Icosapent Ethyl Therapy: Mechanisms, Implications for Current Guidelines, and Populationwide Impact on CVD Prevention

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Presenter Disclosures

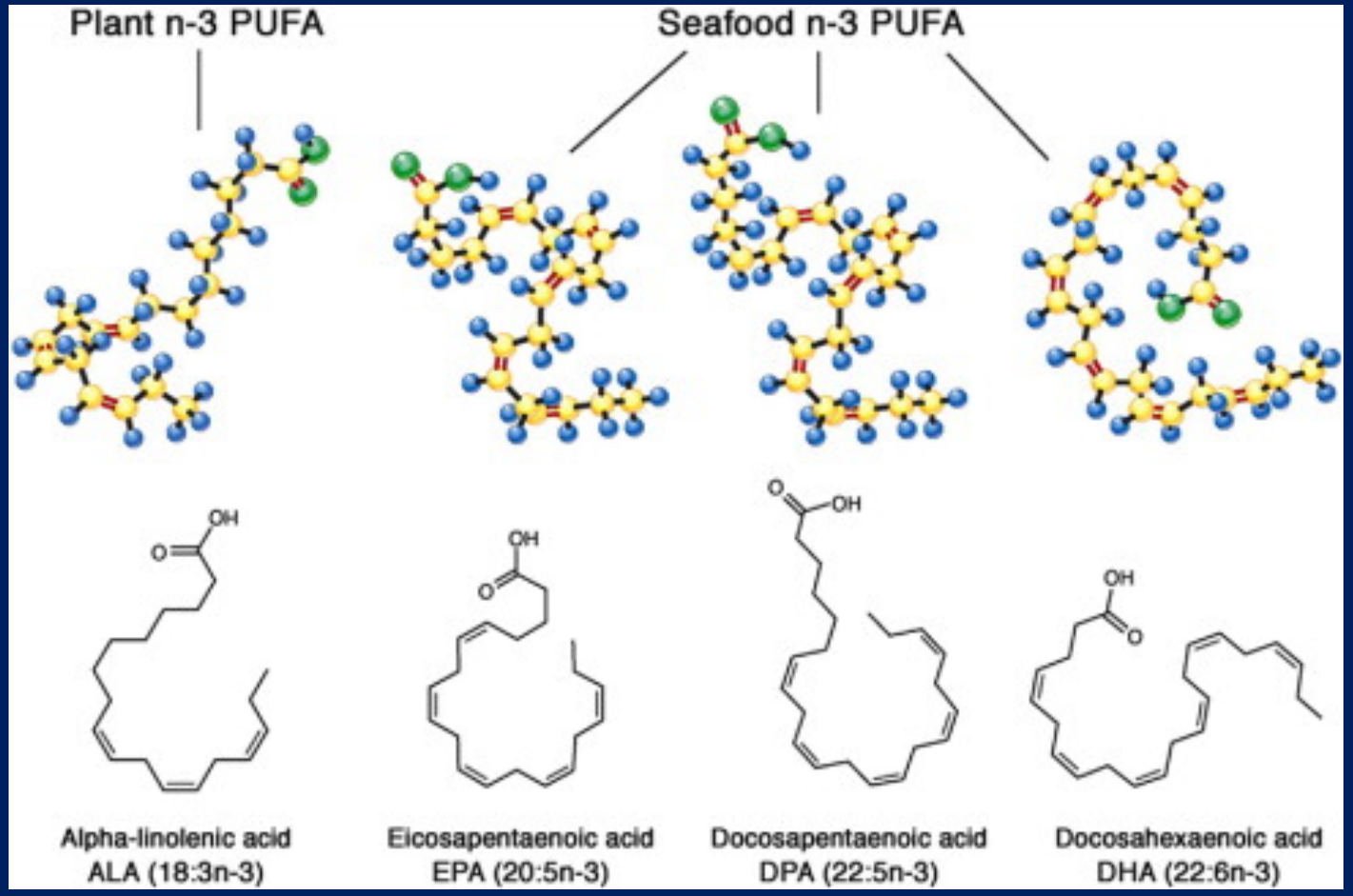
- Research support through institution from Amarin, Amgen, Novartis, and Esperion
- Consultant for Novartis
- Speakers bureau for Amarin and Esperion

What might explain the benefit seen in REDUCE-IT but not other trials of fish oil therapy?

- REDUCE-IT and JELIS are the only omega-3 fatty acid trials to show CV outcomes benefit and involved pure icosapent ethyl added to statin therapy
- Other trials, including those with DHA and EPA combinations have not shown benefit, with amounts of EPA much lower than used in REDUCE-IT
- What are some of the characteristics of EPA that differ from that of DHA?
- Can dietary supplement omega-3 products substitute?

Omega-3 Fatty Acid Molecular Structure

ALA has poor conversion to EPA (0.3–8%) and DHA (<1%) in humans[1]

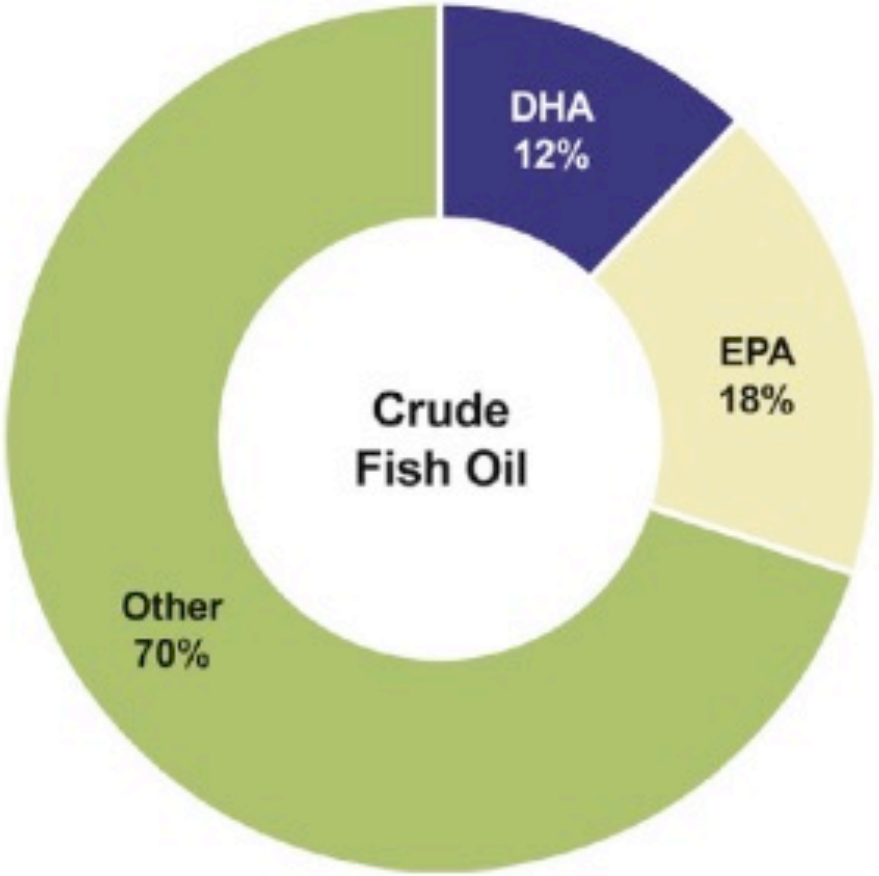


Not for TG-lowering	**Effective for TG-lowering**	**Not approved or indicated for TG-lowering**	**Effective for TG-lowering**

The AHA recommends 2 servings of fish/wk (esp. fatty fish).
A serving is 3.5 ounces cooked, or about ¾ cup of flaked fish.
Fatty fish like salmon, mackerel, herring, lake trout, sardines and albacore tuna are high in n-3 PUFA.[2]

PUFA, polyunsaturated fatty acid. Figure reproduced with permission from Mozaffarian D, Wu JH. *J Am Coll Cardiol*. 2011;58(20):2047-2067.
1. Arterburn LM, et al. *Am J Clin Nutr.* 2006;83(6 Suppl):1467S-1476S. 2. Rimm EB, et al. *Circulation*. 2018 Jul 3;138(1):e35-e47.

EPA and DHA Are Available in Several Forms



Fish Oil Dietary Supplement

~20% DHA
~30% EPA
~50% Other undisclosed fatty acids

Combination OM-3 Prescription Product

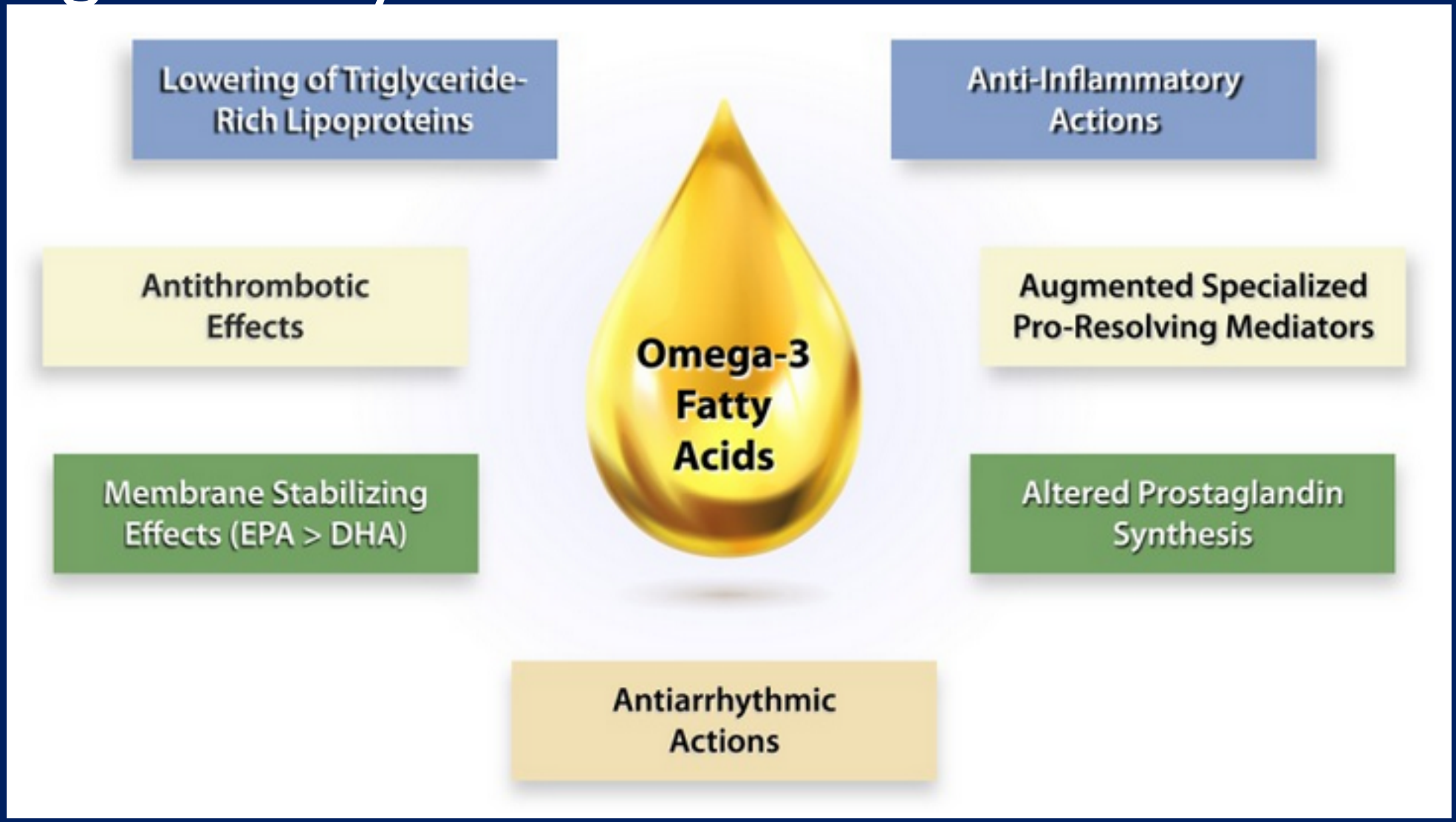
42% DHA
52% EPA
6% Other OM-3 fatty acids

EPA-only Prescription Product

100% icosapent ethyl
(ethyl ester of EPA)

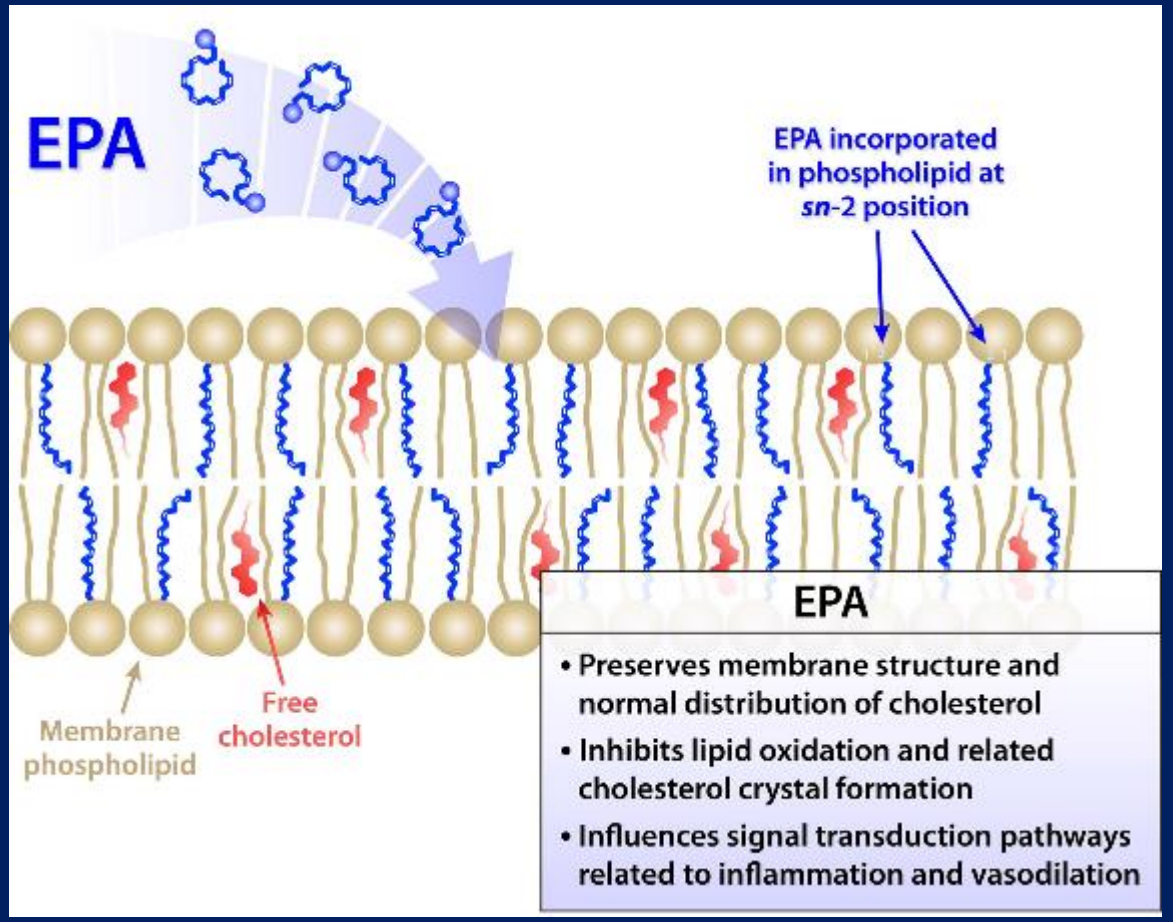
Hilleman DE, et al. *Adv Ther.* 2020;37(2):656-670.

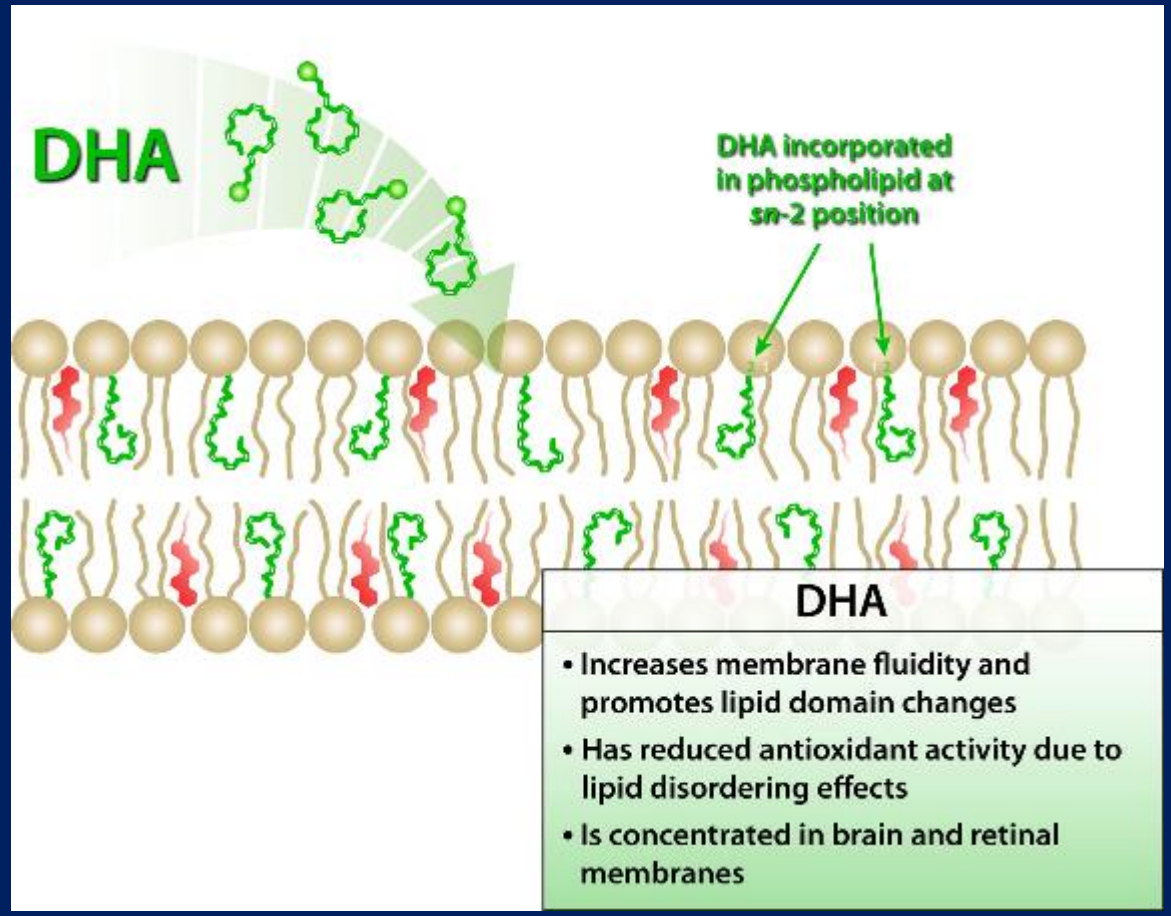
Potential Mechanisms of Cardioprotection for Omega-3 Fatty Acids



Mason, RP, Libby P, Bhatt DL. *Arterioscler Thromb Vasc Biol*. 2020 May; 40(5): 1135–1147.

Contrasting Effects of EPA and DHA

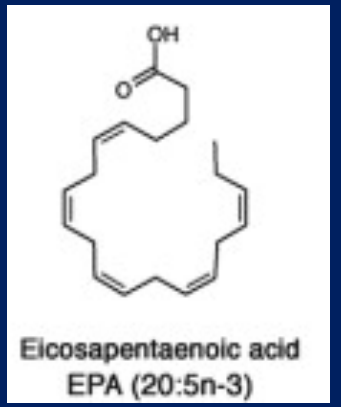


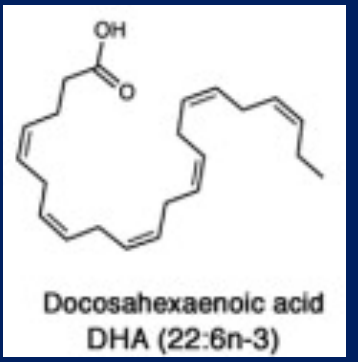


Mason, RP, Libby P, Bhatt DL. *Arterioscler Thromb Vasc Biol*. 2020 May; 40(5): 1135–1147.

EPA (Icosapent Ethyl) and DHA (in Generic Lovaza, etc.) Have Differing Effects on Resolvins,* Oxidation, and **Cell** Membrane Cholesterol

- EPA generates E-series Resolvins (RvE)
- DHA generates D-series Resolvins (RvD)
- EPA →↓oxidation of ApoB-containing lipoproteins (more effective than DHA)
- EPA →↓cell membrane fluidity (→↓glucose-induced pro-atherogenic cholesterol rafts & crystals)
- DHA →↑cell membrane fluidity (→↑pro-atherogenic cholesterol rafts & crystals)

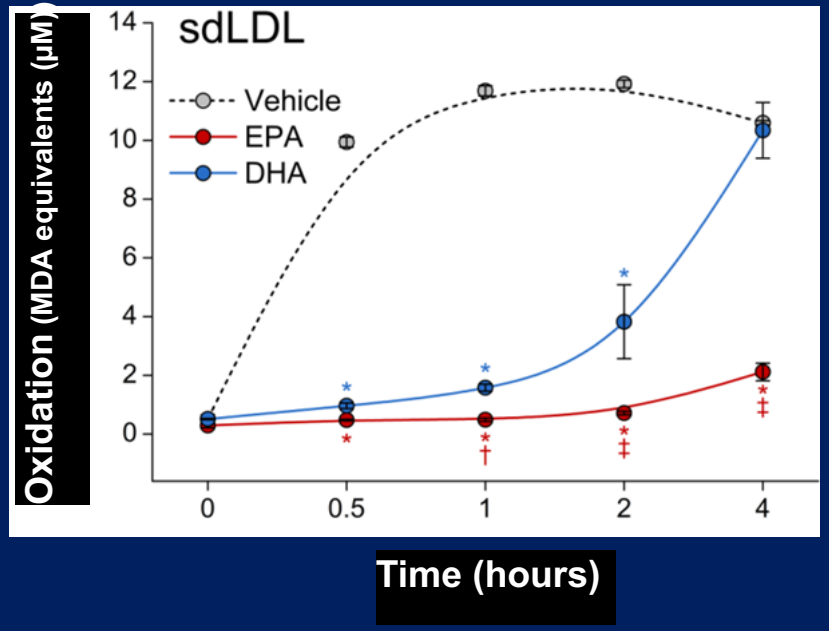


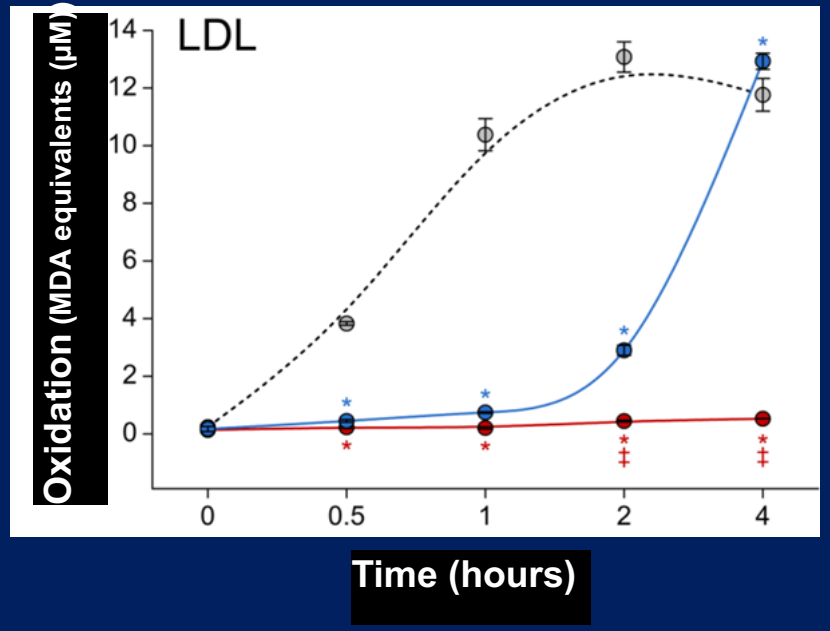


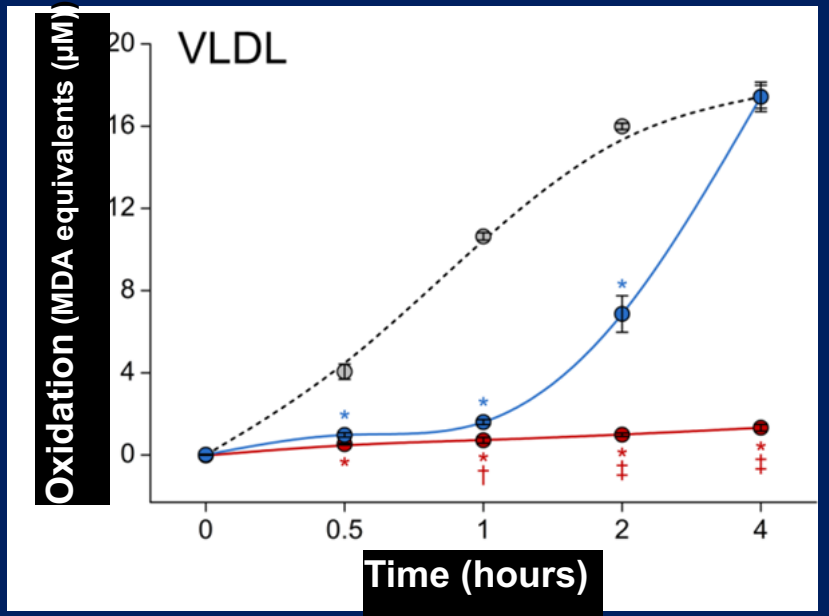
*Resolvins, derived from omega-3 fatty acids, are synthesized during the initial phases of acute inflammatory responses to promote the resolution of inflammation.

 Mason RP, et al. *J Cardiovasc Pharmacol.* 2016;68(1):33-40. Kohli P, Levy BD. *Br J Pharmacol*. 2009;158(4):960-971.

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







Greater lag time in generation of MDA equivalents indicates resistance to oxidation

MDA, malondialdehyde. Malondialdehyde, a marker for oxidative stress, results from lipid peroxidation of polyunsaturated fatty acids. LDL, low-density lipoprotein; sdLDL, small, dense low-density lipoprotein; VLDL, very low-density lipoprotein.

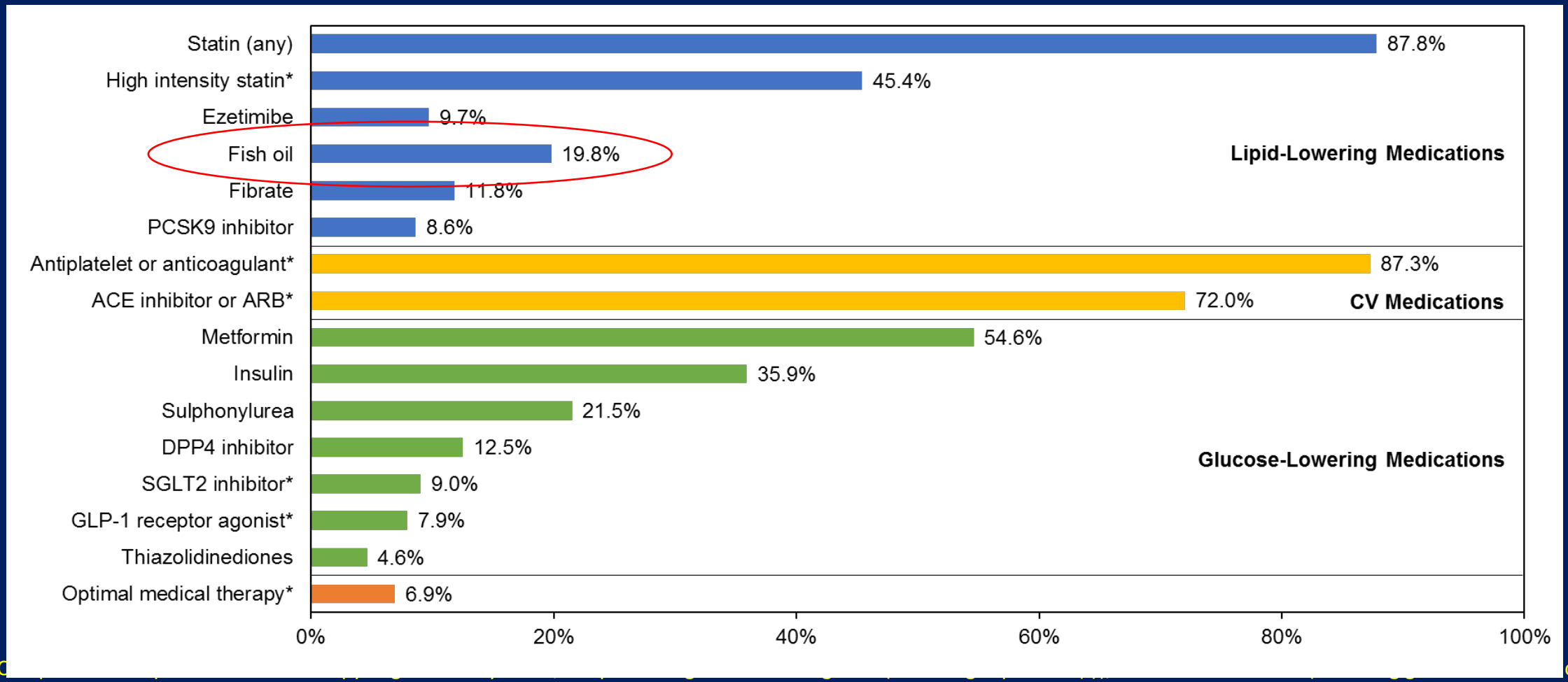
Mason RP et al. *J Cardiovasc Pharmacol* 2016;68(1):33-40.

Various Lipid-Lowering Therapies Have Differing Effects on hsCRP Levels

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

Bays HE, et al. *Am J Cardiovasc Drugs*. 2013;13(1):37-46. Dunbar RL, et al. *Lipids Health Dis.* 2015:14:98. Ridker PM, et al. *N Engl J Med.* 2008;359(21):2195-2207. Bohula EA, et al. *Circulation*. 2015;132(13):1224-1233. Pradhan AD, et al. *Circulation*. 2018;138(2):141-149. Laufs U, et al. *J Am Heart Assoc.* 2019;8(7):e011662

Use of CV and Glucose-Lowering Medications Among Patients with Diabetes and ASCVD in GOULD



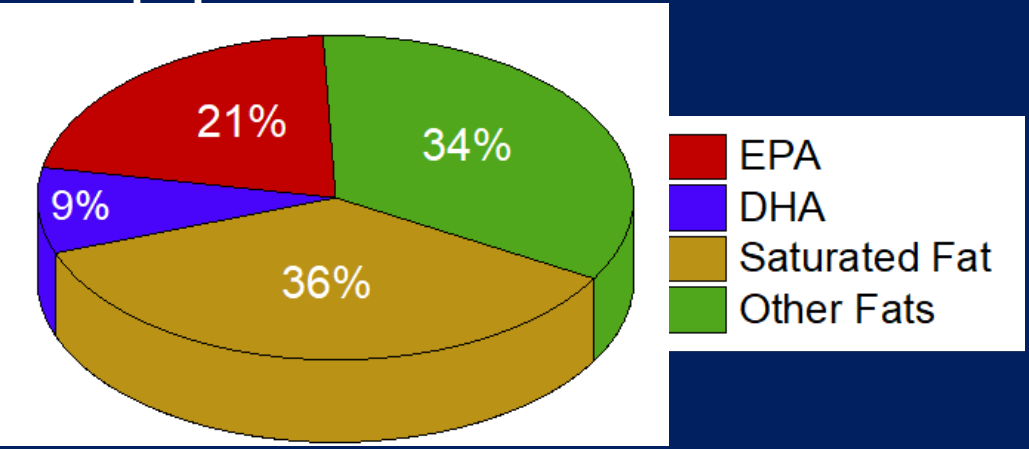
*C…on rate <30 mL/[min·1.73 m^2]), and SGLT2 inhibitor or GLP1 receptor agonist (for type 2 diabetes mellitus; excluding glomerular filtration rate <30 mL/[min·1.73 m^2]). ACE indicates angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CV, cardiovascular; DPP4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide 1; PCSK9, proprotein convertase subtilisin/kexin type 9; and SGLT2, sodium-glucose cotrans-porter-2.

Arnold SV, et al. *Circulation*. 2019;140(7):618-620.

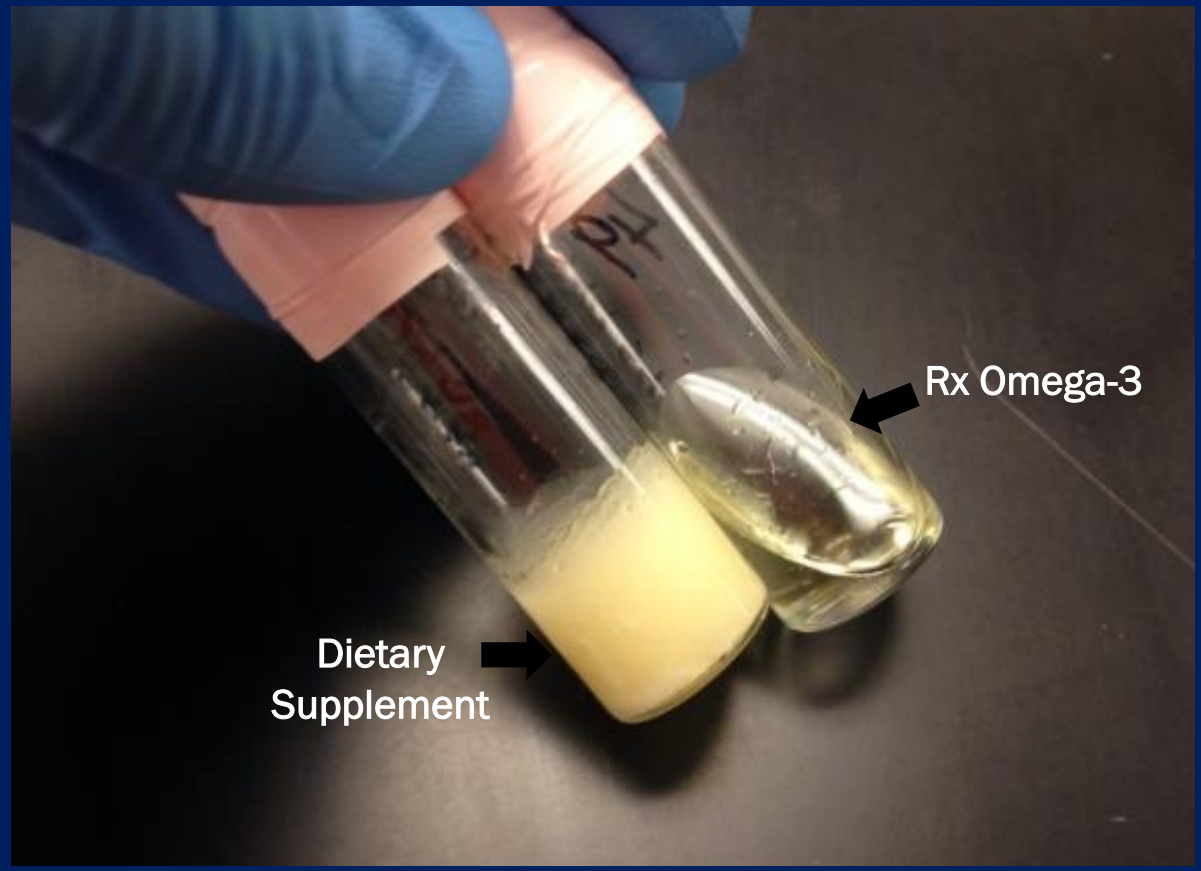
Fish Oil *Dietary Supplements*: Poorly Regulated but Widely Used

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

Dubious Content of *Leading* US Fish Oil Dietary Supplements



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



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

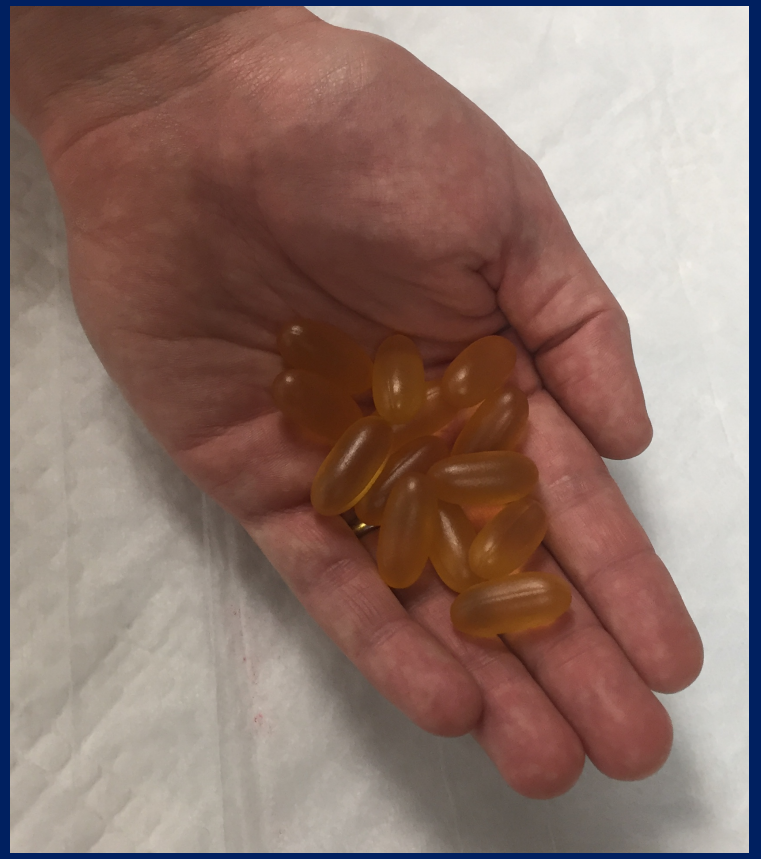
*DS, dietary supplement.

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

Achieving the Recommended 4 gm/day Dose of EPA with Prescription IPE vs Leading Fish-Oil Dietary-Supplements

Prescription pure, stable EPA (Icosapent ethyl)

EPA/DHA Dietary Supplement (per label)



Krill-oil Dietary Supplement (per label)

Photos courtesy of Preston Mason, PhD

Summary

- Distinct differences exist between marine omega-3 fatty acids EPA and DHA
  - Membrane stabilization and fluidity is very different
  - Different resolvins are engaged
  - Activity on oxidized LDL-C is different
  - Anti-inflammatory effects on biomarkers such as hsCRP
- Dietary supplements, though commonly used, have not shown ASCVD event reduction as has icosapent ethyl

Current Prevention Guidelines and Implications for Newer Therapeutic Options

Nutrition Lifestyle Recommendations: Lipids and BP

- **Emphasis on dietary *patterns***
  - Mediterranean or DASH-style
- ↑Fruits, vegetables, and whole grains
- ↑Fiber and ↓Sugar
- Fat intake
  - 30 – 35% total calories
  - <6% saturated fats (avoid *trans* fats)
- *Regular* fish intake
- ↓Highly-processed/pre-prepared food
- Low sodium (<2400 mg/day)
- Healthy eating for a *lifetime*

Best evidence for ↓MI risk is with the Mediterranean diet

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

Physical Activity Guidelines: Lipids and BP

Regular aerobic activity and strength training:

- 3+ sessions per week
- Average ~40 min per session
- Moderate-to-vigorous intensity
- Strength training *also* helpful
- *Patient* chooses most enjoyable and sustainable activities

Best evidence for is brisk walking ~30 min/day ~5 days/week

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

ACC Risk Calculator *Plus* to Assess Risk Category

1. For primary prevention, use the calculator to Assess Risk Category

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

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

- es 40-79
- s to
- n

Current Age *
Age must be between 20-79

Sex * Male | Female

Race * White | African American | Other

Systolic Blood Pressure (mm Hg) *
Value must be between 90-200

Diastolic Blood Pressure (mm Hg)
Value must be between 60-130

Total Cholesterol (mg/dL) *
Value must be between 130 - 320

HDL Cholesterol (mg/dL) *
Value must be between 20 - 100

LDL Cholesterol (mg/dL)
Value must be between 30-300

History of Diabetes? * Yes | No

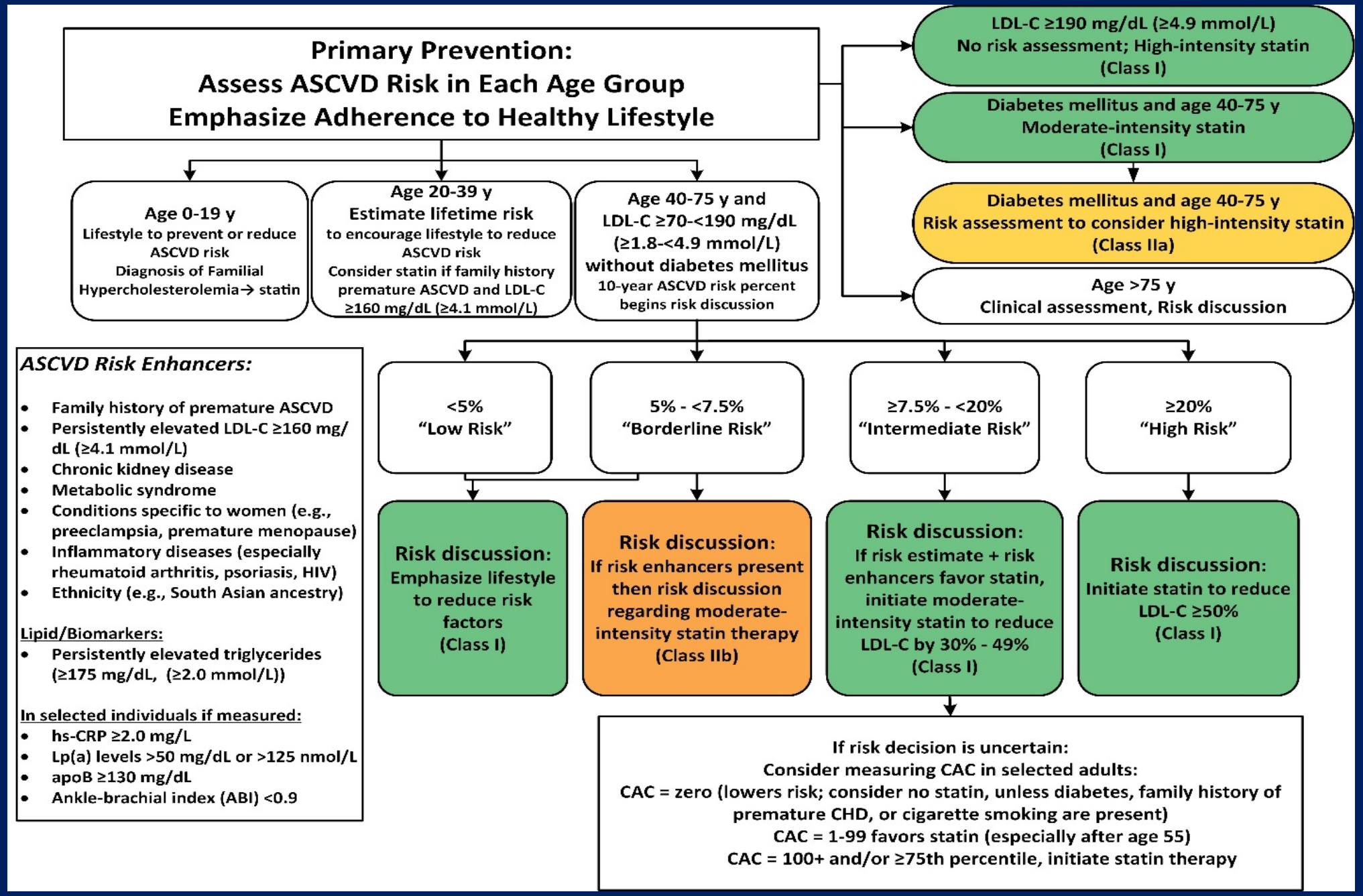
Smoker? * Current | Former | Never

On Hypertension Treatment? * Yes | No

On a Statin? Yes | No

On Aspirin Therapy? Yes | No

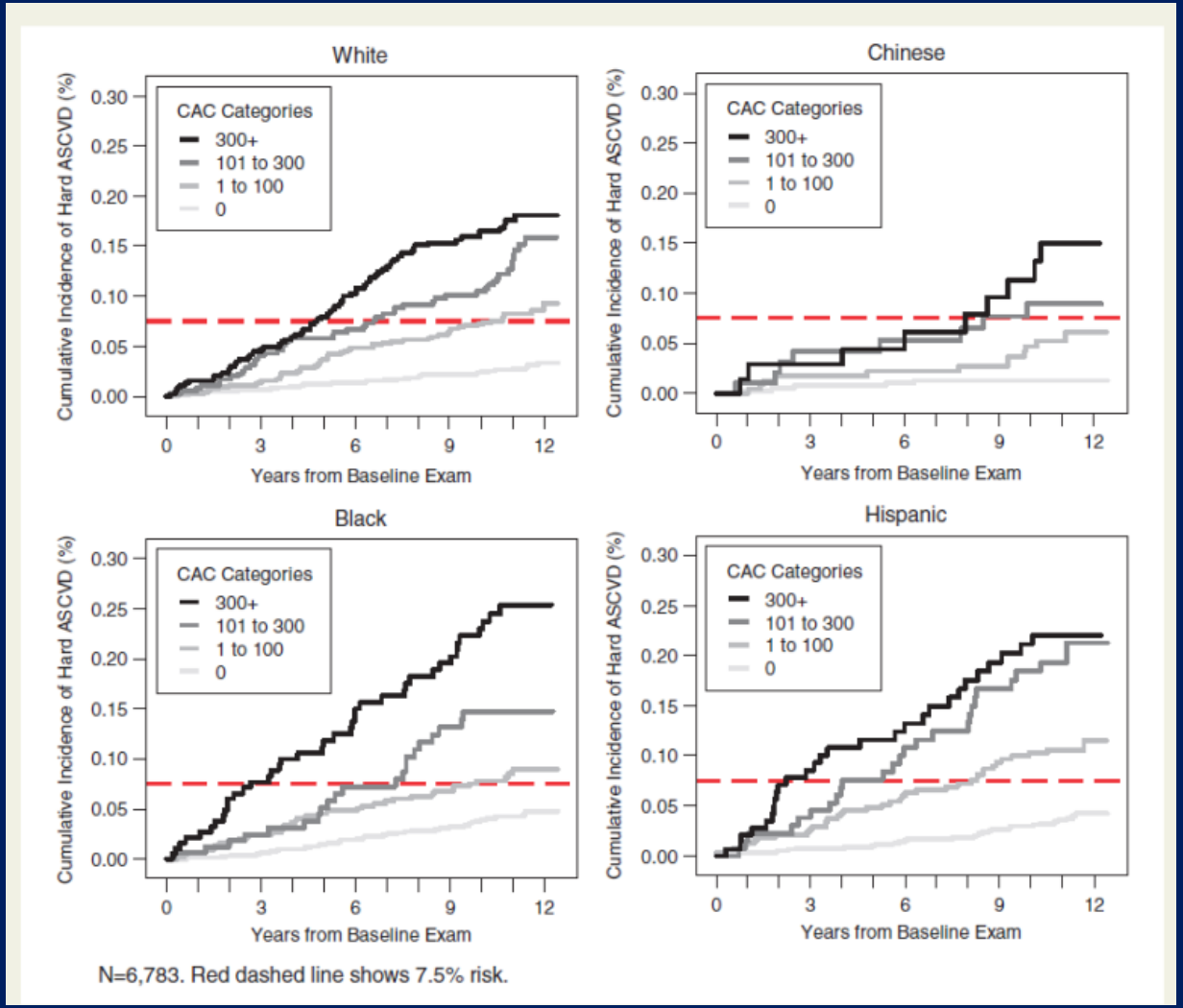
ACC=American College of Cardiology; AHA=American Heart Association; ASCVD=atherosclerotic cardiovascular disease;
tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate



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

Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA) (Budoff et al., Eur Heart J 2018)

- At 10 years of follow-up, all participants with CAC > 100 were estimated to have >7.5% risk regardless of demographic subset.
- Ten-year ASCVD event rates increased steadily across CAC categories regardless of age, sex, or race/ethnicity.
- For each doubling of CAC, there was a 14% increment in ASCVD risk



CAC motivates lifestyle and preventive therapies
"A picture is work a thousand words"

- **In 703 men and women aged 28-84 who received scanning for coronary calcium by EBCT, calcium score remained independently associated with:**
  - **New aspirin usage**
  - **New cholesterol medication**
  - **Consulting with a physician**
  - **Losing weight**
  - **Decreasing dieatary fat**
  - **… but also increased worry**
- **…. Potentially important risk-reducing behaviors may be reinforced by the knowledge of a positive coronary artery scan, independent of preexisting coronary risk factor status**

Wong ND et al, *Am J Cardiol*. 1996 Dec 1;78(11):1220-3

Candidates for CAC Measurement Who Might Benefit from Knowing Their CAC Score

- Patients reluctant to initiate statin therapy who wish to understand their risk and potential for benefit more precisely
- Patients concerned about need to reinstitute statin therapy after discontinuation for statin-associated symptoms
- Older patients (men 55–80 y of age; women 60–80 y of age) with low burden of risk factors who question whether they would benefit from statin therapy
- Middle-aged adults (40–55 y of age) with PCE-calculated 10-year risk for ASCVD 5% to <7.5% with factors that increase their ASCVD risk, although they are in a borderline risk group

Grundy SM, et al. *J Am Coll Cardiol.* 2019;73(24):e285-e350.

Risk Enhancing Factors

- Family history of premature ASCVD (men, age <55y; women, <65 y)
- Primary hypercholesterolemia
- Metabolic syndrome (increased waist circumference, elevated triglycerides, elevated blood pressure, elevated glucose, and low HDL-C
  - 3 or more of 5 factors = Metabolic Syndrome
- Chronic kidney disease
- Chronic inflammatory conditions

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

Additional Risk Enhancing Factors

- History of premature menopause (before age 40 y) *or* pregnancy-associated conditions that ↑ASCVD risk (e.g. preeclampsia)
- High-risk race/ethnicity (eg, South Asian, East Asian, Native American, Middle Eastern)
- High-risk levels of lipids or other biomarkers
- Persistent primary HTG
- If measured:
  - ↑high-sensitivity C-reactive protein
  - ↑Lp(a)
  - ↑apoB
  - ↓ABI

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

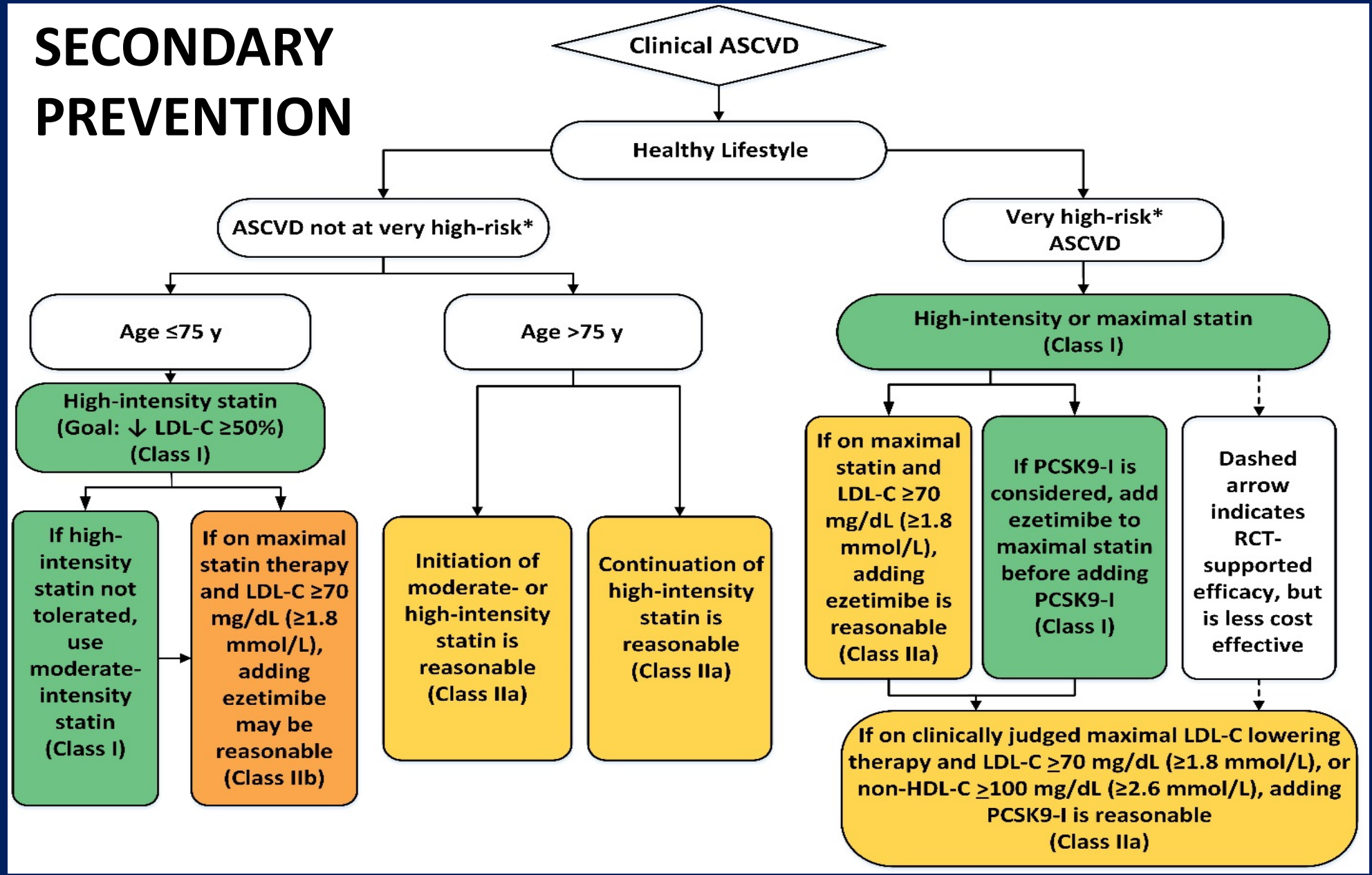
Statin Treatment in Patients with Diabetes

- For patients of all ages with **diabetes *and* ASCVD or 10-year ASCVD risk >20%, high-intensity statin therapy** should be added to lifestyle therapy. (A)
- In patients with **diabetes *without* ASCVD but *with multiple* ASCVD risk factors**, it is reasonable to consider **high-intensity statin therapy**. (C)
- For patients with **diabetes *without* ASCVD, aged 40–75 years** (A), **and >75 years** (B), use **moderate-intensity statin** in addition to lifestyle therapy.
- For patients with **diabetes aged <40 years with additional ASCVD risk factors**, the patient and provider should *consider* using **moderate-intensity statin** in addition to lifestyle therapy. (C)
- For patients who do not tolerate the intended intensity, **the maximum tolerated statin dose should be used**. (E)

(A)= High quality evidence; (B)= Moderate quality evidence; (C)= Limited data; (E)= Consensus of expert opinion based on clinical experience.

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

SECONDARY PREVENTION



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

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 74, NO. 20, 2019

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Identifying the Very-High-Risk Atherosclerotic Cardiovascular Disease Patient

Does It Really Matter?*

Nathan D. Wong, PhD

More than 20 years ago, the 27th Bethesda Conference (1) noted that the intensity of treatment should match the patient risk of future cardiovascular events. The Third Adult Treatment Panel of the National Cholesterol Education Program in 2001 (2) first used risk scoring to stratify the intensity of treatment. The strictest goal intensity statin therapy (with the removal of specific LDL-C goals) was given for all persons with atherosclerotic cardiovascular disease (ASCVD), thus creating and treating all ASCVD patients as "equal" (4).

The American Association of Clinical Endocrinologists (AACE) in 2017 (5) actually was the first to clearly

Wong ND. JACC 2019 (in press)

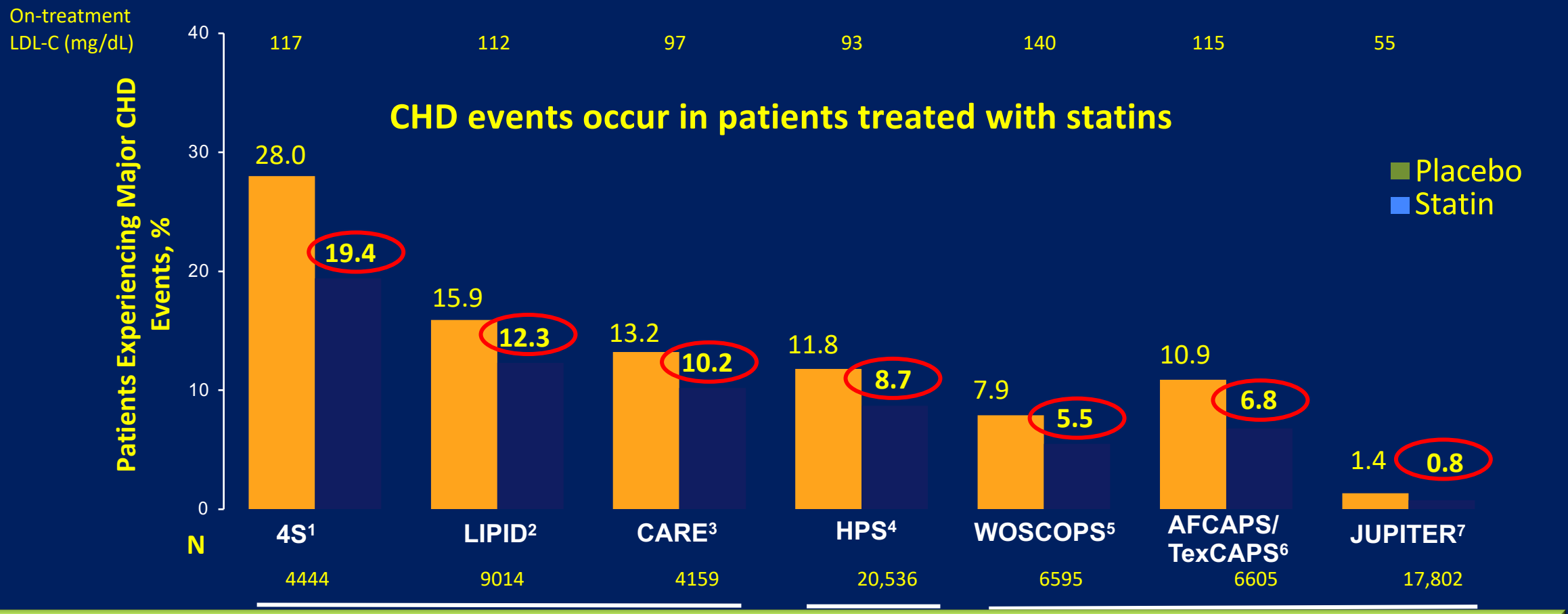
High- and Very High-Risk ASCVD

Major ASCVD Events
Recent ACS
History of MI
History of ischemic stroke
Symptomatic peripheral arterial disease
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

Very High-risk = ≥ 1 Major ASCVD events
or **1 major ASCVD event + ≥ 1 High-risk conditions**

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

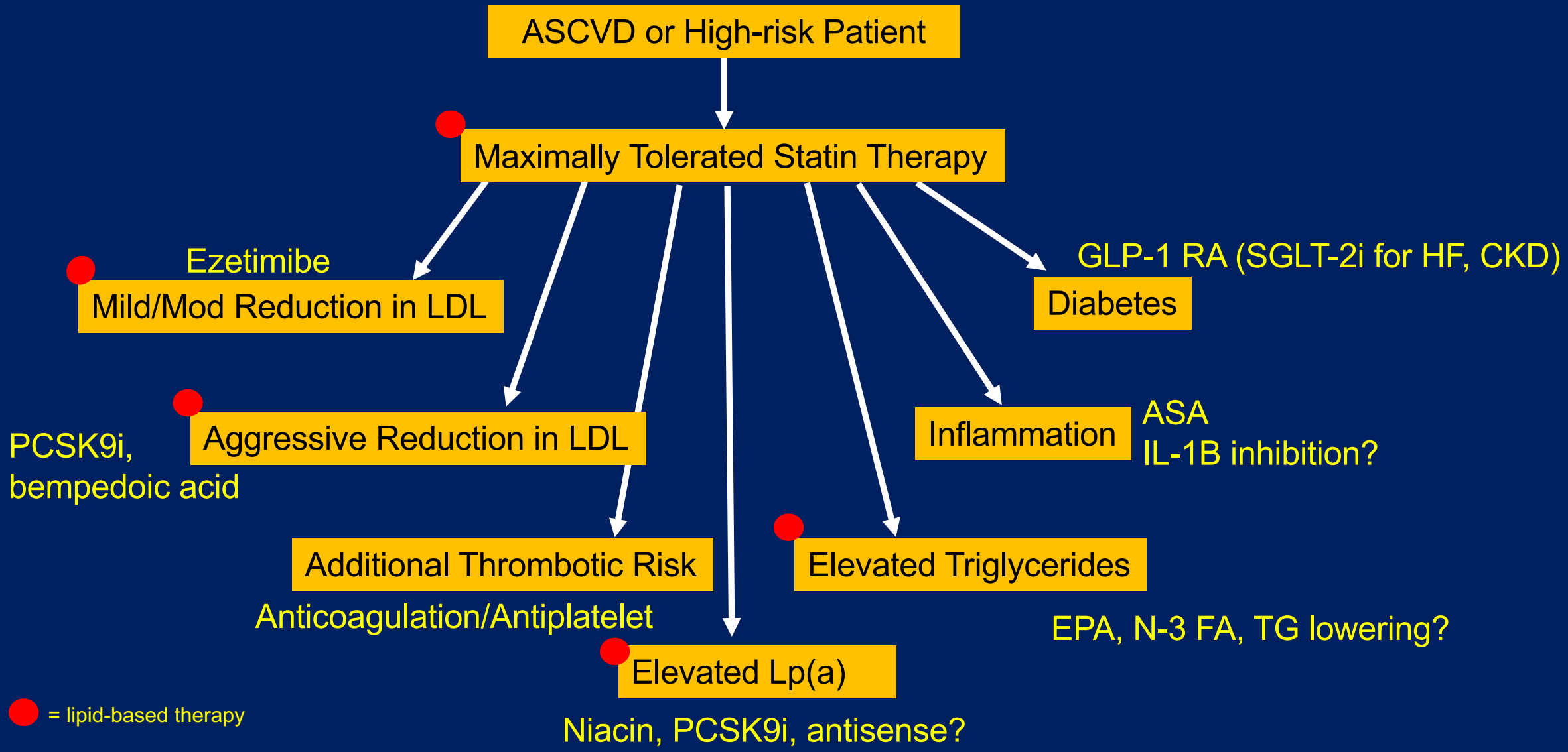
Despite ↓ASCVD with Statin Monotherapy, Substantial CV Risk Remains



Residual CV risk is likely due not only to lipid factors (suboptimal LDL-C, TG), but also other risk factors in 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.

Pharmacologic Approaches to Managing Residual ASCVD Risk



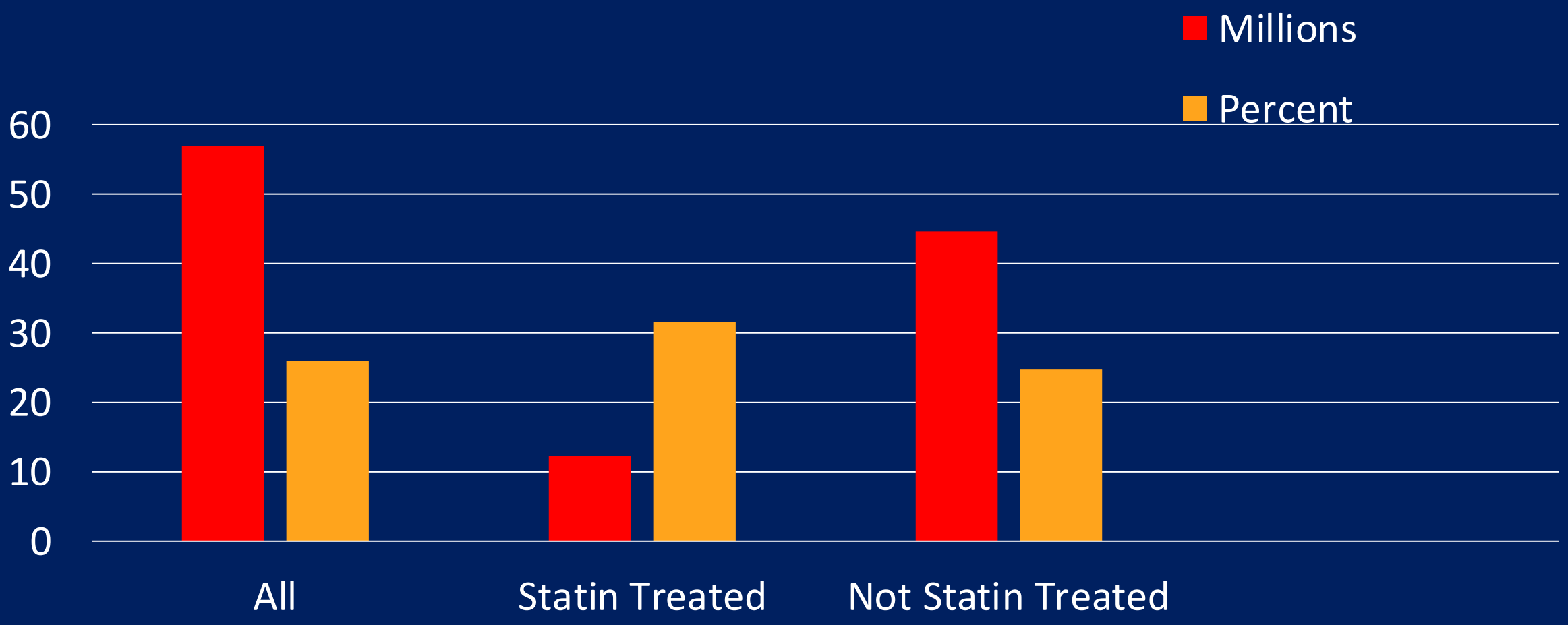
Classification of Fasting TG Levels (2011 AHA/2014 NLA)

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

Jacobson TA et al. *J Clin Lipidol*. 2014;8:473-88.

Miller M et al. *Circulation*. 2011;123:2292-333. American Heart Association (AHA) Scientific Statement. 2014;8:473-88. Miller M et al. *Circulation*. 2011;123:2292-333.

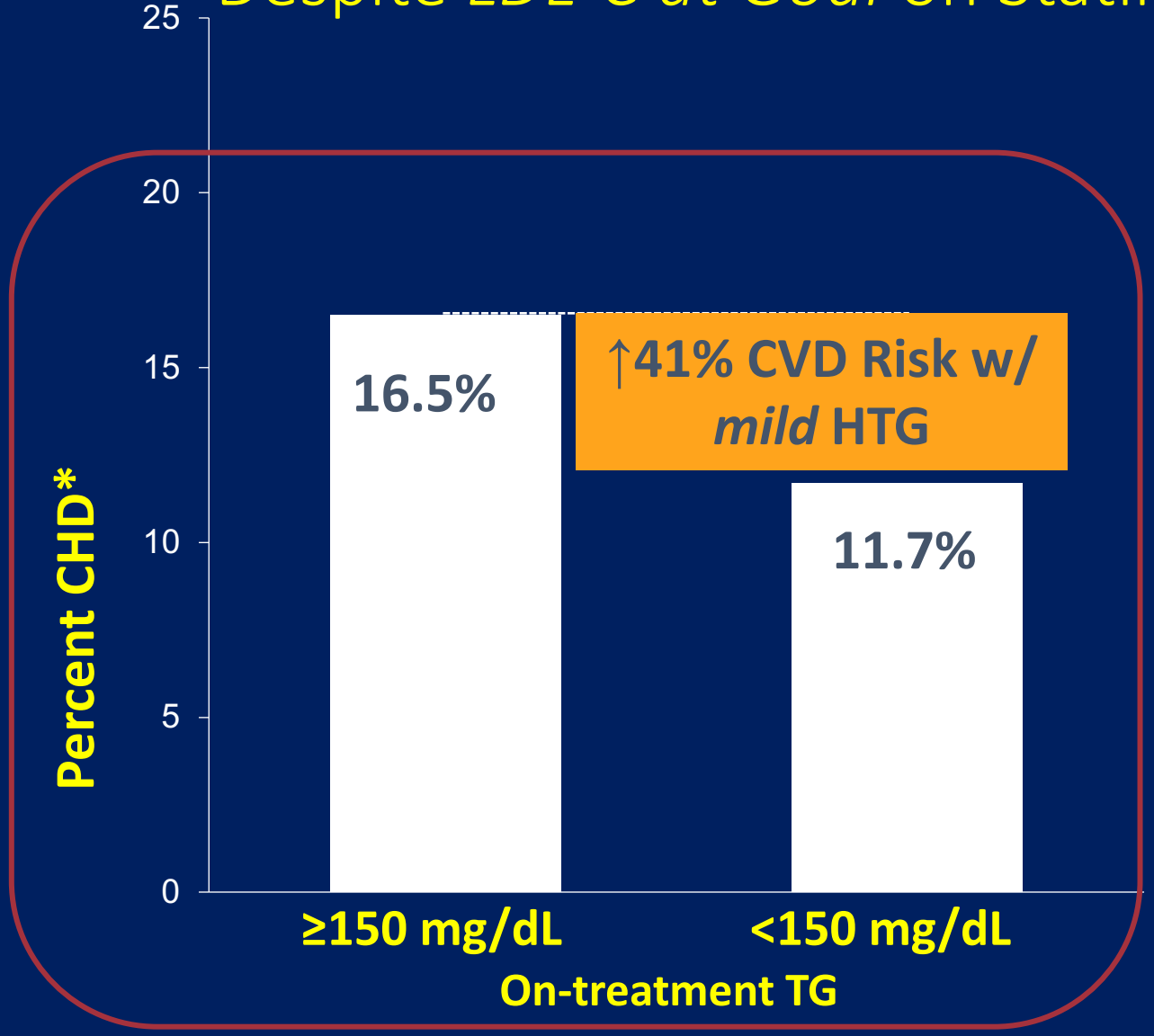
US Prevalence of TG ≥150 mg/dL, On and Off Statin Rx



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

Fan W, et al. *J Clin Lipidol*. 2019;13(1):100-108.

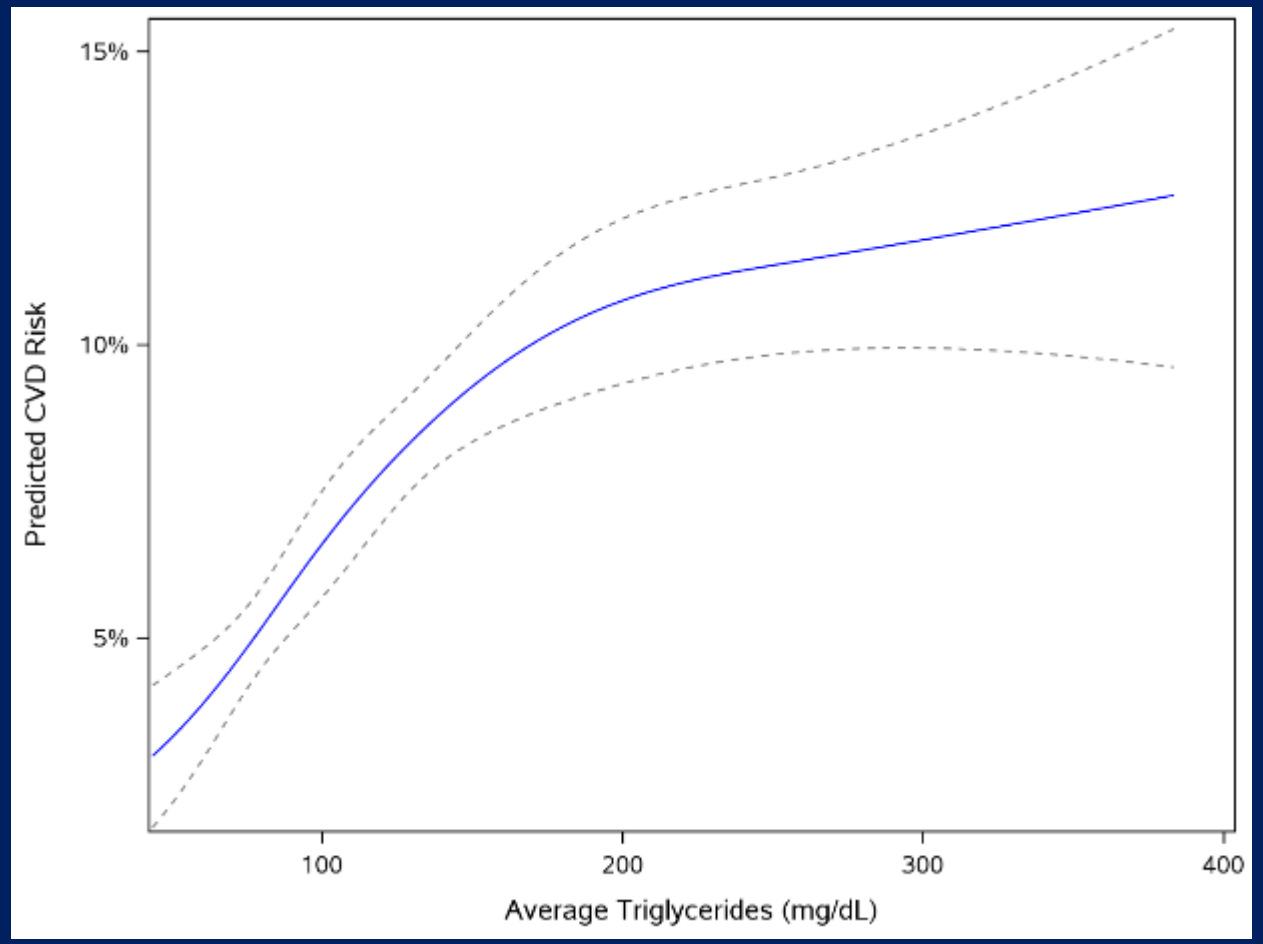
Residual HTG Predicted Residual ASCVD Risk Despite *LDL-C at Goal* on Statin Monotherapy



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

*Death, myocardial infarction, or recurrent acute coronary syndrome, PROVE-IT-TIMI 22, Miller M et al. *J Am Coll Cardiol*. 2008;51:724-30.

Lower is Better: Direct Association between Average TG Level and CVD



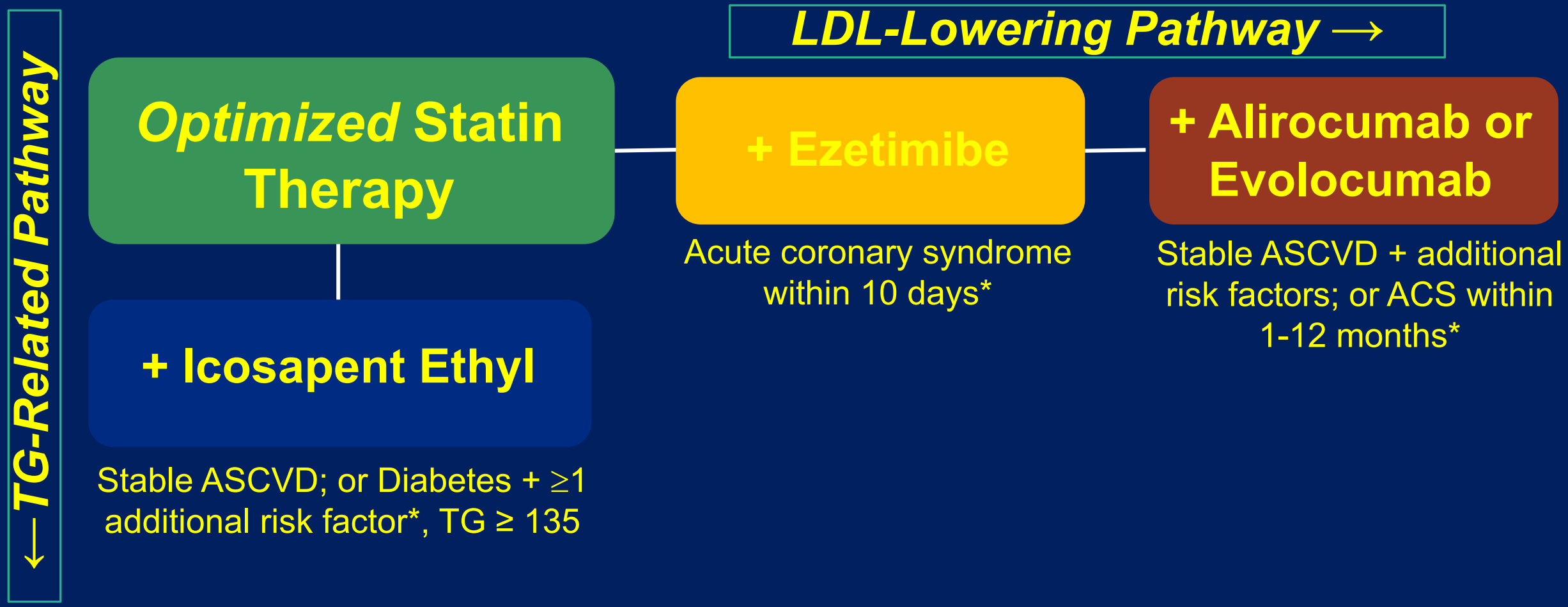
- Data from 8,068 primary prevention patients in Atherosclerosis Risk in Communities Study (ARIC) and Framingham Offspring Study
- Baseline characteristics:
  - 40 to 65 years old
  - No CVD
- ≥ 2 TG measurements on record
- Endpoint: Time to MI, stroke, or CV death
- Follow-up for up to 10 years to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

CVD events increased across the entire range of TG levels to ~ 200 mg/dL, above which the relationship flattened out

Navar AM, Pagidipati N, Mulder H. ACC 2019, New Orleans.

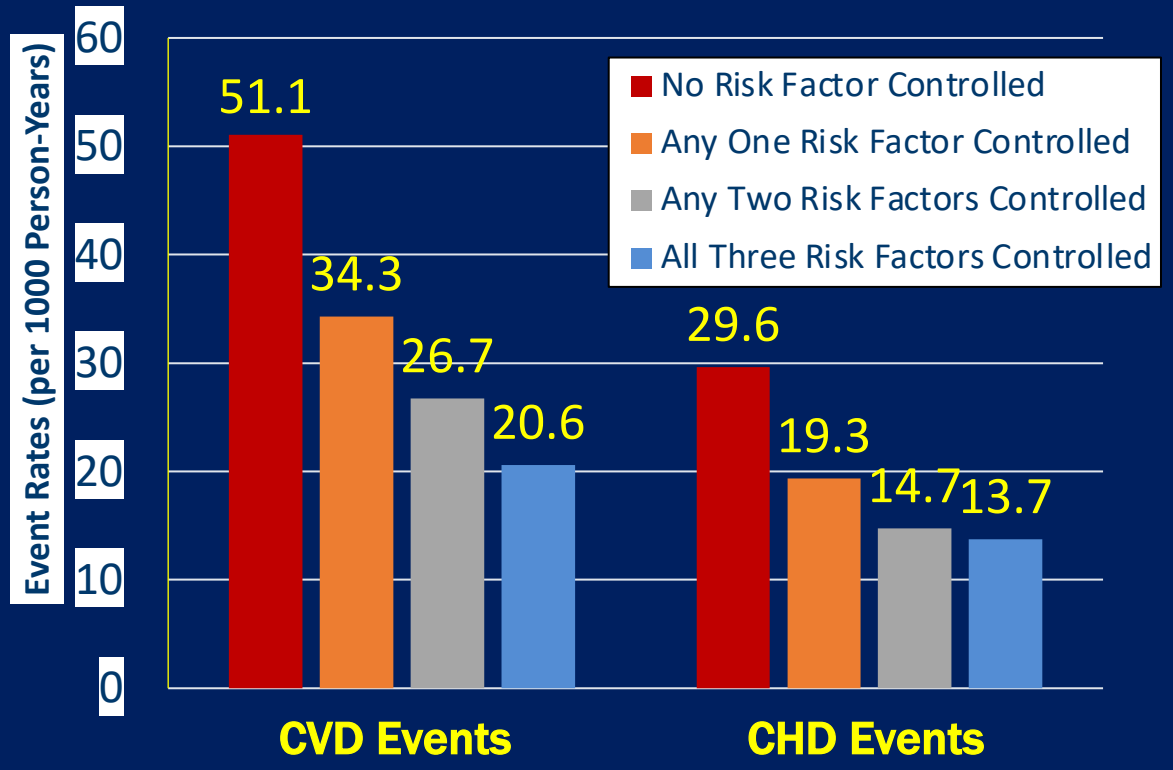
95% confidence intervals shown as dotted lines

Statin Therapy Adjuncts *Proven* to Reduce ASCVD



*Major inclusion criteria for respective CVOTs.
ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease.
After Orringer CE. *Trends in Cardiovasc Med*. 2020;30(3):151-157.

CVD and CHD Event Rates by Number of Risk Factors Controlled (LDL-C, BP, HbA1c): Pooling of ARIC, JACKSON, and MESA Study DM Subjects

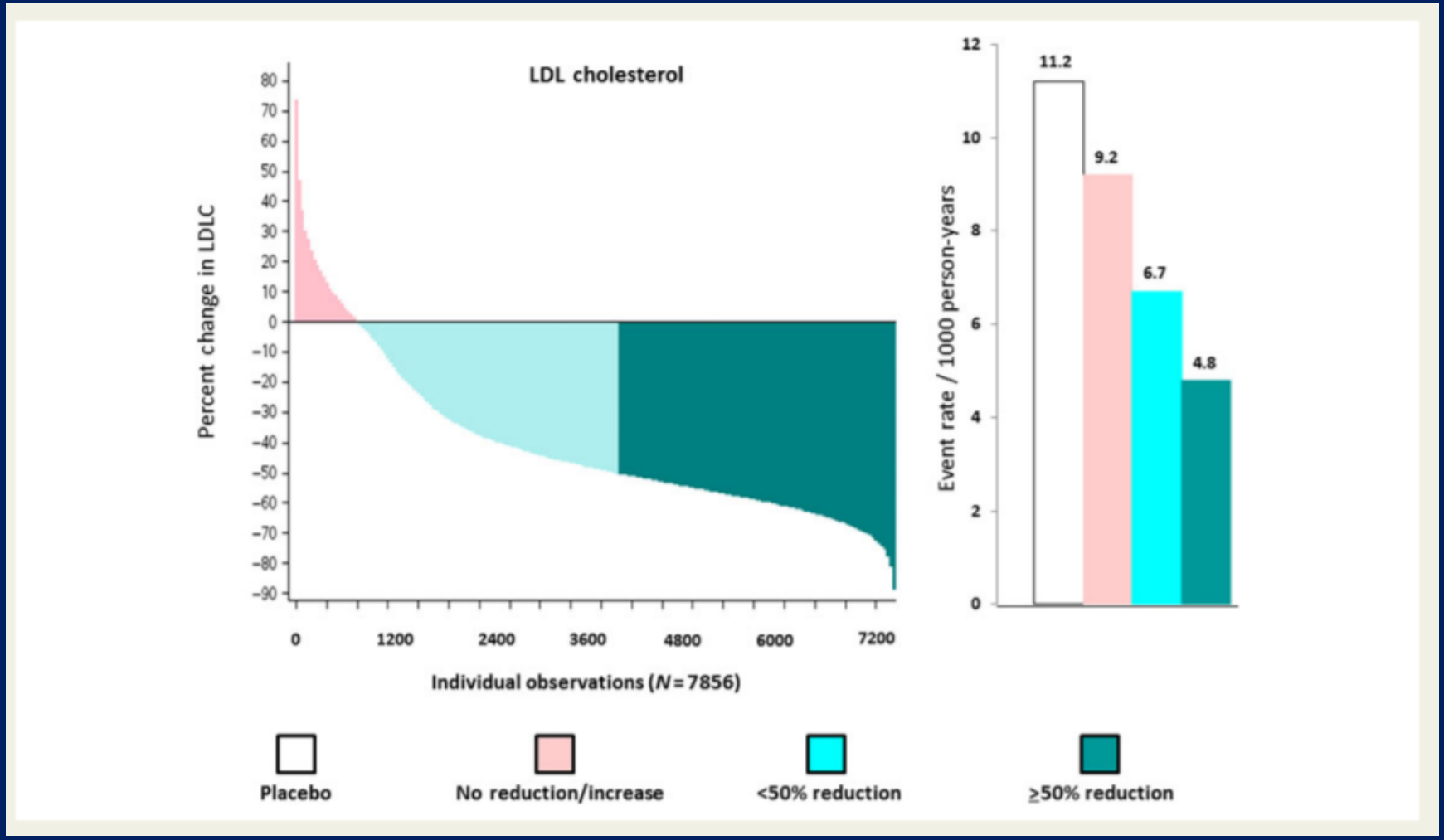


Would IPE Further Reduce DM Residual Risk 20-25%

Multivariable adjusted risks of CVD events 62% lower and CHD events 60% lower with all 3 risk factors controlled (versus none at control)

Wong ND, Zhao Y et al. *Diabetes Care.* 2016;39:668-676

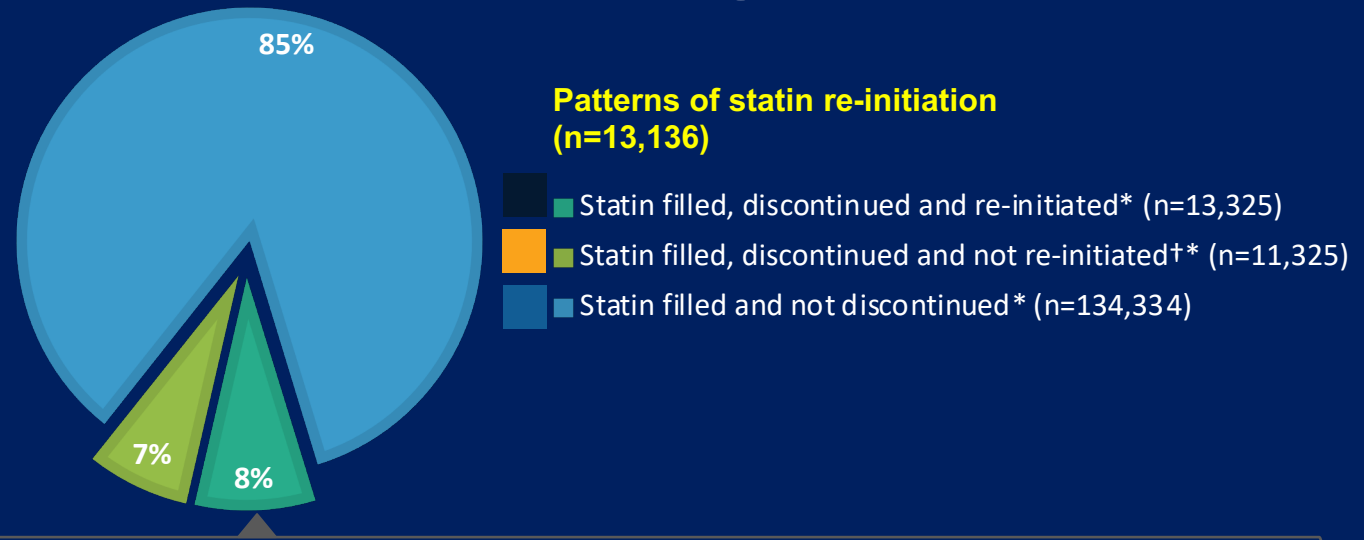
Not All Patients Have the Same LDL-C Response. JUPITER: Variable Change in LDL-C on Rosuvastatin

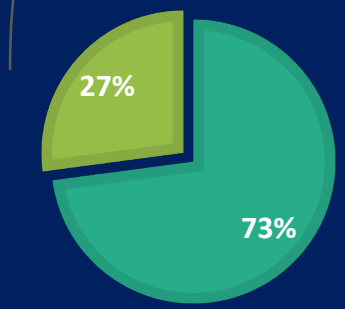


Ridker PM, et al. *Eur Heart J.* 2016;37(17):1373-1379.

Statin Discontinuation Rates are High

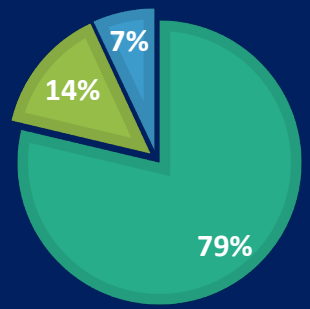
- Medicare beneficiaries with MI 2007-2012
- 15.4% Discontinued within 6 months
  - Only half re-started statin





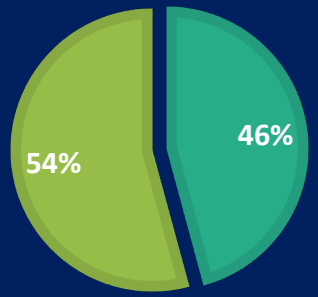
SAME DRUG

- Yes (n=9,574)
- No (n=3,562)



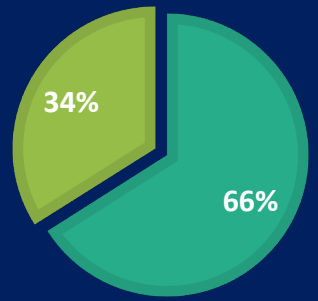
INTENSITY

- Yes (n=9,574)
- No (n=3,562)
- Lower



HIGH STATIN PERSISTENCE±

- Yes (n=6,019)
- No (n=7,117)



SAME DRUG AND INTENSITY

- Yes (n=8,665)
- No (n=4,471)

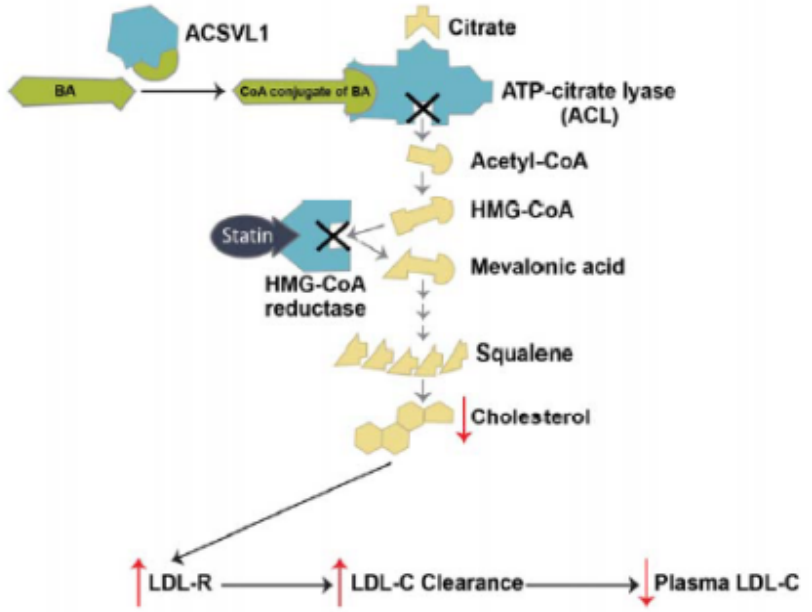
Booth JN. *Circ CV Qual Outcomes* 2017.10:e:003626

Adherence to Statin Therapy Is *Difficult* but *Important*

- Statins are generally well tolerated
  - >Three-quarters of the general population tolerates statin therapy, but
  - 10%-20% of patients prescribed a statin report statin *intolerance*
- Statins are very effective in preventing 1st/recurrent ASCVD across all LDL-C levels
- Rates of serious adverse events are very low
  - The risk of statin-induced serious muscle injury, including rhabdomyolysis, is <0.1%
  - The risk of serious hepatotoxicity is ≈0.001%
  - The risk of statin-induced newly diagnosed diabetes mellitus is ≈0.2% per year of treatment
- Large proportion (40%-70%) of patients *discontinue* statin therapy within 1-2 years, with resulting large *increase* in CVD risk
- Perceived vs real effect may play a role as multiple studies show *nocebo* effect
  - **Many patients *can* tolerate statins on *rechallenge* after reported statin *intolerance***

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

Bempedoic Acid Mechanism of Action



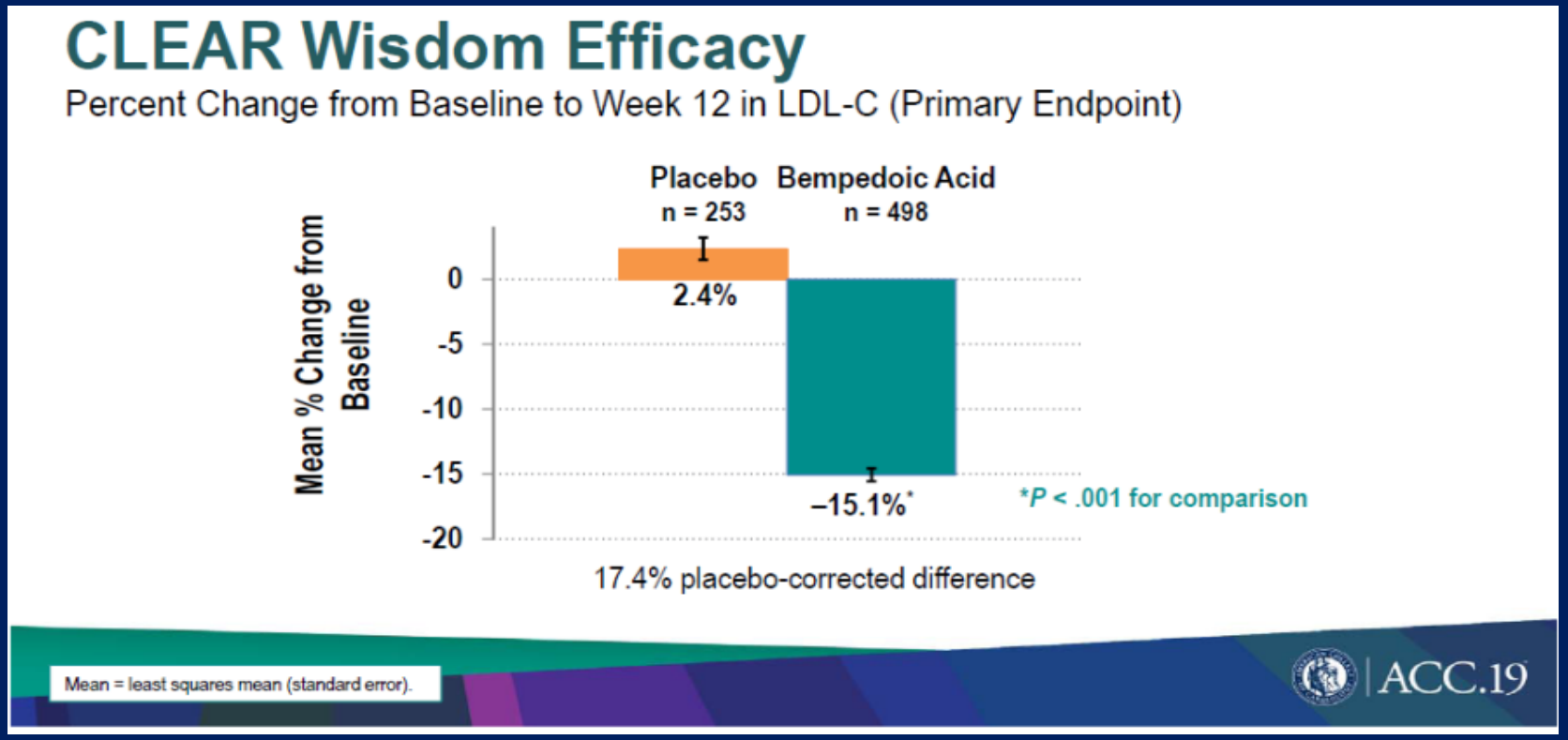
- Bempedoic acid is a prodrug activated in liver by very-long-chain acyl-CoA synthetase-1 (ACSVL1)
- Activated bempedoic acid acts in the same cholesterol synthesis pathway as statins
- Bempedoic acid inhibits ATP-citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase
- Bempedoic acid upregulates LDL receptors and lowers LDL-C
- Activated bempedoic acid is not present in skeletal muscle

For review see: Pinkosky SL, et al. *Nat Commun.* 2016:28;7:13457.
BA, bempedoic acid.

ACC.19

Bempedoic Acid and Bempedoic Acid-Ezebimibe FDA-Approved February 2020

Indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of LDL-C. The effect of on cardiovascular morbidity and mortality has not been determined. First oral, once-daily, non-statin LDL-C lowering medicine approved since 2002 for indicated patients.



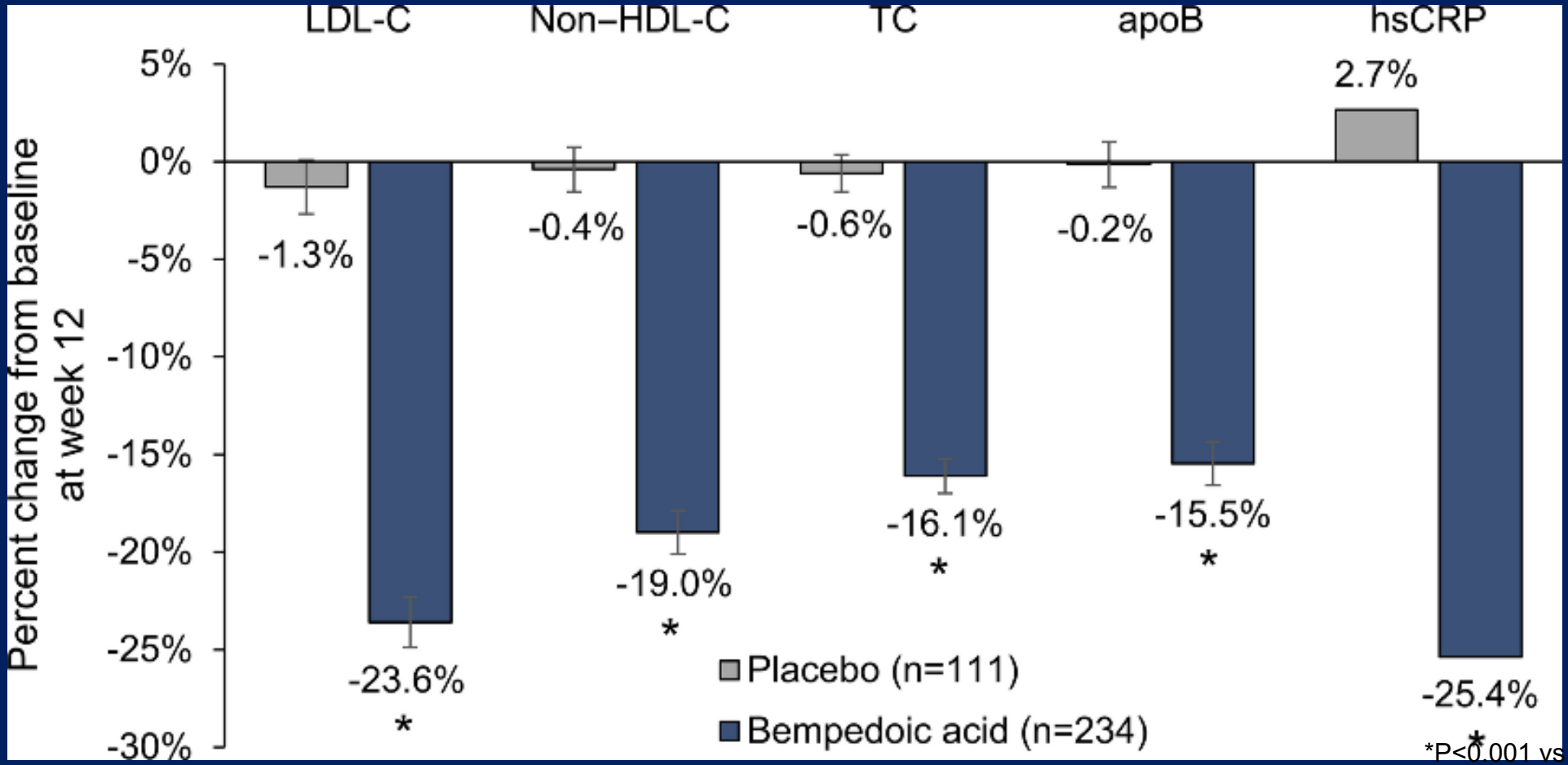
CLEAR HARMONY trial reported at ESC showed in 2000+ pts on maximially tolerated statin therapy placebo corrected LDL-C reduction of 16.8% in treated group.

Bempedoic Acid – Ezetimibe fixed dose combination provides 36% LDL-C lowering

Bempedoic acid trials showed no safety concerns.

CLEAR Serenity Trial Shows Bempedoic Acid Lowers LDL-C in Statin-Intolerant Patients. Now FDA-Approved

345 patients with hypercholesterolemia and a history of intolerance to at least 2 statins (1 at the lowest available dose) 2:1 to bempedoic acid 180 mg or placebo once daily for 24 weeks



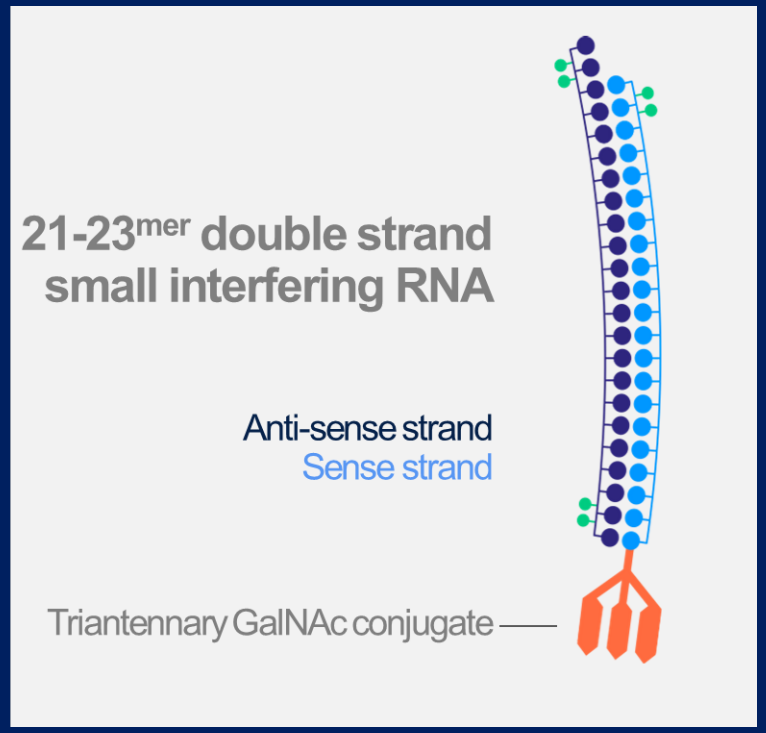
The ongoing CLEAR OUTCOMES trial will demonstrate whether bempedoic acid provides further CV event risk reduction beyond statin therapy

*P<0.001 vs placebo.

Laufs U, et al. *J Am Heart Assoc*. 2019;8:e011662.

ORION-11: Background and rationale

Harnessing the natural process of RNAi



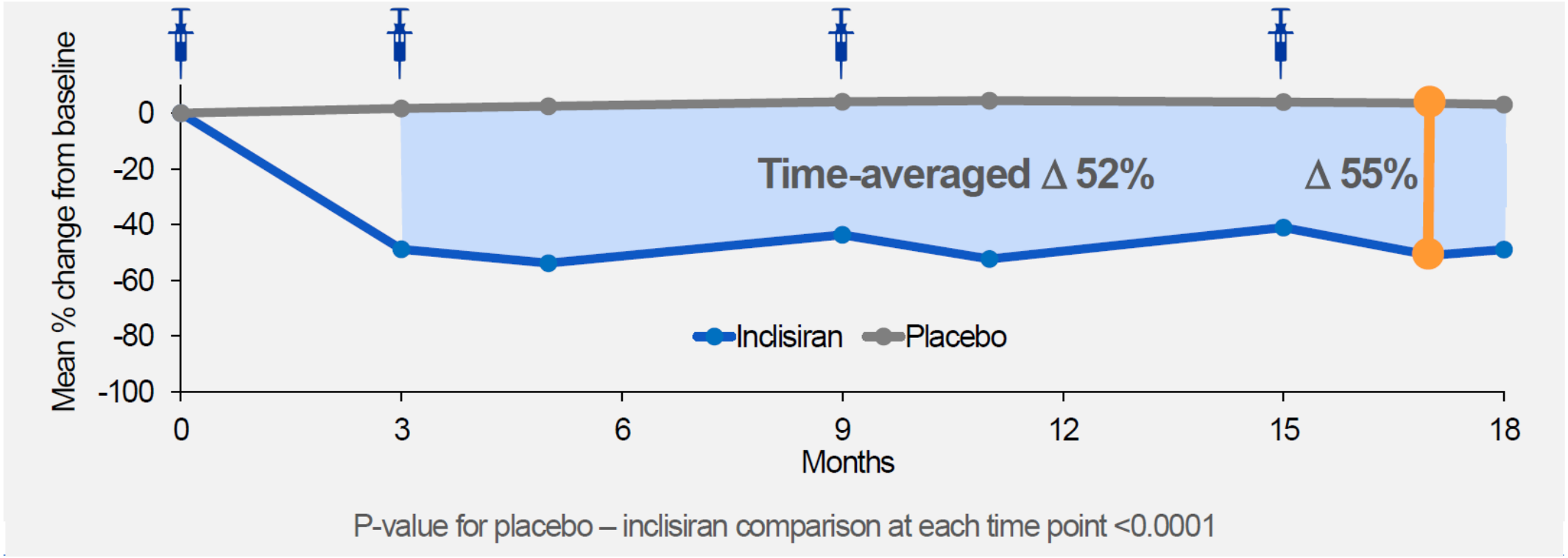
Small interfering double-stranded RNA

- Harnesses the natural process of RNAi
- Nucleotides modified for durability and low immunogenicity
- Distributed to liver due to GalNAc conjugation
- Inhibits production of PCSK9 specifically, durably and potently

ORION Phase III pooled analysis: Efficacy

Durable and potent with consistent effect over 18 months

Percent change in LDL-C over time – observed values in ITT patients



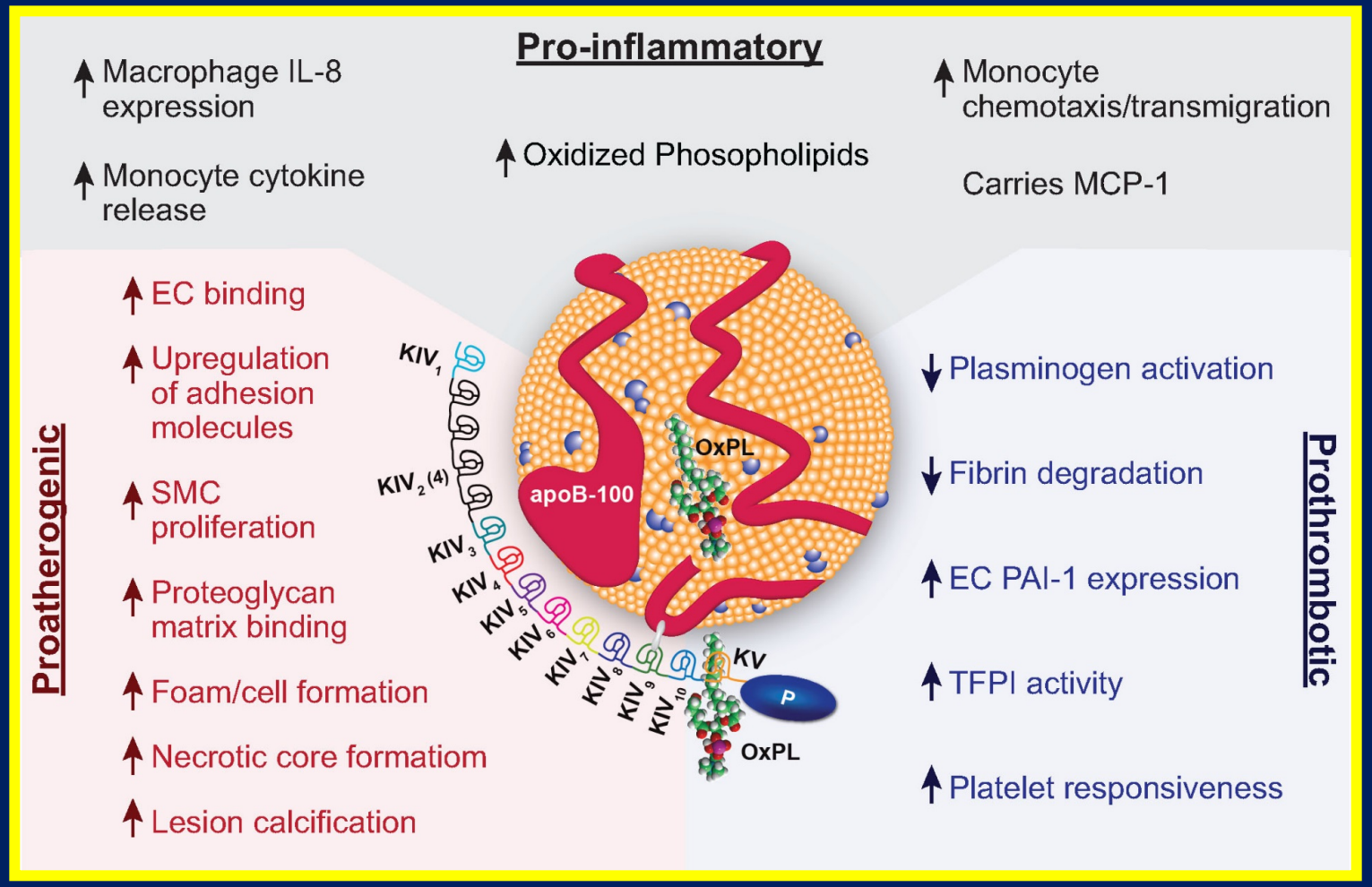
P-value for placebo – inclisiran comparison at each time point <0.0001

1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

Wright RS, et al. Presented at American College of Cardiology Scientific Session; March 28-30, 2020.

Inclisiran's ongoing cardiovascular outcomes trial will examine whether inclisiran provides further CV event reduction beyond statin therapy

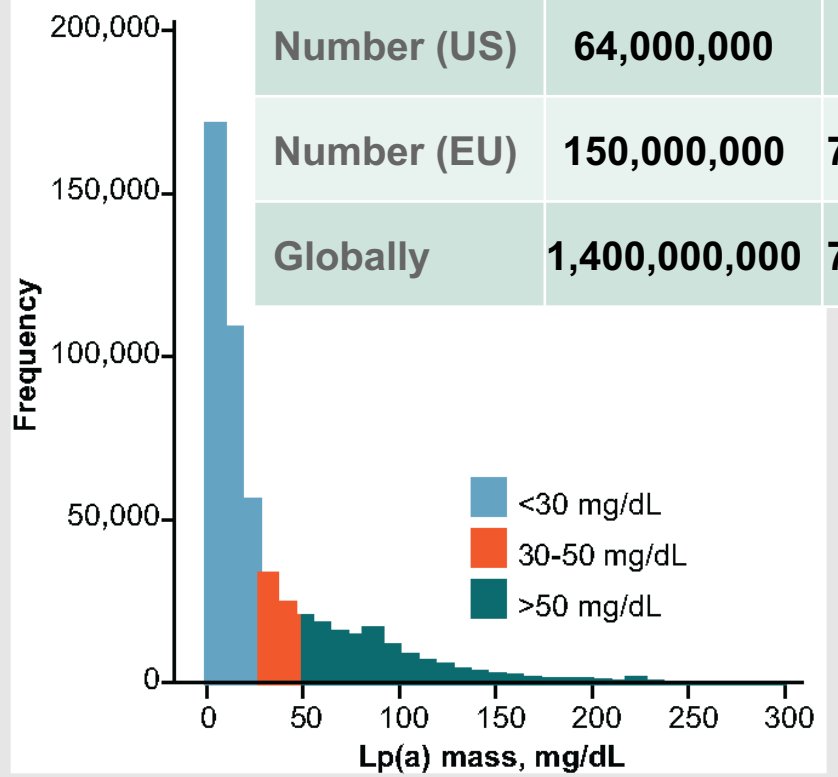
What are the mechanisms through which Lp(a) mediates CVD and Aortic Valve Stenosis?



Tsimikas JACC 2017

Prevalence of Lp(a) Levels in United States in 531,144 patients, and by Inference Globally

Lp(a) distribution in general population extrapolated from the graph					
Prevalence	20%	10%	5%	1%	0.1%
Lp(a) levels	60 mg/dL	90 mg/dL	116 mg/dL	180 mg/dL	245 mg/dL
Number (US)	64,000,000	32,000,000	16,000,000	3,200,000	320,000
Number (EU)	150,000,000	750,000,000	37,500,000	7,500,000	750,000
Globally	1,400,000,000	700,000,000	350,000,000	70,000,000	7,000,000



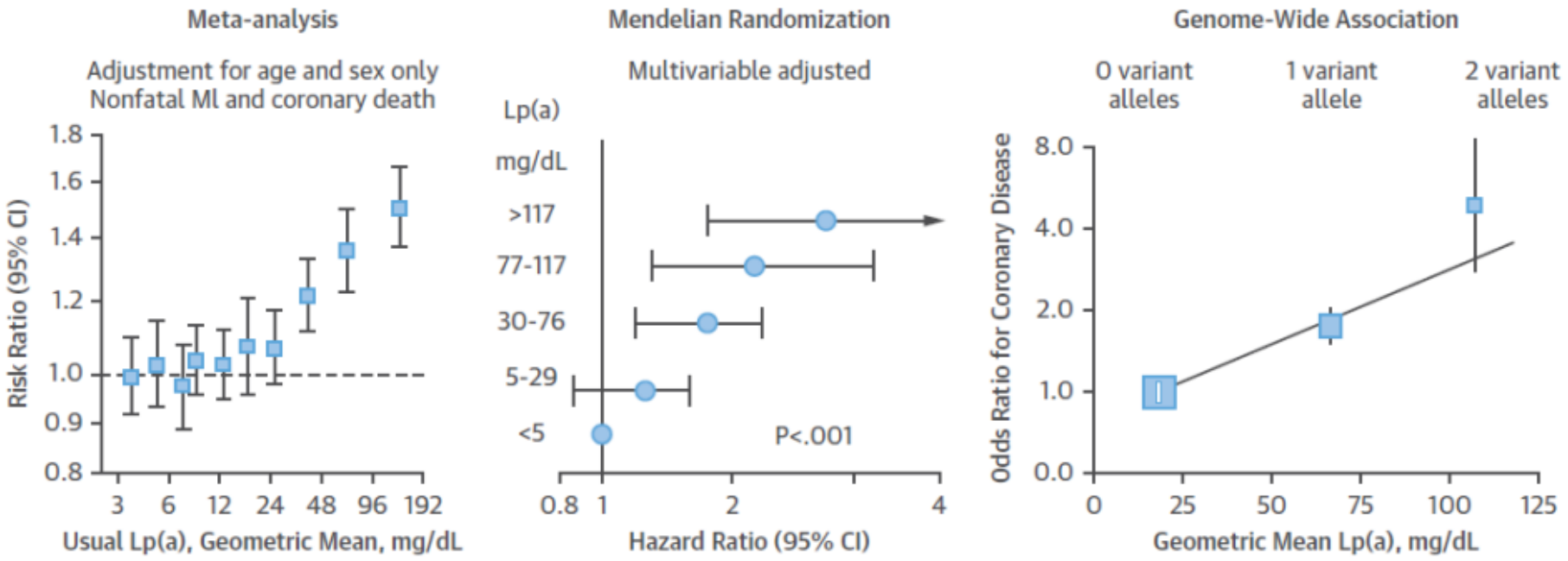
Estimated prevalence assumes:

320M in US, 750M in EU, and 7B globally

US guidelines recommend screening ASCVD pts
ESC guidelines recommend universal screening at least once in adulthood

Varvel et al. ATVB. 2016

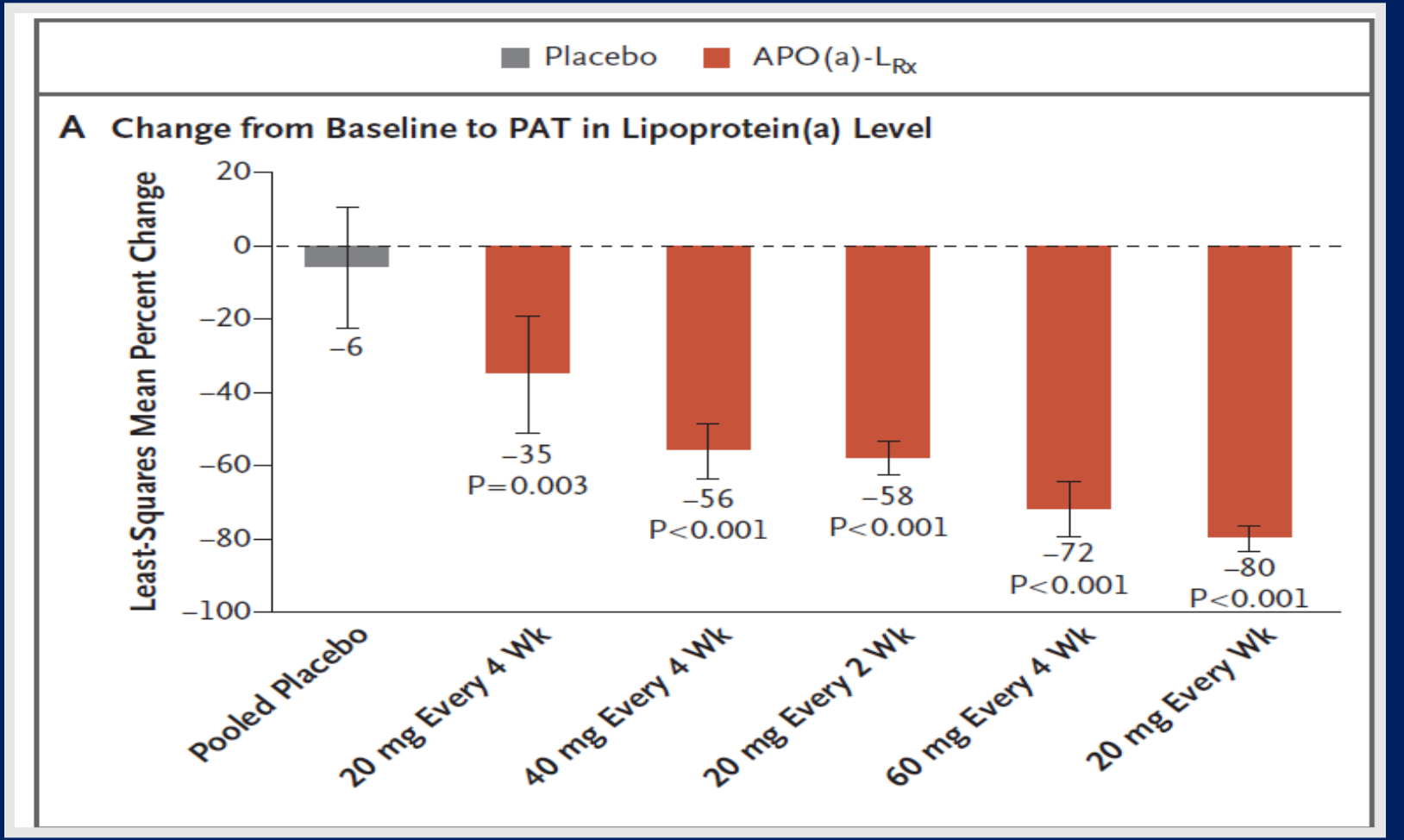
FIGURE 4 Evidence Base for Lp(a) as an Independent, Causal, Genetic Risk Factor for CVD



Epidemiological, meta-analyses, Mendelian randomization, and genome-wide association studies demonstrate that genetically elevated lipoprotein(a) [Lp(a)] leads to higher risk for cardiovascular disease (CVD) events, particularly acute myocardial infarction. Reprinted with permission from the Emerging Risk Factors Collaboration (25), Clarke et al. (27), and Kamstrup et al. (30). CI = confidence interval; MI = myocardial infarction.

Tsimikas JACC 2017

Effect of APO(a)-L_{RX} on Lp(a)

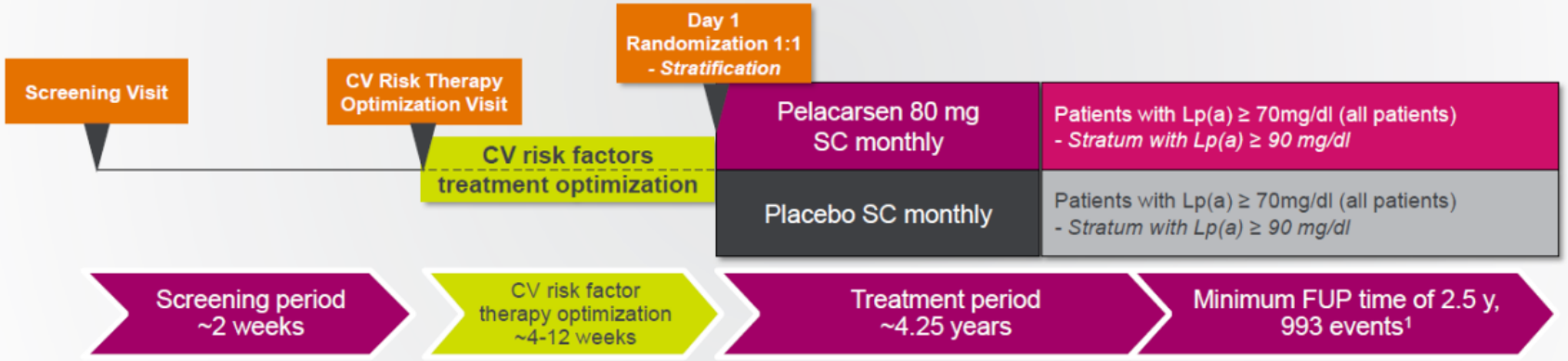


AKCEA-APO(a)-L_{Rx} is an **antisense oligonucleotide** targeting LPA mRNA (which encodes the main Lp(a) constituent, **apolipoprotein**(a)

Tsimikas S., et al. NEJM Jan 1 2020

Pelacarsen Phase 3 Lp(a)HORIZON Study

- Multicenter, randomized, double-blind, placebo-controlled study in 7,680 patients with elevated Lp(a) levels (≥ 70 mg/dL) and history of CVD (myocardial infarction, ischemic stroke, peripheral artery disease)
- Co-Primary endpoints: 1) time to first major adverse cardiovascular event in patients with Lp(a) levels of ≥ 70 mg/dL or 2) patients with Lp(a) levels of ≥ 90 mg/dL. Significance of either endpoint will be considered a positive trial



Enrollment underway • Fast Track Designation
Data expected in 2024

IONIS™

1. A total sample size of 7,680 subjects is required to obtain 993 primary endpoint MACE events. CV: cardiovascular; SC: subcutaneous; MACE: major cardiovascular events

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

New (December 2019)

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

Prior (July 2012)

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

Released December 13, 2019. *After* https://amarincorp.com/docs/Vascepa-PI.pdf

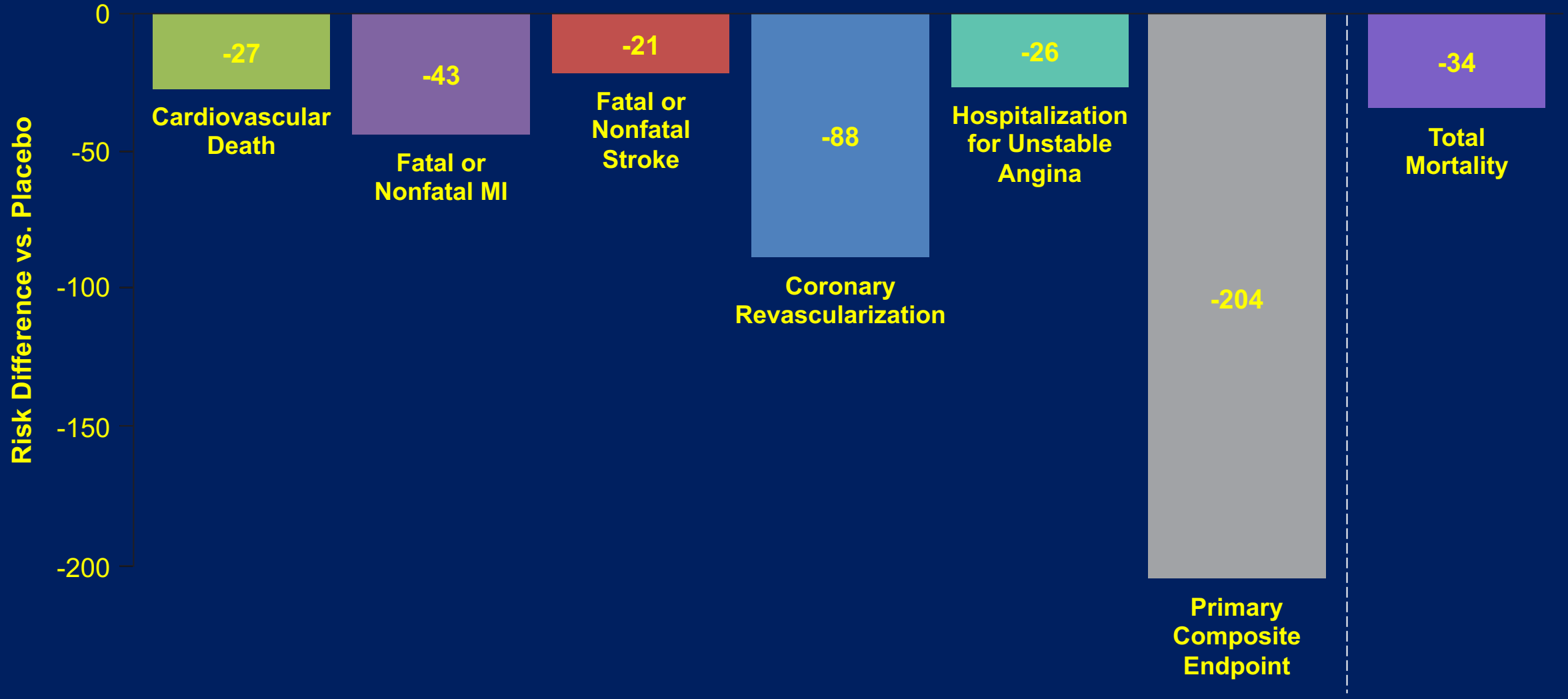
New Guidelines/Recommendations for Icosapent Ethyl to Prevent ASCVD in Patients

Scientific Society	Treatment with Statin and Icosapent Ethyl for ASCVD Risk Reduction
American Diabetes Association (ADA)	In patients with ASCVD or other cardiac risk factors with controlled LDL-C, but elevated triglycerides (135-499)
European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS)	In high-risk (or above) patients with TG levels between 135-499 mg/dL, n-3 PUFAs (icosapent ethyl 2x2 g/day) should be considered in combination with a statin
National Lipid Association (NLA)	For patients 45 years of age or older with clinical ASCVD, or 50 years of age or older with diabetes mellitus requiring medication and ≥1 additional risk factor, with fasting TG 135-499 mg/dL
American Heart Association (AHA)	The use of n-3 FA (4 g/d) for improving atherosclerotic cardiovascular disease risk in patients with hypertriglyceridemia is supported by a 25% reduction in major adverse cardiovascular events in REDUCE-IT
American Association of Clinical Endocrinologists (AACE) / American College of Endocrinology (ACE)	If TG 135-499, add icosapent ethyl 4 g/day if high ASCVD risk on maximally tolerated statins

ASCVD, atherosclerotic cardiovascular disease; HTG, hypertriglyceridemia; LDL-C, low-density lipoprotein cholesterol; PUFA, polyunsaturated fatty acids; TG, triglyceride.

American Diabetes Association [web annotation]. *Diabetes Care.* 2019;42(Suppl. 1):S103-S123. Retrieved from https://hyp.is/JHhz_lCrEembFJ9LIVBZIw. Mach F, et al. *Eur Heart J*. 2020;41(1):111-188. Orringer CE, et al. *J Clin Lipidol.* 2019;13(6):860-872. Skulas-Ray AC, et al. *Circulation.* 2019;140(12):e673-e691. Arnold SV, et al. *Circulation*. 2020;141(19):e779-e806. Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139.

Decrease in Total Events For Every 1000 US Patients on Icosapent Ethyl 4 gm/day for 5 Years



Bhatt DL, et al. *N Engl J Med.* 2019;380(1):11-22. Bhatt DL, et al. *Circulation.* 2019;141(5):367-375.
Bhatt DL. AHA Scientific Sessions 2019, Philadelphia, PA.

REDUCE-IT Eligibility and Preventable Cardiovascular Events in the US Population (from the National Health and Nutrition Examination Survey [NHANES])

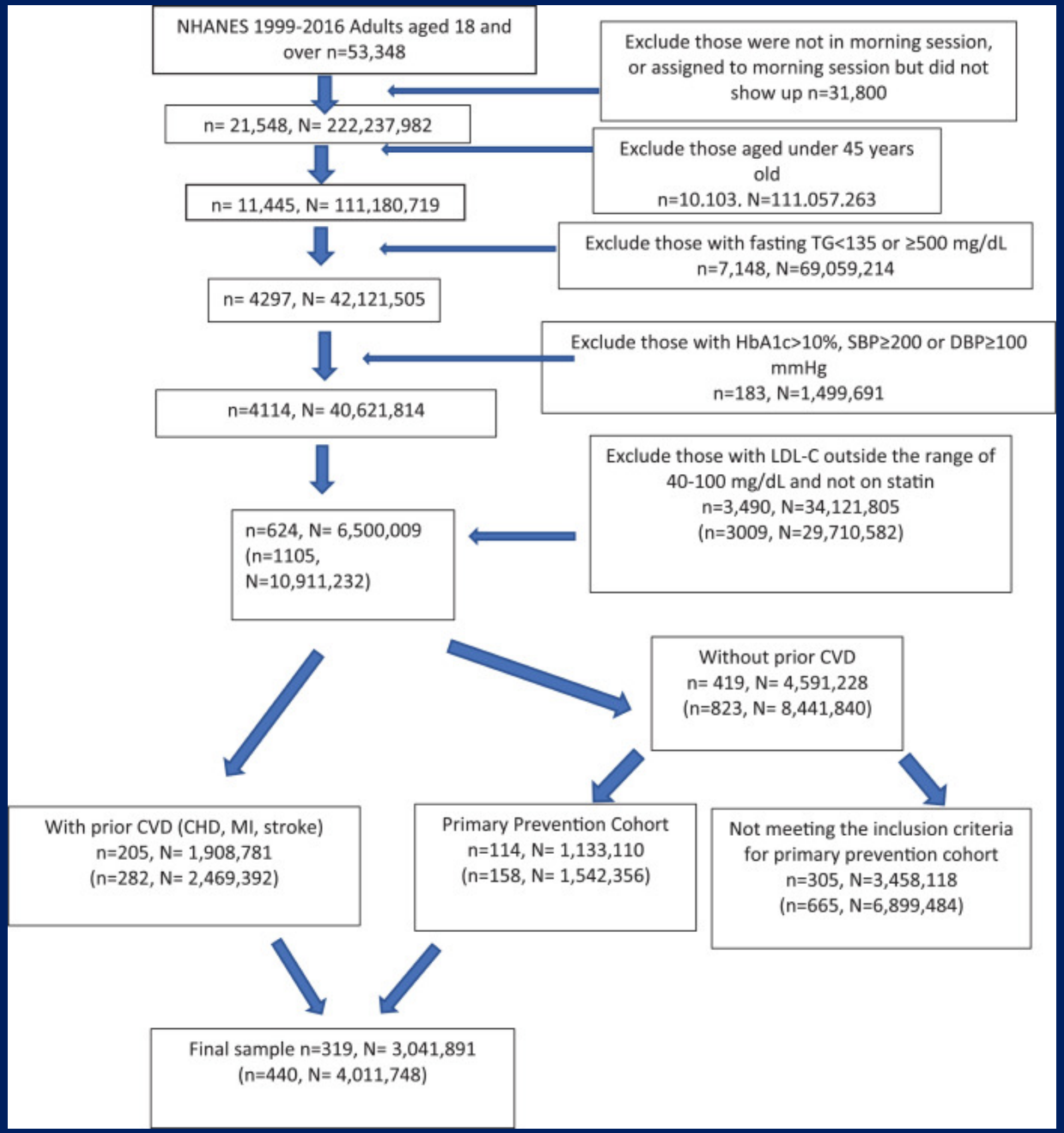
Nathan D. Wong, PhD, MPH[a,*], Wenjun Fan, MD, MS[a], Sephy Philip, RPh, PharmD[b], Craig Granowitz, MD, PhD[b], and Peter P. Toth, MD, PhD[c]

Wong ND et al., Am J Cardio 2020

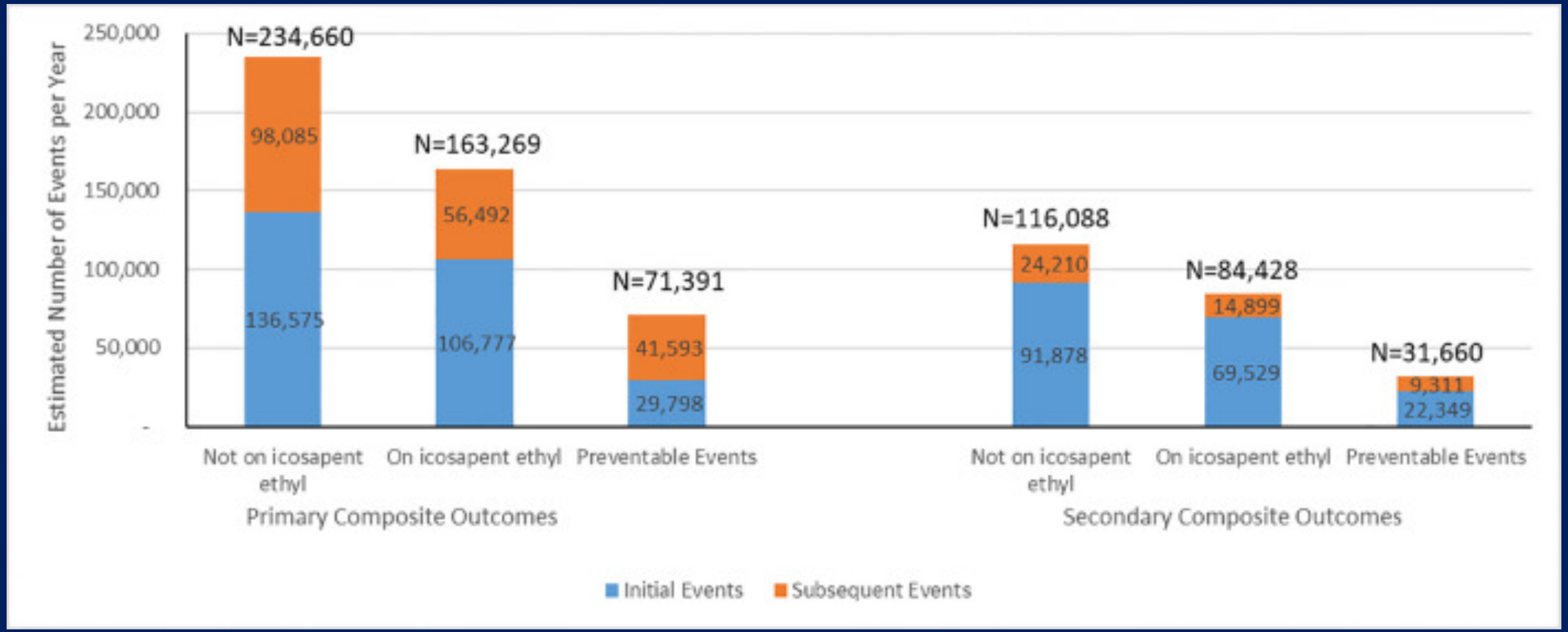
- Given the significant 25% and 30% reductions in the primary and secondary ASCVD endpoints of REDUCE-IT estimated the number of US adults who could potentially benefit from IPE based on REDUCE-IT eligibility criteria or FDA indications
- We also estimated the number of potentially preventable ASCVD events from its use based on REDUCE-IT eligibility criteria and FDA indications.

Methods

- We identified US adults aged ≥20 years with available REDUCE-IT inclusion criteria from the National Health and Nutrition Examination Survey (NHANES) 1999-2016.
- In a secondary analysis, re-calculated the eligible population based on the label approved by the US FDA for IPE: (1) Adults aged 18 and over with elevated triglyceride level (≥150 mg/dL) (2) have either established ASCVD or DM with ≥2 additional risk factors as mentioned above, and (3) statin therapy, but w/o specified LDL-C inclusion levels.
- Estimated expected ASCVD events including primary composite end points (CV death, nonfatal MI, stroke, revascularization, or unstable angina), secondary composite end point (CV death, nonfatal MI, or stroke), and individual endpoints including (CV death, revascularization, nonfatal MI, stroke, and total mortality) from REDUCE-IT initial and total published event rates in the IPE and placebo groups, with the difference being the number of preventable events.


NHANES 1999-2016 Adults aged 18 and over n=53,348
Exclude those were not in morning session, or assigned to morning session but did not show up n=31,800
n= 21,548, N= 222,237,982
Exclude those aged under 45 years old
n=10.103. N=111.057.263
n= 11,445, N= 111,180,719
Exclude those with fasting TG<135 or ≥500 mg/dL
n=7,148, N=69,059,214
n= 4297, N= 42,121,505
Exclude those with HbA1c>10%, SBP≥200 or DBP≥100 mmHg
n=183, N=1,499,691
n=4114, N= 40,621,814
Exclude those with LDL-C outside the range of 40-100 mg/dL and not on statin
n=3,490, N=34,121,805
(n=3009, N=29,710,582)
n=624, N= 6,500,009
(n=1105,
N=10,911,232)
Without prior CVD
n= 419, N= 4,591,228
(n=823, N= 8,441,840)
With prior CVD (CHD, MI, stroke)
n=205, N= 1,908,781
(n=282, N= 2,469,392)
Primary Prevention Cohort
n=114, N= 1,133,110
(n=158, N= 1,542,356)
Not meeting the inclusion criteria for primary prevention cohort
n=305, N=3,458,118
(n=665, N=6,899,484)
Final sample n=319, N= 3,041,891
(n=440, N= 4,011,748)

Annual projected initial and subsequent preventable primary and secondary composite end point events in the United States if on icosapent ethyl, NHANES 1999-2016.



Preventable ASCVD Events: Individual Endpoints

Weighted number and absolute event rate of expected preventable cardiovascular outcomes if on icosapent ethyl, NHANES 1999-2016 (n = 319 weighted to 3.0 M)

	If not on icosapent ethyl			If on icosapent ethyl			Preventable Events		
Variable	No.	%	Events/year	No.	%	Events/year	No.	%	Events/year
Primary composite	669,216	22.0%	136,575	523,205	17.2%	106,777	146,011	4.8%	29,798
Total Primary composite	1,149,835	37.8%	234,660	800,017	26.3%	163,269	349,817	11.5%	71,391
Key secondary composite	450,200	14.8%	91,878	340,692	11.2%	69,529	109,508	3.6%	22,349
Total secondary composite	568,834	18.7%	116,088	413,697	13.6%	84,428	155,136	5.1%	31,660
Cardiovascular death or nonfatal myocardial infarction	377,194	12.4%	76,978	292,022	9.6%	59,596	85,173	2.8%	17,382
Fatal or nonfatal myocardial infarction	264,645	8.7%	54,009	185,555	6.1%	37,868	79,089	2.6%	16,141
Urgent or emergency revascularization	237,267	7.8%	48,422	161,220	5.3%	32,902	76,047	2.5%	15,520
Cardiovascular death	158,178	5.2%	32,281	130,801	4.3%	26,694	27,377	0.9%	5,587
Hospitalization for unstable angina	115,592	3.8%	23,590	79,089	2.6%	16,141	36,503	1.2%	7,450
Fatal or nonfatal stroke	100,382	3.3%	20,486	73,005	2.4%	14,899	27,377	0.9%	5,587
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	514,080	16.9%	104,914	407,613	13.4%	83,186	106,466	3.5%	21,728
*Death from any cause	231,184	7.6%	47,180	203,807	6.7%	41,593	27,377	0.9%	5,587

Eligible sample from NHANES 1999-2016 was 319 (projected to 3,041,891 people). Numbers are displayed as the population weighted sample size based on a median follow-up time of 4.9 years. Absolute event rate of expected CVD and event/person year was based Figure 4 from Bhatt et al.[4]

*Indicates end point that was not statistically significant in the main trial.

Preventable ASCVD Events According to Primary and Secondary Prevention Cohorts

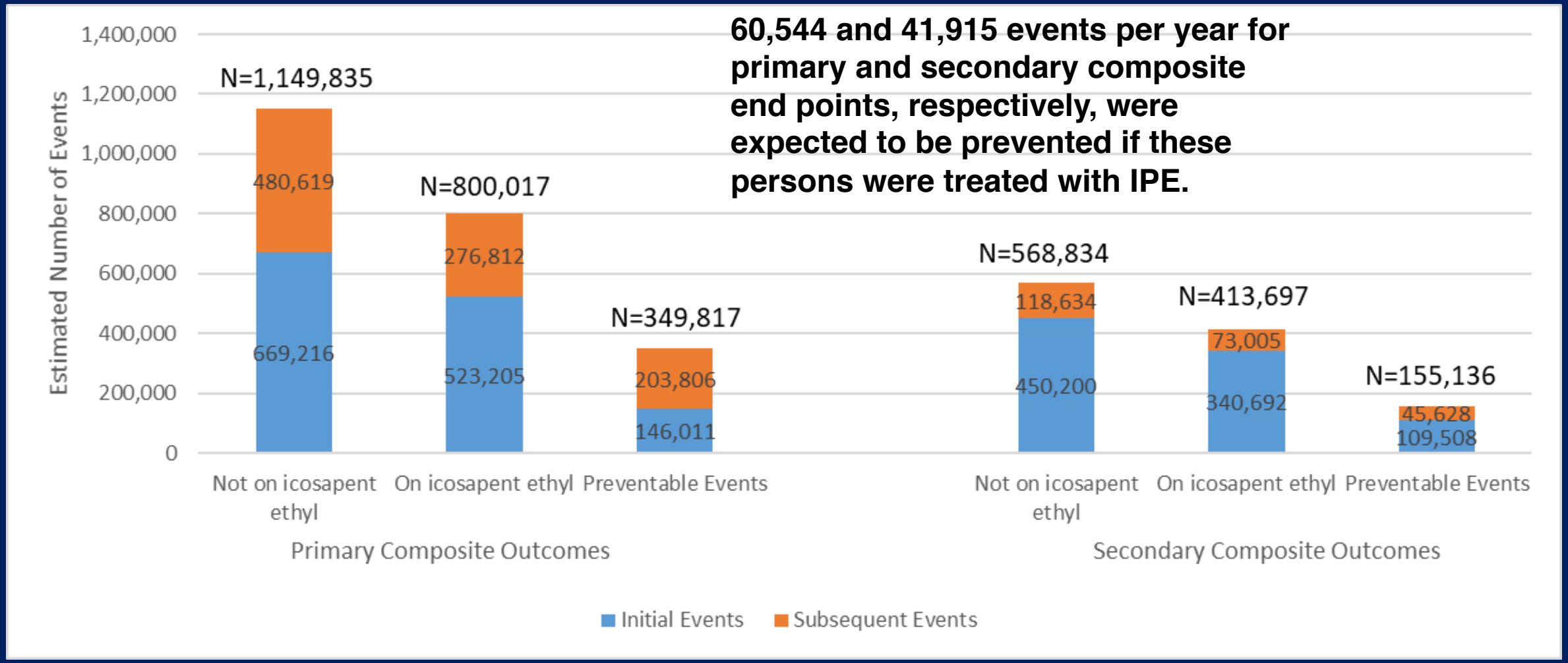
Weighted number and absolute initial event rate of expected preventable cardiovascular outcomes if on icosapent ethyl stratified by risk category, NHANES 1999-2016

	If not on icosapent ethyl			If on icosapent ethyl			Preventable Events		
	No.	%	Events/year	No.	%	Events/year	No.	%	Events/year
***Primary Prevention Cohort (n=114, N= 1,133,110)**									
Primary Composite	154,103	13.6%	31,450	138,239	12.2%	28,212	15,864	1.4%	3,238
Secondary Composite	111,045	9.8%	22,662	92,915	8.2%	18,962	18,130	1.6%	3,670
Secondary Prevention Cohort (n=205, N= 1,908,781)									
Primary Composite	486,739	25.5%	99,334	368,385	19.3%	75,183	118,344	6.2%	24,151
Secondary Composite	322,584	16.9%	65,833	238,598	12.5%	48,693	83,986	4.4%	17,140

Numbers are displayed as the population weighted sample size.

*Indicates subgroup not statistically significant for primary or secondary composite outcomes from the original trial published by Bhatt et al,[4] in subgroup analyses.

Distribution of total projected first and subsequent preventable primary and secondary composite endpoint events in the US if on icosapent ethyl based on FDA Eligibility Criteria, NHANES 1999-2016



Conclusions

- In conclusion, we estimate approximately 3 million US adults would be eligible for IPE with over 70,000 total ASCVD events that could be prevented annually (and nearly 30,000 initial events) based on the REDUCE-IT trial event rates.
- In addition, with the slightly greater risk reductions seen in REDUCE-IT USA,[6] including significant reductions in total mortality, a greater number of preventable events and deaths would be preventable based on these estimates.
- Finally, if FDA indications are utilized, eligible individuals and preventable events are increased by approximately 50%. Further studies should address the economic impact of IPE if applied to eligible patients to inform us of appropriate costs to achieve acceptable cost-effectiveness thresholds, as well as long-term benefits not addressed by REDUCE-IT

Summary

- Therapeutics targeting two lipid pathways, LDL-C, and triglycerides are now proven and approved to reduce ASCVD events
- Statin therapy selection and dosing should be based on the level of ASCVD risk
- While adherence to statin therapy is difficult, many patients can tolerate statins on rechallenge after reported statin intolerance
- New FDA indication (2019) for icosapent ethyl to reduce ASCVD events
- Multiple guidelines and scientific statements support its use for patients w/HTG:
  - *If* TG 135-500, despite LDL-C control with statin therapy, and
  - *If* Prior CVD, or DM2 + additional risk, then
  - IPE 4 g/d recommended to **↓CVD**
  - Non-IPE and dietary supplement omega-3 *not* recommended
- Icosapent ethyl is relatively safe and cost effective

56-year-old male with sudden cardiac death

- 56-year-old South Asian physician with no significant past medical history.
- Cardiac risk factors
  - Dyslipidemia (LDL-C 176 mg/dL and TG 261 mg/dL)
  - FH of premature CAD (father died of an MI at age 45)
- While attending a medical conference, he “felt funny” then went into cardiac arrest.
- Promptly resuscitated by physicians in the area, taken to cath lab where a proximal LAD lesion was stented.

56-year-old male with sudden cardiac death

- Treated for STEMI with guideline directed medical therapy including high intensity statin.
- LDL-C decreased to 88 mg/dL then 65 mg/dL after addition of ezetimibe.
- TG decreased to 190 mg/dL.

Question: What therapy would you recommend now?

1. None; follow-up in 3 months
2. Prescribe a PCSK9 inhibitor
3. Prescribe a fibrate and a PCSK9 inhibitor
4. Prescribe a generic EPA+DHA omega-3 fatty acid
5. Prescribe icosapent ethyl

Preventive Cardiology Program

Take control of your health

Life-threatening cardiac events often can be prevented through early diagnosis, risk assessment, treatment and lifestyle changes.

The UC Irvine Health Preventive Cardiology Program uses the latest evidence-based guidelines for cardiovascular disease prevention. Services include:

- Initial evaluation by cardiologist, plus follow-up to track progress
- Comprehensive laboratory measures for cardiac risk factors and biomarkers, plus further evaluation with optional imaging tests
- Computerized cardiovascular risk profiles and risk scoring
- Comprehensive dietitian consultation with a specific focus on cardiovascular risk factor management
- Physical activity prescriptions and consultations with an exercise specialist
- A full report sent to the patient's referring physician when the program is finished

Our preventive cardiology program's multidisciplinary team includes:

- Cardiologists
- Registered dietitian
- Exercise physiologist
- Prevention researchers/ specialists

Our program can help you if you have been diagnosed with at least one risk factor for cardiovascular disease, including:

- Hypertension
- Hypercholesterolemia/ dyslipidemia
- Metabolic syndrome
- Diabetes
- Cigarette smoking

Patients with pre-existing cardiovascular disease who need more guidance with risk factor modification to prevent disease progression or recurrence are also ideal candidates.

To learn more, call 714-456-6699.

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Thank You!