New Era of ASCVD Lipid Risk Management

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Update on Risk Status in ASCVD

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Faculty Disclosure: James Underberg

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

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

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

<table>
<thead>
<tr>
<th>Men</th>
<th>During a First Myocardial Infarction in Young Adults (18-59 Years) in the US</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>Diabetes Mellitus</td>
<td>34%</td>
</tr>
<tr>
<td>6%</td>
<td>Drug Abuse</td>
<td>5%</td>
</tr>
<tr>
<td>57%</td>
<td>Hypertension</td>
<td>61%</td>
</tr>
<tr>
<td>58%</td>
<td>Dyslipidemia</td>
<td>52%</td>
</tr>
<tr>
<td>16%</td>
<td>Obesity</td>
<td>23%</td>
</tr>
<tr>
<td>54%</td>
<td>Smoking</td>
<td>50%</td>
</tr>
<tr>
<td>92%</td>
<td>Any of these modifiable risk factors</td>
<td>91%</td>
</tr>
</tbody>
</table>

2018 Blood Cholesterol Guidelines: Role of Risk Estimation in Primary Prevention

ACC ASCVD Risk Estimator Plus
App Should Be Used for Primary Prevention Patients (Those Without ASCVD) Only


New Era of ACVD Lipid Risk Management
### 2018 Blood Cholesterol Guidelines: Primary Prevention for Intermediate Risk

#### ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥190 mg/dL (≥4.9 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., premature menopause, inflammatory diseases, especially rheumatoid arthritis, postmenopausal)
- Ethnicity (e.g., South Asian ancestry)

#### Lipid/Biomarkers:
- Persistently elevated triglycerides >573 mg/dL (≥6.5 mmol/L)
- If measured:
  - No CAC ≥2.2 mmol/L
  - Lipid levels ≥300 mg/dL or ≥125 mmol/L
  - Apo B ≥30 mg/dL
  - Arterial-branch index (ABI) <0.9

#### Risk Discussion:
- Emphasize lifestyle to reduce risk factors (Class I)

#### Risk Discussion: If risk enhances present then risk discussion regarding moderate-intensity statin therapy (Class IIa)
- LDL-C ≥190 mg/dL (≥4.9 mmol/L)
- Moderate-intensity statin

#### Risk Discussion: If risk enhances present then risk discussion regarding high-intensity statin therapy (Class IIa)
- LDL-C ≥150 mg/dL (≥4.0 mmol/L)
- High-intensity statin

---

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

<table>
<thead>
<tr>
<th>Patient’s 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimate</th>
<th>&lt;5%</th>
<th>5–7.5%</th>
<th>&gt;7.5–20%</th>
<th>&gt;20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consulting ASCVD risk estimate alone</td>
<td>Statin not recommended</td>
<td>Consider for statin</td>
<td>Recommend statin</td>
<td>Recommend statin</td>
</tr>
<tr>
<td>Consulting ASCVD risk estimate + CAC</td>
<td>Statin not recommended</td>
<td>Statin not recommended</td>
<td>Statin not recommended</td>
<td>Statin not recommended</td>
</tr>
<tr>
<td>If CAC score = 0</td>
<td>Statin not recommended</td>
<td>Statin not recommended</td>
<td>Statin not recommended</td>
<td>Statin not recommended</td>
</tr>
<tr>
<td>If CAC score &gt; 0</td>
<td>CAC not effective for this population</td>
<td>CAC can reclassify risk up or down</td>
<td>CAC can reclassify risk up or down</td>
<td>CAC not effective for this population</td>
</tr>
</tbody>
</table>

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**2018 Blood Cholesterol Guidelines**

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

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

Measurements of LDL-C and Non-HDL-C

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

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


Monitoring Response to Drug Therapy

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

Patients with Primary Severe Hypercholesterolemia

LDL-C levels ≥190 mg/dL [≥4.9 mmol/L]

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


2018 Blood Cholesterol Guidelines

Patients Who Need Primary Prevention

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

2018 Blood Cholesterol Guidelines
Role of PSCK9 in Primary Prevention in Severe Hypercholesterolemia

- In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.

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

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

- Long duration (≥10 years for type 2 diabetes mellitus or ≥20 years for type 1 diabetes mellitus)
- Albuminuria ≥30 mcg of albumin/mg creatinine
- eGFR <60 mL/min/1.73 m²
- Retinopathy
- Neuropathy
- ABI <0.9

ABI = ankle-brachial index; eGFR = estimated glomerular filtration rate
2018 Blood Cholesterol Guidelines
Secondary Prevention in Patients with Clinical ASCVD

**High Risk Conditions**
- Recent ACS
- History of prior MI
- History of ischemic stroke
- Symptomatic PAD

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


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

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


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**Case #1: Ms. P**

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

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

- Next step ??

Case #2: Mr. E

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

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

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David Geffen School of Medicine at UCLA
Co-director, UCLA Program in Preventive Cardiology
Faculty Disclosure: Karol Watson

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

Leading Causes of Death in Perspective

Leading causes of death in perspective

2017 NHS statistics
Agenda

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

AHA’s Life Simple 7
Agenda

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

2013 ACC-AHA Cholesterol Guidelines


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Statin...statin...statin...

Intensity of Statin Therapy

<table>
<thead>
<tr>
<th>HIGH RISK PATIENT</th>
<th>MODERATE RISK PATIENT</th>
<th>LOW RISK PATIENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Intensity Statin</td>
<td>Moderate Intensity Statin</td>
</tr>
<tr>
<td>Daily dose lowers LDL-c ~50%</td>
<td>Daily dose lowers LDL-c ~30% -50%</td>
<td>Daily dose lowers LDL-c &lt;30%</td>
</tr>
<tr>
<td><strong>Atorvastatin (40†)-80 mg</strong></td>
<td>Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20-40 mg‡ Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2-4 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Rosuvastatin 20 (40) mg</strong></td>
<td></td>
<td>Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>

The intensity of statin should match the intensity of risk

Rationale for Pushing LDL-C Even Lower

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

LDL-C Levels and Risk of CV Events

New Era of ACVD Lipid Risk Management

Agenda

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

IMPROVE-IT Trial

18,144 patients with recent ACS

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

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

Vertical axis: Event Rate (%)
Horizontal axis: Years since Randomization

Hazard ratio, 0.936 (95% CI, 0.89–0.99) P=0.016

- Simvastatin monotherapy
- Simvastatin–ezetimibe

**RRR = 6%**
**NNT = 50**

**PCSK9 (proprotein convertase subtilisin/kexin type 9)**

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

**FOURIER Trial Design: Evolocumab**

- 27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)
- Screening, Lipid Stabilization, and Placebo Run-in
- High or moderate intensity statin therapy (± ezetimibe)
- LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL
- Evolocumab SC 140 mg Q2W or 420 mg QM
- Placebo SC Q2W or QM
- Randomized Double Blind
- Follow-up ~ 3 years

**FOURIER Trial Lipid Results**

![Graph showing LDL cholesterol levels over time with Placebo and Evolocumab groups. The graph indicates a 59% mean reduction, *P* < 0.00001. Absolute reduction: 56 mg/dL (95% CI 55-57).](image)

*Placebo*  

*LDL Cholesterol (mg/dL)*  

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
<th>108</th>
<th>120</th>
<th>132</th>
<th>144</th>
<th>156</th>
<th>168</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>90</td>
<td>80</td>
<td>70</td>
<td>60</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
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<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Placebo 59% mean reduction, *P* < 0.00001  

**Absolute reduction: 56 mg/dL (95% CI 55-57)**

*FOURIER Trial: Primary Outcome*

![Graph showing percentage reduction in major cardiovascular events over 24 months with Placebo and Evolocumab groups. The graph indicates a 15% relative risk reduction (RRR) and NNT = 67.](image)

*Placebo*  

*NNT = number needed to treat  
RRR = relative risk reduction*

*Placebo 15% RRR  
NNT = 67*

*Evolocumab*  


New Era of ACVD Lipid Risk Management
FOURIER Trial: MI/Stroke/CV Death

- **Placebo**
- **Evolocumab**

**NNT = 74**

**20% RRR**

NNT = number needed to treat
RRR = relative risk reduction


---

ODYSSEY OUTCOMES Trial

- 18,924 post ACS patients (1-12 months)
- Run-in period of 2-16 weeks on high-intensity or maximum tolerated dose of atorvastatin or rosuvastatin
- At least one lipid entry criterion met
- **Alirocumab SC Q2W**
- **Placebo SC Q2W**
- RANDOMIZED DOUBLE BLIND
- Follow-up: event driven

ACC Scientific Sessions 2018

New Era of ACVD Lipid Risk Management
**ODYSSEY Trial: Primary Outcome**

- **RRR = 15%**
- **NNT = 63**

![Graph showing MACE (%)](image)

- **HR 0.85**
- (95% CI 0.78, 0.93)
- \( P = 0.0003 \)

**ARR = absolute risk reduction**

**NNT = number needed to treat**

**RRR = relative risk reduction**

* based on cumulative incidence

**ODYSSEY: All Cause Mortality**

- **RRR = 15%**
- **NNT = 166**

![Graph showing All-Cause Death (%)](image)

- **HR 0.85**
- (95% CI 0.73, 0.98)
- \( P = 0.026 \)

* nominal P-value
† based on cumulative incidence
Agenda

- Lipid guidelines for primary and secondary prevention of ASCVD

2018 ACC/AHA Guideline on the Management of Blood Cholesterol

Primary Prevention

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

2018 ACC/AHA Guideline on the Management of Blood Cholesterol

Secondary Prevention

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


Thank you!
Managing ASCVD Risk Beyond LDL-C Lowering Therapy

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

Faculty Disclosure: Michael Miller

Dr. Miller discloses that he receives a consulting fee from Amarin Pharma, Inc.
Managing ASCVD Risk Beyond LDL-C Lowering Therapy

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

TG-Rich Lipoproteins (TGRLs) Contribute to Atherosclerosis


New Era of ACVD Lipid Risk Management
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An Apo C-III Loss-of-Function Mutation Causes Very Low TG Levels and Lower Coronary Calcium Scores

Apo C-III=gene encoding apolipoprotein (apo) C-III.
Apo C-III Loss-of-function Mutations Reduce Apo C-III Levels and CHD Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Ancestry</th>
<th>CHD Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHI</td>
<td>EA</td>
<td>0.39</td>
</tr>
<tr>
<td>YHII</td>
<td>AA</td>
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<tr>
<td>FHII</td>
<td>EA</td>
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<td>MCDC-CVA</td>
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<td>ARIC</td>
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<tr>
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<td>PROCARDIS</td>
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<tr>
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<tr>
<td>WTCCC</td>
<td>EA</td>
<td>0.98</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>0.60</td>
</tr>
</tbody>
</table>

AA=African ancestry; EA=European ancestry; HA=Hispanic ancestry; LoF=loss of function.


ANGPTL3 Deficiency: Another Model of Low TG/Reduced CVD

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

ANGPTL3 LoF mutations:
- p.S17X (8 homo, 68 hetero)
- p.S122K fs*3 (1 hetero)
- p.E96del (1 hetero)

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

Managing ASCVD Risk Beyond LDL-C Lowering Therapy

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- Outcomes studies of EPA/DHA; role of drug/dose & population studied
- REDUCE-IT trial results
- REDUCE-IT outcomes point to pleiotropic effect of EPA
- MOA of EPA to reduce ASCVD burden

Negative* Fenofibrate CVOTs (as Statin Adjunct)

<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/CDV or 65-79 yrs w/ ≥2 CV risk factors</td>
<td>All pts: Open-label simvastatin (mean dose: 22 mg/d)</td>
<td>Fenofibrate</td>
<td>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</td>
</tr>
<tr>
<td>(N=5518)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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</td>
<td>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</td>
</tr>
<tr>
<td>(N=9795)</td>
<td></td>
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</tr>
</tbody>
</table>


New Era of ACVD Lipid Risk Management
Negative Niacin Outcome Studies (Added to Statin Therapy)

Managing ASCVD Risk Beyond LDL-C Lowering Therapy

- Pathologic mechanisms contributing to ASCVD via TRL
- Genetic evidence for TRL causal effects
- Outcomes studies on fibrates and niacin
- Outcomes studies of EPA/DHA; role of drug/dose & population studied
- REDUCE-IT trial results
- REDUCE-IT outcomes point to pleiotropic effect of EPA
- MOA of EPA to reduce ASCVD burden
Effect of OM-3 (Supplements/EPA-DHA) on CVD Events: 1999-2018

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>EPA/DHA Dose (mg/d)</th>
<th>EPA / DHA Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIT (2016)</td>
<td>1150 / 890</td>
<td>Dietary supplement</td>
</tr>
<tr>
<td>AREDS-2 (2014)</td>
<td>650 / 350</td>
<td>Dietary supplement</td>
</tr>
<tr>
<td>SLT/FOF/DM3 (2010)</td>
<td>460 / 300</td>
<td>Dietary supplement</td>
</tr>
<tr>
<td>Alpha Omega (2010)</td>
<td>226 / 130</td>
<td>Margarina with dietary supplement</td>
</tr>
<tr>
<td>OMEGA (2010)</td>
<td>460 / 380</td>
<td>Rx EPA/DHA</td>
</tr>
<tr>
<td>RISP (2013)</td>
<td>500 / 500</td>
<td>Rx EPA/DHA</td>
</tr>
<tr>
<td>GISSI-HF (2009)</td>
<td>850 / 950</td>
<td>Rx EPA/DHA</td>
</tr>
<tr>
<td>ORIGIN (2013)</td>
<td>465 / 375</td>
<td>Rx EPA/DHA</td>
</tr>
<tr>
<td>GISSI-P (1999)</td>
<td>850 / 1700</td>
<td>Rx EPA/DHA</td>
</tr>
<tr>
<td>VITAL (2018)</td>
<td>465 / 375</td>
<td>Rx EPA/DHA</td>
</tr>
<tr>
<td>ASCEND (2018)</td>
<td>465 / 375</td>
<td>Rx EPA/DHA</td>
</tr>
</tbody>
</table>


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

**JELIS: 1.8 g/day EPA in Japanese Hypercholesterolemic Patients**

(low-dose background statin doses, high baseline EPA levels)

- Kaplan-Meier Estimates of Incidence of Coronary Events
  - Total Population
  - Primary Prevention Cohort
  - Secondary Prevention Cohort

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


---

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

- HR: 0.47
- 95% CI: 0.23–0.98
- P=0.043

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

Managing ASCVD Risk Beyond LDL-C Lowering Therapy

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- Genetic evidence for TRL causal effects
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- Outcomes studies of EPA/DHA; role of drug/dose & population studied
- REDUCE-IT trial results
- REDUCE-IT outcomes point to pleiotropic effect of EPA
- MOA of EPA to reduce ASCVD burden

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

**Participants**
- Men and women ≥45 years of age
- Established CHD or at high risk for CHD (diabetes + ≥1 risk factor)
- Atherogenic dyslipidemia
  - All patients required to be on stable statin therapy for at least 4 weeks
  - LDL-C >40 mg/dL and ≤100 mg/dL prior to randomization into the study
- Fasting triglyceride level 135–499 mg/dL
- Randomized, double-blind, parallel-group design
- Secondary outcome measures: Incidence of additional CV events, lipid and lipoprotein levels, subgroup analyses such as patients with diabetes, etc.
- International trial; first patient dosed in December 2011
- All potential endpoint events adjudicated by blinded clinical endpoint committee
- 10% of enrolled patients had TGs of 135–150 mg/dL

**Primary Endpoint**
Prevention of 1st major CV event (MACE); defined as:
- CV death
- Nonfatal MI
- Nonfatal stroke
- Coronary revascularization
- Unstable angina requiring hospitalization

**Study duration** ≈ 4–6 years

## REDUCE-IT: Key Baseline Characteristics

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

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

REDUCE-IT: Effects on Biomarkers from Baseline to Year 1

<table>
<thead>
<tr>
<th>Biomarker (mg/dL)</th>
<th>Icosapent Ethyl (N=4089) Median</th>
<th>Placebo (N=4090) Median</th>
<th>Median Between Group Difference at Year 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Year 1</td>
<td>Baseline</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>216.5</td>
<td>175.0</td>
<td>216.0</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>118.0</td>
<td>113.0</td>
<td>118.5</td>
</tr>
<tr>
<td>LDL-C</td>
<td>74.0</td>
<td>77.0</td>
<td>76.0</td>
</tr>
<tr>
<td>HDL-C</td>
<td>40.0</td>
<td>39.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Apo B</td>
<td>82.0</td>
<td>80.0</td>
<td>83.0</td>
</tr>
<tr>
<td>EPA (μg/mL)</td>
<td>26.1</td>
<td>144.0</td>
<td>26.1</td>
</tr>
</tbody>
</table>

*Apo B was measured at year 2.

REDUCE-IT: Primary Endpoint Achieved

**Composite**: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina

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

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

Estimated Kaplan-Meier event rate at approximately 5.7 years
Prespecified Hierarchical Endpoint Testing

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl</th>
<th>Placebo</th>
<th>RRR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite (ITT)</td>
<td>705/4089 (17.2%)</td>
<td>901/4090 (22.0%)</td>
<td>0.75 (0.68-0.83)</td>
<td>25%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Key Secondary Composite (ITT)</td>
<td>459/4089 (11.2%)</td>
<td>606/4090 (14.8%)</td>
<td>0.74 (0.65-0.83)</td>
<td>26%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular Death or Nonfatal Myocardial Infarction</td>
<td>392/4089 (9.8%)</td>
<td>507/4090 (12.4%)</td>
<td>0.75 (0.66-0.86)</td>
<td>25%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatal or Nonfatal Myocardial Infarction</td>
<td>250/4089 (6.1%)</td>
<td>355/4090 (8.7%)</td>
<td>0.69 (0.58-0.81)</td>
<td>31%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent or Emergent Revascularization</td>
<td>216/4089 (5.3%)</td>
<td>321/4090 (7.8%)</td>
<td>0.65 (0.55-0.78)</td>
<td>35%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td>174/4089 (4.3%)</td>
<td>213/4090 (5.2%)</td>
<td>0.80 (0.66-0.98)</td>
<td>20%▼</td>
<td>0.03</td>
</tr>
<tr>
<td>Hospitalization for Unstable Angina</td>
<td>108/4089 (2.6%)</td>
<td>157/4090 (3.8%)</td>
<td>0.66 (0.53-0.87)</td>
<td>32%▼</td>
<td>0.002</td>
</tr>
<tr>
<td>Fatal or Nonfatal Stroke</td>
<td>98/4089 (2.4%)</td>
<td>134/4090 (3.3%)</td>
<td>0.72 (0.55-0.93)</td>
<td>28%▼</td>
<td>0.01</td>
</tr>
<tr>
<td>Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke</td>
<td>549/4089 (13.4%)</td>
<td>690/4090 (16.9%)</td>
<td>0.77 (0.69-0.86)</td>
<td>23%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>274/4089 (6.7%)</td>
<td>310/4090 (7.8%)</td>
<td>0.87 (0.74-1.02)</td>
<td>13%▼</td>
<td>0.09</td>
</tr>
</tbody>
</table>

RRR denotes relative risk reduction.

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

<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 vs 10 placebo; P=0.55)

Positively Adjudicated
Hospitalization for Atrial Fibrillation/Flutter

127 (3.1%) 84 (2.1%) 0.004

Total (First and Subsequent) Events
Primary: CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

Primary Composite Endpoint

RR, 0.70
(95% CI, 0.62–0.78)
P=0.00000000036

HR, 0.75
(95% CI, 0.68–0.83)
P=0.00000001

RR = relative risk

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

![Graph showing patients with an event over years since randomization for Placebo and Icosapent Ethyl.]

**Hazard Ratio, 0.69**
(95% CI, 0.59–0.80)

**RRR = 31%**

**ARR = 6.5%**

**NNT = 15** (95% CI, 11–27)

**P = 0.000001**

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

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

---

All-Cause Mortality: USA Subgroup

![Graph showing all-cause mortality rate over years since randomization for Placebo and Icosapent Ethyl.]

**Hazard Ratio, 0.70**
(95% CI, 0.55–0.90)

**RRR = 30%**

**ARR = 2.6%**

**NNT = 39** (95% CI, 22–154)

**P = 0.004**

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

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

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EPA Has Atheroprotective Properties

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Comparative Effects of TG-lowering Agents on Lipoprotein Oxidation

* MDA Equivalents (µM)

Each agent was tested at 10 µM

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

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

EPA interacts across the CVD continuum to reduce CV events

New Era of ACVD Lipid Risk Management
Practical Considerations to Manage Residual Risk

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

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

2019 Multisociety Cholesterol Guidelines Summary

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

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

- **<5% “Low Risk”**
- **5% to <7.5% “Borderline Risk”**
- **≥7.5% to <20% “Intermediate Risk”**
- **≥20% “High Risk”**

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

- Estimates 10-year hard ASCVD (nonfatal MI, CHD death, stroke) for ages 40-79 and lifetime risk for ages 20-59
- Intended to promote patient-provider risk discussion, and best strategies to reduce risk
- ≥7.5% identifies statin eligibility, not a mandatory prescription for a statin

ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; MI = myocardial infarction; CHD = coronary heart disease; CVD = cardiovascular disease

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

---

**Risk-Enhancing Factors**

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

Additional Risk-Enhancing Factors

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


Using the CAC Score to Guide Statin Therapy

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

2019 Multisociety Cholesterol Guidelines Summary

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

Statin Therapy Adjuncts Proven to Reduce ASCVD

**LDL-Lowering Pathway →**

- **Optimized Statin Therapy**
- + Ezetimibe
- + Alirocumab or Evolocumab

**TG-Related Pathway**

- + Icosapent Ethyl

Stable ASCVD; or Diabetes + ≥1 additional risk factor*, TG ≥ 150

Acute coronary syndrome within 10 days*

Stable ASCVD + additional risk factors; or ACS within 1-12 months*

*Major inclusion criteria for respective CVOTs.

ACS=acute coronary syndrome;
ASCVD=atherosclerotic cardiovascular disease.

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

- Combination therapy statin/fibrate has not been shown to improve ASCVD outcomes and is generally not recommended. (A)

- Combination therapy statin/niacin has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. (A)

- For patients with diabetes and ASCVD, if LDL cholesterol is ≥ 70 mg/dL on high-intensity statin dose, consider adding LDL-lowering therapy such as ezetimibe or PCSK9 inhibitor. (A)
  - Ezetimibe preferred due to lower cost if little additional effect needed
  - PCSK9i preferred if more than 20% LDL-C reduction needed

(A)= High evidence.

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

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


*P<0.001 vs placebo.
**New Guidelines/Recommendations for Icosapent Ethyl to Prevent ASCVD in Patients with TG 135-500 mg/dL**

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

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


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

- There are NO over-the-counter omega-3 products, only dietary supplements (with minimal FDA oversight)
- Dietary supplements are not recommended to treat diseases, but
- Benefits are claimed for heart, brain, weight, vision, inflammation, skin, liver fat, depression, age-related cognitive decline, allergies, bones, pregnancy/neonatal health, childhood behavior…
- Approximately 8% of US adults (19 million) take fish oil dietary supplements
Problems with Content of Leading US Fish Oil Dietary Supplements

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

Dietary Supplement

Prescription pure, stable EPA (icosapent ethyl)  
EPA/DHA Dietary Supplement (per label)  
Krill-oil Dietary Supplement (per label)

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

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

2018 ACC/AHA Multisociety Guidelines

Value Statement: Low Value (LOE: B-NR)
At mid-2018 list prices, PCSK9 inhibitors have a low cost value (>$150,000 per QALY) compared to good cost value (<$50,000 per QALY)

Value Statement: Uncertain Value (B-NR)
Among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 US list prices.

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


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

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Incremental Costs</th>
<th>Incremental LYs</th>
<th>Incremental QALYs</th>
<th>Cost per LY</th>
<th>Cost per QALY</th>
<th>Cost per MACE Avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icosapent Ethyl vs. Medical Management</td>
<td>$9,000</td>
<td>0.54</td>
<td>0.50</td>
<td>$17,000 per LY gained</td>
<td>$18,000 per QALY gained</td>
<td>$53,000 per MACE avoided</td>
</tr>
</tbody>
</table>

Probabilistic Sensitivity Analysis Results

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Cost-Effective at $60,000 per QALY</th>
<th>Cost-Effective at $100,000 per QALY</th>
<th>Cost-Effective at $150,000 per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icosapent Ethyl vs. Medical Management</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

ICER Evidence Rating: B+

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

**Professional Society Recommendations**

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

**Summary— Updates in Lipid Guidelines**

- **2018 Multisociety Cholesterol/2019 ACC/AHA 1st Prevention Guidelines**
  - Improved risk assessment
  - Lifelong healthy lifestyle
  - On-treatment LDL-C levels emphasized (thresholds ≈ goals)
  - Ezetimibe & PCSK9i to ↓**CVD** (if LDL-C > threshold w/ max statin)
- **2019 Five new guidelines/statements for patients w/ HTG:**
  - If TG 135-500, despite LDL-C control with statin therapy, and
  - If Prior CVD, or DM2 + additional risk, then
  - IPE 4 g/d recommended to ↓**CVD**
  - Non-IPE and dietary supplement omega-3 not recommended
- New FDA indication (2019) for icosapent ethyl to ↓**CVD** (≈ to statements)
- Implementing this new guidance:
  - Statin rechallenge often useful
  - Consider statin adjuncts to ↓**CVD**:
    - Ezetimibe and/or PCSK9i for residual LDL-C elevation
    - Icosapent ethyl for TG elevation 135-500 mg/dL (lower is better)