PEER Simplified Lipid Guideline 2023 Update
Prevention/management of CVD in Primary Care

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Guideline Principles

• By Primary Care for Primary Care
  • Evidence-based
  • Patient-centred/patient orientated outcomes
  • Simplified

• Focus on Primary Prevention, Shared Decision Making
• GRADE/Institute of Medicine
• No financial COI

What goes into Evidence-Based Guideline Update?

**Medications**
8 Systematic Review of Systematic Reviews

2015 Simplified Lipid Guideline & Rapid Reviews

Guideline Panel Questions
10 Rapid Reviews

Carry forward a few recommendations

**PEER Simplified Lipid Guideline 2023 ‘Update’**
Recommendations that carry forward

- Start screening at age 40 in males and 50 in females
- No fasting for lipid tests
- For patients with existing CVD, no risk estimation needed
- Lifestyle still recommended (Mediterranean Diet and activity)
- For primary prevention patients, (do a Risk Estimation with all lipid tests)
- No lipid targets and no repeat testing on statins.
- CK & ALT not required

Two Different Beliefs in Lipid Management

Target your Treatment (fire and forget): if a medication ↓ CVEs → discuss possible benefits (and harms) with patients

Patient

CV Risk Estimate → Patient Orientated Outcomes

Lipid Levels → Lipid Targets

Use Medications that ↓ CVE

Veterans 2020, PEER 2015

USPSTF 2020

Treat to Target:
If studies show the association between higher LDL and greater risk of CVD, then meds that ↓ LDL must ↓ CVD and should be offered. The lower the better.

Attempt to achieve targets with any med or combination of medications

CCVS 2021, AHA 2018, ESC 2021

Top 10 Reasons Simplified Guidelines Don’t Have Targets

1. No evidence targets better than fixed dose:
   - 1 RCT (Lodestar) targets vs fixed higher intensity, no diff in CVD or Mortality, but targets led to more test (>7)

2. Attained LDL levels:
   - Should be associated with better CHD reductions. They are not.

3. Statin RCTs use fire & forget.

4. Some RCTs didn’t even enroll for lipids:
   - ASCOT: enrolled on hypertension.
   - Jupiter: enrolled on CRP.

5. Guidelines recommending targets acknowledge lack of evidence,
   - CCS 2021: “no clear target to which LDL-C or non HDL-C or ApoB levels should be lowered is clearly identified in RCTs.”
   - ESC/EAS 2019: “aware of the limitations ... of evidence and accepts that RCTs have not examined different LDL-C goals systematically…”

6. Other Guidelines like the US Preventive Task Force & Veterans Affairs guidelines use risk and have no LDL or surrogate targets.

7. Frustration: Hitting targets is not possible for many (~50% not at LDL target on max statin therapy)*

8. Basing treatment on risk (vs lipids) maximizes benefits
   - Patients with low LDL but higher risk not missed.

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Top 10 Reasons Simplified Guidelines Don’t Have Targets

9. Less testing for patients, less labs for us, less cost (labs and temptation for escalating medications)

10. And,...

We need to Understand Risk

For CVD, it starts with screening to find those at risk of having an event
How often do we test Lipids?

- Variability around cholesterol tests (Total, LDL or HDL) = 10-20%
- Cholesterol changes per year: ≤1%

- Does Cholesterol or Age impact risk more?
- From age 50 to 60: risk up ~70%.
- Total Cholesterol up 1%/yr for 10 yrs (5 to 5.5 mmol/L): risk up ~10%

What about ancillary tests to assess CVD risk?

- Risk Calculators are ~0.75 at prediction (Area-Under-the Curve - AUC)
  - AUC Changes: Large ≥0.1, Moderate 0.05-0.1, Small 0.025-0.05, Very Small <0.025

<table>
<thead>
<tr>
<th>Test</th>
<th>AUC Changes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein (A)</td>
<td></td>
<td>- Adding to risk calculation AUC 0.0017 – 0.004</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td></td>
<td>- Adding to risk calculation AUC 0.002-0.02</td>
</tr>
<tr>
<td>Coronary Artery Ca+ Score</td>
<td></td>
<td>- Alone: AUC 0.70-0.77</td>
</tr>
</tbody>
</table>

Adding Lp(a) Apo(B) or CAC to traditional risk factor calculators results in very small to small improvements in prediction

* Risk Ratios included Hazard Ratios, Relative Risks, and Odds Ratios.
Cholesterol Tests Recommendations

- When reassessing CVD risk in patients not taking lipid-lowering therapy, we suggest reassessing lipids no more than every 5 years and preferably 10, unless risk factors change.
- We recommend against the use of repeat lipid testing and cholesterol targets after a patient begins lipid-lowering therapy.
- We suggest against adding CAC scores to CVD risk assessment.
- We recommend against using Lp(a) or apoB to determine a patient’s CVD risk.

Medications: Kind-of a Big Deal
### Medicines
We included 76 Systematic Reviews (+6 RCTs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Systematic Reviews</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile Acid Sequestrants</td>
<td>(4 RCTs)</td>
<td>53-3,806</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>3</td>
<td>18,921-23,499</td>
</tr>
<tr>
<td>Fibrates</td>
<td>3</td>
<td>16,112-46,099</td>
</tr>
<tr>
<td>Niacin</td>
<td>5</td>
<td>34,294-39,195</td>
</tr>
<tr>
<td>Omega</td>
<td>7</td>
<td>65,819-149,051</td>
</tr>
<tr>
<td>EPA (e.g. icosapent)</td>
<td>2 (2 RCTs)</td>
<td>8,179-18,645</td>
</tr>
<tr>
<td>PCSK-9 inhibitors</td>
<td>26</td>
<td>6,281-97,910</td>
</tr>
<tr>
<td>Statins</td>
<td>30</td>
<td>625-192,977</td>
</tr>
</tbody>
</table>

### Evidence Certainty (GRADE) (for MACE)

<table>
<thead>
<tr>
<th>Drug</th>
<th>All Patients</th>
<th>Primary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile Acid Sequestrants</td>
<td>Very Low</td>
<td>Very Low</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Moderate</td>
<td>Very Low</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Moderate</td>
<td>Very Low</td>
</tr>
<tr>
<td>Niacin</td>
<td>High</td>
<td>No Data</td>
</tr>
<tr>
<td>Omega</td>
<td>Moderate</td>
<td>No Data</td>
</tr>
<tr>
<td>EPA (e.g. icosapent)</td>
<td>Moderate*</td>
<td>Low</td>
</tr>
<tr>
<td>PCSK-9 inhibitors</td>
<td>Moderate</td>
<td>Very Low</td>
</tr>
<tr>
<td>Statins</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Evidence issues: Various MACE definitions, quality concerns, non-representative population, precision of estimate, etc.

* 2 RCTs: one low and one high
### Outcomes for lipid lowering agents

<table>
<thead>
<tr>
<th>Intervention</th>
<th>MACE</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median RR (stat sign/N)</td>
<td>Median RR (stat sign/N)</td>
</tr>
<tr>
<td><strong>Primary Prevention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>0.75 (6/6 SR)</td>
<td>0.91 (4/8 SR)</td>
</tr>
<tr>
<td>PCSK9 Inhibitors</td>
<td>0.84 (14/14 SR)</td>
<td>0.93 (1/17 SR)</td>
</tr>
<tr>
<td>Statins</td>
<td>0.74 (6/6 SR)</td>
<td>0.91 (6/8 SR)</td>
</tr>
</tbody>
</table>

### Medication Evidence Overview

<table>
<thead>
<tr>
<th>Medication</th>
<th>MACE</th>
<th>All-cause Mortality</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins: 1’ prevention: mod dose</td>
<td>25%</td>
<td>10%</td>
<td>Only agent that decreases all-cause mortality. Muscle symptoms (1st year): 15% vs 14%</td>
</tr>
<tr>
<td>Fibrates</td>
<td>0-14%*</td>
<td>NSS</td>
<td>*Overall, no diff when added to statins</td>
</tr>
<tr>
<td>Ezetimibe (added to statins)</td>
<td>~7%</td>
<td>NSS</td>
<td>Limited evidence in 1’ prevention or monotherapy</td>
</tr>
</tbody>
</table>
| PCSK9i (added to statins)      | 15% | NSS | Limited evidence in 1’ prevention or monotherapy. Re-analysis questions results\(^1\) $$ $$
| EPA (Icosapent) added to statins | ~20% | NSS | Limited evidence in 1’ prevention. Risk of AF, bleeding. $$ $$

Niacin, Omega 3s, BAS: no convincing evidence of benefit

\(^1\)BMJ Open 2022;12:e060172. doi:10.1136
Others Issues with Interventions

• Fibrates don’t add any benefit when someone is on a statin
• Eicosapentaenoic acid (EPA) (icosapent, Vascepa®)
  - Efficacy: Reduced MACE (23%), Not all-cause mortality.
  - Issues: 2 RCTs (1 open-label), conflicts with Omega-3s, placebo effect unclear
  - Harms: Increase A fib from 3.9% to 5.3%; Total bleeds up ~0.5% (over 4.5-5 yrs)

Medication Recommendations

• In primary prevention,
  - Patients with 10-y CVD risk of >20%, recommend discussing statins (high-intensity)
  - Patients with a 10-y CVD risk of 10-19%, suggest discussing statins (moderate-intensity).
  - Recommend against non-statin lipid drugs (monotherapy or combined with statins)
• In secondary prevention,
  - Recommend, discuss and encourage high-intensity statin.
  - If additional CVD risk reduction desired, recommend discussing ezetimibe or PCSK9.
  - Due to potential harms (a fib, bleeding), consider icosapent after above.
Issues on Statins:  Life’s Complicated

Statin Intolerance vs muscle aches are common

Meta-analysis: 23 RCTs, 154,664 pts x 4.3 yrs
- 1st year: 14.8% statins vs 14% placebo
- After 1 year, similar event rates (~15.0%)
  - Subgroups similar
  - Mean CK ~2% higher
  - Muscle injury + CK 10x normal – 7.7 vs 4.4 in 100,000

• 3 n-of-1 trials (8-200 patients, statin intolerance): random to 3-4 cycles of ~3-8 weeks of statin, placebo, and no-pill. Muscle symptom scores (0-100):
  - Statin vs placebo: no difference. Statin vs no-pill: 16 versus 8 (no-pill).

**Bottom-Line:** Statins unlikely (~1 in 15) the cause of most muscle symptoms.
Statin Intolerance: Try a Different Drug?

- Statins only med with consistent evidence of benefit
- No RCTs specifically enrolling statin intolerant patients
- In patients who do not tolerate a specific statin regimen due to non-severe muscle adverse effects, we recommend any statin intensity over non-statin lipid therapy.

<table>
<thead>
<tr>
<th>If a patient does not tolerate a statin, discuss statin rechallenge</th>
<th>If a patient is unable to tolerate or unwilling to try a re-challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTIONS</td>
<td>PRIMARY PREVENTION</td>
</tr>
<tr>
<td>Same statin at same dose</td>
<td>Suggest against non-statin lipid lowering therapy</td>
</tr>
<tr>
<td>Different statin</td>
<td>SECONDARY PREVENTION</td>
</tr>
<tr>
<td></td>
<td>Suggest discussing ezetimibe, fibrate, PCSK9 inhibitor or EPA ethyl ester (icosapent)</td>
</tr>
</tbody>
</table>

Special Groups
Statins in Older Adults

**Primary prevention:** For patients 65-75 years, statins likely result in a 16-39% relative ↓ in MACE.
  • For patients >75, the benefit of initiating statins is unclear.

**Secondary Prevention:** >65 years, statins result in consistent ~20% RRR MACE.

CTTC: Lancet 2019; 393(10170):407

Statins and Cognition

• 2014 (TFP) & 2015 (Guideline): No evidence association of statin & cognitive decline. Since then,....

• Systematic rev of RCTs: 1 RCT (20,536 pts x 5 yrs): 0.3% both groups
  - 3 other RCTs (732-2,361 pts), statin vs placebo, x5-7 yrs: No increase risk.

• Systematic revs of observational studies (≤9,162,509), statin vs no, x1-25 yrs:
  - All-cause dementia (16 studies) & Alzheimer’s disease (14 studies): RRR 15-28%
  - Vascular dementia (4 studies): no difference.

• Cognition Scores (4 systematic revs): statin vs placebo with/without baseline cognitive impairment. No difference in MSE, Telephone Interview Cognitive Status, and others.

• Bottom-Line: There is no evidence that statins worsen cognitive function.
Statins in Elderly and Cognition: Recommendations

- In primary prevention patients over the age of 75, we recommend against lipid testing and the assessment of risk using a CVD risk calculator.
- We suggest against the routine initiation of statin therapy for primary prevention in patients over age 75. However, it may be reasonable to discuss the benefits and risks of statin therapy for primary prevention in some patients over age 75 whose overall health status is good.
- In patients over age 75 who have had a cardiovascular event, we recommend clinicians discuss the benefits and risks and encourage the initiation of statin therapy with patients.
- In patients already taking and tolerating a statin, we recommend against stopping the statin or reducing the dose just because patients have aged beyond 75 y.
- We recommend against altering statin prescribing for cognitive concerns.

Guideline take homes
Updated PEER Simplified Decision Aid
Shared Decision Making

https://decisionaid.ca/cvd/

Who to screen and when

Everyone gets Lifestyle

Everyone gets Risk Estimated

Risk <10%, repeat in 5-10 yrs

Risk 10-19%, offer mod statin

Risk ≥20%, offer high statin

On statin: No further lipid test or CK or ALT unless indicated

Potency and benefits
### Lipid Lowering Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prescribing Considerations</th>
<th>CVD Relative Risk Reduction</th>
<th>90-day cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>• Mostly target lipids agents that decrease low-density lipoproteins.</td>
<td>-20%</td>
<td>$90-100</td>
</tr>
<tr>
<td></td>
<td>• Muscle symptoms in first year: 15% versus 10% placebo.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Do not worsen cognitive or dementia.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>• Mostly studied when added to statins in secondary prevention.</td>
<td>7%</td>
<td>$30-45</td>
</tr>
<tr>
<td></td>
<td>• Well tolerated, 1mg daily.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCSK9 inhibitors</td>
<td>• Mostly studied when added to statins in secondary prevention.</td>
<td>-15%</td>
<td>$1500-2400</td>
</tr>
<tr>
<td></td>
<td>• Statin intolerance is common in 10% of patients.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrates</td>
<td>• Mostly studied when added to statins in secondary prevention.</td>
<td>-10%</td>
<td>$600-100</td>
</tr>
<tr>
<td></td>
<td>• Attends less than 1% muscle enzyme abnormality (0% in monotherapy; 1% in combination therapy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe &amp; PCSK9 inhibitors</td>
<td>• Mostly studied when added to statins in secondary prevention.</td>
<td>-30%</td>
<td>$1500</td>
</tr>
<tr>
<td></td>
<td>• Attends less than 1% muscle enzyme abnormality (0% in monotherapy; 1% in combination therapy)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*VP = added to statins, up to 1% if not on statin.

### Management of Muscle Symptoms Related to Statins

#### FAQ & Helpful Resources

**Q:** Why do FPG guidelines recommend against targeting LDL levels?  
**A:** The vast majority of clinical trials have prescribed fixed dose statins based on CVD risk. These studies suggest both strategies (targeting LDL levels or using statins at proven doses) yield similarly effective in reducing CVD risk. Targeting cholesterol levels is more complex than use of proven doses. A simplified approach using proven doses reduces the burden of unnecessary testing for both patients and health professionals. Read more about this issue in the guideline.

**Q:** Does cardiovascular disease add to statin risk?  
**A:** There are many cardiovascular risk calculators. The Framingham model has been validated in Canada. The PREDICT Risk Assessment Tool (https://www.cardio.ca/predict) has been created for this guideline.

**Q:** How can I help patients with positive lifestyle changes?  
**A:** Encourage smoking cessation. Providing assessment and information about the Mediterranean diet (3D program) makes a difference.

### Healthy Patients & Cholesterol Management: Frequently Asked Questions

**What can I do to lower my risk?**

- **Stop smoking:** This is likely the best thing you can do for your health. If you need help, talk to a healthcare provider.
- **Eat a Mediterranean diet:** This diet typically includes lots of vegetables, fruits, fish, nuts, and olive oil.
- **Increase physical activity:** Find an activity you enjoy and can stick with! One type of physical activity is usually not better than another.
- **Consider medicines:** Based on your risk, your healthcare provider may suggest a statin (e.g., atorvastatin and rosuvastatin).

**What is my risk of having a heart attack or stroke?**

Use the PREDICT Cardiovascular Risk Assessment tool for your healthcare provider.

**How well do statins work?**

- **Stop smoking:** This is the best thing you can do for your health. If you need help, talk to a healthcare provider.
- **Eat a Mediterranean diet:** This diet typically includes lots of vegetables, fruits, fish, nuts, and olive oil.
- **Increase physical activity:** Find an activity you enjoy and can stick with! One type of physical activity is usually not better than another.
- **Consider medicines:** Based on your risk, your healthcare provider may suggest a statin (e.g., atorvastatin and rosuvastatin).

**How can I lower my cholesterol level?**

Your cholesterol changes daily, about one percent per month, so we don’t need a check your cholesterol more than every 3 to 5 years. If you are taking a medicine called a statin, you don’t need to recheck your cholesterol. If you help prevent heart attacks and strokes no matter what your cholesterol is.

**Healthcare providers used to check cholesterol.**

They now use cholesterol as part of your overall risk of having a heart attack or stroke.

**What can I do to lower my risk?**

- **Stop smoking:** This is the best thing you can do for your health. If you need help, talk to a healthcare provider.
- **Eat a Mediterranean diet:** This diet typically includes lots of vegetables, fruits, fish, nuts, and olive oil.
- **Increase physical activity:** Find an activity you enjoy and can stick with! One type of physical activity is usually not better than another.
- **Consider medicines:** Based on your risk, your healthcare provider may suggest a statin (e.g., atorvastatin and rosuvastatin).
Thank you

**The PEER Simplified Lipid Guideline**

2023 Update

A simplified approach to lipid management for busy family doctors!

Read the guideline today!

[peerevidence.ca](http://peerevidence.ca)