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Society Guidelines

2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults

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ABSTRACT

The 2021 guidelines primary panel selected clinically relevant questions and produced updated recommendations, on the basis of important new findings that have emerged since the 2016 guidelines. In patients with clinical atherosclerosis, abdominal aortic aneurysm, most patients with diabetes or chronic kidney disease, and those with low-density lipoprotein cholesterol ≥ 5 mmol/L, statin therapy contin-

RÉSUMÉ

Le panel principal responsable des lignes directrices 2021 a sélectionné des éléments cliniquement pertinents et a soumis des recommandations actualisées, basées sur de nouvelles découvertes d'importance apparues depuis les lignes directrices de 2016. Ainsi, le traitement par statine reste recommandé pour les patients atteints d'athérosclérose clinique, d'anévrisme de l'aorte abdominale, pour la

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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.

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ues to be recommended. We have introduced the concept of lipid/lipoprotein treatment thresholds for intensifying lipid-lowering therapy with nonstatin agents, and have identified the secondary prevention patients who have been shown to derive the largest benefit from intensification of therapy with these agents. For all other patients, we emphasize risk assessment linked to lipid/lipoprotein evaluation to optimize clinical decision-making. Lipoprotein(a) measurement is now recommended once in a patient's lifetime, as part of initial lipid screening to assess cardiovascular risk. For any patient with triglycerides > 1.5 mmol/L, either non-high-density lipoprotein cholesterol or apolipoprotein B are the preferred lipid parameter for screening, rather than low-density lipoprotein cholesterol. We provide updated recommendations regarding the role of coronary artery calcium scoring as a clinical decision tool to aid the decision to initiate statin therapy. There are new recommendations on the preventative care of women with hypertensive disorders of pregnancy. Health behaviour modification, including regular exercise and a heart-healthy diet, remain the cornerstone of cardiovascular disease prevention. These guidelines are intended to provide a platform for meaningful conversation and shared-decision making between patient and care provider, so that individual decisions can be made for risk screening, assessment, and treatment.

plupart des patients diabétiques ou atteints d'insuffisance rénale chronique, et chez ceux dont le cholestérol à lipoprotéines de basse densité est ≥ 5 mmol/l. Nous avons introduit la notion de seuils pour le traitement des lipides/lipoprotéines afin d'intensifier le traitement hypolipidémiant avec des agents non-statiniques, et nous avons identifié les patients en prévention secondaire distingués comme ayant tirer le plus grand bénéfice de l'intensification du traitement avec ces agents. Pour tous les autres patients, nous mettons l'accent sur l'appréciation du risque par le biais de l'évaluation des lipides/lipoprotéines afin d'optimiser la prise de décision clinique. Le dosage de la lipoprotéine (a) est maintenant recommandé une fois dans la vie d'un patient, dans le cadre du dépistage initial des lipides pour évaluer le risque cardiovasculaire. Pour tout patient présentant des taux de triglycérides > 1,5 mmol/l, l'apolipoprotéine B ou le cholestérol lié aux lipoprotéines autres que celles de haute densité sont les indices lipidiques à privilégier pour le dépistage, plutôt que le cholestérol à lipoprotéines de basse densité. Nous proposons des recommandations actualisées concernant le rôle du score calcique des artères coronaires en tant qu'outil de décision clinique pour aider à la décision d'administrer un traitement par statine. Il existe de nouvelles recommandations concernant les soins préventifs des femmes souffrant de troubles hypertensifs de la grossesse. Le changement de comportement en matière de santé, incluant l'exercice physique régulier et une alimentation saine pour le coeur, reste la pierre angulaire de la prévention des maladies cardiovasculaires. Ces lignes directrices visent à fournir une plateforme pour une discussion constructive et une prise de décision partagée entre le patient et le prestataire de soins, afin que des décisions individuelles puissent être prises pour le dépistage, l'évaluation et le traitement des risques.

The 2021 Canadian Cardiovascular Society (CCS) dyslipidemia guidelines have been updated to reflect new clinical trial and epidemiologic evidence published since the previous guidelines in 2016.[1] The primary panel posed a number of population, intervention, comparator, and outcomes (PICO) questions to develop recommendations and inform clinical practice on the basis of a detailed literature review. The PICO format is a common standard used for guidelines development, to aid clinicians in determining whether the recommendations apply to their own patients with outcomes relevant to their practice. Initially, 13 different PICO questions were posed and then rated on the basis of the availability and significance of new evidence and importance to be included in the updated guidelines. The primary panel members voted on the initial 13 PICO questions formulated (see Supplemental Appendix S1 Supplemental Appendix S1, S2, S3 etc. Please check throughout.?>), resulting in the identification of 6 key PICO questions, which are included in this update. Using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) standards, individual studies and composite literature were reviewed for each PICO question with regard to the quality of the available evidence and the presence of publication or interpretive bias. We have included the updated recommendations within this update, and the results of voting on each recommendation are shown in Supplemental Appendix S2. For recommendations to go forward a two-thirds voting majority was required. Individuals with conflicts of interest were recused from voting on relevant recommendations.

We have introduced the concept of "treatment thresholds" for intensifying lipid-lowering therapy with nonstatin lipid-lowering agents on the basis of new evidence with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and icosapent ethyl (IPE). Because of the increased focus on apolipoprotein B (ApoB) and non-high-density lipoprotein cholesterol (HDL-C) in this update, values for ApoB and non-HDL-C have been modified (from previous versions of these guidelines) to accurately represent the same percentile equivalents as low-density lipoprotein (LDL) cholesterol (LDL-C) for all recommended thresholds (see Supplemental Appendix S3). The goal of the process was to produce an objective, nonbiased document on the basis of the best available evidence to allow clinicians and patients to make collaborative treatment decisions. These guidelines are not absolute, but are to be used in the context of one-on-one discussion between practitioner and patient and consideration of the patient's values and preferences. Dyslipidemia is an important risk factor for atherosclerotic cardiovascular (CV) disease (ASCVD), and these guidelines inform risk assessment, treatment, and surveillance options for at-risk populations. These guidelines were undertaken under the auspices of the Guideline Committee of the CCS without any support or involvement from outside groups, including industry.

Definitions

ASCVD refers to all clinical conditions of atherosclerotic origin, including acute coronary syndrome (ACS), myocardial infarction (MI), stable or unstable angina, coronary artery disease documented using angiography, coronary or other arterial revascularization (coronary artery bypass graft surgery, femoral popliteal bypass graft surgery, etc), stroke, transient ischemic attack, documented carotid disease, peripheral artery disease, and abdominal aortic aneurysm.

Statin-indicated condition refers to any condition for which pharmacotherapy with statins is indicated, and consists

of all documented ASCVD conditions, as well as other high-risk primary prevention conditions in the absence of ASCVD, such as most patients with diabetes, those with chronic kidney disease (CKD), and those with an LDL-C ≥ 5.0 mmol/L or a diagnosis of familial hypercholesterolemia (FH). This concept was first introduced in the 2016 guidelines and continues to be used in this update.

Primary prevention refers to all efforts aimed at either populations or individuals to prevent or delay the onset of ASCVD.

Secondary prevention refers to the efforts to treat known, clinically significant ASCVD, and to prevent or delay the onset of disease manifestations.

Overview of the Management of Dyslipidemia in Primary Prevention

Screening

We determined that there was insufficient new evidence to recommend major changes to the approach of risk assessment in primary prevention. We continue to recommend lipid/lipoprotein screening (in either fasting or nonfasting state) for men and women older than 40 years of age or at any age with one of the specific conditions listed in Table 1. The nonfasting state is recommended (except for individuals with known triglycerides > 4.5 mmol/L) because it leads to minimal changes in relevant lipid levels and has no effect on apolipoprotein levels compared with the fasting state.[1] Table 2 provides a summary of the recommendations for how to screen patients. We maintain the recommendation for regular CV risk assessments using a validated risk model in Canada (either the **F**ramingham **R**isk **S**core [FRS] or the **C**ardiovascular **L**ife **E**xpectancy **M**odel [CLEM]) every 5 years for men and women aged 40-75 years to guide preventive care through shared decision-making with the patient. Among individuals 30-59 years of age without diabetes, the presence of a history of premature CV disease (CVD) in a first-degree relative (ie, 55 years or younger in male relatives and 65 years or younger in female relatives) increases an individual's calculated FRS percent risk by approximately twofold.[1]

Health behaviour interventions

Health behaviour modifications 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.[2] Evidence from other large prospective cohort studies have also shown that combining low-risk health behaviours that include achieving and maintaining a healthy body weight, consuming a healthy diet, engaging in regular physical activity, smoking cessation, limiting alcohol consumption to no more than moderate, and ensuring a sufficient duration of sleep are associated with benefit for the primary prevention of CVD.[3,4]

We continue to recommend a Mediterranean dietary pattern, which has evidence of CV outcome benefit in systematic reviews and meta-analyses. Additionally, other dietary patterns that share important features such as the Portfolio dietary pattern,[5] Dietary Approaches to Stop Hypertension (DASH) dietary pattern,[6] low-glycemic index/glycemic load dietary pattern,[7] and plant-based dietary pattern,[8] as well as dietary patterns high in nuts,[9,10] legumes,[10] olive oil,[9] fruits and vegetables,[11] total fibre,[12] and whole grains.[13] Dietary therapy using these means can be considered to augment drug therapy with statins; however, their benefits have been shown in terms of surrogate CV measures such as blood pressure and lipoproteins.

We also continue to recommend that all adults should accumulate at least 150 minutes of moderate to vigorous aerobic activity per week. It might also be beneficial to add muscle- and bone-strengthening activities at least 2 days per week. Regular exercise has beneficial effects on diabetes risk,

Table 1. Who to screen for dyslipidemia in adults at risk

Who to screen
Men 40 years of age or older; women 40 years of age or older (or postmenopausal)
• Consider earlier in ethnic groups at increased risk such as South Asian or indigenous individuals
All patients with any of the following conditions, regardless of age
• Clinical evidence of atherosclerosis
• Abdominal aortic aneurysm
• Diabetes mellitus
• Arterial hypertension
• Current cigarette smoking
• Stigmata of dyslipidemia (corneal arcus, xanthelasma, xanthoma)
• Family history of premature CVD*
• Family history of dyslipidemia
• CKD (eGFR ≤ 60 mL/min/1.73 m^2 or ACR ≥ 3 mg/mmol)
• Obesity (BMI ≥ 30)
• Inflammatory diseases (RA, SLE, PsA, AS, IBD)
• HIV infection
• Erectile dysfunction
• COPD
• History of hypertensive disorder of pregnancy

ACR, albumin-to-creatinine ratio; AS, ankylosing spondylitis; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; IBD, inflammatory bowel disease; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematous.

*Men younger than 55 years of age and women younger than 65 years of age in first-degree relatives.Data from Anderson et al.[1]

Table 2. How to screen for dyslipidemia in adults at risk

How to screen
For all
• History and physical examination
• Standard lipid profile*: TC, LDL-C, HDL-C, non-HDL-C,† TG
• FPG or A1c
• eGFR
• Lipoprotein(a)—once in patient's lifetime, with initial screening
Optional
• ApoB
• Urine ACR (if eGFR <60 mL/min/1.73 m^2, hypertension, or diabetes)

A1c, glycated hemoglobin; ACR, albumin-to-creatinine ratio; ApoB, Apolipoprotein B; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

*Nonfasting lipid testing is recommended in most adults for screening; however, for individuals with a history of triglyceride levels > 4.5 mmol/L, measurement of fasting lipid levels are recommended.

†It is now generally preferable to follow non-HDL-C or ApoB levels over LDL-C when interpreting lipid results, particularly when TG are ≥ 1.5 mmol/L.

hypertension, and hypertriglyceridemia, and improves plasma levels of HDL-C.[14]

A summary table of the expected CV outcomes and/or lipid benefits from various health behaviour changes is presented in Supplemental Appendix S4.

Pharmacologic treatment

Studies consistently show a 20%-22% relative risk reduction for each 1 mmol/L reduction in LDL-C.[15] The absolute risk reduction is thus dependent on the baseline risk and the baseline LDL-C, because statin treatment will provide a greater absolute LDL-C lowering in those with higher baseline values. Therefore, we continue to recommend initiation of statin therapy for: (1) all high-risk patients (≥ 20% 10-year risk); or (2) intermediate-risk patients (10%-19.9%) when LDL-C is ≥ 3.5 mmol/L (or ApoB ≥ 1.05 g/L or non-HDL-C ≥ 4.2 mmol/L). In addition, among intermediate-risk individuals with several additional risk factors as evaluated in **H**eart **O**utcomes **P**revention **E**valuation (HOPE) 3[16] (men 50 years of age or older or women 60 years of age or older with 1 additional risk factor including low HDL-C, impaired fasting glucose, increased waist circumference, cigarette smoking, hypertension) the evidence remains in favour of statin initiation to reduce the risk of CV events. The presence of other risk modifiers in intermediate-risk individuals also favours the use of statins (eg, high-sensitivity C-reactive protein ≥ 2.0 mmol/L, family history of premature coronary artery disease, high lipoprotein(a) [Lp(a)] ≥ 50 mg/dL [≥100 nmol/L] or coronary artery calcium score [CAC] > 0 Agatston units [AU]).

For most low-risk subjects (FRS < 10%), health behaviour modification without pharmacotherapy is still recommended; however, the exceptions would be: (1) low-risk individuals with an LDL-C ≥ 5.0 mmol/L (or ApoB ≥ 1.45 g/L or non-HDL-C ≥ 5.8 mmol/L) who have a statin-indicated condition (likely a genetic dyslipidemia such as FH); or (2) individuals with an FRS of 5%-9% with an LDL-C ≥ 3.5 mmol/L (or ApoB ≥ 1.05 g/L or non-HDL-C ≥ 4.2 mmol/L), especially with other CV risk modifiers (eg, family history of premature coronary artery disease, Lp(a) ≥ 50 mg/dL [or ≥ 100 nmol/L] or CAC > 0 AU) because the proportional benefit from statin therapy will be similar to that in other treatment groups. Treatment of this group would follow the intermediate risk approach. The treatment approach recommended for primary prevention patients is outlined in Figure 1. Finally, evidence continues to show the benefits of maintaining low levels of atherogenic lipoproteins throughout life and at any age and any level of risk. Even among primary prevention individuals at low 10-year risk, the benefit of lipid-lowering can be substantial, especially when LDL-C ≥ 3.5 mmol/L.[17] In addition, accumulating evidence suggests continued benefits of lipid-lowering for primary prevention in older adults (older than 75 years).[18]

Other statin-indicated conditions

We continue to recommend statin initiation for the following high-risk conditions (ie, "statin-indicated" conditions, even in the absence of a previous CV event: (1) CKD (except for patients receiving chronic dialysis) defined as patients with an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 and those with preserved estimated glomerular filtration rate in whom CKD is on the basis of an increased urinary albumin to creatinine ratio (≥ 3 mg/mmol) for at least 3 months' duration; (2) diabetes mellitus in patients 40 years of age or older or 30 years of age or older with 15 or more years' duration of diabetes, or the presence of microvascular complications; (3) abdominal aortic aneurysm > 3.0 cm or previous aortic aneurysm surgery.[1] Established ASCVD is also a statin-indicated condition, which is discussed in more detail later in these guidelines. The treatment approach for patients with a statin-indicated condition is summarized in Figure 2.

All of the recommendations from the previous dyslipidemia guidelines that remain unchanged are provided in Supplemental Appendix S5.

New areas of focus

The review of literature and evidence assessment identified several areas for new and/or updated recommendations for primary prevention, specifically in: (1) the preventive care of women with hypertensive disorders of pregnancy; (2) the importance of lipoprotein measurement including non-HDL-C, ApoB, and Lp(a) in assessing CV risk; (3) the role of CAC as a clinical decision-making tool for determining the need to initiate statin treatment; (4) the CV benefit of IPE in patients with triglycerides ≥ 1.5-5.6 mmol/L and a previous CV event or with diabetes and additional risk factors; and (5) the lack of CV benefit of omega-3 fatty acids from dietary sources or other formulations/supplements.

Overview of the Management of Dyslipidemia in Secondary Prevention

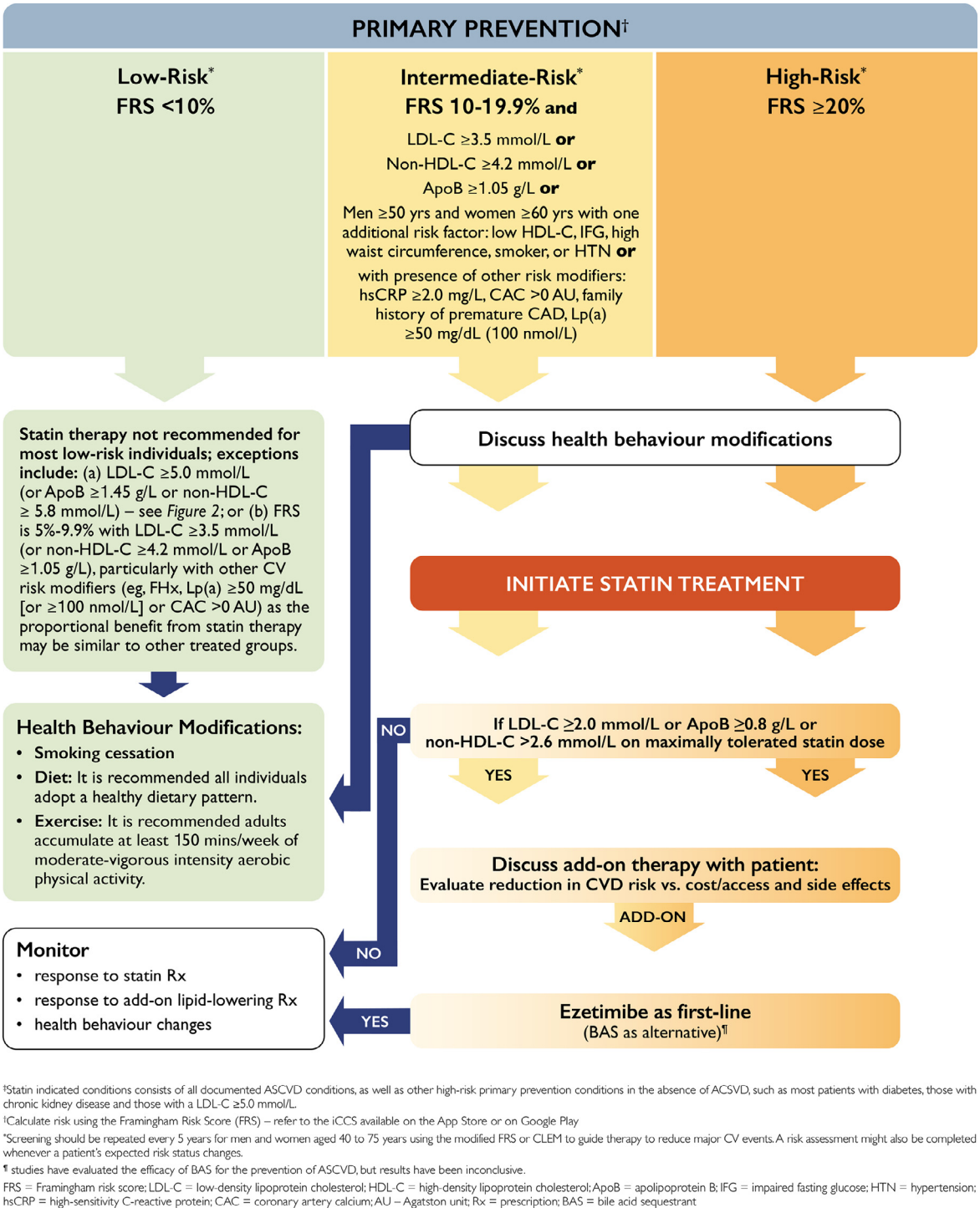
Health behaviour interventions

We continue to recommend health behaviour interventions to optimize CV health in all patients with a previous ASCVD event (refer to the *Health behaviour interventions* in the section on *Overview of the Management of Dyslipidemia in Primary Prevention*). In secondary prevention, limiting sedentary behaviour can be additive to regular physical activity with respect to the reduction of ASCVD 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 in this patient population and remains a cornerstone of management.[19]

Relevant recommendations from the previous dyslipidemia guidelines that remain unchanged are provided in Supplemental Appendix S5.

New areas of focus

Several areas were reviewed by our group that directly affect the care and management of patients with previous ASCVD events and have led to new or updated recommendations, specifically: (1) the role of nonstatin therapies to reduce ASCVD events; (2) the most appropriate lipid/lipoprotein threshold for the intensification of therapy in the management of dyslipidemia; and (3) the lack of CV benefit of omega-3 fatty acids from dietary sources or other formulations/supplements.



‡Statin indicated conditions consists of all documented ASCVD conditions, as well as other high-risk primary prevention conditions in the absence of ACSVD, such as most patients with diabetes, those with chronic kidney disease and those with a LDL-C ≥5.0 mmol/L.

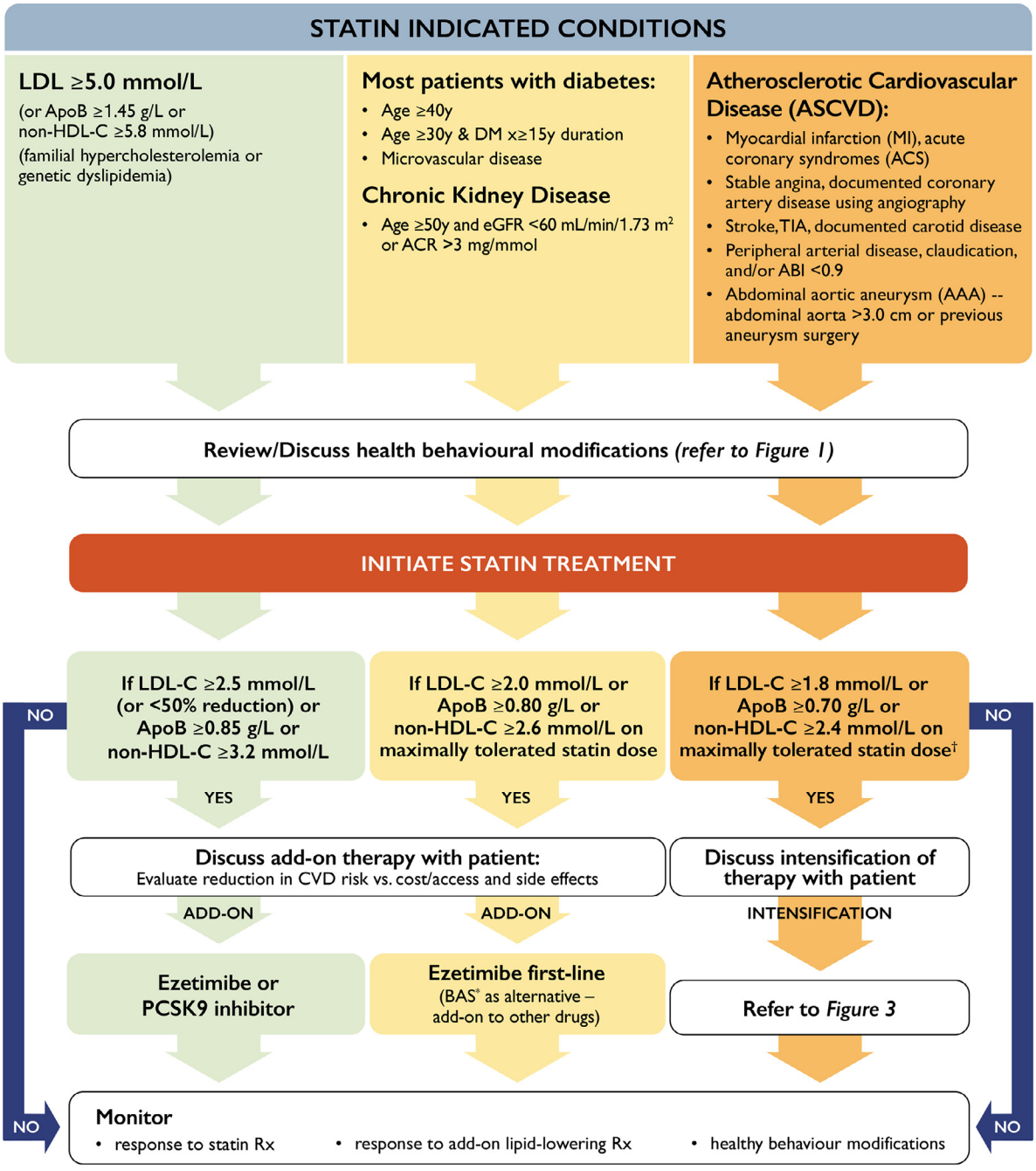
†Calculate risk using the Framingham Risk Score (FRS) – refer to the iCCS available on the App Store or on Google Play

*Screening should be repeated 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.

¶ studies have evaluated the efficacy of BAS for the prevention of ASCVD, but results have been inconclusive.

FRS = Framingham risk score; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; ApoB = apolipoprotein B; IFG = impaired fasting glucose; HTN = hypertension; hsCRP = high-sensitivity C-reactive protein; CAC = coronary artery calcium; AU – Agatston unit; Rx = prescription; BAS = bile acid sequestrant

Figure 1. Treatment approach for primary prevention patients (without a statin-indicated condition*). Statin-indicated conditions consist of all documented ASCVD conditions, as well as other high-risk primary prevention conditions in the absence of ASCVD, such as most patients with diabetes, those with chronic kidney disease, and those with an LDL-C ≥ 5.0 mmol/L. Screening should be repeated every 5 years for men and women aged 40-75 years using the modified FRS or **C**ardiovascular **L**ife **E**xpectancy **M**odel (CLEM) to guide therapy to reduce major CV events. A risk assessment might also be completed whenever a patient's expected risk status changes. ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; AU, Agatston units; BAS, bile acid sequestrant; CAC, coronary artery calcium; CAD, coronary artery disease; CV, cardiovascular; FHx, family history; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; HTN, hypertension; FRS, **F**ramingham **R**isk **S**core; IFG, impaired fasting glucose; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); mins, minutes; Rx, treatment; yrs, years. * Calculate risk using the FRS—refer to the iCCS available on the App Store or on Google Play.



eGFR = estimated glomerular filtration rate; ACR = albumin-to-creatinine; TIA = transient ischemic attack; ABI = ankle-brachial index.
†LDL-C threshold selected on the basis of the PCSK9-inhibitor clinical trials lipid inclusion parameters (references 91 and 92) with percentile equivalents used for ApoB and non-HDL-C (see supplement).
*studies have evaluated the efficacy of BAS for the prevention of ASCVD, but results have been inconclusive.

Figure 2. Treatment approach for patients with a statin-indicated condition. ABI, ankle-brachial index; ACR, albumin to creatinine; ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; Rx, treatment; TIA, transient ischemic attack.

PICO Questions, Evidence Review, and New Recommendations

PICO 1: Do pregnancy-related conditions (hypertensive disorders of pregnancy and other related complications) identify women at increased risk of premature CVD warranting lipid screening?

Pregnancy complications such as preeclampsia and related hypertensive disorders of pregnancy, gestational diabetes, placental abruption, preterm delivery, stillbirth, and delivery of a low birth weight infant are associated with a higher lifetime risk of developing CV risk factors (hypertension; type 2 diabetes mellitus; dyslipidemia, especially hypertriglyceridemia and low HDL-C; metabolic syndrome; and subclinical atherosclerosis) and overt ASCVD.[20,21] The strongest and most abundant evidence linking pregnancy events and ASCVD is for preeclampsia, in which there is a twofold relative risk of developing premenopausal ASCVD, with onset at 10-15 years after delivery[20] compared with women who had uncomplicated pregnancies. This risk is highest if preeclampsia is recurrent (ie, 28% lifetime risk of ASCVD, or within 25 years after delivery[22]), or if associated with preterm delivery (before 37 weeks' gestation) and other adverse conditions (chest pain, dyspnea, low platelet count, elevated liver enzymes, intrauterine growth restriction) or severe complications (eclampsia, stroke, myocardial ischemia, hepatic rupture, acute kidney injury with need for hemodialysis).[23] ASCVD risk is partly mediated by the development of chronic hypertension and metabolic syndrome.[24] There is often silent and subclinical endothelial dysfunction after hypertensive disorders of pregnancy suggesting accelerated vascular aging.[25,26]

National CV societies,[1,27] including the CCS,[1] have recommended performing lipid and metabolic screening in postpartum women who have had these complications, although whether specific thresholds warranting pharmacotherapy differ from those typically used in the general population is not known. Although it is true that these women have a low absolute risk of ASCVD over the short term, the postpartum period might represent "a teachable moment" to engage young women in CV prevention and might result in long-term benefits through health behaviour interventions with or without pharmacological intervention. Treatment decisions should be guided on the basis of lifetime risk in conjunction with patient values and preferences.[28]

RECOMMENDATION

1. Among women who have had a pregnancy complication such as hypertensive disorders of pregnancy, gestational diabetes, preterm birth, stillbirth, low birth weight infant, or placental abruption, we recommend screening with a complete lipid panel in the late postpartum period, because these women have a higher risk of premature CVD and stroke with onset 10-15 years after index delivery (Strong Recommendation; Moderate-Quality Evidence).
2. We recommend counselling women who have any of these pregnancy-related complications of the increased lifetime risk of ASCVD, and reinforcing the importance of healthy behaviours (ie, maintaining a healthy body weight, 150 weekly minutes of moderate intensity aerobic physical activity, avoiding tobacco consumption, no more than moderate alcohol consumption, stress management, and adopting a healthy dietary pattern, such as the Mediterranean diet (Strong Recommendation; Low-Quality Evidence).
3. To assist with decisions about lipid-lowering pharmacotherapy in this patient population, we recommend favouring CV age, over 10-year risk calculators (Strong Recommendation; Low-Quality Evidence).

Values and preferences. Although much of this observed risk among women who have had a pregnancy-related complication might be due to conventional ASCVD risk factors, complications such as preeclampsia might lead to ASCVD through accelerated vascular aging or other pathways warranting additional future research.

There is insufficient evidence to guide decisions about use of lipid-lowering therapy in women on the basis of pregnancy factors alone. The American Heart Association 2019 CV prevention guidelines[27] consider preeclampsia a risk enhancer warranting early screening, healthy behaviour interventions, and possibly shifting of risk category from borderline to intermediate risk (ie, eligible for statin or other lipid-lowering therapy).

We suggest individual discussions about statin or other lipid-lowering pharmacotherapy, considering each patient's lifetime risk/individual risk factors along with severity and recurrence of pregnancy complications (in particular preterm preeclampsia with adverse conditions), balanced against the potential side effects and harms of long-term therapy. Although statins were previously considered teratogenic on the basis of earlier animal studies, this has not been consistently shown in recent human studies.[29,30] A part of the observed increase in risk of congenital malformations might be due to underlying medical conditions rather than treatment with statin therapy itself.[29] Furthermore, there appears to be a differential effect on the basis of the type of compound, with most cases of congenital malformations being seen among infants whose mothers took lipophilic compounds (eg, atorvastatin, lovastatin, simvastatin) as opposed to hydrophilic compounds (eg, pravastatin, rosuvastatin).[31,32] Therefore, in women who are reproductive age and who are eligible and considering statin therapy for ASCVD risk reduction on the basis of CV age or lifetime risk of ASCVD, we suggest the use of hydrophilic compounds over lipophilic compounds because of easier passage through the placenta with the latter molecules. It should be noted that for most reproductive women who take statin therapy for primary prevention of ASCVD, an effective birth control method is recommended with interruption of therapy before a planned pregnancy or at the time of an unplanned positive pregnancy test. These treatments can be resumed after delivery, when breastfeeding is completed. Referral to a specialist in obstetrical medicine or in fetal-maternal medicine should also be considered in the management of statin and nonstatin therapies in pregnant women or in women planning pregnancy.

PICO 2a: Is there evidence to promote non-HDL-C over ApoB or ApoB over non-HDL-C for screening and treatment purposes?

Previous versions of these guidelines have used LDL-C as the primary laboratory measurement for considering initiation of statin treatment and as a treatment target in low-, intermediate-, and high-risk individuals. Beginning with the 2012 guidelines, it has been recommended that non-HDL-C and ApoB could be used as alternate targets to LDL-C in any individual with triglyceride level > 1.5 mmol/L.[1,33] The rationale for this is that above this level of triglyceride, some cholesterol in LDL particles is replaced by triglyceride, which promotes production of more atherogenic small dense LDL particles,[34] and makes the amount of cholesterol in LDL-C an unreliable reflection of LDL particle number.[35] In addition, other particles, such as remnants of chylomicrons and very LDL-C, as well as Lp(a), all accumulate in the artery wall and contribute to atherogenesis, whereas HDL-C does not. Therefore, estimation of the concentration of all atherogenic particles requires a broader focus than a measurement of LDL-C. Non-HDL-C (indirectly) and ApoB (directly) provide a more accurate assessment of the total concentration of atherogenic particles than LDL-C. Non-HDL-C and ApoB are, for this reason, both better predictors of CV event risk and benefit of lipid-lowering therapy compared with LDL-C.[36,37] On the basis of these previous recommendations, non-HDL-C is now routinely reported across Canada at no additional cost, on the basis of the simple calculation of total cholesterol minus HDL-C. ApoB is also available as an insured laboratory test in all provinces except Ontario. Levels of non-HDL-C and ApoB are not significantly changed in the postprandial state in individuals with triglycerides < 4.5 mmol/L, whereas LDL-C can be lowered by up to 10% because of triglyceride enrichment of LDL-C.[38,39] After the guideline recommendation that was introduced in 2016 allowing for nonfasting collections for screening and follow-up lipid testing,[1] it is now generally preferable to follow non-HDL-C or ApoB levels over LDL-C when interpreting lipid results, particularly when triglyceride levels are ≥ 1.5 mmol/L. A recent survey conducted by the Canadian Association of Medical Biochemists and the Canadian Society of Clinical Chemistry indicates that patients across Canada can now present to laboratories nonfasting and receive a complete lipid profile.

Non-HDL-C or ApoB for predicting CVD risk

In population studies, non-HDL-C and ApoB can be considered as equivalent markers of total atherogenic lipoproteins and lipid-related CV risk and this applies to most individuals.[40] Publications since the 2016 update of these guidelines indicate a subgroup of individuals, estimated at between 8% and 23%, have discordance between ApoB and non-HDL-C levels in whom ApoB might be the better predictor of risk for coronary calcification[40] and ASCVD events.[41] Analysis of CV events in the large United Kingdom Biobank,[41] and meta-analysis of 110 prospective cohort registries of patients with or at risk for ASCVD,[42] however, showed an overall similar ability of non-HDL-C and ApoB to predict risk, but confirmed both of these measures to be superior to LDL-C. Recent consensus statements have concluded that non-HDL-C is currently a more practical choice because it incurs no additional expense to the patient or health care system.[43,44] In Canada, the approach has been to allow clinicians to use either non-HDL-C or ApoB as their preferred parameter for assessment of risk and achievement of treatment targets, depending on their comfort level with the two measurements, availability of ApoB testing in their region, and when there might be a concern about discordance between the two measurements, as indicated previously. In the current guidelines, we are continuing this recommendation, while strongly urging the routine use of either non-HDL-C or ApoB instead of LDL-C as the lipid level of interest in initial lipid screening and as a treatment target in all patients with triglyceride level > 1.5 mmol/L.

RECOMMENDATION

4. We recommend that for any patient with triglycerides > 1.5 mmol/L, non-HDL-C or ApoB be used instead of LDL-C as the preferred lipid parameter for screening (Strong Recommendation, High-Quality Evidence).

PICO 2b: Is there evidence to support measurement of Lp (a) to improve risk stratification and dyslipidemia management in patients with and without previous CV events?

Lp(a) is an LDL-like particle in which ApoB is covalently bound to a plasminogen-like molecule called apolipoprotein (a).[45] Plasma concentrations of Lp(a) are not influenced by age, sex, fasting state, inflammation, or lifestyle factors, but are largely controlled by a single gene locus, *LPA* on chromosome 6, and are highly (> 90%) heritable.[46] Individual values are generally stable throughout life, thus, repeat measures are not required for risk assessment.

Mendelian randomization studies have clearly shown that genetic variants in the *LPA* locus uniquely regulating Lp(a) levels are robustly associated with coronary heart disease risk, thereby strongly suggesting a causal association between Lp(a) and CVD.[47,48]

The risk of ASCVD increases with increasing Lp(a) levels > 30 mg/dL in a dose-dependent fashion.[48-50] Among 7524 subjects in the Copenhagen Heart Study followed for 17 years, subjects with an Lp(a) concentration between 30 and 76 mg/dL had a 1.7-fold hazard ratio (HR) for MI and those with an Lp(a) level > 117 mg/dL had an adjusted HR of 2.7.[48] Among 6086 patients with a first MI and 6857 control participants from the INTERHEART study who were stratified according to ethnicity and adjusted for age and sex, Lp(a) concentrations > 50 mg/dL were associated with an increased risk of MI (odds ratio, 1.48; 95% confidence interval [CI], 1.43-1.67), independent of established CVD risk factors including diabetes mellitus, smoking, and high blood pressure.[51] Higher Lp(a) concentrations carried a particularly high population burden in South Asian and Latin American individuals.[51] An Lp(a) level > 50 mg/dL (> 100 nmol/L) is found in approximately 20% of individuals of European and South Asian descent, 40% of African American individuals, and fewer than 10% of East Asian individuals.[51,52] Individuals

with extreme elevations in Lp(a) have been shown to be at markedly high risk, with an event rate similar to that for other genetic dyslipidemias for which family screening is recommended (ie, heterozygous FH). As such, Lp(a) is a common but as yet not routinely measured ASCVD risk marker.

Elevated Lp(a) level also increases the risk of recurrent ASCVD in a dose-dependent manner.[50,53] Among 58,527 subjects from the Copenhagen General Population Study, 2527 subjects aged 20-79 years with a history of ASCVD and elevated Lp(a) were followed over a median of 5 years.[54] The adjusted major adverse CV events (MACE) incidence rate ratios were 1.28 (95% CI, 1.03-1.58) for subjects with an Lp(a) level of 10-49 mg/dL (18-104 nmol/L), 1.44 (95% CI, 1.12-1.85) for 50-99 mg/dL (105-213 nmol/L), and 2.14 (95% CI, 1.57-2.92) for those with Lp(a) ≥ 100 mg/dL (≥ 214 nmol/L).[54] In the randomized, controlled **F**urther Cardiovascular **Ou**tcomes **R**esearch With PCSK9 **I**nhibition in Subjects With **E**levated **R**isk (FOURIER) and Study to Evaluate the Effect of Alirocumab on the Occurrence of Cardiovascular Events in Patients Who Have Experienced an Acute Coronary Syndrome (ODYSSEY OUTCOMES) trials, high levels of Lp(a) were associated with an increased risk of recurrent CVD events in patients with established CVD irrespective of LDL cholesterol.[53,54] Furthermore, alirocumab-associated reductions in Lp(a) reduced MACE in patients with a recent ACS independent of LDL-C.[54]

Although these new data support the potential role of Lp (a) as a target of treatment in the future, there remains no evidence from RCTs that specifically lowering Lp(a) level leads to reductions in CV outcomes. It should also be noted that commonly used lipid-lowering therapies (ie, statins and ezetimibe) do not appreciably lower Lp(a) levels. The only available lipid-lowering therapies that lead to substantial lowering of Lp(a) include PCSK9 inhibitors, niacin, and apheresis, but relatively limited evidence exists for their use in patients with a high Lp(a) level. Newer investigational agents, such as antisense oligonucleotides and small interfering RNAs are currently being evaluated for CVD risk reduction in this patient population. Accordingly, Lp(a) is not currently considered a treatment target and repeat measures are therefore not indicated.

Lp(a) testing is available across Canada, and is currently an insured laboratory test in most provinces, with the exception of Ontario and Manitoba.

RECOMMENDATION

5. We recommend measuring Lp(a) level once in a person's lifetime as a part of the initial lipid screening (Strong Recommendation; High-Quality Evidence).
6. For all patients in the setting of primary prevention with a Lp(a) ≥ 50 mg/dL (or ≥ 100 nmol/L), we recommend earlier and more intensive health behaviour modification counselling and management of other ASCVD risk factors (Strong Recommendation; Expert Consensus).

Values and preferences. There is a large body of evidence supporting the potential causal association between Lp(a) and future ASCVD.[50,51,55-58] The high prevalence of elevated Lp(a) level, the strength of association with incident and recurrent ASCVD events, and the potential to improve CV risk stratification, strongly justify universal screening to identify individuals with very high levels. Identification of high levels of Lp(a) is a useful consideration for shared decision-making in subjects across all ASCVD risk categories, but especially in younger patients, particularly those who have a very strong family history of premature ASCVD. Although further evidence that directly lowering Lp(a) level reduces ASCVD risk is pending, the finding of high Lp(a) should alert primary care practitioners to more actively pursue an overall ASCVD event risk assessment, including careful discussion of current health behaviours, consideration of age-appropriate vascular imaging studies for detecting early evidence of subclinical atherosclerosis in select individuals (eg, CAC score), and earlier introduction of statin or other lipid-lowering therapy, especially in intermediate-risk individuals and/or low-risk individuals with moderate elevations of LDL-C between 3.5 and 5 mmol/L.

In the setting of secondary prevention, the presence of a high Lp(a) level is strongly predictive of recurrent events, and suggests the need for intensification of LDL-lowering therapy, including use of PCSK9 inhibitors. Furthermore, preliminary evidence suggests that treatment with PCSK9 inhibitors post ACS in patients with high Lp(a) reduces MACE independent of LDL-C lowering.[54] When clinicians are uncertain of the implications of elevated Lp(a), consultation with a lipid specialist might be considered.

PICO 3: In primary prevention, what is the evidence for CAC score to improve risk assessment? Specifically, should low CAC (or CAC = 0) score be used to avoid statin therapy in select individuals?

For primary prevention, most guidelines are on the basis of the concept of ASCVD risk assessment to help determine appropriateness and intensity of ASCVD risk factor modification. The primary prevention RCTs on which the recommendations are based, however, use clinical descriptors to identify patients eligible for study and, as a result, the patients eligible for the proven therapy. None of the algorithms available, including the FRS used in Canada, have been used to determine eligibility for any of the successful, primary prevention lipid-lowering trials. Even so, there is evidence to suggest that use of such algorithms is effective on a population level, more so than identification of patients on the basis of trial eligibility criteria.[59,60] Despite this clinical utility, it has been repeatedly shown that typical ASCVD event risk algorithms can lead to substantial over- or underestimation of ASCVD event risk,[61] and consequently, inappropriate risk factor management. Additionally, the value of these algorithms for predicting the presence and burden of atheroma is poor.[62,63]

Atheroma burden, the substrate that portends CV events, directly predicts ASCVD event risk in a graded fashion. This has been shown over decades with invasive angiography and more recently with coronary computed tomography, including noncontrast CAC scoring, the latter being highly applicable for assessment of patients who are asymptomatic, and

possible candidates for primary prevention.[64,65] Accordingly, the literature is replete with clinical studies reinforcing the concept that directly assessing the presence of atheroma, through CAC scoring, significantly improves the appropriate selection of patients who are likely to benefit from lipid modifying therapy.[66]

Noncontrast CAC measurements are sensitive, reproducible, and can be performed rapidly with an average radiation dose of 0.89 mSv (compared with background annual radiation exposure of approximately 3.0 mSv). Evidence for improved C-statistic/net reclassification index after adjustment for standard risk factors (FRS) has been shown in multiple studies.[67,69] The clinical decision-making utility of CAC measurements is best shown in middle-aged, intermediate-risk populations in whom the presence or absence of coronary artery calcification results in reclassification into higher or lower risk populations. A CAC measurement > 0 AU confirms the presence of atherosclerotic plaque. Increasing scores are directly proportional to increased ASCVD event risk.[69-72] A CAC measurement > 100 AU is associated with a high risk (> 2% annual risk) of an ASCVD event within 2-5 years and is generally an indication for intensive CV risk factor modification, including treatment of LDL-C. CAC > 300 AU places the patient in a very high risk category with a 10-year risk of MI/CV death of approximately 28%.[73] A CAC measurement of 0 AU, however, has a very high negative predictive value for ASCVD events in asymptomatic, low-risk adults within 2-5 years (negative predictive value, 95%-99%).[74] Importantly, although a CAC of 0 AU is indicative of a low event rate (1.5% per 10 years; 0.32-0.43 per 1000 person-years; 1.3-5.6 per 11.1 years),[70,75-77] it is not indicative of a 0 event rate. This is likely because noncalcified soft plaque might be present; not all ASCVD events are mediated by vascular atheroma and atheromas might also progress in an unpredictable fashion. The variability in the development of clinical ASCVD with a CAC score of 0 AU is particularly evident in persons younger than 50 years of age, those with a strong family history of premature CVD events, or in the setting of severe CVD risk factors such as smoking, diabetes, poorly controlled hypertension, and in those with lifelong, genetic dyslipidemias (FH or elevated Lp[a]).[78-81] These are patient categories that in general would warrant aggressive ASCVD risk factor modification, even if CAC = 0 AU, to enhance the likelihood of maintaining as low an atheroma burden as possible over a lifetime. Conversely, if such high-risk patients do have CAC > 0 AU, this might provide a strong rationale for adherence to aggressive CVD risk factor modification,[82,83] including lipid-lowering therapy or treatment intensification.[84,85] The effects of statins on the progression of atherosclerosis cannot be assessed through serial CAC scores alone because it does not assess the status of noncalcific plaque. Therapy does not reduce and might even increase CAC scores despite regression of noncalcific plaque components.[86] Accordingly, repeat CAC scanning is not recommended unless risk factor modification has been deferred through patient-physician shared decision-making.

Although CAC provides direct evidence of atherosclerotic plaque and a quantitative assessment of risk of attendant ASCVD events, controversy exists because of a paucity of large placebo-controlled RCTs and its cost-effectiveness for identification of patients suitable for statin therapy is uncertain,[87] even when applied only to the intermediate-risk group identified using risk algorithms. Importantly, at present, CAC scoring is not uniformly available or uniformly funded in Canada, and there are no cost-effectiveness analyses that represent the Canadian context.

RECOMMENDATION

7. We suggest that CAC screening using computed tomography imaging might be considered for asymptomatic adults 40 years of age or older and at intermediate risk (FRS 10%-20%) for whom treatment decisions are uncertain (Strong Recommendation; Moderate-Quality Evidence).
8. We recommend 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).
9. We suggest that CAC screening might be considered for a subset of low-risk individuals 40 years of age or older with a family history of premature ASCVD (men 55 years or younger; women 65 years or younger) in addition to identifying known genetic causes of ASCVD such as elevated Lp(a) level or FH (Weak Recommendation; Low-Quality Evidence).

Values and preferences. Patients with modifiable ASCVD risk factors should be counselled with respect to the potential merit of preventing atherosclerosis itself, the substrate for clinical ASCVD events in the long term, through comprehensive ASCVD risk factor management. As outlined elsewhere, RCTs show the ASCVD risk reduction value of statin therapy in patients with intermediate risk and additional ASCVD risk factors (eg, HOPE 3,[16] **J**ustification for the **U**se of Statins in **P**revention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin [JUPITER][88]) in the absence of CAC testing or any testing to identify preclinical atherosclerosis. Accordingly, the patient-physician decision often does not require CAC scoring but might be strongly influenced by these other factors, including family history of premature ASCVD, other features suggesting genetic causes of dyslipidemia, or side effects of statin therapy. In some low- to intermediate-risk subjects, it might be reasonable to withhold statin therapy for CAC = 0 AU because of a favourable intermediate-term outcome. Exceptions would include cigarette smokers, patients with diabetes, those with poorly controlled hypertension, genetic dyslipidemias such as FH or elevated Lp(a) level, and patients with strong family history of premature ASCVD events. If available, a CAC > 100 AU is an indication for statin therapy regardless of FRS. For those with a CAC of 1-99 AU, individual decision-making is required because risk will not be reclassified and would remain intermediate. If a decision is made to withhold statin or lipid-modifying therapy on the basis of CAC = 0, this decision should be reevaluated during follow-up or if clinical circumstances change. CAC scoring should rarely be performed sooner than within 5 years to aid in this reevaluation. Finally, this section is restricted to

application in patients who are at least 40 years of age for whom the traditional FRS assessment applies. Prevalence of calcification is a sequential aspect of the atherosclerotic process and might be absent in the early phases. Although CAC has been studied extensively for ASCVD risk prediction, the prevalence of CAC is lower in young patients compared with middle-aged and older patients and also in women vs men younger than 50 years of age.

PICO 4: In secondary prevention, what is the most appropriate lipid/lipoprotein threshold for the intensification of therapy?

The totality of evidence from observational, pathophysiological, epidemiological, and Mendelian randomization studies and RCTs of lipid-lowering therapies indicate a causal relationship between LDL-C (as well as non-HDL-C and ApoB) and ASCVD and show that lower concentrations of plasma LDL-C levels are associated with a lower risk of ASCVD events extending to very low LDL-C concentrations (< 0.5 mmol/L).[15,89-96] In RCTs, however, the absolute benefits of therapy were higher in subsets of patients with higher pretreatment LDL-C and/or additional ASCVD event risk enhancers who were at higher absolute risk.

To date, no clear target to which LDL-C or non HDL-C or ApoB levels should be lowered is clearly identified in RCTs, because such trials have generally used thresholds of LDL-C (or non-HDL-C or ApoB) levels for initiation or intensification of lipid-lowering therapies and fixed-dose lipid-lowering drugs (this pertains to statin RCTs and to RCTs that have used the additional use of nonstatin lipid-lowering agents, such as ezetimibe and PCSK9 inhibitors). Exceptions are the **S**candinavian **S**imvastatin **S**urvival **S**tudy (4S) trial in which the statin dose was up- or down-titrated aiming for within-trial total cholesterol levels of 3.0-5.2 mmol/L,[97] the **Imp**roved **R**eduction of **O**utcomes: **V**ytorin **E**fficacy **I**nternational **T**rial (IMPROVE-IT), which allowed for up-titration of simvastatin to 80 mg daily for in-trial LDL-C levels > 2.0 mmol/L,[98] and the ODYSSEY OUTCOMES trial in patients with a recent ACS, which allowed up-and down-titration of alirocumab aiming for an LDL-C target of 0.65-1.3 mmol/L; however, in these trials no randomized comparison with alternate lipid targets was performed.[90] Additionally, a number of trials comparing different intensities of statin treatment (lower vs higher statin dose) in secondary ASCVD prevention showed benefits for more intensive statin therapy; however, these trials did not explore targets of LDL-C lowering.[99,100] One RCT conducted in patients with a recent ischemic stroke showed reductions in major ASCVD events in patients allocated to a strategy of lower LDL-C (< 1.8 mmol/L) vs higher targets (2.3-2.8 mmol/L).[101] Nevertheless, the lower LDL-C target in this trial is similar to the threshold for intensification of lipid-lowering therapy used in other recent trials and recommended in this guideline document.[89,102] A number of studies have shown improved ASCVD outcomes in secondary prevention patients reaching lower in-trial LDL-C levels, but these trials are observational and did not test targets of therapy.[103,104]

Therefore, we recommend the use of thresholds for intensification of lipid therapy in secondary prevention. Most recent large RCTs have used an LDL-C threshold of 1.8 mmol/L for intensification of lipid-lowering therapy with nonstatin drugs in secondary ASCVD prevention patients receiving a maximally tolerated statin dose. Using this threshold, it is expected that most patients will achieve low and very low LDL-C levels, similar to those reached in clinical trials.[90,91]

The IMPROVE-IT trial showed benefit of ezetimibe when used in addition to statin therapy in patients with a recent ACS.[98] The threshold for the additional use of ezetimibe was an LDL-C of 1.3 mmol/L, although in IMPROVE-IT most patients had a higher baseline LDL-C (average 2.45 mmol/L), statin therapy was restricted to only simvastatin (more potent statins were not used) and the modest 6% relative risk reduction was attained only after a long period of treatment (median 6 years). Therefore, we recommend the more robust LDL-C threshold of ≥ 1.8 mmol/L (or percentile equivalent non-HDL-C of ≥ 2.4 mmol/L or ApoB of ≥ 0.7 g/L).

Recent analyses of the large PCSK9 inhibitor trials (FOURIER[89] and ODYSSEY OUTCOMES[90]) have identified subsets of patients with established CVD who are at very high risk and who derived the largest absolute benefit for intensification of lipid-lowering therapy with evolocumab and alirocumab, respectively. This includes patients with recent ACS and those with ASCVD and additional CV risk enhancers including diabetes mellitus, metabolic syndrome, polyvascular disease (vascular disease in ≥ 2 arterial beds), symptomatic peripheral artery disease, history of MI, MI in the past 2 years, previous coronary artery bypass graft surgery, LDL ≥ 2.6 mmol/L, heterozygous FH and Lp(a) ≥ 60 mg/dL.[90,105-113] Intensification of lipid-lowering therapy with PCSK9 inhibitors is especially recommended in these subsets of very high risk patients (see Table 3), with or without the additional use of ezetimibe, which was used in only a small number of patients in these trials. Use of PCSK9 inhibitor therapy in these subsets of patients was shown to result in rapid and large reductions in LDL-C and in significant CVD event reduction. In most other secondary prevention patients, the use of ezetimibe followed by PCSK9 inhibitor therapy is recommended when the LDL-C ≥ 1.8 mmol/L.

The previous 2016 CCS dyslipidemia guidelines did not emphasize the role of plasma triglyceride levels as a threshold or target for lipid-lowering therapy aimed at reducing CVD risk.[1] However, the recent **Redu**ction of **C**ardiovascular **E**vents With Icosapent Ethyl-**I**ntervention **T**rial (REDUCE-IT) showed a CV risk reduction (including reduction in CV death) in patients with ASCVD (as well as in those 50 years old or older with type 2 diabetes requiring medication treatment and at least 1 additional CVD risk factor) receiving moderate and high-intensity statin therapy with triglyceride levels of 1.5-5.6 mmol/L and LDL-C levels of 1.1-2.6 mmol/L.[114]

RECOMMENDATION

10. We recommend use of high-intensity statin therapy in addition to appropriate health behaviour modifications for all secondary prevention CVD patients. For patients who do not tolerate a high-intensity statins,

we recommend the maximally tolerated statin dose (Strong Recommendation; High-Quality Evidence).

11. We recommend intensification of lipid-lowering therapy with a PCSK9 inhibitor (evolocumab or alirocumab)—with or without the additional use of ezetimibe—for secondary CV prevention patients shown to derive the largest benefit from PCSK9 inhibitor therapy in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) while receiving the maximally tolerated statin dose (Fig. 3; Strong Recommendation; Moderate-Quality Evidence). Secondary prevention patients shown to derive the largest benefit from intensification of statin therapy with PCSK9 inhibitor therapy are defined in Table 3.

12. We recommend intensification of lipid-lowering therapy with ezetimibe and/or PCSK9 inhibitor therapy for all secondary prevention CVD patients in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) while receiving the maximally tolerated statin dose. (Strong Recommendation; High-Quality Evidence). If ezetimibe is used initially and LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) PCSK9 inhibitor therapy is recommended (Strong Recommendation; High-Quality Evidence).

It should be noted that one recommendation on the basis of the evidence review of PICO question 4 were overlapping with a recommendation for PICO question 5 and appear as part of that later section (Recommendation 15).

Values and preferences. On the basis of strong evidence for the benefit of intensive LDL-C lowering in secondary prevention, additional lipid-lowering therapy with ezetimibe and PCSK9 inhibitors might also be considered for ASCVD patients with an LDL-C < 1.8 mmol/L, especially for patients considered to be at high risk for recurrent ASCVD events. When initiating intensified lipid-lowering therapy with nonstatin drugs, cost, and access to such therapies should be considered.

There is no evidence to suggest any CV or other risks associated with low and very low LDL-C levels in trials with moderate duration of follow-up.[104,115,116] Therefore, if intensified lipid-lowering therapy initiated for the previously listed thresholds result in low and very low LDL-C levels, lipid-lowering therapy does generally not require down-titration dose adjustment.

Practical tip. Although there is very good evidence supporting the use of PCSK9 inhibitors in patients with ASCVD (especially those listed in Table 3), access might be limited by provincial drug plan coverage in many jurisdictions. Patients with or without private drug plan coverage might need to pay some portion of the cost of these expensive medications. Patient support programs for these medications could be investigated to assist. Clinicians should discuss the indication and potential benefits of a PCSK9 inhibitor with the patient, along with the coverage issues and the potential costs to them. Shared decision-making remains key.

Table 3. Secondary prevention patients shown to derive the largest benefit from intensification of statin therapy with the additional use of a PCSK9 inhibitor

Recent acute coronary event (ACS)
• Hospitalized index ACS to 52 weeks post index ACS
Clinically evident ASCVD and any of the following
• Diabetes mellitus or metabolic syndrome
• Polyvascular disease (vascular disease in ≥ 2 arterial beds)
• Symptomatic PAD
• Recurrent MI
• MI in the past 2 years
• Previous CABG surgery
• LDL-C ≥ 2.6 mmol/L or heterozygous FH
• Lipoprotein(a) ≥ 60 mg/dL (120 nmol/L)

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; FH, familial hypercholesterolemia; LDL-C, low density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral arterial disease; PCSK9, proprotein convertase subtilisin/kexin type 9.

PICO 5: In adults already receiving (or intolerant to) statins, what is the role of nonstatin drugs to reduce CVD risk?

Ezetimibe. Ezetimibe is a cholesterol absorption inhibitor that lowers LDL-C by approximately 20% in addition to a statin regimen or up to 15% as monotherapy. Only in 1 double-blind, RCT has the efficacy of ezetimibe been assessed in reducing CV risk. The IMPROVE-IT showed that ezetimibe 10 mg daily, compared with placebo and used in addition to statin therapy, showed a modest reduction in CV events in 18,144 patients with an ACS within the preceding 10 days.[98] The primary composite outcome of death from CV causes, major coronary events, and nonfatal stroke was 2% lower with ezetimibe (32.7 vs 34.7%; HR, 0.94; 95% CI, 0.89-0.99) for a number need to treat of 50 over 7 years. There were no significant differences between groups in the prespecified safety end points. This evidence informed the 2016 guideline recommendation for ezetimibe as second-line therapy to reduce CV risk in patients with ASCVD if their LDL-C targets were not reached with maximally tolerated statin therapy.[1] Subsequently, in the **H**eart **I**nstitute of **J**apan-**Pr**oper Level of Lipid Lowering With **P**itavastatin and **E**zetimibe in Acute Co**r**onary Syndrome (HIJ-PROPER) trial open-label pitavastatin with ezetimibe (target LDL-C < 1.8 mmol/L) was compared with pitavastatin monotherapy (target LDL-C 2.3-2.6 mmol/L) in 1734 Japanese patients with an ACS. Over 3.9 years, the primary composite outcome of all-cause death, nonfatal MI, nonfatal stroke, unstable angina, and ischemia-driven revascularization was not significantly different between groups (32.8 vs 36.9%; HR 0.89; 95% CI, 0.76-1.04).[117]

PCSK9 inhibitors. Inhibitors of PCSK9 are recently available monoclonal antibodies that lower LDL-C between 50% and 70% when used in addition to statin therapy or as monotherapy.[118] Currently, two PCSK9 inhibitors are approved for use in Canada: alirocumab and evolocumab. Both are approved for the treatment of FH or ASCVD in patients as an adjunct to

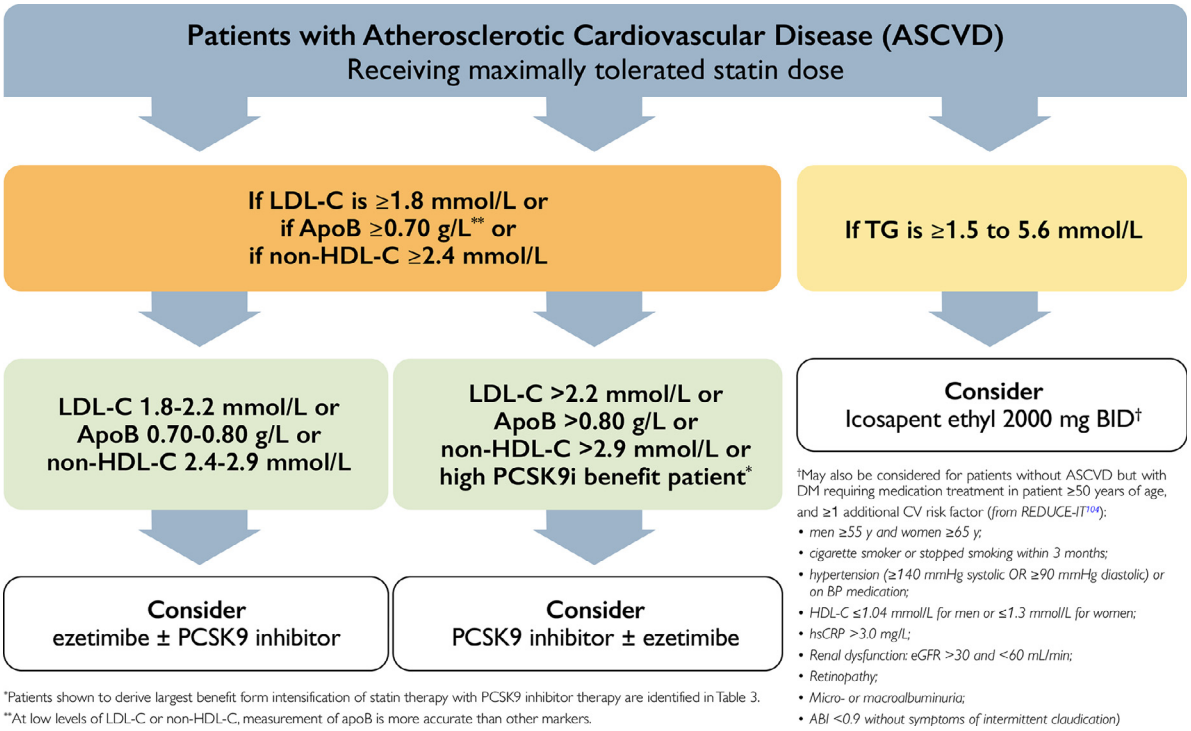


Figure 3. Treatment intensification approach for patients with atherosclerotic cardiovascular disease (ASCVD). ABI, ankle-brachial index; ApoB, apolipoprotein B; BP, blood pressure; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; REDUCE-IT, **Redu**ction of Cardiovascular **E**vents With **I**cosapent Ethyl-**I**ntervention **T**rial.

diet and maximally tolerated statin therapy (with or without ezetimibe) who require additional lowering of LDL-C.

The FOURIER trial enrolled 27,564 patients with clinical ASCVD and additional CVD risk factors whose LDL-C remained ≥ 1.8 mmol/L despite maximally tolerated statin therapy. Patients were randomized to receive evolocumab (140 mg subcutaneously (SC) every 2 weeks or 420 mg SC monthly) or placebo.[89] Baseline LDL-C was 2.4 mmol/L, which after 48 weeks was reduced to a median of 0.8 mmol/L (interquartile range, 0.5-1.2 mmol/L) in the evolocumab group. After 2.2 years of follow-up, the primary outcome of CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, and coronary revascularization was lower with evolocumab (9.8% vs 11.3%; HR, 0.85; 95% CI, 0.79-0.92) for a number needed to treat of 67. Evolocumab also reduced the secondary end point of CV death, nonfatal MI, and nonfatal stroke (5.9% vs 7.4%; HR, 0.80; 95% CI, 0.73-0.88). There was no significant difference in CV or all-cause death. Serious adverse events were similar between groups, although injection site reactions were higher with evolocumab (2.1% vs 1.6%; $P < 0.001$).

In the ODYSSEY OUTCOMES trial alirocumab was evaluated in 18,924 patients with a recent (1-12 months) ACS whose LDL-C was ≥ 1.8 mmol/L despite maximally tolerated statin therapy.[90] Participants were randomized to alirocumab (75 mg SC every 2 weeks to achieve an LDL-C of 0.6-1.3 mmol/L) or placebo. The dose of alirocumab was increased to 150 mg SC every 2 weeks if a participant's LDL-C level remained > 1.3 mmol/L or decreased or discontinued if their LDL-C level was < 0.6 mmol/L. The primary outcome of death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization was lower with alirocumab (9.5% vs 11.1%; HR 0.85; 95% CI, 0.78-0.93) for a number needed to treat of 63 over 2 years. All-cause mortality was numerically lower with alirocumab (3.5% vs 4.1%), but on the basis of the authors' prespecified hierarchical testing, it is debatable whether this can be considered statistically significant. There was no significant difference in CV death between groups. There was no significant difference in serious adverse events, but injection site reactions were more common with alirocumab (3.8% vs 2.1%; $P < 0.001$).

A recent meta-analysis of 23 trials (including FOURIER and ODYSSEY OUTCOMES) compared PCSK9 inhibitors with control in 60,723 patients.[119] There was a significant reduction in MACE (6.2% vs 8.2%; risk ratio, 0.83; 95% CI, 0.78-0.88) with no significant difference in all-cause mortality (risk ratio 0.93; 95% CI, 0.85-1.02) or safety outcomes. Of note, these trials had short follow-up (median of 2.8 years) and therefore might not have been of sufficient duration to observe a mortality benefit.

Although ezetimibe or a PCSK9 inhibitor are reasonable options as monotherapy in patients with complete statin intolerance for LDL-C lowering, there is limited evidence to support either class as an alternative to statin therapy for ASCVD risk reduction. The Study of Alirocumab (REGN727/SAR236553) in Patients With Primary Hypercholesterolemia and Moderate, High, or Very High Cardiovascular (CV) Risk, Who Are Intolerant to Statins (ODYSSEY ALTERNATIVE) trial enrolled 314 patients with statin intolerance who were randomized to alirocumab 75 mg SC every 2 weeks, ezetimibe 10 mg daily, or

atorvastatin 20 mg daily.[120] At 24 weeks, alirocumab reduced LDL-C by a mean difference of 30% compared with ezetimibe. Skeletal muscle-related adverse effects were high overall, but significantly lower with alirocumab (33%) vs atorvastatin (46%) and similar to ezetimibe (41%). The **G**oal **A**chievement After **U**tilizing an Anti-PCSK9 Antibody in **S**tatin Intolerant **S**ubjects-3 (GAUSS-3) trial included 218 patients considered to have previous statin intolerance who were randomized to evolocumab 420 mg SC monthly or ezetimibe 10 mg orally daily.[121] Evolocumab showed a significantly greater reduction in LDL-C compared with ezetimibe (mean difference, 36%) at 24 weeks. The incidence of muscle symptoms was relatively high in both groups, but the difference was not statistically significant (21% vs 29%; $P = 0.17$).

Clinical trials have shown that PCSK9 inhibitors are effective at lowering LDL-C in patients with heterozygous FH[102,120] and in certain patients with homozygous FH,[91] but there is currently a paucity of ASCVD outcome data in these populations.

Primary prevention

There are currently no RCT data supporting the use of PCSK9 inhibitors to reduce CV events in patients who do not have established ASCVD (ie, primary CV prevention) or FH.

IPE. Until recently, contemporary trials of omega-3 fatty acid supplements have not shown a CV benefit in patients with or without CVD.[123,124] Previously, the **J**apan **E**PA **L**ipid **I**ntervention **S**tudy (JELIS) showed a reduction in CV events with 1800 mg daily of eicosapentaenoic acid (EPA) combined with a statin, compared with statin monotherapy, in Japanese patients with a total cholesterol ≥ 6.5 mmol/L; however, it was an open-label trial and the primary outcome was driven by a minor reduction in unstable angina.[125] The REDUCE-IT assessed the effect of a pharmaceutical formulation of purified ethyl EPA (IPE), which was recently approved by Health Canada.[114] In total, 8179 patients were included with established ASCVD (or diabetes and ≥ 1 ASCVD risk factor) who were receiving statin therapy but had an elevated fasting triglyceride level of 1.5-5.6 mmol/L (baseline 2.4 mmol/L). Most patients (71%) were in the secondary prevention cohort. Participants were randomized to 2000 mg of IPE orally twice daily (4 g total per day) or mineral oil as placebo. At 1 year, participants' triglyceride level in the IPE group was modestly reduced by 0.4 mmol/L (approximately 18%) from baseline. IPE reduced the primary outcome of CV death, nonfatal MI, nonfatal stroke, unstable angina, or CV revascularization (17.2% vs 22.0%; HR, 0.75; 95% CI, 0.68-0.83) for a number needed to treat of 21 over 4.9 years. IPE also significantly reduced the composite of CV death, nonfatal MI, and nonfatal stroke (11.2% vs 14.8%; HR, 0.74; 95% CI, 0.65-0.83), as well as CV death (4.3% vs 5.2%; HR, 0.80; 95% CI, 0.66-0.98), but not all-cause death. Atrial fibrillation and peripheral edema were significantly higher with IPE. Because IPE is a purified form of ethyl EPA, the results of REDUCE-IT cannot be extrapolated to other nonprescription omega-3 fatty acids, which typically contain a mixture of EPA and docosahexaenoic acid (DHA).

The Outcomes Study to Assess **St**atin **R**esidual Risk Reduction With **E**pa**n**ova in Hi**g**h CV Risk Patien**t**s With **H**ypertriglyceridemia (STRENGTH) trial aimed to evaluate a pharmaceutical carboxylic acid formulation of EPA and DHA (referred to as omega-3 CA) to prevent MACE in 13,078 patients with hypertriglyceridemia (2.0-5.6 mmol/L), low HDL-C (< 1.2 mmol/L for women and < 1.1 mmol/L for men) who were receiving statin therapy, and were at increased risk of CVD.[128] Patients were randomized to receive 4 g/d of omega-3 CA or corn oil placebo. The trial was discontinued prematurely after a median follow-up of 3.5 years for futility. The primary end point of CV death, nonfatal MI, nonfatal stroke, unstable angina requiring hospitalization, and coronary revascularization was not significantly different between groups (12.0% vs 12.2%; HR, 0.99; 95% CI, 0.90-1.09). Patient-reported gastrointestinal disorders were more common in patients in the omega-3 CA group (24.7% vs 14.7%).

Other therapies. There are no new recommendations regarding the use of fibrates, niacin, and bile acid sequestrants since the 2016 guidelines.[1]

Ongoing trials

There are a number of ongoing trials of nonstatin therapy. Effect of Evolocumab in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke (VESALIUS-CV) is designed to examine the effect of evolocumab at reducing MACE in patients without a previous MI or stroke but who are at high risk of CVD.[127] Inclisiran is an experimental small interfering RNA molecule that inhibits the translation of PCSK9. In the phase III Trial to Evaluate the Effect of Inclisiran Treatment on Low Density Lipoprotein Cholesterol in Subjects With Heterozygous Familial Hypercholesterolemia (ORION-9), Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol (ORION-10), and Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol (ORION-11) trials, inclisiran showed LDL-C lowering in patients with heterozygous FH or with, or at high risk of, atherosclerotic CVD.[128,129] The ongoing phase III A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease (ORION-4) is evaluating whether this LDL-C reduction with inclisiran translates to a reduction in MACE among patients with CVD.[130] The Effect of **Dal**cetrapib vs Placebo on CV Risk in a **Gene**tically Defined Population With a Recent ACS (dalGenE) study aims to assess the effect of dalcetrapib, a cholesteryl ester transfer protein inhibitor (not approved by Health Canada), in patients with a recent ACS and specific genotype.[131] The **C**holesterol **L**owering via B**e**mpedoic Acid, an **A**CL-Inhibiting **R**egimen (CLEAR) Outcomes trial is evaluating the effect of bempedoic acid, a novel adenosine triphosphate (ATP) citrate lyase inhibitor not approved in Canada, in patients with, or at high risk for, ASCVD who are statin-intolerant.[132] Finally, the **P**emafibrate to **R**educe Cardiovascular **O**utco**m**es by Reducing Triglycerides **in** Pati**en**ts With Diabe**t**es (PROMINENT) trial is determining whether pemafibrate, a peroxisome proliferator-activated receptor alpha agonist (which is not approved for use in Canada) reduces MACE in patients with type 2 diabetes mellitus, elevated triglycerides, and low HDL-C.[133]

RECOMMENDATION

13. We recommend the use of IPE to decrease the risk of CV events in patients with ASCVD, or with diabetes and ≥ 1 CVD risk factors, who have an elevated fasting triglyceride level of 1.5-5.6 mmol/L despite treatment with maximally tolerated statin therapy (Strong Recommendation; High-Quality Evidence). Refer to Figure 3.

14. We recommend the use of a PCSK9 inhibitor (alirocumab or evolocumab) to lower LDL-C level in patients with heterozygous FH without clinical ASCVD whose LDL-C remains above the target (ie, LDL-C ≥ 2.5 mmol/L or < 50% reduction from baseline; or ApoB ≥ 0.85 mg/dL or non-HDL-C ≥ 3.2 mmol/L) despite maximally tolerated statin therapy with or without ezetimibe therapy (Strong Recommendation; High-Quality Evidence).

15. We recommend the use of a PCSK9 inhibitor (alirocumab or evolocumab) for patients with heterozygous FH and ASCVD whose LDL-C remains above the threshold ≥ 1.8 mmol/L (or ApoB ≥ 0.7 mg/dL or non-HDL-C ≥ 2.4 mmol/L) despite maximally tolerated statin therapy, with or without ezetimibe (Strong Recommendation; High-Quality Evidence).

It should be noted that 2 recommendations on the basis of the evidence review of PICO question 5 were overlapping with recommendations made for PICO question 4 and appear as part of that earlier section (Recommendations 1 and 2).

Values and preferences. None of these agents have been evaluated in RCTs against each other. Therefore, it is difficult to assess the relative benefit of each therapy. Also, to date these agents have primarily been evaluated in patients with preexisting ASCVD (ie, secondary prevention). The choice of agent should be on the basis of individual patient factors, their values and preferences, and practical considerations, such as access, cost, and adherence. Because ezetimibe lowers LDL-C level by approximately 20% when used in addition to a statin, if a patient's LDL-C is well above the threshold for therapy intensification (ie, > 2.2 mmol/L or > 20% above threshold), it might be preferable to consider a PCSK9 inhibitor as second-line therapy. However, because of cost considerations, some insurance providers might require a trial of ezetimibe before approving the use of a PCSK9 inhibitor. IPE should be preferentially reserved for patients aged ≥ 45 years of age (or ≥ 50 years of age with ≥ 1 CVD risk factor) who are receiving maximally tolerated statin therapy but have a residual elevated triglyceride level (1.5-5.6 mmol/L). Because IPE is a purified form of ethyl EPA, it should not be inferred that the same CV benefits could be derived from the consumption of omega-3 polyunsaturated fatty acid (PUFA) formulations that include EPA alone, EPA and DHA mixtures, or fish oils from supplements or dietary sources.

The recommendation for treatment of patients with FH is on the basis of the 2018 update to the CCS position statement on FH.[134] The recommendation for PCSK9 inhibitors to lower LDL-C level is on the basis of high-quality evidence; however, there is a relative paucity of RCT evidence to support any agent to reduce the risk of CV events in FH patients.

Practical tip. Unlike the use of PCSK9 inhibitors in patients with ASCVD, access to these medications is covered by most provincial drug plans for patients with heterozygous FH (with or without ASCVD) with LDL-C level above the threshold. Although the evidence for IPE to decrease the risk of CV events in patients with ASCVD, or with diabetes and ≥ 1 CVD risk factors is good, it is relatively new and most provincial drug plans do not yet cover this expensive medication. Private plans might cover this drug for patients on the basis of specific criteria and there is a manufacturer patient assistance program that might facilitate access. As part of shared decision-making, clinicians should discuss the indication and potential benefits of IPE, as well as the coverage issues and the potential patient costs.

PICO 6: In primary and secondary prevention, what is the evidence for CV benefit of omega-3 from (1) dietary sources; and/or (2) over-the-counter formulations/ supplements?

Despite the success of the REDUCE-IT trial in showing a purified prescription IPE at 4 g/d reduces major CVD events in statin-treated patients with elevated triglyceride levels who have established CVD or diabetes and at least 1 CVD risk factor,[114] supplementation with over-the-counter long-chain omega-3 PUFAs marketed as natural health products in Canada that include EPA alone, EPA and DHA mixtures, or fish oils from supplements or dietary sources does not offer any clear advantages for CVD event risk reduction. We updated a systematic review and meta-analysis of RCTs with data from 2 subsequently completed RCTs, **A** **S**tudy of **C**ardiovascular **E**vents i**n** **D**iabetes (ASCEND)[135] and **Vit**amin D and Omeg**a**-3 Tria**l** (VITAL),[136] which failed to show a clear CV benefit of supplementation with long chain omega-3 PUFAs in more than 130,000 randomized participants.[137] Another large CVD outcomes trial of a pharmaceutical drug of mixed long-chain omega-3 (largely EPA and DHA) carboxylic acids (omega-3 CA) at 4 g/d with similar entry criteria to the REDUCE-IT trial was also discontinued early by the data safety monitoring board for futility with the drug unlikely to show a benefit to patients.[126] Pooled evidence from RCTs[138-140] and individual large RCTs,[141] however, have shown consistent triglyceride-lowering effects at high doses (2-4 g/d) of omega-3 PUFAs, independent of CVD event risk reduction.

RECOMMENDATION

16. We do not recommend the use of over-the-counter omega-3 polyunsaturated fatty acid supplements (marketed as natural health products in Canada) to reduce CVD risk (Strong Recommendation; High-Quality Evidence).

Values and preferences. Although there is no apparent overall CVD event risk benefit, patients might choose to use these supplements for other indications including the management of high triglycerides, for which very high doses are required (4 g/d), and for which fibrates are generally more effective. Individuals should be aware that, in addition to marine sources, there are different preparations of long-chain omega-3 PUFAs high in DHA and EPA from algal and yeast sources, both of which are suitable for vegans. There is also alpha-linolenic acid from plant sources that do not contain DHA or EPA including flax seeds, chia seeds, and some oils such as canola and soybean oil, which have little or no effect on triglycerides.

Conclusions

In this focused revision of the CCS guidelines for the management of dyslipidemia, the committee has distilled several years of new research in CV risk assessment (especially as it pertains to women), lipoprotein biomarkers, and coronary artery calcium scanning. The committee also reviewed several major landmark RCTs of novel therapies to treat dyslipidemia. On the basis of the best available evidence to date, we have developed several new recommendations for clinicians to more accurately assess their patients' CV risk and optimally manage their lipid disorders. We acknowledge that the science surrounding CV risk and dyslipidemia management is evolving and therefore these recommendations can only be viewed as the best practices on the basis of the currently available evidence. Nonetheless, the objective of any guideline is to provide clinicians with the most up-to-date knowledge and tools to help them make informed decisions with their patients. Appendix 1 provides an at-a-glance, step-wise summary of the management of adult patients with dyslipidemia for the prevention of cardiovascular disease, based on the 2021 CCS dyslipidemia guidelines.

The past few years has realized significant progress in the management of dyslipidemia, with several new therapies currently available and more in development. With continued efforts to prioritize healthy lifestyles and the use of new pharmacotherapeutic options available to treat eligible patients, we hope to realize further reductions in morbidity and mortality from ASCVD in Canada.

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Supplementary Material

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AT A GLANCE: 2021 CCS Guideline for the Management of Dyslipidemia in Adults

1. Who to screen with fasting or non-fasting TC, TG, HDL-C, calculated LDL-C and non-HDL-C with ApoB when appropriate and Lp(a) once:

1. **Men ≥40 yrs old; Women ≥40 yrs old or postmenopausal; at younger age in Indigenous and South Asian individuals**
2. **At any age in patients with:**
   a. Clinical ASCVD
   b. Evidence of preclinical ASCVD (e.g., CACS or carotid ultrasound abnormalities)
   c. Abdominal aortic aneurysm (AAA)
   d. Diabetes
   e. Arterial hypertension
   f. Currently smoking
   g. Stigmata of dyslipidemia: tendinous xanthomas (also corneal arcus, xanthelasmas if <45 yrs old)
   h. Family history of premature CVD in first degree relative (male <55 yrs old; female <65 yrs old)
   i. Family history of dyslipidemia (including elevated Lp(a), especially ≥50 mg/dL or ≥100 nmol/L)
   j. Chronic kidney disease (eGFR ≤60 mL/min/1.73 m^2 or ACR ≥3 mg/mmol)
   k. Obesity (BMI ≥30 kg/m^2)
   l. Inflammatory diseases (e.g., RA, SLE, PsA, AS, IBD)
   m. HIV infection
   n. Erectile dysfunction
   o. Chronic obstructive pulmonary disease
   p. Pregnancy-related complications (hypertensive disease of pregnancy, gestational diabetes, pre-term birth, stillbirth, low birthweight infant, placental abruption)

2. Who to treat based on clinical factors (Framingham Risk Score [FRS] not needed):

1. **Statin-indicated conditions:**
   a. Clinical ASCVD/AAA
   b. Diabetes mellitus if >40 yrs old, or >30 yrs old with microvascular disease or >15 years duration
   c. Chronic kidney disease (non-dialysis, eGFR <60 mL/min or urine ACR ≥3.0 mg/mmol)
   d. FH or LDL-C ≥5.0 or non-HDL-C ≥5.8 mmol/L or ApoB ≥1.45 g/L
2. **Patients with very high TG ≥10 mmol/L and/or history of TG-related pancreatitis.**

3. Who to treat based on FRS:

1. **High FRS (≥20%/10 yrs)**
2. **Intermediate FRS (10-19.9%/10 yrs) and LDL-C ≥3.5 mmol/L or non-HDL-C ≥4.2 mmol/L or ApoB ≥1.05 g/L**
3. **Intermediate FRS (10-19.9%/10-yrs) and LDL-C <3.5 mmol/L or non-HDL-C <4.2 mmol/L or ApoB <1.05 g/L and other risk modifiers FHx, Lp(a) ≥50 mg/dL [or ≥100 mmol/L] or CAC >0 AU)**
4. **Low FRS (5-9.9%/10-yrs) with LDL-C ≥3.5 mmol/L or non-HDL-C ≥4.2 mmol/L or ApoB ≥1.05 g/L or other risk modifiers FHx, Lp(a) ≥50 mg/dl [or ≥100 mmol/L] or CAC >0 AU)**

4. Factors not in FRS suggesting that calculated risk may be underestimated:

1. **From RCTs:**
   a. JUPITER: CRP >2.0 mg/L
   b. HOPE-3: Waist/hip ratio ≥0.85 (women) or ≥0.90 (men), IFG/IGT, (pre-diabetes, metabolic syndrome)
   c. ASCOT: in hypertensives, LVH/other EKG abnormalities
2. **From epidemiology (consider ethnicity and factors g – p Step 1)**

5. Factors not in FRS suggesting that calculated risk may be overestimated:

1. **CAC = 0 AU in moderate FRS patients**

6. What to monitor:

1. **If TG <1.5 mmol/L, monitor treatment with LDL-C, non-HDL-C or ApoB (fasting or non-fasting)**
2. **If TG ≥1.5 mmol/L, monitor treatment with non-HDL-C or ApoB (fasting or non-fasting)**

7. What to use:

1. **Behavioural advice to optimize diet (including alcohol use), weight, and activity levels and to promote smoking cessation (including specific pharmacotherapy when warranted)**
2. **Maximally tolerated statin for those described in Tables 2 and 3**
3. **In CV primary prevention of patients with FH, using threshold of LDL-C ≥2.5 mmol/L, non-HDL-C ≥3.2 mmol/L, ApoB ≥0.85 g/L, or <50% lowering of LDL-C, consider adding PCSK9 inhibitor, with/without ezetimibe**
4. **In other settings of CV primary prevention, using threshold of LDL-C ≥2.0 mmol/L, non-HDL-C ≥2.6, ApoB ≥0.80 g/L or <50% lowering of LDL-C, consider use of ezetimibe (or bile acid sequestrant)**
5. **Add therapy in CV secondary prevention, using thresholds of LDL-C ≥1.8 mmol/L, non-HDL-C ≥2.4, ApoB ≥0.70 g/L**
   a. Ezetimibe ± PCSK9 inhibitor (if LDL-C 1.8 – 2.2 mmol/L, non-HDL-C 2.4 – 2.9 mmol/L, or ApoB 0.7 – 0.8 g/L, ezetimibe may suffice)
   b. PCSK9 inhibitor ± ezetimibe (PCSK9 inhibitor particularly if LDL-C >2.2 mmol/L, non-HDL-C >2.9 mmol/L or ApoB >0.8 g/L) or in very high risk patients who derive the most benefit from PCSK9 inhibitors, e.g., ACS within 1 year, diabetes mellitus or metabolic syndrome, poly-vascular disease, MI within 2 years, recurrent MI, prior coronary artery bypass surgery, symptomatic peripheral arterial disease, FH or residual LDL-C ≥2.6 on maximal statins, elevated Lp(a) ≥60 mg/dL)
6. **Icosapent ethyl in primary prevention patients with diabetes and an additional risk factor or secondary prevention patients when, in both instances, TG is ≥1.5 mmol/L and ≤5.6, on maximally tolerated statin**
7. **When icosapent ethyl is not indicated but TG requires management (e.g., very high TG ≥10 mmol/L or concern about TG-related pancreatitis), use micronized fenofibrate**

AAA = abdominal aortic aneurysm; ACR = albumin-to-creatinine ratio; ACS = acute coronary syndrome ApoB = apolipoprotein B; AS = ankylosing spondylitis; ASCVD = atherosclerotic cardiovascular disease; AU = Agatston unit; BMI = body-mass index; CACS = coronary artery calcium score; CRP = C-reactive protein; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; EKG = electrocardiogram; FH = familial hypercholesterolemia; FHx = family history; FRS = Framingham Risk Score; HIV = human immunodeficiency virus; IBD = inflammatory bowel disease; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein-a; LVH = left ventricular hypertrophy; MI = myocardial infarction; non-HDL-C = non-high-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RCT = randomized control trials; SLE = systemic lupus erythematous; TC = total cholesterol; TG = triglycerides.

Appendix 1. Management of Dyslipidemia at a Glance.