# Canadian Dyslipidemia Guidelines

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# Speaker Disclosures

| | |
|---|---|
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**Relationships with financial sponsor(s)**

## Financial payments/honoraria:

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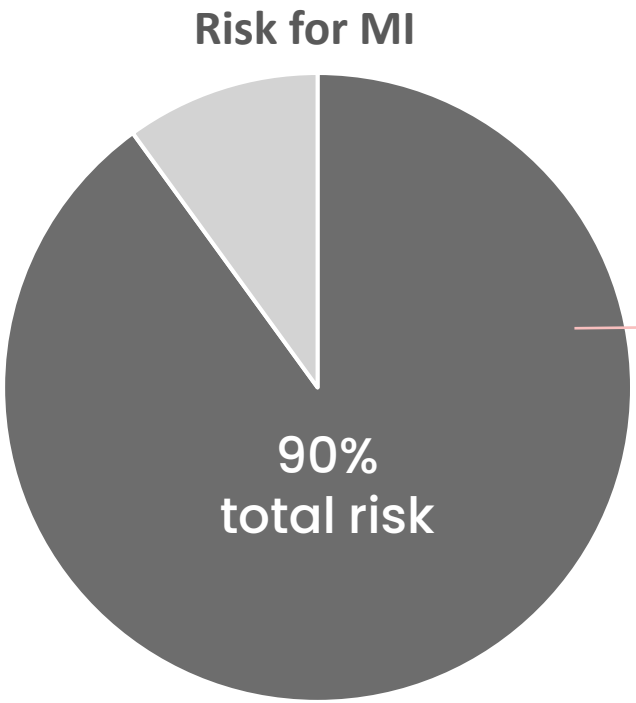
# Objectives

By the end of this presentation, participants will be able to:

- Review key messages from the Canadian Dyslipidemia Guidelines
- Consider new recommendations around investigations and management of dyslipidemia
- Discuss the practicalities of implementing these guidelines in clinical practice

# 90% of MI are explained by 9 modifiable risk factors[1]




**54.1%**
Apo B/Apo A-1 (5 vs. 1)
**DYSLIPIDEMIA** is the greatest risk contributor*

**36.4%**
CURRENT SMOKING

**33.7%**
OBESITY

**28.8%**
PSYCHOSOCIAL FACTORS

**25.5%**
EXERCISE

**23.4%**
BLOOD PRESSURE

**13.9%**
ALCOHOL

**12.9%**
VEGETABLES & FRUIT DAILY

**12.3%**
DIABETES

*Population attributable risk for 5th vs. 1st quintile of Apo B/Apo A-1

Apo A-1: apolipoprotein A-1; Apo B: apolipoprotein B; MI: myocardial infarction; PAR: populations at risk.

1. Yusuf S et al. Lancet. 2004;364(9438):937-952.

# The role of healthcare professionals in CVD

- ✓ Many **CVDs events can be prevented** by addressing risk factors
  - ❑ If not successfully prevented, most **CVDs events can be successfully treated to delay death**
- ✓ Unlike many cancers and neurological diseases, **we can prevent CVD and recurrent** events
- ✓ HCPs **have a key role to play**, perhaps now more than ever

**How do we tackle the rise in cardiovascular diseases?**

CVD, cardiovascular disease; HCP, healthcare professionals.

# The link between LDL-C and ASCVD

**LDL-C**
**A causal factor in ASCVD**
↓
**A major therapeutic target**

### EPIDEMIOLOGIC STUDIES
LDL-C and ASCVD risk have a log-linear association

### HEREDITARY LIPID METABOLISM DISORDERS
FH results in lifelong LDL-C burden and increases the risk of ASCVD

### MECHANISTIC STUDIES
LDL-C has been directly implicated in the initiation and progression of ASCVD

### RANDOMIZED CONTROLLED TRIALS
LDL-C lowering with statins, ezetimibe and PCSK9i mAbs reduce ASCVD risk

### IVUS STUDIES
Plaque progression arrested at LDL-C ≤1.8 mmol/L

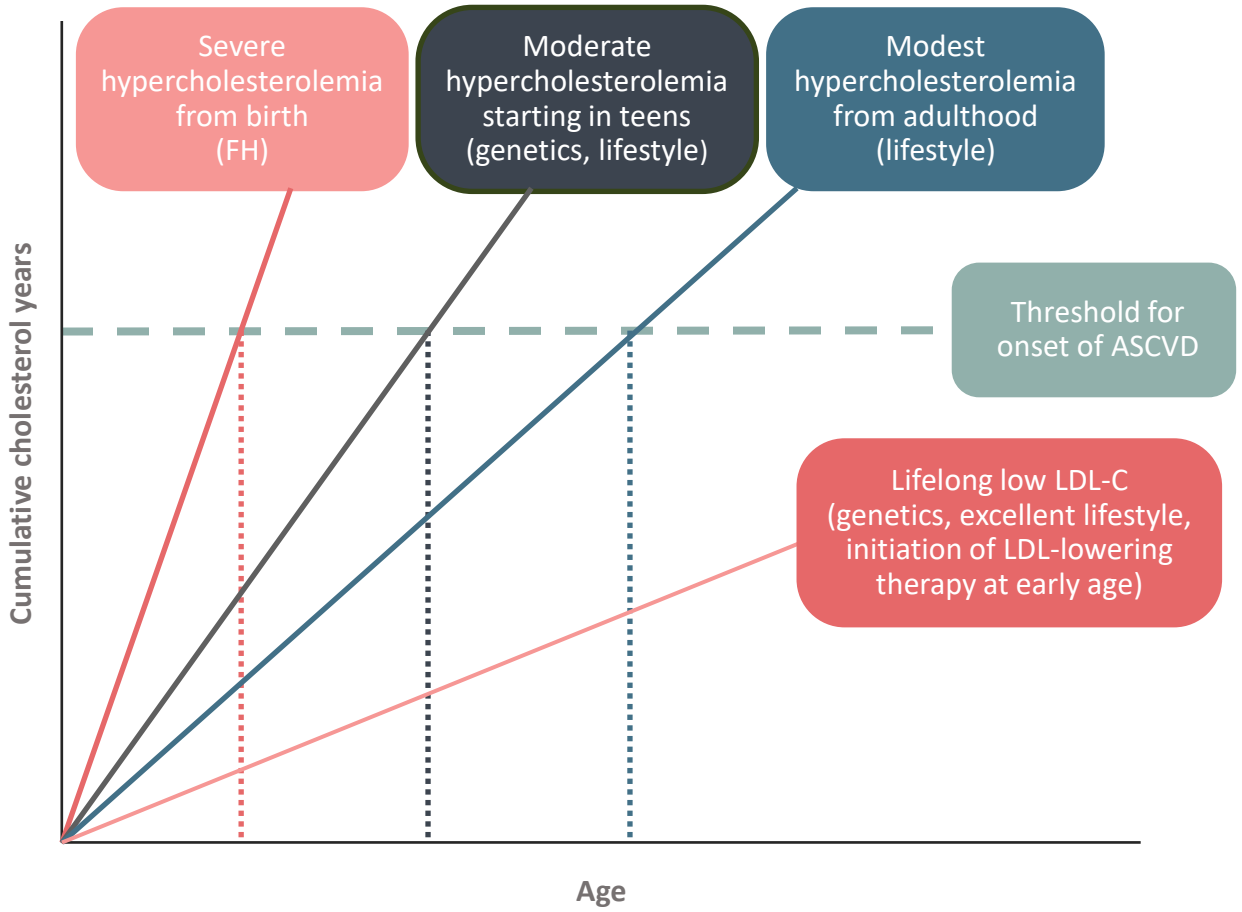
### MENDELIAN RANDOMIZATION STUDIES
LDL-C is a causal risk factor for ASCVD

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; mAb, monoclonal antibody; IVUS, intravascular ultrasound; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors.

# Lifetime exposure to LDL-C associated with greater risk

**Consider long term or lifetime risk:**

**Start early and aim for low LDL-C levels**




ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.
Adapted from Shapiro MD, Bhatt DL. J Am Coll Cardiol. 2020;76(13):1517-1520.

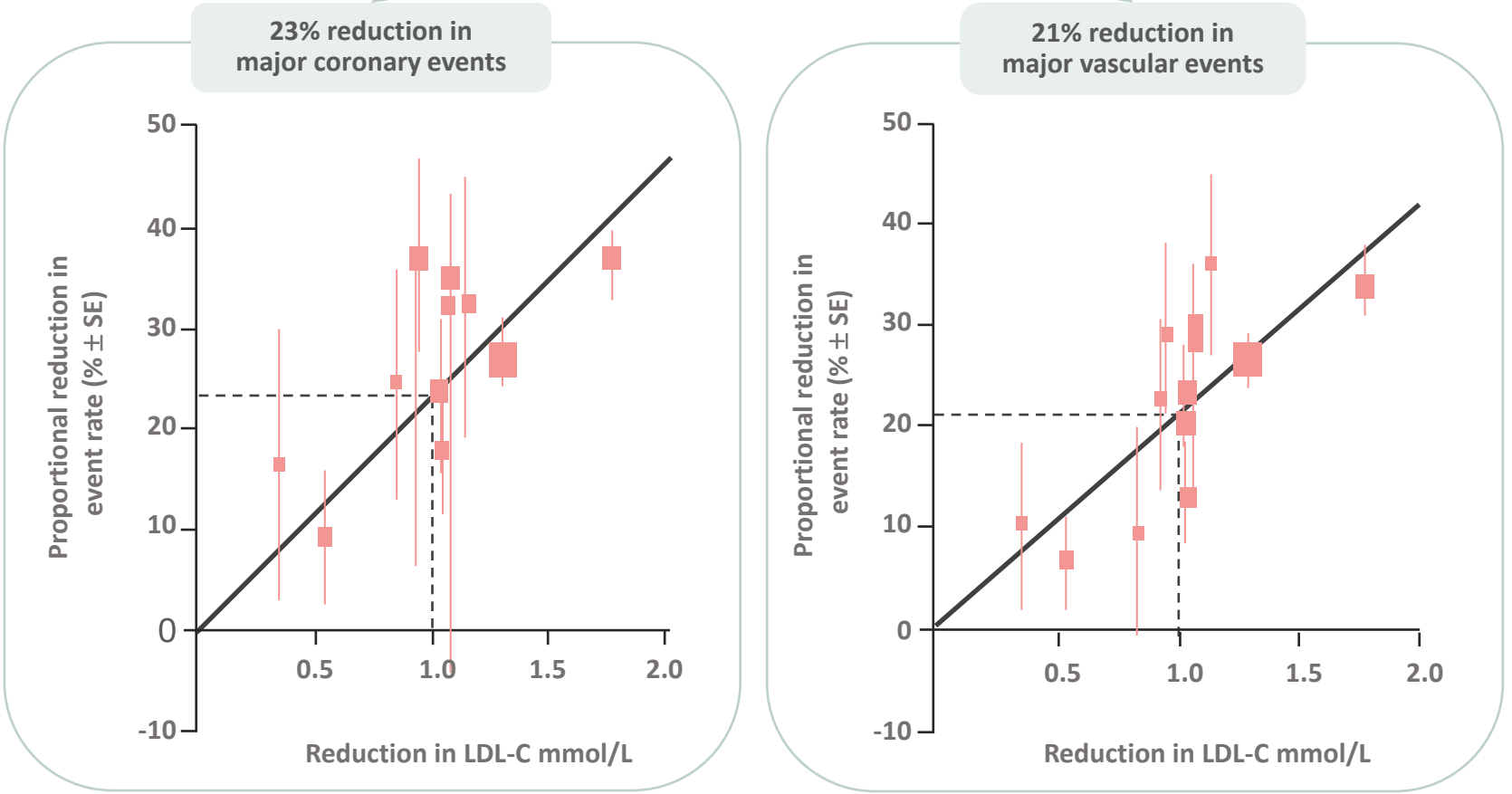
# Correlation between proportional reduction in events and absolute LDL-C reduction at 1 year

**Prospective meta-analysis**

90,056

14 statin trials

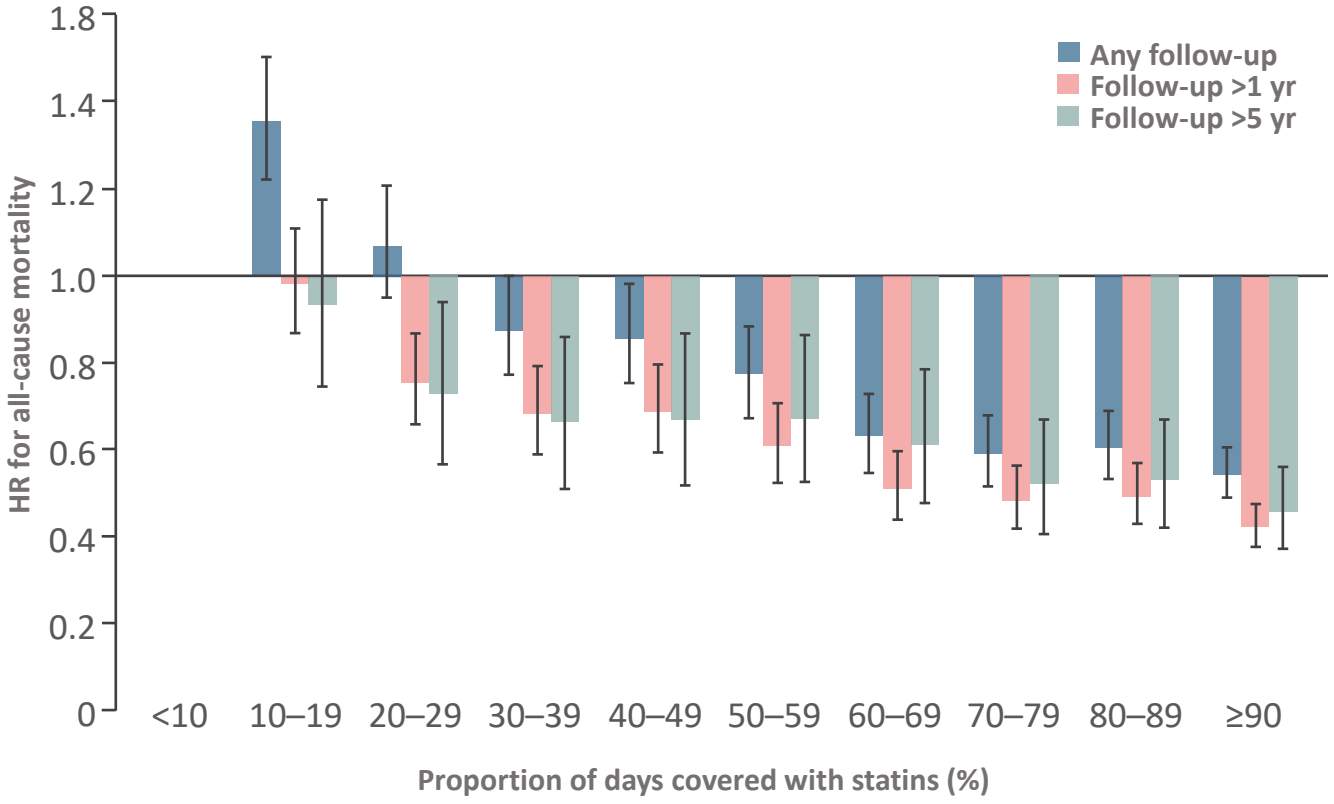
Per 1 mmol/L reduction in LDL-C




LDL-C, low-density lipoprotein cholesterol; SE, standard error.
Adapted from Baigent C et al. Lancet. 2005;366(9493):1267-1278.

# Persistent use of statin is associated with lower risk of all-cause mortality

- A total of 136,052 individuals for the primary prevention group were identified as being newly treated with statin drugs during the study period
- A PDC of ≥90% was associated with a 58% lower hazard of all cause mortality [HR of 0.42 (95% CI, 0.37–0.47)] in the primary prevention cohort relative to PDC of 10%




CI, confidence interval, HR, hazard ratio; PDC, proportion of days covered.
Shalev V et al. Arch Intern Med. 2009;169(3):260-268.

# Take-home messages so far…

LDL-C is well known to be causal for ASCVD and lowering LDL-C is associated with:

- ✓ atherosclerosis regression
- ✓ greater plaque stability
- ✓ reduced risk for ASCVD events

Timely lowering of the LDL-C burden is critical to minimize exposure to elevated levels of circulating LDL-C

Strategies that successfully decrease and maintain low levels of LDL-C are essential to reduce ASCVD risk

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

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

*Canadian Journal of Cardiology* 10.1016/j.cjca.2021.03.016

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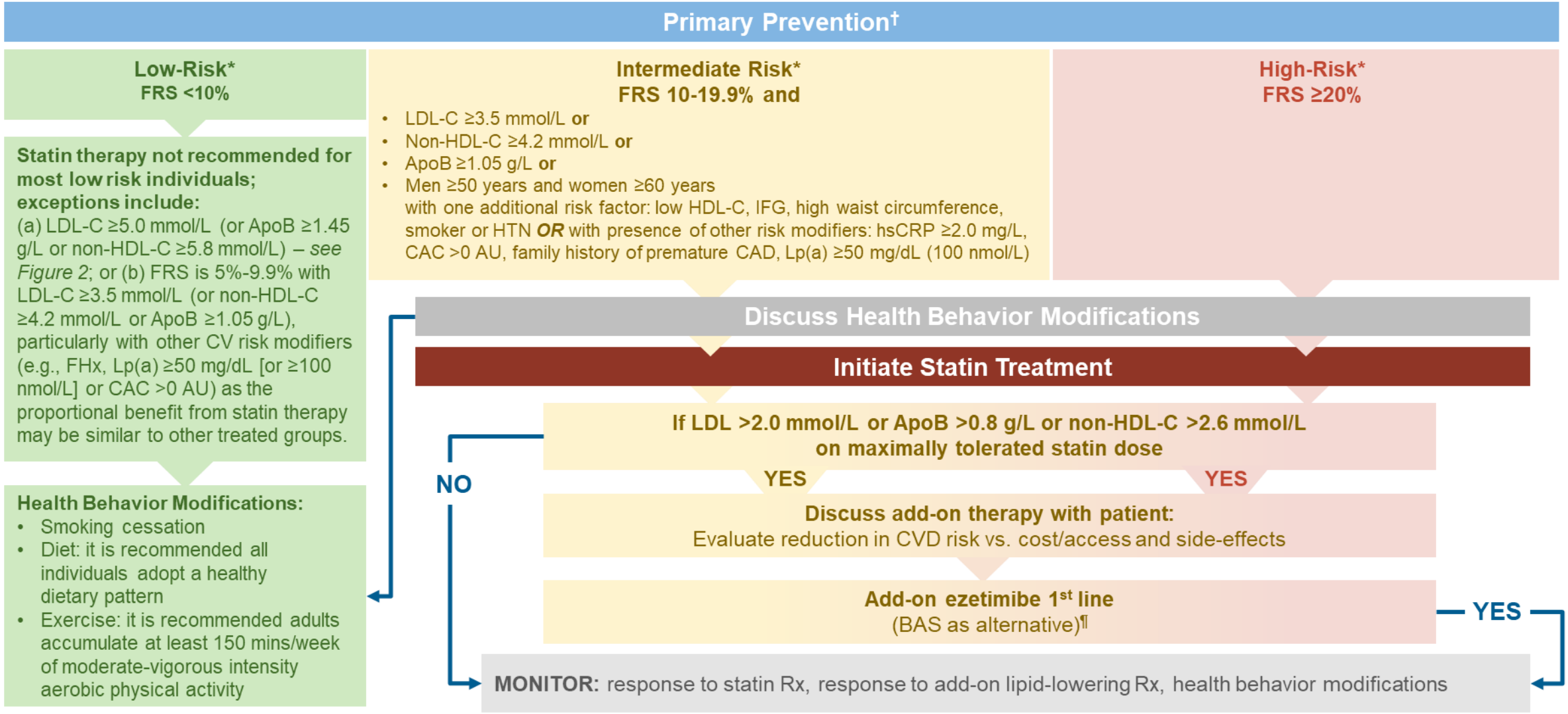
# Figure 1: Treatment Approach for Primary Prevention Patients (Without a Statin Indicated Condition)‡




‡Statin indicated conditions consists of all documented ASCVD conditions, as well as other high-risk primary prevention conditions in the absence of ASCVD, such as most patients with diabetes, those with chronic kidney disease and those with 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. From: https://doi.org/10.1016/j.cjca.2021.03.016, Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Copyright 2021 published by Elsevier Inc. on behalf of Canadian Cardiovascular Society. Reprinted with permission.

# Additional Treatment Recommendations for Primary Prevention Patients

## Health Behaviour Modifications*

Modifiable risk factors for MI in both sexes and all ages as per the INTERHEART[1] Study:

- *Traditional risk factors such as* abdominal lipids, hypertension, smoking, and diabetes

***AND***

- *Other risk factors such as* abdominal obesity, dietary patterns, alcohol consumption, physical activity, and psychological factors

## Other Considerations for Initiating Statin Therapy

Suggest statin initiation among intermediate-risk patients with several additional RFs (as studied in HOPE-3[2]), such as:

Men ≥ 50 or women ≥ 60 years of age with *one* additional RF, including

- low HDL-C,
- impaired fasting glucose,
- increased waist circumference,
- cigarette smoking, ***or***
- HTN

Presence of other risk modifiers in intermediate-risk individuals also favours the use of statins for the following

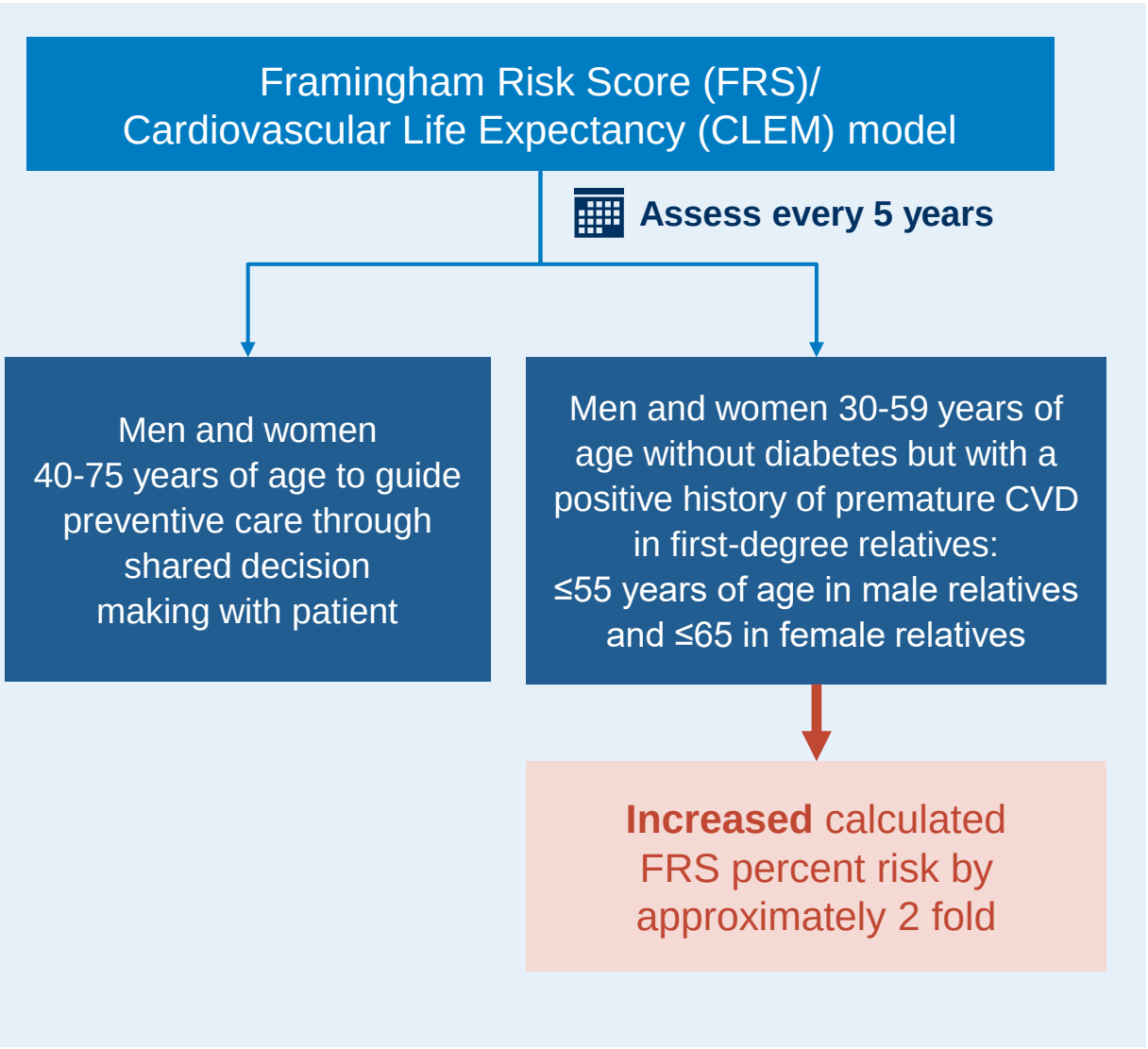
- hsCRP ≥2.0 mmol/L,
- family history of premature CAD,
- high Lp(a) ≥50 mg/dL (≥100 nmol/L), ***or***
- CAC >0

*For most low-risk subjects (FRS <10%), health behavior modification without pharmacotherapy is still recommended; however, the exceptions exist. Please refer to 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult for more detail.

1. Pare G, Caku A, McQueen M, Anand SS, Enas E, Clarke R, et al. Lipoprotein(a) Levels and the Risk of Myocardial Infarction Among 7 Ethnic Groups. Circulation. 2019;139(12):1472-82.
2. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016; 374:2021-2031.

Apo-B, apolipoprotein; CAC, coronary artery calcium; hsCRP, high-sensitivity C-reactive protein; FRS, Framingham risk score; HTN, hypertension; Lp(a), lipoprotein a; MI, myocardial infarction; non-HDL-c, non-high-density lipoprotein cholesterol; RF, risk factors. Content adapted from: Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. From: https://doi.org/10.1016/j.cjca.2021.03.016

# Screening Recommendations for Primary Prevention Patients




## Table 1: Who to screen for dyslipidemia in adults at risk*

**Men and 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 (any age) with any of the following conditions:**

- -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

**Note:** Lipid/lipoprotein screening in non-fasting state is recommended (except for individuals with known TGs >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.

*Adapted from the 2021 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. ACR, albumin-to-creatinine ratio; AS, ankylosing spondylitis; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematous; TG, triglycerides.
Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. From: https://doi.org/10.1016/j.cjca.2021.03.016

# Screening Recommendations for Primary Prevention Patients

## Table 2: How to screen for dyslipidemia in adults at risk*

**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)

| *Non-fasting* lipid testing is recommended in most adults for screening | *Fasting* lipid testing recommended if TGs >4.5 mmol/L |
|---|---|

Now preferable to follow **non-HDL-C** or **ApoB** levels over LDL-C when interpreting lipid results, particularly when TG is ≥1.5 mmol/L

*Adapted from the 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult.
‡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.
A1c, glycated hemoglobin; ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.
Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. From: https://doi.org/10.1016/j.cjca.2021.03.016

# 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[ǂ] associated with increased lifetime risk of developing:

- *CV risk factors*
  - HTN,
  - T2DM,
  - dyslipidemia (especially hypertriglyceridemia and low HDL-C),
  - metabolic syndrome, and
  - subclinical atherosclerosis
- *Overt ASCVD*

Preeclampsia increases RR of developing pre-menopausal ASCVD by 2-fold

## Recommendations:

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, screening with a complete lipid panel in the late postpartum period is recommended, 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).*

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).*

To assist with decisions about lipid-lowering pharmacotherapy in this patient population, recommend favouring CV age, over 10-year risk calculators *(Strong Recommendation; Low Quality Evidence).*

[ǂ]Pregnancy complications include: preeclampsia and related hypertensive disorders of pregnancy, gestational diabetes, placental abruption, preterm delivery, stillbirth, and delivery of a lowbirth weight infant.
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; RR, relative risk; T2DM, type 2 diabetes mellitus.
Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. From: https://doi.org/10.1016/j.cjca.2021.03.016

# PICO 2a: Is There Evidence To Promote Non-HDL-C Over ApoB or ApoB Over Non-HDL-C for Screening and Treatment Purposes?

*non-HDL-C and ApoB have been used as primary laboratory measurement for initiating statins when TGs > 1.5 mmol/L*

Rationale:

- When TGs > 1.5 mmol/L, some cholesterol in LDL particles is replaced by TGs, promoting more atherogenic small dense LDL particles production, therefore making LDL-C cholesterol amount unreliable
- Other particles (e.g. VLDL and Lp(a)) all accumulate in artery wall and contribute to atherogenesis

Decision:

- Estimation of total concentration of all atherogenic particles requires broader focus than measuring LDL-C
- Both non-HDL-C (indirectly) and ApoB (directly) provide a more accurate assessment

Non-HDL-C and ApoB appear to be superior to LDL-C in CV event risk prediction

*Lab Testing in Canada*[ǂ]

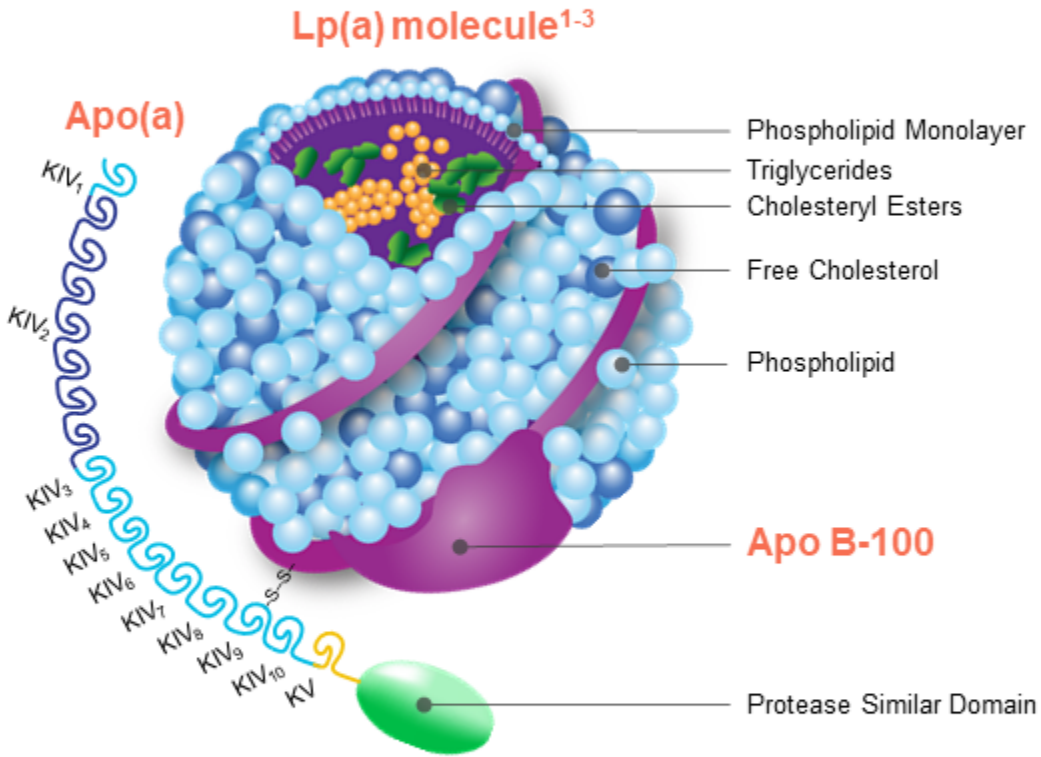
- *non-HDL-C is now routinely reported across Canada at no added cost*
- *ApoB is also available as an insured lab test in all provinces except Ontario*

## Recommendation

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).

[ǂ]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. ApoB, apolipoprotein B; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; TGs, triglycerides; VLDL, very low density lipoprotein. Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. From: https://doi.org/10.1016/j.cjca.2021.03.016

# Lp(a) is Atherogenic, Prothrombotic and Proinflammatory[1,2]




- Lp(a) is produced in the liver and has two main components joined by a covalent disulfide bond[1,2]
  - A lipid core moiety that is an LDL-like particle containing apolipoprotein B-100, which is proatherosclerotic[1,2]

    and
  - A single molecule of apolipoprotein(a)[1-3]

**Lp(a) differs from LDL in that Lp(a) contains a molecule of apo(a)[1,2]**

apo, apoprotein; KI, kringle type I; KII, kringle type II; KIII, kringle type III; KIV, kringle type IV; KV, kringle type V; Lp(a), lipoprotein (a).

1. Cai A, et al. *Dis Markers*. 2013;35(5):551-559. 2. Tsimikas S. *J Am Coll Cardiol*. 2017;69:692-711. 3. Jawi MM, et al. *J Lipids*.2020:1-26. doi.org/10.1155/2020/3491764.

# Lp(a) Concentrations Are Predominantly Controlled by Genetics

**Major influence**

Genetics predominantly control Lp(a) concentrations: (70% to >90%)[1]

**Lesser influence**

Some non-genetic factors may influence Lp(a) levels[1]

- Chronic kidney disease: ↑Lp(a) with ↓GFR (nephrotic syndrome)[1]
- Liver disease: ↓Lp(a)[1]
- Hypothyroidism: ↑Lp(a)[1]
- Menopausal women: ↑Lp(a)[2]
- Acute inflammatory processes (acute phase reactant): transient ↑Lp(a)[3]

**No effect**

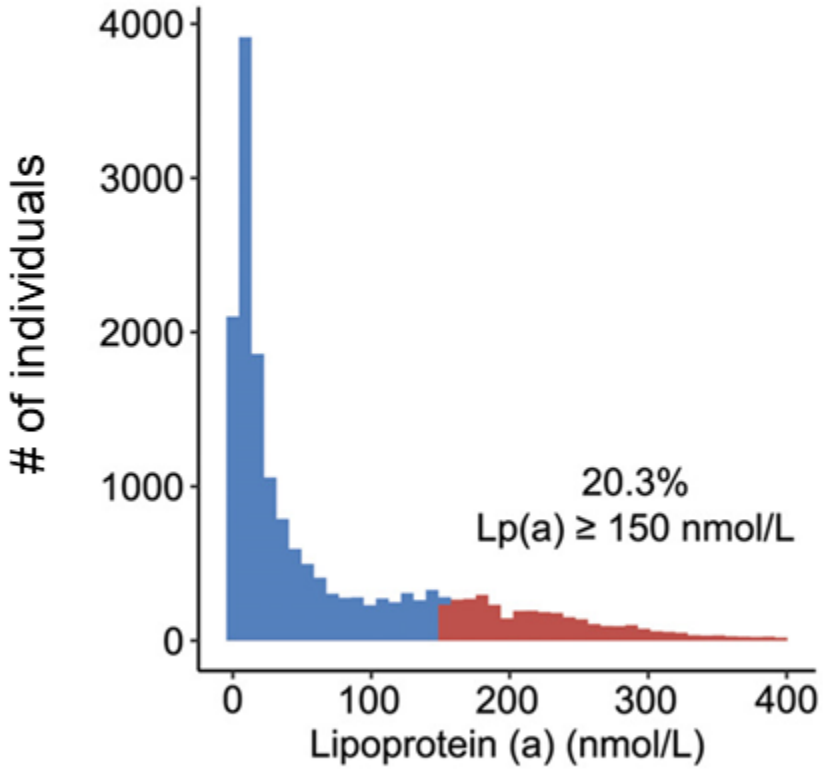
Lifestyle changes such as diet and physical exercise have **NO** significant impact on Lp(a) plasma concentrations[4]

GFR, glomerular filtration rate; Lp(a), lipoprotein(a).

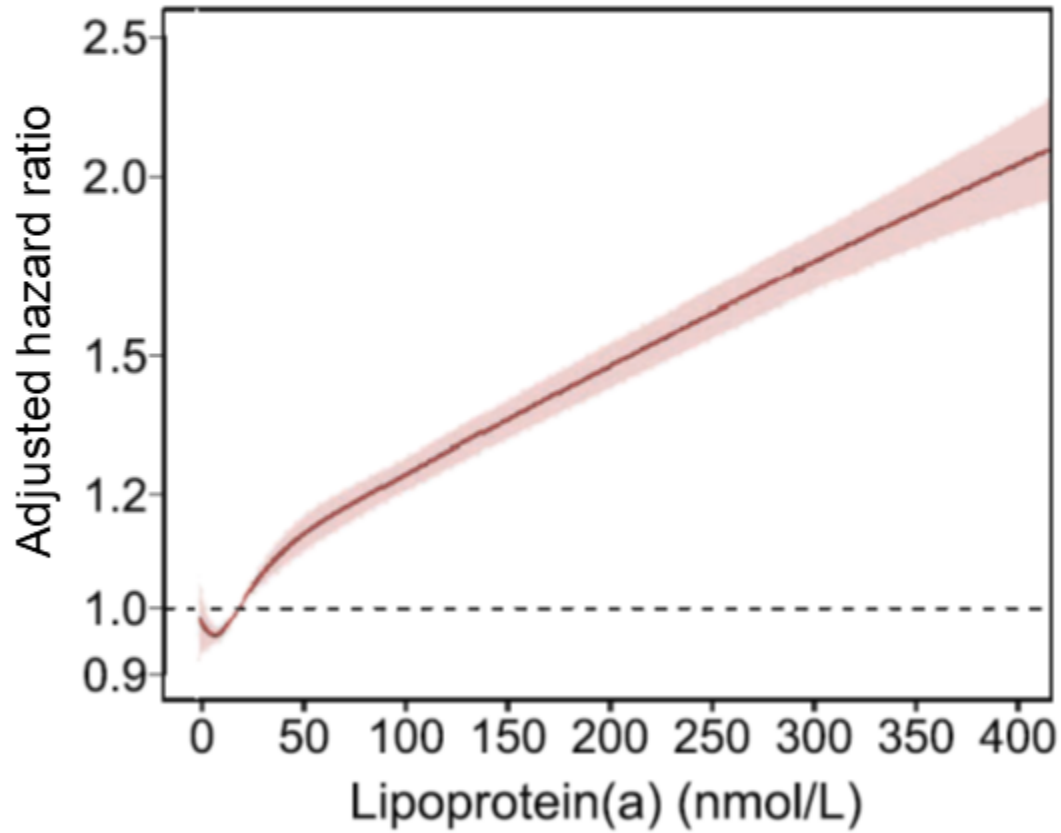
1. Cegla J, et al. *Atherosclerosis*. 2019;291:62-70. 2. Newman CB, et al. *J Clin Endocrinol Metab*. 2020;105:3613-3682.
3. Pirro M, et al. *Pharmacol Res*. 2017;119:178-187. 4. Wilson DP, et al. *J Clin Lipid*ology. 2019;63:374-392.

# Lp(a) and Coronary Heart Disease Risk

**Lp(a) distribution in individuals with established atherosclerotic cardiovascular disease**




**Lp(a) is associated with atherosclerotic cardiovascular disease risk independent of traditional risk factors**






Patel et al., *Arterioscler Thromb Vasc Biol* 2021;41:465-474.

# 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?

- Lp(a) is an LDL-like particle in which ApoB is covalently bound to apolipoprotein (a) molecule
- Plasma concentrations of Lp(a) *not* influenced by age, sex, fasting state, lifestyle factors, but are highly (>90%) heritable
- Individual values are generally stable throughout life, thus, repeat measures are *not* required for risk assessment

## Lp(a) and CVD

- Genetic variants uniquely regulating Lp(a) strongly associated with CHD risk, thereby suggesting association between Lp(a) and CVD

***FOURIER[1] and ODYSSEY OUTCOMES[2] Trials:***

- High Lp(a) levels associated with increased risk of recurrent CVD events irrespective of LDL-C

## Lp(a) and CHD/ASCVD Risk

- Risk of ASCVD increases with increasing Lp(a) levels >30 mg/dL in dose dependent fashion

***INTERHEART[3,4] Study:***

- Lp(a) concentrations >50 mg/dL associated with an increased risk of MI independent of established CVD RFs
- Higher Lp(a) levels particularly seen in South Asians and Latin Americans
- Extreme Lp(a) levels strongly associated with increased event rate similar to that seen for other genetic dyslipidemias (e.g. heterozygous FH)

## Key Points to Consider:

- Elevated Lp(a) appears to increase the risk of recurrent ASCVD in dose dependent manner
- Currently, there is no evidence from RCTs that specifically lowering Lp(a) leads to CV outcome reduction
- Commonly used agents (i.e. statins and ezetimibe) do not adequately lower Lp(a)
- PCSK9 inhibitors, niacin, and apheresis can lower Lp(a) levels, but relatively limited evidence currently exists for their use

### *Lab Testing in Canada[‡]*

- Lp(a) is not currently considered a treatment target. However, Lp(a) testing is available across Canada, and is currently an insured laboratory test in most provinces, except in Ontario and Manitoba.

1. O'Donoghue ML, Fazio S, Giugliano RP, et al. Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk. Circulation 2019;139(12):1483-92; 2. Bittner VA, Szarek M, Aylward PE, et al. Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome. JACC 2020;75(2):133-44; 3. Pare G, Caku A, McQueen M, Anand SS, Enas E, Clarke R, et al. Lipoprotein(a) Levels and the Risk of Myocardial Infarction Among 7 Ethnic Groups. Circulation. 2019;139(12):1472-82; 4. Enkhmaa B, Anuurad E, Berglund L. Lipoprotein (a): impact by ethnicity and environmental and medical conditions. J Lipid Res. 2016;57(7):1111-25.

ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CVD, cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low density lipoprotein cholesterol; Lp(a), lipoprotein a; RCTs, randomized controlled trials; RFs, risk factors.

Content adapted from: Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. From: https://doi.org/10.1016/j.cjca.2021.03.016

# PICO 2b: Recommendations for Measurement of Lp(a) To Improve Risk Stratification and Dyslipidemia Management In Patients With and Without Prior Cardiovascular Events

Measuring Lp(a) level **once** in a person's lifetime as a part of the initial lipid screening is recommended (Strong Recommendation; High Quality Evidence).

For all patients in the setting of primary prevention with a Lp(a) ≥50 mg/dL (or ≥100 nmol/L), earlier and more intensive health behaviour modification counselling and management of other ASCVD risk factors is recommended (Strong recommendation; Expert consensus).

ASCVD, atherosclerotic cardiovascular disease; Lp(a), lipprotein a.

Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult.

# New Areas of Focus in Secondary Prevention

The role of non-statin therapies to reduce ASCVD events

The most appropriate lipid/lipoprotein threshold for the intensification of therapy in the management of dyslipidemia

The lack of CV benefit of omega-3 fatty acids from dietary sources or other formulations/supplements

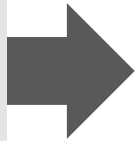
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular.

Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. From: https://doi.org/10.1016/j.cjca.2021.03.016

# PICO 4: In Secondary Prevention, What Is the Most Appropriate Lipid/Lipoprotein Threshold For the Intensification of Therapy?

## Introducing Treatment Thresholds

Recommendation of *thresholds for intensification* of lipid therapy in secondary prevention



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

Most patients anticipated to achieve **low to very low** LDL-C levels using this threshold

## Recommendations

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

ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. From: https://doi.org/10.1016/j.cjca.2021.03.016

# Rationale for a Threshold vs. a Target

To date, no clear target to which LDL-C or non HDL-C or ApoB levels should be lowered is identified in RCTs

Trials have 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

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

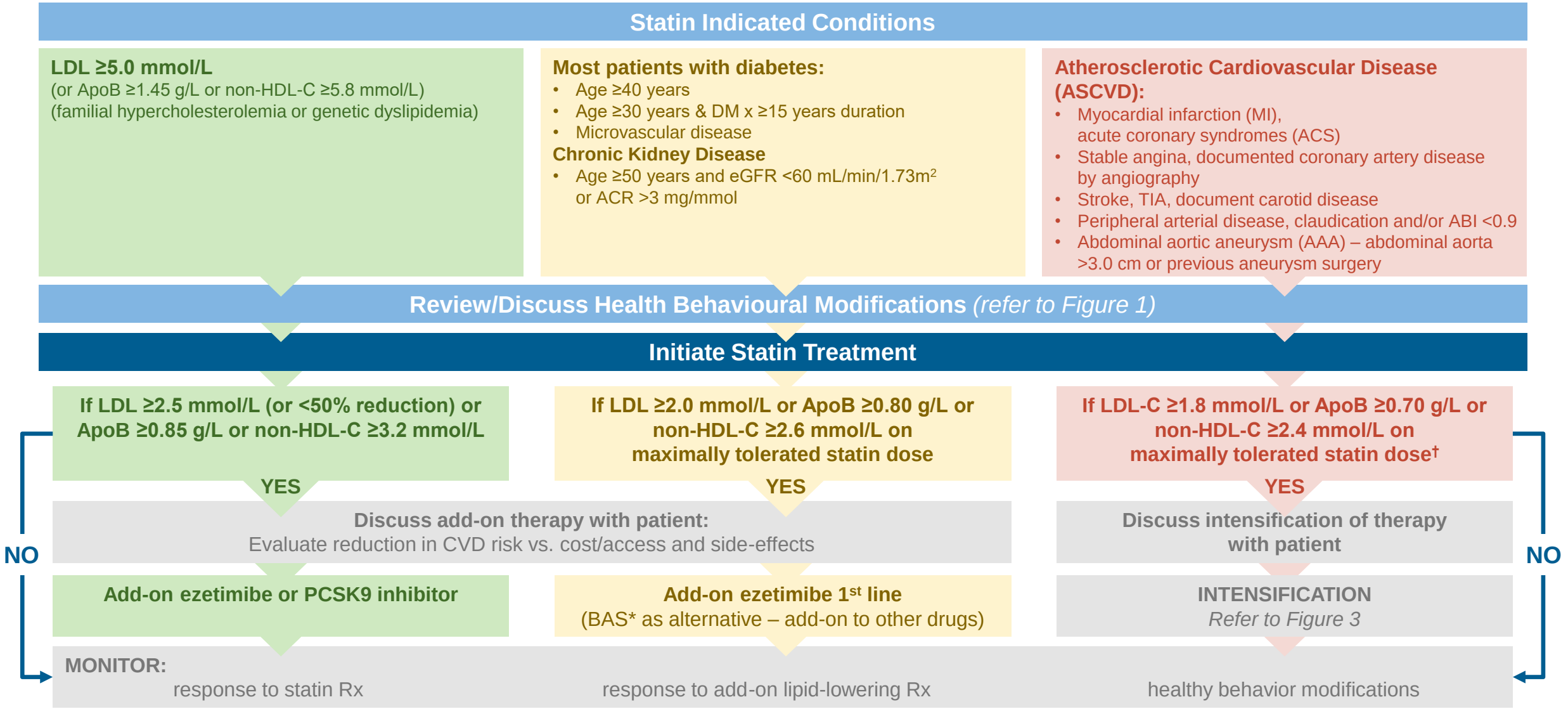
Most recent large RCTs have used an LDL-C threshold of 1.8 mmol/L for intensification of lipid-lowering therapy with non-statin drugs in secondary ASCVD prevention patients on a maximally tolerated statin dose

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

ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RCTs, randomized control trials.

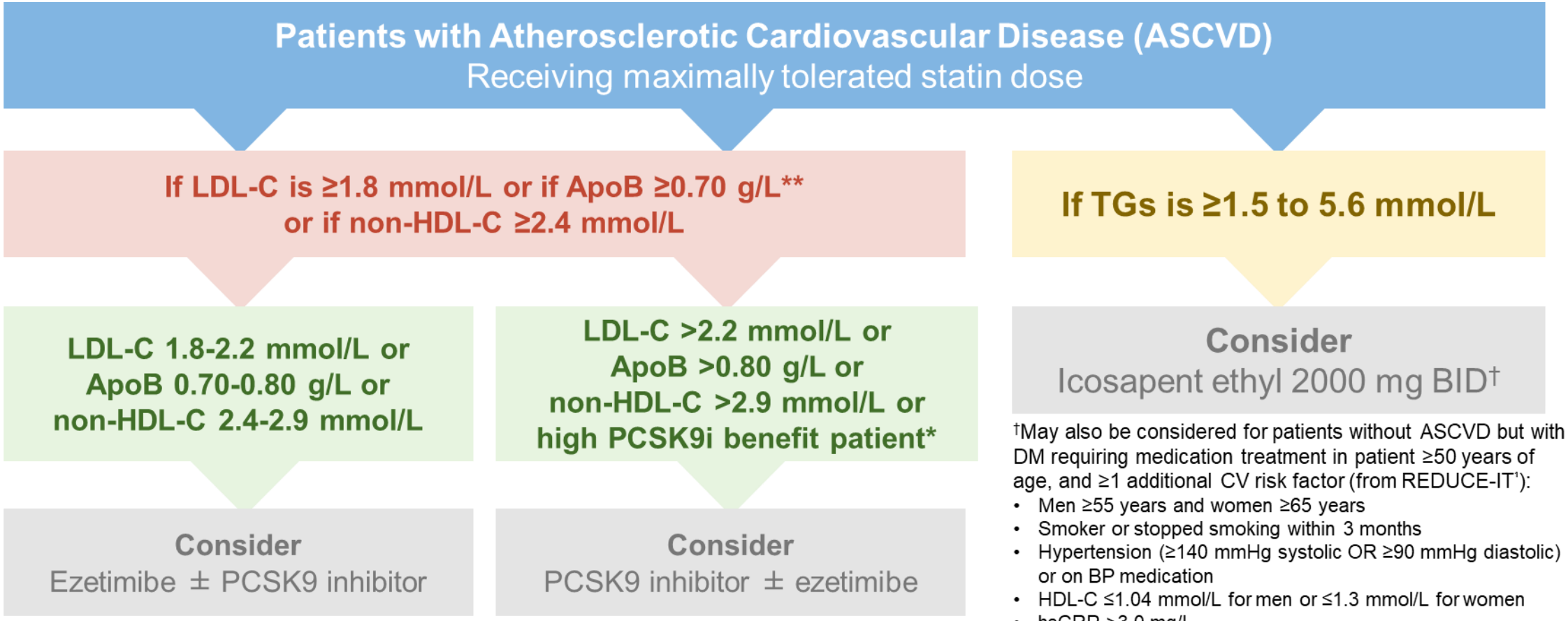
Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. From: https://doi.org/10.1016/j.cjca.2021.03.016

# Figure 2: Treatment Approach for Patients with a Statin Indicated Condition




ABI, ankle-brachial index; ACR, albumin-to-creatinine; ApoB, apolipoprotein B; BAS, bile acid sequestrants; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TIA, transient ischemic attack. †LDL-C threshold selected on the basis of the PCSK9-inhibitor clinical trials lipid inclusion parameters 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. From: https://doi.org/10.1016/j.cjca.2021.03.016. Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Copyright 2021 published by Elsevier Inc. on behalf of Canadian Cardiovascular Society. Reprinted with permission.

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



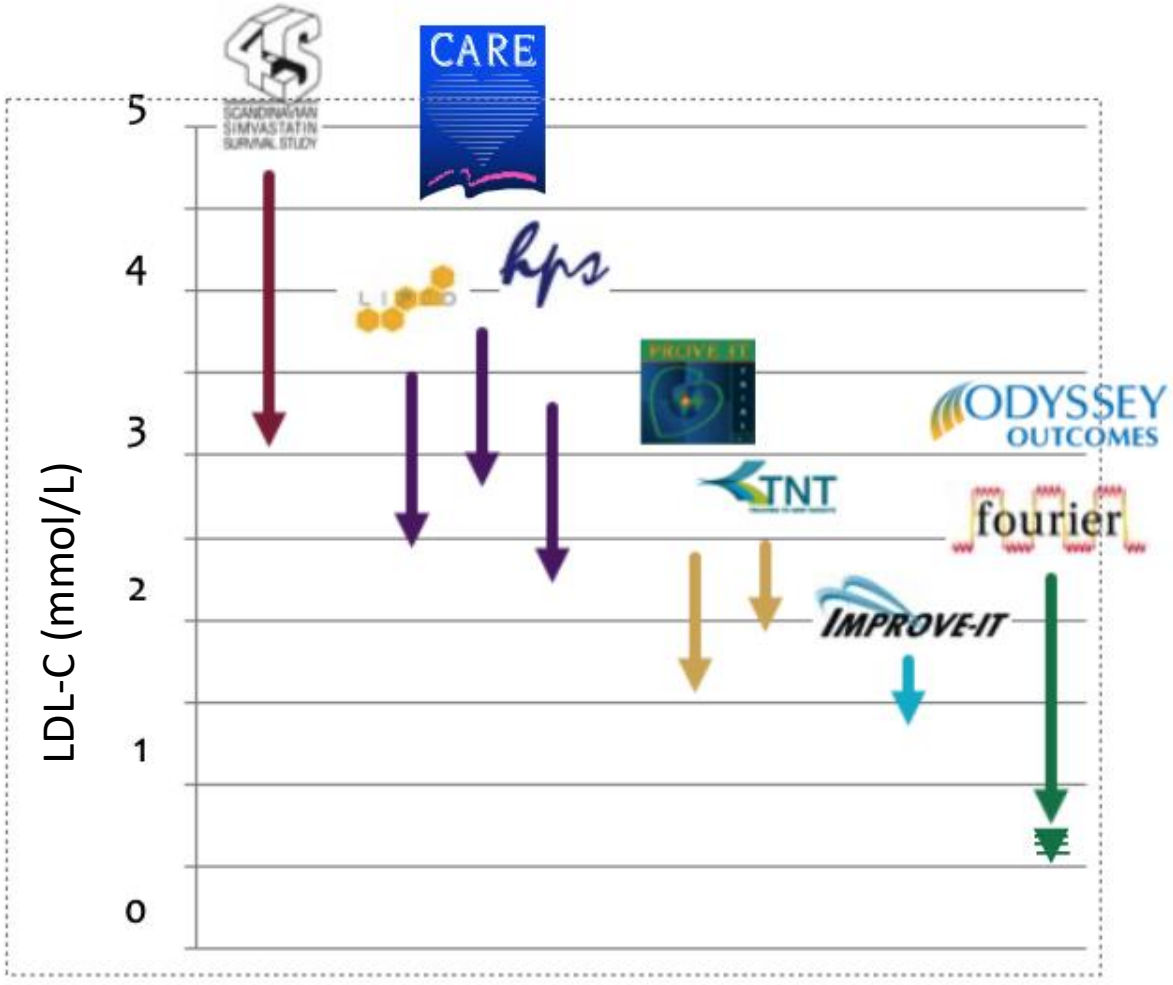

†May also be considered for patients without ASCVD but with DM requiring medication treatment in patient ≥50 years of age, and ≥1 additional CV risk factor (from REDUCE-IT[1]):

- Men ≥55 years and women ≥65 years
- 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

*Patients shown to derive largest benefit from 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.

1. Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, Pedersen TR, LaRosa JC, Waters DD, DeMicco DA, Simes RJ, Keech AC, Colquhoun D, Hitman GA, Betteridge DJ, Clearfield MB, Downs JR, Colhoun HM, Gotto AM Jr, Ridker PM, Grundy SM, Kastelein JJ. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol 2014; 64:485-494. ABI, ankle-brachial index; ApoB, apolipoprotein B; BID, twice daily; BP, blood pressure; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TGs, triglycerides.

# A quarter of a century of treating LDL-C




**High is BAD**

**Average is NOT GOOD**

**Lower is BETTER**

**Even lower is EVEN BETTER**

**Lowest is BEST**

**Using efficacious and SAFE interventions!**



With permission from M S Sabatine

# Statins are a cornerstone of residual risk management in ASCVD but…

- ✓ In Canada, **only 35–50% of patients with ASCVD achieve recommended LDL-C targets**[1-3] despite the established benefit of LDL-C reduction on CV outcomes
- ✓ **Poor statin adherence** has been reported in **up to 50% of patients**[4–5]
- ✓ **Patients frequently discontinue statin therapy** without medical advice because of perceived side effects and consequently increase their risk for CV events

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol.

1. Underberg J et al. Postgrad Med. 2022;134(8):752-762. 2. Goodman SG et al. Can J Cardiol. 2010;26(9):e330-e335. 3. Chen G et al. Can J Cardiol. 2019;35(7):884-891. 4. Gislason GH et al. Eur Heart J. 2006;27(10):1153-5118. 5. Blackburn DF et al. Can J Cardiol. 2005;21(6):485-488.

# Lowering LDL-C: Challenges with very high-risk patients

**<50% = Patients at high risk of recurrent events who achieve optimal LDL-C reduction with statin therapy[1–2]**

- ✓ There is wide heterogeneity in responses and tolerances to therapy
- ✓ Some patients will not attain sufficient reduction of LDL-C levels[1–2]
- ✓ Patients at very high risk of recurrent events are the ones for whom it is most challenging to achieve sufficient LDL-C reduction[1–2]

LDL-C, low-density lipoprotein cholesterol.

1. Kearney PM et al. Lancet. 2008;371(9607):117-125. 2. Foody JM et al. J Clin Lipidol. 2010;4(2):126-132.
Pearson GJ et al. Can J Cardiol. 2021 Mar 26;S0828-282X(21)00165-3. doi: 10.1016/j.cjca.2021.03.016.

# Statin discontinuation: A continuing growing concern[1-4]

- ✓ **Statins are generally well tolerated** and very effective in the prevention and treatment of CVD, regardless of LDL-C levels; **however, they have been associated with various adverse events** (e.g., myalgia, diabetes, etc.)
- ✓ **Patients frequently discontinue statin therapy** without medical advice because of perceived side effects, leaving them at high risk for CV events
- ✓ About **10–20%** of statin-treated patients **have "statin intolerant" side effects**
- ✓ Most (>90%) reports of muscle symptoms by participants that allocated these symptoms to statin therapy were not due to the statin[5]

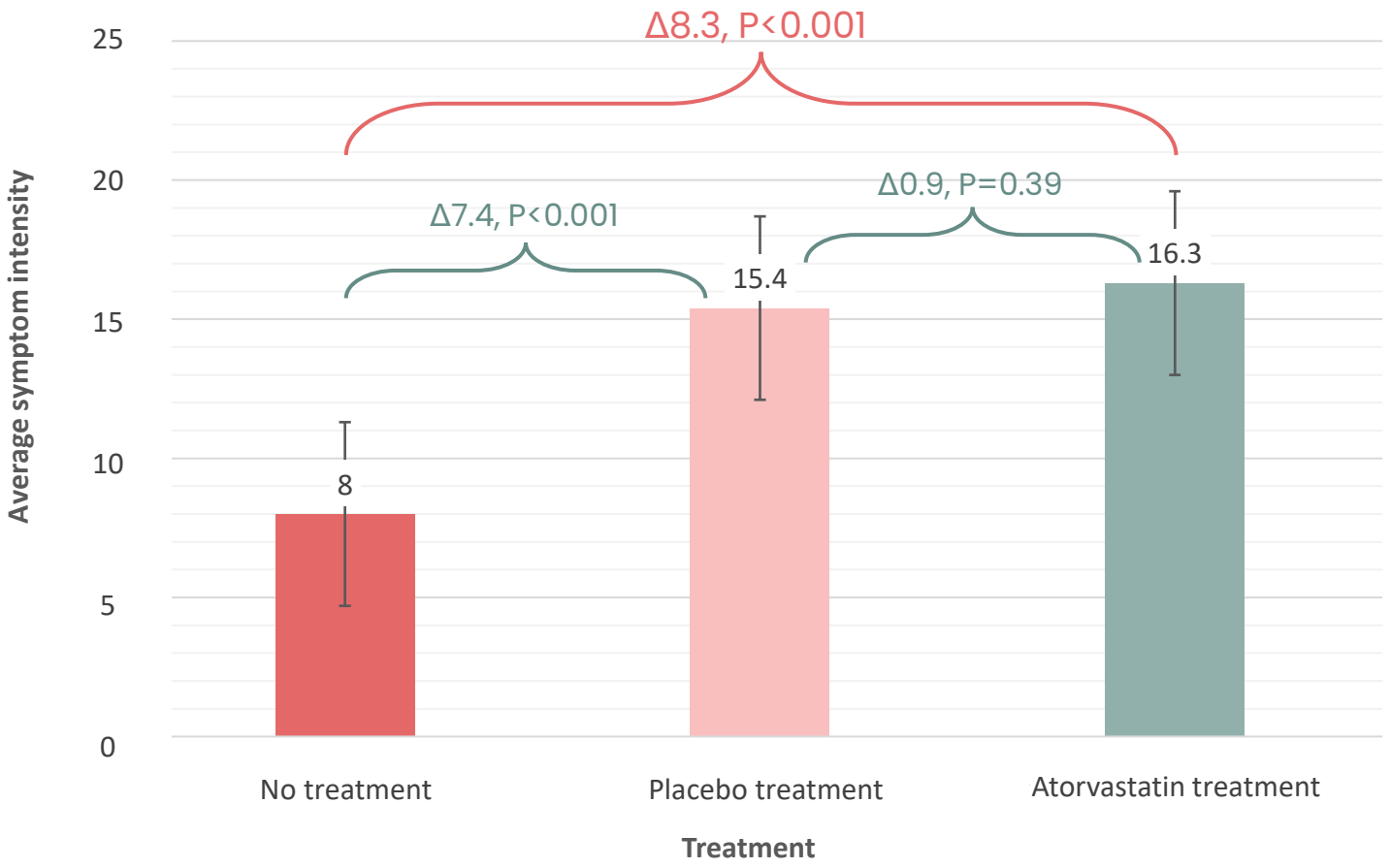
**Statin discontinuation rates remain high, even among patients with CHD (over 50% after 1 year)**

CHD: coronary heart disease, CV, cardiovascular, CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

1. Mancini GBJ et al. Can J Cardiol. 2011;27(5):635-662; 2. Banach M et al. J Cachexia Sarcopenia Muscle. 2016;7(4):396-399. 3. Jackevicius CA et al. JAMA. 2002;288(4):462-467. 4. Evans CD et al. J Manag Care Pharm . 2009;15(6):476-84. 5. Cholesterol Treatment Trialists' Collaboration. Lancet. 2022;400(10355):832-845.

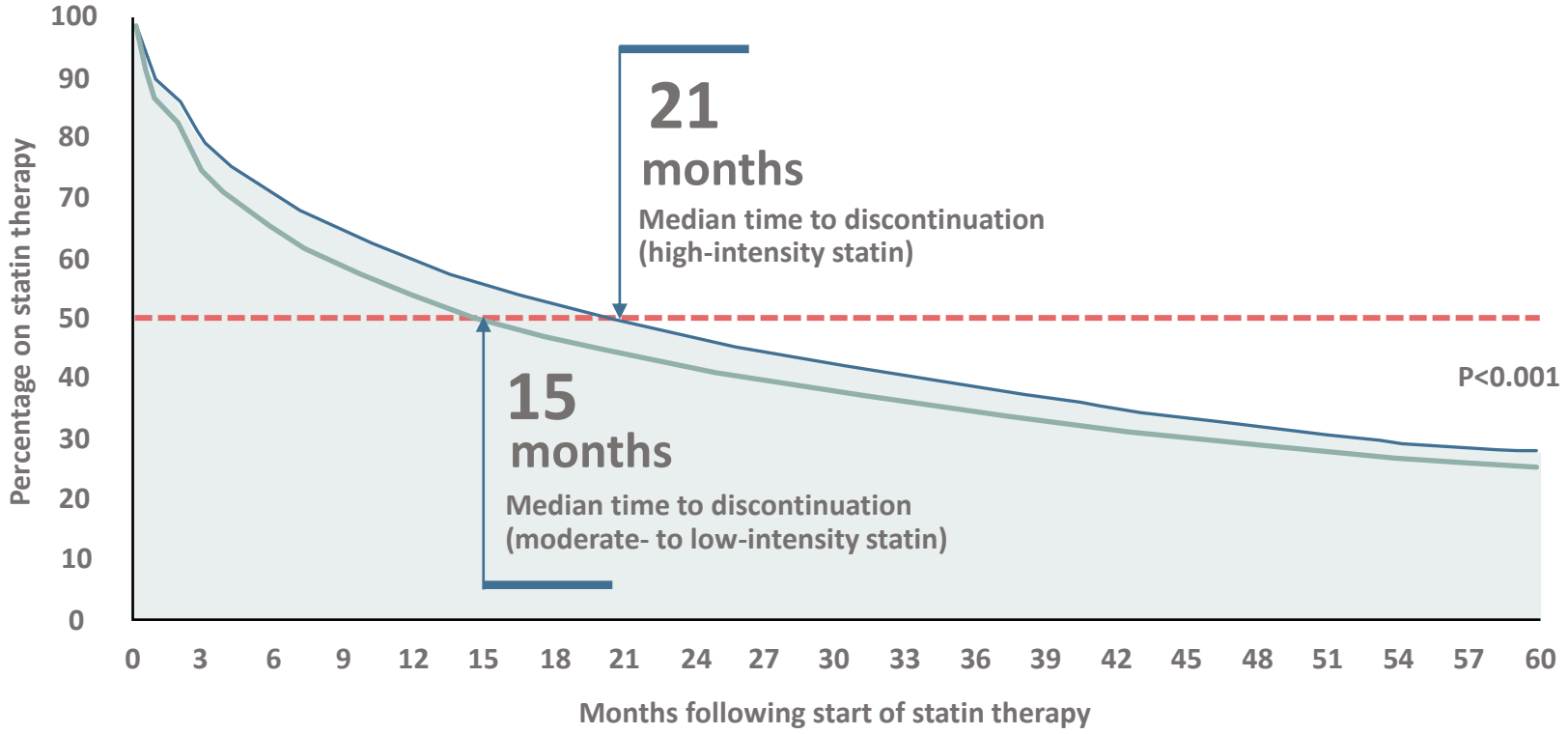
# SAMSON: Side effect symptom intensity difference between placebo and statin treatment

**Side effect symptom intensity is not significantly different between statin treatment and placebo treatment**




Wood FA. N Engl J Med. 2020;383(22):2182-2184.

# In USA, among insured individuals ≥65 years of age, 53% of patients discontinued their statin within 2 years[1]




Perceived side effects are the leading cause of statin discontinuation[2]

According to patient-reported reasons for declining or discontinuing statin therapy (from the PALM Registry)

1. Adapted from Lin I et al. J Manag Care Spec Pharm. 2016;22(6):685-698.
2. Adapted from Bradley CK et al. J Am Heart Assoc. 2019;8:e011765.

# PICO 5: 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

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)[1] trial showed that Ezetimibe 10 mg when added to statin therapy caused modest reduction in CV events in patients with an ACS within the preceding 10 days

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 needed to treat of 50 over 7 years

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

Subsequently, the Heart Institute of Japan Proper Level of Lipid Lowering with Pitavastatin and Ezetimibe in Acute Coronary Syndrome (HIJ-PROSPER)[2] 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 the two groups (32.8 vs. 36.9%, HR 0.89, 95% CI 0.76-1.04)

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

1. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015; 372:2387-97; 2. Hagiwara N, Kawada-Watanabe E, Koyanagi R, et al. Low-density lipoprotein cholesterol targeting with pitavastatin + ezetimibe for patients with acute coronary syndrome and dyslipidaemia: the HIJ-PROPER study, a prospective, open-label, randomized trial. Eur Heart J 2017; 38:2264-75.
Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. From: https://doi.org/10.1016/j.cjca.2021.03.016

# PICO 5: PCSK9 inhibitors - Evolocumab

Inhibitors of PCSK9 are recently available monoclonal antibodies that lower LDL-C between 50-70% when added to statin therapy or as monotherapy. Alirocumab and Evolocumab currently 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[1]) trial

27,564 patients with clinical ASCVD and additional CVD risk factors with LDL-C ≥ 1.8 mmol/L despite maximally tolerated statin therapy

↓

Evolocumab (140 mg subcutaneously (SC) every 2 weeks or 420 mg SC monthly) or placebo

↓

Baseline LDL-C was 2.4 mmol/L, which after 48 weeks was reduced to a median of 0.8mmol/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).

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; FH, familial hypercholesterolemia; MI, myocardial infarction; LDL-C, low density lipoprotein cholesterol.

1. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017; 376:1713-22; Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. From: https://doi.org/10.1016/j.cjca.2021.03.016

# PICO 5: PCSK9 inhibitors - Alirocumab

The Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY OUTCOMES[1]) trial evaluated alirocumab in 18,924 patients with a recent (1-12 months) ACS with an LDL-C ≥ 1.8 mmol/L despite maximally tolerated statin therapy

↓ Randomized

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).

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; LDL-C, low density lipoprotein cholesterol; LDL-C, low-density proprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction.

1. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018; 379:2097-107.
Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. From: https://doi.org/10.1016/j.cjca.2021.03.016

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

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

# What is Icosapent Ethyl (IPE)?

## A Novel Chemical Entity for the Prevention of Cardiovascular Events

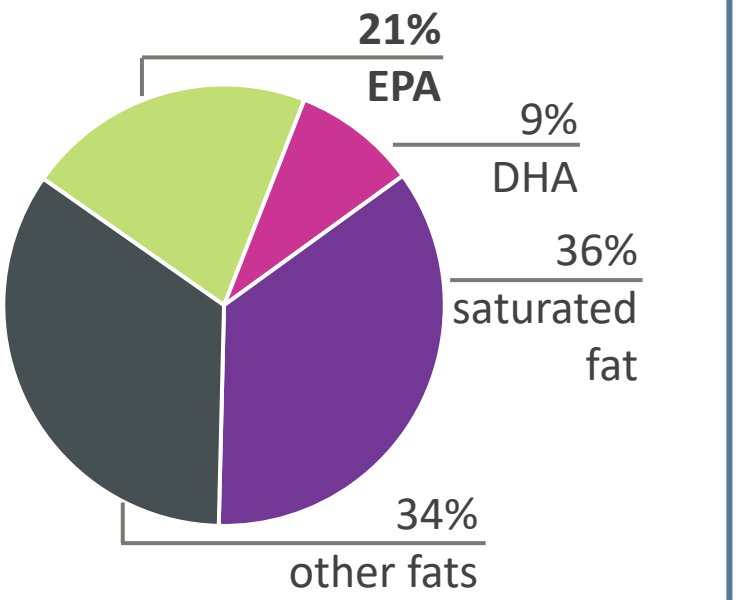
| | |
|---|---|
| **Commercial fish oils** | Consist of mixtures of omega-3 and/or omega-6 fatty acids in variable concentrations and purity |
| **Omega-3** | Comprises various fatty acids, including DHA and EPA |
| **EPA** | Eicosapentaenoic acid |
| **IPE** | **Icosapent ethyl**: A novel chemical entity and prescription drug used in the REDUCE-IT trial |

DHA=docosahexaenoic acid.

Ganda OP et al. *J Am Coll Cardiol*. 2018;72:330-343.

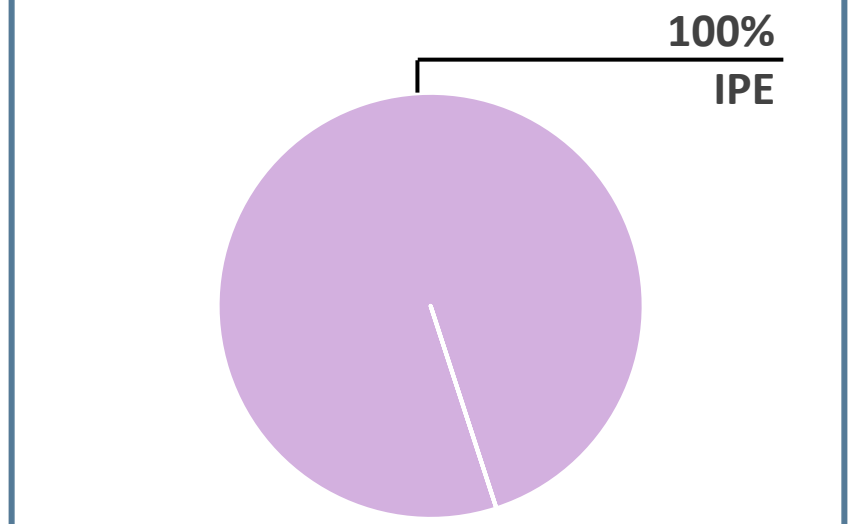
# Icosapent Ethyl (IPE) vs. Omega-3 Mixture Supplements

## Common fish oil (mixtures of omega-3 fatty acids)




VS.

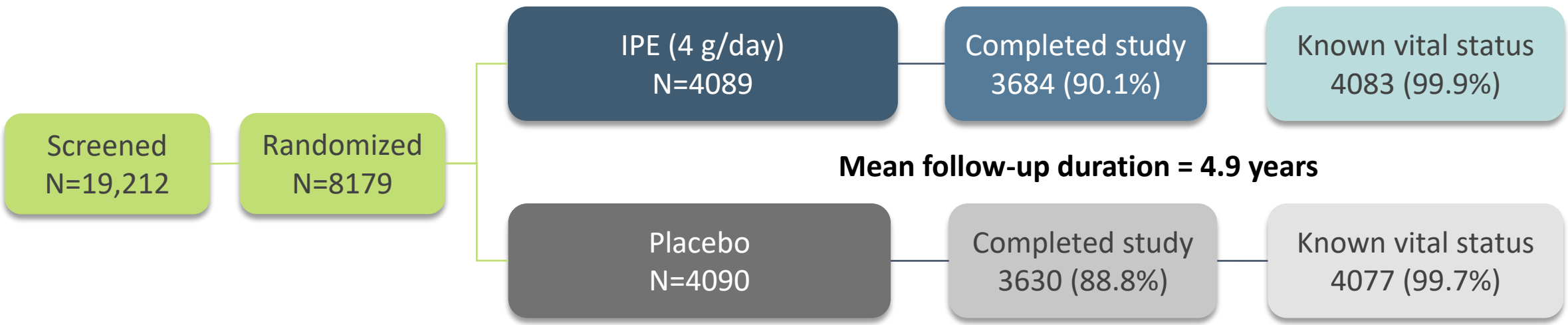
## Icosapent ethyl (IPE)




DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid.

Mason RP, Sherratt SCR. *Biochem Biophys Res Commun*. 2017;483:425-429. Hilleman DE et al. *Adv Ther*. 2020;37:656-670. Amarin – Data on File.

# REDUCE-IT: Multicentre, Randomized, Double-Blinded, Event-Driven, Placebo-Controlled Trial




- **Primary efficacy endpoints** (**5-point MACE**): composite of CV death, MI, stroke, coronary revascularization, unstable angina requiring hospitalization
- **Secondary efficacy endpoint** (**3-point MACE**): composite of CV death, MI, stroke

CV=cardiovascular; IPE=icosapent ethyl; MACE=major adverse cardiovascular event; MI=myocardial infarction.
Bhatt DL et al. *N Engl J Med.* 2019; 380:11-22

# Conclusion: Icosapent Ethyl Significantly Reduced 5-Point MACE by 25%; NNT 21

**Primary Endpoint**
5-Point MACE[a]

**25% RRR**

**NNT = 21**
**ARR = 4.8%**

**HR = 0.75**
**(95% CI, 0.68-0.83)**
***P* = 0.00000001**

**Key Secondary Endpoint**
3-Point MACE[b]

**26% RRR**

**NNT = 28**
**ARR = 3.6%**

**HR = 0.74**
**(95% CI, 0.65-0.83)**
***P* = 0.0000006**

**Individual Components of 3-Point MACE**

**MI Fatal/Nonfatal**

**31% RRR**

**ARR = 2.6%**

**HR = 0.69**
**(95% CI, 0.58-0.81)**
***P* < 0.001**

**Stroke Fatal/Nonfatal**

**28% RRR**

**ARR = 0.9%**

**HR = 0.72**
**(95% CI, 0.55-0.93)**
***P* = 0.01**

**CV Death**

**20% RRR**

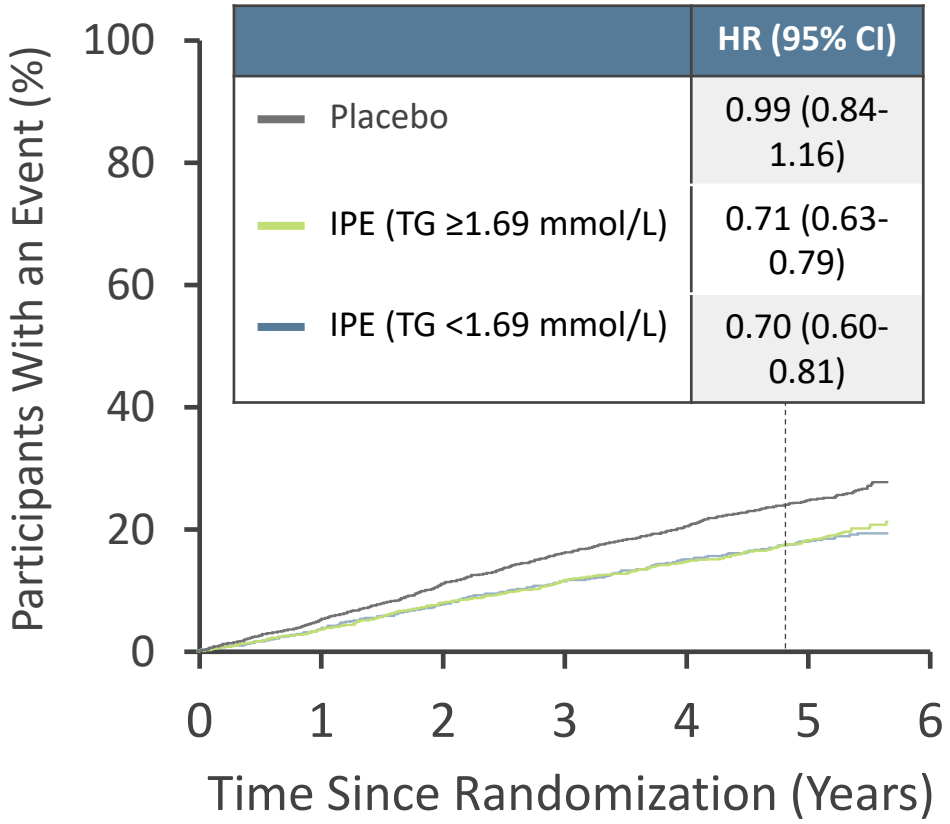
**ARR = 0.9%**

**HR = 0.80**
**(95% CI, 0.66-0.98)**
***P* = 0.03**

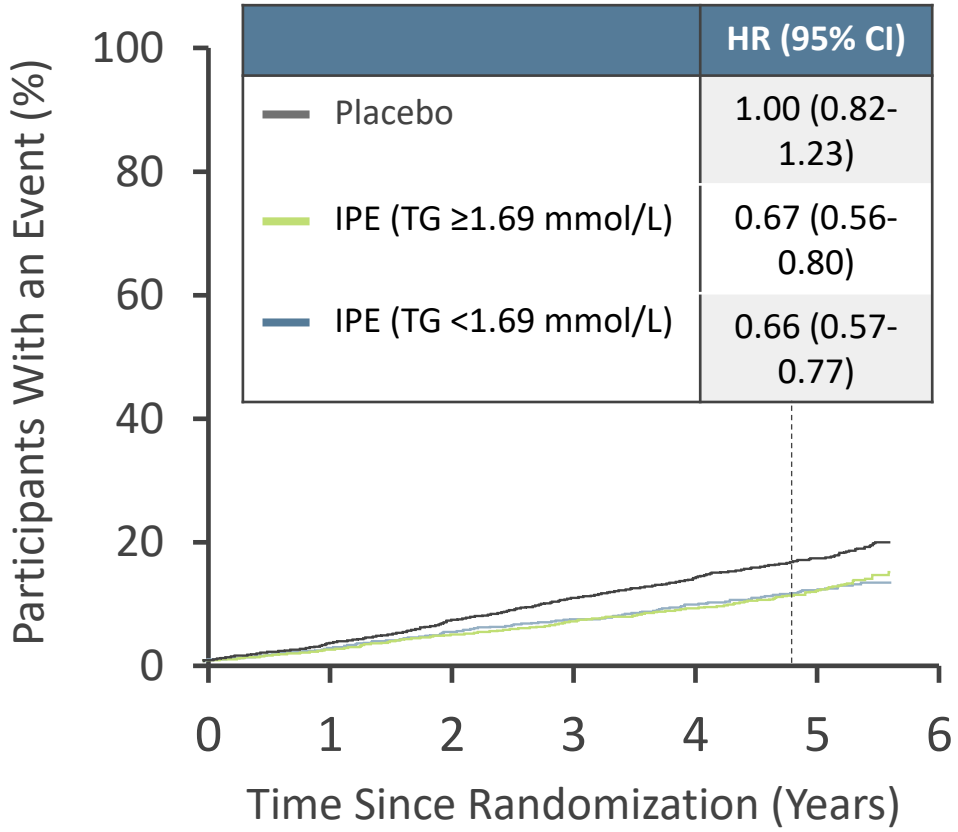
[a] Nonfatal MI, nonfatal stroke, CV death, coronary revascularization, or UA requiring hospitalization. [b] Nonfatal MI, nonfatal stroke, or CV death.
CV=cardiovascular; MACE=major adverse cardiovascular event; MI=myocardial infarction; NNT=number needed to treat; RRR=relative risk reduction; UA=unstable angina.
Bhatt DL et al. *N Engl J Med*. 2019;380:11-22.

# REDUCE-IT: Primary Endpoint by Achieved TG Level at 1 Year

## Primary Endpoint




## Key Secondary Endpoint




Adapted from Bhatt DL et al. *N Engl J Med*. 2019;380:11-22.

# Differences Between Common Fish Oil and Icosapent Ethyl (IPE)

## Common Fish Oil
(Mixtures of omega-3 polyunsaturated fatty acids)


## IPE

### Most fish oil supplements contain DHA
- DHA is an omega-3, which can raise LDL-C

### No demonstrated CV benefit in clinical trials

### Daily dose
- May take up to 10-40 capsules a day to equal the EPA in a daily dose of pure IPE, with an equivalent increase of DHA

### Reported to have fishy taste
- May cause fish-smelling burps

### Stable IPE
- Not shown to raise LDL-C

### Health Canada–approved
- To reduce the risk of ischemic CV events in statin-treated patient with elevated TGs

### Daily dose
- 4 g/day (2 x 1 g capsules BID)

### No reported fishy taste
- Unlikely to have fishy taste or fishy burps taking 4 g/day of pure IPE in a clinical trial

BID=twice daily; CV=cardiovascular; DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid; IPE=icosapent ethyl; LDL-C=low-density lipoprotein cholesterol; TG=triglyceride.

Bhatt DL et al. *N Engl J Med*. 2019;380:11-22. Chang CH et al. *Prostaglandins Leukot Essent Fatty Acids*. 2018;129:1-12. Ganda OP et al. *J Am Coll Cardiol*. 2018;72:330-343. Healthline website: https://www.healthline.com/health-news/should-you-be-taking-prescription-strength-fish-oil. Last Accessed January 17, 2020. Vascepa (icosapent ethyl) Product Monograph. HLS Therapeutics. December 30, 2019. Mason RP, Sherratt SCR. *Biochem Biophys Res Commun*. 2017;483:425-429.

# Health Canada approved: Inclisiran indications

## Primary hypercholesterolemia:

- Inclisiran (Leqvio®) is indicated as an adjunct to lifestyle changes, including diet, to further reduce LDL-C levels in adults with the following conditions who are on maximally tolerated dose of a statin, with or without other LDL-C–lowering therapies:
  - ✓ Heterozygous familial hypercholesterolemia (HeFH)
  - ✓ Non-familial hypercholesterolemia with ASCVD
- The effect of inclisiran (Leqvio®) on CV morbidity and mortality has not yet been determined
- Inclisiran has not been approved for pediatric patients
- No overall differences in safety or efficacy were observed between patients aged ≥65 years and younger patients

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; LDL-C: low-density lipoprotein cholesterol.

Inclisiran product monograph. 2021. Novartis Canada.

# Understanding how inclisiran interacts with mRNA: A refresher on protein synthesis

During protein synthesis, DNA is transcribed and then mRNA is translated into protein

## Transcription

In the nucleus, the **DNA** genetic code is transcribed into an mRNA transcript that can later be decoded for protein synthesis

**mRNA**

## Translation

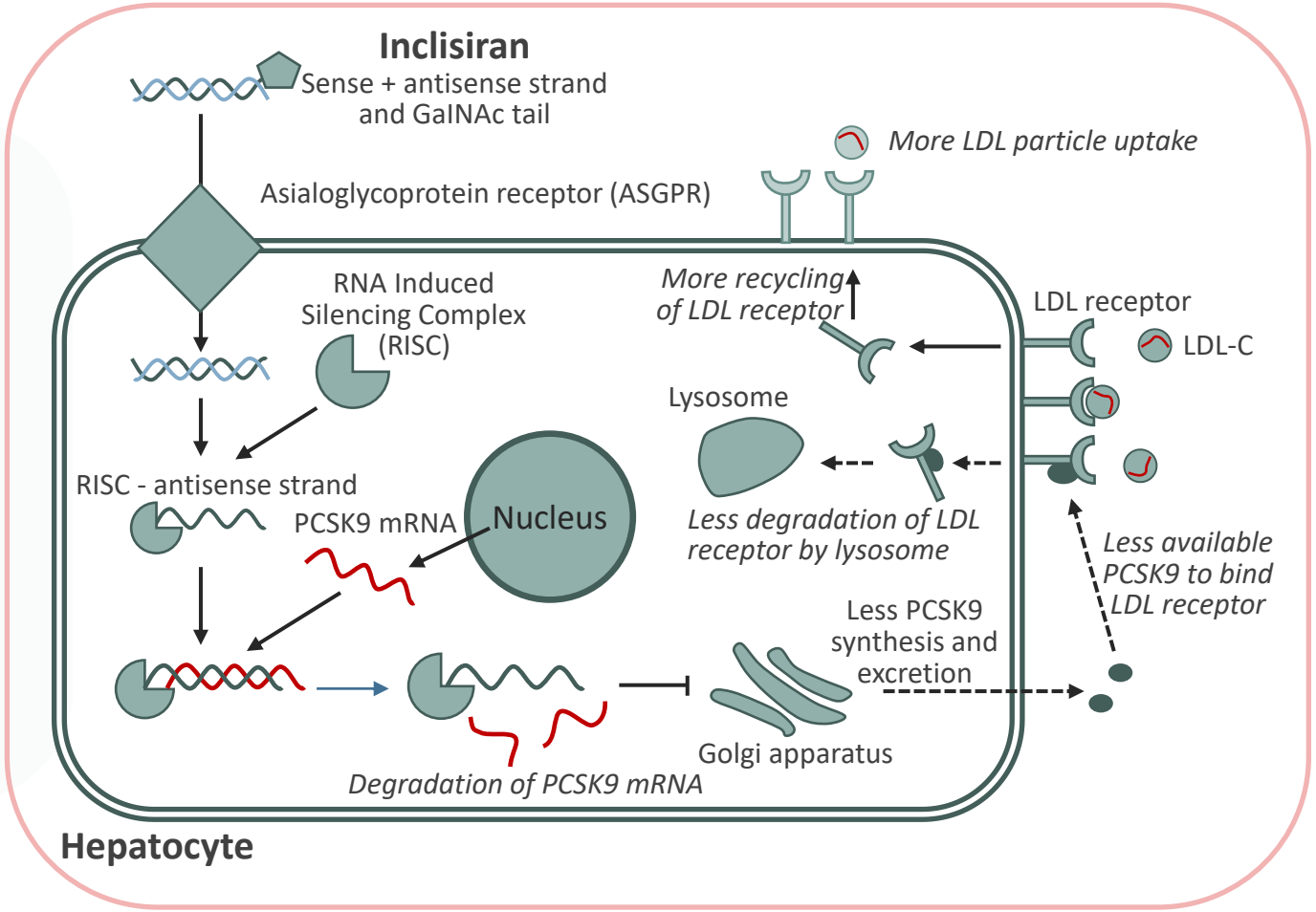
In the cytoplasm, the mRNA genetic code is translated into **protein** by ribosomes

DNA, deoxyribonucleic acid; mRNA, messenger RNA; RNA, ribonucleic acid.

Clancy S et al. Nature Education. 2008;1(1):101.

# Mechanism of action of inclisiran: prevents production of PCSK9 in the liver

- Key to safety is GalNAc conjugation
- Inclisiran binds to ASGPR conferring liver specificity
- Inclisiran plasma levels are undetectable within 48 hours




ASCVD, atherosclerotic cardiovascular disease; GalNAc, N-Acetylgalactosamine; LDL-C, low-density lipoprotein cholesterol; LDLR: low-density lipoprotein receptor; mRNA: messenger ribonucleic acid; PCSK9, proprotein convertase subtilisin/kexin type 9; RNA: ribonucleic acid; RISC: RNA-induced silencing complex.
Adapted from Nordestgaard BG et al. Nat Rev Cardiol. 2018;15(5):261-272.

# Factors explaining the sustained duration of effect of inclisiran: ie given every 6 months

Chemical modifications **increase the stability** of inclisiran by decreasing its susceptibility to degradation from exonucleases and endonucleases[1]

Inclisiran is **slowly released** from the hepatic endosomes into the cytoplasm[1]

Formation of the inclisiran-RISC complex protects inclisiran and **enhances its durability**[1]

RNA undergoes catalytic destruction: a single siRNA (inclisiran)-bound RISC complex can **cleave many mRNA transcripts**[2]

**Inclisiran's chemical modifications and mechanism of action enable it to provide effective LDL-C lowering that is sustained over the course of the extended dosing interval**

mRNA, messenger RNA; LDL-C, low-density lipoprotein cholesterol; RISC, RNA-induced silencing complex; RNA, ribonucleic acid; siRNA, small interfering RNA;

1. Fitzgerald K et al. N Engl J Med. 2017;376(1):41-51. 2. Khvorova A. N Engl J Med. 2017;376(1):4-7.

# Inclisiran dose and administration

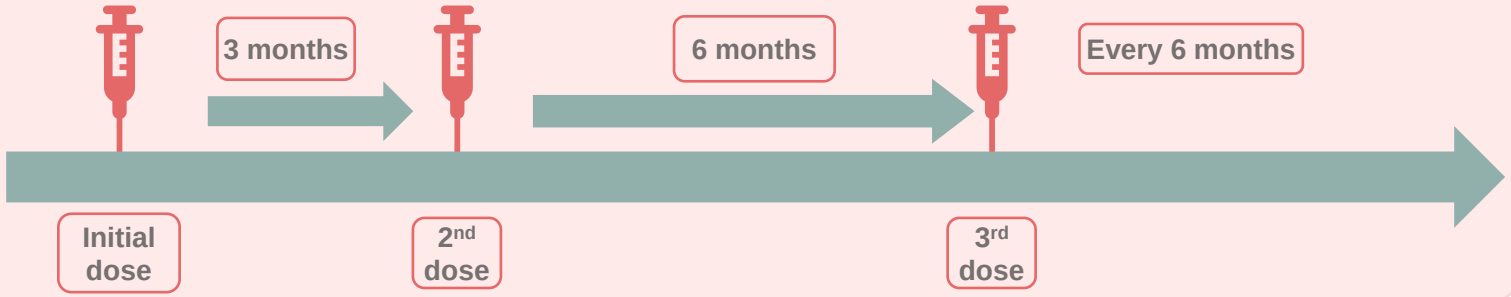
## Injection

- 1.5 mL of solution containing 284 mg inclisiran (equivalent to 300 mg inclisiran sodium)
- Single-dose pre-filled syringe
- Stored at room temperature

## Administration

Subcutaneous injection in the abdomen by a healthcare professional

## Dosage regimen




**2 DOSES A YEAR**

EVERY 6 MONTHS

- ✓ Poor adherence to currently available therapies is an important contributing factor and has been shown to be associated with an increased risk of CVD
- ✓ Inclisiran's infrequent dosing regimen may contribute to higher adherence — even complete adherence if inclisiran is administered by healthcare providers

CVD, cardiovascular disease.

1. Inclisiran Product Monograph, Novartis Canada. 2. Cupido AJ et al. Cardiovasc Research. 2020;116:e126-e139. doi:10.1093/cvr/cvaa.212.

# ORION phase III trials: Patient entry criteria

| ORION 9 | ORION 10 | ORION 11 |
|---|---|---|
| HeFH* | ASCVD | ASCVD + risk equivalents |
| N=482 | N=1561 | N=1671 |
| Stable on a low-fat diet | CHD, CVD, PAD | ✓ ASCVD (CHD, CVD, PAD)<br>✓ ASCVD risk equivalents (T2DM, HeFH* 10-year risk of CV event ≥20%) |
| LDL-C ≥2.6 mmol/L | LDL-C ≥1.8 mmol/L | LDL-C ≥1.8 mmol/L in ASCVD or ≥2.6 mmol/L in risk equivalent |

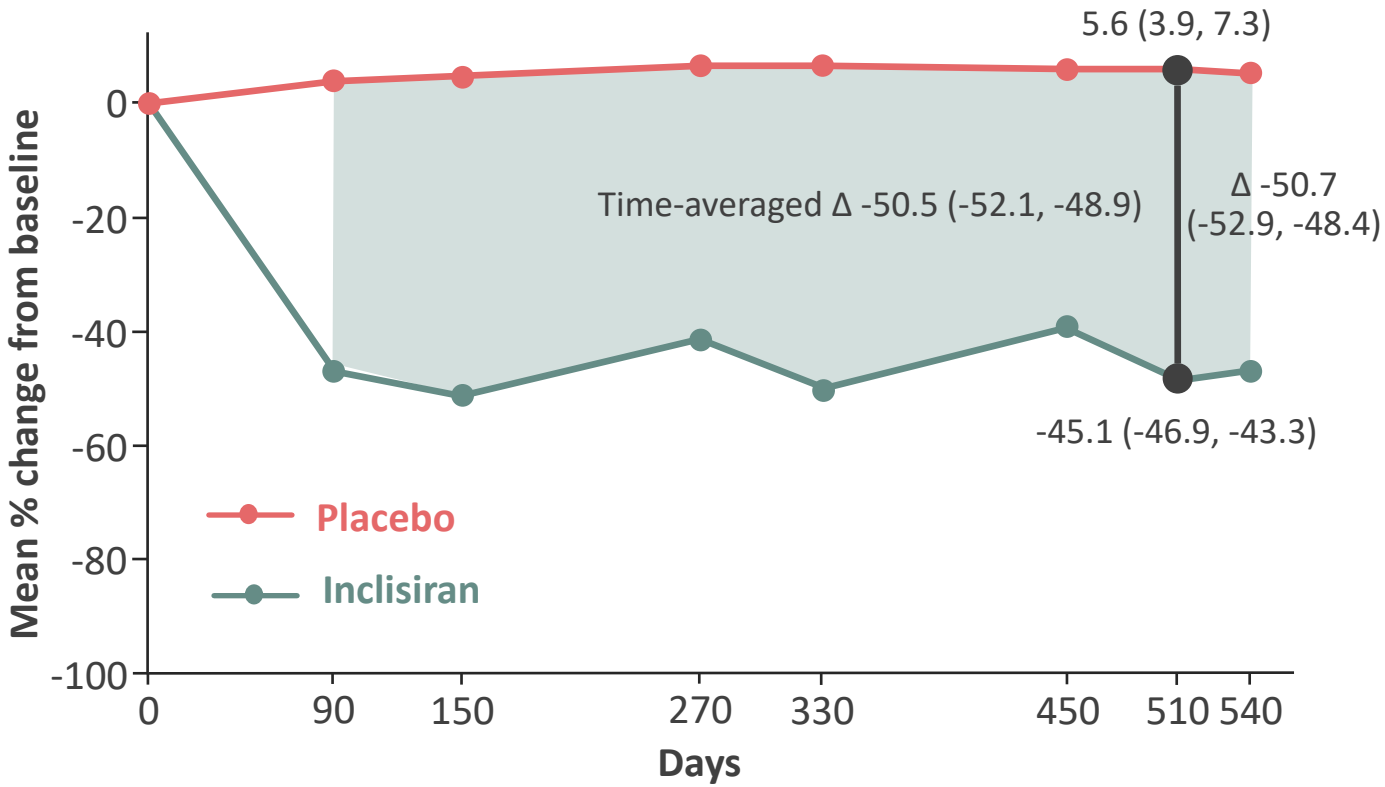
*By genetic testing and/or Simon-Broome criteria

ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CVD, cardiovascular disease; HeFH; heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PAD; peripheral artery disease; T2DM, type 2 diabetes.

Wright RS et al. J Am Coll Cardiol. 2021;77(9):1182-1193.

# Inclisiran provided effective and sustained LDL-C lowering over 18 months vs. placebo

Percent change in LDL-C over time – observed values in ITT patients




The pooled analysis of ORION-9, ORION-10 and ORION-11 comprising 3660 patients was a prespecified analysis to assess the effectiveness and overall safety profile of inclisiran as an adjunct to diet and maximally tolerated statin therapy

ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CVD, cardiovascular disease; HeFH; heterozygous familial hypercholesterolemia; TTT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; PAD; peripheral artery disease; T2DM, type 2 diabetes.

Wright RS et al. J Am Coll Cardiol. 2021;77(9):1182-1193.

# ORION-9,-10,-11: Pooled safety analysis of inclisiran was well tolerated, with a safety profile similar to placebo[1]

| Treatment-emergent Adverse Events (TEAEs) | Placebo | | Inclisiran | |
|---|---|---|---|---|
| **Safety population* – AEs in ≥ 5% patients†** | **N=1822** | | **N=1833** | |
| Patients with at least one TEAE | 1409 | (77.3%) | 1430 | (78.0%) |
| Diabetes mellitus‡ | 207 | (11.4%) | 212 | (11.6%) |
| Nasopharyngitis | 134 | (7.4%) | 140 | (7.6%) |
| Upper respiratory tract infection | 103 | (5.7%) | 105 | (5.7%) |
| Hypertension | 104 | (5.7%) | 104 | (5.7%) |
| Arthralgia | 72 | (4.0%) | 91 | (5.0%) |
| Protocol-defined injection site TEAE‡ | 12 | (0.7%) | 91 | (5.0%) |

**‡TEAEs at the injection site were more frequent with inclisiran than placebo, but were predominantly mild, and none were severe or persistent**

*Included all participants who received at least 1 dose of study medication.
†Participants may have been counted in more than one category.
‡Diabetes TEAE represents worsening of glycemic control as defined in the clinical protocol
1. Wright RS et al. J Am Coll Cardiol. 2021;77(9):1182-1193.

# ORION-9,-10,-11: Pooled safety analysis of inclisiran was well tolerated, with a safety profile similar to placebo[1]

| Serious TEAEs | Placebo | | Inclisiran | |
|---|---|---|---|---|
| **Safety population* – AEs in ≥5% patients†** | **N=1822** | | **N=1833** | |
| Patients with at least one serious TEAE | 419 | (23.0%) | 374 | (20.4%) |
| All-cause death | 27 | (1.5%) | 27 | (1.5%) |
| New, worsening or recurrent malignancy | 49 | (2.7%) | 44 | (2.4%) |
| Liver function | | | | |
| Alanine aminotransferase >3X ULN | 7 | (0.4%) | 9 | (0.5%) |
| Aspartate aminotransferase >3X ULN | 10 | (0.5%) | 8 | (0.4%) |
| Alkaline phosphatase >2X ULN | 5 | (0.3%) | 8 | (0.4%) |
| Bilirubin >2X ULN | 14 | (0.8%) | 14 | (0.8%) |
| Kidney function: creatinine >177 μmol/L | 42 | (2.3%) | 36 | (2.0%) |
| Muscle: creatine kinase >5X ULN | 22 | (1.2%) | 24 | (1.3%) |
| Hematology: platelet count <75 X109/L | 2 | (0.1%) | 1 | (0.1%) |
| TEAEs leading to drug discontinuation | 35 | (1.9%) | 45 | (2.5%) |

*Included all participants who received at least 1 dose of study medication. †Participants may have been counted in more than one category.
AE, adverse event; TEAE, treatment emergent adverse event; ULN, upper limit of normal.
1. Wright RS et al. J Am Coll Cardiol. 2021;77(9):1182-1193.

# Case 1

- 55 year old male
- History of MI
- Has hypertension, PVD
- Meds:
  - Aspirin 81 mg
  - Rosuvastatin 20 mg
  - Perindopril 8 mg
  - Bisoprolol 5 mg

- BMI 24
- BP 120/75, HR 70 bpm

- eGFR 55
- A1c 5.5%
- LDL 2.2

- Would you recommend PCSK9i?
- What about Ezetimibe?

# Case 2

- 67 year old female
- Has T2DM, hypertension, PVD
- No previous CVD
- Meds:
  - Aspirin 81 mg
  - Synjardy bid
  - Ozempic 1 mg per week
  - Perindopril 8 mg

- BMI 32
- BP 130/75, HR 83 bpm

- eGFR 55
- A1c 6.9%
- LDL 2.2

- Refuses statins. What do you suggest?

# Case 3

- 55 year old male
- Has T2DM, hypertension, PVD
- Previous MI
- Meds:
  - Aspirin 81 mg
  - Synjardy bid
  - Ozempic 1 mg per week
  - Perindopril 8 mg
  - Bisoprolol
  - Vascepa
- Tried atorvastatin, rosuvastatin but stopped them both due to myalgias

- BMI 32
- BP 130/75, HR 83 bpm

- eGFR 55
- A1c 6.9%
- LDL 2.2

- What do you suggest?

## Summary

- The new 2021 Canadian Dyslipidemia Guidelines focus on primary and secondary prevention strategies
- The value of Lp(a), Apo B levels, non-HDL cholesterol beyond looking just at LDL is emphasized
- CV risk reduction is most important in considering pharmacotherapy with statins, ezetimibe, PCSK9- inhibitors and IPE
- Novel therapies such as inclisiran may help lower LDL with better adeherence
- The decision regarding therapy is based on the risk of the person with dyslipidemia (patient factors, lipid values, past CV history, etc.)