Guideline for Lipid Testing in Adults (CLP017)

Revised November 2013

1. Purpose

The OAML Guideline for Lipid Testing in Adults (August 2010) has been revised to:

- be consistent with the Canadian Cardiovascular Society's (CCS) 2012 guideline, entitled "Guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult" (CCS's 2012 Dyslipidemia Guidelines);
- introduce the option of using non-fasting samples for the measurement of lipid levels and;
- introduce reporting of non-high density lipoprotein cholesterol (non-HDL-C) levels in addition to total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and calculated low density lipoprotein cholesterol (LDL-C).

The option to use a non-fasting specimen will support patients' compliance with routine screening programs. In addition, it will benefit patients who have difficulty with prolonged fasting. It will also reduce the risk of fainting, especially in seniors, and will help avert metabolic disruptions in patients with diabetes.

Clinicians are encouraged to consult the CCS's 2012 Dyslipidemia Guidelines for a more detailed interpretation and are reminded that OAML Guidelines will not apply to every clinical situation, nor can they serve as a substitute for sound clinical judgment.

2. Lipid Assessment

Assessment of dyslipidemia presently includes the following tests: TC, HDL-C, TG, and LDL-C. These tests may be ordered by checking "Lipid Assessment" on the Ontario Health Insurance Plan's (OHIP) laboratory requisition.

LDL-C level remains the primary marker for monitoring therapy; however, non-HDL-C and apo-lipoprotein B (apo-B) have been recommended by CCS's 2012 Dyslipidemia Guidelines as alternate markers to LDL-C for patients with whom a clear decision to initiate pharmacotherapy or to intensify current pharmacotherapy is not obvious.[1] Although, CCS's 2012 Dyslipidemia Guidelines recommends the use of apo-B as a treatment target, it is not currently an OHIP-insured test.

Non HDL-C is calculated as TC minus HDL-C and is the sum of all cholesterol transported in atherogenic lipoproteins, regardless of triglyceride levels. It will be automatically calculated and reported in mmol/L.

3. Option to Use Non-Fasting Samples for the Measurement of Lipid Levels

Traditionally, fasting samples have been used for the assessment of dyslipidemia. However, the CCS's 2012 Dyslipidemia Guidelines introduced the use of non-fasting specimens for lipid assessment with the introduction of non-HDL-C and apo-B as alternate lipid assessment targets. Neither non-HDL-C nor apo-B are affected by the patient's fasting status.[1 (p 156)]

In addition, Sidhu and Naugler's 2012 community-based population study, published in 2012 in the *Archives of Internal Medicine*, with lipid data from 209,180 patients, also suggests fasting for routine lipid levels is largely unnecessary, as non-fasting lipid profiles change minimally in response to food intake. This study illustrated that the change in measured TC, or HDL-C for fasting compared to non-fasting specimens was less than 2%. Average differences between fasting and non-fasting measurements were less than 10% for LDL-C and less than 20% for TG.[2]

Clinically, fasting carries some risks for patients as noted on the previous page. Therefore, alternative effective markers which do not require fasting have been sought and found. These include non-HDL-C and apo-B. Both may be determined on non-fasting specimens and both are equally effective, if not superior, for determining whether therapeutic targets have been met.[3, 4]

Based on CCS's 2012 Dyslipidemia Guidelines, Sidhu and Naugler's findings, and other peer reviewed literature supporting the use of non-fasting specimens, community laboratories will introduce the option of using non-fasting specimens for the measurement of lipid levels.[1-12]

Note: The clinical significance of fasting vs. non-fasting samples is outlined in OAML Communique C024 available on the OAML website at http://www.oaml.com/res_pract.html.

4. Fasting Samples

- Before ordering a fasting specimen to help facilitate the decision to initiate or alter drug therapy it is recommended that the non-HDL and/or the apo-B levels are first reviewed. Current literature suggests that non-HDL-C & apo-B are more reliable indicators of cardiovascular disease (CVD) than LDL-C. [3, 4] In those instances where LDL-C must be used, the patient should be fasting, since LDL-C is subject to error of up to 10% if calculated on a non-fasting specimen.

- Non-fasting hypertriglyceridemia (triglycerides > 2.00 mmol/L) may warrant fasting analyses to enable an informed treatment decision e.g. prevention of pancreatitis.

Patients at licensed specimen collection centres with orders for lipid assessment will be asked how long they have fasted. This information will be recorded on the laboratory requisition and included on the laboratory report to facilitate lipid result interpretation. Patients must have only water for a minimum of 10 hours to be considered fasting.

Note: Physicians collecting specimens in their own offices must record the number of hours fasting on the laboratory requisition. Specimens received without this information will be considered non-fasting.

5. Other Laboratory Tests for Assessment of CVD Risk

(a) Non-HDL-C

The concentration of non-HDL-C is not affected by fasting status. Non-HDL-C is calculated as the difference between the TC and HDL-C and is the sum of all cholesterol transported in atherogenic lipoproteins, regardless of triglyceride levels. It will be calculated and reported automatically on all patients' lipid reports. The non-HDL-C treatment target for patients at intermediate and high risk for cardiovascular disease (CVD) is less than or equal to 2.60 mmol/L.[1 (p 159)]

It has been suggested that non-HDL-C is a more reliable indicator of CVD than LDL-C and it is identified in the CCS's 2012 Dyslipidemia Guidelines as a reliable alternate lipid marker for monitoring therapy in the non-fasting state.[1, 3, 4]

Note: To order non-HDL-C, when a lipid profile is not required, write "non-HDL-C" on the laboratory requisition.

(b) Apo-B

Apo-B is the primary protein component of the atherogenic lipoproteins LDL and VLDL (very low density lipoprotein). One molecule of apo-B is associated with each LDL and each VLDL molecule, making apo-B a good indicator of the number of LDL and VLDL particles and therefore CVD risk. The apo-B treatment target for patients at intermediate and high risk for CVD is less than or equal to 0.80 g/L.

It has been suggested that apo-B is a more reliable indicator of CVD than LDL-C, since measurement of apo-B is a direct quantitation of cardiac risk markers (LDL-C and VLDL-Cholesterol) rather than a calculated measurement of one.[3, 4] In addition; the apo-B assay is not affected by hypertriglyceridemia, or by fasting status. It is also identified in the CCS's 2012 Dyslipidemia Guidelines as a reliable alternate lipid marker for monitoring therapy in the non-fasting state.[1, 11]

(c) TC/ HDL-C Ratio

In the CCS's 2009 Dyslipidemia Guidelines, the TC/HDL-C ratio was included as a secondary marker for therapy. While not identified as a secondary marker for therapy in the 2012 Guidelines, the ratio will continue to be reported because the 2012 guideline indicates that high risk is defined by hypertension plus three other risk factors, one of which is a TC/HDL-C ratio > 6.0.[1 (p 158)]

Clinicians should be aware that in light of current clinical trial evidence, no recommendations have been made for a specific HDL-C target.

(d) High Sensitivity C-Reactive Protein (hs-CRP)

Quantitation of CRP is not warranted for all patients as part of the primary CVD risk assessment.

Statin therapy may benefit the following groups, if the hs-CRP test result is >2.0 mg/L: [1(p 160)]

- Males >50 years, at moderate risk for CVD and with LDL-C levels <3.5 mmol/L
- Females >60 years, at moderate risk for CVD and with LDL-C levels <3.5 mmol/L[1]

See the CCS's 2012 Dyslipidemia Guidelines for additional information.

Neither apo-B nor hs-CRP is included in the "Lipid Assessment" profile, but either test can be ordered individually by writing the name of the required test(s) in the "Other Tests" section of the OHIP laboratory requisition. Currently, apo-B is not an OHIP-insured test.

6. Ten Year Risk for the Development of CVD

Ten year risk is defined as the probability of a subgroup of the population developing CVD within a 10 year period, if not treated. Assessment of this risk is determined by stratification of patients using clinical and laboratory data entered into the Framingham Risk Score (FRS) Tool.

Limitations to the calculation of the CVD risk using the FRS are well established in the literature. It is found to be sensitive to age, and older individuals are more likely to be assessed with higher risk. These individuals may also have other competing risk factors which affect the accuracy of the FRS. Still, cardiovascular risk assessment has been demonstrated to be helpful in discussing risk with the patient and have a positive impact on the management of their blood pressure and lipid levels.

The following are two risk calculator options:

1. The CardioRiskCalculator is available at http://circl.ubc.ca/cardiorisk-calculator.html. This calculator allows for rapid assessment of Framingham Risk, Cardiovascular Age, Metabolic Syndrome and other factors supporting treatment and management of adults with dyslipidemia and risk of cardiovascular disease.

   Cardiovascular age is calculated as the patient's age corrected for the difference between the individual's life expectancy and the remaining life expectancy for Canadians of the same age and gender. When discussing risk status with the patient, cardiovascular age may be helpful to gain compliance with recommended therapy or changes to lifestyle.

   This calculator also has comparative drug tables and a calculator for determining percentage changes in LDL-C concentration required to reach treatment targets.

2. The FRS calculator included in the CCS's 2012 guideline supplemental material uses age, gender, HDL-C, TC, blood pressure (BP), smoking status and the presence of diabetes in its calculation of CVD risk. This calculator is posted on the OAML website at www.oaml.com.

   Individuals in the following subgroups may be associated with increased risk of CVD and therefore warrant lipid screening: [1(p 153)]

   - Men ≥ 40 years of age, and women ≥ 50-years years of age or postmenopausal
   - All patients with any of the following conditions, regardless of age:

Smoking	HIV infection
Obesity (BMI > 27)	Erectile dysfunction
Diabetes mellitus	Chronic kidney disease
Hypertension*	Chronic obstructive pulmonary disease
Familial hyperlipidemia	Abdominal aortic aneurysm
Family history of premature CVD (< 55y for men or < 65y for women)	Clinical evidence of hyperlipidemia e.g. xanthelasma, xanthoma[14]
Clinical evidence of atherosclerosis or abdominal aortic aneurysm	Inflammatory/ autoimmune disease e.g. rheumatoid arthritis, SLE, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease.

*The Canadian Hypertension Education Program (CHEP) has set treatment targets of less than 140 mmHg for systolic BP and/or less than 90 mmHg for diastolic BP in healthy individuals and less than 130/80 mmHg in individuals with diabetes or chronic kidney disease.[15]

7. Risk Categories and Target Lipid Levels

Summary of the 2012 CCS Treatment Initiation Levels and Lipid Treatment Target Values[1 (p 159)]

*10 Year Risk of CVD	Initiate Therapy	Primary Lipid Treatment Target	Alternate Lipid Treatment Target
**High Risk (FRS ≥ 20%)	Consider in all patients	<2.00 mmol/L or ≥50% decrease of LDL- C from untreated baseline	non-HDL-C ≤ 2.60 mmol/L or Apo B ≤ 0.80 g/L
Intermediate Risk (FRS 10%-19%)	➢ LDL-C ≥3.50 mmol/L ➢ LDL-C < 3.50 mmol/L ***and*** Apo B ≥ 1.2 g/L or non-HDL-C ≥ 4.30 mmol/L	<2.00 mmol/L or ≥50% decrease of LDL- C from untreated baseline	non-HDL-C ≤ 2.60 mmol/L or Apo B ≤ 0.80 g/L
Low Risk (FRS <10%)	LDL-C ≥5.00 mmol/L	≥50% decrease of LDL-C	

*Calculated using FRS Tool (see section 6)
**Patients at high risk of CVD include those with:

- diabetes (over age 40 or over age 30 with 15+ years duration, or any age with microvascular complications);
- peripheral vascular disease;
- atherosclerotic disease;
- abdominal aortic aneurysm and
- chronic kidney disease defined as:
    - estimated Glomerular Filtration Rate (eGFR) < 45 ml/min/1.73m^2;
    - Albumin/Creatinine Ratio (ACR) > 30; [1(p 158)]
- high risk hypertension defined as hypertension plus three of the following risk factors: male, age > 55 years, smoking, TC/HDL-C > 6, left ventricular hypertrophy, family history of premature CVD, ECG abnormalities, microalbuminemia, or chronic kidney disease.

Monitoring Frequency

- For those with FRS ≥ 5%, it is recommended that cardiovascular risk be assessed annually.
- For those with FRS < 5%, it is recommended that cardiovascular risk be assessed every 3-5 years.[1(p 153)]

8. Testing Protocols Prior to Therapy and Monitoring Potential Toxic Effects of Drug Therapies

a) Statins - Pre-treatment Assessment

Initial tests recommended prior to starting statin treatment include the following:

ALT, Creatinine, eGFR, Creatine Kinase (CK), Thyroid–Stimulating Hormone (TSH).

- TSH is recommended because hypothyroidism is a risk factor for statin myopathy as well as a secondary cause of elevated LDL-C

- Baseline urinary protein is recommended to exclude nephrotic syndrome as a cause of secondary dyslipidemia
- eGFR is recommended because significant renal dysfunction is considered to increase the risk of adverse effects from statin drugs.[16]

b) Ongoing Monitoring of Patients on Statins

For patients on chronic statin therapy, ongoing testing for hepatotoxicity need not be performed. True statin-related hepatic damage is exceedingly rare. While ALT elevations are seen in 1-3% of patients on statin therapy (depending on dose), 70% of these resolve spontaneously.[17]

The Canadian Working Group on Statin Intolerance recommends one follow-up ALT and CK after initiation of therapy (3 months) or after dose escalation or statin change. Thereafter, enzyme monitoring would only be indicated to investigate symptoms occurring during long-term therapy.[16 (p 642)]

Evidence shows that ongoing CK monitoring for myotoxicity is not required.[1 (p 162)] Elevated CK levels in asymptomatic patients receiving a constant dose of medication are commonly due to physical exertion or muscle injury rather than being drug-induced.

If signs/symptoms of myotoxicity or hepatotoxicity develop in statin-treated patients, further testing should be performed to determine the cause(s).

c) **On-going Monitoring of Patients on Fibrates and/or Niacin**

Unlike patients on statin drugs, patients on fibrates and/or niacin **do** require monitoring for toxicity every 6 months, or earlier if symptoms develop, using the tests indicated.

- Monitor patients on niacin with ALT, glucose, HbA1c, Uric Acid, INR[18]
- Monitor patients on fibrates with creatinine[19]

Note:
If a dose change of any of the above drugs is implemented, additional toxicity testing at dose change and 3 months post change is recommended.

If elevations of any of these analytes persist and a decision is made to continue with drug therapy, albeit at reduced dosages, more frequent monitoring is warranted.

9. References

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Acknowledgements

The OAML gratefully acknowledges the contributions of the members of the expert panel:

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