PEER simplified lipid guideline 2023 update

Prevention and management of cardiovascular disease in primary care

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Abstract

Objective To update the 2015 clinical practice guideline and provide a simplified approach to lipid management in the prevention of cardiovascular disease (CVD) for primary care.

Methods Following the Institute of Medicine's *Clinical Practice Guidelines We Can Trust*, a multidisciplinary, pan-Canadian guideline panel was formed. This panel was represented by primary care providers, free from conflicts of interest with industry, and included the patient perspective. A separate scientific evidence team performed evidence reviews on statins, ezetimibe, proprotein convertase subtilisin-kexin type 9 inhibitors, fibrates, bile acid sequestrants, niacin, and omega-3 supplements (docosahexaenoic acid with eicosapentaenoic acid [EPA] or EPA ethyl ester alone [icosapent]), as well as on 11 supplemental questions. Recommendations were finalized by the guideline panel through use of the Grading of Recommendations Assessment, Development and Evaluation methodology.

Recommendations All recommendations are presented in a patient-centred manner designed with the needs of family physicians and other primary care providers in mind. Many recommendations are similar to those published in 2015. Statins remain first-line therapy for both primary and secondary CVD prevention, and the Mediterranean diet and physical activity are recommended to reduce cardiovascular risk (primary and secondary prevention). The guideline panel recommended against using lipoprotein a, apolipoprotein B, or coronary artery calcium levels when assessing cardiovascular risk, and recommended against targeting specific lipid levels. The team also reviewed new evidence pertaining to omega-3 fatty acids (including EPA ethyl ester [icosapent]) and proprotein convertase subtilisin-kexin type 9 inhibitors, and outlined when to engage in informed shared decision making with patients on interventions to lower cardiovascular risk.

Conclusion These updated evidence-based guidelines provide a simplified approach to lipid management for the prevention and management of CVD. These guidelines were created by and for primary health care professionals and their patients.

Editor's key points

- This guideline provides an update of the 2015 PEER simplified lipid guidelines. Focusing on the needs of primary care providers and their teams, this guideline was designed to be applicable and feasible in practices.
- Similar to the 2015 recommendations, attainment of lipid targets is not recommended. Statins remain first-line therapy for primary cardiovascular disease prevention based on a patient's estimated cardiovascular risk and shared decision making. Currently there is no role for lipoprotein a, apolipoprotein B, or coronary artery calcium in risk assessment.
- Non-statin therapies, such as ezetimibe and proprotein convertase subtilisin-kexin type 9 inhibitors, may be added to statins in secondary prevention when there is a need for additional cardiovascular risk reduction.
- Statin rechallenge should be performed in patients with nonsevere statin intolerance.
- A 2-page guideline summary, a patient handout, and an updated online decision aid were created to assist with shared decision making between patients and clinicians.

Cardiovascular diseases (CVDs) are the leading cause of mortality globally.[1] Cardiovascular-related conditions (eg, hypertension, diabetes) are common reasons for visiting primary care providers.[2] There is an increasing number of lipid-lowering agents used to reduce CVD risk including statins, ezetimibe, proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, fibrates, bile acid sequestrants (BAS), niacin, and omega-3 supplements (docosahexaenoic acid [DHA] with eicosapentaenoic acid [EPA] or EPA ethyl ester alone [icosapent]). Owing to emerging evidence on diagnostic testing and therapeutic options, as well as recent publications of other lipid-related guidelines,[3-7] we have updated our 2015 PEER simplified lipid guideline.[8] Similar to the 2015 guideline, this update focuses on primary prevention, prioritizes high-level evidence, incorporates shared decision making, and provides simplified recommendations designed for use in primary care.

Family physicians deliver most health care services in Canada, including most primary prevention for CVDs.[9,10] Therefore, our intended audience consists of family physicians and other primary care providers, as well as their teams. For this reason, recommendations must be accessible, applicable, and feasible to implement in primary care settings. The concept of *time needed to treat* is also introduced in this updated guideline.[11] Most primary care providers lack sufficient time to provide all the care required in their communities of practice,[12] and most guidelines do not consider the time needed to implement recommendations for eligible patients.[11] In our evidence-to-decision framework, based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology,[13] we considered the time needed for clinicians and patients to implement guideline recommendations in light of opportunity costs and competing demands.[14]

Methods

We followed the principles of the Institute of Medicine's *Clinical Practice Guidelines We Can Trust*,[15] the Guidelines International Network,[16] and the GRADE methodology.[13]

Panel membership

Nine health professionals (5 family physicians [M.R.K., M. Cauchon, M. Cotterill, N. Duggan, R.W.]; 2 internal medicine specialists [A.S.H., S.K.]; 1 nurse practitioner [R.D.M.]; 1 pharmacist [L.R.]), 1 patient (T.P.), and 1 non-voting member (pharmacist and guideline methodologist, A.J.L.), comprised the guideline panel. Member selection was based on profession, practice setting, location, and absence of conflicts of interest with the pharmaceutical industry. A separate evidence team of 19 health professionals (A.J.L., M.R.K., G.M.A., E.B., N. Dugré, J.F., L.F., S.R.G., J.E.M.K., C.S.K., J.P.M., S.S.M., J.P., A.P., D.P., B.S.T., J.T., J.W., J.Y.) with expertise in evidence synthesis were responsible for the evidence review. No member of the guideline panel or evidence team had conflicts of interest with industry (Appendix 1, available from **CFPlus***). Recommendations created by the guideline panel were based on evidence reviews performed by the evidence team.

Evidence review

The evidence team performed a systematic review of systematic reviews of randomized controlled trials (RCTs) on the effects of 7 classes of lipid-lowering therapies—statins, ezetimibe, PCSK9 inhibitors, fibrates, BAS, niacin, and omega-3 supplements (DHA with EPA or EPA ethyl ester alone [icosapent])—on patient-oriented outcomes, such as major adverse cardiovascular events (MACE), cardiovascular mortality, and all-cause mortality. Methods and results of these systematic reviews are available elsewhere (**page 701**).[17,18] We categorized our findings into subgroups for primary and secondary CVD prevention. We collected adverse event data—primarily overall, serious, and withdrawals due to adverse events, as well as adverse events specifically relevant to the intervention (eg, muscle-related adverse events for statins). We excluded evidence specifically pertaining to pediatric patients, pregnant or lactating patients, or patients with familial hypercholesterolemia.

Additionally, the evidence team completed rapid reviews to answer 11 supplemental clinical questions chosen by the guideline panel (Appendix 1*). These supplemental questions included the following:

- For patients without CVD who are not taking lipid-lowering therapy, does repeat lipid testing as part of CVD risk estimation every 5 to 10 years meaningfully change risk estimates compared with more frequent testing?
- In patients without established CVD, does the use of apolipoprotein B (apoB) measurement meaningfully change CVD risk estimation more than standard risk estimates alone?
- In patients without established CVD, does the use of lipoprotein a (Lp[a]) meaningfully change CVD risk estimation more than standard risk estimates alone?
- In patients without established CVD, does the use of coronary artery calcium (CAC) scores meaningfully change CVD risk estimation more than standard risk estimates alone?
- In patients with or at risk of CVD, does attainment of specific low-density lipoprotein (LDL), apoB, or non–high-density lipoprotein levels decrease the risk of CVD compared with use of statins without achieving specific targets?
- In patients taking statin therapy, do statins negatively affect cognition, memory, cognitive decline, or dementia compared with not taking statins?

*__Appendices 1__ to __3__ and the __2-page guideline summary__ (__Figure 1__) are available from __https://www.cfp.ca__. Go to the full text of the article online and click on the __CFPlus__ tab.

- In patients reporting muscle-related symptoms associated with statins, does rechallenging, switching statins, using a lower dose, or using an alternative dosing strategy improve statin use?
- In patients intolerant to statins, do any lipid-lowering drugs (PCSK9 inhibitors, BAS, icosapent, fibrates, niacin, or ezetimibe) lower the risk of CVD compared with not taking statins?
- In patients older than age 75, do statins reduce cardiovascular events compared to placebo, without substantially increasing harms?
- In patients with or at risk of CVD, does increasing physical activity (including cardiac rehabilitation) reduce the risk of CVD?
- In patients with or at risk of CVD, does the Mediterranean diet reduce the risk of CVD?

Other nonlipid-related CVD prevention strategies beyond lipid-lowering therapies (eg, acetylsalicylic acid, colchicine) were beyond the scope of this guideline.

Guideline process

The work of the guideline panel was iterative and involved multiple rounds of discussion on clinical question creation, evidence review, and drafting and approving recommendations. Following the principles of the GRADE methodology, recommendations were developed by taking into account the trade-off between favourable and unfavourable outcomes, the quality of evidence, patient preferences and values, and resource use (including medication costs and time to implement recommendations).[13] The evidence standard was informally set higher for primary than secondary prevention. This is because primary prevention involves asking those who are asymptomatic to undergo screening and potential treatments, with potential harms, costs, and inconvenience. Regarding the strength of the recommendations, the word *recommend* indicates a strong recommendation, while *suggest* indicates a weak recommendation.[13]

This guideline provides an update of the 2015 PEER simplified lipid guidelines.[8] Select recommendations from the 2015 guideline were carried forward (Appendix 1*).

Recommendations

Box 1 summarizes all recommendations. Full evidence reviews are available in the systematic review (**page 701**)[18] and Appendix 1.* The GRADE certainty of evidence and strengths of each individual recommendation are listed in **Table 1** and Appendix 1,* respectively.

A 2-page guideline summary (**Figure 1**, available from **CFPlus***), a patient handout (Appendix 2, available from **CFPlus***), and an updated decision aid (**https://decisionaid.ca/cvd/**) were created to assist with shared decision making between patients and clinicians. The guideline and accompanying tools underwent external peer review by 32 clinicians and patients (Appendix 3, available from **CFPlus***).

Recommendations in this guideline are general recommendations designed for most patients. However, they may require adaptation for individual patient encounters, integrating evidence-based recommendations with the clinician's experience and the patient's values, preferences, and expectations. Recommendations do not apply to pregnant or lactating patients, pediatric patients, or those with familial hypercholesterolemia.

Screening and testing

Recommendations:

- In patients without CVD (primary prevention), we *suggest* lipid testing as part of global CVD risk estimation in men aged 40 or older and women aged 50 or older.
  -Testing can be considered earlier for patients with known traditional CVD risk factors including, but not limited to, hypertension, family history of premature CVD, chronic kidney disease, diabetes, and smoking.
- When reassessing cardiovascular risk in patients not taking lipid-lowering therapy, we *suggest* reassessing lipid levels no more than every 5 years and preferably every 10 years, unless risk factors change.
- We *recommend against* fasting for lipid testing. Nonfasting lipid levels can be used to calculate global CVD risk.
- We *recommend against* risk estimation for those with preexisting CVD, as they are already considered to be at high risk.
- We *recommend against* using Lp(a) or apoB to determine a patient's cardiovascular risk.
- We *suggest against* adding CAC scores to cardiovascular risk assessment.

Lipid levels are one of many risk factors for CVD, with age having the largest impact on risk.[8] A validated CVD risk calculator is needed to estimate a patients' future CVD risk, as well as the potential benefits and harms of treatments. As variability exists among risk calculators, practitioners should estimate risk with the same calculator, preferably one validated for their population. For this guideline, our recommendations were based on the Framingham risk score (FRS) calculator, which has been validated in Canada.[8] For primary prevention, a patient's CVD risk should be determined regardless of the presence or absence of higher risk conditions (eg, diabetes).[8] This risk calculation will allow patients to make informed choices about the potential benefits and risks of therapy.

Testing lipid levels more frequently than every 5 to 10 years is generally unnecessary owing to minimal annual changes in lipid levels (about 1%) and considerable variability (10% to 20%) in both analytic and biological results (Appendix 1*).

In patients younger than 75, traditional cardiovascular risk factors have a reasonable accuracy in predicting cardiovascular events, with a C statistic of about 0.75.[19] Adding Lp(a) and apoB measurements to traditional cardiovascular risk factors improves the C statistic by 0.0017 and 0.0004, respectively (Appendix 1*). Adding CAC levels to traditional risk factors improves the C statistic by 0.04 (Appendix 1*). Since changes in C statistics of 0.025 to 0.05 are considered

Box 1. Recommendations summary

Screening and testing

1. In patients without CVD (primary prevention), we **suggest** lipid testing as part of global CVD risk estimation in men age ≥40 y and women age ≥50 y
   - Testing can be considered earlier for patients with known traditional CVD risk factors including but not limited to hypertension, family history of premature CVD, chronic kidney disease, diabetes, and smoking
2. When reassessing CVD risk in patients not taking lipid-lowering therapy, we **suggest** reassessing lipids no more than every 5 y and preferably 10 y, unless risk factors change
3. We **recommend against** fasting for lipid testing. Nonfasting lipids can be used to calculate global CVD risk
4. We **recommend against** risk estimation for those with pre-existing CVD as they are already considered at high risk
5. We **suggest against** adding CAC scores to cardiovascular risk assessment
6. We **recommend against** using Lp(a) or apoB to determine a patient's cardiovascular risk

Interventions

7. We **suggest** encouraging patients to participate in physical activity. The specific type, duration, and intensity are likely less important than adherence
8. We **recommend** the Mediterranean diet to reduce cardiovascular risk
9. For primary prevention in patients with a 10-y CVD risk of ≥20%, we **recommend** clinicians discuss the initiation of statins (preferably high-intensity statins) with patients
10. For primary prevention in patients with a 10-y CVD risk of 10% to 19%, we **suggest** clinicians discuss the initiation of statins (preferably moderate-intensity statins) with patients
11. For primary prevention in patients with a 10-y CVD risk of <10%, we **suggest** retesting lipid levels in 5 y at the earliest and preferably in 10 y, with risk estimation
12. In primary prevention, we **recommend against** using non-statin lipid-lowering drugs as monotherapy or in combination with statins
13. In secondary prevention, we **recommend** clinicians discuss the risks and benefits and encourage initiation of high-intensity statin therapy with patients
14. In secondary prevention, if additional cardiovascular risk reduction is desired beyond maximized statin therapy, we **recommend** a discussion of ezetimibe or PCSK9 inhibitors. Given potential adverse effects (atrial fibrillation, bleeding), we **suggest** adding icosapent to statins only after considering ezetimibe or PCSK9 inhibitors

Considerations in patients older than 75 y

15. For primary prevention in patients older than 75 y, we **recommend against** lipid testing and the assessment of risk using a CVD risk calculator
16. We **suggest against** the routine initiation of statin therapy for primary prevention in patients older than 75 y. However, it may be reasonable to discuss the benefits and risks of statin therapy for primary prevention in some patients older than 75 y whose overall health status is good
17. In patients older than 75 y who have had a cardiovascular event, we **recommend** clinicians discuss the benefits and risks with patients and encourage the initiation of statin therapy
18. 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
19. We **recommend against** altering statin prescribing for cognitive concerns

Statin intolerance

20. In patients who do not tolerate a specific statin regimen due to nonsevere muscle adverse effects, we **recommend** any statin intensity over non-statin lipid therapy. This could include the same or different statins, doses, or alternate daily dosing, based on shared decision making
21. For primary prevention in patients unable to tolerate any statin rechallenge, we **suggest against** use of non-statin pharmacologic therapies
22. For secondary prevention in patients unable to tolerate any statin rechallenge, we **suggest** discussion of ezetimibe, fibrates, or PCSK9 inhibitors. Given potential adverse events of icosapent (atrial fibrillation, bleeding), it should be considered only once other options have been explored

Follow-up

23. We **recommend against** the use of repeat lipid testing and cholesterol targets after a patient begins lipid-lowering therapy
24. We **suggest against** testing for baseline CK or ALT levels in healthy, asymptomatic individuals before starting statin therapy. Testing may be appropriate based on symptoms or other risk factors

ALT—alanine aminotransferase, apoB—apolipoprotein B, CAC—coronary artery calcium, CK—creatine kinase, CVD—cardiovascular disease, Lp(a)—lipoprotein a, PCSK9—proprotein convertase subtilisin-kexin type 9.

small and changes of less than 0.025 are considered very small,[20] it is unlikely that these results are clinically meaningful. Additionally, the lack of widespread availability of CAC testing limits its current use in primary care.

Nonpharmacologic interventions

Recommendations:

- We *suggest* encouraging patients to participate in physical activity. The specific type, duration, and intensity are likely less important than adherence.
- We *recommend* the Mediterranean diet to reduce cardiovascular risk.

For patients with established CVD, exercise-based cardiac rehabilitation decreases all-cause mortality by 10% (relative risk reduction) and cardiovascular mortality and myocardial infarction by 20% to 40% (relative risk reduction) at 3 years (Appendix 1*). Evidence for physical activity in primary prevention is less robust (Appendix 1*). Regardless, physical activity provides other noncardiac benefits and has minimal harms.

Table 1. GRADE certainty-of-evidence table for all recommendations

TOPIC	GRADE CERTAINTY OF EVIDENCE
Screening and testing	
• Lipid testing	High
• CAC in cardiovascular risk assessment	Moderate
• Lp(a) and apoB in cardiovascular risk assessment	High
Interventions	
• Physical activity	Low
• Mediterranean diet	Moderate
• Statins for primary prevention (CVD risk ≥20%)	High
• Statins for primary prevention (CVD risk 10%-19%)	High
• Non-statins for primary prevention	Moderate
• Statins for secondary prevention	High
• Non-statins for secondary prevention	High
Considerations in patients older than 75 y	
• Lipid testing for primary prevention	Moderate
• Statins for primary prevention	Moderate
• Statin initiation for secondary prevention	High
• Statin continuation for secondary prevention	Moderate
• Statins and cognition	Low
Statin intolerance	
• Statin intolerance (rechallenging)	High
• Statin intolerance in primary prevention (other drugs)	Low
• Statin intolerance in secondary prevention (other drugs)	Low
Follow-up	
• Lipid targets and repeat testing after lipid-lowering therapy	Not applicable
• Baseline CK and ALT testing before lipid-lowering therapy	Not applicable

ALT—alanine aminotransferase; apoB—apolipoprotein B; CAC—coronary artery calcium; CK—creatine kinase; CVD—cardiovascular disease; GRADE—Grading of Recommendations Assessment, Development and Evaluation; Lp(a)—lipoprotein a.

Compared with low-fat diets, the Mediterranean diet results in a 25% to 30% relative reduction in future cardiovascular events in both primary and secondary prevention populations over approximately 5 to 7 years (Appendix 1*). Additional approaches to reducing CVD risk (eg, smoking cessation, treatment of hypertension) should be discussed with patients but were not explicitly reviewed in this guideline.

Pharmacologic interventions

Recommendations:

- In primary prevention for patients with a 10-year CVD risk of 20% or greater, we *recommend* clinicians discuss the initiation of statins (preferably high-intensity statins) with patients.
- In primary prevention for patients with a 10-year CVD risk of 10% to 19%, we *suggest* clinicians discuss the initiation of statins (preferably moderate-intensity statins) with patients.
- In primary prevention for patients with a 10-year CVD risk of less than 10%, we *suggest* retesting lipid levels in 5 years at the earliest, and preferably at 10 years, with risk estimation.
- In primary prevention, we *recommend against* using non-statin lipid-lowering drugs as monotherapy or in combination with statins.
- In secondary prevention, we *recommend* clinicians discuss the risks and benefits and encourage initiation of high-intensity statin therapy with patients.
- In secondary prevention, if additional cardiovascular risk reduction is desired beyond maximized statin therapy, we *recommend* discussing the initiation of ezetimibe or PCSK9 inhibitors. Given potential adverse effects (atrial fibrillation, bleeding), we *suggest* adding EPA ethyl ester (icosapent) to statins only after ruling out ezetimibe or PCSK9 inhibitors.

In primary prevention, only statins have substantial evidence of benefit, decreasing MACE, cardiovascular mortality, and all-cause mortality (risk ratio [RR]=0.75, 0.83, and 0.91, respectively).[18] Fibrates decrease MACE but have no effect on cardiovascular or all-cause mortality. Fibrates also have increased incidence of renal dysfunction (increased serum creatinine, RR=1.88 to 5.01), liver dysfunction (altered liver test results, RR=19.1), and pancreatitis (RR=1.74 to 2.74).[18] The other medication classes either showed no benefit in primary prevention, lacked evidence as monotherapy, or predominantly enrolled special populations (such as patients with familial hypercholesterolemia) in primary prevention.[18]

We recognize that cardiovascular risk is continuous and the relative benefit of statins is likely consistent across spectrums of risk. The primary prevention risk categories (<10%, 10% to 19%, or ≥20%) are arbitrary and not evidence based. In secondary prevention, statins remain first-line therapy. Adding ezetimibe and PCSK9 inhibitors to statin therapy in secondary prevention decreases MACE but not cardiovascular mortality or all-cause mortality. Clinicians could consider discussing these agents with patients who have had recent or recurrent CVD or for secondary prevention in those with considerable ongoing risk factors. While EPA ethyl ester (icosapent) was shown to decrease MACE and cardiovascular mortality in systematic reviews of mixed (primary and secondary prevention) patient populations, it increases the risk of atrial fibrillation (RR=1.35; 95% CI 1.10 to 1.66) and bleeding (RR=1.49; 95% CI 1.20 to 1.84).[18]

Figure 1. PEER simplified lipid guideline 2023 summary

PEER Simplified Lipid Guideline 2023: Summary

Simplified approach Shared decision making Reduce unnecessary testing

Treatment Algorithm

(Excludes familial hypercholesterolemia)

Primary Prevention (no previous CVD)

Men 40-75 years
Women 50-75 years
or
Compelling risk factor (examples: family history, diabetes, smoking)

Secondary Prevention (previous CVD)

Calculate patient's 10-year cardiovascular risk*

Risk <10%	Risk 10-19%	Risk ≥20%
Encourage healthy lifestyle.† Suggest re-estimate cardiovascular risk in 5-10 years.	Encourage healthy lifestyle.† Suggest discussing statins (preferably moderate intensity).	Encourage healthy lifestyle.† Recommend discussing statins (preferably high intensity).

Statin initiated?

No

- Suggest re-estimating cardiovascular risk in 5-10 years, sooner if risk factors change.

Yes

- No repeat lipid testing.
- No baseline creatine kinase or alanine transaminase unless clinically indicated.

For secondary prevention, if additional cardiovascular risk reduction is desired beyond maximum statin dose:

- Recommend discussing ezetimibe or PCSK9 inhibitors.
  - Due to adverse events, suggest EPA ethyl ester (icosapent) only after ezetimibe or PCSK9 inhibitor considered.

* Risk levels based on Framingham, the only 10-year calculator validated in Canada.

† Lifestyle includes smoking cessation, physical activity and the Mediterranean diet

CVD = cardiovascular disease
EPA = eicosapentaenoic acid
PCSK9 = proprotein convertase subtilisin-kexin type 9

Statin Intensity

Statin (mg)	Low	Moderate	High
Atorvastatin	5	10-20	40-80
Pravastatin	10-20	40-80	-
Rosuvastatin	2.5	5-10	20-40
Simvastatin	5-10	20-40	-

Benefit of Statin Therapy

Sample Patient, CVD Risk over 10 years	Statin Option	Relative Risk Reduction	Absolute Risk Reduction	New 10 year Risk on Therapy
20%	Moderate Intensity	25%	5%	15%
	High Intensity	35%	7%	13%

Figure 1 *continued on page 681*

Figure 1 *continued from page 680*

PEER Simplified Lipid Guideline 2023: Summary

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 every 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 twice daily.	~20%	$1000

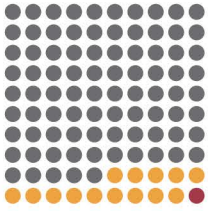
* 0% if added to statins; up to 14% if not on a statin

[1]*RxFiles PEER/ACFP Pricing Document*

EPA = eicosapentaenoic acid; CVD = cardiovascular disease;
PCSK9 = proprotein convertase subtilisin-kexin type 9

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 Same statin at same dose Lower dose or intensity Different statin Alternate day dosing	**Primary prevention** Suggest against non-statin lipid lowering therapy **Secondary prevention** Suggest discussing ezetimibe, fibrate, PCSK9 inhibitor or EPA ethyl ester (icosapent)

FAQ & Helpful Resources

Q: Why do PEER guidelines recommend against targeting low-density lipoprotein (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

Risk estimation

Risk estimation varies with different populations, over different time frames (eg, 5 vs 10 years), with different outcomes included, and when different models and calculators are used.[21] Recently, researchers attempted to recalibrate and validate the FRS within a large Canadian population.[22] Reporting on 5-year estimates, the recalibrated FRS may also overestimate risk, albeit not to the same extent as traditional FRS estimates. However, uncertainty exists on how to best estimate 10-year risk based on 5-year data. Therefore, until 10-year data are available, we will continue to use the traditional 10-year Framingham model in our patient decision aid and risk calculator, with the understanding that risk in some Canadians may be overestimated by roughly 30%.

Considerations in older adults

Recommendations:

- In primary prevention for patients older than 75 years of age, 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 older than 75.
  - It may be reasonable to discuss the benefits and risks of statin therapy for primary prevention in some patients older than 75 whose overall health status is good.
- 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 years.
- In secondary prevention for patients older than 75, we *recommend* clinicians discuss the benefits and risks and encourage the initiation of statin therapy with patients.
- We *recommend against* altering statin prescribing for cognitive concerns.

Many commonly used risk calculators (eg, FRS) exclude patients older than 75. In addition, the diagnostic accuracy of predicting future cardiovascular events is lower for those older than 75 (C statistic=0.62)[23] than for younger adults (C statistic approximately 0.75).[19] Best evidence suggests that statins for primary prevention in patients older than 75 does not statistically significantly decrease MACE (Appendix 1*), therefore routine initiation of statin therapy in this population is not encouraged. It may be reasonable, however, for practitioners to discuss statin therapy for primary prevention in some patients older than 75 whose overall health status is good. In addition, for older adults taking statins for primary prevention, there currently is no evidence to support stopping statins just because they have reached 75 years of age. In 2015, the use of pravastatin in patients 65 years and older was not recommended owing to a potential increase in cancer incidence.[8] However, updated evidence including 2 large systematic reviews found no increased risk of cancer incidence or death with statins (Appendix 1*). Additionally, we recommend against altering statin prescribing owing to cognitive concerns, as the evidence does not support a link between decreased cognition and statin use (Appendix 1*).

Statin intolerance

Recommendations:

- In patients who do not tolerate a specific statin regimen owing to nonsevere muscle adverse effects, we *recommend* any statin intensity over non-statin lipid therapy. This could include the same or different statins, doses, or alternate daily dosing, based on shared decision making.
- For primary prevention in patients unable to tolerate any statin rechallenge, we *suggest against* the use of non-statin pharmacologic therapies.
- For secondary prevention in patients unable to tolerate any statin rechallenge, we *suggest* discussion of ezetimibe, fibrates, or PCSK9 inhibitors. Given potential adverse events of EPA ethyl ester (icosapent) (atrial fibrillation, bleeding), it should be considered only after other options are ruled out.

Most muscle-related complaints in people taking statins are not statin-induced. For patients in their first year of statin therapy, the risk of muscle symptoms is approximately 15% compared with 14% among those taking placebo (Appendix 1*). After a year, the differences in muscle symptoms between statin and placebo are not statistically significant. Given the benefits of statins in primary and secondary CVD prevention, and that most patients will tolerate a statin retrial (Appendix 1*), statin rechallenge should be undertaken for patients who experience nonsevere muscle complaints. Rechallenge options could include using the same or a different statin or dose, or using every-other-day dosing. There is no evidence that one approach is superior to another for tolerability (Appendix 1*).

In the unlikely event that a patient does not tolerate any statin (or dose), there are limited data to guide practice. Ezetimibe, PCSK9 inhibitors, EPA ethyl ester (icosapent), and fibrates have not been adequately studied in patients who cannot tolerate statins. In addition, PCSK9 inhibitors, ezetimibe, and EPA ethyl ester (icosapent) have minimal evidence as monotherapy or in primary prevention (Appendix 1*).[18] For these reasons, we recommend against non-statin therapies in primary prevention. However, in secondary prevention, where the risk of recurrent disease is higher (but recognizing the paucity of evidence), patients and clinicians may wish to explore these non-statin alternatives.

Follow-up

Recommendations:

- We *recommend against* the use of repeat lipid testing and cholesterol targets after a patient begins lipid-lowering therapy.
- We *suggest against* testing for baseline creatine kinase or alanine aminotransferase levels before

starting statin therapy in healthy, asymptomatic individuals. Testing may be appropriate based on symptoms or other risk factors.

At the time of the evidence review, the best available evidence did not prove whether targeting treatment to specific LDL levels or simply using or adding medications that have been shown to reduce the risk of CVD is best for patients (Appendix 1*). Most clinical trials have used fixed-dose (mostly moderate-intensity) statins based on CVD risk and have found benefit occurs irrespective of LDL levels achieved (Appendix 1*). Given the large degree of analytic and biological variation in lipid testing, the associated costs and inconvenience of repeat testing (including visits to discuss repeat test results), and the challenge in achieving targets, the treat-to-target approach is less desirable (Appendix 1*).[24,25] Since the evidence review was completed, a key RCT[26] demonstrated that a high-potency statin strategy was not inferior to the treat-to-target strategy in preventing recurrent CVD (**Table 2**).[26-29]

Since completion of our evidence review, several relevant studies have been published (**Table 2**).[26-29]

Discussion

This guideline represents an update to our 2015 PEER simplified lipid guideline.[8] We conducted 7 medication class systematic reviews of systematic reviews and reviewed the evidence pertaining to 11 supplemental questions. While many of our recommendations are similar to those from 2015, we have new recommendations pertaining to Lp(a), apoB, and CAC, as well as for omega-3 fatty acids, EPA ethyl ester (icosapent), and PCSK9 inhibitors.

Key additions to this guideline pertain to the recommendations on non-statin lipid therapies, with the introduction of new medication classes and the emergence of new evidence. While statins continue to be recommended for primary and secondary CVD prevention, ezetimibe or PCSK9 inhibitors can be added for patients

Table 2. New studies since evidence review

STUDY	STUDY OVERVIEW OR CHARACTERISTICS	KEY RESULTS	COMMENTS AND CONSISTENCY WITH GUIDELINE RECOMMENDATION
LODESTAR[26]	4400 Korean patients with CAD randomized to treat-to-target LDL level (1.3 to 1.8 mmol/L) or high-intensity statin (20 mg of rosuvastatin or 40 mg of atorvastatin) Mean age 65 y, 72% male Noninferiority study	At 3 y (per protocol analysis): composite of death, MI, stroke, or coronary revascularization: 8.3% target, 8.5% high intensity (not inferior) Mortality: 2.5% for each	Lipid levels checked at least 7 times in 3 y in target group; 73% of patients had no statin titration Supports recommendation against lipid targets
PROMINENT[27]	10,497 patients with diabetes (67% with CVD) taking statins with elevated TG levels or low HDL levels randomized to pemafibrate or placebo	At 3.4 y, MACE, CV mortality, or all-cause mortality: no difference	No difference when analyzed by primary or secondary prevention Adding fibrates to statin does not change CV outcomes. Supports recommendation
CLEAR Outcomes[28]	13,970 patients with CVD or at "high risk," unable or unwilling to take statins. Randomized to bempedoic acid or placebo Mean age 66 y, 70% secondary prevention	At 3.5 y, bempedoic acid decreased 4-point MACE (11.7% vs 13.3% placebo) No difference in CV mortality or all-cause mortality. Gout and cholelithiasis increased by 1% (absolute risk)	23% of patients were taking statins in the trial Bempedoic acid was not available in Canada at the time of publication No change in recommendation regarding statin intolerance
Comparison of 7 popular dietary programs and risk of mortality and CV events: systematic review and network meta-analysis[29]	To determine the relative efficacy of structured named diet and health behaviour programs (dietary programs) for prevention of mortality and major CV events in patients at increased risk of CVD	Mediterranean dietary programs proved superior to minimal intervention for the prevention of all-cause mortality, CV mortality, stroke, and nonfatal MI	Supports Mediterranean diet recommendation

CAD—coronary artery disease; CLEAR—Cholesterol Lowering via Bempedoic Acid (ECT1002), an ACL-Inhibiting Regimen; CV—cardiovascular; CVD—cardiovascular disease; HDL—high-density lipoprotein; LDL—low-density lipoprotein; LODESTAR—Low-Density Lipoprotein Cholesterol-targeting Statin Therapy versus the Intensity-based Statin Therapy in Patients with Coronary Artery Disease; MACE—major adverse cardiovascular events; MI—myocardial infarction; PROMINENT—Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes; TG—triglyceride.

with CVD when additional risk reduction is desired. Due to increased risk of atrial fibrillation and bleeding, EPA ethyl ester (icosapent) should be considered only for secondary prevention in patients already taking statins and in whom ezetimibe and PCSK9s were considered. Statin rechallenge should be performed for patients with presumed nonsevere statin intolerance. Finally, for patients taking statin therapy, we recommend against repeat lipid testing and attempting to achieve cholesterol level targets. This is based on the variability of lipid results; the time required to repeat lipid testing, discuss the results, and implement new treatment strategies; and the challenge of achieving targets. In addition, a recent RCT[26] found that using a maximum-tolerated statin dose results in similar outcomes compared with the treat-to-target strategy (**Table 2**).[26-29]

Strengths and weaknesses of the guideline

A strength of this guideline is that we followed the Institute of Medicine's best practices.[15] We formed a multidisciplinary guideline panel free from conflicts of interests that consisted mainly of primary care providers and a patient to generate recommendations. We used systematic reviews of systematic reviews of RCTs to evaluate patient-oriented outcomes of potential benefit and harm. We incorporated the principle of *time needed to treat* to help with our evidence-to-decision framework.[11] Finally, we valued simplification when possible and promoted shared decision making. One weakness is that we did not assess the quality of the individual RCTs beyond what the systematic reviews reported. Additionally, we found repetitive inclusion of the same RCTs in multiple systematic reviews. For example, we included 26 systematic reviews related to PCSK9 inhibitors, but most of the evidence stemmed from 2 RCTs.[18] To prevent these issues, future guideline updates may consider extracting RCT-level evidence. Finally, we recognize that solely relying on RCTs for adverse events is not optimal.

Future guideline updates

Updates to this guideline could occur when additional key evidence is published. For example, the STAREE (Statins in Reducing Events in the Elderly) trial is randomizing about 10,000 primary prevention patients older than 70 years to atorvastatin or placebo to determine the effect on death, disability, and MACE.[30] The SITE (Statins in the Elderly) trial is randomizing primary prevention patients 75 years or older who are taking statins to either a discontinuation or continuation arm to determine the effect on all-cause mortality.[31] In addition, 2 RCTs are currently examining how CAC level scores compare with traditional risk factors for predicting future cardiovascular events.[32,33] Finally, we will consider updating our guideline when 10-year Canadian Framingham risk estimate data are reported.

We encourage future research on non-statin medications as monotherapy in primary prevention, as well as on the effects of currently available non-statin therapies on CVD in patients with true statin intolerance. We also encourage consistent definitions of MACE (eg, 3-point end point of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) as current MACE definitions vary between studies and commonly contain end points of lesser clinical relevance as defined by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative.[34]

Other guidelines

Our guideline is most similar to the 2020 US Veterans Affairs–Department of Defense (VA-DoD) guideline.[5] Both guidelines included multidisciplinary panels with no conflicts of interest and systematically evaluated literature to provide evidence for recommendations on key clinical questions. Both recommend infrequent lipid testing, recommend against using LDL levels to adjust treatment intensity, and encourage statin rechallenge for patients with presumed statin intolerance. For secondary prevention, the VA-DoD guideline recommends adding ezetimibe or PCSK9 inhibitors to statins in those patients "willing to intensify treatment"[5] or icosapent if triglyceride levels remain elevated. We were less enthusiastic about icosapent due to potential adverse events. Another slight difference is the approach to "lower-risk" patients. The VA-DoD guideline recommends statins for primary prevention in patients with a 10-year risk of 6% to 12% and who "prefer statin treatment."[5] The US Preventive Services Task Force recommends prescribing statins to those with a risk of 7.5%.[35] To calculate risk, the US Preventive Services Task Force uses the pooled cohort equation (PCE), the VA-DoD uses PCE or FRS, while we use FRS. Outcomes from the PCE include coronary artery disease death, nonfatal myocardial infarction, and fatal and nonfatal strokes, while the FRS outcomes include myocardial infarction, angina or coronary insufficiency, heart failure, strokes, and claudication. As a result, an FRS of about 10% is similar to a PCE risk score of about 6%.

Finally, the time needed to treat must be considered in all primary care guidelines. While we did not formally calculate the time needed to treat for every recommendation, we understand that clinicians may have many competing priorities with each patient encounter. We therefore ensured that recommendations were feasible and practical in busy clinicians' offices.

Conclusion

Using the best available evidence, GRADE methodology, and a guideline panel well represented by family medicine, we present a simplified approach to the prevention and management of CVD in primary care. This simplified guideline and knowledge translation tool will empower family physicians and other primary health care providers and will allow them to discuss potential benefits and harms of pharmacologic and nonpharmacologic choices with their patients through shared decision making.

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Competing interests

There are no conflicts involving the pharmaceutical industry. Any other potential competing interests are presented in Appendix 1, available from **CFPlus**.*

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