2016 Canadian Cardiovascular Society
GUIDELINES FOR THE MANAGEMENT OF DYSLIPIDEMIA FOR THE PREVENTION OF CARDIOVASCULAR DISEASE IN THE ADULT


*equal contribution

Short title: 2016 CCS Dyslipidemia Guidelines

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BRIEF SUMMARY

The 2016 Canadian Cardiovascular Society Dyslipidemia guidelines provide guidance to clinicians for the assessment of risk and appropriate treatment of dyslipidemia for the prevention of cardiovascular disease. The focus is on shared decision making between the clinician and patient. We now recommend non-fasting determination of lipids and expanded definitions of subjects who will benefit from statin therapy. There is also new information on the use of health behavior modifications and non-statin medications.
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ABSTRACT

Since the publication of the 2012 guidelines new literature has emerged to inform decision making. The 2016 guidelines primary panel selected a number of clinically relevant questions and has produced updated recommendations, based on important new findings. In subjects with clinical atherosclerosis, abdominal aortic aneurysm, most subjects with diabetes or chronic kidney disease and those with low-density lipoprotein (LDL) cholesterol ≥ 5 mmol/L, statin therapy is recommended. For all others, there is an emphasis on risk assessment linked to lipid determination to optimize decision making. We have recommended non-fasting lipid determination as a suitable alternative to fasting levels. Risk assessment and lipid determination should be considered in individuals over 40 years of age or in those at increased risk regardless of age. Pharmacotherapy is generally not indicated for those at low Framingham Risk Score (FRS) <10%. A wider range of patients are now eligible for statin therapy in the intermediate risk category (10-19%) and in those at high FRS (>20%). Despite the controversy, we continue to advocate for LDL-C targets for subjects who are started on therapy. Detailed recommendations are also presented for health behavior modification which is indicated in all subjects. Finally, recommendation for the use of non-statin medications is provided. Shared decision making is vital as there are many areas where clinical trials do not fully inform practice. The guidelines are meant to be a platform for meaningful conversation between patient and care provider so that individual decisions can be made for risk screening, assessment and treatment.
INTRODUCTION AND PROCESS:

The 2012 Canadian Cardiovascular Society (CCS) Dyslipidemia Guidelines have been updated to reflect new clinical trial and epidemiologic evidence. The primary panel posed a number of PICO (population, intervention, comparator, outcomes) questions to create recommendations based on detailed literature review. The PICO format is a common standard used for guidelines implementation, aiding clinicians in determining if the recommendations apply to their own patients with outcomes relevant to their practice. Using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) standards, individual studies and composite literature was reviewed for quality and bias. We have included both strong and conditional recommendations within the main manuscript. The literature review and results of voting on each PICO question are included in the Supplement. For recommendations to go forward a 2/3 voting majority was required. Individuals with conflicts of interest were recused from voting. We have introduced a recommendation for non-fasting lipid determination and retained the concept of LDL-C targets of treatment. Global risk assessment is discussed recognizing there are several approaches in a primary prevention setting. The overall goal of the process was to produce a document based on the best available evidence that would allow clinicians and patients to make collaborative treatment decisions (Table 1). These guidelines are not absolute, but are meant to launch one on one discussion between practitioner and patient. As dyslipidemia is an important risk factor for cardiovascular disease, these guidelines will allow appropriate risk assessment, treatment and surveillance options of our at risk population. These guidelines were undertaken under the auspices of the Guideline Committee of the CCS without any support or involvement from outside groups including industry.

DEFINITIONS:

CVD events: cardiovascular death, non-fatal myocardial infarction, ischemic stroke, revascularization, acute coronary syndromes hospitalizations

NNT: number needed to treat to prevent one CVD event for 5 years of treatment per 1 mmol/L reduction in LDL-C. NNT of <50 are generally regarded as desirable by physicians with some patients wishing to see NNT<30 to deem an intervention as acceptable.
RISK ASSESSMENT FOR PRIMARY PREVENTION

PICO: In adults, does the use of one of the currently recommended risk engine in comparison to no risk assessment improve the management of dyslipidemia to reduce CVD events?

The primary goals of CVD risk assessment should be (1) to re-assure individuals without any treatable risk factors that they are doing well; (2) to advise individuals with treatable risk factors or unhealthy behaviors; and (3) to identify subjects most likely to benefit from pharmacotherapy. Several studies have also demonstrated that the potential benefits of risk assessment are maximized when results are directly communicated to the patient.1-5

The American Heart Association and American College of Cardiology have recently proposed the use of a new Atherosclerotic Cardiovascular Disease Risk Score.6 This risk algorithm has been shown to shift treatment recommendations to older individuals, at the expense of younger individuals where benefits may be greater, compared to the currently recommended CCS approach.7

Although risk algorithms are useful in determining high-risk groups, several shortcomings must be recognized with all 10 year risk assessment strategies including the Framingham Heart Study risk score (FRS). Firstly, short-term risk estimates over 10 years are overly sensitive to the patient’s age such that older individuals are more likely to be targeted for therapy. Secondly, cardiovascular risk scoring strategies tend to be better calibrated among middle aged individuals as traditional cardiovascular risk factors such as dyslipidemia, are most strongly associated with premature CVD.8,9 It has been estimated that many younger individuals (especially those with elevated LDL-C) will benefit substantially from long-term therapy even if they are at low risk over the short term. Indeed these patients can present a high life-long risk of CVD.10,11 Furthermore for patients above 75 years of age, the Framingham model is not well validated.12

Based on the limitations of 10 year risk models, there is increasing interest in risk calculations that assess 30 year risk, lifetime risk, or metrics such as “cardiovascular age”, “vascular age”, or “cardiovascular age risk”.13-17 Cardiovascular age using the Cardiovascular Life Expectancy
Model (CLEM) is calculated as the patient's age minus the difference between his or her estimated remaining life expectancy (adjusted for coronary and stroke risk) and the average remaining life expectancy of Canadians of the same age and sex. For example, a 50-year-old with a life expectancy of 25 more years (vs 30 more years for the average Canadian male who lives to be 80 years) would be assigned a cardiovascular age of 55 years (http://www.chiprehab.com/). When primary health care providers engage Canadian patients by discussing their “cardiovascular age” uncertainty surrounding prescribed therapy is reduced and the management of dyslipidemia and hypertension is improved.\textsuperscript{2,18}

Among individuals 30-59 years of age without diabetes, the presence of a positive parental history of premature CVD (less than 55 years in first degree male relatives and less than 65 in female relatives) increases an individual’s calculated FRS percent risk by approximately 2 fold.\textsuperscript{19} The 10 year Framingham risk percentdoubled for family history of premature CVD will be referred to as the “modified FRS” (http://www.ccs.ca). The Cardiovascular Life Expectancy Model automatically adjusts the annual risk for a positive family history. To date only the FRS model and the CLEM have been validated and shown to accurately estimate risk among Canadians.\textsuperscript{20} It is acknowledged that these models are not validated for South Asian, first Nations or new immigrant populations. Therefore we would recommend these two methods of risk assessment for use, with these caveats in mind.

**RECOMMENDATIONS**

1. We recommend that a cardiovascular risk assessment be completed every 5 years for men and women age 40 to 75 using the modified Framingham risk score or Cardiovascular Life Expectancy Model to guide therapy to reduce major cardiovascular events. A risk assessment may also be completed whenever a patient’s expected risk status changes. (Strong Recommendation, High Quality Evidence)

2. We recommend sharing the results of the risk assessment with the patient to support shared decision making and improve the likelihood that patients will reach lipid targets. (Strong Recommendation, High Quality Evidence)
Practical Tip:

While there is good evidence to support the use of statins in secondary prevention in patients over the age of 75 years for some outcomes, a mortality benefit has not been demonstrated. In addition, the evidence for statin use in primary prevention is lacking in this population, mainly because they have not been extensively studied. For robust elderly patients felt to be at higher risk a discussion about the importance of statin therapy in overall management should be undertaken as these patients are often at high risk where a CVD event has importance consequences for morbidity.

WHOM TO CONSIDER FOR SCREENING:

Screening should be considered for men and women > 40 years of age or at any age with the conditions listed in Figure 1. These conditions are associated with an increased risk of CVD. They represent both traditional CVD risk factors and a variety of inflammatory conditions that were reviewed in the 2012 guidelines. In addition, we addressed the following PICO question.

PICO: Among women of any age with previously documented hypertensive diseases of pregnancy should lipid screening be recommended to identify those at an increased risk of CVD events?

Women with a previous history of hypertensive disorders of pregnancy (HDP) which includes pre-eclampsia and pregnancy induced hypertension, represent among the highest-risk populations for premature cardiovascular disease (CVD). The average age of onset of the first vascular event in this group is 38 years (for those who develop an event) and the 30-year survival rate is markedly attenuated compared with uncomplicated pregnancies. HDP is independently associated with increased risk of CVD death: 2.14 (1.3-3.6) for women with preeclampsia and 9.5 (4.5-20.3) for severe preeclampsia. The 2011 American Heart Association (AHA) Guidelines on the prevention of CVD in women now include HDP as an independent CV risk factor.

Answer: Women diagnosed with HDP should be approached for screening with a lipid panel regardless of age. There is insufficient evidence to classify these individuals in the high risk (ie. Statin indicated condition) category. However, drug therapy could be discussed with the patient given the high long term risk. Statins are contraindicated during pregnancy so risk-benefit ratios
must be particularly assessed for treatment in women of child bearing age (See Supplemental material for full narrative).

HOW TO SCREEN: FASTING OR NON-FASTING LIPID DETERMINATION

PICO: Among adults in whom screening is recommended is non-fasting lipid determination equivalent to fasting lipid determination for risk assessment?

In contrast to changes seen in triglycerides following a large oral fat load, triglyceride and low density lipoprotein cholesterol (LDL-C) levels change relatively little after normal meals in the majority of the population. General and community-based population studies found that triglyceride levels increase only 0.2-0.3 mmol/L or 20% after eating normal meals, typically peaking 4 hours postprandially. LDL-C levels are reduced after eating, by an average of 0.1-0.2 mmol/L or 10%, either due to hemodilution, to exchange of cholesterol on LDL by triglycerides or due to calculation using the Friedewald formula. Total cholesterol, HDL-cholesterol (HDL-C), non-HDL-cholesterol (non-HDL-C), and apolipoprotein B100 (apo B) do not vary appreciably after eating. Recent data from the NHANES study demonstrated that the ability to predict CVD events was identical for non-fasting and fasting LDL-C determination.

Non-fasting lipid testing increases convenience for patients and laboratory operations. Non-fasting testing does not affect risk assessment strategies, since total and HDL-cholesterol, used to estimate 10 year CVD risk, are not altered significantly in the non-fasting state.

Since the major studies that determined changes in non-fasting lipids excluded individuals with prior triglyceride levels >4.5 mmol/L, we do not have data on changes in lipid levels in this subgroup of patients (estimated to be 1.5-2% of the population) after eating. Moreover, triglyceride replacement of cholesterol on LDL occurs with elevated triglyceride levels, meaning reported LDL-C levels do not reliably indicate LDL particle number when triglycerides are >1.5 mmol/L. For this reason it remains the recommendation to use the non-HDL-C level (or apo B), which is not altered after eating or by triglycerides, as the treatment target of choice when triglyceride levels are >1.5 mmol/L. Finally, individuals with a previous triglyceride level >4.5 mmol/L should have their lipids tested in the fasting state.
The purpose of this guideline change is to provide physicians and patients with the option to have screening and follow-up non-fasting lipid testing, however it is recognized that some physicians will prefer that patients have their lipid profiles tested fasting (Figure 2). While non-fasting triglycerides are predictive of increased CVD and mortality risk, and increased levels are indicators of insulin resistance and atherogenic remnant lipoproteins, non-fasting triglyceride targets are not currently included in any national lipid guidelines. A non-fasting approach has recently been advocated in Europe. 

**RECOMMENDATION:**

1. We recommend non-fasting lipid and lipoprotein testing which can be performed in adults in whom screening is indicated as part of a comprehensive risk assessment to reduce CVD events (Strong Recommendation, High Quality Evidence).
2. We suggest that for individuals with a history of triglyceride levels > 4.5 mmol/L that lipid and lipoprotein levels be measured fasting (Conditional Recommendation, Low Quality Evidence).

**Practical Tip:** Compared to fasting lipid values, there will be minimal change with non HDL-C, a slight decrease in LDL-C and small increase in triglyceride concentrations when individuals do not fast.

**PRIMARY AND SECONDARY LIPOPROTEIN DETERMINANTS**

**PICO:** In adult patients, are apo B and non-HDL-C still appropriate as alternate targets to evaluate risk?

There is no significant new literature on this topic since the publication of the 2012 guidelines. Non HDL-C is derived from the simple calculation of total cholesterol minus HDL-C and is the sum of all the cholesterol transported in atherogenic lipoproteins (Figure 3). One molecule of apo B is present in all atherogenic lipoproteins including LDL, very LDL, remnants and
lipoprotein (a). Multiple observational and RCTs have demonstrated that non-HDL-C and/or apo B predict risk similarly or better than LDL-C. The Emerging Risk Factors Collaboration, in an analysis of 302,430 people without vascular disease from 68 prospective trials published in 2009, concluded that both apo B and non–HDL-C, predicted risk similarly to directly measured LDL-C and that fasting did not affect the hazard ratios. Another meta-analysis by Sniderman and colleagues, including 233,455 subjects from 12 reports and published in 2011, concluded that apo B was the best predictor of CV risk, followed by non-HDL-C, followed by LDL-C.

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<th>RECOMMENDATION:</th>
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<td>We recommend that non-HDL-C and apo B should continue to be considered alternate targets to LDL-C to evaluate risk in adults (Strong Recommendation, High Quality Evidence).</td>
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*Values and preferences:* As clinicians are most familiar with LDL-C we continue to recommend its use as the primary target, but anticipate a shift to preferential use of non-HDL-C or apo B in the future.

WHEN TO CONSIDER PHARMACOLOGICAL TREATMENT IN RISK MANAGEMENT

**PICO:** In adults, do current dyslipidemia treatment recommendations based on levels of risk reduce CVD events?

When deciding on whom to consider for pharmacotherapy we would suggest the following approach (Figure 4). 1) *Statin-indicated conditions:* Identify those patients who are in the 5 statin-indicated conditions listed below. Risk assessment is not required for these individuals as statin therapy is indicated. 2) *Primary prevention:* Perform a risk assessment for those who do not have the above high risk conditions. If the preference is to calculate total CVD risk using the Framingham risk score, modified for family history then one would identify those at low risk (<10%) in whom pharmacotherapy is not indicated. In addition, those with a FRS of >20% (high risk) should be approached for treatment. Those in the intermediate risk (IR) category may be considered for statin therapy based on randomized trial criteria and patient preference. (Table 2)

1. **Statin indicated conditions**
This group achieves the greatest absolute benefit from lipid lowering therapy as they are at high risk. This includes subjects with: 1) clinical atherosclerosis, i.e. previous MI, or coronary revascularization by percutaneous coronary intervention or coronary artery bypass graft surgery, other arterial revascularization procedures, angina pectoris, cerebrovascular disease including transient ischemic attack, or peripheral arterial disease (claudication and/or ABI < 0.9) (NNT = 20); 2) abdominal aortic aneurysm (> 3.0 cm diameter); 3) diabetes mellitus - age ≥ 40 years, ≥ 15 years duration for age ≥ 30 years (type I DM), or with the presence of microvascular disease (NNT = 20-25); 4) chronic kidney disease (CKD) – see next section for definition (NNT = 20), or 5) LDL-C ≥ 5.0 mmol/L (including genetic dyslipidemias), (NNT = 25). Statins are the initial lipid lowering agent of choice for all of these groups (see Figure 2). We have not made specific recommendations on statin intensity or dose. However, for most conditions we have targeted a 50% reduction in LDL-C which usually requires moderate to high dose of a potent statin depending on the response to lifestyle interventions.

2. Primary Prevention

Studies consistently demonstrate a 20-22% relative risk reduction for each 1 mmol/L reduction in LDL-C. The absolute risk reduction is thus dependent upon the baseline risk and to some degree the baseline LDL-C as statin treatment will provide a greater absolute LDL-C lowering in those with higher baseline values.

a) The low risk category applies to individuals with a modified 10 year FRS < 10%. The vast majority of these individuals do not require pharmacologic therapy. The exceptions are subjects with an LDL-C ≥ 5.0 mmol/L, many of whom have a genetic dyslipidemia such as familial hypercholesterolemia (see statin indicated conditions). In individuals with modified FRS of 5%-9%, yearly monitoring could be utilized to evaluate change in risk. Based on a consistent relative risk reduction observed in the CTT meta-analysis, certain individuals in the low risk category might decide to start statin therapy with a view to long term risk reduction.

b) The high risk category is the least common in the general population until age increases beyond 65 years. It is defined as an adjusted FRS 10 year risk ≥ 20%. Statin therapy is indicated for these subjects (NNT =35).

c) The intermediate risk (IR) group encompasses a significant proportion of Canadians (up to 25%). Statin therapy, in addition to health behavior interventions might be appealing to a
broad group of individuals in the IR group. The strongest evidence for treatment is based on the inclusion criteria from the primary prevention studies outlined below.

a. Those with an LDL-C $\geq 3.5$ mmol/L, or an apo B $\geq 1.2$ g/L or non-HDL-C $\geq 4.3$ mmol/L as per the previous 2012 CCS dyslipidemia guidelines.

b. Men $\geq 50$ or women $\geq 60$ years and one additional risk factor including low HDL-C, impaired fasting glucose, increased waist circumference, cigarette smoking, and hypertension (with additional risk factors including LVH).

c. Consideration could be given to subjects with other factors including sub-clinical atherosclerosis (coronary artery calcium score $>100$), hs CRP $\geq 2$ mmol/L, lipoprotein (a) $\geq 30$ mg/dL. These should be considered as less well studied indications for therapy.

Primary prevention studies

The primary prevention studies have included subjects without vascular disease who on average were in the intermediate risk group. However, several of the studies included those with lower risk (5-9% FRS) and those in the high risk group (>20%). There was no major heterogeneity for benefit across the risks in these studies. These studies showed benefit of statin therapy including the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS, NNT =28),\textsuperscript{40} the West of Scotland Coronary Prevention Study (WOSCOPS, NNT = 38),\textsuperscript{41} the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT, NNT = 58),\textsuperscript{42} and JUPITER (NNT = 25).\textsuperscript{43} These studies included subjects with baseline LDL-C near or above 3.5 mmol/L except for JUPITER where the entry criteria was based on LDL-C < 3.5 mmol/L with an elevated CRP. In addition, based on the recently published Heart Outcomes Prevention Evaluation (HOPE) - 3 study a broader group of patients in the intermediate risk category may gain benefit from statin therapy. The study included male $\geq 55$ or female $\geq 65$ years and one additional risk factor. There was a demonstrated reduction in CVD events with rosuvastatin 10 mg daily regardless of LDL-C levels (mean LDL-C 3.3 mmol/L). With a fixed dose of statin, the 0.9 mmol/L reduction in LDL-C resulted in a 25% reduction in events (NNT = 70).\textsuperscript{44} Also of importance was the fact that 49% of the HOPE-3 population was Asian, with outcomes similar to Caucasian population, increasing the evidence for primary prevention in this population.
Shared decision making is central to all discussions related to the introduction of medications to reduce cardiovascular risk. As discussed below, the initial and backbone of cardio-metabolic risk management is health behavior intervention.

**RECOMMENDATIONS**

1. **Statin indicated conditions:** We recommend management that includes statin therapy in high risk conditions including clinical atherosclerosis, abdominal aortic aneurysm, most diabetes mellitus, chronic kidney disease (age > 50 years) and those with LDL-C ≥ 5.0 mmol/L to lower the risk of CVD events and mortality (Strong Recommendation, High Quality Evidence).

2. **Primary prevention:**
   
   a. We recommend management that does not include statin therapy for individuals at low risk (modified FRS < 10 %) to lower the risk of CVD events (Strong Recommendation, High Quality Evidence).
   
   b. We recommend management that includes statin therapy for individuals at high risk (modified FRS ≥ 20%) to lower the risk of CVD events (Strong Recommendation, High Quality Evidence).

   c. We recommend management that includes statin therapy for individuals at intermediate risk (modified FRS 10-19%) with LDL-C ≥ 3.5 mmol/L to lower the risk of CVD events. Statin therapy should also be considered for intermediate risk persons with LDL-C <3.5 mmol/L but with apo B ≥ 1.2 g/L or non-HDL-C ≥ 4.3 mmol/L or in men ≥ 50 and women ≥ 60 years of age with ≥ 1 CV risk factor (Strong Recommendation, High Quality Evidence).

**Values and Preferences:**

This recommendation applies to individuals with an LDL-C ≥ 1.8 mmol/L. Any decision regarding pharmacological therapy for CV risk reduction in IR persons needs to include a thorough discussion of risks, benefits, and cost of treatment, alternative non-pharmacological methods for CV risk reduction and each individual’s preference. The proportional risk reduction associated with statin therapy in RCTs in (IR) persons is of similar magnitude to that attained in high-risk persons. Moreover, irreversible severe side effects are very rare and availability of generic statins results in low cost of therapy. However, the absolute risk reduction is lower. Statin therapy may be considered in persons with FRS of 5%-9% with LDL-C ≥ 3.5 mmol/L or other CV risk factors as the proportional benefit from statin therapy will be similar in this group as well.
CHRONIC KIDNEY DISEASE

PICO: In adults with chronic kidney disease, who will benefit from statin therapy to reduce CVD events?

Randomized trials have demonstrated benefit of statins or statins plus ezetimibe in subjects with CKD. This includes subjects with an eGFR <60 mL/min/1.73 m² and those with preserved eGFR in whom CKD is based on an increased urinary albumin:creatinine ratio (≥ 3 mg/mmol) for at least 3 months duration. The Study Heart and Renal Protection (SHARP) randomized 9270 subjects (40-80 years) with a serum creatinine > 150 µmol/L for men and 130 µmol/L for women. Combination therapy with simvastatin and ezetimibe resulted in a 17% reduction in the primary end-point of MI, coronary death, ischemic stroke or revascularization. A recent Cochrane review and meta-analysis evaluated 38 studies (n= 37,274) with a HR of 0.72 for major CV events and 0.79 for all-cause mortality. The NNT was 20 for various outcomes over a 5 year period.

The Kidney Disease: Improving Global Outcomes (KDIGO) group published an extensive set of recommendations in late 2013. The group recommended treatment for all above 50 years and only in those with enhanced risk factors below 50 years. Secondly, the meta-analysis demonstrated a beneficial effect of statins in patients with CKD in those with or without albuminuria. This group has used 3 mg/mmol as the cut-off, while the Canadian Diabetes Association defined 2 mg/mmol as an abnormal level. Since LDL-C is a poor risk marker for subjects with CKD, treatment is recommended regardless of lipid values.
SECONDARY TESTING

**PICO:** In adults, does the measurement of risk markers improve cardiovascular risk assessment in intermediate risk subjects to aid in dyslipidemia management?
We recommend limited testing in subjects in whom a clear decision about the use of statin therapy by the patient and clinician is not evident. This would generally be confined to those at low to intermediate risk in a primary prevention setting. A full review was not undertaken for all of the potential biomarkers, instead we focused on areas where new literature was evident. The strongest evidence exists for the assessment of sub-clinical atherosclerosis with coronary artery calcium.

**Coronary Artery Calcium (CAC, Agatston Score) Measurement**

Non-contrast, CAC measurements are sensitive, reproducible, and rapid with an average radiation dose of 0.89 mSev (background annual radiation exposure is ~3.0 mSev). Evidence for improved C-statistic/net reclassification index after adjustment for standard risk factors (FRS) has been provided by multiple studies. The ability to reclassify to a lower or higher risk category and, therefore clinical utility, is greatest for middle aged, intermediate risk subjects. CAC of 0 has a very high negative predictive value for CHD events in asymptomatic, low-risk adults of any CVD event within 2 to 5 years (negative predictive value, 95%–99%). CAC >0 confirms the presence of atherosclerotic plaque. Rising scores are directly proportional to increased CVD risk. CAC >100 is associated with a high risk (>2% annual risk) of a CVD event within 2 to 5 years and is generally an indication for intensive treatment of LDL-C as well as other treatable CV risk factors. CAC >300 places the patient in a very high risk category with a 10 year risk of MI/CV death of approximately 28%. The effects of statin on progression of atherosclerosis cannot be accessed through serial CAC scores as therapy does not attenuate and may even increase CAC progression. Accordingly, repeat screening to determine CAC progression is not recommended.
Lipoprotein (a)

Lp(a) is an LDL-like particle in which apo B is covalently bound to a plasminogen-like molecule designated (a). Plasma concentrations of Lp(a) are controlled by a single gene, LPA, and are highly (> 90%) heritable. Mendelian randomization studies have clearly demonstrated that genetic variants in the LPA gene regulating Lp(a) levels are robustly associated with CHD risk, supporting a causal role. Individual values are generally stable throughout life, thus repeat measures are not required for risk assessment. The Copenhagen Heart Study determined the risk of MI by Lp(a) concentrations in the general population including 7,524 subjects, followed for 17 years. Subjects with an Lp(a) concentration between 30 and 76 mg/dL had a 1.7 fold hazard ratio (HR) whereas those with an Lp(a) level above 117 mg/dL exhibited a multivariate adjusted HR of 2.7. The Emerging Risk Factors Collaboration similarly demonstrated that Lp(a) concentrations above 30 mg/dL were associated with a progressive increase in risk. A
continuous increase in CVD risk is evident in the 30% of the population with Lp (a) levels above 30 mg/dL.\textsuperscript{55}

**RECOMMENDATION:**

We suggest that Lp(a) may aid risk assessment in subjects at intermediate Framingham risk or with a family history of premature CAD (Conditional recommendation, moderate quality evidence).

**Values/preferences:** Lp(a) is a marker of CVD risk. Particular attention should be given to individuals with Lp(a) levels above 30 mg/dL for whom CVD risk is increased by approximately 2 fold. Although no randomized clinical trials are available to support basing treatment decisions solely on the basis of an elevated Lp(a), identification of high levels of Lp(a) may be particularly useful for mutual decision-making in the situation indicated above. Moreover, in younger patients who have a very strong family history of premature CVD suspected to be related to atherogenic dyslipidemia but who by virtue of young age, do not meet usual risk criteria for treatment, detection of high Lp(a) may help inform mutual decision making regarding treatment. Lp(a) is not considered a treatment target and repeat measures are not indicated.

**MONITORING, SURVEILLANCE AND TARGETS**

**PICO:** In adults started on pharmacotherapy does the use of treatment targets reduce CVD events?

We recognize there is controversy regarding the use of lipid treatment targets. There is no conclusive evidence for using targets for lipid-lowering therapy, as no randomized controlled trials have tested specific lipid targets. However, we believe that titrating statin therapy to achieve target lipid levels will have beneficial effects on CVD outcomes, particularly for high risk (statin indicated conditions) patients. We considered the following:

a) There is high inter-individual variability in LDL-C levels attained with statin therapy, and evidence from in-trial achieved lipid parameters indicates that lower LDL-C are associated with a lower risk for cardiovascular events.\textsuperscript{56}
b) Randomized controlled trials and meta-analyses of statin trials show that the proportional reduction in major CVD events is directly related to the absolute LDL-C reduction that is achieved. In five trials conducted in populations targeted for secondary prevention, high-intensity statin therapy resulted in further significant reductions in major CVD events compared to moderate-intensity statin therapy. Relative risk reductions were similar across various levels of baseline risk, and if anything there was a greater relative risk reduction amongst lower risk individuals (<1%/year event rates) targeted for primary prevention. There was no evidence of any threshold within the cholesterol ranges studied.57

Another meta-analysis of 8 randomized controlled trials (N=38,153) of statin therapy assessed the risk of cardiovascular events at very low levels of LDL-C.56 Patients who achieved an in-trial LDL-C level of <1.3 mmol/L, had a 19% (adjusted) lower risk of major cardiovascular events when compared to patients who achieved an LDL-C between 1.9-2.6 mmol/L. To date, no clear lower limit of LDL-C below which there is no additional benefit, specifically with statin therapy, has been identified. However, recent analyses from randomized trials have demonstrated lower event rates in subjects who achieved at least a 50% reduction in on treatment LDL-C levels.59,60

c) New evidence from the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT),61 in which patients with a recent acute coronary syndrome were treated for an average of seven years, indicates that the addition of ezetimibe to moderate-intensity statin therapy reduces both LDL-C and CVD events. In this trial, LDL-C was lowered below 2 mmol/L (average in-trial LDL-C level achieved with statin monotherapy and statin plus ezetimibe were 1.8 mmol/L and 1.4 mmol/L, respectively). Thus, this provides further evidence for more aggressive LDL-C lowering in high risk patients. However, we acknowledge that more aggressive LDL-C lowering with other non-statin lipid-lowering therapies have not resulted in a reduction in cardiovascular events. In both the AIM-HIGH62 and HP2-THRIVE63 trials, patients achieved an LDL-C level <2 mmol/L with the combination of a statin (+/- ezetimibe) and niacin (+/- laropiprant), but this did not translate into a reduction in cardiovascular events. The reasons for the lack of benefit with niacin in these trials is not clear but may relate to the population studied already having optimum lipid values;

d) Very recently both the ESC and ACC/AHA have recommended the use of targets.64,65

e) The use of lipid targets may aid clinicians in optimizing lipid-lowering therapy, and may reinforce patient adherence and provide evidence for patients of the efficacy of treatment.
**RECOMMENDATIONS:**

1. We recommend a treat-to-target approach in the management of dyslipidemia to mitigate CVD risk. (Strong Recommendation, Moderate Quality Evidence).

**Statin indicated conditions**

1. We recommend a target LDL-C consistently $<2.0$ mmol/L or $>50\%$ reduction of LDL-C for individuals for whom treatment is initiated to lower the risk of CVD events and mortality (Strong Recommendation, Moderate-Quality Evidence). Alternative target variables are apoB $<0.8$ g/L or non-HDL-C $<2.6$ mmol/L (Strong Recommendation, Moderate Quality Evidence).

2. We recommend a $>50\%$ reduction of LDL-C for patients with LDL-C $>5.0$ mmol/L in individuals for whom treatment is initiated to decrease the risk of CVD events and mortality (Strong Recommendation, Moderate Quality Evidence).

**Values and Preferences:** Based on the IMPROVE-IT trial, for those with a recent acute coronary syndrome and established coronary disease consideration should be given to more aggressive targets (LDL-C $<1.8$ mmol/L or $>50\%$ reduction). This might require the addition of ezetimibe (or other non-statin medications) to maximally tolerated statin. This would value more aggressive treatment in higher risk individuals.

**Primary prevention conditions warranting therapy:**

**All risk groups:**

3. We recommend a target LDL-C consistently $<2.0$ mmol/L or $>50\%$ reduction of LDL-C in individuals for whom treatment is initiated to lower the risk of CVD events (Strong Recommendation, Moderate Quality Evidence). Alternative target variables are apoB $<0.8$ g/L or non-HDL-C $<2.6$ mmol/L (Strong Recommendation, Moderate Quality Evidence).

**Values and preferences:** From randomized trials in primary prevention, achieving these levels will reduce CVD events. The mortality reduction is statistically significant but modest (NNT $=250$). Treatment in primary prevention values morbidity reduction preferentially.
HEALTH BEHAVIOR INTERVENTIONS

PICO: In adults with high cholesterol and increased cardiovascular risk do lifestyle interventions compared with usual care decrease lipid values or CVD events?

Lifestyle interventions remain the cornerstone of chronic disease prevention, including CVD. Data from the INTERHEART study indicate that, in addition to the traditional risk factors (abnormal lipids, hypertension, smoking and diabetes), abdominal obesity, dietary patterns, alcohol consumption, physical inactivity, and psychosocial factors are modifiable risk factors for MI worldwide in both sexes and at all ages. Evidence from other large prospective cohort studies have also shown that combining low-risk health behaviors which include achieving and maintaining a healthy body weight, healthy diet, regular physical activity, smoking cessation, moderate alcohol consumption, and sufficient sleep duration is associated with benefit for the primary prevention of CVD. The REasons for Geographic and Racial Differences in Stroke (REGARDS) prospective cohort study showed similar benefit in the secondary prevention of CHD and all-cause mortality. These observational studies suggest that low-risk lifestyle behaviors are associated with 60-80% lower risk.

Smoking cessation

Smoking cessation is probably the most important health behavior intervention for the prevention of CVD. Smoking also has an adverse effect on lipids. There is a linear and dose dependent association between the number of cigarettes smoked per day and CVD risk. Pharmacotherapy is associated with an increased likelihood of smoking abstinence.

Nutrition therapy

Primary goals of nutrition therapy are to maintain and achieve a healthy body weight, improve the lipid profile, and importantly reduce the risk of cardiovascular events. There are many dietary pathways to achieve cardiovascular risk reduction and adherence is probably the most important determinant of success. A registered dietitian may be of value to provide advice and follow-up.
Traditional dietary approaches to cardiovascular risk reduction have focused on macronutrient-based strategies with an emphasis on saturated fat and dietary cholesterol reduction. A systematic review and meta-analysis of 37 trials using the US National Cholesterol Education Program (NCEP) Step I (≤30% total energy as fat, ≤10% of energy as saturated fat, ≤300 mg/d dietary cholesterol), and Step II (≤7% of energy as saturated fat, ≤200 mg/d dietary cholesterol) diets confirmed significant lowering of plasma lipids and lipoproteins, and CVD risk factors. LDL-C levels decreased by an average of 12% with the Step I diet and 16% with the Step II diet. A World Health Organization (WHO) systematic review and meta-analysis of randomized control trials demonstrated that low saturated fat diets decrease combined CVD events compared with high saturated fat intakes. The benefit, however, appears to be restricted to the replacement of saturated fats with polyunsaturated fatty acids (PUFAs), especially those from mixed omega-3/omega-6 sources in these trials. Replacement of saturated fat with higher quality sources of mono-unsaturated fatty acids (MUFAs) from olive oil, canola oil, nuts, and seeds and carbohydrates from whole grains and low glycemic index carbohydrates is associated with benefit.

Supplementation with long chain omega-3 PUFAs does not appear to result in cardiovascular risk reduction. Systematic reviews and meta-analyses of randomized trials involving 75,000 participants have failed to show a cardiovascular benefit of supplementation with long chain omega-3 PUFAs. Pooled evidence from randomized controlled trials and individual large randomized controlled trials, however, have shown advantages for lowering triglycerides at high doses (2-4g/day).

Recognizing that nutrient-based approaches may miss important cholesterol lowering interactions, there has been a move toward more food and dietary pattern-based approaches to cardiovascular risk reduction. The Prevención con Dieta Mediterránea (PREDIMED) study was a Spanish, multicentre, randomized trial of the effect of a Mediterranean diet supplemented with either extra-virgin olive oil or mixed nuts compared with a low-fat control diet on major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) in 7447 participants at high cardiovascular risk. The primary outcome was reduced by 30% in both Mediterranean diet groups after the trial was stopped early for benefit at a median follow-up of 4.8 years. Other dietary patterns that include shared elements of a Mediterranean dietary pattern have also shown some evidence of cardiovascular benefit in systematic reviews and meta-analyses. These include a Portfolio dietary pattern (please see Supplemental Table S2), Dietary Approaches to Stop Hypertension (DASH) dietary pattern, low-glycemic index
(GI)/glycemic load (GL) dietary pattern (please see Supplemental Table S3), as well as dietary patterns high in nuts, legumes, olive oil, fruits and vegetables, total fibre, and whole grains. Dietary therapy by these means can be considered to augment drug therapy with statins.

Supplemental Table S4 summarizes the expected cardiovascular and lipid-lowering benefits of the various evidence-based dietary patterns for dyslipidemia management. Canadian nutrition practice guidelines for cardiac rehabilitation and cardiovascular disease prevention are cited elsewhere.

Physical Activity

Many studies have shown the benefits of regular exercise in maintaining health and preventing CVD. Regular exercise also has beneficial effects on diabetes risk, hypertension, and hypertriglyceridemia, and improves plasma levels of HDL-C. In several studies, a lower frequency of CVD was noted in physically active individuals independent of known CVD risk factors. Adults should accumulate at least 150 minutes of moderate to vigorous aerobic activity per week in bouts of 10 minutes or more. It is also beneficial to add muscle- and bone-strengthening activities at least 2 days per week. A greater amount of activity will be associated with greater benefits. Limiting sedentary behavior can be additive to regular activity with respect to the reduction of CVD events. A certified exercise physiologist may be of value to provide advice and follow-up. Cardiac rehabilitation has been clearly shown to be of benefit particularly in secondary prevention scenarios.

Psychological factors

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

**RECOMMENDATIONS:**

We recommend that adults who smoke should receive clinician advice to stop smoking to reduce CVD risk (Strong Recommendation, High Quality Evidence).

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**RECOMMENDATIONS:**

1. We recommend that all individuals are offered advice about healthy eating and activity and adopt the Mediterranean dietary pattern to lower 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.

2. We recommend that omega-3 polyunsaturated fatty acids supplements not be used to reduce CVD events (Strong Recommendation, High Quality Evidence).

*Values and preferences:* Although there is no apparent cardiovascular benefit, patients may 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 (DHA) and eicosapentaenoic (EPA) acid from marine, algal, and yeast sources and that high doses are required (2-4 g/day).

3. 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).
RECOMMENDATIONS:

4. We suggest that to increase the probability of achieving a cardiovascular benefit, individuals should replace saturated fats with polyunsaturated fats (Conditional Recommendation, Moderate-Quality Evidence), emphasizing those from mixed omega-3/omega-6 polyunsaturated fatty acids (PUFAs) sources (e.g. 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 mono-unsaturated fatty acids (MUFAs) and carbohydrates, then people should choose plant sources of MUFAs (e.g. olive oil, canola oil, nuts, and seeds) and high-quality sources of carbohydrates (e.g. whole grains and low glycemic index carbohydrates) (Conditional Recommendation, Low-Quality Evidence).

Values and preferences: Industrial trans fats are no longer generally regarded as safe (GRAS) 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 may 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.
**RECOMMENDATIONS:**

We suggest that all individuals be encouraged to moderate energy (caloric) intake to achieve and maintain a healthy body weight (Conditional Recommendation, Moderate-Quality Evidence) and adopt a healthy dietary pattern to lower their CVD risk:

(a) Mediterranean dietary pattern (Strong Recommendation/High-Quality Evidence)

(b) Portfolio dietary pattern (Conditional Recommendation, Moderate-Quality Evidence)

(c) DASH dietary pattern (Conditional Recommendation, Moderate-Quality Evidence)

(d) Dietary patterns high in nuts (≥ 30 g/day) (Conditional Recommendation, Moderate-Quality Evidence)

(e) Dietary patterns high in legumes (≥ 4 servings/week) (Conditional Recommendation, Moderate-Quality Evidence)

(f) Dietary patterns high in olive oil (≥ 60mL/day) (Conditional Recommendation, Moderate-Quality Evidence)

(g) Dietary patterns rich in fruits and vegetables (≥ 5 servings/day) (Conditional Recommendation, Moderate-Quality Evidence)

(h) Dietary patterns high in total fibre (≥ 30 g/day) (Conditional Recommendation, Moderate-Quality Evidence) and whole grains (≥ 3 servings/day) (Conditional Recommendation, Low-Quality Evidence)

(i) Low-glycemic load (GL) (Conditional Recommendation, Moderate-Quality Evidence) or low-glycemic index (GI) (Conditional Recommendation, Low-Quality Evidence) dietary patterns

(j) Vegetarian dietary patterns (Conditional Recommendation, Very Low-Quality Evidence)

Values and preferences. Adherence is one of the most important determinants for attaining the benefits of any diet. High food costs (e.g. fresh fruits and vegetables), allergies (e.g. peanut and tree nut allergies), intolerances (e.g. lactose intolerance), and gastrointestinal (GI) side effects (e.g. flatulence and bloating from fibre) may present as important barriers to adherence. Other barriers may include culinary (e.g. ability and time to prepare foods), cultural (e.g. culturally specific foods), and ecological/environmental (e.g. sustainability of diets) considerations. 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.
RECOMMENDATIONS:

1. We recommend the following dietary *components* for LDL-C lowering:

   (a) Portfolio dietary pattern (Strong Recommendation, High-quality Evidence)
   
   (b) Dietary patterns high in nuts (≥ 30 g/day) (Strong Recommendation, High Quality Evidence)
   
   (c) Dietary patterns high in soy protein (≥ 30 g/day) (Strong Recommendation, High Quality Evidence)
   
   (d) Dietary patterns with plant sterols/stanols (≥ 2 g/day) (Strong Recommendation, High Quality Evidence)
   
   (e) Dietary patterns high in viscous soluble fibre from oats, barley, psyllium, pectin, or konjac mannan (≥ 10 g/day) (Strong Recommendation, High Quality Evidence)
   
   (f) NCEP Step I and II dietary patterns (Strong Recommendation, High Quality Evidence)

2. We suggest the following dietary *patterns* for LDL-C lowering:

   (a) Dietary patterns high in dietary pulses (≥ 1 serving/day or ≥ 130 g/day) (beans, peas, chickpeas, and lentils) (Conditional Recommendation, Moderate-Quality Evidence)
   
   (b) Low-glycemic index (GI) dietary patterns (Conditional Recommendation, Moderate-Quality Evidence)
   
   (c) DASH dietary pattern (Conditional Recommendation, Moderate-Quality Evidence)

*Values and preferences.* Individuals may choose to use an LDL-C lowering dietary pattern alone or as an add-on to lipid-lowering therapy to achieve targets. Dietary patterns based on single-food interventions (high plant sterols/stanols, viscous soluble fibre, nuts, soy, dietary pulses) may be considered additive (that is, the ~5-10% LDL-C lowering effect of each food can be summed) based on the evidence from the Portfolio dietary pattern.
RECOMMENDATIONS:

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).

| NON-STATIN THERAPY |

| VALUES AND PREFERENCES: Low risk lifestyle behaviours are variably defined as follows: a healthy body weight (BMI 18.5-25 to <30kg/m2 or WC of <88 inches females or <95 to <102 inches males), healthy diet (higher fruits & vegetables to Mediterranean dietary pattern), regular physical activity (≥ 1 time/week to 40 min/day plus 1 hour/week of intense exercise), smoking cessation (never smoked to smoking cessation >12 months), moderate alcohol consumption (≥ 12-14g/month to 46g/day), and moderate sleep duration (6 to 8 hours/night). Individuals can achieve benefits in a dose-dependent manner. |
PICO: In adults already taking statins, does the addition of other lipid modulating drugs compared with placebo reduce CVD events?

Ezetimibe

The results of IMPROVE-IT,⁹⁴ are of major significance for a number of reasons.⁹⁵ This is the first time that a non-statin, when added to a statin in high-risk patients, resulted in a significant (albeit relatively small) reduction in clinical events (NNT = 70). Further, this benefit was seen in patients who already had LDL-C levels at or below guideline-recommended targets (control group LDL-C on statin of 1.8 mmol/L). This supports the LDL hypothesis, reaffirms the excellent safety and tolerability profile of ezetimibe and provides further evidence for treating to lower LDL-C levels.

Niacin

Both AIM HIGH⁶² and HPS-2 THRIVE,⁶³ failed to demonstrate any CV benefit of adding niacin to statins in high-risk patients who had achieved target levels of LDL-C. Furthermore, there was significant expected and unexpected toxicity of this strategy in HPS-2 THRIVE. While it is possible that this toxicity was partly due to the laropiprant component of the particular niacin preparation that was used there was also an excess of previously described side effects with extended-release niacin alone in AIM HIGH. The routine use of niacin, added to statin therapy for CV prevention in patients who have achieved lipid targets, cannot be recommended in light of recent clinical trials. Use in subjects who do not achieve appropriate LDL-C levels despite statins could be considered.

Fibrates

Both FIELD,⁹⁶ (not all patients on background statin therapy) and ACCORD LIPID,⁹⁷ failed to show a benefit of fenofibrate on CV outcomes when added to statin therapy in patients with diabetes, with or without concomitant CAD. A meta-analysis suggests a nominal benefit in the sub-group of patients with high TG/low HDL at baseline (heterogeneous populations from 5 trials).⁹⁸ Given the safety profile of fenofibrate, clinicians may consider fenofibrate in high-risk patients with residual high TG/low HDL, recognizing that the potential for benefit on CVD is based on pooled sub-group analysis, and far from definitive.

Bile acid sequestrants
Cholestyramine was shown to significantly reduce CV events in monotherapy in the LRC-CPPT study (pre-dating statins). There has been no RCT adding a BAS to statin therapy in the modern era. However, colesevelam, representing a new BAS with better GI tolerability and some degree of glycemic benefit, offers roughly the same LDL-C lowering as ezetimibe, with no major toxicity. Therefore, it may be reasonable to consider adding a BAS to maximally tolerated statin therapy +/- ezetimibe in high risk patients who are unable to achieve LDL-C targets.

**PCSK9 inhibitors**

Evolocumab and alirocumab were both recently approved in Canada as well as the US and Europe. A third PCSK9 inhibitor, bococizumab is undergoing phase 3 outcome trials and is currently not approved anywhere in the world. The definitive outcome trials for these agents (FOURIER, ODYSSEY OUTCOMES, SPIRE-1 and SPIRE-2) are ongoing, but results are expected beginning in early 2017.

In their large phase 2/3 clinical program, both alirocumab and evolocumab have demonstrated excellent LDL-C lowering capacity (50-70%), regardless of background therapy, in a wide variety of patients including those on statins. The observation of a large and concordant relative reduction (roughly 50%) in clinical outcomes, in their LDL-C efficacy studies (OSLER and ODYSSEY LONG TERM) is consistent with the LDL hypothesis, and with the meta-regression results from the CTTC. The large phase 3 end-point trials are required to confirm these results.

Approved indications for these agents to date are for patients with established clinical atherosclerotic vascular disease or familial hypercholesterolemia whose LDL-C remains above target despite maximally-tolerated statin dosing +/- ezetimibe (see supplement for recommendations). See Figure 5 for suggested treatment algorithms.
RECOMMENDATIONS:

1. We recommend ezetimibe as second-line therapy to lower LDL-C in patients with clinical cardiovascular disease if targets are not reached on maximally tolerated statin therapy. (Strong Recommendation, High Quality evidence)

2. We recommend that niacin not be added to statin therapy for CVD prevention in patients who have achieved LDL-C targets. (Strong Recommendation, High Quality Evidence)

Values and Preferences: It remains unclear whether niacin offers CV benefits in other patient groups, such as those with LDL-C above target or those with low HDL-C or high TG.

3. We recommend that fibrates not be added to statin therapy for CVD event prevention in patients who have achieved LDL-C targets (Strong recommendation, High Quality evidence).

Values and preferences: In sub-group analysis, patients with elevated triglycerides and low HDL-C may benefit from fibrate therapy.
4. We suggest that bile acid sequestrants be considered for LDL-C lowering in high risk patients who remain above target despite statin +/- ezetimibe therapy (Conditional Recommendation, Low Quality Evidence)

5. We suggest the use of PCSK9 inhibitors (evolocumab, alirocumab) to lower LDL-C for patients with heterozygous familial hypercholesterolemia whose LDL-C remains above target despite maximally tolerated statin therapy (Conditional Recommendation, Moderate Quality Evidence). We suggest that Evolocumab be added to background therapy in patients with homozygous familial hypercholesterolemia and continued if LDL-C lowering is documented (Conditional Recommendation, Moderate Quality Evidence).

6. We suggest that PCSK9 inhibitors be considered to lower LDL-C for patients with atherosclerotic cardiovascular disease in those not at LDL-C goal despite maximally tolerated statin +/- ezetimibe therapy. (Conditional Recommendation, Moderate Quality Evidence).

Values and preferences: Definitive outcome trials with PCSK9 inhibitors are underway but have not yet been completed. However, phase 3 efficacy trials show consistent reduction in LDL-C and reassuring trends towards reduced CV events, even though not powered for such. Given the very high lifetime risk faced by patients with FH or ASCVD, clinicians should balance the anticipated benefits of robust LDL-C lowering with PCSK9 inhibitors against the lack of definitive outcomes data.

7. We suggest lomitapide and mipomersen* may be considered exclusively in patients with homozygous familial hypercholesterolemia (Conditional Recommendation, Moderate Quality Evidence).

* not approved in Canada
Statin intolerance and adverse effects remain of great interest in the media and in lay materials readily available to patients. Additionally, this field generates many academic publications that have been previously reviewed and synthesized into principles of management that remain applicable. The term goal inhibiting statin intolerance has been advanced to describe this phenomenon. 103-105

Rhabdomyolysis remains very rare with currently marketed statins as previously reviewed. Because myalgia is the most common complaint underlying suspected statin intolerance, the quest for supplements that alleviate or prevent myalgia while taking statins continues but none have been identified to date.106-110 The small additional risk of diabetes associated with statin use was previously reviewed. While the mechanism of effect remains speculative, a recent analysis suggests that there may be a relationship between LDL receptor mediated cholesterol transport and new onset diabetes as well as an effect mediated by direct inhibition of HMG CoA reductase.111,112 The long ago dismissed association of statins and cataract formation has re-emerged from several cohort studies, most of which suggest a positive association.113 HOPE-3 is the first RCT to demonstrate this as well. The risks of these are not material enough to override the anticipated CVD risk reduction in patients with guideline-based indications for statin therapy.

Cognitive impairment in association with statin therapy has been evaluated in several systematic reviews, and meta-analyses indicating that this relationship is not well-founded.114-121

Practical Tip: Always confirm that there is an indication for statin use which, if present, would suggest that benefits, clearly communicated to the patient, far outweigh the potential occurrence of any of the many side effects purported to be associated with statin use. Assess patient features that might limit dosage or preclude use of statins (eg potential drug-drug interactions) and always emphasize dietary, weight and exercise interventions to facilitate achievement of lipid goals and other benefits of comprehensive, CV prevention. Shared decision making remains key.
**RECOMMENDATIONS:**

1. We recommend that despite concerns about a variety of possible adverse effects, all purported statin-associated symptoms should be evaluated systematically, incorporating observation during cessation, re-initiation (same or different statin, same or lower potency, same or decreased frequency of dosing) to identify a tolerated, statin-based therapy for chronic use (Strong recommendation, Low Quality Evidence).

2. We recommend that vitamins, minerals, or supplements for symptoms of myalgia perceived to be statin-associated not be used (Strong Recommendation, Low Quality Evidence).

**Values and preferences:** Always confirm that there is an indication for statin use which, if present, would suggest that benefits, clearly communicated to the patient, far outweigh the potential occurrence of any of the many side effects purported to be associated with statin use. Assess patient features that might limit dosage or preclude use of statins (eg potential drug-drug interactions) and always emphasize dietary, weight and exercise interventions to facilitate achievement of lipid goals and other benefits of comprehensive, CV prevention.

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**PRACTICAL APPROACH**

The backbone of risk reduction involves a concerted effort to impact lifestyle choices.\textsuperscript{122} We recognize that there is controversy when it comes to the use of treatment targets. The primary panel continues to believe that monitoring and surveillance of LDL-C levels to achieve consistent target levels or > 50% reduction from baseline will have beneficial effects on outcomes, particularly for high risk secondary prevention patients. We recognize that several groups have not recommended targets. The optimal approach is certainly in flux and will evolve.
further as ongoing phase 3 clinical trials of lipid lowering therapy will provide further cardiovascular outcome evidence about combination therapy in the next 2-3 years. The determination of adherence is not easy without follow-up measurements and variability of response to any selected pharmacologic intervention is also incontrovertible. Regardless of whether one adopts the use of targets with close monitoring, our primary goal is to increase appropriate screening, emphasize more widespread risk assessment so as promote shared decision making to use proven effective therapy to reduce the risk to our population.

CONCLUSION

The primary panel has tried to capture the recent excitement in the study of dyslipidemia within the current document. While guidelines cannot always reflect the expected changes in the field, we feel that we have added several important recommendations that will move us in that direction. The use of non-fasting lipid determinations will be of great value for patients and service providers. Risk assessment with shared decision making is meant to recognize that population based recommendations with 10 year risk engines have some limitations. Clinical trials evidence has expanded our recommendations for IR subjects and allowed conditional recommendations for the use of some exciting new drugs for difficult to treat patients. Definitive data will be available from several studies in the next 1-2 years. Finally, we must also not lose sight of the fact that atherosclerotic vascular disease could be mainly prevented with population based health behavior interventions. Until a time when that is the case, we can advocate for our patients with appropriate screening, risk assessment, treatment and monitoring as outlined in the current guidelines.
Figure Legends

Figure 1 Whom to screen for dyslipidemia in adults at risk
*Men <55 and women <65 yrs of age in first degree relative.

Figure 2 How to screen for dyslipidemia in adults at risk

Figure 3 Non-HDL-Cholesterol measures cholesterol in all atherogenic lipoproteins

Figure 4 Conditions where pharmaco-therapy with statins is indicated

Figure 5 Non-statin treatment algorithms;
†http://ccs.ca
‡Statins are first line therapy but add-on or alternative therapy may be required as per the algorithm.
¶Consider more aggressive targets for recent ACS patients.
**PCSK9 inhibitors have not been adequately studied as add-on to statins for patients with diabetes and other co-morbidities.
apoB: apolipoprotein B; BAS: bile acid sequestrants; BMI: body mass index; CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; HIV: human immunodeficiency virus; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin kexin 9; TC: total cholesterol; TG: triglycerides; Rx: prescription.
Table 1. Summary of 2016 Guidelines Changes and Highlights

<table>
<thead>
<tr>
<th>Change or Highlight</th>
</tr>
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<tbody>
<tr>
<td>Lipid screening for both men and women ≥ 40 years of age</td>
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<tr>
<td>Inclusion of screening for women with a history of hypertensive diseases of pregnancy</td>
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<tr>
<td>Non-fasting lipid determination recommendation</td>
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<tr>
<td>LDL-C as primary, non-HDL-C or apoB as alternative targets</td>
</tr>
<tr>
<td>Risk assessment with modified Framingham Risk Score to determine risk category</td>
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<tr>
<td>Alternate approach is use of Cardiovascular Life Expectancy Model (CLEM) to calculate cardiovascular age</td>
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<tr>
<td>Shared decision making</td>
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<tr>
<td>Retention of treatment targets for those on therapy</td>
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<tr>
<td>Broader treatment recommendations for those in intermediate risk category</td>
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<tr>
<td>New expanded definition of CKD as high risk phenotype</td>
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<tr>
<td>Statins remain drugs of choice</td>
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<tr>
<td>New recommendation for non-statin drugs</td>
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<tr>
<td>Nutritional guidelines that focus on dietary patterns – Mediterranean, DASH or Portfolio diet</td>
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<tr>
<td>Detailed review of the impact of nutritional components on lipids and CV events</td>
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</table>

LDL-C – low density lipoprotein cholesterol; apo B – apolipoprotein B; CKD – chronic kidney disease; DASH – Dietary Approaches to Stop Hypertension
### Table 2 – Pharmacological Treatment Indications and Targets

<table>
<thead>
<tr>
<th>Category</th>
<th>Consider Initiating pharmaco-therapy if</th>
<th>Target</th>
<th>NNT</th>
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</thead>
<tbody>
<tr>
<td>Primary prevention</td>
<td>High FRS (≥20%) all</td>
<td>LDL-Ch ≥ 2.0 mmol/L or &gt; 50% ↓</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Intermediate FRS (10-19%)</td>
<td>Apo B &lt; 0.8 g/L</td>
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<tr>
<td></td>
<td>LDL-Ch ≥ 3.5 mmol/L or Non-HDL ≥ 4.3 mmol/L or Apo B ≥ 1.2 g/L or Men ≥ 50 and women ≥ 60 yrs and one additional CVD RF</td>
<td>Or</td>
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<td></td>
<td></td>
<td>non-HDL-Ch &lt; 2.6 mmol/L</td>
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<tr>
<td>Statin indicated conditions**</td>
<td>Clinical atherosclerosis*</td>
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<tr>
<td></td>
<td>Abdominal aortic aneurysm</td>
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<td></td>
<td>Diabetes mellitus ≥40 yrs 15 yrs duration for age ≥30 yrs (DM 1)</td>
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<td></td>
<td>Microvascular disease</td>
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<td></td>
<td>Chronic kidney disease (age ≥ 50 yrs) eGFR &lt; 60 mL/min/1.73 m² or ACR &gt; 3 mg/mmol</td>
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<tr>
<td></td>
<td>LDL-Ch ≥ 5.0 mmol/L</td>
<td>&gt;50% ↓ in LDL-Ch</td>
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</tbody>
</table>

FRS – modified Framingham Risk Score; ACR – albumin:creatinine ratio; * consider LDL-Ch < 1.8 mmol/L for subjects with ACS within last 3 months; ** statins indicated as initial therapy
BIBLIOGRAPHY


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81. Schwingshackl L, Hoffmann G. Diet quality as assessed by the healthy eating index, the alternate healthy eating index, the dietary approaches to stop hypertension score, and health outcomes: A systematic review and meta-analysis of cohort studies. *J Acad Nutr Diet.* 2015;115(5):780-800.e5.


## WHO TO SCREEN

<table>
<thead>
<tr>
<th>Men ≥40 years of age; women ≥40 years of age (or postmenopausal)</th>
<th>All patients with the following conditions regardless of age:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider earlier in ethnic groups at increased risk such as South Asian or First Nations individuals</td>
<td>• Clinical evidence of atherosclerosis</td>
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<tr>
<td></td>
<td>• Abdominal aortic aneurysm</td>
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<td>• Diabetes</td>
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<td>• Arterial hypertension</td>
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<td>• Current cigarette smoking</td>
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<td>• Stigmata of dyslipidemia (arcus cornea, xanthelasma or xanthoma)</td>
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<td></td>
<td>• Family history of premature CVD*</td>
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<td></td>
<td>• Family history of dyslipidemia</td>
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<td>• Chronic kidney disease</td>
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<td>• Obesity (BMI ≥30 kg/m²)</td>
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<td></td>
<td>• Inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>• HIV infection</td>
</tr>
<tr>
<td></td>
<td>• Erectile dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td></td>
<td>• Hypertensive diseases of pregnancy</td>
</tr>
</tbody>
</table>
HOW TO SCREEN

For all:
• History and physical examination
• Standard lipid panel (TC, LDL-C, HDL-C, TG)
• Non-HDL-C (will be calculated from profile)
• Glucose
• eGFR

Optional:
• ApoB
• Urine albumin:creatinine ratio
  (if eGFR <60 mL/min/1.73m², hypertension or diabetes)

NON-FASTING LIPID TESTING IS ACCEPTABLE
Non-HDL-C = Total Cholesterol – HDL-C

Atherogenic Apo B-containing Lipoproteins

Chylomicron Remnants

VLDL
Very low-density lipoprotein

IDL
Intermediate-density lipoprotein

Lp(a)
Lipoprotein(a)

LDL-C
Calculated from standard Lipid Profile

ApoB
Measured separately

HDL
High-density lipoprotein
<table>
<thead>
<tr>
<th><strong>CLINICAL ATHROSCLEROSIS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction, acute coronary syndromes</td>
</tr>
<tr>
<td>Stable angina, documented coronary disease by angiography (&gt;10% stenoses)</td>
</tr>
<tr>
<td>Stroke, TIA, documented carotid disease</td>
</tr>
<tr>
<td>Peripheral artery disease, claudication and/or ABI &lt; 0.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>ABDOMINAL AORTIC ANEURYSM</strong></th>
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</thead>
<tbody>
<tr>
<td>Abdominal aorta &gt; 3.0 cm or</td>
</tr>
<tr>
<td>Previous aneurysm surgery</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>DIABETES MELLITUS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 40 years of age or</td>
</tr>
<tr>
<td>&gt; 15 years duration and age ≥ 30 years or</td>
</tr>
<tr>
<td>Microvascular complications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>CHRONIC KIDNEY DISEASE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3 months duration and</td>
</tr>
<tr>
<td>ACR &gt; 3.0 mg/mmol or</td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/min/1.73m²</td>
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</table>

<table>
<thead>
<tr>
<th><strong>LDL-C ≥ 5.0 MMOL/L</strong></th>
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</thead>
<tbody>
<tr>
<td>LDL-C ≥ 5.0 mmol/L or</td>
</tr>
<tr>
<td>Document familial hypercholesterolemia</td>
</tr>
<tr>
<td>Excluded 2nd causes</td>
</tr>
</tbody>
</table>
RISK ASSESSMENT, STRATIFICATION & TREATMENT CONSIDERATION

Calculate risk (unless statin-indicated condition) using the Framingham Risk Score (FRS) or Cardiovascular Life Expectancy Model (CLEM). Repeat screening every 5 years for FRS <5% or every year for FRS ≥5%.

No Pharmacotherapy

Primary Prevention Conditions

- Low Risk
  - FRS <10%

- Intermediate Risk
  - FRS 10-19%
  - LDL-C ≥3.5 mmol/L
  - Non-HDL-C ≥4.3 mmol/L
  - ApoB ≥1.2 g/L
  - Men ≥50 and women ≥60 with one additional risk factor: low HDL-C, impaired fasting glucose, high waist circumference, smoker, hypertension

- High Risk
  - FRS ≥20%
  or alternative method

Statin-indicated Conditions

- Clinical atherosclerosis
- Abdominal aortic aneurysm
- Most diabetes including:
  - Age ≥40y
  - Age ≥30y & 15y duration (type 1 DM)
  - Microvascular disease
- Chronic kidney disease

LDL-C >5mmol/L (genetic dyslipidaemia)

Discuss behavioural modifications

Health Behavioural Modifications

- Smoking cessation
- Diet: It is recommended all individuals adopt a healthy dietary pattern
- Exercise: It is recommended adults should accumulate at least 150 minutes per week of moderate-vigorous intensity aerobic physical activity

Initiate Statin Treatment: Treat to Target Approach

Confirm adherence and barriers to use

YES

Target achieved on maximally tolerated dose?

NO

NO

NO ADD-ON

Discuss add-on therapy with patient:

Evaluate reduction in CVD risk vs. additional cost & side effects

ADD-ON

ADD-ON

ADD-ON

Monitor

- Response to statin Rx
- Health behaviours

Add-on Therapy

Ezetimibe as 1st line (BAS as alternative)

Ezetimibe 1st line (BAS as alternative)
PCSk9 inhibitors as 2nd line (add-on to other drugs)

Ezetimibe (or BAS) or PCSk9 inhibitors