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

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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 evolved. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in circumstances of 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.

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

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

Brief summary

The 2021 dyslipidemia guidelines provide updated recommendations based on important new evidence. The concept of lipid/lipoprotein treatment thresholds for intensifying lipid-lowering therapy with non-statin agents is introduced, and secondary prevention patients demonstrated to derive the largest benefit from intensification of therapy are identified. There are new recommendations for when to use non-HDL-C or ApoB be instead of LDL-C as the preferred lipid screening parameter, and for the role lipoprotein(a) to improve risk stratification and management.

Abstract

The 2021 guidelines primary panel selected clinically relevant questions and produced updated recommendations, on the basis of important new findings emerging since the 2016 guidelines. In subjects with clinical atherosclerosis, abdominal aortic aneurysm, most subjects with diabetes or chronic kidney disease, and those with low-density lipoprotein cholesterol (LDL-C) ≥5 mmol/L, statin therapy continues to be recommended. We have introduced the concept of lipid/lipoprotein treatment thresholds for intensifying lipid-lowering therapy with non-statin 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 LDL-C. 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.

Introduction and Process

The 2021 Canadian Cardiovascular Society (CCS) dyslipidemia guidelines have been updated to reflect new clinical trial and epidemiologic evidence published in the field 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 based on 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 Supplementary Material), resulting in the identification of six 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 the manuscript and the results of voting on each recommendation can be found in the *PICO Voting Results Summary* section of the Supplementary Material. 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 non-statin lipid-lowering agents based on new evidence with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and icosapent ethyl (IPE). Given the increased focus on apolipoprotein B (apoB) and non-HDL-C in this revision, values for apoB and non-HDL-C have been modified (from prior versions of these guidelines) to accurately represent the same percentile equivalents as LDL-C for all recommended thresholds (see Supplementary Material). The goal of the process was to produce an objective, non-biased document based on 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 (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

Atherosclerotic cardiovascular (ASCVD): refers to all clinical conditions of atherosclerotic origin, including acute coronary syndrome (ACS), myocardial infarction (MI), stable or unstable angina, coronary artery disease document by angiography, coronary or other arterial revascularization (coronary artery bypass graft [CABG] surgery, femoral popliteal [Fem-Pop] bypass graft surgery, etc.) stroke, transient ischemic attack (TIA), documented carotid disease, peripheral artery disease (PAD) and abdominal aortic aneurysm.

Statin-indicated condition: refers to any condition for which pharmacotherapy with statins in indicated, and 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 low-density lipoprotein cholesterol (LDL-C) ≥5.0 mmol/L or a diagnosis of familial hypercholesterolemia. 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 non-fasting state) for men and women > 40 years of age or at any age with one of specific conditions listed in *Table 1*. The non-fasting state is recommended (except for individuals with known triglycerides >4.5 mmol/L) as it leads to minimal changes in relevant lipid levels and has no effect on apolipoprotein levels compared to the fasting state.[1] *Table 2* provides a summary of the recommendations for how to screen patients. We maintain the recommendation for regular cardiovascular risk assessments using a validated risk model in Canada (either the Framingham Risk Score [FRS] or the Cardiovascular Life Expectancy [CLEM] model) every 5 years for men and women aged 40-75 to guide preventive care through shared decision making with the patient. Among individuals 30-59 years of age without diabetes, the presence of a positive history of premature CVD in first degree relative (i.e. ≤55 years in male relatives and ≤65 in female relatives) increases an individual's calculated FRS percent risk by approximately 2 fold.[1]

Health Behaviour Interventions

Health behavior 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 lipids, hypertension, smoking and diabetes), abdominal obesity, dietary patterns, alcohol consumption, physical inactivity, and psychosocial factors are modifiable risk factors for myocardial infarction (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 behaviors which 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 (GI)/glycemic load (GL) 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 by these means can be considered to augment drug therapy with statins; however, their benefits have been demonstrated 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 may also be beneficial to add muscle- and bone-strengthening activities at least 2 days per week. Regular exercise has beneficial effects on diabetes risk, 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 can be found in the Supplementary Material.

Pharmacologic Treatment

Studies consistently demonstrate a 20-22% relative risk reduction for each 1 mmol/L reduction in low-density lipoprotein cholesterol (LDL-C).[15] The absolute risk reduction is thus dependent upon the baseline risk and the baseline LDL-C, as 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 apolipoprotein B [ApoB] ≥ 1.05 g/L or non-high-density lipoprotein [non-HDL]-C ≥ 4.2 mmol/L). In addition, among intermediate risk individuals with several additional risk factors as evaluated in HOPE-3[16] (men ≥ 50 or women ≥ 60 years of age with one 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 favors the use of statins (e.g. hsCRP ≥ 2.0 mmol/L, family history of premature CAD, high lipoprotein(a) [Lp(a)] ≥ 50 mg/dL (≥100 nmol/L) or CAC > 0).

For most low-risk subjects (FRS <10%), health behavior modification without pharmacotherapy is still recommended; however, the exceptions would be: (a) 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 familial hypercholesterolemia); or (b) individuals a 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 (e.g., family history of premature CAD, Lp(a) ≥50 mg/dL [or ≥100 nmol/L] or Coronary Artery Calcium score [CAC] >0 AU) since the proportional benefit from statin therapy will be similar to other treatment groups. Treatment of this group would follow the intermediate risk approach. *Figure 1* outlines the

treatment approach recommended for primary prevention patients. Finally, evidence continues to demonstrate 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 $\geq$ 3.5 mmol/L.[17] In addition, accumulating evidence suggests continued benefits of lipid-lowering for primary prevention in older adults (> 75 years).[18]

Other statin-indicated conditions:

We continue to recommend statin initiation for the following high-risk conditions (i.e. "statin-indicated" conditions, even in the absence of a prior CV event: (1) chronic kidney disease (CKD) (except for patients on chronic dialysis) defined as patients with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 and those with preserved eGFR in whom CKD is based on 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 ≥30 years of age with ≥15 years duration of diabetes or the presence of microvascular complications; (3) abdominal aortic aneurysm (AAA) >3.0 cm or prior aortic aneurysm surgery.[1] Established ASCVD is also a statin-indicated condition which is discussed in more detail later in these guidelines. *Figure 2* summarizes the treatment approach for patients with a statin-indicated condition.

All of the recommendations from the previous dyslipidemia guidelines which remain unchanged are provided in the *Ongoing Recommendations from the 2016 Guidelines* section of the Supplementary Material.

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 lipoprotein(a) (Lp[a]) in assessing cardiovascular risk; (3) the role of coronary artery calcium as a clinical decision making tool for determining the need to initiate statins; and (4) the CV benefit of icosapent ethyl in patients with triglycerides ≥1.5-5.6 mmol/L and a prior cardiovascular 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 prior ASCVD event (refer to section on primary prevention). In secondary prevention, limiting sedentary behavior can be additive to regular physical activity with respect to the reduction of ASCVD events. A certified exercise physiologist may be of value to provide advice and follow-up. Cardiac rehabilitation has been clearly shown to be of benefit in this patient population and remains a cornerstone of management.[19]

Relevant recommendations from the previous dyslipidemia guidelines which remain unchanged are provided in the *Ongoing Recommendations from the 2016 Guidelines* section of the Supplementary Material.

New areas of focus

Several areas were reviewed by our group that directly impact on the care and management of patients with prior ASCVD events and have led to new or updated recommendations, specifically: (1) the role of non-statin 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.

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 cardiovascular disease 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 2-fold relative risk of developing pre-menopausal ASCVD, with onset at 10 to 15 years after delivery[20] compared to women who had uncomplicated pregnancies. This risk is highest if preeclampsia is recurrent (i.e., 28% lifetime risk of ASCVD, or within 25 years after delivery[22]), or if associated with preterm delivery (prior to 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 following hypertensive disorders of pregnancy suggesting accelerated vascular aging.[25,26]

National cardiovascular societies[1,27], including the Canadian Cardiovascular Society (CCS)[1] have recommended performing lipid and metabolic screening in postpartum women who have had these complications, though whether specific thresholds warranting pharmacotherapy differ from that typically used in the general population is not known.[28] While it is true that these women have a low absolute risk of ASCVD over the short term, the postpartum period may represent “a teachable moment” to engage young women in CV prevention and may result in long-term benefits through health behaviour interventions with or without pharmacological intervention.[28] Treatment decisions should be guided based on lifetime risk in conjunction with patient values and preferences.[29]

RECOMMENDATIONS:

1. Among women who have had a pregnancy complication such as hypertensive disorders of pregnancy, gestational diabetes, pre-term birth, stillbirth, low birthweight infant, or placental abruption, we recommend screening with a complete lipid panel in the late postpartum period, since 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 (i.e. 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:

While much of this observed risk among women who have had a pregnancy-related complication may be due to conventional ASCVD risk factors, complications such as preeclampsia may 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 based on pregnancy factors alone. The American Heart Association (AHA) 2019 Cardiovascular Prevention Guidelines[27] considers preeclampsia a *risk enhancer* warranting early screening, healthy behavior interventions and possibly shifting of risk category from borderline to intermediate risk (i.e., 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 pre-term preeclampsia with adverse conditions), balanced against the potential side effects and harms of long-term therapy. Although statins were previously considered teratogenic based on earlier animal studies, this has not been consistently found in recent human studies.[30,31] A part of the observed increase in risk of congenital malformations may be due to underlying medical conditions rather than treatment with statin therapy itself.[30] Furthermore, there appears to be a differential effect based on the type of compound, with most cases of congenital malformations being seen among infants whose mothers took lipophilic compounds (e.g., atorvastatin, lovastatin, simvastatin) as opposed to hydrophilic compounds (e.g., pravastatin, rosuvastatin).[32] Therefore, in women who are reproductive age and who are eligible and considering statin therapy for ASCVD risk reduction based on CV age or lifetime risk of ASCVD, we suggest the use of hydrophilic compounds over lipophilic compounds due to 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 prior to 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 non-statin 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.[1,34] 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,[35] and makes the amount of cholesterol in LDL-C an unreliable reflection of LDL particle number.[36] In addition, other particles, such as remnants of chylomicrons and very low density lipoprotein (VLDL), 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. Both 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 when compared to LDL-C.[37,38] Based on these previous recommendations, non-HDL-C is now routinely reported across Canada at no additional cost, based on the simple calculation of total cholesterol minus HDL-cholesterol. 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% due to triglyceride enrichment of LDL-C.[39,40] Following the guideline recommendation that was introduced in 2016 allowing for non-fasting collections for both 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 TG is ≥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 non-fasting 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.[41] 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 where ApoB may be the better predictor of risk for coronary calcification[41] and ASCVD events.[42] Analysis of CV events in the large UK Biobank[42], and meta-analysis of 110 prospective cohort registries of patients with or at risk for ASCVD[43], however, found 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 as it incurs no additional expense to the patient or healthcare system.[44,45] In Canada, the approach has been to allow clinicians to utilize 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 in their region and when there may be a concern about discordance between the two measurements, as indicated above. 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.

RECOMMENDATIONS:

1. 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 prior cardiovascular events?

Lipoprotein (a) [Lp(a)] is an LDL-like particle in which ApoB is covalently bound to a plasminogen-like molecule called apolipoprotein (a).[46] 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.[47] 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 CHD risk, thereby strongly suggesting a causal association between Lp(a) and CVD.[48,49] The risk of ASCVD increases with increasing Lp(a) levels >30 mg/dL in a dose dependent fashion.[49-51] 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 myocardial infarction (MI) and those with an Lp(a) level >117 mg/dL had an adjusted HR of 2.7.[49] Among 6086 cases of first MI and 6857 controls from the INTERHEART study that were stratified by ethnicity and adjusted for age and sex, Lp(a) concentrations >50 mg/dL were associated with an increased risk of MI (OR 1.48, CI 1.43-1.67), independent of established CVD risk factors including diabetes mellitus, smoking and high blood pressure.[52] Higher Lp(a) concentrations carried a particularly high population burden in South Asians and Latin Americans.[52] An Lp(a) level above 50 mg/dL (100 nmol/L) is found in approximately 20% of individuals of European and South Asian descent, 40% of African Americans and fewer than 10% of East Asians.[52,53] Individuals with extreme elevations in Lp(a) have been shown to be at markedly high-risk, with an event rate similar to that seen for other genetic dyslipidemias for which family screening is recommended (i.e. heterozygous familial hypercholesterolemia [FH]). As such, Lp(a) is a common but as yet not routinely-measured ASCVD risk marker.

Elevated Lp(a) also increases the risk of recurrent ASCVD in a dose dependent manner.[51,54] Among 58527 subjects from the Copenhagen General Population Study, 2527 subjects aged 20 to 79 with a history of ASCVD and elevated Lp(a) were followed over a median of 5 years.[55] The adjusted major adverse CV events (MACE) incidence rate ratios were 1.28 (95% CI, 1.03–1.58) for subjects with a Lp(a) level of 10 to 49 mg/dL (18–104 nmol/L), 1.44 (1.12–1.85) for 50 to 99 mg/dL (105–213 nmol/L), and 2.14 (1.57–2.92) for those with Lp(a) ≥100 mg/dL (214 nmol/L).[55] In the randomized,

controlled FOURIER and 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.[54,56] Furthermore alirocumab-associated reductions in Lp(a) reduced MACE in patients with a recent acute coronary syndrome (ACS) independent of LDL-C.[56]

Although these new data support the potential role of Lp(a) as a target of treatment in the future, there remains no evidence from randomized controlled trials (RCT's) that specifically lowering Lp(a) leads to reductions in CV outcomes. It should also be noted that commonly used lipid-lowering therapies (i.e. statins and ezetimibe) do not appreciably lower Lp(a). 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 high Lp(a). 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.

RECOMMENDATIONS

1. 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).
2. 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.[51,52,57-60] The high prevalence of elevated Lp(a), 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. While further evidence that directly lowering Lp(a) 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 (e.g. coronary artery calcium [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 3.5-5 mmol/L.

In the setting of secondary prevention, the presence of high Lp(a) 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.[56] When clinicians are uncertain of the implications of elevated Lp(a), consultation with a lipid specialist may be considered.

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

For primary prevention, most guidelines are based upon the concept of ASCVD risk assessment to help determine appropriateness and intensity of ASCVD risk factor modification. The primary prevention RCT's upon 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, has 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.[61,62] In spite of 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 [63], and consequently, inappropriate risk factor management. Additionally, the value of these algorithms for predicting the presence and burden of atheroma is poor.[64-65]

Atheroma burden, the substrate that portends CV events, directly predicts ASCVD event risk in a graded fashion. This has been demonstrated over decades with invasive angiography and more recently with coronary computed tomography, including non-contrast, CAC scoring, the latter being highly applicable for assessment of patients who are asymptomatic, and possible candidates for primary prevention.[66,67] Accordingly, the literature is replete with clinical studies reinforcing the concept that directly assessing the presence of atheroma, through CAC, significantly improves the appropriate selection of patients who are likely to benefit from lipid modifying therapy.[68]

Non-contrast, CAC measurements are sensitive, reproducible, and can be performed rapidly with an average radiation dose of 0.89 mSv (compared to 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.[69,70] The clinical decision-making utility of CAC measurements is best demonstrated in middle-aged, intermediate risk populations where the presence or absence of coronary artery calcification results in reclassification into higher or lower risk populations. A CAC measurement > 0 Agatston units (AU) confirms the presence of atherosclerotic plaque. Increasing scores are directly proportional to increased ASCVD event risk.[71-74] A CAC measurement > 100 AU is associated with a high risk (> 2% annual risk) of a 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%.[75] A CAC measurement of 0 AU, on the other hand, has a very high negative predictive value for ASCVD events in asymptomatic, low-risk adults within 2-5 years (negative predictive value, 95%-99%).[76] Importantly, although a CAC of 0 AU is indicative of a low event rate (1.5%/10 years; 0.32 to 0.43 per 1000 person-years; 1.3-5.6/11.1years)[72,77-79] it is not indicative of a zero event rate. This is likely because non-calcified soft plaque may be present, not all ASCVD events are mediated by vascular atheroma and atheromas may also progress in an

unpredictable fashion. The variability in the development of clinical ASCVD with a CAC of 0 AU is particularly evident in persons < 50 years of age, those with a strong family history of premature CVD events, 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)).[80-83] These are patient categories that in general would warrant aggressive ASCVD risk factor modification, even if CAC = 0 AU, in order 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 may provide a strong rationale for adherence to aggressive CVD risk factor modification[84,85], including lipid-lowering therapy or treatment intensification[86-87]. 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 non-calcific plaque. Therapy does not reduce and might even increase CAC Agatston scores in spite of regression of non-calcific plaque components.[88] 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 due to a paucity of large placebo-controlled RCT's and its cost-effectiveness for identification of patients suitable for statin therapy is uncertain[89], even when applied only to the intermediate risk group identified using risk algorithms. Importantly, at present, CAC is not uniformly available or uniformly funded in Canada, and there are no cost-effectiveness analyses that represent the Canadian context.

RECOMMENDATIONS:

1. We suggest that CAC screening using computed tomography imaging may be considered for asymptomatic adults ≥ 40 years and at intermediate risk (FRS 10%-20%) for whom treatment decisions are uncertain (Strong Recommendation, Moderate-Quality Evidence).
2. 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).
3. We suggest that CAC screening may be considered for a subset of low-risk individuals ≥ 40 years with a family history of premature ASCVD (men ≤ 55 years; women ≤ 65 years) in addition to identifying known genetic causes of ASCVD such as elevated Lp(a) 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, RCT's show the ASCVD risk reduction value of statin therapy in patients with intermediate risk and additional ASCVD risk factors (e.g. HOPE 3 Trial[16], JUPITER Trial[90]) in the absence of CAC testing or any testing to identify pre-clinical atherosclerosis. Accordingly, the patient-physician decision often does not require CAC but may 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-intermediate risk subjects, it may be reasonable to withhold statin therapy for CAC=0 AU given a favorable 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) 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 since risk will not be reclassified and would remain intermediate. If a decision is made to withhold statin or lipid modifying therapy based on CAC=0, this decision should be re-evaluated during follow-up or if clinical circumstances change. CAC should rarely be performed sooner than within 5 years to aid in this re-evaluation. 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 may be absent in the early phases. While CAC has been studied extensively for ASCVD risk prediction, the prevalence of CAC is lower in young patients compared to middle-aged and older patients and also in women vs. men <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, Mendelian randomization studies and RCT's 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).[15,91-98] In RCT's, however, the absolute benefits of therapy were higher in subsets of patients with higher pre-treatment 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, as 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 RCT's and to RCT's which have used the addition of non-statin lipid-lowering agents, such as ezetimibe and PCSK9 inhibitors). Exceptions are the 4S trial where the statin dose was up-or-down-titrated aiming for within trial total cholesterol levels of 3.0-5.2 mmol/L,[99] the IMPROVE-IT trial which allowed for up-titration of simvastatin to 80 mg daily for in trial LDL-C levels > 2.0 mmol/L,100 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.[92] Additionally, a number of trials comparing different intensity 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.[101,102] 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).[103] 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.[91,104] A number of studies have demonstrated 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.[105,106]

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 non-statin drugs in secondary ASCVD prevention patients on 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.[92,93]

The IMPROVE-IT trial showed benefit of ezetimibe in addition to statin therapy in patients with a recent ACS.[100] The threshold for the addition of ezetimibe was 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[91] and ODYSSEY-OUTCOMES[92]) 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 ASCVD and additional CV risk enhancers including diabetes mellitus, metabolic syndrome, polyvascular disease (vascular disease in ≥2 arterial beds), symptomatic peripheral artery disease (PAD), history of MI, MI in the past 2 years, previous coronary artery bypass graft (CABG) surgery, LDL ≥2.6 mmol/L, heterozygous FH and Lp (a) ≥60 mg/dl.[92,107-115] 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 addition of ezetimibe, which was used in only a minority 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 PSCK9 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 REDUCE-IT demonstrated CV risk reduction (including reduction in CV death) in patients ASCVD, as well as in those ≥50 years old with type 2 diabetes requiring medication treatment and at least one additional CVD risk factor) receiving moderate and high intensity statin therapy with triglyceride levels of 1.5 to 5.6 mmol/L and LDL-C levels of 1.1 to 2.6 mmol/L.[116]

RECOMMENDATIONS:

1. 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 statin, we recommend the maximally tolerated statin dose (Strong Recommendation; High-Quality Evidence).
2. We recommend intensification of lipid-lowering therapy with a PCSK9 inhibitor (evolocumab or alirocumab) – with or without the addition of ezetimibe – for secondary CV prevention patients shown to derive the largest benefit from PSCK9 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) on maximally tolerated statin dose. Refer to *Figure 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.

3. 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) on 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 based on the evidence-review of PICO question #4 were overlapping with a recommendation for PICO question #5 and appear as part of that later section (recommendations 3).

Values and preferences:

Based on strong evidence for the benefit of intensive LDL-C lowering in secondary prevention, additional lipid-lowering therapy with ezetimibe and PCSK9 inhibitors may 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 non-statin 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.[106,117,118] Therefore, if intensified lipid-lowering therapy initiated for the above listed thresholds results in low and very low LDL-C levels, lipid-lowering therapy does generally not require down titration dose adjustment.

Practical tip:

While there is very good evidence supporting the use of PCSK9 inhibitors in patients with ASCVD (especially those listed in Table 3), access may be limited by provincial drug plan coverage in many jurisdictions. Patients with or without private drug plan coverage may 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.

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

Ezetimibe

Ezetimibe is a cholesterol absorption inhibitor that lowers LDL-C by roughly 20% in addition to a statin regimen or up to 15% as monotherapy. Only one double-blind, RCT has assessed the efficacy of ezetimibe in reducing cardiovascular risk. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) demonstrated that ezetimibe 10 mg daily, as compared to placebo and when added to statin therapy, showed a modest reduction in cardiovascular events in 18,144 patients with an ACS within the preceding 10 days.[100] 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%, hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.89-0.99) for a number need to treat of 50 over seven years. There were no significant differences between groups in the pre-specified safety endpoints. 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, the Heart Institute of Japan Proper Level of Lipid Lowering with Pitavastatin and Ezetimibe in Acute Coronary Syndrome (HIJ-PROSPER) trial compared open-label pitavastatin plus ezetimibe (target LDL-C < 1.8 mmol/L) vs. 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).[119]

PCSK9 Inhibitors

Inhibitors of PCSK9 are recently available monoclonal antibodies that lower LDL-C between 50-70% when added to statin therapy or as monotherapy.[120] 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 diet and maximally tolerated statin therapy (with or without ezetimibe) who require additional lowering of LDL-C.

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (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 (subq) every 2 weeks or 420 mg subq monthly) or placebo.[91] 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 endpoint 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, though injection site reactions were higher with evolocumab (2.1 vs. 1.6%, p<0.001).

The Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY OUTCOMES) trial evaluated alirocumab in 18,924 patients with a recent (1-12 months) ACS whose LDL-C was ≥ 1.8 mmol/L despite maximally tolerated statin therapy.[92] Participants were randomized to alirocumab (75 mg subq every 2 weeks to achieve an LDL-C 0.6-1.3 mmol/L) or placebo. The dose of alirocumab was increased to 150 mg subq 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 based on the authors' pre-specified 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 to control in 60,723 patients.[121] 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 may not have been of sufficient duration to observe a mortality benefit.

While both 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 ODYSSEY ALTERNATIVE trial enrolled 314 patients with statin intolerance who were randomized to alirocumab 75 mg subq every 2 weeks, ezetimibe 10 mg daily, or atorvastatin 20 mg daily.[122] At 24 weeks, alirocumab reduced LDL-C by a mean difference of -30% compared to ezetimibe. Skeletal muscle-related adverse effects were high overall, but significantly lower with alirocumab (33%) vs. atorvastatin (46%) and similar to ezetimibe (41%). The GAUSS-3 trial included 218 patients considered with previous statin intolerance who were randomized to evolocumab 420 mg subq monthly or ezetimibe 10 mg orally daily.[123] Evolocumab demonstrated a significantly greater reduction in LDL-C compared to 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 demonstrated that PCSK9 inhibitors are effective at lowering LDL-C in patients with heterozygous FH[104,124] and in certain patients with homozygous FH[93], 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 (i.e., primary CV prevention) or FH.

Icosapent Ethyl

Until recently, contemporary trials of omega-3 fatty acid supplements have not demonstrated a CV benefit in patients with or without CVD.[125,126] Previously, the Japan EPA Lipid Intervention Study (JELIS) showed a reduction in CV events with 1800 mg daily of eicosapentaenoic acid (EPA) when combined with a statin, as compared to 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.[127] The Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial (REDUCE-IT) assessed the effect of a pharmaceutical formulation of purified ethyl EPA (icosapent ethyl or IPE), which was recently approved by Health Canada.[116] 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 one year, participants' triglyceride level in the IPE group was modestly reduced by 0.4 mmol/L (~ 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. As IPE is a purified form of ethyl EPA, the results of REDUCE-IT cannot be extrapolated to other non-prescription omega-3 fatty acids, which typically contain a mixture of EPA and docosahexaenoic acid (DHA).

The Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High CV Risk Patients with Hypertriglyceridemia (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 on statin therapy with hypertriglyceridemia (2.0-5.6 mmol/L), low HDL-C (< 1.2 mmol/L for women and < 1.1 mmol/L for men), and increased risk of CVD.[128] Patients were randomized to receive 4 g per day 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 endpoint 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. The 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 prior MI or stroke but who are at high risk of CVD.[129] Inclisiran is an experimental small interfering RNA molecule that inhibits the translation of PCSK9. In the phase 3 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 demonstrated LDL-C lowering in patients with heterozygous FH or with, or at high risk of, atherosclerotic CVD.[130,131] The ongoing phase 3 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.132 The Effect of Dalcetrapib vs. Placebo on CV Risk in a Genetically Defined Population With a Recent ACS (dal-GenE) 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.[133]

The Evaluation of Major Cardiovascular Events in Patients With, or at High Risk For, Cardiovascular Disease Who Are Statin Intolerant Treated with Bempedoic Acid (ETC-1002) or Placebo (CLEAR Outcomes) trial is evaluating the effect of bempedoic acid, a novel ATP citrate lyase inhibitor not approved in Canada, in patients with, or at high risk for, ASCVD who are statin intolerant.[134] Finally, the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients With Diabetes (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.[135]

RECOMMENDATIONS

1. We recommend the use of icosapent ethyl to lower 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*.
2. We recommend the use of a PCSK9 inhibitor (alirocumab or evolocumab) to lower LDL-C in patients with heterozygous FH without clinical ASCVD whose LDL-C remains above the target (i.e., LDL-C ≥2.5 mmol/L or < 50% reduction from baseline; or Apo-B≥ 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).
3. 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 two recommendations based on 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 RCT's 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 pre-existing ASCVD (i.e., secondary prevention). The choice of agent should be based on individual patient factors, their values and preferences, and practical considerations, such as access, cost and adherence. As ezetimibe lowers LDL-C by approximately 20% when added to a statin, if a patient's LDL-C is well above the threshold for therapy intensification (i.e., >2.2 mmol/L or >20% above threshold), it may be preferable to consider a PCSK9 inhibitor as second-line therapy. However, due to cost considerations, some insurance providers may 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) on maximally tolerated statin therapy but have residual elevated triglycerides (1.5-5.6 mmol/L). As 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 based on the 2018 update to the Canadian Cardiovascular Society position statement on FH.[136] The recommendation for PCSK9 inhibitors to lower LDL-C is based on 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 mediations is covered by most provincial drug plans for patients with heterozygous FH (with or without ASCVD) with LDL-C above the threshold. While the evidence for IPE to lower 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 yet cover this expensive medication. Private plans may cover this drug for patients based on specific criteria and there is a manufacturer patient assistance program that may 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 cardiovascular benefit of omega-3 from (i) dietary sources, and/or (ii) OTC formulations/supplements?

Despite the success of the REDUCE-IT trial in showing a purified prescription IPE at 4 g daily reduces major CVD events in statin-treated patients with elevated triglycerides who have established CVD or diabetes and at least one CVD risk factor[116], 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 RCT's with data from two subsequently completed RCTs, ASCEND (A Study of Cardiovascular Events in Diabetes)[137] and VITAL (Vitamin D and Omega-3 Trial)[138], which failed to show a clear CV benefit of supplementation with long chain omega-3 PUFAs in more than 130,000 randomized participants.139 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 4g/day 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 demonstrate a benefit to patients.[128] Pooled evidence from RCTs[140-142] and individual large RCTs[143], however, have shown consistent triglyceride-lowering effects at high doses (2-4 g/day) of omega-3 PUFAs, independent of CVD event risk reduction.

RECOMMENDATION:

1. We do not recommend the use of over-the-counter omega-3 polyunsaturated fatty acids 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 may choose to use these supplements for other indications including the management of high triglycerides, for which very high doses are required (4 g/day), 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 acid from algal and yeast sources, both of which are suitable for vegans.

There is also alpha-linolenic acid (ALA) 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 cardiovascular risk assessment (especially as it pertains to women), lipoprotein biomarkers and coronary artery calcium scanning. The committee also reviewed several major landmark randomized controlled trials of novel therapies to treat dyslipidemia. Based on 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 cardiovascular risk and dyslipidemia management is evolving and therefore these recommendations can only be viewed as the best practices based on 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.

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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Figure legends

Figure 1. Treatment Approach for Primary Prevention Patients (without a statin indicated condition[‡])

[‡]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 2. Treatment Approach for Patients with a Statin Indicated Condition

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 3: Treatment Intensification Approach for Patients with Atherosclerotic Cardiovascular Disease (ASCVD)

*Patients shown to derive largest benefit form intensification of statin therapy with PCSK9 inhibitor therapy are identified in *Table 3.*
***At low levels of LDL-C or non-HDL-C, measurement of apoB is more accurate than other markers.*
[†]May also be considered for patients without ASCVD but with DM requiring medication treatment in patient ≥50 years of age, and ≥1 additional CV risk factor (*from REDUCE-IT*[105]):

- *men ≥55 y and women ≥65 y;*
- *cigarette smoker or stopped smoking within 3 months;*
- *hypertension (≥140 mmHg systolic OR ≥90 mmHg diastolic) or on BP medication;*
- *HDL-C ≤1.04 mmol/L for men or ≤1.3 mmol/L for women;*
- *hsCRP >3.0 mg/L;*
- *Renal dysfunction: eGFR >30 and <60 mL/min;*
- *Retinopathy;*
- *Micro- or macroalbuminuria;*
- *ABI <0.9 without symptoms of intermittent claudication)*

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Table 1: Who to screen for dyslipidemia in adults at risk.[1*]

Who To Screen	
Men ≥40 years of age; **Women ≥40 years of age** **(or post-menopausal)** 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 (AAA) • diabetes mellitus • arterial hypertension • current cigarette smoking • stigmata of dyslipidemia (corneal arcus, xanthelasma, xanthoma) • family history of premature CVD[†] • family history of dyslipidemia • chronic kidney disease (eGFR ≤60 mL/min/1.73 m^2 or ACR ≥3 mg/mmol) • obesity (BMI ≥30 kg/m^2) • inflammatory diseases (RA, SLE, PsA, AS, IBD) • HIV infection • erectile dysfunction • COPD • history of hypertensive disorder of pregnancy

[*] Adapted from the *2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult*.
[†] Men younger than 55 years of age and women younger than 65 years of age in first degree relatives.
CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ACR = albumin-to-creatinine ratio; BMI = body mass index; RA = rheumatoid arthritis; SLE = systemic lupus erythematous; PsA = psoriatic arthritis; AS = ankylosing spondylitis; IBD = inflammatory bowel disease; HIV = human immunodeficiency virus; COPD = chronic obstructive pulmonary disease

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:** • Apolipoprotein B (ApoB) • Urine ACR (if eGFR <60 mL/min/1.73 m^2, hypertension, or diabetes**)**

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

[†]Non-fasting 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.

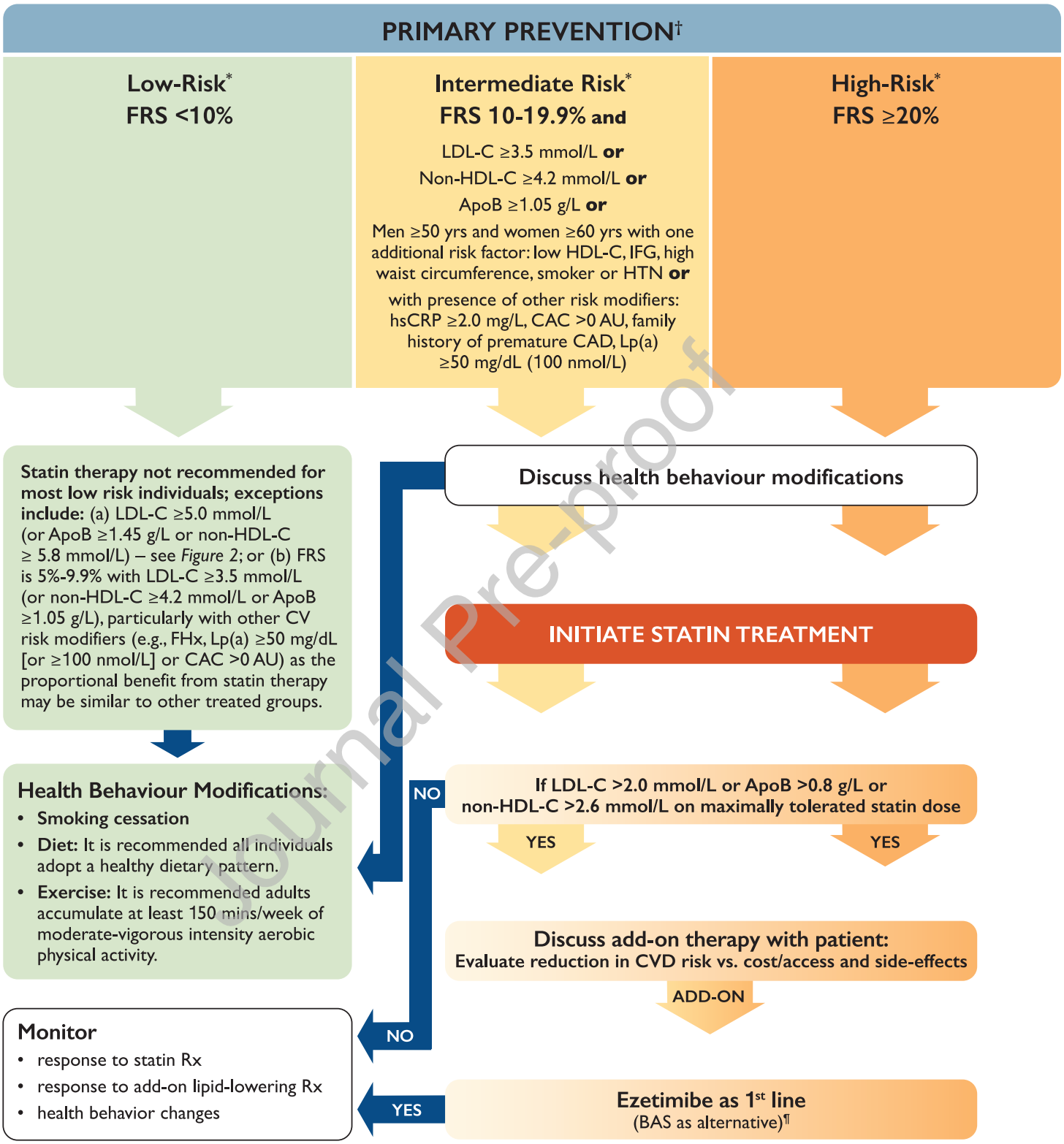
[*]it is now generally preferable to follow non-HDL-C or ApoB levels over LDL-C when interpreting lipid results, particularly when TG is ≥1.5 mmol/L.

Table 3: Secondary prevention patients shown to derive the largest benefit from intensification of statin therapy with the addition 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: i. diabetes mellitus or metabolic syndrome ii. polyvascular disease (vascular disease in ≥2 arterial beds) iii. symptomatic PAD iv. recurrent MI v. MI in the past 2 years vi. previous CABG surgery vii. LDL-C ≥ 2.6 mmol/L or heterozygous FH viii. lipoprotein (a) ≥ 60 mg/dL (120 nmol/L)

ASCVD = atherosclerotic cardiovascular disease; PAD = peripheral arterial disease; MI = myocardial infarction; CABG = coronary artery bypass graft; LDL-C = low density lipoprotein cholesterol; FH = familial hypercholesterolemia

Figure 1. Treatment Approach for Primary Prevention Patients (without a statin indicated condition‡)



‡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.

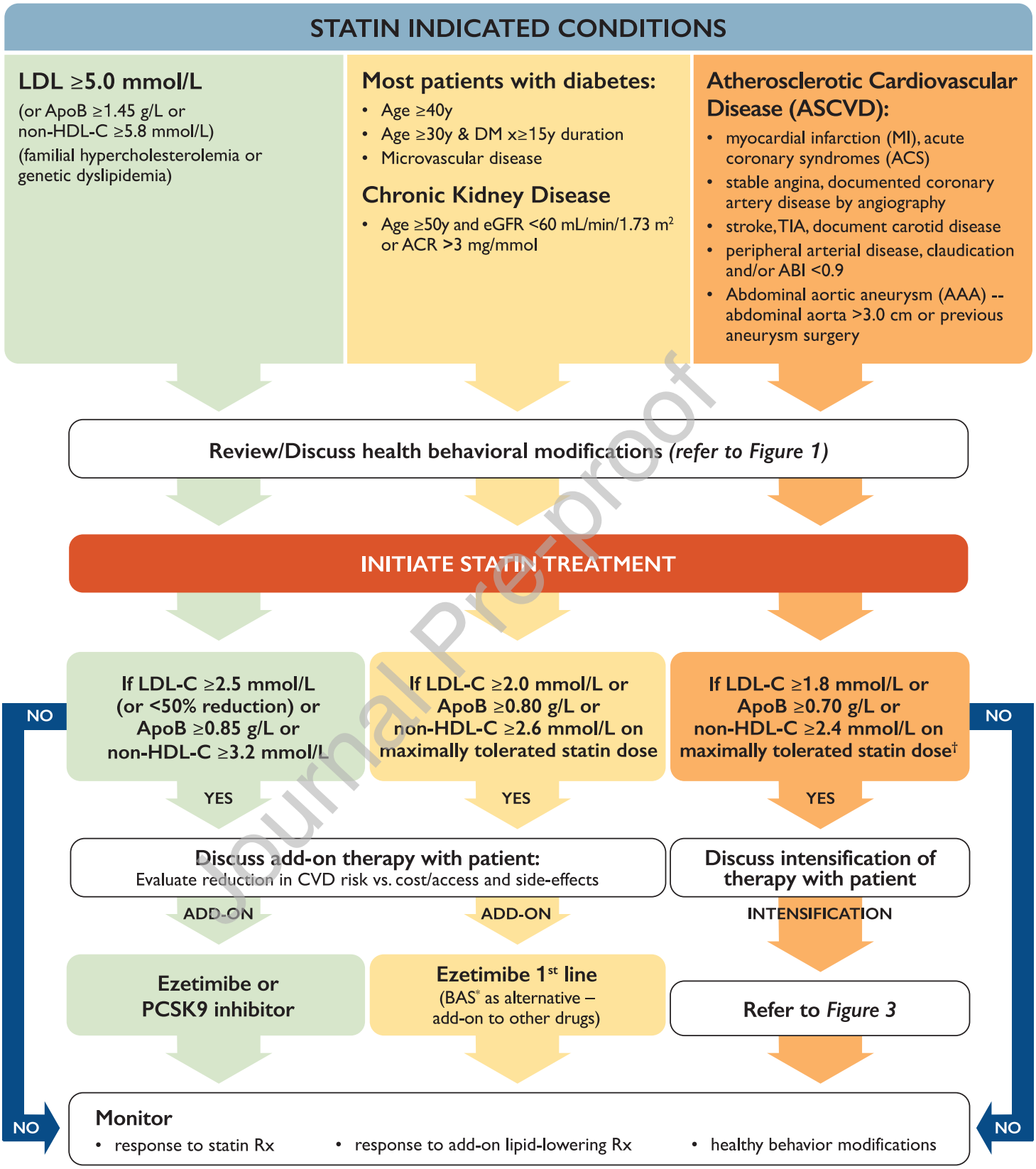
†Calculate risk using the Framingham Risk Score (FRS) – refer to the iCCS available on the App Store or on Google Play

*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.

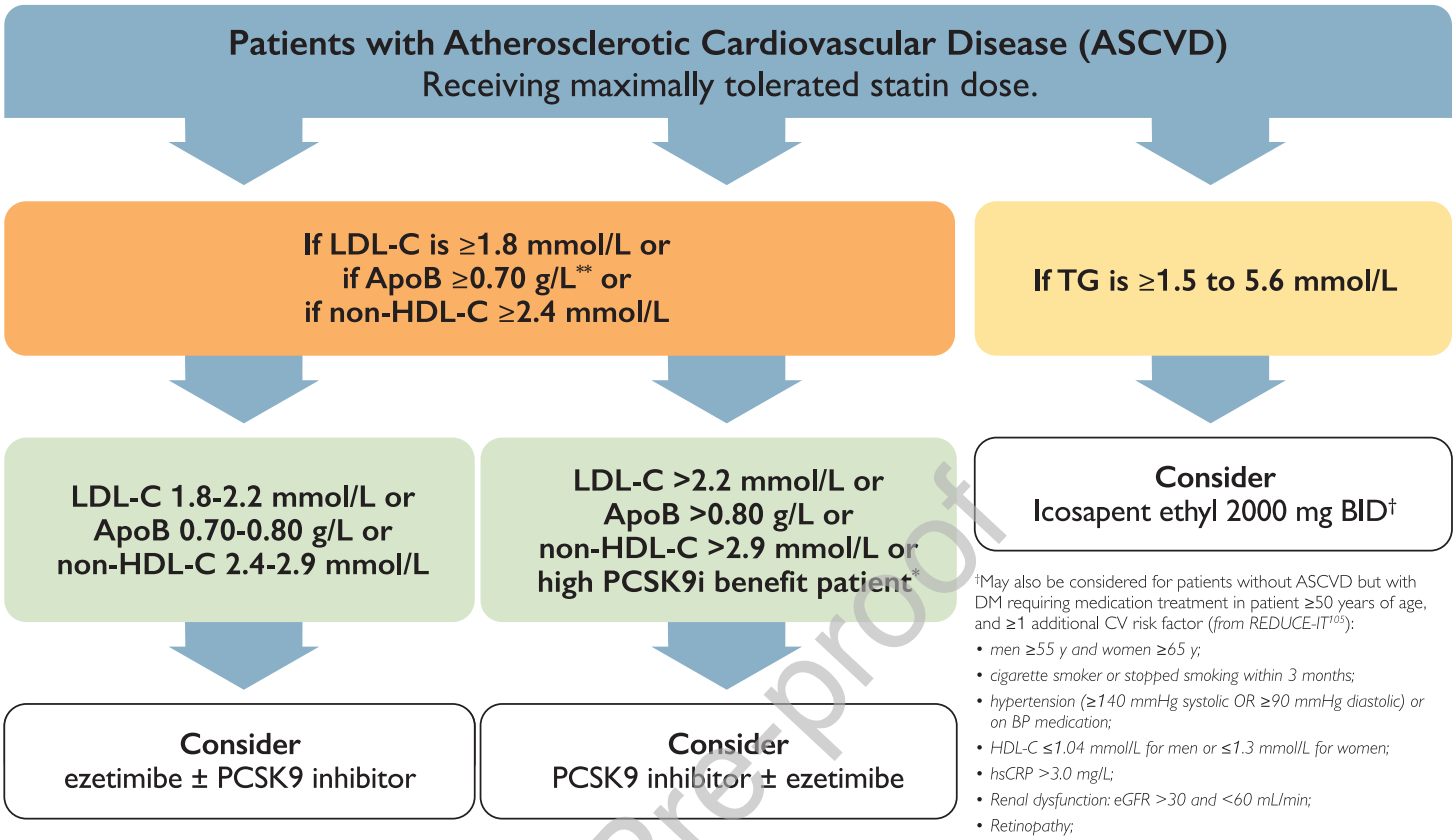
FRS = Framingham risk score; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; ApoB = apolipoprotein B; IFG = impaired fasting glucose; HTN = hypertension; hsCRP = high-sensitivity C-reactive protein; CAC = coronary artery calcium; AU – Agatston unit; Rx = prescription;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

Figure 2. Treatment Approach for Patients with a Statin Indicated Condition



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 3. Treatment Intensification Approach for Patients with Atherosclerotic Cardiovascular Disease (ASCVD)



*Patients shown to derive largest benefit form intensification of statin therapy with PCSK9 inhibitor therapy are identified in Table 3.

**At low levels of LDL-C or non-HDL-C, measurement of apoB is more accurate than other markers.

†May also be considered for patients without ASCVD but with DM requiring medication treatment in patient ≥50 years of age, and ≥1 additional CV risk factor (*from REDUCE-IT*[105]):

- *men ≥55 y and women ≥65 y;*
- *cigarette smoker or stopped smoking within 3 months;*
- *hypertension (≥140 mmHg systolic OR ≥90 mmHg diastolic) or on BP medication;*
- *HDL-C ≤1.04 mmol/L for men or ≤1.3 mmol/L for women;*
- *hsCRP >3.0 mg/L;*
- *Renal dysfunction: eGFR >30 and <60 mL/min;*
- *Retinopathy;*
- *Micro- or macroalbuminuria;*
- *ABI <0.9 without symptoms of intermittent claudication)*