New Options and Strategies for CV Risk Reduction in Diabetes: What the Data Tell Us

June 7, 2019 | InterContinental San Francisco | San Francisco, CA

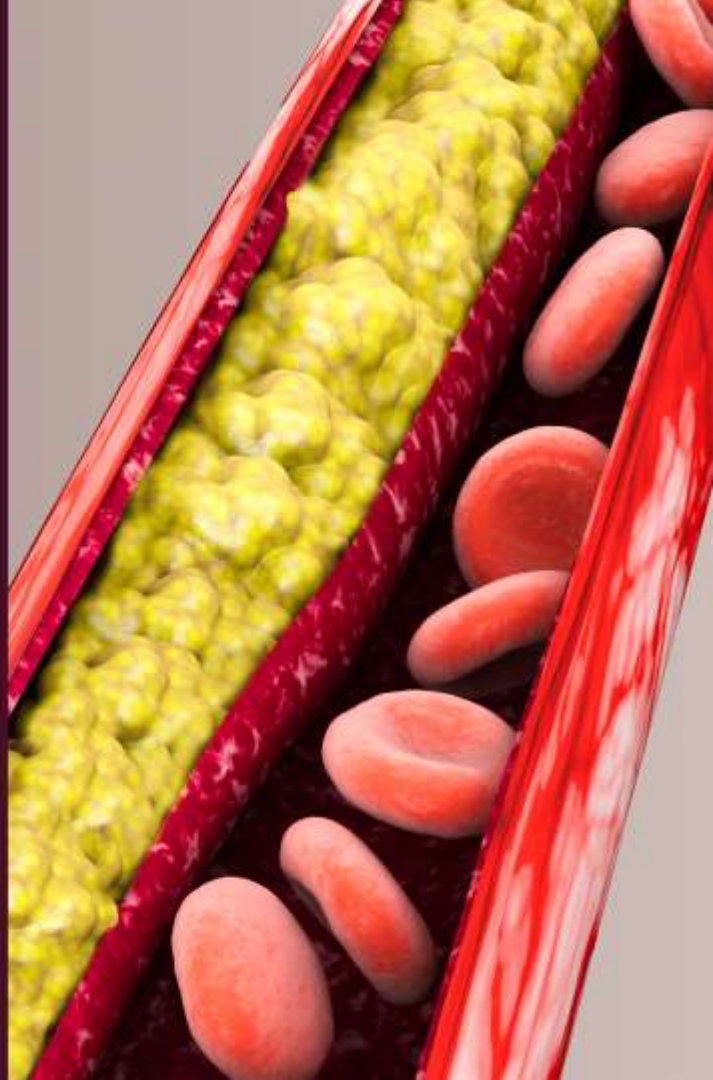
Agenda

6:30 PM	Registration and Buffet Dinner
7:00	Program Overview *Robert H. Eckel, MD, Chair*
7:15	New Cholesterol Guidelines: What You Should Know *Robert H. Eckel, MD, Chair*
7:35	Omega-3 FAs and their Use in Patients with ASCVD *Deepak L. Bhatt, MD, MPH*
7:55	Roundup of Recent Clinical Trial Evidence to Reduce ASCVD Events *Sergio Fazio, MD, PhD*
8:15	Panel Discussion and Q&A
8:35	Case-based Learning on Personalization of Care in Patients with Diabetes and High-risk ASCVD *All Faculty*
8:50	Closing Comments *Robert H. Eckel, MD, Chair*
9:00 PM	Adjourn

Faculty slides are available online: medtelligence.net/june7
Scroll to the "Related" section and click on "Syllabus"

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

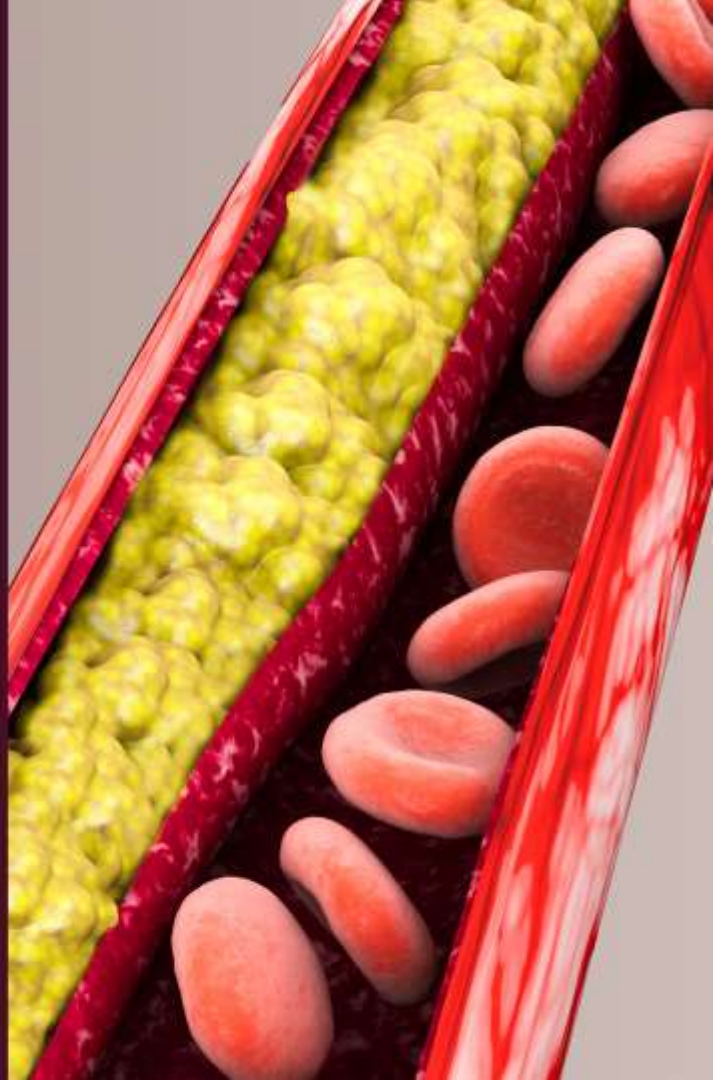
It is being provided as a useful reference that we encourage you to use during and after the activity.



New Options and Strategies for CV Risk Reduction in Diabetes:

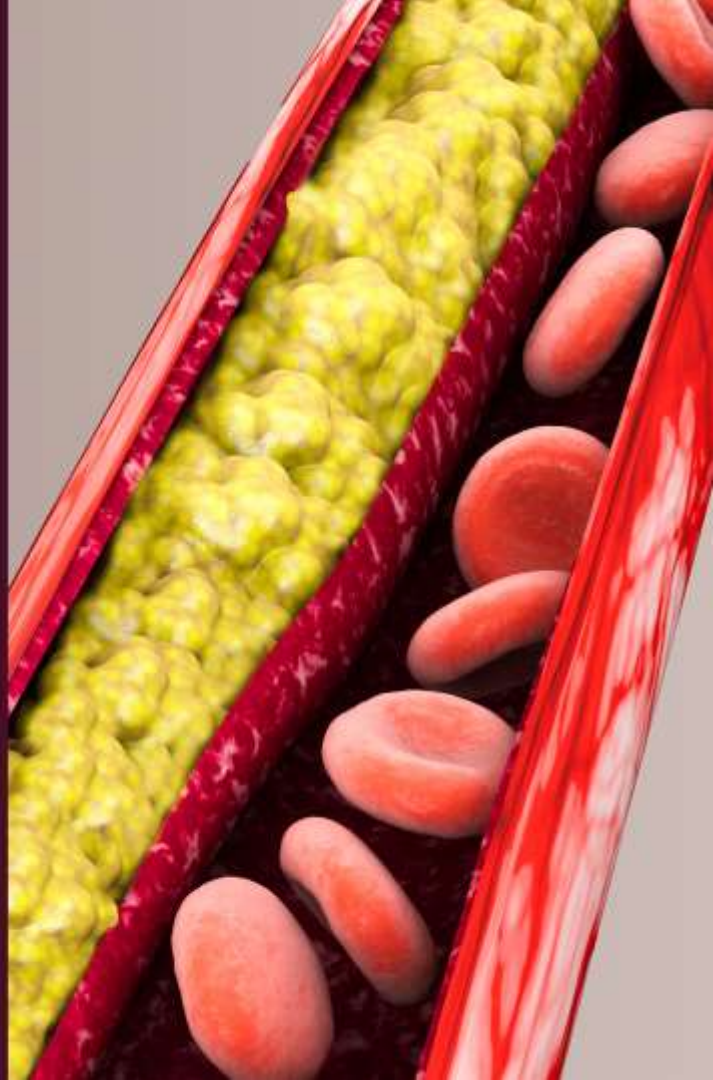
What the Data Tell Us

June 7, 2019



Welcome and Program Overview

Robert H. Eckel, MD, *Chair*



Robert H. Eckel, MD, *Chair*

Charles A. Boettcher II Endowed Chair in Atherosclerosis
Professor of Medicine – Division of Endocrinology, Metabolism and Diabetes, and Cardiology
Professor of Physiology and Biophysics
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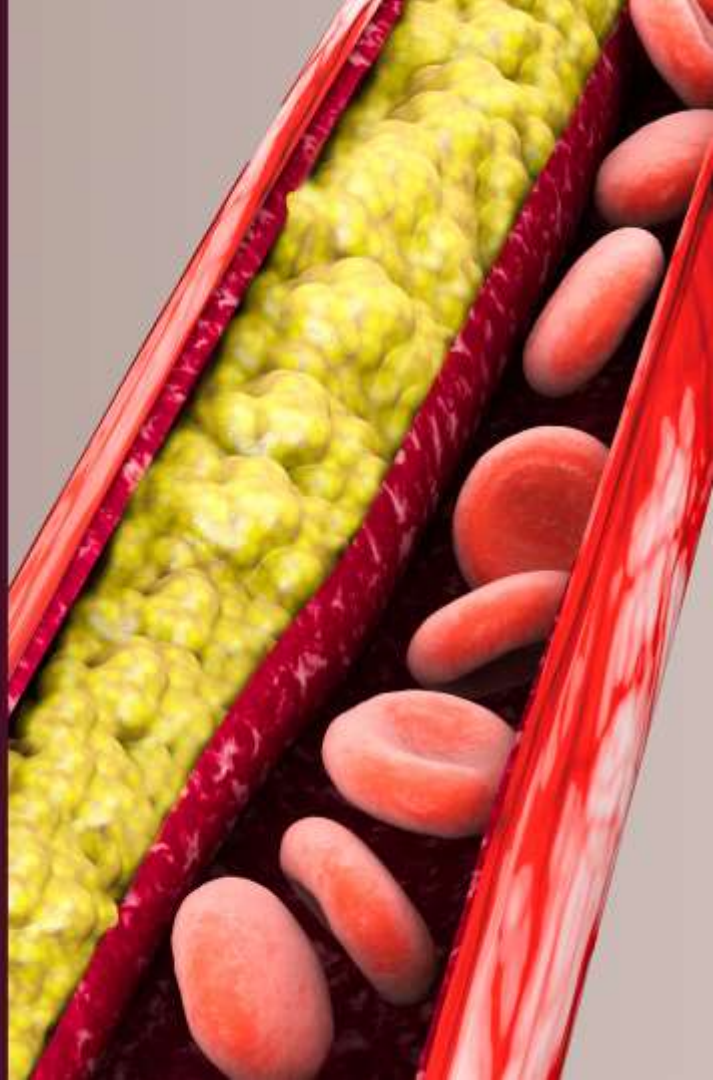
- Disclosures: Consulting Fees: Novo Nordisk, Sanofi; Contracted Research: ENDEC

New Cholesterol Guidelines: What You Should Know

Robert H. Eckel, MD, *Chair*



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: Secondary Prevention

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

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.

Eggs, Dietary Cholesterol and Cardiovascular Disease Revisited

EDITORIAL

Reconsidering the Importance of the Association of Egg Consumption and Dietary Cholesterol With Cardiovascular Disease Risk

Robert H. Eckel, MD

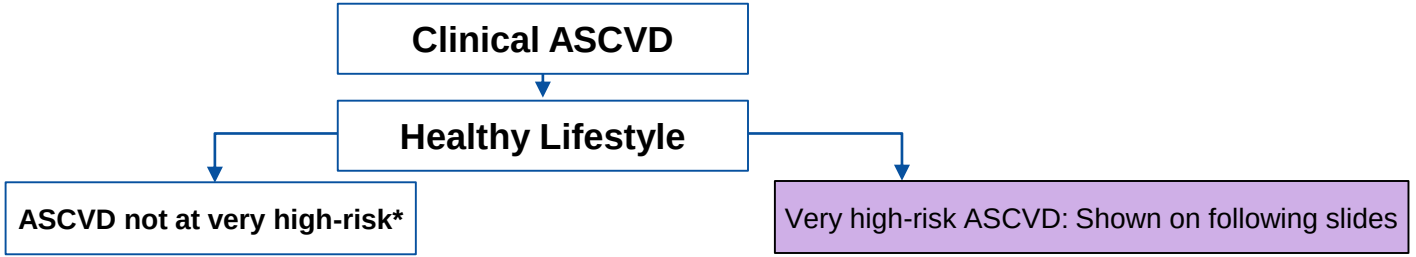
Nutrition research, in contrast with randomized clinical trials that compare a drug with placebo, is more difficult for many reasons, including complexities in data gathering and changes in human behavior over time. In this issue of *JAMA*, Zhong and colleagues[1] report new insights about a controversial topic, the association of egg consumption and dietary cholesterol with cardiovascular disease (CVD) incidence and all-cause mortality. Clearly, the topic of this study is important to clinicians, patients, and the public at large because the association of egg consumption and dietary cholesterol with CVD, although debated for decades, has more recently been thought to be less important. Compared with the meta-analyses and reviews previously published, this

Related article page 1081

In the report by Zhong et al,[1] a harmonized approach was used to analyze self-reported baseline nutritional data on macronutrient intake in 29 615 adults from 6 prospective US cohorts, a group with high racial and ethnic diversity, to examine cardiovascular disease outcomes over a median of 17.5 years. The main finding was that higher consumption of eggs and dietary cholesterol (which included eggs and meats) was significantly associated with incident CVD and all-cause mortality, with a dose-response relationship. Another important finding in the study was that associations between dietary cholesterol and incident CVD and all-cause mortality were no longer significant after adjusting for consumption of eggs and processed and unprocessed red meat. Moreover, the dietary cholesterol content of eggs fully explained the association between egg consumption and inci-

Eckel RH. *JAMA*. 2019;321:1055-6.

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.

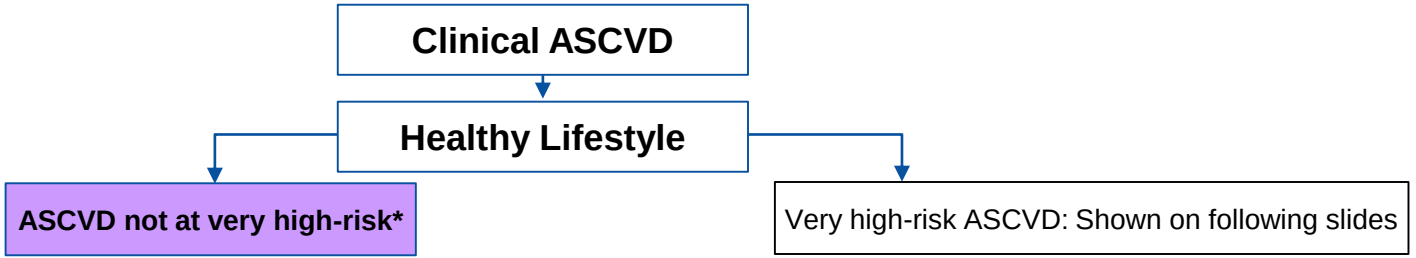
- Class I (Strong). Benefit >>> Risk.
- Class IIa (Moderate). Benefit >> Risk.
- Class IIb (Weak). Benefit ≥ Risk.

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

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

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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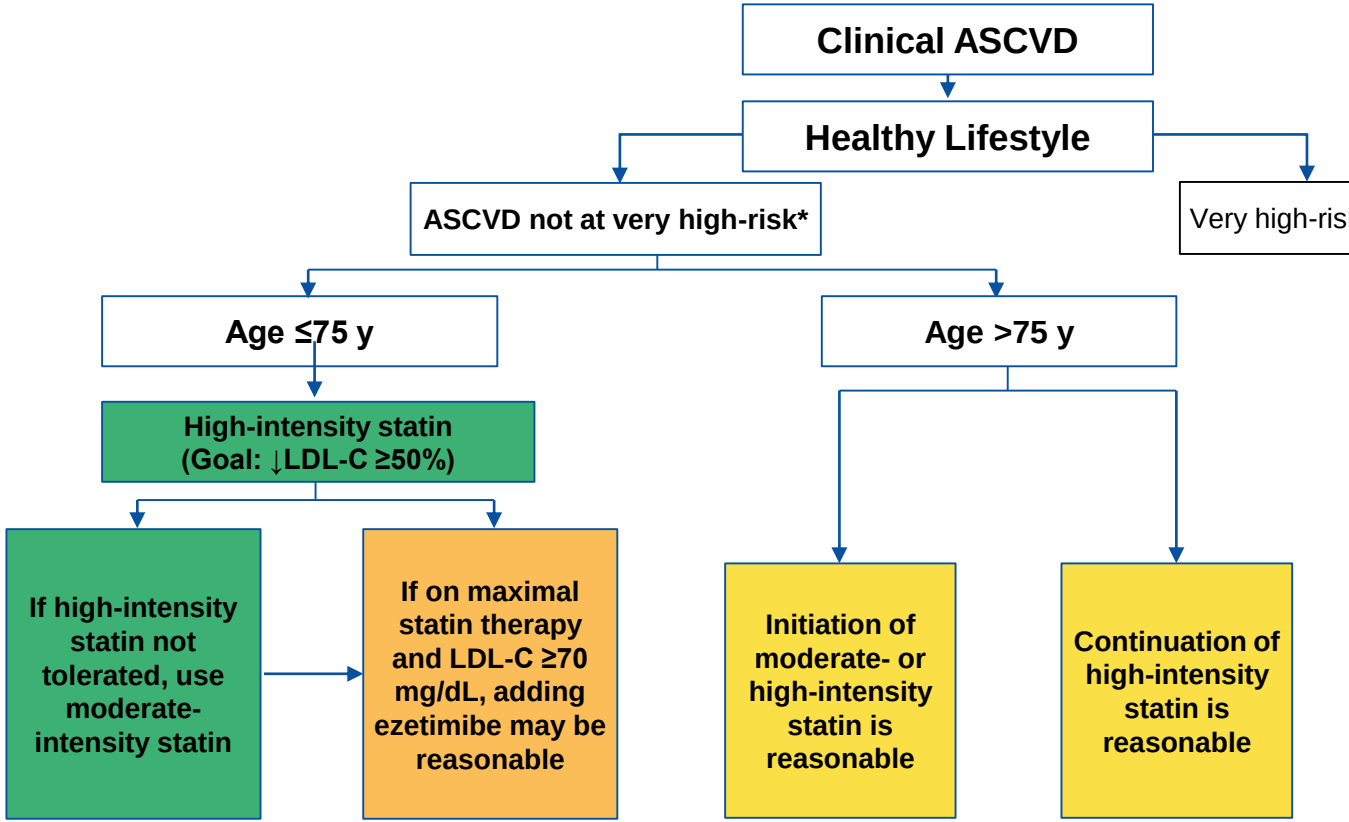

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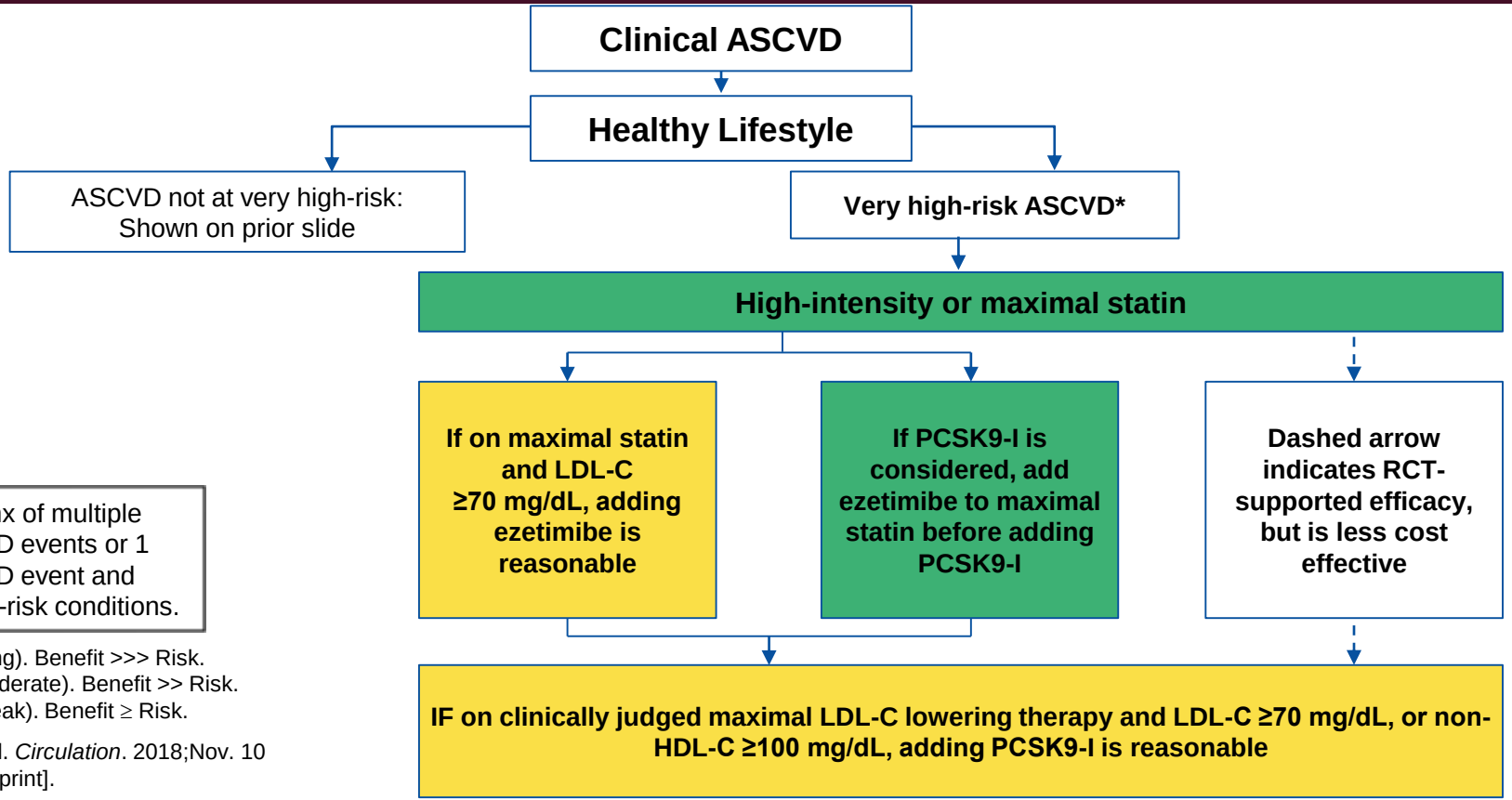

*Includes a hx of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

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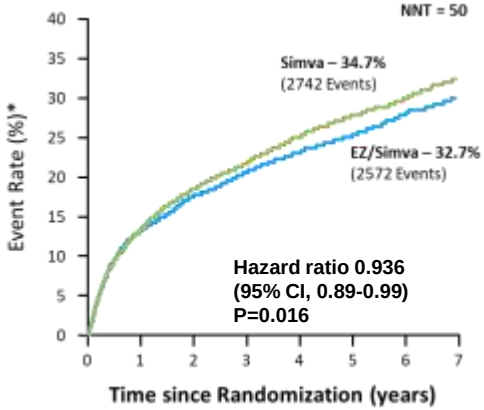
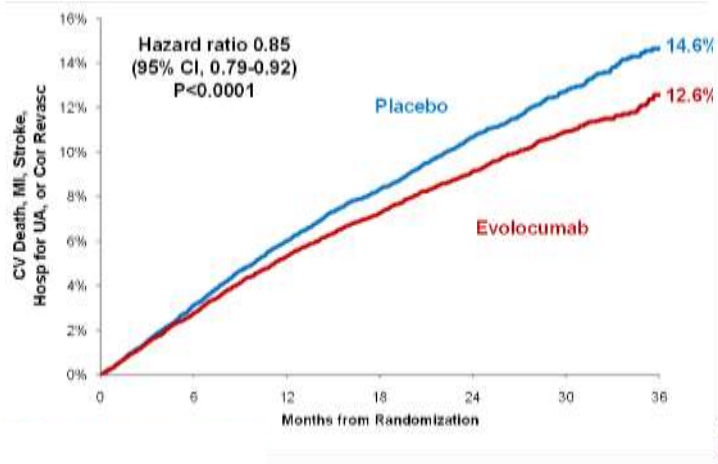
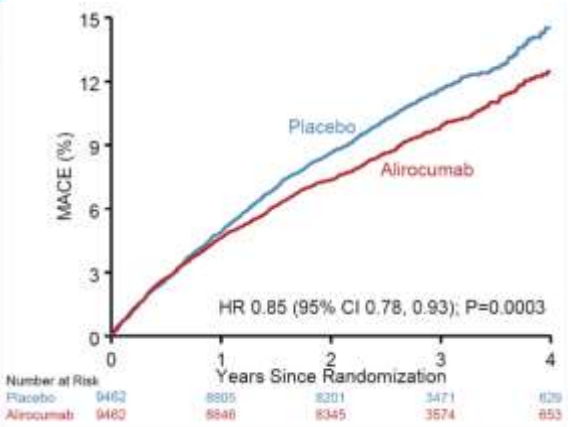
Successful Statin Add-on Trials (5–15% RRR)



IMPROVE-IT[1]



FOURIER[2]

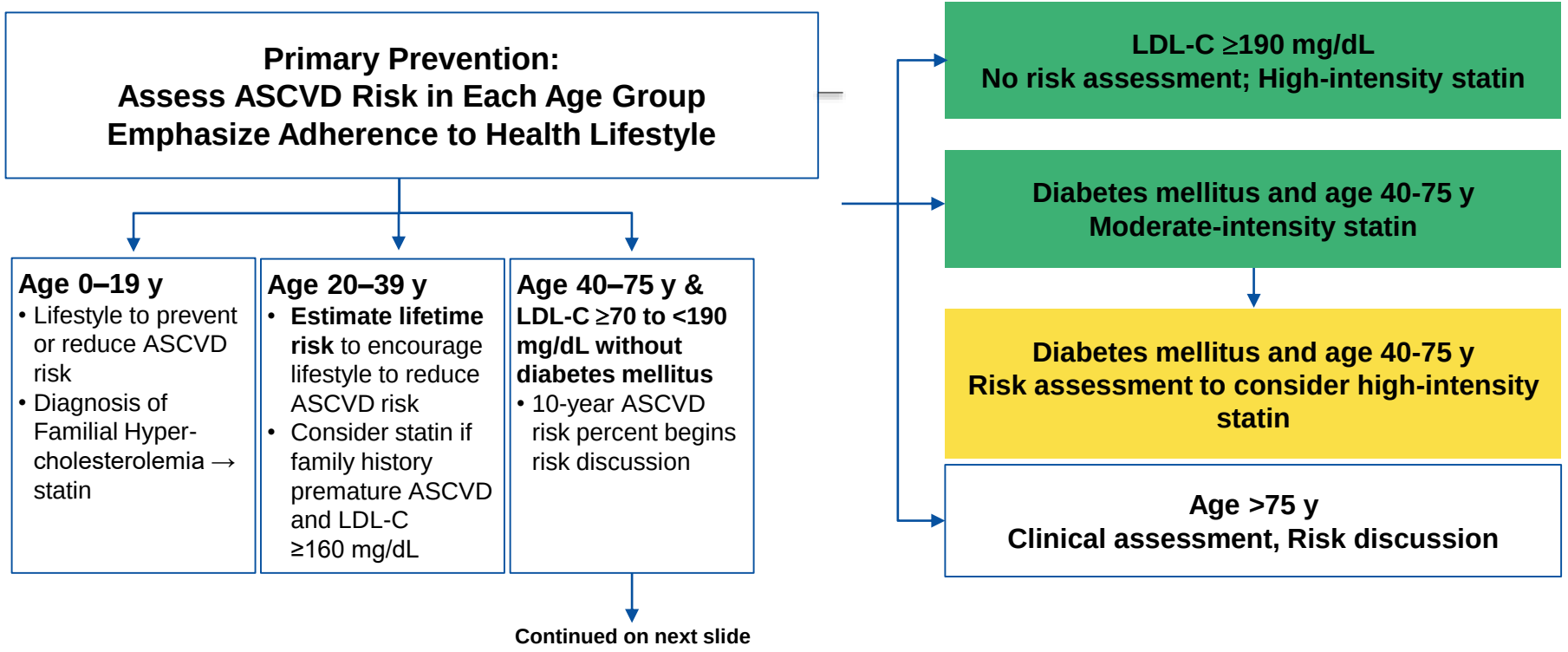


ODYSSEY Outcomes[3]

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.

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



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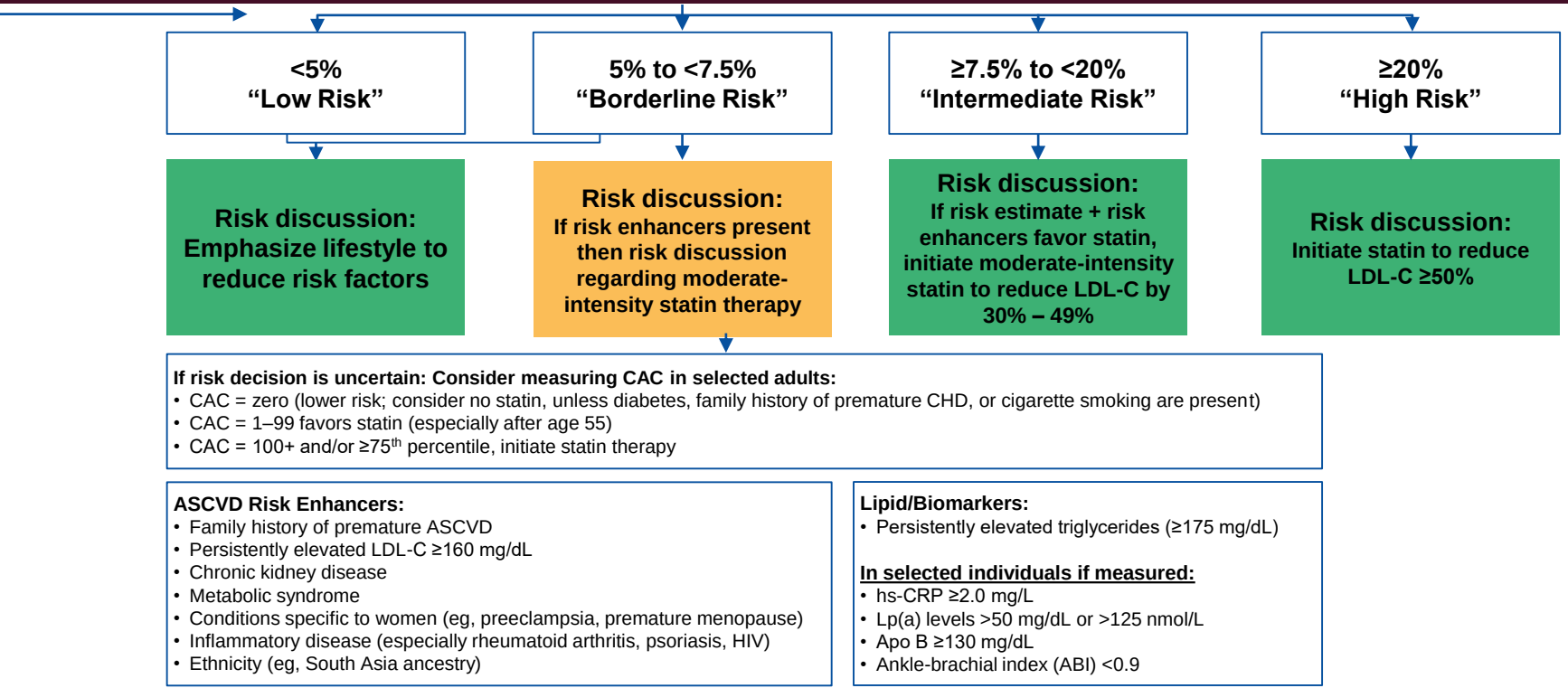
Grundy SM et al. *Circulation*. 2018;Nov. 10 [Epub ahead of print]. Although high TG was noted as a CVD risk factor, treatment of HTG was covered only briefly and prescription omega-3 was not mentioned. (Published simultaneously with REDUCE-IT.)

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



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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]

Severe Hypertriglyceridemia

REVIEW

Annals of Internal Medicine

The Chylomicronemia Syndrome Is Most Often Multifactorial

A Narrative Review of Causes and Treatment

Alan Chait, MD, and Robert H. Eckel, MD

The chylomicronemia syndrome occurs when triglyceride levels are severely elevated (usually >16.95 mmol/L [1500 mg/dL]) and is characterized by such clinical features as abdominal pain, acute pancreatitis, eruptive xanthomas, and lipemia retinalis. It may result from 1 of 3 conditions: the presence of secondary forms of hypertriglyceridemia concurrent with genetic causes of hypertriglyceridemia, termed *multifactorial chylomicronemia syndrome* (MFCS); a deficiency in the enzyme lipoprotein lipase and some associated proteins, termed *familial chylomicronemia syndrome* (FCS); or familial partial lipodystrophy. Most chylomicronemia syndrome cases are the result of MFCS; FCS is very rare. In all these conditions, triglyceride-rich lipoproteins accumulate because of impaired plasma clearance. This review describes the 3 major causes of the chylomicronemia syndrome; their consequences; and the approaches to treatment, which differ considerably by group.

Ann Intern Med. 2019;170:626-634. doi:10.7326/M19-0203 Annals.org
For author affiliations, see end of text.
This article was published at Annals.org on 30 April 2019.

The term *chylomicronemia syndrome* first appeared in the scientific literature in 1981 to describe clinical features attributed to marked elevations in plasma triglyceride levels in a small number of patients (1). Features included abdominal pain, acute pancreatitis, eruptive xanthomas, lipemia retinalis, mental confusion, memory loss, and flushing with minimal alcohol intake (1). Several of these characteristics resembled those chylomicronemia syndrome, with an emphasis on acute pancreatitis; and an approach to therapy.

Methods

This update used PubMed Central. Search terms included *chylomicronemia*; *chylomicronemia syndrome*; *chylomicronemia treatment*; *chylomicronemia genetics*;

Ann Int Med. 2019;170:626-34.

Major Secondary Causes of Hypertriglyceridemia

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

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

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]

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*. 2018;Nov. 10 [Epub ahead of print].

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*. 2018;Nov. 10 [Epub ahead of print].

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*. 2018;Nov. 10 [Epub ahead of print].

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*. 2018;Nov. 10 [Epub ahead of print].

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*. 2018;Nov. 10 [Epub ahead of print].

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*. 2018;Nov. 10 [Epub ahead of print].

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*. 2018;Nov. 10 [Epub ahead of print].

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*. 2018;Nov. 10 [Epub ahead of print].

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*. 2018;Nov. 10 [Epub ahead of print].

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*. 2018;Nov. 10 [Epub ahead of print].

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*. 2018;Nov. 10 [Epub ahead of print].

Residual Cardiovascular Risk in Statin-Treated Patients with Elevated Triglycerides: Now We Can REDUCE-IT

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

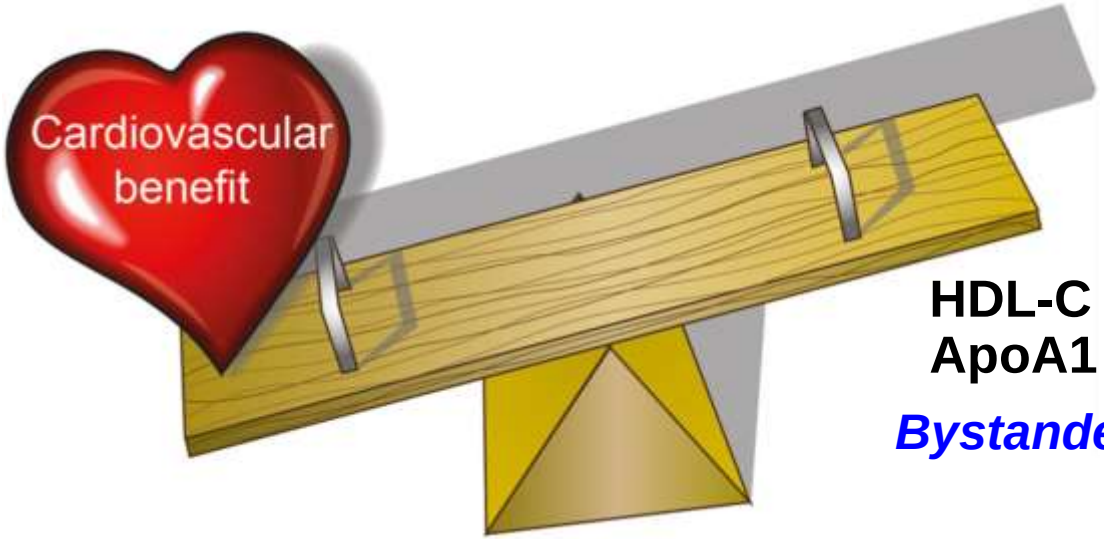
Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, 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), 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, 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

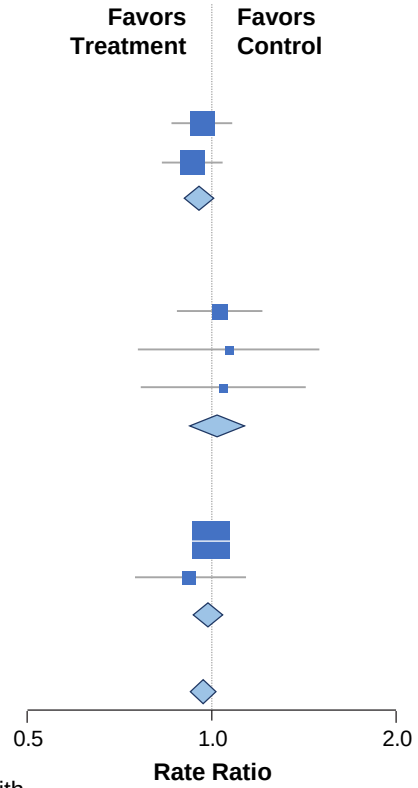
Causal risk factors?

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

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

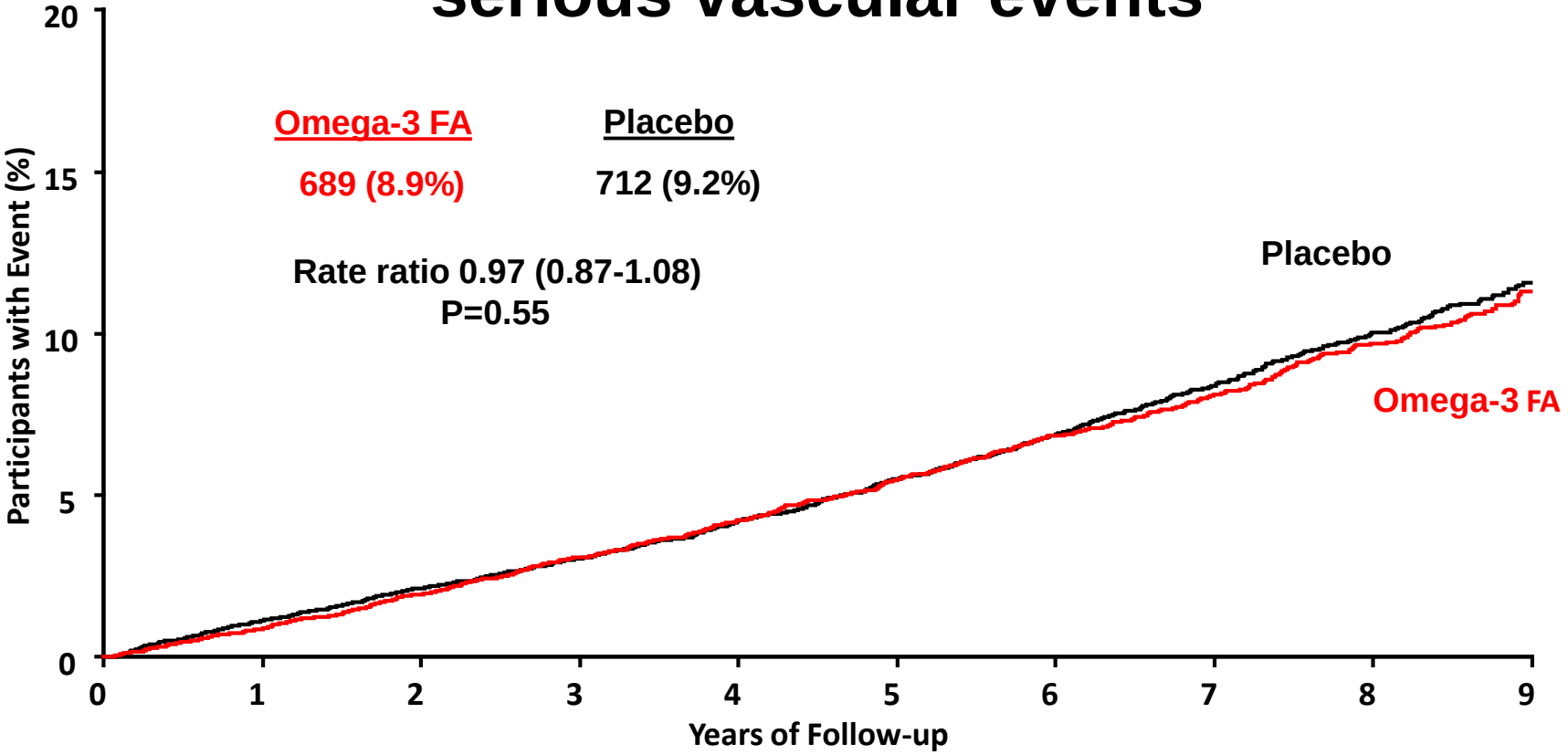
ASCEND trial design

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



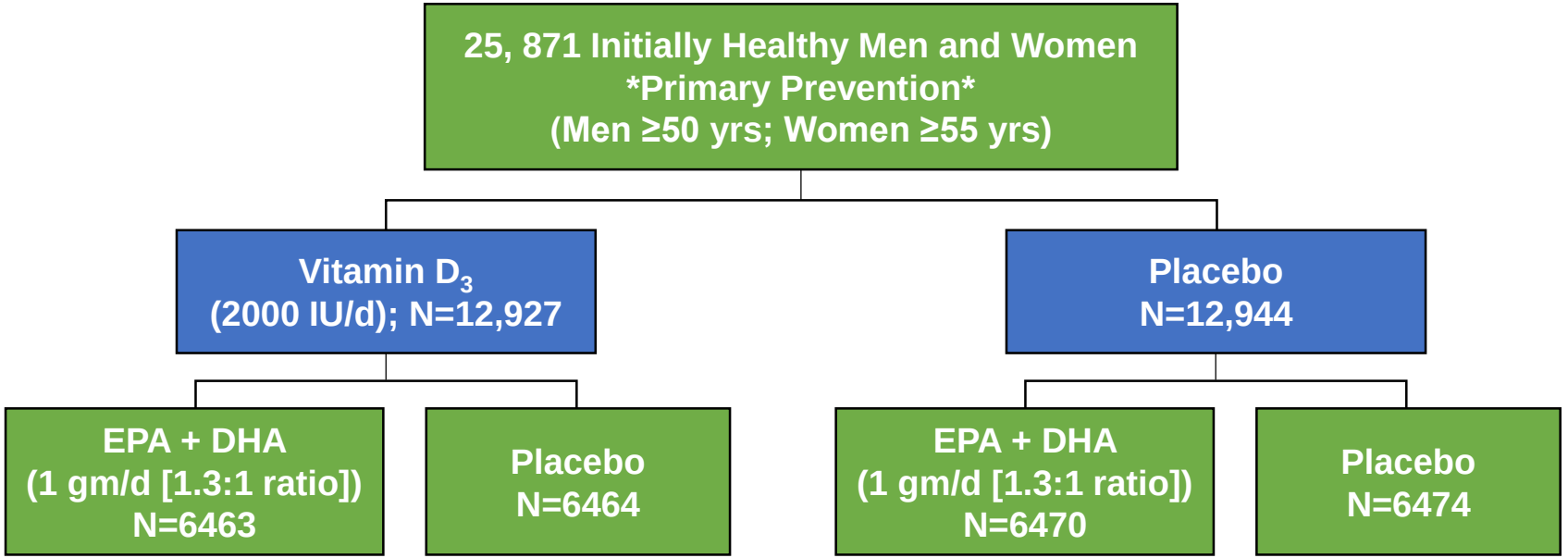
The NEW ENGLAND JOURNAL of MEDICINE

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*

The **VIT**amin D and Omega**A**-3 Tria**L (VITAL):** Design



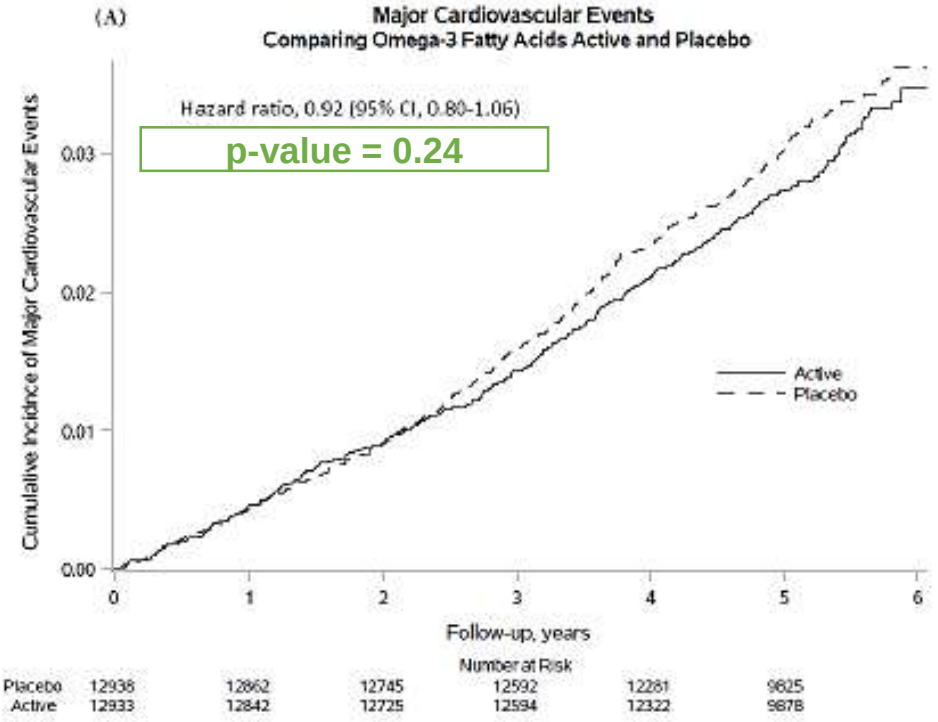
Median Treatment Period = 5.3 years.

5106 African Americans.

Blood collection in ~16, 953 at baseline, follow-up bloods in ~6000.

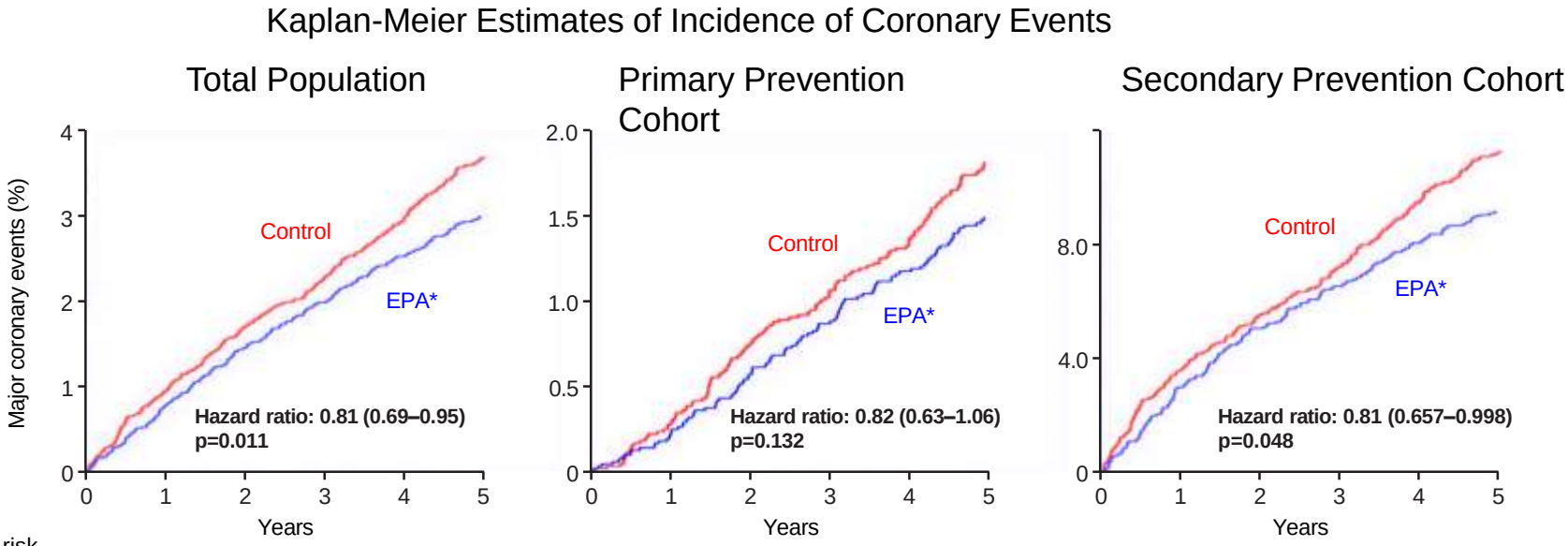
Adapted from: Manson JE, Bassuk SS, Lee I-M, et al. *Cont Clinical Trials*, 2011.

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

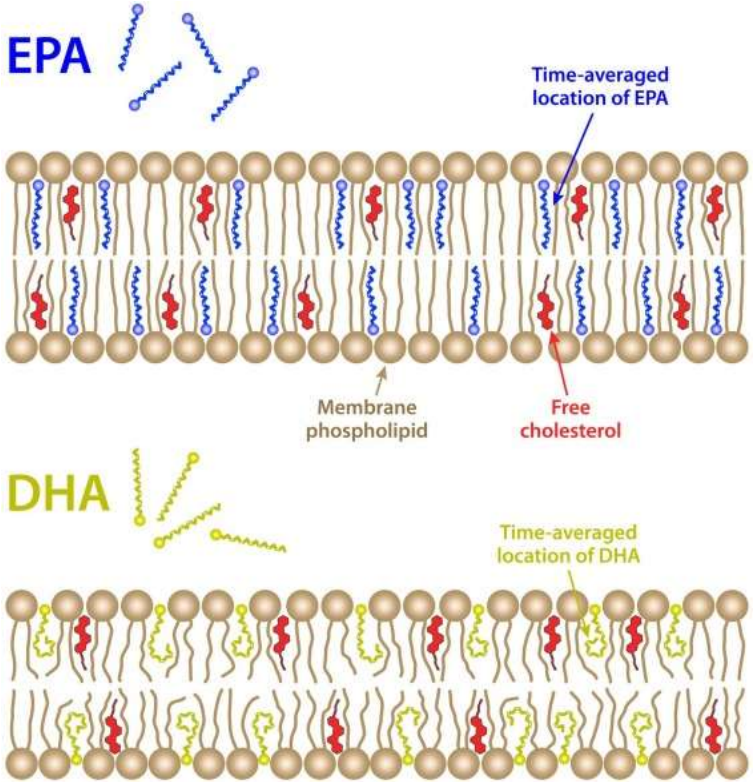
JELIS Suggests CV Risk Reduction with EPA in Japanese Hypercholesterolemic Patients



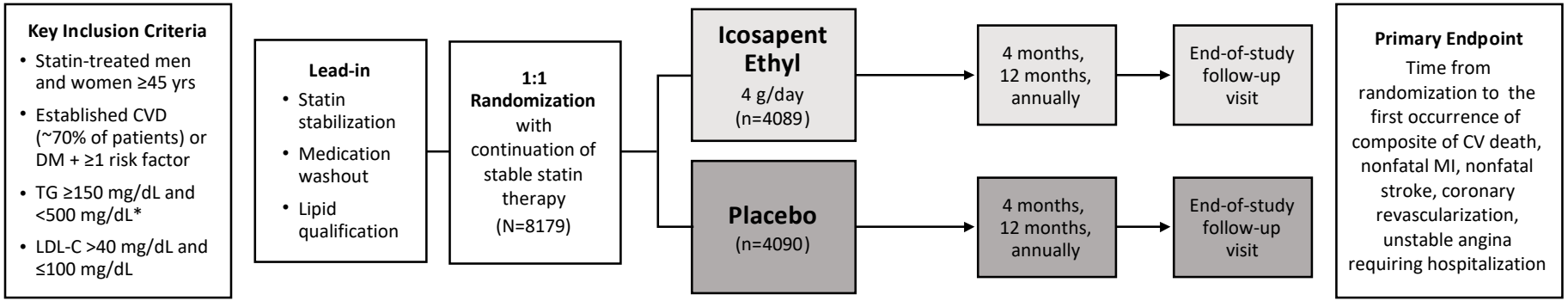
*1.8 g/day

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



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

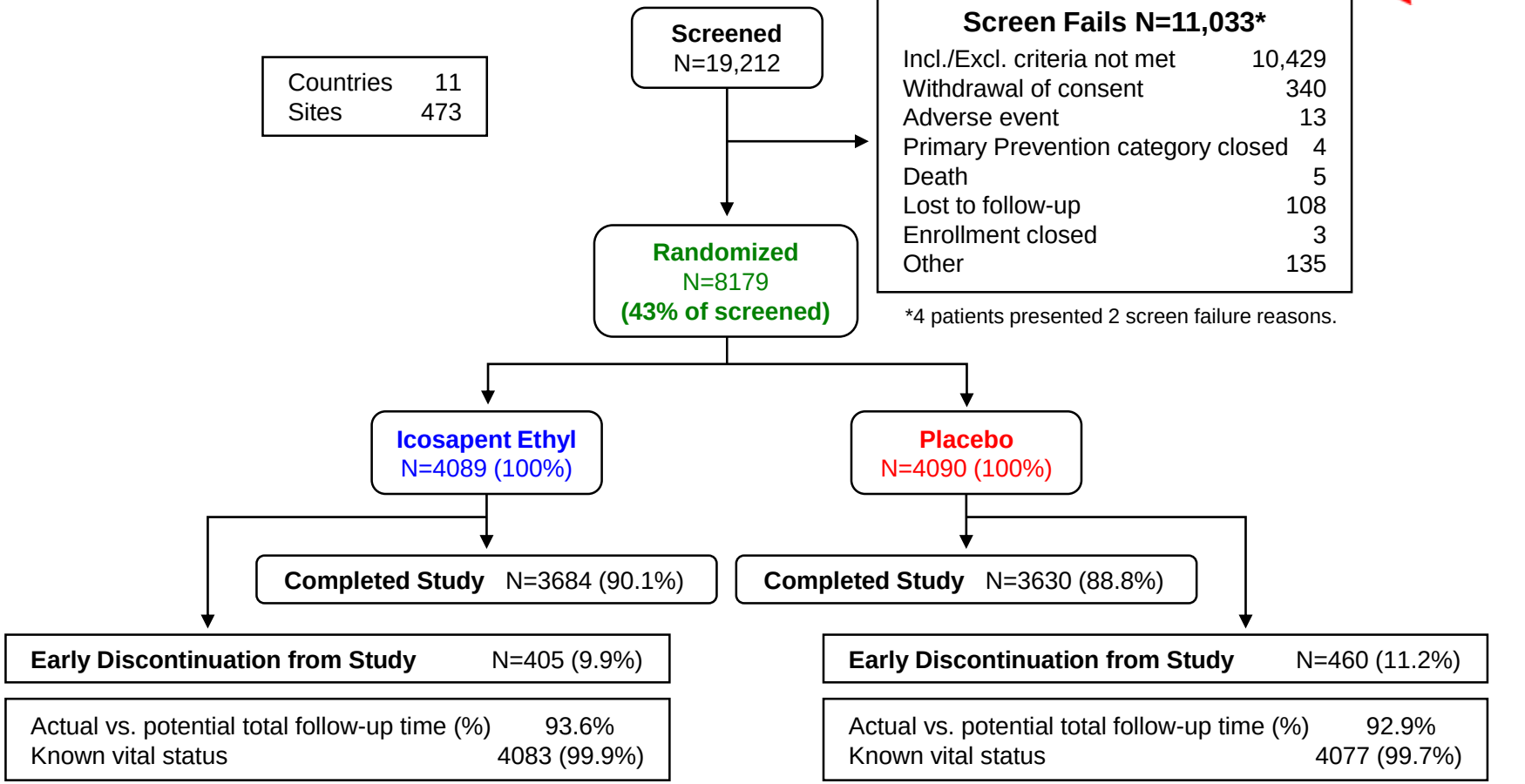
*Due to the variability of triglycerides, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability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

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

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.

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.

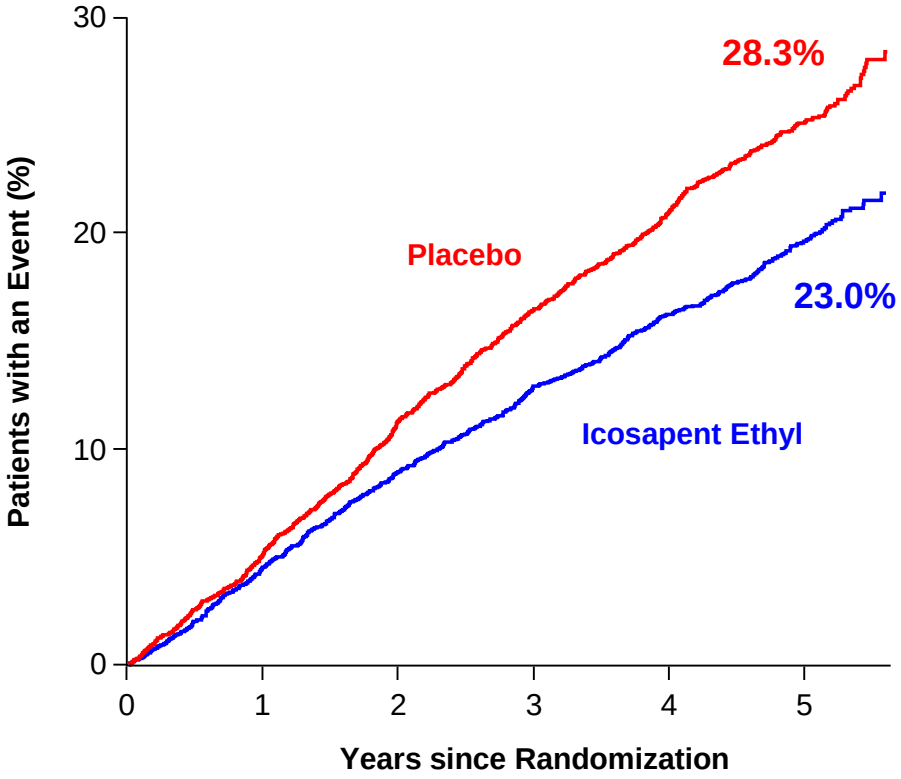
Effects on Biomarkers from Baseline to Year 1

	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%

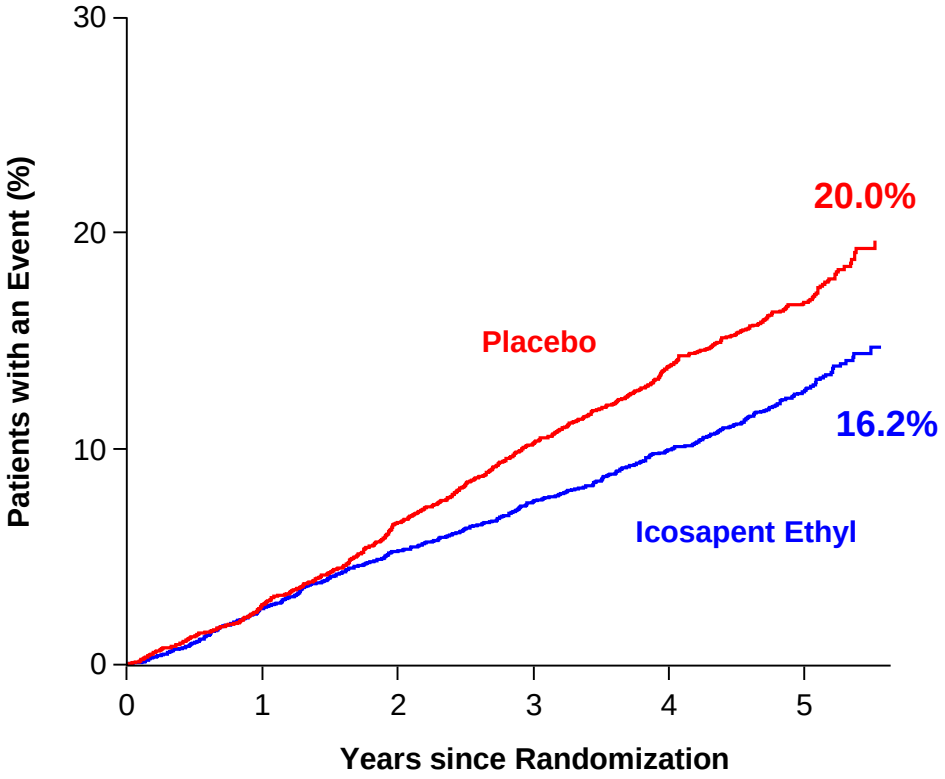
ARR = 4.8%

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%

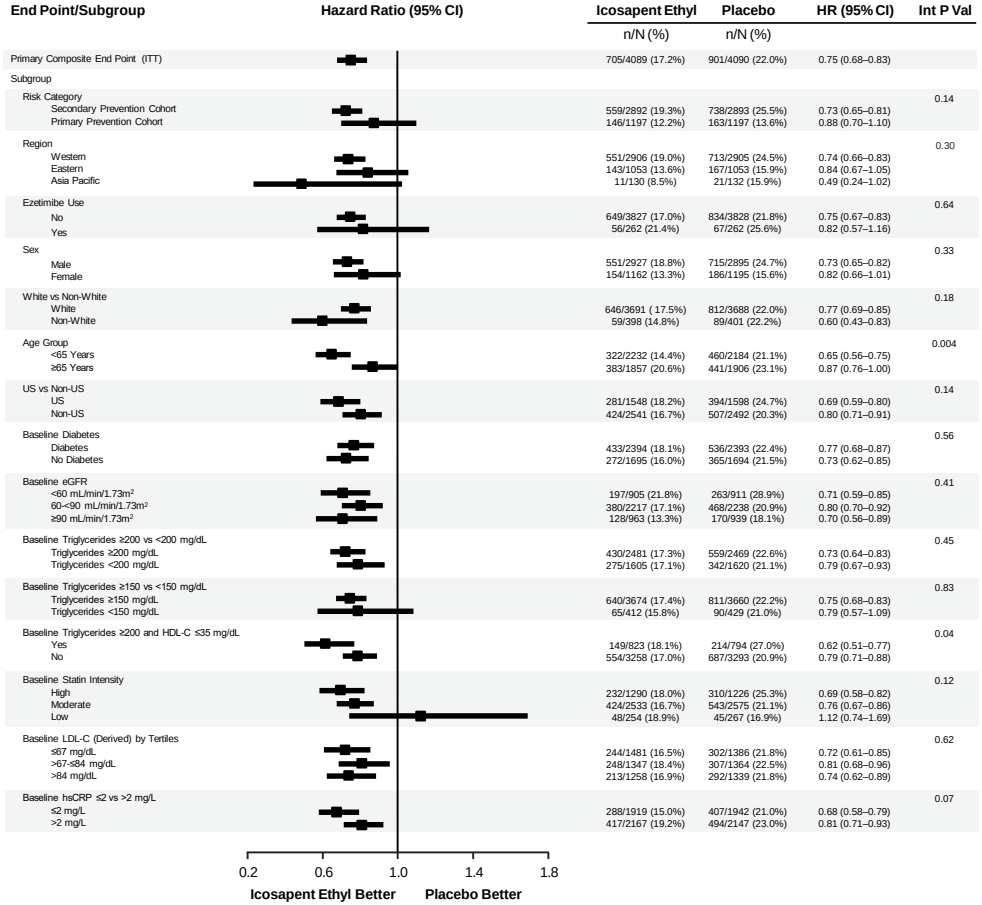
ARR = 3.6%

NNT = 28 (95% CI, 20–47)

P=0.0000006

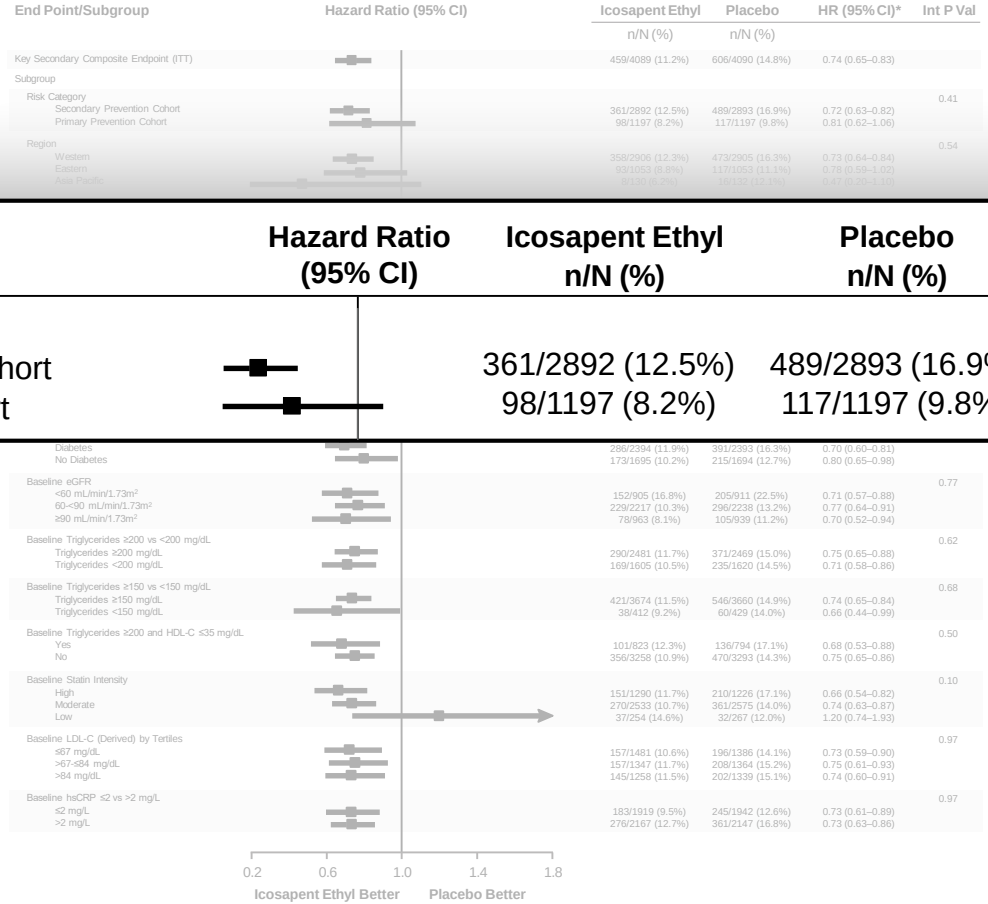
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019. Bhatt DL. AHA 2018, Chicago.

Primary End Point in Subgroups



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

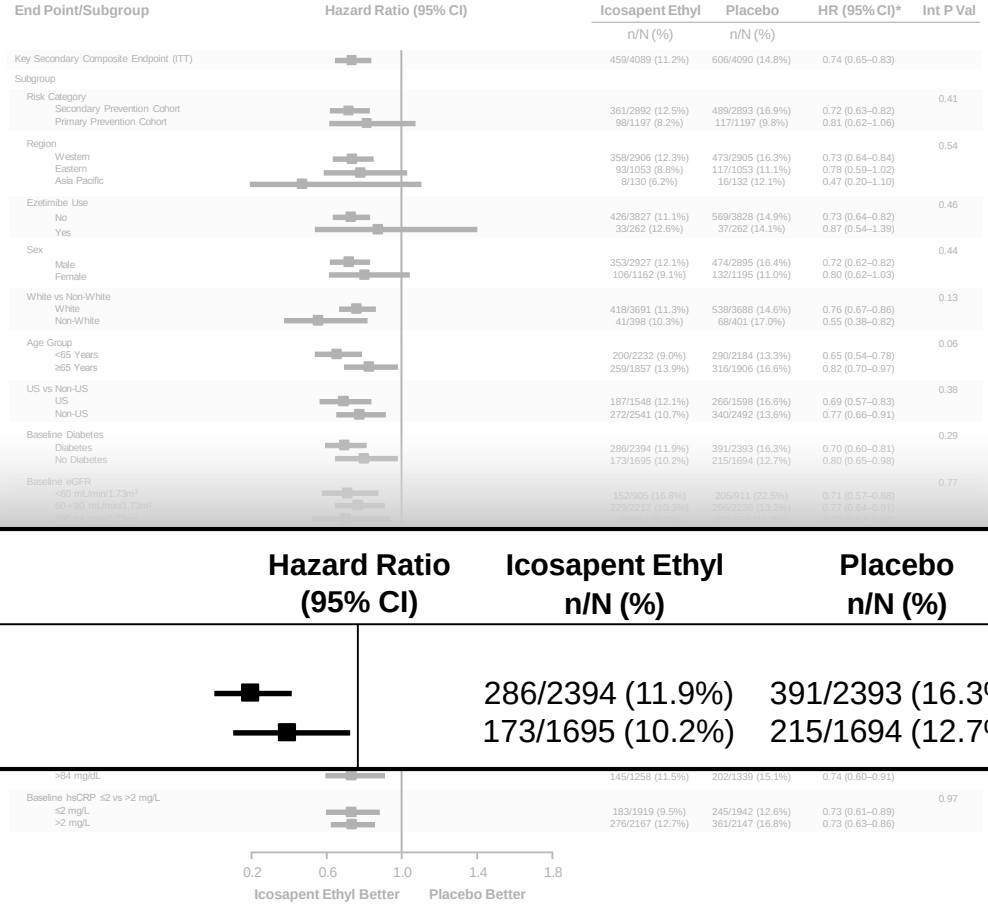
Key Secondary End Point in Subgroups



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
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.

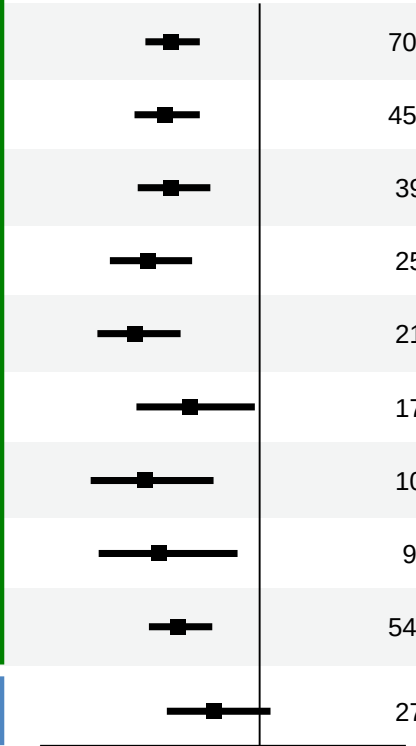
Key Secondary End Point in Subgroups

Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Triglycerides ≥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.

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

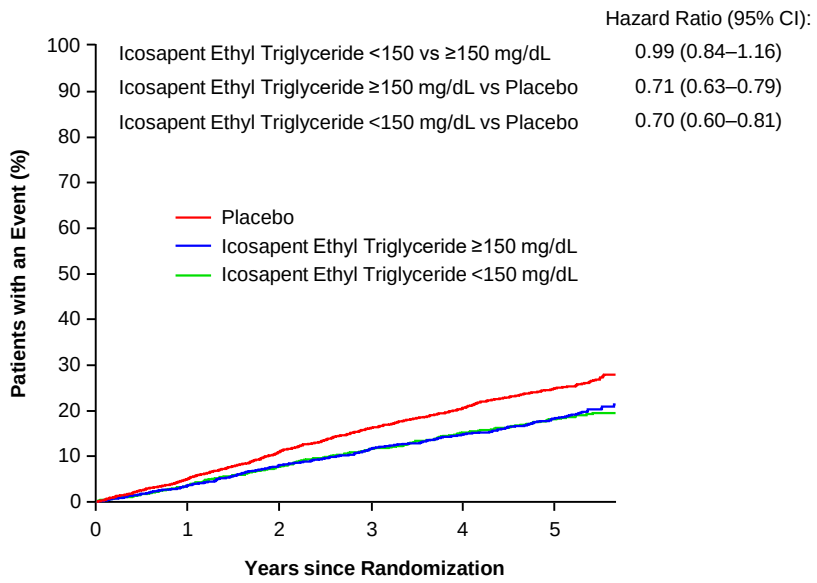
Primary System Organ Class Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Positively Adjudicated Atrial Fibrillation/Flutter[1]	127 (3.1%)	84 (2.1%)	0.004

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.

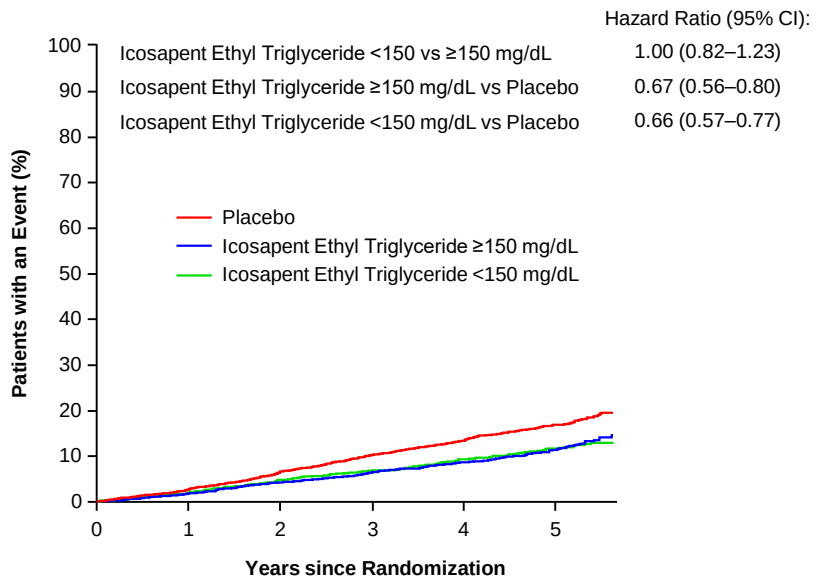
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22.

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

A Primary End Point by Achieved Triglyceride Level at 1 Year



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



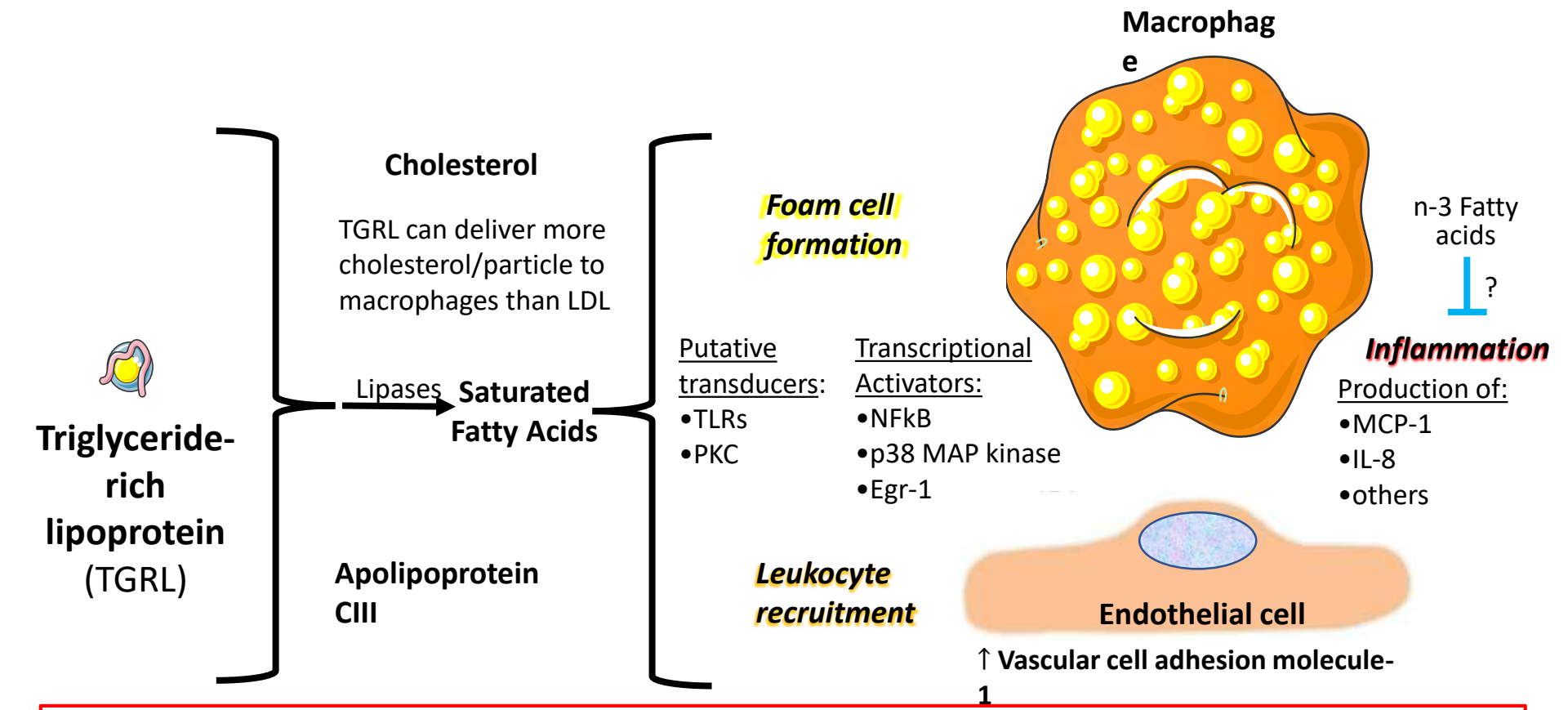
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22.

Potential Benefits of EPA

Effects of EPA on Plaque Progression

	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

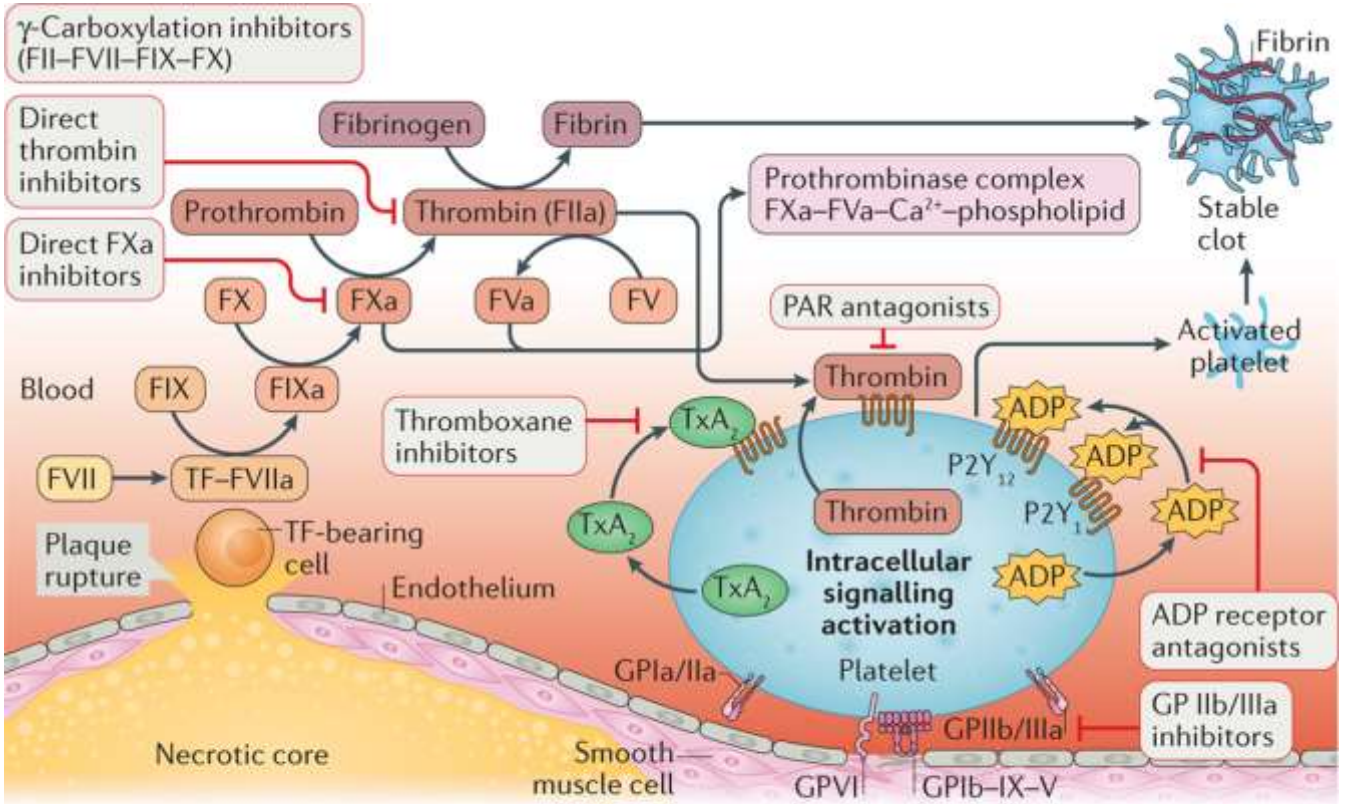
Adapted with permission* from Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol*. 2018;72:330-343. [*https://creativecommons.org/licenses.org/by-nc/4.0/]



Possible Mechanisms by which Triglyceride-Rich Lipoproteins Give Rise to Inflammation and Accentuate Atherogenesis

Courtesy of Dr. Peter Libby 2019

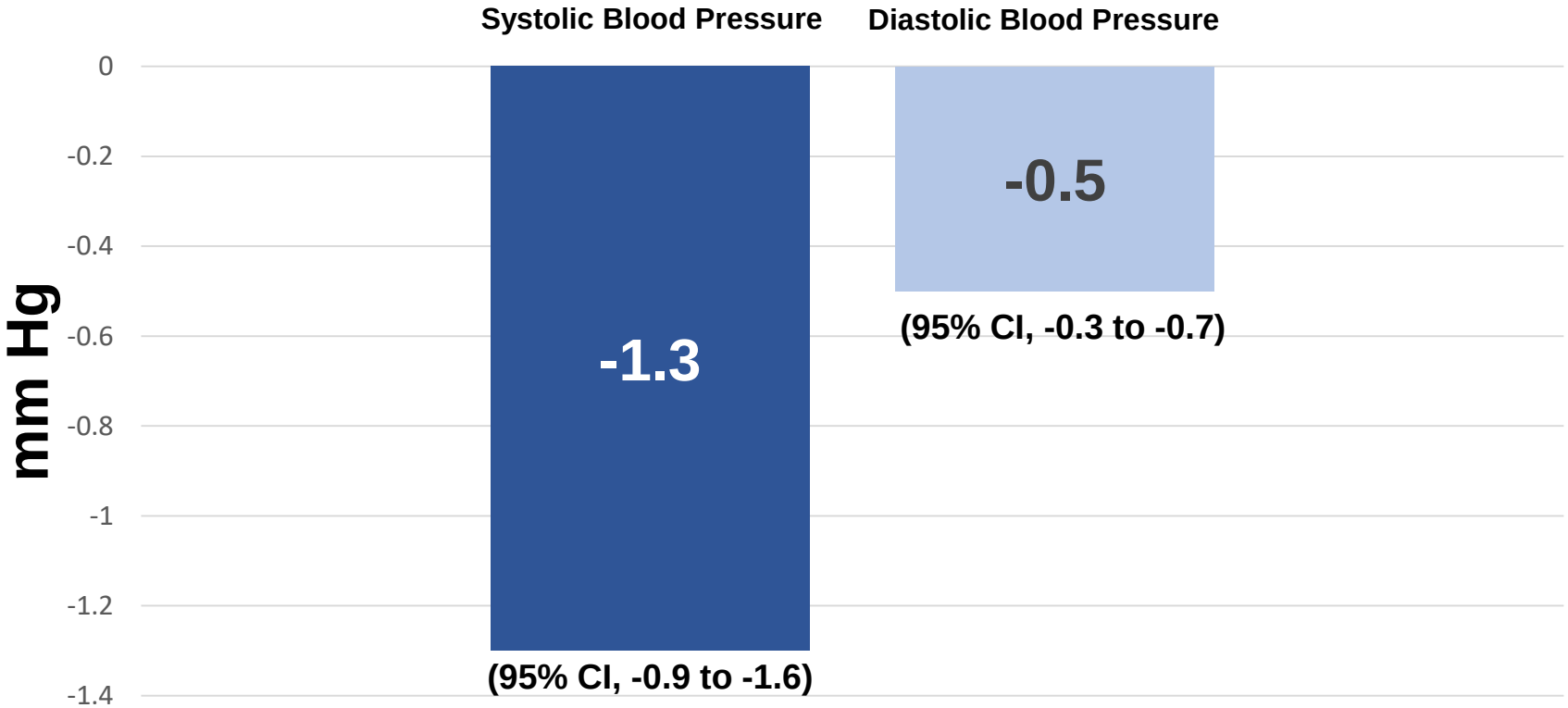
Antiplatelet and Anticoagulant Pathways



Nature Reviews | Cardiology

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

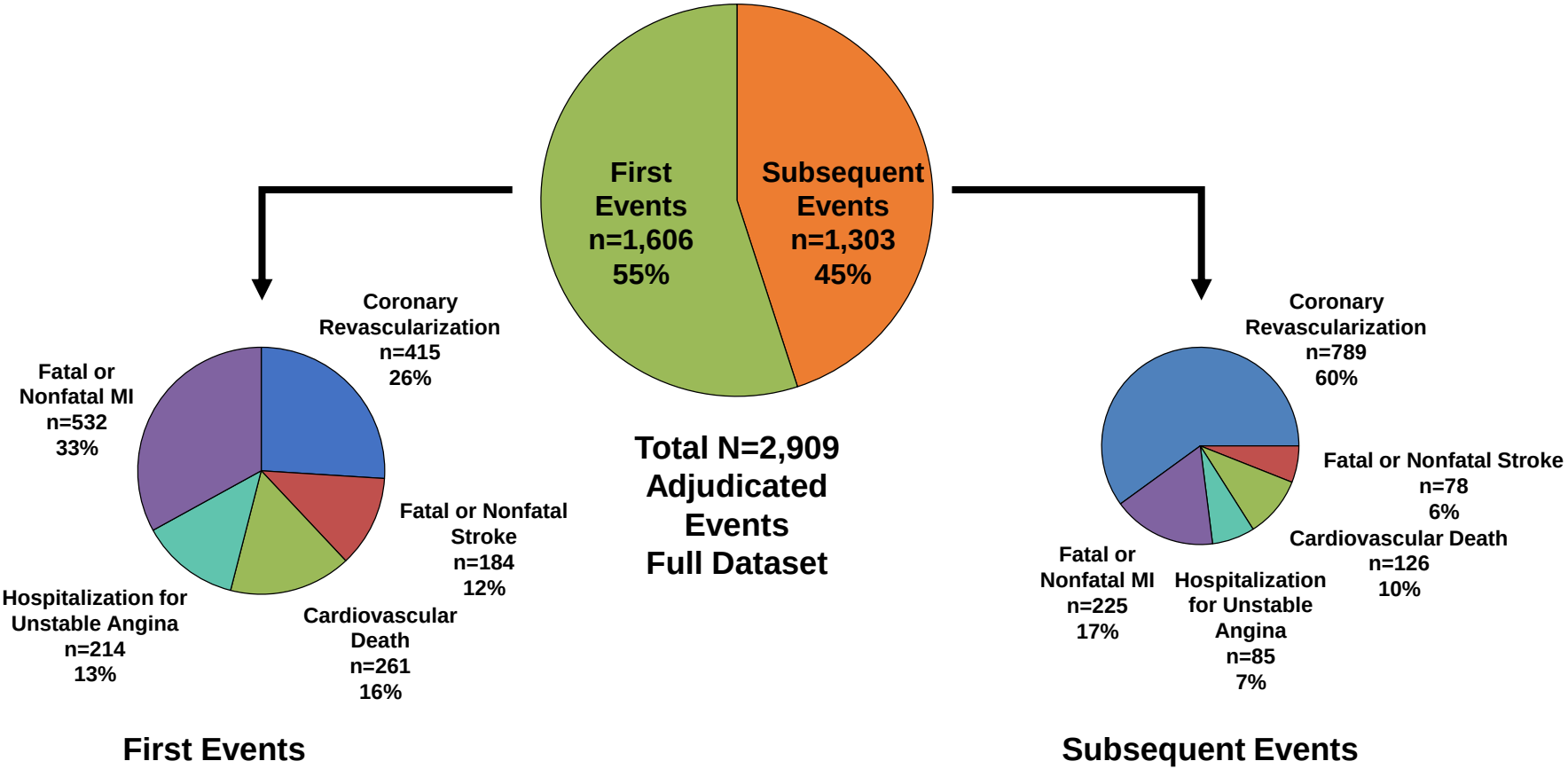
Placebo-corrected Reductions in Blood Pressure from Baseline with Icosapent Ethyl 4g/day



Prespecified exploratory analysis with no adjustment for multiple comparisons.

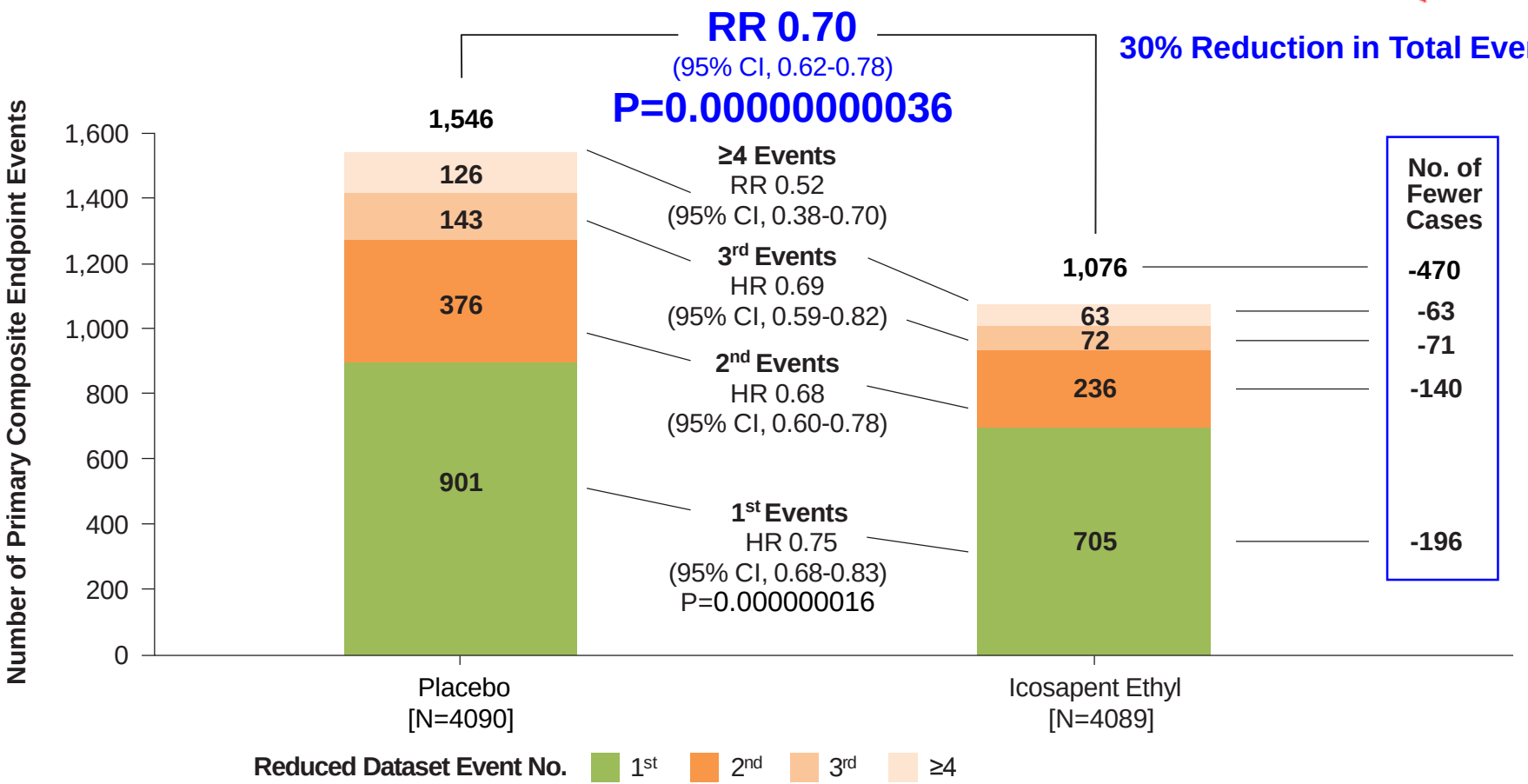
Bhatt DL, Steg PG, Miller M. *N Engl J Med*. 2019;380:1678.

Proportions of First and Subsequent Events



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

First and Subsequent Events



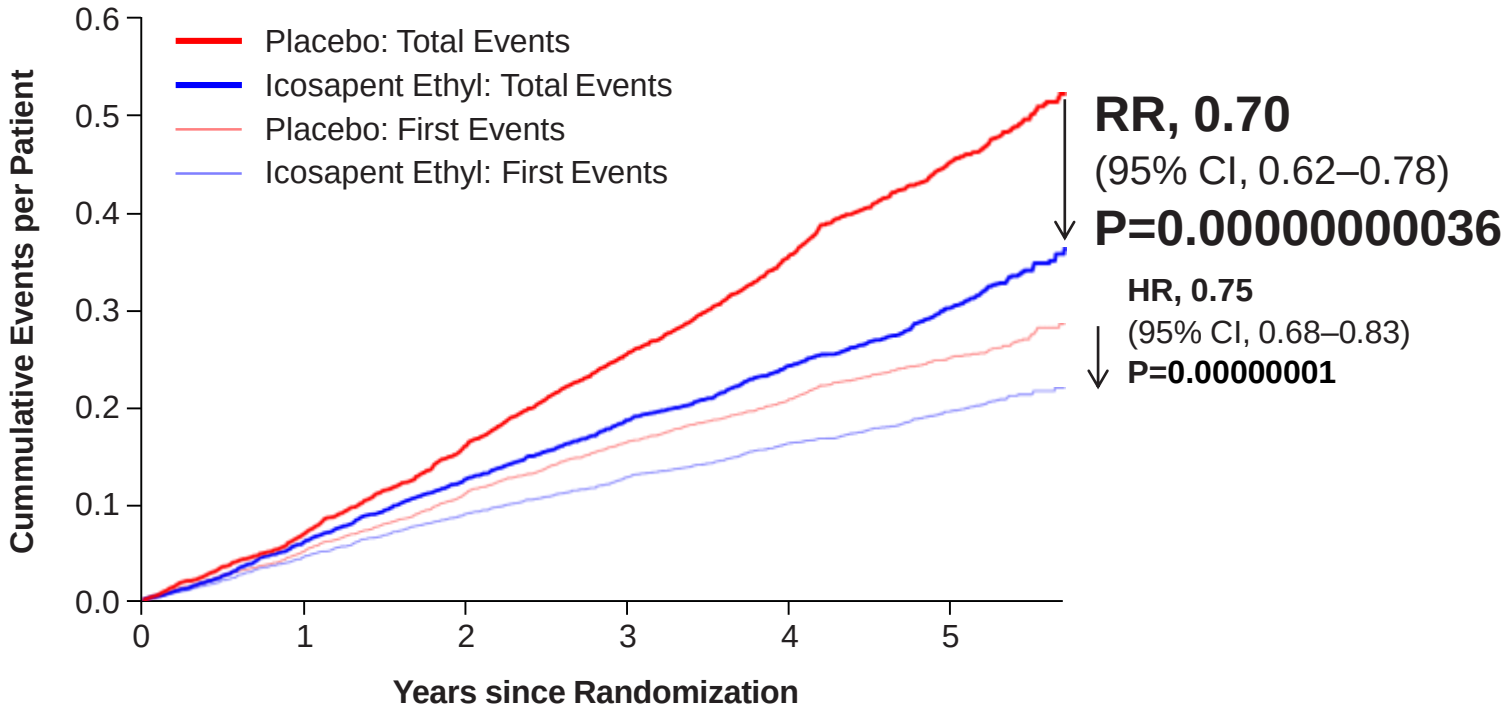
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

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

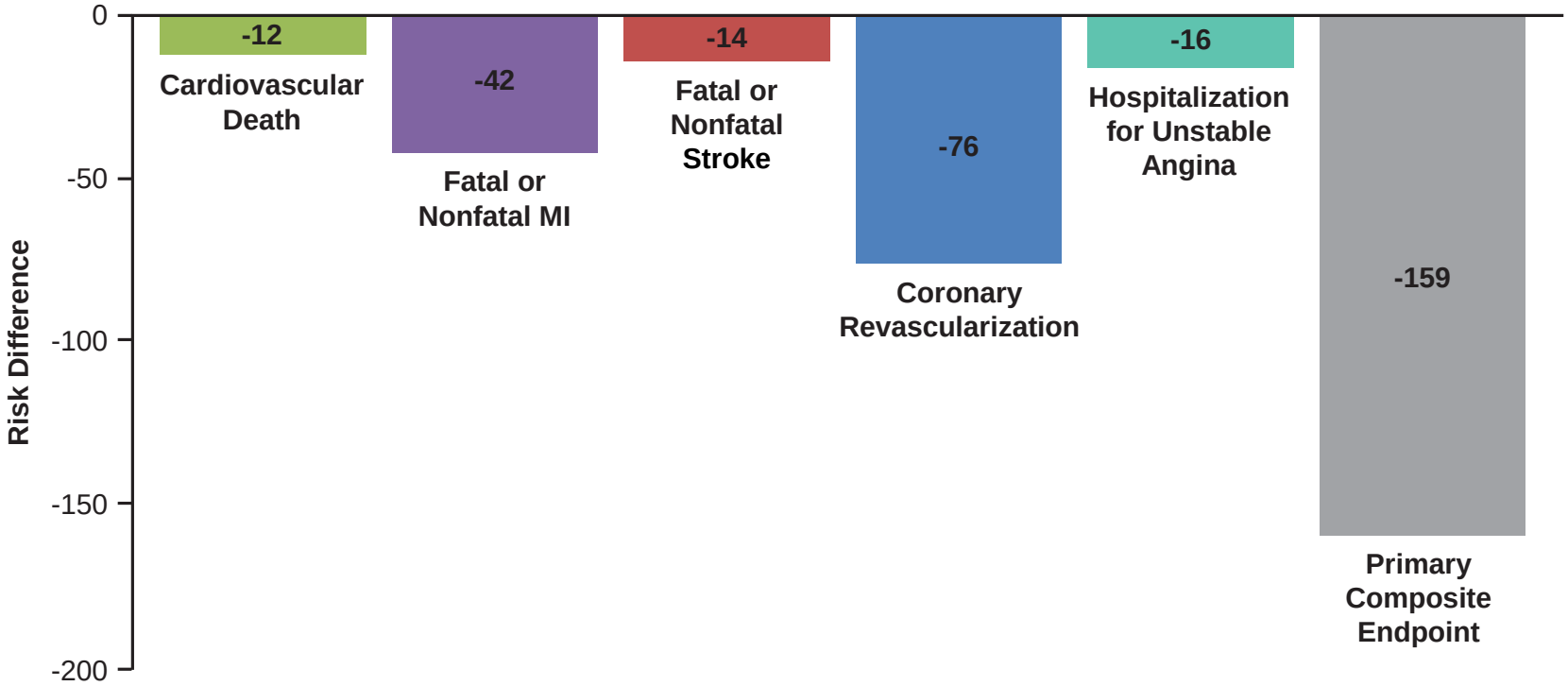
Primary: CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

Primary Composite Endpoint



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

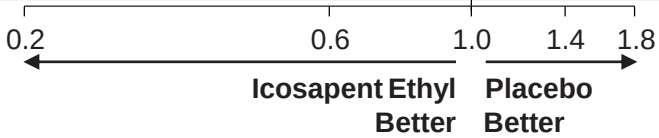
For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:



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 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

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.

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

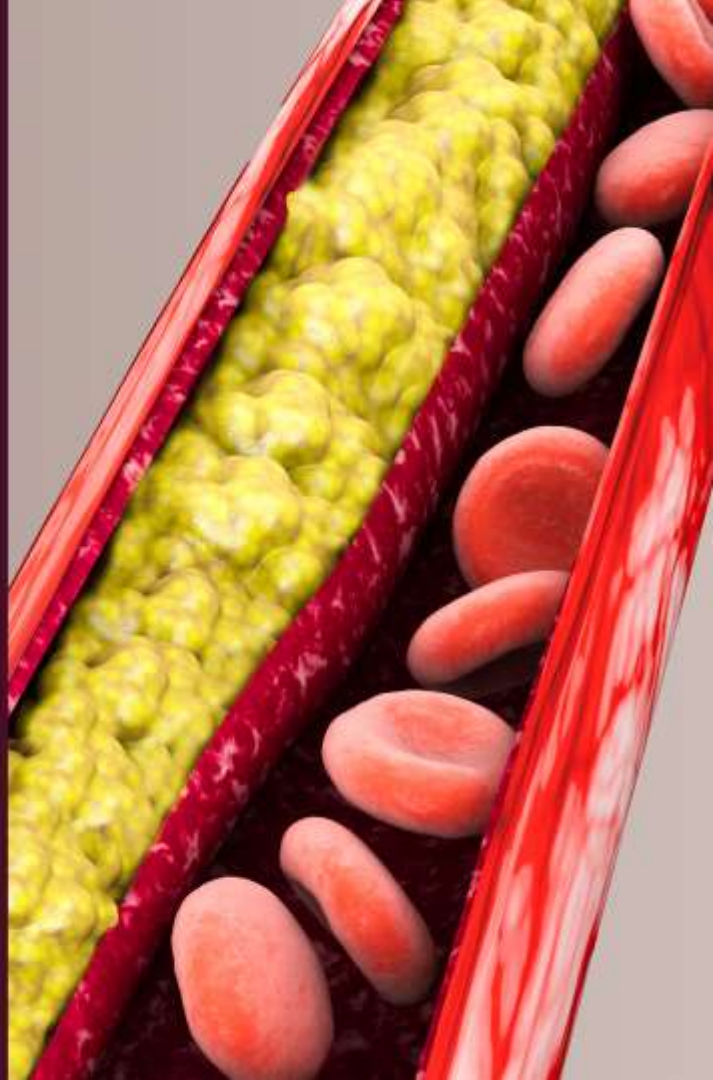
Section 10 – Cardiovascular Disease and Risk Management: Lipid Management[1]

- 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.

Roundup of Recent Clinical Trial Evidence to Reduce ASCVD Events

Sergio Fazio, MD, PhD



Sergio Fazio, MD, PhD

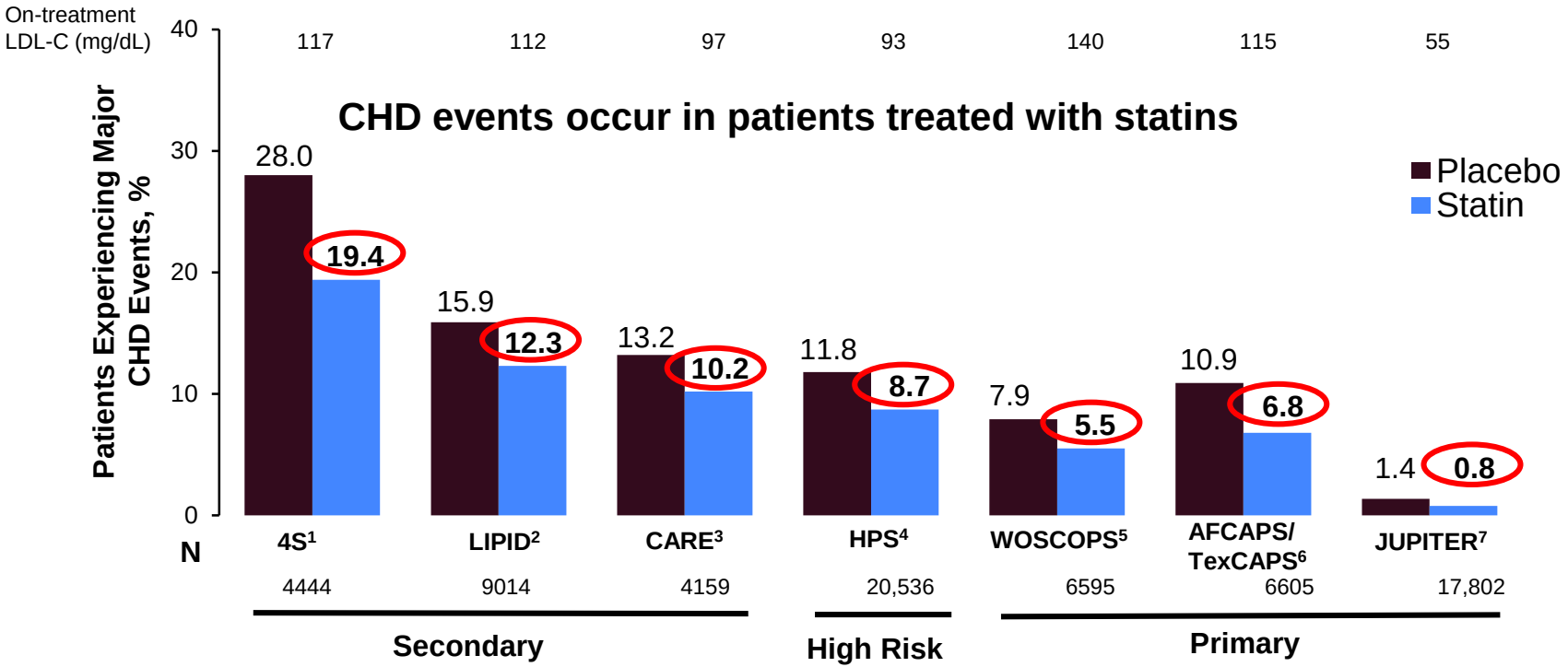
William and Sonja Connor Chair of Preventive Cardiology
Professor of Medicine, Physiology & Pharmacology
Director, Center for Preventive Cardiology
Knight Cardiovascular Institute
Oregon Health & Science University
Portland, OR

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

A 68-year-old gentleman with 30 years of continuous exposure to statin therapy and recent finding of calcified coronaries (Agatston 2450)

“I thought the statin was supposed to protect me”

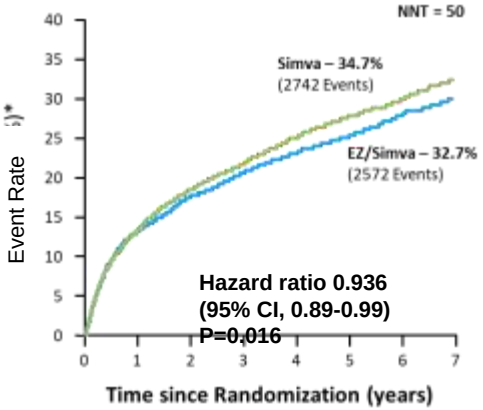
Residual CV Risk in Subjects on Statin Monotherapy



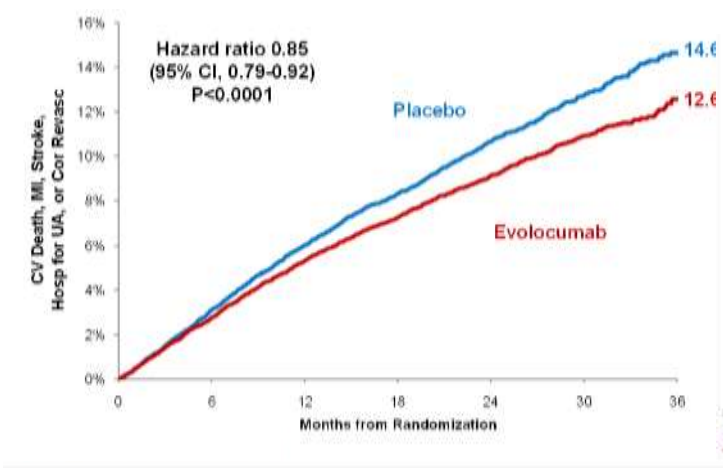
Residual CV risk may be due not only to other lipid measures that may not be controlled, but other risk factors at suboptimal control such as hypertension, diabetes, or smoking.

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

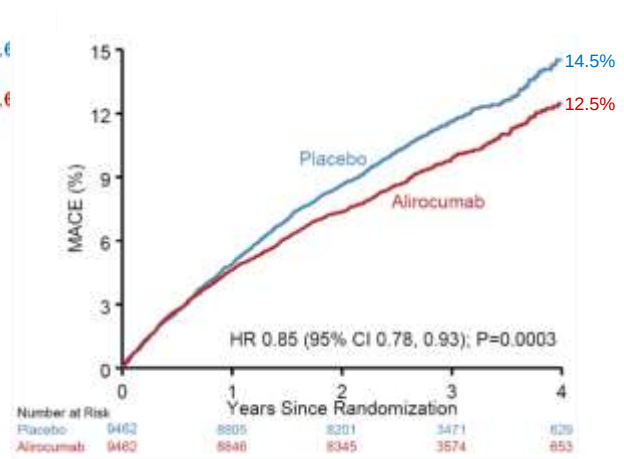
Additional LDL-C Lowering in Subjects on Statin Monotherapy Reduces CV Risk



IMPROVE-IT[1]



FOURIER[2]

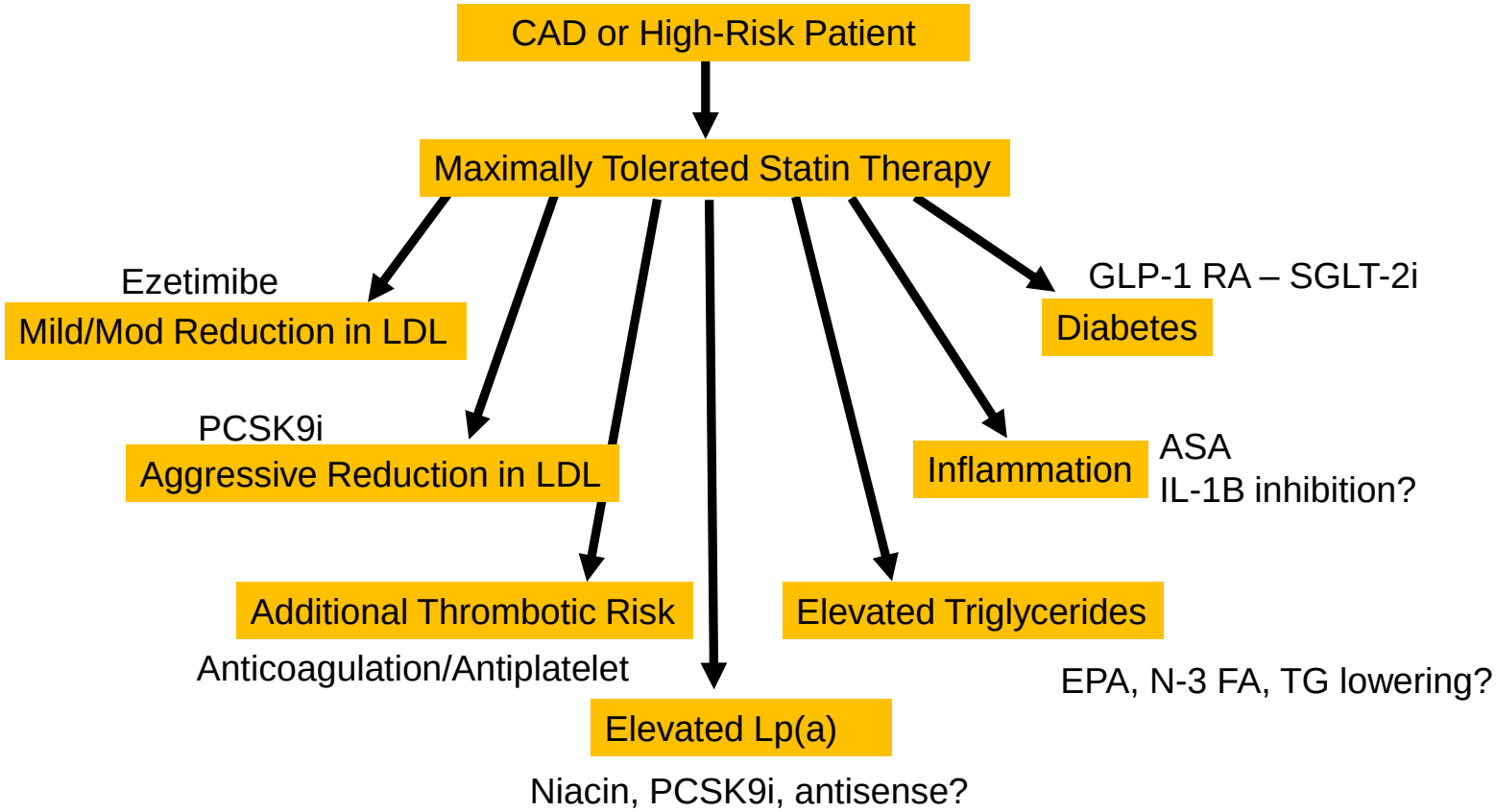


ODYSSEY Outcomes[3]

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.

Pharmacologic Approaches to Managing Residual CV Risk



Fenofibrate Outcome Trials

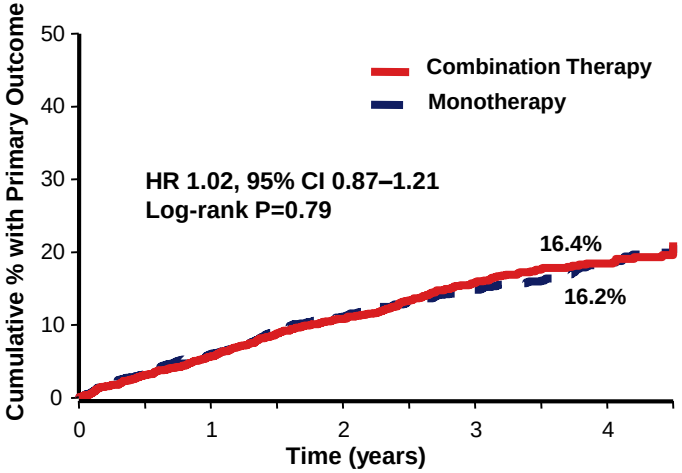
Study	CV Risk Profile	Statin Use	Daily Inter-vention	Median Baseline TG Level	Effect on TG Level	Primary Outcome	Primary Outcome Results
ACCORD (N=5518)	• T2DM • 40-79 yrs w/CVD ***or*** • 55-79 yrs w/ ≥2 CV risk factors	All pts: Open-label simvastatin (mean dose: 22 mg/d)	Fenofibrate	162 mg/dL	–26%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

***Note that *post hoc* analysis for both studies found statistically significant benefit in the subgroup of patients with TG≥204 mg/dL & HDL-C ≤34 md/dL (Sacks FM et al. *N Engl J Med*. 2010;363:692-4).**

ACCORD Study Group et al. *N Engl J Med*. 2010;362:1563-74. Keech A et al. *Lancet*. 2005;366:1849-61.

Niacin Outcome Trials

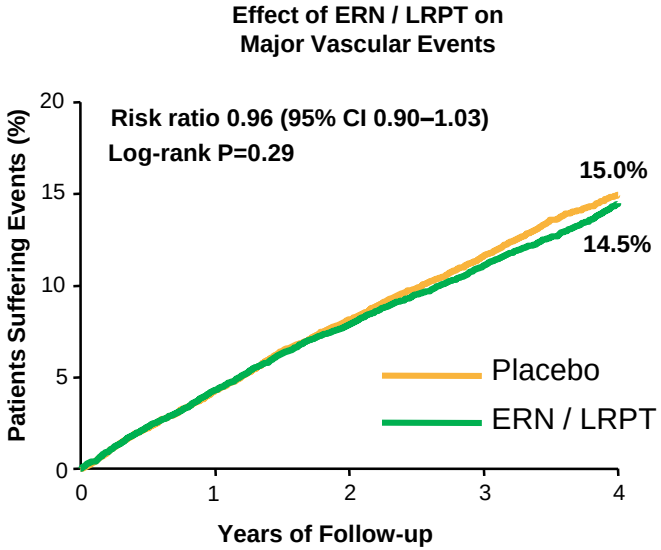
AIM-HIGH *(–29% TG)*



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

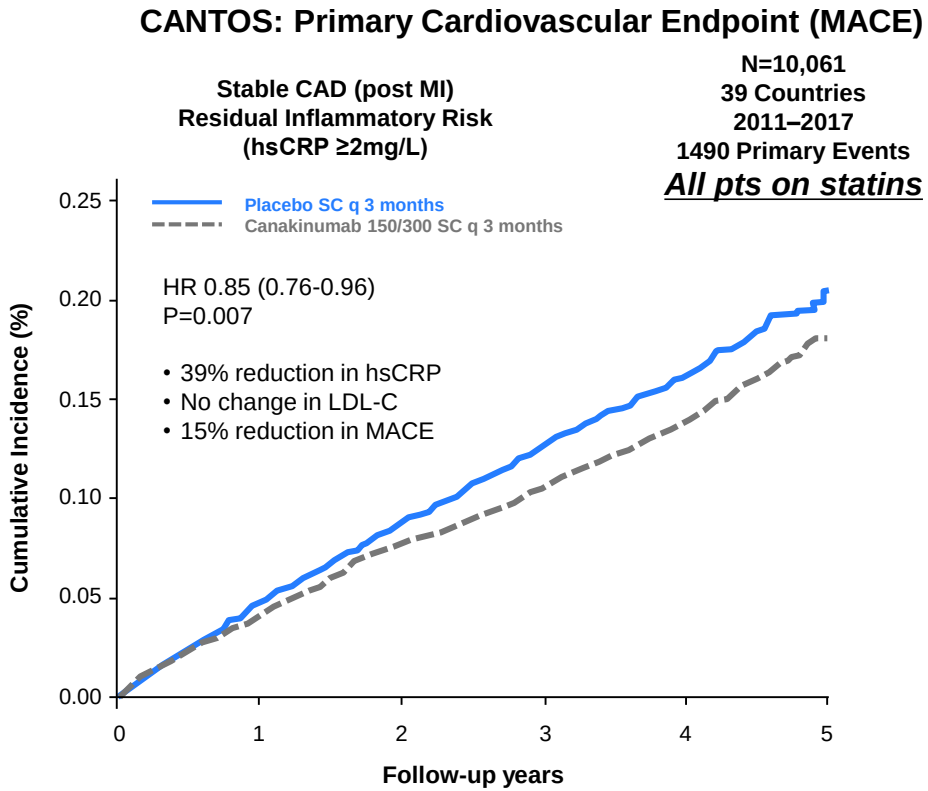
Boden WE et al. *N Engl J Med.* 2011;365:2255-67

HPS2-THRIVE *(–26% TG)*



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

CANTOS: Reducing Inflammation by Blocking IL1-beta Reduces CV Events in Subjects on Statin Therapy



NEJM 2018

Reducing Inflammation Doesn't Always Work

2011 – 2017

Interleukin-1β Inhibition

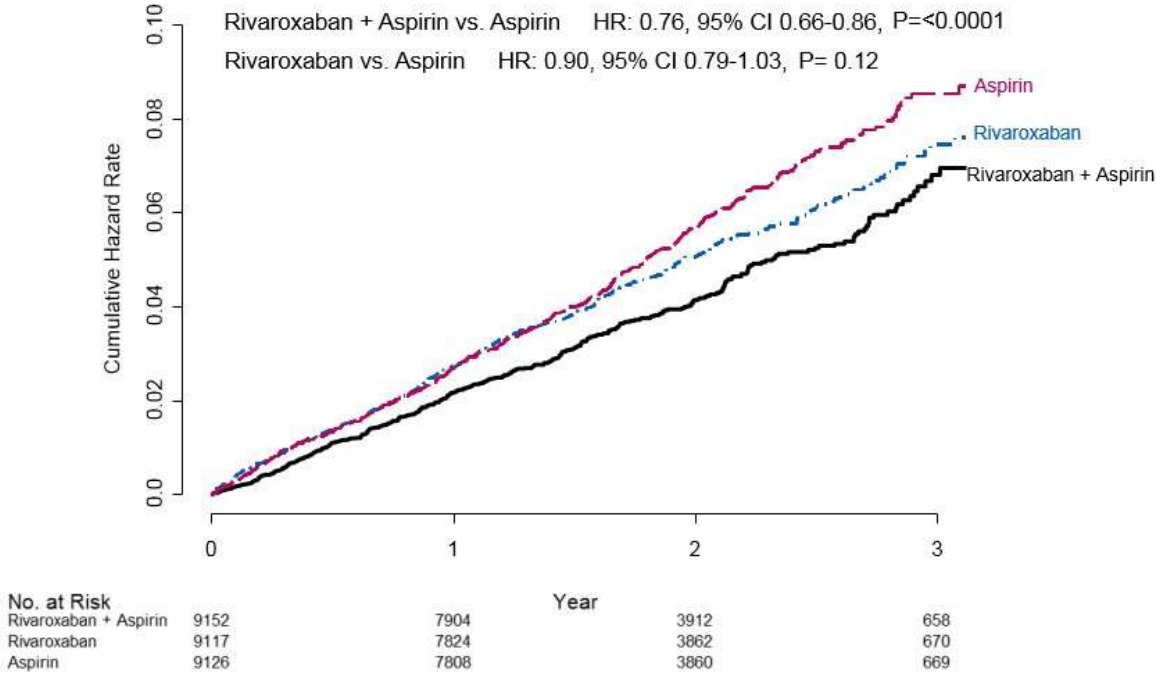
- ↓ IL-1β
- ↓ IL-6
- ↓ hsCRP
- ↓ 17% reduction in MACE+
- ↔ LDL, BP, coagulation

2013 – 2018

Low-dose Methotrexate

- ↔ IL-1β
- ↔ IL-6
- ↔ hsCRP
- ↔ No reduction in MACE+

Anticoagulation and CVD Risk Reduction: The COMPASS Trial



Eikelboom JW et al. *N Eng J Med*. 2017;377:1319-30.

Risk Reduction of R+A vs A
Rivaroxaban plus aspirin (R+A) vs aspirin (A)

	Absolute RR	Relative RR	P
Primary outcome	↓1.3%	↓24%	<0.0001
All-cause death	↓0.7%	↓18%	0.01
Bleeding	↑1.2%	↑70%	0.01

Primary Endpoint Components

	R + A N=9152	A N=9126	Rivaroxaban + Aspirin vs Aspirin	
Outcome	**N (%)**	**N (%)**	**HR (95% CI)**	**P**
CV death	160 (1.7%)	203 (2.2%)	0.78 (0.64-0.96)	0.02
Stroke	83 (0.9%)	142 (1.6%)	0.58 (0.44-0.76)	<0.001
MI	178 (1.9%)	205 (2.2%)	0.86 (0.70-1.05)	0.14

COMPASS Trial: Net Clinical Benefit

Outcome	Rivarox+ASA (N, %)	ASA Alone (N, %)	Rivarox+ASA vs ASA Alone (HR, P Value)
Major Bleeding	288 (3.1)	170 (1.9)	1.70, <0.001
Fatal Bleeding	15 (0.2)	10 (0.1)	1.49, 0.32
Nonfatal ICH	21 (0.2)	19 (0.2)	1.10, 0.77
Nonfatal Bleed Critical Organ	42 (0.5)	29 (0.3)	1.43, 0.14
Other Major Bleeding	210 (2.3)	112 (1.2)	1.88, <0.001
Minor Bleeding	838 (9.2)	503 (5.5)	1.70, <0.001
Major GI Bleed	140 (1.5)	65 (0.7)	2.15, <0.001
Net Clinical Benefit*	431 (4.7)	534 (5.9)	0.80, <0.001

*Net clinical benefit=CV death, stroke, MI, fatal bleed, symptomatic bleed into a critical organ. Eikelboom JW et al. *N Eng J Med.* 2017;377:1319-30.

CV Outcome Trials in Diabetes

Study (N)	Drug (Class)	Primary endpoint	Hazard ratio
EMPA-REG[1] 7,020	Empagliflozin SGLT-2	CV death, non-fatal myocardial infarction, or non-fatal stroke	0.86, (95% CI, 0.74, 0.99) P=0.0382
LEADER[2] 9,340	Liraglutide GLP-1 RA		0.87, (95% CI, 0.78-0.97) P=0.001 for non-inferiority P=0.01 for superiority
SUSTAIN-6[3] 3,297	Semaglutide GLP-1 RA		0.74, (95% CI, 0.58–0.95) P<0.001 for noninferiority P=0.02 for superiority
CANVAS[4] 10,134	Canagliflozin SGLT-2		0.86, (95% CI, 0.75-0.97) P<0.0001 for noninferiority P=0.0158 for superiority
HARMONY[5] 10,793	Albiglutide GLP-1 RA		0.78, (95% CI, 0.68–0.90) P<0.0001 for non-inferiority P=0.0006 for superiority
DECLARE TIMI-58[6] 17,160	Dapagliflozin SGLT-2	CV death, non-fatal myocardial infarction, or ischemic stroke	0.93, (95% CI, 0.84-1.03) P<0.001 for noninferiority P=0.17 for superiority

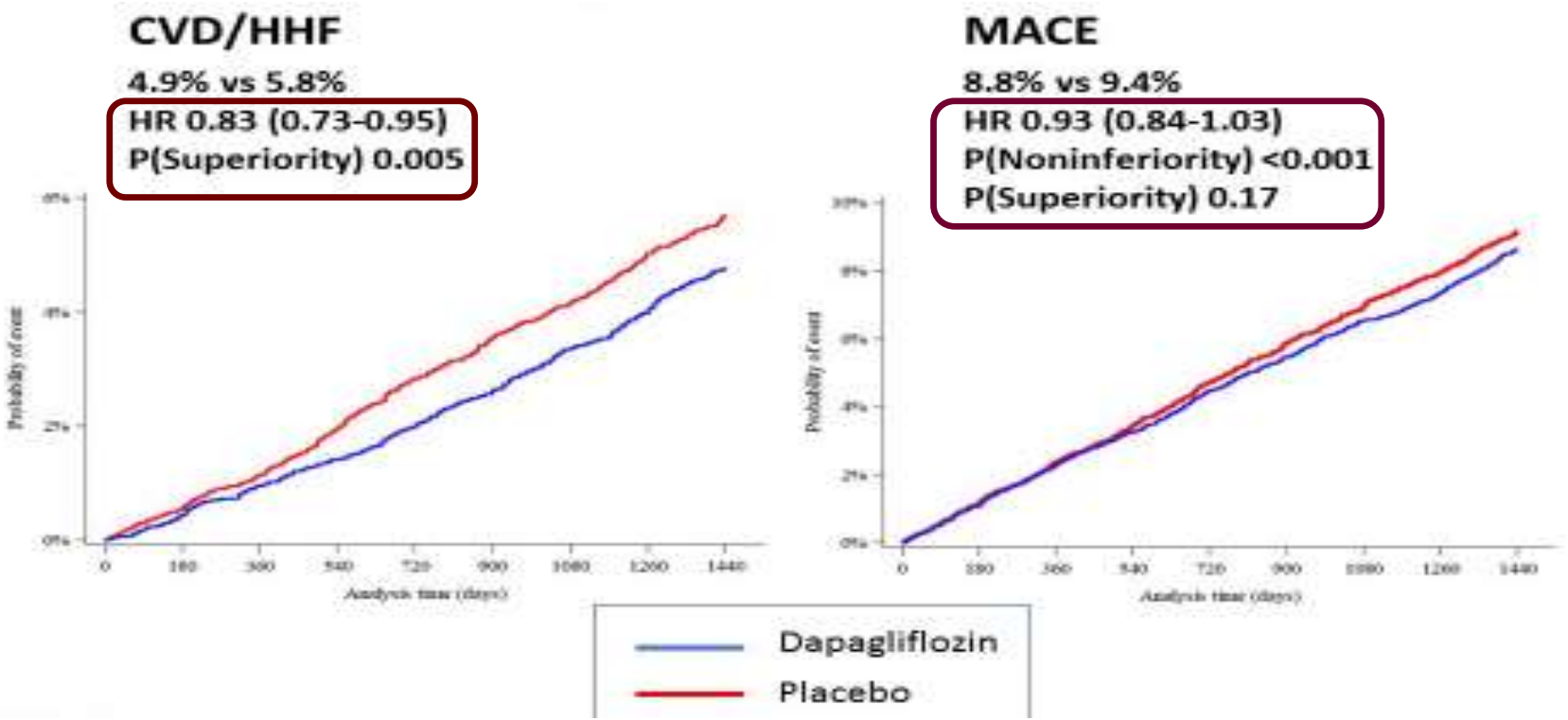
[1]Zinman B et al. *N Engl J Med.* 2015;373:2117-28. [2]Marso SP et al. *N Engl J Med.* 2016;375:311-22. [3]Marso SP et al. *N Engl J Med.* 2016;375:1834-44. [4]Neal B et al. *N Engl J Med.* 2017;377:644-57. [5] Hernandez AF et al. *Lancet.* 2018;392;1519-29. [6]Wiviott SD et al. *N Engl J Med.* 2019;380:347-57.

SGLT2 inhibitors: CV Outcome Studies

- Empa-Reg (Empagliflozin): 2015
- CANVAS (Canagliflozin): 2017
- DECLARE (Dapagliflozin): 2018
- VERTIS-CV (Ertugliflozin): ~2020

DECLARE TIMI-58: Dual Primary Outcomes

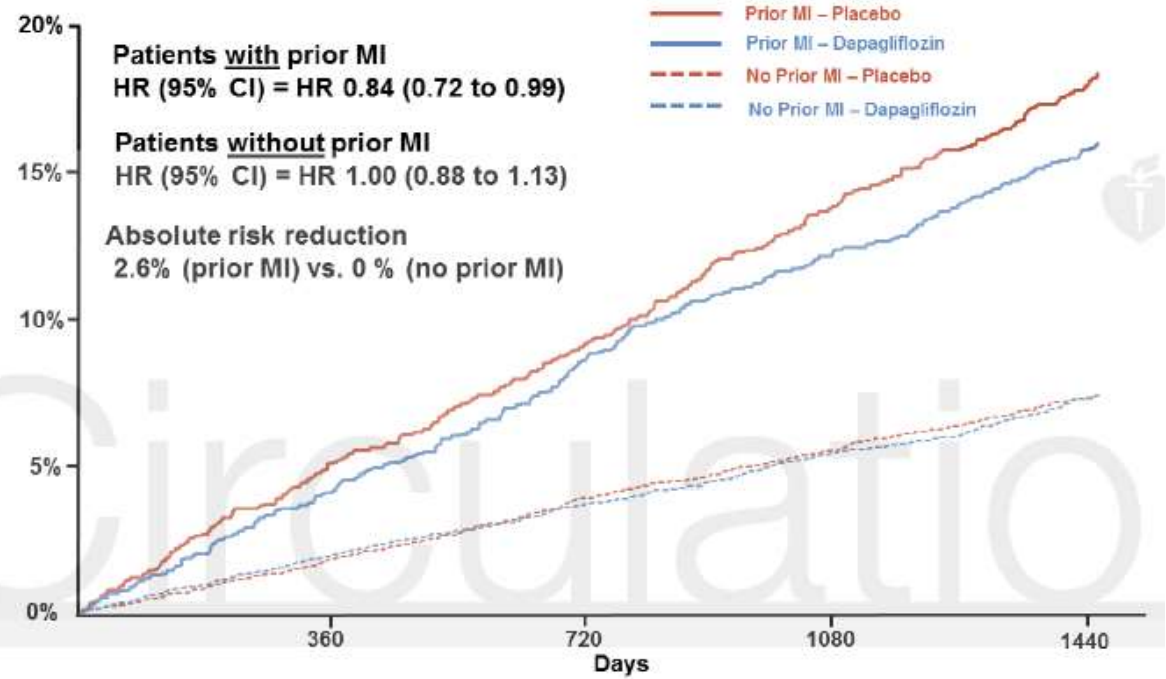
Dapagliflozin vs placebo n=17,160, 60% with no prior ASCVD, median f/u 4.2 yr.



Wiviott SD et al. *N Engl J Med*. 2019;380:347-57.

Hospitalization for Heart Failure, HR 0.73 (0.61-0.88)

DECLARE: MACE by Prior MI

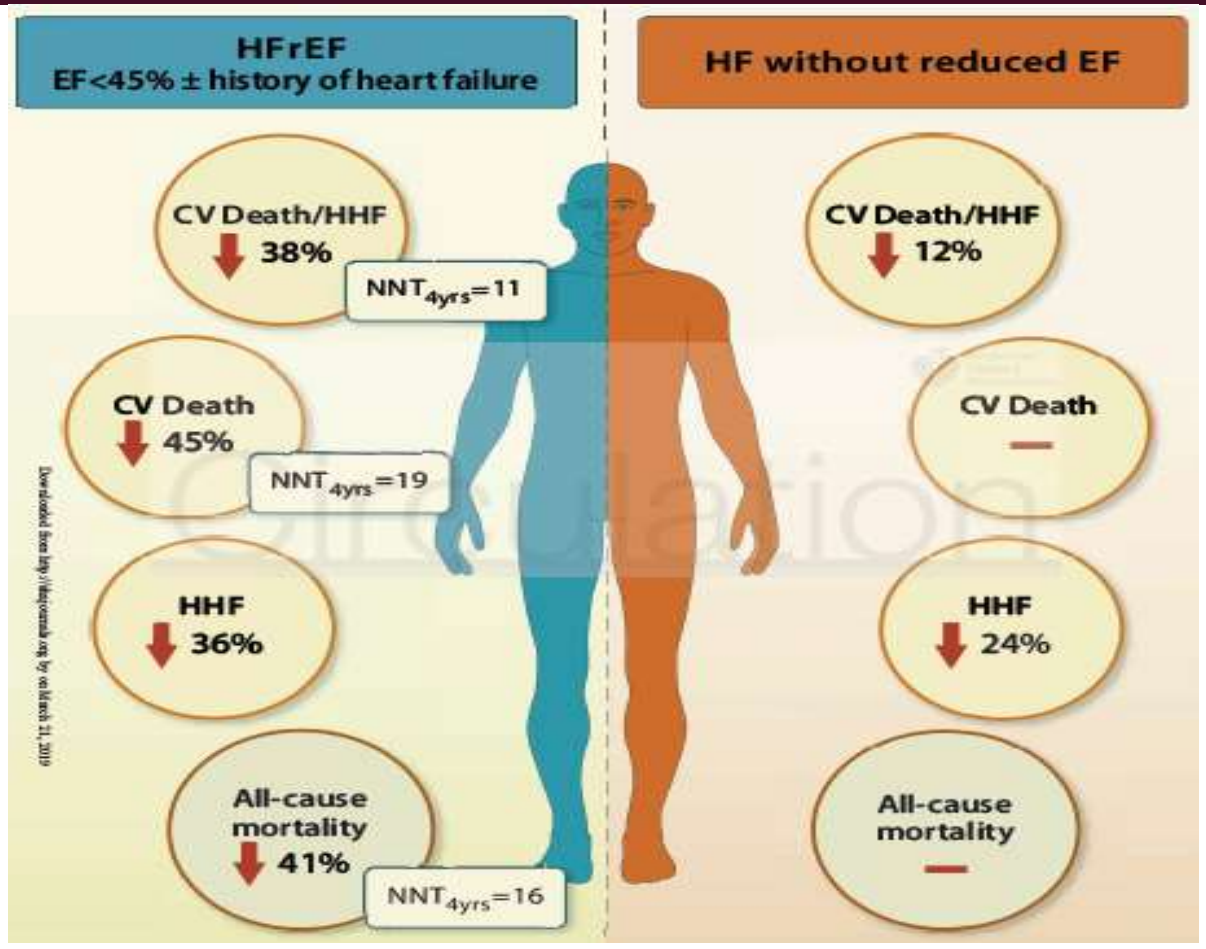


Number at risk:

Prior MI - Placebo	1807	1698	1607	1498	989
Prior MI - Dapagliflozin	1777	1687	1591	1504	1011
No Prior MI - Placebo	6771	6583	6362	6151	4169
No Prior MI - Dapagliflozin	6805	6616	6426	6204	4214

Furtado RHM et al. *Circulation*. 2019;139:2516-27.

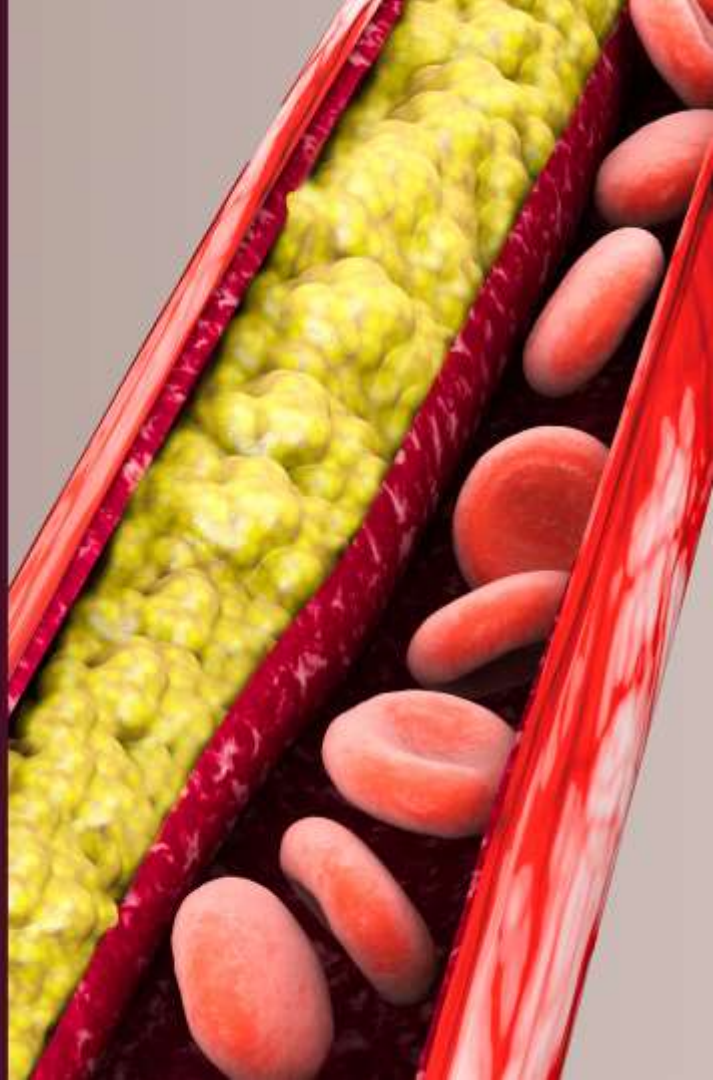
DECLARE: HHF Outcomes by EF



Verma S, McMurray JJV
Circulation. 2019: March 21-on line;

Kato, ET et al
Circulation. 2019: March 21-on line

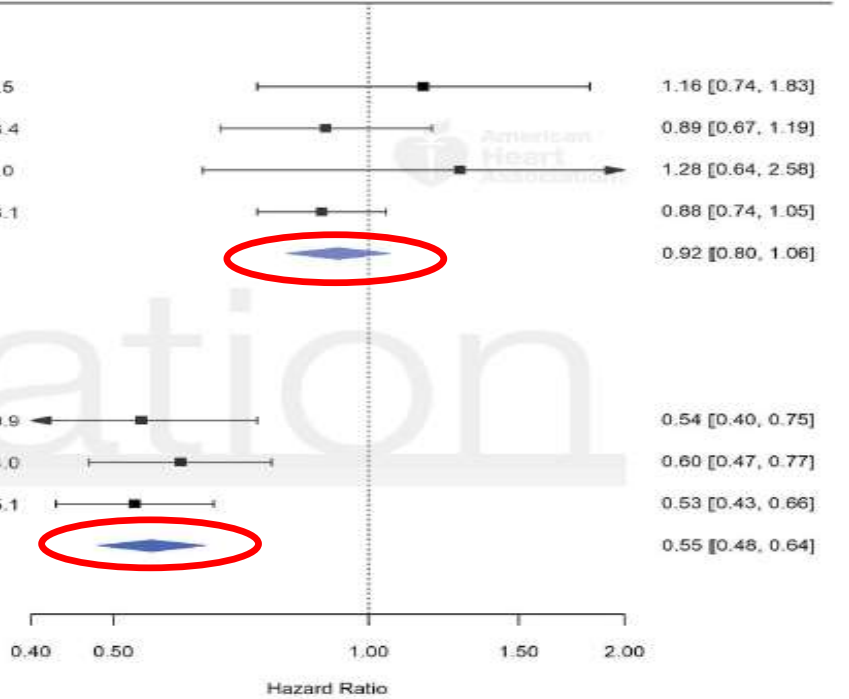
Renal Outcomes with SGLT-2 Inhibitors



Renal Outcomes: GLP1ra vs SGLT2i

Progression to sustained doubling of creatinine, ≥40% decline in eGFR, ESRD, or death from renal disease.

Trials	Patients	Events	Treatment n/N	Placebo n/N	Weights	HR [95% CI]
GLP1-RA						
ELIXA	6063	76	35/3032	41/3031	9.5	1.16 [0.74, 1.83]
LEADER	9340	184	87/4668	97/4672	23.4	0.89 [0.67, 1.19]
SUSTAIN-6	3297	32	18/1648	14/1649	4.0	1.28 [0.64, 2.58]
EXSCEL	12914	519	246/6456	273/6458	63.1	0.88 [0.74, 1.05]
Fixed Effects for GLP1-RA (P-value=0.24)						0.92 [0.80, 1.06]
SGLT2i						
EMPA-REG OUTCOME	6968	152	81/4645	71/2323	20.9	0.54 [0.40, 0.75]
CANVAS Program	10142	249	NA	NA	34.0	0.60 [0.47, 0.77]
DECLARE-TIMI 58	17160	365	127/8582	238/8578	45.1	0.53 [0.43, 0.66]
Fixed Effects for SGLT2i (P-value<0.001)						0.55 [0.48, 0.64]



Zelniker TA et al. *Circulation*. 2019;13:2022-31.

SGLT2i and Renal Outcome Trials

- CREDENCE (Canagliflozin)

  NCT 02065791; (stopped early - July 2018)

- DAPA-CKD (Dapagliflozin)

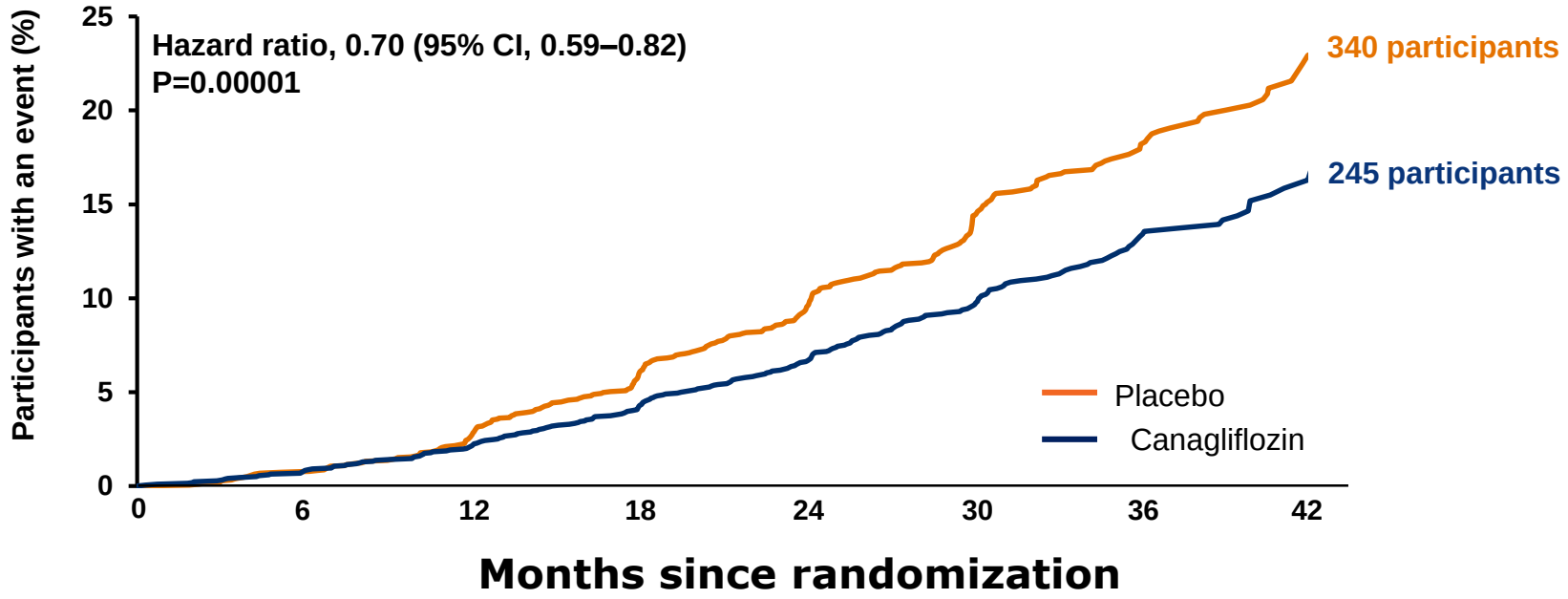
  NCT 03036150 (completion date ~2020)

- EMPA-KIDNEY (Empagliflozin)

  NCT 03594110 (~2022)

CREDENCE: ESRD, Doubling of Serum Creatinine, Renal or CV Death

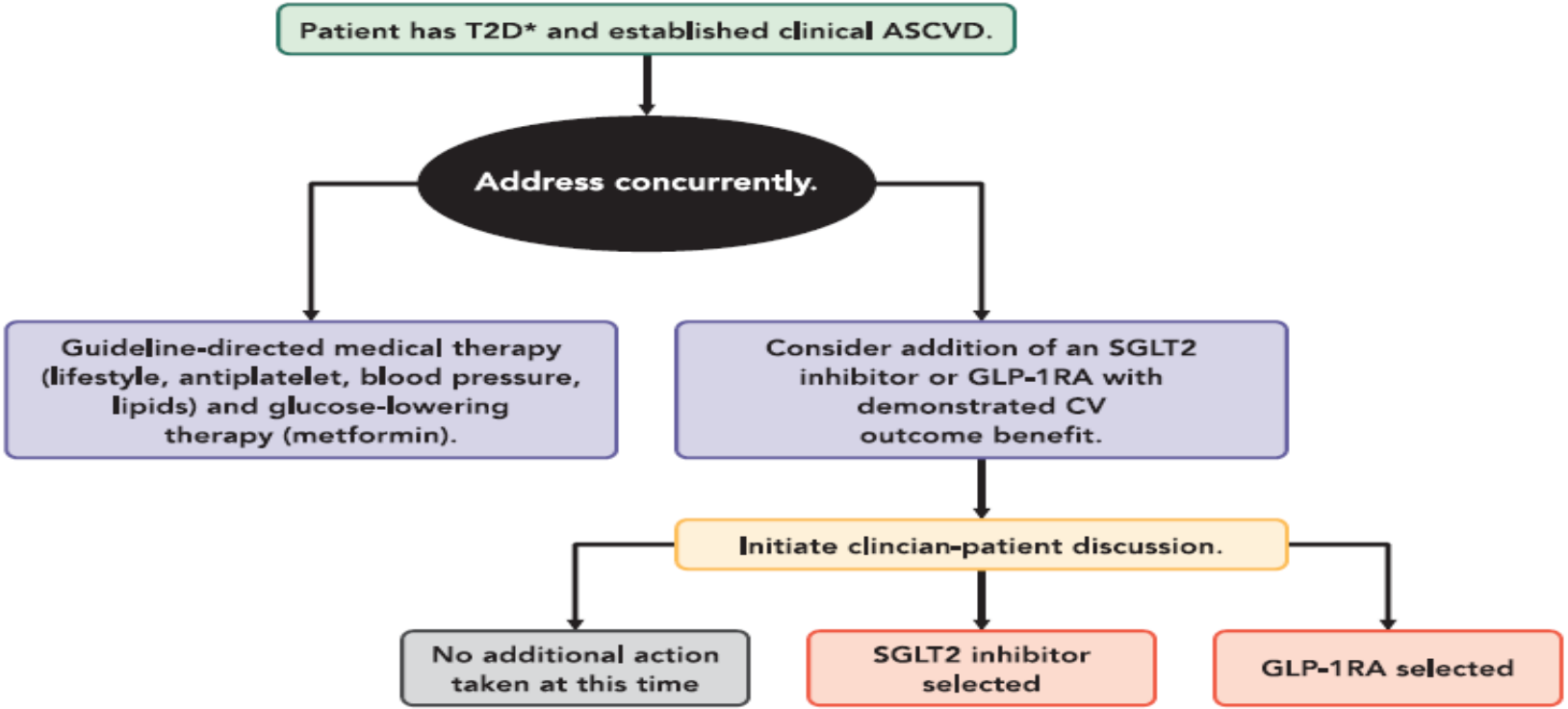
n=4401, eGFR <60 mL/min in 60%, <45 mL/min in 31%



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Perkovic V et al. *N Engl J Med*. 2019;Apr 14. [Epub ahead of print]

T2DM and CVD: 2018 ACC/ADA Decision Pathway



*Most trials of SGLT2i and GLP-1RA required baseline A1C ≥7% (Example: EXSCEL Trial required HbA1c ≥ 6.5%), and most patients were already on metformin as first-line therapy if tolerated and not contraindicated

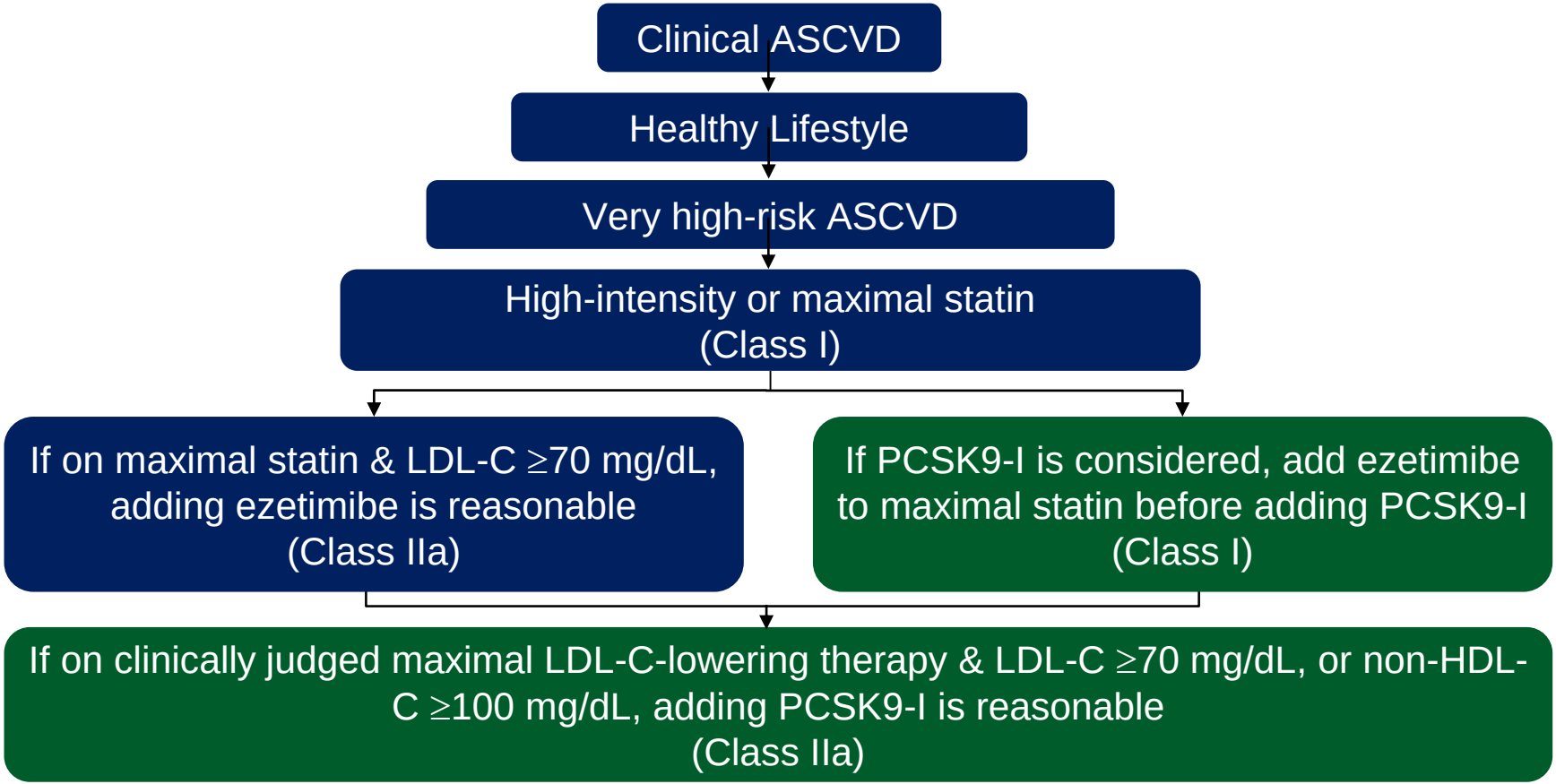
Das SR et al. *J Am Coll Cardiol*. 2018;72:3200-23

ASCVD Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – DM or stage 3 or 4 CKD with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10%-20% – DM or stage 3 or 4 CKD with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

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

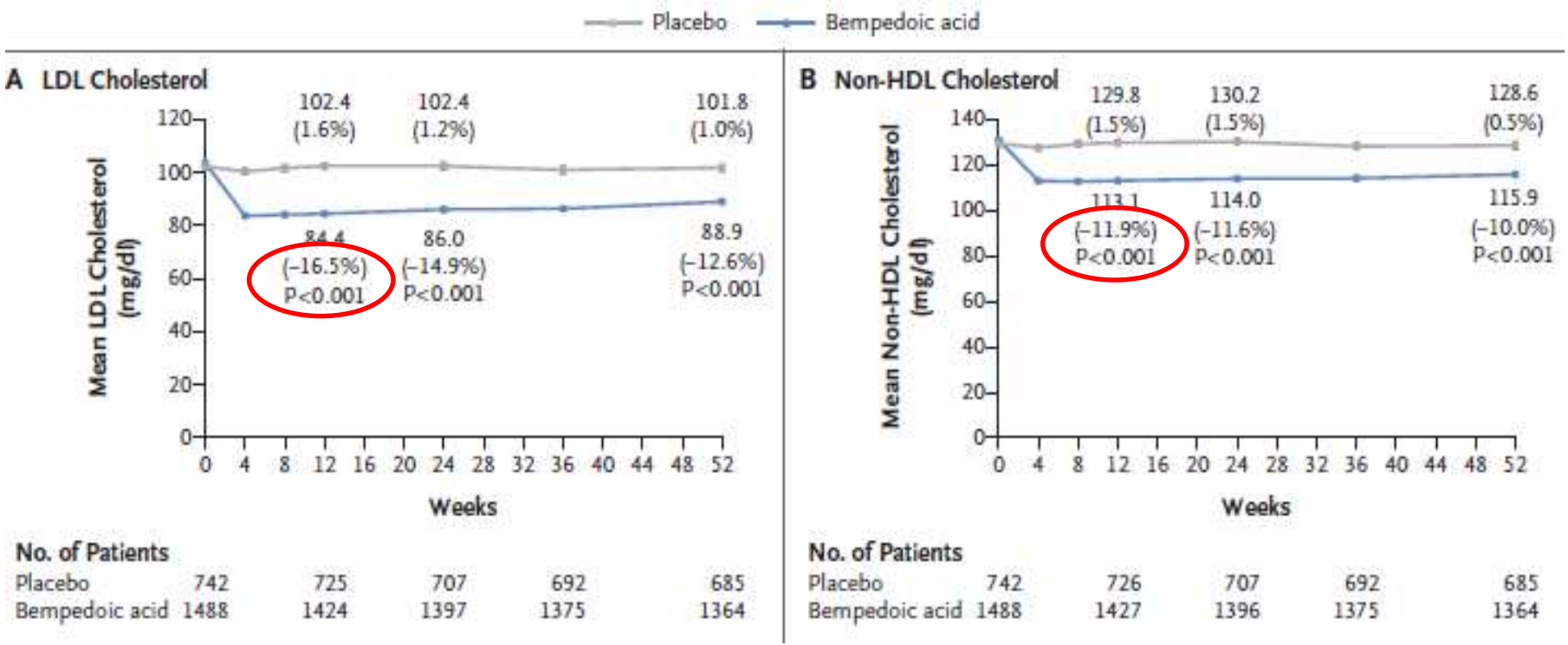
AHA/ACC 2018 Cholesterol Guidelines



Grundy SM et al. *Circulation*. 2018;Nov. 10

CLEAR Harmony: 52-week Lipid Efficacy with Bempedoic Acid, an ATP Citrate Lyase inhibitor

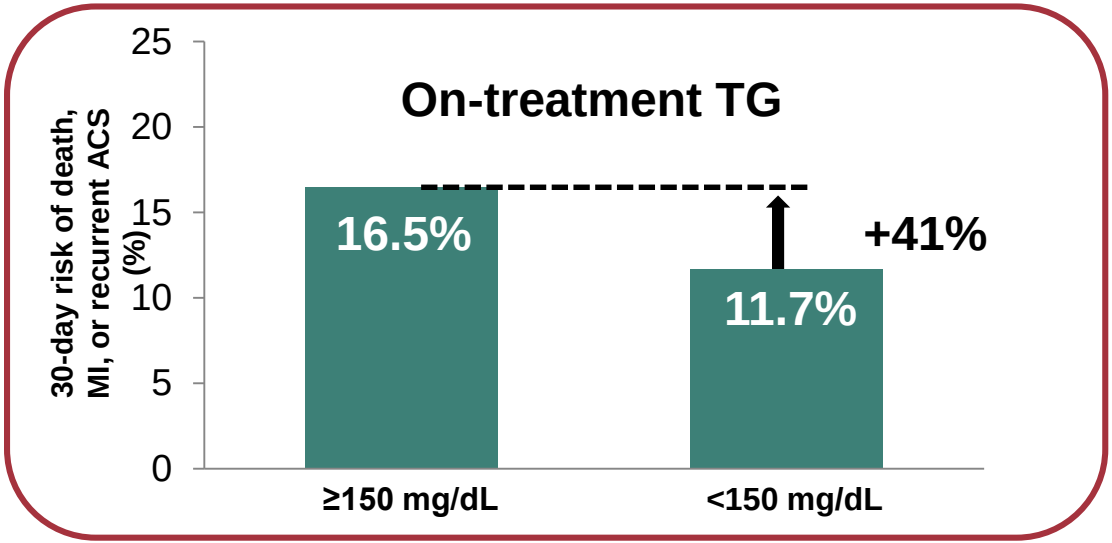
n= 2230 patients with ASCVD or FH or both, on max tolerated statin ± other lipid Rx



Ray KK et al. *N Engl J Med*. 2019;380:1022-32.

Residual HTG Predicts Residual ASCVD Risk Despite LDL-C at Goal on Statin Monotherapy

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



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

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

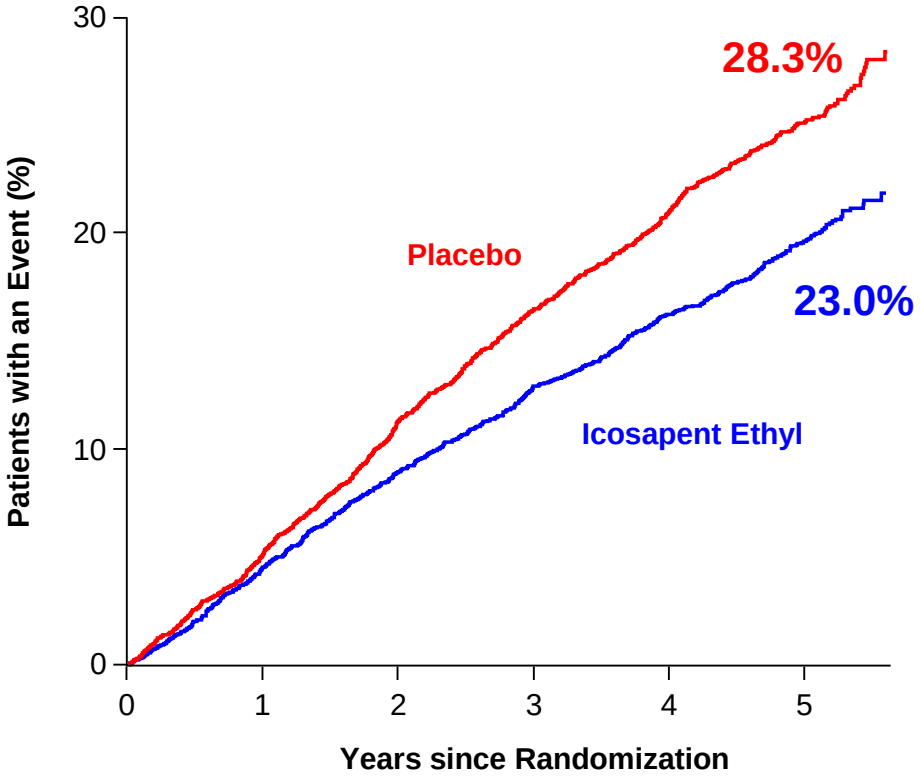
CV Outcomes Trials in Patients with HTG

	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	8,179	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	4.8 years	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.

REDUCE-IT Study of EPA: Effect on the Primary Endpoint
(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

ARR=absolute risk reduction; CI=confidence interval; Revasc=revascularization; RRR=relative risk reduction.

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

Mechanism-based Statin-adjunct Therapy for ASCVD Prevention

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

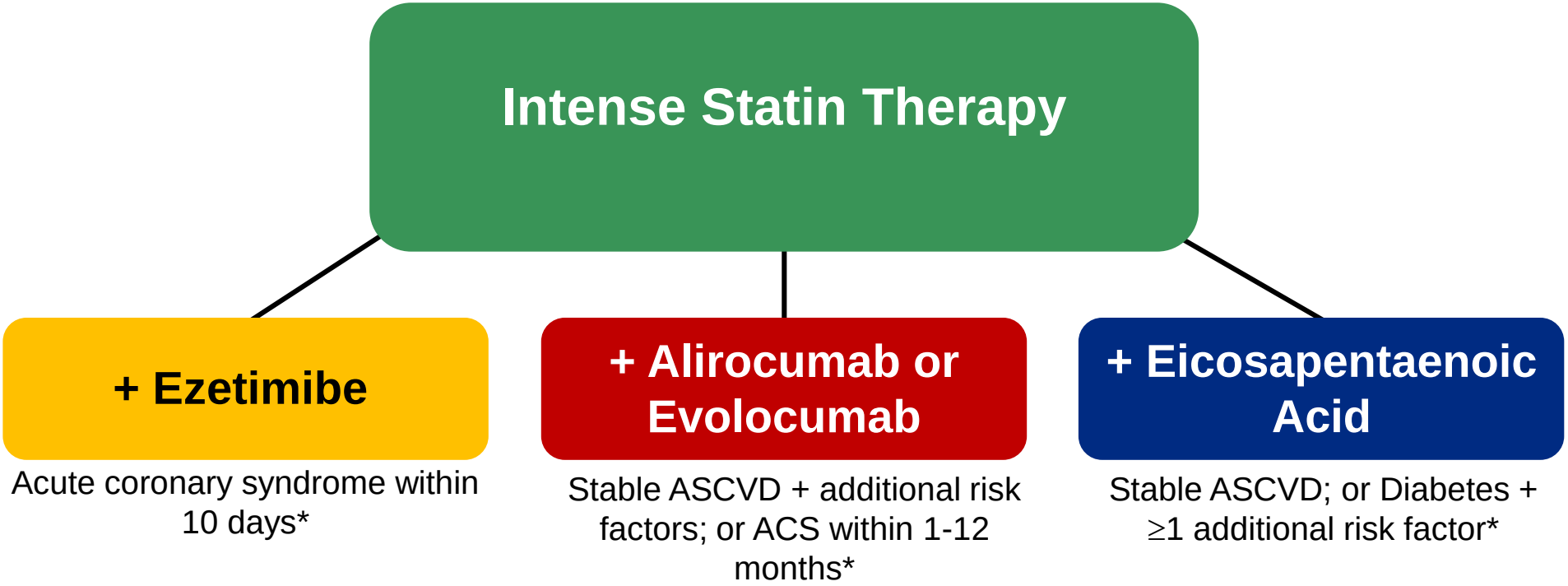
Residual Risk Factors

↑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.

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]

ADA Standards of Care: Update, March 2019

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.

(Grade A)

Conclusions

- After a long drought, a plethora of clinical studies has provided evidence for additional pharmacologic avenues to reduce CVD risk in statin-treated
- 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