PEER Simplified Lipid Guideline 2023 Update

Prevention/management of CVD in Primary Care

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- Speakers Bureau/Honoraria: Alberta College of Family Physicians, Saskatchewan College of Family Physicians, Alberta Pharmacists Association, University of Saskatchewan, , MEME, CSHP-SK
- Consulting Fees: N/A
- Grants/Research Support: N/A
- Patents: N/A
- Other: Salary – College of Family Physicians of Canada

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- **Relationships with financial sponsors:**
  - **Grants/Research Support:** CIHR (BedMed Study)
  - **Expenses or Honoraria:** only not for profit organizations
    - ACFP, Alberta Health (Expert Drug Committee), SRPC, AMA, CCFP
  - **Consulting Fees or Patents:** N/A
  - **Other:** Employee University of Alberta
    - EMPRSS: Electronic Medical Procedure Reporting Systems
    - Medical Director: Backcountry ski lodge

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- Consulting Fees: N/A
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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

JAMA 2013; 309 (2): 139

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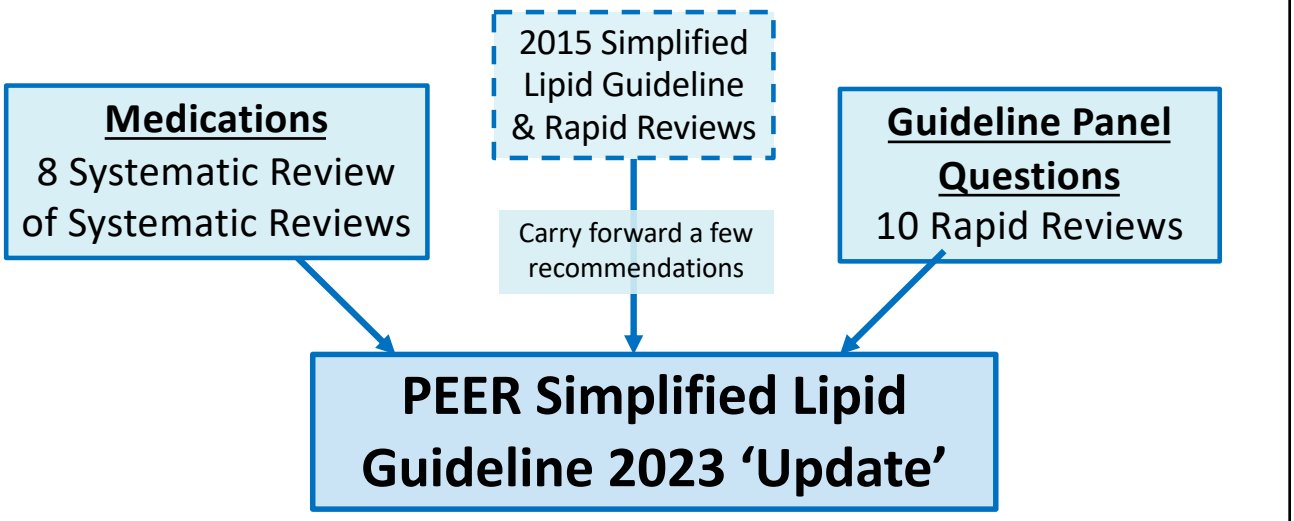
What goes into Evidence-Based Guideline Update?



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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

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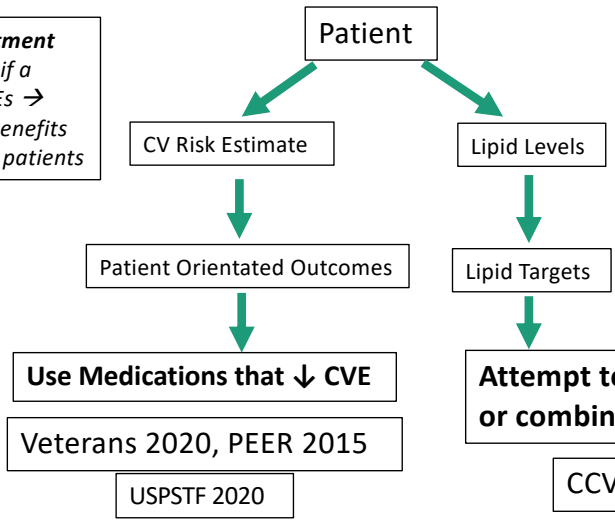
Two Different Beliefs in Lipid Management

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



***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.*

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Circulation 2019;139(25):e1046; Ann Intern Med 2020;173(10):822; Can J Cardio 2021;37(8):1129; CFP 2015; 61(10): 857, Eur Heart J 2021;42(34):3227

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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.

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1) JAMA. doi:10.1001/jama.2023.2487 2) Lancet. 2003;361:1149-58. 3) NEJM 2008;359:2195-207.

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Top 10 Reasons Simplified Guidelines Don't Have Targets

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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* CMAJ 2008;178(5):576-84.

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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,…

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We need to Understand Risk

For CVD,
It starts with screening to find those at risk of having an event

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How often do we test Lipids?

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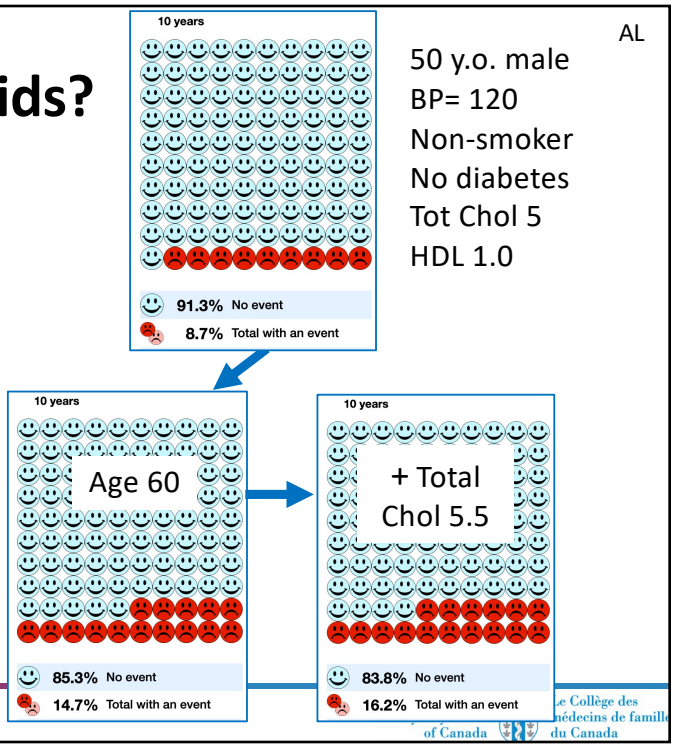
- Variability around cholesterol tests (Total, LDL or HDL) = 10-20%
- Cholesterol changes per year: ≤1%

- 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%

50 y.o. male
BP= 120
Non-smoker
No diabetes
Tot Chol 5
HDL 1.0



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What about ancillary tests to assess CVD risk?

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- 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

Lipoprotein (A)	Apolipoprotein B	Coronary Artery Ca+ Score
- Adding to risk calculation AUC 0.0017 – 0.004 - Alone: RR 1.00-2.21	- Adding to risk calculation AUC 0.002-0.02 - Alone: RR 1.03-2.87	- Alone: AUC 0.70-0.77 - Adding to risk calculation: AUC 0.036-0.05 better - RCTs coming

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

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* Risk Ratios included Hazard Ratios, Relative Risks, and Odds Ratios.

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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.

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Medications: Kind-of a Big Deal

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

Medicines

We included **76** Systematic Reviews (+6 RCTs)

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Evidence Certainty (GRADE)

(for MACE)

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

Drug	All Patients	Primary Prevention
Bile Acid Sequestrants	Very Low	Very Low
Ezetimibe	Moderate	Very Low
Fibrates	Moderate	Very Low
Niacin	High	No Data
Omega	Moderate	No Data
EPA (e.g. icosapent)	Moderate*	Low
PCSK-9 inhibitors	Moderate	Very Low
Statins	Moderate	Moderate

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* 2 RCTs: one low and one high

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Outcomes for lipid lowering agents

Intervention	MACE	All-cause mortality
	Median RR (stat sign/N)	Median RR (stat sign/N)
BAS		)
Ezetim		)
Fibrate		)
Niacin		)
Omega		)
EPA on		)
PCSK9 Inhibitors	0.84 (14/14 SR)	0.93 (1/17 SR)
Statins	**0.74 (6/6 SR)**	**0.91 (6/8 SR)**

Primary Prevention

	MACE	All-Cause Mortality
Statins	0.75 (6/6 SR)	0.91 (4/8 SR)

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Medication Evidence Overview

Medication	MACE	All-cause Mortality	Notes
Statins: **1' prevention: mod dose**	25%	10%	**Only agent that decreases all-cause mortality.** Muscle symptoms (1st year): 15% vs 14%
Fibrates	0-14%*	NSS	*Overall, no diff when added to statins
Ezetimibe **(added to statins)**	~7%	NSS	**Limited evidence in 1' prevention or monotherapy**
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			

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[1]BMJ Open 2022;**12**:e060172. doi:10.1136

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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)

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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.

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Issues on Statins: Life's Complicated

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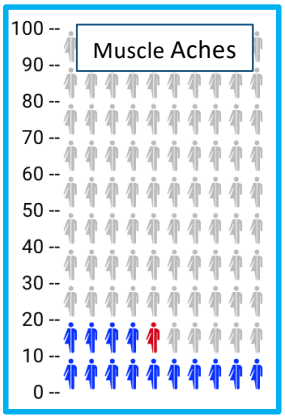
Statin Intolerance vs muscle aches are common

Meta-analysis: 23 RCTs, 154,664 pts x4.3 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.

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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.

If a patient does not tolerate a statin, discuss statin rechallenge

OPTIONS

Same statin at same dose	Lower dose or intensity
Different statin	Alternate day dosing

If a patient is unable to tolerate or unwilling to try a re-challenge

PRIMARY PREVENTION

Suggest against non-statin lipid lowering therapy

SECONDARY PREVENTION

Suggest discussing ezetimibe, fibrate, PCSK9 inhibitor or EPA ethyl ester (icosapent)

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Special Groups

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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

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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.

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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.

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Guideline take homes

Updated PEER Simplified Decision Aid

Shared Decision Making

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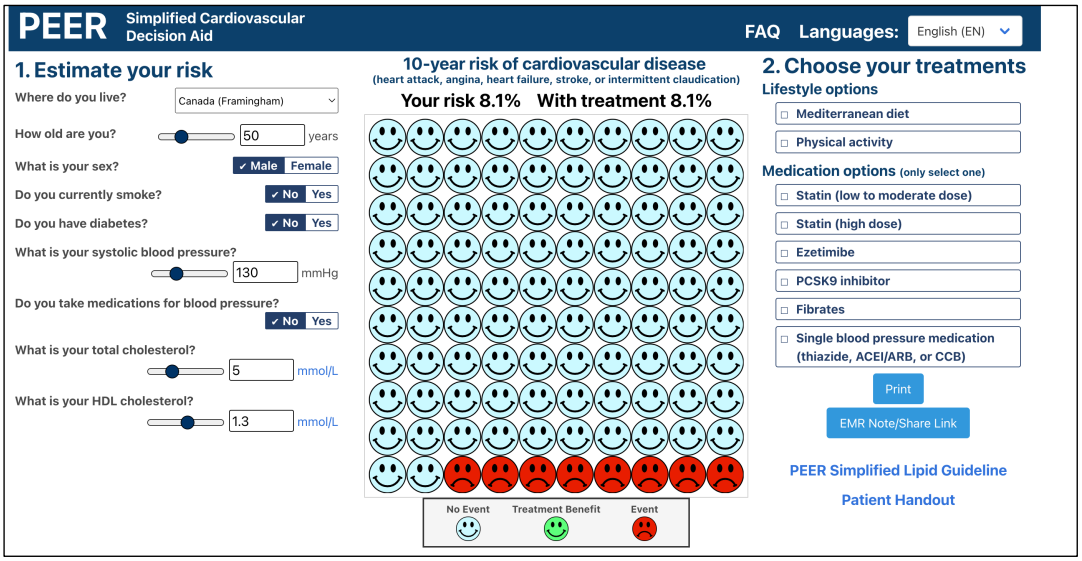

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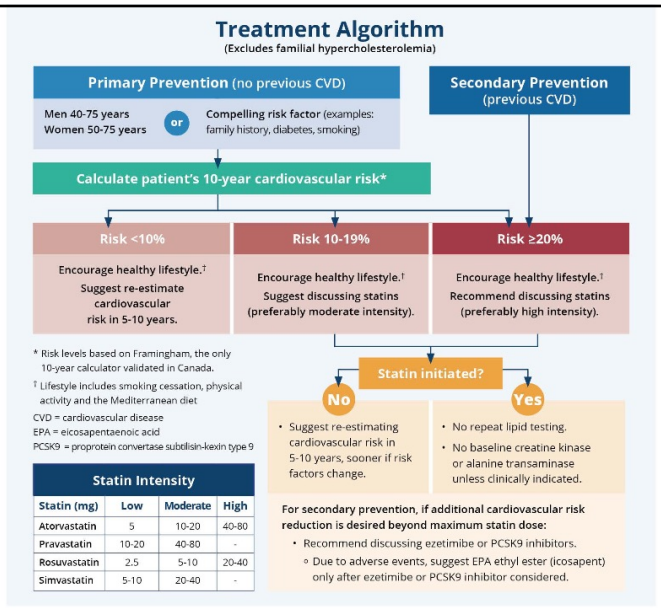

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- Who to screen and when
- Everyone gets Lifestyle
- Everyone gets Risk Estimated
- Risk <10%, repeat in 5-10 yrs
- Risk 10-19%, offer mod statin
- Risk ≥20%, offer high statin
- On statin: No further lipid test or CK or ALT unless indicated
- Potency and benefits

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Benefits, Adverse Effects and Costs and some evidence

Risk of muscle symptoms on statins and what to do

Frequently asked questions & QR code links to resources

Lipid Lowering Agents

Drug	Prescribing Considerations	CVD Relative Risk Reduction	90-day cost[1]
Statins	• The only lipid lowering agent that decreases all-cause mortality. • Muscle symptoms in first year: 15% versus 14% placebo. • Do not worsen cognition or dementia.	25-35%	$30-50
Ezetimibe	• Mostly studied when added to statins in secondary prevention. • Well tolerated; 10mg daily.	7%	$30-45
PCSK9 inhibitors	• Mostly studied when added to statins in secondary prevention. • Injection site reactions: 3.5% versus 2.1% placebo. • Subcutaneous injections q 2 weeks: Alirocumab 75-150mg or evolucumab 140mg.	~15%	$1500-2400
Fibrates	• Increase serum creatinine (2-11% more than placebo), pancreatitis (~0.1% more), altered liver function tests (~5% more); example: fenofibrate.	0-14%*	$60-150
EPA ethyl ester (icosapent)	• Mostly studied when added to statins. • Atrial fibrillation (5.3% versus 3.9% placebo), serious bleeds (2.7% versus 2.1% placebo); 2g BID.	~20%	$1000

* 0% if added to statins; up to 14% if not on a statin

[1] *RxFiles PEER/ACFP Pricing Document*

EPA = eicosapentaenoic acid; CVD = cardiovascular disease

Management of Muscle Symptoms Related to Statins

Out of 100 patients on statins, 15 report muscle symptoms, but only 1 is due to statins

If a patient does not tolerate a statin, discuss statin rechallenge		If a patient is unable to tolerate or unwilling to try a re-challenge
OPTIONS		PRIMARY PREVENTION Suggest against non-statin lipid lowering therapy
Same statin at same dose	Lower dose or intensity	SECONDARY PREVENTION Suggest discussing ezetimibe, fibrate, PCSK9 inhibitor or EPA ethyl ester (icosapent)
Different statin	Alternate day dosing	

FAQ & Helpful Resources

Q: Why do PEER guidelines recommend against targeting LDL levels?

A: The vast majority of clinical trials have prescribed fixed statin doses based on CVD risk. Best evidence suggests both strategies (targeting LDL levels or using statins at proven doses) are similarly effective in reducing CVD risk. Targeting cholesterol levels is more complex than use of proven doses. A simplified approach of using proven doses reduces the burden of unnecessary testing for both patients and health professionals. Read more about this issue in the guideline.

Q: Which cardiovascular decision aid should I use?

A: There are many cardiovascular risk calculators. The Framingham model has been validated in Canada. The PEER Cardiovascular Decision Aid (https://decisionaid.ca/cvd/), based on Framingham, has been created for this guideline.

Q: How can I help patients with positive lifestyle changes?

A: Encourage smoking cessation. Providing exercise prescription and information about the Mediterranean diet may be helpful.

RXFILES EXERCISE PRESCRIPTION

MEDITERRANEAN DIET

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Patient Handout

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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).

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Healthy Patients & Cholesterol Management: Frequently Asked Questions

For people who have not had a heart attack or stroke

Your cholesterol is one of many known risk factors for heart attack or stroke. Other risk factors include age, sex, smoking, blood pressure, and other conditions such as diabetes.

How often should I have my cholesterol checked?

Your cholesterol changes slowly, about one percent every year, so we don't need to check your cholesterol more than every 5 to 10 years. If you are taking a medicine called a statin, you don't need to recheck your cholesterol. Statins help prevent heart attacks and strokes no matter what your cholesterol is.

Health care providers used to check cholesterol every year. They now use cholesterol as one part of your overall risk of having a heart attack or stroke.

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

Use this link to the PEER Cardiovascular Decision Aid and talk to your health care provider

How well do statins work?

Statins may lower the risk of heart attacks and strokes by 25 percent. For example, if your 10-year risk of having a heart attack or stroke is 20 percent, a statin can lower your risk to 15 percent. Statins are the only cholesterol medicine that may lower your risk of dying. Statins are generally well tolerated. Some patients report muscle pains; however, muscle pains occur as often with a placebo (a pill that contains no medicine) as they do with statins.

If you have questions about this information, go to the PEER cardiovascular decision aid or talk to your healthcare provider.

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Consider medicines: Based on your risk, your healthcare provider may suggest a statin (e.g., atorvastatin and rosuvastatin).

The information provided in this pamphlet is based on recommendations from the 2023 PEER Simplified Lipid Guideline Update.

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Thank you

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2023 Update

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