Top Concepts in Recent Cholesterol Management Guidelines That Clinicians Need to Know

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Disclosure

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Member/Steering Committee: Patient and Provider Assessment of Lipid Management (PALM), Registry at the Duke Clinical Research Institute
The writing committee consisted of medical experts including cardiologists, internists, interventional cardiologists, a nurse practitioner, pharmacists, a physician assistant, a pediatrician, a nephrologist and a lay/patient representative.

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Guideline Summary
121 pages
72 Recommendations
Class I 29
Class II a 26
Class II b 14
Class III 3
2 Value Based Recommendations

Objectives

- Discuss the rationale for recommendations for the treatment of 3 primary prevention populations (LDL-C ≥190 mg/dl, patients with diabetes, and those without elevated LDL-C or diabetes [pure primary prevention population]).
- Why and how we calculate ASCVD risk?
- How do we personalize ASCVD risk?
- How do we reclassify ASCVD risk when there is uncertainty on the part of the clinician or the patient?
- Discuss major recommendations for cholesterol treatment in patients for secondary ASCVD prevention.

Primary Prevention of ASCVD
Primary Prevention: Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

Age 0-19 y
Lifestyle to prevent development of premature ASCVD

Age 20-39 y
Evaluate lifetime risk to manage lifestyle to reduce ASCVD risk
Consider statins if history of premature ASCVD or LDL-C >190 mg/dL (4.9 mmol/L)

Age 40-75 y
Consider statin therapy if history of premature ASCVD or LDL-C >190 mg/dL (4.9 mmol/L) without diabetes mellitus

Age >75 y
Clinical assessment, risk discussion

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., precocious puberty, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

LDL/Crit biomarkers:
- Persistently elevated triglycerides (≥375 mg/dL, ≥4.0 mmol/L)

In selected individuals if measured:
- In e-CRP ≥2.0 mg/L
- In LDL ≥190 mg/dL or ≥4.9 mmol/L
- ApoB ≥130 mg/dL
- Arterial-branch index (ABI) <0.9

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

- Low Risk: ≤5%
- Borderline Risk: 5% - 7.5%
- Intermediate Risk: ≥7.5% - <20%

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

- High Risk: ≥20%

If risk decision is uncertain:
Consider CAC score
- CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
- CAC = 1-99 (favor statin, especially if age 55)
- CAC = 100+ (favor statin, especially if age 55 and/or CAC percentile)

Long-term Mortality End points at 20 Years of Follow-up, Overall, and Stratified by LDL-C Levels at Baseline.

<table>
<thead>
<tr>
<th></th>
<th>CHD death</th>
<th>Cardiovascular death</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall primary prevention cohort</td>
<td>LDL-C &lt;190 mg/dL</td>
<td>p = 0.456</td>
<td>0.75 (0.69, 0.83)</td>
</tr>
<tr>
<td></td>
<td>LDL-C &lt;130 mg/dL</td>
<td>p = 0.157</td>
<td>0.91 (0.73, 1.13)</td>
</tr>
<tr>
<td></td>
<td>LDL-C &lt;190 mg/dL</td>
<td>p = 0.213</td>
<td>0.88 (0.67, 1.00)</td>
</tr>
<tr>
<td></td>
<td>LDL-C &lt;190 mg/dL</td>
<td>p = 0.184</td>
<td>0.79 (0.50, 1.26)</td>
</tr>
</tbody>
</table>

- **CHD death**
- **Cardiovascular death**
- **All-cause mortality**


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 of premature ASCVD and LDL-C ≥190 mg/dL (4.9 mmol/L)

- **Age 40-75 y**
  - LDL-C ≥190 mg/dL (4.9 mmol/L) without diabetes mellitus or ASCVD risk present begins risk discussion

- **Age >75 y**
  - Clinical assessment, risk discussion

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., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Obesity (especially south Asian ancestry)

LDL-C ≥210 mg/dL (5.4 mmol/L)
- No risk assessment; high-intensity statin (Class I)

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

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

Risk discussion: If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class IIa)

Risk discussion: If risk estimate × risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30-49% (Class IIa)

Risk discussion: If risk estimate × risk enhancers favor statin, initiate high-intensity statin therapy (Class IIa)

## Efficacy of Cholesterol-lowering Therapy in 18,686 People with Diabetes in 14 Randomised Trials of Statins

4.5 year of follow-up; 3247 major vascular events

<table>
<thead>
<tr>
<th>Major vascular event and prior diabetes</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event</td>
<td>27/6 (8.3%)</td>
<td>979 (105%)</td>
<td>0.78 (0.69-0.87)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>34 (1.2%)</td>
<td>176 (5.5%)</td>
<td>0.67 (0.57-0.80)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>43 (1.4%)</td>
<td>144 (4.8%)</td>
<td>0.77 (0.66-0.90)</td>
</tr>
<tr>
<td>Test for heterogeneity within subgroup: $\chi^2 = 0.1; p = 0.8$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary revascularisation</td>
<td>149 (5.7%)</td>
<td>627 (6.7%)</td>
<td>0.75 (0.64-0.88)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>2129 (5.0%)</td>
<td>2807 (7.9%)</td>
<td>0.76 (0.72-0.81)</td>
</tr>
<tr>
<td>Any coronary revascularisation</td>
<td>2520 (5.8%)</td>
<td>3434 (7.6%)</td>
<td>0.76 (0.73-0.80)</td>
</tr>
<tr>
<td>Test for heterogeneity within subgroup: $\chi^2 = 0.1; p = 0.8$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>467 (4.4%)</td>
<td>501 (5.4%)</td>
<td>0.97 (0.93-0.97)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>933 (2.7%)</td>
<td>1116 (3.2%)</td>
<td>0.84 (0.76-0.93)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>1340 (3.3%)</td>
<td>1617 (3.7%)</td>
<td>0.83 (0.77-0.88)</td>
</tr>
<tr>
<td>Test for heterogeneity within subgroup: $\chi^2 = 0.0; p = 0.4$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major vascular event</td>
<td>1782 (19.2%)</td>
<td>6384 (14.1%)</td>
<td>0.79 (0.72-0.86)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7998 (17.8%)</td>
<td>8684 (19.0%)</td>
<td>0.79 (0.72-0.81)</td>
</tr>
</tbody>
</table>


### Diabetes-Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes Mellitus

<table>
<thead>
<tr>
<th>Risk Enhancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long duration (≥10 years for type 2 diabetes mellitus (S.4.3-20) or ≥20 years for type 1 diabetes mellitus)</td>
</tr>
<tr>
<td>Albuminuria ≥30 mcg of albumin/mg creatinine</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Retinopathy</td>
</tr>
<tr>
<td>Neuropathy</td>
</tr>
<tr>
<td>ABI &lt;0.9</td>
</tr>
</tbody>
</table>
Primary Prevention: Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

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., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

Lipid/Biomarkers:
- Persistently elevated triglycerides (≥300 mg/dL, ≥8.3 mmol/L)

In selected individuals if measured:
- HDL ≥40 or >1.65 mmol/L
- Apo B/apolipoprotein B (Apo B) ≥0.9

Risk discussion: Emphasize lifestyle to reduce risk factors (Class II)

Risk discussion: if risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class II)

Risk discussion: if risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 40% (Class II)

Risk discussion: initiate statins to reduce LDL-C ≥50% (Class I)

If risk decision is uncertain:
Consider measuring CAC in select adults:
CAC = zero (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

Optimal risk factors:
- TC = 170 mg/dL
- HDL-C = 50 mg/dL
- Systolic BP = 110 mmHg
- Not taking medications for HTN
- Not a diabetic
- Not a smoker

ACC/AHA ASCVD Risk Estimator

10-year risk of non-fatal MI, coronary heart disease death, and fatal and non-fatal stroke

Intended for use if no ASCVD and LDL-C is <190 mg/dL

2017 Hypertension Guidelines

Blood Pressure (BP) Thresholds and Recommendations for Treatment and Follow-Up

BP Thresholds and Recommendations for Treatment and Follow-Up

Normal BP (BP < 120/80 mm Hg)
- Promote optimal lifestyle habits
- Nonpharmacologic therapy (Class I)

Elevated BP (120–129/80–89 mm Hg)
- Reassess in 1 y (Class IIa)

Stage 1 Hypertension (BP 130–139/80–89 mm Hg)
- Nonpharmacologic therapy (Class I)

Stage 2 Hypertension (BP ≥ 140/90 mm Hg)
- Clinical ASCVD or estimated 10-y CVD risk ≥ 10%
  - No
  - Yes
- Nonpharmacologic therapy and BP-lowering medication (Class I)

2018 Cholesterol Guidelines

Primary Prevention: Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

Age 0–18 y
- Hypertension in patients with ASCVD risk factors

Age 19–39 y
- Estimate lifetime risk in patients with ASCVD risk factors

Age 40–74 y
- Estimate lifetime risk in patients with ASCVD risk factors
- Consider moderate-intensity statin therapy

Age 75 y and older
- Clinical assessment, risk discussion

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C (≥ 190 mg/dL)
- ESRD
- Congestive heart failure
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (e.g., rheumatoid arthritis, psoriasis, HHV-1)
- Ethnicity (e.g., South Asian ancestry)

LDL-C: ≤ 100 mg/dL (2.6 mmol/L)
- No risk assessment; high-intensity statin

LDL-C 100–129 mg/dL (2.6–3.3 mmol/L)
- Moderate-intensity statin

LDL-C ≥ 130 mg/dL (3.4 mmol/L)
- High-intensity statin

Diabetes mellitus and age 40–75 y
- Moderate-intensity statin

Diabetes mellitus and age 75 y and older
- Clinical assessment, risk discussion
**Pooled Cohort Equations (PCE)**

- Recommended for use based on:
  - Broad utilization and desired endpoint of hard ASCVD
  - Most widely validated score in contemporary US populations
    - SR identified 23 manuscripts evaluating PCE in diverse populations
  - PCE are well calibrated near decision thresholds (e.g., 7.5% 10-year risk) in broad US clinical population
  - As with all risk scores, PCE can under- and over-estimate true risk in some subgroups
  - Reclassification by CAC well understood

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1. **Absolute Risk Estimation Helps Target Preventive Therapies to Patients Most Likely to Benefit**

- Allows identification of patients at sufficient risk to merit treatment with higher likelihood of net individual and societal benefit
- Allows direct comparison of potential benefits and harms from drug therapy

**Cholesterol Treatment Trialists**

**Blood Pressure Lowering Treatment Trialists**

CTT, Lancet 2012. BPLTTC, Lancet 2014. Lloyd-Jones et al., Circ and JACC 2018
2. Threshold for Statin Benefit In Primary Prevention?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Age/sex eligibility Criteria</th>
<th>Lipid/other eligibility criteria (mg/dL)</th>
<th>Mean LDL-C reduction and absolute reduction versus placebo at 1 y</th>
<th>RRR for ASCVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEGA</td>
<td>Pravastatin 10-20 mg</td>
<td>Men &lt;45 years of age; postmenopausal women 45-70 years of age</td>
<td>Total cholesterol 220-275 (LDL-C &lt;160-210)</td>
<td>-77%, 128 vs 156 (&gt;28 mg/dL)</td>
<td>24% 5.1%</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>Lovastatin 20-40 mg</td>
<td>Men &lt;57 years of age; postmenopausal women 55-75 years of age</td>
<td>LDL-C 130-192, triglycerides &lt;400, HDL-C &gt;45 for men and &lt;57 for women</td>
<td>-27%, 115 vs 156 (&gt;41 mg/dL)</td>
<td>26% 6.9%</td>
</tr>
<tr>
<td>JUPITER</td>
<td>Rosuvastatin 20 mg</td>
<td>Men &gt;50 years of age; women 260-70 years of age</td>
<td>hs-CRP &gt;2 mg/L; LDL-C &gt;130, triglycerides &lt;500</td>
<td>-50%, 55 vs 110 (&gt;35 mg/dL)</td>
<td>44% 7.6%</td>
</tr>
</tbody>
</table>

*AFCAPS/TexCAPS indicates Air Force/Texas Coronary Atherosclerosis Prevention Study: ASCVD, atherosclerotic cardiovascular disease; JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER); HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; and RRR, relative risk reduction.

Adapted from the supplement to the 2013 American College of CardiologyAmerican Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease in Adults.

3. Refining Risk Estimates for Individual Patients

**Risk-Enhancing Factors for Clinician-Patient Risk Discussion**

- Family history of premature ASCVD: (males, age <55 y; females, age <65 y)
- Primary hypercholesterolemia (LDL-C, 160-189 mg/dL [4.1-4.8 mmol/L]; non-HDL-C 190-219 mg/dL [4.9-5.6 mmol/L])*
- Metabolic syndrome [increased waist circumference, elevated triglycerides (>150 mg/dL), elevated blood pressure, elevated glucose, and low HDL-C (<40 mg/dL in men; <50 in women mg/dL) are factors; tally of 3 makes the diagnosis]
- Chronic kidney disease (eGFR 15-59 mL/min/1.73 m² with or without albuminuria, not treated with dialysis or kidney transplantation)
- Chronic inflammatory conditions such as psoriasis, RA, or HIV/AIDS
- History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as pre-eclampsia
- High-risk race/ethnicities (e.g. South Asian ancestry)
- Lipid/biomarkers: Associated with increased ASCVD risk
  - Persistently* elevated, primary hypertriglyceridemia (>175 mg/dL);
  - If measured:
    - Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)
    - Elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥ 50 mg/dL or ≥125 nmol/L constitutes a risk enhancing factor especially at higher levels of Lp(a)
    - Elevated apoB ≥130 mg/dL - A relative indication for its measurement would be triglyceride ≥ 200 mg/dL. A level ≥ 130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk enhancing factor
    - ABI (ABI) <0.9

Salim Virani, MD
Cholesterol Management Guidelines
4. Refining Risk Estimates for Individual Patients

Identifies pts with event rates below net statin benefit range

Except if baseline 10-y risk ≥20%


Estimate Absolute 10-year ASCVD Risk

Low Risk 0 - <5%
Borderline Risk 5% - <7.5%
Intermediate Risk 7.5% - <20%
High Risk ≥20%

Clinician-patient discussion considering risk-enhancing factors and net benefit of therapy

Lifestyle modification
Lifestyle and drug therapy
Putting It all Together in Intermediate Risk Patients

Clinicians and patients may not wish to postpone therapy in patients with a CAC score of 0 and diabetes mellitus, heavy current cigarette smoking, or strong family history of premature ASCVD.


Putting it All Together

Primary Prevention: Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C (≥160 mg/dL or ≥4.9 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., premenopausal, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

LDL-C = LDL cholesterol

LDL-C < 100 mg/dL (2.6 mmol/L)
No risk assessment; High-intensity statin
(Class I)

LDL-C ≥ 100 mg/dL (2.6 mmol/L)
Risk assessment to consider high-intensity statin
(Class IIa)

LDL-C < 100 mg/dL (2.6 mmol/L) or ≥ 100 mg/dL (2.6 mmol/L) without diabetes mellitus
5-year ASCVD risk per 10% risk equation

Reclassify (CAC)


Putting it All Together

Primary Prevention: Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C (≥160 mg/dL or ≥4.9 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., premenopausal, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

LDL-C = LDL cholesterol

LDL-C < 100 mg/dL (2.6 mmol/L)
No risk assessment; High-intensity statin
(Class I)

LDL-C ≥ 100 mg/dL (2.6 mmol/L)
Risk assessment to consider high-intensity statin
(Class IIa)

LDL-C < 100 mg/dL (2.6 mmol/L) or ≥ 100 mg/dL (2.6 mmol/L) without diabetes mellitus
5-year ASCVD risk per 10% risk equation

Reclassify (CAC)

**Take Home Messages (Primary Prevention)**

- Emphasize a heart-healthy lifestyle
- Treat patients with LDL-C $\geq 190 \text{ mg/dl}$ and those with diabetes early and aggressively

**Calculate ASCVD risk:**
- 20-39 years: Lifetime risk estimation
- 40-75 years: 10 year ASCVD risk;

- If 40-75 years, diabetes $\rightarrow$ moderate intensity statin
- If 40-75 years, no diabetes and intermediate risk (7.5-19.9%)
  - strong evidence for benefit with statins based on multiple RCTs

- Clinician-patient risk discussion occurs before statin Rx
  - Enhancing factors personalize a risk decision re statins
  - When a risk decision uncertain, coronary artery calcium score can target statin use to those most likely to benefit (reclassify).

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**Secondary ASCVD Prevention**
Patients with Clinical ASCVD (Definition)

- Acute coronary syndrome including those with history of myocardial infarction or unstable angina
- Stable angina
- Coronary or other arterial revascularization
- Stroke or transient ischemic attack
- Peripheral artery disease including aortic aneurysm of atherosclerotic origin.


Secondary ASCVD Prevention

Older Adults with ASCVD

Table 5: Effects on Major Vascular Events per mmol/L reduction in LDL cholesterol, by baseline prognostic factors in 5 more vs less trials

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events (% p.a.)</th>
<th>Unweighted RR (CI)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous vascular disease:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>3837 (4.5)</td>
<td>0.72 (0.65 - 0.80)</td>
<td></td>
</tr>
<tr>
<td>Non-CHD vascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>8 (3.3)</td>
<td>0.74 (0.52 - 1.06)</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>769 (17.0)</td>
<td>0.79 (0.69 - 0.91)</td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>3286 (4.2)</td>
<td>0.71 (0.63 - 0.80)</td>
<td></td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5145 (4.8)</td>
<td>0.71 (0.63 - 0.80)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6774 (4.8)</td>
<td>0.70 (0.60 - 0.83)</td>
<td></td>
</tr>
<tr>
<td>Age (years):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>2177 (4.3)</td>
<td>0.72 (0.62 - 0.83)</td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>1356 (4.7)</td>
<td>0.71 (0.66 - 0.84)</td>
<td></td>
</tr>
<tr>
<td>&gt; 75</td>
<td>310 (6.3)</td>
<td>0.78 (0.52 - 1.21)</td>
<td></td>
</tr>
</tbody>
</table>

Lancet 2010; 376:1670-81
Secondary ASCVD Prevention

Healthy Lifestyle

ASCVD not at very high-risk*

Age ≤75 y
High-intensity statin (Goal: LDL-C <100 mg/dL) (Class I)
If high-intensity statin not tolerated, use moderate-intensity statin (Class IIa)

Age >75 y
Initiation of moderate- or high-intensity statin is reasonable (Class IIa)
Continuation of high-intensity statin is reasonable (Class IIa)

Very high-risk* ASCVD

High-intensity or maximal statin (Class I)
If on maximal statin and LDL-C ≥70 mg/dL (1.8 mmol/L), adding ezetimibe may be reasonable (Class IIa)
If PCSK9 is considered, add ezetimibe to maximal statin before adding PCSK9-β (Class I)

Dashed arrow indicates RCT-supported efficacy, but is less cost effective
If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (1.8 mmol/L), or non-HDL-C ≥100 mg/dL (2.6 mmol/L), adding PCSK9-β is reasonable (Class IIa)

Which Secondary Prevention Patients to Use Non-Statins in?

Healthy Lifestyle

ASCVD not at very high-risk*

Age ≤75 y
High-intensity statin (Goal: LDL-C <100 mg/dL) (Class I)
If high-intensity statin not tolerated, use moderate-intensity statin (Class IIa)

Age >75 y
Initiation of moderate- or high-intensity statin is reasonable (Class IIa)
Continuation of high-intensity statin is reasonable (Class IIa)

Very high-risk* ASCVD

High-intensity or maximal statin (Class I)
If on maximal statin and LDL-C ≥70 mg/dL (1.8 mmol/L), adding ezetimibe may be reasonable (Class IIa)
If PCSK9 is considered, add ezetimibe to maximal statin before adding PCSK9-β (Class I)

Dashed arrow indicates RCT-supported efficacy, but is less cost effective
If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (1.8 mmol/L), or non-HDL-C ≥100 mg/dL (2.6 mmol/L), adding PCSK9-β is reasonable (Class IIa)

Why Do we Have a Very-High Risk Clinical ASCVD Category?- Learnings from IMPROVE-IT

Identification of Very-high Risk ASCVD Patients in Trials of PSCK9 Inhibitors

The Use of Major and Minor Criteria in FOURIER Trial

Major subgroups showing large ARR in trials of PCSK9 inhibitors for e.g. recent MI, more than one MI, multivessel CAD, those with PAD, and those with LDL-C >100mg/dl.2,3,4

References:
**Very High-Risk ASCVD Patients**

### Major ASCVD Events
- Recent ACS (within the past 12 mo)
- History of MI (other than recent ACS event listed above)
- History of ischemic stroke
- Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)

### High-Risk Conditions
- Age ≥65 y
- Heterozygous familial hypercholesterolemia
- History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
- Diabetes mellitus
- Hypertension
- CKD (eGFR 15-59 mL/min/1.73 m²)
- Current smoking
- Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
- History of congestive HF

*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions*
Which Non-statins to Use and in What Order?

Clinical ASCVD

Healthy Lifestyle

ASCVD not at very high-risk

Age ≤ 75 y

High-intensity statin (Goal: LDL-C < 50 mg/dL)

Age > 75 y

If high-intensity statin not tolerated, use moderate-intensity statin (Class IIa)

If on maximal statin therapy and LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L), adding ezetimibe may be reasonable (Class IIa)

Initiation of moderate- or high-intensity statin is reasonable (Class IIa)

Continuation of high-intensity statin is reasonable (Class IIa)

If on maximal statin and LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L), adding ezetimibe is reasonable (Class IIa)

If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L), or non-HDL-C ≥ 100 mg/dL (≥ 2.6 mmol/L), adding PCSK9-i is reasonable (Class IIa)

Very high-risk ASCVD

High-intensity or maximal statin (Class I)

If PCSK9-i is considered, add ezetimibe to maximal statin before adding PCSK9-i (Class I)

Dashed arrow indicates RCT-supported efficacy, but is less cost effective

Percent ASCVD Patients who will drop their LDL-C levels to <70 mg/dl with treatment intensification (total cohort size = 631,855)

Titrated to high-intensity statin therapy alone 18.7%

Addition of ezetimibe therapy alone 50.7%

Titrated to high-intensity statin therapy plus ezetimibe use 59.8%

Percent ASCVD Patients who will drop their LDL-C levels to <70 mg/dl with treatment intensification (total cohort size = 10,342)

Titrated to high-intensity statin therapy alone 33%

Addition of ezetimibe therapy alone 42.5%

Titrated to high-intensity statin therapy plus ezetimibe use 65.3%


Cannon CP, et al. JAMA Cardiol. 2017 1;2(9):959-966
Take Home Messages (Secondary Prevention)

- High-intensity statin therapy plus healthy lifestyle remains the first step in secondary prevention.
- The 2018 AHA/ACC multi-society cholesterol guidelines identify a “very high-risk ASCVD group” among secondary prevention patients.
- These very high-risk ASCVD patients have the highest absolute event rates and consequently, highest ARR with the use of non-statin therapies.
- Statin use and emphasis on statin adherence remains the first step before stepwise addition of ezetimibe or a PCSK9i in very high-risk patients.