

Simplified lipid guidelines

Prevention and management of cardiovascular disease in primary care

G. Michael Allan MD CCFP Adrienne J. Lindblad ACPR PharmD Ann Comeau MN NP CCN(C) John Coppola MD CCFP
 Brienne Hudson MD CCFP Marco Mannarino MD CCFP Cindy McMinis Raj Padwal MD MSc
 Christine Schelstraete Kelly Zarnke MD MSc FRCPC Scott Garrison MD PhD CCFP Candra Cotton
 Christina Korownyk MD CCFP James McCormack PharmD Sharon Nickel Michael R. Kolber MD CCFP MSc

Abstract

Objective To develop clinical practice guidelines for a simplified approach to primary prevention of cardiovascular disease (CVD), concentrating on CVD risk estimation and lipid management for primary care clinicians and their teams; we sought increased contribution from primary care professionals with little or no conflict of interest and focused on the highest level of evidence available.

Methods Nine health professionals (4 family physicians, 2 internal medicine specialists, 1 nurse practitioner, 1 registered nurse, and 1 pharmacist) and 1 nonvoting member (pharmacist project manager) comprised the overarching Lipid Pathway Committee (LPC). Member selection was based on profession, practice setting, and location, and members disclosed any actual or potential conflicts of interest. The guideline process was iterative through

online posting, detailed evidence review, and telephone and online meetings. The LPC identified 12 priority questions to be addressed. The Evidence Review Group answered these questions. After review of the answers, key recommendations were derived through consensus of the LPC. The guidelines were drafted, refined, and distributed to a group of clinicians (family physicians, other specialists, pharmacists, nurses, and nurse practitioners) and patients for feedback, then refined again and finalized by the LPC.

Recommendations Recommendations are provided on screening and testing, risk assessments, interventions, follow-up, and the role of acetylsalicylic acid in primary prevention.

Conclusion These simplified lipid guidelines provide practical recommendations for prevention and treatment of CVD for primary care practitioners. All recommendations are intended to assist with, not dictate, decision making in conjunction with patients.

EDITOR'S KEY POINTS

- Clinical practice guidelines are often developed with little input from the primary care practitioners who will be implementing the recommendations, and contributors to guideline development often have actual or potential conflicts of interest, many of which go undeclared.
- The process used to develop these guidelines aimed to include more primary care practitioners with little or no conflict of interest in order to create simplified lipid guidelines that were relevant and easy to implement in primary care. Patient input was also sought.
- The resulting guidelines provide an implementation algorithm and practical recommendations on screening and testing, risk assessments, interventions, follow-up, and the role of acetylsalicylic acid in primary prevention. Supplementary documents include a patient handout and the extensive evidence review that was completed to develop the guidelines.



This article is eligible for Mainpro-M1 credits. To earn credits, go to www.cfp.ca and click on the Mainpro link.

This article has been peer reviewed.
Can Fam Physician 2015;61:857-67

La traduction en français de cet article se trouve à www.cfp.ca dans la table des matières du numéro d'octobre 2015 à la page e439.

Numerous clinical practice guidelines exist on managing dyslipidemia, sometimes with widely varying recommendations.¹⁻⁵ Adherence to and realization of these guidelines in primary care is often lacking.⁶ Primary care uptake might be hampered by the limited involvement of primary care physicians (17% of contributors) in the development of national clinical practice guidelines.⁷ It is also clear that many of the targets recommended in clinical practice guidelines are not attainable for most patients even in clinical trials designed specifically to address targets.⁸ Furthermore, the amount of time required to adhere to chronic disease management and preventive care recommendations might be unrealistic.^{9,10} Additionally, approximately 50% of recommendations in guidelines are based on the lowest-level evidence (primarily expert opinion).^{11,12} Although some level of expert opinion is reasonable, such a high percentage is

Recommendations summary

Screening and testing

- Initiating screening: In patients without CVD (primary prevention), we suggest lipid testing as part of global CVD risk estimation in men at age ≥ 40 y and women at age ≥ 50 y (moderate-level evidence).
 - Testing can be considered earlier for patients with known traditional CVD risk factors including, but not limited to, hypertension, family history of premature CVD, diabetes, and smoking (low-level evidence).
- Repeat screening: For patients not taking lipid-lowering therapy, we suggest lipid testing as part of global CVD risk estimation, performed no more than every 5 y (moderate-level evidence). Global CVD risk estimation can be repeated sooner if other CVD risk factors develop in the interim.
- Patients do not need to fast for lipid testing. Nonfasting lipid levels can be used to calculate global CVD risk (moderate-level evidence).

Risk assessments

- Primary prevention: We encourage risk estimation with a CVD risk calculator (eg, Framingham) every time lipid testing is performed. Testing and risk estimation should be performed starting at age 40 y in men and 50 y in women (or earlier if indicated by other risk factors) until age 75 y (low-level evidence).
 - Primary prevention in patients with diabetes mellitus: We encourage risk estimation as above (low-level evidence).
 - Primary prevention in patients with CKD: We recommend using a CVD risk calculator (eg, QRISK2) that includes CKD in its estimation of risk (low-level evidence).
- We discourage risk estimation for the following patients:
 - Those with pre-existing CVD, as they are automatically at high risk (high-level evidence).
 - Those < 40 y (without additional risk factors) and those > 75 y, as risk equations are not based on patients in these age ranges (low-level evidence).
 - Patients taking lipid therapy, as calculators are not designed to adjust for changes with lipid therapy (low-level evidence). If risk calculation is desired for patients taking lipid therapy, pretreatment lipid levels should be used and risk should be adjusted for known benefits of statin or ASA therapy.
- We discourage the use of biomarkers as part of risk assessment until further evidence is available (moderate-level evidence).

Interventions

- Lifestyle interventions, including but not limited to smoking cessation, Mediterranean diet, and exercise, should be discussed with all patients (high-level evidence).
- Secondary-prevention patients: We strongly encourage clinicians to discuss the risks and benefits of high-intensity statin therapy with patients (high-level evidence).
- Primary-prevention patients: We suggest clinicians discuss the risks and benefits of moderate- or high-intensity statins with their patients based on an individual's risk of CVD (high-level evidence).
 - For patients with a 10-y CVD risk of $< 10\%$, we suggest retesting lipid levels in 5 y with risk estimation (moderate-level evidence).
 - For patients with a 10-y CVD risk of 10% – 19% , we suggest clinicians discuss initiation of statins (preferably moderate-intensity statins) with patients (high-level evidence).
 - For patients with a 10-y CVD risk of $\geq 20\%$, we strongly encourage clinicians to discuss initiation of statins (preferably high-intensity) with patients (high-level evidence).
- Patients who are elderly (based on frailty as much as age) or those with renal impairment can be offered lower-intensity statin therapy (low-level evidence).
- Primary prevention patients > 75 y: We discourage routinely testing lipid levels, estimating CVD risk, and prescribing statins (moderate-level evidence).
 - Some patients > 75 y whose life expectancy and overall health status are good can be offered statin therapy for primary prevention, but this should be left to the clinician and patient's discretion (low-level evidence).
- Secondary prevention patients > 75 y: We strongly encourage clinicians to discuss the risks and benefits of moderate-intensity statins with patients (high-level evidence).
 - Patients already taking and tolerating a statin should not have their statin stopped or reduced just because they have aged beyond 75 y (low-level evidence).
- In patients ≥ 65 y, pravastatin should likely not be considered first-line therapy until uncertainty surrounding cancer in this subgroup with this drug is resolved (moderate-level evidence).
- Patients who do not tolerate a specific statin regimen should be offered a lower-intensity regimen, with either the same or a different statin, or a short drug holiday followed by rechallenge to help clarify if statins are related to the intolerance (low-level evidence).
 - Any statin intensity is preferred to non-statin lipid-lowering therapy (moderate-level evidence).
 - Alternate daily dosing can be considered if a patient does not tolerate daily dosing (low-level evidence).
 - In patients who have severe reactions like rhabdomyolysis, retreatment might not be appropriate (low-level evidence).
- In primary prevention, non-statin lipid-lowering drugs should not be used as first-line monotherapy or in combination with statins (high-level evidence).
- In secondary prevention, ezetimibe can be considered in discussion with patients as add-on therapy to statins, but owing to the higher relative benefit of statins, statin therapy should be maximized first (to high intensity) (high-level evidence).

Follow-up

- The use of cholesterol targets for reducing CVD is not required (high-level evidence).
- We suggest that the monitoring of repeat lipid levels after a patient begins lipid-lowering therapy is not required (low-level evidence).
 - Adherence to statins can be improved with patient reinforcement.
- We suggest that testing for baseline CK or ALT levels in healthy individuals before starting statin therapy is generally unnecessary (low-level evidence). The evidence against testing baseline ALT or CK levels is poor and some clinicians might prefer to test one or both.
- Routine monitoring of CK and ALT levels should be reserved for those patients who are symptomatic or who are at higher risk of adverse events. Frequency should be determined at the discretion of the attending clinician (moderate-level evidence).

Primary prevention with ASA

- We discourage the use of ASA for patients without previous CVD and an estimated 10-y CVD risk $< 20\%$ (high-level evidence).
- We suggest ASA can be considered in primary prevention if the 10-y CVD risk is $\geq 20\%$ and bleeding risk is low (low-level evidence).
 - Use of ASA for primary CVD prevention should be considered after statin therapy has been discussed (high-level evidence).
- Patients offered ASA should be informed of the potential benefits and harms of ASA use (low-level evidence).

ALT—alanine transaminase, ASA—acetylsalicylic acid, CT—creatinine kinase, CKD—chronic kidney disease, CVD—cardiovascular disease.

disconcerting when many guideline contributors have conflicts of interest.^{7,13}

To address these challenges, our objective was to follow the recommendations of the Institute of Medicine from their document “Clinical Practice Guidelines We Can Trust.”¹⁴ We attempted to increase the contribution of primary care professionals, seek participants with little or no conflict of interest, and focus on the highest level of evidence. The purpose of this guideline is to develop a simplified approach to primary prevention of cardiovascular disease (CVD), concentrating on CVD risk estimation and lipid management for primary care clinicians and their teams. All recommendations within this document are to assist with, not dictate, decision making in conjunction with the patient. Other factors that should be considered in therapy decisions include, but are not limited to, patient preference, comorbidities, potential adverse effects, drug interactions, and cost. Patient preference and shared, informed decision making should guide all patient care decisions.

There is considerable controversy about the management of dyslipidemia, and whether the use of cholesterol targets is evidence-based. As this document is based on the best available evidence with a focus on use in primary care, the results of this guideline might differ from other Canadian guidelines on the same topic, and are more in line with the 2013 American guidelines.¹⁻³ Clinicians are encouraged to discuss their approach to CVD risk management with their patients, letting each patient decide what is best for him or her. A patient handout is available at **CFPlus**.*

It should be noted that genetic hypercholesterolemia should be considered in patients with markedly elevated lipid levels (eg, low-density lipoprotein [LDL] >5 mmol/L) despite appropriate lifestyle changes. These guidelines do not apply to patients meeting the diagnostic criteria for familial hypercholesterolemia (which include elevated LDL levels, physical findings, and family or personal history of CVD).⁴ Additionally, treatment of hypertension is important in managing CVD risk. However, blood pressure management is beyond the scope of this guideline.

METHODS

Nine health professionals (4 family physicians [G.M.A., J.C., B.H., M.M.], 2 internal medicine specialists [R.P., K.Z.], 1 nurse practitioner [A.C.], 1 registered nurse [C.S.], and

*The **evidence review** document,¹⁵ a **patient handout**, the **full disclosure** of competing interests, and an easy-to-print version of the **algorithm** including statin dosing and treatment benefit tables are available at www.cfp.ca. Go to the full text of the article online and click on **CFPlus** in the menu at the top right-hand side of the page.

1 pharmacist [C.M.]) and 1 nonvoting member (pharmacist project manager [A.J.L.]) comprised the overarching Lipid Pathway Committee (LPC) tasked with creating and approving the guideline. Member selection was based on profession, practice setting, and location, in order to represent a variety of primary care providers from rural and urban settings. Members disclosed any actual or potential conflicts of interest, including predisposition bias (financial conflicts are disclosed within these guidelines; the full disclosure is available at **CFPlus**).

Overall, the guideline process was iterative through online posting, detailed evidence review, and telephone and online meetings. To start, members of the LPC were asked to identify 10 priority questions to be addressed in the guideline. Questions were then grouped and members were asked to independently rank what they thought the 10 priority questions were. These were ranked and the top 10 were identified.

1. When should screening for cardiovascular risk begin, who should be screened, and how often should patients be screened for risk?
2. Do we have evidence to support the use of biomarkers in risk assessment or monitoring?
3. According to evidence, ease of use, and principles of shared, informed decision making, which risk calculators should be recommended?
4. Which lipid-lowering drugs decrease the risk of CVD (myocardial infarction, stroke), by how much, and what are the harms?
5. Does evidence support decreasing LDL, triglyceride, or total cholesterol levels, or total cholesterol to high-density lipoprotein (HDL) ratio; increasing HDL levels; or attaining specific lipid targets to decrease CVD?
6. Is it necessary to test serum lipid levels after starting lipid-lowering therapy?
7. How should patients who are taking statins be monitored for safety and efficacy?
8. How should statins be dosed? What is the evidence for high-dose compared with standard-dose statin therapy? What is the evidence for low-dose compared with standard-dose statin therapy?
9. How should we treat patients who do not tolerate statin therapy?
10. Which patient characteristics (eg, post-myocardial infarction, diabetes mellitus, level of CVD risk) warrant consideration of lipid-lowering therapy?

Two additional questions were added after the first 10 were answered.

11. How should we approach statin use in the elderly?
12. Who, if anyone, should receive daily acetylsalicylic acid (ASA) for primary prevention?

The Evidence Review Group, consisting of 5 health professionals (A.J.L., M.R.K., S.G., C.C., G.M.A.) with expertise in literature searching, critical analysis, and knowledge translation, answered these questions. The

search strategy for each question varied based on the nature of the question; generally, relevant guidelines were reviewed for evidence, followed by a search of the Cochrane Database of Systematic Reviews and PubMed. The focus was on systematic reviews and meta-analyses, with use of randomized controlled trial (RCT) data when needed. At times, lower levels of evidence were considered when necessary (such as for the examination of biomarkers), but these were given low weighting. When relevant, only studies with hard CVD outcomes (myocardial infarction, stroke, and death) were included. The quality of evidence was rated (Table 1).² Further information on the search strategy and answers to the questions can be found in the evidence review.^{15*}

After review of the answers, key recommendations were derived through consensus of the LPC. Five members of the LPC (M.M., B.H., J.C., C.M., G.M.A.) volunteered to draft the summarized guideline (pathway) from the available evidence and to establish recommendations. Once the draft guideline was complete, the

document was posted for the LPC and a meeting was convened. The guideline was then refined and distributed to a group of clinicians (family physicians, other specialists, pharmacists, nurses, and nurse practitioners) and patients for feedback, then refined again and finalized by the LPC.

RECOMMENDATIONS

The lipid algorithm developed for these guidelines is outlined in Figure 1, and the original version is available at **CFPlus**.^{16*} Specific recommendations are detailed below.

Screening and testing

What is screening? For these guidelines, *screening* refers to lipid testing accompanied by an overall CVD risk assessment. Using only 1 risk factor (such as lipid levels) to target therapy will miss many higher-risk patients. Without a risk assessment tool (eg, the Framingham risk calculator), clinicians and patients will estimate risk less accurately and either start treatment when it is not warranted or fail to start treatment in higher-risk individuals. Therefore, we recommend that a CVD risk assessment using a risk calculator be done with every measurement of lipid levels. **Box 1** lists some suggested calculators.

When to start screening? Mass population-based screening and interventions (including “annual physicals” or periodic health assessments) for cardiac risk factors in patients without CVD do not appear to reduce CVD or all-cause mortality.¹⁵ However, this evidence is limited; many studies predated statin therapy or used lifestyle counseling as the only intervention.

Cardiovascular disease is most strongly associated with advancing age and traditional CVD risk factors.¹⁵

Table 1. Evidence quality rating

QUALITY RATING	EVIDENCE
High	<ul style="list-style-type: none"> High-quality RCTs: High-quality includes good design, low risk of bias, and confidence in the estimate Systematic reviews of high-quality RCTs
Moderate	<ul style="list-style-type: none"> RCTs with important limitations: Limitations of RCTs could include inadequate power, poor follow-up, missing quality elements like allocation concealment, per-protocol analysis, etc High-quality observational studies: High-quality observational studies typically include prospective cohort studies of large populations mirroring Canadian populations and adequate adjustment for confounding Systematic reviews of RCTs with important limitations or high-quality observation studies
Low	<ul style="list-style-type: none"> RCTs with profound limitations: Profound limitations in RCTs include those listed above but larger and multiple concerns (eg, a trial grossly underpowered for clinical outcomes, CIs that include meaningful harm and benefit, 50% loss to follow-up, etc) Observational studies with important limitations: Observational studies with important limitations might include retrospective studies, small or specific subpopulations, high-risk confounding, etc Other lower evidence studies like case series or studies without patient-oriented outcomes (physiologic studies) Systematic reviews including any of these studies

RCT—randomized controlled trials.
Adapted from Stone et al.²

Box 1. Possible cardiovascular risk calculators*

University of Edinburgh Cardiovascular Risk Calculator:
<http://cvrisk.mvm.ed.ac.uk/calculator/calc.asp>

- Offers 3 different databases to compare calculated risk; has different display options (some will show statin risk reduction)

Best Science Medicine: <http://bestsciencemedicine.com/chd/calc2.html#basic>

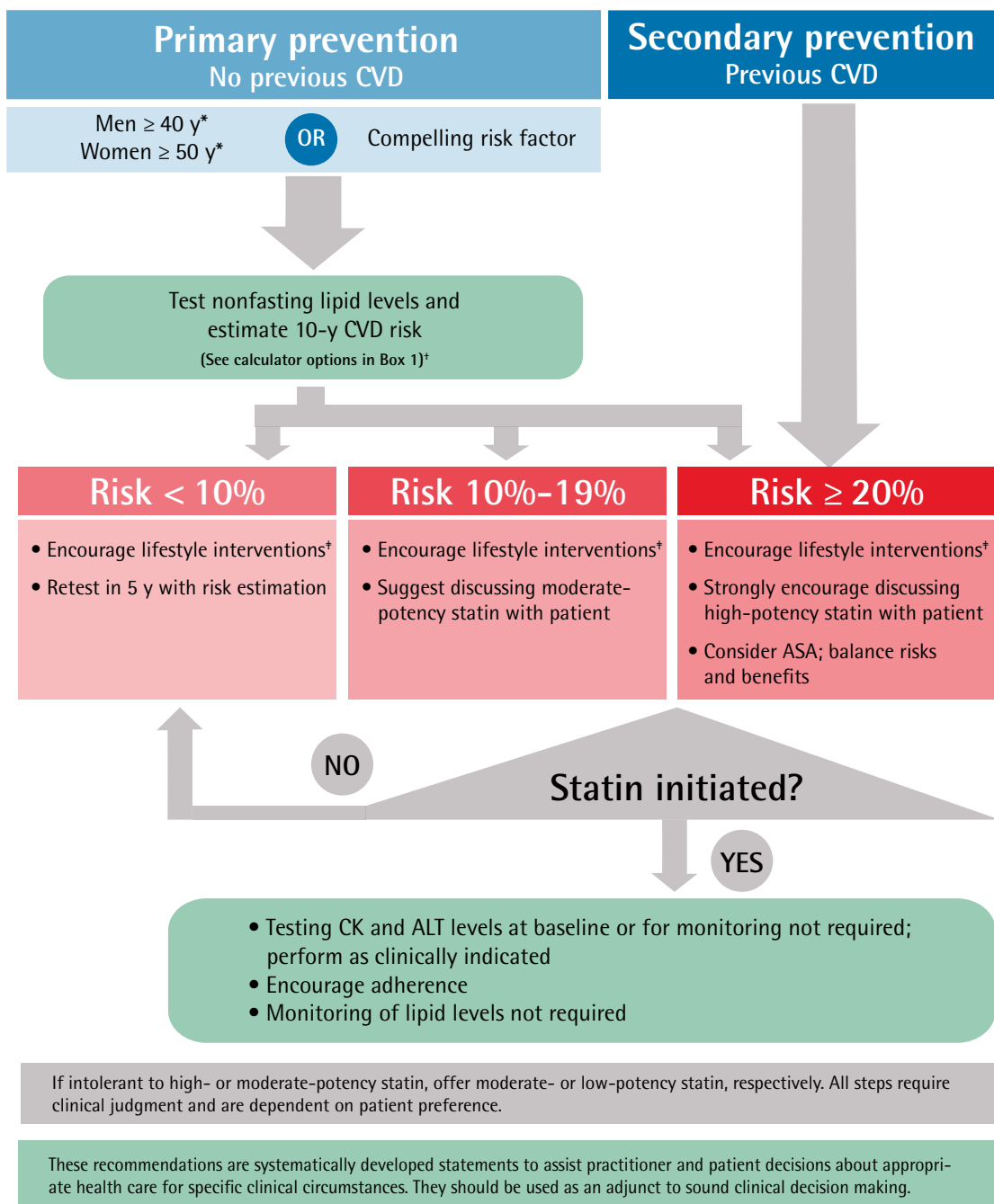
- Offers 3 different databases, including Framingham and QRISK2, to compare risks; shows potential benefit of different interventions

QRISK2: www.qrisk.org

- Includes chronic kidney disease in risk estimation

*This list is not meant to be all encompassing or to encourage use of one over another. It is simply some suggestions of possible calculators.

Figure 1. Lipid algorithm: For primary or secondary prevention; excludes those with familial hypercholesterolemia.



ALT—alanine transaminase, ASA—acetylsalicylic acid, CK—creatinine kinase, CVD—cardiovascular disease.

*Clinicians can initiate lipid testing and risk estimation early if high clinical suspicion exists (ie, if there are compelling risk factors such as family history, hypertension, diabetes, or smoking). Regardless, testing before age 35 y is not recommended for by far most patients, and risk estimation tools do not include patients younger than 35 y. Primary prevention screening beyond age 75 y is generally not recommended.

[†]Risk can be calculated using a number of risk calculators, but each clinician should use the same one consistently. The Framingham risk calculator has been validated in a Canadian population and is likely preferred. The following calculator has been created for this guideline: <http://chd.bestsciencemedicine.com/calc2html#basic>.

[‡]Lifestyle interventions include smoking cessation, exercise, and the Mediterranean diet. Exercise should include > 150 min in > 4 sessions of moderate (brisk walking) to vigorous exercise weekly.

Adapted from Toward Optimized Practice.¹⁶

Patients with 1 CVD risk factor are more likely to have another CVD risk factor.¹⁵ More evidence is needed to determine which ethnicities and which noncardiac chronic medical conditions (such as chronic autoimmune inflammatory conditions like rheumatoid arthritis) are truly independently associated with elevated CVD risk.

In association with age increasing CVD risk, we support starting screening for men at age 40 and women at age 50. We debated screening all patients at age 40, but most women would be too low risk at this age, and the recommendation would not follow the best available evidence. Screening can be considered earlier for patients with known risk factors like hypertension or diabetes.

How often should I repeat lipid level measurement and CVD screening for patients not taking therapy?

For patients not taking lipid-lowering therapy, there is substantial short-term variability and minimal long-term change in lipid levels.¹⁵ Frequent lipid level testing is likely to reflect the short-term variability and is unlikely to meaningfully alter global CVD risk assessment.¹⁵ Because lipid levels change minimally over the long term and constitute only 1 variable in determining global CVD risk assessment, the same lipid profile remains relevant for many years.¹⁵ There is no need to frequently repeat the lipid profile to update risk estimation in untreated patients. Therefore, for those not taking statin therapy, screening (repeat lipid levels and risk assessment) is not required more often than every 5 years.

Do patients need to fast to have their cholesterol level checked?

Minimal differences exist between fasting and nonfasting HDL, LDL, and total cholesterol levels.¹⁵ The differences that occur are less than the within-person variability from repeat lipid testing.¹⁵ Tests of nonfasting HDL and non-HDL levels correlate with future CVD events.¹⁵ Although triglycerides are most susceptible to change without fasting, triglycerides contribute minimally to total cholesterol levels, and triglyceride levels are not consistently associated with CVD.¹⁵ Removing the fasting restriction should improve test adherence and reduce potential patient harm (eg, hypoglycemia in patients with diabetes).¹⁵

Risk assessments

Why estimate risk? Overall risk, not lipid levels, is the best predictor of benefit from statins.¹⁷ Estimating risk without a risk assessment tool (like Framingham) is challenging; both patients and clinicians frequently err in their estimations.¹⁸ An overreliance on lipid levels and lack of appreciated risk might contribute to why many high-risk patients go without treatment.¹⁸ Additionally, estimation of risk promotes shared, informed decision making, allowing a discussion with patients about their

baseline risk and, as a result, the potential absolute benefit of taking a statin. Low-potency statins reduce baseline estimated CVD risk by about 25% and high-potency statins reduce baseline risk by about 35%.¹⁵ As an example, a patient with a 20% 10-year risk of CVD would have his or her risk reduced by 5% with low-potency (25% of 20%) or 7% with high-potency (35% of 20%) statin therapy.

We recognize that risk calculators are not without limitations. For example, in paired comparisons risk calculators disagree about risk level (high, moderate, or low) approximately 33% of the time.¹⁹ That said, risk calculation is the most reliable way to estimate patients' CVD risk and the potential benefit from statin or ASA therapy.¹⁸ Although the Framingham risk calculator might tend to overestimate risk somewhat, it presents risks of combined CVD outcomes and has some research with validation in a Canadian population.¹⁵ To account for the issues around overestimation of risk with the Framingham tool, we used the traditional risk cutoffs of 10% and 20% compared with the US guideline (7.5%), which uses a different calculator.²

Diabetes and chronic kidney disease. Patients with diabetes or chronic kidney disease (CKD) are at increased risk of CVD, although the risk is not equivalent to the risk in patients with coronary artery disease.¹⁵ The Framingham calculator can include diabetes in its calculation of risk. For patients with CKD, a risk calculator that includes CKD in the risk equation is recommended (eg, QRISK2).

Some clinicians might choose to simply prescribe statins to all patients with diabetes or CKD. In most cases, an individual's risk might be above 10%, but without risk estimation it will be difficult to allow patients to make an informed choice understanding their absolute risk and the potential benefits of statin therapy.

Biomarkers. A number of risk factors and biomarkers are statistically significantly associated with CVD. For simplicity, we will collectively refer to these as *biomarkers*. Interpretation of the research is challenged by multiple limitations. For any biomarker to have utility in risk estimation, it should add meaningfully to established risk assessment tools. Currently only one biomarker (coronary artery calcium level) appears to offer a potentially meaningful improvement in all measures of performance when added to Framingham risk scores.¹⁵ However, this biomarker requires further validation, safety assessment, and cost-effectiveness analyses.¹⁵ Commonly promoted biomarkers (like lipoproteins and C-reactive protein) have a substantial body of evidence demonstrating that they do not add meaningfully to risk prediction.¹⁵ There is currently no high-level evidence to support testing and monitoring of any biomarker in the management of CVD risk.

When is risk estimation unnecessary?

Secondary prevention: In patients with known CVD (such as a history of myocardial infarction or stroke), risk assessment is not appropriate. These patients have risk greater than 20% and are good candidates for statin therapy, particularly high-dose or high-intensity therapy.²⁰⁻²² In patients with previous CVD, clinicians are strongly encouraged to discuss and recommend the highest approved dose and intensity statin the patient tolerates.¹⁵

Young and old patients: In primary prevention (those without previous CVD), risk assessment tools like Framingham and ASSIGN include patients aged 35 to 75 years, while the ASCVD risk estimator includes patients aged up to 79 years. As mentioned above, we recommend screening begin at age 40 in men and 50 in women (or earlier if there are identified risks). Given the uncertainty around primary prevention treatment of the elderly and limits in risk assessment after age 75, we recommend risk assessment stop at age 75.

Patients taking lipid-lowering medication: Once patients are taking lipid medications, risk assessment is inaccurate. Some medicines modify lipid levels with little or no effect on cardiovascular risk; this might cloud global risk estimation. In the case of statins, the most reliable risk estimation would be to use lipid levels from before treatment began for risk estimation and then reduce the risk estimate by 25% to 35%, based on statin dose and potency.

Interventions

Table 2¹⁶ outlines the benefits of lifestyle and pharmaceutical interventions reviewed in this guideline.

Lifestyle. Lifestyle (nondrug) interventions are considered the cornerstone of therapy and should be initiated as a first-line intervention to reduce CVD and improve health.

Unfortunately, we do not have space or resources to provide a full review of lifestyle interventions but strongly recommend the following 3 be advocated for all patients.

Smoking cessation: Evidence shows that concerted smoking cessation efforts reduce mortality and other outcomes,²³⁻²⁵ and some studies show benefits far exceeding those seen with pharmaceutical intervention²⁵ (high-level evidence).

Exercise: Exercise in high-risk individuals results in CVD and mortality reductions similar to or better than reductions seen in trials for most pharmaceutical treatments^{26,27} (high-level evidence). At least 150 minutes (30 to 60 minutes 4 to 7 times a week) of moderate- or high-intensity exercise (moderate intensity includes brisk walking) is consistently recommended.^{1,28,29}

Mediterranean diet: Three clinical trials demonstrate reduction in CVD in patients following the Mediterranean diet, with a relative reduction in primary prevention similar to that seen with statins³⁰⁻³² (high-level evidence).

Statins. Statins are the only class of lipid-lowering therapy that has evidence for reduction of all-cause mortality (relative risk reduction of about 10%) and cardiovascular events (about 25%).¹⁵ Statins are therefore recommended as first-line therapy in all patients for whom pharmaceutical intervention is considered. As mentioned previously, risk estimation should stop beyond age 75 years. Further, data on starting statin therapy for primary prevention are very limited for patients beyond age 75 years, with no evidence for patients in their 80s.¹⁵ The evidence for statins (moderate intensity) in secondary prevention is stronger, and they should be considered regardless of age in secondary prevention.¹⁵ Owing to uncertainty around a possible risk of cancer with pravastatin in patients

Table 2. Benefits of therapies

THERAPY	ESTIMATED BENEFIT (RELATIVE RISK REDUCTION), %	EXAMPLE IF BASELINE RISK ESTIMATED AT 20% OVER 10 Y		
		ABSOLUTE RISK REDUCTION, %	NUMBER NEEDED TO TREAT	NEW RISK ESTIMATE, %
Smoking cessation	Recalculate risk without smoking	9*	12*	11*
Mediterranean diet	30	6	17	14
Exercise	30	6	17	14
Statin intensity				
• Low	25	5	20	15
• Moderate	30	6	17	14
• High	35	7	15	13
Acetylsalicylic acid	12	2	50	18

*Example used a male smoker, 53 y old, with total cholesterol level of 5.0 mmol/L, high-density lipoprotein level of 1.2 mmol/L, and systolic blood pressure of 128 mm Hg; estimated risk from the Framingham risk assessment tool (from <http://cvrisk.mvm.ed.ac.uk/calculator/calc.asp> and <http://bestsciencemedicine.com/chd/calc2.html>) to attain a 20% risk over 10 y.

Adapted from Toward Optimized Practice.¹⁶

65 years and older, other statins should likely be considered for this age group.¹⁵ There is no evidence of risk for other statins in patients of any age or for pravastatin in patients younger than 65 years of age.¹⁵ Finally, for elderly patients already taking statins and tolerating them, advancing age is not a reason to stop statin therapy.

How should statins be dosed? There is no evidence to recommend adjusting doses to achieve specific LDL targets, as only fixed doses are tested in trials.¹⁵ Patients at equivalent levels of risk get the same benefit regardless of pretreatment LDL levels. There is evidence from secondary prevention that higher doses or higher-potency statins reduce CVD more than lower doses or lower-potency statins do.¹⁵ Therefore, recommended dosing should be based on intensity (representing both potency in the type of statin and dose) of statin therapy (Table 3).²

Evidence favours the use of moderate- or high-intensity statin therapy in all patients. The additional benefit of high-intensity statin therapy, relative to low- or moderate-intensity therapy, in secondary prevention is about 10% (ie, relative risk reduction improves from 25% to 35%).¹⁵ There are no trials comparing statin doses for primary prevention.

What should I do if a statin is not tolerated? The incidence of adverse events, including myalgias and elevation in transaminase levels, increases with increasing statin doses (the section on follow-up includes more information about the harms of statins). Side effects can lead to discontinuation of statin therapy and must be addressed. About 70% of patients with an adverse reaction to a statin will be able to tolerate an alternate statin regimen.¹⁵ The benefit of being on any statin is greater than the difference in benefit between being on a high versus a low dose, so getting and keeping the patient on a statin is key.

Non-statin therapy. Non-statins include fibrates, niacin, ezetimibe, and bile-acid sequestrants. Fibrates given alone have evidence of a reduction in nonfatal myocardial infarction but considerably less overall CVD reduction than statins and no mortality benefit.¹⁵ Added to statins, they have no benefit.¹⁵ Niacin has 1 old trial suggesting benefit, but studies since the introduction of

statins have failed to show a benefit with niacin added to statin therapy.¹⁵ Fibrates, niacin, and bile-acid sequestrants generally have a higher incidence of adverse effects compared with statins.¹⁵

Ezetimibe is well tolerated but has no demonstrated effect on mortality or CVD in primary prevention.¹⁵ The IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study, in which 10 mg of ezetimibe was added to 40 mg of simvastatin compared with 40 mg of simvastatin alone, demonstrated a 6% relative reduction in CVD events.³³ In secondary prevention, ezetimibe might be a reasonable option after statin therapy, but it needs to be stressed that the benefit of low-intensity statins far exceeds the benefit of ezetimibe, and the benefit of an increase to high-intensity statin therapy is almost double that seen from adding ezetimibe. If the relative benefits could be extrapolated to primary prevention, the absolute benefit would be only about 1% over 10 years for high-risk patients (and less in moderate-risk patients). For this reason, ezetimibe cannot be advocated in primary prevention. Finally, it is important to note that the relative benefit from ezetimibe did not differ between patients with high and low baseline LDL levels, indicating again that treating patients based on LDL level is inappropriate.

Follow-up

What lipid level should I target for my patients?

Traditionally, clinical practice guidelines have recommended the use of lipid targets for different cardiovascular risk groups (eg, LDL <2 mmol/L, 50% reduction in LDL).¹⁵ However, evidence is lacking for the use of particular targets to guide titration of statin therapy. The RCTs showing a benefit in CVD outcomes with statin use have compared fixed-dose statin therapy with placebo, or high- versus low-dose statin therapy.¹⁵ There are no RCT data showing a significant benefit of particular lipid targets on CVD outcomes.¹⁵

When should I repeat measurement of lipid levels after starting a statin?

As discussed above, the lack of evidence for titrating statin therapy to particular lipid targets brings into question whether lipid levels need to be monitored after a statin is initiated. Currently, there is no evidence of benefit for re-measuring lipid levels after initiation of statin therapy.¹⁵ While some argue that repeating measurement of lipid levels is helpful in assessing adherence to statin therapy, there is no evidence that this increases adherence.¹⁵ However, there is some evidence that statin adherence is improved through patient reinforcement and reminders (eg, telephone calls, pharmacist medication reviews, medication calendars).¹⁵

Patients taking statins might (and likely will) have their risk increase as they age or develop new risk

Table 3. Statin dosing ranges and intensity

INTENSITY	STATIN OPTIONS
Low	Pravastatin 10–20 mg; lovastatin 10–20 mg; simvastatin 5–10 mg; atorvastatin 5 mg; rosuvastatin 2.5 mg
Moderate	Pravastatin 40–80 mg; lovastatin 40–80 mg; simvastatin 20–40 mg; atorvastatin 10–20 mg; rosuvastatin 5–10 mg
High	Atorvastatin 40–80 mg; rosuvastatin 20–40 mg

Adapted from Stone et al.²

factors. As mentioned previously, ordering lipid panels for patients taking lipid-modifying agents and using the findings of these new panels in CVD risk calculators will give inaccurate estimations of risk. Clinicians would be better to use the pretreatment lipid levels, as they generally change little over time, and add in the new risk factors. The overall risk can be adapted to reflect the lipid therapy by reducing the risk by the anticipated relative reduction from statin therapy (25% to 35% based on intensity of therapy).

What are the main harms of statins? Harms associated with statins include muscle and liver injury and elevation of blood glucose levels. Myalgia is a common adverse effect associated with statin use, but serious adverse effects such as rhabdomyolysis and liver failure are exceedingly rare (Table 4).^{15,34} Increases in creatine kinase (CK) and liver enzyme levels in asymptomatic patients can occur, and many of these enzyme elevations will return to baseline with continued statin use.¹⁵ In fact, a trial with a subgroup analysis of patients with elevated liver test results (assumed primarily nonalcoholic fatty liver disease) found that patients randomized to statins were more likely to have a decrease in abnormal liver test findings, while the placebo arm was more likely to see an increase.³⁵ Confounding factors, including patient comorbidities and other medications, might increase the chance of muscle and liver damage.¹⁵

Table 4. Incidence rates per 100 000 person-years for muscle- and liver-related adverse effects with statins

ADVERSE EFFECT	INCIDENCE PER 100 000 PERSON-Y		DIFFERENCE (95% CI)
	STATIN	PLACEBO	
Elevated ALT level (>3 times ULN)	300	200	100 (64 to 140)
Liver failure	~0.5	NA	NA
Elevated CK level (>10 times ULN)	83	60	23 (-4 to 50)
Myalgia (muscle pain, tenderness, weakness)	5150	4960	190 (-38 to 410)
Myopathy (muscle pain, tenderness, weakness severe enough to stop pills; CK level not always specified)	97	92	5 (-17 to 27)
Rhabdomyolysis (poorly defined, except for CK >10 times ULN)	4.4	2.8	1.6 (-2.4 to 5.5)

CK—creatinine kinase, NA—not applicable, ULN—upper limit of normal.
Data from Law and Rudnicka.³⁴

There are no RCT data to support routine monitoring of CK and alanine transaminase (ALT) levels in patients taking statin therapy¹⁵; RCTs have shown that rates of elevation of ALT and CK levels are similar between placebo and treatment groups.¹⁵ There are cohort data showing that even if ALT levels are elevated at baseline, this does not correlate with an increased likelihood of severe elevations in liver enzymes.¹⁵ Routine monitoring of ALT and CK levels has the potential to do harm to patients if statins are stopped unnecessarily.

Low-potency statin use increases the risk of developing type 2 diabetes by approximately 1 in 250 over 5 years.³⁶ High-potency (over low-potency) statins might increase the risk a further 1 in 125 over 5 years.³⁶ To keep this in perspective, approximately 1 patient will be diagnosed with diabetes for every 2 to 15 avoiding CVD or death.

Use of ASA in primary prevention

Use of ASA for primary CVD prevention decreases the risk of CVD but at the expense of increased risk of bleeding, without altering all-cause or CVD mortality. The relative reduction in vascular events with ASA is approximately 12%, about half the benefit seen with low-intensity statin therapy.¹⁵ The risk of gastrointestinal bleeding increases with ASA use by about 0.5% to 4% over 10 years, with lower risk in younger women and higher risk in older men.¹⁵ Unfortunately, patients at increased risk of future CVD are often also at increased risk of bleeding.¹⁵ Compared with statins, ASA has less relative benefit and higher risk of serious adverse events, and therefore ASA should be considered for primary CVD prevention after statin therapy.

Based on the best available evidence, patients whose 10-year CVD risk is 20% or higher might have a small net benefit derived from ASA use, and therefore it might be reasonable to consider ASA therapy in these patients. For example, in 1000 men aged 65 years with a 20% chance of CVD over 10 years, ASA use would result in 64 fewer myocardial infarctions, but 1 additional hemorrhagic stroke and 24 serious gastrointestinal bleeds. In net terms, this equates to about 40 fewer CVD events than serious bleeds.

Patients must be made aware of these potential benefits and harms, and for most patients without CVD who are at relatively low risk of future CVD, the benefits of ASA use are offset or outweighed by the potential harms.

Conclusion

We based our lipid pathway on the highest-quality evidence and the need to keep management of lipid levels and CVD risk reduction simple. Screening for cardiovascular risk should begin at age 40 for men and 50 for women, and fasting for lipid tests is not required. Using the principles of shared, informed decision making, we recommend calculating a patient's baseline CVD risk.

A statin can be expected to lower that risk by 25% to 35% (eg, if baseline risk is 20%, a statin will lower it to 15% to 13%). This information can be used to help the patient determine if they are willing to take a statin. No other class of medication has the same volume of high-quality, consistent data on CVD and mortality reduction as statins do. Current evidence does not support targeting specific lipid levels, and repeated measurement of lipid levels for patients already taking statins is not required. Lifestyle changes are recommended for all patients, while ASA can be considered after statin therapy in high-risk individuals with low risk of bleeding.

The removal of lipid targets and associated monitoring of lipid levels, as well as other streamlining measures, has substantially simplified the management of lipid levels and CVD risk. Additionally, the targeting of risk identifies patients most likely to benefit from intervention while actively involving patients in their care. ✨

Dr Allan is Professor and Director of Evidence-based Medicine in the Department of Family Medicine at the University of Alberta in Edmonton and Director of the Evidence and CPD program of the Alberta College of Family Physicians. **Dr Lindblad** is Knowledge Translation and Evidence Coordinator for the Alberta College of Family Physicians and Associate Clinical Professor in the Department of Family Medicine at the University of Alberta. **Ms Comeau** is Primary Care Manager and a nurse practitioner for the Edmonton Southside Primary Care Network. **Dr Coppola** is Clinical Assistant Professor in the Department of Family Medicine in the Cumming School of Medicine at the University of Calgary in Alberta. **Dr Hudson** is a family physician in Grande Prairie, Alta. **Dr Mannarino** is Assistant Clinical Professor and Clinic Preceptor in the Department of Family Medicine at the University of Alberta. **Ms McMinis** is Clinical Practice Leader in Pharmacy Services for Alberta Health Services in Wainwright, Alta. **Dr Padwal** is Associate Professor in Clinical Epidemiology, Clinical Pharmacology, and General Internal Medicine and Director of the Hypertension Clinic at the University of Alberta. **Ms Schelstraete** is a virtual care nurse for MyHome Health pilot project in the Sherwood Park-Strathcona County Primary Care Network in Alberta. **Dr Zarnke** is Associate Professor of Medicine and Head of the Division of General Internal Medicine in the Faculty of Medicine at the University of Calgary and Section Chief of General Internal Medicine for the Alberta Health Services Calgary Zone. **Dr Garrison** is Associate Professor in the Department of Family Medicine at the University of Alberta. **Ms Cotton** is a clinical pharmacist at Saint-Vincent Hospital in Ottawa, Ont. **Dr Korownyk** is Associate Professor in the Department of Family Medicine at the University of Alberta. **Dr McCormack** is Professor in the Faculty of Pharmaceutical Sciences at the University of British Columbia in Vancouver. **Ms Nickel** is Coordinator of the Evidence and CPD program of the Alberta College of Family Physicians. **Dr Kolber** is Associate Professor in the Department of Family Medicine at the University of Alberta.

Acknowledgment

This guideline was sponsored by Toward Optimized Practice, supported by the Alberta College of Family Physicians, and endorsed by the College of Family Physicians of Canada.

Contributors

The Evidence Review Group comprised **Drs Lindblad, Kolber, Garrison, and Allan** and **Ms Cotton**. The Lipid Pathway Committee comprised **Drs Allan, Mannarino, Coppola, Hudson, Padwal, and Zarnke** and **Ms Comeau, Ms McMinis, and Ms Schelstraete**; **Dr Lindblad** was a nonvoting member. The Pathway Review Group consisted of **Drs Kolber and Korownyk**. **Drs McCormack, Nickel, and Allan** were responsible for knowledge translation.

Competing interests

Dr Padwal has participated on advisory boards on renal denervation for resistant hypertension for Medtronic, has received grants or honoraria from Abbott, Servier, and Merck for hypertension-related continuing medical education, and has participated in clinical trials for Novo Nordisk, CVRx, Vanencia, and PharmaSmart. The full disclosure including predisposition bias is available at [CFPlus](#).*

Correspondence

Dr G. Michael Allan; e-mail mgallan@ualberta.ca

References

1. Anderson TJ, Grégoire J, Hegele RA, Couture P, Mancini GB, McPherson R, et al. 2012 Update of the Canadian Cardiovascular Society guidelines for the

diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol* 2013;29(2):151-67.

2. Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(25 Suppl 2):S1-45. Epub 2013 Nov 12. Erratum in: *Circulation* 2014;129(25 Suppl 2):S46-8.

3. Tobe SW, Stone JA, Brouweres M, Bhattacharyya O, Walker KM, Dawes M, et al. Harmonization of guidelines for the prevention and treatment of cardiovascular disease: the C-CHANGE initiative. *CMAJ* 2011;183(15):E1135-50. Epub 2011 Sep 12. Erratum in: *CMAJ* 2012;184(3):327.

4. European Association for Cardiovascular Prevention & Rehabilitation; Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, et al. ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011;32(14):1769-818. Epub 2011 Jun 28.

5. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;33(13):1635-701. Epub 2012 May 3. Erratum in: *Eur Heart J* 2012;33(17):2126.

6. Liddy C, Singh J, Hogg W, Dahrouge S, Deri-Armstrong C, Russell G, et al. Quality of cardiovascular disease care in Ontario, Canada: missed opportunities for prevention—a cross sectional study. *BMC Cardiovasc Disord* 2012;12:74.

7. Allan GM, Kraut R, Crawshaw A, Korownyk C, Vandermeer B, Kolber MR. Contributors to primary care guidelines. What are their professions and how many of them have conflicts of interest? *Can Fam Physician* 2015;61:52-8.

8. Lindblad AJ, Makowsky M, Allan GM. Treating to target: ready, fire, aim. *Can Fam Physician* 2014;60:541.

9. Østbye T, Yamall KS, Krause KM, Pollak KI, Gradison M, Michener JL. Is there time for management of patients with chronic diseases in primary care? *Ann Fam Med* 2005;3(3):209-14.

10. Yamall KS, Pollak KI, Østbye T, Krause KM, Michener JL. Primary care: is there enough time for prevention? *Am J Public Health* 2003;93(4):635-41.

11. Tricoci P, Allen JM, Kramer JM, Calif RM, Smith SC Jr. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA* 2009;301(8):831-41.

12. Lee DH, Vilemeyer O. Analysis of overall level of evidence behind Infectious Diseases Society of America practice guidelines. *Arch Intern Med* 2011;171(1):18-22.

13. Neuman J, Korenstein D, Ross JS, Keyhani S. Prevalence of financial conflicts of interest among panel members producing clinical practice guidelines in Canada and United States: cross sectional study. *BMJ* 2011;343:d5621.

14. Greenfield S, Steinberg EP, Auerbach A, Avorn J, Galvin R, Gibbons R, et al. *Clinical practice guidelines we can trust*. Washington, DC: Institute of Medicine; 2011. Available from: www.iom.edu/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx. Accessed 2014 Aug 15.

15. Lindblad AJ, Kolber MR, Garrison S, Cotton C, Allan GM. Simplified lipid guidelines: evidence review of 12 key clinical questions [CFPlus]. *Can Fam Physician* 2015;61:857-67.

16. Toward Optimized Practice. *Simplified lipid pathway: CVD risk in primary care. Summary of the clinical practice guideline. Lipid algorithm*. Edmonton, AB: Toward Optimized Practice; 2015. Available from: www.topalbertadoctors.org/cpgs/54252506. Accessed 2015 Aug 26.

17. Cholesterol Treatment Trialists' (CTT) Collaborators; Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;380(9841):581-90. Epub 2012 May 17.

18. Allan GM, Garrison S, McCormack J. Comparison of cardiovascular disease risk calculators. *Curr Opin Lipidol* 2014;25(4):254-65.

19. Allan GM, Nouri F, Korownyk C, Kolber MR, Vandermeer B, McCormack J. Agreement among cardiovascular risk calculators. *Circulation* 2013;127(19):1948-56. Epub 2013 Apr 10.

20. Kerr AJ, Broad J, Wells S, Riddell T, Jackson R. Should the first priority in cardiovascular risk management be those with prior cardiovascular disease? *Heart* 2009;95(2):125-9. Epub 2008 Apr 1.

21. Wilt TJ, Bloomfield HE, MacDonald R, Nelson D, Rutks I, Ho M, et al. Effectiveness of statin therapy in adults with coronary heart disease. *Arch Intern Med* 2004;164(13):1427-36.

22. Josan K, Majumdar SR, McAlister FA. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. *CMAJ* 2008;178(5):576-84.

23. Moreno-Palanco MA, Ibáñez-Sanz P, Ciriá-de Pablo C, Pizarro-Portillo A, Rodríguez-Salvanes F, Suárez-Fernández C. Impact of comprehensive and intensive treatment of risk factors concerning cardiovascular mortality in secondary prevention: MIRVAS study. *Rev Esp Cardiol* 2011;64(3):179-85. Epub 2011 Feb 16.

24. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005;142(4):233-9.

25. Mohiuddin SM, Mooss AN, Hunter CB, Grollmes TL, Cloutier DA, Hilleman DE. Intensive smoking cessation intervention reduces mortality in high-risk smokers with cardiovascular disease. *Chest* 2007;131(2):446-52.
26. Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2011;(7):CD001800.
27. Hambrecht R, Walthert C, Möbius-Winkler S, Gielen S, Linke A, Conradi K, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. *Circulation* 2004;109(11):1371-8. Epub 2004 Mar 8.
28. Eckel RH, Jakicic J, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63(25 Pt B):2960-84. Epub 2013 Nov 12. Erratum in: *J Am Coll Cardiol* 2014;63(25 Pt B):3027-8.
29. Hackam DG, Quinn RR, Ravani P, Rabi DM, Dasgupta K, Daskalopoulou SS, et al. The 2013 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol* 2013;29(5):528-42. Epub 2013 Mar 29.
30. De Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL, Monjaud I, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343(8911):1454-9. Erratum in: *Lancet* 1995;345(8951):738.
31. Singh RB, Dubnov G, Niaz MA, Ghosh S, Singh R, Rastogi SS, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. *Lancet* 2002;360(9344):1455-61.
32. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368(14):1279-90. Epub 2013 Feb 25. Erratum in: *N Engl J Med* 2014;370(9):886.
33. Braunwald E, Califf R, Cannon C, Giugliano R, McCagg A, Pelland C, et al. *Improved Reduction of Outcomes: Vytorin Efficacy International Trial* [slide presentation]. Dallas, TX: American Heart Association; 2014. Available from: http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_469669.pdf. Accessed 2014 Nov 29.
34. Law M, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol* 2006;97(8A):52C-60C. Epub 2006 Feb 3.
35. Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study: a post-hoc analysis. *Lancet* 2010;376(9756):1916-22. Epub 2010 Nov 23.
36. Turgeon R, Allan GM. Statin-induced diabetes: too sweet a deal? *Can Fam Physician* 2013;59:e311. Available from: www.cfp.ca/content/59/7/e311.full.pdf+html. Accessed 2015 Aug 19.
