Hyperlipidemia continues to be a major risk factor for cardiovascular disease, affecting up to 45% of adult Canadians. Optimal diagnosis and treatment of cholesterol disorders is definitely a cornerstone of preventative care for the Canadian population.

Objective One

Screen appropriate patients for hyperlipidemia

Currently guidelines per CCS 2021 recommend screening all adults at age 40 and above. Other patient groups include those with clinical evidence of atherosclerosis, aneurysm, diabetes, smokers, family history of premature heart disease, family heart of dyslipidemia, kidney disease, obesity, an inflammatory disorder, erectile dysfunction, COPD, and some other conditions. No current specific guidelines on pediatric patients. American cardiology and also pediatric societies do recommend screening at ages 9-11 and 16-18 again as well. Lack of screening guidelines in pediatrics is universal everywhere, largely due to the lack of RCTs performed in kids. Nonetheless, humans can build coronary plaque at any age.

Newest Canadian Task Force guidelines on dyslipidemia are from 1993.

Objective Two

In all patients whose cardiovascular risk is being evaluated, include the assessment of lipid status.

Screening lipid markers: HDL, (calculated) LDL, triglycerides and total cholesterol. Usually reported is also the non-HDL cholesterol. We know the HDL to be the "good" cholesterol and LDL to be the "bad" cholesterol. Non-HDL is generally a compilation of LDL and all other "bad" lipid particles. Triglycerides are excluded from the total cholesterol but are important in knowing how accurate our LDL number is (high triglycerides = inaccurate LDL!). Screening can be done nonfasted but if concern for high triglycerides, then a fasted sample should be obtained.

Useful lipid markers: ApoB and lipoprotein(a) (aka Lp(a)). ApoB is essentially the universal marker for all bad cholesterol. It includes IDL, VLDL, LDL, Lp(a) as it essentially measures all atherogenic lipid markers. Lp(a) is an independent risk factor and significant elevation serves as an isolated risk variable. No approved therapies (and unclear if treating it even improves outcomes). New Canadian guidelines (CCS - 2021) recommend utilizing ApoB instead of LDL

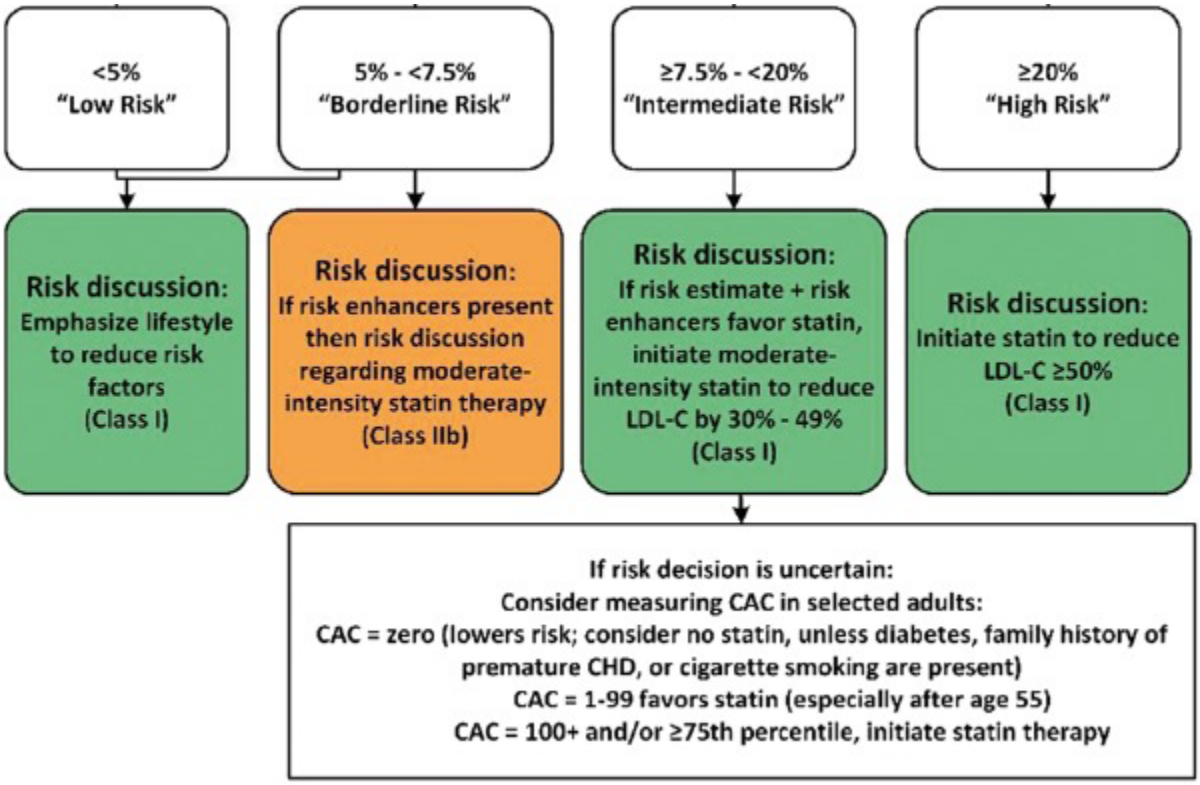
when the patient has elevated triglycerides and also **recommend once in lifetime screening for Lp(a) for all patients.**

Other lipid markers: Apo A-1, IDL, VLDL, chylomicrons + others. Apo A-1 can be thought of as the good marker (aka attached to HDL). IDL and VLDL are atherogenic and chylomicrons should not be found circulating in healthy patients but should be checked in true cases of familial hypertriglyceridemia (ex. extreme elevations while fasted).

If a patient does have significantly elevated LDL (>5.0 mmol/L), it would be reasonable to complete an appropriate physical exam.

Physical exam findings: There are two prominent physical features for hyperlipidemia. The first is tendon xanthomas, which are essentially cholesterol deposits in the tendons. You can usually see them over the achilles tendons and these are highly specific for a lipid disorder. The other feature is a corneal arcus; lipid deposits on the edge of the cornea. In the elderly these are often more age related but in those under the age of 40-45, it can be highly suggestive of a lipid disorder. The cumulative findings of the LDL number, physical exam, medical and family history can be used in the Dutch Lipid clinic or Simon Broom calculator for familial hypercholesterolemia.

ASCVD:



ASCVD risk calculation can help guide statin initiation decisions for primary prevention. Patients who are high risk should be started on a high intensity statin with the goal of LDL reduction of 50%. Intermediate risk assessment needs shared decision making and can factor in other risk factors too. There are additional calculators and lab markers that can be utilized to aid this decision. Coronary calcium scoring is also a tool, depending on patient hesitancy. Low risk patients generally do not need statins for primary prevention.

Objective Three

When hyperlipidemia is present, take an appropriate history, and examine and test the patient for modifiable causes (e.g., alcohol abuse, thyroid disease).

Diet, Physical Activity and Other Lifestyle Risks:

- High consumption of red meat likely does worsen hyperlipidemia and contributes to an elevated LDL + general consumption of trans fats and saturated fats
- Alcohol consumption

- Sedentary lifestyle can be a major contributor to a low HDL
- Smoking has been shown to lower HDL and also impair its function
- Obesity

Secondary Causes of Hyperlipidemia:

- Uncontrolled hypothyroidism (generally excluding subclinical hypothyroidism) does cause hyperlipidemia and all patients should have a TSH screen done if diagnosed with a true high cholesterol diagnosis. Can monitor vs treat the cholesterol depending on how high the cholesterol is and how uncontrolled the thyroid is.
- Nephrotic syndrome can cause elevated triglycerides and total cholesterol/LDL and select patients should be screened with a urine protein:creatinine ratio (even with a normal creatinine). If identified, while diagnosis and treatment of the underlying disorder is crucial, therapy for the high cholesterol is still indicated.
- Cholestatic liver disease can cause hyperlipidemia, such as primary biliary cholangitis. This is often due to elevated of lipoprotein X
- Chronic renal disease is associated with elevated LDL and hypertriglyceridemia though there isn't always a direct relationship
- Some medications can play a role in dyslipidemia, specifically certain antihypertensives such as thiazides or beta blockers. OCPs can also induce dyslipidemia at times. Antipsychotics are another major class of medications which often do induce metabolic changes that goes beyond dyslipidemia (certain ones more likely to do so than others). Other specific classes would be HIV medications, specifically protease inhibitors.
- Anabolic steroid use can cause both a high LDL and a low to very low HDL; appropriate history should be taken if this is suspected.
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Objective Four

<u>Ensure that patients diagnosed with hyperlipidemia receive appropriate lifestyle and dietary advice. Periodically reassess compliance with this advice (especially in patients at overall low or moderate CV risk).</u>

Dietary and Physical Activity Recommendations:

From Canadian Cardiovascular Society:

Recommendation: We recommend that adults should accumulate at least 150 minutes of moderate to vigorous-intensity aerobic physical activity per week, in bouts of 10 minutes or more to reduce CVD risk (Strong Recommendation; High-Quality Evidence).

Recommendation: We recommend combining low-risk lifestyle behaviours that include achieving and maintaining a healthy body weight, healthy diet, regular physical activity, moderate alcohol consumption, and moderate sleep duration to achieve maximal CVD risk reduction (Strong Recommendation; High-Quality Evidence).

Values and preferences: Low-risk lifestyle behaviours are variably defined as follows: a healthy body weight (body mass index of 18.5-25 to < 30 kg/m2 or waist circumference of < 88 cm for women or < 95 to < 102 cm for men), healthy diet (higher fruits and vegetables Mediterranean dietary pattern), regular physical activity (> 1 time per week to 40 min/d plus 1 h/wk of intense exercise), smoking cessation (never smoked to smoking cessation for > 12 months), moderate alcohol consumption (> 12-14 g/mo to 46 g/d), and moderate sleep duration (6-8 hours per night). Individuals can achieve benefits in a dose-dependent manner.

Recommendation: We recommend that all individuals are offered advice about healthy eating and activity and adopt the Mediterranean dietary pattern to decrease their CVD risk (Strong Recommendation; High-Quality Evidence).

Values and preferences: Adherence is one of the most important determinants for attaining the benefits of any diet. Individuals should choose the dietary pattern that best fits with their values and preferences, allowing them to achieve the greatest adherence over the long-term.

Recommendation: We recommend that omega-3 PUFAs supplements not be used to reduce CVD events (Strong Recommendation; High-Quality Evidence).

Values and preferences: Although there is no apparent CV benefit, patients might choose to use these supplements for other indications including the management of high triglycerides. Individuals should be aware that there are different preparations of long chain omega-3 PUFAs high in docosahexaenoic acid and eicosapentaenoic acid from marine, algal, and yeast sources and that high doses are required (2-4 g/d).

The recommendation on Omega 3s is based on insufficient data on the benefits of fish oil supplements. Prescription strength omega 3s (combined DHA/EPA) are useful for lowering triglycerides only. Supplemental forms of omega 3s can be oxidized and perhaps harmful

too. High dose EPA in prescription form has been shown to improve cardiac outcomes in select populations.

Recommendation: We suggest that individuals avoid the intake of trans fats and decrease the intake of saturated fats for CVD disease risk reduction (Conditional Recommendation; Moderate-Quality Evidence).
Recommendation: We suggest that to increase the probability of achieving a CV benefit, individuals should replace saturated fats with polyunsaturated fats (Conditional Recommendation; Moderate-Quality Evidence), emphasizing those from mixed omega-3/omega-6 PUFA sources (eg, canola and soybean oils) (Conditional Recommendation; Moderate-Quality Evidence), and target an intake of saturated fats of < 9% of total energy (Conditional Recommendation; Low-Quality Evidence). If saturated fats are replaced with MUFAs and carbohydrates, then people should choose plant sources of MUFAs (eg, olive oil, canola oil, nuts, and seeds) and high-quality sources of carbohydrates (eg, whole grains and low GI carbohydrates) (Conditional Recommendation; Low-Quality Evidence).
Values and preferences: Industrial trans fats are no longer generally regarded as safe in the United States and there are monitoring efforts aimed at reducing them to the lowest level possible in Canada. These conditions make it increasingly difficult for individuals to consume trans fats in any appreciable amount. Individuals might choose to reduce or replace different food sources of saturated fats in the diet, recognizing that some food sources of saturated fats, such as milk and dairy products and plant-based sources of saturated fats, have not been reliably associated with harm.

Specific dietary recommendations:

I. Mediterranean dietary pattern (Strong Recommendation; High-Quality Evidence);
II. Portfolio dietary pattern (Conditional Recommendation; Moderate-Quality Evidence);
III. DASH dietary pattern (Conditional Recommendation; Moderate-Quality Evidence);
IV. Dietary patterns high in nuts (> 30 g/d) (Conditional Recommendation; Moderate-Quality Evidence);
V. Dietary patterns high in legumes (> 4 servings per week) (Conditional Recommendation; Moderate-Quality Evidence);
VI. Dietary patterns high in olive oil (> 60 mL/d) (Conditional Recommendation; Moderate-Quality Evidence);

VII. Dietary patterns rich in fruits and vegetables (> 5 servings per day) (Conditional Recommendation; Moderate-Quality Evidence);

VIII. Dietary patterns high in total fibre (> 30 g/d) (Conditional Recommendation; Moderate- Quality Evidence), and whole grains (> 3 servings per day) (Conditional Recommendation; Low-Quality Evidence);

IX. Low glycemic load (Conditional Recommendation; Moderate-Quality Evidence); or low GI (Conditional Recommendation; Low-Quality Evidence) dietary patterns;

X. Vegetarian dietary patterns (Conditional Recommendation; Very Low-Quality Evidence).

Objective Five

<u>In treating hyperlipidemic patients, establish target lipid levels based on overall CV risk.</u>

Both patients with hyperlipidemia and coronary artery disease will have lipid targets to achieve but the evidence for specific targets is better for CAD patients. The marker we always tend to target is the LDL and this target will be lower depending on the risk profile. A patient with a borderline familial hypercholesterolemia diagnosis who has 0 other risk factors will have a different LDL target than someone who has 3 stents placed for a STEMI and has a long list of comorbidities. The former is likely to be part of a shared decision-making process while the latter generally has more firm evidence based targets to achieve. This is important because we want to minimize the future risk for everyone but we also don't want to overburden the patient either. For example, a very low target LDL for a patient with borderline high LDL as their only risk factor, could possibly require more than just statin therapy to achieve the goal. They may also get adverse effects when they are moved to a high-intensity statin dose. So having an appropriate target for these folks is important.

CAD patients – target LDL is often 2.0 mmol/L. Similar target can be used for familial hypercholesterolemia. For primary prevention, there isn't as robust evidence for certain targets. Mortality rates and their association with LDL have been variable. 2.5-3.0 mmol/L is a reasonable target for those who do not have cardiovascular disease and no suspected genetic disease.

Objective Six

In patients receiving medication for hyperlipidemia, periodically assess compliance with and side effects of treatment.

Patient diagnosed with hyperlipidemia will generally be starting on a statin and have their lipid markers periodically checked to assess for improve and meeting of targets. If unable to tolerate a statin, can look at trialing a different statin. Failure to tolerate multiple statins is a good reason to move on and initiate other therapies. If the patient is tolerating high intensity statin therapy but still not meeting their lipid goals, then it would be ideal to add a 2nd line therapy. Occasionally, some patients require more than 2 medications to meet their goals and/or require more intensive medications such as PSCK9 inhibitors.

Statins

High-Intensity Statin	Moderate-Intensity Statin	Low-Intensity Statin
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg	Simvastatin 10 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg	Pravastatin 10–20 mg
	Simvastatin 20–40 mg	Lovastatin 20 mg
	Pravastatin 40–80 mg	Fluvastatin 20–40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg bid	
	Pitavastatin 2–4 mg	

[a]From: Stone NJ, Robinson JG, Lichtenstein AH et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2014;63:2889–934.

doi:10.1371/journal.pone.0154952.t001

High intensity – Lowers LDL by >50%

Medium intensity – lowers LDL by 30-49%

Low intensity – Lowers LDL by <30%

Side effects

Most common: Myalgias/myopathy – 2-10% depending on severity and if creatine kinase elevation occurs. Less likely to occur with hydrophilic statins (rosuvastatin & pravastatin). Next step management can be less frequent dosing & changing the specific drug or lowering the dose. Some patients may tolerate every other day dosing as well.

Uncommon: Liver disease / Drug induced liver injury (DILI) - <1% prevalence. Mild transaminitis is not a contraindication to statin use. Statins often improve liver enzyme numbers with patients who have fatty liver disease! If liver enzymes rise to 3x upper limit, that is often a good reason to discontinue and re evaluate.

Rare: anti-HMGCR myopathy – Very rare adverse effect with very high CK levels & proximal weakness.

As a side point, studies did not show any benefit for coenzyme q10 supplementation to prevent statin adverse effects.

Ezetimibe

Often the general 2nd line medication after statins to help further lower LDL. It is also used in those who cannot tolerate statins but may not be optimal in reaching LDL goals on its own. LDL reduction is generally on par with a low intensity statin or even less at 15-20%.

Fibrates

Pharmacotherapy for hypertriglyceridemia (especially if familial). Generally, you would use this medication as monotherapy if the patient has failed dietary & lifestyle changes, and does not need statins. Also would use as monotherapy if the triglycerides are in a severe range. The goal is improvement of triglycerides but there is some benefit to HDL as well, but not as much with LDL. It can cause some of the same adverse effects as statins with myopathy and CK elevations but unlike statins, it can affect the kidneys and liver much more extensively. It is actually contraindicated in liver disease for example.

Bile acid resins

Can be utilized for the treatment of hyperlipidemia. An example medication is cholestyramine. There is usually a dose dependent reduction of LDL seen and main adverse effects are related to fat absorption and sometimes fat-soluble vitamin absorption. It is the only lipid therapy that can be used during pregnancy as of 2022.

PCSK9 inhibitors

2 current drugs: evolocumab & alirocumab.

Indications: Treatment of CAD in patients not meeting LDL targets on other therapy (usually statins +/- ezetimibe) or patients with familial hypercholesterolemia who require further LDL lowering. Those who cannot tolerate statins but require significant LDL reduction are also good candidates. LDL reduction is >50% and there are minimal adverse effects. Cost is a general barrier but improving. Patients require close lipid monitoring (4-12 weeks after initiation).

Inclisiran – siRNA inhibitor which is a PSCK9 inhibitor variant essentially. Newly approved by FDA in USA in December 2021, offers significant LDL reduction (>50%).

Adjuncts

Icosapent ethyl (high dose EPA) – indicated for patients who have CAD to help lower triglycerides further. It does improve mortality rates but clinical trials did show elevated risk of atrial fibrillation! Supplement omega 3s are not effective in improving mortality. In fact, supplements have been found to be rancid and oxidized, hence potentially inflicting harm. Other prescription omega 3s (EPA/DHA combined) can be used for the treatment of hypertriglyceridemia but not have shown isolated cardiac benefits.

Bempedoic Acid

Newer agent for helping further lower LDL to meet targets. Usually see about a 20-30% reduction in LDL with minimal adverse effects (usually nasopharyngitis) but does elevate the risk of gout so monitoring uric acid levels would probably be wise.

Niacin

While it does improve LDL numbers in isolation, current guidelines and literature do not recommend its use as it does not improve mortality. Interestingly, it is one of the very few drugs which improves Lp(a). But it does cause uncomfortable flushing sensations and can cause liver toxicity. Not recommended for anyone at this time.

New novel medications:

Evinacumab – ANGPTL3 inhibitor – utilized for homozygous FH. Other therapies for HoFH include lomitapide and mipomersen. These are novel therapies which should only be prescribed by a lipid specialist.

References

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