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15th ANNIVERSARY

New Guidelines and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

Margo B. Minissian, PhD, ACNP
Eliot Brinton, MD, FAHA, FNLA

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Objectives

- Screen and diagnose female patients at high risk of cardiovascular events during their annual visit
- Describe the impact of residual ASCVD risk that remains beyond statin therapy
- Apply evidence-based guidelines and recent randomized clinical trial evidence to lifestyle and pharmacologic adjuncts to statin therapy to manage women at risk of ASCVD events

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Identifying Women at Risk for ASCVD

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Clinical Lipid Specialist, Barbra Streisand Women's Heart Center
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Faculty Disclosure

Dr. Minissian receives consulting fees from Amgen

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Only ~Half of Women* Know That Heart Disease Is Their #1 Killer

- **Heart disease is the leading cause of death for women** in the US, killing 299,578 women in 2015 (22.3% of all deaths)
  - Heart disease kills **4 times *more women than breast cancer***
- **Stroke is the 4th leading cause of death for women** in the US
  - In 2011, stroke caused the death of 76,597 females (59.4% of total stroke deaths)
- **Women are *more likely to die*** from heart disease and stroke **than men**

*56%

https://www.cdc.gov/heartdisease/women.htm https://www.cdc.gov/women/lcod/2015/race-ethnicity/index.htm
https://www.heart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_472913.pdf

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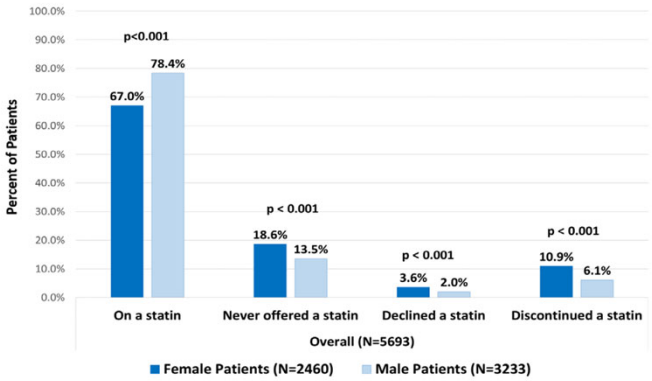
Undertreatment: Women Receive *Less* Statin Therapy Than Men*



Women also receive less therapy than men for hypertension,and CAD, heart failure

*Patient and Provider Assessment of Lipid Management (PALM) Registry; N=5693 (43% women) eligible for statins per 2013 ACC/AHA Guidelines

Nanna MG, et al. Circ Cardiovasc Qual Outcomes. 2019;12:e005562. Epub ahead of print.

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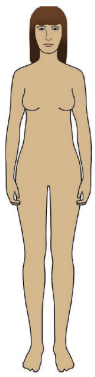
The Evaluation of CV Risk Factors and Symptoms in Women Remains Challenging

- Established risk factors common to both genders
- Psychological stress
- Smoking
- Hypertension
- History of CAD or other atherosclerotic vascular disease
- Diabetes mellitus
- Chronic kidney disease
- Inflammatory disorders e.g. RA
- Dyslipidemia: high LDL and/or low HDL
- Age >55 years
- Family history of premature CAD



- Risk factors specific to women
- Postmenopausal
- Pregnancy complications:
  - pre-eclampsia
  - gestational diabetes

Influence of Gender on ASCVD Symptoms	
Common in both sexes	Greater impact on Women
Pain, pressure, or squeezing in chest	Report milder symptoms
Radiation of pain to neck, shoulder, back, arm, jaw	Sudden onset of weakness, shortness of breath, fatigue feeling of systematic illness (w/o chest pain)
Palpitations	Diabetes
Difficulty in breathing	Autoimmune diseases
Dizziness	Heartburn, nausea, vomiting, abdominal pain
	Cold sweats, clamminess

Cardiac/coronary symptoms in women are "atypical" and therefore ACS/MI/Angina are way UNDER-diagnosed in women, creating a very dangerous situation

After Keteepe-Arachi T, Sharma S. European Cardiology Review 2017;12:10-13.

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ASCVD Risk Assessment, Hypertriglyceridemia, and Management Strategies in Women

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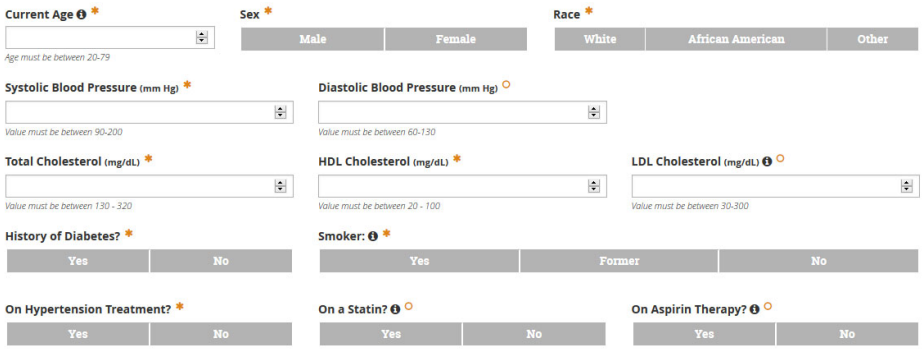
ACC Risk Calculator Plus to Assess Risk Category



Then use the new AHA/ACC Blood Cholesterol Guideline Algorithm for Primary Prevention to guide management

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ACC/AHA Guidelines: Risk-Enhancers for ASCVD

- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL
- Chronic kidney disease
- Metabolic syndrome
- **Conditions specific to women (e.g., gestational diabetes, preeclampsia, premature menopause, post-menopausal state)**
- Inflammatory disease (generally **more common in women**)
- Ethnicity (e.g., South-Asian ancestry)

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

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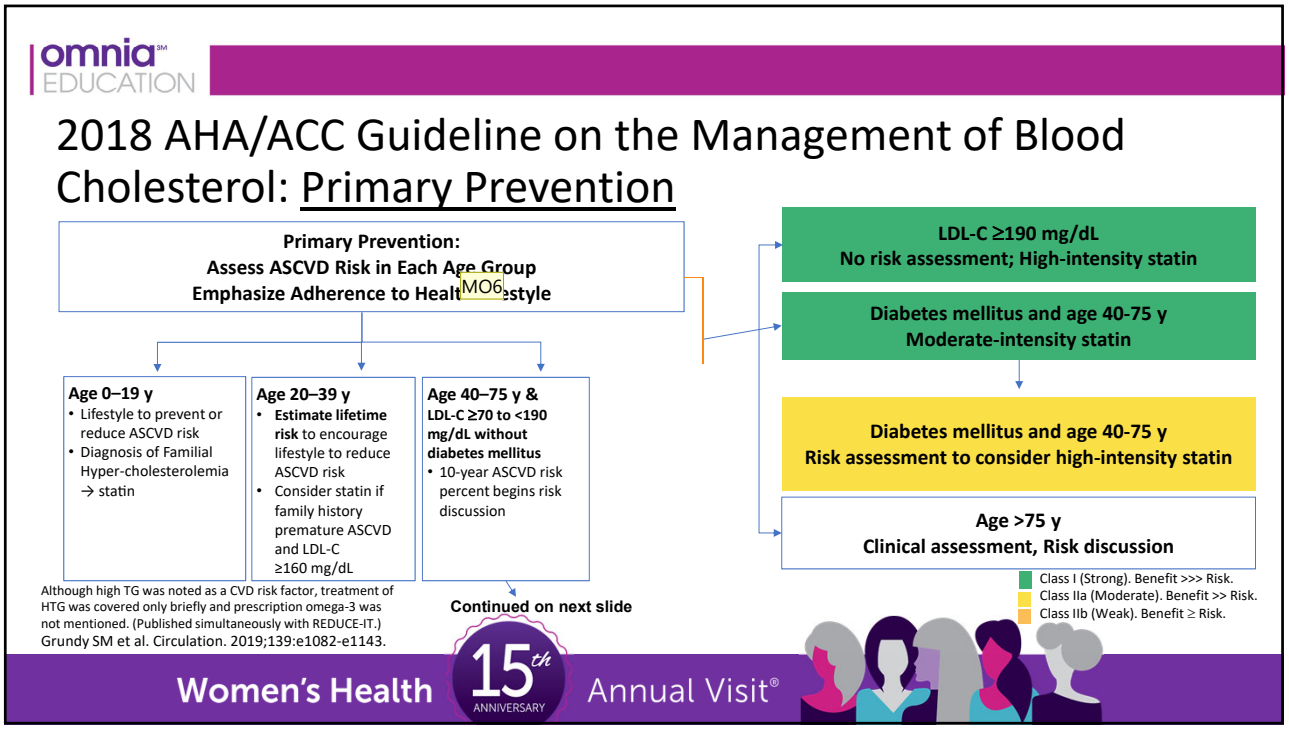

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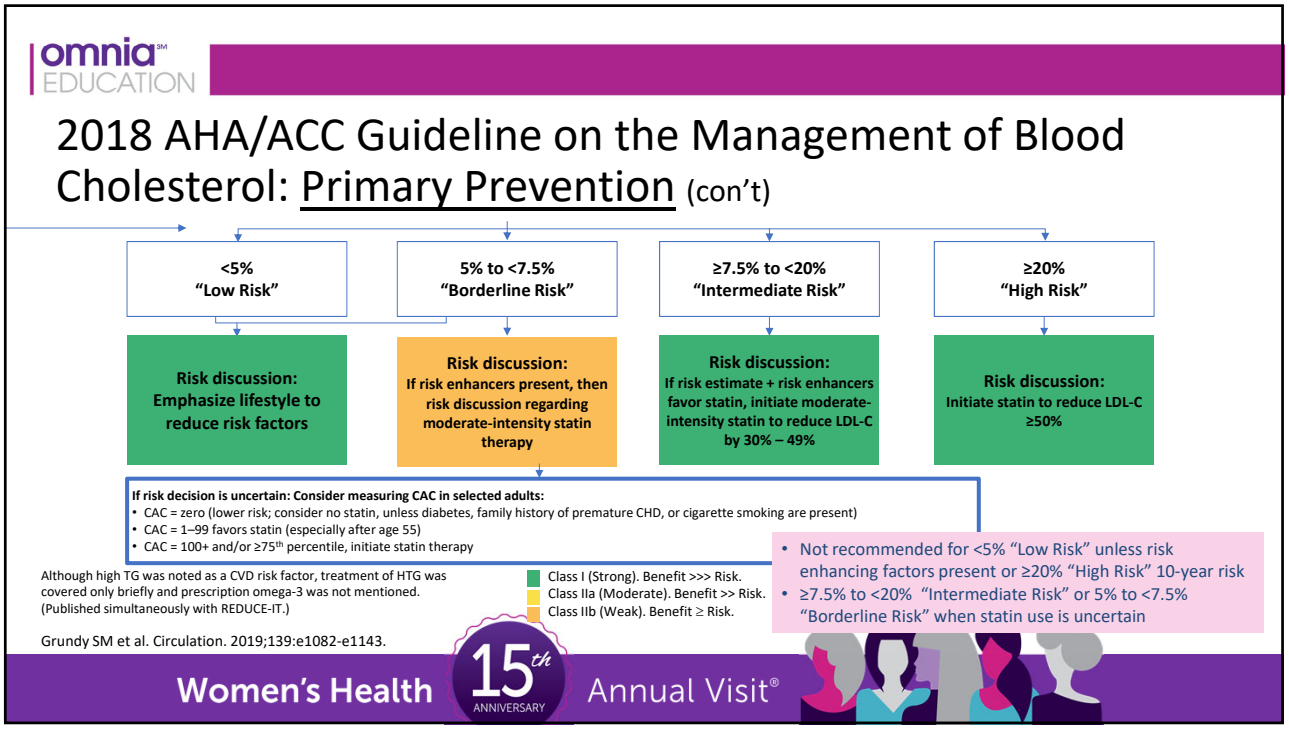

12

New Guidelines and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

Slide 11

MO6 I think this should he Healthy Lifestyle, not Health Lifestyle
Meghan Orner, 9/11/2019

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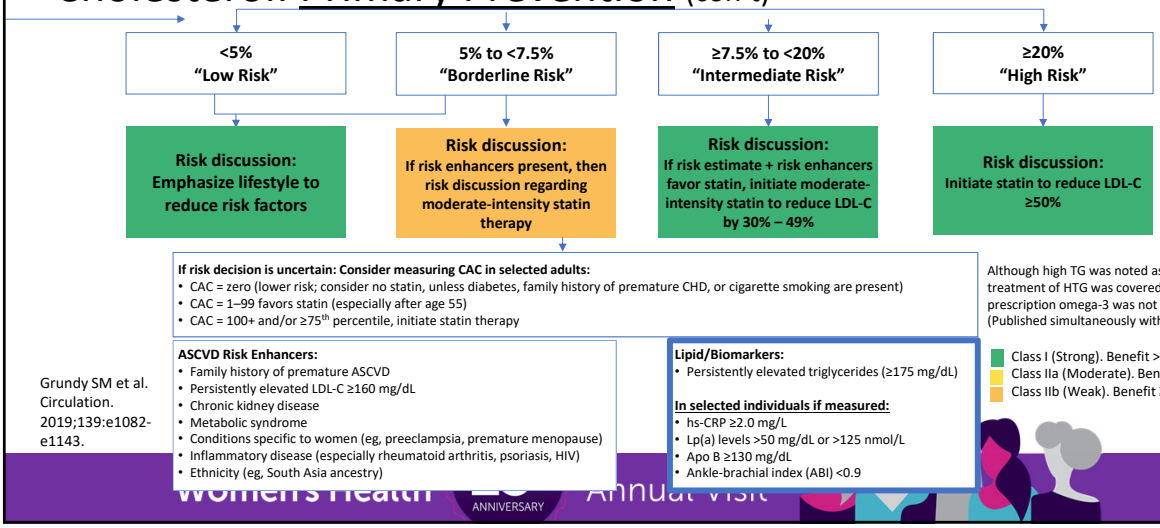
2018 AHA/ACC Guideline on the Management of Blood Cholesterol: Primary Prevention (con't)



Although high TG was noted as a CVD risk factor, treatment of HTG was covered only briefly and prescription omega-3 was not mentioned. (Published simultaneously with REDUCE-IT.)

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

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

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Very High Risk of Future CVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation (S4.1-39))
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2) (S4.1-15, S4.1-17)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

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

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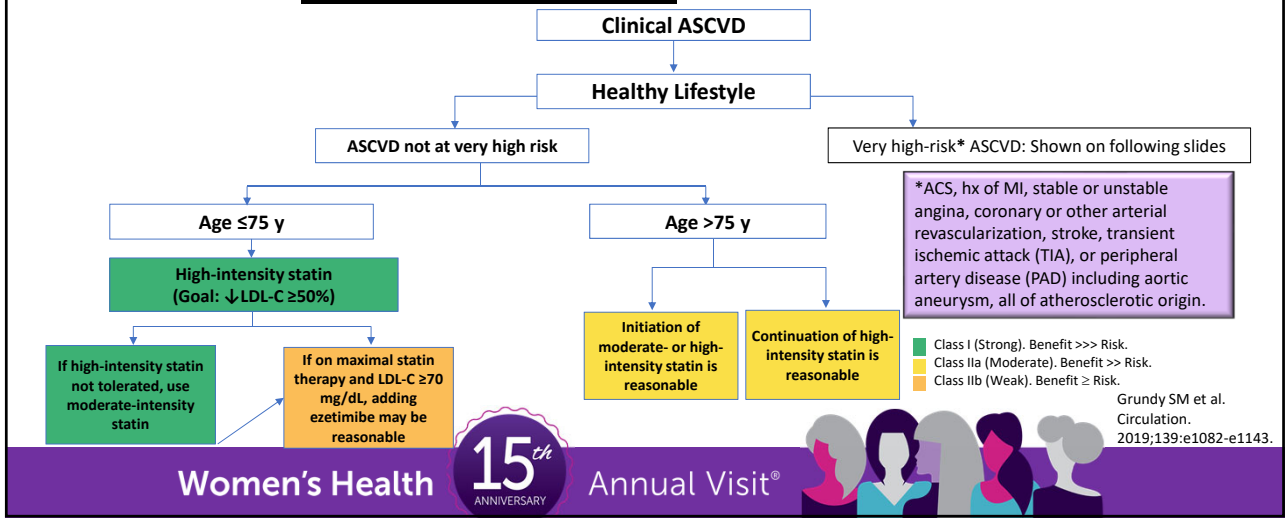
2018 AHA/ACC Guideline on the Management of Blood Cholesterol: Primary Prevention



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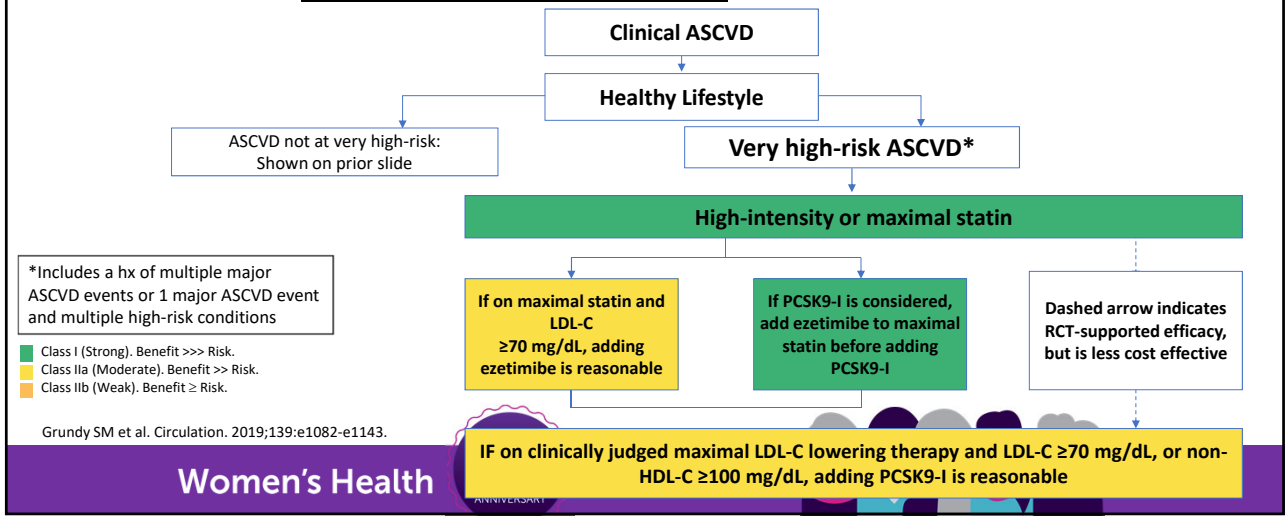
2018 AHA/ACC Guideline on the Management of Blood Cholesterol: Secondary Prevention (con't)



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Hypertriglyceridemia (HTG)

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

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

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Hypertriglyceridemia (HTG)

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

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Major Secondary Causes of HTG

- Diabetes mellitus, insulin resistance
- Obesity
- Alcohol
- Chronic kidney disease
- Nephrotic syndrome
- Hypothyroidism
- HIV
- Hepatocellular disease
- Inflammatory diseases

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

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Medications That Can Cause HTG

Agents Which Often Have Clinically Relevant Effects

- Oral estrogens (effects vary by unclear patient-specific factors)
- Antiretroviral HIV regimens
- Phenothiazines – (2nd generation)
- Glucocorticoids (systemic only, ***not*** topical creams or nasal)
- Immunosuppressants
- Tamoxifen
- Isotretinoin
- Ethanol

Agents Which Rarely Have Clinically Relevant Effects

- Bile-acid sequestrants
- Nonselective beta-blockers
- Diuretics

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

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New Guidelines and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

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ACC/AHA 2018 Cholesterol Guidelines — Top 10 Take-Home Messages

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

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

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

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

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Nutrition Lifestyle Recommendations: Lipids and BP

- **Dietary patterns emphasis-based:**
  - DASH and Mediterranean-style eating plans
- Fruits, vegetables, and whole grains
- 30-35% fat intake
  - <6% saturated fats, no trans fats
- Low sodium (<2400 mg/day), high potassium
- Cut down on "processed" (dietary fiber removed/sugar added) or pre-prepared food
- Healthy eating for a lifetime

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

New Guidelines and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

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Physical Activity Guidelines: Lipids and BP

- Advise adults to engage in aerobic physical activity
  - 3 to 4 sessions a week
  - lasting on average 40 min per session
  - involving moderate-to-vigorous intensity physical activity

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

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ACC/AHA 2018 Cholesterol Guidelines — Top 10 Take-Home Messages

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

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

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

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

New Guidelines and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

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ACC/AHA 2018 Cholesterol Guidelines — Top 10 Take-Home Messages

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

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

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

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ACC/AHA 2018 Cholesterol Guidelines — Top 10 Take-Home Messages

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

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

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

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ACC/AHA 2018 Cholesterol Guidelines — Top 10 Take-Home Messages

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

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

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

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ACC/AHA 2018 Cholesterol Guidelines — Top 10 Take-Home Messages

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

Risk discussion should include a review of:

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

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

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ACC/AHA 2018 Cholesterol Guidelines — Top 10 Take-Home Messages

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

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

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

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

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ACC/AHA 2018 Cholesterol Guidelines — Top 10 Take-Home Messages

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

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

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

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

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

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ACC/AHA 2018 Cholesterol Guidelines — Top 10 Take-Home Messages

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

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

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

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ACC/AHA 2018 Cholesterol Guidelines — Top 10 Take-Home Messages

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

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

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

New Guidelines and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

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Evidence-Based Approaches for Managing Patients at High Risk of ASCVD Events

Eliot Brinton, MD, FAHA, FNLA
President
Utah Lipid Center
Salt Lake City, UT

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Faculty Disclosure

Consulting Fees: Amarin, Esperion, Kowa

Commercial Interest Speakers Bureau: Amarin, Amgen, Boehringer, Kowa, Merck, Nova, Regeneron, Sanofi

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New Guidelines and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

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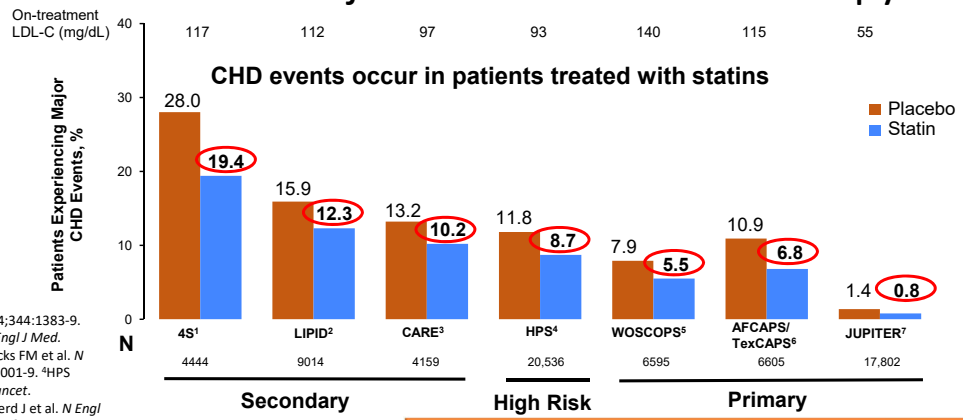
Residual CV Risk in Subjects on Statin Monotherapy



[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.

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

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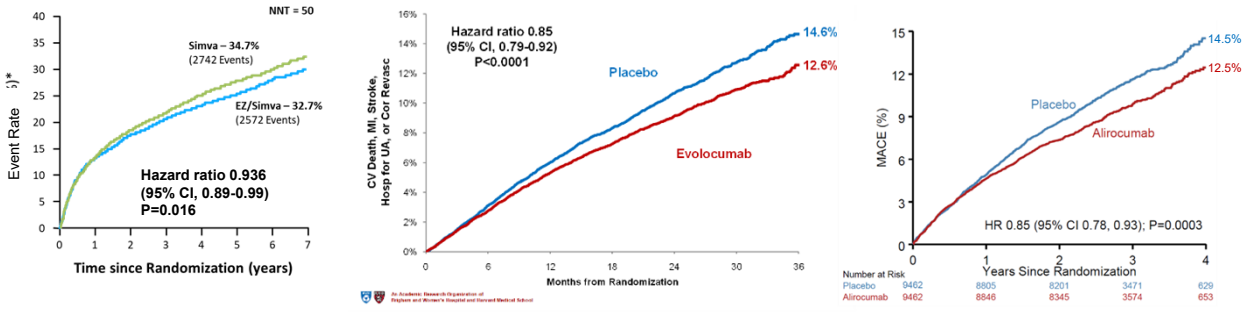
Additional LDL-C Lowering in Subjects on Statin Monotherapy Reduces CV Risk



1. Cannon CP et al. N Engl J Med. 2015;372:2387-97.
2. Sabatine MS et al. N Engl J Med. 2017;376:1713-22.
3. Schwartz GG et al. N Engl J Med. 2018;379:2097-107.

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

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Fenofibrate Outcome Trials

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

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

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

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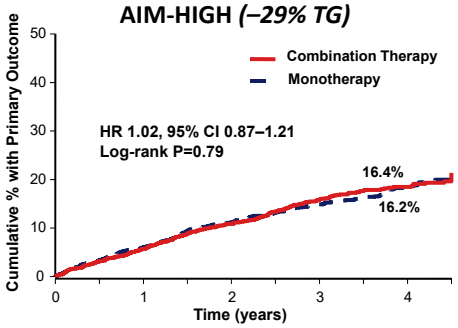
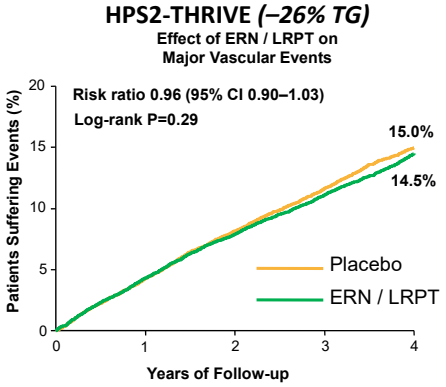
Niacin Outcome Trials

AIM-HIGH *(–29% TG)*



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

HPS2-THRIVE *(–26% TG)*



Boden WE et al. N Engl J Med. 2011;365:2255-67.
HPS2-THRIVE Collaborative Group. N Engl J Med. 2014;371:203-12.

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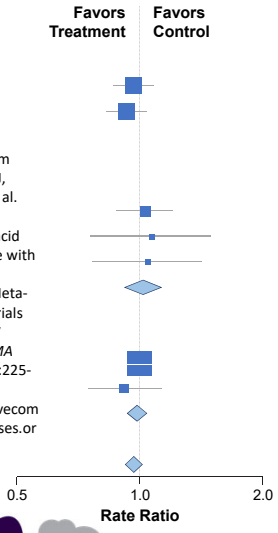
Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

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



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

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How May EPA and DHA Differ Re: Anti-Atherosclerotic Mechanisms?

Pros of EPA

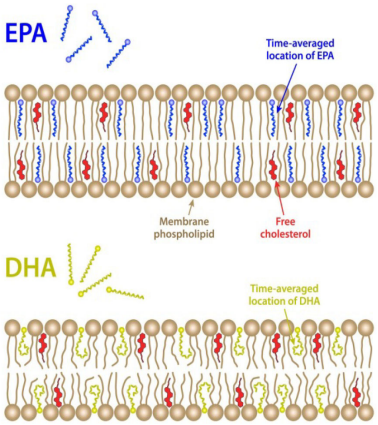
Fits between PL legs (in lipoproteins & cells):
- More stable in PL mono/bilayer
- Longer/better antiox effect
- No ↑chol crystals (vs. ↑ w/ DHA)

Fits in AA-series enzymes:
- ↓AA→pro-inflam cytokines
- ↓hsCRP
- No inhibition of LDL-R → modest ↓LDL-C/apoB

Pros of DHA

Coils up between PL legs:
- ↑↑Membrane fluidity

Modest ↑HDL-C (vs. ↓ w/ EPA)



EPA and DHA Appear to be *Similar* Re:
- ↓TG
- Anti-platelet
- Anti/pro-arrhythmia

Bottom Line:
EPA may be better than DHA, but this is *not* yet proven clinically. More research is needed.

Reprinted with permission* from Sherratt SCR, Mason RP. Chem Phys Lipids. 2018;212:73-79.
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New Guidelines and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

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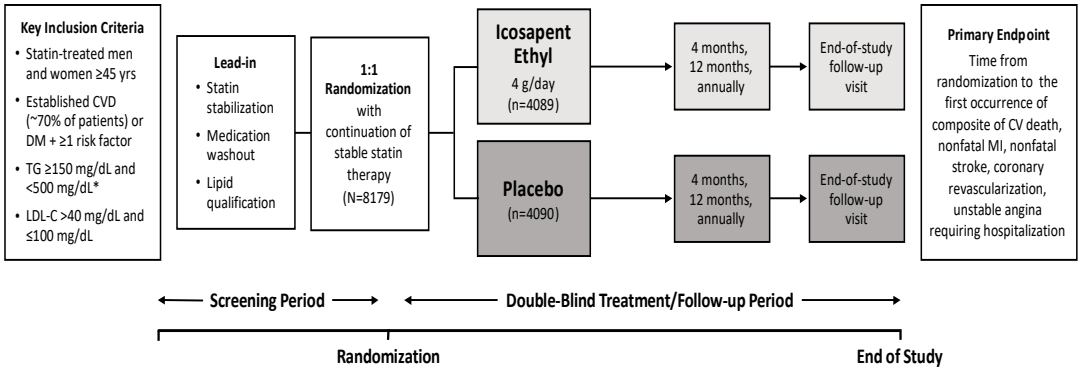
REDUCE-IT Design



After Bhatt DL, Steg PG, Brinton EA, et al. Clin Cardiol. 2017;40:138-148.

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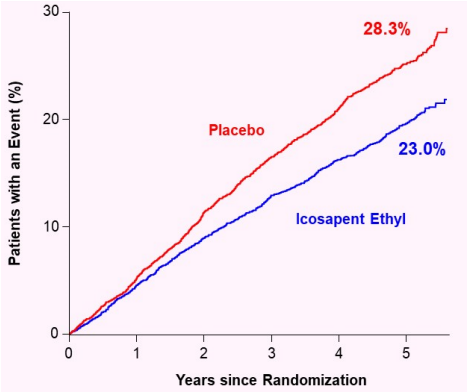
Primary Endpoint: CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

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

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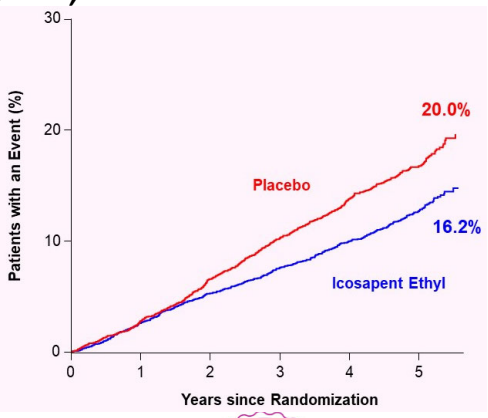
Key Secondary Endpoint: CV Death, MI, Stroke



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

RRR = 26.5%

ARR = 3.6%

NNT = 28 (95% CI, 20–47)

P=0.0000006

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

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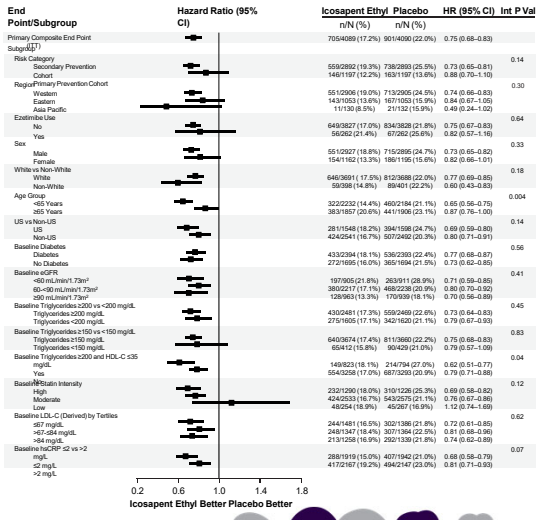
Primary Endpoint in Subgroups



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

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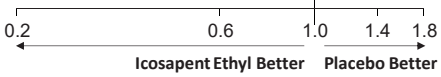
Primary Composite Endpoint: Time to First Event by Baseline TG Tertiles

TIME TO FIRST EVENT – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	HR (95% CI)	P-value
	n/N (%)	n/N (%)		
Primary Composite Endpoint (ITT)	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68–0.83)	<0.0001
Baseline Triglycerides by Tertiles*				
≥81 to ≤190 mg/dL	233/1378 (16.9)	291/1381 (21.1)	0.79 (0.66–0.94)	0.0069
>190 to ≤250 mg/dL	246/1370 (18.0)	283/1326 (21.3)	0.80 (0.68–0.95)	0.0121
>250 to ≤1401 mg/dL	226/1338 (16.9)	327/1382 (23.7)	0.68 (0.57–0.80)	<0.0001



***P (interaction) = 0.33**

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

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Treatment-Emergent Adverse Events

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

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

New Guidelines and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

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Treatment-Emergent Adverse Event of Interest: Serious Bleeding

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

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

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

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Adjudicated Events: Hospitalization for Atrial Fibrillation or Atrial Flutter

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

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

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

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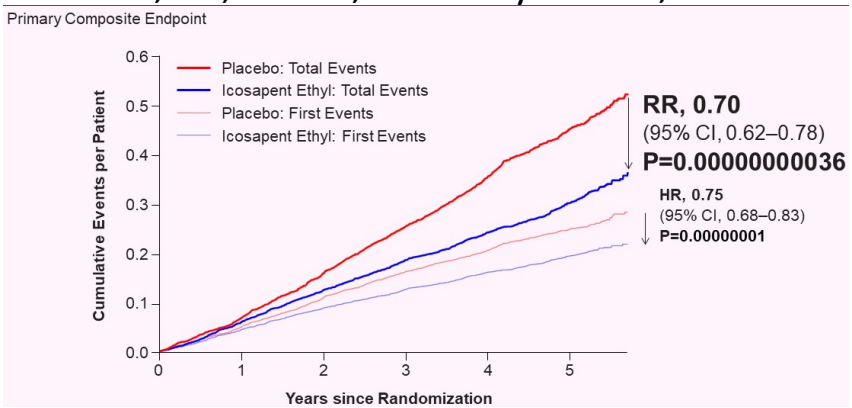
Total (First and Subsequent) Events

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



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

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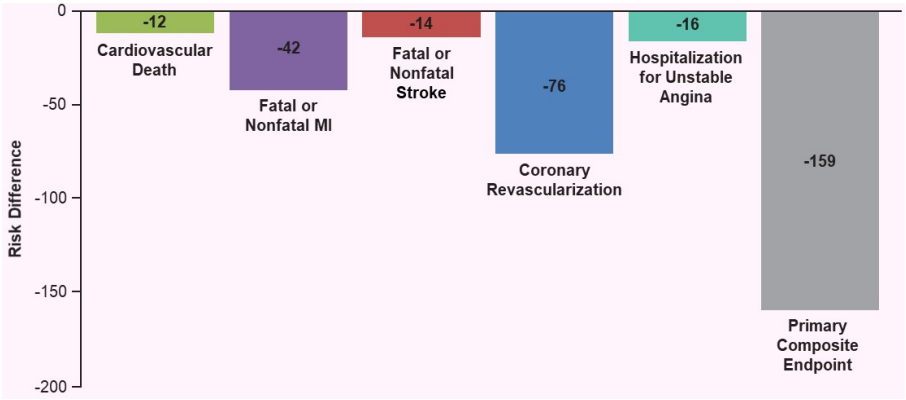
For Every 1,000 Patients Treated with Icosapent Ethyl for 5 Years:



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

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

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

- Treatment of Other Lipoprotein Fractions or Targets
  - In patients with ASCVD or other cardiac risk factors on a statin with controlled LDL-C, but elevated triglycerides (135-499), the addition of icosapent ethyl should be considered to reduce cardiovascular risk. **A**
  - "It should be noted that data are lacking with other omega-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products."
- Other Combination Therapy
  - Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. **A**
  - Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. **A**

1. American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes—2019 [web annotation]. Diabetes Care 2019;42(Suppl.1):S103–S123. https://hyp.is/JHhz_lCrEembFJ9LIVBZIw/care.diabetesjournals.org/content/42/Supplement_1/S103. Updated March 27, 2019. Accessed March 28, 2019.

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

FDA Product Classification[1] → Food

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

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

Ability to reduce ASCVD → **Not demonstrated**

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

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

New Guidelines and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

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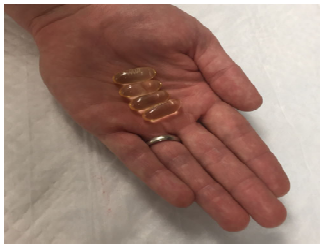
Besides the Other Issues with Dietary Supplements, You Need Huge Amounts to = 4g Rx EPA



Icosapent ethyl

EPA Dietary Supplement from label

Krill oil from label

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Conclusions

- Compared with placebo, icosapent ethyl 4g/day significantly reduced important CV events by 25%, including:
  - 20% reduction in death due to cardiovascular causes
  - 31% reduction in heart attack
  - 28% reduction in stroke
- Low rate of adverse effects, including:
  - Small but significant increase in atrial fibrillation/flutter
  - Non-statistically significant increase in serious bleeding
- Consistent efficacy across multiple subgroups
  - Including baseline triglycerides from 135-500 mg/dL
  - Including secondary and primary prevention cohorts

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New Guidelines and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

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Conclusions

- Compared with placebo, icosapent ethyl 4g/day significantly reduced total cardiovascular events by 30%, including:
  - 25% reduction in first cardiovascular events
  - 32% reduction in second cardiovascular events
  - 31% reduction in third cardiovascular events
  - 48% reduction in fourth or more cardiovascular events
- Analysis of first, recurrent, and total events demonstrates the large burden of ischemic events in statin-treated patients with baseline triglycerides >~100 mg/dL and the potential role of icosapent ethyl in reducing this residual risk

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Case: 65-yo African-American Woman with No Prior CHD Events, with HTG

Eliot Brinton, MD, FAHA, FNLA
Margo B. Minissian, PhD, ACNP

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New Guidelines and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

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Case: 65-yo African-American Woman with No Prior CVD Events, Postmenopause, with HTG

Meds:

HCTZ 50 mg/d

Exam:

BMI=33 kg/m2, BP=126/84 mm Hg, Waist=36", Non-smoker

Labs:

Fasting glucose	115 mg/dL
A1c	6.2%
TC	201 mg/dL
TG	320 mg/dL
HDL-C	36 mg/dL
LDL-C	98 mg/dL
Non-HDL-C	174 mg/dL

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2018 AHA/ACC Guideline on the Management of Blood Cholesterol: Primary Prevention

Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

MO11

Age 0–19 y
- Lifestyle to prevent or reduce ASCVD risk
- Diagnosis of Familial Hyper-cholesterolemia → statin

Age 20–39 y
- **Estimate lifetime risk** to encourage lifestyle to reduce ASCVD risk
- Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL

Age 40–75 y & LDL-C ≥70 to <190 mg/dL without diabetes mellitus
- 10-year ASCVD risk percent begins risk discussion

Continued on next slide

LDL-C ≥190 mg/dL
No risk assessment; High-intensity statin

Diabetes mellitus and age 40-75 y
Moderate-intensity statin

Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin

Age >75 y
Clinical assessment, Risk discussion

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

Although high TG was noted as a CVD risk factor, treatment of HTG was covered only briefly and prescription omega-3 was not mentioned. (Published simultaneously with REDUCE-IT.)
Grundy SM et al. Circulation. 2019;139:e1082-e1143.

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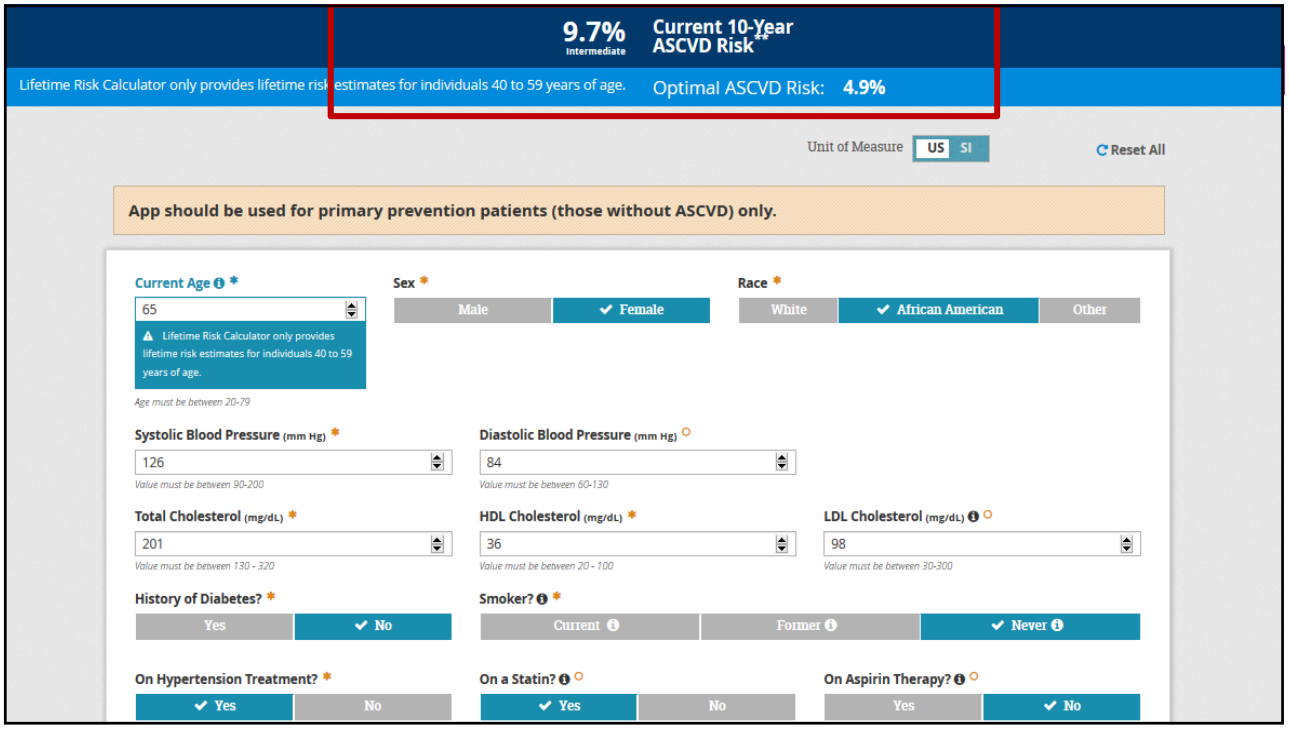
New Guidelines and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

Slide 58

MO11 Think this should be "Healthy Lifestyle"
Meghan Orner, 9/11/2019



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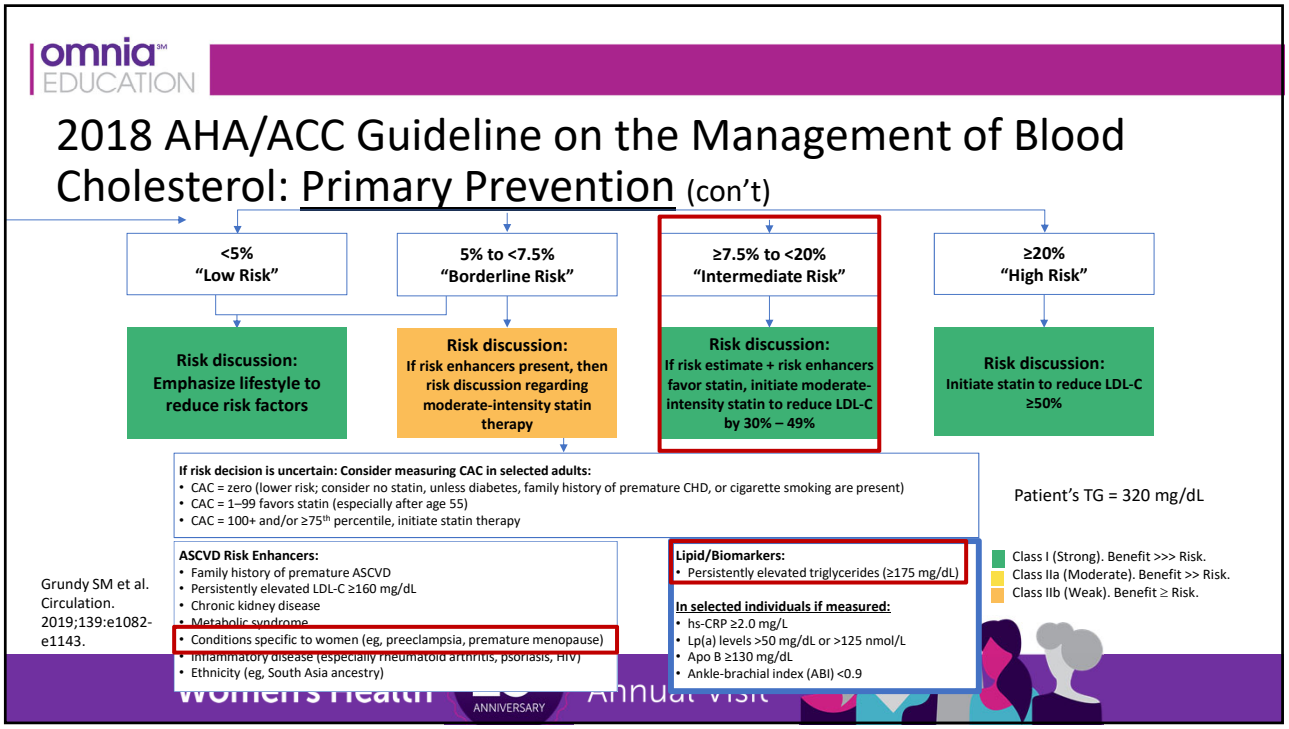

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Final Comments

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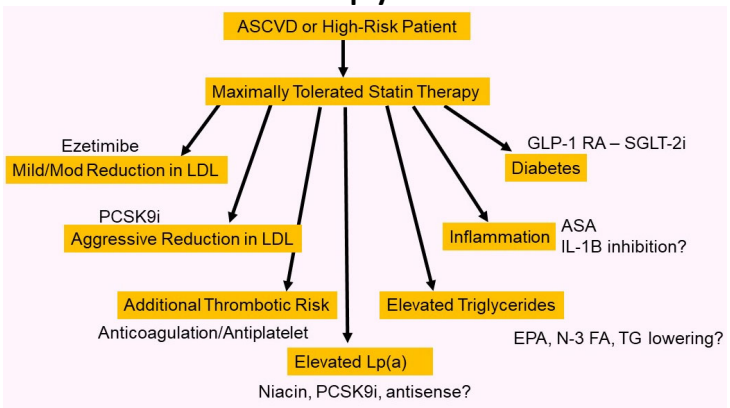
Pharmacologic Approaches to Managing Residual ASCVD Risk After Statin Therapy



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