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

Erin D. Michos, MD, MHS, FACC, FAHA, FASE
Michael Miller, MD, FACC, FAHA

Identified or perceived conflict of interest has been resolved in accordance with ACCME guidelines.

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
Faculty Disclosure

Dr. Michos has nothing to disclose.

Dr. Miller receives consulting fees from Amarin.

Identifying Women at Risk for ASCVD

New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
Only ~Half of Women* Know that Heart Disease Is Their #1 Killer

- **Heart disease is the #1 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 #4 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.heart.org/lko/groups/heart-public/@wcm/@spj@smi/documents/downloadable/ucm_472913.pdf

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

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

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

New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
The Evaluation of CV Risk Factors and Symptoms in Women Remains Challenging

<table>
<thead>
<tr>
<th>Risk factors specific to women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established risk factors common to both genders</td>
</tr>
<tr>
<td>Psychological stress</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>History of CAD or other atherosclerotic vascular disease</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Inflammatory disorders e.g. RA</td>
</tr>
<tr>
<td>Dyslipidemia: high LDL, low HDL</td>
</tr>
<tr>
<td>Age ≥65 years</td>
</tr>
<tr>
<td>Family history of premature CAD</td>
</tr>
</tbody>
</table>

Influence of Gender on ASCVD Symptoms

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

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


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

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)

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

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

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 ≥190 mg/dL
  No risk assessment; High-intensity statin
- Diabetes mellitus and age 40–75 y
  Moderate-intensity statin

Age >75 y
- Clinical assessment, Risk discussion

LDL-C ≥70 to <190 mg/dL without diabetes mellitus
- 10-year ASCVD risk percent begins risk discussion

Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% – 49%

Risk discussion:
If risk estimation + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by ≥50%

Risk discussion:
If risk decision is uncertain: Consider measuring CAC in selected adults:
- CAC = zero (lower risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
- CAC <10th percentile, initiate statin therapy
- CAC = 10th+ and/or ≥75th percentile, initiate statin therapy

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.)

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

**Clinical ASCVD**

- **ASCVD not at very high-risk**
  - Age ≤75 y
  - High-intensity statin (Goal: ↓LDL-C ≥50%)
  - If high-intensity statin not tolerated, use moderate-intensity statin
  - If on maximal statin therapy and LDL-C ≥70 mg/dL, adding ezetimibe may be reasonable

- **Continuation of high-intensity statin is reasonable**

**Healthy Lifestyle**

- Very high-risk* ASCVD: Shown on following slides

*ACS, hx of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin.


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

**Clinical ASCVD**

- **ASCVD not at very high-risk:** Shown on prior slide

**Healthy Lifestyle**

- **Very high-risk ASCVD***

**High-intensity or maximal statin**

- If on maximal statin and LDL-C ≥70 mg/dL, adding ezetimibe is reasonable
- If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I
- Dashed arrow indicates RCT-supported efficacy, but is less cost effective

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


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

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>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.</td>
</tr>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>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.).</td>
</tr>
</tbody>
</table>

Major Secondary Causes of HTG

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

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

New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
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, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction.

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


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

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


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 will be subsequent risk reduction.

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

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.


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.

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%.


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.

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%.


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)


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


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).

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

Residual CV Risk in Subjects on Statin Monotherapy

On-treatment LDL-C (mg/dL)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>LDL-C</th>
<th>CHD events in patients treated with statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>4444</td>
<td>28.0</td>
<td>0.8</td>
</tr>
<tr>
<td>LIPID</td>
<td>9014</td>
<td>15.9</td>
<td>16.2</td>
</tr>
<tr>
<td>CARE</td>
<td>4159</td>
<td>12.3</td>
<td>13.2</td>
</tr>
<tr>
<td>HPS</td>
<td>20,036</td>
<td>11.8</td>
<td>5.5</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>6,595</td>
<td>7.9</td>
<td>10.9</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>6,605</td>
<td>5.5</td>
<td>6.8</td>
</tr>
<tr>
<td>JUPITER</td>
<td>17,802</td>
<td>1.4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

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.

New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
Additional LDL-C Lowering in Subjects on Statin Monotherapy Reduces CV Risk

**Table: Fenofibrate Outcome Trials**

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

*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 mg/dL (Sacks FM et al. N Engl J Med. 2010;363:692-4).*
New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

### Niacin Outcome Trials

**AIM-HIGH (−29% TG)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1696</td>
<td>1718</td>
</tr>
<tr>
<td>10</td>
<td>1581</td>
<td>1606</td>
</tr>
<tr>
<td>20</td>
<td>1381</td>
<td>1366</td>
</tr>
<tr>
<td>30</td>
<td>910</td>
<td>903</td>
</tr>
<tr>
<td>40</td>
<td>436</td>
<td>428</td>
</tr>
</tbody>
</table>

Risk ratio 1.02, 95% CI 0.87–1.21
Log-rank P=0.79 (NS)

**HPS2-THRIVE (−26% TG)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1301</td>
<td>1394</td>
</tr>
<tr>
<td>1</td>
<td>1305</td>
<td>1394</td>
</tr>
<tr>
<td>2</td>
<td>1291</td>
<td>1384</td>
</tr>
<tr>
<td>3</td>
<td>1255</td>
<td>1363</td>
</tr>
<tr>
<td>4</td>
<td>1050</td>
<td>1155</td>
</tr>
</tbody>
</table>

Risk ratio 0.96 (95% CI 0.90–1.03)
Log-rank P=0.29 (NS)

#### Rate Ratios (CI)

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events (%)</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratios (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td>1321 (3.9)</td>
<td>1155 (3.0)</td>
<td>0.97 (0.87–1.08)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td></td>
<td>1301 (3.3)</td>
<td>1394 (3.6)</td>
<td>0.93 (0.83–1.03)</td>
</tr>
<tr>
<td>Any</td>
<td></td>
<td>3081 (7.9)</td>
<td>3188 (8.2)</td>
<td>0.96 (0.90–1.01)</td>
</tr>
</tbody>
</table>

P=0.12

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events (%)</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratios (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td></td>
<td>574 (1.9)</td>
<td>554 (1.8)</td>
<td>1.03 (0.88–1.21)</td>
</tr>
<tr>
<td>Ischemic</td>
<td></td>
<td>117 (0.4)</td>
<td>109 (0.4)</td>
<td>1.07 (0.79–1.45)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td></td>
<td>142 (0.4)</td>
<td>135 (0.3)</td>
<td>1.03 (0.77–1.39)</td>
</tr>
<tr>
<td>Unclassified/other</td>
<td></td>
<td>870 (2.2)</td>
<td>843 (2.2)</td>
<td>1.03 (0.93–1.13)</td>
</tr>
</tbody>
</table>

P=0.60

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events (%)</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratios (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revascularization</td>
<td></td>
<td>3044 (9.3)</td>
<td>3040 (9.3)</td>
<td>1.00 (0.93–1.07)</td>
</tr>
<tr>
<td>Coronary</td>
<td></td>
<td>305 (2.7)</td>
<td>330 (2.9)</td>
<td>0.92 (0.75–1.11)</td>
</tr>
<tr>
<td>Noncoronary</td>
<td></td>
<td>3290 (10.0)</td>
<td>3315 (10.2)</td>
<td>0.99 (0.94–1.04)</td>
</tr>
</tbody>
</table>

P=0.60

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events (%)</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratios (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any major vascular event</td>
<td></td>
<td>5930 (15.2)</td>
<td>6071 (15.6)</td>
<td>0.97 (0.93–1.01)</td>
</tr>
</tbody>
</table>

P=0.10

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### Low-Dose Omega-3 Mixtures Show No CV Benefit

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events (%)</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratios (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td>5511 (3.3)</td>
<td>5295 (3.1)</td>
<td>1.00 (0.93–1.07)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td></td>
<td>5416 (3.3)</td>
<td>5408 (3.1)</td>
<td>1.00 (0.93–1.07)</td>
</tr>
<tr>
<td>Any</td>
<td></td>
<td>11211 (5.5)</td>
<td>11105 (5.4)</td>
<td>1.00 (0.93–1.07)</td>
</tr>
</tbody>
</table>

P=0.60

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

**Pros of EPA**
- Fits between PL legs (in lipoprt & cells):
  - More stable in PL mono/bilayer
  - Longer/better antioxidant effect
  - No ↑cholesterol crystals (vs. ↑ w/ DHA)
- Fits in AA-series enzymes:
  - ↓AA → pro-inflammatory 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.

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**REduce-IT Design**

**Key Inclusion Criteria**
- Statin-treated men and women ≥45 yrs
- Established CVD (≥70% of patients) or DM + ≥2 risk factors
- TG ≥150 mg/dL and <500 mg/dL
- LDL-C ≥40 mg/dL and ≤100 mg/dL

**Lead-in**
- Statin stabilization
- Medication washout
- Lipid qualification

**1:1 Randomization with continuation of stable statin therapy**
- Icosapent Ethyl 4 g/day (n=4090)
- Placebo (n=4089)

**Primary Endpoint**
- Time from randomization to first occurrence of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina requiring hospitalization

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

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

- **Hazard Ratio, 0.75**
  (95% CI, 0.68–0.83)
  - RRR = 24.8%
  - ARR = 4.8%
  - NNT = 21 (95% CI, 15–33)
  - P=0.0000001

Key Secondary End Point: CV Death, MI, Stroke (“hard” CVD endpoints)

- **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
New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
Adjudicated Events: Hospitalization for Atrial Fibrillation or Atrial Flutter

<table>
<thead>
<tr>
<th>Primary System Organ Class Preferred Term</th>
<th>Icosapent Ethyl (N=4089)</th>
<th>Placebo (N=4090)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positively Adjudicated Atrial Fibrillation/Flutter[^1]</td>
<td>127 (3.1%)</td>
<td>84 (2.1%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

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.


Total (First and Subsequent) Events

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


New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:

-12
Cardiovascular Death

-42
Fatal or Nonfatal MI

-14
Fatal or Nonfatal Stroke

-76
Coronary Revascularization

-159
Hospitalization for Unstable Angina

Primary Composite Endpoint


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

Section 10 – Cardiovascular Disease and Risk Management: Lipid Management

- 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


New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
New Recommendations for Drug Treatment of Patients with Hypertriglyceridemia: European Society of Cardiology (ESC) and National Lipid Association (NLA)

**Recommendations**

<table>
<thead>
<tr>
<th>Statin treatment is recommended as the first drug of choice to reduce CVR risk in high-risk individuals with hypertriglyceridemia (TG levels &gt;2.3 mmol/L [&gt;200 mg/dL]).</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients 45 years of age or older with clinical ASCVD, or 50 years of age or older with type 2 diabetes requiring medication and ≥1 additional risk factor*, and fasting triglycerides 135–499 mg/dL on maximally tolerated statin, with or without ezetimibe, treatment with icosapent ethyl is recommended for ASCVD risk reduction. (I B–R)</td>
</tr>
</tbody>
</table>

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

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

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

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

Icosapent ethyl  
EPA Dietary Supplement (per label)  
Krill oil (per label)

Conclusions

• Compared with placebo, icosapent ethyl 4g/day significantly reduced CV events
  — **time to first event**, primary endpoint—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 **TG 135-500 mg/dL**
    – Including **women** and secondary and primary prevention cohorts

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

• Compared with placebo, icosapent ethyl 4g/day significantly reduced total CV 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 TG >~135 mg/dL and the potential role of icosapent ethyl in reducing this residual risk

Case: 59-‐yo African American Woman with No Prior CHD Events, with HTG

New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
Case: 59-yr African American Woman with No Prior CVD Events, Post-Menopausal, w/moderate HTG & HBP (treated)

**Meds:**
HCTZ 25 mg/d

**Exam:**
BMI=31 kg/m², BP=126/84 mm Hg, Waist=38”, Non-smoker

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

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

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

- **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 ≥190 mg/dL

- **Age 40–75 y & LDL-C ≥190 mg/dL**
  - Diabetes mellitus and age 40-75 y
  - Moderate-intensity statin
  - Risk assessment to consider high-intensity statin

- **Age >75 y**
  - Clinical assessment, Risk discussion

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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