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

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

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
Identifying Women at Risk for ASCVD

Margo B. Minissian, PhD, ACNP, FAHA, FNLA
Nurse Scientist, Cardiology Nurse Practitioner
Clinical Lipid Specialist, Barbra Streisand Women’s Heart Center
Cedars-Sinai Heart Institute
Los Angeles, CA

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 #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.cdc.gov/heartdisease/women.htm
https://www.heart.org/hcmj/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_472913.pdf

Undertreatment: Women Receive Less Statin Therapy Than Men*

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

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

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

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.

ASCVD Risk Assessment, Hypertriglyceridemia, and Management Strategies in Women

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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)

ACC Risk Calculator Plus to Assess Risk Category

Then use the new AHA/ACC Blood Cholesterol Guideline Algorithm for Primary Prevention to guide management
New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

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

Age >75 y
Clinical assessment, Risk discussion

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 = 1–99 favors statin (especially after age 55)
• CAC = 100+ and/or ≥75th percentile, initiate statin therapy

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

Risk levels and management:

- **<5% “Low Risk”**
  - Risk discussion: Emphasize lifestyle to reduce risk factors

- **5% to <7.5% “Borderline Risk”**
  - 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 = 1–99 favors statin (especially after age 55)
    - CAC = ≥100 and/or ≥75th percentile, initiate statin therapy

- **≥7.5% to <20% “Intermediate Risk”**
  - Risk discussion: If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
  - Risk discussion: If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% – 49%

- **≥20% “High Risk”**
  - Risk discussion: Initiate statin to reduce LDL-C ≥50%

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (eg, preeclampsia, premature menopause)
- Inflammatory disease (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (eg, South Asia ancestry)

Lipid/Biomarkers:
- Persistently elevated triglycerides (≥175 mg/dL)
- In selected individuals if measured:
  - hs‐CRP ≥2.0 mg/L
  - Lp(a) levels >50 mg/dL or >125 nmol/L
  - Apo B ≥130 mg/dL
  - Ankle‐brachial index (ABI) <0.9


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.

Very High Risk of Future CVD Events


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)
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**


New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
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 $\geq 50\%$.


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


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.

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%.


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.


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

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%.


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.


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).


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

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

Faculty Disclosure

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

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

<table>
<thead>
<tr>
<th>N</th>
<th>4S1</th>
<th>LIPID2</th>
<th>CARE3</th>
<th>HPS4</th>
<th>WOSCOPS5</th>
<th>AFCAPS/TexCAPS6</th>
<th>JUPITER7</th>
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<tr>
<td>117</td>
<td>28.0</td>
<td>17.9</td>
<td>13.2</td>
<td>11.8</td>
<td>10.9</td>
<td>0.8</td>
<td>1.4</td>
</tr>
<tr>
<td>112</td>
<td>19.4</td>
<td>15.9</td>
<td>12.3</td>
<td>8.7</td>
<td>6.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>97</td>
<td></td>
<td>11.8</td>
<td>10.2</td>
<td>5.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93</td>
<td></td>
<td>9.9</td>
<td>8.7</td>
<td>6.8</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>140</td>
<td></td>
<td>11.8</td>
<td>10.2</td>
<td>5.5</td>
<td></td>
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<tr>
<td>115</td>
<td></td>
<td>9.9</td>
<td>8.7</td>
<td>6.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55</td>
<td></td>
<td>11.8</td>
<td>10.2</td>
<td>5.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CHD events occur in patients treated with statins

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Event Rate</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPROVE-IT</td>
<td>14.5%</td>
<td>0.936</td>
<td>0.89-0.99</td>
<td>0.016</td>
</tr>
<tr>
<td>FOURIER</td>
<td>12.5%</td>
<td>0.85</td>
<td>0.78-0.93</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ODYSSEY Outcomes</td>
<td>14.5%</td>
<td>0.85</td>
<td>0.78-0.93</td>
<td>0.0003</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.

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


New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
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>All pts: 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) P=0.32 (NS)</td>
<td></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 Median f/u: 5 yrs</td>
<td>HR=0.89* (95% CI: 0.75-1.05) P=0.16 (NS)</td>
<td></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).


Niacin Outcome Trials

**AIM-HIGH (~29% TG)**

- Combination Therapy
- Monotherapy

<table>
<thead>
<tr>
<th>N at risk</th>
<th>Time (years)</th>
<th>Cumulative % with Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>1586</td>
<td>1531</td>
</tr>
<tr>
<td>Combination Therapy</td>
<td>1718</td>
<td>1606</td>
</tr>
</tbody>
</table>

| HR 1.02, 95% CI 0.87-1.21 | Log-rank P=0.79 (NS) |

**HPS2-THRIVE (~26% TG)**

Effect of ERN / LRPT on Major Vascular Events

<table>
<thead>
<tr>
<th>Risk ratio 0.96 (95% CI 0.90-1.03)</th>
<th>Log-rank P=0.29 (NS)</th>
</tr>
</thead>
</table>


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

Low-Dose Omega-3 Mixtures Show No CV Benefit

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events (%)</th>
<th>Rate Ratios (CI)</th>
<th>Favors</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1132 (2.9)</td>
<td>1155 (3.0)</td>
<td>0.97 (0.87–1.08)</td>
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</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>1301 (3.3)</td>
<td>1394 (3.6)</td>
<td>0.93 (0.83–1.03)</td>
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</tr>
<tr>
<td>Coronary heart disease</td>
<td>3085 (7.9)</td>
<td>3188 (8.2)</td>
<td>0.96 (0.90–1.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P=.012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>574 (1.9)</td>
<td>554 (1.8)</td>
<td>1.03 (0.88–1.21)</td>
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<tr>
<td>Hemorrhagic</td>
<td>117 (0.4)</td>
<td>109 (0.4)</td>
<td>1.07 (0.76–1.51)</td>
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<tr>
<td>Unclassified/other</td>
<td>142 (0.4)</td>
<td>135 (0.3)</td>
<td>1.05 (0.77–1.43)</td>
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<tr>
<td>Any</td>
<td>870 (2.2)</td>
<td>843 (2.2)</td>
<td>1.03 (0.93–1.13)</td>
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</tr>
<tr>
<td></td>
<td>P=.60</td>
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<tr>
<td>Revascularization</td>
<td></td>
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<tr>
<td>Coronary</td>
<td>3044 (9.3)</td>
<td>3040 (9.3)</td>
<td>1.00 (0.93–1.07)</td>
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<tr>
<td>Noncoronary</td>
<td>305 (2.7)</td>
<td>330 (2.9)</td>
<td>0.92 (0.79–1.08)</td>
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<tr>
<td>Any</td>
<td>3290 (10.0)</td>
<td>3313 (10.2)</td>
<td>0.99 (0.94–1.04)</td>
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</tr>
<tr>
<td></td>
<td>P=.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>5930 (15.2)</td>
<td>6071 (15.6)</td>
<td>0.97 (0.93–1.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P=.10</td>
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</table>

Adapted with permission from Aung T, 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/]

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

**REDUCE-IT Design**

**Key Inclusion Criteria**
- Statin-treated men and women ≥45 yrs
- Established CVD (~70% of patients) or DM + ≥1 risk factor
- TG ≥150 mg/dL and <500 mg/dL
- LDL-C >40 mg/dL and ≤100 mg/dL

**Lead-in**
- Icosapent Ethyl
- Placebo (n=4090)

**Icosapent Ethyl**
- 4 g/day
- 1:1 Randomization with continuation of stable statin therapy (N=8179)
- 4 months, 12 months, annually

**Placebo**
- 4 months, 12 months, annually

**End of Study**
- End-of-study follow-up visit

**Randomization**
- Time from randomization to the first occurrence of composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina requiring hospitalisation

**Primary Endpoint**

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

**Patients with an Event (%)**

- Icosapent Ethyl
- Placebo

**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**
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


Primary End Point in Subgroups


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**Primary Composite Endpoint:**

Time to First Event by Baseline TG Tertiles

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

*P (interaction) = 0.33


**Treatment-Emergent Adverse Events**

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

Treatment-Emergent Adverse Event of Interest: Serious Bleeding

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

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


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


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


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

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridemia (TG levels &gt;2.3 mmol/L [&gt;200 mg/dL]).</td>
<td>I</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>In high-risk (or above) patients with TG levels between 1.5–5.4 mmol/L (135–499 mg/dL), despite statin treatment, e-3 PUFA's (icosapent ethyl 2–2 g/day) should be considered in combination with a statin.</td>
<td>IIa</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>In primary prevention patients who are on LDL-C goal with TG levels &gt;2.3 mmol/L (&gt;200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statin.</td>
<td>IIb</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>In high-risk patients who are on LDL-C goal with TG levels &gt;2.3 mmol/L (&gt;200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statin.</td>
<td>IIb</td>
<td>C</td>
<td></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)

*≥1 of the following:
- Age: men ≥55 years and women ≥65 years
- Cigarette smoker or stopped smoking within 3 months
- Hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) or on antihypertensive medication
- HDL-C <40 mg/dL, for men or <50 mg/dL, for women
- hs-CRP >2.0 mg/L
- Renal dysfunction: Creatinine clearance ≤30 and <60 mL/min
- Retinopathy
- Meto- or macro-albuminuria
- ABI <0.9 without symptoms of intermittent claudication


New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
Dietary Supplement Fish Oil: *Not* Useful for ASCVD Prevention

<table>
<thead>
<tr>
<th>FDA Product Classification¹</th>
<th>Food</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Trials/FDA Pre-Approval¹</td>
<td>Not Required</td>
</tr>
<tr>
<td>Content &amp; Purity²</td>
<td>Often difficult to achieve high doses likely needed for efficacy</td>
</tr>
<tr>
<td></td>
<td>Often have high saturated fat content</td>
</tr>
<tr>
<td></td>
<td>Omega-3 content often overstated</td>
</tr>
<tr>
<td></td>
<td>Tend to contain relatively high amounts of oxidized lipids which may increase CV risk</td>
</tr>
<tr>
<td>Ability to reduce ASCVD</td>
<td>Not demonstrated</td>
</tr>
<tr>
<td>Use for Treatment of Disease</td>
<td>Not Recommended</td>
</tr>
</tbody>
</table>


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)

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 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

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

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

Case: 59-yo 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

New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
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 ≥70 to <190 mg/dL without diabetes mellitus
• 10-year ASCVD risk percent begins risk discussion

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.)


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

New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
2018 AHA/ACC Guideline on the Management of Blood Cholesterol: Primary Prevention (con’t)

- <5% “Low Risk”
  - Risk discussion: Emphasize lifestyle to reduce risk factors

- 5% to <7.5% “Borderline Risk”
  - Risk discussion: If risk enhancers present then risk discussion regarding moderate-intensity statin therapy

- ≥7.5% to <20% “Intermediate Risk”
  - Risk discussion: If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% – 49%

- ≥20% “High Risk”
  - Risk discussion: Initiate statin to reduce LDL-C ≥50%

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory disease (especially rheumatoid arthritis and psoriasis, HIV)
- Ethnicity (e.g., South Asia ancestry)

Lipid/Biomarkers:
- Persistently elevated triglycerides (≥175 mg/dL)
- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 nmol/L
- Apo B ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9

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 = 1–99 favors statin (especially after age 55)
- CAC = 100+ and/or ≥75th percentile, initiate statin therapy

Patient’s TG = 320 mg/dL


Final Comments

New Guideline and Evidence to Improve Management of Patients with or at High-Risk of Atherosclerotic Cardiovascular Disease (ASCVD)
Pharmacologic Approaches to Managing Residual ASCVD Risk After Statin Therapy

ASCVD or High-Risk Patient

Maximally Tolerated Statin Therapy
- Ezetimibe
- PCSK9i
- Aggressive Reduction in LDL

GLP-1 RA – SGLT-2i

Diabetes

Inflammation

ASA, IL-1β inhibition?

Elevated Triglycerides

EPA, N-3 FA, TG lowering?

Elevated Lp(a)

Niacin, PCSK9i, antisense?

Additional Thrombotic Risk
- Anticoagulation/Antiplatelet

Women’s Health Annual Visit®

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