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

Glen J. Pearson, BSc, BScPhm, PharmD, FCSHP; Ann E. Thompson, BScPharm, ACPR; William Semchuk, BSP, MSc, PharmD, FCSHP

Introduction

Despite the observation that age-specific mortality rates from coronary artery disease (CAD) have declined by nearly 40% in Canada over the past several decades, this disease continues to be the leading cause of death and morbidity for Canadians.[1] Hyperlipidemia (especially an elevated low-density lipoprotein cholesterol [LDL-C] level and/or elevated total cholesterol to high-density lipoprotein cholesterol [TC:HDL-C] ratio) is recognized as a major independent risk factor for CAD. Recently, the large international case-controlled INTERHEART study demonstrated that an abnormal lipid profile was the most important modifiable risk factor associated with myocardial infarction.[2] Consequently, national guidelines have been promulgated and regularly updated on the basis of accumulating clinical trial evidence to assist health care practitioners with diagnosis and treatment of patients with dyslipidemia. In Canada, these guidelines were updated and published in September 2006.[1]

Given advancements in pharmacy practice and current expectation that pharmacists take a more active role in and responsibility for medication management and patient health outcomes, pharmacists should be taking steps to identify and collaboratively manage patients with dyslipidemia. To emphasize where the knowledge and skills of pharmacists should be applied in the management of patients with dyslipidemia, the 2006 Canadian Cardiovascular Society [CCS] position statement (Recommendations for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease[1]) has been adapted and expanded. These Canadian pharmacist practice guidelines are a part of the continuing national effort to recognize and advance "the responsible and patient-centred role of the pharmacist"[3] in chronic disease management.

As key players in the health care system, pharmacists should use their knowledge, skills, and relationship with patients to improve the management of dyslipidemia and prevent cardiovascular disease. Consequently, these guidelines emphasize the role of the pharmacist in all aspects of managing the disease:

- Identification and screening of patients
- Individual cardiovascular (CV) risk assessment
- Establishing appropriate lipid targets, based on CV risk
- Lifestyle modification
- Recommending and monitoring appropriate drug treatment
- Ensuring patient adherence with treatment
- Specialty clinic referral

Readers interested in more detail or background on any of the above should refer to the full recommendations.[1]

Websites
UKPDS Risk Engine (www.dtu.ox.ac.uk/riskengine)
Framingham Risk Score (www.nhlbi.nih.gov/about/framingham/index.html)
Cardiovascular Life Expectancy Model (www.myhealthcheckup.com)

Identification and screening of patients with dyslipidemia and/or increased cardiovascular risk

1. As accessible community-based practitioners, pharmacists should actively recommend dyslipidemia screening, by a qualified health professional, with a complete fasting lipid profile every 1 to 3 years for the following patients:
   - All men ≥40 years old
   - All women ≥50 years old or postmenopausal

This information was originally published in and/or adapted from The Canadian Journal of Cardiology *2006;22:913-27.*

2. Pharmacists should actively identify and recommend dyslipidemia screening, by a qualified health professional, with a complete fasting lipid profile for patients of any age with:
   - Diabetes mellitus (DM)
   - Current or recent (within last year) cigarette smoking
   - Hypertension
   - Abdominal obesity
   - Waist circumference >102 cm in men and >88 cm in women (lower cutoffs are appropriate for South and East Asians)
   - Family history of premature CAD, especially first-degree relatives: men <55 years and women <65 years
   - Stigmata of hyperlipidemia (e.g., xanthelasma, xanthoma, corneal arcus)
   - Exertional chest discomfort, dyspnea, erectile dysfunction, claudication, chronic kidney disease
   - Evidence of atherosclerosis (CAD, cerebrovascular disease, or peripheral arterial disease [PAD])

Cardiovascular risk assessment

1. Take appropriate steps to risk-stratify patients in order to guide treatment recommendations and set targets for lipid-lowering (Table 1).
2. Automatically consider the following patients to be at high-risk (≥20% 10-year risk of CAD-death or non-fatal myocardial infarction [MI]) for cardiovascular events:
   - Patients with evidence of atherosclerotic vascular disease, such as CAD, cerebrovascular disease or PAD
   - Most patients with DM (type 1 or 2) — exceptions would include younger adults with type 1 or 2 DM with shorter duration of disease and without complications of DM (including established cerebrovascular disease) and without other cerebrovascular disease risk factors, for whom vascular risk should be calculated (UKPDS risk engine appropriate)[4]
   - Patients with chronic kidney disease (glomerular filtration rate ≤30 mL/min/1.73 m^2)
3. For all other primary prevention patients, calculate their 10-year risk estimate for CAD-death or non-fatal MI according to the Framingham Risk Score (FRS).
4. For patients with a family history of CAD in a first-degree relative before the age of 55 years in a male or 65 years in a female, the calculated 10-year CAD risk should be multiplied by a factor of 2.0.
5. For the purpose of evaluating the overall benefit of dyslipidemia treatment or other risk factor modification, consider use of the Cardiovascular Life Expectancy Model.

TABLE 1 Cardiovascular risk categories and lipid targets

Risk level	10-year CAD risk	Recommendations	Grade, level of evidence*
High†	≥20%	Treatment target Primary target: LDL-C <2.0 mmol/L	 Class I, Level A
		Secondary target: TC/HDL-C <4.0	 Class IIa, Level A
Moderate	10%–19%	Treat when: TC/HDL-C ≥5.0 *or* LDL-C ≥3.5 mmol/L	 Class I, Level A Class I, Level A
Low	<10%	Treat when: TC/HDL-C ≥6.0 *or* LDL-C ≥5.0 mmol/L	 Class IIa, Level A Class IIa, Level A

*Evidence grading criteria: Class I = evidence and/or general agreement that a given diagnostic procedure or treatment is beneficial, useful, and effective; Class IIa = conflicting evidence and/or divergence of opinion about the usefulness and/or efficacy of the treatment; weight of evidence in favor; Level A = data from multiple randomized controlled trials or meta-analyses.[1]
†High risk includes coronary artery disease, cerebrovascular disease, peripheral arterial disease, and most patients with diabetes.

Pharmacist recommendations for lipid targets

1. Recommend to patients and providers that patients identified as *high risk* (those with established atherosclerotic vascular disease, diabetes mellitus, chronic kidney disease, or a calculated 10-year risk of CAD-death or non-fatal MI of ≥20% by FRS) achieve an LDL-C <2.0 mmol/L (primary target) and TC/HDL-C <4.0 (secondary target).
2. Recommend to patients and providers that patients identified as *moderate risk* (a calculated 10-year risk of CAD-death or non-fatal MI of 10%–19% by FRS) be treated when the LDL-C ≥3.5 mmol/L or TC/HDL-C ≥5.0.
3. Recommend to patients and providers that patients identified as *low risk* (a calculated 10-year risk of CAD-death or non-fatal MI of <10% by FRS) be treated when the LDL-C ≥5.0 mmol/L or TC/HDL-C ≥6.0.

Pharmacist recommendations for lifestyle changes to control dyslipidemia and cardiovascular risk

1. Encourage all patients with dyslipidemia and/or increased cardiovascular risk to adopt a healthy lifestyle to lower their risk of CAD as follows:
   - Refrain from smoking
   - Adopt healthy eating habits consistent with Canada's Food Guide:
     - Limit intake of simple sugars, refined carbohydrates, saturated and trans fatty acids
     - Emphasize a diet rich in vegetables, fruit, whole grain cereals, poly- and monounsaturated oils, including omega-3 fatty acids
   - Achieve and maintain a healthy weight

Monitoring of cholesterol-lowering therapies

It is important to be aware that cholesterol-lowering therapies are generally well tolerated and this point should be emphasized to patients. Drug therapy monitoring pertains to both efficacy and safety. It is essential to ensure that cholesterol targets are achieved with the therapeutic regimen prescribed while avoiding or minimizing known toxicities, which requires access to the patient's laboratory values.

Monitoring for potential or real toxicities requires that the pharmacist take a thorough medication history and an evaluation of patient-specific laboratory data may provide further evidence to support any adverse drug reaction. Not all adverse reactions or intolerances will be confirmed by laboratory data. Careful consideration of the clinical scenario, patient factors and the temporal relationship between the drug and the adverse reaction should dictate the correct course of action.

Since other medical conditions, such as hypothyroidism or a rheumatologic condition, can cause myotoxicity, it is important to consider these and recommend appropriate baseline monitoring to include or exclude these possibilities.[5] Table 2 expands on known toxicities, while Tables 3 and 4 provide a guide for determining appropriate baseline monitoring parameters as well as follow-up laboratory monitoring for the various lipid-lowering agents.

TABLE 2 Toxicities reported with lipid-lowering therapies

Myotoxicity[5,6]	Hepatotoxicity[5,8,9]
• Divided into myopathy (muscle aches or weakness without CK rise), myositis (muscle symptoms with ↑CK levels), and rhabdomyolysis (see below). • Myopathy and myositis are bothersome but benign conditions; no long-term damage. • Usually involves symptoms although can be asymptomatic. • Class effect and tends to be dose-related; more potent agents at lower doses may be effective at minimizing occurrence. • Characteristics that increase risk of development include advanced age, female gender, small body frame, renal insufficiency, diabetes, hypothyroidism and drug interactions such as combination lipid-lowering therapy, or statins prescribed with agents that influence their metabolism, such as erythromycin, cyclosporine and fluconazole. • TSH should be monitored at baseline because it is known that hypothyroidism may cause myopathy, and this secondary cause needs to be ruled out. • There is insufficient evidence to prove that co-enzyme Q reduces the incidence of statin-induced myopathy. Fortunately, there are no known risks associated with co-enzyme Q, and some anecdotal reports demonstrate it may be effective for reducing statin-induced myopathy.[7]	• Occurs in <1% of patients, approximately 1 per million person-years of use. • Statins and fibrates are not recommended in patients with active liver disease or unexplained persistent increases in liver enzymes (ALT/AST); however, in patients with fatty liver disease (nonalcoholic; obesity-related), the associated elevation in liver enzymes may improve with treatment of the underlying dyslipidemia. • Statin-induced increases in ALT levels are generally dose-related. • ALT is more specific in identifying liver injury; AST is more nonspecific, and located in cardiac and muscle tissue. If AST is elevated without ALT elevation, cardiac or muscle injury is more likely.[10] ALT is the important parameter to monitor. • Statins specifically do not need to be avoided in patients with chronic liver disease. There is no evidence to suggest that drug-induced liver injury is increased with their use; however, using low doses is recommended when initiating therapy. • Liver damage or failure is not well predicted by routine monitoring of AST/ALT, according to Expert Panel of National Lipid Association[8]; instead, they recommend, if liver damage is suspected, a bilirubin should be ordered and assessed. Product monographs for individual statins, fibrates and niacin still advocate annual monitoring.
Rhabdomyolysis[5,6]	
• Very rare; not predicted by the development of myopathy. • Associated with severe and progressive muscle aches, weakness and pain (as a result of muscle breakdown) accompanied by large ↑CK (>10x the upper limit of normal) *and* marked serum creatinine elevation (as evidenced by yellow-brown urine and myoglobin in the urine) leading to renal failure.	

CK = creatine kinase; TSH = thyroid-stimulating hormone; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Medication adherence

Nonadherence to cholesterol-lowering therapies is a significant problem. In 2001, Tsuyuki and Bungard reviewed the literature and reported that although discontinuation rates within clinical trials and lipid clinics are low, at approximately 2%–38% over 1 to 5 years, nonadherence rates in nonselected populations are much higher, at up to 78% at 1 year.[13] More recently, continued poor adherence rates have been noted in 2 Canadian cohorts.[14,15] Adherence rates in Ontario seniors were reported to range between 25.4% in primary prevention and 40.1% following an acute coronary syndrome event.[14] In another study, 1- and 5-year adherence rates to statins following a first cardiovascular event were reported to be 60.3% and 48.8% within the Saskatchewan Prescription Drug Database.[15] It has also been shown in a cohort of myocardial infarction patients that medication discontinuation is independently associated with increased mortality rates (HR 3.81; 95% CI 1.88-7.72).[16] Rasmussen et al. demonstrated that individuals who were classified as low adherers (to statins) were 1.25 times as likely to die following a myocardial infarction compared to high adherers.[17]

Recently, 2 clinical trials have demonstrated the significant impact of pharmacist intervention in adherence. Wu et al. established that periodic telephone counselling by pharmacists significantly decreased total mortality in a group of 502 patients receiving 5 or more drugs for chronic disease.[18] In this 2-year randomized trial, patients allocated to the intervention group received a 10–15 minute telephone call from a pharmacist at the midpoint between clinic visits throughout the study period. The pharmacist asked about the patient's treatment regimens; clarified any misconceptions; explained the nature of any side effects; reminded patients of their next clinic appointment; and reinforced the importance of compliance with treatment and relevant aspects of self-care, such as diet, exercise, and self-monitoring. At the end of the 2-year follow-up, patients in the intervention group had received 6 to 8 telephone calls from the pharmacist and mortality was 11% in the intervention group vs 17% in the controlled group.[18]

Subsequently, the FAME study (Federal Study of Adherence to Medication in the Elderly) demonstrated that a comprehensive pharmacy program led to substantial improvements in adherence among elderly patients receiving complex medical regimens, and that improving adherence can result in better health outcomes. This trial included 200 patients with an average age of 78 years who were prescribed 4 or more daily medications for multiple chronic conditions. Patients received education and oral instructions from pharmacists and individual blister packs of their medications. Patients met every 2 months with a pharmacist. Adherence rates increased from 61% to 97% after 6 months. Improvements were seen in multiple physiologic parameters, including blood pressure and cholesterol.[19]

  - Waist circumference: optimally <94 cm for men and <80 cm for women
  - Lower cutoffs are appropriate for South and East Asian males (<90 cm)
  - BMI <27 kg/m^2 as a minimum goal and optimally, <25 kg/m^2
- Engage in regular physical activity
  - 60 minutes of light, 30–60 minutes of moderate or 20–30 minutes of vigorous activity 4 to 7 days/week

2. Collaborate and, where appropriate, refer patients to other health professionals (smoking cessation counsellors, dieticians, exercise physiologists, etc.) to assist them in adopting a healthy lifestyle to lower their risk of CAD.

Pharmacist recommendations for treatment in patients with dyslipidemia and cardiovascular risk factors

1. Recommend that appropriate drug treatment be started immediately, concomitant with diet and therapeutic lifestyle changes, in all high-risk patients to achieve both primary

TABLE 3 Baseline monitoring recommended before initiating lipid-lowering therapy

- Fasting lipid profile to determine target(s)
- TSH to rule out underlying hypothyroidism
- AST/ALT to assess baseline levels
- Serum creatinine to evaluate renal function
- CK for baseline comparison if possible future myotoxicity*
- Fasting glucose to assess for diabetes mellitus
- Uric acid†

Suggested follow-up laboratory monitoring

6–8 weeks
- Fasting lipid profile to determine if target has been achieved; modify therapy if needed
- AST/ALT, especially if on combination therapy

Annual
- Fasting lipid profile to ensure target(s) maintained
- AST/ALT, especially if receiving combination lipid-lowering therapy

TSH = thyroid-stimulating hormone; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CK = creatine kinase.
*Baseline CK is not absolutely necessary,[5] but should elevations occur after therapy is commenced, it helps to determine if increase is secondary to statin or was present initially with no change after initiation of therapy.
†Uric acid elevations occur as dose of niacin increased; avoid in patients who had recent gout attack and are not on uric-acid-lowering therapy.[11]

and secondary lipid targets (LDL-C ≤2.0 mmol/L and TC/HDL-C ≤4.0).
2. For high-risk patients with established atherosclerosis, recommend drug therapy to lower LDL-C by at least 50%.
3. Recommend a statin as initial therapy for most patients for achievement of target LDL-C concentrations. Where necessary, a cholesterol absorption inhibitor (ezetimibe) or a bile acid sequestrant (cholestyramine or colestipol) should be combined with the statin to achieve the LDL-C target.
4. Among low- and moderate-risk patients who are candidates for treatment, recommend drug therapy to lower LDL-C by at least 40%.
5. Once LDL-C targets have been achieved, recommend one of the following approaches for achievement of the TC/HDL-C ratio target:
   - For patients with ↑TGs (triglycerides), intensify dietary therapy and exercise, with a focus on weight loss, restriction of refined carbohydrates and alcohol and increased intake of omega-3 fatty acids
   - For patients with ↓HDL-C, increased aerobic exercise, increased intake of monounsaturated fats, moderate alcohol intake (if TGs are not significantly elevated), weight loss and smoking cessation are beneficial
   - For patients with ↓HDL-C or mild ↑TGs, a further increase in statin dose may achieve the TC/HDL-C ratio target, even if the LDL-C target has been reached
   - For patients with combined dyslipidemia and ↓HDL-C, the combination of a statin with niacin or a fibrate should be considered
6. Whenever drug therapy is recommended, suggest appropriate laboratory testing (or order the labs where they are permitted) and ensure that the patient receives ongoing monitoring for the efficacy and safety of the drug regimen.

Pharmacist-recommended adherence strategies for patients

Pharmacists have a major role to play in encouraging patients to take their lipid-lowering medications in order to achieve the full benefit of cardiovascular risk reduction and protection. Consequently, pharmacists should:

- Educate patients about the benefits of drug therapy in real terms, the relative safety of the agent selected and indicate that the most common outcome for a patient is reduction of cholesterol and risk for CAD events without side effects.
- Work with patients to simplify medication and dosing regimens.
- Use adherence aids such as blister packaging, as well as educating elderly patients about multiple medications.
- Participate in the education of patients and their families about dyslipidemia, vascular disease and their treatment regimen.
- Assess adherence to both pharmacologic and nonpharmaco-

TABLE 4 Monitoring of various lipid-lowering drugs*

Parameter	Lipid-lowering therapies in which parameters should be monitored	Signs and symptoms that may accompany parameter	Drug-drug combinations that ↑ likelihood of adverse event
AST/ALT	Statins Fibrates Niacin IR and SR Ezetimibe	Abdominal pain, jaundice, dark urine, malaise, fatigue	Statin + fibrate† Statin + ezetimibe Statin + niacin
CK	Statins Ezetimibe[12]	Muscle aches, pains, cramps, weakness, absent reflexes, fatigue	Statin + ezetimibe Statin + fibrate Statin + niacin
Glucose	Niacin IR and SR	Asymptomatic	
Uric acid	Niacin IR and SR	Asymptomatic; may develop gout	
TSH	Statins Niacin IR and SR	Muscle aches, pains, cramps, weakness, fatigue	
Gastrointestinal upset	Bile acid resins Fibrates Statins Niacin	Abdominal bloating/pain, belching, flatulence, nausea, constipation, GERD	

AST = aspartate aminotransferase; ALT = alanine aminotransferase; CK = creatine kinase; TSH = thyroid-stimulating hormone; GERD = gastroesophageal reflux disease.
*The bile acid sequestrants (e.g., cholestyramine) do not require laboratory monitoring.
†Gemfibrozil appears to confer a greater risk when used in combination with statins compared to bezafibrate or fenofibrate.

logic lipid-lowering therapy at each visit.
• Contact patients if they appear to be neglecting to renew prescriptions, in order to assess reasons for discontinuing therapy and encourage patients about the benefit of long-term therapy.
• Encourage patients to fit medication-taking into their daily routine.

Specialty clinic referrals

Collaborate with other health professionals and encourage or recommend the referral of appropriate patients, such as those with extremes of lipoprotein disorders or a lack of response to conventional therapies, to specialized, tertiary-care, lipid or cardiovascular risk reduction clinics. ■

From the Division of Cardiology, University of Alberta (Pearson) and Capital Health Regional Pharmacy Services (Thompson), Edmonton, Alberta; and the Regina Qu'Appelle Health Region (Semchuk). Contact Glen.Pearson@ualberta.ca.

This document has been endorsed by the following groups:

The Canadian Cardiovascular Society (CCS) recognizes the importance of this project and its objectives as it relates to cardiovascular health and care. However, the content has not been peer reviewed by the Society and does not necessarily represent the views of the CCS.

The Canadian College of Clinical Pharmacy (CCCP) acknowledges the expanding role of pharmacists and realizes the importance of screening patients at risk for cardiovascular disease as well as the need for monitoring therapy. The Dyslipidemia Guidelines for Pharmacists provide useful and specific information to assist pharmacists in fulfilling this role. While CCCP recognizes that any therapeutic area may be controversial and we encourage a healthy evidence-based debate regarding recommendations, we believe that the guidelines are in alignment with the mission and objectives of CCCP (to advance patient health by supporting and enhancing direct patient care practice), and CCCP endorses this initiative.

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