PRACTICAL IMPLEMENTATION OF LIPID LOWERING FOR CARDIOVASCULAR RISK REDUCTION IN PRIMARY CARE

Introduction
With the advent of safe lipid-lowering drugs, particularly statins and non-statin agents such as ezetimibe, and with the emergence of newer therapeutics such as monoclonal antibodies and RNA technologies, it has become apparent that major adverse cardiovascular (CV) events can be reduced both in primary and secondary prevention by 20–50% through lowering of low-density lipoprotein cholesterol (LDL-C) by 1–2 mmol/L. The purpose of this paper is to provide a pragmatic approach to the implementation of the 2021 Canadian Cardiovascular Society Guideline for managing dyslipidemia in adults.

A) Screening and Identification of an Atherogenic Lipid Profile
Adults ≥40 years of age should have a complete lipid screen which need not be fasting. However, screening should occur at younger ages in women who are postmenopausal or have a history of hypertensive disorders of pregnancy. Similarly, younger adults of South Asian or Indigenous heritage and of either sex should be screened. Regardless of age, a full lipid profile should also be measured in any individual with evidence of preclinical or clinical atherosclerosis (including abdominal aortic aneurysm or erectile dysfunction [ED] in males); a family history of either dyslipidemia or early CV events; the presence of non-lipid CV risk factors such as diabetes, obesity, chronic kidney disease, hypertension or smoking; and the presence of inflammatory diseases (rheumatoid arthritis [RA]; systemic lupus erythematosus [SLE]; psoriatic arthritis [PsA]; ankylosing spondylitis [AS]; inflammatory bowel disease [IBD]; human immunodeficiency virus [HIV]; and chronic obstructive pulmonary disease [COPD]). Lipid screening should now routinely include not only a measure of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and LDL-C but also a one-time measurement of Lp (a), a particularly malignant, apolipoprotein B containing atherogenic particle with additional atherothrombotic and inflammatory properties that is almost entirely genetically determined and, therefore, imparts a lifelong risk that runs in families. Its elevation cannot be deduced from any other component of the lipid panel; therefore, it must be specifically measured to know if it is imparting additional vascular risk.

Lipid screening should now routinely include not only a measure of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and LDL-C but also a one-time measurement of Lp (a), a particularly malignant, apolipoprotein B containing atherogenic particle with additional atherothrombotic and inflammatory properties that is almost entirely genetically determined and, therefore, imparts a lifelong risk that runs in families. Its elevation cannot be deduced from any other component of the lipid panel; therefore, it must be specifically measured to know if it is imparting additional vascular risk. Otherwise, it may cause damage “under the radar” and not be suspected as playing a critical role until events have occurred either prematurely or recurrently.

Clinical trials are underway to determine if agents that can specifically and profoundly lower this atherogenic...
A particle will be associated with CV risk reduction. For now, detection of an elevation warrants "risk enhancement" i.e., the individual is at higher risk than implied by other risk factors; therefore earlier and more aggressive management of all modifiable CV risk factors should be considered. Repeated measurements are not warranted. However, because the levels are genetically determined, screening for high Lp (a) as part of a full lipid profile in first degree relatives should be considered (Figure 1).

Interpreting the Lipid Profile: Consider Triglycerides First
In patients found to have a TG ≥1.5 mmol/L, it is important to know that the LDL-C may be misleading when calculated in the usual fashion and that it is only one component of atherogenicity (Figure 2). Simple arithmetic indicates that as TG elevates, the calculated LDL-C must decline for any given measure of TC and HDL-C. Under these circumstances, the atherogenicity of the lipid profile is more accurately reflected by an apolipoprotein B measurement, specifically apolipoprotein B100. The latter correlates somewhat with the non-HDL-C. Figure 3 (cholesterol "triads") summarizes the comparable levels of LDL-C, non-HDL-C and apolipoprotein B that warrant therapy and/or intensification of therapy when statins are insufficient. Note that when HDL-C, "the good cholesterol," is subtracted from the total cholesterol, the result is non-HDL-C which reflects "the bad cholesterol". Thus, non-HDL-C is a measure of the cholesterol in lipid particles containing an apolipoprotein B and which are atherogenic. Finally, if a patient is known or found to have TG >4.5 mmol/L, fasting lipid profiles are warranted during on-going care. However, even though the LDL-C is not calculated or reported by most laboratories when the TG is >4.5 mmol/L, non-HDL-C and apolipoprotein B can still guide risk assessment and therapy.
Figure 2. Atherogenic lipid particles and their relationship to cholesterol measurements and specific assays. Depicted are the largest (and generally the fewest) atherogenic particles, chylomicron remnants associated with an apolipoprotein B48 (derived from the intestine), followed by smaller and progressively more numerous atherogenic particles (particularly LDL) associated with apolipoprotein B100 (derived from the liver). The illustration shows how the commonly-employed Friedewald equation is used to calculate LDL-C from measures of total cholesterol, HDL-C and TG divided by 2.2. In addition, the figure emphasizes how LDL and LDL-C are not the sole determinants of atherogenicity. More specific assays for apolipoprotein B100 and for Lp (a) help to clarify the atherogenicity of any given lipid profile. Specialized laboratories and research laboratories may measure particles directly; however, such assays, beyond those for lipoprotein (a), are not used in clinical practice; courtesy of G.B. John Mancini, MD, FRCPC, FACC.

Figure 3. The Lipid Triads. When TG is <1.5 mmol/L, the LDL-C is adequate for diagnostic and therapeutic purposes. However, when TG is ≥1.5 mmol/L, the non-HDL-C and apolipoprotein B equivalents are important to consider. Therefore, the first step in interpreting the lipid profile is to determine if the TG is completely normal or even mildly elevated; courtesy of G.B. John Mancini, MD, FRCPC, FACC.
### Statin-indicated Conditions

<table>
<thead>
<tr>
<th>Secondary Prevention</th>
<th>ASCVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Prevention</td>
<td>DM &gt; 40 yo, or &gt; 30 yo with microvascular disease or &gt; 15 y duration</td>
</tr>
<tr>
<td></td>
<td>CKD (non-dialysis, eGFR &lt;60ml/min/1.73m², UACR ≥ 3 mg/mmol)</td>
</tr>
<tr>
<td></td>
<td>LDL-C ≥ 5mmol/L (or non-HDL-C ≥ 5.8 mmol/L or apolipoprotein B ≥ 1.45 g/L) or patient with familial hypercholesterolemia</td>
</tr>
</tbody>
</table>

### Treatment Warranted Based on FRS Stratification

<table>
<thead>
<tr>
<th></th>
<th>FRS &gt; 20%/10y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FRS ≥ 10%/10y and LDL-C ≥ 3.5 mmol/L (or non-HDL-C ≥ 4.2 mmol/L or apolipoprotein B ≥ 1.05 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>FRS ≥ 10%/10y and LDL-C &lt; 3.5 mmol/L but in association with risk enhancers*</td>
</tr>
<tr>
<td></td>
<td>FRS ≥ 5%-9.9%/10y and LDL-C ≥ 3.5 mmol/L (or non-HDL-C ≥ 4.2 mmol/L or apolipoprotein B ≥ 1.05g/L) and presence of risk enhancers*</td>
</tr>
</tbody>
</table>

### *Risk Modifiers Not Reflected in Framingham Risk Scoring or Statin-indicated Conditions

#### *Risk Enhancers From Randomized Clinical Trials:

- hs-CRP >2.0 mg/L
- Elevated waist-to-hip ratio
- Prediabetes, metabolic syndrome, IFG or IGT
- LVH/other EKG abnormalities in hypertensive patients

#### *Risk Enhancers From Epidemiological Studies:

- Family history of premature CVD
- Elevated Lp (a)
- Preclinical ASCVD (e.g., CAC score >0)
- Obesity
- Inflammatory diseases
- ED
- Pregnancy-related complications
- Indigenous and South Asian ethnicity

#### Risk De-enhancers:

- CAC Score = 0 in moderate FRS patient

---

Table 1. Summary of patient profiles warranting lipid lowering for reduction of CV risk; courtesy of G.B. John Mancini, MD, FRCPC, FACC. ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus; FRS = Framingham risk score; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; hsCRP = High-Sensitivity C-Reactive Protein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; LVH = left ventricular hypertrophy; EKG = electrocardiogram; CVD = cardiovascular disease; CAC = coronary artery calcium; ED = erectile dysfunction.
B) Who to Treat (Table 1)

Framingham Risk Score Considerations
Statin-indicated conditions are those that can be identified clinically, without the need for risk calculation. Clinical trials have proven the benefit of lipid-lowering therapy for secondary prevention i.e., those with clinical atherosclerotic cardiovascular disease (ASCVD). Similarly, for primary prevention, most patients with Type 2 diabetes mellitus (T2DM) (those >40 years of age; or with over 15 years’ duration of T2DM or evidence of microvascular disease[MVD]) and those with chronic kidney disease (CKD) (eGFR <60 mL/min/1.73m² or urine albumin-creatinine ratio [ACR] ≥3.0 mg/mmol) have been shown to benefit. While this is not based on clinical trials, it is known that patients with very high LDL-C (≥5.0 mmol/L) and those with familial hypercholesterolemia have improved CV outcomes through long- term LDL-C lowering.

Subjects Identified with Framingham Risk Stratification
In patients who do not meet the obvious statin-indicated criteria, the current recommendation is to stratify risk based on the Framingham Risk Score (FRS) and to treat patients at high risk (≥20% risk of events/10 years). The clinician should also advocate therapy in patients with moderate risk (10%-19% risk of CV events/10 years) and LDL-C ≥3.5 mmol/L. Even in those with risk of 5%-9.9%, therapy is warranted if the LDL-C is ≥3.5 mmol/L if other risk enhancers are also present. Patients with LDL-C <3.5 mmol/L would warrant therapy if the risk is moderate and other risk enhancers studied in clinical trials but not part of the FRS or the statin-indicated conditions are also present (e.g., c-reactive protein) [CRP] >2.0 mg/L, presence of end-organ damage such as left ventricular hypertrophy [LVH] in hypertensive patients, or presence of metabolic syndrome/prediabetes/impaired fasting glucose [IFG]/impaired glucose tolerance [IGT]/high waist-to-hip ratio). Other risk enhancers supported through epidemiologic evidence should also be factored in (e.g., family history of premature ASCVD; Lp (a) >50mg/dL or >100 nmol/L; pregnancy-related complications; Indigenous or South Asian ethnicity; evidence of preclinical atherosclerosis; concomitant HIV; or inflammatory diseases). Therapy is generally not advocated in adults if FRS is <5%/10 years and if none of these other risk enhancers are present.

Coronary Artery Calcium Scoring: Primary Value is in the Treatment-restrictant Patient
It must be emphasized that any disposition formulated by the physician will always be subject to patient-physician discussions prior to implementation or lack of implementation. When a patient conforms to a profile, as outlined above, of having a high likelihood of reaping benefit from lipid lowering, but remains reluctant to accept the rationale for therapy, the demonstration of already established atherosclerosis may facilitate acceptance of recommended therapy. This is important to consider particularly if the risk has been estimated as moderate (≥10%-19.9% by the Framingham equation) wherein clinical studies have shown optimal utility. However, even above and below this level of risk, some patients may not accept treatment recommendations. Although not generally recommended in these circumstances, a coronary artery calcium scoring (CACS) may aid in patient counseling. This is especially the case when features such as a family history of premature ASCVD, high Lp(a), or high LDL-C (≥3.5%) are present and patients remain reluctant to accept therapy (Figure 4). For practical purposes, if the calcium score is above 100 Agatston units, it suggests that a moderate FRS is likely an underestimation and that the patient should be reclassified to high risk. A score of 1-99 suggests that the patient is still indeed at least at moderate risk. With the additional knowledge that atherosclerosis is already established, the patient may view the value of the indicated therapy more favourably. The finding of a zero score generally portends a good, short-term prognosis (the patient is re-classified to a low risk). Some patients may prefer to forego preventive therapy based on the zero calcium score when their perception of the negative impact of taking daily medications is high. Others, however, may accept preventive therapy as a way to try to maintain the low atherosclerotic burden status implied by the zero calcium score. It is imperative to re-evaluate the situation, at least within five years, if modifiable risk factors, particularly LDL-C, remain untreated. It is also essential that the decision to forego therapy is truly the patient’s decision because clinicians are obliged to indicate that in the setting of a CACS of zero Agatston units the rate of events is low, but it is not in fact zero. Part of this may be due to the fact that non-calcified plaque may still be present when the CACS is zero and non-calcified plaque may progress in the presence of untreated risk factors. In general, physicians should be advocating therapy for modifiable risk factors as this is the safest long-term strategy. In addition, every effort should be made to treat all modifiable risk factors in patients with T2DM, on-going smoking and family history of premature CV disease wherein the reclassification role of CACS is less well-accepted.

A) Limited Therapeutic Options
At the time of writing, according to the 2021 guidelines and for most practical purposes, LDL-C-related CV risk can be addressed with statins, ezetimibe and proprotein convertase subtilisin/ kexin type 9 (PCSK9) inhibitors although the armamentarium continues to be augmented with novel medications. Another therapeutic tool, icosapent ethyl, is discussed in the context of residually elevated TG levels while on statins. Fenofibrate, also in the setting of high TG, is discussed however, it is not used to lower CV risk (Figure 5).

The busy clinician should focus on being able to optimally use statins and ezetimibe initially. As there are many statins, another practical point is to become comfortable with the use of rosuvastatin and atorvastatin which are
**Coronary Artery Calcium Scoring in Treatment-Reluctant Patients**

Use of CACS for re-classification of risk not recommended but may be required for patient counselling.

**Figure 4.** Practical use of CACS. The application of CACS is best-established in patients with a moderate risk but who are reluctant to accept risk reduction therapy. In such patients, the risk can be modified upwards or downwards. Applications outside this realm are less well accepted and are not generally recommended (i.e., in subjects with high Framingham risk, family history of premature CVD, ongoing smoking, T2DM, and familial hypercholesterolemia); courtesy of G.B. John Mancini, MD, FRCPC, FACC.

<table>
<thead>
<tr>
<th>DM, Ongoing Smoking, Family History of Premature CVD, Familial Hypercholesterolemia</th>
<th>OR</th>
<th>High FRS ≥ 20%/10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate FRS ≥ 10% - 19.9%/10 years</td>
<td>OR</td>
<td>Low Risk ≥ 5 – 9.9%/10 years with LDL-C ≥ 3.5 mmol/l and risk enhancers</td>
</tr>
<tr>
<td><strong>CACS = 0:</strong> low risk, document if patient wishes to defer therapy, reassess over time</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CACS = 1 – 99:</strong> reassess and document patient wishes regarding accepting/deferring therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CACS ≥ 100:</strong> high risk, reassess and document patient wishes regarding accepting/deferring therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 5.** The cholesterol therapeutic armamentarium. Practitioners should be comfortable with use of these agents in patients found to warrant lipid-related CV risk reduction in primary and secondary prevention. Fenofibrate is not used for CV risk reduction; however, it is generally used to prevent pancreatitis in patients with TG > 10 mmol/L, or at lower levels when there is a history of recurrent pancreatitis; courtesy of G.B. John Mancini, MD, FRCPC, FACC.

<table>
<thead>
<tr>
<th>Standard Therapy</th>
<th>Non-Statin Therapies</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>Ezetimibe</td>
<td>PCSK9 Inhibitor</td>
</tr>
</tbody>
</table>

* Appropriate for patients with ASCVD alone, particularly those with high risk features such as recent acute coronary syndromes, recurrent events, prior bypass surgery, peripheral vascular disease, elevated lipoprotein (a), diabetes etc. Access will depend on province, private insurance or willingness to pay out of pocket. Inclisiran is an alternative to PCSK9 inhibitors but was not evaluated for the current lipid guideline.
very effective at low, moderate or high doses, and even with intermittent dosing as might be required in patients with intolerance to daily doses of statins. Finally, although theoretically it may make sense to bypass the relatively modest LDL-C-lowering effect of ezetimibe and to proceed directly to PCSK9 inhibitors when patients remain substantially above threshold on statins, access to this class is often contingent upon proof of a trial of ezetimibe. Optimal utilization of these three agents can achieve a 50%, 20% and 60% lowering of LDL-C respectively. Used together, a net lowering from baseline of approximately 85% can be achieved.

Some clinicians may wish to expand their armamentarium with the use of resins (e.g., colesevelam which provides an anticipated 20% lowering of LDL-C if tolerated at full dose) or small interfering RNA (siRNA) medications such as inclisiran which yields a 50% lowering with injections every six months. However, currently it is quite reasonable to leave these agents to the purview of specialists.

Using a Threshold as an Objective

The adequacy of LDL-C-lowering therapies and the need for statin add-ons are evaluated with respect to achieving LDL-C levels past the threshold. For most primary prevention settings in adults, using a statin add-on is warranted if the LDL-C remains >2.0 mmol/L or in the secondary prevention setting when the LDL-C remains >1.8 mmol/L while on a maximally tolerated statin (Figure 3). If the TG level is ≥1.5 mmol/L, it is important to use the non-HDL-C or preferably the apolipoprotein B thresholds shown in Figure 3 to determine if intensification of therapy is warranted.

Unique Considerations When Triglycerides are Elevated

As indicated above, triglyceride values ≥1.5 mmol/L require care in properly evaluating the atherogenicity of the lipid profile, at least warranting consideration of non-HDL-C (a simple approximation of cholesterol in the apolipoprotein B bearing, atherogenic lipid particles) or preferably by measuring apolipoprotein B directly. Beyond this diagnostic implication, there is also a therapeutic implication for patients with ASCVD or high-risk T2DM who are already receiving statins and with remaining TG levels between 1.5 mmol/L and 5.6 mmol/L. In these settings, a unique, pharmaceutical grade formulation of eicosapentanoic acid (isopent ethyl) has been demonstrated to reduce CV risk whereas over-th-counter (OTC) fish oils and other formulations containing both eicosapentanoic acid and docosahexaenoic acid (known as omega-3s) have failed to confer this CV risk reduction. The only other tool to consider for the therapeutic armamentarium is fenofibrate, not for CV risk reduction but rather for reduction of the risk of pancreatitis if TG >10 mmol/L.

Conclusion

This brief overview attempts to provide a practical distillation of the 2021 Guidelines for the Management of Dyslipidemia in Adults. The discussion is designed to provide “clinical pearls” and to help navigate the more sophisticated concepts that extend well beyond a focus merely on LDL-C. The new emphasis on weighing the implications of genetically elevated Lp (a), as well as the impact of even modestly elevated TG levels, both for the interpretation of the lipid profile and for therapeutic implications, are demonstrated. The objective is to provide the clinician with a rationale for implementing statins, intensifying statins, using statin add-ons such as ezetimibe and PCSK9 inhibitors, and considering novel agents such as icosapent ethyl in appropriate patients. Additional resources are available to augment this overview: (The CCS Dyslipidemia Guideline Pocket Guide [https://ccs.ca/pocket-guides/], The CCS Dyslipidemia Guideline “At a Glance” [https://ccs.ca/companion-resources/] and the CardioRisk Calculator [https://www.circl.ubc.ca/cardiorisk-calculator.html]).

Correspondence

Dr. G.B. John Mancini
Email: mancini@mail.ubc.ca

Financial Disclosures

Advisory Board: Amgen, Sanofi, Esperion, NovoNordisk, Boehringer-Ingelheim/Lilly, HLS Therapeutics, Glaxo Smith Kline, Pfizer.

Reference