Summary Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult[1]

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 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 behavior modification that is indicated in all subjects. Finally, recommendation for the use of nonstatin medications is provided. Shared decisionmaking 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.

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.

Risk Assessment for Primary Prevention

Does risk assessment improve the management of dyslipidemia to reduce CVD events?

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?

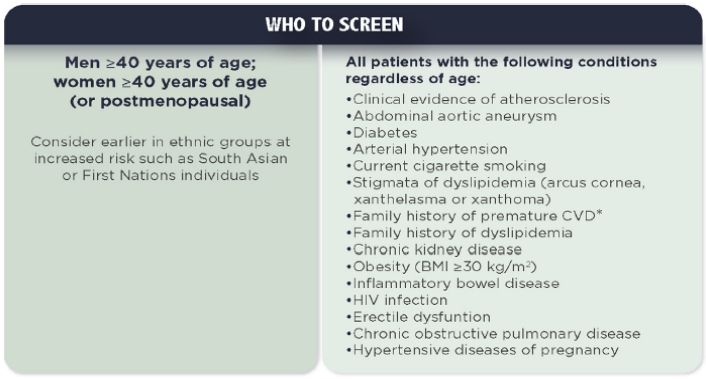


Figure 1. Whom to screen for dyslipidemia in adults at risk. *Men younger than 55 years and women younger than 65 years of age in first-degree relative. BMI, body mass index.

How to Screen: Fasting or Nonfasting Lipid Determination?

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

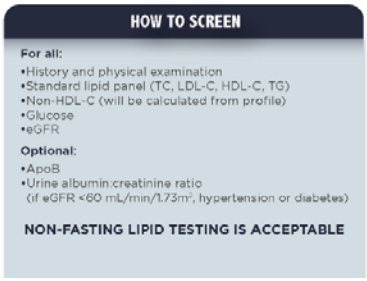


Figure 2. How to screen for dyslipidemia in adults at risk. ApoB, apolipoprotein B; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

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).

Background:

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 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 because of hemodilution, 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.

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) 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 apoB), 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.

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

In adult patients, are apoB and non-HDL-C still appropriate as alternate targets to evaluate risk?

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.

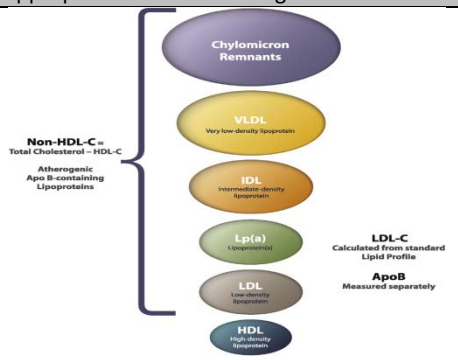


Figure 3. Non-HDL-cholesterol measures cholesterol in all atherogenic lipoproteins. ApoB, apolipoprotein B; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LP(a), lipoprotein(a); VLDL, very low-density lipoprotein.

When to Consider Pharmacological Treatment in Risk Management

Do current dyslipidemia treatment recommendations on the basis of levels of risk reduce CVD events?

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 $\geq$ 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 $\geq$ 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 $\geq$ 1.2 g/L or non-HDL-C $\geq$ 4.3 mmol/L or in men 50 years of age and older and women 60 years of age and older with $\geq$ 1 CV risk factor (Strong Recommendation; High-Quality Evidence).

Values and preferences. This recommendation applies to individuals with an LDL-C $\geq$ 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.

Table 2. Pharmacological treatment indications and targets

Category	Consider initiating pharmacotherapy if	Target	NNT
Primary prevention	High FRS (≥ 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†		20
	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	

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.

Secondary Testing

PICO: In adults, does the measurement of risk markers improve CV risk assessment in IR subjects to aid in dyslipidemia management?

Lp(a)

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?

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.

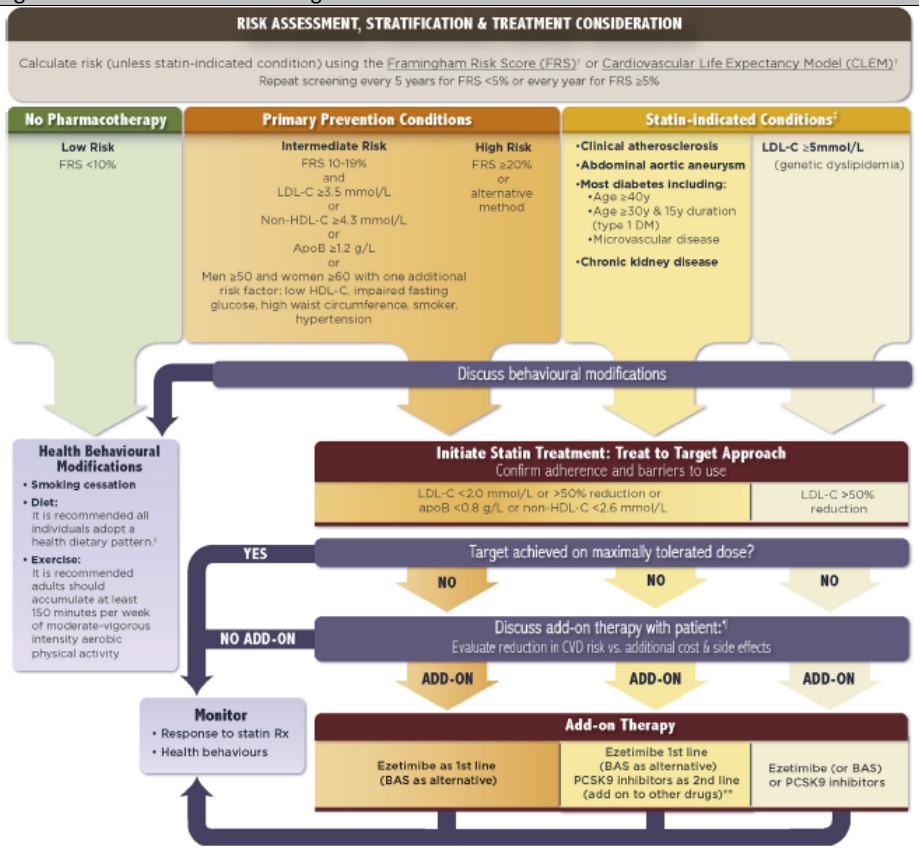
Primary prevention conditions warranting therapy, all risk groups

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.

Figure 5. Nonstatin treatment algorithms.



http://ccs.ca; z 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, highdensity lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin kexin 9; Rx, prescription.

References

1. Anderson, T. J. *et al.* 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Can. J. Cardiol.* **32,** 1263–1282 (2016).