Dyslipidemia Management

Cardiovascular disease (CVD) causes one third of deaths in Canada. (1) Due to an increase in diabetes, obesity and sedentary lifestyle, the prevalence in of CVD Canada is expected to increase. (1) Mortality from coronary artery disease has decreased over recent decades which can most likely be attributed to improvements in control of known cardiovascular risk factors in these patients, specifically, blood pressure, smoking, and cholesterol levels. (1)

Assessment

Screening of plasma lipids is recommended in adult men 40 and over and women that are 50 years of age or older or who are postmenopausal. While adults at any age with the following risk factors should be screened for lipids at any age:

- modifiable factors: smoking, diabetes, hypertension, obesity
- others: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), chronic HIV infection, chronic kidney disease (CKD), abdominal aortic aneurysm (AAA), erectile dysfunction (ED)
- individuals of First Nation or South Asian ancestry are at increased risk and consideration should be given for screening at an earlier age

Cardiovascular risk assessment has been shown to help health care providers to identify patients most likely to benefit from primary prevention therapies. Key points to discuss with patients include reassuring low risk patients that they are doing well, and advising individuals with treatable risk factors or unhealthy behaviours to address these factors while identifying those that are most likely to benefit from pharmacotherapy.

Recommendations by the 2012 Update to the CCS Guidelines suggests initial risk assessment be completed using the Framingham Risk Score (FRS) to estimate the 10 year risk of developing “total” cardiovascular events. (2)

(See Cardiovascular Disease risk calculation module)

The categories of risk are displayed in Table 1. Low risk is considered to be those with an FRS of less than 10%. (2) The intermediate risk group are those with a FRS of 10-19% and encompasses a significant proportion of the Canadian population. (2) The high risk group has a FRS that exceeds 20% and are the principle beneficiaries of statin therapy. (2) They are those with clinical evidence of atherosclerosis, previous MI, coronary revascularization, coronary artery bypass graft (CABG) surgery or other revascularization procedures as well as those with cerebrovascular disease including transient ischemic attack (TIA) or peripheral arterial disease. (2) The 2012 guidelines have added abdominal aortic aneurysm (AAA) because atherosclerosis is the primary aetiology of this type of aneurysm. (2) This group also includes those with an FRS score of greater than 20%, or those with clinical valvular disease, diabetes and age ≥ 40 or diabetes of 15 yrs duration and age≥30 with silent or documented microvascular disease. (2) Those with CKD are at increase risk of CVD depending on their level of glomerular filtration rate (GFR) and urinary albumin excretion.(2) Anyone with a GFR of less than or equal to 45 mL/min/1.73m^2 or albumin-to-creatinine ratio (ACR) of ≥ 30 mg/mmol (≥ 300 mg/day) is considered high risk. Those with a GFR of ≤ 60 mL/min/1.73m^2 and an ACR of ≥ 3 mg/mmol are also at higher risk as shown in the SHARP study that showed benefit of lipid lowering therapy with a combination of statin and ezetimibe in this patient population. High risk can also be defined by hypertension plus three of the following risk factors: male, age > 55 years, smoking, total cholesterol/HDL-C ratio > 6, left ventricular hypertrophy (LVH), family history of premature CVD, electrocardiogram (ECG) abnormalities, or micoalbuminuria. Patients with all of the above characteristics were all shown to gain benefit from statin therapy. In those with a family history of premature atherosclerosis in a first degree relative, the calculated Framingham risk score should be doubled.

Treatment

For those considered low risk treatment is initiated if LDL-C is greater than or equal to 5 mmol/L, a level that usually indicates a genetic lipoprotein disorder. The goal for treatment is for a greater than or equal to a 50% reduction in LDL-C. (2)

In the intermediate risk group of patients treatment is initiated if LDL-C is greater than 3.5 mmol/L. Pharmacologic therapy is recommended in this patient group after initiation and compliance with health behaviour modifications among individuals whose LDL-C remains above 3.5 mmol/L because the absolute benefit is estimated to be significant in these patients. (2) Treatment targets for this population are for less than or equal to 2 mmol/L or a greater than 50% reduction in the untreated baseline LDL-C. (1) Nearly all clinical trials in cholesterol treatment used LDL-C as an indicator of response to therapy. Every 1 mmol/L reduction in LDL-C is associated with a corresponding 20-25% reduction in CVD mortality and non fatal myocardial infarction (MI). (2)

Table 1 Summary of treatment thresholds and targets based on Framingham Risk Score (FRS) (1)

Risk level	**Health Behaviour Modification**	**Initiate Drug therapy if:**	**Primary target: LDL-C**
High (FRS ≥ 20%)	For all	Consider treatment in all	≤ 2 mmol/L or ≥ 50% ↓ LDL-C
Moderate (FRS 10 to 19%)	Consider as first line treatment, If no improvement initiate drug therapy	LDL-C ≥ 3.5 mmol/L For LDL-C < 3.5	≤ 2 mmol/L or ≥ 50% ↓ LDL-C
Low (FRS < 10%)	For all	LDL-C ≥ 5 mmol/L Familial hypercholesterolemia	≥ 50% ↓ LDL-C

Treatment is to be initiated in all of those considered to be in the high risk category. This group achieves the greatest absolute benefit from pharmacotherapy and statins remain as the primary first line therapy. (1) The target of treatment, similar to the intermediate risk group is an LDL-C of less than or equal to 2 mmol/L. (1) In those with a severe baseline dyslipidemia or in patients in whom therapy is limited by drug intolerance and who fail to achieve the 2 mmol/L goal, a 50% or greater reduction of LDL-C from baseline is recommended. (1) In some individuals with recurrent vascular disease or very high risk on the basis of established vascular disease and multiple major coronary risk factors an LDL-C of less than 1.8 mmol/L is justified based on the finding that

that the Cholesterol Treatment Trialists (CTT) Collaboration of 2010 showed that individuals achieving this target with a standard statin regimen showed additional benefit and no increase in major side effects with this goal. (6)

Health Behaviours Modification

Health behaviours remain the cornerstone of chronic disease prevention including cardiovascular disease. Smoking cessation is one of the most important health behaviour interventions for the prevention of CVD. (1) There is a linear and dose dependent association between the number of cigarettes smoked per day and CVD risk. (7) Pharmacological therapy is associated with an increased likelihood of smoking abstinence. (2)

Nutrition therapy is an integral component to help improve the lipid profile and importantly reduces the risk of cardiovascular events. Dietary therapy augments statin therapy and remains an important therapeutic tool with few side effects and little harm. (2) Diets low in sodium & simple sugars, substitution of unsaturated fats for saturated and trans fats and caloric restrictions to maintain an ideal body weight are just some of the ways to improve lipid profiles. (2)

Physical activity is an important cardiovascular disease prevention strategy. Regular exercise has beneficial effects on diabetes risk, hypertension, hypertriglyceridemia and improves plasma HDL-C levels. Adults should accumulate at least 150 minutes of moderate to vigorous aerobic activity per week in bouts of 10 minutes or more. (2, 8) It can also be beneficial to add bone and muscle strengthening activities at least 2 days per week. (2)

The INTERHEART study confirmed the importance of stress as a CVD risk factor. (7) After MI, patients with depression have a worse prognosis but it remains unclear whether pharmacological management reduces this risk. (7) Health care providers should explore stress management techniques with this population to optimize quality of life.

Alcohol consumption is not contraindicated in patients with CVD but should be used in moderation. (1) Females should consume no more than 0-2 standard drinks per day and a maximum of 10 standard drinks per week. (9)

Males should consume no more than 0-3 standard drinks per day and a maximum of 15 standard drinks per week. (9)

Pharmacotherapy

Pharmacotherapy is to be initiated in all high risk patients used along with health behaviour modification. (1) In intermediate risk patients lifestyle changes should be implemented first, followed by medications if targets are not reached. (1)

In high risk patients treatment should be started immediately, the majority of patients will be able to achieve target LDL-C levels on **statin monotherapy**. (1) However, a significant minority may require combination therapy with an agent that inhibits cholesterol absorption (ezetimibe), or bile acid re-absorption (cholestyramine, colestipol), or concomitant use of niacin. These alternate therapies are usually for use in patients that do not tolerate statin therapy, or used in combination with a statin for those that can only tolerate them at low dose. Favourable effects on LDL-C can be achieved with ezetimibe, bile acids or niacin. Niacin therapy alone has been shown to decrease CVD events. (10)

In patients with extreme hypertriglyceridemia (> 10 mmol/L) fibrates may prevent pancreatitis. Combinations are safe and generally reduce LDL-C by an additional 10-15%.

See table below for summary of recommendations available pharmacotherapy choices and recommended dosage ranges.

Table 2 Lipid-lowering medications (1)

Generic name	Trade name	Recommended dose range (daily)
Statins		
Atorvastatin	Lipitor	10 mg – 80 mg
Fluvastatin	Lescol	20 mg – 80 mg
Lovastatin	Mevacor	20 mg – 80 mg
Pravastatin	Pravachol	10 mg – 40 mg
Rosuvastatin	Crestor	5 mg – 40 mg
Simvastatin	Zocor	10 mg – 80 mg*
Bile acid and/or cholesterol absorption inhibitors		
Cholestyramine	Questran	2 g – 24 g
Colestipol	Colestid	5 g – 30 g
Ezetimibe	Ezetrol	10 mg
Fibrates		
Bezafibrate	Bezalip	400 mg
Fenofibrate†	Lipidil Micro/Supra/EZ	48 mg – 200 mg
Gemfibrozil†‡	Lopid	600 mg – 1200 mg
Niacin		
Nicotinic acid	Generic crystalline niacin	1 g – 3 g
	Niaspan	0.5 g – 2 g

*Increased myopathy on 80 mg;
†Reduce dose or avoid in renal impairment;
‡Should not be used with a statin because of an increased risk of rhabdomyolysis

Preliminary and safety Monitoring

Before initiation of pharmacological therapy for dyslipidemias, baseline lipoprotein profile should be obtained after 10-12 hr fast, preferably with patient refraining from alcohol for 24-48 hours. The profile should include Total Cholesterol, HDL-C, and triglycerides. A fasting blood glucose level should also be obtained at baseline to identify the presence of impaired fasting blood glucose or diabetes. In patients with Low HDL-C, baseline Thyroid stimulating hormone level helps uncover the occasional hypothyroid induced hyperlipidemia.

Statins are generally well tolerated, the most common intolerance issues are adverse muscle effects and abnormal elevations in Liver function tests (LFT's). These side effects occur in approximately 5% of patients. (1) Baseline alanine aminostrasferase (ALT), and aspartate aminotransferase (AST), serum creatinine (Secr), creatinine kinase (CK) are useful to monitor potential side effects associated with therapy.

Follow-up Monitoring

Re-checking of the lipoprotein panel is based on risk assessment with FRS. If the FRS is less than 5% then lipoprotein levels are to be checked every 3-5 years. (2) If FRS is greater than or equal to 5% then lipoprotein levels should be monitored yearly. Follow up of LFT's and CK levels is not indicated unless driven by symptoms. Myalgias are one of the most common side effects of statins and can occur in approximately 5 % of patients on statin therapy. They are characterized by dull muscle aches that worsen with exercise but can occur in patients that are sedentary as well. CK levels may remain normal, and a diagnosis can be made with drug discontinuation and re-challenge.

Myositis is an inflammation of skeletal muscles and the diagnosis can be made based on muscle discomfort and elevation of CK to more than three times the upper limit of normal. It is a serious condition that can potentially be caused by strenuous exercise. Management of myositis in a patient taking a statin involves a dose reduction and close monitoring of CK levels. Discontinuation of the statin is often required.

Rhabdomyolysis is a syndrome characterized by muscle necrosis and the release of intracellular muscle constituents into the circulation. It is a life threatening condition with a prevalence of less than 1 in 100,000 statin treated patients. It is characterized by severe muscle pains, myoglobinuria, and possibly acute renal failure (ARF) and a CK level greater than 10,000U/L. Prompt discontinuation of the statin and hospitalization for supportive treatment is required.

A very small percentage of patients taking statins (0.3-2.0%) can have significant elevations in hepatic transaminases defined as an ALT level of greater than three times the upper limit of normal. It is generally considered to be dose related.

Treatment with niacin preparations can result in persistent significant elevations in ALT in approximately 1% of patients. (1) Generally is recommended to assess ALT at baseline and between one and three months after initiating therapy. Fasting blood glucose and glycosylated hemoglobin should be monitored every 6-12 months in these patients as niacin has a tendency to increase blood glucose levels. (1) Uric acid levels should also be monitored in patients taking niacin.

In patients taking fibrates, increases in serum creatinine of 15-20% are commonly seen. (1) More significant increases can be seen in those with underlying kidney disease. Fibrates should be initiated at the lowest available dose and increased only after re-evaluation of renal function and lipid parameters. (1)

Drug interactions.

There an increased risk of myopathy with statins and gemfibrozil; therefore, this combination is not recommended. Statins metabolized by the CYP3A4 enzyme system. (E.g. Simvastatin, Atorvastatin) are more prone than those metabolized by the CYP2C9 enzyme system (E.g. Rosuvastatin) to drug-drug interactions causing myopathy when used concomitantly with inhibitors of CYP3A4 (amiodarone, verapamil, diltiazem, and amlodipine). The guidelines recommend that the Simvastatin dose not exceed 20mg when used concomitantly with amlodipine, and it should not exceed 10 mg if amiodarone, verapamil, or diltiazem are being used. Simvastatin (and Atorvastatin) should not be used at all with antifungal agents, cyclosporine, or the macrolide antibiotics.

Patient Information

Health behaviours remain the cornerstone of management of dyslipidemias. These include smoking cessation, diet restrictions, exercise, stress management and limitations on alcohol consumption. They should be

universally applied to all patients for the prevention of chronic disease and are outlined under Health behaviours under treatments for dyslipidemias.

Patients should be advised to stop statin therapy and contact prescribing health care provider if worrisome symptoms develop. The effort spent preserving statin therapy in subjects with adverse effects should be directly related to the level of risk for each individual patient. In high risk patients all options should be exercised before changing to alternative therapy or withdrawing treatment. Lower dose combination therapy remains an option for those patients, with emphasis on more aggressive non-pharmacologic approach such as diet modification and exercise. For subjects with lower risk, re-evaluation of the need for the lipid lowering therapy should precede a change to alternative therapy because outcomes studies are not as robust.

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