Cardiology CV Prevention
Review of the most important studies of 2018
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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 and emphasizes intensive lifestyle efforts.
In all age groups, **lifestyle therapy** is the primary intervention for metabolic syndrome.

The **more** LDL-C is reduced on statin therapy, the **greater** will be subsequent risk reduction.

In patients with **clinical ASCVD**, reduce low-density lipoprotein cholesterol (LDL-C) with **high intensity statin therapy** or maximally tolerated statin therapy.
Use a maximally tolerated statin to lower LDL-C levels by ≥50%.

**Very High-Risk - definition**

- History of multiple major ASCVD events
  - or
- 1 major ASCVD event
  - and multiple high-risk conditions

In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) 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 (≥1.8 mmol/L).

In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) 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.

Severe primary Hypercholesterolemia
(LDL-C level ≥190 mg/dL
[≥4.9 mmol/L])
Severe Primary Hypercholesterolemia

Initiate high-intensity statin therapy without calculating 10-year ASCVD risk.

If the LDL-C level remains ≥100 mg/dL (≥2.6 mmol/L), adding ezetimibe is reasonable.

Severe primary Hypercholesterolemia

If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL (≥2.6 mmol/L) and the patient has multiple factors that increase subsequent risk of ASCVD events, PCSK9 inhibitor may be considered.

Severe primary Hypercholesterolemia

Remember with PCSK29 drugs: the long-term safety (>3 years) is uncertain and economic value is low at mid 2018 list prices.
In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), 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%.
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:
- cigarette smoking
- elevated blood pressure
- LDL-C
- hemoglobin A1C (if indicated)
- calculated 10-year risk of ASCVD
- the presence of risk-enhancing factors
- the potential benefits of lifestyle and statin therapies
- the potential for adverse effects and drug–drug interactions
- consideration of costs of statin therapy
- patient preferences and values in shared decision-making

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.
Risk enhancing factors

- Include family history of premature ASCVD;
- Persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L);
- 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)

Risk enhancing factors

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Persistent elevations of triglycerides ≥175 mg/dL (≥1.97 mmol/L)
MAY BE measured in selected individuals,
1. apolipoprotein B ≥130 mg/dL
2. high-sensitivity C-reactive protein (hsCRP) ≥2.0 mg/L
3. ankle-brachial index (ABI)

In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL to 189 mg/dL (≥1.8–4.9 mmol/L), 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 = 0
treatment with statin therapy may be withheld or delayed except
1. cigarette smokers
2. diabetes mellitus
3. strong family history of premature ASCVD.
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.

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.
Cardiology 2019

Does Vitamin D or Omega 3 reduce CV events?

Vital Trial

Vital Trial- Description

• Description:
  • The goal of the trial was to assess the cardiovascular (CV) and cancer benefits of n-3 (also called omega-3) fatty acid and vitamin D3 supplementation compared with placebo among healthy participants.
Study Design

• In a 2 x 2 factorial design, healthy participants were randomized in a 1:1 fashion to either vitamin D3 (at a dose of 2000 IU per day) (n = 12,927) or placebo (n = 12,944), or n–3 fatty acids (1 g per day as a fish-oil capsule containing 840 mg of n-3 fatty acids, including 460 mg of eicosapentaenoic acid [EPA] and 380 mg of docosahexaenoic acid [DHA]) (n = 12,933) or matching placebo (n = 12,938).

Vital Trial

• Total number of enrollees: 25,871
• Duration of follow-up: 5.3 years
• Mean patient age: 67.1 years
• Percentage female: 51%

Vital trial

Inclusion criteria:
- Men >50 years or women >55 years
- No known cardiovascular disease or cancer

Exclusion criteria:
- Renal failure or dialysis
- Cirrhosis
- History of hypercalcemia
Vital Trial – salient features/characteristics

• African American: 20%
• Mean body mass index: 28 kg/m²
• Diabetes: 13.7%

Vital Study – Principal Findings

• The primary CV outcome of CV death, nonfatal myocardial infarction (MI), or stroke, for vitamin D3 vs. placebo, was 3.1% vs. 3.2%, hazard ratio (HR) 0.97, 95% confidence interval (CI) 0.85-1.1, p = 0.69.
• CV death: 1.1% vs. 1.1%, for vitamin D3 vs. placebo, respectively
• Stroke: 1.1% vs. 1.1%
• MI: 1.1% vs. 1.5%, HR 0.72, 95% CI 0.59-0.90
• Primary cancer outcome, invasive cancer: 6.1% vs. 6.4%, HR 0.96, 95% CI 0.88-1.06, p = 0.47

Vital Study – Principal Findings

• The primary CV outcome of CV death, nonfatal MI, or stroke, for n–3 fatty acid vs. placebo, was 3.0% vs. 3.2%, HR 0.92, 95% CI 0.80-1.06, p = 0.24.
• CV death: 1.2% vs. 1.1%, for n–3 fatty acid vs. placebo, respectively
• Stroke: 1.1% vs. 1.1%
• MI: 1.3% vs. 1.3%
• Primary cancer outcome, invasive cancer: 6.3% vs. 6.2%, HR 1.03, 95% CI 0.99-1.13, p = 0.56
Vital Secondary - D3 vs placebo outcomes

- Secondary outcomes for vitamin D3 vs. placebo:
- All-cause mortality: 3.8% vs. 3.8%

Secondary outcomes — n-3 fatty acid vs placebo

- Total coronary heart disease: 0.3% vs. 0.4%
- All-cause mortality: 3.8% vs. 3.7%

Vital Trial - Conclusion

- The **VITAL trial** showed that supplementation with either n-3 fatty acid at a dose of 1 g/day or vitamin D3 at a dose of 2000 IU/day was not effective for primary prevention of CV or cancer events among healthy middle-aged men and women over 5 years of follow-up.
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**Cardiology 2019**

Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial

REDUCE-It Trial
Reduce-IT Trial – Contribution to Literature

- The REDUCE-IT trial showed that use of icosapent ethyl 2 g twice daily was superior to placebo in reducing TGs, CV events, and CV death among patients with high TGs and either known CV disease or those at high risk for developing it, and who were already on statin therapy with relatively well-controlled LDL levels.

Reduce-IT Trial – Study Design

- The REDUCE-IT trial showed that use of icosapent ethyl 2 g twice daily was superior to placebo in reducing TGs, CV events, and CV death among patients with high TGs and either known CV disease or those at high risk for developing it, and who were already on statin therapy with relatively well-controlled LDL levels.

Reduce-IT Trial – Inclusion

- Age >45 years with established CV disease or age >50 years with diabetes and ≥1 additional risk factor
- Fasting TG level from 150-499 mg/dl
- Low-density lipoprotein (LDL) cholesterol level from 41 and 100 mg/dl
- Stable dose of statin for ≥4 weeks
Reduce-IT Trial –Exclusion

• Severe heart failure
• Active severe liver disease
• Glycated hemoglobin level >10.0%
• Planned coronary intervention or surgery
• History of acute or chronic pancreatitis
• Known hypersensitivity to fish, shellfish, or ingredients of icosapent ethyl or placebo

Reduce-IT Trial –Other salient features/characteristics

• Secondary prevention cohort: 70.7%
• Ezetimibe use: 6.4%
• Moderate- or high-intensity statin: 94%
• Diabetes: 59%
• Median TG levels at baseline: 216 mg/dl, LDL: 75 mg/dl, high-density lipoprotein: 40 mg/dl, high-sensitivity C-reactive protein: 2.2

Reduce-IT Trial –Principal Findings

The primary CV outcome of CV death, nonfatal myocardial infarction (MI), stroke, coronary revascularization, or unstable angina, for icosapent ethyl vs. placebo, was 17.2% vs. 22.0%, hazard ratio 0.75, 95% confidence interval 0.68-0.83; p < 0.0001
**Reduce-IT Trial** — Secondary outcomes icosapent ethyl vs placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Icosapent Ethyl</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in TG levels at 1 year</td>
<td>-39.0 mg/dl</td>
<td>4.5 mg/dl</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Change in LDL at 1 year</td>
<td>2 mg/dl</td>
<td>7 mg/dl</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CV death or MI</td>
<td>9.6%</td>
<td>12.4%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>All MI</td>
<td>6.1%</td>
<td>8.7%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Revascularization</td>
<td>5.3%</td>
<td>7.8%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6.7%</td>
<td>7.6%</td>
<td>not significant</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>5.3%</td>
<td>3.9%</td>
<td></td>
</tr>
<tr>
<td>Serious adverse bleeding events</td>
<td>2.7%</td>
<td>2.1%</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Reduce-IT Trial - Interpretation**

The results of this trial indicate that the use of icosapent ethyl 2 g twice daily was superior to placebo in reducing TGs, CV events, and CV death among patients with high TGs and either known CV disease or those at high risk for developing it, and who were already on statin therapy with relatively well-controlled LDL levels.

Rates of revascularization and MI were lower, while atrial fibrillation/flutter and bleeding were higher with icosapent ethyl.

**Reduce-IT Trial**

One aspect of this medication is that it has a higher dose of purified eicosapentaenoic acid (EPA) (4 g/day) than what was tested in other clinical trials.

These are very interesting findings, and come on the heels of several negative trials with n-3 fatty acid supplementation.
Reduce-IT Trial

This is one of the first non-LDL targeted trials to show a CV benefit, and will likely be featured in future guidelines.

Currently there are other additional trials with moderate to high doses of EPA that are ongoing.

Cardiology 2019

What is the value of moderate dose aspirin in older adults without cardiovascular disease, dementia or disability?

ASPREE Trial

Aspree Trial- Contribution To Literature

• The ASPREE trial showed that aspirin did not prevent disability-free survival, but did increase major bleeding compared with placebo.
Aspree Trial - Description

- The goal of the trial was to evaluate low-dose aspirin compared with placebo among healthy elderly patients.
- Study Design
  - Randomized
  - Parallel
  - Stratified

Aspree Trial

- Healthy elderly patients were randomized to aspirin 100 mg daily (n = 9,525) versus placebo (n = 9,589).
- Total number of enrollees: 19,114
- Duration of follow-up: median 4.7 years
- Median patient age: 74 years
- Percentage female: 56%
- Percentage with diabetes: 11%

Aspree Trial

Inclusion criteria:
- Healthy individuals ≥70 years of age (or ≥65 years of age for blacks and Hispanics)

Exclusion criteria:
- Cardiovascular or cerebrovascular disease
- Dementia
- High risk of bleeding
- Contraindication to aspirin
Aspree Trial – Principal findings

• The primary outcome, all-cause death, dementia, or physical disability, was 21.5 events per 1,000 person-years in the aspirin group compared with 21.2 events per 1,000 person-years in the placebo group (p = 0.79).

Aspree Trial – Secondary outcomes

• Major hemorrhage: 8.6 events per 1,000 person-years in the aspirin group vs. 6.2 events per 1,000 person-years in the placebo group (p < 0.001)
• Any intracranial bleeding: 2.5 events per 1,000 person-years in the aspirin group vs. 1.7 events per 1,000 person-years in the placebo group (p < 0.05)

• Upper gastrointestinal bleeding: 2.1 events per 1,000 person-years in the aspirin group vs. 1.1 events per 1,000 person-years in the placebo group (p < 0.05)
• Cardiovascular disease (fatal cardiovascular disease, myocardial infarction, stroke, or hospitalization for heart failure): 10.7 events per 1,000 person-years in the aspirin group
Aspree Trial - Secondary outcomes

- All-cause mortality: 5.9% in the aspirin group vs. 5.2% in the placebo group (p < 0.05)
- Cancer mortality: 3.1% in the aspirin group vs. 2.3% in the placebo group (p < 0.05)

Aspree Trial - Secondary outcomes

- Cardiovascular disease (fatal cardiovascular disease, myocardial infarction, stroke, or hospitalization for heart failure): 10.7 events per 1,000 person-years in the aspirin group vs. 11.3 events per 1,000 person-years in the placebo group (p = not significant)

Aspree Trial – Interpretation

Among healthy elderly patients, low-dose aspirin therapy was not beneficial.
Compared with placebo, aspirin did not improve disability-free survival or reduce major adverse cardiovascular events at a median of 4.7 years.
Aspirin was associated with a significant increase in major bleeding, which was attributed to excess intracranial and upper gastrointestinal bleeding.
Aspree Trial – Interpretation

Aspirin was also associated with an increase in all-cause mortality, which was attributed to excess cancer mortality. While the increase in all-cause and cancer mortality is compelling, these findings have not been observed previously and should likely be interpreted with caution.

- The ARRIVE trial showed that among younger individuals with moderate risk of coronary heart disease, the use of aspirin was not beneficial.
- The ASCEND Aspirin trial showed that among diabetic patients, aspirin reduced the incidence of major adverse cardiovascular events; however, this was somewhat counterbalanced by an increase in major bleeding.