



Society Guidelines

2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult

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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, on the basis of 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 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 nonfasting lipid determination as a suitable alternative to fasting levels. Risk assessment and lipid determination

RÉSUMÉ

Depuis la publication des lignes directrices de 2012, la nouvelle littérature qui est apparue favorise la prise de décision éclairée. Le principal panel sur les lignes directrices de 2016 a choisi un certain nombre de questions pertinentes sur le plan clinique et a procédé à l'actualisation des recommandations en se basant sur les dernières conclusions importantes. Chez les sujets ayant des signes cliniques d'athérosclérose, un anévrisme de l'aorte abdominale, chez la plupart des sujets atteints d'un diabète ou d'une néphropathie chronique, et chez ceux ayant un cholestérol à lipoprotéines de faible densité ≥ 5 mmol/l, le traitement par statines est recommandé. Pour les autres, l'accent est mis sur l'évaluation des risques liée à la détermination des

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The disclosure information of the authors and reviewers is available from the CCS on their guidelines library at www.ccs.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary

experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

should be considered in individuals older than 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 FRS intermediate risk category (10%-19%) and in those with a high FRS (> 20%). Despite the controversy, we continue to advocate for low-density lipoprotein cholesterol targets for subjects who start therapy. Detailed recommendations are also presented for health behaviour modification that is indicated in all subjects. Finally, recommendation for the use of nonstatin medications is provided. Shared decision-making is vital because there are many areas in which 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 population, intervention, comparator, and outcomes (PICO) questions to create recommendations on the basis of detailed literature review. The PICO format is a common standard used for guidelines implementation, to aid clinicians in determining whether the recommendations apply to their own patients with outcomes relevant to their practice. Using the Grading of Recommendations, Assessment, Development, and Evaluation standards, individual studies and composite literature were reviewed for quality and bias. We have included strong and conditional recommendations within the main article. The results of voting on each PICO question are included in the *Voting Results Summary Table* section of the [Supplementary Material](#). For recommendations to go forward a 2 of 3 voting majority was required. Individuals with conflicts of interest were recused from voting. We have introduced a recommendation for nonfasting lipid determination and retained the concept of low-density lipoprotein (LDL) cholesterol (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 on the basis of 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. Because dyslipidemia is an important risk factor for cardiovascular (CV) disease (CVD), these guidelines will allow appropriate risk assessment, treatment, and surveillance options of our at-risk population. These guidelines

lipides pour optimiser la prise de décision. Nous avons recommandé la détermination des lipides chez les sujets non à jeun comme alternative convenable à la détermination des concentrations chez les sujets à jeun. L'évaluation des risques et la détermination des lipides devraient être considérées chez les individus de plus de 40 ans ou chez ceux exposés à un risque accru, quel que soit l'âge. La pharmacothérapie n'est généralement pas indiquée chez ceux dont le score de risque de Framingham est faible (SRF; < 10 %). Un plus grand nombre de patients sont maintenant admissibles au traitement par statines, soit ceux de la catégorie de risque intermédiaire du SRF (10 % à 19 %) et ceux de la catégorie de risque élevé du SRF (> 20 %). En dépit de la controverse, nous continuons de préconiser des valeurs cibles du taux de cholestérol à lipoprotéines de faible densité chez les sujets qui commencent le traitement. Nous présentons également des recommandations détaillées sur la modification du comportement en matière de santé indiquée chez tous les sujets. Finalement, nous recommandons l'utilisation de médicaments n'appartenant pas au groupe des statines. La prise de décision partagée est indispensable puisqu'il existe de nombreux domaines dans lesquels les essais cliniques n'éclairent pas pleinement la pratique. Les lignes directrices sont censées servir de plateforme à des échanges significatifs entre le patient et le prestataire de soins de sorte que des décisions individuelles sur le dépistage et l'évaluation des risques, et le traitement puissent être prises.

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: CV death, nonfatal myocardial infarction (MI), ischemic stroke, revascularization, and acute coronary syndromes hospitalizations.

Number needed to treat (NNT): NNT to prevent 1 CVD event for 5 years of treatment per 1 mmol/L reduction in LDL-C. NNT of < 50 is 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 engines compared with no risk assessment improve the management of dyslipidemia to reduce CVD events?

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

The American Heart Association (AHA) 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

Table 1. Summary of 2016 guidelines changes and highlights

Lipid screening for men and women 40 years of age and older
Inclusion of screening for women with a history of hypertensive diseases of pregnancy
Nonfasting lipid determination recommendation
LDL-C as primary, non-HDL-C or apoB as alternative targets
Risk assessment with modified Framingham Risk Score to determine risk category
Alternate approach is use of CLEM to calculate cardiovascular age
Shared decision-making
Retention of treatment targets for those receiving therapy
Broader treatment recommendations for those in the intermediate risk category
New expanded definition of CKD as high risk phenotype
Statins remain drugs of choice
New recommendation for nonstatin drugs
Nutritional guidelines that focus on dietary patterns—Mediterranean, DASH, or Portfolio diet
Detailed review of the effect of nutritional components on lipids and CV events

apoB, apolipoprotein B; CKD, chronic kidney disease; CLEM, Cardiovascular Life Expectancy Model; CV, cardiovascular; DASH, Dietary Approaches to Stop Hypertension; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

individuals in whom benefits might be greater, compared with 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). First, 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. Second, CV risk scoring strategies tend to be better calibrated among middle-aged individuals because traditional CV 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 levels) 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 lifelong risk of CVD.^{10,11} Furthermore, for patients older than 75 years of age, the Framingham model is not well validated.¹²

On the basis of 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 CV 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 individual with a life expectancy of 25 more years (vs 30 more years for the average Canadian man who lives to be 80 years old) would be assigned a CV 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.^{2,18}

Among individuals 30-59 years of age without diabetes, the presence of a positive parental history of premature CVD (younger than 55 years in first-degree male relatives and younger than 65 years in female relatives) increases an individual's calculated FRS percent risk by approximately

twofold.¹⁹ The 10-year FRS percent doubled for family history of premature CVD will be referred to as the “modified FRS” (<http://www.ccs.ca/en/guidelines/guideline-resources>). The CLEM 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 Canadian individuals.²⁰ It is acknowledged that these models are not validated for South Asian, First Nations, or new immigrant populations. Therefore, we would recommend these 2 methods of risk assessment for use, with these caveats in mind.

RECOMMENDATION

1. We recommend that a CV risk assessment be completed every 5 years for men and women aged 40 to 75 years using the modified FRS or CLEM to guide therapy to reduce major CV events. A risk assessment might 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. Although there is good evidence to support the use of statins in secondary prevention in patients older than the age of 75 years for some outcomes, a mortality benefit has not been shown.²¹ In addition, the evidence for statin use in primary prevention is lacking in this population, mainly because they have not been extensively studied.²² For robust elderly patients believed to be at higher risk a discussion about the importance of statin therapy in overall management should be undertaken because these patients are often at high risk because a CVD event has important consequences for morbidity.

Whom to Consider for Screening

Screening should be considered for men and women older than 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 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 history of hypertensive disorders of pregnancy (HDP), which includes preeclampsia and pregnancy-induced hypertension, represent among the highest-risk populations for premature CVD.²³ The average age of onset of the first vascular event in this group is 38 years (for those who develop an event),²⁴ and the 30-year survival rate is markedly

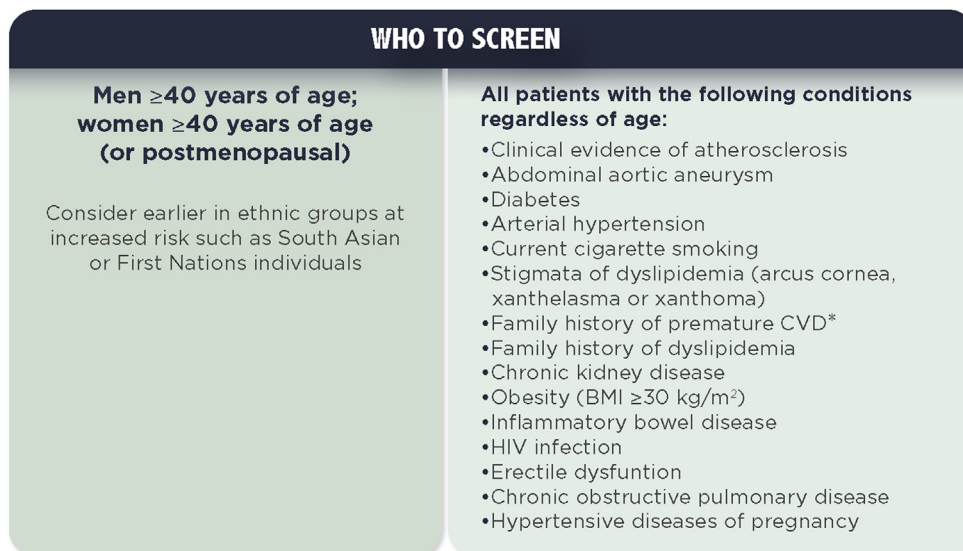


Figure 1. Whom to screen for dyslipidemia in adults at risk. *Men younger than 55 years and women younger than 65 years of age in first-degree relative. BMI, body mass index.

attenuated compared with women with uncomplicated pregnancies.²⁵ 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.²⁵ The 2011 AHA guidelines on the prevention of CVD in women now include HDP as an independent CV risk factor.²⁶

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 because of 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 the *Hypertensive Disorders of Pregnancy and Cardiovascular Risk* section of the [Supplementary Material](#) for a full narrative).

How to Screen: Fasting or Nonfasting Lipid Determination

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

In contrast to changes in triglyceride levels after a large oral fat load, triglyceride and LDL-C levels change relatively little after normal meals in most of the population. General and community-based population studies reported that triglyceride levels increase only 0.2-0.3 mmol/L or 20% after eating normal meals,^{27,28} typically peaking 4 hours postprandially.^{29,30} LDL-C levels are reduced after eating, by an average of 0.1-0.2 mmol/L or 10%,^{27,28} either because of hemodilution,²⁷ exchange of cholesterol on LDL by triglycerides, or because of calculation using the Friedwald formula. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and apolipoprotein (apo)B100 do not vary appreciably after eating. Recent data from the National Health and Nutrition Survey (NHANES) showed that the ability to predict CVD events was identical for nonfasting and fasting LDL-C determination.³¹

Nonfasting lipid testing increases convenience for patients and laboratory operations. Nonfasting testing does not affect risk assessment strategies, because total and HDL-C, used to estimate 10-year CVD risk, are not altered significantly in the nonfasting state.

Because the major studies that determined changes in nonfasting lipids excluded individuals with previous 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^{27,28}) 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.³² For this reason it remains the recommendation to use the non-HDL-C level (or apoB), which is not altered

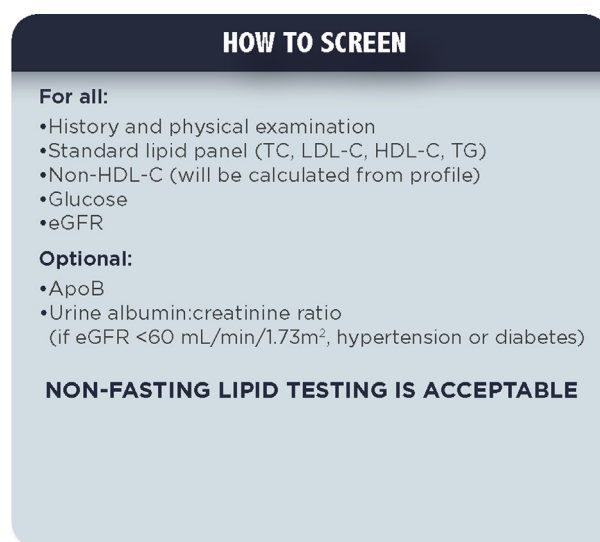


Figure 2. How to screen for dyslipidemia in adults at risk. ApoB, apolipoprotein B; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

after eating or by triglycerides, as the treatment target of choice when triglyceride levels are > 1.5 mmol/L.³³ 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 nonfasting lipid testing, however, it is recognized that some physicians will prefer that patients have their lipid profiles tested fasting (Fig. 2). Although nonfasting triglycerides are predictive of increased CVD and mortality risk, and increased levels are indicators of insulin resistance and atherogenic remnant lipoproteins,^{34,35} nonfasting triglyceride targets are not currently included in any national lipid guidelines. A nonfasting approach has recently been advocated in Europe.³⁶

RECOMMENDATION

1. We recommend nonfasting lipid and lipoprotein testing 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 with 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 apoB 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 lipoprotein (Fig. 3). One molecule of apoB is present in all atherogenic lipoprotein including LDL, very LDL, remnants, and lipoprotein(a) (Lp(a)). Multiple observational and randomized controlled trials (RCTs) have shown that non-HDL-C and/or apoB predict risk similarly or better than LDL-C. The Emerging Risk Factors Collaboration,³⁷ in an analysis of 302,430 people without vascular disease from 68 prospective trials published in 2009, concluded that apoB and non-HDL-C predicted risk similar to directly measured LDL-C and that fasting did not affect the hazard ratios (HRs).

RECOMMENDATION

We recommend that non-HDL-C and apoB should continue to be considered alternate targets to LDL-C to evaluate risk in adults (Strong Recommendation; High-Quality Evidence).

Values and preferences. Because 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 apoB in the future.

When to Consider Pharmacological Treatment in Risk Management

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

When deciding on whom to consider for pharmacotherapy we suggest the following approach (Fig. 4). (1) For statin-indicated conditions: identify patients who are in the 5 statin-indicated conditions listed in the section on “*Statin-indicated Conditions.*” Risk assessment is not required for these individuals as statin therapy is indicated. (2) For primary prevention: perform a risk assessment for those who do not have the previously-mentioned high-risk conditions. If the preference is to calculate total CVD risk using the FRS,⁷ 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 might be considered for statin therapy on the basis of randomized trial criteria and patient preference (Table 2).

Statin-indicated conditions

This group achieves the greatest absolute benefit from lipid-lowering therapy because they are at high risk. This includes subjects with: (1) clinical atherosclerosis (ie, previous MI, or coronary revascularization using percutaneous coronary

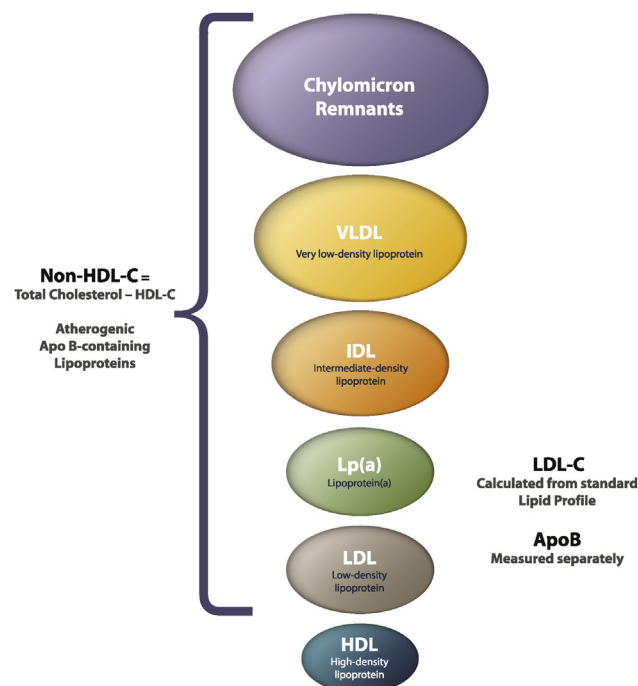


Figure 3. Non-HDL-cholesterol measures cholesterol in all atherogenic lipoproteins. ApoB, apolipoprotein B; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); VLDL, very low-density lipoprotein.

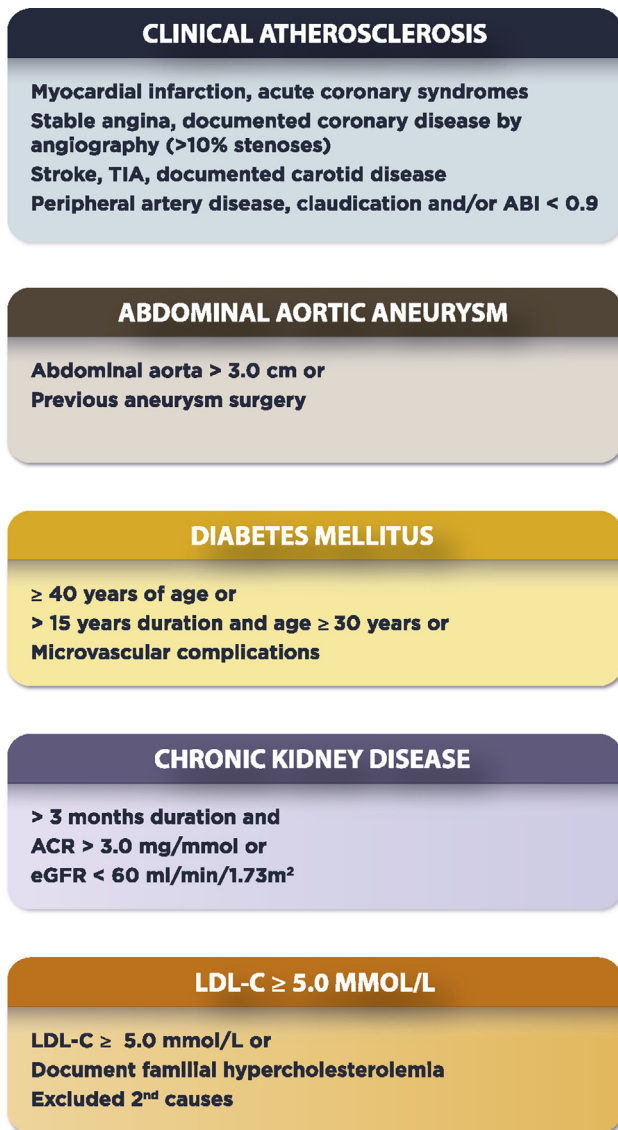


Figure 4. Conditions for which pharmacotherapy with statins is indicated. ABI, ankle-brachial index; ACR, albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; TIA, transient ischemic attack.

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 ankle-brachial index < 0.9; NNT = 20); (2) abdominal aortic aneurysm (> 3.0 cm diameter); (3) diabetes mellitus (DM) with age \geq 40 years, > 15-year duration for age \geq 30 years (type 1 diabetes mellitus [DM]), or with the presence of microvascular disease (NNT = 20-25); (4) chronic kidney disease (CKD)—see the next section for the definition (NNT = 20); or (5) LDL-C \geq 5.0 mmol/L (including genetic dyslipidemias; NNT = 25).³⁸ Statins are the initial lipid-lowering agent of choice for all of these groups (Fig. 2).³⁹ 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 a moderate to high dose of a potent statin depending on the response to lifestyle interventions.

Primary prevention

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

1. The low-risk category applies to individuals with a modified 10-year FRS < 10%. Most of these individuals do not require pharmacologic therapy. The exceptions are subjects with an LDL-C \geq 5.0 mmol/L, many of whom have a genetic dyslipidemia such as familial hypercholesterolemia (see the section on *Statin-indicated conditions*). In individuals with a modified FRS of 5%-9%, yearly monitoring could be used to evaluate change in risk. On the basis of a consistent relative risk reduction observed in the Cholesterol Treatment Trialists' meta-analysis,³⁹ certain individuals in the low-risk category might decide to start statin therapy with a view to long-term risk reduction.
2. 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 \geq 20%. Statin therapy is indicated for these subjects (NNT = 35).
3. The IR group encompasses a significant proportion of Canadians (up to 25%). Statin therapy, in addition to health behaviour interventions might be appealing to a broad group of individuals in the IR group. The strongest evidence for treatment is on the basis of the inclusion criteria from the primary prevention studies outlined in the section, *Primary prevention studies*.
 - i. Those with an LDL-C \geq 3.5 mmol/L, or an apoB \geq 1.2 g/L or non-HDL-C \geq 4.3 mmol/L as per the previous 2012 CCS dyslipidemia guidelines.
 - ii. Men 50 years of age and older or women 60 years of age and older and 1 additional risk factor including low HDL-C, impaired fasting glucose, increased waist circumference, cigarette smoking, and hypertension (with additional risk factors including left ventricular hypertrophy).
 - iii. Consideration could be given to subjects with other factors including subclinical atherosclerosis (coronary artery calcium [CAC] score > 100), high-sensitivity C-reactive protein \geq 2 mmol/L, or Lp(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 IR group. However, several of the studies included those with lower risk (5%-9% FRS) and those in the high-risk group (FRS > 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),⁴⁰ the **West of Scotland Coronary Prevention Study** (WOSCOPS; NNT = 38),⁴¹ the **Anglo-Scandinavian Cardiac Outcomes Trial** (ASCOT; NNT = 58),⁴² and **Justification for the Use of Statins in Prevention: An Intervention**

Table 2. Pharmacological treatment indications and targets

Category	Consider initiating pharmacotherapy if	Target	NNT
Primary prevention	High FRS ($\geq 20\%$) All	LDL-C < 2.0 mmol/L or $> 50\%$ ↓ Or	35
	Intermediate FRS (10%-19%) LDL-C ≥ 3.5 mmol/L or non-HDL-C ≥ 4.3 mmol/L or ApoB ≥ 1.2 g/L or men ≥ 50 and women ≥ 60 years and 1 additional CVD RF	ApoB < 0.8 g/L Or non-HDL-C < 2.6 mmol/L	40
Statin-indicated conditions*	Clinical atherosclerosis† Abdominal aortic aneurysm Diabetes mellitus Age ≥ 40 years 15-Year duration for age ≥ 30 years (DM 1) Microvascular disease Chronic kidney disease (age ≥ 50 years) eGFR < 60 mL/min/1.73 m ² or ACR > 3 mg/mmol LDL-C ≥ 5.0 mmol/L	$> 50\%$ ↓ in LDL-C	20

ACR, albumin:creatinine ratio; ACS, acute coronary syndrome; apoB, apolipoprotein B; CVD, cardiovascular disease; DM 1, type 1 diabetes mellitus; eGFR, estimated glomerular filtration rate; FRS, modified Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NNT, number needed to treat; RF, risk factor.

* Statins indicated as initial therapy.

† Consider LDL-C < 1.8 mmol/L for subjects with ACS within past 3 months.

Trial Evaluating Rosuvastatin (JUPITER; NNT = 25).⁴³ These studies included subjects with baseline LDL-C near or > 3.5 mmol/L except for JUPITER, in which the entry criteria was on the basis of LDL-C < 3.5 mmol/L with an elevated C-reactive protein level. In addition, on the basis of the recently published **Heart Outcomes Prevention Evaluation (HOPE)-3** study, a broader group of patients in the IR category might gain benefit from statin therapy. The study included men 55 years of age and older, and women 65 years of age and older, with 1 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).⁴⁴ Also of importance was the fact that 49% of the HOPE-3 population was Asian, with outcomes similar to those in the 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 CV risk. As discussed below, the initial and backbone of cardiometabolic risk management is health behaviour intervention.

RECOMMENDATION

1. Statin-indicated conditions: We recommend management that includes statin therapy in high-risk conditions including clinical atherosclerosis, abdominal aortic aneurysm, most DM, CKD (age older than 50 years), and those with LDL-C ≥ 5.0 mmol/L to decrease the risk of CVD events and mortality (Strong Recommendation; High-Quality Evidence).

2. Primary prevention:

- i. We recommend management that does not include statin therapy for individuals at low risk (modified FRS $< 10\%$) to decrease the risk of CVD events (Strong Recommendation; High-Quality Evidence).
- ii. We recommend management that includes statin therapy for individuals at high risk (modified FRS $\geq 20\%$) to decrease the risk of CVD events (Strong Recommendation; High-Quality Evidence).
- iii. We recommend management that includes statin therapy for individuals at IR (modified FRS 10%-19%) with LDL-C ≥ 3.5 mmol/L to decrease the risk of CVD events. Statin therapy should also be considered for IR persons with LDL-C < 3.5 mmol/L but with apoB ≥ 1.2 g/L or non-HDL-C ≥ 4.3 mmol/L or in men 50 years of age and older and women 60 years of age and older 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 nonpharmacological 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 magnitude similar to that attained in high-risk persons. Moreover, irreversible severe side effects are very rare and availability of generic statins results in a low cost of therapy. However, the absolute risk reduction is lower. Statin therapy might be considered in persons with

FRS of 5%-9% with LDL-C \geq 3.5 mmol/L or other CV risk factors because the proportional benefit from statin therapy will be similar in this group as well.

CKD

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

Randomized trials have shown benefit of statins or statins combined with ezetimibe in subjects with CKD. This includes subjects with an estimated glomerular filtration rate $<$ 60 mL/min/1.73 m² and those with preserved estimated glomerular filtration rate in whom CKD is determined on the basis of an increased urinary albumin:creatinine ratio (\geq 3 mg/mmol) for at least a 3-month duration. The **Study Heart and Renal Protection (SHARP)**⁴⁵ randomized 9270 subjects (aged 40-80 years) with a serum creatinine level $>$ 150 μ mol/L for men and 130 μ mol/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.⁴⁶ 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 2013.⁴⁷ The group recommended treatment for all older than 50 years and only in those with enhanced risk factors younger than 50 years. Second, the meta-analysis showed a beneficial effect of statin use in patients with CKD with or without albuminuria. This group has used 3 mg/mmol as the cutoff, whereas the Canadian Diabetes Association defined 2 mg/mmol as an abnormal level. Because LDL-C is a poor risk marker for subjects with CKD, treatment is recommended regardless of lipid values.

RECOMMENDATION

1. We recommend treatment with a statin or a statin/ezetimibe combination to reduce CVD events in adults 50 years of age and older with CKD not treated with dialysis or a kidney transplant (Strong Recommendation; High-Quality Evidence).

Values and preferences. If the preference is to partake in early prevention and long-term risk reduction, in subjects younger than 50 years the absolute risk of events is lower but studies suggest that statins will result in a relative risk reduction similar to those older than 50 years. The statin/ezetimibe combination recommendation is on the basis of the SHARP study, which used 20 mg of simvastatin and 10 mg of ezetimibe.

2. We suggest that lipid-lowering therapy not be initiated in adults with dialysis-dependent CKD (Conditional Recommendation; Moderate-Quality Evidence).

Values and preferences. In younger individuals who might become eligible for kidney transplantation or with a longer life expectancy, statin or statin/ezetimibe combination therapy might be desirable although high-quality studies have not been done in this population.

3. We suggest that lipid-lowering therapy be continued in adults already receiving it at the time of dialysis initiation (Conditional Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation reflects that fact that a substantial number of patients in SHARP transitioned to dialysis during the study and there was no heterogeneity of results for the population as a whole. The evidence is of low quality overall and there is substantial debate about best practice in this situation.

4. We suggest the use of statin therapy in adults with kidney transplantation (Conditional Recommendation; Moderate-Quality Evidence).

Secondary Testing

PICO: In adults, does the measurement of risk markers improve CV risk assessment in IR 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 IR in a primary prevention setting. A full review was not undertaken for all of the potential biomarkers, instead we focused on areas in which new literature was evident. The strongest evidence exists for the assessment of subclinical atherosclerosis with CAC.

CAC (Agatston score) measurement

Noncontrast, CAC measurements are sensitive, reproducible, and rapid with an average radiation dose of 0.89 mSv (background annual radiation exposure is approximately 3.0 mSv). Evidence for improved C-statistic/net reclassification index after adjustment for standard risk factors (FRS) has been provided by multiple studies.⁴⁸ The ability to reclassify to a lower or higher risk category and, therefore clinical utility, is greatest for middle-aged, IR subjects. A CAC measurement of 0 has a very high negative predictive value for coronary heart disease (CHD) events in asymptomatic, low-risk adults of any CVD event within 2-5 years (negative predictive value, 95%-99%). A CAC measurement $>$ 0 confirms the presence of atherosclerotic plaque. Increasing scores are directly proportional to increased CVD risk.⁴⁹ A CAC measurement $>$ 100 is associated with a high risk ($>$ 2% annual risk) of a CVD event within 2-5 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%.⁵⁰ The effects of statin on progression of atherosclerosis cannot be accessed through serial CAC scores because therapy does not attenuate and might even increase CAC progression.⁵¹ Accordingly, repeat screening to determine CAC progression is not recommended.

RECOMMENDATION

1. We suggest that CAC screening using computed tomography imaging might be appropriate for asymptomatic, middle-aged adults (FRS 10%-20%) for whom treatment decisions are uncertain (Conditional Recommendation; Moderate-Quality Evidence).
2. We suggest that CAC screening using computed tomography imaging not be undertaken for: (1) high-risk individuals; (2) patients receiving statin treatment; or (3) most asymptomatic, low-risk adults (Strong Recommendation; Moderate-Quality Evidence).
3. We suggest that CAC screening might be considered for a subset of low-risk middle-aged individuals with a family history of premature CHD (men younger than 55 years; women younger than 65 years) (Conditional Recommendation; Low-Quality Evidence).
4. We suggest that in patients who warrant risk factor management on the basis of usual criteria, CAC scoring not be undertaken. Moreover, CAC scoring (seeking a result with a value of 0) should not be used as a rationale for withholding otherwise indicated, preventive therapies (Strong Recommendation; Low-Quality Evidence).

Lp(a)

Lp(a) is an LDL-like particle in which apoB 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.⁵² Mendelian randomization studies have clearly shown 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 according to Lp(a) concentrations in the general population including 7524 subjects followed for 17 years.⁵³ Subjects with an Lp(a) concentration between 30 and 76 mg/dL had a 1.7-fold HR whereas those with an Lp(a) level > 117 mg/dL exhibited a multivariate adjusted HR of 2.7. The Emerging Risk Factors Collaboration⁵⁴ similarly showed that Lp(a) concentrations > 30 mg/dL were associated with a progressive increase in risk. A continuous increase in CVD risk is evident in 30% of the population with Lp(a) levels > 30 mg/dL.⁵⁵

RECOMMENDATION

1. We suggest that Lp(a) might aid risk assessment in subjects with intermediate FRS or with a family history of premature coronary artery disease (Conditional Recommendation; Moderate-Quality Evidence).

Values and preferences. Lp(a) is a marker of CVD risk. Particular attention should be given to individuals with Lp(a) levels > 30 mg/dL for whom CVD risk is increased by approximately twofold. Although no randomized clinical trials are available to support basing treatment decisions solely on the basis of an elevated Lp(a) level, identification of high levels of Lp(a) might be

particularly useful for mutual decision-making in intermediate-risk subjects. 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) might 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 who have started 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, because no RCTs 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:

- (1) There is high interindividual variability in LDL-C levels attained with statin therapy, and evidence from in-trial achieved lipid parameters indicates that lower LDL-C levels are associated with a lower risk for CV events.⁵⁶
- (2) RCTs 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 5 trials conducted in populations targeted for secondary prevention, high-intensity statin therapy resulted in further significant reductions in major CVD events compared with 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 among lower-risk individuals (< 1% per 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 RCTs (N = 38,153) of statin therapy assessed the risk of CV events at very low levels of LDL-C.⁵⁸ Patients who achieved an in-trial LDL-C level of < 1.3 mmol/L, had a 19% (adjusted) lower risk of major CV events compared with patients who achieved an LDL-C level between 1.9 and 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 shown lower event rates in subjects who achieved at least a 50% reduction in on-treatment LDL-C levels.^{59,60}

- (3) 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 7 years, indicates that the combination of ezetimibe with moderate-intensity statin therapy reduces LDL-C levels and CVD events. In this trial, LDL-C was decreased to < 2 mmol/L (average in-trial LDL-C level achieved with statin monotherapy and statin with 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 nonstatin lipid-lowering therapies have not resulted in a reduction in CV events. In the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH)⁶² and Heart Protection Study 2 - Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)⁶³ trials, patients achieved an LDL-C level < 2 mmol/L with the combination of a statin (with or without ezetimibe) and niacin (with or without laropiprant), but this did not translate into a reduction in CV events. The reasons for the lack of benefit with niacin in these trials is not clear but might relate to the population studied already having optimum lipid values.

- (4) Very recently the European Society of Cardiology and American College of Cardiology have recommended the use of targets.^{64,65}
- (5) The use of lipid targets might aid clinicians in optimizing lipid-lowering therapy, and might reinforce patient adherence and provide evidence for patients of the efficacy of treatment.

RECOMMENDATION

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 level consistently < 2.0 mmol/L or > 50% reduction of LDL-C for individuals for whom treatment is initiated to decrease 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. On the basis of 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 combination of ezetimibe (or other nonstatin medications) with 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 decrease 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. According to evidence 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 Behaviour Interventions

PICO: In adults with high cholesterol levels and increased CV 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 lipid levels, 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.⁶⁶ Evidence from other large prospective cohort studies have also shown that combining low-risk health behaviours, 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.^{67,68} 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.⁶⁹ Results of these observational studies suggest that low-risk lifestyle behaviours are associated with 60%-80% lower risk.

Smoking cessation

Smoking cessation is probably the most important health behaviour 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.⁶⁶ 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 CV events. There are many dietary pathways to achieve CV risk reduction and adherence is probably the most important determinant of success. A registered dietitian might be of value to provide advice and follow-up.

Traditional dietary approaches to CV 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 Step I ($\leq 30\%$ total energy as fat, $\leq 10\%$ of energy as saturated

fat, ≤ 300 mg/d dietary cholesterol), and Step II ($\leq 7\%$ of energy as saturated fat, ≤ 200 mg/d dietary cholesterol) diets confirmed significant lowering of plasma lipid and lipoprotein levels, 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.⁷⁰ A World Health Organization systematic review and meta-analysis of randomized control trials reported that low saturated fat diets decrease combined CVD events compared with high saturated fat intake diets. The benefit, however, appears to be restricted to the replacement of saturated fats with polyunsaturated fatty acids (PUFAs),⁷¹ especially those from mixed omega-3/omega-6 sources in these trials.⁷² 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 (GI) carbohydrates is associated with benefit.^{73,74}

Supplementation with long chain omega-3 PUFAs does not appear to result in CV risk reduction. Systematic reviews and meta-analyses of randomized trials involving 75,000 participants have failed to show a CV benefit of supplementation with long chain omega-3 PUFAs.⁷⁵ Pooled evidence from RCTs⁷⁶ and individual large RCTs,⁷⁷ however, have shown advantages for decreasing triglycerides at high doses (2-4 g/d).

Recognizing that nutrient-based approaches might miss important cholesterol-lowering interactions,⁷⁸ there has been a move toward more food and dietary pattern-based approaches to CV risk reduction. The **Prevenición 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 CV events (MI, stroke, or death from CV causes) in 7447 participants at high CV risk.⁷⁹ 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.⁷⁹ Other dietary patterns that include shared elements of a Mediterranean dietary pattern have also shown some evidence of CV benefit in systematic reviews and meta-analyses ([Supplemental Table S1](#)). These include a Portfolio dietary pattern ([Supplemental Table S2](#)),⁸⁰ Dietary Approaches to Stop Hypertension (DASH) dietary pattern,⁸¹ low-glycemic index/glycemic load dietary pattern ([Supplemental Table S3](#)),⁸² and vegetarian dietary pattern,⁸³ as well as dietary patterns high in nuts,^{79,84} legumes,⁸⁴ olive oil,⁷⁹ fruits and vegetables,⁸⁵ total fibre,⁸⁶ and whole grains.⁸⁷ Dietary therapy using these means can be considered to augment drug therapy with statins.

In [Supplemental Table S4](#) the expected CV and lipid-lowering benefits of the various evidence-based dietary patterns for dyslipidemia management are summarized. Canadian nutrition practice guidelines for cardiac rehabilitation and CVD prevention are cited elsewhere.⁸⁸

Physical activity

Many studies have shown the benefits of regular exercise in maintaining health and preventing CVD.^{89,90} Regular exercise also has beneficial effects on diabetes risk, hypertension, and hypertriglyceridemia, and improves plasma levels of

HDL-C.⁹¹ In several studies, a lower frequency of CVD was noted in physically active individuals independent of known CVD risk factors.⁹² 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.⁹³ Limiting sedentary behaviour can be additive to regular activity with respect to the reduction of CVD events. A certified exercise physiologist might 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.⁶⁶ 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.

RECOMMENDATION

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

RECOMMENDATION

1. 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.

2. 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).

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).

RECOMMENDATION

4. 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.

RECOMMENDATION

1. 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:

- 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).

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

RECOMMENDATION

1. We recommend the following dietary components for LDL-C lowering:
 - i. Portfolio dietary pattern (Strong Recommendation; High-Quality Evidence);
 - ii. Dietary patterns high in nuts (≥ 30 g/d) (Strong Recommendation; High-Quality Evidence);
 - iii. Dietary patterns high in soy protein (≥ 30 g/d) (Strong Recommendation; High-Quality Evidence);
 - iv. Dietary patterns with plant sterols/stanols (≥ 2 g/d) (Strong Recommendation; High-Quality Evidence);
 - v. Dietary patterns high in viscous soluble fibre from oats, barley, psyllium, pectin, or konjac mannan (≥ 10 g/d) (Strong Recommendation; High-Quality Evidence);
 - vi. US National Cholesterol Education Program Steps I and II dietary patterns (Strong Recommendation; High-Quality Evidence);
2. We suggest the following dietary patterns for LDL-C lowering:
 - i. Dietary patterns high in dietary pulses (≥ 1 serving per day or ≥ 130 g/d) (beans, peas, chickpeas, and lentils) (Conditional Recommendation; Moderate-Quality Evidence);
 - ii. Low GI dietary patterns (Conditional Recommendation; Moderate-Quality Evidence);
 - iii. DASH dietary pattern (Conditional Recommendation; Moderate-Quality Evidence).

Values and preferences. Individuals might choose to use an LDL-C lowering dietary pattern alone or as an add-on to lipid-lowering therapy to achieve targets. Dietary patterns on the basis of single-food interventions (high plant sterols/stanols, viscous soluble fibre, nuts, soy, dietary pulses) might be considered additive (that is, the

approximate 5%-10% LDL-C lowering effect of each food can be summed) on the basis of the evidence from the Portfolio dietary pattern.

RECOMMENDATION

1. 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

1. 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.

Nonstatin Therapy

PICO: In adults already receiving statins, does the combination of other lipid-modulating drugs compared with placebo reduce CVD events?

Ezetimibe

The results of IMPROVE-IT,⁶¹ are of major significance for a number of reasons.⁹⁴ This is the first time that a non-statin, when combined with 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 with statin treatment 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

AIM HIGH⁶² and HPS-2 THRIVE⁶³ failed to show any CV benefit of combining niacin with 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. Although it is possible that this toxicity was partly because of the laropiprant component of the particular niacin preparation that was used, there was also an excess of the previously described side effects with extended-release niacin alone in AIM HIGH. The routine use of niacin, combined with statin therapy for CV prevention in patients who have achieved lipid targets, cannot be recommended in light of recent clinical trials. Its use in subjects who do not achieve appropriate LDL-C levels despite statin use could be considered.

Fibrates

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)⁹⁵ (not all patients receiving background statin therapy) and ACCORD (Action to Control Cardiovascular Risk in Diabetes) Lipid⁹⁶ studies failed to show a benefit of fenofibrate on CV outcomes when combined with statin therapy in patients with diabetes, with or without concomitant coronary artery disease. Results of a meta-analysis suggest a nominal benefit in the subgroup of patients with high triglyceride/low HDL-C levels at baseline (heterogeneous populations from 5 trials).⁹⁷ Because of the safety profile of fenofibrate, clinicians might consider fenofibrate for high-risk patients with residual high triglyceride/low HDL-C levels, recognizing that the potential for benefit on CVD is on the basis of a pooled subgroup analysis, and far from definitive.

Bile acid sequestrants

Cholestyramine was shown to significantly reduce CV events in patients receiving monotherapy in the Lipid Research Council - Cardiovascular Primary Prevention Trial (LRC-CPPT) study (predated statins).⁹⁸ There has been no RCT that combined a bile acid sequestrant (BAS) with statin therapy in the modern era. However, colesevelam, representing a new BAS with better gastrointestinal tolerability and some degree of glycemic benefit, offers approximately the same LDL-C lowering as ezetimibe, with no major toxicity. Therefore, it might be reasonable to consider combining a BAS with maximally tolerated statin therapy doses with or without ezetimibe in high-risk patients who are unable to achieve LDL-C targets.

Proprotein convertase subtilisin kexin 9 inhibitors

Evolocumab and alirocumab were both recently approved in Canada as well as in the United States and Europe. A third proprotein convertase subtilisin kexin 9 (PCSK9) inhibitor, bococizumab is undergoing phase III outcome trials and is currently not approved anywhere in the world. The definitive outcome trials for these agents (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk [FOURIER], Study to Evaluate the Effect of Alirocumab on the Occurrence of Cardiovascular Events in Patients Who Have Experienced an Acute Coronary Syndrome [ODYSSEY OUTCOMES], Studies of PCSK9 Inhibition and the Reduction of Vascular Events [SPIRE]-1, and SPIRE-2) are ongoing, with results expected beginning in early 2017.⁹⁹

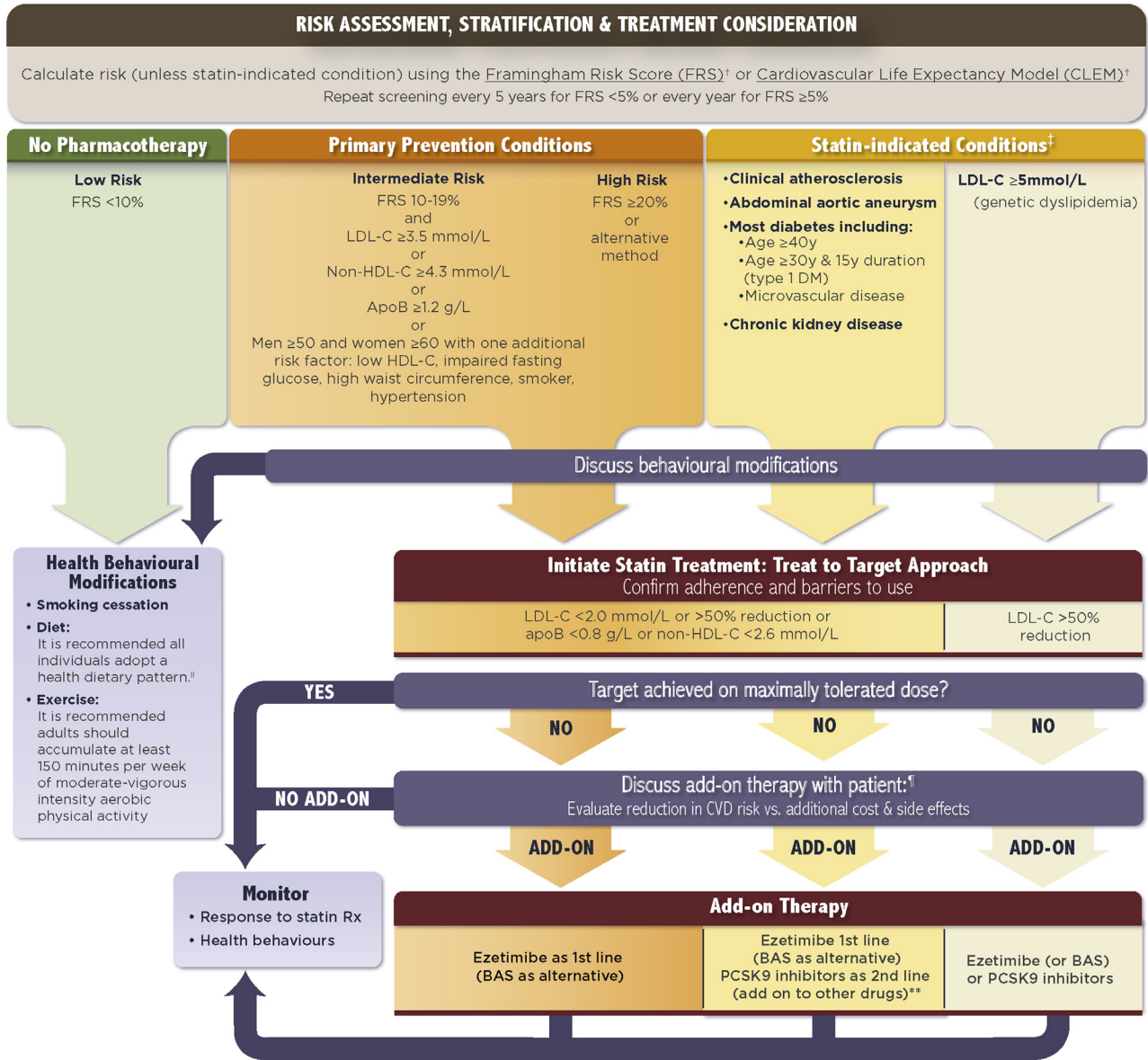


Figure 5. Nonstatin treatment algorithms. [†] <http://ccs.ca>; [‡] Statins are first-line therapy but add-on or alternative therapy might be required as per the algorithm; [¶] Consider more aggressive targets for recent ACS patients; ^{**}PCSK9 inhibitors have not been adequately studied as add-on to statins for patients with diabetes and other comorbidities. ACS, acute coronary syndrome; ApoB, apolipoprotein B; BAS, bile acid sequestrants; CLEM, Cardiovascular Life Expectancy Model; CVD, cardiovascular disease; DM, diabetes mellitus; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin kexin 9; Rx, prescription.

In their large phase II/III clinical program, alirocumab and evolocumab have shown excellent LDL-C lowering capacity (50%-70%), regardless of background therapy, in a wide variety of patients including those receiving statins. The observation of a large and concordant relative reduction (approximately 50%) in clinical outcomes, in their LDL-C efficacy studies (Open-Label Study of Long-Term Evaluation Against LDL-C [OSLER] and Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy [ODYSSEY LONG TERM]) is consistent with the LDL hypothesis, and with the meta-regression results from the CTT.^{100,101} Large phase III 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 level remains above target despite maximally-tolerated statin dosing with or without ezetimibe. See Figure 5 for suggested treatment algorithms.

RECOMMENDATION

1. We recommend ezetimibe as second-line therapy to lower LDL-C levels in patients with clinical CVD if targets are not reached with maximally tolerated statin therapy (Strong Recommendation; High-Quality Evidence).

2. We recommend that niacin not be combined with 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 levels or those with low HDL-C or high triglyceride levels.

3. We recommend that fibrates not be combined with statin therapy for CVD event prevention in patients who have achieved LDL-C targets (Strong Recommendation; High-Quality Evidence).

Values and preferences. In subgroup analysis, patients with elevated triglyceride levels and low HDL-C levels might benefit from fibrate therapy.

4. We suggest that BASs be considered for LDL-C lowering in high-risk patients whose levels remain above target despite statin treatment with or without 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 level remains above target level despite maximally tolerated statin therapy (Conditional Recommendation; Moderate-Quality Evidence).

We suggest that evolocumab be combined with 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 level for patients with atherosclerotic CVD in those not at LDL-C goal despite maximally tolerated statin doses with or without ezetimibe therapy (Conditional Recommendation; Moderate-Quality Evidence).

Values and preferences. Definitive outcome trials with PCSK9 inhibitors are under way but have not yet been completed. However, phase III efficacy trials show consistent reduction in LDL-C levels and reassuring trends toward reduced CV events, although not powered for such. Because of the very high lifetime risk faced by patients with familial hypercholesterolemia 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 that lomitapide and mipomersen (not approved in Canada) might be considered exclusively in patients with homozygous familial hypercholesterolemia (Conditional Recommendation; Moderate-Quality Evidence).

Potential Adverse Effects of Statins

Statin intolerance and adverse effects remain of great interest in the media and in lay materials readily available to patients. Additionally, this 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.¹⁰²⁻¹⁰⁴

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 during statin treatment continues but none have been identified to date.¹⁰⁵⁻¹⁰⁹ The small additional risk of diabetes associated with statin use was previously reviewed. Although the mechanism of effect remains speculative, a recent analysis suggested that there might be a relationship between LDL receptor-mediated cholesterol transport and new-onset diabetes as well as an effect mediated by direct inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG Co A reductase).^{110,111} The long-ago dismissed association of statins and cataract formation has re-emerged from several cohort studies, most of which suggest a positive association.¹¹² HOPE-3 is the first RCT to show 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 indicate that this relationship is not well founded.¹¹³⁻¹²⁰

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.

RECOMMENDATION

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, reinitiation (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.

Practical Approach

The backbone of risk reduction involves a concerted effort to affect lifestyle choices.¹²¹ 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 III clinical trials of lipid-lowering therapy will provide further CV 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, and emphasize more widespread risk assessment so as promote shared decision-making to use proven effective therapy to reduce the risk to our population.

Conclusions

The primary panel has tried to capture the recent excitement in the study of dyslipidemia within this document. Although guidelines cannot always reflect the expected changes in dyslipidemia research, we believe that we have added several important recommendations that will move us in that direction. The use of nonfasting 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 behaviour 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.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at <http://dx.doi.org/10.1016/j.cjca.2016.07.510>.