Prevention of ASCVD in Women Through Lipid Management in the New Era

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Prevention of ASCVD in Women Through Lipid Management in the New Era with focus on LDL-C lowering

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Case 1 – G.S. (con’t)

Exam:
• 5’3”, 148lb (BMI 26 kg/m²) waist 35 inches
• Normal cardiac exam
• BP 136/78 mm Hg

Lipids:
– TC= 210 mg/dL
– TG 160 mg/dL
– HDL-C 42 mg/dL
– LDL-C 136 mg/dL

Fasting glucose 105 mg/dL; A1c 5.7
• hsCRP= 2.8 mg/L
• ASCVD 10-year Risk: 5.2% & Lifetime Risk: 39%

FDVH47 # J IV1

• 58 yo G3P3 South Asian with no history of heart disease here for ASCVD risk assessment
• HTN taking HCTZ 25 mg/d
• No smoking or diabetes
• Menopause at age 40
• Mother died of MI age 60
• Takes care of her toddler grandchild but otherwise is sedentary

RISK ENHANCERS
• 1 birth preterm (34 weeks)
• 2 pregnancies gestational DM
• Premature menopause
• Family history premature CAD
• South Asian
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Does she need a statin?

Female-Specific Risk Enhancers
CVD Mortality Gap Between Men and Women Has Narrowed But Plateaued

U.S. data from AHA Statistics Report

- Additionally, CVD on rise in middle aged women in US
- The heart disease death rate for women aged 45–64 declined 23% from 1999 (96.8) to 2011 (74.9) but then increased 7% in 2017 (80.1)

Female-Specific Risk Enhancers Are Across the Lifespan

- Younger Women
  - Early or late menarche
  - PCOS
  - OCPs
  - Premature menopause
  - Primary ovarian insufficiency

- Pregnancy
  - Gestational diabetes
  - Gestational hypertension
  - Preeclampsia
  - Preterm birth

- Older Women
  - Menopause


American Journal of Preventive Cardiology
State-of-the-Art Review
Identification of female-specific risk enhancers throughout the lifespan of women to improve cardiovascular disease prevention
Petal Elder†, Garima Sharma‡, Martha Galati‡, Erin D. Michos‡, §
Adverse Pregnancy Outcomes (APOs) and Future Maternal CVD Risk

• Ask about pregnancy history
• Risk seen even more than 10 years out from adverse pregnancy


Pre-Eclampsia, Pre-term Delivery and Subsequent Maternal CVD: Meta-analysis

• >20 studies, with ~6 million women including >25,800 with preeclampsia & 338,000 with previous preterm delivery
• Preeclampsia is associated with a 4-fold increase in incident HF and a 2-fold increased risk in CHD, stroke, and CVD death
• Preterm delivery is associated with an increase in future maternal adverse CV outcomes, including a 2-fold increase in deaths caused by CHD
  – Highest risks occurred when the PTD occurred before 32 weeks’ gestation or were medically indicated

Wu P et al. J Am Heart Assoc. 2018;7:e007809. DOI: 10.1161/JAHA.117.007809
Gestational Diabetes Mellitus (GDM) and Risk of Maternal CVD

Nationwide: All births 2007-2008 in France: 7-year follow-up; 1,518,990 deliveries with 62,958 with GDM, After adjusting for age, DM, obesity and hypertensive disorders in pregnancy, GDM was significantly associated with a higher risk of CVD (adjusted Odds Ratio = 1.25 [1.09–1.43])


APOs and Future Maternal CVD Risk

APO= Adverse Pregnancy Outcome

Pregnancy as Nature’s Free Stress Test

Premature Menopause and Incident CVD in UK Biobank

Premature menopause (before age 40) was associated with increased risk of CVD (HR: 1.36; 95% CI: 1.19 to 1.56; p < 0.001) after adjustment for conventional risk factors.


Peters SA and Woodward M. Heart 2018;104:1069-1075.

CVD Risk Reduction Through LDL-C lowering Therapy for PRIMARY PREVENTION
Nutrition Lifestyle Recommendations: Lipids and BP

- Emphasis on dietary patterns (esp. Mediterranean or DASH-style):
  - ↑Fruits, vegetables, and whole grains
  - ↑Fiber and ↓Sugar
  - Fat intake
    - 30 – 35% total calories
    - <6% saturated fats (avoid trans fats)
  - Regular fish intake
  - ↓Highly-processed/pre-prepared food
  - Low sodium (<2400 mg/day)
  - Healthy eating for a lifetime

Best evidence for ↓MI risk is with the Mediterranean diet

Physical Activity Guidelines: Lipids and BP

Regular aerobic activity and strength training:

- 3+ sessions per week
- Average ~40 min per session
- Moderate-to-vigorous intensity
- Strength training also helpful
- Patient chooses most enjoyable and sustainable activities

Best evidence for is brisk walking ~30 min/day ~5 days/week

2019 ACC/AHA Guideline on Primary Prevention

Statins: Key Take-Home Message

• Statin therapy is first-line treatment for primary prevention of ASCVD in patients with:
  – Elevated LDL-C levels (≥190 mg/dL)
  – Diabetes mellitus who are age 40 to 75 years
  – Determined to be at sufficient ASCVD risk after a clinician–patient risk discussion


ACC Risk Calculator Plus to Assess Risk Category

1. For primary prevention, use the calculator to Assess Risk Category

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

• 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

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

ACC=American College of Cardiology; AHA=American Heart Association; ASCVD=atherosclerotic cardiovascular disease; tools.acc.org/ascvd-risk-estimator-plus#!/calculate/estimate
2019 ACC/AHA Primary Prevention Guidelines: Risk Enhancing Factors

Risk-Enhancing Factors

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


2019 ACC/AHA Primary Prevention Guidelines: Risk Enhancing Factors (con’t)

Additional Risk-Enhancing Factors

- History of premature menopause (before age 40 y) or pregnancy-associated conditions that ↑ASCVD risk (e.g. preeclampsia)
- High-risk race/ethnicity (eg South Asian, East Asian, Native American, Middle Eastern)
- High-risk levels of lipids or other biomarkers
- Persistent primary HTG
- If measured:
  - ↑high-sensitivity C-reactive protein
  - ↑Lp(a)
  - ↑apoB
  - ↓ABI

Using The CAC Score to Guide Statin Therapy

• A CAC score predicts ASCVD events in a graded fashion
  – 0; useful for reclassifying patients to a lower-risk group, often allowing statin therapy to be withheld or postponed unless higher risk conditions are present
  – 1-99 favors statin therapy
  – 100+ initiate statin therapy

• For patients >75 y/o, RCT evidence for statin therapy is not strong, so clinical assessment of risk status in a clinician–patient risk discussion is needed to decide whether to continue or initiate statin treatment

• European Society of Cardiology guidelines also support CAC scoring:
  – “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.”


Case 1 – G.S. (con’t)

• Borderline 10-year risk – 5.2%
• Has multiple risk enhancing factors
• Lifestyle: encourage healthy diet, increase activity, weight loss
• BP control
• Moderate intensity statin recommended to reduce LDL-C by ≥30%
• Engaged in shared decision making
• Patient was reluctant to start statin, worried about side effects of statins based on some posts she has seen in her Facebook group
• After further discussion, CAC score was obtained
  – CAC score 24, which is 81st percentile for age/sex/race
  – Images reviewed with patient; she agreed to initiate statin
Adherence to Statin Therapy is Difficult but Important

• Statins are generally well-tolerated
  – >Three-quarters of the general population tolerates statin therapy, but
  – 10-20% of patients prescribed a statin report statin intolerance
• Statins are very effective in preventing 1st/recurrent ASCVD across all LDL-C levels
• Rates of serious adverse events are very low
  – The risk of statin-induced serious muscle injury, including rhabdomyolysis, is <0.1%
  – The risk of serious hepatotoxicity is ≈0.001%
  – The risk of statin-induced newly diagnosed diabetes mellitus is ≈0.2% per year of treatment
• Large proportion (40-70%) of patients discontinue statin therapy within 1-2 years, with resulting large increase in CVD risk
• Perceived vs real effect may play a role as multiple studies show nocebo effect
  – Many patients can tolerate statins on rechallenge after reported statin intolerance


Case 2 – C.R.

• A 68-year-old Hispanic woman with a 20-year history of T2DM, also history of HTN and dyslipidemia, but no history of clinical CVD
• A prior chest CT 2 yrs ago for evaluation of pneumonia incidentally noted severe coronary artery calcifications
  – She is a nonsmoker with family history of T2DM and HTN; her mother died at 75 of CHF
• Physical exam:
  – Unremarkable; BP 148/80 mm Hg bilaterally, heart rate 90 bpm; height 5'5", weight 174 lb, BMI 29 kg/m2, waist 37 inches
Case 2 – C.R. (con’t)

- TC: 206 mg/dL
- TG: 300 mg/dL
- HDL-C: 42 mg/dL
- LDL-C: 104 mg/dL
- Non-HDL-C: 164 mg/dL
- Glucose: 150 mg/dL
- A1C: 7.3%

Current medications:

- lisinopril 20 mg & HCTZ 12.5 mg/day
- metformin 1000 mg bid
- **pravastatin 10 mg daily**

Does she need any change to lipid lowering therapy?

Statin Treatment in Patients with Diabetes

- For patients of all ages with diabetes and ASCVD or 10-year ASCVD risk >20%, **high-intensity statin therapy** should be added to lifestyle therapy. (A)

- In patients with diabetes without ASCVD but with multiple ASCVD risk factors, it is reasonable to consider **high-intensity statin therapy**. (C)

- For patients with diabetes without ASCVD, aged 40–75 years (A), and >75 years (B), use **moderate-intensity statin** in addition to lifestyle therapy.

- For patients with diabetes aged <40 years with additional ASCVD risk factors, the patient and provider should consider using **moderate-intensity statin** in addition to lifestyle therapy. (C)

- For patients who do not tolerate the intended intensity, the **maximum tolerated statin dose should be used**. (E)

(A)= High quality evidence; (B)= Moderate quality evidence; (C)= Limited data; (E)= Consensus of expert opinion based on clinical experience.

Diabetes-Specific Risk Enhancers

*Independent of Other Risk Factors in Diabetes Mellitus*

- Long duration
  - ≥10 years for T2DM
  - ≥20 years for type 1 DM
- Albuminuria ≥30 mcg albumin/mg creatinine
- eGFR <60 mL/min/1.73 m2
- Retinopathy
- Neuropathy
- ABI <0.9

Arnett DK et al. *J Am Coll Cardiol*. 2019 Mar 17. [Epub ahead of print]

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Selecting the Appropriate Statin

<table>
<thead>
<tr>
<th></th>
<th>High-Intensity</th>
<th>Moderate-Intensity</th>
<th>Low-Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C Lowering†</td>
<td>≥50%</td>
<td>30% to 49%</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Statins</td>
<td>Atorvastatin (40 mg†) 80 mg Rosuvastatin 20 (40 mg)</td>
<td>Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20–40 mg§</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1–4 mg</td>
<td>Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg</td>
</tr>
</tbody>
</table>

Statin Therapy Adjuncts *Proven* to Reduce ASCVD

**Optimized Statin Therapy**

- + Ezetimibe
  - Acute coronary syndrome within 10 days*

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

- + Alirocumab or Evolocumab
  - 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; CVOTs, cardiovascular outcomes trials.


CVD Risk Reduction Through Triglyceride-lowering Therapy

**John R. Nelson MD, FACC, FNLA, FASNC**

Director, California Cardiovascular Institute
ACC-Ca Governmental Relations Committee Member
Past President, Founding Member - Pacific Lipid Association
Past Member, Board of Directors - National Lipid Association
Fresno, CA
**Case 2 – C.R. (con’t)**

- Lifestyle changes were encouraged.
- Pravastatin 10 mg/d was changed to rosuvastatin 20 mg/d.

- She returns for repeat labs
  - TC: 163 mg/dL
  - TG: 225 mg/dL
  - HDL-C: 44 mg/dL
  - LDL-C: 74 mg/dL
  - Non-HDL-C: 119 mg/dL
  - A1C: 6.9%

Does she need any change to lipid lowering therapy?

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**Residual HTG Predicted Residual ASCVD Risk Despite LDL-C at Goal on Statin Monotherapy**

- ↑41% CVD Risk w/ mild HTG

Despite LDL-C <70 mg/dL on high-dose statin, patients with TG ≥150 have a 41% higher risk of coronary events*

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Fasting TG Is Strongly Related to CVD Risk, Even at Very Low Levels

- Data from 8,068 primary prevention patients in Atherosclerosis Risk in Communities Study (ARIC) and Framingham Offspring Study
- Baseline characteristics:
  - 40 to 65 years old
  - No CVD
- ≥2 fasting TG measurements on record
- Endpoint: Time to MI, stroke, or CV death
- Follow-up for up to 10 years to first event

CVD events increased across the range of TG levels ~50 to ~200 mg/dL, above which the relationship flattened out

Classification of Fasting TG Levels (2011 AHA/2014 NLA)

<table>
<thead>
<tr>
<th>Fasting Triglycerides (mg/dL)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>Optimal</td>
</tr>
<tr>
<td>&lt;150</td>
<td>Normal</td>
</tr>
<tr>
<td>150–199</td>
<td>Borderline high</td>
</tr>
<tr>
<td>200–499</td>
<td>High</td>
</tr>
<tr>
<td>≥500</td>
<td>Very high</td>
</tr>
</tbody>
</table>

Current Guidance Regarding Available Statin Adjuncts: Fibrates & Niacin

**Negative Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD Fenofibrate</td>
<td>0.92</td>
<td>0.79-1.08</td>
<td>0.32</td>
</tr>
<tr>
<td>FIELD Fenofibrate</td>
<td>0.89</td>
<td>0.75-1.05</td>
<td>0.16</td>
</tr>
<tr>
<td>AIM-HIGH Extended-release niacin</td>
<td>1.02</td>
<td>0.87-1.21</td>
<td>0.79</td>
</tr>
<tr>
<td>HPS2-THRIVE Extended-release niacin/forticaptan</td>
<td>0.96</td>
<td>0.90-1.03</td>
<td>0.29</td>
</tr>
</tbody>
</table>

- 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)

(A)= High evidence.

Fatty Acids in Primary Prevention: ASCEND & VITAL (EPA+DHA 1g/d) Failed to Meet Primary Endpoint

ASCEND Trial

VITAL Trial

**JELIS: Rx Pure EPA + Statins Led to ↓ Major Coronary Events* in Hypercholesterolemic Patients on Statins and in HTG Subgroup†**

N=18,645 Japanese pts with TC ≥ 251 mg/dL prior to baseline statin Rx. Baseline TG=153 mg/dL. Statin up-titrated to 20 mg pravastatin or 10 mg simvastatin for LDL-C control.

*Primary endpoint: Sudden cardiac death, fatal and non-fatal MI, unstable angina pectoris, angiolast, stenting, or coronary artery bypass graft.


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**REDUCE-IT Primary and Secondary Endpoints**

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

**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

**Key Secondary End Point:** CV Death, MI, Stroke

**Hazard Ratio, 0.74**

(95% CI, 0.65–0.83)

RHR = 26.5%

ARR = 3.6%

NNT = 28 (95% CI, 20–47)

P = 0.0000006

Decrease in Total Events For Every 1000 US Patients on Icosapent Ethyl 4g/day for 5 Years

Risk Difference vs. Placebo

- Cardiovascular Death
- Fatal or Nonfatal MI
- Fatal or Nonfatal Stroke
- Hospitalization for Unstable Angina
- Coronary Revascularization
- Total Mortality


Annual Projected Initial and Subsequent Preventable Primary and Secondary Composite Endpoint Events based on REDUCE-IT

Estimated number of events per year

Primary composite outcomes

- Not on Icosapent ethyl: 136,575
- On Icosapent ethyl: 106,777
- Preventable events: 29,798

Secondary composite outcomes

- Not on Icosapent ethyl: 24,210
- On Icosapent ethyl: 14,499
- Preventable events: 9,311

REDUCE-IT: Time to First & Total Primary Endpoint Events by CV Risk Category & Diabetes Status at Baseline

Interaction P value between patients with established CVD with diabetes and patients with established CVD without diabetes = 0.98
Interaction P value between patients with diabetes and other risk factors, patients with established CVD with diabetes, and patients with established CVD without diabetes = 0.32

CVD with IPE Did NOT Vary by TG Decrease *(HR similar with achieved TG ≥ or < 150 mg/dL)*

Statin + Placebo (Reference)
- Statin + IPE TG ≥150 mg/dL, HR 0.71 (0.63-0.79)
- Statin + IPE TG <150 mg/dL, HR 0.71 (0.60-0.81)

Primary Endpoint by On-Treatment Serum EPA

CV Death, MI, Stroke, Coronary Revascularization, Unstable Angina

Hazard Ratio: Reference to EPA = 26 µg/mL
- Median placebo
- Median 4g/day IPE (EPA)

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>5196</th>
<th>2400</th>
<th>756</th>
<th>87</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC-Derived Daily Average EPA (µg/mL)</td>
<td>26</td>
<td>100</td>
<td>200</td>
<td>300</td>
</tr>
</tbody>
</table>

Median placebo Median 4g/day IPE (EPA)

Adapted from Bhatt DL. Abstract presented at: ACC.20/WCC Virtual Meeting; March 30, 2020.
Reported Clinical and Biologic Cardiovascular Benefits of Omega-3 Fatty Acids

Arrhythmias
- Sudden death (GISSI-P and REDUCE-IT)
- Atrial fibrillation harmful (vs apparent and beneficial ventricular arrhythmias)
- Heart rate variability improvement

Anti-atherogenic
- Non-HDL-C
- TG
- Chylomicrons
- VLDL- and Chylomicron-remnants
- HDL-C (only in DHA-containing, w/ EPA-alone)
- LDL and HDL particle size (DHA only)
- Plaque stabilization

Antithrombotic
- Platelet aggregation
- Blood flow (viscosity)

Anti-inflammatory and endothelial-protective effects
- C-reactive protein (hsCRP)
- Endothelial adhesion molecules & Leukocyte adhesion receptors
- Proinflammatory eicosanoids
- Proinflammatory leukotrienes
- NO production/vasodilation

Systolic and diastolic BP


Fish Oil Dietary Supplements: Poorly Regulated but Widely Used

- Approximately 8% of US adults (19 million) take fish-oil dietary supplements, but
- There are NO over-the-counter omega-3 products in USA (FDA-regulated and non-prescription), and
- Only non-Rx omega-3s in USA are dietary supplements
  - Minimal FDA oversight, lots of saturated fat, etc.
- Dietary supplements are NOT recommended to treat diseases, yet
- Benefits claimed for heart, brain, weight, etc., etc.
- NO CVD benefits seen in dietary supplement trials!
Dubious 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 tends to be high (even those meeting industry standards are more oxidized than Rx meds)
- Contamination risk (pesticides, PCBs, etc.)
- Difficult to achieve EPA+DHA doses similar to Rx meds

High saturated fatty acid content of common fish oil dietary supplement makes it solid at room temperature


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

Prescription pure, stable EPA (Icosapent ethyl)  
EPA/DHA Dietary Supplement (per label)  
Krill Oil Dietary Supplement (per label)

Photos courtesy of Preston Mason, PhD
Icosapent Ethyl (IPE), Rx Only, Now Indicated by the FDA for CVD Event Reduction

New December 2019

- As an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and
  - Established cardiovascular disease or
  - Diabetes mellitus and 2 or more additional risk factors for cardiovascular disease.

Prior July 2012

- As an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.
- Limitations of Use: The effect of IPE on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.
- The daily dose is 4 grams per day


New Guidelines/Recommendations for IPE to Prevent ASCVD in Patients with TG 135-500 mg/dL (mild to moderate HTG)*

<table>
<thead>
<tr>
<th>Scientific Society</th>
<th>Publication</th>
<th>Treatment with Statin and IPE for ASCVD Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Diabetes Association (ADA)</td>
<td>#10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes—2019</td>
<td>In patients with ASCVD or other cardiac risk factors with controlled LDL-C, but elevated triglycerides (135-499)</td>
</tr>
<tr>
<td>European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS)</td>
<td>2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce CV Risk</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>NLA Scientific Statement on the Use of Icosapent Ethyl in Statin-treated Patients with Elevated Triglycerides and High- or Very-high ASCVD Risk</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>AHA Science Advisory: Omega-3 Fatty Acids for the Management of Hypertriglyceridemia</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>

*1. All 4 guidelines include TG 135-499, per REDUCE-IT design, but the FDA indication is TG>150
2. Three of 4 guidelines/statements mention “LDL-C control” on a statin, per REDUCE-IT design, but the NLA and FDA mention a “maximally-tolerated” statin, NOT used in REDUCE-IT

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFAs = polyunsaturated fatty acids; TG = triglyceride.
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**Optimized Statin Therapy**
- + Ezetimibe
  - Acute coronary syndrome within 10 days*
- + Icosapent Ethyl
  - Stable ASCVD; or Diabetes + ≥1 additional risk factor*, TG ≥ 150
- + Alirocumab or Evolocumab
  - 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.

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**Summary— *Updates in Lipid Guidelines***

- **2018 Multi-Society Cholesterol/2019 ACC/AHA 1° Prevention Guidelines**
  - *Improved* risk assessment
  - *Lifelong* healthy lifestyle
  - *On-treatment* LDL-C levels emphasized (thresholds ≈ goals)
  - Ezetimibe & PCSK9i to ↓ **CVD** (if LDL-C > threshold w/ max statin)
Summary—Updates in Lipid Guidelines

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• 2019 *Four* 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 4g/d recommended to ↓CVD
  – Non-IPE and dietary-supplement omega-3 *not* recommended

• New FDA indication (2019) for IPE to ↓CVD (≈ to Statements)
Summary—*Updates in Lipid Guidelines*

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• New FDA indication (2019) for IPE 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 in the case of *residual* TG elevation