New Opportunities to Improve Management of Patients with or at High Risk of ASCVD Events: *You Weigh the Evidence*

SEPTEMBER 25, 2019 | LOEWS PHILADELPHIA HOTEL | PHILADELPHIA, PA

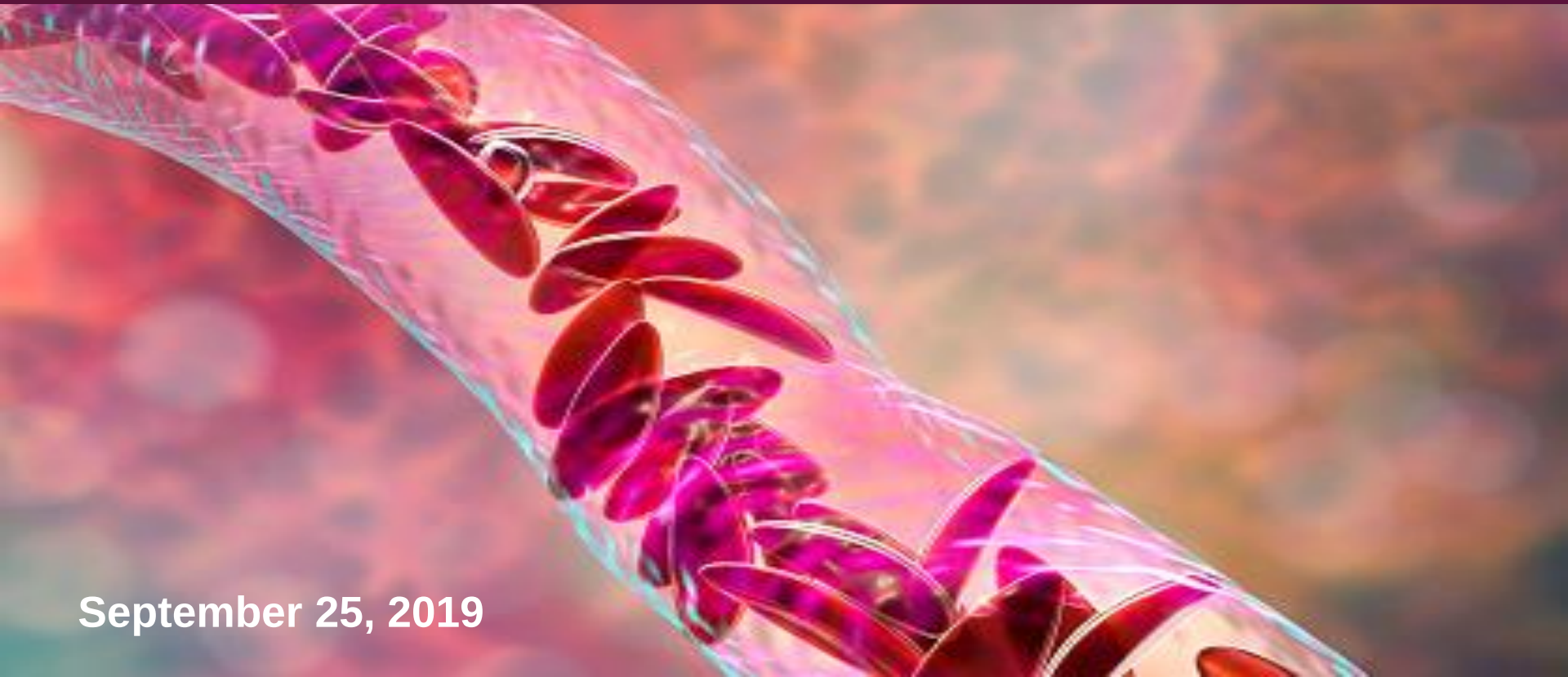
AGENDA

6:00 PM	Registration and Buffet Dinner
6:30 PM	Program Overview
6:40 PM	New Cholesterol Guidelines: What You Should Know
6:55 PM	Update on Cardiovascular Outcomes Trials of Adjunctive Therapies to Statins
7:15 PM	Personalizing Management of ASCVD Risk Factors
7:30 PM	Case Presentations on ASCVD Prevention
7:45 PM	Panel Discussion and Question & Answer Session
8:00 PM	Adjourn

Faculty slides are available online: **medtelligence.net/Sept25**

Scroll to the "Related" section and click on "Syllabus"

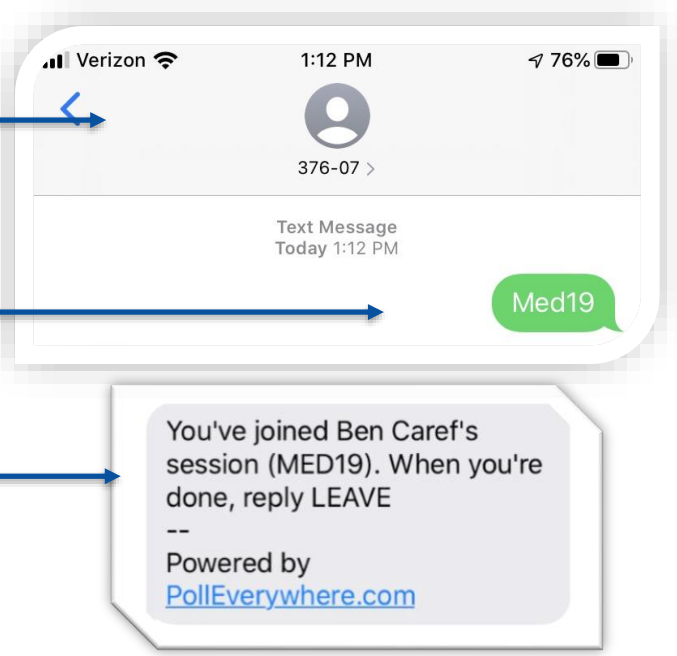
New Opportunities to Improve Management of Patients with or at High Risk of ASCVD Events: *You Weigh the Evidence*



September 25, 2019

Instructions for Audience Response

- Use your smartphone text messaging app
  - Message To: 37607
  - Text Message: MED19
  - You should receive a text message back



- To answer a presenter's question, text message to 37607 and press A, B, C, D, etc.

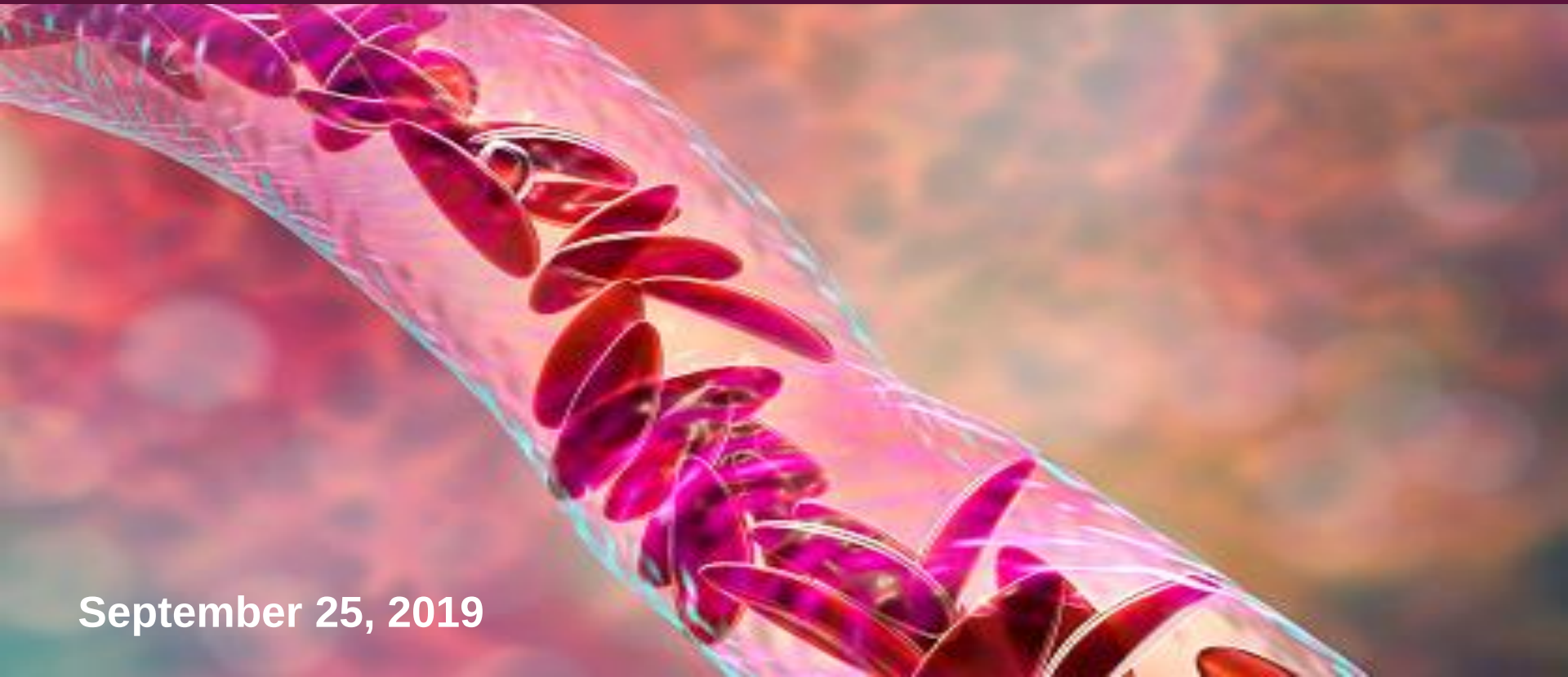
What best describes your profession?

A. Family practice
B. Resident
C. Student
D. Life member
E. Other healthcare provider
F. Not involved in patient care

How many patients with dyslipidemia(s) do you typically see each week?

A. None
B. 1-20
C. 21-40
D. 41-60
E. >60

New Opportunities to Improve Management of Patients with or at High Risk of ASCVD Events: *You Weigh the Evidence*



September 25, 2019

Welcome and Program Overview

DEEPAK L. BHATT, MD, MPH, CHAIR

Tonight's Faculty

Deepak L. Bhatt, MD, MPH, Chair
Executive Director of Interventional Cardiovascular Programs
Brigham and Women's Hospital Heart and Vascular Center
Professor of Medicine
Harvard Medical School
Boston, MA

Erin D. Michos, MD, MHS
Associate Professor of Medicine and Epidemiology
Ciccarone Center for the Prevention of Cardiovascular Disease
Division of Cardiology
Johns Hopkins School of Medicine
Baltimore, MD

Meeting Announcements

- In your folder:
  - Agenda
  - Faculty bios
  - Learning objectives
  - CME information
- Question cards on table
- No unauthorized recording devices allowed (audio, video, cell, camera)
- Place cell phones on vibrate or silence mode
- Submit questions to faculty by using a question card

Online materials for this CME activity

Access slides online

- Faculty slides are available here: medtelligence.net/sept25
- Scroll to the “Related” section and click on “Syllabus”

Online CME credit

- All attendees will receive an email with a link to the evaluation form
- Once you complete the online evaluation form, you will receive an email with a link to download your CME certificate
  - Or, you can access your certificate within your Medtelligence/ReachMD Profile

Grab your smartphones or iPads!

Learning Assessment 1

What does the 2018 ACC/AHA Guideline on Blood Cholesterol Management algorithm recommend for a 69 y/o man with clinical ASCVD?

A. Put patient on low-intensity statin therapy and healthy lifestyle
B. Put patient on moderate-intensity statin therapy
C. Put patient on high-intensity statin therapy
D. Treat to obtain an LDL-C reduction of 25%

ACC=American College of Cardiology; AHA=American Heart Association; ASCVD=atherosclerotic cardiovascular disease; LDL-C=low-density lipoprotein cholesterol.

Learning Assessment 2

You have a patient with clinical ASCVD who has a TG level of 212 mg/dL and an LDL-C of 69 mg/dL. Which of the following should you recommend?

A. Fibrate (eg, fenofibrate)
B. Nicotinic acid (eg, niacin)
C. Prescription EPA
D. Omega-3 dietary supplement
E. Nothing

ASCVD=atherosclerotic cardiovascular disease; EPA=eicosapentaenoic acid; LDL-C=low-density lipoprotein cholesterol; TG=triglyceride(s).

Learning Assessment 3

Compared with placebo in REDUCE-IT, pure eicosapentaenoic acid (EPA) 4 g/day reduced the primary endpoint (5-point MACE) by

A. 15%

B. 25%

C. 50%

D. No difference in events

MACE=major adverse cardiovascular events; REDUCE-IT=Reduction of CV Events with Icosapent Ethyl – Intervention Trial.

New Cholesterol Guidelines: What You Should Know

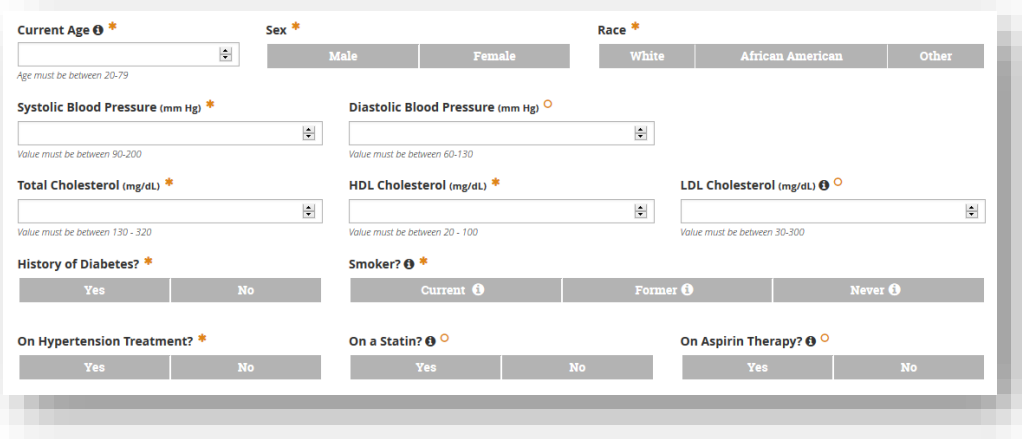
ERIN MICHOS, MD, MHS

ACC Risk Calculator Plus to Assess Risk Category

1. For primary prevention, 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

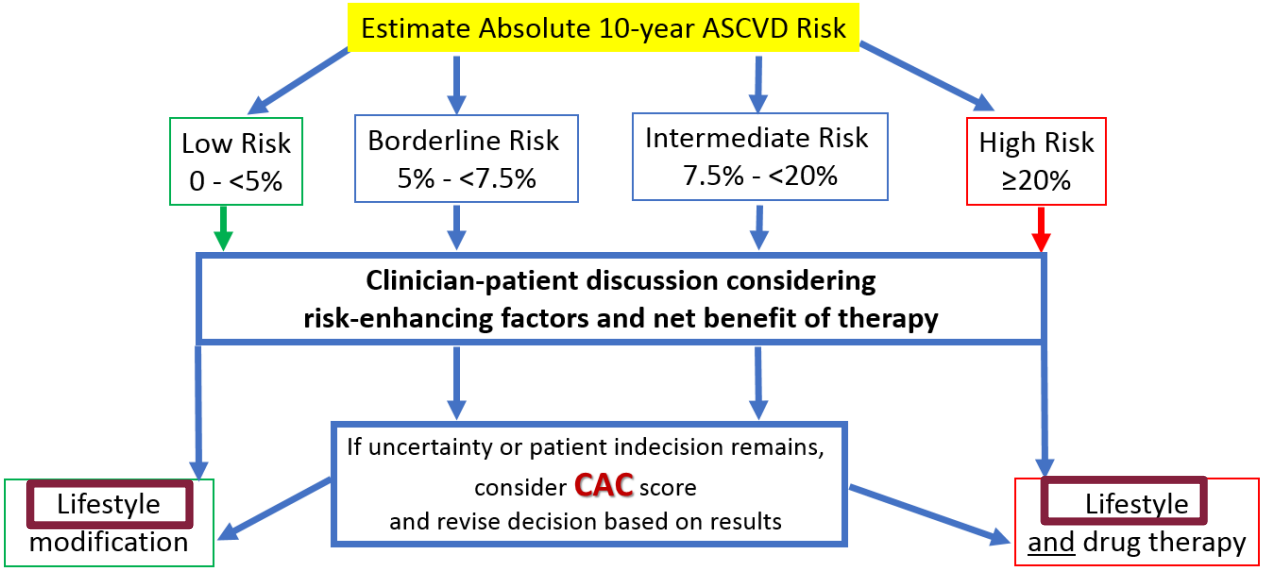


2. Then use the new ACC/AHA Blood Cholesterol guideline algorithms to guide management

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

2019 ACC/AHA Primary Prevention Guideline

Assessment of ASCVD: Lifelong Lifestyle



Courtesy of Erin Michos.

Nutrition Lifestyle Recommendations: Lipids and BP

- **Dietary patterns emphasis-based**:
  - DASH and Mediterranean-style eating plans
- Fruits, vegetables, and whole grains
- 30 – 35% fat intake
  - <6% saturated fats, no *trans* fats
- Low sodium (<2400 mg/day)
- Cut out processed or pre-prepared food
- Healthy eating for a lifetime

Eckel RH et al, *Circulation* 129 (25 Suppl 2):S76-99, 2014.

Physical Activity Guidelines: Lipids and BP

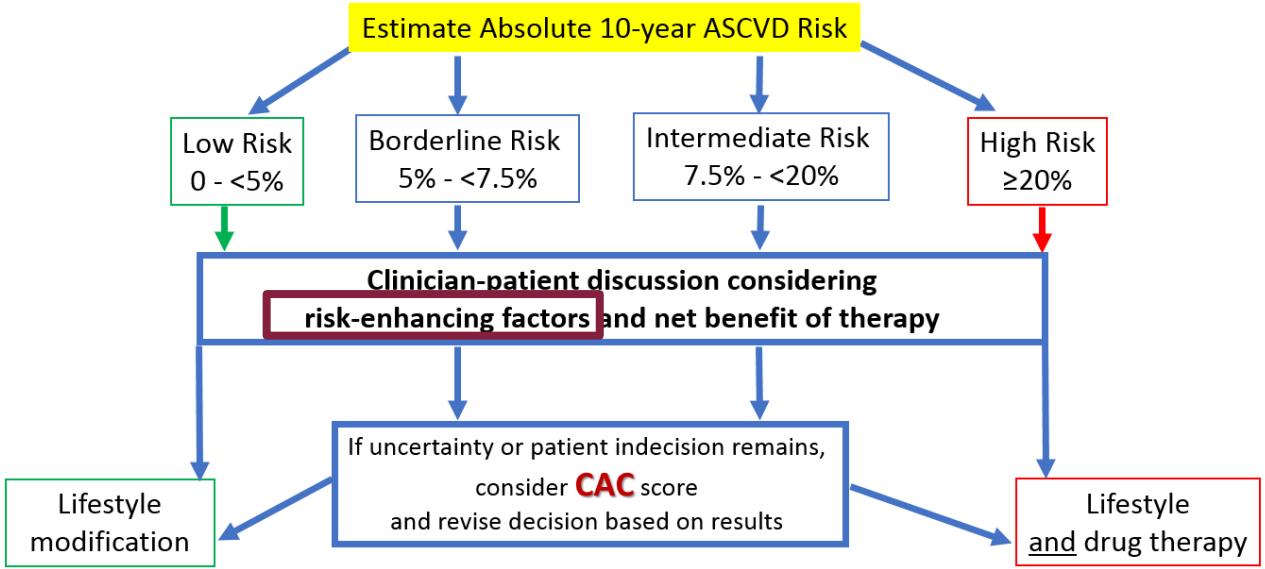
Advise adults to engage in aerobic physical activity

- 3 to 4 sessions a week
- lasting on average 40 min per session
- involving moderate-to-vigorous intensity physical activity.

Eckel RH et al, *Circulation* 129 (25 Suppl 2):S76-99, 2014.

2019 ACC/AHA Primary Prevention Guideline

Assessment of ASCVD: Risk Enhancing Factors



Courtesy of Erin Michos.

2019 ACC/AHA Primary Prevention Guideline: Risk Enhancing Factors

Risk-Enhancing Factors
• **Family history of premature ASCVD (men, age <55y; women, <65 y)**
• **Primary hypercholesterolemia** (LDL-C 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])
• **Metabolic syndrome** (**increased waist circumference** [by ethnically appropriate cutpoints], **elevated triglycerides [>150 mg/dL, nonfasting**], **elevated blood pressure, elevated glucose**, and low HDL-C [<40 mg/dL in men; <50 mg/dL in women] are factors; a tally of 3 makes the diagnosis)
• **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
• **Chronic inflammatory conditions,** such as psoriasis, RA, lupus, or HIV/AIDS

Grundy SM et al. Circulation. 2019;139:e1082-e1143.

2019 ACC/AHA Prevention Guideline: Risk Enhancing Factors, cont'd

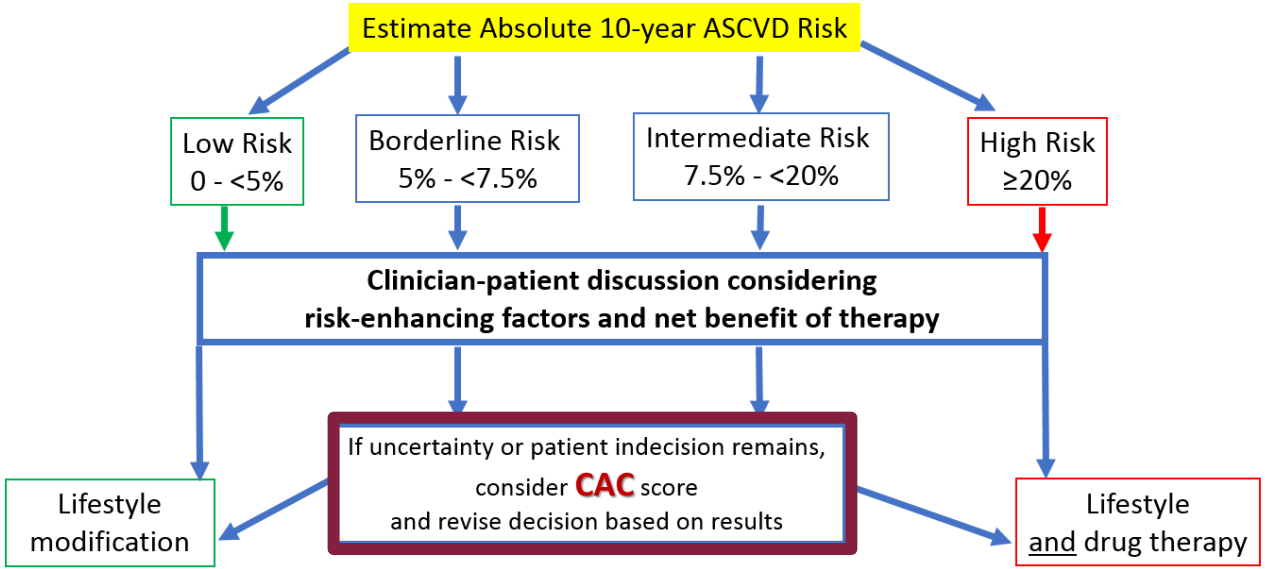
Risk-Enhancing Factors

- **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia**
- **High-risk race/ethnicity** (e.g., South Asian ancestry)
- **Lipids/biomarkers**: associated with increased ASCVD risk
- Persistently elevated, primary hypertriglyceridemia (≥175 mg/dL, nonfasting);
- If measured:
  - **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
  - **Elevated Lp(a):** Lp(a) ≥50 mg/dL or ≥125 nmol/L, especially at higher levels of Lp(a)
  - **Elevated apoB** (≥130 mg/dL): A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL
  - **ABI** <0.9

Grundy SM et al. Circulation. 2019;139:e1082-e1143.

2019 ACC/AHA Primary Prevention Guideline

Assessment of ASCVD: Use of CAC



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. Circulation. 2019;139:e1082-e1143.

Major Secondary Causes of Hypertriglyceridemia

- Diabetes Mellitus, Insulin Resistance
- Obesity
- Alcohol
- Chronic Kidney Disease
- Nephrotic syndrome
- Hypothyroidism
- HIV
- Hepatocellular disease
- Inflammatory diseases

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

Medications that Cause of Hypertriglyceridemia

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

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Hypertriglyceridemia

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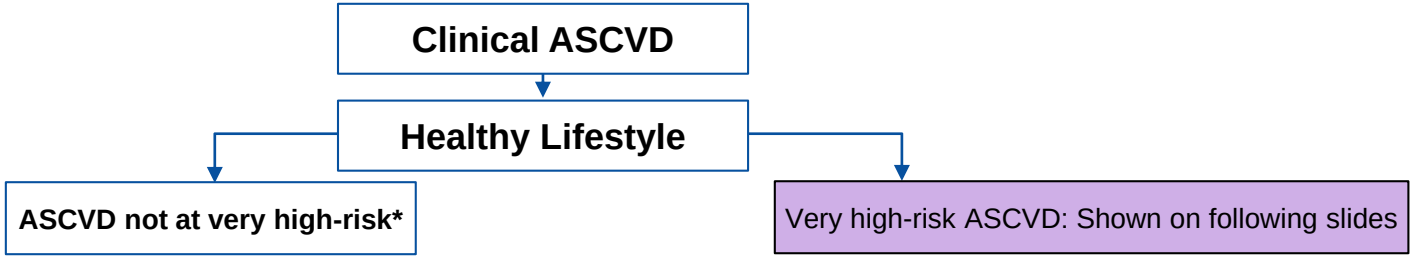
2018 AHA/ACC/ Multi-Society Guideline on the Management of Blood Cholesterol: Secondary Prevention

2018 AHA/ACC/ Multi-Society 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. 2019;139:e1082-e1143.

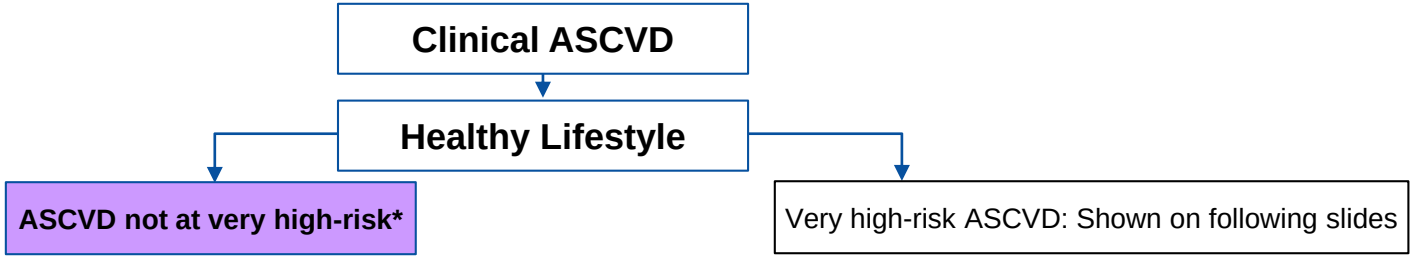
Very High-Risk ASCVD Patients

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)
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)
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

***Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions**.

Grundy SM, Stone NJ et al. AHA/ACC/Multi-Society 2018 Chol Guidelines. Circulation. 2019;139:e1082-e1143.

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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Grundy SM et al. *Circulation*. Circulation. 2019;139:e1082-e1143.

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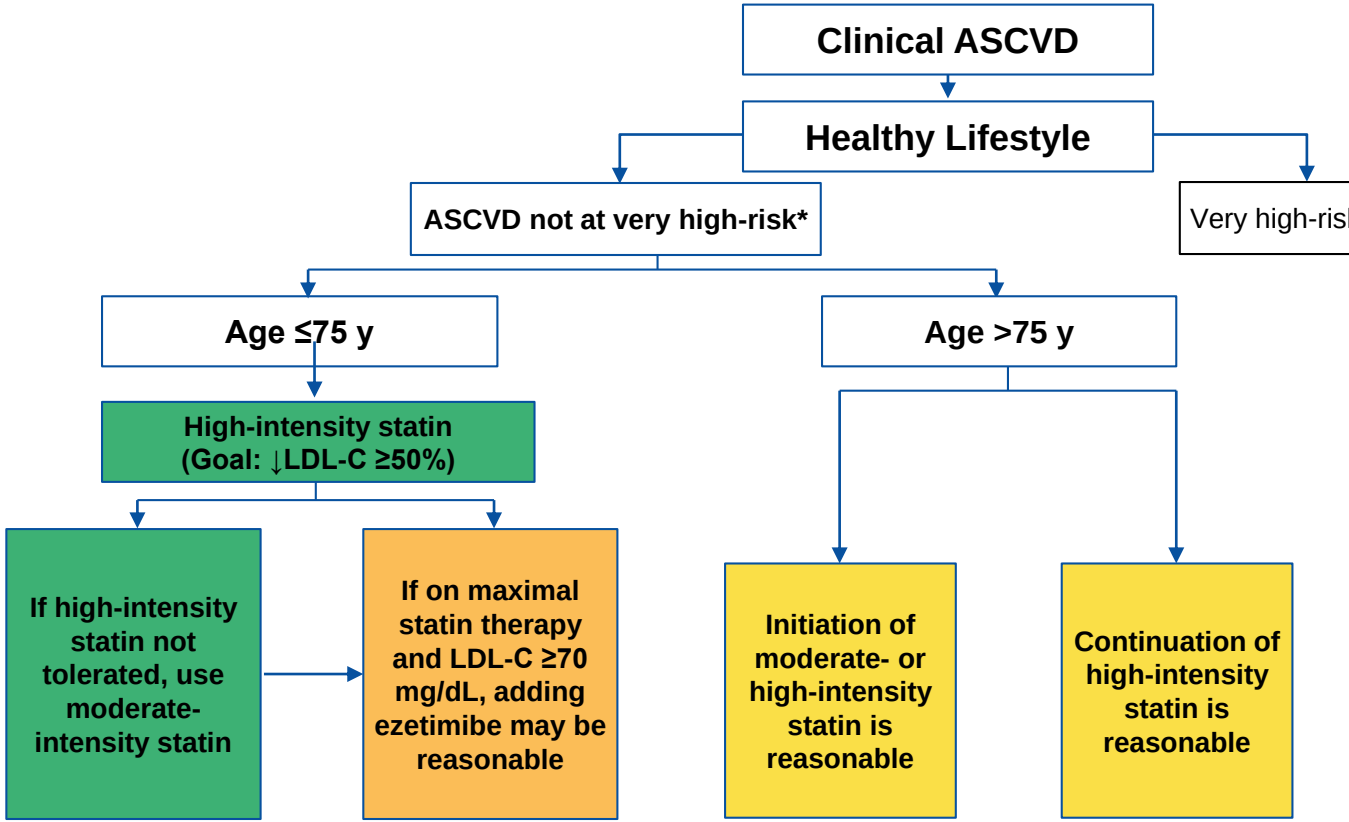

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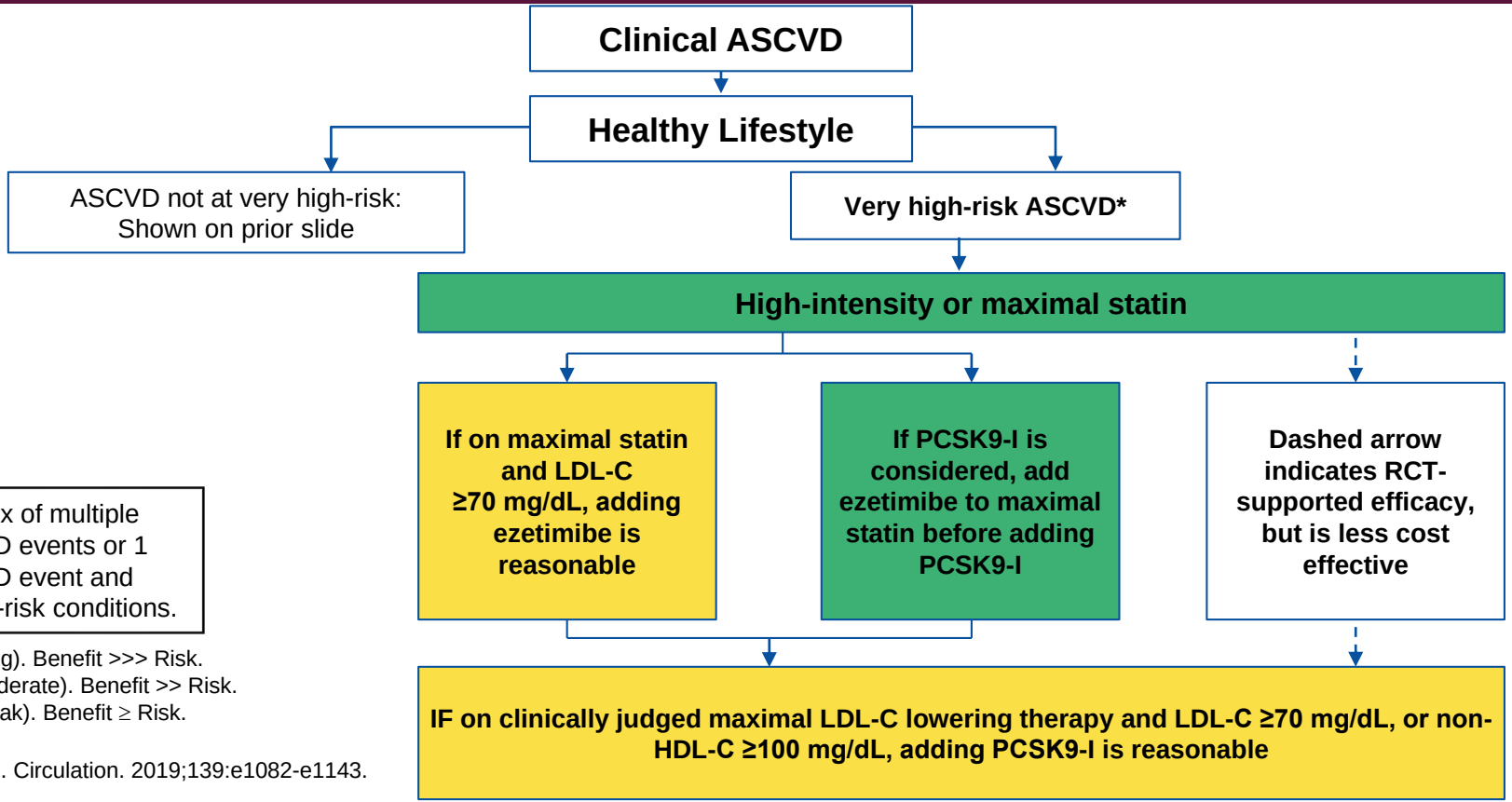

*Includes a hx of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

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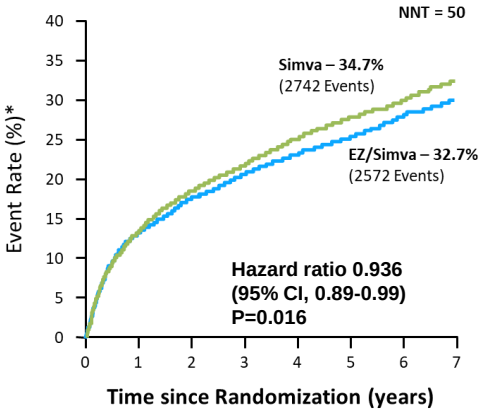
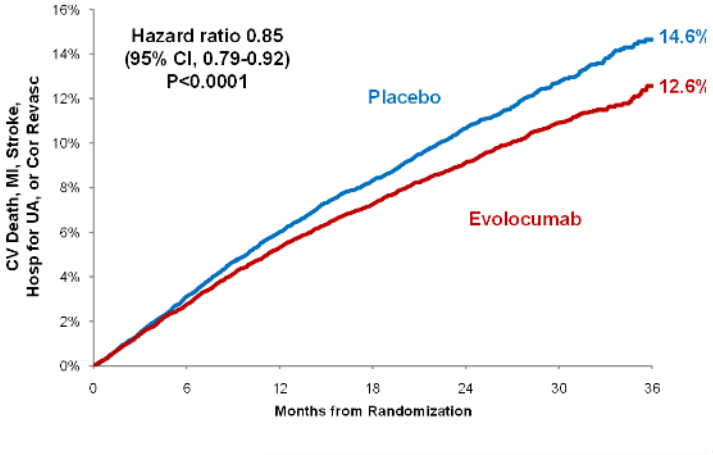
Grundy SM et al. Circulation. 2019;139:e1082-e1143.

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

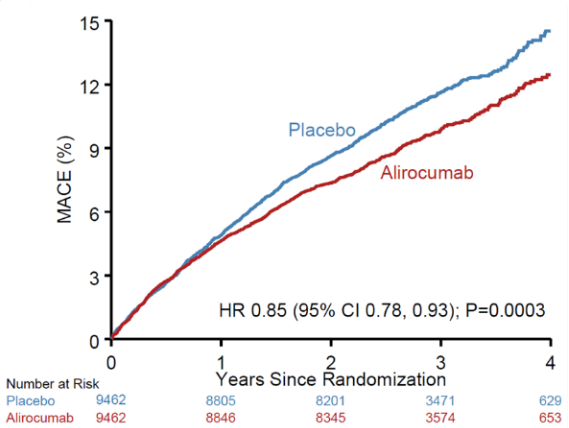
IMPROVE-IT[1]



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. Schwartz GG et al. *N Engl J Med*. 2018;379:2097-107.

Cholesterol Guidelines – Top 10 Take Home Messages

1. **In all individuals, emphasize a heart-healthy lifestyle across the life course**.

A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction.

In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.

Grundy SM et al. Circulation. 2019;139:e1082-e1143.

Top 10 Take Home Messages

2. **In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.**

The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction.

Use a maximally tolerated statin to lower LDL-C levels by ≥50%.

Grundy SM et al. Circulation. 2019;139:e1082-e1143.

Top 10 Take Home Messages

3. In very high-risk ASCVD, use an LDL-C threshold of 70 mg/dL to consider addition of nonstatins to statin therapy.

- Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
- In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL.
- In patients at very high risk whose LDL-C level remains ≥70 mg/dL on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost-effectiveness is low at mid-2018 list prices.

Grundy SM et al. Circulation. 2019;139:e1082-e1143.

Top 10 Take Home Messages

4. **In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL) without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.**

- If the LDL-C level remains ≥100 mg/dL, adding ezetimibe is reasonable
- If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL & the patient has multiple factors that increase subsequent risk of ASCVD events, PCSK9 inhibitor may be considered.

Grundy SM et al. Circulation. 2019;139:e1082-e1143.

Top 10 Take Home Messages

5. **In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL, start moderate-intensity statin therapy without calculating 10-year ASCVD risk.**

In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.

Grundy SM et al. Circulation. 2019;139:e1082-e1143.

Top 10 Take Home Messages

6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.

Risk discussion should include a review of

- major risk factors (eg, cigarette smoking, elevated blood pressure, LDL-C, hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD);
- the presence of risk-enhancing factors (see No. 8);
- the potential benefits of lifestyle and statin therapies;
- the potential for adverse effects and drug–drug interactions;
- the consideration of costs of statin therapy; and
- the patient preferences & values in shared decision-making.

Grundy SM et al. Circulation. 2019;139:e1082-e1143.

Top 10 Take Home Messages

7. **In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL, at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.**

Risk-enhancing factors favor statin therapy (see No. 8).

If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.

Grundy SM et al. Circulation. 2019;139:e1082-e1143.

Top 10 Take Home Messages

8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).

Risk-enhancing factors include

- family history of premature ASCVD;
- persistently elevated LDL-C levels ≥160 mg/dL;
- metabolic syndrome;
- chronic kidney disease;
- history of preeclampsia or premature menopause (age <40 yrs);
- chronic inflammatory disorders (eg, rheumatoid arthritis, psoriasis, or chronic HIV);
- high-risk ethnic groups (eg, South Asian);
- persistent elevations of triglycerides ≥175 mg/dL

Grundy SM et al. Circulation. 2019;139:e1082-e1143.

Top 10 Take Home Messages

8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).

Risk-enhancing factors include family history of premature ASCVD; persistently elevated LDL-C levels ≥160 mg/dL; metabolic syndrome; chronic kidney disease; history of preeclampsia or premature menopause (age <40 years); chronic inflammatory disorders (eg, rheumatoid arthritis, psoriasis, or chronic HIV); high-risk ethnic groups (eg, South Asian); persistent elevations of triglycerides ≥175 mg/dL; and, if measured in selected individuals

- apolipoprotein B ≥130 mg/dL;
- high-sensitivity C-reactive protein ≥2.0 mg/L;
- ankle-brachial index <0.9 and Lp(a) ≥50 mg/dL, especially at higher values of Lp(a).

Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5–7.5% (borderline risk)

Grundy SM et al. Circulation. 2019;139:e1082-e1143.

Top 10 Take Home Messages

9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL – 189 mg/dL, at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

- If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.
- A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age.
- For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician-patient risk discussion.

Grundy SM et al. Circulation. 2019;139:e1082-e1143.

Top 10 Take Home Messages

10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

- Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline.
- In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).

Grundy SM et al. Circulation. 2019;139:e1082-e1143.

THANK YOU!

Update on Cardiovascular Outcomes Trials of Adjunctive Therapies to Statins

Deepak L. Bhatt, MD, MPH

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

BWH BRIGHAM AND WOMEN'S HOSPITAL
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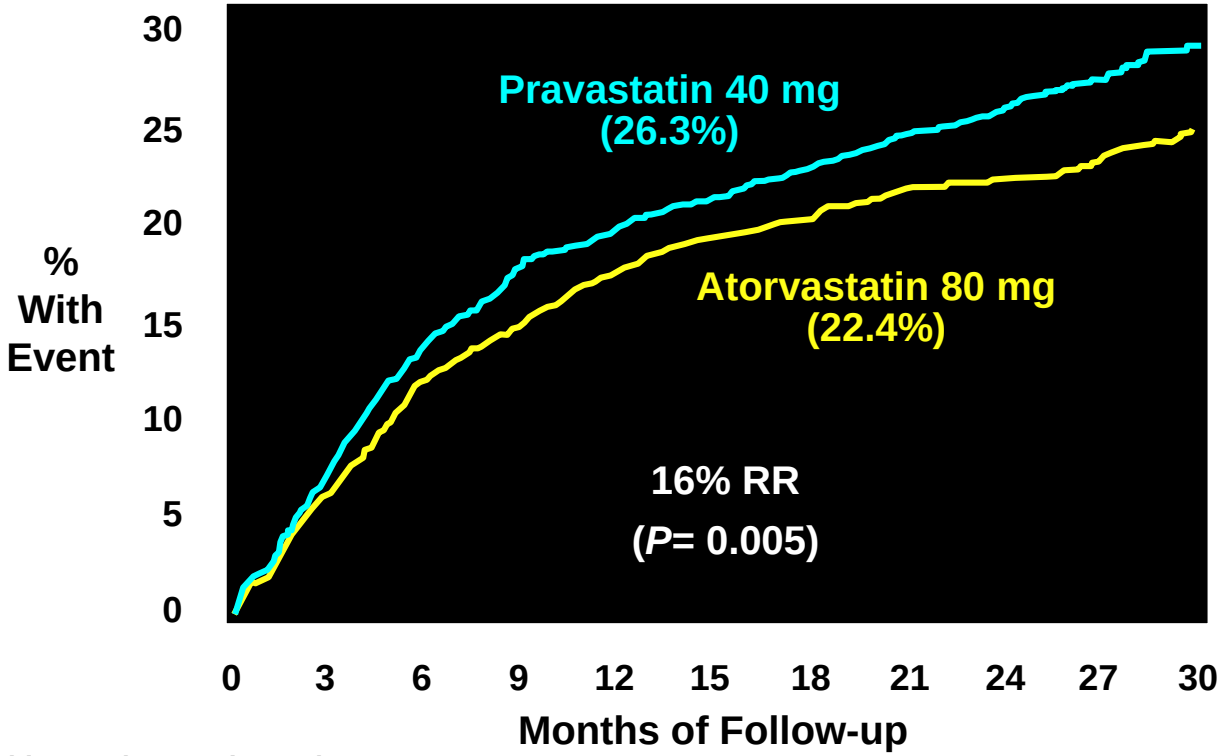
TEACHING HOSPITAL

Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific, 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; AEGIS-II executive committee funded by CSL Behring), 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), Medtelligence/ReachMD (CME steering committees), 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, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, 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.

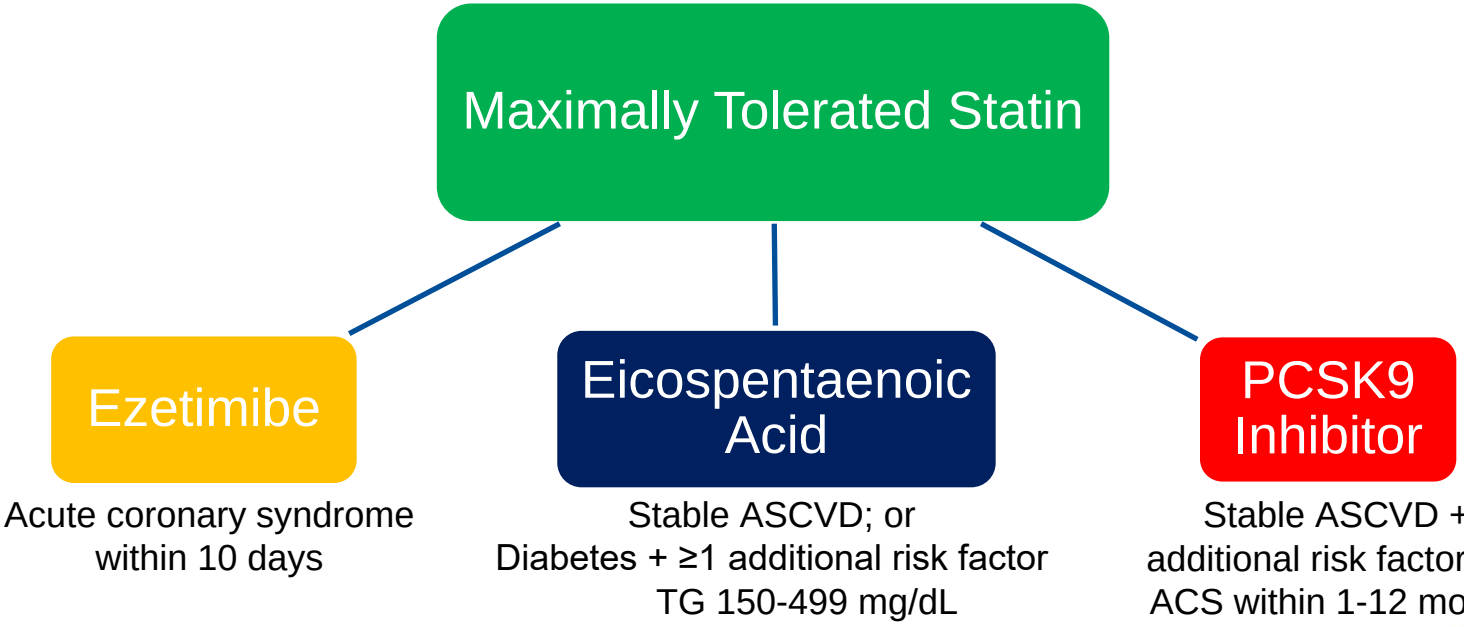
This presentation includes off-label and/or investigational uses of drugs.

All-Cause Death or Major CV Events in All Randomized Subjects



Cannon CP, Braunwald E, et al. *N Engl J Med.* 2004;350:1495-1504.

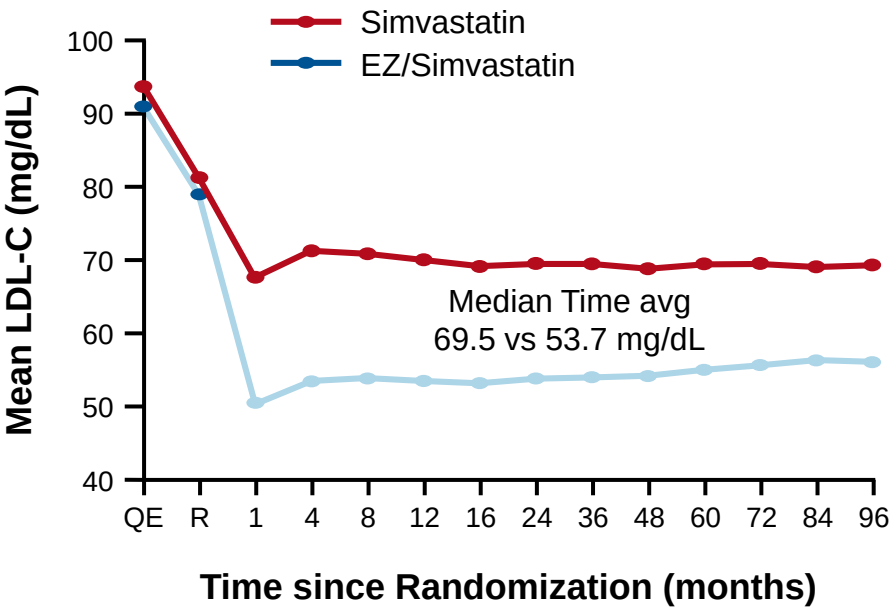
RCT-Proven Non-Statin Additive Therapies for ASCVD Risk Reduction in High-Risk Patients

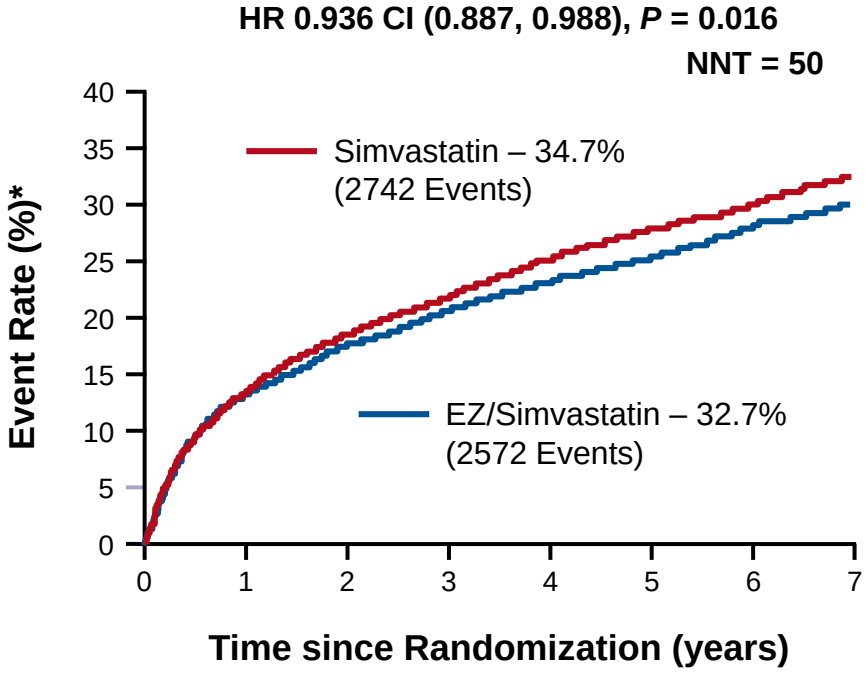


Courtesy of Dr. Carl Orringer, LBCT discussant. AHA 2018, Chicago.
Orringer CE. *Trends in Cardiovasc Med*. 2019. May 4. pii: S1050-1738(19)30054-4.

IMPROVE-IT: Primary Results

18,144 ACS patients randomized to simvastatin alone or ezetimibe (EZ)/simvastatin, 6-year median follow up



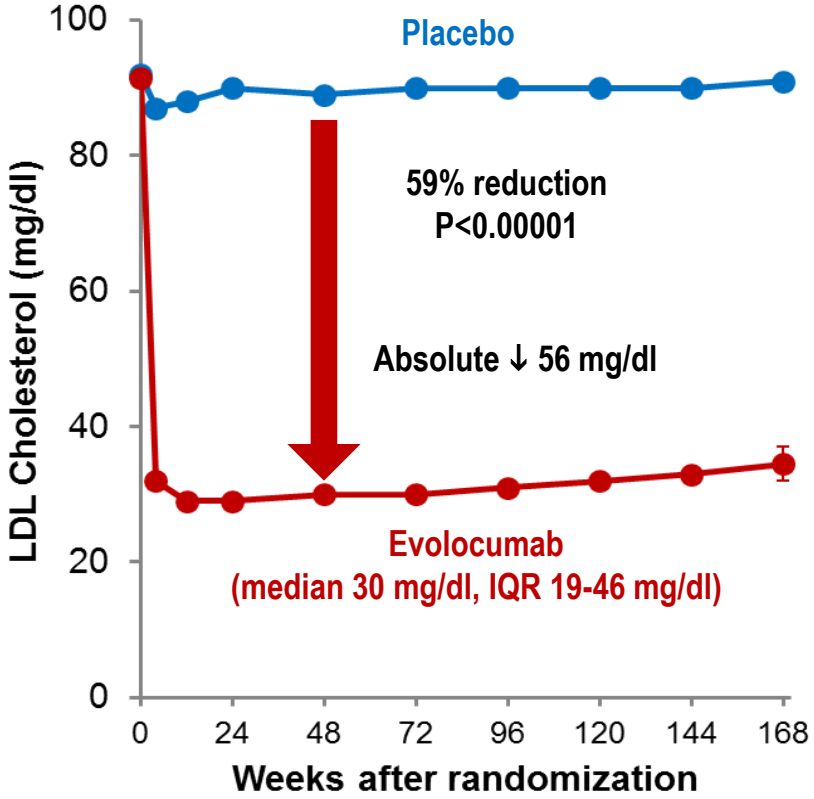


*Primary endpoint (cardiovascular death, MI, UA, coronary revascularization, or stroke).

Cannon CP, Blazing MA, Giugliano RP, et al…. Braunwald E, Califf RM. *N Engl J Med.* 2015;372(25):2387–2397.

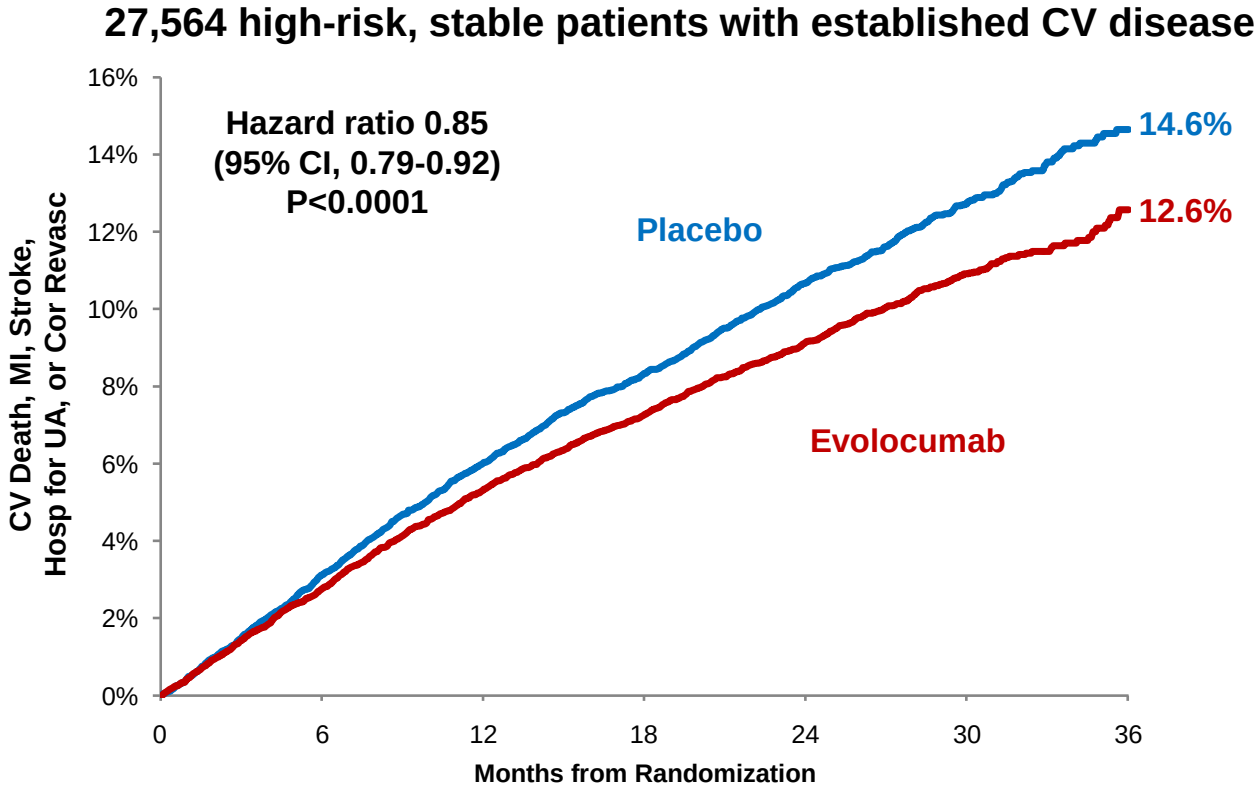
FOURIER: Effects of PCSK9i Evolocumab on LDL-C

27,564 high-risk, stable patients with established CV disease



Sabatine MS, et al. *NEJM.* 2017;376:1713-22.

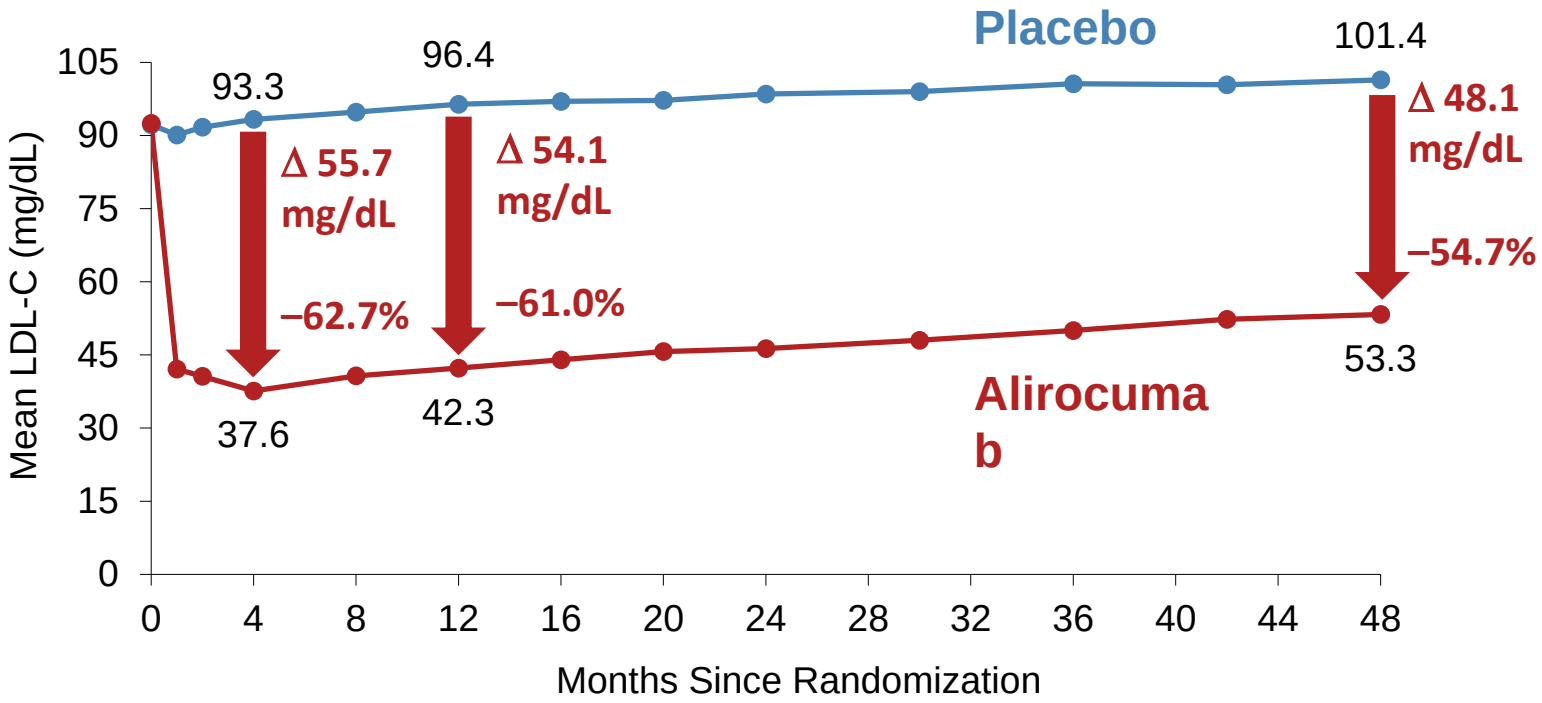
FOURIER: Effects of PCSK9i Evolocumab, Primary Endpoint



An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Sabatine MS, et al. *NEJM.* 2017;376:1713-22.

ODYSSEY OUTCOMES: LDL-C On-Treatment Analysis

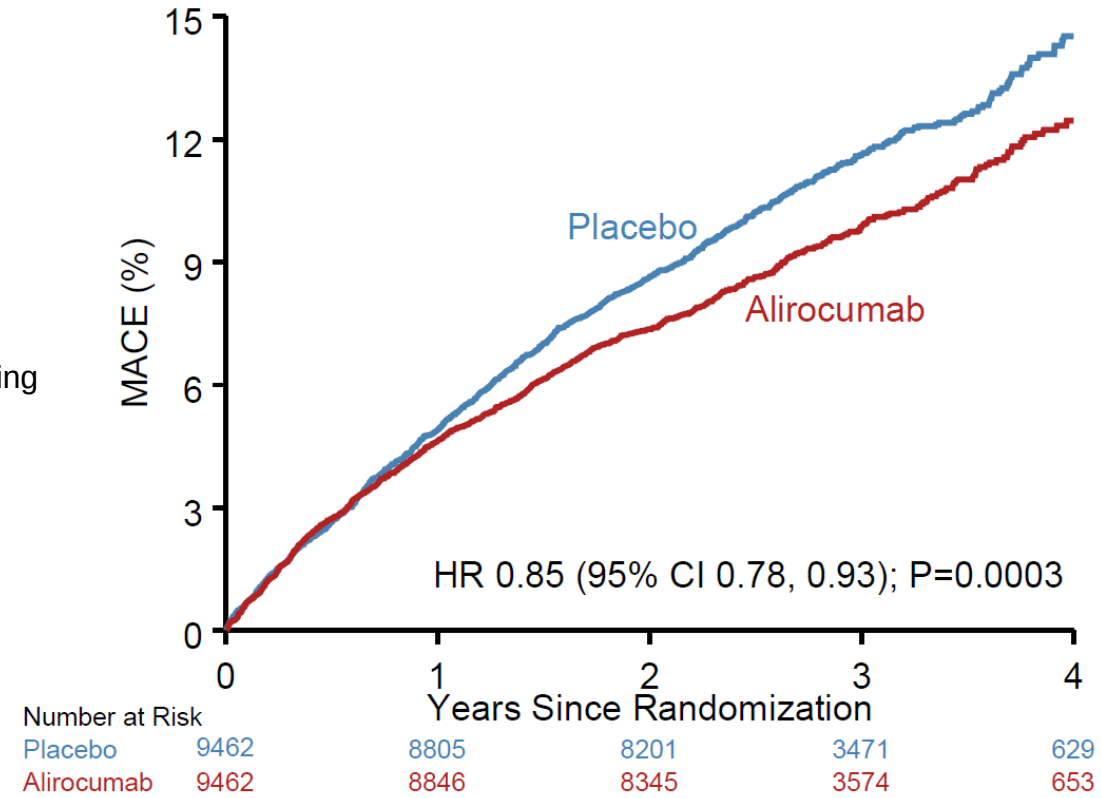


Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo. Approximately 75% of months of active treatment were at the 75 mg dose.

Schwartz GG, Steg PG, et al. *NEJM* Nov 7, 2018 doi: 10.1056/NEJMoa1801174. Steg PG, ACC 2018, Orlando, FL.

Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

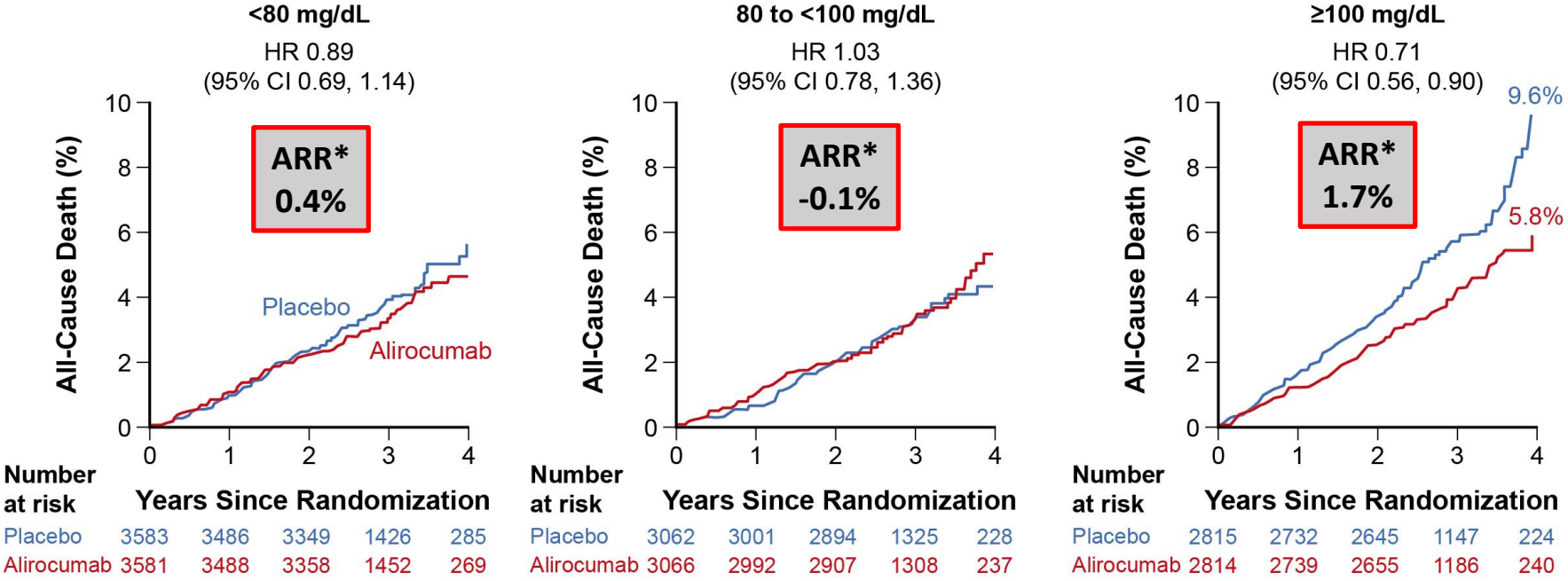


NNT 49 for 4 years

Schwartz GG, Steg PG, et al. NEJM Nov 7, 2018 doi: 10.1056/NEJMoa1801174. Steg PG, ACC 2018, Orlando, FL.

ODYSSEY OUTCOMES

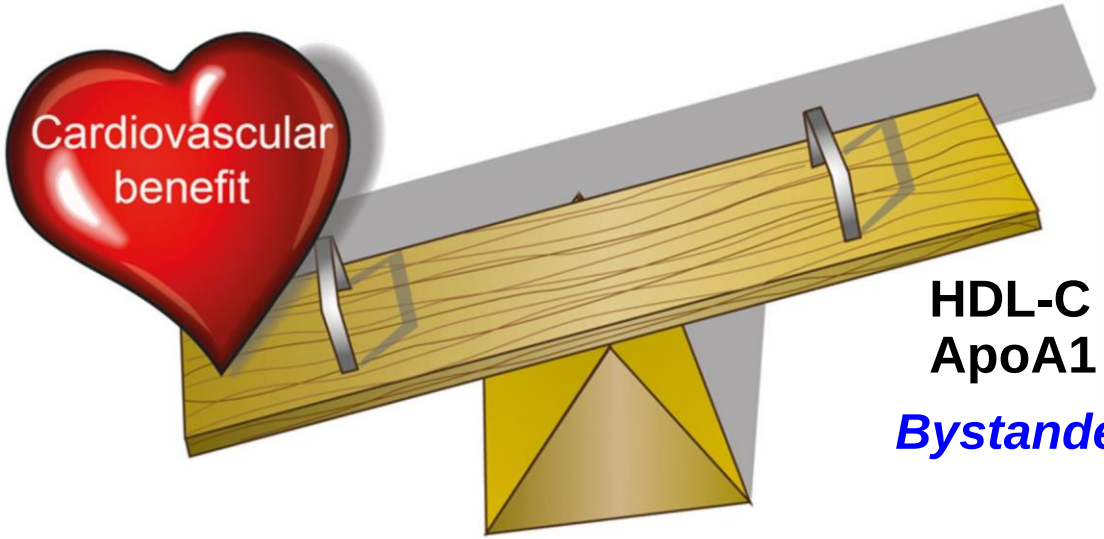
All-cause Death in Three Predefined Categories of Baseline LDL-C



*Absolute risk reduction: Interaction P=0.005
Post hoc analysis

Steg PG, Szarek M, Bhatt DL, et al., *Circulation* 2019;140:103-112.

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.

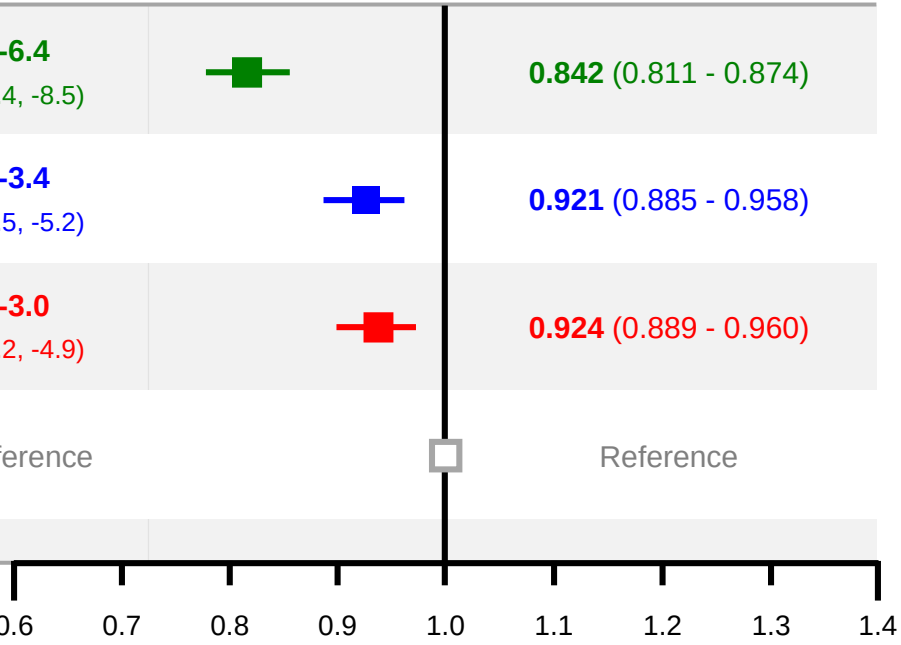
A naturally randomized trial evaluating the potential clinical benefit of triglyceride lowering therapies on the risk of coronary heart disease

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

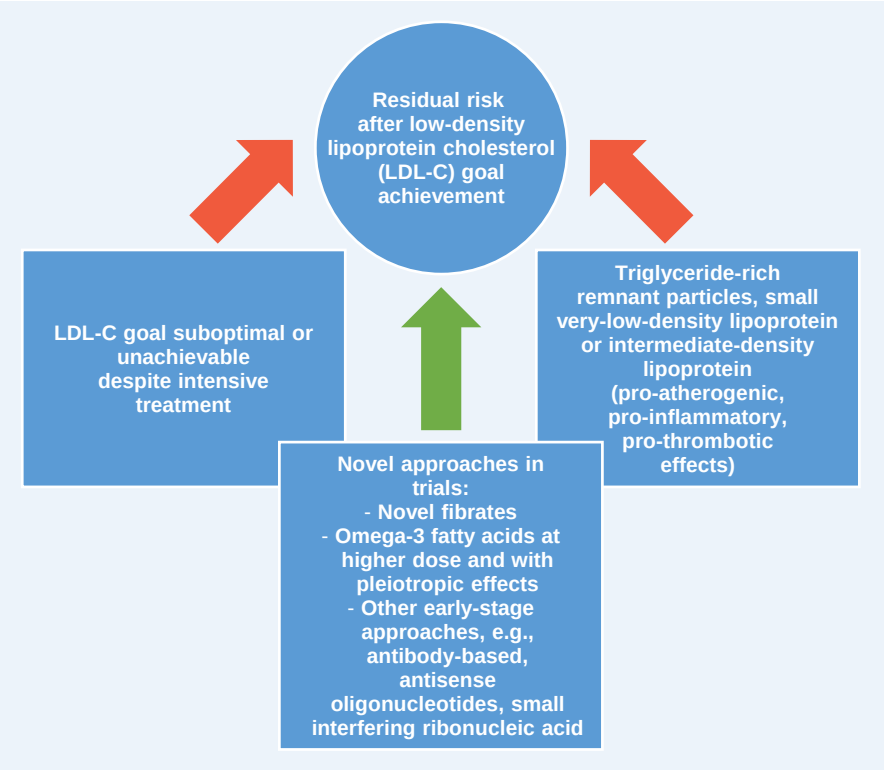
2x2 Group	Δ Triglycerides, mg/dL (95% CI)	Δ LDL-C, mg/dL (95% CI)	Δ apoB, mg/dL (95% CI)	OR $_{CHD}$ (95% CI)
Both scores > median N = 104,694	**-24.3** (-16.2, -32.4)	**-4.9** (-2.1, -7.7)	**-6.4** (-4.4, -8.5)	**0.842** (0.811 - 0.874)
***LDLR* score > median** N = 112,018	**-3.8** (-15.1, -7.5)	**-4.8** (-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.

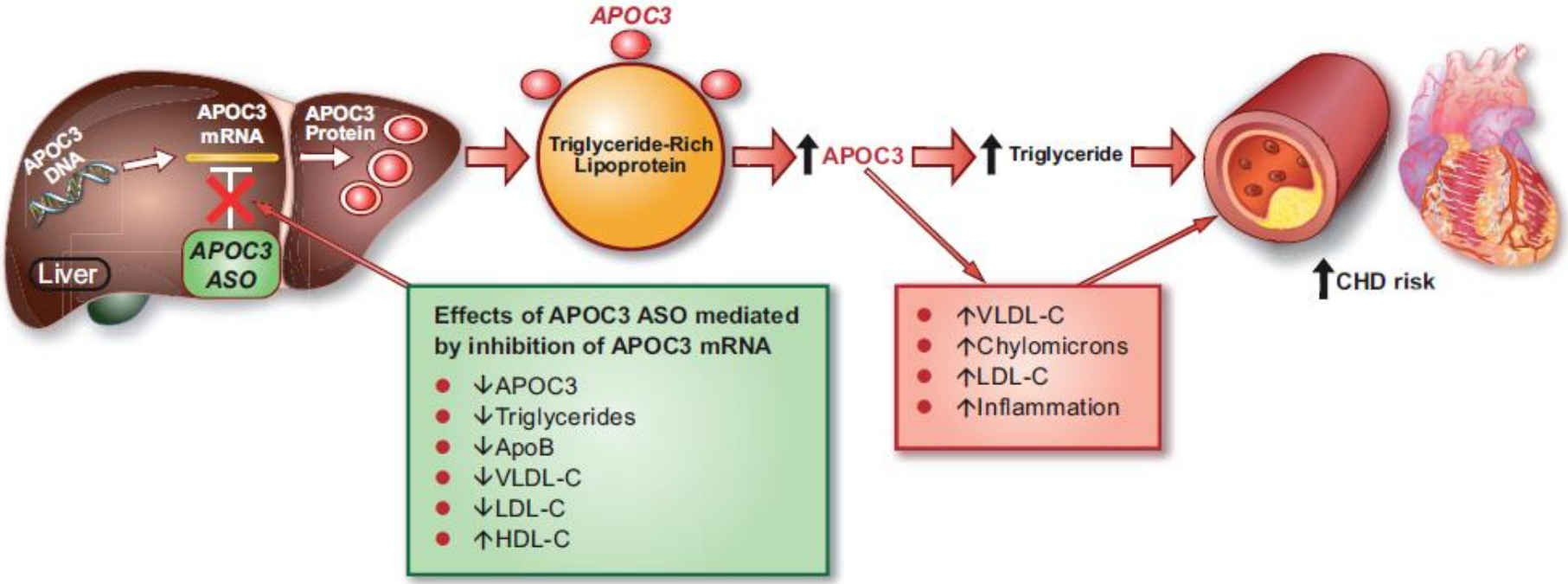
Adapted from Ference BA, Kastelein JJP, Ray KK, et al. Association of Triglyceride-Lowering LPL Variants and LDL-C-Lowering LDLR Variants With Risk of Coronary Heart Disease. *JAMA*. 2019;321:364-373.

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/]

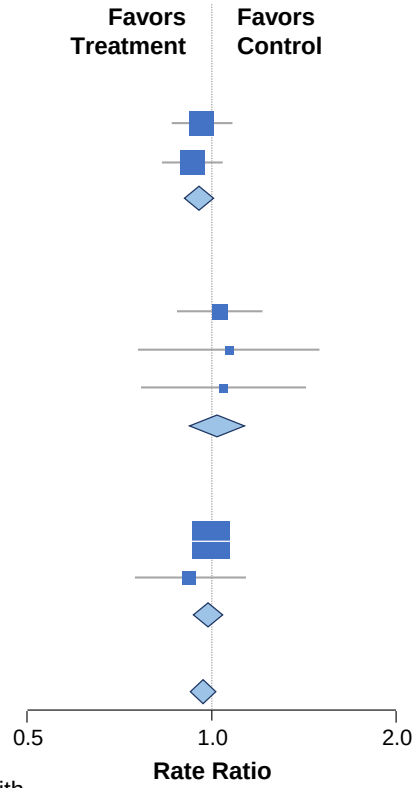
Targeting RNA to Lower Triglycerides:
Long Strides from Short Molecules



Qamar A, Libby P, Bhatt DL. Targeting RNA to lower triglycerides: long strides from short molecules. *European Heart Journal*. 2019;40:2797–2800.

Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
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



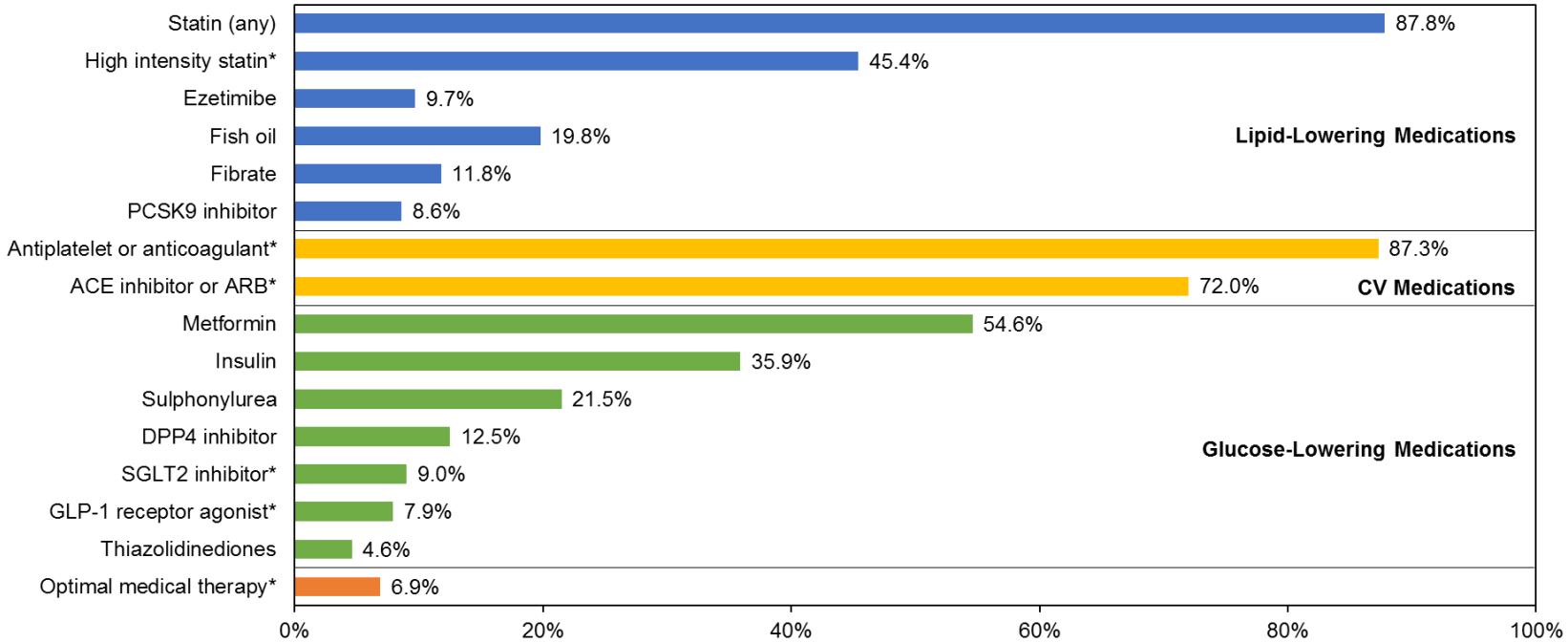
Adapted with permission* from Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77917 individuals. *JAMA Cardiol.* 2018;3:225-234. [*https://creativecommons.org/licenses.org/by-nc/4.0/]

Confusion Regarding Fish Oil Dietary Supplements

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

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

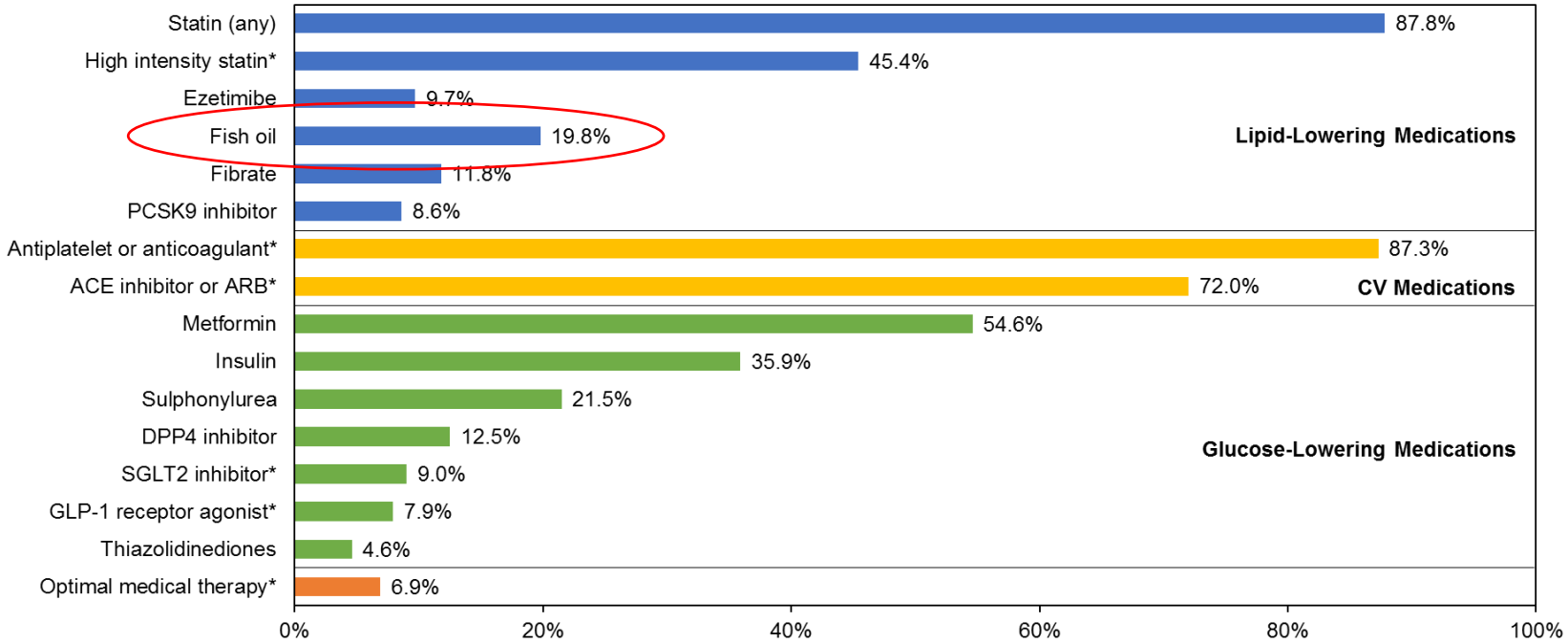
Use of CV and Glucose-lowering Medications among Patients with DM and ASCVD in GOULD



*Components of optimal medical therapy: high-intensity statin, antiplatelet agent or anticoagulant (excluding triple therapy), ACE inhibitor or ARB (excluding glomerular filtration rate <30 mL/[min·1.73 m2]), and SGLT2 inhibitor or GLP1 receptor agonist (for type 2 diabetes mellitus; excluding glomerular filtration rate <30 mL/[min·1.73 m2]). ACE indicates angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CV, cardiovascular; DPP4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide 1; PCSK9, proprotein convertase subtilisin/kexin type 9; and SGLT2, sodium-glucose cotrans-porter-2.

Arnold SV, de Lemos JA, Rosenson RS, et al. *Circulation*. 2019;140:618–620. DOI: 10.1161/CIRCULATIONAHA.119.041730

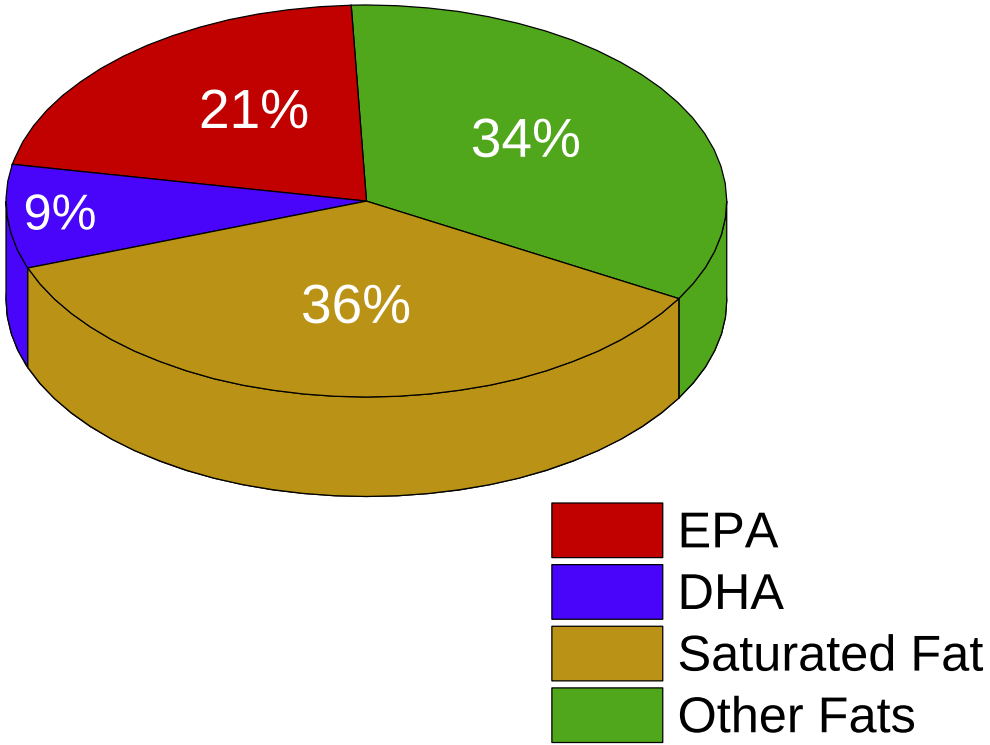
Use of CV and Glucose-lowering Medications among Patients with DM and ASCVD in GOULD



*Components of optimal medical therapy: high-intensity statin, antiplatelet agent or anticoagulant (excluding triple therapy), ACE inhibitor or ARB (excluding glomerular filtration rate <30 mL/[min·1.73 m2]), and SGLT2 inhibitor or GLP1 receptor agonist (for type 2 diabetes mellitus; excluding glomerular filtration rate <30 mL/[min·1.73 m2]). ACE indicates angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CV, cardiovascular; DPP4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide 1; PCSK9, proprotein convertase subtilisin/kexin type 9; and SGLT2, sodium-glucose cotrans-porter-2.

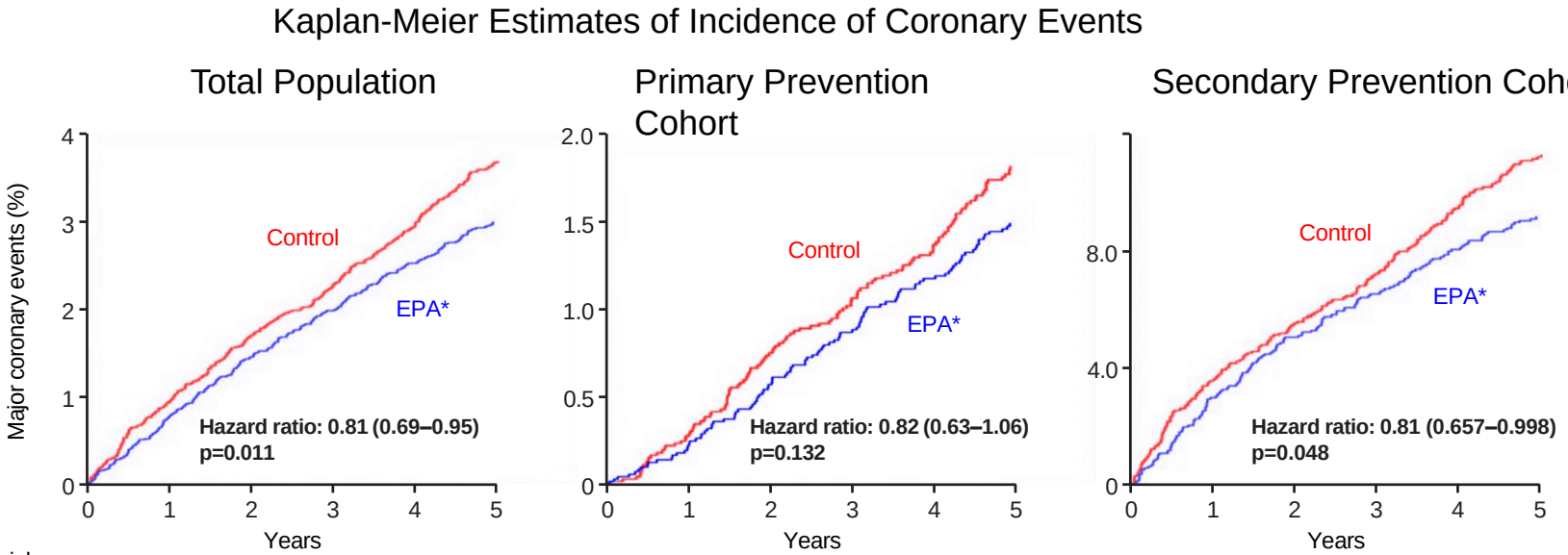
Arnold SV, de Lemos JA, Rosenson RS, et al. *Circulation*. 2019;140:618–620. DOI: 10.1161/CIRCULATIONAHA.119.041730

Fatty Acid Content of Leading U.S. Fish Oil Supplement



Adapted with permission* from Mason RP, Sherratt SCR. *Biochem Biophys Res Commun.* 2017;483 :425-429. [*https://creativecommons.org/licenses.org/by-nc/4.0/]

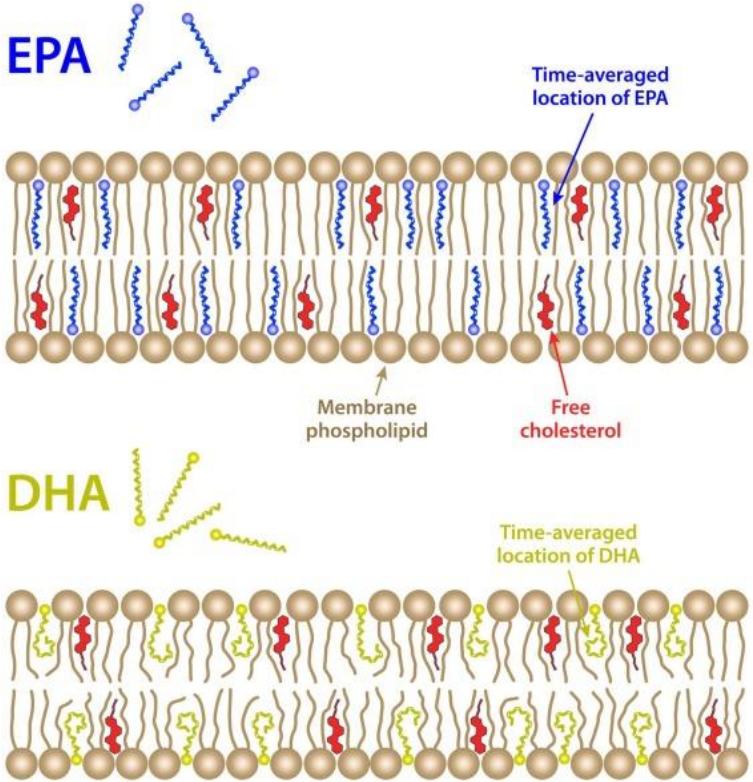
JELIS Suggests CV Risk Reduction with EPA in Japanese Hypercholesterolemic Patients



*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



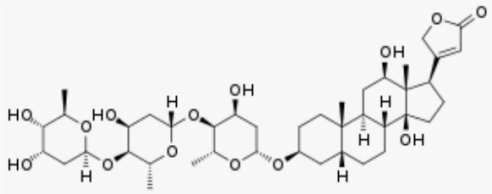
Reproduced with permission* from Sherratt SCR, Mason RP. Eicosapentaenoic acid and docosahexaenoic acid have distinct membrane locations and lipid interactions as determined by X-ray diffraction. *Chem Phys Lipids*. 2018;212:73-79. [*https://creativecommons.org/licenses.org/by-nc/4.0/]

Transformational Medicines Isolated from Nature:

Unique Molecules from these Sources have Proven Clinical Efficacy

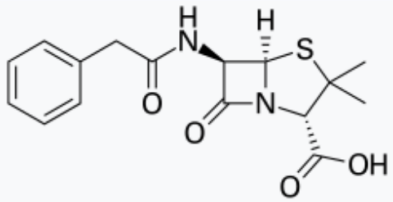
Digoxin

Purple Foxglove



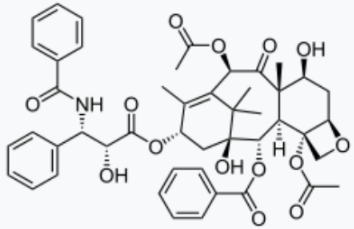
Penicillin

Penicillium Mold



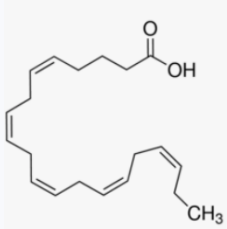
Paclitaxel

Pacific Yew



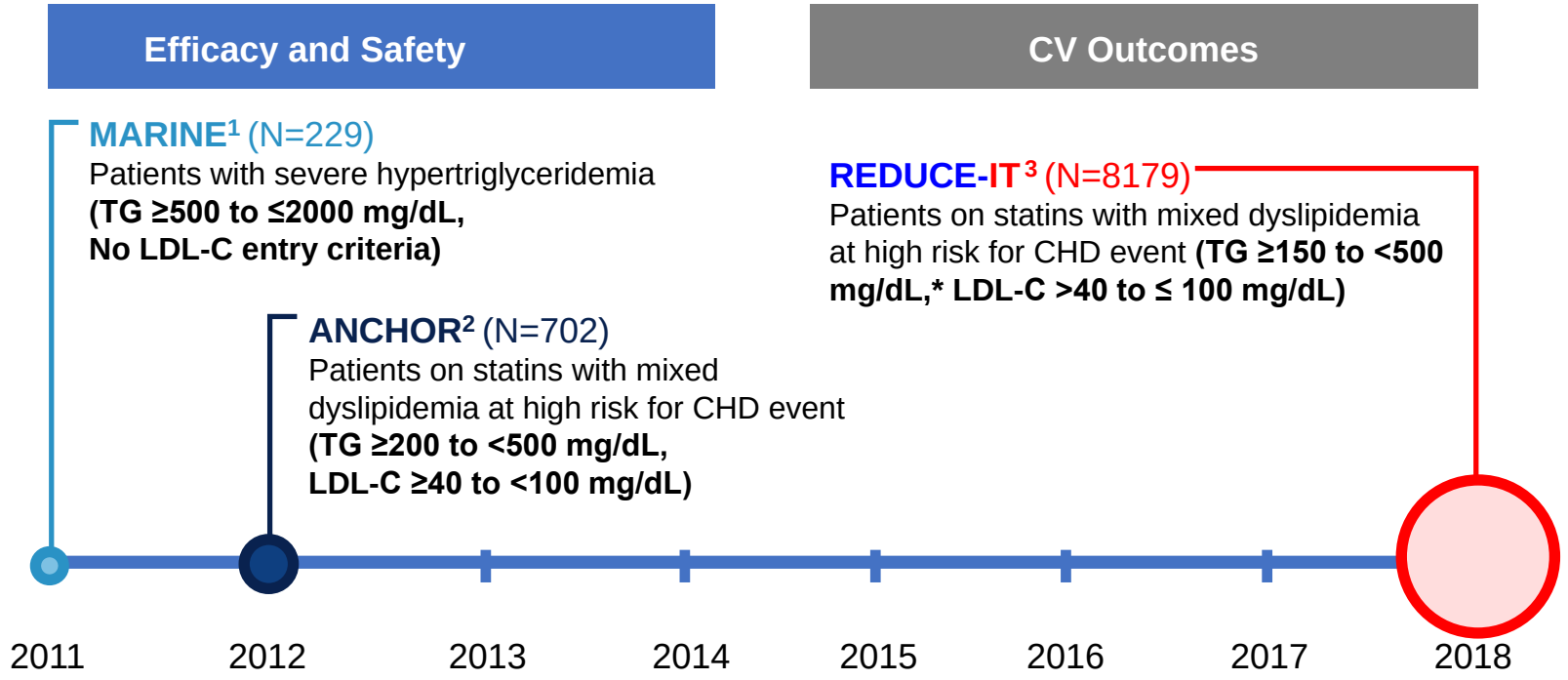
Icosapent Ethyl

Marine Fish



Lero M, Sherratt SCR, Mason RP (2019)

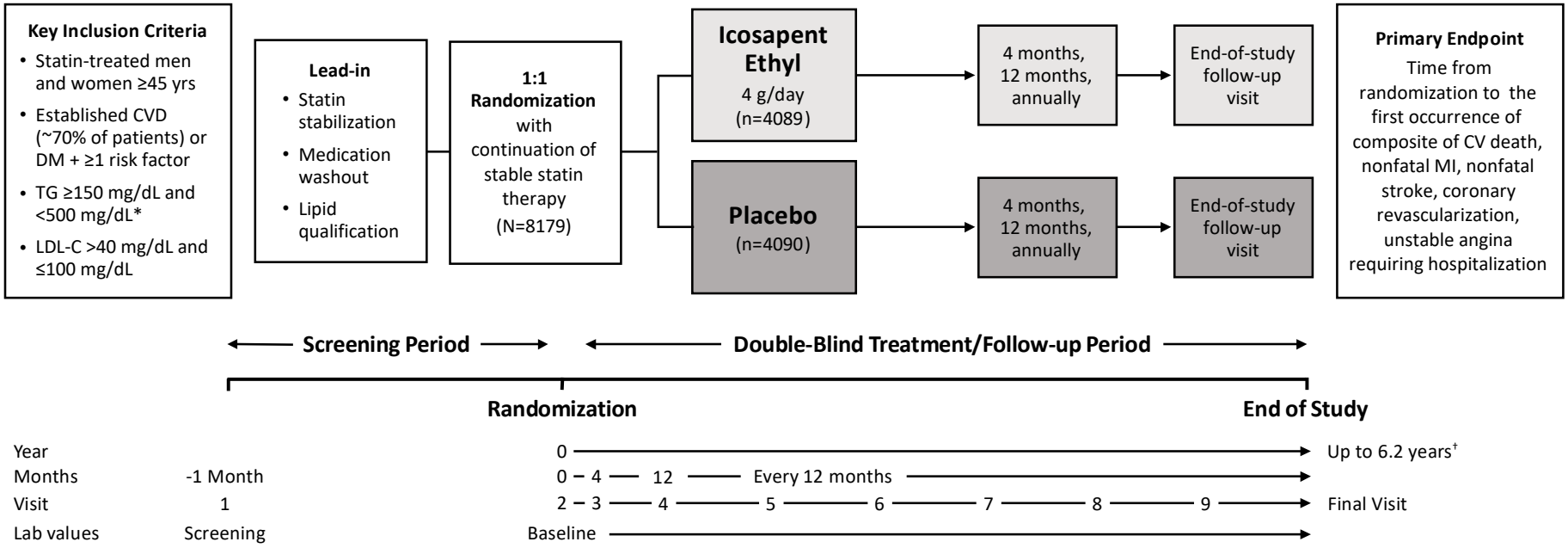
Pure EPA Icosapent Ethyl Clinical Program



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*. 2019;380:11-22.

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.

[‡https://creativecommons.org/licenses/by-nc/4.0/]

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%)

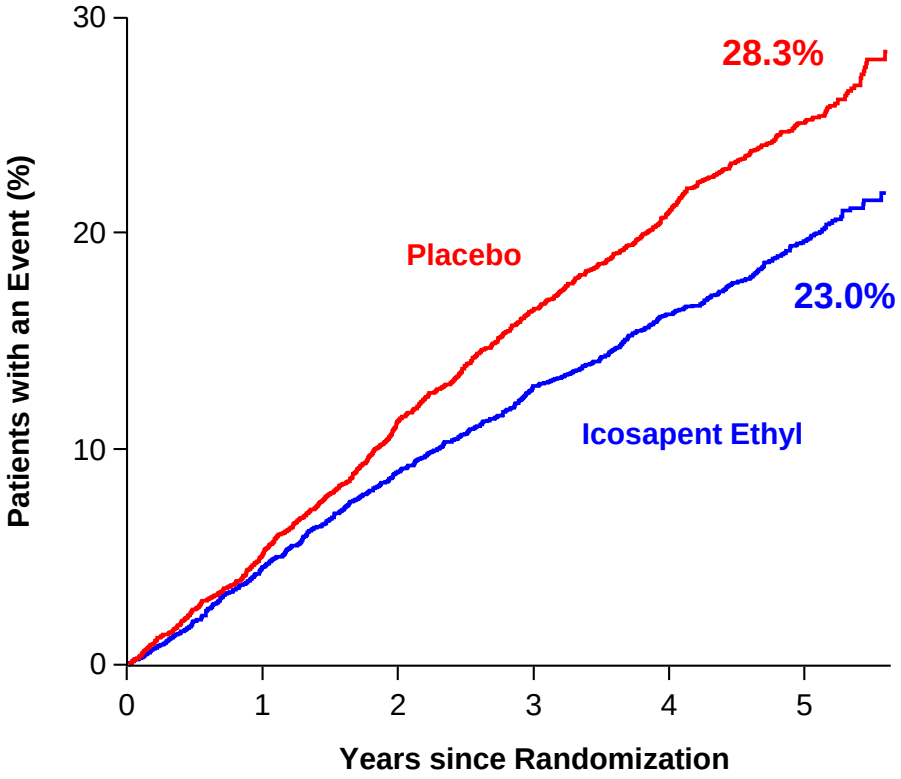
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22.

Key Medical Therapy

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

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

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



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

RRR = 24.8%

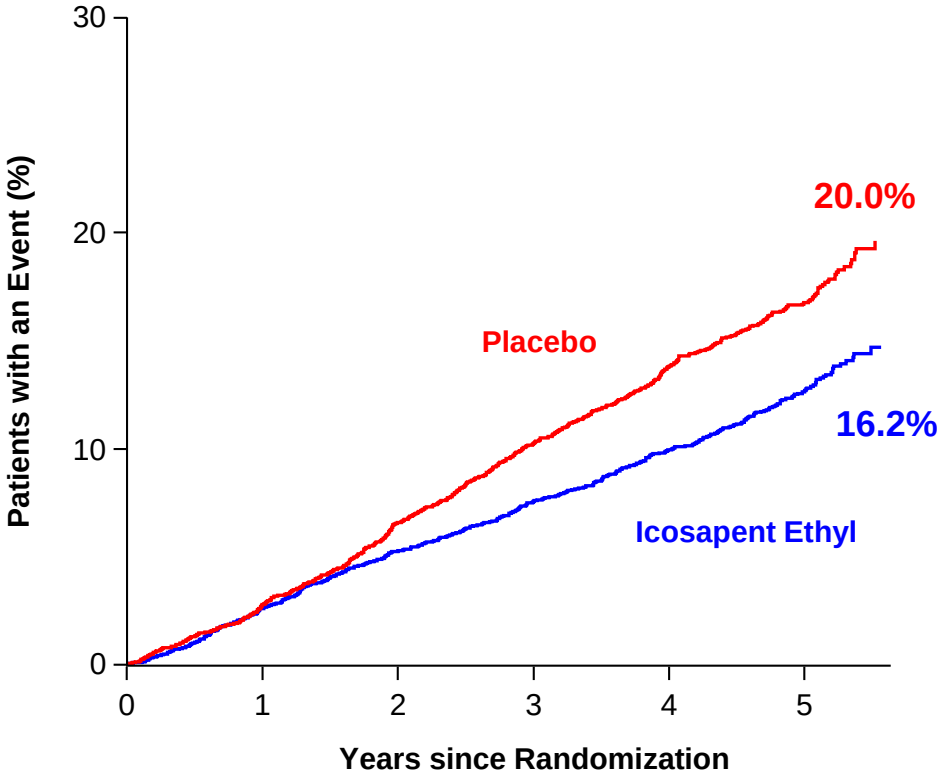
ARR = 4.8%

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%

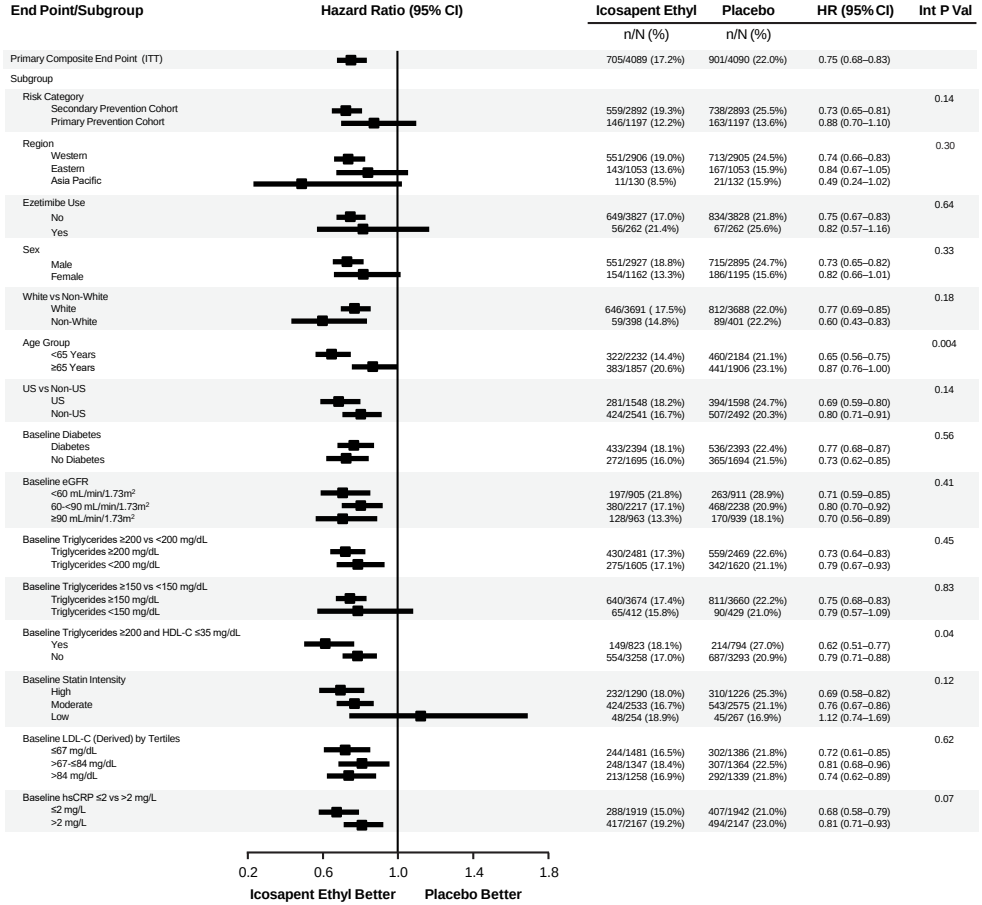
ARR = 3.6%

NNT = 28 (95% CI, 20–47)

P=0.0000006

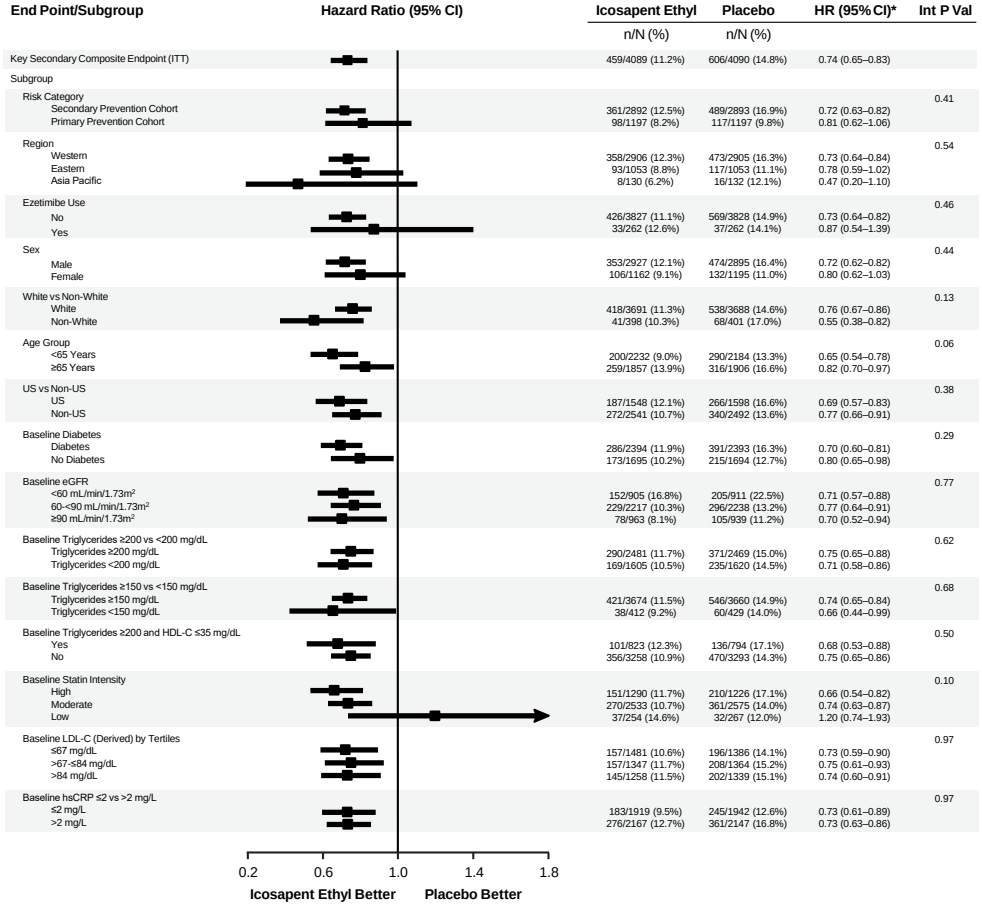
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019. Bhatt DL. AHA 2018, Chicago.

Primary End Point in Subgroups



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

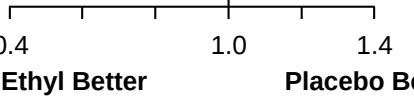
Key Secondary End Point in Subgroups



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

Prespecified Hierarchical Testing

Endpoint	Hazard Ratio (95% CI)	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.

Treatment-Emergent Adverse Events

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Subjects with at Least One TEAE, n (%)	3343 (81.8%)	3326 (81.3%)	0.63
Serious TEAE	1252 (30.6%)	1254 (30.7%)	0.98
TEAE Leading to Withdrawal of Study Drug	321 (7.9%)	335 (8.2%)	0.60
Serious TEAE Leading to Withdrawal of Study Drug	88 (2.2%)	88 (2.2%)	1.00
Serious TEAE Leading to Death	94 (2.3%)	102 (2.5%)	0.61

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

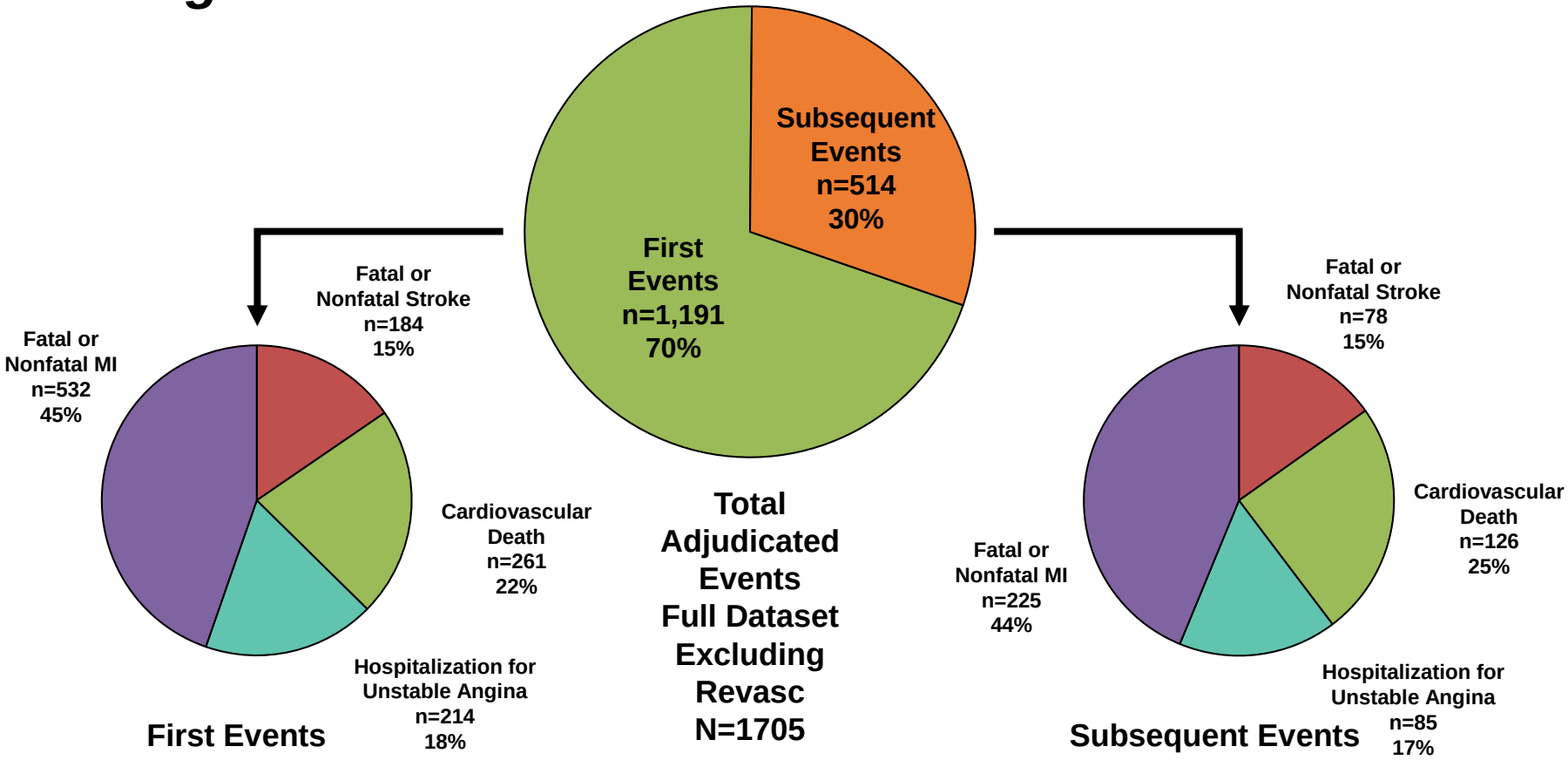
Primary System Organ Class Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Positively Adjudicated Atrial Fibrillation/Flutter[1]	127 (3.1%)	84 (2.1%)	0.004

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.

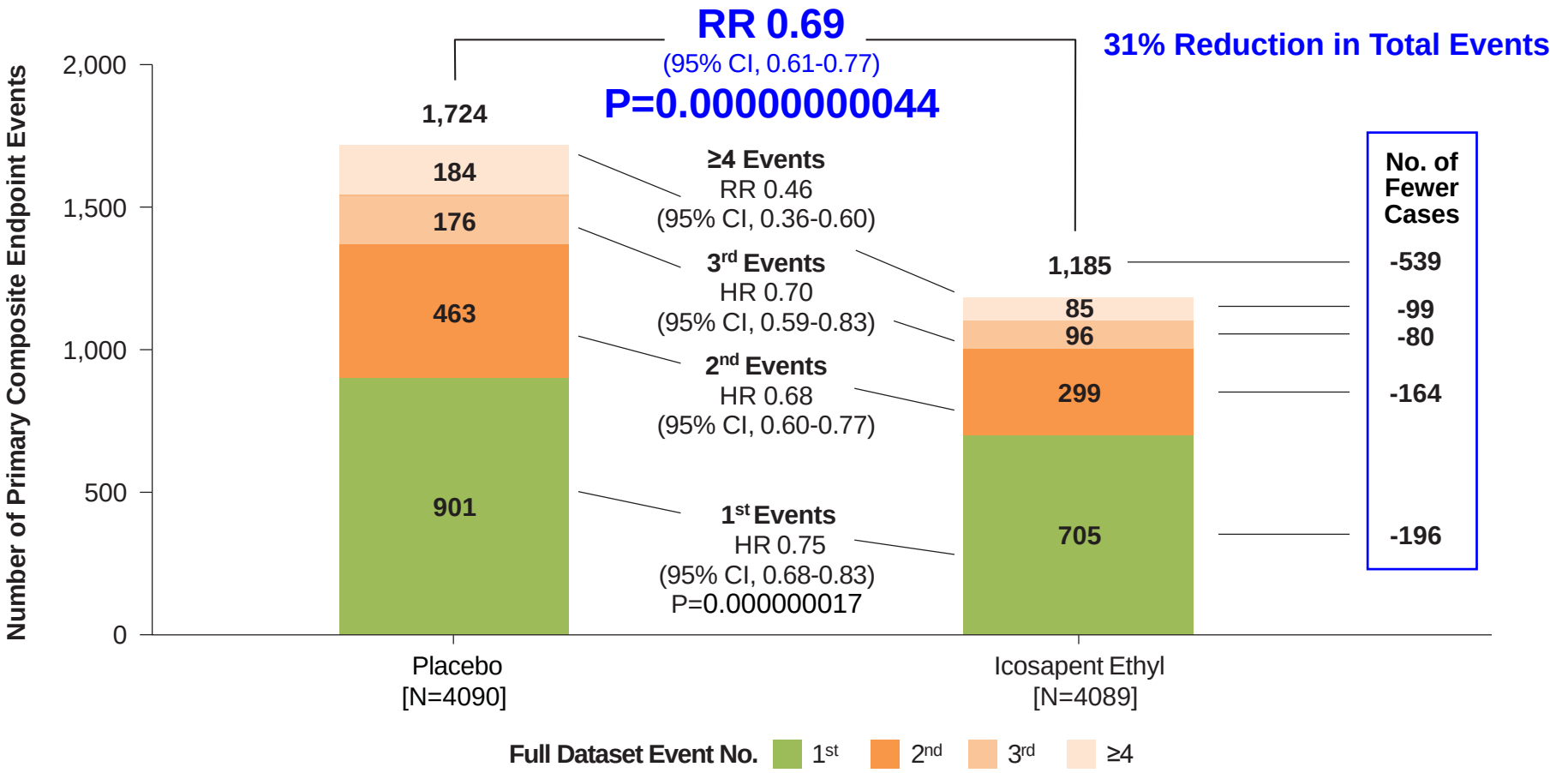
Proportions of First and Subsequent Events

Excluding Revascularization



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

First and Subsequent Events – Full Data



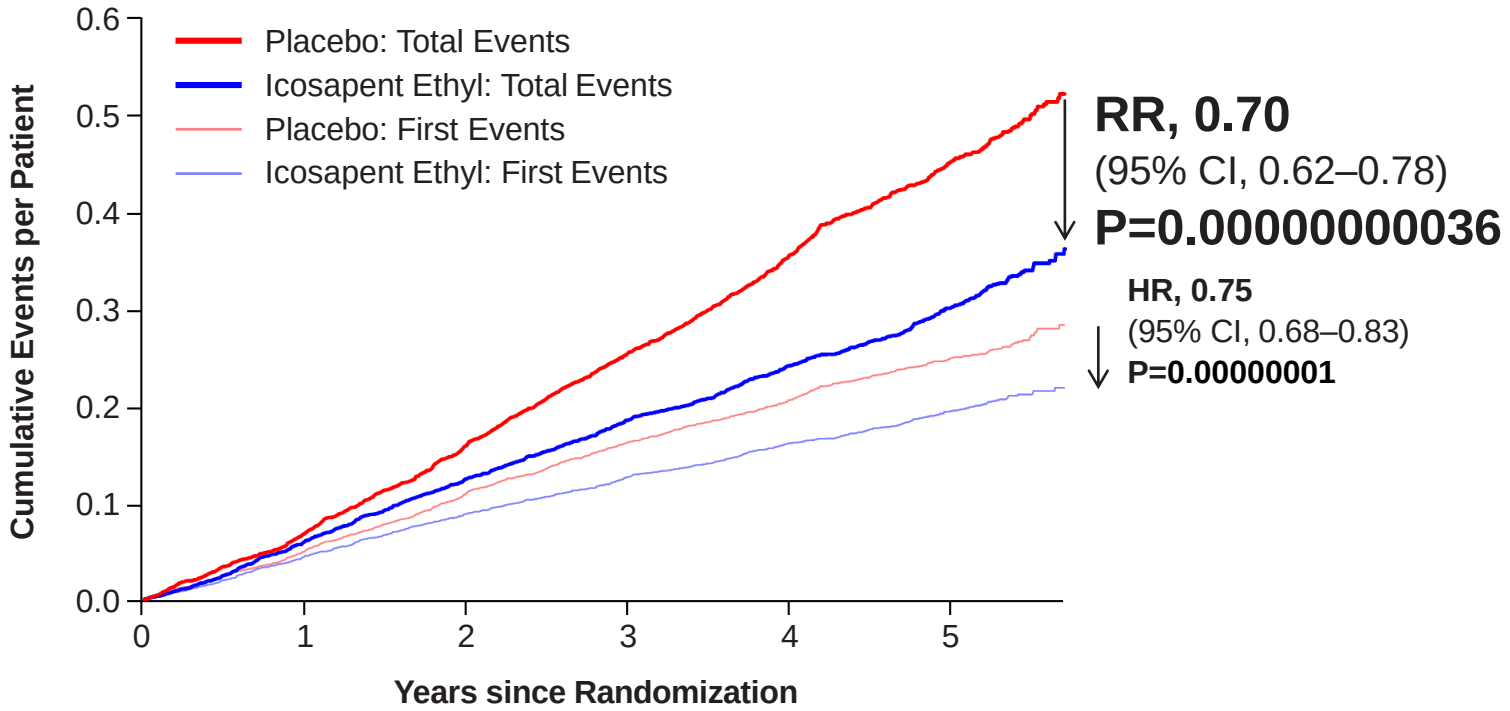
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802.

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

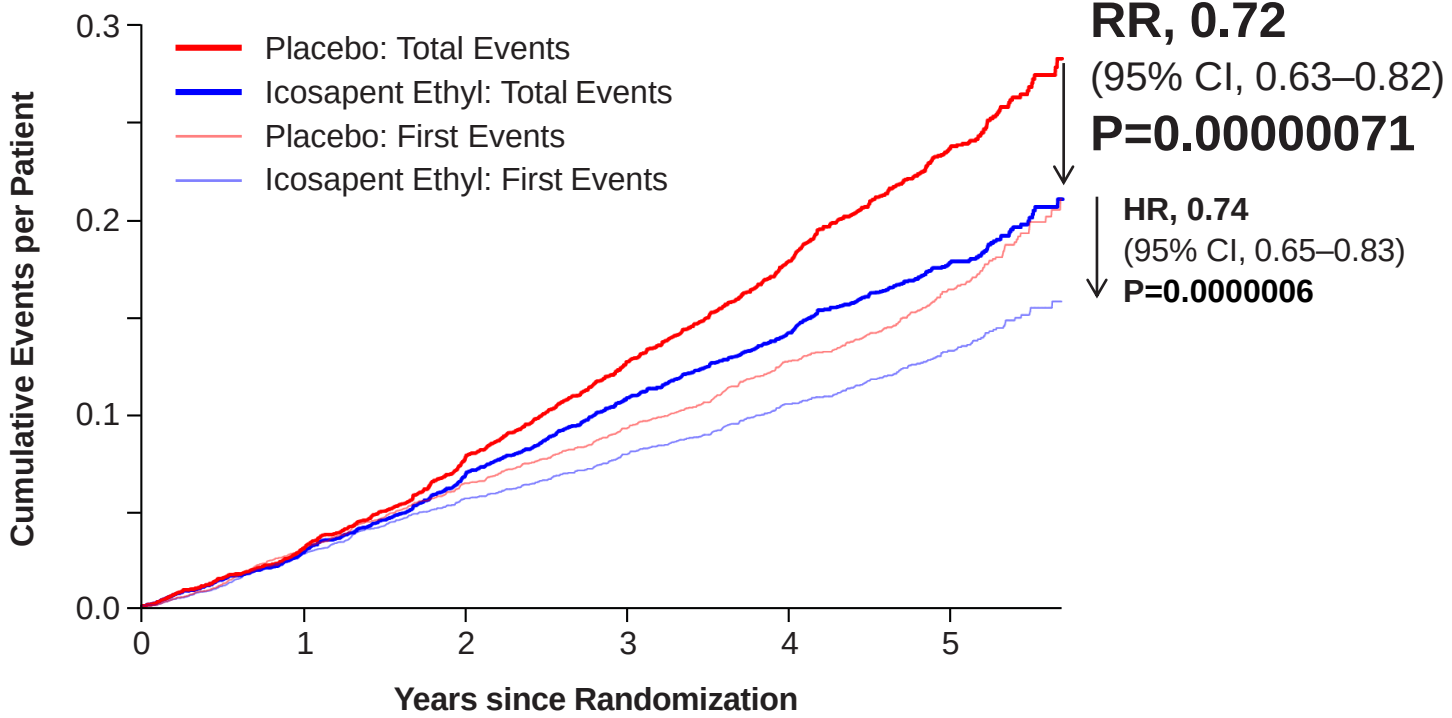


Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

Total (First and Subsequent) Events

Key Secondary: CV Death, MI, Stroke

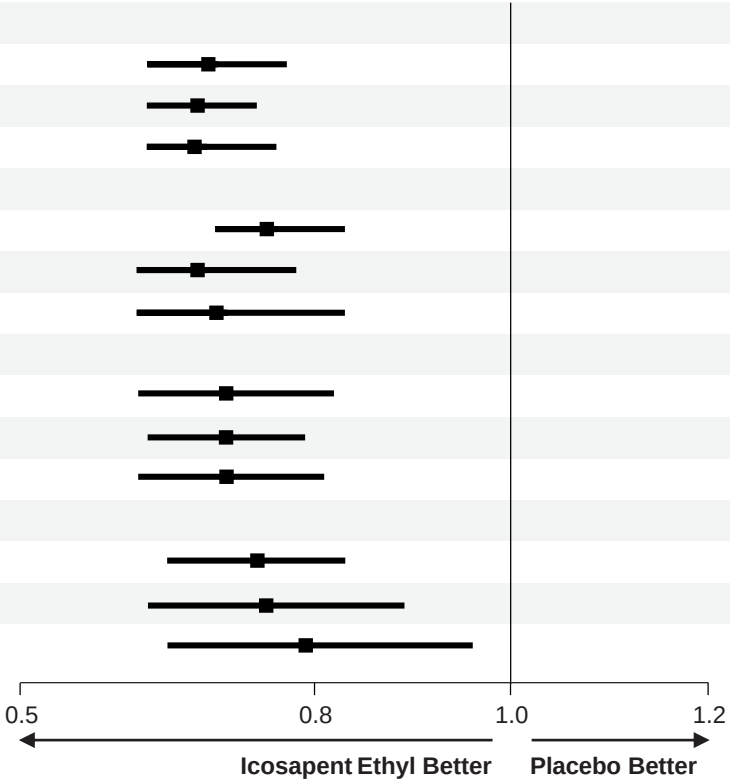
Key Secondary Composite Endpoint



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

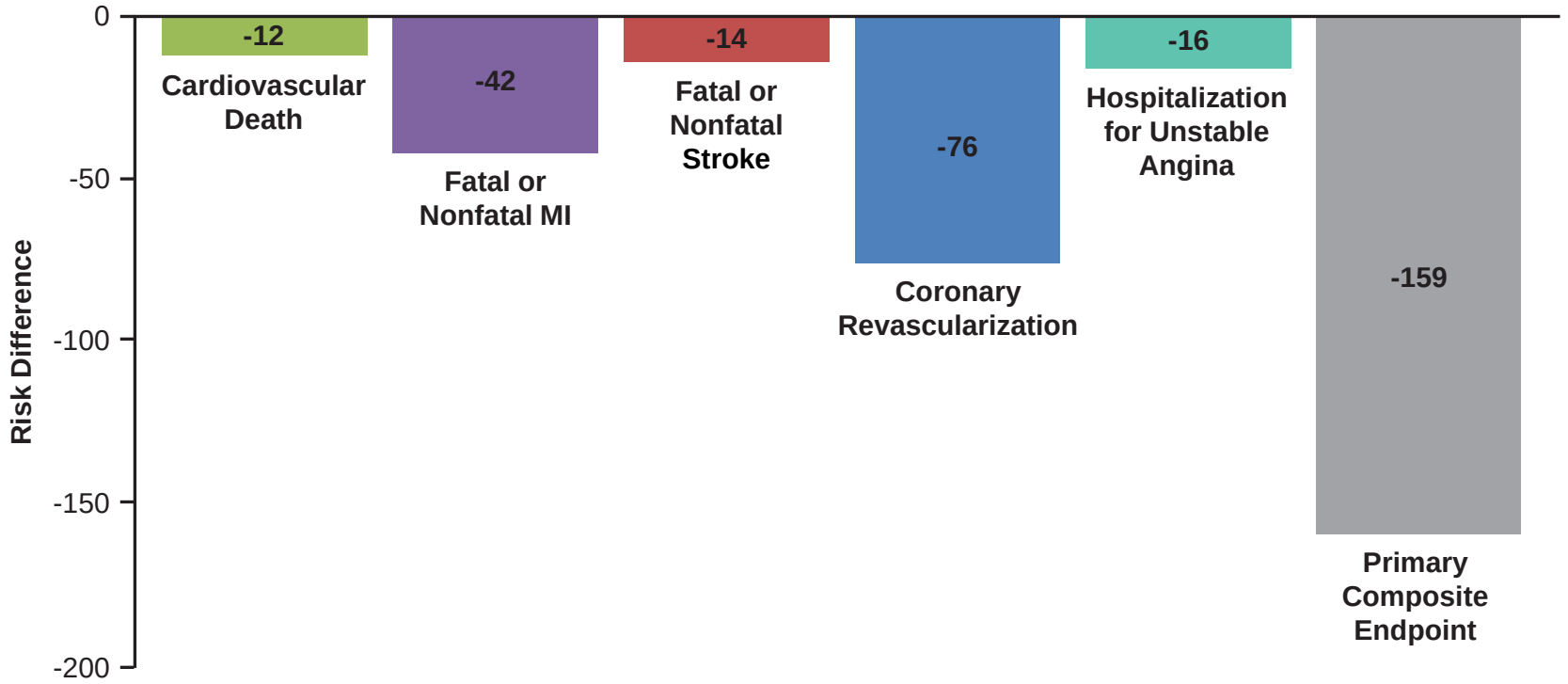
Total Primary and Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences (Full Dataset, Adjusted)

Endpoint/Model	Adjusted Rate/Hazard Ratio (95% CI)	Adjusted P-value
Primary Composite Endpoint		
Negative binomial	0.69 (0.61, 0.77)	4.4×10^{-10}
Andersen-Gill (I)	0.68 (0.63, 0.74)	3.0×10^{-22}
Andersen-Gill (II)	0.68 (0.61, 0.76)	3.4×10^{-11}
Modified WLW		
First event	0.75 (0.68, 0.83)	1.7×10^{-8}
Second event	0.68 (0.60, 0.78)	3.1×10^{-9}
Third event	0.70 (0.60, 0.83)	2.1×10^{-5}
Key Secondary Composite Endpoint		
Negative binomial	0.71 (0.62, 0.82)	1.2×10^{-6}
Andersen-Gill (I)	0.71 (0.63, 0.79)	1.7×10^{-10}
Andersen-Gill (II)	0.71 (0.62, 0.81)	3.4×10^{-7}
Modified WLW		
First event	0.74 (0.65, 0.83)	7.1×10^{-7}
Second event	0.75 (0.63, 0.89)	0.0011
Third event	0.79 (0.65, 0.96)	0.0171



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

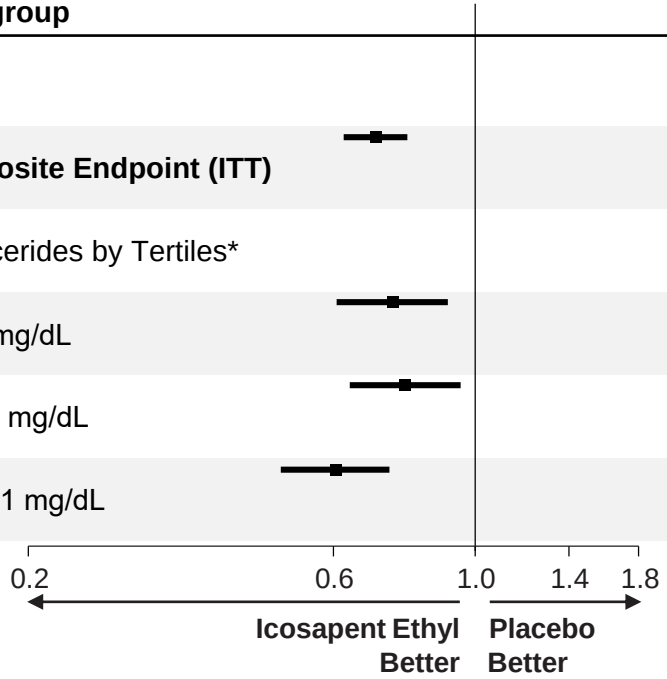
For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:



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

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

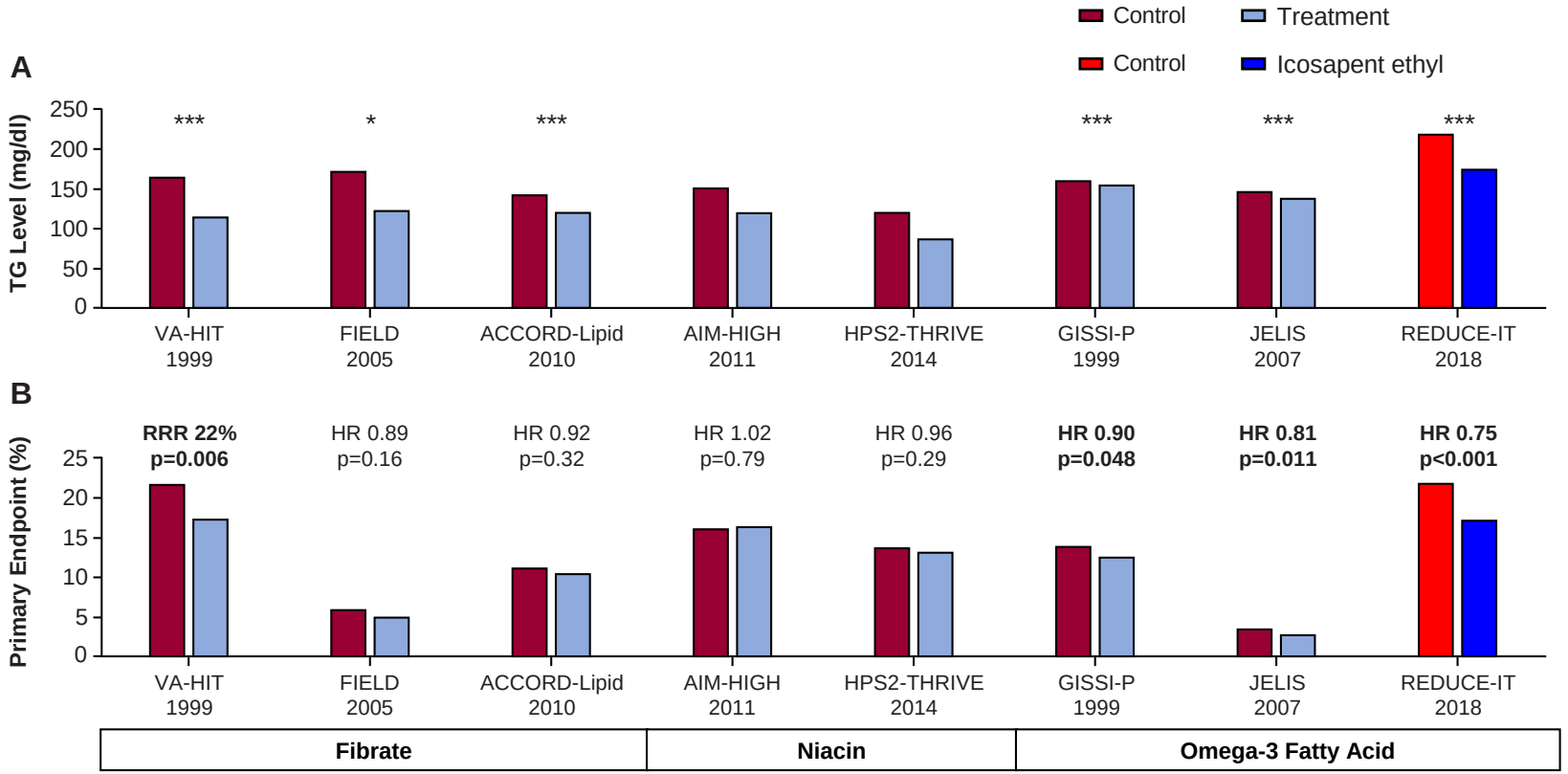
Total Ischemic Events by Baseline TG and Achieved TG at 1 Year

		Total Primary Composite Endpoint		Total Key Secondary Composite Endpoint	
	n (%)† (N=8179)	RR (95% CI)	Interaction p-value	RR (95% CI)	Interaction p-value
Baseline triglycerides			0.26		0.89
≥200 mg/dl	4950 (60.5)	0.66 (0.57-0.77)		0.71 (0.60-0.84)	
<200 mg/dl	3225 (39.4)	0.76 (0.63-0.91)		0.72 (0.58-0.90)	
Baseline triglycerides			0.94		0.88
≥150 mg/dl	7334 (89.7)	0.70 (0.62-0.78)		0.72 (0.62-0.82)	
<150 mg/dl	841 (10.3)	0.71 (0.49-1.03)		0.69 (0.44-1.08)	
Baseline triglycerides tertiles			0.17		0.18
≥81 to ≤190 mg/dl	2759 (33.7)	0.74 (0.61-0.90)		0.68 (0.54-0.87)	
>190 to ≤250 mg/dl	2696 (33.0)	0.77 (0.63-0.95)		0.85 (0.67-1.08)	
>250 to ≤1401 mg/dl	2720 (33.3)	0.60 (0.50-0.73)		0.63 (0.51-0.78)	
Achieved triglycerides at 1 year*	(N=4089)		-		-
Icosapent ethyl TG ≥150 mg/dl vs Placebo	2364 (57.8)	0.66 (0.57-0.75)		0.63 (0.54-0.74)	
Icosapent ethyl TG <150 mg/dl vs Placebo	- 1325 (32.4)	0.62 (0.53-0.74)		0.65 (0.53-0.78)	

* Statistical comparisons of each icosapent ethyl triglyceride group (≥150 mg/dl or <150 mg/dl at 1 year) against the entire placebo group; no interaction p values are generated.
†Number and percentage of patients in each baseline TG subgroup across combined icosapent ethyl and placebo groups; and number and percentage of patients in each 1-year TG group (≥150 mg/dl or <150 mg/dl) for icosapent ethyl.

Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol.* 2019: 1845-50. In press.

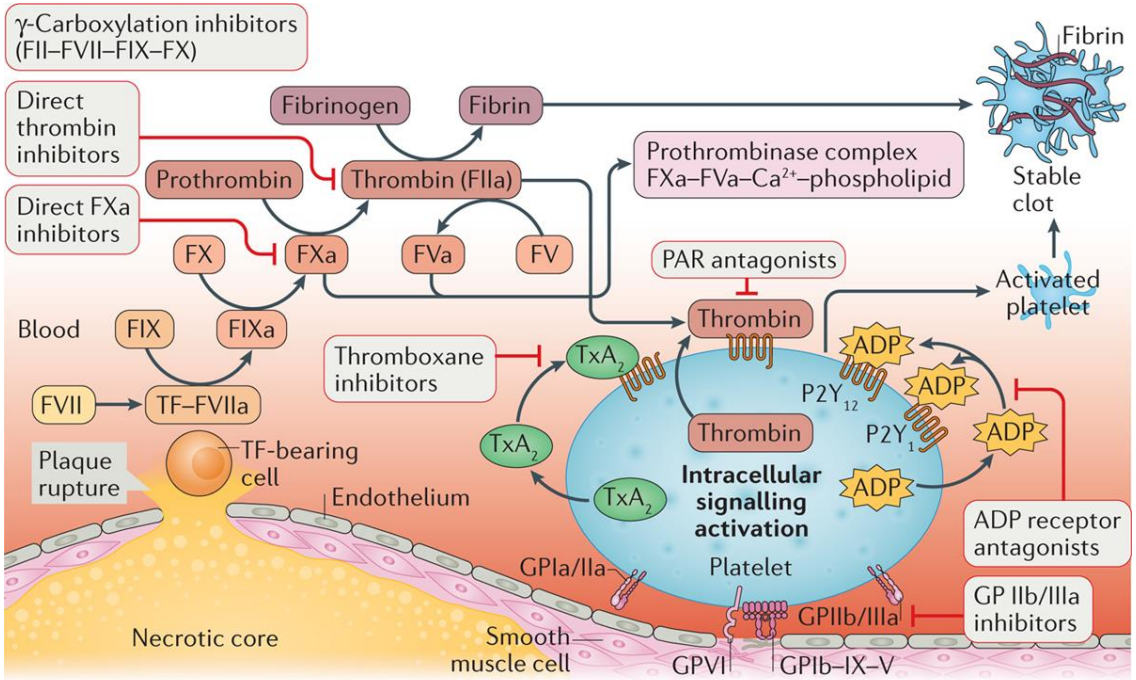
Key Triglyceride-Lowering Trials and Effects on CV Outcomes



Patel PN, Patel SM, Bhatt DL. *Curr Opin Cardiol.* 2019;34 (in press).

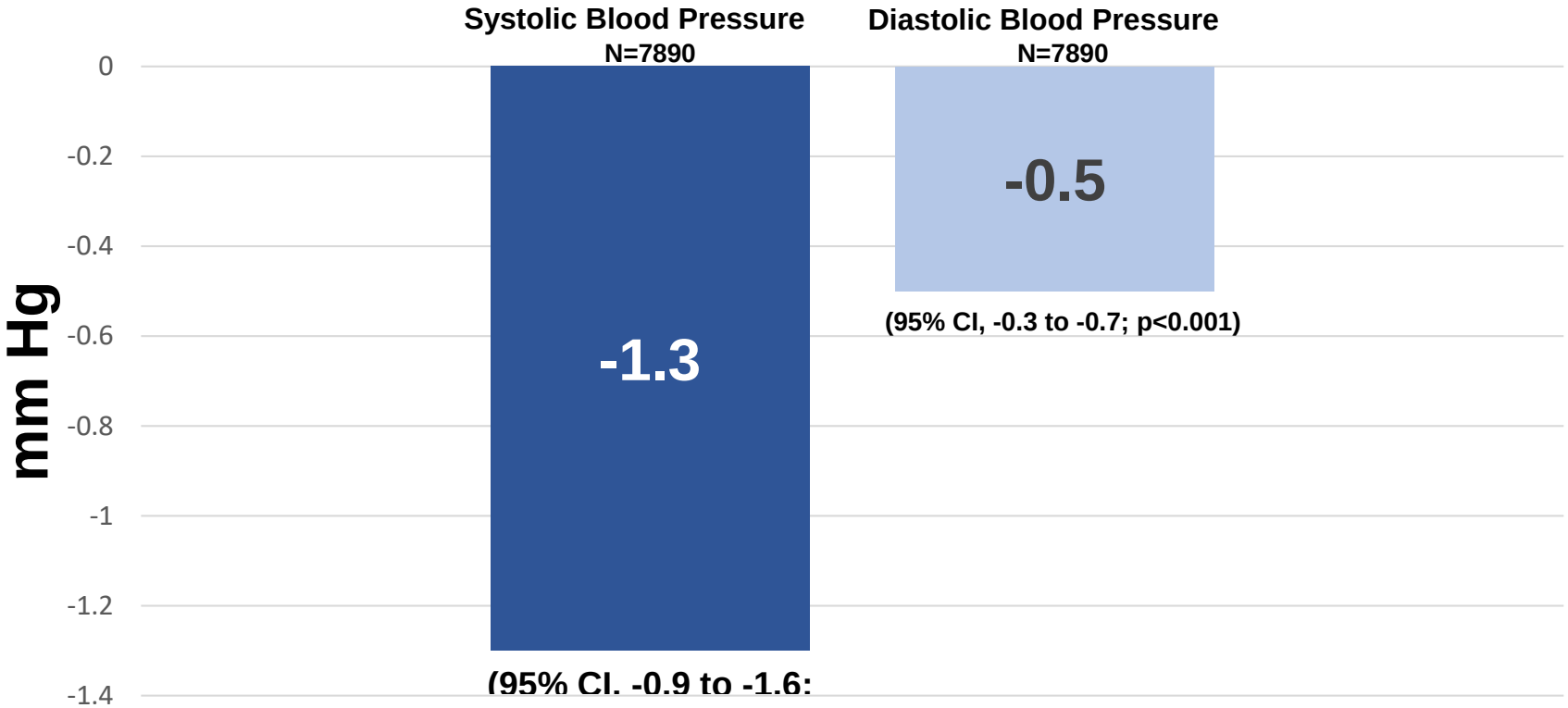
*** P<0.001; * P<0.05

Antiplatelet and Anticoagulant Pathways



Reproduced with permission from Bhatt DL. Advances in atherosclerosis, atrial fibrillation, and valvular disease. *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2017.212. 2018.

Placebo-corrected Reductions in Blood Pressure from Baseline with Icosapent Ethyl 4g/day



Prespecified exploratory analysis with no adjustment for multiple comparisons. Repeated-measurements analysis of change from baseline blood pressure over time by mixed-effects model. ITT population. Icosapent ethyl n=4089, Placebo n=4091. Maximum number of observations per patient = 6.

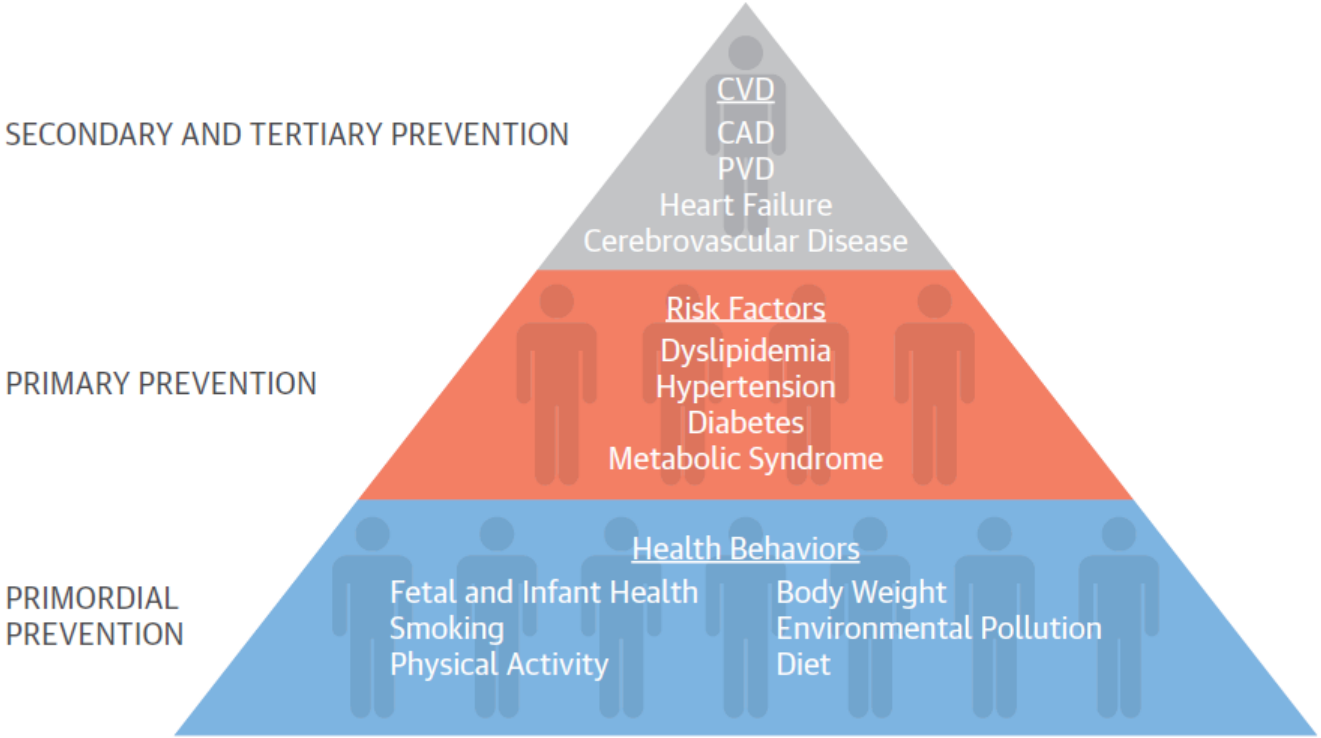
Bhatt DL, Steg PG, Miller M. *N Engl J Med*. 2019;380:1678.

Potential Benefits of EPA

	Endothelial Dysfunction/ Oxidative Stress	Inflammation/ Plaque Growth	Unstable Plaque
Increase	Endothelial function Nitric oxide bioavailablity	EPA/AA ratio IL-10	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 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/]

Pyramid of Risk



Hong KN, Fuster V, Rosenson RS, Rosendorff C, Bhatt DL. JACC 2017. Permission pending.

BRIGHAM AND WOMEN'S HOSPITAL

Heart & Vascular Center

Thank You!

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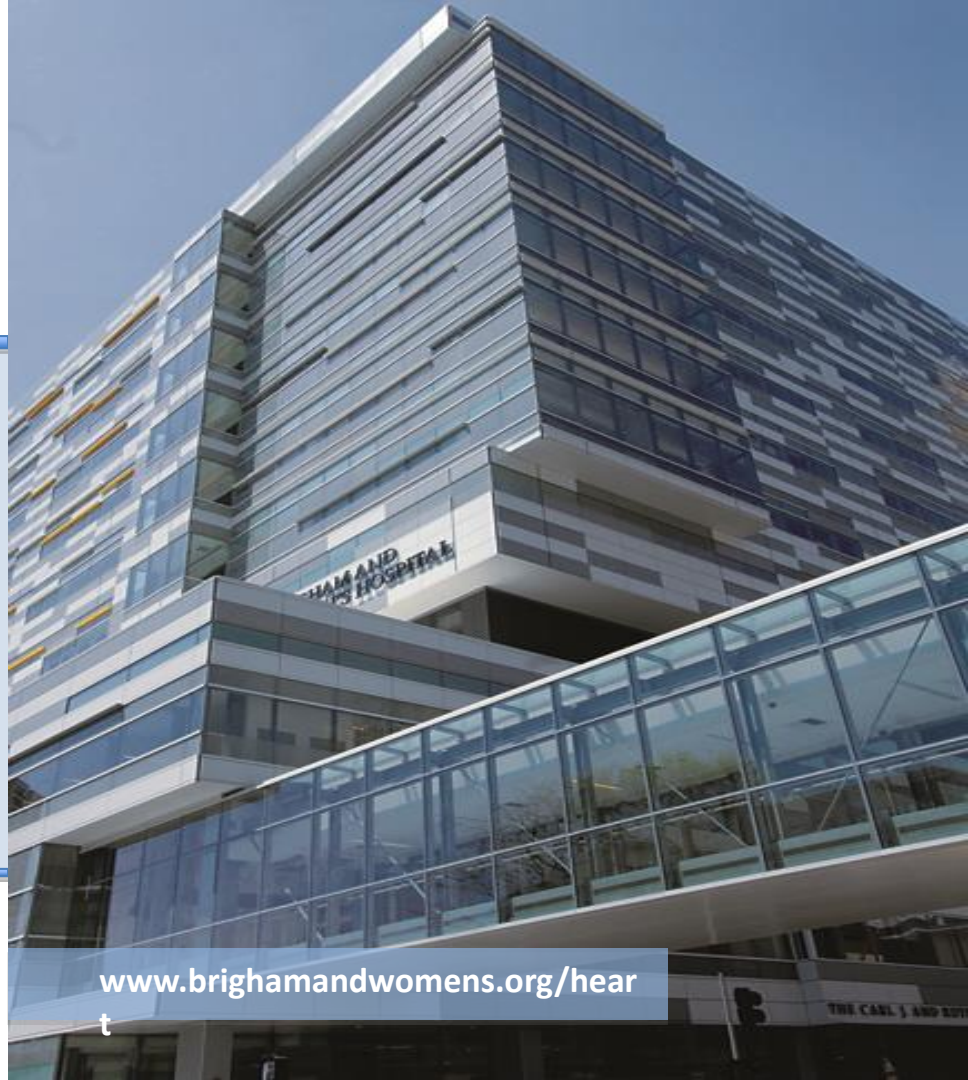
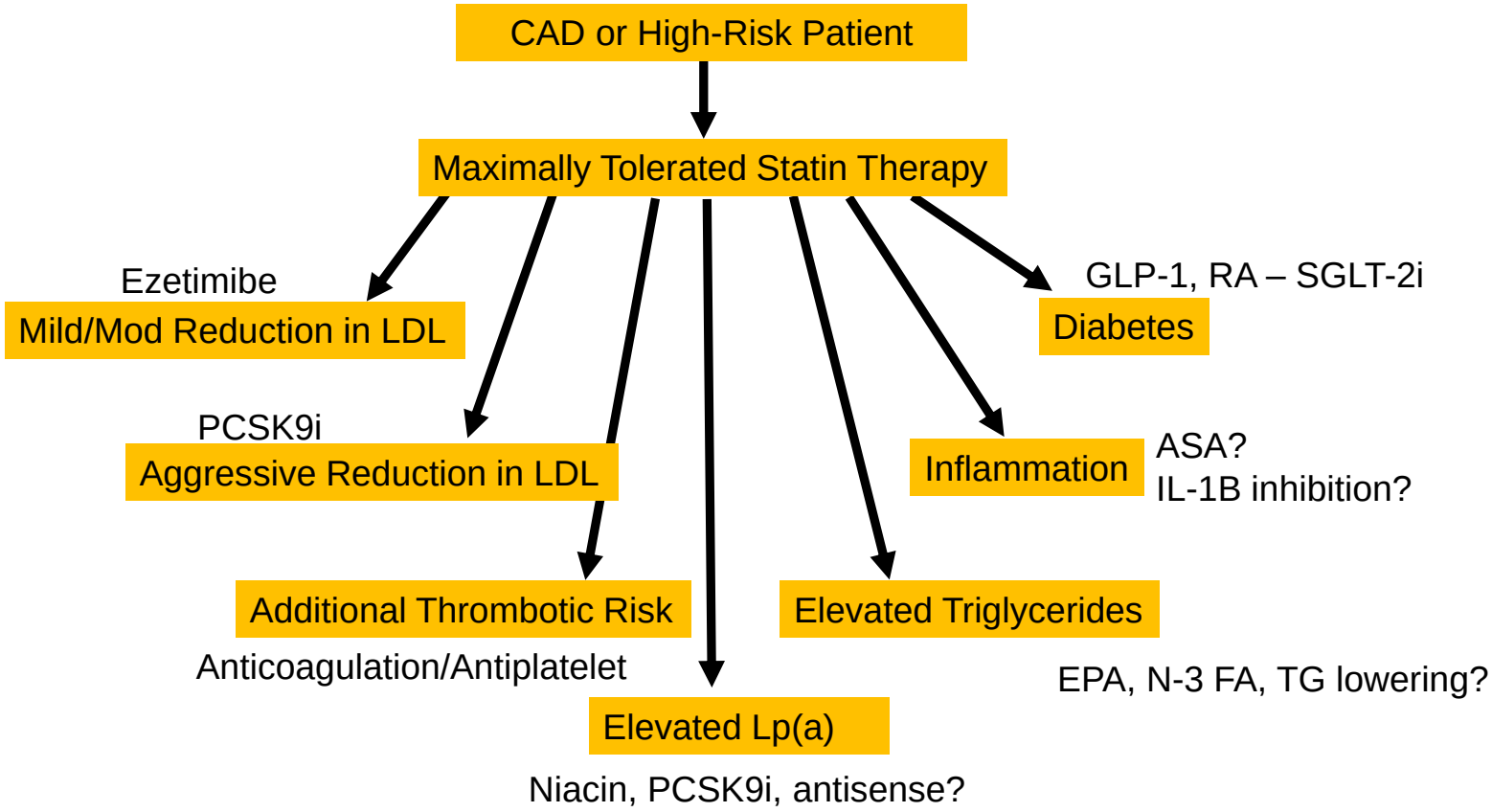
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL



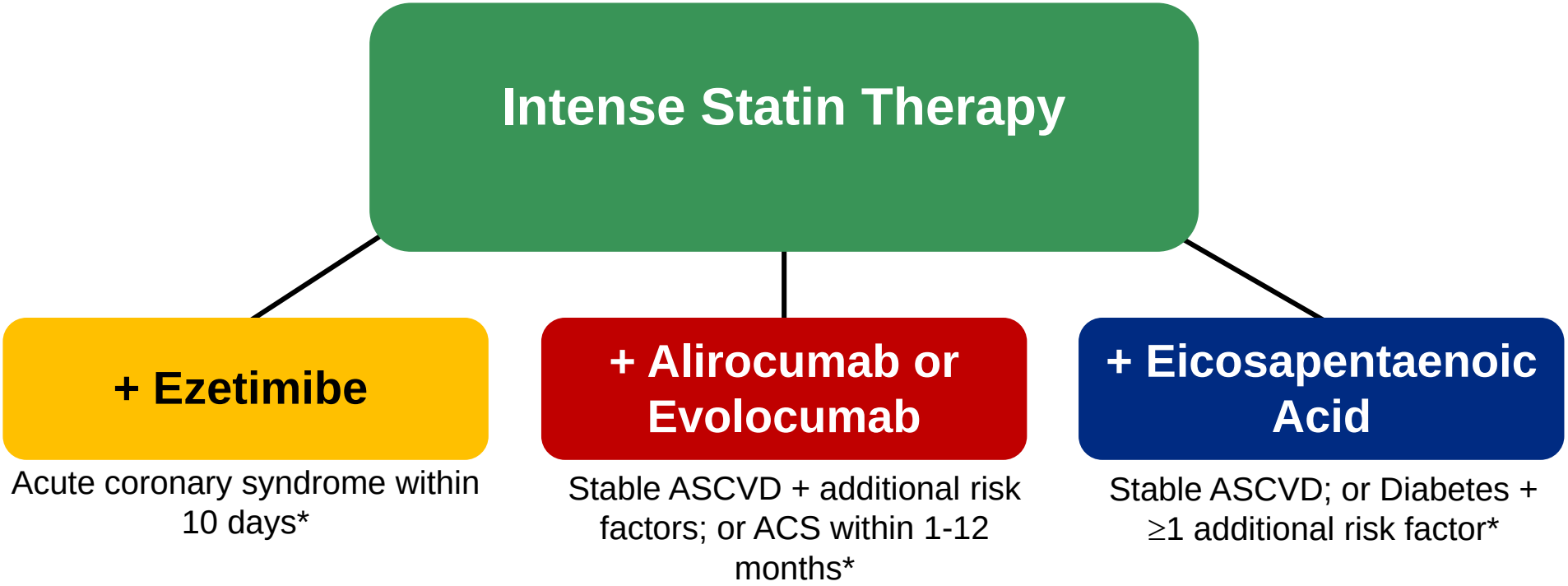
Personalizing Management of ASCVD Risk Factors

ERIN MICHOS, MD, MHS

Pharmacologic Approaches to Managing Residual CV Risk



Statin Therapy Adjuncts Proven to Reduce ASCVD



*Major inclusion criteria for each trial.
ACS=acute coronary syndrome; ASCVD=atherosclerotic cardiovascular disease.
After Orringer CE. *Trends in Cardiovasc Med*. 2019. May 4. [Epub ahead of print]

American Diabetes Association (ADA) Issues Updates to the *2019 Standards of Medical Care in Diabetes*

Section 10 – Cardiovascular Disease and Risk Management: Lipid Management[1]

- 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."
- Other Combination Therapy
  - Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. **A**
  - Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. **A**

1. 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. https://hyp.is/JHhz_ICrEembFJ9LIVBZIw/care.diabetesjournals.org/content/42/Supplement_1/S103. Updated March 27, 2019. Accessed March 28, 2019.

New Recommendations for Drug Treatment of Patients with Hypertriglyceridemia: European Society of Cardiology (ESC) and National Lipid Association (NLA)

ESC

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)].[355]	I	B
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2×2 g/day) should be considered in combination with a statin.[194]	IIa	B
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	B
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	C

© ESC 2019

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = polyunsaturated fatty acids; TG = triglyceride. a=Class of recommendation; b=Level of evidence.

NLA

NLA Position on the Use of Icosapent Ethyl in High and Very-high-risk Patients

- For patients 45 years of age or older with clinical ASCVD, or 50 years of age or older with type 2 diabetes requiring medication and ≥1 additional risk factor*, and fasting triglycerides 135-499 mg/dL on maximally tolerated statin, with or without ezetimibe, treatment with icosapent ethyl is recommended for ASCVD risk reduction. (I B-R)

CLASS I (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

*
- Age: men ≥55 years and women ≥65 years
- Cigarette smoker or stopped smoking within 3 months
- Hypertension (≥140 mmHg systolic OR ≥90 mmHg diastolic) or on antihypertensive medication
- HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women
- hs-CRP >3.0 mg/L
- Renal dysfunction: Creatinine clearance >30 and <60 mL/min
- Retinopathy
- Micro- or macro-albuminuria
- ABI <0.9 without symptoms of intermittent claudication

https://www.lipid.org/nla/nla-position-use-icosapent-ethyl-high-and-very-high-risk-patients

Dietary Supplement Fish Oil: *Not* Useful for ASCVD Prevention

FDA Product Classification[1] → Food

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

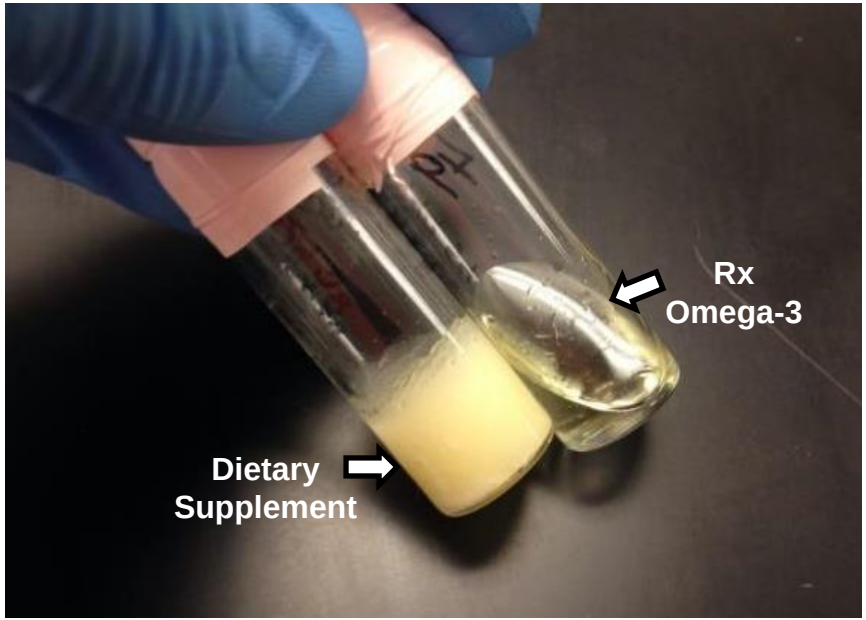
Content & Purity[2-9] →
- Often difficult to achieve high doses likely needed for efficacy
- Often have high saturated fat content
- Omega-3 content often overstated
- Tend to contain relatively high amounts of oxidized lipids which may increase CV risk
- Can contain PCBs and dioxins at harmful levels

Ability to reduce ASCVD → **Not demonstrated**

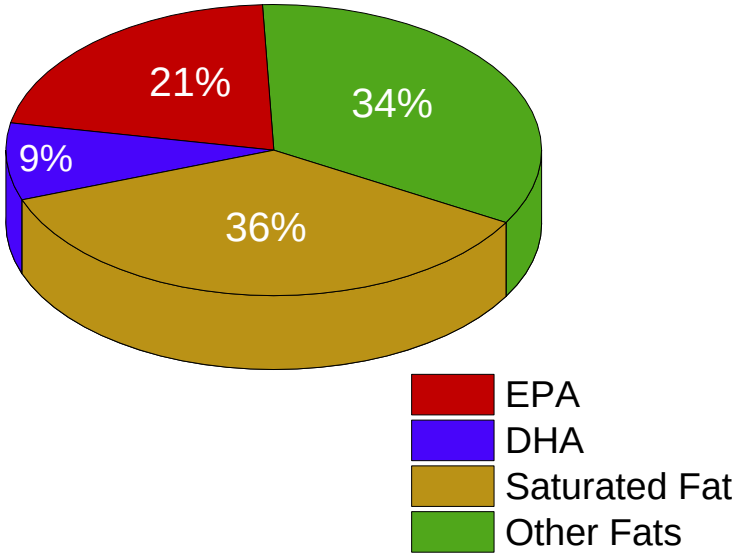
Use for Treatment of Disease → ***Not Recommended***

1. US Food and Drug Administration. www.fda.gov/Food/DietarySupplements/default.htm. Updated April 4, 2016. Accessed Nov. 4, 2018. 2. Hilleman D and Smer A. *Manag Care*. 2016;25:46-52. 3. Mason RP and Sherratt SCR. *Biochem Biophys Res Commun.* 2017;483:425-9. 4. Albert BB et al. *Sci Rep*. 2015;5:7928. 5. Kleiner AC et al. *J Sci Food Agric*. 2015;95:1260-7. 6. Ritter JC et al. *J Sci Food Agric*. 2013:93:1935-9. 7. Jackowski SA et al. *J Nutr Sci*. 2015;4:e30. 8. Rundblad A et al. *Br J Nutr*. 2017;117:1291-8. 9. European Medicines Agency, 2018: 712678.

Fatty Acid Content of Leading U.S. Fish Oil Supplement



Saturated fatty acid content in fish oil supplement results in solid mass following isolation



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

Besides the Other Issues with Dietary Supplements, You Need Huge Amounts to = 4g Rx EPA

Icosapent ethyl

EPA Dietary Supplement from label

Krill oil from label

Conclusions

- After a long drought, a plethora of clinical studies has provided evidence for additional pharmacologic avenues to reduce CVD risk in statin-treated patients
- Cardio-protective agents should be preferred for diabetes management
- Control of coagulation and inflammation still needs to be positioned for wider scopes in CVD risk reduction
- The value of additional LDL lowering is proven, but use of EPA for subjects with elevated TG produces even larger CV benefits

Panel Discussion and Q&A

ALL FACULTY

Erin Michos
Deepak Bhatt

CASE: 69-YO AFRICAN AMERICAN WOMAN WITH NO PRIOR CHD EVENTS, TYPE 2 DIABETES, WITH HTG

Case: 69-yo African American Woman with *No* Prior CVD Events, Post-Menopausal, Type 2 Diabetes, w/moderate HTG & HBP (treated)

Meds:

HCTZ 25 mg/d; atorvastatin 40 mg/d

Exam:

BMI=31 kg/m^2, BP=126/84 mm Hg, Waist=38”, Non-smoker

Labs:

Fasting glucose	115 mg/dL
A1c	6.2%
TC	201 mg/dL
TG	320 mg/dL
HDL-C	38 mg/dL
LDL-C	98 mg/dL
Non-HDL-C	163 mg/dL

What would you prescribe?

A. Increase atorvastatin dose to 80 mg/dL
B. Ezetimibe
C. PCSK9 inhibitor
D. Dietary-supplement fish-oil
E. Icosapent ethyl (pure EPA) 2g bid
F. Fibrate

Closing Comments

DEEPAK L. BHATT, MD, MPH, *CHAIR*

Learning Assessment 1

What does the 2018 ACC/AHA Guideline on Blood Cholesterol Management algorithm recommend for a 69 y/o man with clinical ASCVD?

A. Put patient on low-intensity statin therapy and healthy lifestyle
B. Put patient on moderate-intensity statin therapy
C. Put patient on high-intensity statin therapy
D. Treat to obtain an LDL-C reduction of 25%

ACC=American College of Cardiology; AHA=American Heart Association; ASCVD=atherosclerotic cardiovascular disease; LDL-C=low-density lipoprotein cholesterol.

Learning Assessment 2

You have a patient with clinical ASCVD who has a TG level of 212 mg/dL and an LDL-C of 69 mg/dL. Which of the following should you recommend?

A. Fibrate (eg, fenofibrate)
B. Nicotinic acid (eg, niacin)
C. Prescription EPA
D. Omega-3 dietary supplement
E. Nothing

ASCVD=atherosclerotic cardiovascular disease; EPA=eicosapentaenoic acid; LDL-C=low-density lipoprotein cholesterol; TG=triglyceride(s).

Learning Assessment 3

Compared with placebo in REDUCE-IT, pure eicosapentaenoic acid (EPA) 4 g/day reduced the primary endpoint (5-point MACE) by

A. 15%

B. 25%

C. 50%

D. No difference in events

MACE=major adverse cardiovascular events; REDUCE-IT=Reduction of CV Events with Icosapent Ethyl – Intervention Trial.

Online materials for this activity

Access slides online

- Faculty slides are available here: medtelligence.net/sept25
- Scroll to the “Related” section and click on “Syllabus”

Online CME credit

- All attendees will receive an email with a link to the evaluation form
- Once you complete the online evaluation form, you will receive an email with a link to download your CME certificate

Adjourn

DEEPAK L. BHATT, MD, MPH, *CHAIR*