
New Era of ASCVD Lipid Risk Management

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Update on Risk Status in ASCVD

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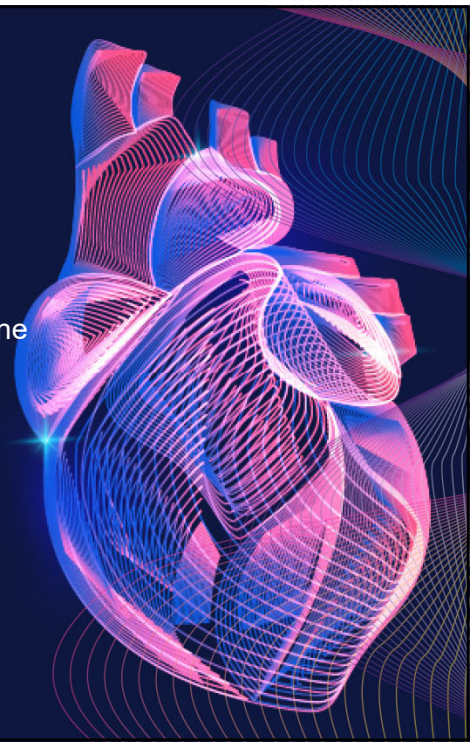

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Faculty Disclosure: James Underberg

Dr. Underberg discloses that he received grant/research support from Aegerion Pharmaceuticals and Pfizer, is a consultant for Amarin Corporation, Ambry, and Amgen, and receives honoraria from Amgen, Amarin, Regeneron, and Sanofi.

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Outline

- Who is at high risk for CVD events?
- ACC/AHA/Multisociety cholesterol guidelines approach to diagnosis: What's new?
- Screening and diagnosis, including fasting and nonfasting blood samples, non-HDLc assessment and CAC scoring
- Risk assessment based on ACC/AHA/Multisociety guidelines

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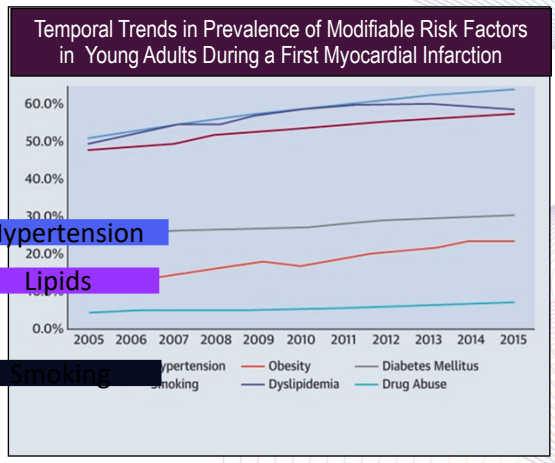
Modifiable Risk Factors in Acute Myocardial Infarction (AMI): Young Adults

Men	During a First Myocardial Infarction in Young Adults (18-59 Years) in the US		Women
25%	Diabetes Mellitus	> 1 in 4	34%
6%	Drug Abuse	> 1 in 20	5%
57%	Hypertension	> 1 in 2	61%
58%	Dyslipidemia	> 1 in 2	52%
16%	Obesity	> 1 in 6	23%
54%	Smoking	> 1 in 2	50%
92%	Any of these modifiable risk factors	> 9 in 10	91%



Yandrapalli S, et al. *J Am Coll Cardiol.* 2019;73(5):573-584

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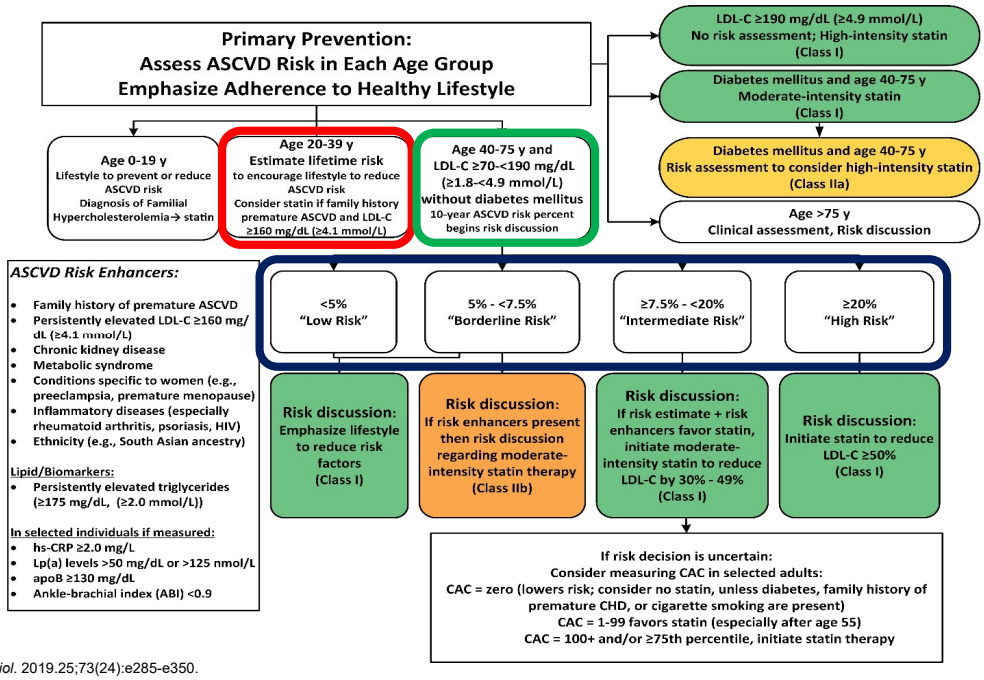
2018 Blood Cholesterol Guidelines:

Role of Risk Estimation in Primary Prevention



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

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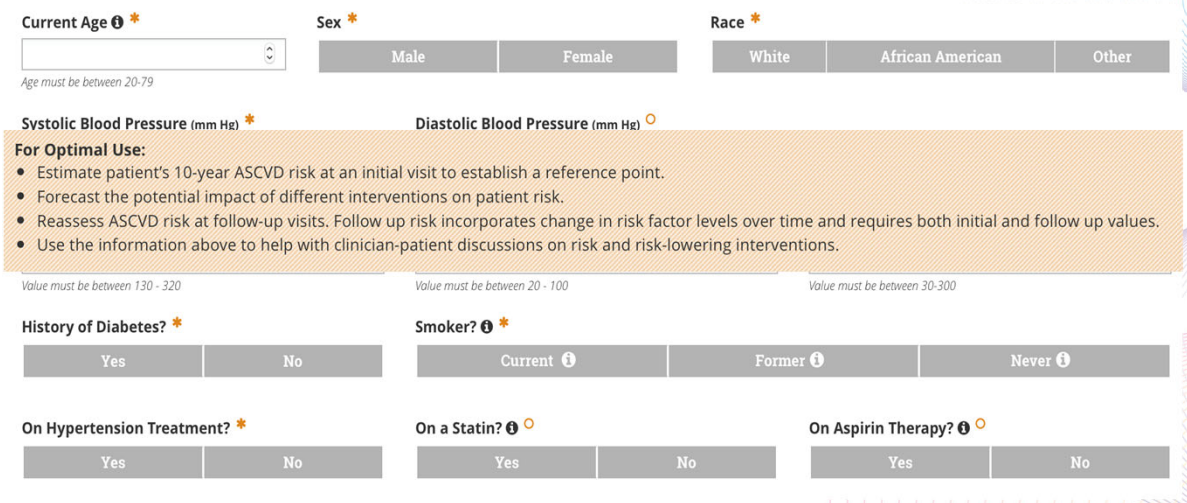
ACC ASCVD Risk Estimator Plus

App Should Be Used for Primary Prevention Patients (Those Without ASCVD) Only



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

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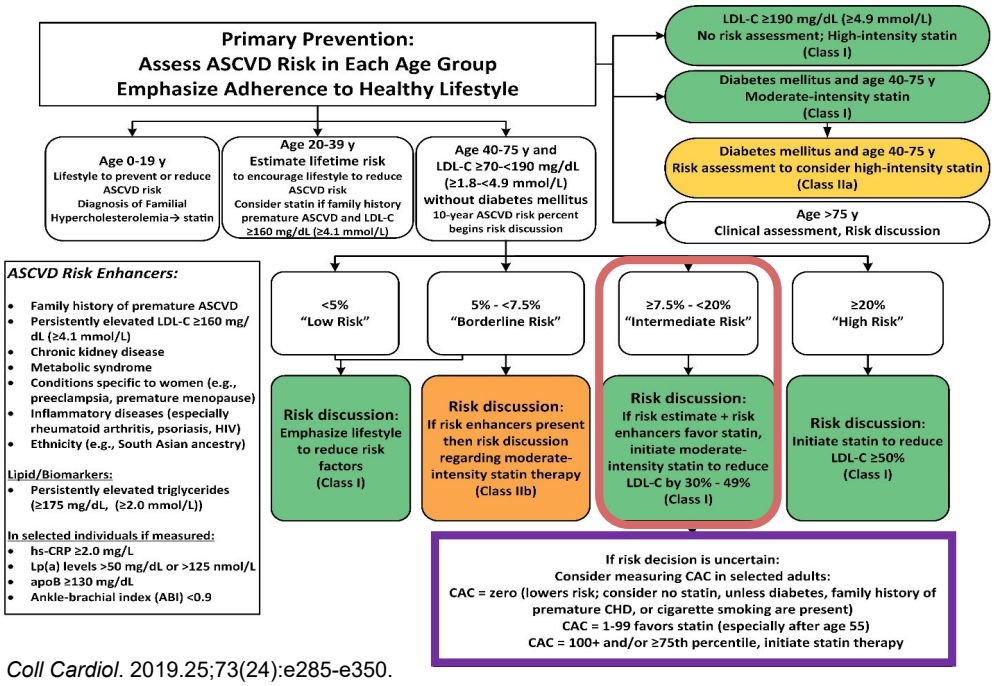
2018 Blood Cholesterol Guidelines:

Primary Prevention for Intermediate Risk



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

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Using 10-year ASCVD Risk Estimate Plus Coronary Artery Calcium (CAC) Score to Guide Statin Therapy

Patient's 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimate	<5%	5–7.5%	>7.5–20%	>20%
Consulting ASCVD risk estimate alone	Statin not recommended	Consider for statin	Recommend statin	Recommend statin
Consulting ASCVD risk estimate + CAC				
If CAC score = 0	Statin not recommended	Statin not recommended	Statin not recommended	Recommend statin
If CAC score > 0	Statin not recommended	Consider for statin	Recommend statin	Recommend statin
Does CAC score modify treatment plan?	CAC not effective for this population	CAC can reclassify risk up or down	CAC can reclassify risk up or down	CAC not effective for this population

Greenland P, et al. *J Am Coll Cardiol*. 2018;72(4):434–47.

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2018 Blood Cholesterol Guidelines

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

- Patients reluctant to initiate statin 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*. 2019.25;73(24):e285-e350.

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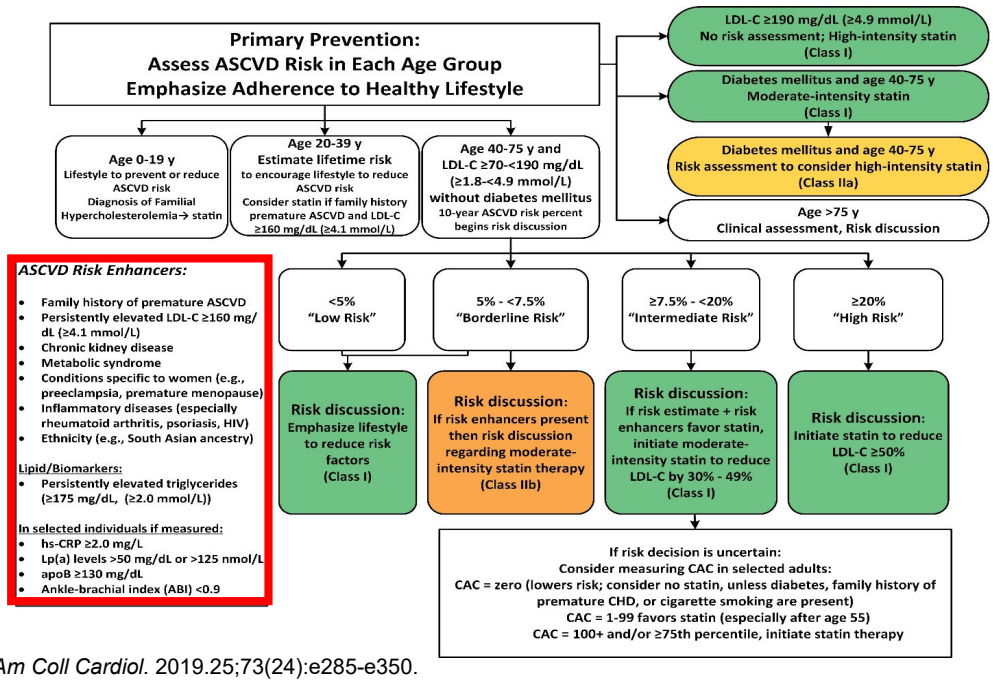
2018 Blood Cholesterol Guidelines:

ASCVD Risk Enhancers



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

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Measurements of LDL-C and Non-HDL-C

Recommendations for Measurements of LDL-C and Non-HDL-C		
COR	**LOE**	**Recommendations**
I	B-NR	In adults who are 20 years of age or older and not on lipid-lowering therapy, measurement of either a fasting or a nonfasting plasma lipid profile is effective in estimating ASCVD risk and documenting baseline LDL-C.
I	B-NR	In adults who are 20 years of age or older and in whom an initial nonfasting lipid profile reveals a triglycerides level of 400 mg/dL (≥4.5 mmol/L) or higher, a repeat lipid profile in the fasting state should be performed for assessment of fasting triglyceride levels and baseline LDL-C.

Recommendations for Measurements of LDL-C and Non-HDL-C		
COR	**LOE**	**Recommendations**
IIa	C-LD	For adults with an LDL-C level less than 70 mg/dL (<1.8 mmol/L), measurement of direct LDL-C or modified LDL-C estimate is reasonable to improve accuracy over the Friedewald formula.
IIa	C-LD	In adults who are 20 years of age or older and without a personal history of ASCVD but with a family history of premature ASCVD or genetic hyperlipidemia, measurement of a fasting plasma lipid profile is reasonable as part of an initial evaluation to aid in the understanding and identification of familial lipid disorders.

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

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Monitoring Response to Drug Therapy

- Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes and
  - Repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment
  - Repeat every 3 to 12 months as needed
- Responses to lifestyle and statin therapy are defined by percentage reductions in LDL-C levels compared with baseline.

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

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Patients with Primary Severe Hypercholesterolemia
LDL-C levels ≥190 mg/dL [≥4.9 mmol/L]

- Diagnosed Clinically
  - Patients with primary severe hypercholesterolemia (LDL-C levels ≥190 mg/dL [≥4.9 mmol/L]) have a high risk of ASCVD and premature and recurrent coronary events
  - Dutch Lipid Clinic Network, Simon Broome, MEDPED, AHA Criteria
  - Use FH Diagnosis app
- Diagnosed Genetically
  - Increased risk with positive mutation
- No FH Diagnosis with LDL >220 mg/dL
  - Very high risk and warrant aggressive LDL-lowering therapy

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

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2018 Blood Cholesterol Guidelines
Patients Who Need Primary Prevention

- Severe hypercholesterolemia – do not need risk-reduction scoring
- Patients with diabetes – role of assessing ASCVD risk
- Risk-reduction evaluation in patients without diabetes or severe hypercholesterolemia

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

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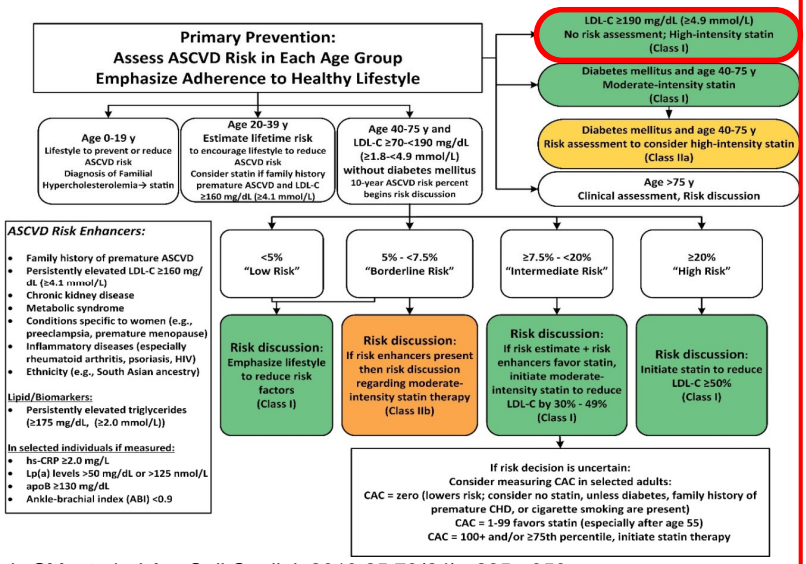
2018 Blood Cholesterol Guidelines

Role of PSCK9 in Primary Prevention in Severe Hypercholesterolemia



- In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered
- In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL (≥5.7 mmol/L) or higher and who achieve an on-treatment LDL-C level of 130 mg/dL (≥3.4 mmol/L) or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered

NYU Langone Health

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

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Diabetes-Specific Risk Enhancers Independent of Other Risk Factors (AHA/ACC Guidelines)

- Long duration (≥10 years for type 2 diabetes mellitus or ≥20 years for type 1 diabetes mellitus)
- Albuminuria ≥30 mcg of albumin/mg creatinine
- eGFR <60 mL/min/1.73 m^2
- Retinopathy
- Neuropathy
- ABI <0.9

ABI = ankle-brachial index; eGFR = estimated glomerular filtration rate

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

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2018 Blood Cholesterol Guidelines

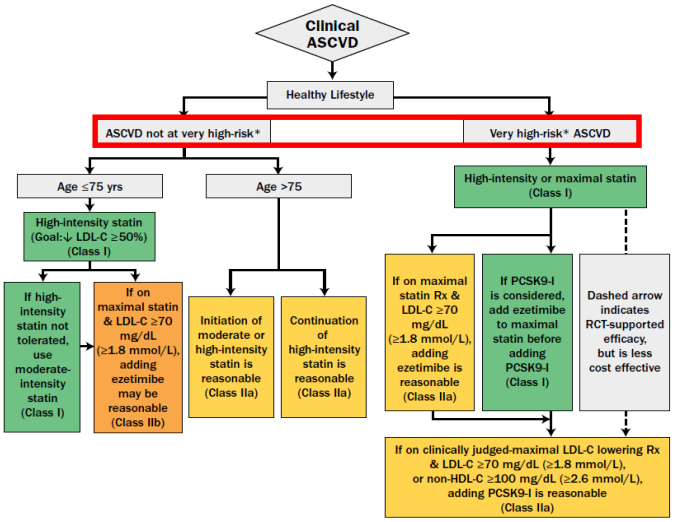
Secondary Prevention in Patients with Clinical ASCVD

High Risk Conditions

- Recent ACS
- History of prior MI
- History of ischemic stroke
- Symptomatic PAD

Additional Risk Factors

- Age ≥65 years
- HeFH
- Prior CABG or PCI
- Diabetes
- Hypertension
- Chronic kidney disease
- Current smoking
- LDL-C ≥ 2.6 mmol/L (100 mg/dL) despite maximally tolerated statin and ezetimibe
- History of HF
- Recurrent ASCVD events
- Major ASCVD event with ≥1 risk conditions



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

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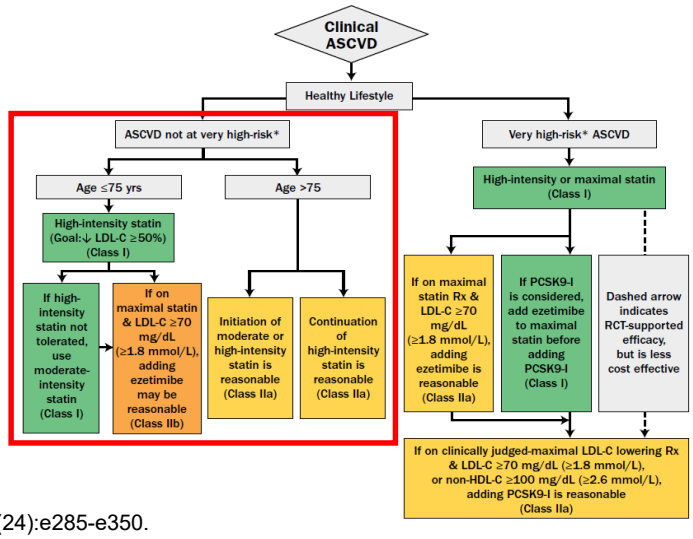
2018 Blood Cholesterol Guidelines

Secondary Prevention in Patients with Clinical ASCVD

In patients with *ASCVD **NOT** at VERY high risk*, it may be reasonable to add ezetimibe if inadequate lowering of LDL-C on maximally tolerated statin therapy.



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

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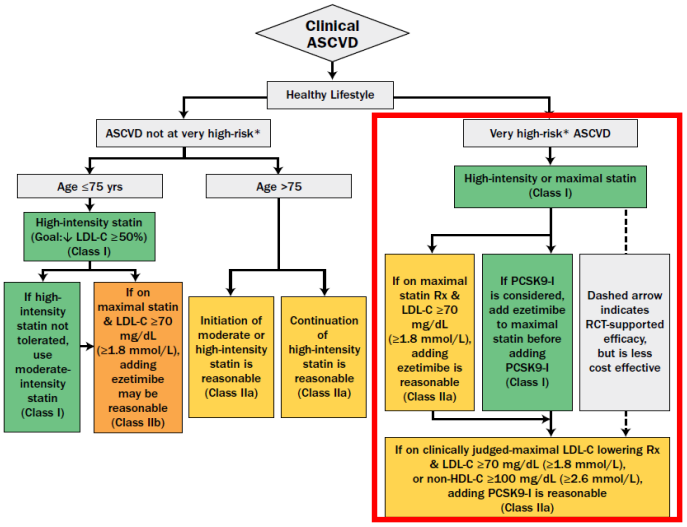
2018 Blood Cholesterol Guidelines

Secondary Prevention in Patients with Clinical ASCVD

In patients with ASCVD at **VERY** high risk, initiate ezetimibe prior to consideration of PCSK9i if inadequate lowering of LDL-C on maximally tolerated statin therapy.



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

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Case #1: Ms. P

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

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Case #1 (continued)

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

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Case #2: Mr. E

- 58-year-old male, nonsmoker
- Following aggressive diet and lifestyle program, has lost 18 lbs over past 4 months
- Diet mostly vegan with occasional shellfish
- T2 DM for 11 years, taking metformin, SGLT2 inhibitor, HbA1c 7.1%
- Rosuvastatin 20 mg
- BMI 27, father died of MI age 55
- Labs: LDLc 84, HDLc 38 mg/dL, TG 167 mg/dL, Total Cholesterol 155 mg/dL
- Next step ??

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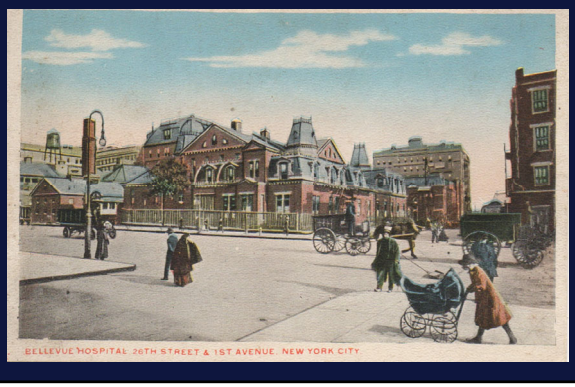
Thank You !



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New Approaches to the Management of Patients at High-Risk of ASCVD Events

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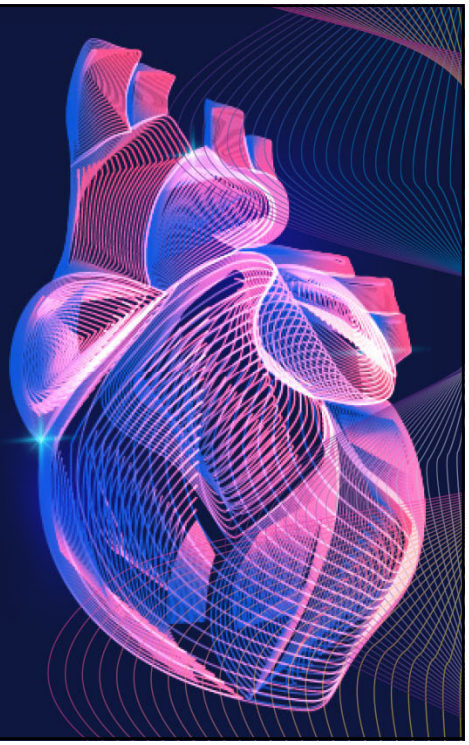

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Faculty Disclosure: Karol Watson

Dr. Watson discloses that she participates on the speaker's bureau for Boehringer Ingelheim and Eli Lilly and Company and is on the advisory board for Amgen, Amarin, Boehringer Ingelheim, Eli Lilly and Company, and Esperion.

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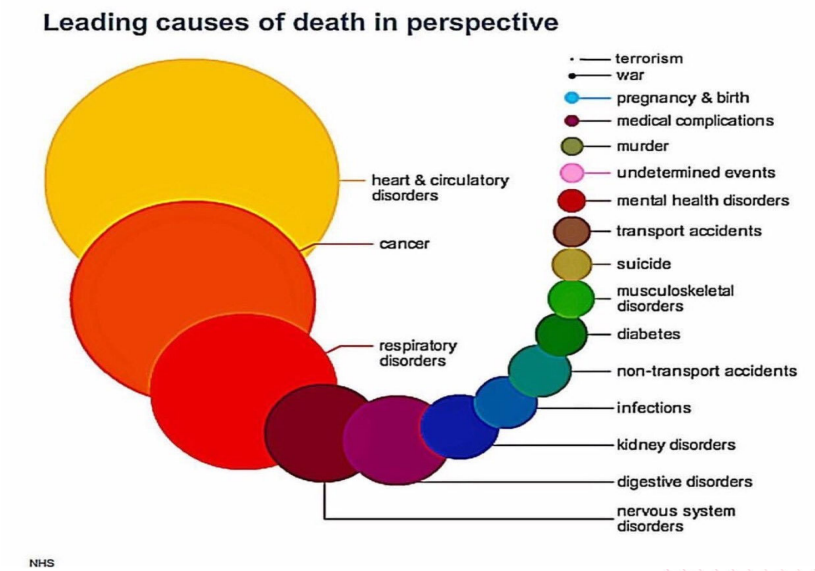
Leading Causes of Death in Perspective



2017 NHS statistics

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Agenda

- AHA's simple 7
- LDL-C lowering with statins
- LDL-C lowering beyond statins: ezetimibe and PCSK9 inhibitors
- Lipid guidelines for primary and secondary prevention of ASCVD

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AHA's Life Simple 7

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Agenda

- AHA's simple 7
- LDL-C lowering with statin intensification
- LDL-C lowering beyond statins: ezetimibe and PCSK9 inhibitors
- Lipid guidelines for primary and secondary prevention of ASCVD

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2013 ACC-AHA Cholesterol Guidelines

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Neil J. Stone, Jennifer Robinson, Alice H. Lichtenstein, C. Noel Bairey Merz, Conrad B. Blum, Robert H. Eckel, Anne C. Goldberg, David Gordon, Daniel Levy, Donald M. Lloyd-Jones, Patrick McBride, J. Sanford Schwartz, Susan T. Shero, Sidney C. Smith, Jr, Karol Watson and Peter W.F. Wilson

Circulation. published online November 12, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Stone NJ, et al. *Circulation*. 2014;129:S1-45

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Statin…statin…statin…

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Intensity of Statin Therapy

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

Stone NJ, et al. *Circulation*. 2014;129:S1-45.

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The intensity of statin should match the intensity of risk

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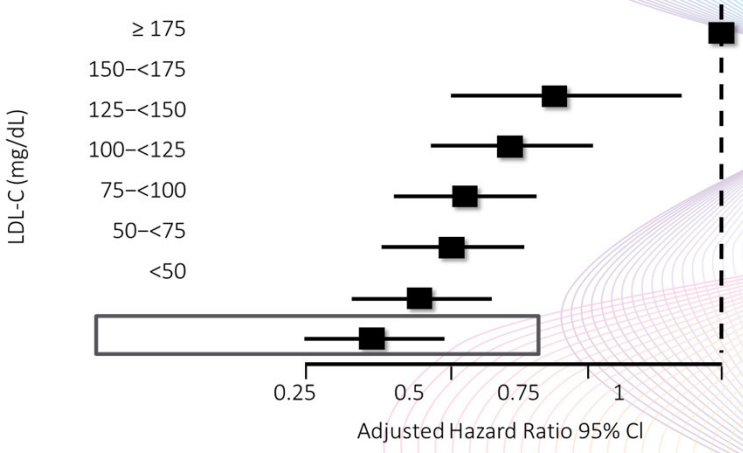
Rationale for Pushing LDL-C Even Lower

Meta-analysis of 38,153 patients from 8 randomized statin trials

LDL-C Levels and Risk of CV Events



Boekholdt SM, et al. *J Am Coll Cardiol.* 2014;64:485-494.

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Agenda

- AHA's simple 7
- LDL-C lowering with statin intensification
- LDL-C lowering beyond statins: ezetimibe and PCSK9 inhibitors
- Lipid guidelines for primary and secondary prevention of ASCVD

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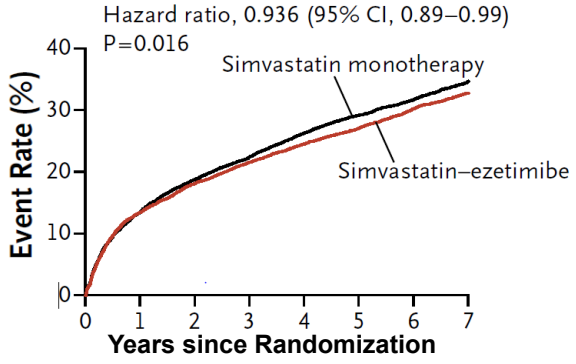
IMPROVE-IT Trial

18,144 patients with recent ACS

Simvastatin 40 mg vs. ezetimibe 10 mg + simvastatin 40 mg for 7 years



- Simvastatin alone (median LDL 69 mg/dL)
- Simvastatin + ezetimibe (median LDL 54 mg/dL)

RRR = 6%

NNT = 50

NNT = number needed to treat
RRR = relative risk reduction

Cannon CP, et al. *N Engl J Med*. 2015;372:2387-2397.

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PCSK9 (proprotein convertase subtilisin/kexin type 9)

- Secreted protein which targets the LDL receptor for degradation
- Gain of function mutations cause high LDL-C
- Loss of function mutations cause low LDL-C
- Inhibition lowers LDL-C levels
- Up-regulated by statin therapy

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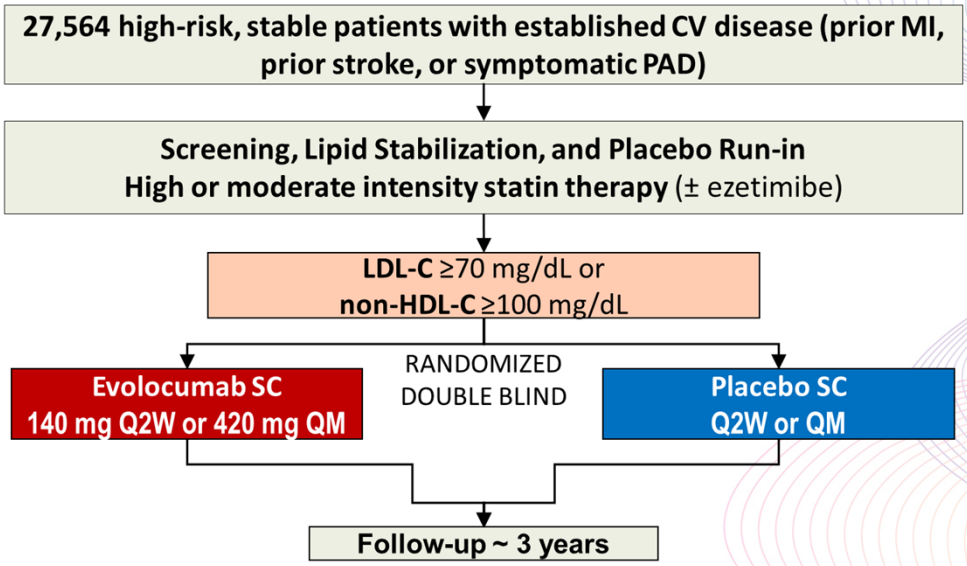
FOURIER Trial Design: Evolocumab



Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.

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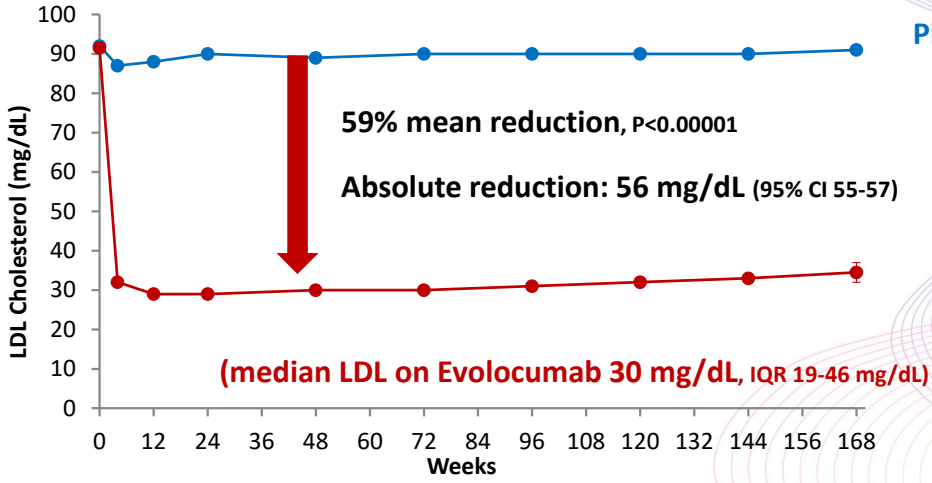
FOURIER Trial Lipid Results



Sabatine MS, et al. *Am Heart J* 2016;173:94-101.

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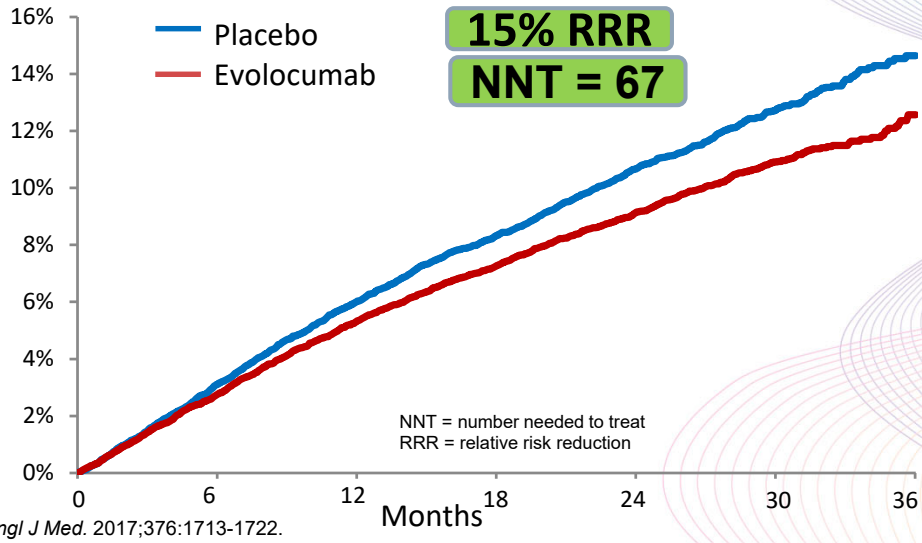
FOURIER Trial: Primary Outcome



Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722.

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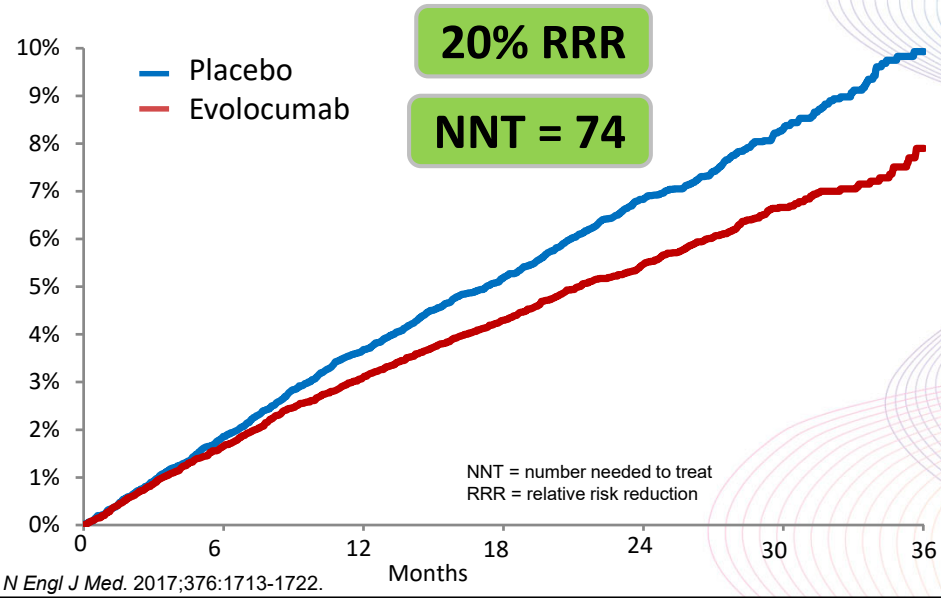
FOURIER Trial: MI/Stroke/CV Death



Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722.

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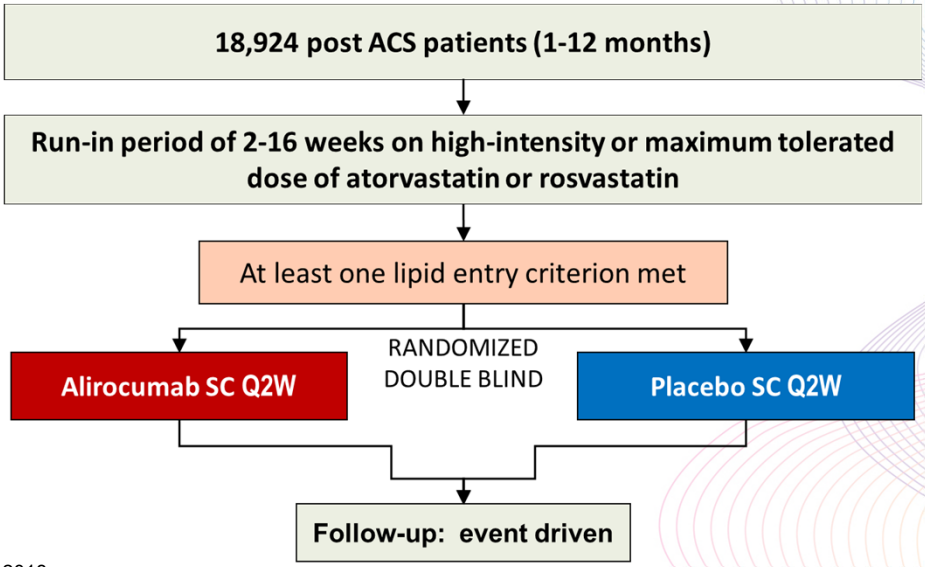
ODYSSEY OUTCOMES Trial



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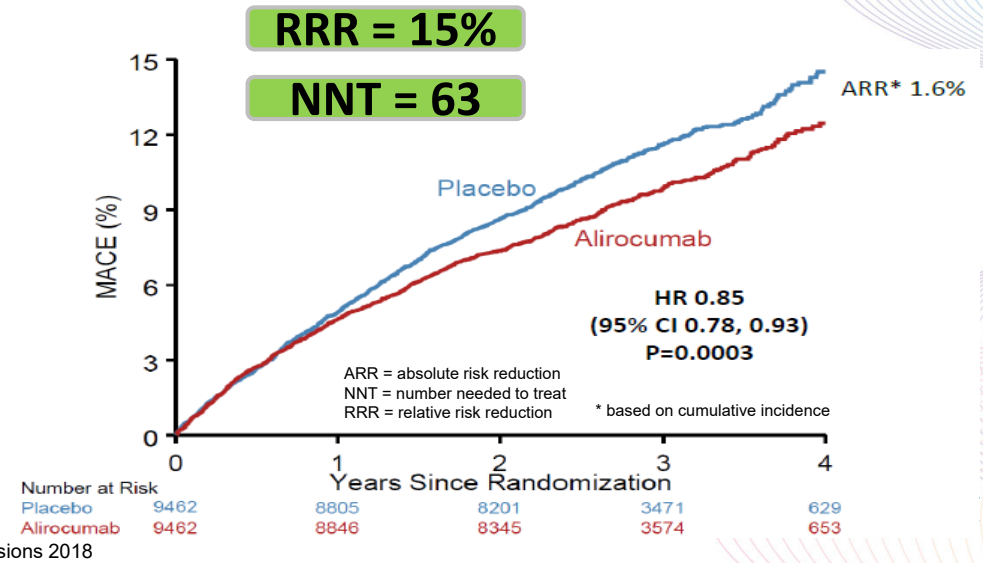
ODYSSEY Trial: Primary Outcome



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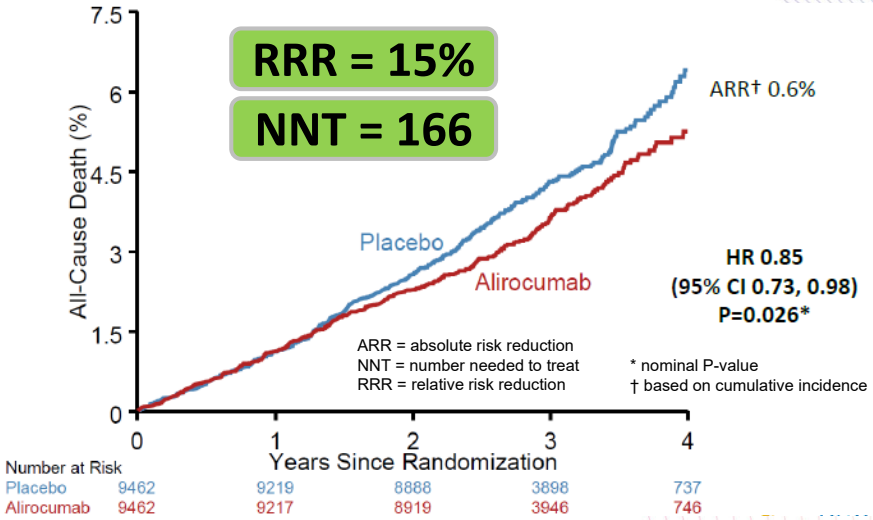
ODYSSEY: All Cause Mortality



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Agenda

- Lipid guidelines for primary and secondary prevention of ASCVD

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2018 ACC/AHA Guideline on the Management of Blood Cholesterol

Primary Prevention

- 10-year ASCVD risk should guide therapy
  - For intermediate risk patients, consider moderate or high intensity statin therapy
  - For high risk patients, LDL-C should be reduced > 50%
  - It may be reasonable to add ezetimibe to maximally tolerated statin in patients with intermediate risk who would benefit from more aggressive LCL-C lowering

Grundy SM, et al. *Circulation*. 2019;139:e1046-e1081.

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2018 ACC/AHA Guideline on the Management of Blood Cholesterol

Secondary Prevention

- High intensity statin therapy is indicated for clinical ASCVD, but if this cannot be used, moderate-intensity statin therapy can be utilized
- The first goal to achieve ≥ 50% reduction in LDL-c
- If LDL-c remains > 70 mg/dL, adding ezetimibe may be reasonable
- If LDL-c remains > 70 mg/dL, after addition of ezetimibe, adding PCSK9 inhibitor may be reasonable

Grundy SM, et al. *Circulation*. 2019;139:e1046-e1081.

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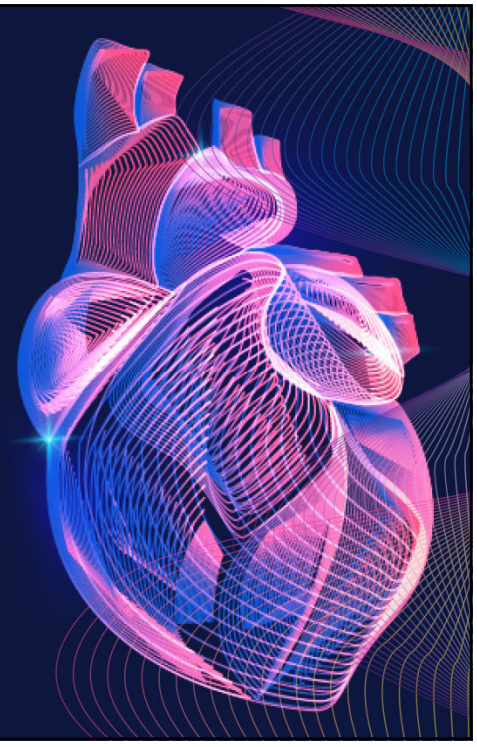
Thank you!



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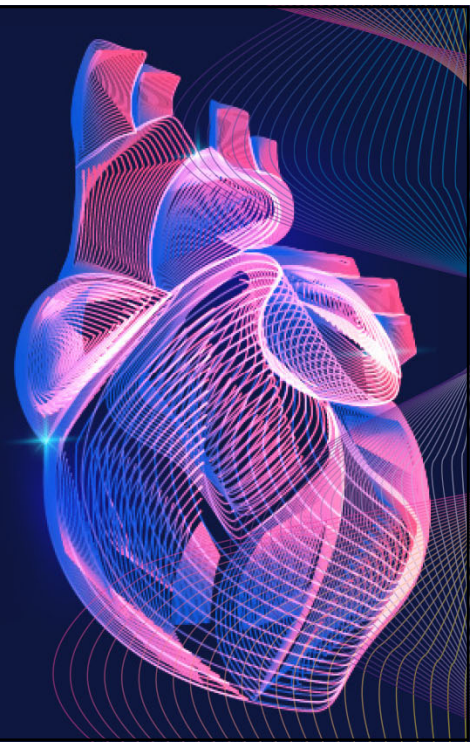
Managing ASCVD Risk Beyond LDL-C Lowering Therapy

Michael Miller, MD, FACC, FAHA
Professor of Cardiovascular Medicine
University of Maryland School of Medicine



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Faculty Disclosure: Michael Miller

Dr. Miller discloses that he receives a consulting fee from Amarin Pharma, Inc.

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Managing ASCVD Risk Beyond LDL-C Lowering Therapy

- Pathologic mechanisms contributing to ASCVD via TRL
- Genetic evidence for TRL causal effects
- Outcomes studies on fibrates and niacin
- Outcomes studies of EPA/DHA; role of drug/dose & population studied
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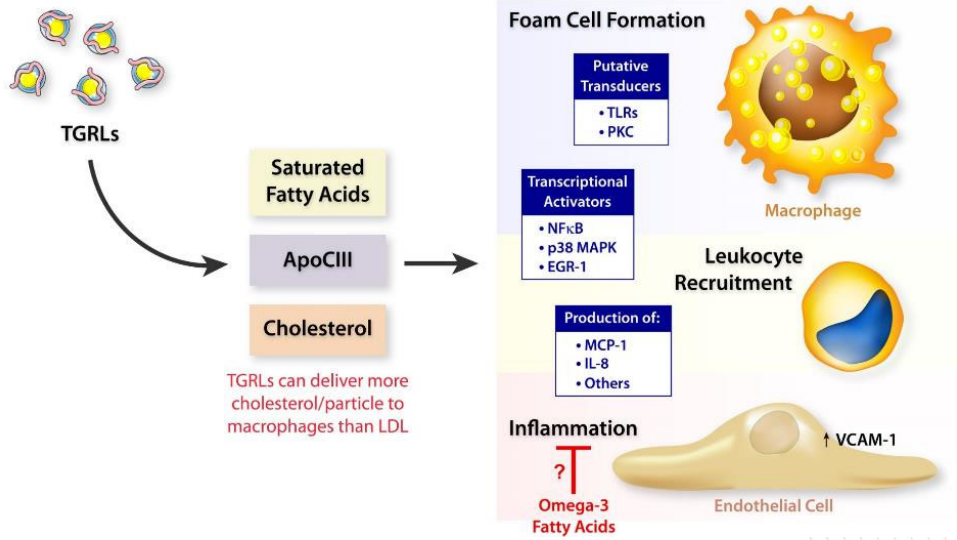
- REDUCE-IT outcomes point to pleiotropic effect of EPA
- MOA of EPA to reduce ASCVD burden

53

TG-Rich Lipoproteins (TGRLs) Contribute to Atherosclerosis



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

54

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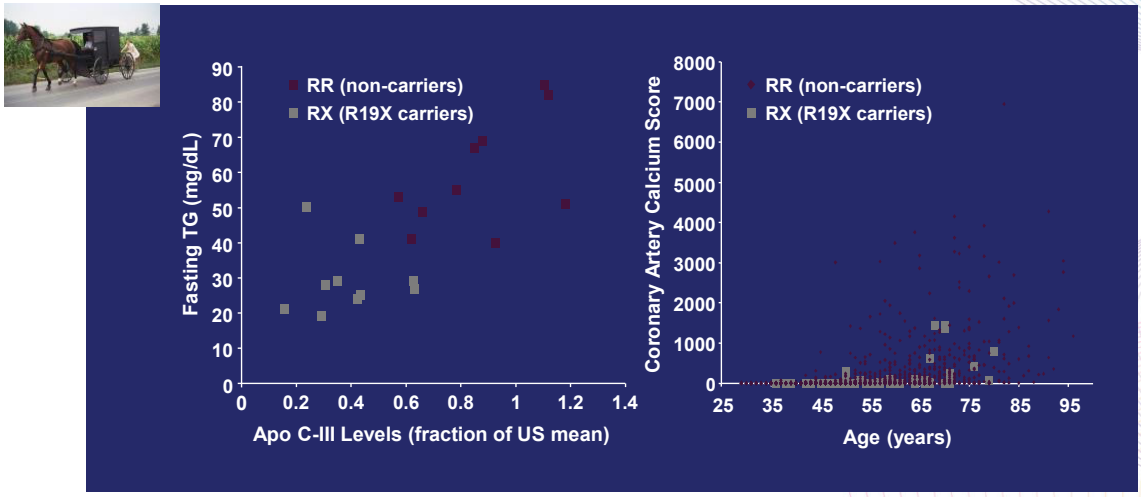
55

An Apo C-III Loss-of-Function Mutation Causes Very Low TG Levels and Lower Coronary Calcium Scores

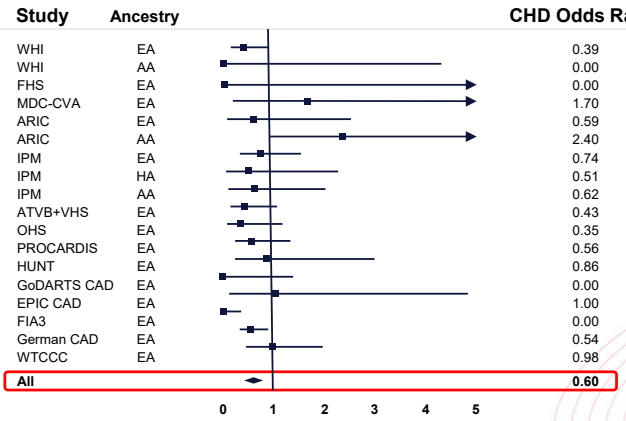


Apo C-III=gene encoding apolipoprotein (apo) C-III.
Pollin TI, et al. *Science.* 2008;322:1702-5.

56

Apo C-III Loss-of-function Mutations Reduce Apo C-III Levels and CHD Risk

Odds ratio of CHD of subjects with any of 4 Apo C-III LoF mutations
15 Studies
N=110,970 participants
34,002 w/CHD
76,968 controls



Apo C-III LoF mutations:
- ↓TG 39%
- ↓CHD 40%

AA=African ancestry; EA=European ancestry; HA=Hispanic ancestry; LoF=loss of function.
The TG and HDL Working Group of the Exome Sequencing Project, NHLBI. *New Engl J Med*. 2014;371:22-31.

57

ANGPTL3 Deficiency: Another Model of Low TG/Reduced CVD

Italian community with large cohort of familial combined hypolipidemia (FHBL2)

Minicocci I, et al. *J Clin Endocrinol Metab*. 2012;97:E1266-75.

ANGPTL3 LoF mutations:

p.S17X (8 homo, 68 hetero)
p.S122K fs*3 (1 hetero)
p.E96del (1 hetero)

9.4% = estimated prevalence in the populations of inactivating ANGPTL3 mutations

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Negative* Fenofibrate CVOTs (as Statin Adjunct)

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

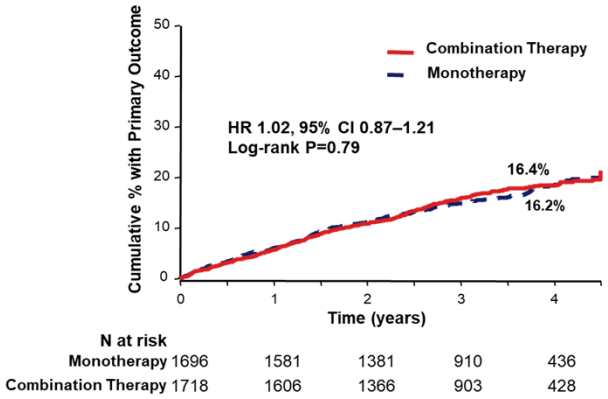
*Note *post hoc* analysis for both studies found statistically significant benefit in subgroup of patients with TG ≥ 204 mg/dL & HDL-C ≤ 34 md/dL (Sacks FM, et al. *N Engl J Med*. 2010;363:692-4).

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

60

Negative Niacin Outcome Studies (Added to Statin Therapy)

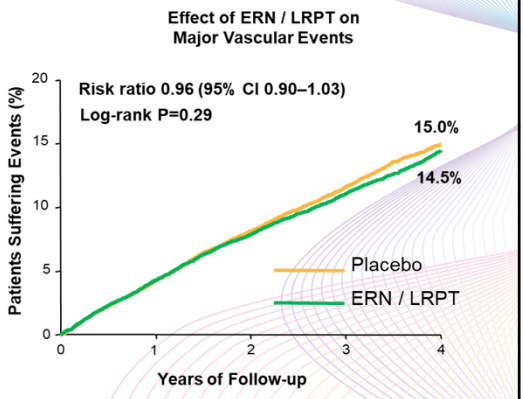
AIM-HIGH *(–29% TG)*



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.

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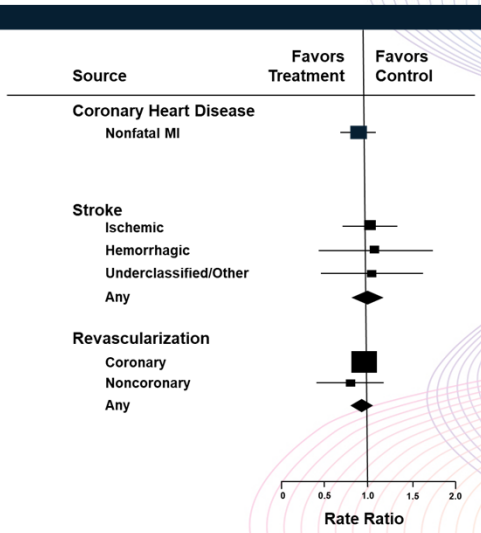
Effect of OM-3 (Supplements/EPA-DHA) on CVD Events: 1999-2018

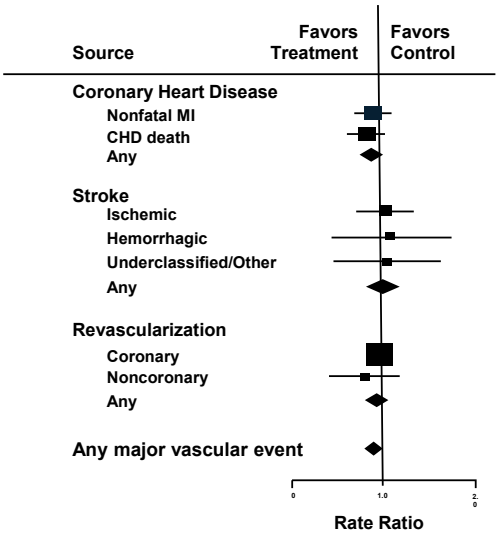
Study (Year)	EPA/DHA Dose (mg/d)	EPA / DHA Source
DOIT (2010)	1150 / 800	Dietary supplement
AREDS-2 (2014)	650 / 350	Dietary supplement
SU.FOL.OM3 (2010)	400 / 200	Dietary supplement
Alpha Omega (2010)	226 / 150	Margarine with dietary supplement
OMEGA (2010)	460 / 380	Rx EPA/DHA
R&P (2013)	500 / 500	Rx EPA/DHA
GISSI-HF (2008)	850 / 950	Rx EPA/DHA
ORIGIN (2012)	465 / 375	Rx EPA/DHA
GISSI-P (1999)	850 / 1700	Rx EPA/DHA
VITAL (2018)	465 / 375	Rx EPA/DHA
ASCEND (2018)	465 / 375	Rx EPA/DHA



Aung T et al. *JAMA Cardiol*. 2018;3:225-34.

63

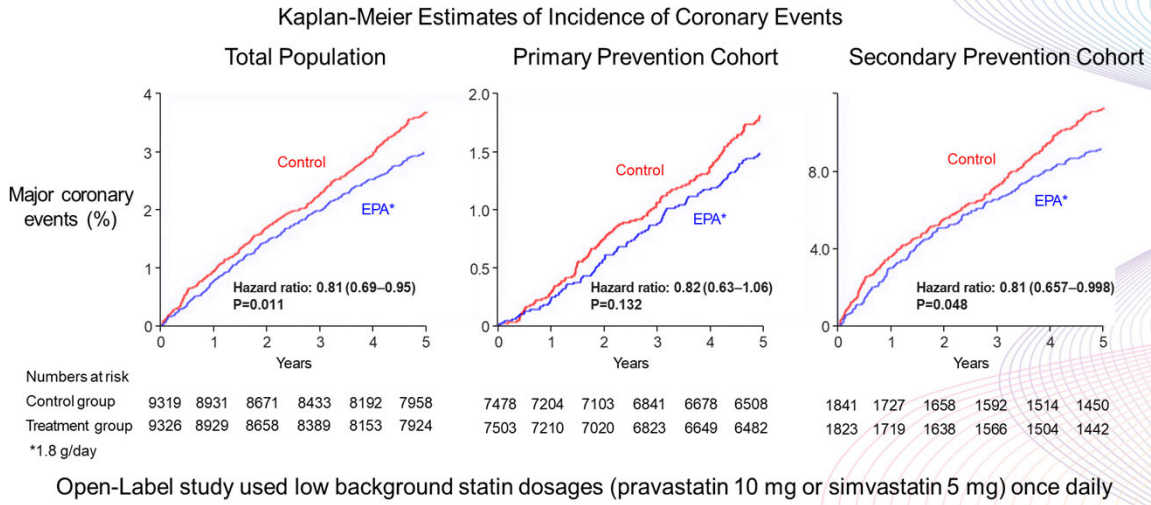
Lack of Apparent Effect of OM-3 on ASCVD May Be Due to Low Doses, Use of Dietary Supplements, or Lack of HTG Subjects



Aung T, et al. *JAMA Cardiol*. 2018;3:225-34.

64

JELIS: 1.8 g/day EPA in Japanese Hypercholesterolemic Patients (low-dose background statin doses, high baseline EPA levels)

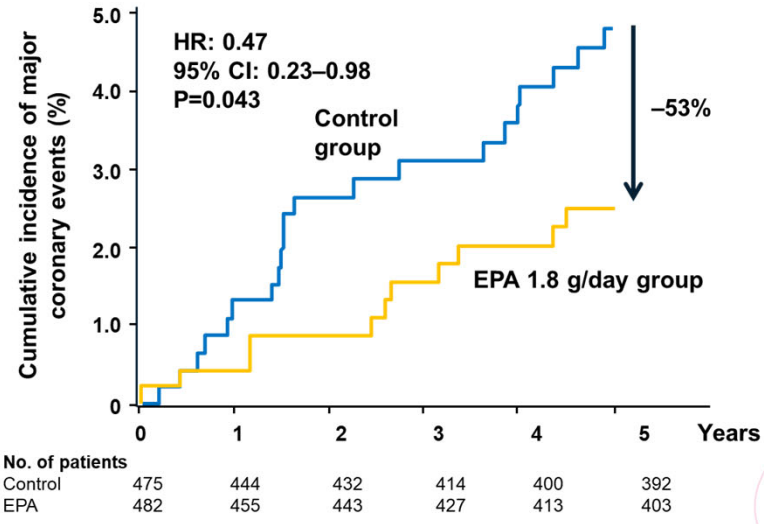


Open-Label study used low background statin dosages (pravastatin 10 mg or simvastatin 5 mg) once daily

Yokoyama M, et al. *Lancet.* 2007;369:1090-8.

65

JELIS: Larger Decrease in MACE in Those with TG >150 mg/dL and HDL-C <40 mg/dL*



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

*Pre-specified. Saito Y, et al. *Atherosclerosis*. 2008;200:135-40.

66

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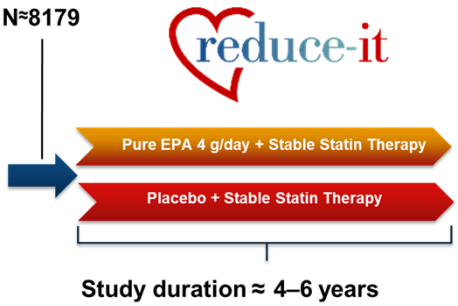
REDUCE-IT: Reduction of CV Events with Icosapent Ethyl – Intervention Trial

Participants

- Men and women ≥45 years of age
- Established CHD or at high risk for CHD (diabetes + ≥1 risk factor)
- Atherogenic dyslipidemia
  - All patients required to be on stable statin therapy for at least 4 weeks
  - LDL-C >40 mg/dL and ≤100 mg/dL prior to randomization into the study
- Fasting triglyceride level 135–499 mg/dL



Primary Endpoint
Prevention of 1st major CV event (MACE); defined as:

- CV death
- Nonfatal MI
- Nonfatal stroke
- Coronary revascularization
- Unstable angina requiring hospitalization

- Randomized, double-blind, parallel-group design
- Secondary outcome measures: Incidence of additional CV events, lipid and lipoprotein levels, subgroup analyses such as patients with diabetes, etc.
- International trial; first patient dosed in December 2011
- All potential endpoint events adjudicated by blinded clinical endpoint committee
- 10% of enrolled patients had TGs of 135–150 mg/dL

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

http://www.clinicaltrials.gov/ct2/show/NCT01492361

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REDUCE-IT: Key Baseline Characteristics

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age (years)	64	64
Female, %	28.4%	29.2%
CV Risk Category, %		
Secondary Prevention Cohort	70.7%	70.7%
Primary Prevention Cohort	29.3%	29.3%
Prior Atherosclerotic Coronary Artery Disease, %	58.4%	58.5%
Prior Atherosclerotic Cerebrovascular Disease, %	15.7%	16.2%
Prior Atherosclerotic Peripheral Artery Disease, %	9.5%	9.5%
Type 2 Diabetes, %	57.9%	57.8%
Triglycerides (mg/dL), Median (Q1-Q3)	217 (177 - 272)	216 (176 - 274)
Triglyceride Category (by Tertiles)*		
≥81 to ≤190 mg/dL	median 163 mg/dL	
>190 to ≤250 mg/dL	median 217 mg/dL	
>250 to ≤1401 mg/dL	median 304 mg/dL	

*Baseline TG calculated as average of final screening TG and subsequent TG value from date of randomization.

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

69

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REDUCE-IT: 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 (mg/dL)*	Baseline	Year 1	Baseline	Year 1	Absolute Change from Baseline	% Change from Baseline	% Change P-value
Triglycerides	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	112.6	393.5	<0.001

*Apo B was measured at year 2.

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

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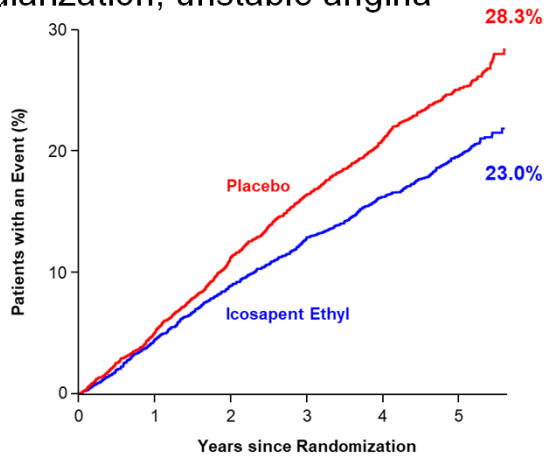
REDUCE-IT: Primary Endpoint Achieved

Composite: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, 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

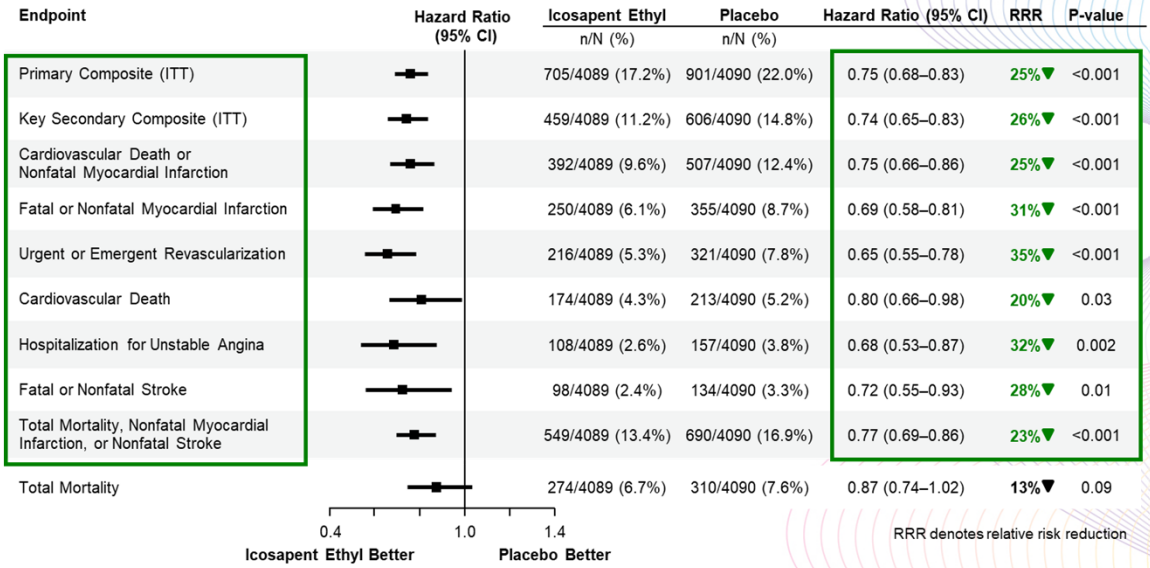
ARR = absolute risk reduction
NNT = number needed to treat
RRR = relative risk reduction

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

Estimated Kaplan-Meier event rate at approximately 5.7 years

72

Prespecified Hierarchical Endpoint Testing



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

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REDUCE-IT: Adverse Events of Interest – Serious Bleeding and AFib

	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 vs 10 placebo; P=0.55)

Positively Adjudicated Hospitalization for Atrial Fibrillation/Flutter	127 (3.1%)	84 (2.1%)	0.004

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

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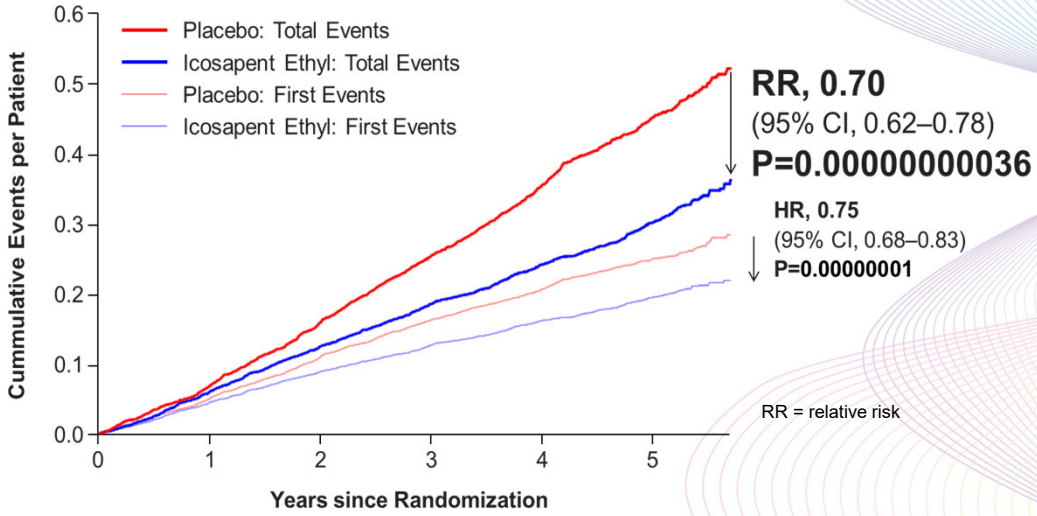
Total (First and Subsequent) Events

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

Primary Composite Endpoint



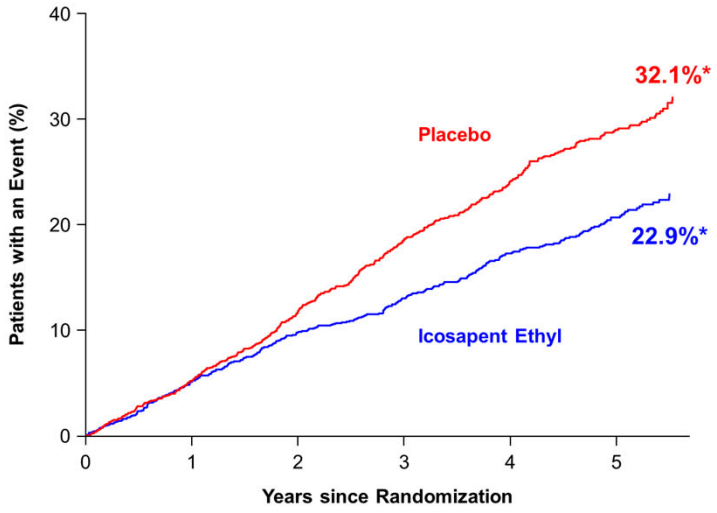
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802.

75

reduce-it USA

76

Primary Endpoint: USA Subgroup
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.69
(95% CI, 0.59–0.80)
RRR = 31%
ARR = 6.5%
NNT = 15 (95% CI, 11–27)
P = 0.000001

ARR = absolute risk reduction
NNT = number needed to treat
RRR = relative risk reduction

*Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

Bhatt DL, Miller M, Brinton EA, et al. *Circulation.* 2020;141:367-375.

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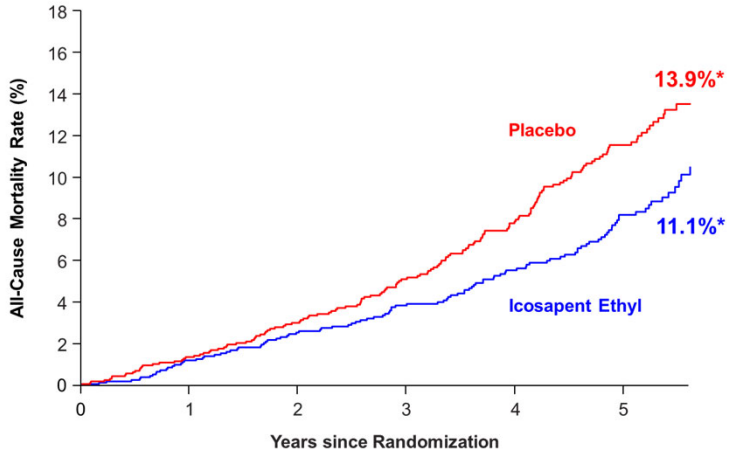
All-Cause Mortality: USA Subgroup



Hazard Ratio, 0.70
(95% CI, 0.55–0.90)
RRR = 30%
ARR = 2.6%
NNT = 39 (95% CI, 22–154)
P = 0.004

ARR = absolute risk reduction
NNT = number needed to treat
RRR = relative risk reduction

*Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

Bhatt DL, Miller M, Brinton EA, et al. *Circulation.* 2020;141:367-375.

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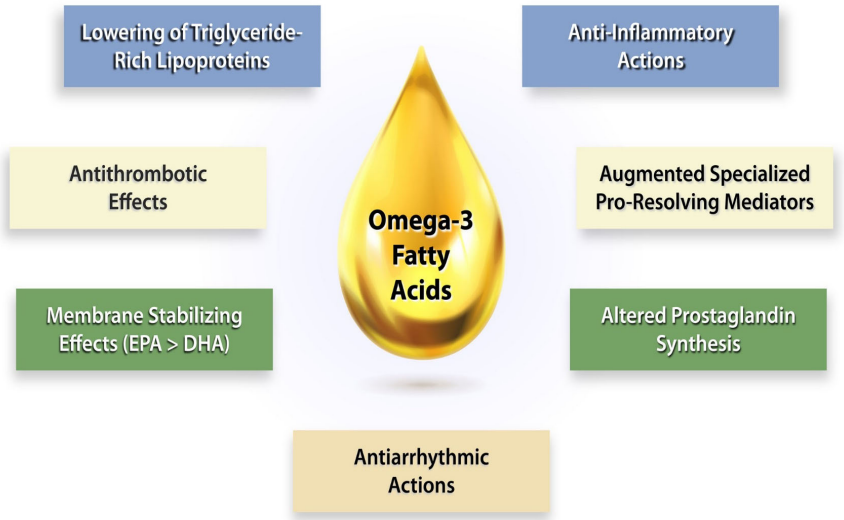
EPA Has Atheroprotective Properties



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

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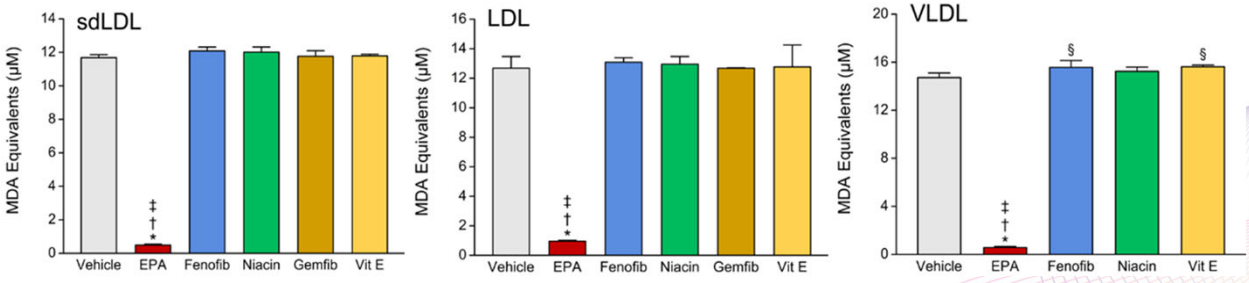
Comparative Effects of TG-lowering Agents on Lipoprotein Oxidation

Each agent was tested at 10 μM



* p < 0.001 versus vehicle-treated control; † p < 0.001 versus fenofibrate, niacin, or gemfibrozil; ‡ p < 0.001 versus vitamin E; § p < 0.05 versus vehicle-treated control

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

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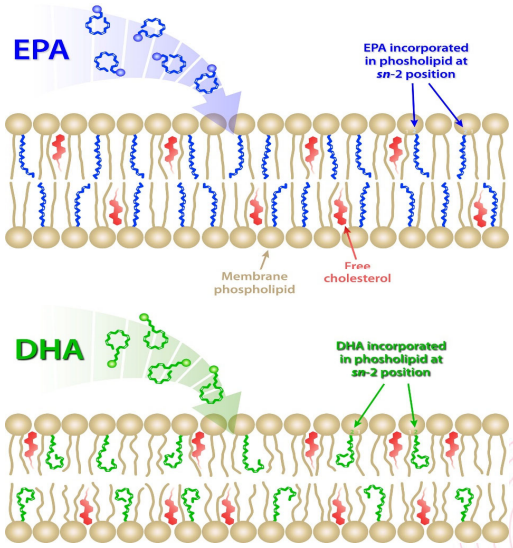
Biophysical Analysis: EPA Has Stable Extended Conformation in the Cell Membrane While DHA Has Disordering Effect



Sherratt SCR, Mason RP. *Chem Phys Lipids* 2018;212:73-79; Mason, et al. *Arterioscler Thromb Vasc Biol*. 2020;40(5):1135-1147.

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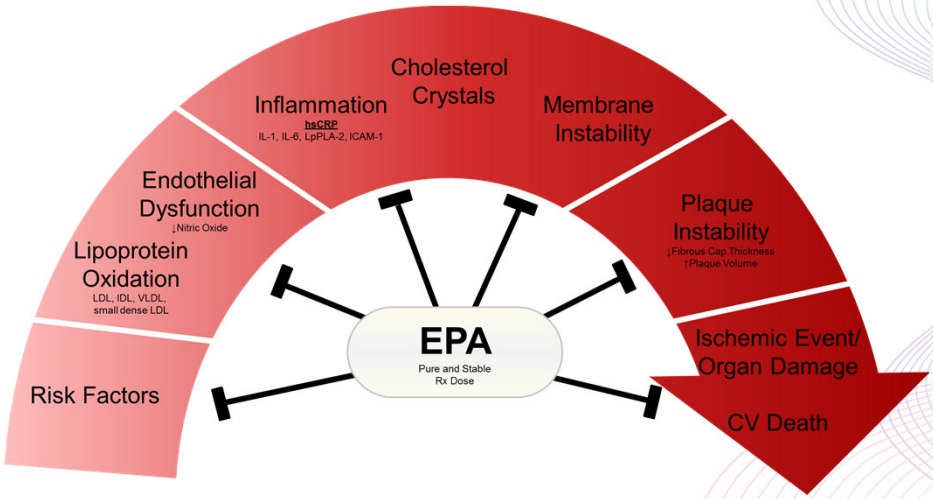
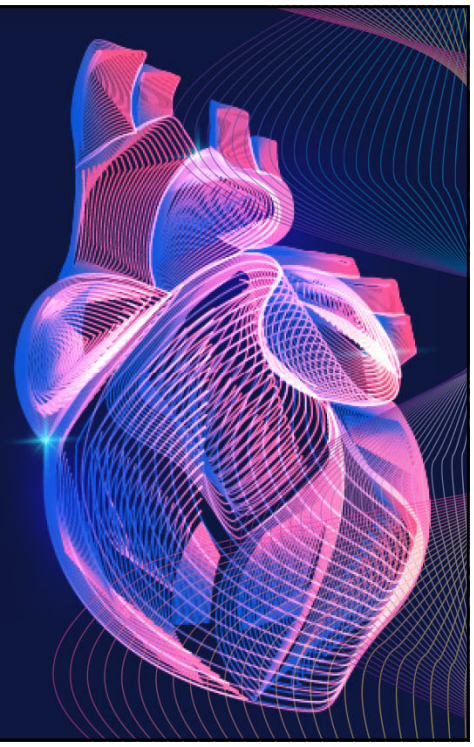
EPA Interacts Across the CVD Continuum to Reduce CV Events



Bays HE, et al. *Am J Cardiovasc Drugs*. 2013;13:37-46; Borow KM, Nelson JR, Mason RP. *Atherosclerosis*. 2015;242:357-66; Bhatt DL, et al. *N Engl J Med*. 2019;380:11-22; Ganda OP, et al. *J Am Coll Cardiol*. 2018;72:330-43; Jia X, et al. *Curr Atheroscler Rep*. 2019;21:1; Mason RP, et al. *Biomed Pharmacother*. 2018;103:1231-7; Ference BA, et al. *JAMA*. 2019;321:364-73. Sherratt SCR, Juliano RA, Mason RP. *Biochim Biophys Acta Biomembr*. 2020;1862(7):183254.

84

Thank you!



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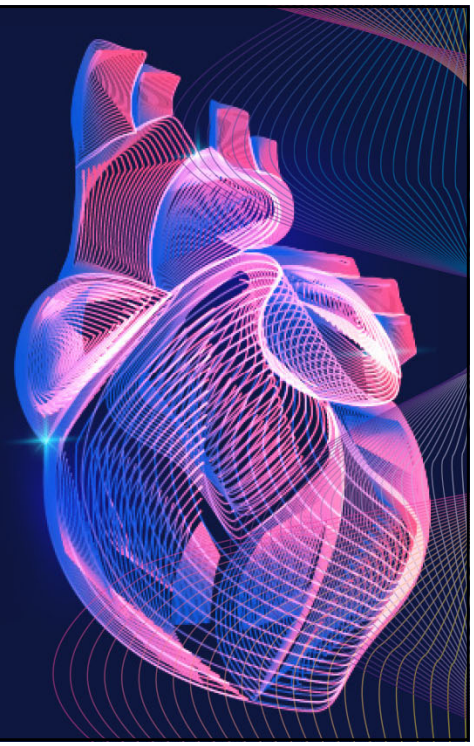
Practical Considerations to Manage Residual Risk

Sergio Fazio, MD, PhD
Professor of Medicine
Director, Center for Preventive Cardiology
Oregon Health & Science University
Editor-in-Chief
The American Journal of Preventive Cardiology



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Faculty Disclosure

Dr. Fazio discloses that he receives consulting fees from Amarin, Amgen, Astra, Kowa, and Novo Nordisk

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2019 Multisociety Cholesterol Guidelines Summary

- Lifelong healthy lifestyle reinforced
- Improved ASCVD Risk Estimator Plus
  - can project potential **benefit** of risk-lowering interventions
  - can **track change** in risk over time
- CACS for improved diagnostic prediction and shared decision-making
- Identify risk-enhancing factors to help in deciding management
- Risk stratification of absolute 10-year ASCVD risk score into four buckets: Low, Borderline, Intermediate, and High

Grundy SM, et al. *Circulation*. 2019;139:e1082-e1143.
https://www.acc.org/tools-and-practice-support/mobile-resources/features/2013-prevention-guidelines-ascvd-risk-estimator

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ACC Risk Calculator *Plus* to Assess Risk Category

1. For CVD risk calculation in the primary prevention setting:

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

- 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

2.

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

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Risk-Enhancing Factors

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

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

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Additional Risk-Enhancing Factors

- History of premature menopause (before age 40 y) *or* pregnancy-associated conditions that ↑ASCVD risk (e.g., preeclampsia or GD)
- High-risk race/ethnicity (South East Asian, Middle Eastern, etc.)
- Persistent primary HTG
- Biochemistries and vascular Imaging:
  - ↑high-sensitivity C-reactive protein
  - ↑Lp(a)
  - ↑apoB
  - ↑uric acid
  - ↓ABI
  - ↑CIMT

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

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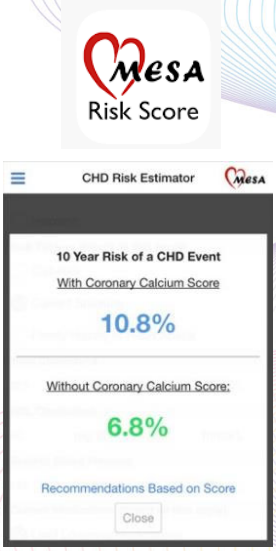
Using the CAC Score to Guide Statin Therapy

- CAC scores predict ASCVD events
  - 0 Reclassify patients to a lower-risk group, statin therapy withheld or postponed
  - 1-99 initiate statin therapy
  - 100+ initiate statin therapy with lowest LDL goal
- For patients >75 y/o, RCT evidence for statin therapy is not strong, so clinical assessment of risk status and shared decision-making is needed
- European Society of Cardiology guidelines:
  - "CAC score assessment with CT should be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate risk."



Grundy SM, et al. *Circulation*. 2019;139:e1082-e1143. *Atherosclerosis* 2019;290:140-205.

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2019 Multisociety Cholesterol Guidelines Summary

- High- and Very High-Risk ASCVD categories clarified
- Reinforced usage of statin therapy as first-line with high/maximum intensity for most in ASCVD
- New adjuncts (ezetimibe and PCSK9i evolocumab and alirocumab) now recommended when further LDL-C reduction warranted
- Presented same day as REDUCE-IT results were presented, so no guidance on TG-lowering provided

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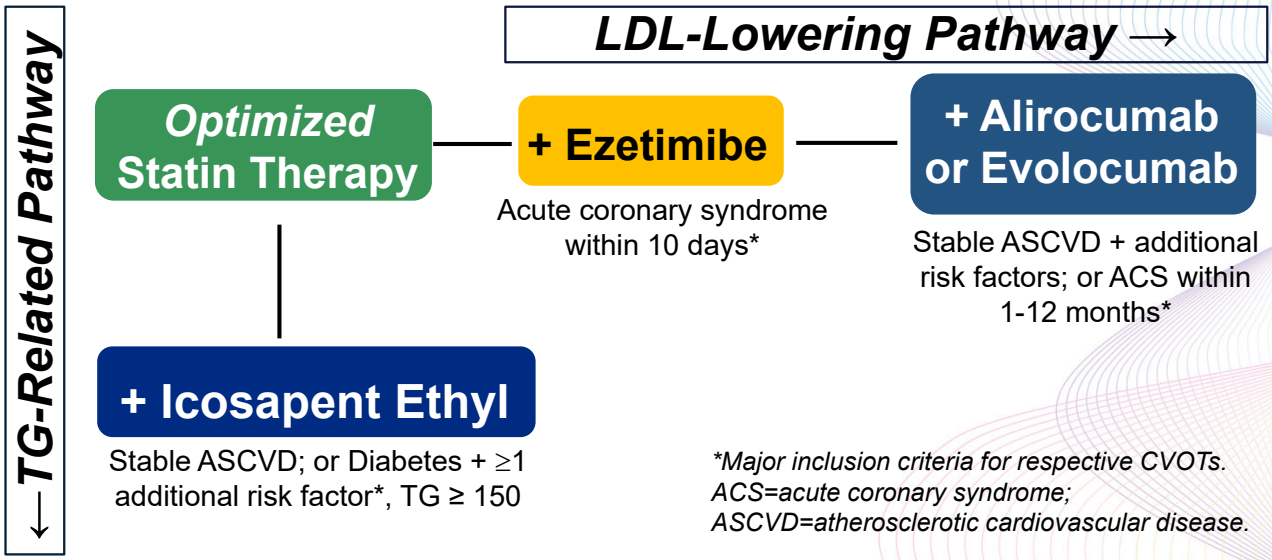
Statin Therapy Adjuncts *Proven* to Reduce ASCVD



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

94

Current Guidance Regarding Statin Adjuncts: Fibrates, Niacin, Ezetimibe, or PCSK9i

- Combination therapy **statin/fibrate** has not been shown to improve ASCVD 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)
- For patients with **diabetes and ASCVD, if LDL cholesterol is ≥70 mg/dL on high-intensity statin dose, consider adding LDL-lowering therapy** such as ezetimibe or PCSK9 inhibitor. (A)
  - Ezetimibe preferred due to lower cost if little additional effect needed
  - PCSK9i preferred if more than 20% LDL-C reduction needed

(A)= High evidence.

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

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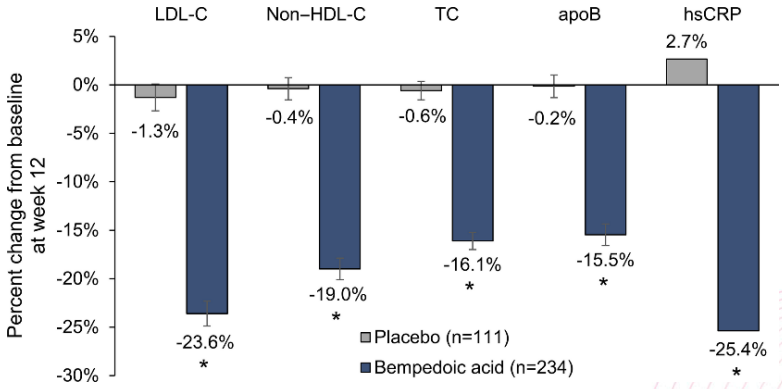
CLEAR Shows Bempedoic Acid Benefits in Statin *Intolerance—Now FDA Approved*

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



*P<0.001 vs placebo.

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

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New Guidelines/Recommendations for Icosapent Ethyl to Prevent ASCVD in Patients with TG 135-500 mg/dL

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; 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_ICrEembFJ9LIVBZIw. *Eur Heart J*. 2020;41(1):111-188. Orringer CE, et al. *J Clin Lipidol*. November 2019. AHA Science Advisory. Skulas-Ray AC, et al. *Circulation*. 2019;140:e673-e691. Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139.

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

- There are *NO* over-the-counter omega-3 products, *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

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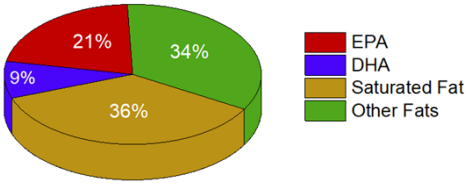
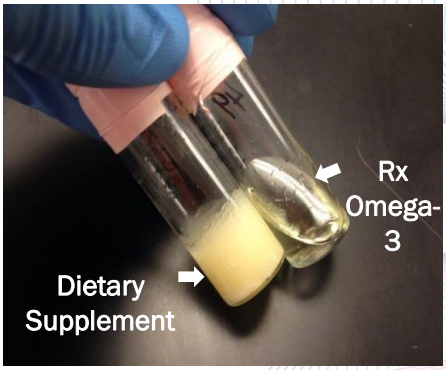
Problems with Content of *Leading* US Fish Oil Dietary Supplements



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



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

Mason RP, Sherratt SCR. *Biochem Biophys Res Commun*. 2017;483:425-429. Hilleman D, Smer A. *Manag Care*. 2016;25:46-52. Albert BB, et al. *Sci Rep*. 2015;5:7928. Kleiner AC, et al. *J Sci Food Agric*. 2015;95:1260-7. Ritter JC, et al. *J Sci Food Agric*. 2013:93:1935-9. Jackowski SA, et al. *J Nutr Sci*. 2015;4:e30. Rundblad A, et al. *Br J Nutr*. 2017;117:1291-8. European Medicines Agency. 2018:712678.

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Achieving the Recommended 4 g/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

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2018 ACC/AHA Multisociety Guidelines

Value Statement: Low Value (LOE: B-NR)	At mid-2018 list prices, PCSK9 inhibitors have a low cost value (>$150,000 per QALY) compared to good cost value (<$50,000 per QALY)
Value Statement: Uncertain Value (B-NR)	Among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 US list prices.

NOTE: Based on initial wholesale acquisition price of $14K per year

Price was reduced by 60% in October 2018

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

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ICER Base-Case and Sensitivity Analyses Show Cost-Effectiveness of Icosapent Ethyl

Base-Case Incremental Results

Intervention	Incremental Costs	Incremental LYs	Incremental QALYs	Cost per LY	Cost per QALY	Cost per MACE Avoided
Icosapent Ethyl vs. Medical Management	$9,000	0.54	0.50	$17,000 per LY gained	$18,000 per QALY gained	$53,000 per MACE avoided

Probabilistic Sensitivity Analysis Results

Intervention	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY
Icosapent Ethyl vs. Medical Management	100%	100%	100%

ICER Evidence Rating: B+

LY= life year; MACE = major cardiovascular event; QALY = quality adjusted life year.

Institute for Clinical and Economic Review (ICER). Draft Evidence Report. Additive Therapies for Cardiovascular Disease: Effectiveness and Value. https://icer-review.org/wp-content/uploads/2019/02/ICER_CVD_Draft_Evidence_Report_072419.pdf. Posted July 24, 2019. Accessed July 24, 2019.

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Professional Society Recommendations

- **March 2019 (reaffirmed in 2020)**: American Diabetes Association
  - Secondary prevention patients and patients with ASCVD risk factors with controlled LDL-C and TG levels of 135-499 mg/dL
  - Level A = "can be considered"
- **September 2019**: European Society of Cardiology/European Atherosclerosis Society
  - High-risk patients with TG levels of 135-499 mg/dL despite statins
  - Level B, Class IIa = "should be considered"
- **September 2019**: National Lipid Association
  - Recommended in the population studied in REDUCE-IT
  - Class I, Level B-R = "is recommended"

Diabetes Care. 2020;43(Suppl. 1):S111-S134. *Eur Heart J*. 2020;41:111-188. *J Clin Lipidol*. 2019;13(6):860-872.

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Summary—*Updates* in Lipid Guidelines

- 2018 Multisociety Cholesterol/2019 ACC/AHA 1° Prevention Guidelines
  - *Improved* risk assessment
  - *Lifelong* healthy lifestyle
  - *On-treatment* LDL-C levels emphasized (thresholds ≈ goals)
  - Ezetimibe & PCSK9i to ↓**CVD** (if LDL-C > threshold w/ max statin)
- 2019 *Five* new guidelines/statements 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
- New FDA indication (2019) for icosapent ethyl to ↓CVD (≈ to statements)
- Implementing this new guidance:
  - Statin *rechallenge* often useful
  - Consider statin *adjuncts* to ↓**CVD**:
    - Ezetimibe and/or PCSK9i for *residual LDL-C* elevation
    - Icosapent ethyl for *TG* elevation 135-500 mg/dL (lower is better)

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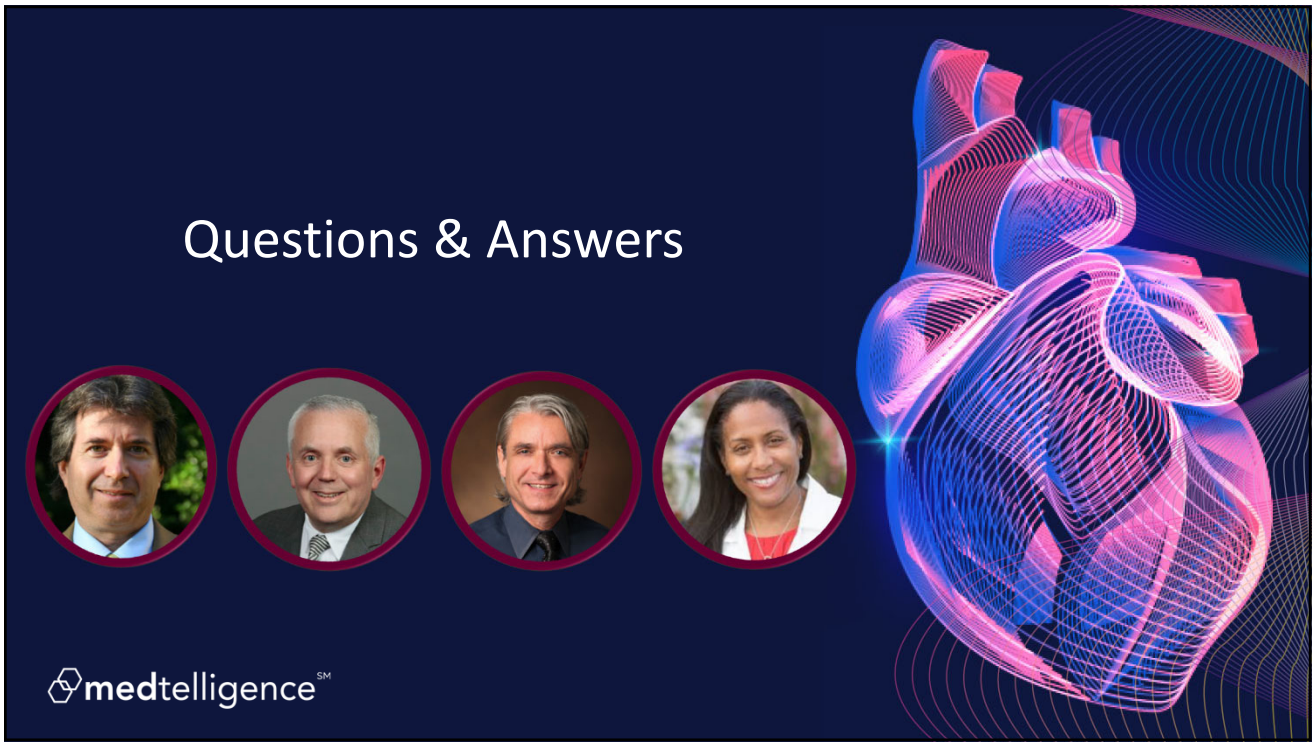

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