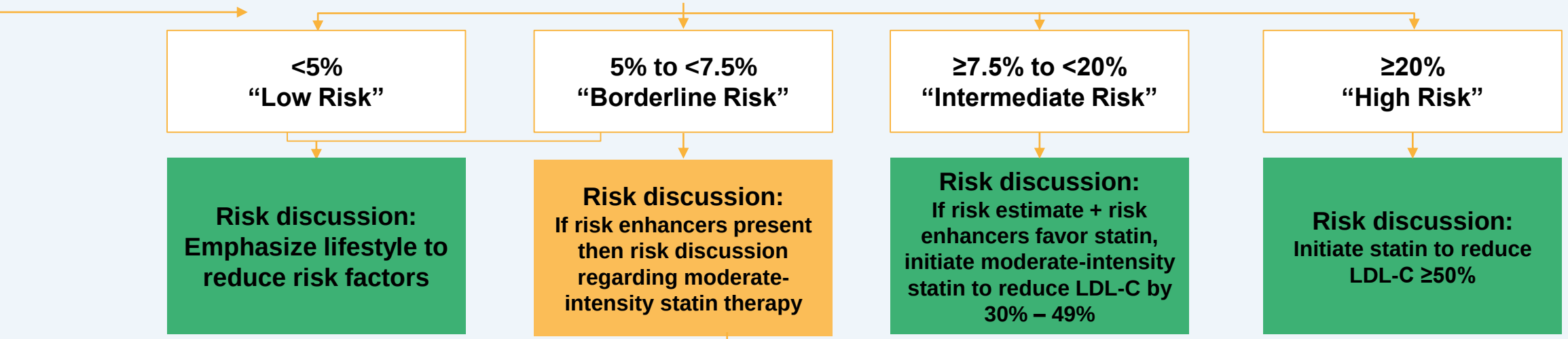

If risk decision is uncertain: Consider measuring CAC in selected adults:

- CAC = zero (lower risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
- CAC = 1–99 favors statin (especially after age 55)
- CAC = 100+ and/or ≥75th percentile, initiate statin therapy

ASCVD Risk Enhancers:

- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (eg, preeclampsia, premature menopause)
- Inflammatory disease (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (eg, South Asia ancestry)

Lipid/Biomarkers:

- Persistently elevated triglycerides (≥175 mg/dL)

In selected individuals if measured:

- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 nmol/L
- Apo B ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9

Class I (Strong). Benefit >>> Risk.
Class IIa (Moderate). Benefit >> Risk.
Class IIb (Weak). Benefit ≥ Risk.

Grundy SM et al. *Circulation*. 2018;Nov. 10 [Epub ahead of print]. Although high TG was noted as a CVD risk factor, treatment of HTG was covered only briefly and prescription omega-3 was not mentioned. (Published simultaneously with REDUCE-IT.)

Hypertriglyceridemia

Recommendations for Hypertriglyceridemia		
COR	**LOE**	**Recommendations**
I	**B-NR**	**In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL [1.9 to 5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides.**
IIa	**B-R**	**In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy (see Section 4.4.2.).**

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology Foundation/ American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;Nov 8:[Epub ahead of print]

Hypertriglyceridemia

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2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology Foundation/ American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;Nov 8:[Epub ahead of print]

AHA Scientific Statement: *Secondary Causes of HTG*

- Alcohol
- Hypothyroidism
- Diabetes
- Liver disease
- Nephrotic syndrome
- Pregnancy
- Lipodystrophy

Medications

- Estrogens
- Beta blockers
- Corticosteroids
- Retinoic Acid
- Protease inhibitors
- Antipsychotic meds

UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE

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

Hypertriglyceridemia

Recommendations for Hypertriglyceridemia		
COR	**LOE**	**Recommendations**
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2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology Foundation/ American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;Nov 8:[Epub ahead of print]

Managing Residual Risk Beyond LDL-C Lowering Therapy

Deepak L. Bhatt, MD, MPH

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

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

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

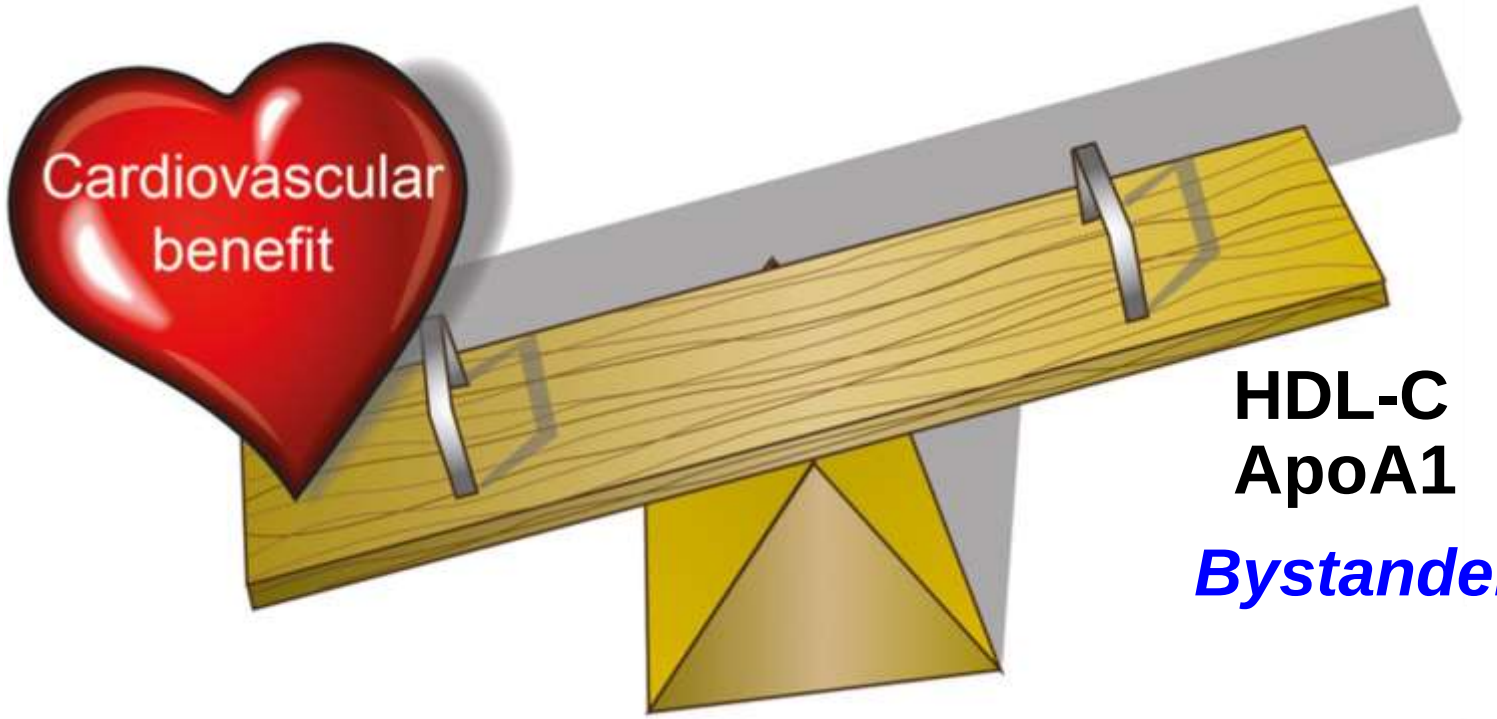
Disclosures

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

This presentation includes off-label and/or investigational uses of drugs.

REDUCE-IT was sponsored by Amarin Pharma, Inc.

Triglycerides a Causal Risk Factor?



HDL-C
ApoA1

Bystanders?

Triglyceride-rich lipoproteins
ApoC3, ApoA5, AngPTL4

Causal risk factors?

European Heart Journal

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

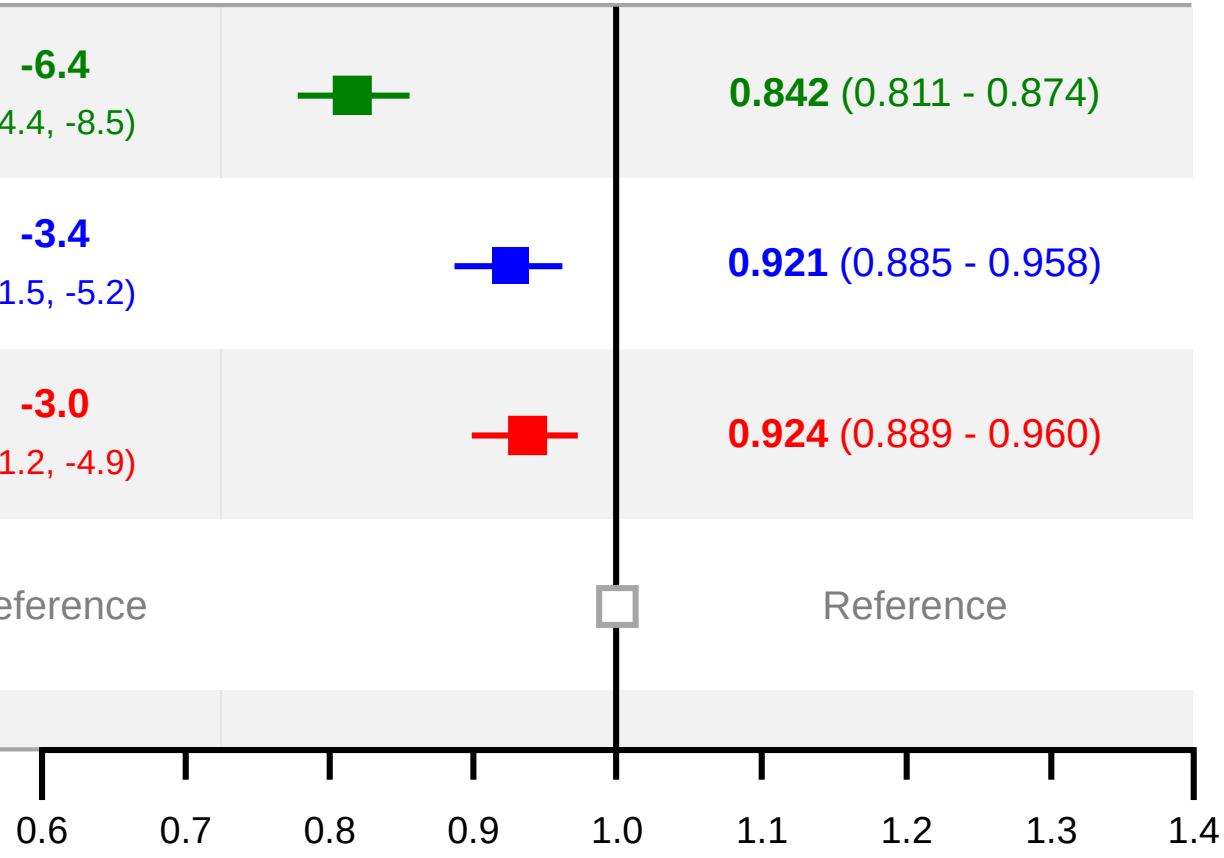
A naturally randomized trial evaluating the potential clinical benefit of triglyceride lowering therapies on the risk of coronary heart disease

Brian A. Ference MD, MPhil, MSc, John J. P. Kastelein MD, PhD, Kausik K. Ray MD, MPhil, Henry N. Ginsberg MD, M. John Chapman PhD, DSc, Chris J. Packard DSc, Ulrich Laufs MD, PhD, Adam S. Butterworth PhD, Emanuele Di Angelantonio, MD, John Danesh FRCP, DPhil, Stephen J. Nicholls MBBS, PhD, Deepak L. Bhatt, MD, MPH, Marc S. Sabatine MD, MPH, and Alberico L. Catapano PhD

UNIVERSITY OF CAMBRIDGE | Centre for Naturally Randomized Trials

Combined Effect of LPL and LDLR Scores on Lipids & CHD: 2 x 2 factorial analysis

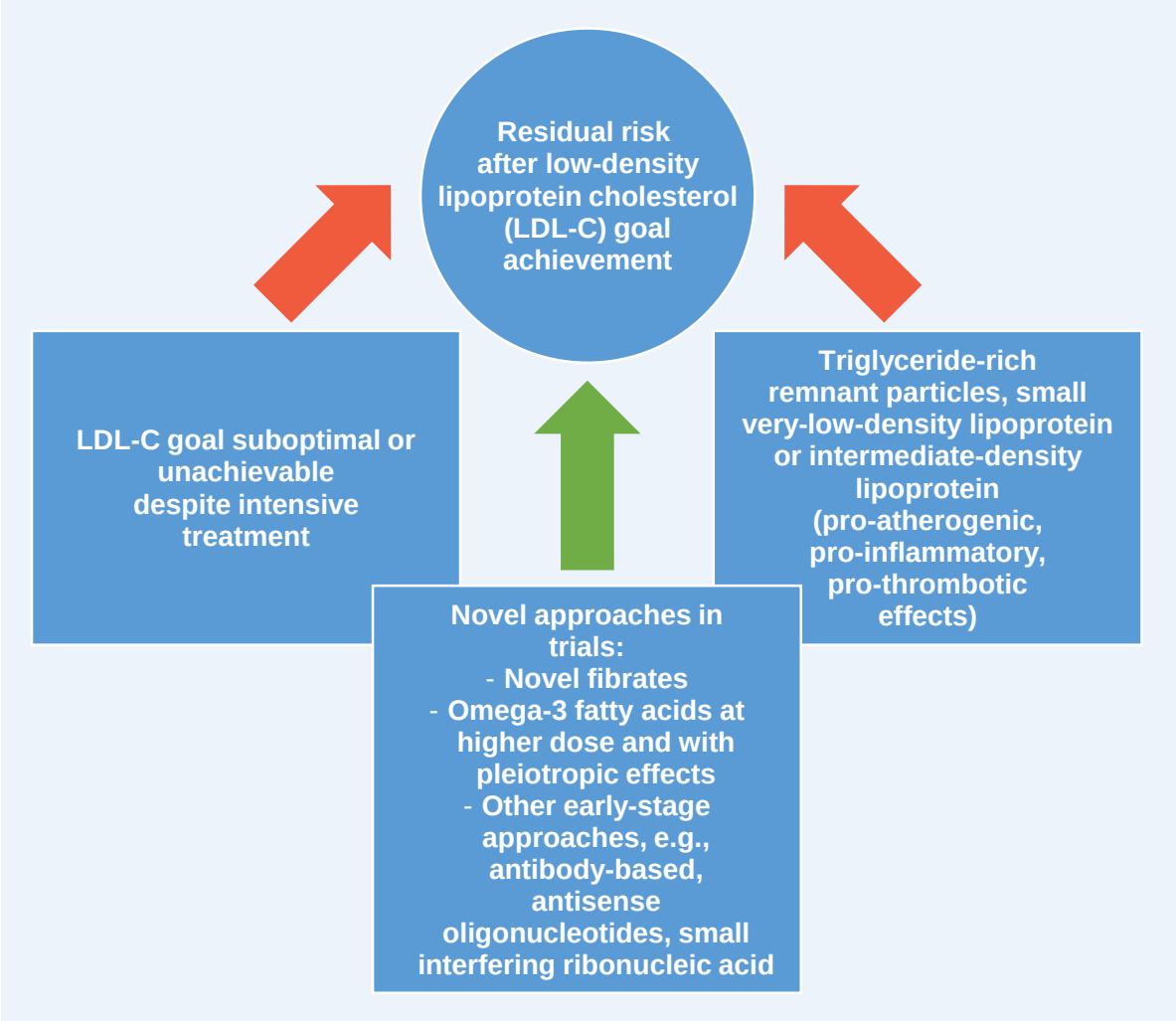
2x2 Group	Δ Triglycerides, mg/dL (95% CI)	Δ LDL-C, mg/dL (95% CI)	Δ apoB, mg/dL (95% CI)	OR_{CHD} (95% CI)
Both scores > median N = 104,694	**-24.3** (-16.2, -32.4)	**-4.9** (-2.1, -7.7)	**-6.4** (-4.4, -8.5)	**0.842** (0.811 - 0.874)
***LDLR* score > median** N = 112,018	**-3.8** (-15.1, -7.5)	**-4.8** (-2.0, -7.6)	**-3.4** (-1.5, -5.2)	**0.921** (0.885 - 0.958)
***LPL* score > median** N = 122,599	**-20.1** (-13.3, -28.8)	**-0.1** (-0.5, 0.3)	**-3.0** (-1.2, -4.9)	**0.924** (0.889 - 0.960)
Both scores ≤ median N = 131,167	Reference	Reference	Reference	Reference



apoB=apolipoprotein B; CHD=coronary heart disease; LDL-C=low-density lipoprotein cholesterol; LDLR=low-density lipoprotein receptor; LPL=lipoprotein lipase; OR_{CHD}=odds ratio coronary heart disease.

Adapted from Ference BA, Kastelein JJP, Ray KK, et al. A naturally randomized trial evaluating the potential clinical benefit of triglyceride lowering therapies on the risk of coronary heart disease. *JAMA*. 2019.

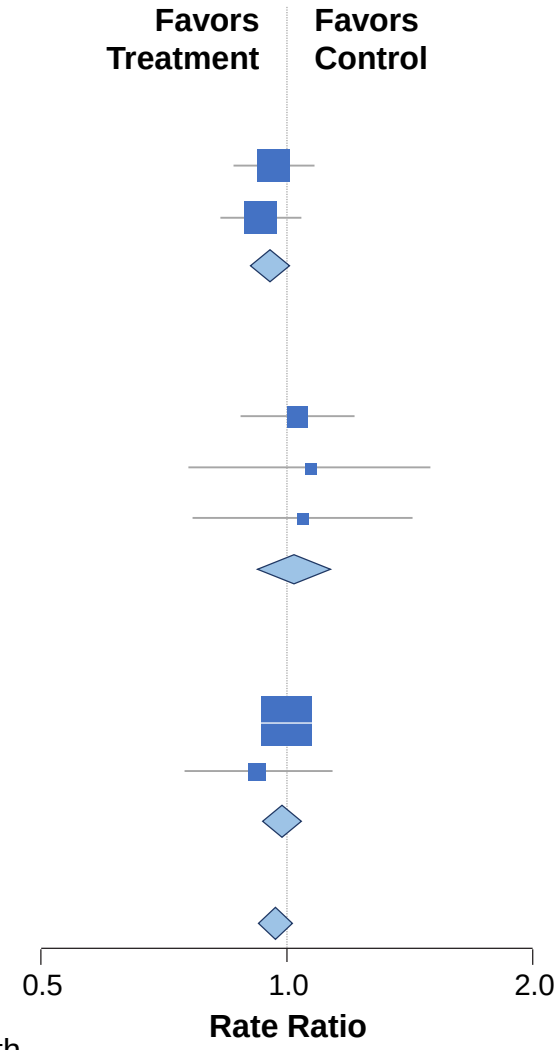
Promising Therapies for Hypertriglyceridemia



Adapted with permission* from Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol*. 2018;72:330-343. [*https://creativecommons.org/licenses.org/by-nc/4.0/]

Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

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



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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*

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

Jane Armitage and Louise Bowman

on behalf of the ASCEND Study Collaborative Group

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

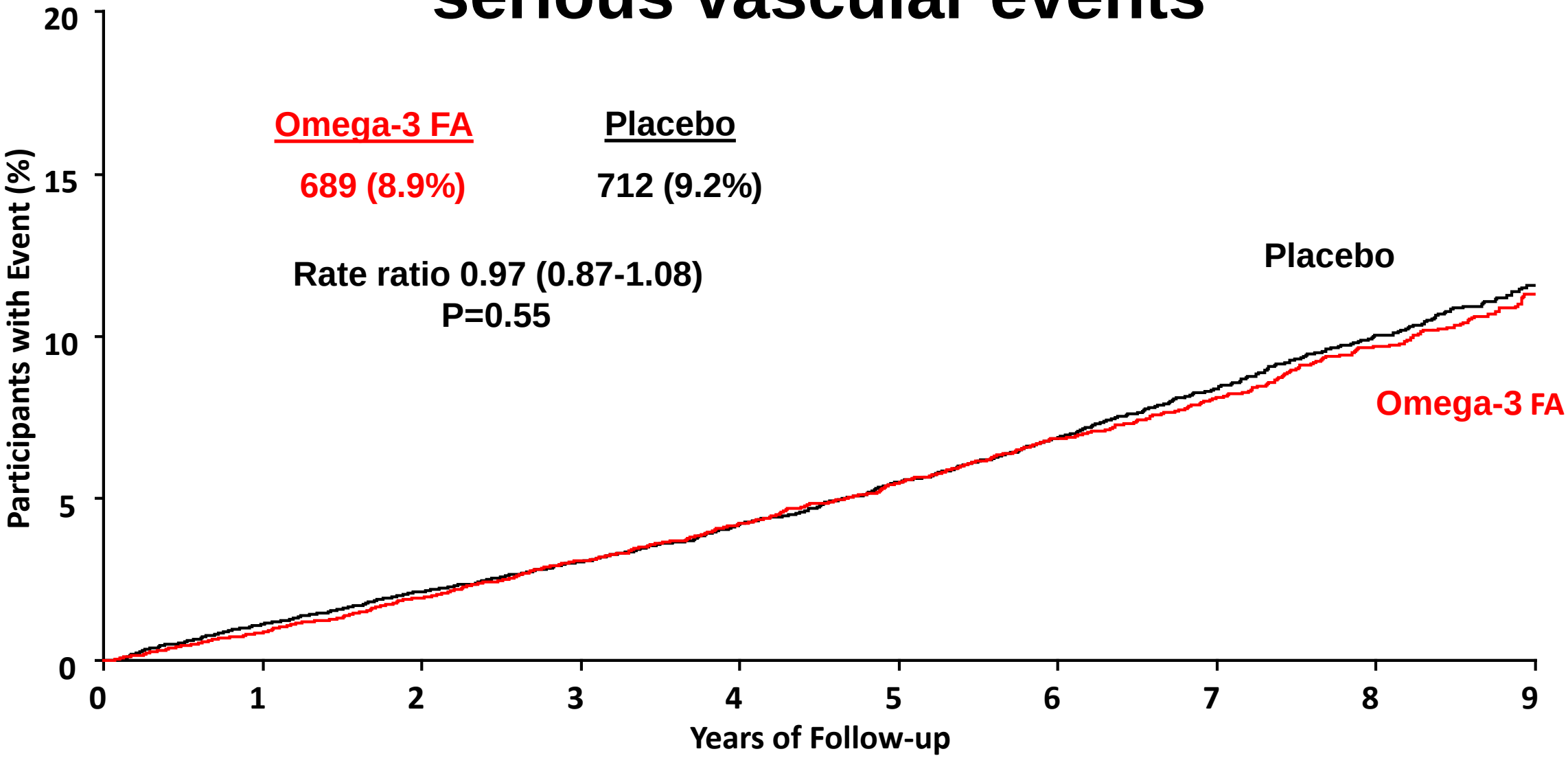
ASCEND trial design

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

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

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

Effect of omega-3 FA supplements on serious vascular events



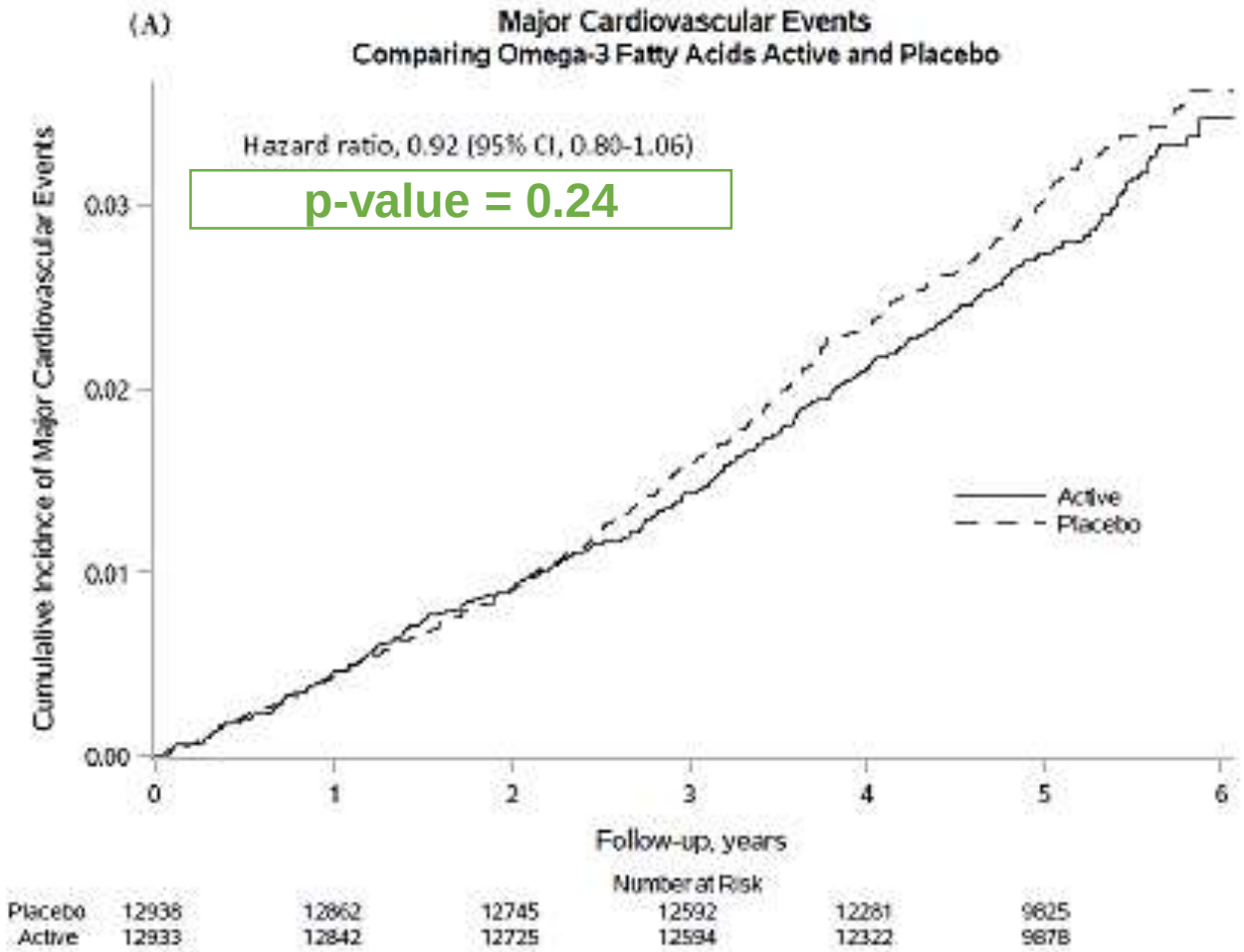
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

JoAnn E. Manson, M.D., Dr.P.H., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., Sc.D., William Christen, Sc.D., Shari S. Bassuk, Sc.D., Samia Mora, M.D., M.H.S., Heike Gibson, Ph.D., Christine M. Albert, M.D., M.P.H., David Gordon, M.A.T., Trisha Copeland, M.S., R.D., Denise D'Agostino, B.S., Georgina Friedenberg, M.P.H., Claire Ridge, M.P.H., Vadim Bubes, Ph.D., Edward L. Giovannucci, M.D., Sc.D., Walter C. Willett, M.D., Dr.P.H., and Julie E. Buring, Sc.D., for the VITAL Research Group*

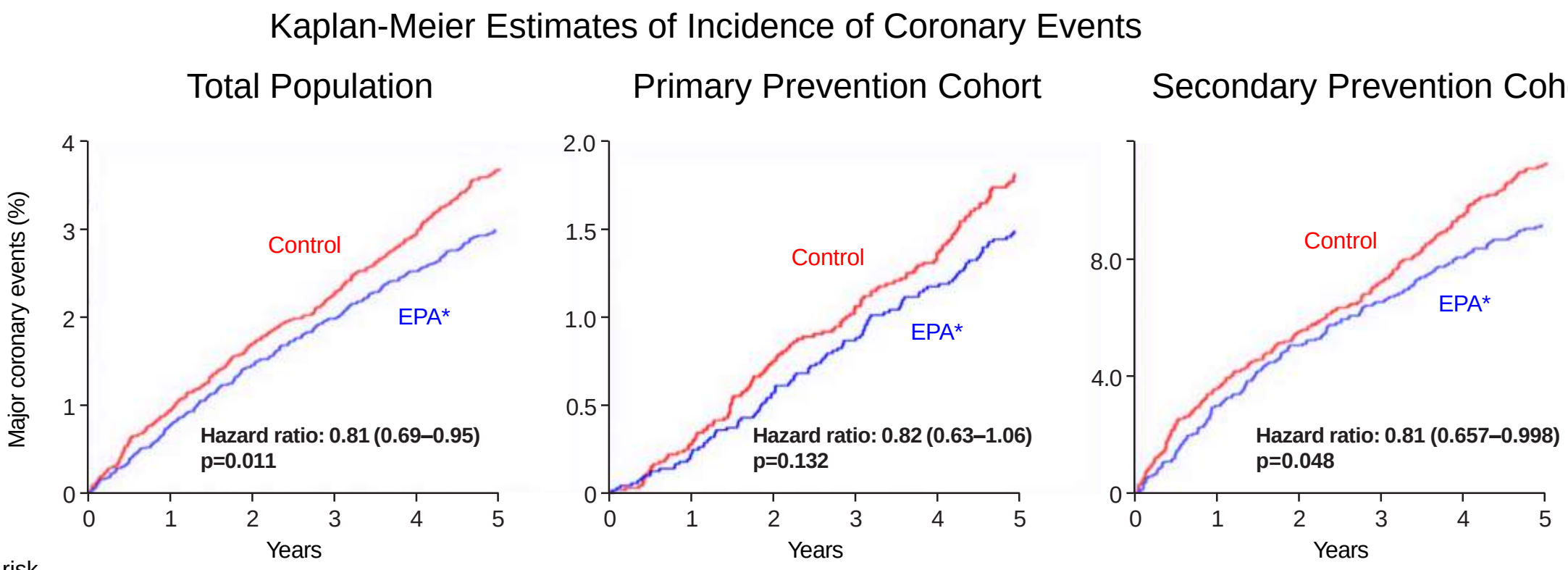
Cumulative Incidence Rates of Major CVD Events by Year of Follow-up: Omega-3s vs. Placebo



Manson JE, Cook NR, Lee I-M, et al. *NEJM.* 2018

JELIS Suggests CV Risk Reduction with EPA in Japanese Hypercholesterolemic Patients

Kaplan-Meier Estimates of Incidence of Coronary Events



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

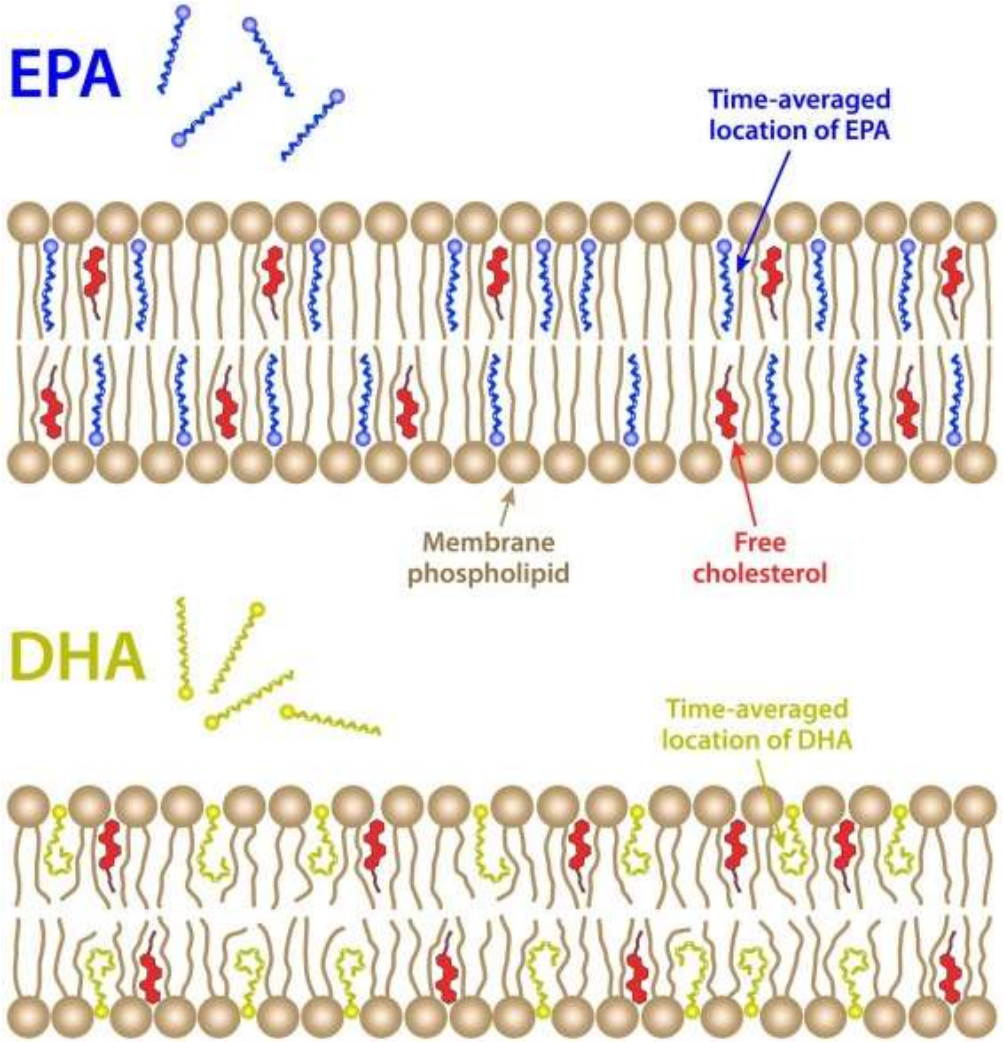
7478	7204	7103	6841	6678	6508
7503	7210	7020	6823	6649	6482

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

*1.8 g/day

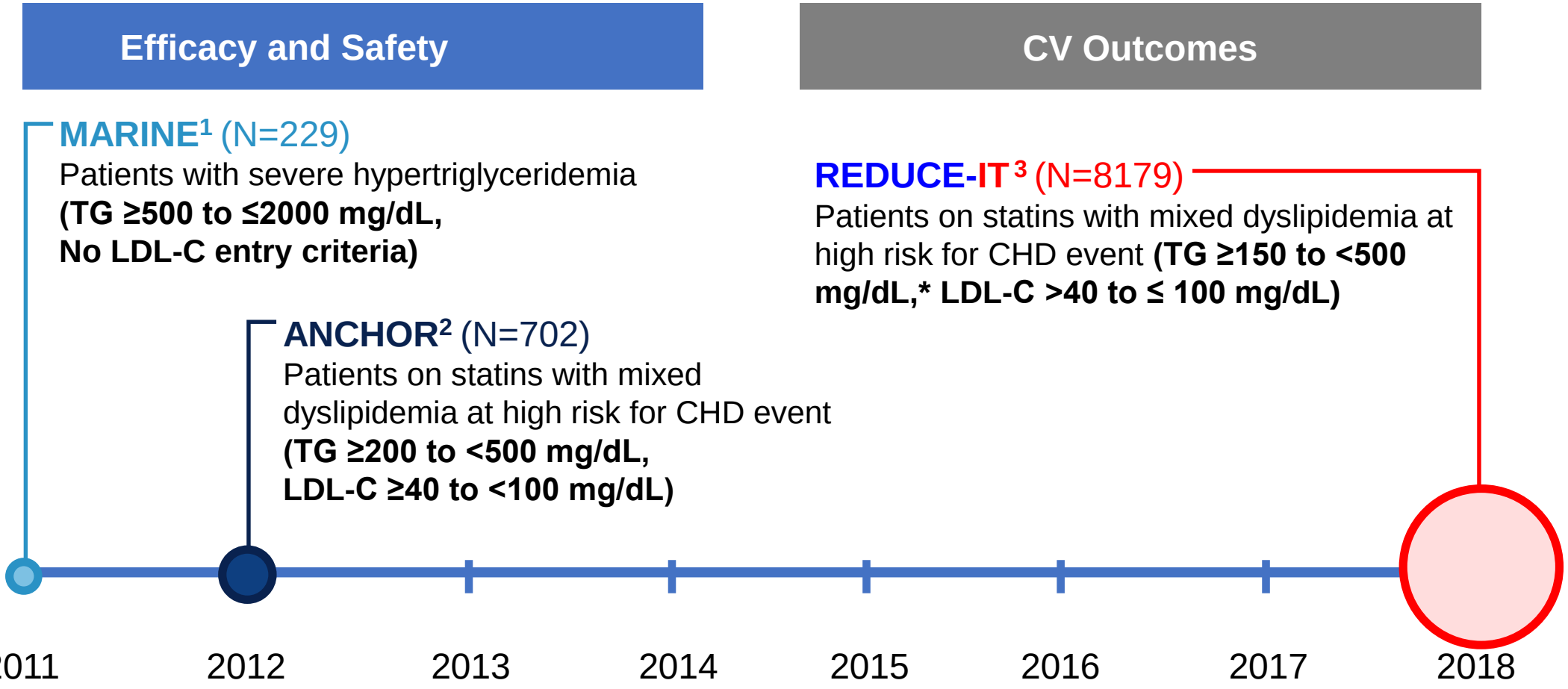
Adapted with permission from Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet.* 2007;369:1090-1098.

EPA and DHA Have Differing Effects on Cellular Membranes



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

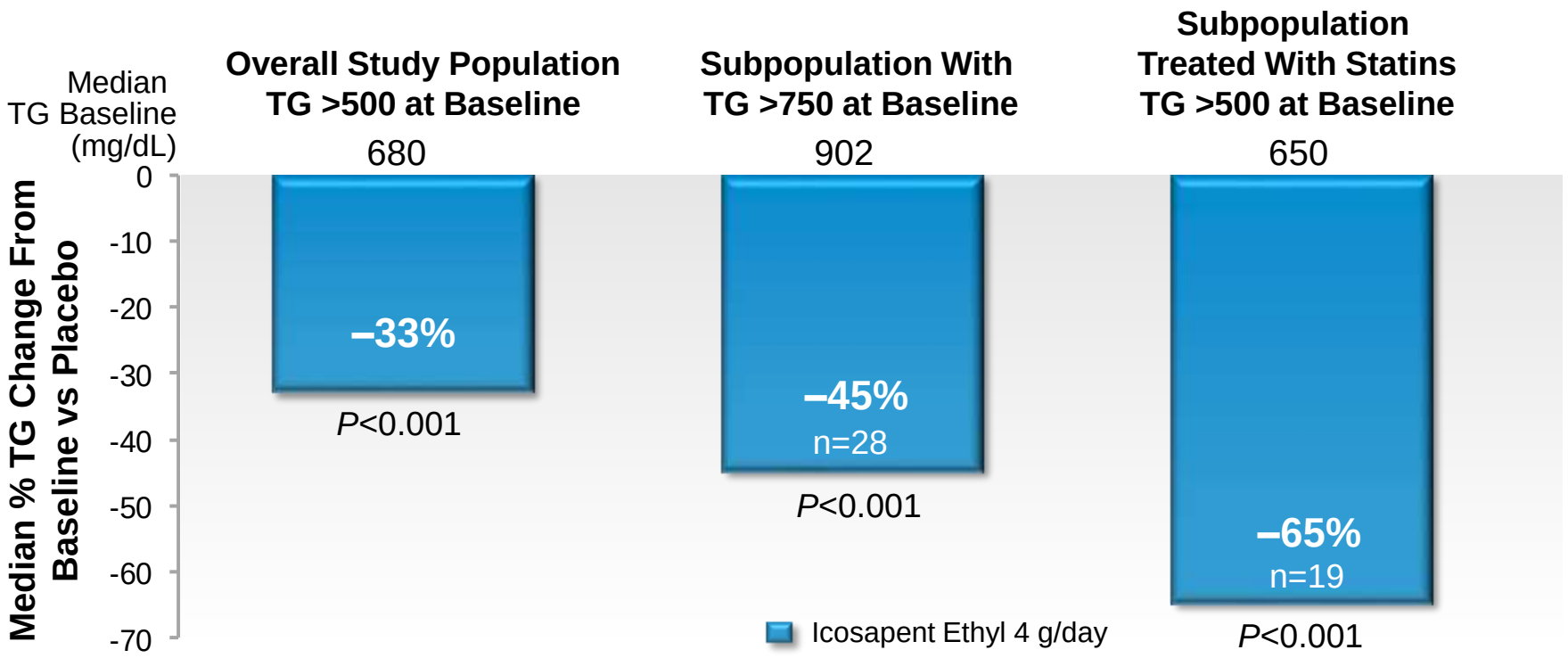
Pure EPA Icosapent Ethyl Clinical Program



CHD=coronary heart disease; CV=cardiovascular; LDL-C=low-density lipoprotein cholesterol; TG=triglyceride.
*Original protocol criteria specified a TG level of 150 to <500 mg/dL. A 2013 protocol amendment modified qualifying TG levels to ≥200 to <500 mg/dL.

1. Bays HE et al. *Am J Cardiol.* 2011;108(5):682-690; 2. Ballantyne CM et al. *Am J Cardiol*. 2012;110(7):984-992; 3. Bhatt DL et al. NEJM. 2018 (epub ahead of print).

MARINE: Pure EPA Icosapent Ethyl Demonstrated Significant TG Reductions Across Populations

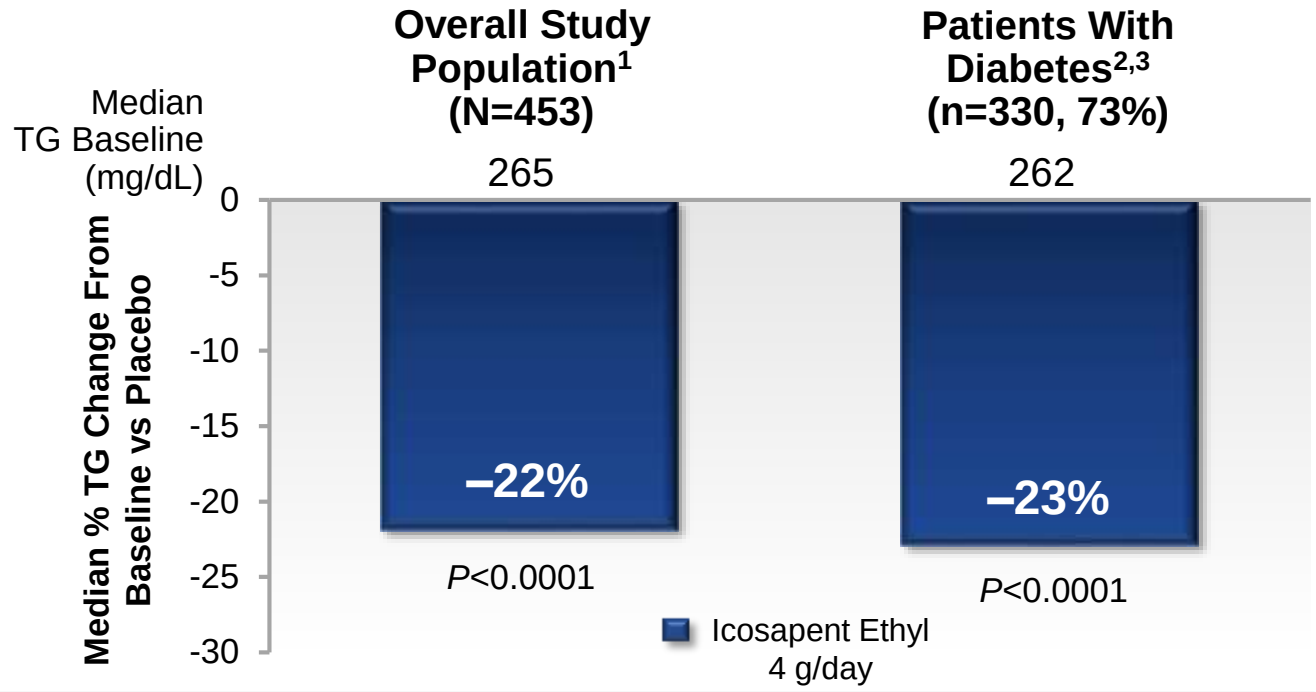


Icosapent Ethyl median % change vs baseline	–27%	–27%	–30%
Placebo median % change vs baseline	+10%	+19%	+32%

Overall study population: icosapent ethyl (n=76), placebo (n=75); patients with baseline TG >750 mg/dL: icosapent ethyl (n=28), placebo (n=32); on statin therapy: icosapent ethyl (n=19), placebo (n=18). *P* values reflect differences between icosapent ethyl and placebo.

Bays HE et al. *Am J Cardiol*. 2011;108(5):682-690.

ANCHOR: Pure EPA Icosapent Ethyl Demonstrated Significant TG Reductions Overall and in Patients With Diabetes



Icosapent Ethyl median % change vs baseline	–18%	–19%
Placebo median % change vs baseline	+6%	+6%

Overall study population: icosapent ethyl 4 g/day, n=226; placebo, n=227.
Diabetes subpopulation: icosapent ethyl 4 g/day, n=165; placebo, n=165.
P values reflect differences between icosapent ethyl and placebo.

1. Ballantyne CM et al. *Am J Cardiol*. 2012;110(7):984-992; 2. Brinton EA et al. *Cardiovasc Diabetol*. 2013;12:100; 3. Data on file. Amarin Pharma, Inc.

Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

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

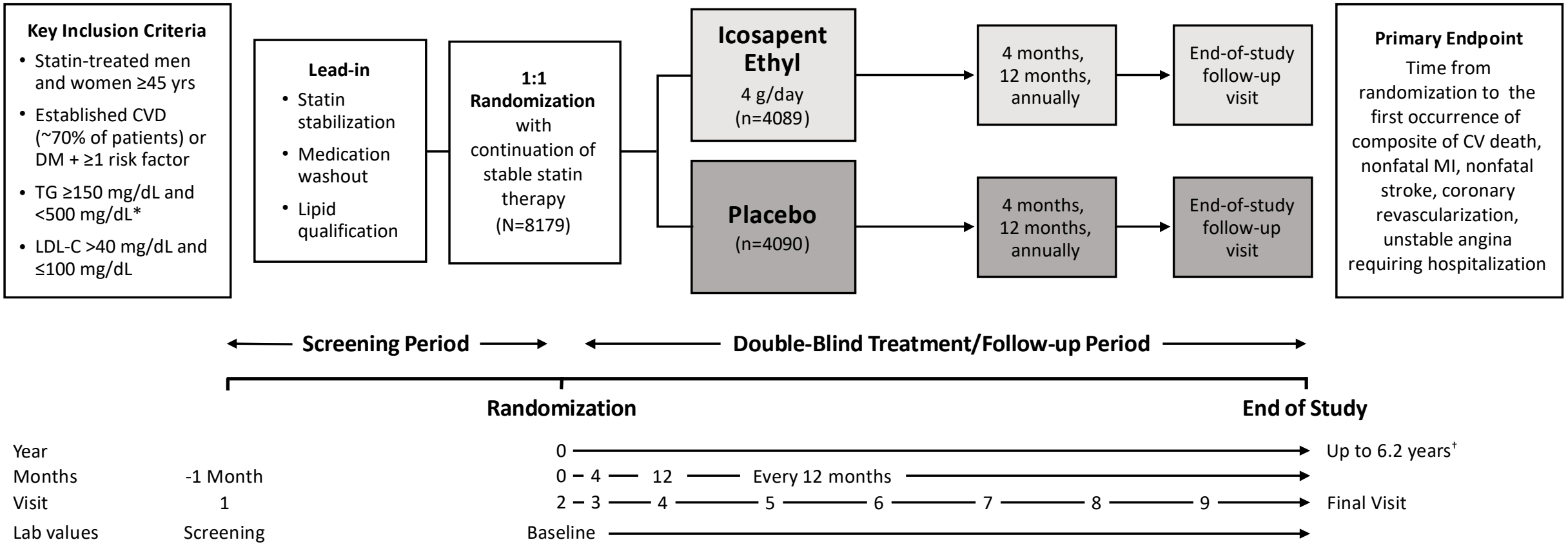
Eliot A. Brinton, MD, Terry A. Jacobson, MD, Steven B. Ketchum, PhD,

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

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

on Behalf of the REDUCE-IT Investigators

REDUCE-IT Design



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

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

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

Key Inclusion Criteria – REDUCE-IT

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

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

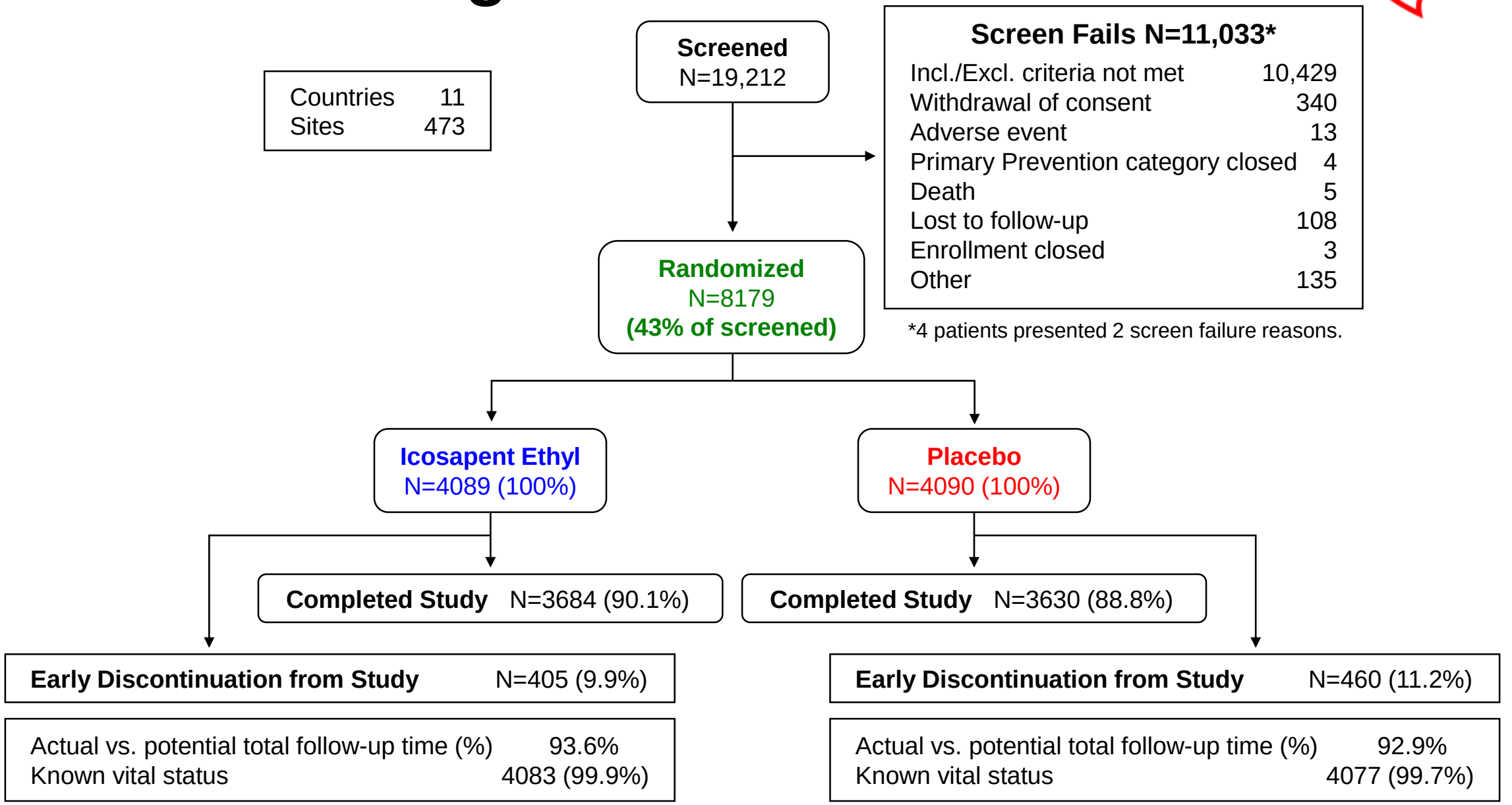
3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

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

Key Exclusion Criteria

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

CONSORT Diagram



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

Median trial follow up duration was 4.9 years.

The NEW ENGLAND JOURNAL of MEDICINE

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

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

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

Article available at https://www.nejm.org
Slides available for download at https://professional.heart.org
or at https://www.ACC.org

Key Baseline Characteristics

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

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

Effects on Biomarkers from Baseline to Year 1

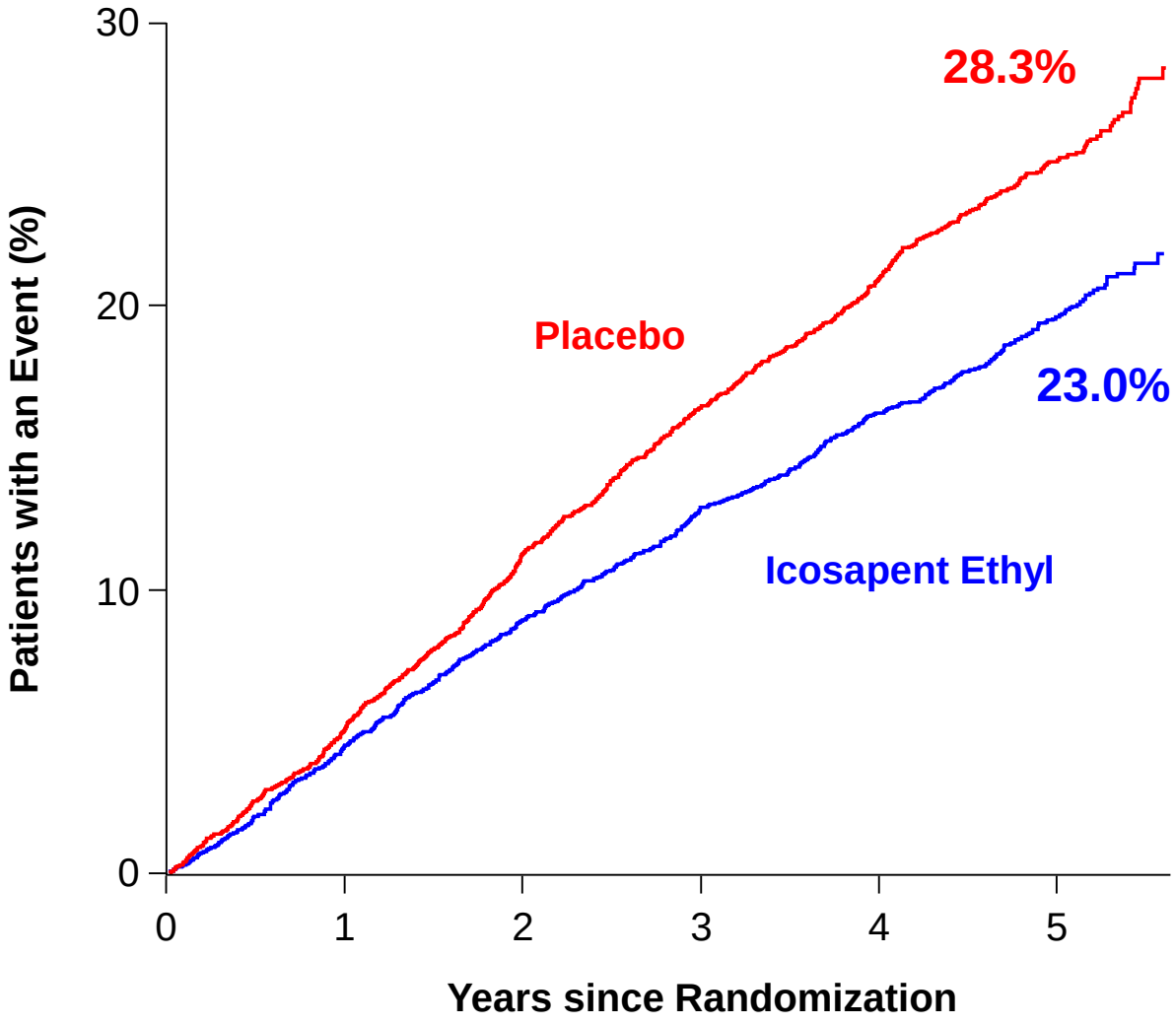
	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
Biomarker*	**Baseline**	**Year 1**	**Baseline**	**Year 1**	**Absolute Change from Baseline**	**% Change from Baseline**	**% Change P-value**
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7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

*Apo B and hsCRP were measured at Year 2.

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

Primary End Point:

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



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

RRR = 24.8%

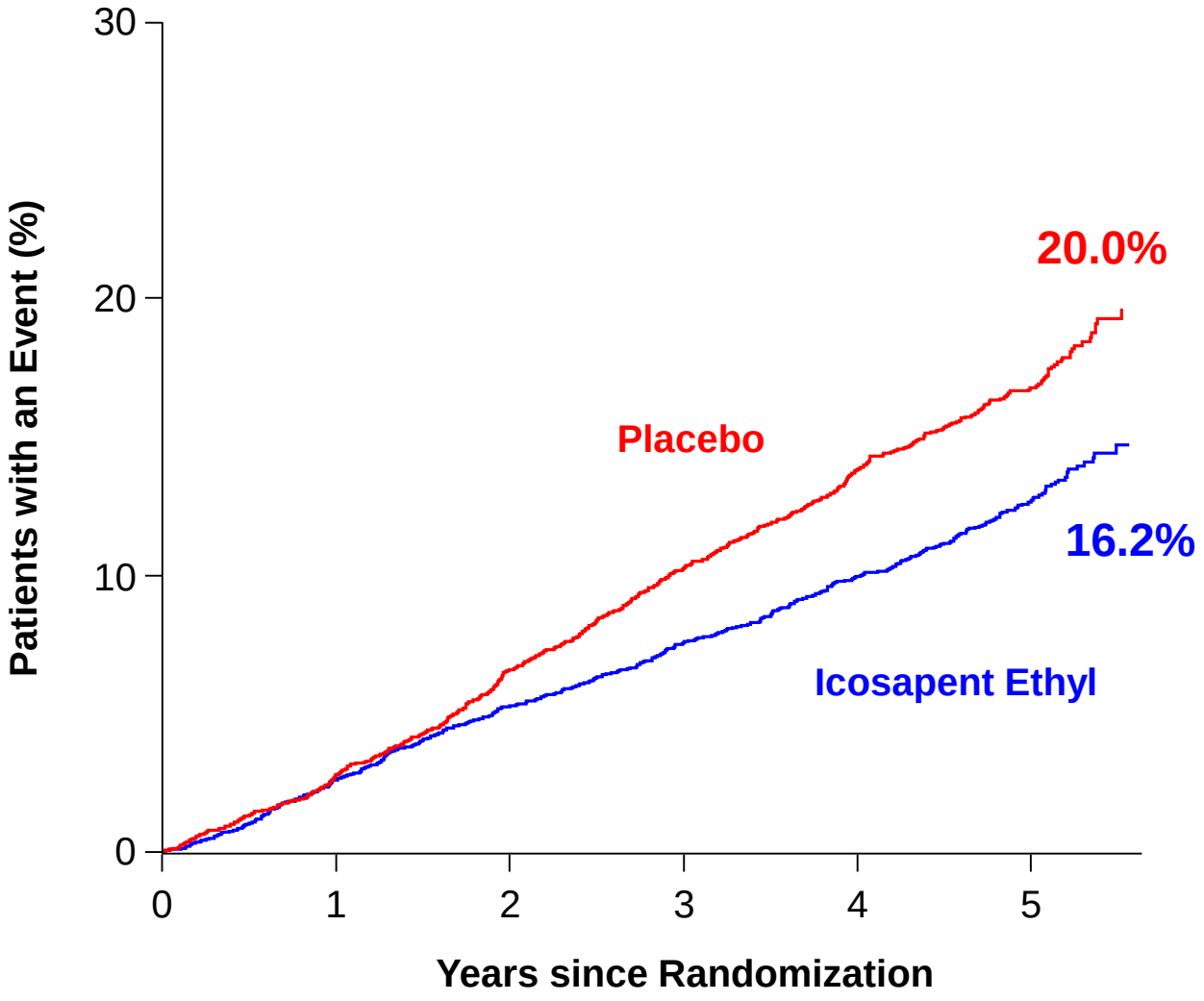
ARR = 4.8%

NNT = 21 (95% CI, 15–33)

P=0.00000001

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019. Bhatt DL. AHA 2018, Chicago.

Key Secondary End Point:
CV Death, MI, Stroke



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

RRR = 26.5%

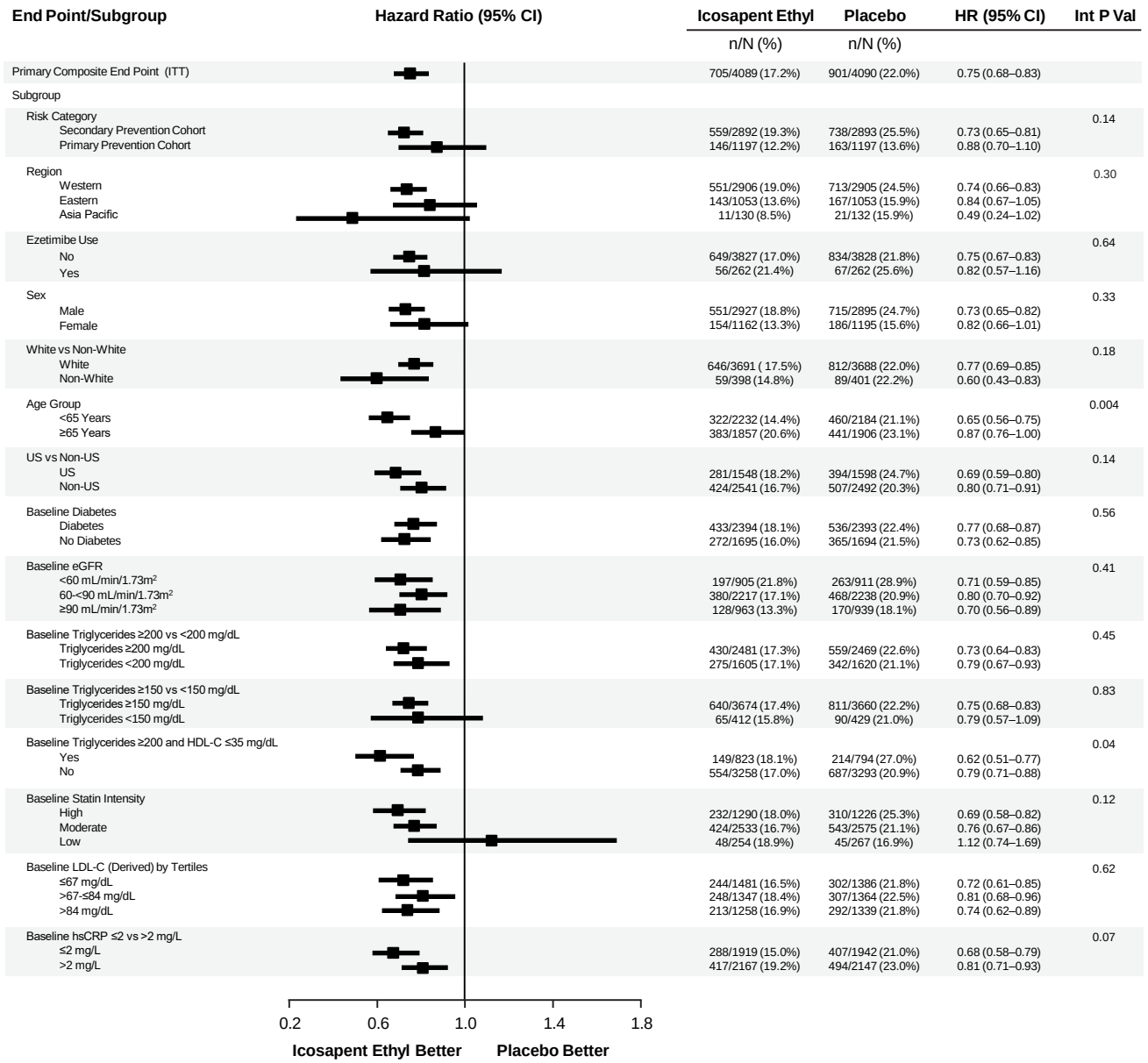
ARR = 3.6%

NNT = 28 (95% CI, 20–47)

P=0.0000006

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019. Bhatt DL. AHA 2018, Chicago.

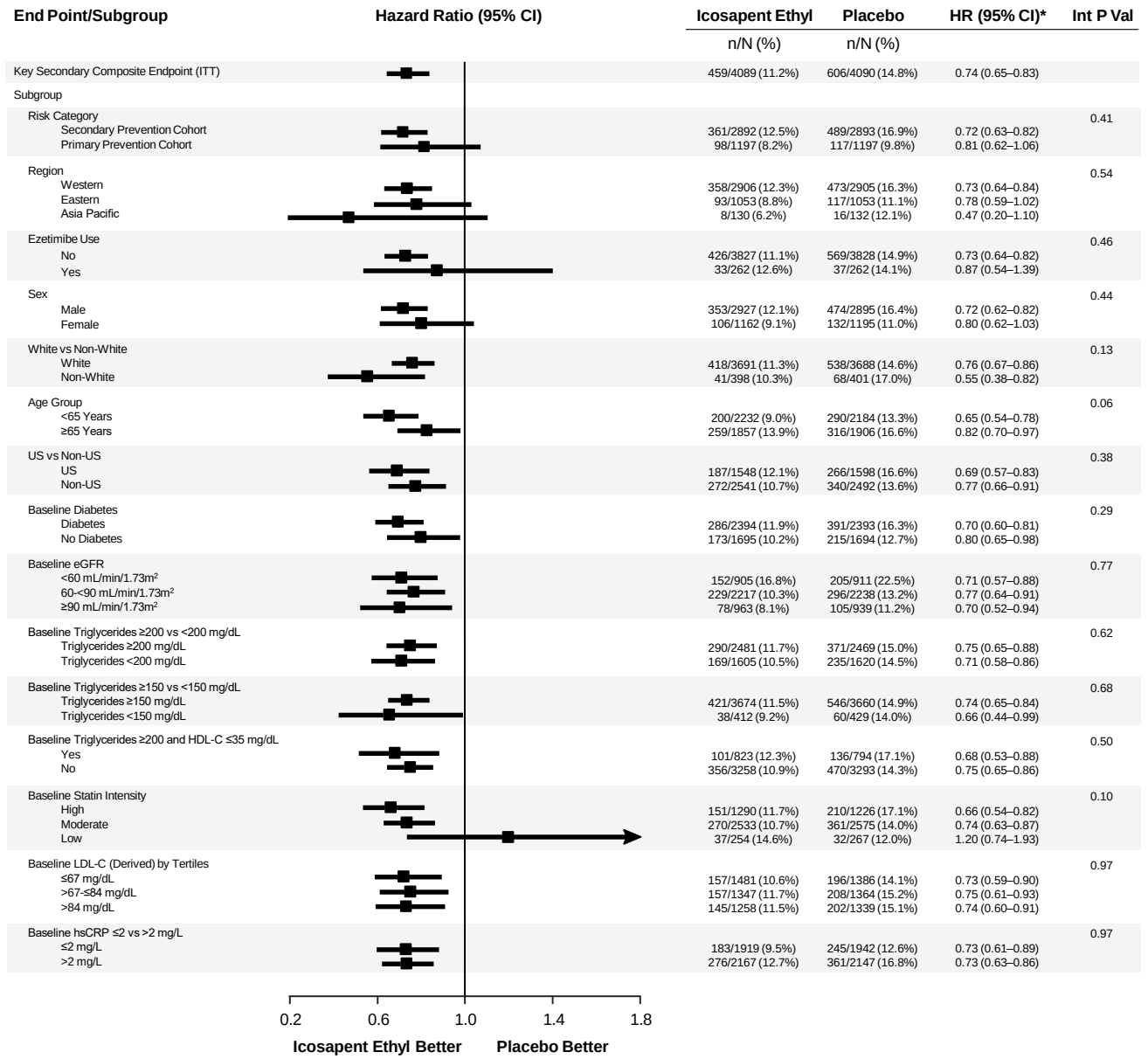
Primary End Point in Subgroups



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

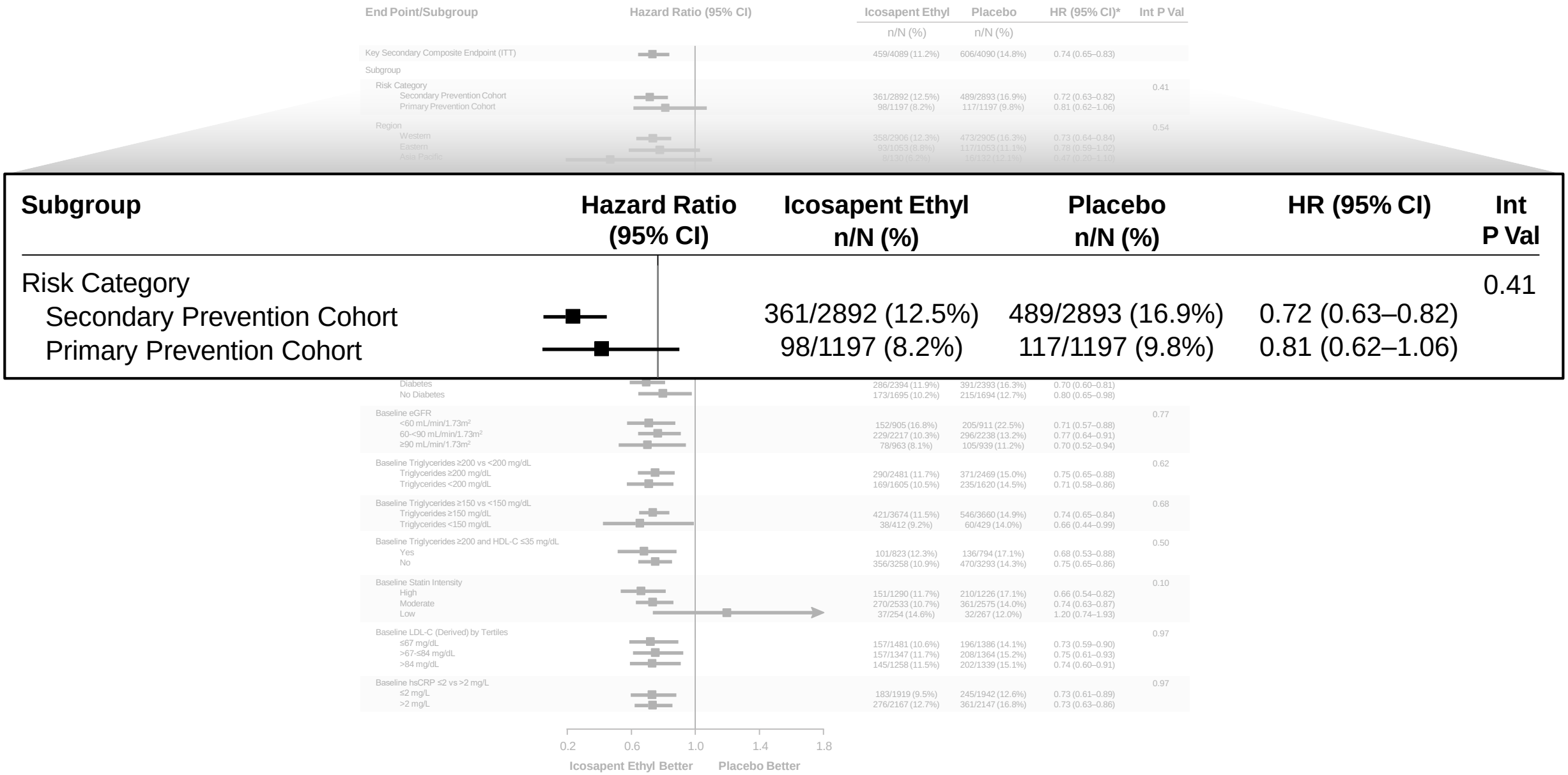
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22.

Key Secondary End Point in Subgroups



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

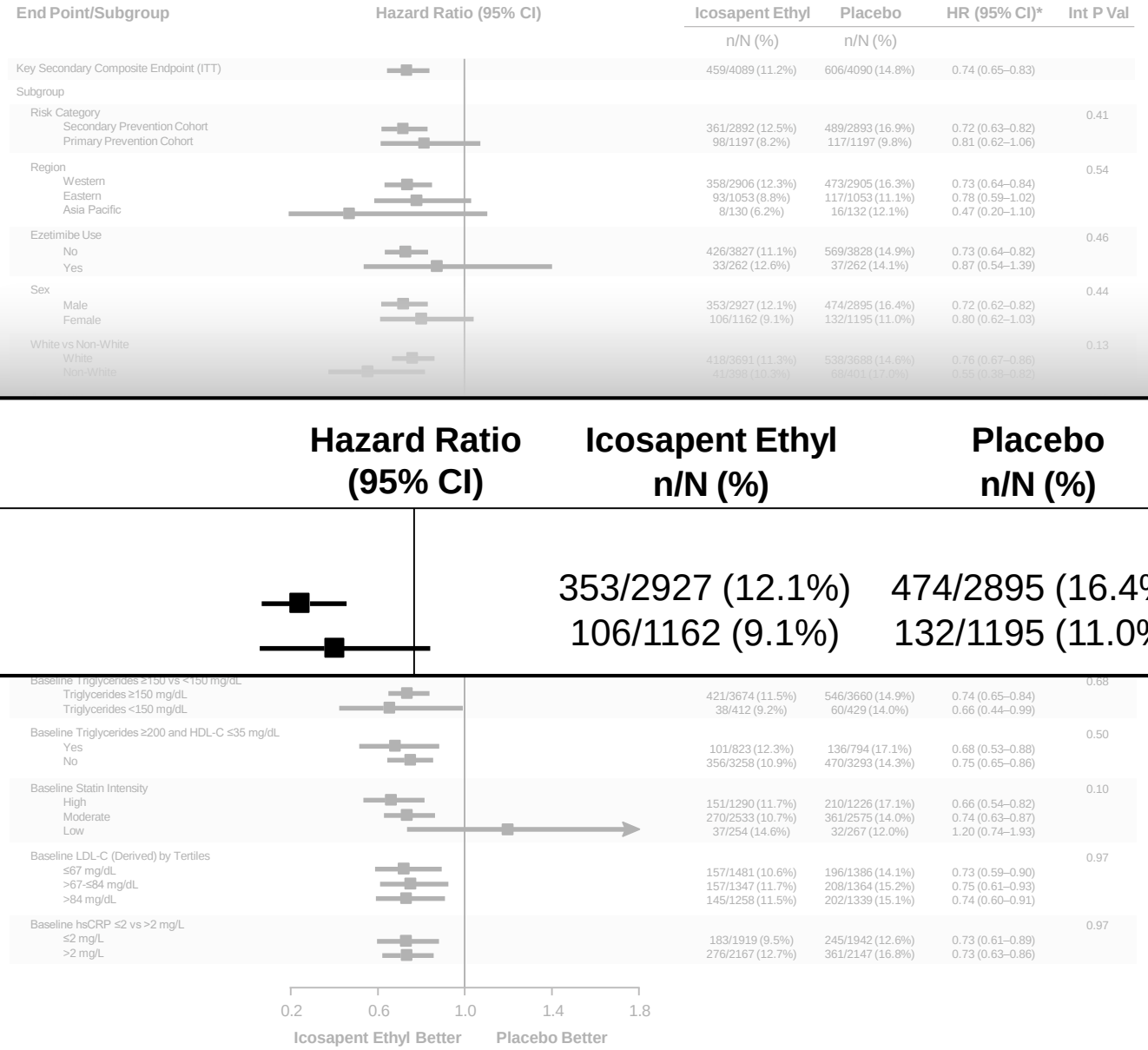
Key Secondary End Point in Subgroups



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

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

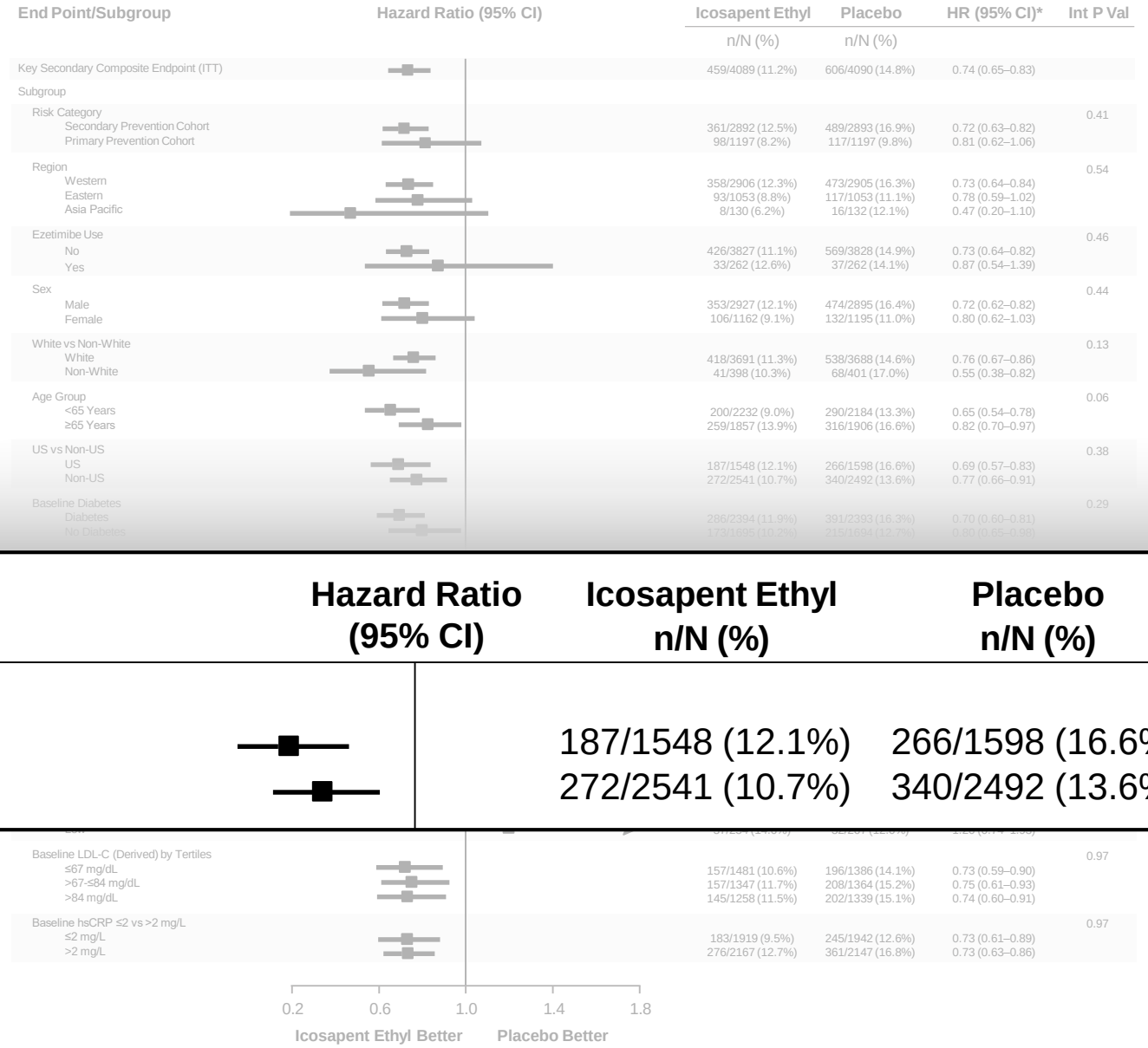
Key Secondary End Point in Subgroups



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

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

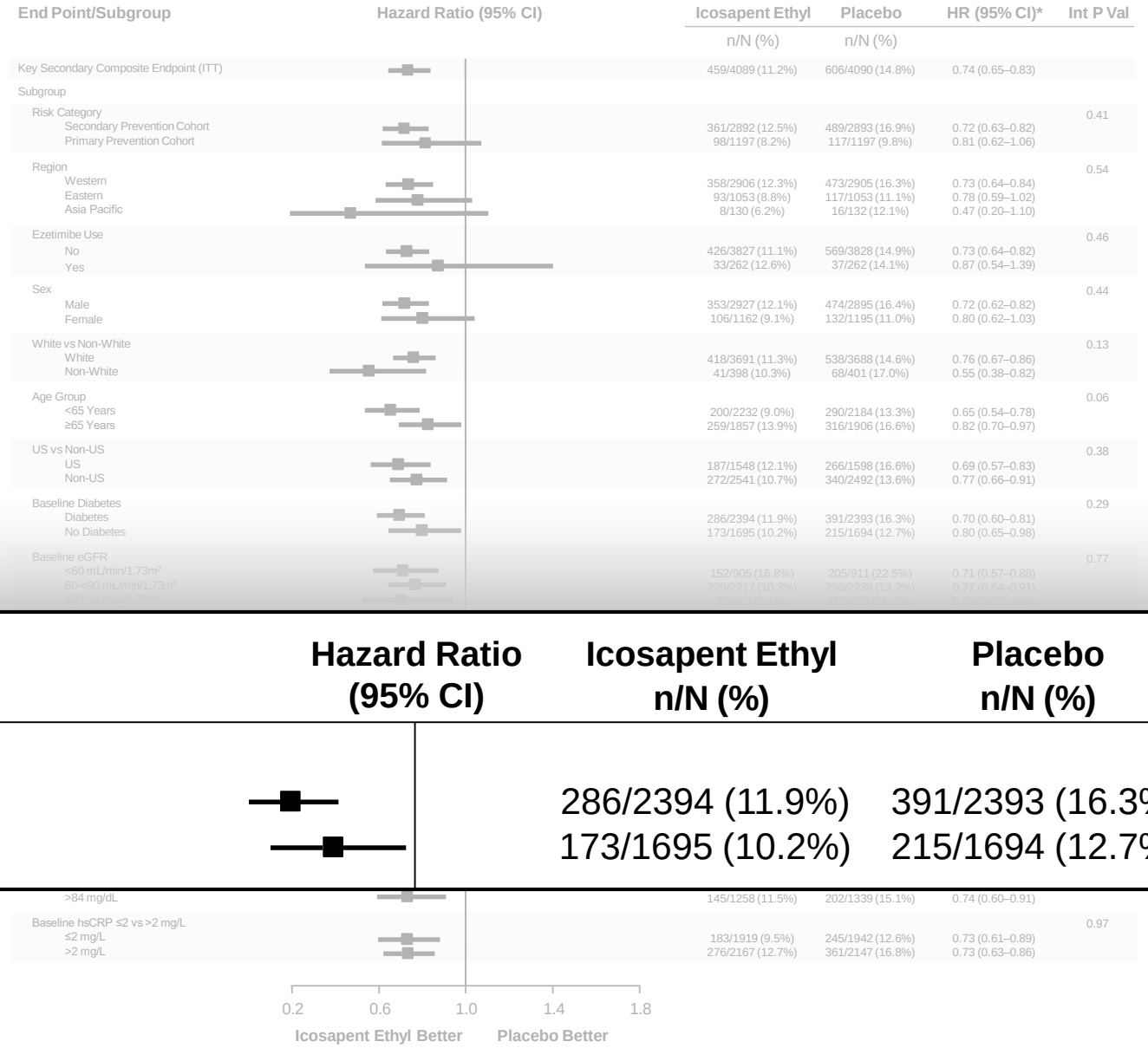
Key Secondary End Point in Subgroups



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

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

Key Secondary End Point in Subgroups



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

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

Key Secondary End Point in Subgroups

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

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

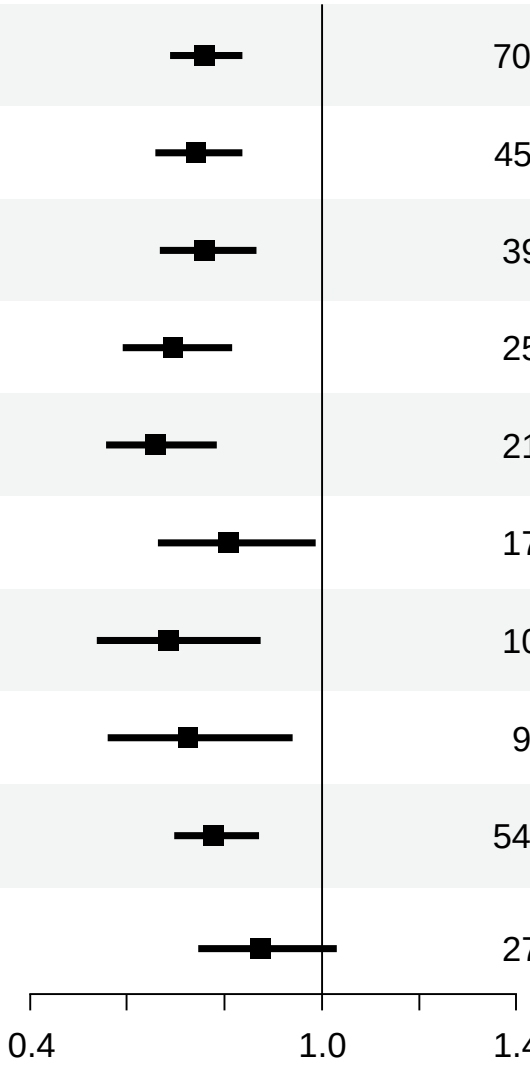
Key Secondary End Point in Subgroups

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

Icosapent Ethyl Better Placebo Better

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

Prespecified Hierarchical Testing



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

RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

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

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

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

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

REDUCE-IT Tertiary Endpoints: Revascularization

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

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

Treatment-Emergent Adverse Event of Interest: Serious Bleeding

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

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

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

Adjudicated Events: Hospitalization for Atrial Fibrillation or Atrial Flutter

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

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

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

“Miracle of EPA”

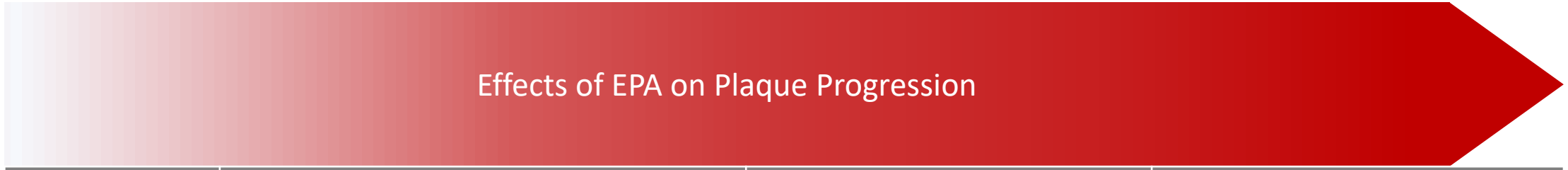
The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

FISHing for the Miracle of Eicosapentaenoic Acid

John J.P. Kastelein, M.D., Ph.D., and Erik S.G. Stroes, M.D., Ph.D.

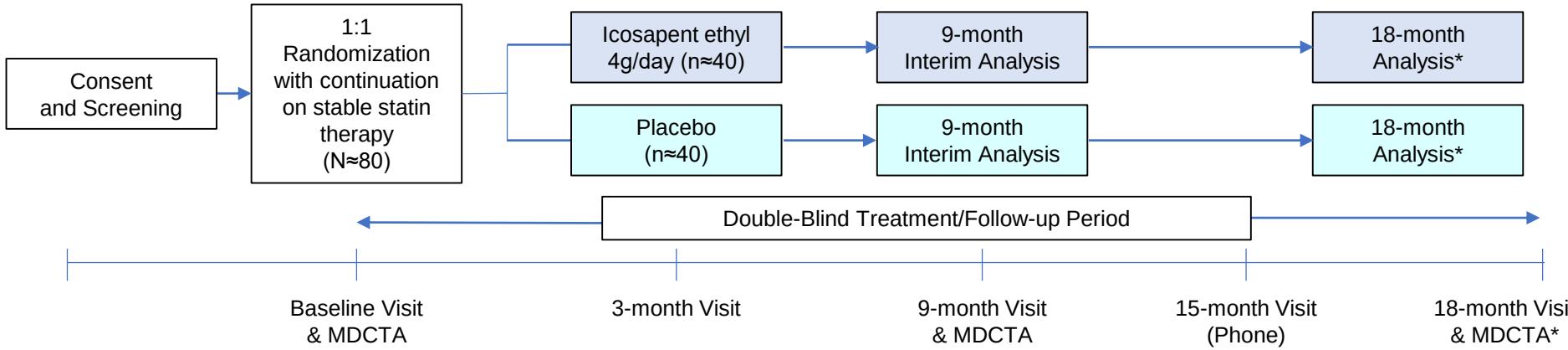
Potential Benefits of EPA



	Endothelial Dysfunction/ Oxidative Stress	Inflammation/ Plaque Growth	Unstable Plaque
Increase	Endothelial function Nitric oxide bioavailablity	EPA/AA ratio	Fibrous cap thickness Lumen diameter Plaque stability
Decrease	Cholesterol crystalline domains Ox-LDL RLP-C Adhesion of monocytes Macrophages Foam cells	IL-6 ICAM-1 IL-10 hsCRP Lp-PLA_2 MMPs	Plaque volume Arterial stiffness Plaque vulnerability Thrombosis Platelet activation

Adapted with permission* from Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol*. 2018;72:330-343. [*https://creativecommons.org/licenses.org/by-nc/4.0/]

EVAPORATE Study Design



Primary Endpoint

Change in low-attenuation plaque volume measured by multidetector computed tomography angiography.

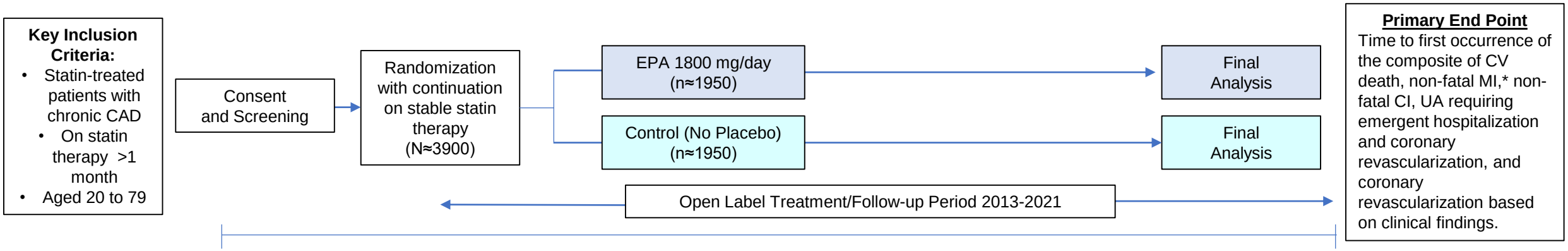
At baseline and 9 months, assessments will include blood pressure, height, weight, laboratory blood testing, physical exams, MDCTA (to assess progression of low-attenuation plaque volume) and safety evaluation.

Safety will also be assessed at 3 months for all patients and at 15 months for patients continuing for a total of 18 months of treatment.

*If a statistician and the Data Safety and Monitoring Board find that efficacy is not achieved at 9 months, patients will be followed for an additional 9 months to assess progression of low-attenuation plaque volume by MDCTA. If a P value of ≤0.006 is achieved at 9 months, then the study will terminate because the efficacy boundary will have been achieved. Abbreviations: BP, blood pressure; EVAPORATE, Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy study; MDCTA, multi-detector computed tomography angiography.

Adapted from: Budoff et al, Clinical Cardiology. 2018;41:13-19.

RESPECT EPA Study Design



CAD is defined as having at least one of the following criteria:
(1) History of acute coronary syndrome (acute myocardial infarction or unstable angina)
(2) History of coronary revascularization (PCI or CABG)
(3) Clinically diagnosed ischemic heart disease and severe coronary artery stenosis (75% or higher according to AHA classification) demonstrated in coronary angiography

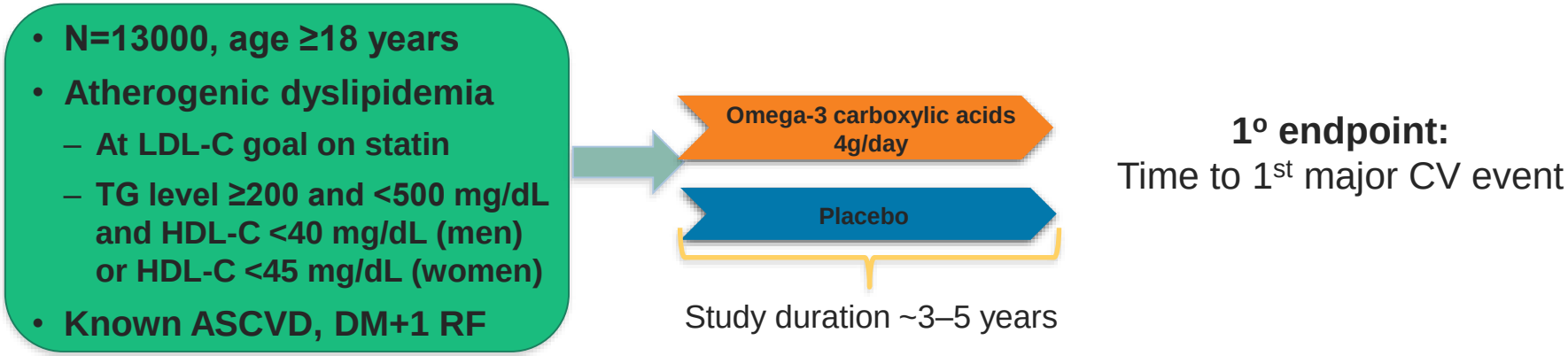
* Indicates not including percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) related MI.

CI, cerebral infarction; CV, cardiovascular; EPA, eicosapentaenoic acid MI, myocardial infarction, UA unstable angina.

Funding Source: Japan Heart Foundation

RESPECT-EPA: UMIN000012069 (https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000002496).

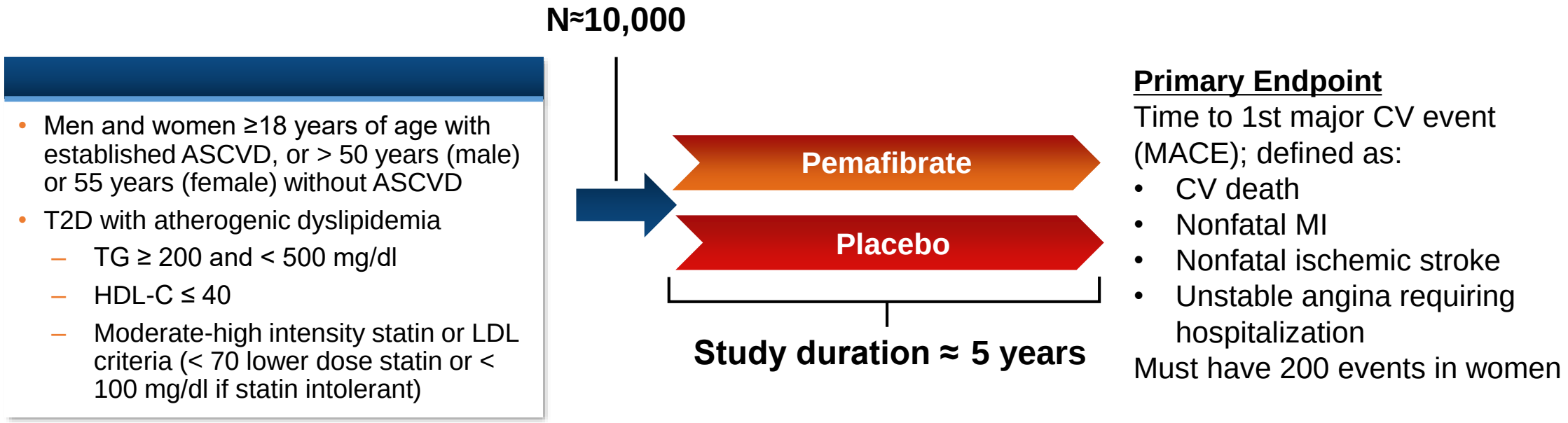
Outcome Study to Assess Statin Residual Risk Reduction with Omega-3-carboxylic acids in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH)



- Randomized, double-blind, parallel group design
- Primary outcome: time to first occurrence of CV death, nonfatal MI, nonfatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina

ClinicalTrials.gov. http://www.clinicaltrials.gov: STRENGTH; NCT02104817.

PROMINENT: Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN PatiENts with DiabeTes



- International, randomized, double-blind, parallel-group design
- All potential endpoint events adjudicated by blinded Clinical Endpoint Committee
- Secondary and tertiary endpoints include hospitalization for heart failure, any coronary revascularization, new or worsening PAD, lipid and lipoprotein parameters, inflammation and glucose parameters

SPPARM-α: selective peroxisome proliferator-activated receptor alpha modulator

Pradhan AD, Paynter NP, Everett BM, et al, … Libby P, Ridker PM. Am Heart J 2018;206:80-93. https://clinicaltrials.gov/ct2/show/NCT03071692

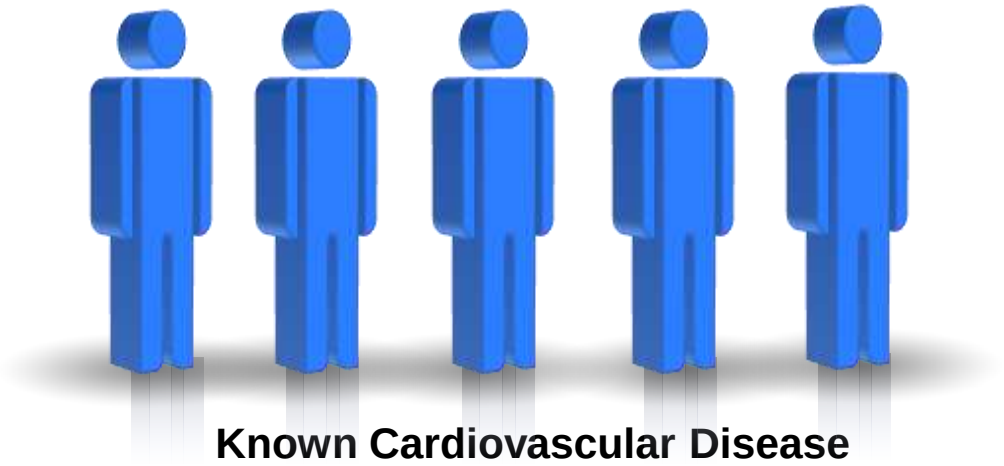
CV Outcomes Trials in Patients with HTG

	REDUCE-IT*	STRENGTH*	PROMINENT*
Agent **Dose**	**EPA (EE)** **4 g/d**	**EPA+DHA (FFA)** **4 g/d**	**SPPARMα – Pemafibrate** **0.2 mg bid**
N	~8000	Estimated 13,000	Estimated 10,000
Age	≥45 years	≥18 years	≥18 years
Risk Profile	CVD (70%) or ↑CVD risk (30%)	CVD (50%) or ↑CVD risk (50%)	T2DM only CVD (2/3) or ↑CVD risk (1/3)
Follow-up	4–6 years (planned)	3–5 years (planned)	5 years (planned)
Statin Use	100% (at LDL-C goal)	100% (at LDL-C goal)	Moderate- / high-intensity or LDL <70 mg/dL
Primary Endpoint	Expanded MACE	Expanded MACE	Expanded MACE
Entry TG **Entry HDL-C**	200–499 mg/dL N/A	200–499 mg/dL <40 mg/dL M, <45 mg/dL W	200–499 mg/dL ≤40 mg/dL

*Locations: International sites; Statistics: Powered for 15% RRR.

ClinicalTrials.gov. http://www.clinicaltrials.gov; REDUCE-IT: NCT01492361; STRENGTH: NCT02104817; PROMINENT: NCT03071692.

Redefining Residual Risk



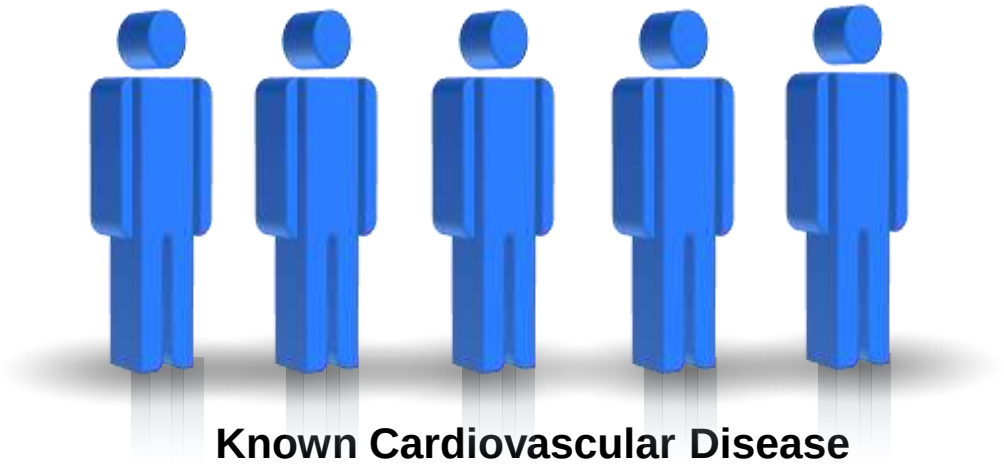
Known Cardiovascular Disease

High Intensity Statin

Biologic Issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk
Critical Biomarker	LDL-C >100mg/dL	hsCRP >2mg/L	No simple biomarker	TG >135mg/dL HDL <40mg/dL	Lp(a) >50mg/dL
Potential Intervention	Targeted LDL / Apo B Reduction	Targeted Inflammation Reduction	Targeted Antithrombotic Reduction	Targeted Triglyceride Reduction	Targeted Lp(a) Reduction
Randomized Trial Evidence	IMPROVE-IT FOURIER, SPIRE, ODYSSEY	CANTOS	PEGASUS, COMPASS	REDUCE-IT STRENGTH PROMINENT	Planned

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

Redefining Residual Risk



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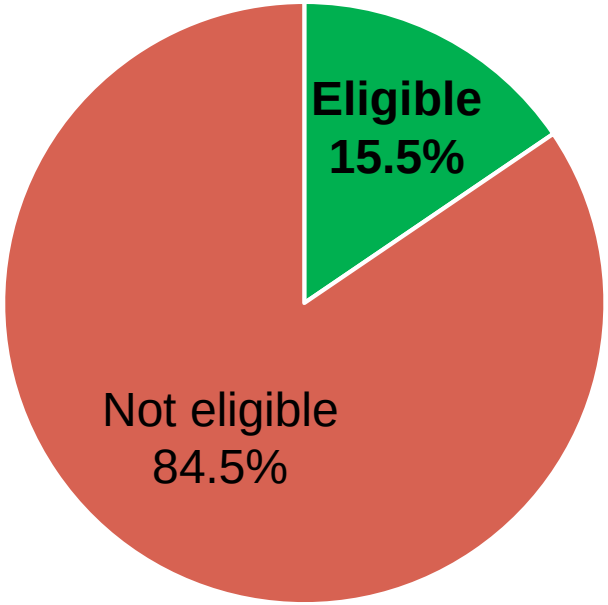
Randomized Trial Evidence	IMPROVE-IT FOURIER, SPIRE, ODYSSEY	CANTOS	PEGASUS, COMPASS	REDUCE-IT STRENGTH PROMINENT	Planned

REDUCE-IT?

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

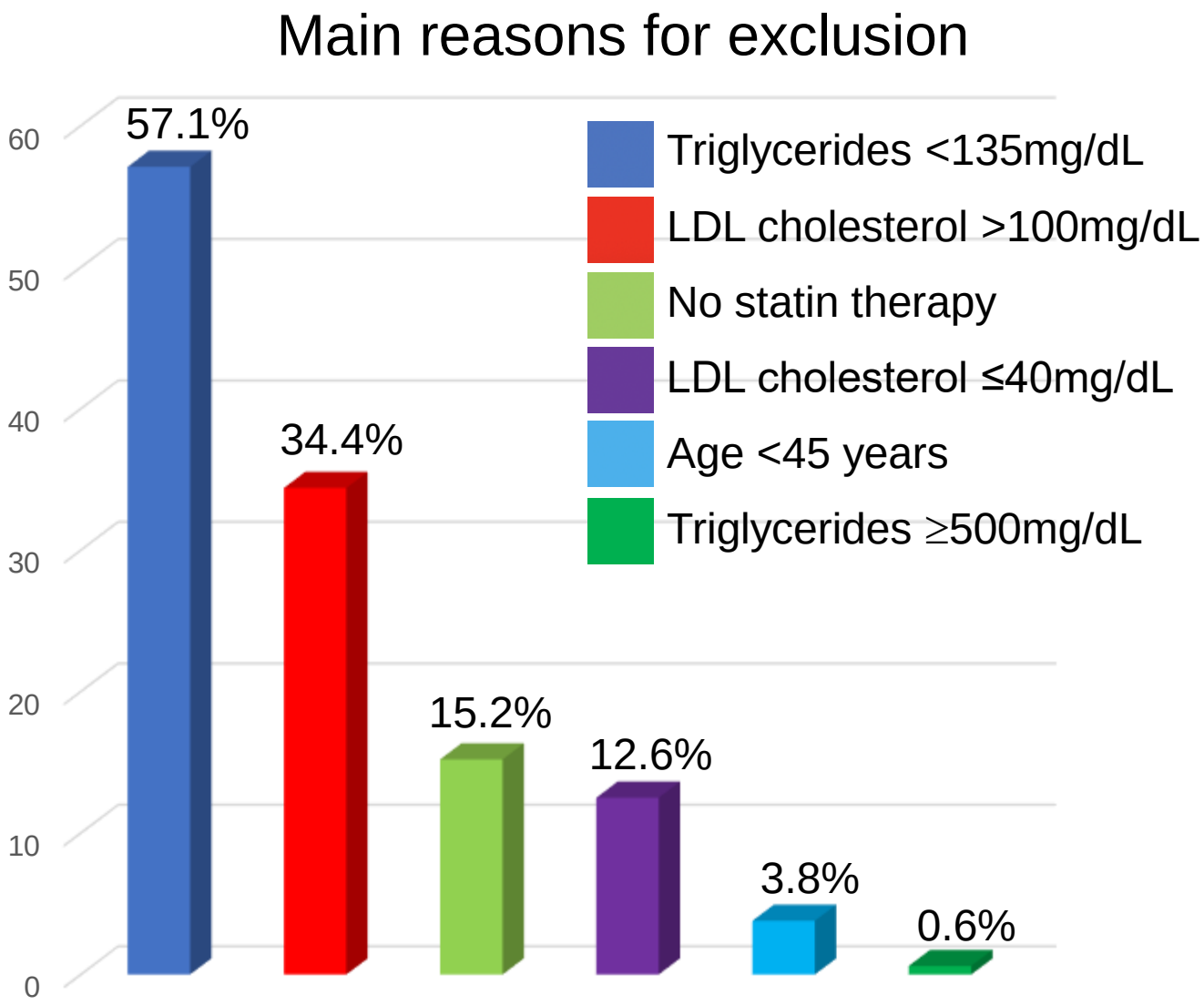
Generalizability of REDUCE-IT in Patients with Stable CAD

An analysis of 24,146 patients from the CLARIFY registry



Key Inclusion Criteria for CLARIFY Analysis

- Statin-treated men or women
- Age ≥45 years with either established CV disease OR age ≥50 years with diabetes mellitus and at least one additional CV risk factor
- AND triglycerides ≥135 and <500 mg/dL
- AND LDL-cholesterol >40 and ≤100 mg/dL



Picard F, Bhatt DL, Ducrocq G, et al. Steg PG. *JACC.* 2019.

Generalizability of REDUCE-IT in Patients with Stable CAD

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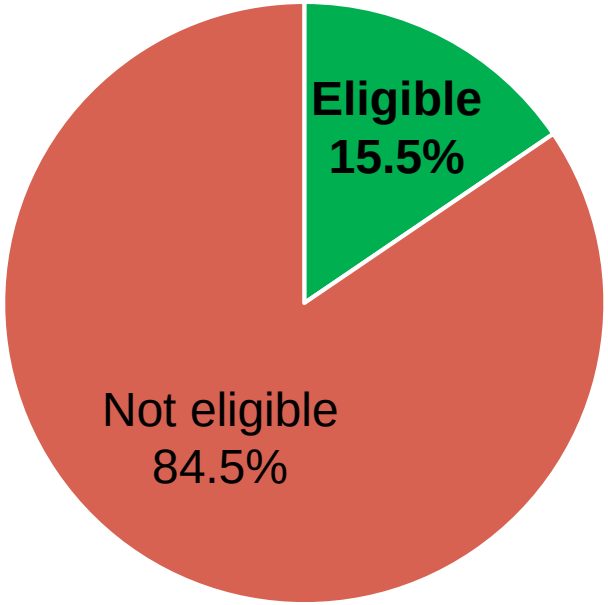
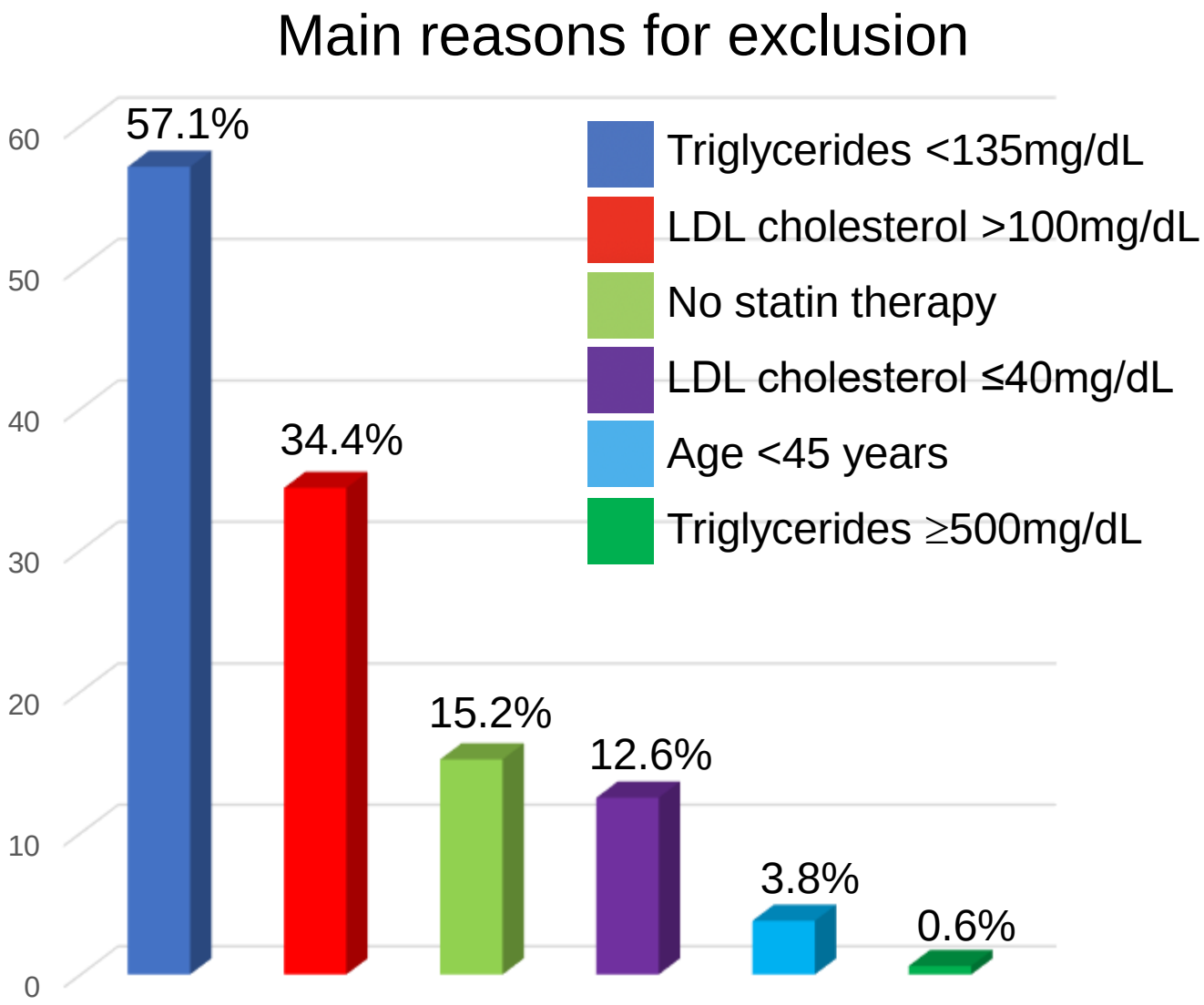


Key Inclusion Criteria for CLARIFY Analysis

- Statin-treated men or women
- Age ≥45 years with either established CV disease OR age ≥50 years with diabetes mellitus and at least one additional CV risk factor
- AND triglycerides ≥135 and <500 mg/dL
- AND LDL-cholesterol >40 and ≤100 mg/dL

NOTE: REDUCE-IT also enrolled patients with PAD, CVD, and DM with at least one risk factor



Picard F, Bhatt DL, Ducrocq G, et al. Steg PG. *JACC.* 2019.

Conclusions

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

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

Low rate of adverse effects, including:

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

Consistent efficacy across multiple subgroups

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

Reduction in Total Ischemic Events in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

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

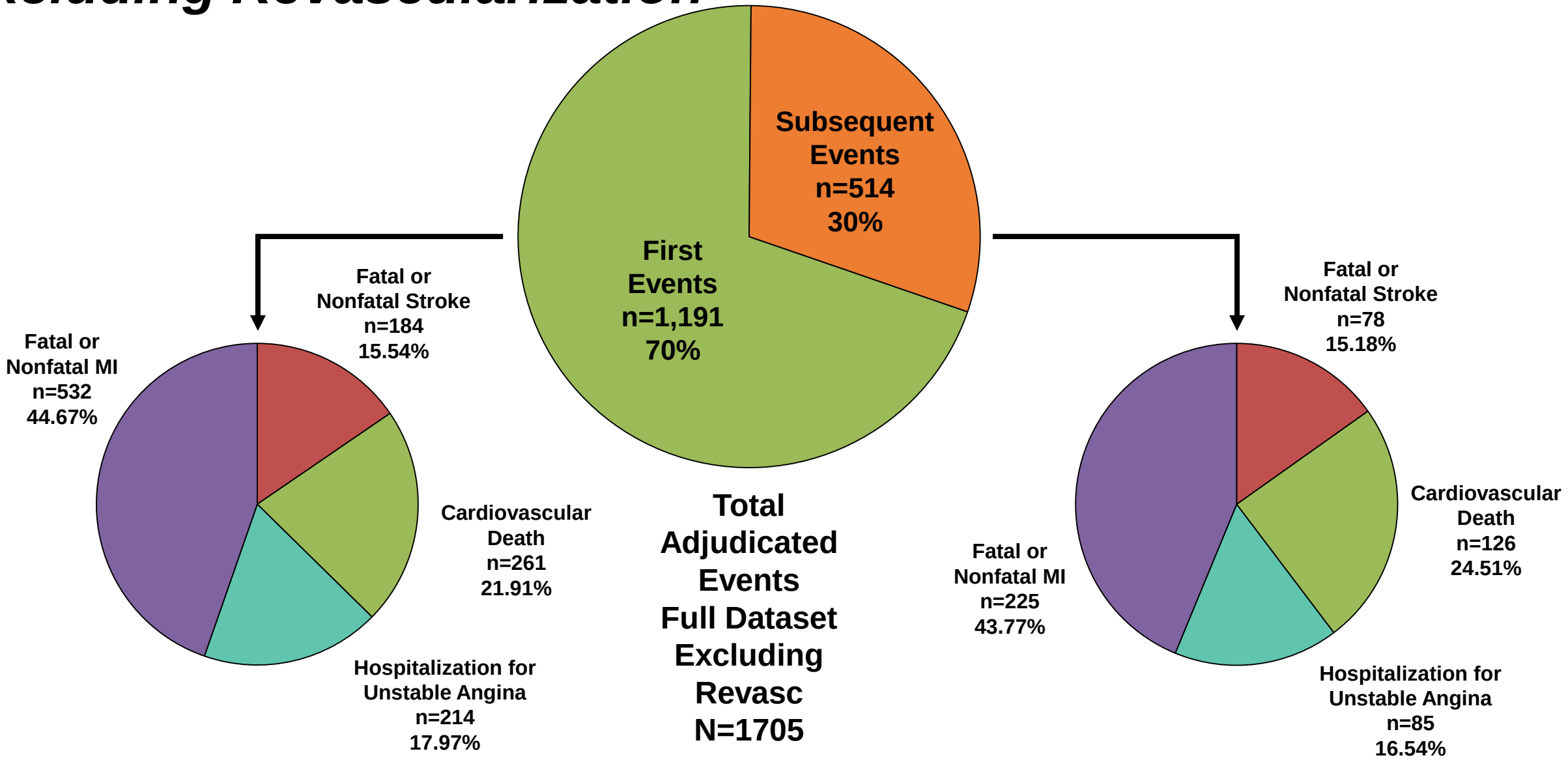
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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

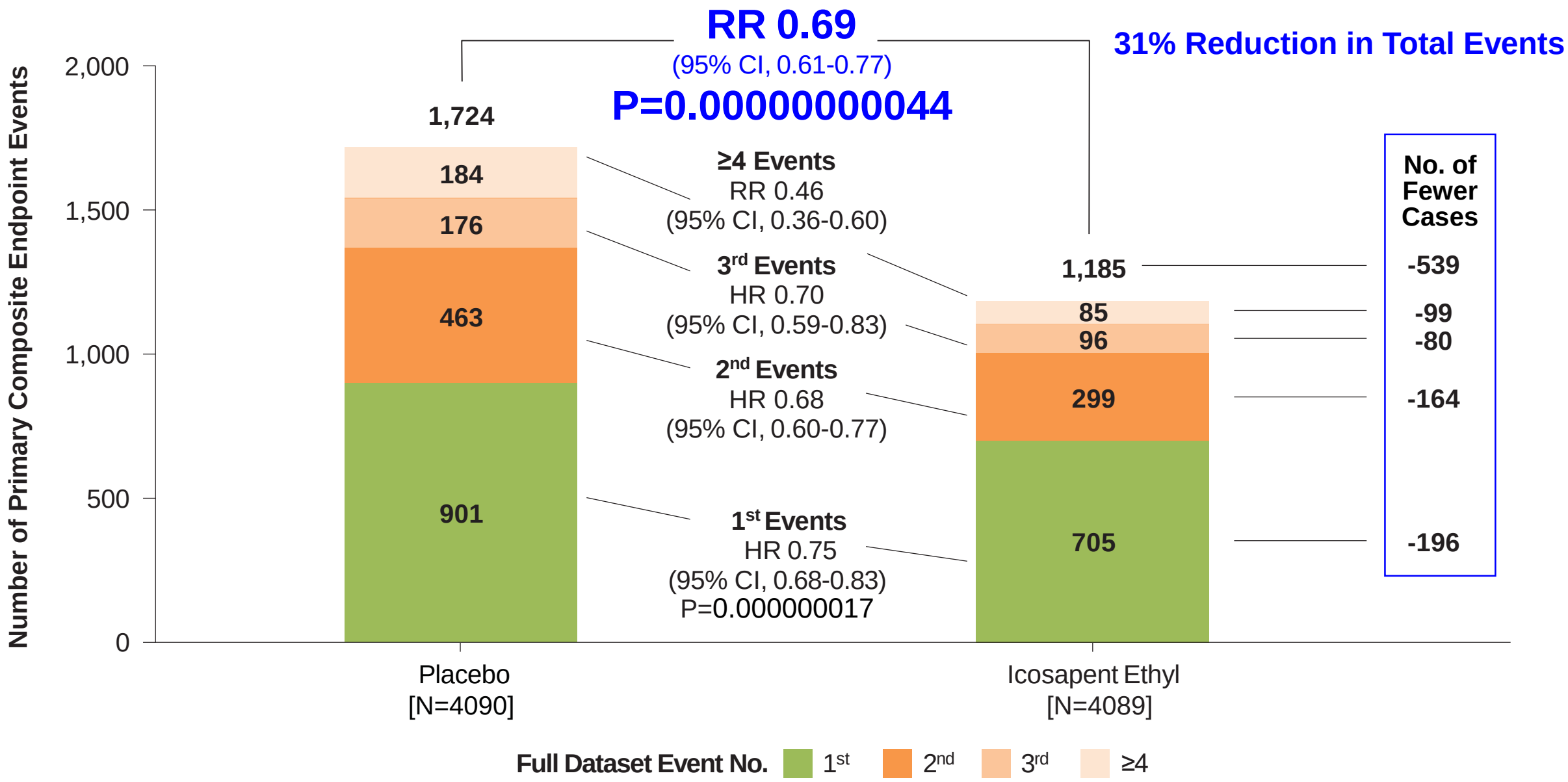
Deepak L. Bhatt, MD, MPH,[a] Ph. Gabriel Steg, MD,[b,c] Michael Miller, MD,[d] Eliot A. Brinton, MD,[e] Terry A. Jacobson, MD,[f] Steven B. Ketchum, PhD,[g] Ralph T. Doyle, Jr, BA,[g] Rebecca A. Juliano, PhD,[g] Lixia Jiao, PhD,[g] Craig Granowitz, MD, PhD,[g] Jean-Claude Tardif, MD,[h] John Gregson,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

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

Proportions of First and Subsequent Events
Excluding Revascularization



First and Subsequent Events – Full Data



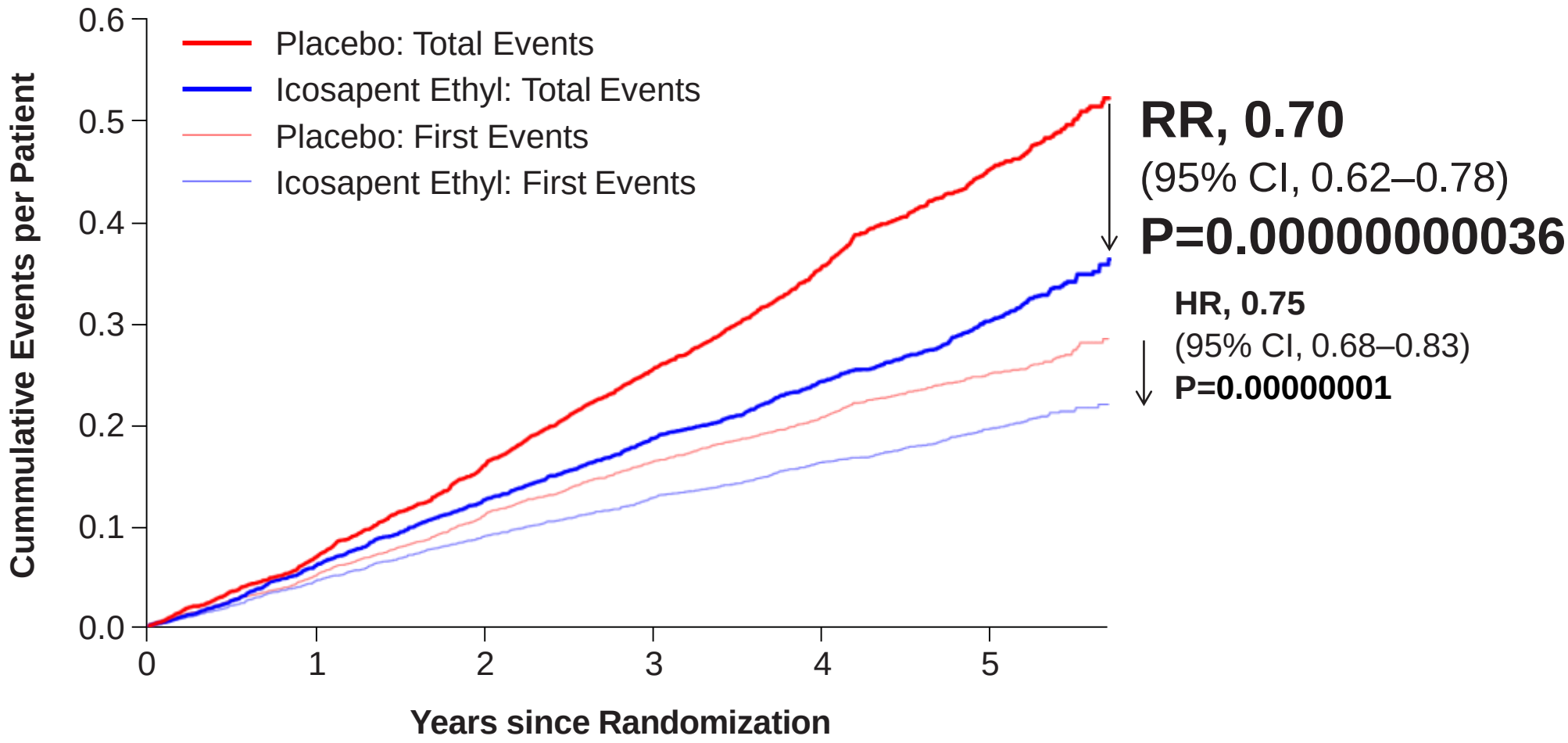
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

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

Total (First and Subsequent) Events

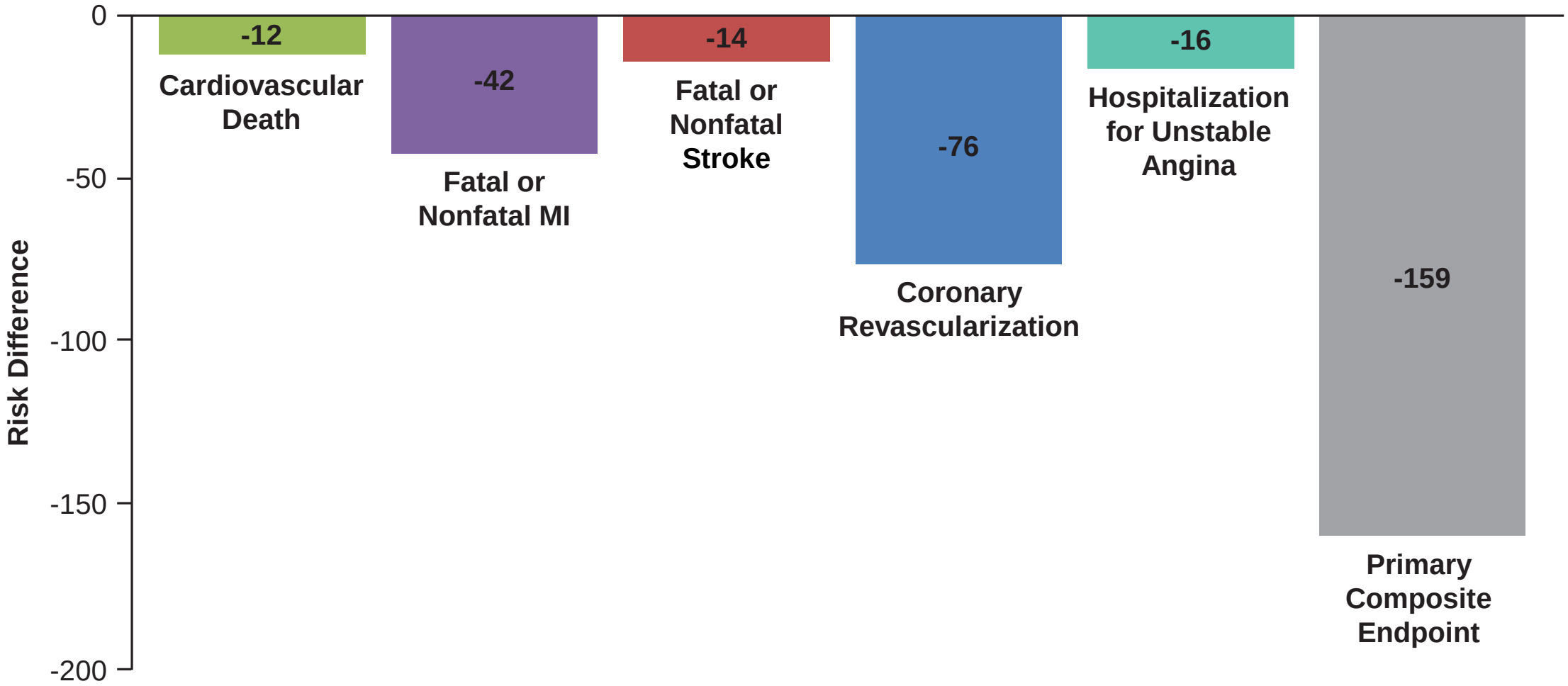
Primary: CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

Primary Composite Endpoint



Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

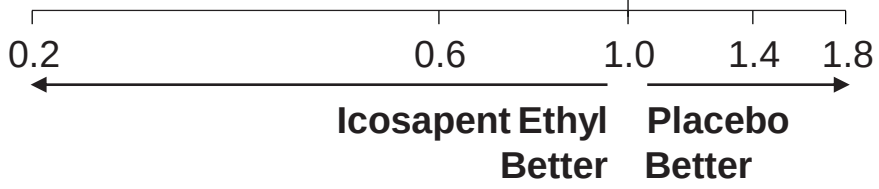
For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:



Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

Primary Composite Endpoint: Total Endpoint Events by Baseline TG Tertiles

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



***P (interaction) = 0.17**

Bhatt DL. ACC 2019, New Orleans.

Conclusions

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

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

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

Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019. Bhatt DL. ACC 2019, New Orleans.

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

Treatment of Other Lipoprotein Fractions or Targets:

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

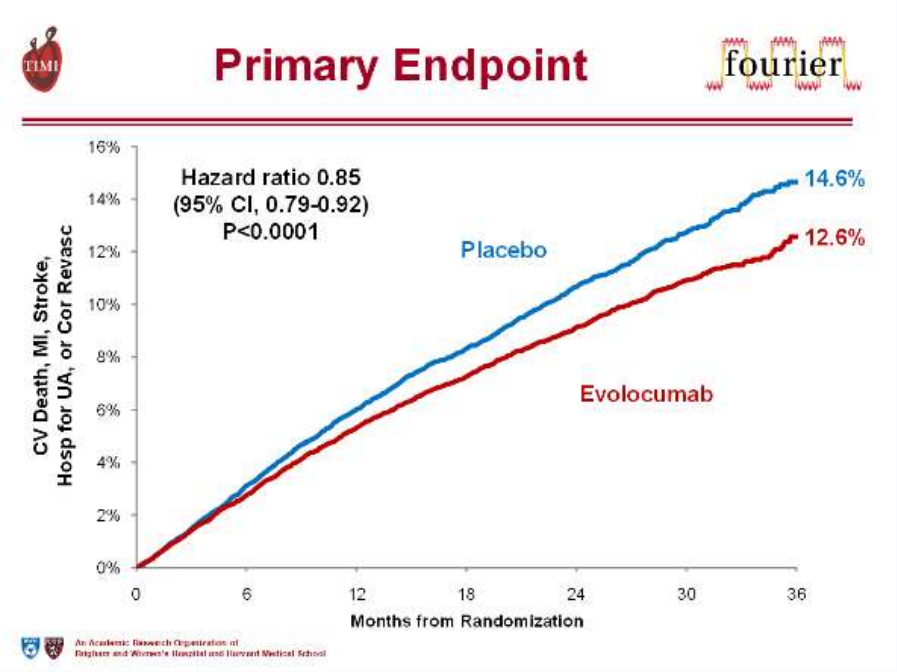
“It should be noted that data are lacking with other omega-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products."

American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes—2019 [web annotation]. Diabetes Care 2019;42(Suppl. 1):S103–S123. Retrieved from https://hyp.is/JHhz_lCrEembFJ9LIVBZIw

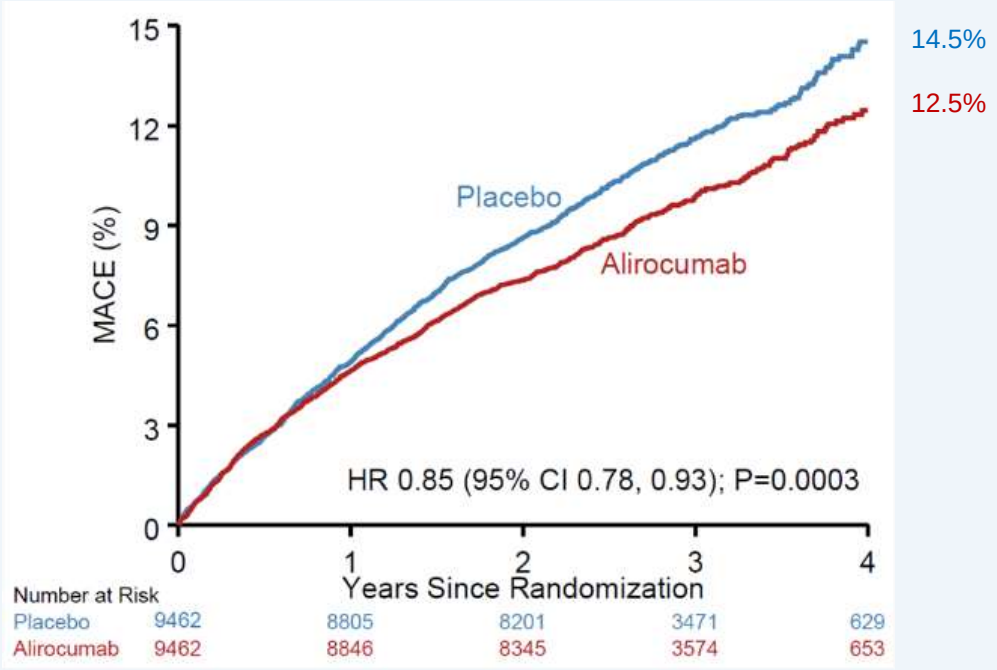
Practical Considerations to Manage Residual Risk

Sergio Fazio, MD, PhD

Maximal LDL-C Lowering with PCSK9 inhibitors Reduces MACE Events without Affecting hsCRP Levels



FOURIER[1]

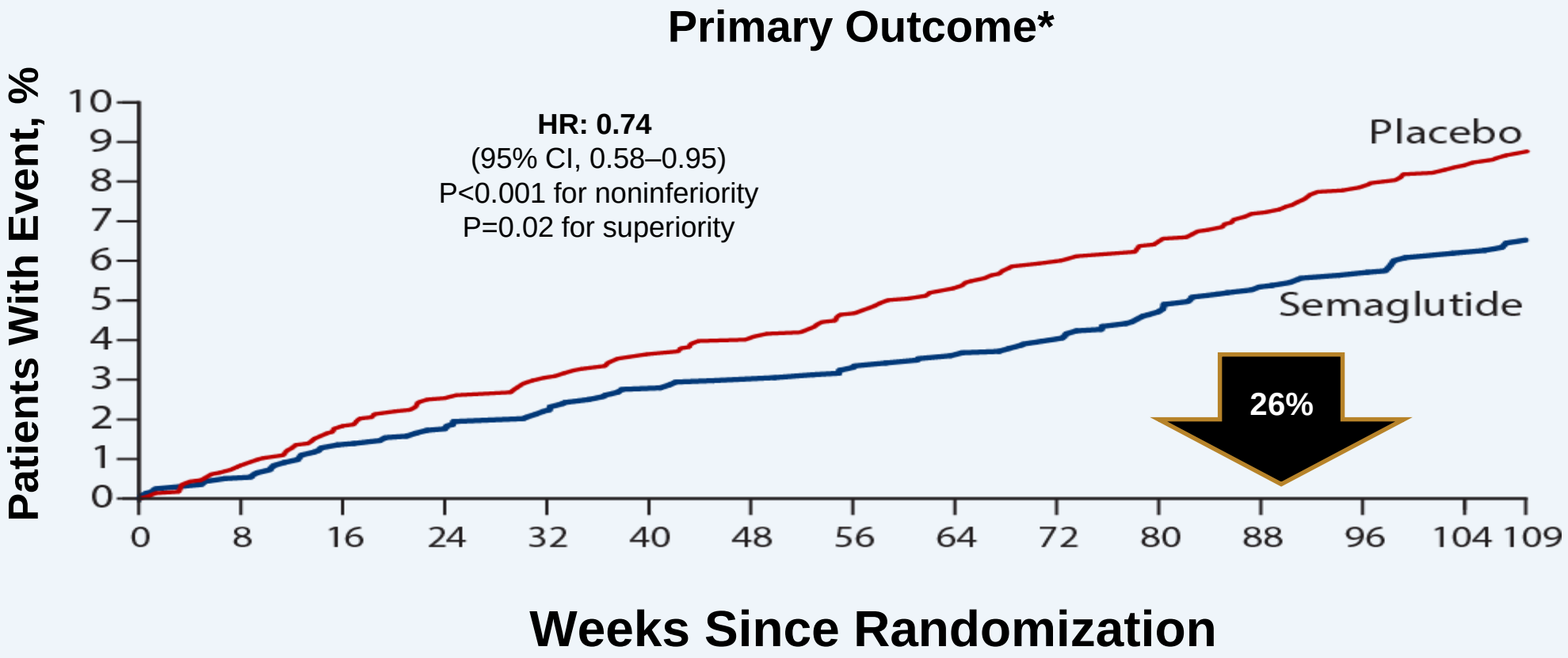


ODYSSEY Outcomes[2]

CI=confidence interval; Cor Revasc=coronary revascularization; HR=hazard ratio; MACE=major adverse cardiovascular events; MI=myocardial infarction; UA=unstable angina.

1. Sabatine MS et al. *N Engl J Med.* 2017;376:1713-22. 2. Schwartz GG et al. *N Engl J Med*. 2018;379:2097-107.

SUSTAIN-6 Study: *Semaglutide vs Placebo*

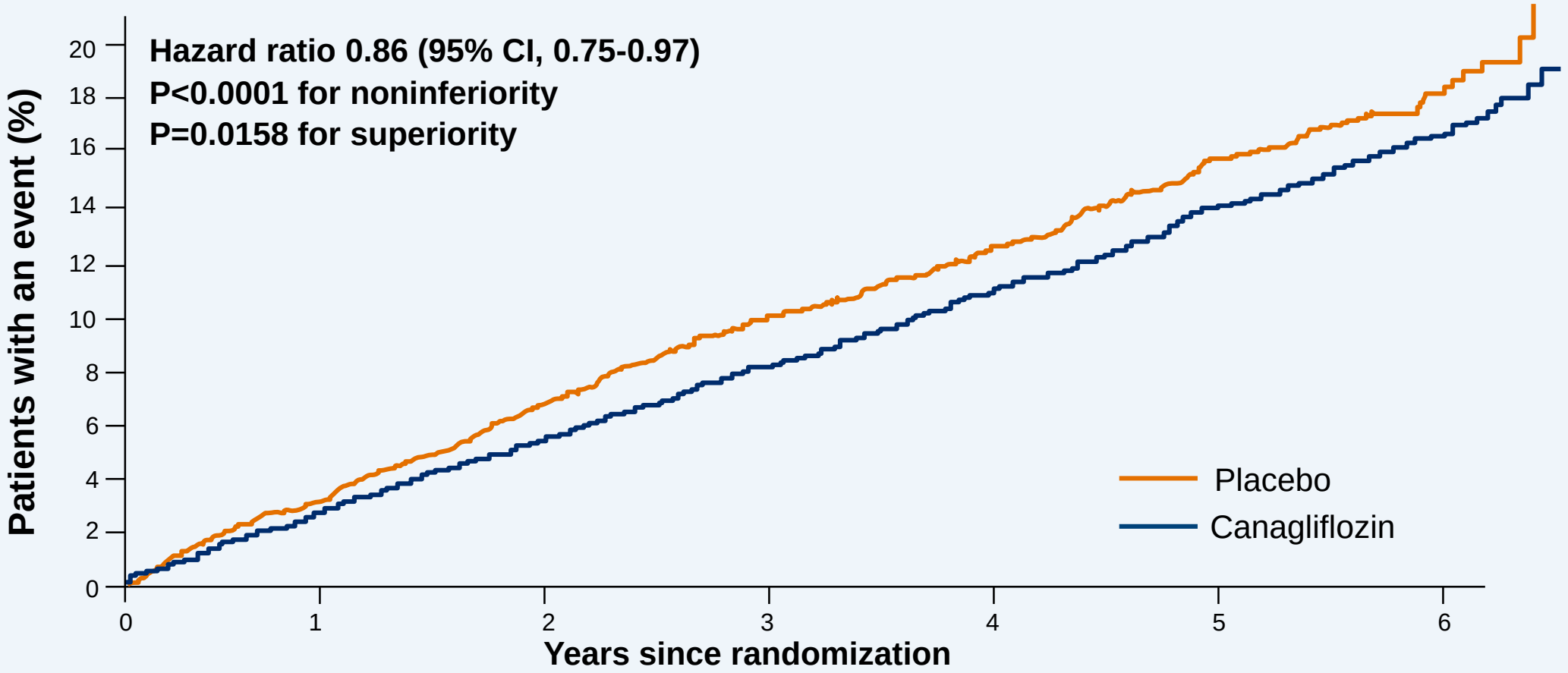


*Death from CV causes, nonfatal MI, or nonfatal stroke.

Marso SP et al. *N Engl J Med*. 2016;375:1834-44.

Primary MACE Outcome CANVAS

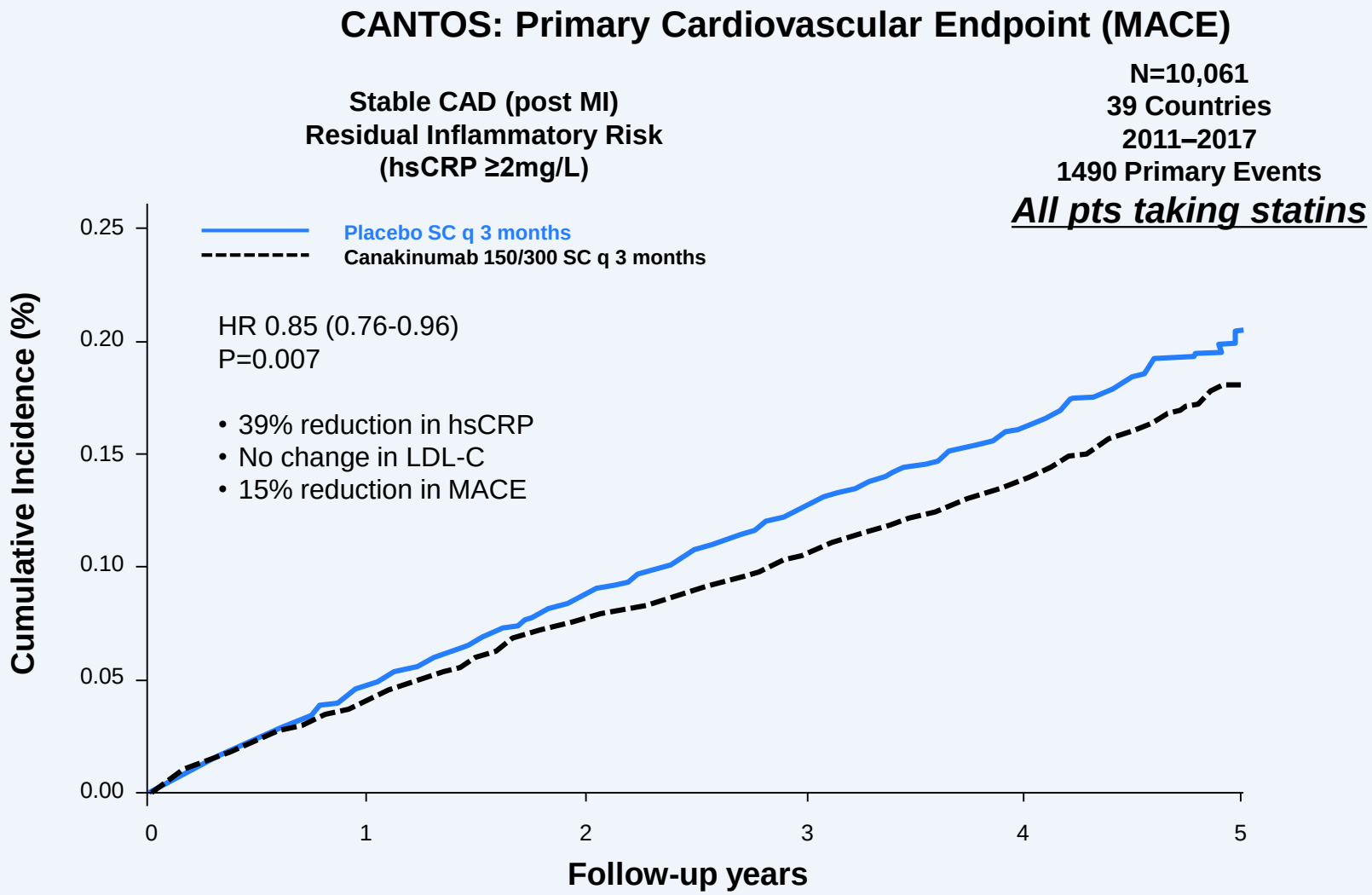
CV Death, Nonfatal Myocardial Infarction, or Nonfatal Stroke



No. of patients							
Placebo	4347	4153	2942	1240	1187	1120	789
Canagliflozin	5795	5566	4343	2555	2460	2363	1661

Intent-to-treat analysis. d'Emden M et al. *Diabetes Res Clin Pract*. 2018;136:23-31.

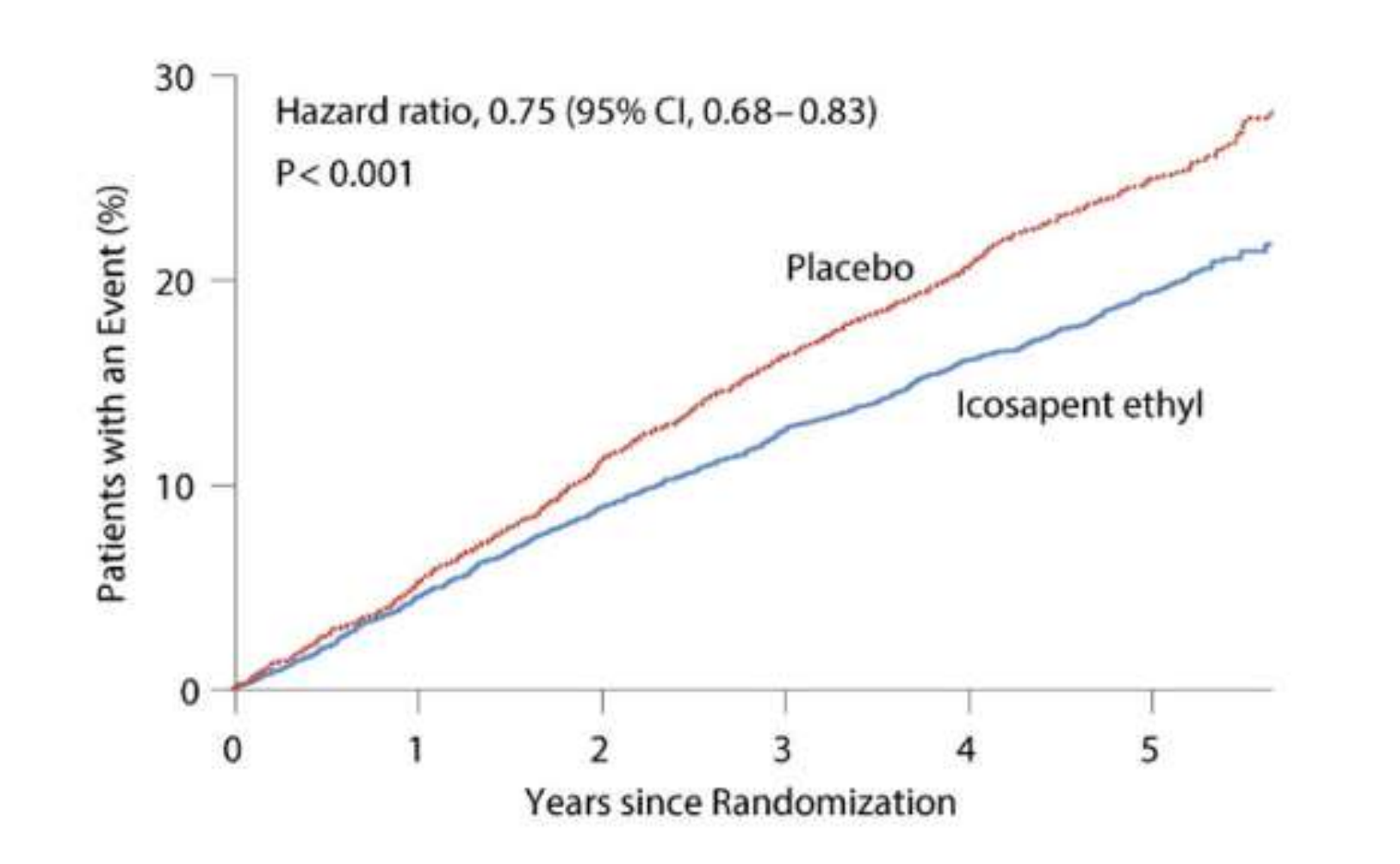
CANTOS: Reducing hsCRP Levels with an Anti IL1-beta mAb Reduces CV Events without Affecting LDL-C levels



Ridker PM et al. *N Engl J Med*. 2017;377:1119-31.

REDUCE-IT:

EPA Drastically Lowers CVD Risk in Hypertriglyceridemic Subjects with LDL-C At Goal



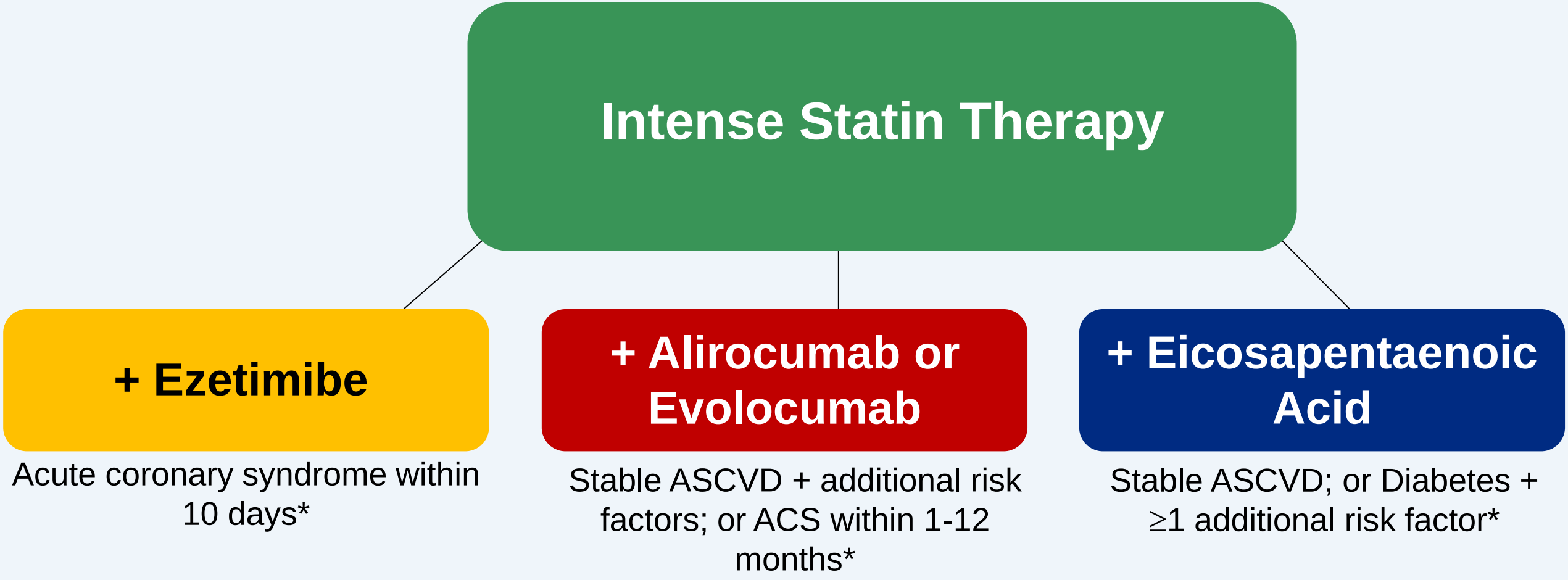
Bhatt DL et al. *N Engl J Med.* 2019;380:11-22.

Why Did EPA Significantly Reduce CVD Events When Other OM-3s Did Not?

- REDUCE-IT & JELIS: Highest doses among all OM-3 CVOTs[1]
- EPA: ≥96% pure single-molecule agent
- EPA ↓hepatic VLDL-TG synthesis and/or secretion & enhances TG clearance
- EPA appears to improve ASCVD risk factors beyond TG-lowering[2]
  - ↓LDL oxidation
  - ↓CV-related inflammatory parameters
  - ↓Platelet aggregation
  - ↓Cholesterol crystal formation
  - ↑Cell-membranes stability
  - ↑Endothelial function
  - ↑HDL function

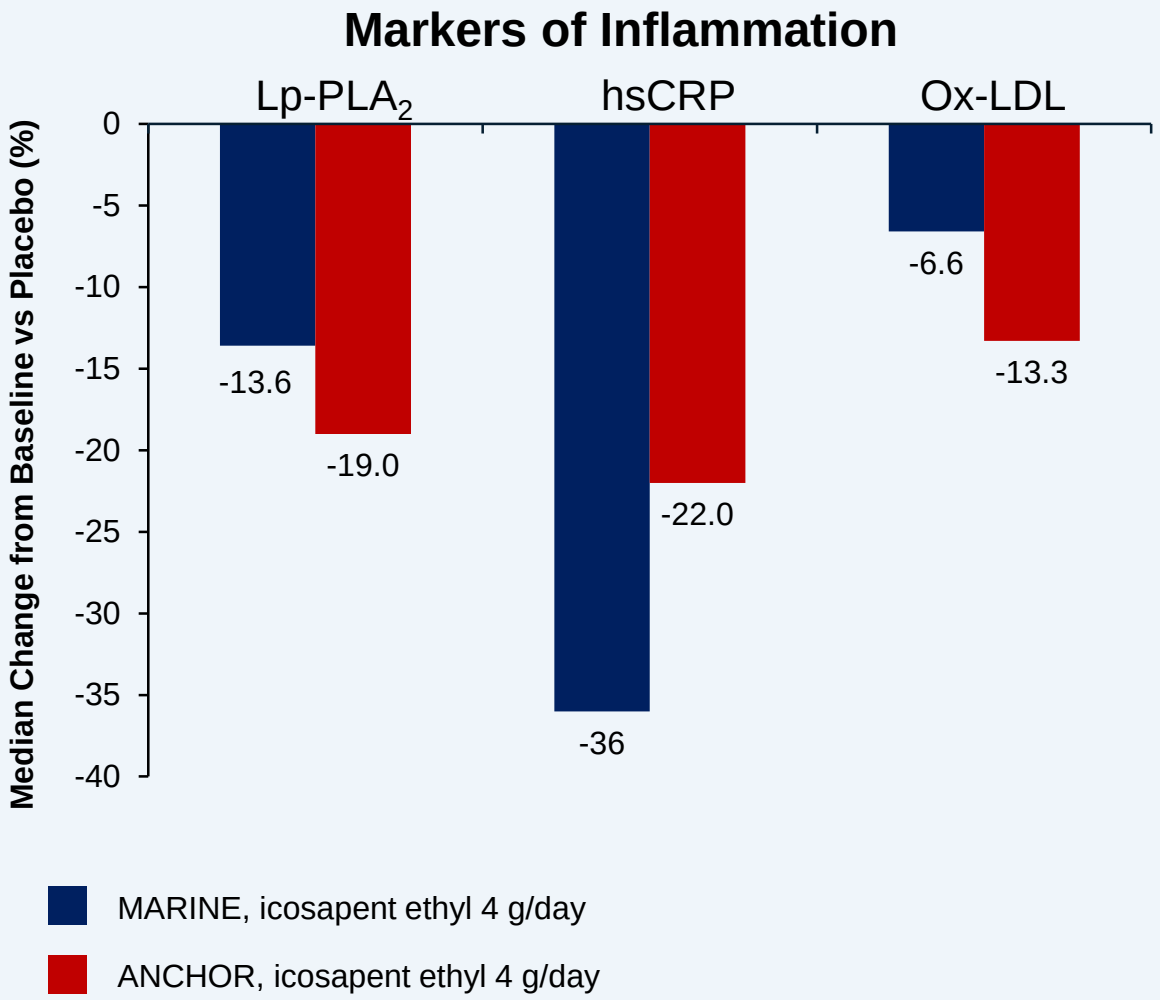
1. Aung T et al. *JAMA Cardiol*. 2018;3:225-34. 2. Mason RP. *Curr Atheroscler Rep.* 2019;21:2. Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46. Dunbar RL et al. *Lipids Health Dis*. 2015:14:98. Ridker PM et al. *N Engl J Med*. 2008;359:2195-207. Bohula EA et al. *Circulation*. 2015;132:1224-33. Mason RP et al. *J Cardiovasc Pharmacol*. 2016;68:33-40. Sherratt SCR, Mason RP. *Chem Phys Lipids.* 2018; 212:73-9. Mason RP et al. *Biochim Biophys Acta*. 2016;1858:3131-40. Mason RP, Jacob RF. *Biochim Biophys Acta*. 2015;1848:502-9. Mason RP et al. *Biomed Pharmacother*. 2018;103:1231-7. Tanaka N et al. *Atherosclerosis*. 2014;237:577-83. Tanaka N et al. *Circ J*. 2018;82:596-601. Sherratt SCR, Mason RP. *Biochem Biophys Res Comm*. 2018;496:335-8.

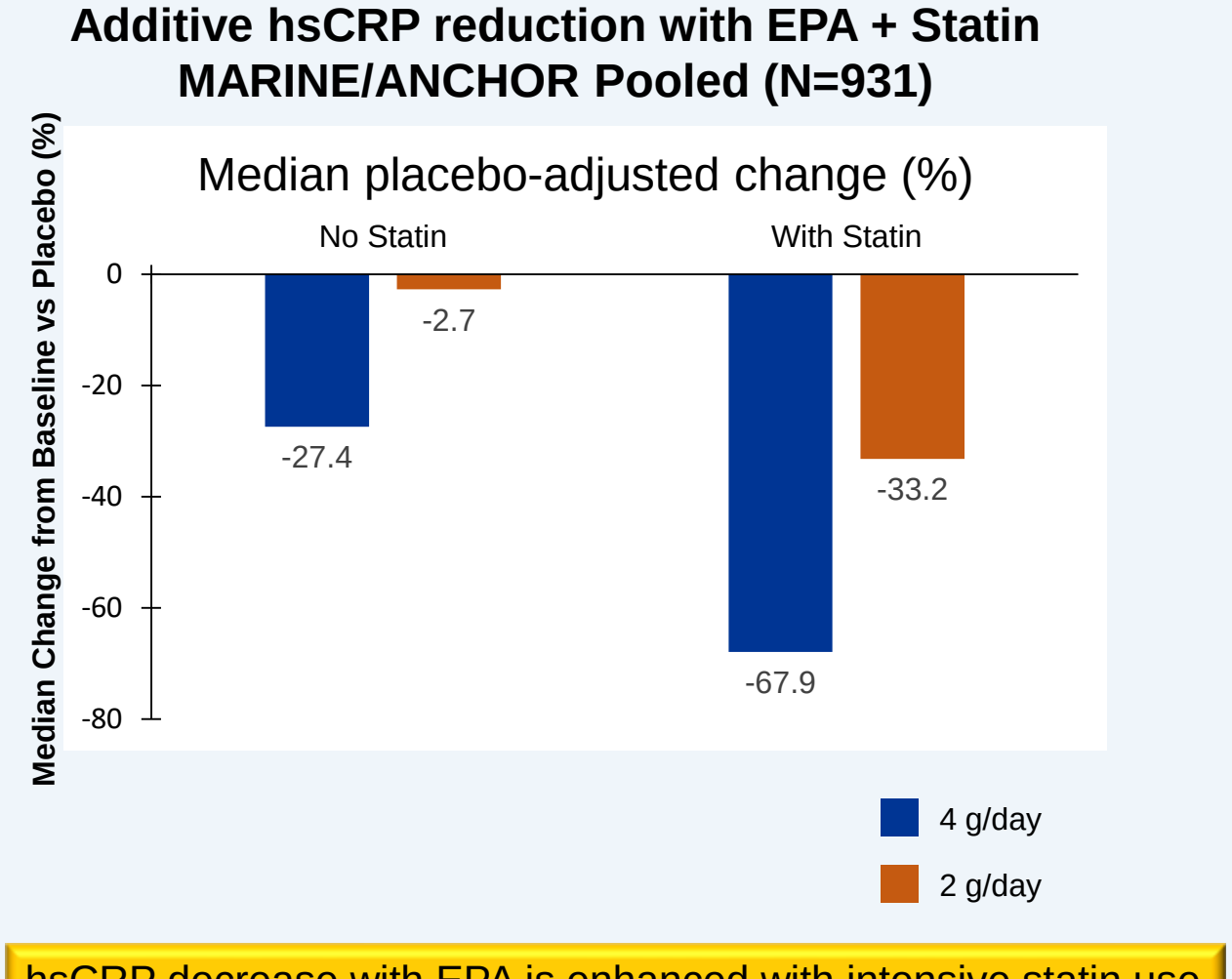
Statin Therapy Adjuncts Proven to Reduce ASCVD



*Major inclusion criteria for each trial.
ACS=acute coronary syndrome; ASCVD=atherosclerotic cardiovascular disease.
After Orringer C. Oral Discussion of REDUCE-IT presentation; AHA 2018, Chicago.

EPA Treatment Lowers Levels of Inflammatory and Oxidative Markers





hsCRP decrease with EPA is enhanced with intensive statin use

MARINE studied 229 patients with very high TG levels ≥500 mg/dL. ANCHOR studied 702 patients with well-controlled LDL-C and residually high TG levels 200–500 mg/dL.
Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46.

Lipid Therapies and hsCRP Levels

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

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

Mechanism-based Statin-adjunct Therapy for ASCVD Prevention

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

Residual Risk Factors

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

REDUCE-IT?

ASO=antisense oligonucleotide.

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

CV Outcomes Trials in Patients with HTG

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

*Locations: International sites; Statistics: Powered for 15% RRR.

REDUCE-IT: Bhatt DL et al. *N Engl J Med.* 2019;380:11-22. STRENGTH: NCT02104817. PROMINENT: NCT03071692.

Omega-3 FA Products
Prescription

- Omega-3 *fatty acid ethyl esters*
  - Lovaza® + generics
    - 2 g BID with food or 4 g Qday with food
- EPA *ethyl esters*
  - Vascepa®
    - 2 g BID with food
- Omega-3 *carboxylic acids* (free fatty acid form)
  - Epanova®
    - 2-4 g daily with/without food
    - Product currently not available commercially

Backes J et al. *Lipids Health Dis*. 2016;15:118.

Fish Oil – Prescription

- Pros
  - Pure
  - Consistent
  - Value of prescription
    - Counseling
    - Monitoring
  - Greater adherence
  - Adverse effects
- Cons
  - Cost
    - High copay
    - Formulary coverage
  - Insurance changes
  - Patient perception
  - Expanded indication for EPA-only product
  - Guideline recommendation for EPA-only product

Dietary Supplements vs Rx Fish Oil

	Prescription	Dietary Supplements
FDA Product Classification	**Drug**	**Food**
Clinical Trials Required Pre-approval	**Yes**	**Not required** **FDA has to prove that a supplement is not safe to restrict use or remove from the market**
FDA Pre-approval	**Yes**	**No** **Proof of efficacy not required**
Content and Purity	• **Adhere to strict standards for content and purity** • **Digested content is pure**	• **Contains variable amounts of omega-3 FA** • **Most do not contain labelled content of omega-3 FA** • **Up to 36% dietary supplement omega-3 FA content is saturated fat** • **Oxidation** • **Contamination**
Substitution	**DHA/EPA combination products are not equivalent to EPA-only products**	**OM-3 FA dietary supplements are not equivalent to and should not be substituted for Rx OM-3 FA products**

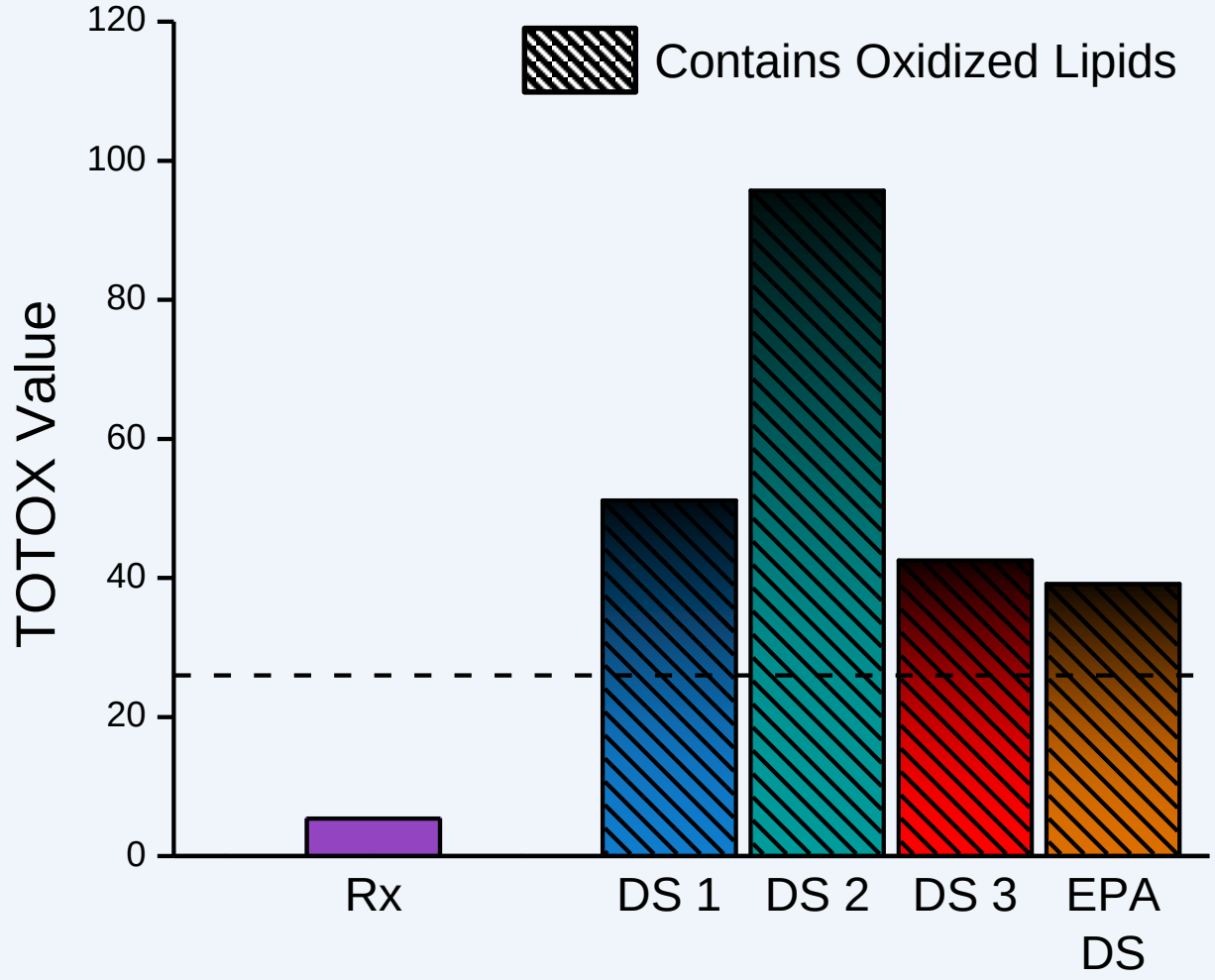
- Leading DS taken by US adults is fish oil[1]
  - 19 million fish oil DS consumed each month[1]
- ~80% of PharmDs and MDs who recommend fish oil supplements think that they are OTC[2]
  - 30% of PharmDs and 22% of MDs believe Rx and DS are similar in strength and content[2]

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

Fish Oil Dietary Supplements Are Widely Used

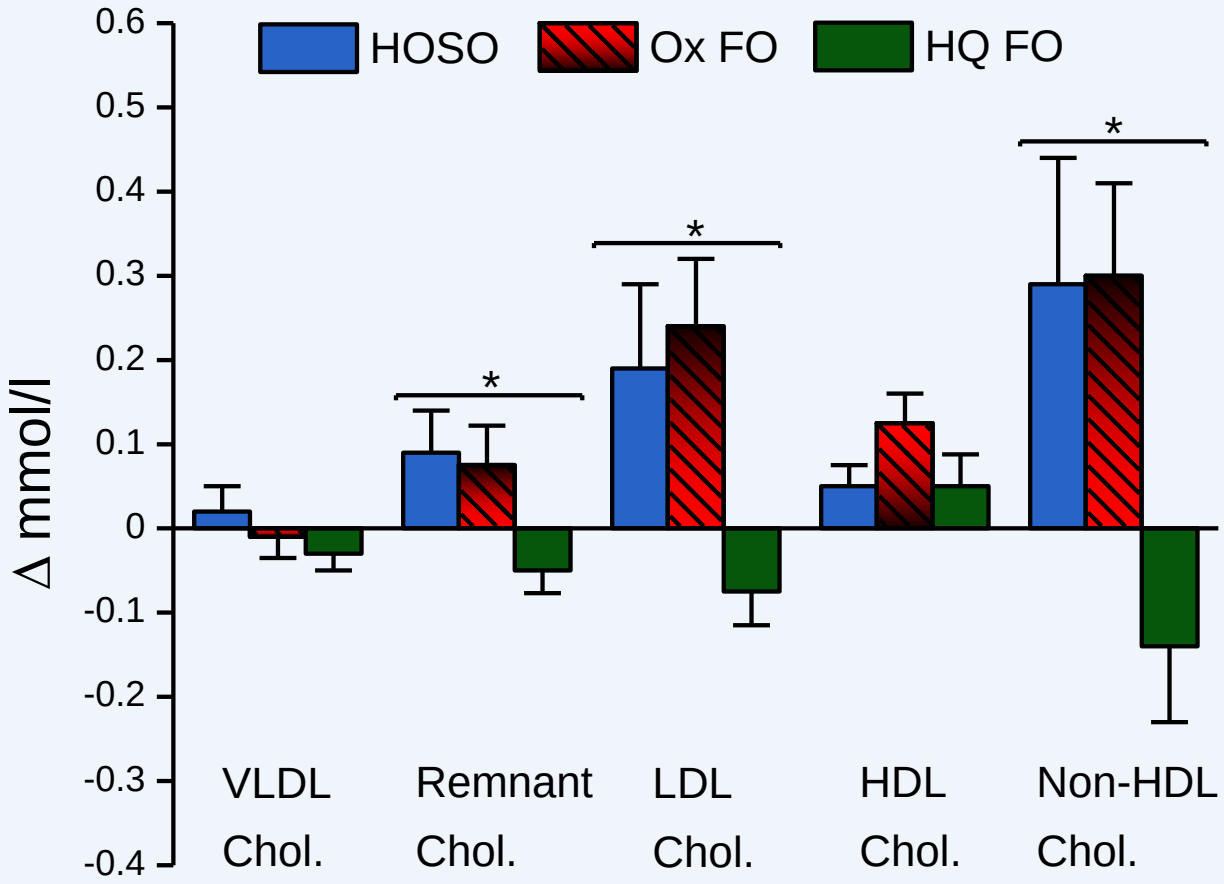
- Not over-the-counter but unregulated dietary supplements
- Estimated global market for omega-3 products was $31 billion in 2015
- In a large UK prospective study, 31% of adults reported taking fish oils
- Estimates suggest 7.8% of US population (19 million people) take fish oil supplements
- Benefits claimed on the heart, brain, weight, vision, inflammation, skin, pregnancy and early life, liver fat, depression, childhood behavior, mental decline, allergies, bones…

Supplement Total Oxidation Values Exceed International Thresholds



International threshold for oxidation (US Council for Responsible Nutrition. Voluntary Monograph: Omega-3 DHA, Omega-3 EPA, Omega-3 DHA & EPA (2006). Available at: http://www.crnusa.org/pdfs/O3FINALMONOGRAPHdoc.pdf. [Date of access: 09/04/2015].
Adapted from: Mason RP, Sherratt SCR. *Biochem Biophys Res Commun.* 2017;483:425-9.

Oxidized Fish Oil Negatively Impacts Key Lipid Factors



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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 December 2018
EMA/712678/2018

Omega-3 fatty acid medicines no longer considered effective in preventing heart disease

EMA has concluded that omega-3 fatty acid medicines are not effective in preventing further heart and blood vessels problems in patients who have had a heart attack. The conclusion, based on a review of data accumulated over the years, means that these medicines will no longer be authorised for such use.

Omega-3 fatty acid medicines have been authorised for use after a heart attack, in combination with other medicines, in several EU countries since 2000, at a dose of 1 g per day. At the time of their authorisation, available data showed some benefits in reducing serious problems with the heart and blood vessels, although the benefits were considered modest. Further data that have become available since then have not confirmed the beneficial effects of these medicines for this use.

Although there are no new safety concerns, EMA's human medicines committee (CHMP) concluded that the balance between the benefits and risks of these medicines to prevent recurrence of heart disease or stroke is now negative.

These medicines can still be used to reduce levels of certain types of blood fat called triglycerides.

Conclusions

- We are now faced with several options to reduce CVD risk by addressing different components of residual risk
- LDL control, inflammation control, use of cardio-protective anti-diabetic agents, and use of EPA are effective strategies in appropriate patients
- Treatment with EPA affects the CVD risk attributable to hypertriglyceridemia, although risk reduction is not explained by TG lowering
- Omega 3 supplements are not likely to provide similar benefits