# Supplementary Material

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

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## *Supplemental Appendix S1:* **Original 13 PICO Questions**

1. In primary prevention, which risk algorithm provides the best performance for cardiovascular risk estimation? (modified Framingham, PCE, or other?)
2. In primary prevention, what ancillary approaches can physicians use to counsel individuals toward lifestyle change and identify individuals for earlier treatment? (vascular age, lifetime risk, benefit approach)
3. In both primary and secondary prevention, what is the most appropriate lipid or lipoprotein measure for (i) estimating cardiovascular risk and (ii) for determining the adequacy of therapy?
4. Can consideration of women's health issues, including pregnancy-related conditions, enhance cardiovascular risk assessment in primary prevention?
5. Can consideration of ethnicity and ethnic-specific factors enhance cardiovascular risk assessment?
6. Can consideration of inflammatory-conditions, including autoimmune disease and arthritis, enhance cardiovascular risk assessment?
7. Can consideration of additional lipid or lipoproteins, such as triglyceride-rich lipoproteins and/or lipoprotein(a) improve risk assessment?
8. 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?
9. In adults already receiving or intolerant to statins, what is the role of other lipid-modulating drugs compared with placebo reduce CVD events? (PCSK9-inhibitors)
10. In secondary prevention, what is the most appropriate lipid/lipoprotein threshold for intensification of therapy?
11. In adults with high cholesterol levels and increased CV risk, do any diets or dietary interventions, compared with usual care, decrease lipid values or CVD events.
12. In primary and secondary prevention, what is the evidence for cardiovascular benefit of omega-3 from (i) dietary sources, (ii) OTC formulations/supplements and (iii) purified prescription formulations?
13. In primary and secondary prevention populations, what is the evidence for potential harm (on lipid levels and CV outcomes) from cannabis and cannabis-related products?

## *Supplemental Appendix S2:* PICO Voting Results Summary

**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?**

Recommendation 1: Among women whose pregnancy was complicated by the hypertensive disorders of pregnancy -- gestational hypertension and/or preeclampsia -- or a preterm birth before 34 weeks' gestation, a stillbirth and/or a placental abruption, we recommend screening with a comprehensive lipid panel at least 12 weeks postpartum. These women have a higher risk of premature CVD and stroke within 10-15 years after the affected pregnancy (Strong Recommendation, Moderate Quality Evidence). *Values and preferences: The observed increased risk of CVD after preeclampsia may be due to shared conventional CVD risk factors, or through accelerated vascular aging or other pathways warranting additional research.*

| | | |
|---|---|---|
| Agree | 65.38% | 17 |
| Agree - but have concerns with wording, quality or strength (see comments) | 30.77% | 8 |
| Disagree (see comments) | 0.00% | 0 |
| Recuse (if you have any conflicts related to the content of this recommendation, please recuse) | 3.85% | 1 |
| Comments regarding the above recommendation: | | 9 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

Recommendation 2: We recommend informing women who have had one of these pregnancy complications, and their primary care physicians, of the increased lifetime risk of CVD, and to reinforce the importance of implementing a heart healthy lifestyle, including a healthy body weight, engaging in 150 weekly minutes of moderate intensity cardiovascular activity, avoidance of tobacco, limiting alcohol consumption to no more than one beverage per day, stress management, and eating a heart healthy diet such as the Mediterranean diet. We recommend calculating and sharing their cardiometabolic age (www.cardiometabolicage.com) to support patient engagement and shared decision-making. (Strong Recommendation; Moderate Quality Evidence).

| | | |
|---|---|---|
| Agree | 76.92% | 20 |
| Agree - but have concerns with wording, quality or strength (see comments) | 19.23% | 5 |
| Disagree (see comments) | 0.00% | 0 |
| Recuse (if you have any conflicts related to the content of this recommendation, please recuse) | 3.85% | 1 |
| Comments regarding the above recommendation: | | 5 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

Recommendation 3: To assist with decisions about initiating lipid-lowering pharmacotherapy in a non-pregnant woman who had one or more of these pregnancy complications, we recommend referral to a specialized postpartum cardiovascular health clinic or specialized lipid clinic, if locally available. If such resources are not locally available, we recommend using standard risk assessment tools to decide about lipid-lowering pharmacotherapy. However, when interpreting their 10-year CVD risk using a risk

calculator, it is important to note that most women in this group will be found to have a low calculated absolute risk of CVD, short-term, which may give a false sense of reassurance to both the patient and her health care provider. (Weak Recommendation; Low-Quality Evidence)

| | | |
|---|---|---|
| Agree | 76.92% | 20 |
| Agree - but have concerns with wording, quality or strength (see comments) | 15.38% | 4 |
| Disagree (see comments) | 3.85% | 1 |
| Recuse (if you have any conflicts related to the content of this recommendation, please recuse) | 3.85% | 1 |
| Comments regarding the above recommendation: | | 6 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

*Values and preferences:*

1. 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 (8) considers preeclampsia a risk 'enhancer' warranting early screening and possibly shifting of risk category from borderline to intermediate risk (i.e., eligible for statin or other lipid-lowering therapy)
2. Consideration for pharmacotherapy should incorporate patient preferences, the severity or recurrence of pregnancy complications such as preeclampsia, and family history of premature CVD, among other important metabolic factors such as obesity, and must be balanced against the potential side effects and harms of long-term therapy. Alternative lifetime CVD risk calculators (https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.108.816694), or calculation of cardiometabolic age (www.cardiometabolicage.com; https://www.thelancet.com/journals/landia/article/PIIS2213-8587(14)70229-3/fulltext) should be considered in lieu of 10-year risk calculators in this population.
3. Initiating lipid lowering pharmacotherapy in reproductive aged women is complex. Statins have been found to have teratogenic potential based on earlier animal studies, but this has not been consistently found in recent human studies (12, 13). It has been suggested that a part of observed increase in the risk of congenital malformations may be due to underlying medical conditions rather than treatment with statin therapy itself (12). 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 (eg., simvastatin, lovastatin, atorvastatin) as opposed to hydrophilic compounds (eg., pravastatin)(14). There is limited data about the safety of ezetimibe in pregnancy. Owing to the many uncertainties surrounding safety of lipid-lowering pharmacotherapy during pregnancy, we recommend careful counseling, with the aid of specialists in dyslipidemia and obstetric medicine when considering initiating lipid lowering pharmacotherapy in reproductive aged-women.
5. For most reproductive women who already take statin therapy for primary prevention of CVD, therapy should be interrupted prior to a planned pregnancy, or stopped at the time of a positive pregnancy test in the case of an unplanned pregnancy. These can be resumed after delivery, when exclusive breastfeeding is completed.

| | | |
|---|---|---|
| Agree | 76.92% | 20 |
| Changes required | 23.08% | 6 |

| | | |
|---|---|---|
| Comments regarding the above values and preferences: | | 6 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

**PICO 2: Can consideration of additional lipid or lipoproteins, such as triglyceride-rich lipoproteins and/or lipoprotein(a) improve risk assessment?**

Recommendation 1: For any patient with triglycerides > 1.5mM, use non-HDL-C or apoB instead of LDL-C as the preferred lipid parameter for initial screening and treatment target (< 2.6 mM for non-HDL-C or < 0.8 g/L for apoB) in intermediate or high risk individuals (Strong Recommendation, High-Quality Evidence).

| | | |
|---|---|---|
| Agree | 65.38% | 17 |
| Agree - but have concerns with wording, quality or strength (see comments) | 19.23% | 5 |
| Disagree (see comments) | 15.38% | 4 |
| Recuse (if you have any conflicts related to the content of this recommendation, please recuse) | 0% | 0 |
| Comments regarding the above recommendation: | | 9 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

Recommendation 2: We recommend measuring lipoprotein (a) level once in a person's lifetime as a part of the initial lipid screening (Strong Recommendation; High-Quality Evidence).

| | | |
|---|---|---|
| Agree | 69.23% | 18 |
| Agree - but have concerns with wording, quality or strength (see comments) | 23.08% | 6 |
| Disagree (see comments) | 0% | 0 |
| Recuse (if you have any conflicts related to the content of this recommendation, please recuse) | 0% | 0 |
| Comments regarding the above recommendation: | | 8 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

Recommendation 3: For all patients with a lipoprotein (a) >50 mg/dL or >100 nmol/L, we recommend more aggressive LDL lowering in secondary prevention, and consideration of earlier initiation of LDL lowering therapy in primary prevention (Strong Recommendation;Moderate-Quality Evidence).
Recommendation changed to:
"For all patients with a lipoprotein (a) >50 mg/dL or >100 nmol/L, we recommend intensifying LDL lowering in secondary prevention (Strong Recommendation; Moderate-Quality Evidence), and we recommend earlier screening and management of cardiovascular risk factors in the setting of primary prevention (Strong recommendation; High-Quality Evidence).
*Values and Preferences:*
Lp(a) is an independent risk factor for CVD, ischemic stroke, aortic valve stenosis and abdominal aortic aneurysm (19, 20, 24-27). The risk of cardiovascular disease increases in a linear fashion with Lp(a) levels

>30 mg/dL. There is a large body of evidence supporting the causal association between Lp(a) and future cardiovascular disease. Furthermore, there is now evidence that treatment with PCSK9 inhibitors post ACS in patients with Lp(a) reduces MACE independently of LDL-C lowering. Identification of high levels of Lp(a) is particularly useful for mutual decision-making in subjects across all cardiovascular risk categories, but especially in younger patients who have a very strong family history of premature CVD and in whom detection of high Lp(a) might help inform decision-making regarding treatment. The high frequency and strength of Lp(a) as a CVD risk factor and its ability to inform CV risk stratification strongly justify its use as a routinely-measured test. While further evidence that directly lowering Lp(a) reduces major CVD risk is pending, the finding of high Lp(a) should alert primary care physicians to more actively pursue overall CVD risk assessment, including consideration of age-appropriate vascular imaging studies and earlier introduction of statin or other lipid-lowering therapy. 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. Where physicians are uncertain of the significance of elevated Lp(a), consultation with a lipid specialist may be considered.

| | | |
|---|---|---|
| Agree | 61.54% | 16 |
| Agree - but have concerns with wording, quality or strength (see comments) | 30.77% | 8 |
| Disagree (see comments) | 7.69% | 2 |
| Recuse (if you have any conflicts related to the content of this recommendation, please recuse) | 0% | 3 |
| Comments regarding the above recommendation: | | 10 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

**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?**

Recommendation 1: We suggest that CAC screening using computed tomography imaging may be considered for asymptomatic adults 40 years or older and at intermediate risk (FRS 10%-20%) for whom treatment decisions are uncertain (Weak Recommendation, Moderate-Quality Evidence).

| | | |
|---|---|---|
| Agree | 69.23% | 18 |
| Agree - but have concerns with wording, quality or strength (see comments) | 26.92% | 7 |
| Disagree (see comments) | 3.85% | 1 |
| Recuse (if you have any conflicts related to the content of this recommendation, please recuse) | 0.00% | 0 |
| Comments regarding the above recommendation: | | 8 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

Recommendation 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).

| | | |
|---|---|---|
| Agree | 96.15% | 25 |
| Agree - but have concerns with wording, quality or strength (see comments) | 3.85% | 1 |
| Disagree (see comments) | 0.00% | 0 |
| Recuse (if you have any conflicts related to the content of this recommendation, please recuse) | 0.00% | 0 |
| Comments regarding the above recommendation: | | 1 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

Recommendation 3: We suggest that CAC screening may be considered for a subset of low-risk individuals 40 years or older, in addition to identifying known genetic causes of ASCVD such as elevated Lp(a) or Familial hypercholesterolemia) in those with a family history of premature CVD (men younger than 55 years; women younger than 65 years) (Weak Recommendation; Low-Quality Evidence).

| | | |
|---|---|---|
| Agree | 73.08% | 19 |
| Agree - but have concerns with wording, quality or strength (see comments) | 19.23% | 5 |
| Disagree (see comments) | 7.69% | 2 |
| Recuse (if you have any conflicts related to the content of this recommendation, please recuse) | 0.00% | 0 |
| Comments regarding the above recommendation: | | 7 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

*Values and preferences:* Patients with modifiable CV risk factors should be counselled with respect to the potential merit of preventing atherosclerosis itself, the substrate for clinical cardiovascular events in the long-term, through comprehensive risk factor management. As outlined elsewhere, RCT's show the CV risk reduction value of statin therapy in patients with intermediate risk and additional CV risk factors (e.g. HOPE 3 Trial, JUPITER Trial) in the absence of CAC testing or any testing to identify pre-clinical atherosclerosis. Accordingly, the patient-physician decision often does not require CAC and, instead, may be strongly influenced by these other factors, including family history of premature CVD, other features suggesting genetic causes of CVD or side effects of statin therapy. In low-intermediate risk subjects it is reasonable to withhold statin therapy for CAC=0 given a favorable intermediate term outcome. The exceptions here would be cigarette smokers, diabetes, poorly controlled hypertension, lifelong, genetic dyslipidemias such as FH or Familial Elevated Lp(a) and patients with strong family history of premature CV events. If obtained, a CAC >100 is an indication for statin therapy regardless of Framingham risk. For those with a CAC of 1-99, individual decision making is required but even this low range is indication of presence of atherosclerosis. If a decision is made to withhold statin for lipid lowering based on CAC, this decision should be re-evaluated during follow-up or if clinical circumstance 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 early phases. While CAC has been studied extensively for risk prediction, prevalence of CAC is lower in young patients vs middle-aged and older patients and also in women vs men.

| | | |
|---|---|---|
| Agree with current wording | 73.08% | 19 |
| Changes required | 26.92% | 7 |
| Comments regarding the above values and preferences: | | 8 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

**PICO 4: In Secondary Prevention, what is the most appropriate lipid/lipoprotein threshold for the intensification of therapy?**

Recommendation 1: High intensity statin or when high intensity statin is associated with side effects maximum tolerated statin dose (Strong Recommendation, High-Quality Evidence).

| | | |
|---|---|---|
| Agree | 80.77% | 21 |
| Agree - but have concerns with wording, quality or strength (see c | 15.38% | 4 |
| Disagree (see comments) | 3.85% | 1 |
| Recuse (if you have any conflicts related to the content of this rec | 0.00% | 0 |
| Comments regarding the above recommendation: | | 5 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

Recommendation 2: Intensification of lipid lowering therapy with PCSK9 inhibitor (with or without the addition of ezetimibe) for patients in whom LDL-C remains ≥ 1.8 mmol/L or non-HDL-C ≥ 2.6 mmol/L or Apo-B ≥ 80 mg/dL (Strong Recommendation; High-Quality).

| | | |
|---|---|---|
| Agree | 73.08% | 19 |
| Agree - but have concerns with wording, quality or strength (see c | 15.38% | 4 |
| Disagree (see comments) | 7.69% | 2 |
| Recuse (if you have any conflicts related to the content of this rec | 3.85% | 1 |
| Comments regarding the above recommendation: | | 8 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

Recommendation 3: If LDL-C remains ≥ 1.8 mmol/L on maximum tolerated statin and PCSK9 inhibitor therapy additional lipid lowering interventions can be considered (Weak Recommendation; Low-Quality Evidence)

| | | |
|---|---|---|
| Agree | 57.69% | 15 |
| Agree - but have concerns with wording, quality or strength (see c | 19.23% | 5 |
| Disagree (see comments) | 19.23% | 5 |
| Recuse (if you have any conflicts related to the content of this rec | 3.85% | 1 |
| Comments regarding the above recommendation: | | 11 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

High-Risk Patients with Chronic Stable CVD

Recommendation 1: High intensity statin or when high intensity statin is associated with side effects maximum tolerated statin dose (Strong Recommendation, High-Quality Evidence).

| | | |
|---|---|---|
| Agree | 84.62% | 22 |
| Agree - but have concerns with wording, quality or strength (see | 11.54% | 3 |
| Disagree (see comments) | 3.85% | 1 |
| Recuse (if you have any conflicts related to the content of this rec | 0.00% | 0 |
| Comments regarding the above recommendation: | | 5 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

Recommendation 2: Intensification of lipid lowering therapy with ezetimibe and/or PCSK-9 inhibitor therapy (Strong recommendation; High Quality Evidence). If ezetimibe is used initially and LDL-C remains ≥ 1.8 mmol/L or non-HDL-C ≥ 2.6 mmol/L or Apo-B ≥ 80 mg/dL PCSK-9 inhibitor therapy is recommended (Strong Recommendation; High-Quality).

| | | |
|---|---|---|
| Agree | 73.08% | 19 |
| Agree - but have concerns with wording, quality or strength (see | 15.38% | 4 |
| Disagree (see comments) | 7.69% | 2 |
| Recuse (if you have any conflicts related to the content of this rec | 3.85% | 1 |
| Comments regarding the above recommendation: | | 8 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

Recommendation 3: Treatment intensification of lipid lowering therapy with Icosapent Ethyl for patients on maximum tolerated statin dose with fasting triglyceride levels of 1.69-2.59 mmol/L and LDL-C ≤ 1.8 mmol/L (Strong Recommendation; High-Quality Evidence).

| | | |
|---|---|---|
| Agree | 42.31% | 11 |
| Agree - but have concerns with wording, quality or strength (see | 19.23% | 5 |
| Disagree (see comments) | 34.62% | 9 |
| Recuse (if you have any conflicts related to the content of this rec | 3.85% | 1 |
| Comments regarding the above recommendation: | | 13 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

*Values and preferences*: No clear target to which LDL-C or non HDL-C or Apo-B should be lowered is clearly identified in clinical trials, although in trials of intensified lipid lowering therapy with ezetimibe and/or PCSK-9 inhibitors patients in the active treatment groups reached on average levels of 0.8-1.4 mmol/L (large number of patients had substantially lower levels). One RCT of patients with recent ACS used an LDL-C target of 0.65 – 1.3 mmol/L, although no randomized comparison with an alternate target was done. One RCT conducted in patients with recent ischemic stroke showed reduced major vascular events in patients allocated to a strategy of lower LDL-C targets (<1.8 mmol/L) vs higher targets (2.3-2.8 mmol/L).The totality of evidence from observational pathophysiological, observational epidemiological studies, epigenetic studies and randomized RCTs of lipid lowering therapies indicates that LDL-C causes atherosclerotic CV disease and that lower concentrations of plasma LDL-C levels are associated with lower CV risk extending to very low LDL-C concentrations (<0.5 mmol/L), although in RCTs the absolute benefits of therapy are higher in subsets of patients with higher pre-treatment LDL-C and/or additional risk markers.PCSK-9 inhibitor trials have enrolled patients with LDL-C ≥ 1.8 mmol/L and demonstrate highest absolute benefit in patients in the very high-risk secondary prevention group as defined above. However, PCSK-9 inhibitors may be considered also for very-high patients with LDL-C <1.8 mmol/L.After moderate duration of follow-up there is no risk associated with low and very low LDL-C levels. Therefore, if intensified lipid lowering therapy initiated for above listed thresholds results in low and very low LDL-C levels, lipid lowering therapy does generally not require dose adjustment. When initiating PCSK-9 inhibitor therapy cost and availability should be considered.

| | | |
|---|---|---|
| Agree | 84.62% | 22 |
| Disagree (see comments) | 15.38% | 4 |
| Comments regarding the above values and preferences: | | 7 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

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

Recommendation 1: We recommend the use of ezetimibe to lower the risk of cardiovascular events in patients with atherosclerotic CVD whose LDL-C remains above the threshold of ≥1.8 mmol/L despite maximally tolerated statin therapy (Strong Recommendation, High-Quality Evidence).

| | | |
|---|---|---|
| Agree | 80% | 20 |
| Agree - but have concerns with wording, quality or strength (see comments) | 12% | 3 |
| Disagree (see comments) | 4% | 1 |
| Recuse (if you have any conflicts related to the content of this recommendation, please recuse) | 4% | 1 |
| Comments regarding the above recommendation: | | 6 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

Recommendation 2: We recommend the use of a PCSK9 inhibitor (alirocumab or evolocumab) to lower the risk of CV events in patients with atherosclerotic CVD whose LDL-C remains above the threshold of ≥1.8 mmol/L despite maximally tolerated statin therapy (Strong Recommendation; High-Quality).

| | | |
|---|---|---|
| Agree | 64% | 16 |
| Agree - but have concerns with wording, quality or strength (see comments) | 28% | 7 |
| Disagree (see comments) | 4% | 1 |
| Recuse (if you have any conflicts related to the content of this recommendation, please recuse) | 3.85% | 1 |
| Comments regarding the above recommendation: | | 6 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

TWO OPTIONS - CHOOSE ONE:

(A) Recommendation 3a: We recommend the use of icosapent ethyl to lower the risk of cardiovascular events in patients with atherosclerotic CVD, or with diabetes and ≥1 cardiovascular risk factor, who have an elevated fasting triglyceride level of 1.5-5.6 mmol/L and an optimized LDL-C level (Strong Recommendation; High-Quality Evidence).

OR

(B) Recommendation 3b: We recommend the use of icosapent ethyl to lower the risk of cardiovascular events in patients with atherosclerotic CVD, or with diabetes and ≥1 cardiovascular risk factor, who have an elevated fasting triglyceride level of 1.5-5.6 mmol/L and LDL-C level of 1.1-2.6 mmol/L (Strong Recommendation; High-Quality Evidence).

Answer Choices Responses
Option A: 48.00% (12)
Option B: 36.00% (9)
Agree - but have concerns with wording, quality or strength (see comments): 8.00% (2)
Disagree (see comments): 4.00% (1)
Recuse (if you have any conflicts related to the content of this recommendation): 4.00% (1)
Comments regarding the above recommendation: 8
Answered: 25
Skipped: 0
PICO Group: We recommend proceeding with option A based on simple majority (48% vs 36%).

*Values and preferences:* None of these agents have been evaluated in a head-to-head randomized controlled trial with 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 CVD (i.e., secondary prevention). The choice of agent should be based on individual patient factors, their values and preferences, and practical considerations, such as cost and adherence. Due to cost considerations, some insurance providers may require a trial of ezetimibe before approving the use of a PCSK9 inhibitor. Icosapent ethyl should be preferentially reserved for patients whose LDL-C is optimized but have residual elevated triglycerides. Although icosapent ethyl contains EPA, this recommendation does not imply that the same cardiovascular benefits can be derived from the consumption of high doses (4g/day) of EPA alone, EPA and DHA blends, or fish oils from supplements or dietary sources. It also does not imply that the same cardiovascular benefits can be derived from triglyceride-lowering alone.

| | | |
|---|---|---|
| Agree | 88% | 22 |
| Agree - but have concerns with wording, quality or strength (see comments) | 0 | 0 |
| Disagree (see comments) | 8% | 2 |
| Recuse (if you have any conflicts related to the content of this recommendation, please recuse) | 4% | 1 |
| Comments regarding the above recommendation: | | 6 |
| | **Answered** | **25** |
| | **Skipped** | **0** |

**PICO 6: Omega-3 and Secondary Prevention**
**Recommendation 1:** 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 in primary or secondary prevention (Strong Recommendation, High-Quality Evidence).
***Values and preferences:*** Although icosapent ethyl (a prescription pharmaceutical that is an ethyl ester of eicosapentaenoic acid [EPA]) is recommended to reduce major CVD events in statin-treated patients who have elevated triglycerides with established CVD or diabetes and at least one cardiovascular risk factor, it should not be inferred that the same cardiovascular benefits can be derived from the consumption of omega-3 polyunsaturated fatty acid formulations that include EPA alone, EPA and DHA mixtures, or fish oils from supplements or dietary sources. Patients may still choose to use omega-3 polyunsaturated fatty acid supplements for other indications including the management of high triglycerides, for which very high doses are required (2-4 g/day) but there should be no expectation of a cardiovascular benefit.

| | | |
|---|---|---|
| Agree | 80.77% | 21 |
| Agree - but have concerns with wording, quality or strength (see comments) | 19.23% | 5 |
| Disagree (see comments) | 0.00% | 0 |
| Recuse (if you have any conflicts related to the content of this recommendation, please recuse) | 0.00% | 0 |
| Comments regarding the above recommendation: | | 5 |
| | **Answered** | **26** |
| | **Skipped** | **0** |

Recommendation 2: INCLUDED FOR REFERENCE ONLY - NO VOTE**this recommendation will appear as part of the non-statin therapy section
Recommendation 2: We recommend icosapent ethyl to reduce major CVD events in statin-treated patients who have elevated triglycerides with established CVD or diabetes and at least one cardiovascular risk factor (Strong Recommendation, High-Quality Evidence).
*Values and preferences*: Although icosapent ethyl is a purified ethyl ester of EPA, this recommendation does not imply that the same cardiovascular benefits can be derived from the consumption of high doses (4 g/day) of EPA alone, EPA and DHA blends, or fish oils from supplements or dietary sources. It also does not imply that the same cardiovascular benefits can be derived from triglyceride-lowering alone.

## *Supplemental Appendix S3:* **ApoB and Non-HDL-C Threshold Selection**

Given the increased emphasis on apoB and non-HDL-C in the 2021 CCS dyslipidemia guideline document, we have reviewed the evidence from several large cohorts and have provided percentile equivalents for apoB and non-HDL-C for each LDL-C threshold referenced in the guideline document.

For untreated individuals, data from NHANES was evaluated to determine percentile equivalents. These results were also validated by reviewing available data from the UK biobank (not shown).

| percentile | LDL-C (mmol/L) | apoB (g/L) | non-HDL-C (mmol/L) |
|---|---|---|---|
| 10th | 1.8 | 0.61 | 2.1 |
| 15th | 2.0 | 0.65 | 2.4 |
| 22nd | 2.2 | 0.70 | 2.7 |
| 33rd | 2.5 | 0.78 | 3.0 |
| 75th | 3.5 | 1.05 | 4.2 |
| 97th | 5.0 | 1.49 | 6.1 |

For individuals on lipid-lowering therapy, data from NHANES participants on lipid-lowering therapy was evaluated to determine the percentile equivalents:

| percentile | LDL-C (mmol/L) | apoB (g/L) | non-HDL-C (mmol/L) |
|---|---|---|---|
| 10th | 1.68 | 0.63 | 2.28 |
| 15th | 1.84 | 0.67 | 2.48 |
| 22nd | 2.07 | 0.71 | 2.69 |
| 33rd | 2.30 | 0.78 | 2.95 |
| 75th | 3.23 | 1.06 | 4.11 |
| 98th | 4.97 | 1.45 | 6.1 |

Based on these data, the following equivalent thresholds were selected for the 2021 CCS dyslipidemia guidelines:

| | LDL-C | apoB | non-HDL-C |
|---|---|---|---|
| | (mmol/L) | (g/L) | (mmol/L) |
| | 1.8 | 0.7 | 2.4 |
| | 2.0 | 0.8 | 2.6 |
| | 3.5 | 1.05 | 4.2 |
| | 5.0 | 1.45* | 5.8* |

*these values were selected to remain closer to the 95th percentile as defined by the CCS guidelines for familial hypercholesterolemia.

***Supplemental Appendix S4:*** **Expected Benefits of Various Health Behaviour Changes**

This information is carried forward from the 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult[1] Supplementary material.

| **Intervention (minimal dose for effect)** | **Expected CV outcomes** | **Expected lipid outcomes** |
|---|---|---|
| Mediterranean dietary pattern | ↓ major CV events 28-30% (0.6-1% absolute risk reduction [NNT=100-167]) | |
| Portfolio dietary pattern | ↓10y-FRS by 11% | Efficacy: ↓ LDL-C 21-29% (comparable to Lovastatin 20mg)<br>Effectiveness: ↓ LDL-C 8-14% |
| DASH (Dietary Approaches to Stop Hypertension) dietary pattern | ↓ CVD 20%; ↓10y-FRS by 13% | ↓ LDL-C 3% |
| Dietary patterns high in nuts (≥ 30 g/day) | ↓ Major CV events 28% (1% absolute risk reduction [NNT=100]) | ↓ LDL-C 5-7%, ↓ TG 5-10% |
| Dietary patterns high in legumes (≥ 4 servings/week) | ↓ CHD events 14% | |
| Dietary patterns high in Olive oil (≥ 60 mL/day) | ↓ major CV events 30% (0.6% absolute risk reduction [NNT=167]) | |
| Dietary patterns rich in fruits and vegetables (≥ 5 servings/day) | ↓ CV mortality 4% per serving/day | |
| Dietary patterns high in total fibre (≥ 30 g/day) | ↓ CVD events 9% reduction per 7g/day | |
| Dietary patterns high in whole grains (≥ 3 servings/day) | ↓ CVD events 21% | |
| Low-glycemic index (GI)/glycemic load (GL) dietary patterns | ↓ CHD and CVD events 10-12%/19-21% | ↓ LDL-C 5% (for low-GI dietary patterns) |
| Vegetarian dietary patterns | ↓ CHD events 19% | |
| Saturated fats intake ≤ 9% energy 107 | ↓ CVD events 21% | |
| Replacement of Saturated fats with polyunsaturated fats (PUFAs) especially from omega-3/omega-6 sources | ↓ CVD events 28% (5.4% absolute risk reduction [NNT=18.5]) | |
| Replacement (≥ 5% energy) of Saturated fats with polyunsaturated fats (MUFAs) from plant sources | ↓ CHD events 15% for 5% energy replacement | |
| Replacement of saturated fats with whole grains | ↓ CHD events 9% for 5% energy replacement | |

| | | |
|---|---|---|
| Replacement (≥ 5% energy) of Saturated fats with low-GI carbohydrates | ↓ CHD events 23% for 5% energy replacement | |
| Omega -3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from marine, algal, or yeast sources (2-4 g/day) | No CV benefit | ↓ TG 25-30% in hypertriglyceridemia |
| Reduced saturated fats/dietary cholesterol<br>NCEP Step I diet: ≤10% energy/≤300 mg/day<br>NCEP Step II diet: ≤7% energy/≤ 200 mg/day | | ↓ LDL-C<br>10-12%<br>12-16% |
| Dietary patterns supplemented with plant sterols/stanols 1-2 gm/day | | ↓ LDL-C 6-12%; |
| Dietary patterns high in soy protein ≥30g/day | | ↓ LDL-C 3-5%; ↓ TG 4% |
| Dietary patterns high viscous soluble fibre from oats, barley, psyllium, pectin, or konjac mannan (≥10 g/day) | | ↓ LDL-C 5-10%; |
| Dietary patterns high in dietary pulses (beans, peas, chickpeas, and lentils) (≥ 1 serving/day or ≥130 g/day) | | ↓ LDL-C 5% |
| Moderate Alcohol intake 1-2 drinks/day | ↓ CHD events 32% | ↑ HDL-C 5-10%, |
| Weight loss and reduction of abdominal obesity 5-10% of body weight loss | ↓ CVD risk 6% per 4.56 kg/m$^2$ lower BMI and 9% per 12.6cm lower waist circumference (based on a minimum BMI of 20 kg/m$^2$) | ↓ LDL-C 11%, ↑ HDL-C 3% (12% once weight stable), ↓ TG 32% |
| Exercise<br>30-60 min/day moderate to vigorous intensity | ↓ CVD events 20-30% | ↑ HDL-C 5-10% |
| Smoking cessation | ↓ CV mortality 52% for never smoking and 10-39% for smoking cessation (< 5 years to ≥ 20 years) | ↑ HDL-C 7-12% |
| Combined low-risk lifestyle behaviours (healthy body weight, healthy diet, regular exercise, smoking cessation, moderate alcohol intake, moderate sleep duration). | ↓ CVD events and mortality 75% | |

## *Supplemental Appendix S5:* Ongoing Recommendations from the 2016 Guidelines

1. We recommend that a cardiovascular risk assessment be completed every 5 years for men and women age 40 to 75 using the modified Framingham risk score or Cardiovascular Life Expectancy Model to guide therapy to reduce major cardiovascular events. A risk assessment may also be completed whenever a patient's expected risk status changes. (Strong Recommendation, High Quality Evidence)
2. We recommend sharing the results of the risk assessment with the patient to support shared decision making and improve the likelihood that patients will reach lipid targets. (Strong Recommendation, High Quality Evidence)
3. We recommend non-fasting lipid and lipoprotein testing which can be performed in adults in whom screening is indicated as part of a comprehensive risk assessment to reduce CVD events (Strong Recommendation, High Quality Evidence).
4. We suggest that for individuals with a history of triglyceride levels > 4.5 mmol/L that lipid and lipoprotein levels be measured fasting (Conditional Recommendation, Low Quality Evidence).
5. *Statin indicated conditions:* We recommend management that includes statin therapy in high risk conditions including clinical atherosclerosis, abdominal aortic aneurysm, most diabetes mellitus, chronic kidney disease (age > 50 years) and those with LDL-C ≥ 5.0 mmol/L to lower the risk of CVD events and mortality (Strong Recommendation, High Quality Evidence).
6. *Primary prevention:*
    a. We recommend management that does not include statin therapy for individuals at low risk (modified FRS < 10 %) to lower the risk of CVD events (Strong Recommendation, High Quality Evidence).
    b. We recommend management that includes statin therapy for individuals at high risk (modified FRS ≥ 20%) to lower the risk of CVD events (Strong Recommendation, High Quality Evidence)
    c. We recommend management that includes statin therapy for individuals at intermediate risk (modified FRS 10-19%) with LDL-C ≥ 3.5 mmol/L to lower the risk of CVD events. Statin therapy should also be considered for intermediate risk persons with LDL-C <3.5 mmol/L but with apo B ≥ 1.2 g/L or non-HDL-C ≥ 4.3 mmol/L or in men ≥ 50 and women ≥ 60 years of age with ≥ 1 CV risk factor (Strong Recommendation, High Quality Evidence).
7. We recommend treatment with a statin or statin/ezetimibe combination to reduce CVD events in adults ≥ 50 years with chronic kidney disease not treated with dialysis or a kidney transplant. (Strong Recommendation, High Quality Evidence).
8. We suggest that lipid lowering therapy not be initiated in adults with dialysis dependent CKD. (Conditional Recommendation, Moderate Quality Evidence)
9. We suggest that lipid lowering therapy be continued in adults already it at the time of dialysis initiation. (Conditional Recommendation, Low Quality Evidence).
10. We suggest the use of statin therapy in adults with kidney transplant. (Conditional Recommendation, Moderate Quality Evidence).
11. We suggest that in patients warranting risk factor management based on usual criteria, CAC scoring not be undetaken. Moreover, CAC scoring (seeking a result with a value of zero) should not be used as a rationale for withholding otherwise indicated, preventive therapies. (Strong recommendation, Low Quality Evidence)

*Statin indicated conditions*
*Primary prevention conditions warranting therapy:*
*All risk groups:*

12. We recommend that adults who smoke should receive clinician advice to stop smoking to reduce CVD risk (Strong Recommendation, High Quality Evidence).
13. We recommend that all individuals are offered advice about healthy eating and activity and adopt the Mediterranean dietary pattern to lower their CVD risk: (Strong Recommendation, High Quality Evidence)
14. We suggest that individuals avoid the intake of trans fats and decrease the intake of saturated fats for CVD disease risk reduction (Conditional Recommendation, Moderate-Quality Evidence).
15. We suggest that to increase the probability of achieving a cardiovascular benefit, individuals should replace saturated fats with polyunsaturated fats (Conditional Recommendation, Moderate-Quality Evidence), emphasizing those from mixed omega-3/omega-6 polyunsaturated fatty acids (PUFAs) sources (e.g. canola and soybean oils) (Conditional Recommendation, Moderate-Quality Evidence), and target an intake of saturated fats of <9% of total energy (Conditional Recommendation, Low-Quality Evidence). If saturated fats are replaced with mono-unsaturated fatty acids (MUFAs) and carbohydrates, then people should choose plant sources of MUFAs (e.g. olive oil, canola oil, nuts, and seeds) and high-quality sources of carbohydrates (e.g. whole grains and low glycemic index carbohydrates) (Conditional Recommendation, Low-Quality Evidence).
16. We suggest that all individuals be encouraged to moderate energy (caloric) intake to achieve and maintain a healthy body weight (Conditional Recommendation, Moderate-Quality Evidence) and adopt a healthy dietary pattern to lower their CVD risk:
    a) Mediterranean dietary pattern (Strong Recommendation/High-Quality Evidence)
    b) Portfolio dietary pattern (Conditional Recommendation, Moderate-Quality Evidence)
    c) DASH dietary pattern (Conditional Recommendation, Moderate-Quality Evidence)
    d) Dietary patterns high in nuts (≥ 30 g/day) (Conditional Recommendation, Moderate-Quality Evidence)
    e) Dietary patterns high in legumes (≥ 4 servings/week) (Conditional Recommendation, Moderate-Quality Evidence)
    f) Dietary patterns high in olive oil (≥ 60mL/day) (Conditional Recommendation, Moderate-Quality Evidence)
    g) Dietary patterns rich in fruits and vegetables (≥ 5 servings/day) (Conditional Recommendation, Moderate-Quality Evidence)
    h) Dietary patterns high in total fibre (≥ 30 g/day) (Conditional Recommendation, Moderate-Quality Evidence) and whole grains (≥ 3 servings/day) (Conditional Recommendation, Low-Quality Evidence)
    i) Low-glycemic load (GL) (Conditional Recommendation, Moderate-Quality Evidence) or low-glycemic index (GI) (Conditional Recommendation, Low-Quality Evidence) dietary patterns
    j) Vegetarian dietary patterns (Conditional Recommendation, Very Low-Quality Evidence)
17. We recommend the following dietary *components* for LDL-C lowering:
    a) Portfolio dietary pattern (Strong Recommendation, High-quality Evidence)
    b) Dietary patterns high in nuts (≥ 30 g/day) (Strong Recommendation, High Quality Evidence)
    c) Dietary patterns high in soy protein (≥ 30 g/day) (Strong Recommendation, High Quality Evidence)
    d) Dietary patterns with plant sterols/stanols (≥2 g/day) (Strong Recommendation, High Quality Evidence)
    e) Dietary patterns high in viscous soluble fibre from oats, barley, psyllium, pectin, or konjac mannan (≥ 10 g/day) (Strong Recommendation, High Quality Evidence)
    f) NCEP Step 1 and II dietary patterns (Strong Recommendation, High Quality Evidence)
18. We suggest the following dietary *patterns* for LDL-C lowering:

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

19. We recommend that adults should accumulate at least 150 minutes of moderate-to-vigorous intensity aerobic physical activity per week, in bouts of 10 minutes or more to reduce CVD risk (Strong Recommendation, High Quality Evidence).
20. We recommend combining low-risk lifestyle behaviors that include achieving and maintaining a healthy body weight, healthy diet, regular physical activity, moderate alcohol consumption, and moderate sleep duration to achieve maximal CVD risk reduction (Strong Recommendation, High Quality Evidence).
21. We recommend that niacin not be added to statin therapy for CVD prevention in patients who have achieved LDL-C targets. (Strong Recommendation, High Quality Evidence)
22. We recommend that fibrates not be added to statin therapy for CVD event prevention in patients who have achieved LDL-C targets (Strong recommendation, High Quality evidence).
23. We recommend that despite concerns about a variety of possible adverse effects, all purported statin-associated symptoms should be evaluated systematically, incorporating observation during cessation, re-initiation (same or different statin, same or lower potency, same or decreased frequency of dosing) to identify a tolerated, statin-based therapy for chronic use (Strong recommendation, Low Quality Evidence).
24. We recommend that vitamins, minerals, or supplements for symptoms of myalgia perceived to be statin-associated not be used (Strong Recommendation, Low Quality Evidence).