Canadian Lipid Guidelines and Clinical Practice: Closing the Treatment Gap

In this review, Dr. Lau shows how proper patient education and counselling, along with the assistance of other health professionals and strategies to implement more aggressive lipid lowering, will go a long way to reduce CVD risks as well as the burden on our patients and our society.

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CVD is the leading cause of death in Canada and globally. Among the modifiable risk factors for CVD, elevated lipid levels are by far the most important, as reported in the Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction in 52 countries (the INTERHEART study): case-control study involving > 15,000 subjects.

Benefits of cholesterol lowering

Evidence for the more aggressive treatment targets for high-risk individuals emanates from recent clinical trials with hard CVD endpoints and regression studies that have investigated the impact of therapy on atherosclerotic burden. Many studies have shown that the greater the reduction in LDL-C, the greater the coronary artery disease (CAD) risk reduction. Indeed, for every 1 mmol/L reduction in LDL-C, there is a 23% reduction in major coronary events and a 21% reduction in major vascular events, according to a meta-analysis of 14 large statin trials involving > 90,000 patients.

Lower lipid treatment targets

Aggressive lowering of LDL-C has been widely accepted as the most effective strategy to reduce CVD risk in high-risk patients, which includes a vast majority of people with diabetes. The 2006 Canadian Cardiovascular Society (CCS) position statement on the diagnosis and treatment of dyslipidemia recommends lowering LDL-C from 2.5 mmol/L to < 2.0 mmol/L and, optimally, at least a 50% reduction in LDL-C levels in individuals with CAD or a calculated 10-year CVD risk of > 20%.

This new target was chosen as the primary lipid-lowering goal since it has been consistently shown that intensive lipid-lowering provides

<table>
<thead>
<tr>
<th>10-year CV risk*</th>
<th>Primary: LDL-C level (mmol/L)</th>
<th>Secondary: TC/HDL-C ratio</th>
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</thead>
<tbody>
<tr>
<td>High (≥ 20%) **</td>
<td>&lt; 2.0</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>Moderate (10%-19%)</td>
<td>&lt; 3.5</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Low (&lt; 10%)</td>
<td>&lt; 5.0</td>
<td>&lt; 6</td>
</tr>
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TC: Total cholesterol
* 10-year risk for CVD is based on Framingham risk score calculation for men and women.
** Most patients with diabetes are considered at high short-term risk even in the absence of CVD.
additional CVD risk reduction in high-risk patients. Once this new, low LDL-C target is met, attempts should be made to reduce the total cholesterol (TC)/HDL-C ratio to < 4.0, again in high-risk patients. The CCS risk stratification and lipid treatment goals are listed in Table 1.

**Highlights of the 2006 Canadian lipid guidelines**

The following highlights the 2006 Canadian lipid guidelines:

- LDL-C remains the primary target and TC/HDL-C ratio is the secondary target for therapy
- For high-risk individuals with a 10-year Framingham CVD risk of ≥ 20%, new LDL-C treatment target is now lowered to ≤ 2.0 mmol/L and the TC/HDL-C ratio < 4
- For most low-risk individuals with 10-year risk of ≤ 10%, a slightly higher intervention point for the initiation of therapy (LDL-C of 5.0 mmol/L or a TC/HDL-C ratio < 6.0)

- Statins are the drugs of choice for lowering LDL-C
- Ezetimibe, bile acid sequestrants, nicotinic acid or fibrates can be used in combination therapy with a statin to achieve treatment targets

### Lifestyle modification and lipid-lowering agents

Lifestyle modification remains the cornerstone for the treatment of dyslipidemia. Achieving a healthy weight, limiting saturated, trans fat and cholesterol intake, incorporating regular physical activity in the daily routine will significantly reduce CVD risk. Pharmacotherapy, when indicated, should be initiated with the lowest effective dose of statin and then titrated to a dose which achieves the lipid target. The six statins available on the Canadian market differ markedly in their efficacies in lowering LDL-C, triglycerides and the TC/HDL-C ratio (Table 2). Rosuvastatin is the most effective in lowering LDL-C, ranging from 45% to 55% and the best in reducing the TC/HDL-C ratio, which is one of the best indices of future risk of coronary disease. It should be noted that doubling the statin dose will only lower LDL-C levels by another 5% to 6%.

The shift in the guidelines toward a lower LDL-C target may require higher doses of statin therapy, as demonstrated in numerous recent statin trials. In the PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) study, 40 mg of pravastatin q.d. and 80 mg of atorvastatin q.d. led to mean LDL-C levels of 2.47 mmol/L and 1.61 mmol/L, respectively. The difference between pravastatin and atorvastatin over 2.5 years was an almost 4% absolute difference (16% relative risk reduction) in major CVD outcomes.6 In the Treating to New Targets

<table>
<thead>
<tr>
<th>Statins in order of potency</th>
<th>Dosage (mg)</th>
<th>LDL-lowering (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>5, 10, 20, 40</td>
<td>45-55</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10, 20, 40, 80</td>
<td>40-50</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10, 20, 40, 80</td>
<td>35-45</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10, 20, 40, 80</td>
<td>25-35</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>10, 20, 40, 80</td>
<td>20-35</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20, 40, 80</td>
<td>10-20</td>
</tr>
</tbody>
</table>

* Each doubling of statin dosage decreases LDL-C by an additional 5%-6%.
(TNT) study, a difference in LDL-C between 2.60 mmol/L, in patients receiving 10 mg of atorvastatin and 2 mmol/L in those receiving 80 mg of atorvastatin, resulted in an absolute reduction in the rate of major CV events of 2.2% and a 22% relative reduction in risk.7 Similarly, A Study To Evaluate the effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden (ASTEROID) trial on atheromatous plaque regression quantified by intravascular ultrasound imaging, 40 mg of rosuvastatin q.d. produced a significant 53% decrease in LDL-C and a 59% reduction in the LDL-C/HDL-C ratio.8 Importantly, plaque regression was more likely in patients with LDL-C < 2.0 mmol/L than in those with higher levels, especially LDL-C > 2.6 mmol/L.

It is estimated that about 50% to 75% of patients will achieve the new lower LDL-C target with higher doses of simvastatin, atorvastatin or rosuvastatin. After the LDL-C levels, the guidelines continue to emphasize the TC/HDL-C ratio in primary prevention as a secondary target.

**Table 3**

**Other lipid-modifying medications**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Generic names</th>
<th>Principal actions</th>
<th>Considerations</th>
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</table>
| Bile acid sequestrants                   | - Cholestyramine
- Colestipol                | - Lower LDL-C                  | - May raise TG
- GI side-effects                |
| Cholesterol absorption inhibitors        | - Ezetimibe                     | - Lower LDL-C                          | - Less effective than statins as monotherapy        |
| Nicotinic acid:                         | - Niacin, non-prescription
- Extended-release Niacin, prescription | - Lower LDL-C
- Lower TG
- Raise HDL-C                  | - May worsen glycemic control
- Long-acting niacin should not be used because of increased hepatotoxicity |
| Fibrates                                 | - Fenofibrate,
- Bezafibrate,
- Gemfibrozil                  | - Lower TG
- Variable effect on LDL-C
- Raise HDL-C                  | - May increase LDL-C,
- creatinine and homocysteine levels
- Gemfibrozil should not be used with a statin due to increased risk of myopathy and rhabdomyolysis |

TG: Triglyceride
Lipid Guidelines

Statins have been proven effective in saving lives in both primary and secondary CVD prevention. Their cost-effectiveness in the treatment of CVD is much less of a concern.

Combination therapy

If the lipid target is not achieved with monotherapy, combination therapy with another lipid lowering agent should be considered (Table 3). Achieving LDL-C targets rapidly while minimizing adverse effects of medication may be best achieved with combination therapy. Combining a statin with the cholesterol absorption inhibitor ezetimibe has proven to be a reasonable initial strategy to bring more people to target LDL-C levels.

For the same lipid levels achieved with statins or other lipid-lowering agents, it is unclear whether the hard CVD outcomes are comparable to those achieved with statin monotherapy. We await with interest results from ongoing clinical trials on combination therapy of statin with ezetimibe or nicotinic acid.

Adverse side-effects

In general, statins are well tolerated with few side-effects. Myalgia and liver enzyme abnormalities are more likely to occur with higher doses. If a patient experiences adverse side-effects from one statin, such as myopathy, it is reasonable to switch to another statin at comparable doses. Rhabdomyolysis is exceedingly rare and is often associated with renal insufficiency or with combination therapy with gemfibrozil.

Conclusions

The latest Canadian lipid guidelines recommend aggressive lowering of LDL-C as a primary target, followed by TC/HDL-C ratio as a secondary target for treatment. Higher doses of statins are often required to achieve the lower LDL-C levels and combination therapy may be necessary in some cases. Statins have been proven to save lives and are generally tolerated with few side-effects. The biggest challenges in clinical practice are achieving treatment targets and patient adherence.

A significant proportion of treated patients are not achieving targets, as shown in a recent Canadian study. Proper patient education and counselling, along with assistance of other health professionals and strategies to implement more aggressive lipid lowering, will go a long way to help reduce the CVD risks as well as the health and financial burden on our patients and our society.

References