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MEETING REPORT

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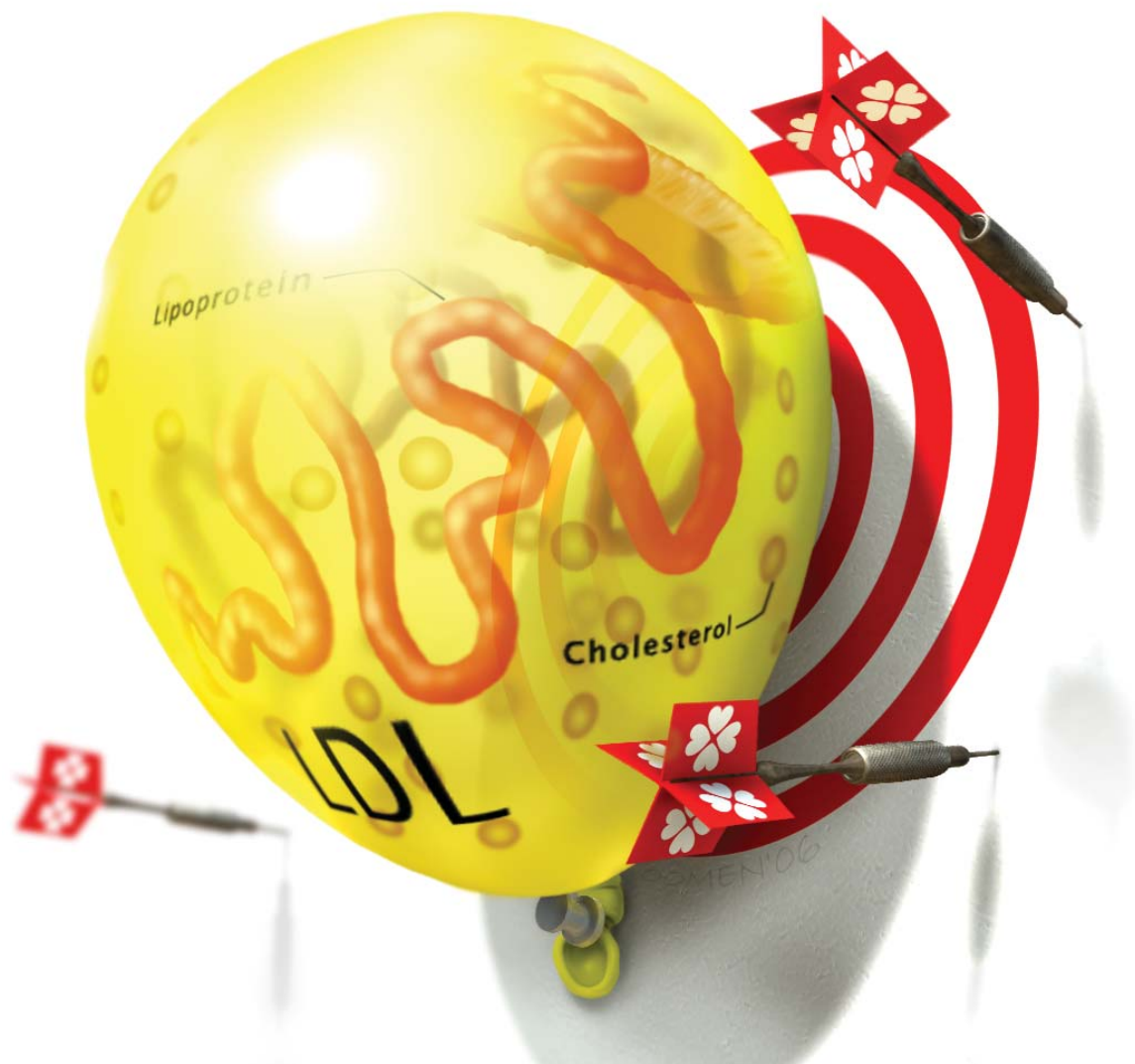
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Canadian Lipid Guidelines Update

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Update on Lipid Management in Canada

Since the last publication of recommendations for the management and treatment of dyslipidemia,^{1,2} important new clinical data has emerged to support more intensive lipid lowering in certain patient groups. Recent studies in subjects with both stable coronary artery disease (CAD) as well as in those with an acute coronary syndrome (ACS), such as the Treatment to New Targets (TNT),³ Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL)⁴ and PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT)⁵ studies have shown that lowering LDL-cholesterol more intensively, to a value of at least <2.0 mmol/L is associated with additional cardiovascular risk reduction in these high-risk individuals. This has been further supported by two surrogate endpoint studies, REVERSal of Atherosclerosis with Lipitor (REVER-SAL)⁶ and A Study To Evaluate the effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden (ASTEROID),⁷ which both demonstrated slowing or regression of atherosclerosis using intravascular ultrasound (IVUS). Treatment benefit in intermediate- and high-risk (5-10% of the study population) groups was also shown in the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT),⁸ even in those patients without overt dyslipidemia. As a result of some of this data, the National Cholesterol Education Program Adult Treatment Panel III updated their treatment recommendations in 2004 to reflect an optional lower LDL-C target in “very high risk” patients.⁹

Updates to Canadian Recommendations for Lipid Management

In light of these recent data, Canadian guidelines for the management of dyslipidemia have been updated and recently published, by both the Canadian Cardiovascular Society (CCS)¹⁰ and the Canadian Diabetes Association (CDA).¹¹ The CCS position statement was developed based on reviews of meta-analyses of studies of the efficacy and safety of lipid-lowering therapies, and of the predictive value of established and emerging risk factors. Emerging risk factors may play a role in moving patients at intermediate risk to a higher or lower risk category. These risk factors include: laboratory measurements such as apo B, hsCRP, Lp(a), and A1C (in patients with elevated plasma glucose); assessment of exercise capacity by graded exercise stress testing; non-invasive assessment of atherosclerosis, such as determination of ankle-brachial index (ABI) and carotid imaging. In high-risk patients, pharmacological treatment is recommended immediately with diet and exercise. The primary treatment goal for most high-risk patients is to achieve an LDL-C of <2.0 mmol/L. Once the LDL-C target has been achieved, attempts should be made to achieve a TC/HDL-C ratio of <4.0 by further lifestyle modification, or through the addition of further lipid-modifying therapy. Weight loss (if required) and increased physical activity can increase HDL-C levels by approximately 7-10%. If HDL-C is not sufficiently increased using these lifestyle modifications, niacin can increase HDL-C levels by 15-20%, or fibrates can induce an increase of 6-10%. It is noted that people considered to be at low or moderate risk may actually have high lifetime risk, because of other comorbidities such as obesity. It is known that the reduction in CAD and stroke events and overall cost-effectiveness of therapy is proportional to the decrease in LDL-C.¹² It is therefore recommended that one consider pharmacologic therapy for an LDL-C >3.5 mmol/L in patients at moderate risk, and >5.0 mmol/L for those at low risk, and aiming for an LDL-C reduction of at least 40% is considered to be generally appropriate. A 40% LDL reduction can generally be achieved with atorvastatin 20 mg, rosuvastatin 10 mg, simvastatin 40 mg, or lovastatin 80 mg.

A recently published national chart audit study of 2473 Canadian patients with type 2 diabetes revealed that 55% of patients with a diagnosis of diabetes of 2 years had dyslipidemia. This proportion rose to 66% in those who had had diabetes for ≥15 years.¹³ Despite this, less than 50% of diabetic patients in Canada are treated with any lipid-lowering agent. This high burden of dyslipidemia in patients with diabetes, as well as the increasing compelling trial evidence on the benefits of intensive management of dyslipidemia in diabetes, led to a review of the lipid recommendations published in the Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. The 2006 Lipid Expert Committee used the same evidence-based methodological principles of the 2003 guidelines to develop revised recommendations for adults with diabetes. Once again, it is recommended that the vast majority of people with established diabetes be considered at high risk of a vascular event, and should be treated accordingly. The targets for people with diabetes previously considered at “moderate risk” of a vascular event have been eliminated in these new recommendations. Instead, the LDL-C target has been lowered from <2.5 mmol/L to ≤2.0 mmol/L and is now recommended as the

primary goal in the management of dyslipidemia. First-line treatment should consist of optimally dosed statin therapy. This means giving an appropriate statin at an appropriate dose. If the LDL-C remains ≥2 mmol/L, despite the maximum tolerated dose of an effective statin, the addition of a cholesterol absorption inhibitor such as ezetimibe should be considered, and is typically associated with a further 20% LDL-C lowering. Once the LDL-C target has been achieved, physicians can consider additional lifestyle and pharmacologic therapies to achieve the secondary target of a TC/HDL-C ratio of <4.0.

Challenges to Achieving Lower LDL-C Targets

There is a major challenge in lipid management today in achieving the recommended LDL-C treatment goal. An analysis from 8182 patients in two prospective Canadian registries (Vascular Protection [VP] and the Guideline Orientated Approach to Lipid Lowering [GOALL])¹⁴ showed that 78% of high-risk patients (with either established cardiovascular disease or diabetes) were receiving a lipid-lowering agent. However, only 51.2% of these patients had achieved the then recommended LDL-cholesterol target of <2.5 mmol/L. For patients with diabetes without cardiovascular disease, the target was achieved in only 44.7% of patients. Persons with both vascular disease and diabetes are at the highest CV risk, yet only 59% of these individuals had an LDL-C ≤2.5 mmol/L. Similarly, the Canadian Lipid Study-Observational (CALIPSO)¹⁵ studied 3721 patients on statin therapy, and showed that 68% of these subjects were at high risk for coronary artery disease. Of these high-risk patients, 36% had not achieved the then target LDL-C of <2.5 mmol/L. When the new target of <2.0 mmol/L was applied, 70% of these high-risk patients were not at goal.

The ACTFAST study¹⁶ was a 12-week, open-label trial that examined 2113 high-risk patients requiring treatment with a statin, who had their statin dose selected based on a predefined algorithm in an attempt to achieve LDL-C targets quickly. The majority (81%) of the statin-naïve patients achieved LDL-C targets using a flexible starting dose of atorvastatin, plus one titration if necessary, but only 61% of previously statin-treated patients achieved their LDL-C goals. Patients not achieving LDL-C goals appeared to be more refractory to atorvastatin monotherapy, or experienced side effects, thus limiting the up-titration of the dose.

One reason for LDL-C targets not being achieved in all patients is a result of a lack of dose titration. The hesitancy to titrate statin doses up may stem from fears of increased side effects on both the patient's and physician's part, despite the fact that there have been careful evaluations of statin safety, both in randomized clinical trials and meta-analyses, all of which have reaffirmed the extremely safe side effect profiles of the currently available statins. Another factor that may be contributing to the lack of LDL-C control among patients is the choice of statin. The “right” statin must be capable of achieving the required LDL-C lowering in a given patient, and must be prescribed at the appropriate dose. Clinical studies have shown that atorvastatin, rosuvastatin, simvastatin, or lovastatin are the most effective choices (see Table 1).

Table 1. Efficacy of selected statins in lowering LDL-C

Statin	Appropriate dose	% reduction in LDL-C achieved
Atorvastatin ¹⁷	10, 20, 40, 80 mg	37-51%
Lovastatin ¹⁸	20, 40, 80 mg	29-54%
Rosuvastatin ¹⁷	10, 20, 40 mg	46-55%
Simvastatin ¹⁷	10, 20, 40, 80 mg	28-46%

The Benefits of Dual Inhibition

The majority of patients, including those with metabolic syndrome, diabetes mellitus and combined dyslipidemia, are able to achieve target levels of LDL-C with statin monotherapy. When titrating statins, in general, an additional 6% lowering in LDL-C can be expected for each doubling of the statin dose. However, not all patients are able to tolerate higher doses of statins, as the risk of side effects (particularly myositis), although low, tends to increase with higher doses. Such patients may be candidates for combination therapy with an agent that inhibits cholesterol absorption (ezetimibe) or bile acid reabsorption (resins; e.g., cholestyramine or colestipol). The addition of a resin can lower LDL-C levels by an additional 20-25% at maximal doses, but these drugs are often not well tolerated, especially at higher doses. Therefore, when further LDL-C lowering is required, the combination of ezetimibe with statins is useful, as this combination has been shown to provide, on average, an additional 20% reduction in LDL-C. ▣

Combination therapy may also be required in many patients to achieve the TC/HDL-C ratio of <4.0. In patients with dyslipidemia and low HDL-C levels, the combination of a statin with niacin is very effective, and has been reported in small studies to significantly reduce CAD events. For patients who do not tolerate, or who are not candidates for niacin and exhibit significant hypertriglyceridemia despite statin monotherapy, a combination of a statin with a fibrate may also be used. Recommended fibrates for combination therapy include fenofibrate and bezafibrate. Gemfibrozil should not be used in combination with statins, due to the increased risk of myopathy and rhabdomyolysis. Fibrates are also recommended as first-line therapy for patients with diabetes and fasting TG levels >10 mmol/L who do not respond to other measures, such as improved glycemic control, weight loss, and restriction of refined carbohydrates and alcohol.

Conclusion

In the absence of new treatment strategies, the introduction of the new LDL-C and TC/HDL-C ratio targets will likely increase the number of Canadians not achieving their lipid targets. Currently, about 50% of

patients with diabetes are not receiving lipid-lowering therapy, despite the fact that trials such as CARDS have shown that statin treatment is associated with a 37% reduction in major cardiovascular events. It is therefore important to establish a simple, effective pharmacological protocol for the treatment of our dyslipidemic patients, such as:

- Start with an effective statin dose that is calculated to achieve the target LDL-C based on the starting and target LDL-C levels (e.g., atorvastatin 10 mg, lovastatin 80 mg, rosuvastatin 10 mg, or simvastatin 40 mg)
- If the patient does not achieve target, increase the statin to its maximum therapeutic or tolerated dose
- If LDL-C is still not at target, add a cholesterol absorption inhibitor (e.g., ezetimibe 10 mg)

By following these simple steps in order to achieve lipid targets, we should be well on our way to closing the “care gap” that currently exists with our dyslipidemic patients in Canada. ■

<p>Disclosure of faculty</p> <p>Jacques Genest, MD Dr. Genest has received honoraria for speaking and/or advisory board and/or research from sanofi-aventis, AstraZeneca, Bayer, Fujisawa, Merck Frosst/Schering, Pfizer, Servier, Novartis and Biotech like Liponex, ResverLogix and Bruin/Centcor.</p> <p>Lawrence A. Leiter, MD Dr. Leiter has received research funding from, provided CME on behalf of, and has acted as a consultant to AstraZeneca, Bayer, Biovail, Bristol-Myers Squibb, Eli Lilly, Fournier, GlaxoSmithKline, Merck Frosst, Merck Frosst/Schering, Novartis, Pfizer, sanofi-aventis and Servier.</p>	<p>Rafik Habib, MD Dr. Habib has received research funding and honoraria for speaking, for advisory boards and for consultant meetings from AstraZeneca, sanofi-aventis, Servier, GlaxoSmithKline, Merck Frosst/Schering, Pfizer and Eli Lilly.</p> <p>J. Robin Conway, MD Dr. Conway has received speaker honoraria and research grants in the past year from GlaxoSmithKline, Pfizer, NovoNordisk, Merck Frosst, sanofi-aventis, AstraZeneca and Servier.</p>
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Canadian Diabetes Association 2006 Recommendations for the Management of Dyslipidemia

Lipid targets for adults with diabetes at high risk for CVD

Index	Target value
Primary target	
LDL-C	≤2.0 mmol/L*
Secondary target	
TC/HDL-C ratio	<4.0

* Clinical judgment should be used to decide whether additional LDL-C lowering is required for patients with an on-treatment LDL-C of 2.0 to 2.5 mmol/L.
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
TC = total cholesterol

2006 Recommendations for the Management of Dyslipidemia

Note: Readers are referred to the original guidelines document for supporting references and evidence grading.

◆ = New Recommendation

Prevention

People with type 1 or type 2 diabetes should be encouraged to adopt a healthy lifestyle to lower their risk of CVD. This entails adopting healthy eating habits, achieving and maintaining a healthy weight, engaging in regular physical activity, and smoking cessation.

Risk Assessment

◆ Most people with type 1 or type 2 diabetes should be considered at high risk for vascular disease. The exceptions are younger people with type 1 or type 2 diabetes with shorter duration of disease and without complications of diabetes (including established CVD) and without other CVD risk factors. A computerized risk engine (e.g., UKPDS risk engine, Cardiovascular Life Expectancy Model) can be used to estimate vascular risk.

Screening

Fasting lipid levels (TC, HDL-C, TG and calculated LDL-C) should be measured at the time of diagnosis of diabetes and then every 1 to 3 years as clinically indicated. More frequent testing should be performed if treatment for dyslipidemia is initiated.

Targets

◆ The primary target of therapy is the LDL-C; the secondary target is the TC/HDL-C ratio.

◆ If the TC/HDL-C ratio is ≥4.0, consider strategies to achieve a TC/HDL-C ratio <4.0, such as improved glycemic control, intensification of lifestyle (weight loss, physical activity, smoking cessation) and, if necessary, pharmacologic interventions.

Plasma apo B can be measured, at the physician's discretion, in addition to LDL-C and TC/HDL-C, to monitor adequacy of lipid-lowering therapy in the high-risk patient. Target apo B should be <0.9 g/L.

Treatment

- ◆ Patients at high risk of a vascular event should be treated with a statin to achieve an LDL-C ≤2.0 mmol/L. Clinical judgment should be used as to whether additional LDL-C lowering is required for patients with an on-treatment LDL-C of 2.0 to 2.5 mmol/L.
- ◆ In patients with serum TG >10.0 mmol/L, despite best efforts at optimal glycemic control and other lifestyle interventions, a fibrate should be prescribed to reduce the risk of pancreatitis. For those with moderate hyper-TG (4.5-10.0 mmol/L), either a statin or a fibrate can be attempted as first-line therapy, with the addition of a second lipid-lowering agent of a different class if target lipid levels are not achieved after 4 to 6 months on monotherapy.

For patients not at target(s), despite optimally dosed first-line therapy as described above, combination therapy can be considered. Although there are as yet no completed trials demonstrating clinical outcomes in patients receiving combination therapy, pharmacologic treatment options include (listed in alphabetical order):

- Statin plus ezetimibe
- Statin plus fibrate
- Statin plus niacin

- Adapted from Canadian Diabetes Association Clinical Practice Guidelines Expert Committee¹¹

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Canadian Cardiovascular Society 2006 Guidelines for the Management and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease

GLOBAL RISK ASSESSMENT

Framingham Risk Factor score screening

- Screen with a full lipid profile, every one to three years, all men who are 40 years of age or older and all women who are postmenopausal or 50 years of age or older.
- In addition, adults with the following risk factors should be screened at any age:
 - Diabetes mellitus;
 - Current or recent (within past year) cigarette smoking;
 - Hypertension;
 - Abdominal obesity (metabolic syndrome) – waist circumference of greater than 102 cm for men and greater than 88 cm for women (lower cut-offs are appropriate for South and East Asians);
 - Family history of premature coronary artery disease (CAD);
 - Stigmata of hyperlipidemia (e.g., xanthoma);
 - Exertional chest discomfort, dyspnea, erectile dysfunction, claudication, chronic kidney disease; or
 - Evidence of atherosclerosis.
- Screen children who have a family history of severe hypercholesterolemia or chylomicronemia.
- Other patients may be screened at the discretion of their physician, particularly when lifestyle changes are indicated.

Risk categories

Risk level	10-year CAD risk	Recommendations
High	≥20%	<i>Treatment targets:</i> Primary target: LDL-C <2.0 mmol/L Secondary target: TC/HDL-C <4.0
Moderate	10% - 19%	<i>Treat when:</i> LDL-C ≥3.5 mmol/L or TC/HDL-C ≥5.0
Low	<10%	<i>Treat when:</i> LDL-C ≥5.0 mmol/L or TC/HDL-C ≥6.0

High risk includes coronary artery disease (CAD), peripheral artery disease, cerebrovascular disease and most patients with diabetes.

OTHER FACTORS INFLUENCING CAD RISK

Apolipoprotein B

Plasma apolipoprotein B measurement may be used to determine CAD risk, especially in hypertriglyceridemia, and to monitor treatment. Optimal levels of apolipoprotein B are less than 0.85 g/L in high-risk patients, less than 1.05 g/L in moderate-risk patients and less than 1.2 g/L in low-risk patients.

Lipoprotein (a)

A lipoprotein (a) concentration greater than 0.3 g/L in an individual with a total cholesterol to high-density lipoprotein cholesterol ratio of greater than 5.5 or other major risk factors indicates the need for earlier, more intensive low-density lipoprotein cholesterol (LDL-C) lowering.

High-sensitivity C-reactive protein

High-sensitivity C-reactive protein may be clinically useful in identifying individuals who are at higher risk for CAD than that predicted by a global risk assessment, in particular in patients with abdominal obesity or a calculated 10-year risk between 10% and 20%. A high-sensitivity C-reactive protein level of less than 1.0 mg/L indicates low risk for cardiovascular disease, between 1.0 mg/L to 3.0 mg/L indicates moderate risk and more than 3.0 mg/L indicates high risk.

Indexes of glycemia

Fasting glucose should be measured every one to three years in adults 40 years of age or older and in younger adults with abdominal obesity and/or a family history of type 2 diabetes. Measurement of glycated hemoglobin is not recommended unless

fasting glucose is elevated. Moderate elevations in glycated hemoglobin may indicate increased CAD risk.

Homocysteine

Although it is a marker of CAD risk, treatment with vitamins to lower homocysteine is not recommended.

NONINVASIVE INVESTIGATIONS

After a careful history review and physical examination, noninvasive investigations that may be useful for patients in the moderate-risk category to detect subclinical atherosclerosis and/or to further define future CAD risk are the ankle-brachial index, carotid ultrasound and graded exercise testing.

TREATMENT

Lifestyle

An important focus should be to decrease caloric consumption by decreasing saturated and trans fat intake, reducing intake of sugar and refined carbohydrates, and by increasing exercise (to more than 200 min per week) as needed to achieve and maintain a body mass index of less than 27 kg/m² (ideally less than 25 kg/m²).

Medication

- In high-risk individuals, treatment should be started immediately and concomitantly with diet and exercise. The treatment goal for most high-risk patients is first to achieve an LDL-C of less than 2.0 mmol/L; an optimal reduction in LDL-C for most CAD patients is at least 50%. Once the LDL-C target has been reached, attempts should be made to achieve a total cholesterol to high-density lipoprotein cholesterol ratio of less than 4.0 by further lifestyle modification. Adjuvant lipid-modifying therapy may also be considered.
- Patients in the low- or moderate-risk categories may be at high long-term cardiovascular risk. This group includes many patients with abdominal obesity. The reduction in CAD and stroke events and overall cost-effectiveness of therapy is proportional to the decrease in LDL-C.
- For those low- and moderate-risk individuals who are candidates for statin therapy, treatment to lower LDL-C by at least 40% is generally appropriate.

Generic name	Trade name	Recommended dose range
Statins		
Atorvastatin	Lipitor (Pfizer Canada Inc)	10 mg - 80 mg
Fluvastatin	Lescol (Novartis Pharmaceuticals Canada Inc)	20 mg - 80 mg
Lovastatin	Mevacor (Merck Frosst Canada)	20 mg - 80 mg
Pravastatin	Pravachol (Bristol-Myers Squibb, Canada)	10 mg - 40 mg
Rosuvastatin	Crestor (AstraZeneca Canada)	5 mg - 40 mg
Simvastatin	Zocor (Merck Frosst Canada)	10 mg - 80 mg
Bile acid and/or cholesterol absorption inhibitors		
Cholestyramine	Generic	2 g - 24 g
Colestipol	Colestid (Pfizer Canada Inc)	5 g - 30 g
Ezetimibe	Ezetrol (Merck Frosst/Schering Pharmaceuticals Canada)	10 mg
Fibrates*		
Bezafibrate	Bezalip (Hoffman-La Roche Limited, Canada)	400 mg
Fenofibrate	Lipidil Micro/Lipidil Supra/Lipidil EZ (Fournier Pharma Inc, Canada)	200 mg/160 mg/145 mg
Gemfibrozil	Lipid (Pfizer Canada Inc)	600 mg - 1200 mg
Niacins		
Nicotinic acid	Generic crystalline niacin	1 g - 3 g
	Niaspan (Oryx Pharmaceuticals Inc, Canada)	0.5 g - 2 g

* Fibrates should generally be reserved if triglyceride levels are greater than 10 mmol/L despite lifestyle changes; follow creatinine levels.

- Adapted from McPherson et al¹⁰

