

In the Know: Canadian Guidelines for Dyslipidemia, 2003

In his reviews of Canadian dyslipidemia guidelines, Dr. Curnew explores the impact of major trials, the assessment and categories of risk, and both pharmacologic and non-pharmacologic treatment options.

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The management of hyperlipidemia continues to evolve. In order to keep pace, clinical guidelines require ongoing reassessment in response to new information and challenges.

Obesity, of which 31% of Canadian adults suffer, is associated with an increased prevalence of diabetes, hypertension, and cardiovascular disease (CVD). Furthermore, with obesity prevalence rates reaching epidemic proportions, the incidence of Type 2 diabetes has also increased; Type 2 diabetes is a major risk factor for coronary artery disease.

New clinical trials (MIRACL, VA-HIT, and the Heart Protection Study) form the basis upon which indications for drug therapy are determined. These new dyslipidemia guidelines attempt to harmonize cardiovascular risk assessment across North America using these studies, along with the Framingham study equations published in the National Cholesterol Education Program Adult Treatment Panel III (ATP-III).

How is risk assessed?

The NCEP ATP-III risk estimation algorithm will be used to harmonize risk assessment across North America. The Canadian Diabetes Association stipulates one additional categorical risk factor (*e.g.*, over age 40, hypertension, smoking, or total cholesterol/high-density lipoprotein cholesterol [TC/HDL-C] > 5.0) is required to categorize diabetes as a CAD equivalent. The panel agrees that while a young, diet-controlled patient

Table 1

Groups for which screening is indicated

- Healthy men over age 40 and women over 50 should have a full lipid profile done every 5 years to ensure they remain at low risk.
- Diabetes patients, especially those over 30, are now recognized to be at an extremely high risk. Patients with Type 2 diabetes, who are apparently healthy and over 50, have a 5% yearly vascular risk. All diabetes patients over 30 should be screened yearly and have their lipids treated more aggressively.
- Patients with genetic dyslipidemias or manifestations of hyperlipidemia (*e.g.*, xanthelasma, xanthoma, arcus, or extremely positive family history) should be screened at an earlier age, depending on clinical judgment.
- Patients with vascular disease (*e.g.*, carotid, peripheral and coronary atherosclerosis) should be screened annually and treated for aggressive lipid management control.
- Patients of any age may be screened at the physician's discretion, particularly where lifestyle changes are indicated.

with diabetes may have a relatively low 10-year risk estimate, long-term risk remains very high and should be considered in making treatment decisions.

Who should be screened?

Table 1 outlines patients who should be screened for hyperlipidemia.

Table 2

Risk categories and target levels

Risk category	10-year risk estimate of CVD	LDL-C* (mmol/L)	TC/HDL-C ratio
High**	≥ 20% Diabetes Atherosclerotic disease	< 2.5	< 4.0
Moderate	10% to 20%	< 3.5	< 5.0
Low	≤ 10%	< 4.5	< 6.0

* apo B may be used as an alternative risk measurement, particularly for followup of patients on statins.

** An optimal level of apo B in a high-risk patient is < 0.9 g/L.

CVD: Cardiovascular disease

LDL-C: Low-density lipoprotein cholesterol

TC/HDL-C: Total cholesterol/high-density lipoprotein cholesterol

Risk categories

Three categories of risk are recognized (Table 2). High-risk patients include those with established CAD, cerebrovascular disease, and peripheral arterial disease; adult diabetics; and asymptomatic patients in whom the 10-year risk of cardiovascular death or non-fatal myocardial infarction (MI) is > 20%. Those with moderate risk include individuals with a > 10-year risk < 20%. Treatment may be deferred if the 10-year risk estimate of coronary heart disease (CHD) is < 5% and low-density lipoprotein cholesterol (LDL-C) is < 5.0 mmol/L. This avoids the over-treatment of patients at very low overall cardiovascular risk.

What is the impact of the new trials?

Heart Protection Study

The Heart Protection Study was a landmark study involving 20,556 subjects aged 40 to 80 with total cholesterol > 3.5 mmol/L. Two major criteria were pivotal for patient selection:

- physicians believed the patient was at high-risk of future vascular insults (e.g., CHD, MI, peripheral vascular disease, CVD, Type 2 diabetes, and/or hypertension);
- physicians were unclear of the benefit of lipid intervention, (e.g., patients with established vascular disease and very low cholesterol values, the elderly, and healthy diabetes patients).

The major finding was that the use of simvastatin, 40 mg/day, decreased mortality by 13% and reduced all cardiovascular endpoints by 24%, regardless of starting cholesterol level.

Predefined subgroup analysis showed a benefit in men and women, young and old, patients with or without established disease, and extending across all ranges of total or LDL-C.

In light of these findings, the Canadian guidelines now suggest high-risk individuals be treated with the equivalent of simvastatin, 40 mg/day, and that the minimum target of therapy be an LDL-C of 2.5 mmol/L and a total cholesterol/high-density lipoprotein-C ratio < 4.0.

Controversy still exists as to the optimal level of LDL-C in high-risk subjects and large clinical trials are underway examining “how low to go” in high-risk individuals. Personally, I now treat high-risk patients with a higher-dose statin. In time, I foresee we will be treating lipid status more aggressively. We will be aiming for lower LDL values and treat-

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ing more broadly, with a focus on other lipid parameters (*i.e.*, high-density lipoprotein [HDL] and triglycerides [TG]). I also believe we will be using more combination lipid-lowering agents.

MIRACL trial

The MIRACL trial compared atorvastatin, 80 mg/day, to best treatment and angioplasty in patients with stable CAD. A 16% reduction in cardiovascular events was noted, with the benefit being attributable to hospitalization for recurrent angina. The MIRACL trial showed that high-dose atorvastatin is safe and may acutely reduce cardiovascular events.

VA-HIT

The Veterans Administration HDL intervention Trial (VA-HIT) examined patients with established CAD, normal LDL-C, and reduced HDL-C (1.0 mmol/L). The use of gemfibrozil, 1,200 mg/day, was associated with a 22% decrease in recurrent coronary events without lowering LDL-C.

DAIS

The Diabetes Atherosclerosis Intervention Study (DAIS), a small angiographic trial of fenofibrate in patients with diabetes and dyslipidemia, reported a reduction in clinical endpoints, although the study was not powered to evaluate clinical events.

HATS

The Hyperlipidemia Atherosclerosis Treatment Study (HATS), an angiographic trial of low dose simvastatin (10 mg/day to 20 mg/day) plus niacin (1,500 mg/day), with or without antioxidant vitamins or placebo, found angiographic improvement of CAD and a 90% reduction in major cardiovascular events. While HATS is only a small trial of just over 150 patients, the findings suggest a broader approach to lipid management with attention to all lipid parameters, including LDL, TG, and HDL.

Table 3

Current lipid-lowering medications

Drug	Recommended dose
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Statins

Atorvastatin	10 mg to 80 mg
Fluvastatin	20 mg to 80 mg
Lovastatin	20 mg to 80 mg
Pravastatin	10 mg to 40 mg
Rosuvastatin	10 mg to 40 mg
Simvastatin	5 mg to 80 mg

Bile acid and/or Cholesterol Absorption inhibitors

Cholestyramine	2 g to 24 g
Colestipol	5 g to 30 g
Colesevelam	3.8 g to 4.5 g
Ezetimibe	10 mg

Fibrates*

Bezafibrate	400 mg
Fenofibrate	67 mg to 200 mg
Gemfibrozil	600 mg to 1,200 mg

Niacin†

Nicotinic acid	1 g to 3 g
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* Avoid in patients with renal insufficiency

† Use with caution in patients with diabetes or glucose intolerance. Do not use Gemfibrozil in combination with statins.

How is dyslipidemia treated?

What's the role of lifestyle and diet?

Significant improvement in dietary composition over the past four decades, in particular decreases in saturated fat and cholesterol intake, have been partially offset by a continuing increase in the prevalence of obesity. Dietary changes should be part of a larger strategy of lifestyle modifications aimed at increasing exercise, fruit and vegetable intake, and the proportion of monosaturated and polyunsaturated fats in the diet. Emphasis should be placed on decreasing caloric consumption, in particular by reduction of refined carbohydrates and sugar, to achieve and maintain a body mass index < 27.

I feel lifestyle and diet considerations have been underemphasized in this report. While I believe most patients at high risk should start lipid management immediately upon hospital discharge, patients at low risk can wait six months, trying lifestyle changes first.

Lifestyle changes and pharmacologic therapy are complimentary; dietary advice lowers cholesterol by an average of 5%. However, a high-fat diet has been clearly demonstrated to promote vasoconstriction.

The Lyon Diet Heart Trial Study reported a one-to two-third reduction in future cardiovascular events on a healthy diet of fruits, vegetables, and high fibre. In short, diet should be viewed as the foundation to good health. Furthermore, people who exercise regularly have a 25 % reduction in fatal heart attacks following a first MI.

Medication

Target lipid levels

Table 3 lists currently available lipid-lowering agents and corresponding doses. In high-risk individuals, treatment should be started immediately, concomitant with diet and therapeutic lifestyle changes. The priority for treatment is a reduction of LDL-C to < 2.5 mmol/L and TC/HDL-C to < 4.0. My focus is on the LDL cholesterol.

Dietary advice lowers cholesterol by an average 5%.

The majority of patients, including those with the metabolic syndrome, Type 2 diabetes, and combined dyslipidemia, will be able to achieve target levels for LDL-C on statin monotherapy. However, a significant minority of patients will require combination therapy with a bile acid sequestrant (*e.g.*, cholestyramine) or an agent which inhibits cholesterol absorption (*e.g.*, ezetimibe). These combinations are safe and can decrease LDL-C by an additional 10% to 20%, or even 30% in a motivated patient with an aggressive dietary approach.

Elevated triglycerides

Ideally, epidemiologic evidence suggests TG should be < 1.7 mmol/L. Current recommendations call for implementing and maintaining lifestyle changes rather than attempting to lower TG by pharmacologic means. Achievement of a target TC/HDL-C ratio generally entails the modification of elevated TG levels. However, severe hypertriglyceridemia poses a significant risk of pancreatitis for patients on optimal lifestyle therapy with TG > 6 mmol/L. Available options include a fibrate, niacin, or salmon oil supplementation.

When should I refer?

Physicians are often confronted with difficult cases, unexplained atherosclerosis, extremes of lipoprotein disorders, or a lack of response to conventional therapies. In such cases, referral to a specialized centre may be warranted.

What does it all mean?

Both the Canadian and American recommendations are a step in the right direction. While there are more agreements between the two recommendations than ever before, some differences still exist in the suggested management of hyperlipidemia.

Most notably, while the Americans recommend screening cholesterol earlier in life (age 20), Canadians wait until later in life, due to data on cost-efficiency. Although it is clear that heart disease starts early, it is difficult to know the best time to intervene with drug therapy. I aim for lifestyle changes earlier in life; adding drug therapy is important as the level of risk increases.

While both countries use Framingham data to predict a 10-year vascular risk, the Americans place a stronger emphasis on lifestyle change. Although the Framingham scale has its limitations, I think it's very reasonable and probably the best way to screen and treat levels of risk.

One should not treat cholesterol in isolation, but treat the total burden of risk factors. It is

remarkable that lipid-lowering agents can decrease cardiovascular events by 33%, possibly more considering there are 200 associated factors that can potentially damage arteries.

While we do not know the most effective statin, the targets recommended by the Canadian consensus are very reasonable. Debate on this topic will always exist, but the reality is that the vast majority of high-risk patients are poorly treated in Canada. This must change, as both the financial and mortal burden of atherosclerosis are increasing.

What's new?

Since the publication of the Canadian guidelines, new information has emerged. Aggressive treatment with statin drugs is intended to drive cholesterol far below current standards, prevent new vascular problems, and save lives. These drugs are already a cornerstone of cardiac care, routinely prescribed for high risk patients, including those with:

- established past disease,
- diabetes with another risk factor, and
- those with multiple cardiac risk factors.

However, new results of randomized, controlled trials suggest doctors and patients should opt for higher doses of cholesterol medications aiming for LDL cholesterol close to 1.5 mmol/L below the target LDL of 2.5 mmol/L set by both the Canadian and American guidelines.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study suggests lowering LDL cholesterol levels substantially below current target levels in acute coronary syndrome (ACS) patients is beneficial.

The second trial, PROVE-IT – TIMI 22, was designed to show that standard lipid-lowering with an LDL target of 2.5 mmol/L would be just as beneficial as intensive LDL-lowering to 1.6 mmol/L with high-dose atorvastatin. Some 4,162 patients hospitalized for ACS within the previous 10 days

were randomized to either the pravastatin or the atorvastatin management protocols. The study proved just the opposite. Intense atorvastatin treatment significantly reduced the primary composite endpoint of:

- risk of death,
- myocardial infarction (MI),
- unstable angina,
- stroke, and
- revascularization in ACS patients (by an additional 16%).

With pravastatin, patients reached a median LDL level of 2.46 mmol/L while the atorvastatin patients' LDL levels dropped to 1.60 mmol/L for two years. There was a 16% reduction in the hazard ratio with atorvastatin compared to pravastatin. Death due to coronary heart disease, MI, or urgent revascularization decreased by 25% in the atorvastatin group.

Benefits were especially marked in patients whose baseline LDLs were > 125 mg/dL. This group saw a 34% decrease in the hazard ratio. Adverse effects were minor in both trials and with both treatments.

Patients had to have a total cholesterol level of < 240 mg/dL, measured within the first 24 hours after ACS onset. Patients receiving long-term statin therapy at the time of their index ACS onset were included in the study if total cholesterol measured at screening was < 200 mg/dL. Most patients were concomitantly administered aspirin (93%), beta blockers (85%), clopidogrel/ticlopidine (72%), and angiotensin-converting enzyme (ACE) inhibitors (69%) during treatment.

The benefit of atorvastatin compared with pravastatin emerged as early as 30 days into the trial and was consistent over time. These data suggest this population with ACS, who have a culprit lesion and often additional vulnerable plaques, can derive particular benefit from early and intensive lipid-lowering with statins.

Table 4

Primary composite endpoint

Primary endpoint	Pravastatin 40 mg (n=1973)	Atorvastatin 80 mg (n=2003)	Relative risk reduction (%)
All-cause mortality/MI/unstable angina/revascularization (PCI or CABG)/stroke	26.3	22.4	16

MI: Myocardial Infarction
 PCI: Prophylactic cranial irradiation
 CABG: Coronary artery bypass grafting

ALLIANCE

A second trial, the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) study, was undertaken to assess whether aggressive, LDL cholesterol lowering (with titrated doses of atorvastatin in patients with CHD) reduces cardiovascular complications compared with patients receiving usual care. A total 2,442 hyperlipidemic patients with CHD from managed-care organizations or veterans affairs hospitals were randomized to an aggressive, focused-care program of atorvastatin (10 mg/day to 80 mg/day), or usual care of a lipid treatment program prescribed by patients' primary care physicians (and could include diet, behaviour modification, and antihyperlipidemic medication).

In the focused-care group, atorvastatin was titrated to achieve an LDL cholesterol < 2.00 mmol/L, or a maximum dosage of 80 mg/day. The mean dosage of atorvastatin achieved in the study was 40.5 mg/day. Eligible patients had a history of CHD, defined as an acute MI > 3 months before screening, a percutaneous coronary intervention > 6 months before screening, or coronary artery bypass graft surgery > 3 months before screening.

The percentage of patients reaching the pri-

mary endpoint (the composite of cardiac death, MI, stroke, and hospitalization) was reduced by 17% among atorvastatin recipients at a mean 52 months after randomization. There were 333 total events in the usual care group vs. 289 events in the group receiving atorvastatin.

The risk of non-fatal MI was reduced by 47% in the atorvastatin-treated patients compared with the usual care group. The rates of serious adverse events were the same in each treatment group.

ALLIANCE demonstrated incremental clinical benefit with aggressive LDL cholesterol lowering without safety concerns in patients with CHD.

***L*ipid-lowering agents can decrease cardiovascular events by 33%.**

Physician comments

Lower is better, at least for LDL. PROVE-IT is the first of a series of landmark trials that has already changed my practice of lipid management in high-risk patients. Over 4,000 patients were hospitalized for ACS; with pravastatin, patients reached a median LDL level of 2.5 mmol/L. While using a more potent statin such as atorvastatin, LDL levels dropped to 1.60 mmol/L and provided an additional 16% reduction in future vascular events. My target LDL in very high-risk patients is 1.5 mmol/L.

Safety

Muscle toxicity may manifest as the following:

- Myositis (elevated creatinine kinase [CK] levels, with or without muscle symptoms);
- Myalgia (muscle symptoms without CK elevations);
- Myopathy (muscle pain or weakness, typically with an elevation of CK to 10 x the upper limit of normal).
- Rhabdomyolysis (potentially fatal condition that occurs in some patients in association with acute oliguric renal failure secondary to lysis of skeletal myocyte with attendant myoglobinemia/myoglobinuria).

Myopathy is more likely when statins are used in combination with other drugs, particularly cytochrome P450 monooxygenase inhibitors or substrates, including:

- cyclosporine,
- fibrates,
- macrolide antibiotics,
- azoles antifungal agents,
- warfarin, and
- calcium channel blockers.

Niacin appears to elevate the risk of statin myopathy through a non-CYP-related mechanism. Dose-related abnormalities of liver function (particularly asymptomatic, clinically insignificant elevations in hepatic transaminases) are also infrequently (< 2%) associated with statin treatment.

Monitoring

Patients taking statins should be advised to report any muscle soreness, tenderness, or other discomfort (particularly symptoms unexplained by recent exertion), as well as brown-tinged urine, which is a hallmark of evolving rhabdomyolysis.

A baseline CK level should be obtained in addition to a thyroid-stimulating hormone level, because thyroid abnormalities predispose some patients to myopathy.

If the patient presents later with muscle pain or tenderness, the CK level should be determined at that time. If the CK level is > 10 x the upper limit of normal in any patient complaining of muscle pain or tenderness, statin therapy should be discontinued immediately. Statins may also need to be discontinued in some patients with asymptomatic CK elevations > 10 x the upper limit of normal.

One hallmark of effective myopathy prevention is identification of patients at elevated risk. In general, high-dose statins should be monitored more closely in older persons, especially elderly, and/or thin or frail women, and individuals with multisystem disease (including chronic renal failure associated with diabetes).

In order to limit the myotoxic risk of statins, potentially desirable pharmacologic properties should include:

- low systemic exposure through low doses,
- low oral bioavailability,
- high first-pass hepatic extraction or high plasma protein binding, and
- high selectivity for hepatocytes over skeletal myocytes.


Hydrophilic statins, such as pravastatin and rosuvastatin, and agents not appreciably metabolized by CYP3A4, such as pravastatin, possibility of rosuvastatin and fluvastatin, have been associated with low incidences of myopathy in combination regimens.

Side-effects are rare and vascular disease is common. I use higher doses of statins, such as atorvastatin (which has extensive safety, efficacy, and clinical trial data at low and high doses) and rosuvastatin (starting dose can lower LDL by 50%,).

In patients at higher risk for side-effects, I start low and go slow. In high risk patients, especially

younger patients with vascular disease, those with diabetes, and those admitted with ACS, I start with much higher doses. Despite our current arsenal of lipid lowering agents, many of my patients cannot achieve target lipid values on high-dose (and often combination) lipid-lowering therapy. Higher-dose statins, ezetimibe, and combination therapy are important additions to this arsenal.

My personal monitoring guidelines include:

- Baseline AST, ALT, FBS, BUN, CR, TSH, CK;
- Repeat CK with symptoms compatible with “muscle ache syndrome”;
- Repeat CK, ALT within one to three months after starting or changing dose;
- Measure CK, ALT every six months in asymptomatic high-risk individuals;
- In combination lipid therapy measure CK, ALT every three months;
- It is unclear when to monitor low-risk individuals; however, I suggest once a year ALT, CK. 

References available—contact *Perspectives in Cardiology* at cardio@sta.ca.

Take-home message

- Healthy men over age 40 and women over 50 should be screened every five years to ensure they remain at low risk.
- High-risk patients include those with CAD, cerebrovascular disease, adults with diabetes, and those in whom 10-year risk of cardiovascular death or non-fatal MI is > 20%.
- Priority for treatment in high-risk individuals is a reduction of LDL-C to < 2.5 mmol/L and TC/HDL-C to < 4.0.



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