Canadian Lipid Guidelines Update
Update on lipid management in Canada

Since the last publication of recommendations for the management and treatment of dyslipidemia, important new clinical data has emerged to support more intensive lipid lowering in certain patient groups. Recent data in subjects with clinical cardiovascular disease (CVD) as well as in those with an acute coronary syndrome (ACS), such as the Treatment to New Targets (TNT), Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) and Pravastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) studies have shown that lowering LDL-cholesterol more intensively, to a level of <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 Liraglutide (REVER- SAL) and a Study to Evaluate the Effectiveness of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden (ASTEROS), both of which demonstrated a relationship between LDL-cholesterol lowering and a reduced burden 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 Outcomes Trial (ASCOT), even in those patients without overt dyslipidaemia. 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.

Updates to Canadian Recommendations for Lipid Management

In light of these recent data, Canadian guidelines for the management of dyslipidaemia have been updated and recently published, by both the Canadian Cardiovascular Society (CCS) and the Canadian Diabetes Association (CDA). 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 age, HDL-C, triglycerides, and HbA1c (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 in people with established coronary artery disease is 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 10-20%. If HDL-C is not sufficiently increased using these lifestyle modifications, niacin can increase HDL-C levels by 15-25%, or fibrates by 30-40%. It is noted that people considered to be at low or moderate risk may actually have higher lifetime risk because of their lifestyle choices 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. 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-C 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 2,473 Canadian patients with type 2 diabetes revealed that 55% of patients with a diagnosis of diabetes of 2 years had dyslipidaemia. This proportion rose to 66% in those who had had diabetes for 12 years or more. Despite this, less than 50% of diabetic patients in Canada are treated with any lipid-lowering agent. This high burden of dyslipidaemia in patients with diabetes, as well as the increasing compelling trial evidence on the benefits of intensive management of dyslipidaemia 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 primary 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 cardiovascular event and should be treated accordingly. The targets for people with diabetes previously considered at “moderate risk” at 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 dyslipidaemia. First-line treatment should consist of optimally dosed statin therapy. This means giving an appropriate statin at an appropriate dose. If this does not lower LDL to ≤2.0 mmol/L, then the addition of a cholesterol absorption inhibitor such as ezetimibe should be considered in certain patients with low LDL-cholesterol. Once the LDL-C target has been achieved, physicians can consider additional 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 new LDL-C targets. The primary treatment goal in people with established coronary artery disease is to achieve a TC/HDL-C ratio of <4.0 by further lifestyle modification, or through the addition of further lipid-modifying therapy. A recently published national chart audit study of 2,473 Canadian patients with type 2 diabetes revealed that 55% of patients with a diagnosis of diabetes of 2 years had dyslipidaemia. This proportion rose to 66% in those who had had diabetes for 12 years or more. Despite this, less than 50% of diabetic patients in Canada are treated with any lipid-lowering agent. This high burden of dyslipidaemia in patients with diabetes, as well as the increasing compelling trial evidence on the benefits of intensive management of dyslipidaemia 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 primary 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 cardiovascular event and should be treated accordingly. The targets for people with diabetes previously considered at “moderate risk” at 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 dyslipidaemia. First-line treatment should consist of optimally dosed statin therapy. This means giving an appropriate statin at an appropriate dose. If this does not lower LDL to ≤2.0 mmol/L, then the addition of a cholesterol absorption inhibitor such as ezetimibe should be considered in certain patients with low LDL-cholesterol. Once the LDL-C target has been achieved, physicians can consider additional therapies to achieve the secondary target of a TC/HDL-C ratio of <4.0.

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The Benefits of Dual Inhibition

The majority of patients, including those with metabolic syndrome, diabetes mellitus, and combined dyslipidaemia, are able to achieve target levels of LDL-C with statin monotherapy. When titrating statins, in general, an additional 40% 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 myopathy), 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 (Cholestyramine or colestevast). The addition of cholestyramine can lower LDL-C levels in those patients treated with high doses of statins (as these are typically not well tolerated). Therefore, when further LDL-C lowering is required, the combination of atorvastatin with statins is useful, as this combination has been shown to provide, on average, an additional 20% reduction in LDL-C.

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

<table>
<thead>
<tr>
<th>Statin</th>
<th>Appropriate dose</th>
<th>% reduction in LDL-C achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>10, 20, 40, 80 mg</td>
<td>55-60%</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>10, 20, 40 mg</td>
<td>25-40%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10, 20, 40, 80 mg</td>
<td>35-51%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10, 20, 40, 80 mg</td>
<td>46-50%</td>
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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 nicotinic acid 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 nicotinic acid and exhibit significant hypertriglyceridemia despite statin monotherapy, a combination of a statin and a fibrate may also be used. Recommended fibrates for combination therapy include fenofibrate and bezafibrate. Gemfibrozil is not recommended as first-line therapy for diabetic patients with fasting TG levels >10 mmol/L who do not respond to other measures, such as tight glycemic control, weight loss and restriction of refined carbohydrates and alcohol.

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Conclusion
The introduction of the new LDL-C and TC/HDL-C ratio targets will 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, rosvastatin 10 mg, or simvastatin 40 mg)
- If the patient does not achieve target, increase the statin to its maximum tolerated dose, or add another lipid-lowering agent (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 within our dyslipidemic patients in Canada.

2006 Recommendations for the Management of Dyslipidemia

**Lipid targets for adults with diabetes at high risk for CVD**

<table>
<thead>
<tr>
<th>Index</th>
<th>Target value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary target</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>≤2.0 mmol/L*</td>
</tr>
<tr>
<td>Secondary target</td>
<td></td>
</tr>
<tr>
<td>TC/HDL-C ratio</td>
<td>&lt;4.0</td>
</tr>
</tbody>
</table>

*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.

**Note:** Readers are referred to the original guidelines document for supporting references and 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 (i.e., with <10 years of disease) and those with a history of diabetes without complications (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 TG/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 of ≤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 fenofibrate
- Statin plus niacin

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REFERENCES:

High-Risk level 10-year CAD risk Recommendations
• Other patients may be screened at the discretion of their physician, particularly screen children who have a family history of severe hypercholesterolemia.
• 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.

Moderate 10%-19% Treat when:
- HDL-C ≥ 1.0 mmol/L
- Fasting glucose ≤ 5.5 mmol/L
- LDL-C ≤ 2.5 mmol/L
- Has goal LDL-C of less than 2.0 mmol/L

Low 6%-9% Treat when:
- HDL-C ≥ 1.0 mmol/L
- Fasting glucose ≤ 5.5 mmol/L
- LDL-C < 2.5 mmol/L

OTHER FACTORS INFLUENCING CAD RISK

Apolipoproteins
Plasma apolipoprotein B measurement may be used to determine CAD risk, especially in hyperlipidaemia, 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.

Catepsin D
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 further, 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.

NONINVASIVE INVESTIGATIONS

- • Adapted from McPherson et al.10

Echocardiography
- • Appropriate for South and East Asians);
- • Adequate for assessment of left ventricular systolic function in selected patients.

Stress Testing
- Low-risk individuals: chest pain, electrocardiographic changes and angina with exercise.
- Intermediate-risk individuals: chest pain and/or electrocardiographic changes with exercise.
- High-risk individuals: chest pain and/or electrocardiographic changes, angina with exercise, and abnormal test results.

CT coronary angiography
- • Appropriate when echocardiography and stress testing are inadequate or inconclusive.
- • Not appropriate in chronic renal failure or when severe atherosclerotic plaques interfere with proper visualization.

Magnetic resonance imaging
- • Not appropriate in chronic renal failure or when severe atherosclerotic plaques interfere with proper visualization.
- • Appropriate when echocardiography and stress testing are inadequate or inconclusive.

Supporting Clinical Impact — Meeting Report