



## New Canadian Dyslipidemia Guidelines

### What's New and How Does it Affect Practice?

Cardiovascular disease (CVD) remains the leading cause of death for Canadians; the most recent data shows CVD claimed 71,000 Canadians in 2005, including 3000 Saskatchewan residents<sup>1</sup>. Of all the causes of CVD, coronary artery disease (CAD) has been found to be the most common<sup>2</sup>. The most significant risk factor for developing CAD is elevated low-density lipoprotein (LDL-C). There are numerous strategies to reduce LDL-C, but optimal approaches in screening and managing complex patients have often not been implemented. In response, Canadian specialists and several organizations released the 2006 Dyslipidemia Guidelines to aid practitioners in identification and treatment of patients at risk for primary and secondary CVD events<sup>3</sup>.

Since the completion of the 2006 guidelines, several landmark studies have brought new information and evidence into practice. The committee reviewed all literature focused on the screening and treatment of dyslipidemia published between January 1<sup>st</sup>, 2006 and February 1<sup>st</sup>, 2009 and only included blinded, randomized studies that focused on cardiovascular outcomes<sup>4</sup>. The analysis of literature has enabled several key features to be incorporated into the 2009 guidelines: new screening tools and markers are available, lipid targets are simplified, and more patient-specific treatment recommendations are suggested.

### What has changed from the 2006 guidelines?

#### Screening criteria<sup>4,5</sup>

The 2009 guidelines include more sharply defined guidelines on who should have a fasting plasma lipid profile and be screened for CVD risk. The 2009 guidelines also suggest re-assessment of CVD risk every 3-5 years in appropriate patients. Differences compared to the 2006 guidelines are noted in green text.

<p>Who should be screened with a fasting plasma lipid profile?</p>	<ul style="list-style-type: none"> <li>• All Men <math>\geq</math> 40 years</li> <li>• All Women <math>\geq</math> 50 years or postmenopausal</li> <li>• Children of parents with severe lipid disorder (ie., familial hypercholesterolemia, chylomicronemia)</li> <li>• Adults of any age who have one or more of the following risk factors:             <ul style="list-style-type: none"> <li>○ Diabetes mellitus</li> <li>○ Physical signs of hyperlipidemia (xanthelasma, xanthoma, etc.)</li> <li>○ <b>Current smokers (vs. current smokers and recently quit in last year)</b></li> <li>○ Hypertension</li> <li>○ HIV treated with highly active antiretroviral therapy</li> <li>○ Obesity, increased waist circumference, or <b>BMI <math>&gt;27\text{kg}/\text{m}^2</math> (vs. just waist circumference)</b></li> <li>○ Premature CAD in first-degree relative <math>&lt;60</math> years of age <b>(vs. <math>&lt;55</math> men, <math>&lt;60</math> women)</b></li> <li>○ Chronic kidney disease, <b>eGFR <math>&lt;60\text{mL}/\text{min}/1.73\text{m}^2</math> (vs. no eGFR defined)</b></li> <li>○ Autoimmune disease (systemic lupus, <b>psoriasis, rheumatoid arthritis vs. just lupus included</b>)</li> <li>○ Any evidence of atherosclerosis</li> <li>○ Erectile dysfunction</li> </ul> </li> </ul>
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## Risk Assessment

The new guidelines have changed recommendations for stratifying patients to high, moderate or low risk, especially in the moderate risk category; low risk stratification remains the same. New assessment tools include the use of both a modified Framingham Risk Score (FRS) model (<http://www.framinghamheartstudy.org/risk/gencardio.html>) and a Reynolds Risk Score (RRS, <http://www.reynoldsriskscore.org/Default.aspx>)<sup>4</sup>. Framingham has been modified to officially include diabetes<sup>7</sup>. The RRS uses the same criteria of FRS, except it includes the use of high-sensitivity C-reactive protein (hs-CRP) and family history, but is based on non-diabetic individuals<sup>8</sup>.

The combination of the new tools allows for the use of more markers, namely hs-CRP in moderate risk, to better define a patient's risk of CVD. C-reactive protein (CRP) is a component of the immune system which causes inflammation and subsequent immune system activity. CRP acutely rises in the event of trauma or illness but cannot reliably predict any cardiovascular risk. Hs-CRP has the same function but is also a marker of chronic inflammation in the body<sup>9</sup>. Individuals with high hs-CRP have chronic inflammation, which leads to white blood cell invasion and damage to the arterial walls, early initiation of atherosclerotic plaques within the arteries, and acute rupturing of these plaques, increasing the likelihood of a cardiovascular event<sup>10,11</sup>. How well hs-CRP correlated with CVD risk was largely speculative until the JUPITER trial showed treating patients with elevated hs-CRP, but normal LDL, had clinically significant benefits<sup>12</sup>. Thus, hs-CRP levels can help with the decision to initiate treatment in moderate risk individuals, noted below. Levels of hs-CRP levels can be elevated by acute inflammatory processes, infections and injuries.<sup>13</sup> This should be taken into consideration when evaluating initial high values of hs-CRP.<sup>13</sup>

### **CVD Risk Stratification for 2009<sup>4</sup>**

<b>Risk Level</b>	<b>FRS Score</b>	<b>RRS Score</b>	<b>LDL-C</b>	<b>TC/HDL – C Ratio</b>	<b>Hs-CRP</b>
High Risk*	≥20%	<b>≥20%</b>	NA	NA	NA
Moderate Risk	10%-19%	NA	>3.5mmol/L	>5.0	<b>Men &gt;50: &gt;2mg/L</b> <b>Women &gt;60: &gt;2mg/L</b>
Low Risk	<10%	NA	NA	NA	NA

\*Patient with CAD, peripheral vascular disease, atherosclerosis and most patients with diabetes are automatically high risk, regardless of other markers

**Bold / Green are new recommendations compared to the 2006 guidelines**

## Initiating Treatment and Target Levels

The decision to initiate treatment in moderate risk patients with borderline lipids (LDL-C >3.5mmol/L and TC/HDL-C >5) was often a difficult choice. The 2009 guidelines introduce using hs-CRP and family history as a marker for initiating treatment in moderate risk patients to help make the decision easier<sup>4</sup>.

Another important change is the primary and secondary target goals. The previous guidelines focused on LDL-C <2mmol/L as a primary target and the TC/HDL ratio of <4.0 as a secondary target; the new guidelines now define a primary target as LDL-C <2mmol/L, a 50% decrease or more of LDL-C, or apoB <0.8g/L<sup>4,5</sup>. Going for a 50% decrease or more of LDL-C may be a more aggressive approach than some clinicians are accustomed to. It should be noted, however, that several of the landmark lipid trials (4S, CARE, HPS, CARD, ASCOT) which had strong outcome data on reduction of MI and death reduced LDL by only 18 – 35 percent.<sup>13</sup> Also, there is no outcome evidence to support the addition of a second drug to a patient's medication regimen to achieve the new targets.<sup>13</sup>

ApoB is a primary apolipoprotein—a protein responsible for carrying cholesterol to tissues—for LDL-C. The higher a patient's apoB, the more LDL-C is transferred to tissues, and an increase in plaque formation and CVD risk results<sup>15</sup>. The inclusion of apoB in the guidelines more clearly identifies its role in dyslipidemia as a primary treatment target, as some studies have found apoB is a better predictor of CVD than LDL-C, though treatment is the same

regardless of the treatment parameter<sup>14</sup>. The aim of these new primary targets is to keep realistic goals while still maximizing benefits<sup>4</sup>.

### Treatment Initiation and Primary Targets for 2009<sup>4,5</sup>

Risk Level	When to Initiate Treatment	Primary Target Levels	Grade of Recommendation and Level of Evidence
High Risk	All patients, immediately	LDL-C <2mmol/L Or <b>&gt;50% decrease in LDL-C or apoB &lt;0.8g/L</b>	Grade I, Level A
Moderate Risk	LDL – C > 3.5mmol/L TC/HDL-C > 5.0 <b>Hs-CRP &gt; 2mg/L in men &gt;50 or women &gt;60</b> <b>If family history increases risk according to RRS</b>	LDL-C <2mmol/L Or <b>&gt;50% decrease in LDL-C or apoB &lt;0.8g/L</b>  *The benefits of this target in moderate risk is less clear; guidelines suggest using clinical judgment to decide if targets are appropriate	Grade IIa, Level A
Low Risk	LDL-C > 5mmol/L TC/HDL-C > 6 with high triglycerides	<b>&gt;50% decrease in LDL-C</b>	Grade IIa, Level A

\*Bold / green indicate new or different recommendations compared to the 2006 guidelines

There are also new secondary targets that can be pursued instead of just the TC/HDL ratio<sup>4</sup>.

### Secondary Targets for CVD Risk Reduction for 2009

Secondary Treatment Goals	Consider these targets after achieving target LDL-C or apoB: <ul style="list-style-type: none"> <li>• TC/HDL-C ratio &lt;4</li> <li>• <b>Non-HDL cholesterol &lt;3.5 mmol/L</b></li> <li>• <b>apoB/apoA1 ratio &lt;0.8</b></li> <li>• <b>Triglycerides &lt;1.7mmol/L</b></li> <li>• <b>hs-CRP &lt;2 mg/L</b></li> </ul> *Clinical benefits of achieving these targets are unknown
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Adapted from Pharmacist's Letter<sup>6</sup>

### Treatment Recommendations<sup>4,5,6</sup>

The major differences in treatment recommendations are aimed at helping achieve secondary targets through more specific medication indications and lifestyle changes. The same battery of medications, and doses, are recommended in the new guidelines.

#### *Lifestyle Changes*

The usual recommendations of smoking cessation and eating healthy remain. However, instead of suggesting 150-200 minutes of exercise per week to patients, the new guidelines suggest 30-60 minutes of moderate intensity exercise per day. Stress management, a lower BMI goal (<25 instead of <27), and a reduction of alcohol consumption (one drink per day for women, two per day for men permitted) are also included in the new guidelines. Finally, omega-3 supplementation (as opposed to specifically salmon oil) is recommended in those with elevated triglycerides.

## Achieving Primary and Secondary Targets

Major changes include new, detailed suggestions for lower triglycerides, raising HDL-C and the inclusion of hs-CRP as an official treatment target.

### Treatments to achieve Targets

Target	First-line Medication	Second-line Medication
LDL-C	Lifestyle plus Statin	Add: bile-acid sequesterant; or cholesterol absorption inhibitor; <b>or</b> <b>Niacin (Niaspan or generic crystalline— flush free niacin ineffective)</b>
HDL-C	Lifestyle: smoking cessation, weight loss ( <b>BMI &lt;25</b> ), exercise ( <b>30-60 min/d</b> ), moderate alcohol intake  <b>Niacin or fibrate* (less effective), plus statin (for LDL-C).</b>	N/A
Triglycerides	Life-style: exercise ( <b>30-60 min/d</b> ), weight loss ( <b>BMI &lt;25</b> ), restrict refined carbohydrates, <b>reduce alcohol intake, increase omega-3 fatty acids</b>  <b>Triglycerides &gt;10 mmol/L: Fibrate* (to reduce pancreatitis risk)</b>  <b>Triglycerides 5 mmol/L to 10 mmol/L: Fibrate* or omega-3 fatty acid</b>  <b>Triglycerides 2 to 5 mmol/L on statin, and high risk: Add fibrate* or niacin (unclear impact on CAD risk if LDL-C is at target)</b>	N/A
hs-CRP	<b>Statin</b>	N/A

\*Fenofibrate recommended in combination with statin therapy; less risk of myotoxicity compared to gemfibrozil

### Monitoring Recommendations<sup>4,6</sup>

Previous guidelines did not have details on monitoring treatment; the new guidelines now have official monitoring parameters.

<b>Monitoring Safety</b>	<p>Baseline: Fasting lipid panel, glucose, TSH (as hypothyroidism contributes to hyperlipidemia), liver function, creatinine, creatine kinase, apoB and apoA1 (if targeting as treatment goals)</p> <p>Follow-up measurements: Repeat liver function tests and creatine kinase every six to 12 months, with any change in lipid therapy, and in the event of symptoms.</p> <p>Niacin: ALT at baseline and one and three months after starting niacin; fasting glucose and A1C every six to 12 months; uric acid</p> <p>Fibrates: May increase serum creatinine; start with lowest dose and increase after follow-up measurements of creatinine and lipids.</p>
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Adapted from Pharmacist's Letter<sup>6</sup>

## What Does it All Mean?

The ultimate question with the new guidelines is, “will it change how I practice?” The short answer is no. Much of what is now recommended is what clinicians have been doing for some time; the only difference is the new body of evidence that affirms what everyone has been doing.

The differences in screening criteria will prevent high-risk patients from “slipping under the radar”, such as those with rheumatoid arthritis who may not have been screened in the past. The addition of the Reynold’s Risk Score will also help clinicians provide more accurate risk assessment for those potentially in the moderate risk category, or ensure validity of a Framingham Risk Assessment. Moderate risk patients are now more easily identified with the inclusion of hs-CRP as a monitoring tool.

The addition of treating elevated hs-CRP may also mean patients who would normally be left untreated will now receive potentially beneficial therapy. The JUPITER trial found that treating patients (rosuvastatin studied) with elevated hs-CRP, but normal lipid levels, significantly reduced primary outcome events (MI, stroke, arterial revascularization, hospitalization for unstable angina or death from CV causes). The NNT reported was 31 over 4 years<sup>9</sup>. The NNT for 1.9 years, the actual length of the study, works out to 82 which is quite similar to the results of other statin drug trials.<sup>13</sup>

ApoB has also been included as a primary treatment target, but whether laboratories or clinicians will adopt it as a primary target has yet to be seen. Some studies have found apoB predicts coronary event risk better than LDL-C<sup>10</sup>; however, since there are no specific treatment recommendations to lower apoB that differ from traditional treatment, treatment will remain the same even if a clinician is targeting apoB as the primary treatment parameter.

Regarding treatment, there are not many differences in the new guidelines that will alter practice. The main change is the suggestion to target a LDL-C decrease of greater than 50%, which may be more aggressive treatment than some clinicians have implemented. The drug treatment recommendations are what has been practiced for some time, such as using niacin to further lower LDL-C or raise HDL and using fibrates to lower triglycerides. The new guidelines provide a specific place in therapy for these treatments, whereas before they were just general recommendations.

The new guidelines help provide continuity in treatment between clinicians, open up treatment to new patients, and make stratifying risk more reliable and accurate. Concerns regarding the new guidelines include a) the potential to increase the number of patients using a second lipid-modifying drug without outcome data to verify benefit and b) with more lower risk people qualifying for therapy, the potential for very long-term treatment (again with some uncertainty regarding the relative benefits and risks).

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