Lipid Management update 2019

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Disclosures:

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Research Grants from: Amgen, Boehringer-Ingelheim (BI), Bristol-Myers Squibb (BMS), Daiichi Sankyo, Janssen, Merck

Consulting fees from Aegerion, Alnylam, Amarin, Amgen, BI, BMS, Corvidia, Eisai, Innovent, Janssen, Kowa, Merck, Pfizer, Regeneron, Sanofi.
## A Half-Century of Research in LDL-C Lowering Drugs for Preventing CV Events

<table>
<thead>
<tr>
<th>Method</th>
<th>Study</th>
<th>Chol/LDL</th>
<th>CHD↓</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Oslo I 1970</td>
<td>T-C 14%</td>
<td>25%</td>
<td>0.05</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>LRC–CPPT 1984</td>
<td>LDL-C 13%</td>
<td>19%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ileal bypass</td>
<td>POSCH 1990</td>
<td>LDL-C 38%</td>
<td>35%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin</td>
<td>4S 1994</td>
<td>LDL-C 35%</td>
<td>30%</td>
<td>0.0003</td>
</tr>
<tr>
<td>HD Statin</td>
<td>PROVE IT 2004</td>
<td>LDL-C 33mg/dl</td>
<td>16%</td>
<td>0.005</td>
</tr>
<tr>
<td>Fibrates</td>
<td>FIELD 2005</td>
<td>LDL-C 12%</td>
<td>11%</td>
<td>NS</td>
</tr>
<tr>
<td>Niacin</td>
<td>HPS2 2014</td>
<td>LDL-C 10mg/dl</td>
<td>4%</td>
<td>NS</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>IMPROVE IT 2016</td>
<td>LDL-C 17mg/dl</td>
<td>6.4%</td>
<td>0.016</td>
</tr>
<tr>
<td>PCSK9</td>
<td>FOURIER 2017</td>
<td>LDL-C 62mg/dl</td>
<td>20%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CETP</td>
<td>REVEAL 2017</td>
<td>LDL-C 11mg/dl</td>
<td>9%</td>
<td>0.004</td>
</tr>
</tbody>
</table>
CTT: Benefits of Statins on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol

<table>
<thead>
<tr>
<th></th>
<th>Statin/More statin</th>
<th>Control/Less statin</th>
<th>Relative risk (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI</td>
<td>3485 (1.0)</td>
<td>4593 (1.3)</td>
<td>0.73 (0.69 - 0.78)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1887 (0.5)</td>
<td>2281 (0.6)</td>
<td>0.80 (0.74 - 0.87)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>5105 (1.4)</td>
<td>6512 (1.9)</td>
<td>0.76 (0.73 - 0.78)</td>
</tr>
<tr>
<td>CABG</td>
<td>1453 (0.4)</td>
<td>1857 (0.5)</td>
<td>0.75 (0.69 - 0.82)</td>
</tr>
<tr>
<td>PTCA</td>
<td>1767 (0.5)</td>
<td>2283 (0.7)</td>
<td>0.72 (0.65 - 0.80)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>2133 (0.6)</td>
<td>2667 (0.8)</td>
<td>0.76 (0.70 - 0.82)</td>
</tr>
<tr>
<td>Any coronary revascularisation</td>
<td>5353 (1.5)</td>
<td>6807 (2.0)</td>
<td>0.75 (0.72 - 0.78)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>1427 (0.4)</td>
<td>1751 (0.5)</td>
<td>0.79 (0.72 - 0.87)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>257 (0.1)</td>
<td>220 (0.1)</td>
<td>1.12 (0.88 - 1.43)</td>
</tr>
<tr>
<td>Unknown stroke</td>
<td>618 (0.2)</td>
<td>709 (0.2)</td>
<td>0.88 (0.76 - 1.01)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>2302 (0.6)</td>
<td>2680 (0.8)</td>
<td>0.84 (0.79 - 0.89)</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>10973 (3.2)</td>
<td>13350 (4.0)</td>
<td>0.78 (0.76 - 0.80)</td>
</tr>
</tbody>
</table>

Effect of Lowering LDL-C on CHD Events

Ballantyne CM. Am J Cardiol. 1998
O'Keefe JH et al, JACC 2004
2013 ACC/AHA Cholesterol Guidelines: Recommendations for the 4 Statin Benefit Groups

- **ASCVD**:
  - NO
  - **LDL>190**
    - NO
    - **DM**
      - NO
      - YES: Risk >7.5%
      - YES: Risk ≤7.5%
      - YES: Estimate 10-y ASCVD Risk with Pooled Cohort Equations
    - YES: YES: Statin (High Intensity)
    - YES: Statin (M/H Intensity)
    - YES: Statin (Mod Intensity)
  - YES: Statin (High Intensity)

- **Statin (High Intensity)**
- **Statin (Mod Intensity)**
- **Statin (M/H Intensity)**
IMPROVE-IT: Primary Results
18,144 ACS patients randomized to simvastatin alone or ezetimibe (EZ)/simvastatin, median follow-up 6 years

*Primary end point (cardiovascular death, MI, unstable angina, coronary revascularization, or stroke).

IMPROVE-IT vs CTT: CV Benefit Proportional to LDL-C for Both Ezetimibe and Statins

*Using CTT methods: LDL difference between groups using baseline LDL for Pts without blood samples. Endpoint of CV Death, MI, stroke or revascularization >30days post Rand. Cox HR reported.

No statistically significant differences in cancer or muscle- or gallbladder-related events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Simva n=9077 (%)</th>
<th>EZ/Simva n=9067 (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT and/or AST≥3x ULN</td>
<td>2.3</td>
<td>2.5</td>
<td>0.43</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>1.5</td>
<td>1.5</td>
<td>0.96</td>
</tr>
<tr>
<td>Gallbladder-related AEs</td>
<td>3.5</td>
<td>3.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Rhabdomyolysis*</td>
<td>0.2</td>
<td>0.1</td>
<td>0.37</td>
</tr>
<tr>
<td>Myopathy*</td>
<td>0.1</td>
<td>0.2</td>
<td>0.32</td>
</tr>
<tr>
<td>Rhabdo, myopathy, myalgia with CK elevation*</td>
<td>0.6</td>
<td>0.6</td>
<td>0.64</td>
</tr>
<tr>
<td>Cancer* (7-yr KM %)</td>
<td>10.2</td>
<td>10.2</td>
<td>0.57</td>
</tr>
</tbody>
</table>

*% = n/N for the trial duration.
Safety Events – 6 years f/u

Giugliano RP et al. JAMA Cardiology March 2017
Effect of ezetimibe treatment on the primary end-point
A composite of the atherosclerotic cardiovascular events
(Sudden cardiac death, myocardial infarction, PCI or CABG, and/or stroke)

Hazard Ratio: 0.659 (95% CI, 0.504-0.862)

p = 0.002
PCSK9 Regulates LDL-R Expression

LDL-C Reduction via PCSK9 Inhibition

COMBO II: PCSK9i Alirocumab vs Ezetimibe Added to Max-tolerated Statin in High CV-Risk Patients

LDL-C reduction over 52 weeks on background of max-tolerated statin

Ezetimibe + Placebo Q2WK SC (n=241)
Alirocumab 75-150 mg Q2W + Placebo Ezetimibe (n=479)

LDL-C, LS Mean (SE), mg/dL

Dose ↑ if LDL-C >70 mg/dL at wk8

Impact of PCSK9 Inhibition on Lipid Levels

Meta-analysis of 35 randomized controlled trials comparing treatment with and without PCSK9 inhibitors

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Δ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>↓ 54.7</td>
</tr>
<tr>
<td>TC</td>
<td>↓ 34.9</td>
</tr>
<tr>
<td>HDL-C</td>
<td>↑ 6.9</td>
</tr>
<tr>
<td>apoB</td>
<td>↓ 45.5</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>↓ 26.5</td>
</tr>
</tbody>
</table>

GLAGOV: Evolocumab Added to Statins

Primary Endpoint: Percent Atheroma Volume

-0.95

P <0.001

-0.02

P = NS

-0.08

Evolocumab: LDL-C 36.6 mg/dL

Placebo LDL-C 93.0 mg/dL

# of Patients

Placebo  484  446  441  447  441  425  418

Alirocumab  484  456  452  444  449  449  434

GLAGOV: Evolocumab added to statin
On-treatment LDL-C vs. Regression of Coronary Plaque

FOURIER: Effects of PCSK9i Evolocumab

27,564 high-risk, stable patients with established CV disease

Evolocumab (median 30 mg/dl, IQR 19-46 mg/dl)

Placebo

59% reduction
P<0.00001

Absolute ↓ 56 mg/dl

HR 0.85 (0.79-0.92)
P<0.0001

HR 0.80 (0.73-0.88)
P<0.0001

CVD, MI, stroke
UA, cor revascularization

KM Rate (%) at 3 Years

Sabatine MS et al. NEJM. 2017; 376: 1713-22.
Total Key Secondary EP Events: CVD/MI/Stroke

- Total Events: RR 0.81 (95% CI 0.73-0.90), P<0.001
- Additional Events: RR 0.79 (0.61-1.02)
- 1st Event: HR 0.80 (0.73-0.88)

- Placebo: 1013 events
- Evolocumab: 816 events

- 1268 total events
- 255 additional events
- 1014 total events
- 198 additional events

- Difference: Evolocumab vs Placebo
  - Total Events: 0.81
  - Additional Events: 0.79
  - 1st Event: 0.80
Total Primary Endpoint Events

Number of Events Prevented for 1,000 Patients
Treated with Evolocumab for 3 Years

First Event Only
-22

Total Events
-52

Events per 1,000 Patients
CV Death, MI or Stroke in Patients with and without Peripheral Artery Disease

Placebo
Evolocumab

CV Death, MI or Stroke

PAD
No PAD

N=3,642
N=23,922

27% RRR
HR 0.73
(0.59 – 0.91)
P=0.0040

PAD
3.5% ARR
NNT 2.5y 29

No PAD
1.4% ARR
NNT 2.5y 72

p-interaction = 0.41
**Major Adverse Limb Events**

Placebo vs. Evolocumab

**All Patients**  
N=27,564

42% RRR  
HR 0.58  
(0.38 – 0.88)  
P=0.0093

Outcome  
MALE  
HR  
95% CI

- ALI or major amputation: 0.52  
  (0.31 – 0.89)
- ALI: 0.55  
  (0.31 – 0.97)
- Major amputation: 0.57  
  (0.17 – 1.95)
- Urgent revascularization: 0.69  
  (0.38 – 1.26)
FOURIER – Lower CV Event Rates with Lower LDL-C Levels*, Even Down to 20 mg/dL

*Relationship between the achieved LDL-cholesterol concentration at 4 weeks and the risk of CVD, MI, or stroke.
ORION-1: Efficacy of Single-dose Inclisiran in Patients at High CV Risk with Elevated LDL-C

ODYSSEY OUTCOMES

Post-ACS patients (1 to 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

Randomization

Alirocumab SC Q2W

Placebo SC Q2W

Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

We attempted to maximize the number of patients in the target range and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W) or blindly switching to placebo.
LDL-C: On-Treatment Analysis

Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
Approximately 75% of months of active treatment were at the 75 mg dose
Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

*Based on cumulative incidence

HR 0.85
(95% CI 0.78, 0.93)
P=0.0003
## Primary Efficacy and Components

<table>
<thead>
<tr>
<th>Endpoint, n (%)</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
<th>HR (95% CI)</th>
<th>Log-rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>903 (9.5)</td>
<td>1052 (11.1)</td>
<td>0.85 (0.78, 0.93)</td>
<td>0.0003</td>
</tr>
<tr>
<td>CHD death</td>
<td>205 (2.2)</td>
<td>222 (2.3)</td>
<td>0.92 (0.76, 1.11)</td>
<td>0.38</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>626 (6.6)</td>
<td>722 (7.6)</td>
<td>0.86 (0.77, 0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>111 (1.2)</td>
<td>152 (1.6)</td>
<td>0.73 (0.57, 0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>37 (0.4)</td>
<td>60 (0.6)</td>
<td>0.61 (0.41, 0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>CV death</td>
<td>240 (2.5)</td>
<td>271 (2.9)</td>
<td>0.88 (0.74, 1.05)</td>
<td>0.15</td>
</tr>
<tr>
<td>All-cause death</td>
<td>334 (3.5)</td>
<td>392 (4.1)</td>
<td>0.85 (0.73, 0.98)</td>
<td>0.026*</td>
</tr>
</tbody>
</table>
LDL-C Levels for Optimal CV Risk Reduction: What We Know Now

- High is bad
- Average is not good
- Lower is better
- Even lower is even better
- Lowest is best
Treatment algorithm for hypercholesterolemia

Step 1:
Statin

Step 2:
Check low-density lipoprotein cholesterol (LDL-C)

Step 3:
Add prescription as needed

Post-acute coronary syndrome/coronary artery disease patient with hypercholesterolemia

American College of Cardiology/American Heart Association Guidelines: Optimize statin therapy

LDL-C <70 mg/dl
Add ezetimibe

LDL-C ≥70 mg/dl
Add proprotein convertase subtilisin/kexin type 9 inhibitors or other lipid-lowering therapy

LDL-C target <50 mg/dl for very high risk atherosclerotic cardiovascular disease

Results: LDL-C Distribution and LLT Utilization at Baseline and after Full Treatment Intensification

Before Treatment Intensification

- HIS + EZE (1%)
- MIS + EZE (1%)
- HIS Only (14%)
- MIS Only (37%)
- EZE Only (1%)
- No Statin or EZE (46%)

After Treatment Intensification

- HIS + EZE + ALI 150 (2%)
- HIS + EZE + ALI 75 (12%)
- HIS + EZE (17%)
- MIS + EZE (1%)
- HIS Only (25%)
- MIS Only (43%)

ALI 75 = alirocumab 75 mg; ALI 150 = alirocumab 150 mg; EZE = ezetimibe; HIS = high-intensity statin; MIS = moderate- to low-intensity statin.

### Implementation

#### Recommendations for Implementation

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>Interventions focused on improving adherence to prescribed therapy are recommended for management of adults with elevated cholesterol levels, including telephone reminders, calendar reminders, integrated multidisciplinary educational activities, and pharmacist-led interventions, such as simplification of the drug regimen to once-daily dosing.</td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
<td>Clinicians, health systems, and health plans should identify patients who are not receiving guideline-directed medical therapy and should facilitate the initiation of appropriate guideline-directed medical therapy, using multifaceted strategies to improve guideline implementation.</td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
<td>Before therapy is prescribed, a patient-clinician discussion should take place to promote shared decision-making and should include the potential for ASCVD risk-reduction benefit, adverse effects, drug-drug interactions, and patient preferences.</td>
</tr>
</tbody>
</table>

Grundy SM, et al JACC/Circulation 2018 online
Brigham Lipid Optimization (B-LO) Program

• 1012 pts with high ASCVD risk

• Remote management program executed by non-physician navigators with physician oversight and decision-support software utilizing Benson M, Plutzky J, et al. ACC.18

Patient satisfaction with program (scale 0-10):

• 10 - 77%
• 9 – 8%
• 8 – 8 %
Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

- **Age 0-19 y**
  - Lifestyle to prevent or reduce ASCVD risk
  - Diagnosis of Familial Hypercholesterolemia → 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 (≥4.1 mmol/L)

- **Age 40-75 y**
  - LDL-C ≥190 mg/dL (≥4.9 mmol/L)
  - No risk assessment; High-intensity statin (Class I)

- **Diabetes mellitus and age 40-75 y**
  - Moderate-intensity statin (Class I)

- **Diabetes mellitus and age 40-75 y**
  - Risk assessment to consider high-intensity statin (Class Ila)

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

**ASCVD Risk Enhancers:**
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)
- Lipid/Biomarkers:
  - Persistently elevated triglycerides (≥175 mg/dL, ≥2.0 mmol/L)
  - 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

**Risk Discussion:**
- **<5% “Low Risk”**
  - Risk discussion: Emphasize lifestyle to reduce risk factors (Class I)

- **5% - <7.5% “Borderline Risk”**
  - Risk discussion: If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class IIb)

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

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

If risk decision is uncertain:
Consider measuring CAC in selected adults:
- CAC = 0 (lowers 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

Grundy SM, et al  JACC/Circulation 2018 online
Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: (MESA)

N=6,783. Red dashed line shows 7.5% risk.

Budoff MJ et al. EHJ 2018;39, 2401–2408,
European Atherosclerosis Society Consensus Panel: Adverse effects of statin therapy: perception vs. the evidence

Highly favourable Benefit / Risk Ratio for statin therapy

**POTENTIAL RISKS**
- Modest risk of new-onset diabetes (~0.1% annually), higher in those with the metabolic syndrome cluster
- Muscle symptoms, but be aware of the nocebo effect
- Very rarely, clinically relevant liver injury
- Possible increase in risk of haemorrhagic stroke in patients with a prior stroke suggested by SPARCL; not confirmed in the substantive evidence base of RCTs, cohort and case-control studies

**BENEFITS**
- Reduction in LDL-C levels
- Regression of coronary atheroma
- Reduction in ASCVD events

No evidence to support adverse effects of statins on cognitive function, clinically significant renal deterioration, or risk for cataract, or haemorrhagic stroke in patients without prior stroke.

Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol

REDUCE-IT Design

1. Age ≥45 years with established CVD (Secondary Prevention Cohort) or ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)

2. Fasting TG levels ≥135 mg/dL and <500 mg/dL

3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

Primary Endpoint Events: CV death, nonfatal MI, nonfatal stroke, coronary revasc, hospitalization for unstable angina

Key Secondary Endpoint Events: CV death, nonfatal MI, nonfatal stroke

Double-blind study; Events adjudicated by CEC that was blinded to treatment during adjudication

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

![Graph showing event rates over time for Placebo and Icosapent Ethyl with hazard ratio, RRR, ARR, and NNT calculations.]

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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>RRR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite (ITT)</td>
<td></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></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></td>
<td>392/4089 (9.6%)</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></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></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></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></td>
<td>108/4089 (2.6%)</td>
<td>157/4090 (3.8%)</td>
<td>0.68 (0.53–0.87)</td>
<td>32%▼</td>
<td>0.002</td>
</tr>
<tr>
<td>Fatal or Nonfatal Stroke</td>
<td></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></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></td>
<td>274/4089 (6.7%)</td>
<td>310/4090 (7.6%)</td>
<td>0.87 (0.74–1.02)</td>
<td>13%▼</td>
<td>0.09</td>
</tr>
</tbody>
</table>

RRR denotes relative risk reduction.
First and Subsequent Events

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

30% Reduction in Total Events

Placebo [N=4090]
1,546
126
143

1,076
63
72

901
376
236

Icosapent Ethyl [N=4089]

No. of Fewer Cases
-470
-63
-71
-140
-196

Note: WLW method for the 1st events, 2nd events, and 3rd events categories; Negative binomial model for ≥4 events and overall treatment comparison.
Omega-3 fatty acids for Cardiovascular Prevention

→ **Diet:** Apparent benefit of fish consumption (observational studies)

→ **Low-dose Supplementation**
  - Initial trials suggested benefit (JELIS - with medium dose EPA)
  - Meta-analysis (trials to 2018), ASCEND and VITAL trials: No overall CV benefit

→ **High-dose omega-3 FA:** Positive CV Benefit
  → REDUCE-IT trial (4 gm EPA) shows 25% ↓ in CV events, 30%↓ in total CV events
  → STRENGTH trial with Epanova (4 gm mixed EPA/DHA agent) – due in late 2019
Conclusions

• New 2018 ACC/AHA guidelines
  – Recommend statins for 4 benefit groups
  – Then add non-statins if LDL > 70 mg/dl for secondary prev. and >100 mg/dl for FH
• IMPROVE IT, REVEAL, FOURIER, and ODYSSEY OUTCOMES have shown
  – *Non-statin* agents (ezetimibe and PSCK9 inhibitors) lowering LDL-C and CV events
  – Achieving lower LDL levels (< 50 mg/dL) shown to be safe and significantly reduces the risk of cardiovascular events in very high risk ASCVD
• PCSK9 inhibitors: FH or Clinical ASCVD on max tolerated statin with LDL> goal
• High-dose eicosapent ethyl (EPA) – CV benefit in Pts. with elevated Triglycerides
• BUT: We need to use the therapies we have proven to have benefit!