2016 Guidelines for the management of dyslipidemia and the prevention of cardiovascular disease in adults by pharmacists

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Introduction

In 2007 and subsequently in 2015, the *Canadian Pharmacists Journal* published dyslipidemia guidelines tailored to pharmacists based on recommendations from the Canadian Cardiovascular Society (CCS).^{1,2} Since the latest CCS guideline iteration, numerous publications have clarified the role of widely used lipid-lowering agents and have introduced a brand-new class of agents, the proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors. Additionally, the recently published RxACT and Rx EACH trials demonstrated that pharmacist-led dyslipidemia management increased appropriate statin use and low-density lipoprotein cholesterol (LDL-C) target attainment.^{3,4} In this article, we provide an update based on the 2016 CCS guidelines⁵ and highlight key evidence supporting these recommendations. Table 1 summarizes the major changes since the previous iteration of these guidelines.

Role of the pharmacist

Traditionally, pharmacists have taken a supportive role in the management of dyslipidemia, providing patient education, drug therapy recommendations, drug interaction assessments and adverse effect and adherence monitoring.^{1,2} In 2007, pharmacists in Alberta received the ability to apply for independent prescribing authority as well as order and interpret laboratory tests.

Two trials demonstrated the value of pharmacist screening for dyslipidemia and prescribing in improving control of dyslipidemia when added to usual care.^{3,4}

In the RxACT trial, the addition of pharmacist prescribing to patients with uncontrolled dyslipidemia increased the odds of achieving lipid targets by approximately 3-fold after 6 months.³ In the Rx EACH trial of patients with high risk of cardiovascular disease (CVD), most of whom were already prescribed a statin for dyslipidemia, pharmacist prescribing increased the proportion of individuals achieving lipid targets from 46% to 56% after 3 months.⁴ This resulted from a 0.4 mmol/L (20%) LDL-C reduction in the pharmacist prescribing group, whereas LDL-C did not change in the usual care group.⁴

Based on this evidence, pharmacists should practice to the full scope of practice possible in their province in order to take an active role in the management of dyslipidemia.

Screening

The CCS guidelines recommend screening all individuals 40 years of age or older as well as all individuals with one or more predisposing factors listed in Table 2 regardless of age. Notable changes in who to screen in the CCS 2016 guidelines include (1) reducing the age to start screening women from 50 years to 40 years, which was a pragmatic adjustment for the purpose of

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TABLE 1 Summary of major changes in 2016 guidelines⁵

Screening	<p>Who</p> <ul style="list-style-type: none"> • Women should be screened starting at age ≥ 40 (<i>changed from ≥ 50</i>). • All women with a history of hypertensive disease of pregnancy should be screened. <p>How</p> <ul style="list-style-type: none"> • Lipid panel testing does not need to be performed in the fasting state, except in individuals with a history of triglyceride concentrations >4.5 mmol/L.
Cardiovascular disease risk assessment	No major change
Who to treat	<ul style="list-style-type: none"> • Changed “secondary prevention” category to 5 statin-indicated conditions • Added a category for intermediate-risk patients for whom treatment with a statin should be considered
Lipid targets	No major change
Nonstatin drugs	<p>Specific recommendations provided for role of various drugs as add-on to statin</p> <ul style="list-style-type: none"> • Consider in certain circumstances: bile-acid sequestrants, ezetimibe and proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors • Avoid combining with statin: fibrates, niacin

simplifying the recommendations, and (2) adding hypertensive disorders of pregnancy as a CVD risk factor warranting screening, based on the observations of premature onset of first vascular events (average age of 38 years for those who develop CVD) and reduced 30-year survival rates among this population compared with those who have uncomplicated pregnancies.^{6,7}

For patients who should be screened, the CCS guidelines recommend the following screening tests in addition to clinical history and physical examination: standard lipid panel (total cholesterol, LDL-C, high-density lipoprotein cholesterol [HDL-C] and triglycerides), non-HDL-C (calculated from the lipid panel as total cholesterol–HDL-C), blood glucose and estimated glomerular filtration rate (eGFR). Optional tests include urine albumin-creatinine ratio (ACR) in patients with hypertension, diabetes or eGFR <60 mL/min and apolipoprotein-B (apoB). Additionally, the CCS guidelines now recommend nonfasting lipid testing, unless patients have a history of triglycerides greater than 4.5 mmol/L (in which case LDL-C cannot be calculated by the Friedewald equation). The guideline panel based this decision on substantial new evidence demonstrating that meals minimally influence lipid levels (Table 3) and that nonfasting lipids predict long-term outcomes the same as fasting determinations.

Cardiovascular disease risk assessment

1. Pharmacists should actively engage patients in discussion of CVD risk.
2. Pharmacists should assess patients for the 5 “statin-indicated conditions,” which confer a high cardiovascular (CV) risk ($\geq 20\%$ over 10 years) and for which statins have demonstrated the largest absolute benefit, including:
 - A. Clinical atherosclerosis, history of any:
 - Coronary: myocardial infarction (MI), angina pectoris, percutaneous intervention or coronary artery bypass graft surgery
 - Cerebrovascular disease: stroke or transient ischemic attack
 - Peripheral artery disease: intermittent claudication and/or ankle-brachial index ≤ 0.90
 - Arterial revascularization
 - B. Abdominal aortic aneurysm (diameter >3 cm) or previous aneurysm surgery
 - C. Diabetes mellitus plus either age ≥ 40 years, diabetes duration >15 years and age ≥ 30 years (type 1 diabetes) or presence of microvascular disease (retinopathy, nephropathy or neuropathy)
 - D. Chronic kidney disease (CKD): eGFR <60 mL/min/1.73 m² and/or urinary

TABLE 2 CCS recommendations for who to screen and how⁵

Who	How
<ul style="list-style-type: none"> Men or women ≥ 40 years of age (or postmenopausal women) Consider screening at an earlier age for at-risk ethnic groups (e.g., First Nations, South Asians) 	<ul style="list-style-type: none"> Dyslipidemia: standard lipid panel (total cholesterol, HDL, LDL-C and triglycerides) $\pm$ apoB <ul style="list-style-type: none"> Fasting or nonfasting Non-HDL can easily be calculated from total cholesterol–HDL-C
<p>Or any of the following, regardless of age</p> <ul style="list-style-type: none"> Family history: <ul style="list-style-type: none"> Of premature CVD in a first-degree relative (females < 65 years old or males < 55 years old) Of dyslipidemia Clinical evidence of atherosclerosis, including: <ul style="list-style-type: none"> Cerebrovascular disease (stroke or transient ischemic attack) Coronary artery disease (stable angina or previous acute coronary syndrome) Peripheral artery disease (intermittent claudication and/or ankle-brachial index ≤ 0.90) Abdominal aortic aneurysm Clinical manifestations of hypercholesterolemia* Current tobacco use Chronic kidney disease (eGFR < 60 mL/min/1.73 m² and/or urinary ACR ≥ 3 mg/mmol) Chronic obstructive pulmonary disease Diabetes mellitus Erectile dysfunction HIV infection Hypertension Hypertensive diseases of pregnancy Inflammatory disease (e.g., inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis) Obesity (BMI ≥ 30 kg/m²) 	<ul style="list-style-type: none"> History and physical examination Blood pressure using proper manual technique or device approved by Hypertension Canada Fasting plasma glucose or hemoglobin A1c eGFR $\pm$ urinary ACR

ACR, albumin-to-creatinine ratio; apoB, apolipoprotein-B; BMI, body mass index; CCS, Canadian Cardiovascular Society; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol.

*Includes corneal arcus (white ring around the iris of the eye), xanthelasma (yellow papules around the eyelids), xanthoma (yellowish cholesterol deposit under skin around joints or tendons, most commonly on the hands, elbows or Achilles tendons). Examples demonstrated in Hovingh et al.¹²

ACR ≥ 3 mg/mmol for at least 3 months among patients ≥ 50 years old (CKD definition expanded and harmonized with the Kidney Disease: Improving Global Outcomes [KDIGO] recommendations⁸) not undergoing chronic dialysis

E. LDL-C ≥ 5 mmol/L or documented familial hypercholesterolemia.

3. For patients without a statin-indicated condition (so-called primary prevention patients), pharmacists should estimate a patient's long-term CV risk using a risk

calculator that incorporates validated CV risk factors (i.e., age, sex, smoking status, blood pressure, lipid profile, presence of diabetes and use of CV medications).

A. The CCS continues to recommend calculating a patient's 10-year CV risk using the modified Framingham Risk Score (FRS; versions available in the CCS guideline app for phones) or by calculating a patient's "cardiovascular age" using the Cardiovascular Life Expectancy Model (online calculator available in the CCS guideline app

TABLE 3 Summary of key new evidence

Nonfasting vs fasting lipid panel	Multiple studies found little change in lipid levels based on fasting. For example, a cross-sectional study of 209,180 Canadians found that fasting for up to 16 hours changed total cholesterol and HDL by <2%, calculated LDL-C by ≤10% and triglycerides by ≤20%. ¹³ In another study, fasting increased total cholesterol and LDL-C by ≤0.2 mmol/L, increased HDL by ≤0.1 mmol/L and reduced triglycerides by ≤0.3 mmol/L. ¹⁴ These differences are less than the variability expected from repeat testing. ¹⁵
Statins in patients with CKD	A 2012 Cochrane review evaluated use of statins in 51,099 patients with CKD, including patients enrolled in the SHARP trial. ¹⁶ This review identified no benefit in initiating statin therapy in patients with CKD already receiving dialysis. For CKD patients not receiving dialysis, statins reduced the risk of major CV events (NNT ~20), including all-cause mortality (NNT ~50), MI and stroke.
Statins in primary prevention patients at intermediate risk	The recently published HOPE-3 trial randomized 12,705 primary prevention patients with an estimated 10-year CV risk of 10% to either rosuvastatin 10 mg orally daily or placebo. ¹⁷ Patients were enrolled, regardless of LDL-C, if they met the following criteria: men ≥55 years or women ≥65 years of age plus 1 risk factor (family history of premature coronary artery disease, current/recent smoking, elevated waist circumference, low HDL, CKD or dysglycemia) or women 60-64 years plus 2 CV risk factors. At a median follow-up of 5.6 years, rosuvastatin 10 mg/d reduced LDL-C by 1 mmol/L, leading to a 24% relative risk reduction in CV death, MI or stroke (NNT 91). The proportions of patients reporting muscle pain or weakness were 5.8% with rosuvastatin and 4.7% with placebo (NNH 91).
Nonstatin lipid-lowering therapies	
Ezetimibe	The IMPROVE-IT trial randomized 18,144 stable patients hospitalized for ACS within the preceding 10 days with LDL-C 1.3-3.2 mmol/L (1.3-2.6 mmol/L if receiving lipid-lowering therapy at baseline) to treatment with either simvastatin 40 mg/d plus ezetimibe 10 mg/d or simvastatin 40 mg/d plus placebo. ¹⁸ Ezetimibe lowered LDL-C by 0.4 mmol/L more than placebo. At a median follow-up of 6 years, ezetimibe reduced the composite CV outcome (NNT 50), which was driven by a reduction in nonfatal MI and stroke. Ezetimibe did not result in any increased risk of adverse events or discontinuation.
PCSK9 inhibitors	<p>The FOURIER trial randomized 27,564 patients with CVD, LDL-C ≥1.8 mmol/L on maximum-tolerated statin therapy and additional risk factors to evolocumab or placebo.¹⁹ The study intervention was administered subcutaneously every 2 weeks (140 mg) or every 4 weeks (420 mg) based on patient preference. Evolocumab lowered LDL-C by 1.45 mmol/L (~60%) more than placebo, to a median of 0.78 mmol/L. At a median follow-up of 2.2 years, evolocumab reduced the composite CV outcome (NNT 67). As with ezetimibe, this reduction was driven by nonfatal MI and stroke, and evolocumab did not significantly reduce the risk of death. Evolocumab did not increase the risk of any adverse effects except for injection-site reactions (number needed to harm [NNH] = 200).</p> <p>The large definitive CV outcome trial for alirocumab is ongoing.</p> <p>Two smaller trials of PCSK9 inhibitors in a total of 6806 patients corroborate the findings of FOURIER.^{20,21}</p>

ACS, acute coronary syndrome; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NNH, number needed to harm; NNT, number needed to treat; PCSK9, proprotein convertase subtilisin/kexin 9.

or at <http://myhealthcheckup.com/cvd/?lang=en>.

B. Some patients, particularly primary prevention patients at intermediate

risk, may undergo coronary artery calcium (CAC) score testing. This involves a computed tomography (CT) scan of the chest to quantify

calcification of the coronary arteries, which is a marker of atherosclerotic plaque buildup. Higher CAC scores, particularly those >300 Agatston units, are associated with a greater risk of CV events (e.g., 10-year risk of myocardial infarction or cardiovascular death of ~28%).⁹ For patients with a CAC score available, practitioners can integrate the score into the patient's estimated 10-year risk of CV events using the calculator available at <https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx>.

Who should receive treatment?

1. Pharmacists should share the results of the CVD risk assessment with the patient and engage the patient in a shared decision-making process. The decision to initiate and continue drug therapy to reduce CV risk ultimately belongs to the patient. Pharmacists should ensure that patients are fully informed about their decision and that any potential misconceptions and misinformation about CV risk and available therapies have been corrected.
2. With the above point in mind, the CCS guidelines generally recommend initiating lipid-lowering therapy in:
 - A. All patients with a statin-indicated condition;
 - B. High-risk primary prevention patients (defined as an FRS 10-year risk $\geq 20\%$);
 - C. Intermediate-risk primary prevention patients (FRS 10%-19%) with LDL-C ≥ 3.5 mmol/L, non-HDL ≥ 4.3 mmol/L, apoB ≥ 1.2 g/L; or
 - D. Men age ≥ 50 or women ≥ 60 years plus 1 additional risk factor (low HDL, impaired fasting glucose, increased waist circumference, cigarette smoker or hypertension) (modified HOPE-3 criteria, see Table 3).
3. The CCS guidelines recommend *against* initiating lipid-lowering therapy in
 - A. Patients with CKD receiving dialysis
 - This recommendation applies to patients who are dialysis-dependent at the time of considering initiation of treatment; however, it is suggested that lipid-lowering therapy be continued in adults already receiving it at the time of dialysis initiation.
 - B. Low-risk (FRS <10%) primary prevention patients
 - For those with 10-year risk of 5%-9%, consider reassessing CV risk yearly.

Lipid targets

1. For all patients initiating lipid-lowering therapy, the target LDL-C is either a value <2 mmol/L or a >50% reduction from baseline
 - Consider further lowering LDL-C beyond this target in patients at very high CV risk (as achieved with addition of ezetimibe and evolocumab in the IMPROVE-IT and FOURIER trials, respectively; refer to Table 3).
2. Alternate targets include non-HDL <2.6 mmol/L or apoB <0.8 g/L.
 - These targets may be particularly useful for certain subsets of patients, such as those for whom LDL-C cannot be calculated due to triglycerides >4.5 mmol/L.

Despite the controversy regarding lipid targets summarized in the 2015 update for pharmacists,² the CCS guidelines continue to recommend treating to achieve lipid targets. Notably, most of the new evidence for nonstatin lipid-lowering therapies is based on trials with specific lipid enrolment criteria. The guideline panel concluded that there is likely a beneficial effect on CV outcomes that results from titrating statin therapy to achieve lipid targets, especially in patients with statin-indicated conditions, based on the following considerations:

- There is significant interindividual variability in the LDL-C concentrations that are achieved with statin therapy.
- The evidence from lipid parameters achieved in statin trials consistently demonstrates that lower LDL-C concentrations are associated with lower risk for CV events.
- Randomized clinical trials and meta-analyses of the statin studies demonstrate a reduction in major cardiovascular events that is directly proportional to the absolute LDL-C reduction that is achieved.

FIGURE 1 Risk assessment, stratification and treatment consideration

- Both the European Society of Cardiology (ESC) and American College of Cardiology (ACC) have recently recommended the use of lipid targets.^{10,11}

Furthermore, the CCS guideline panel members anticipated that lipid targets will provide useful guidance to clinicians in optimizing a patient's lipid-lowering therapy and might reinforce patient adherence to therapy and provide evidence of treatment efficacy.

Nonstatin lipid-lowering therapy

Statins have the most robust evidence for benefit among lipid-lowering pharmacologic agents. New evidence provides clarity on the role of nonstatin

agents, generally added to statin therapy or used in statin-intolerant individuals (Table 3).

The CCS guidelines recommend use of non-statin lipid-lowering in the following scenarios:

1. Addition of ezetimibe to maximum-tolerated statin in patients with clinical atherosclerosis who have not reached their lipid target (i.e., as second-line therapy)
2. Addition of bile-acid sequestrants in high-risk patients who remain above their lipid target despite statin ± ezetimibe (i.e., as third-line therapy)
3. PCSK9 inhibitors in patients who have not reached their lipid target on maximum-tolerated statin ± ezetimibe (i.e., as third-

and fourth-line therapy) in the following patients:

- A. Heterozygous familial hypercholesterolemia—either evolocumab or alirocumab.
- B. Homozygous familial hypercholesterolemia—evolocumab only.
- C. Clinical atherosclerosis—either evolocumab or alirocumab.

Notably, the cost (currently approximately \$8000 per year) and limited third-party insurance coverage of these agents may restrict patient access.

The CCS guidelines also recommend to:

4. Avoid the addition of a fibrate or niacin to statin therapy in patients who have reached their lipid target.

Lifestyle advice

The 2016 CCS guidelines recommend that clinicians provide the following lifestyle advice to *all* patients to reduce CV risk:

1. Encourage all users of tobacco products to quit.
2. Encourage moderate alcohol consumption.
3. Encourage moderate sleep duration (6-8 hours per night).

4. Offer advice about healthy eating and activity, such as adopting the Mediterranean diet to lower CV risk.
5. Recommend avoidance of all trans fat.
6. Recommend substitution of dietary polyunsaturated fats for saturated fats.
7. Encourage patients to moderate energy (caloric) intake to achieve and maintain a healthy body weight.

Conclusion

The 2016 CCS dyslipidemia guidelines⁵ implemented a number of changes relevant to pharmacists who provide care to this population of patients, and these have been reviewed in detail in this article. Figure 1 summarizes the risk assessment, stratification and treatment approach and provides an algorithm for the guideline-based management of dyslipidemia and prevention of CVD in adults. We encourage readers to refer to the full guidelines published in the *Canadian Journal of Cardiology*⁵ for more details, supplemental material and the evidence tables compiled for each of the PICO (patient, intervention, comparator and outcome) questions that guided the recommendations. Additionally, pharmacists may find a number of useful practice tools and educational resources related to the dyslipidemia guidelines on the CCS website (www.ccs.ca/en/guidelines/guideline-resources). ■

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