

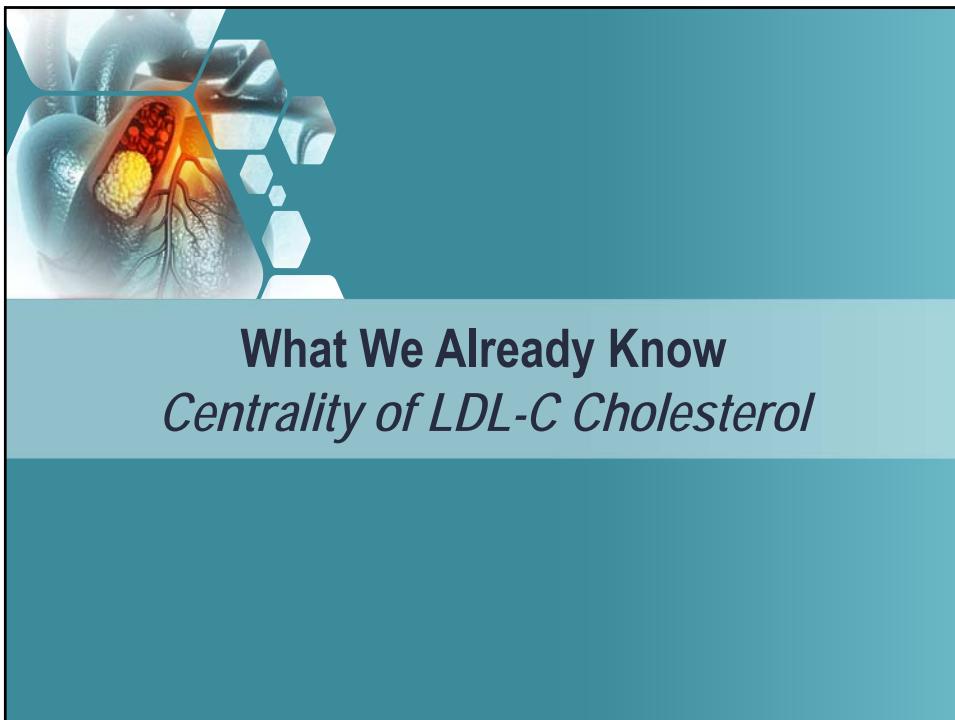
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Learning Objectives

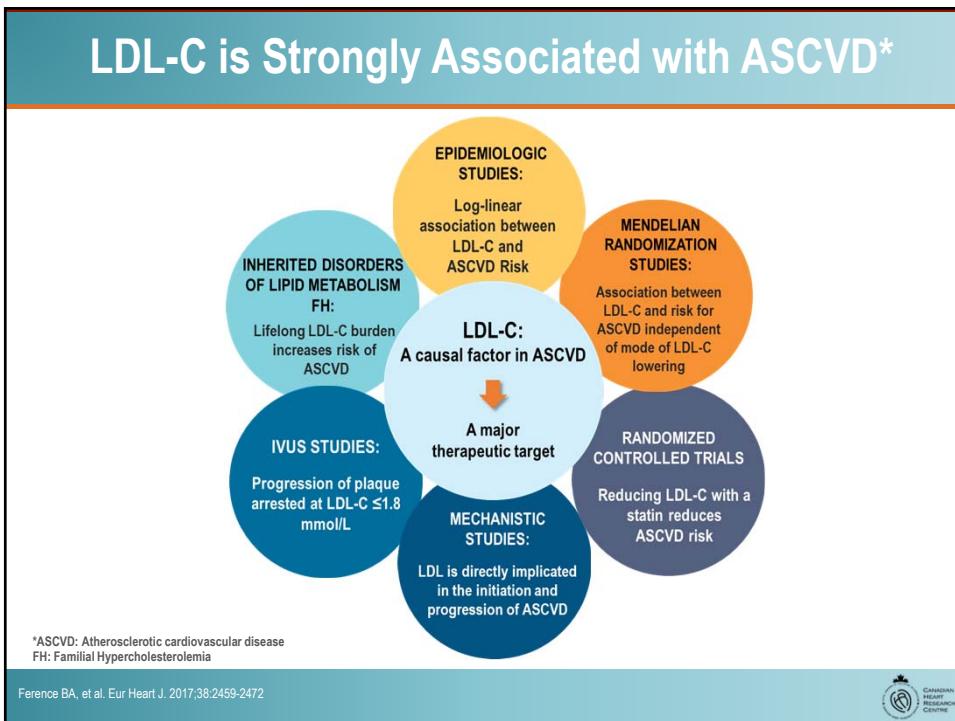
Upon completion of this activity, participants will be able to:

- 01** Explain the key updates to the 2021 CCS Dyslipidemia Guidelines for primary and secondary prevention
- 02** Identify those patients who would benefit from additional therapy beyond statins to reduce CV risk
- 03** Appropriately apply the new 2021 CCS Dyslipidemia Guideline recommendations into routine clinical practice





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Evidence for LDL-C as a Main Priority for Risk Reduction

- LDL-C compromises 75% of the cholesterol carried by circulating apo-B containing lipoproteins
- LDL-C meets multiple criteria for causality related to ASCVD
- LDL-C is the most studied lipid parameter in RCTs and the primary priority for lipid-lowering therapy

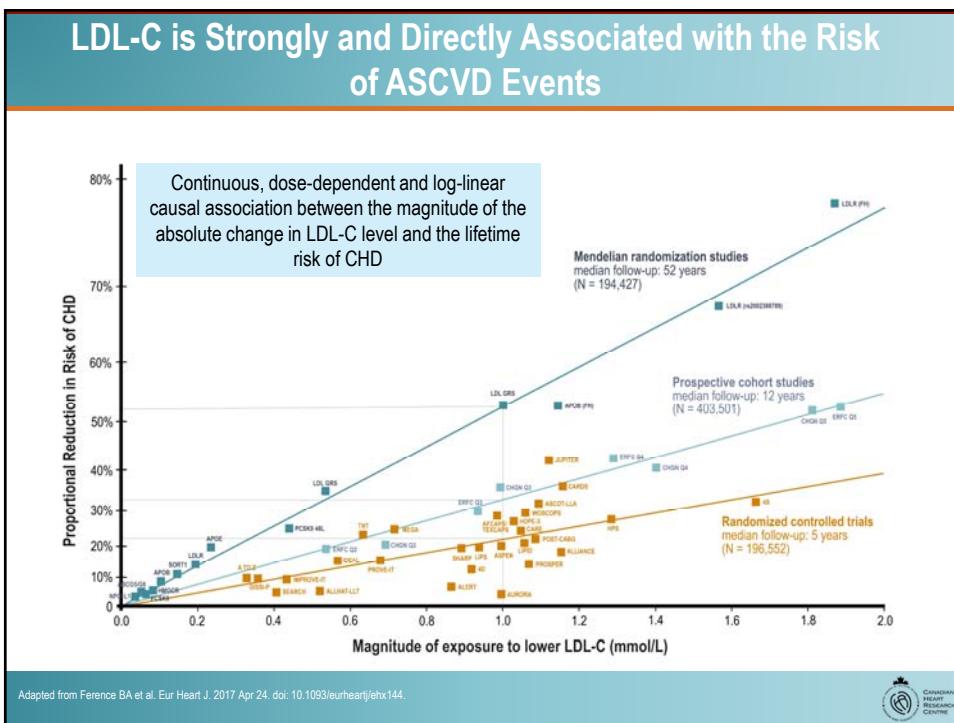
RCTs: Randomized Clinical Trials

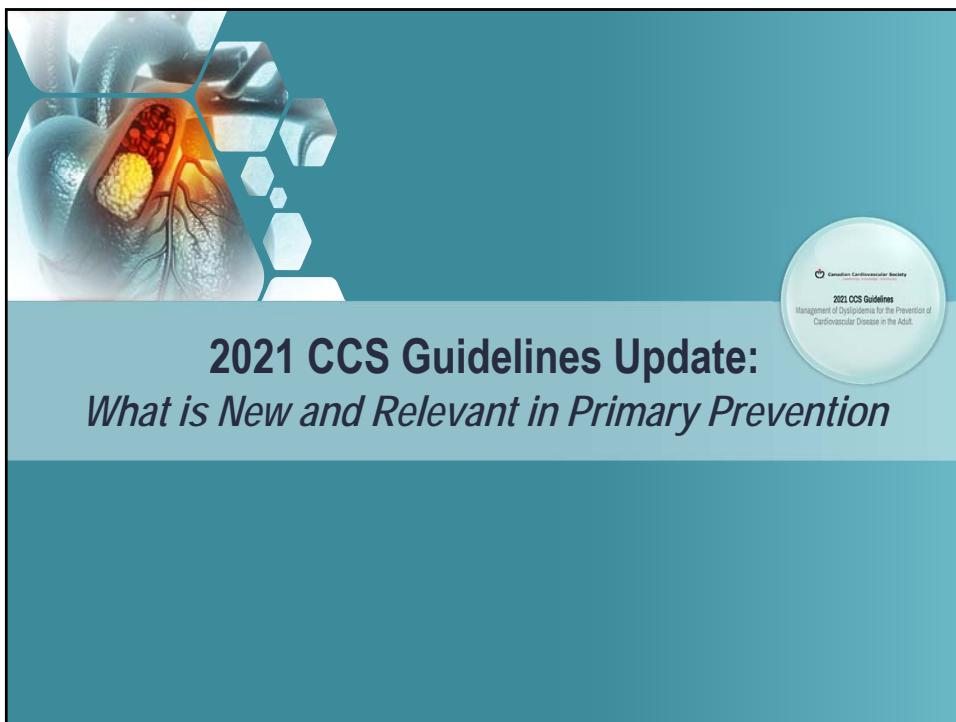
Stone NJ, et al. The 2018 AHA/ACC/Multi-Society Cholesterol guidelines: Looking at past, present and future, Progress in Cardiovascular Diseases, Volume 62, Issue 5, 2019, 375-383,



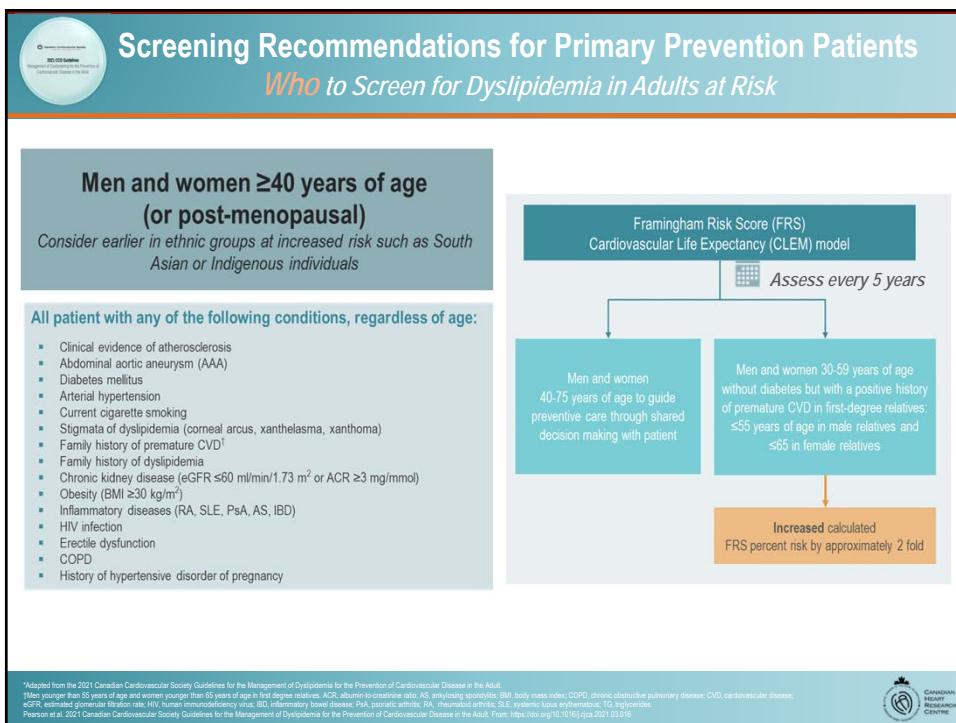
LDL-C reduction remains the main focus in guidelines

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NEW

Pregnancy Related Disorders - Recommendation

Pregnancy complications[†] 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

- Among women who have had a pregnancy complication such as hypertensive diseases of pregnancy, gestational diabetes, pre-term birth, stillbirth, low birthweight infant, or placental abruption, **screening with a 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*)
- **Counselling women** who have any of these pregnancy-related complications of the **increased lifetime risk of ASCVD** and reinforcing the importance of healthy behaviours is recommended. (*Strong Recommendation: Low Quality Evidence*)
- To assist with decisions about lipid-lowering pharmacotherapy in this patient population, **favouring CV age, over 10-year risk calculators is recommended.** (*Strong Recommendation: Low Quality Evidence*)

[†]Pregnancy complications include: preeclampsia and related hypertensive disorders of pregnancy, gestational diabetes, placental abruption, preterm delivery, stillbirth, and delivery of a low birth 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.cca.2021.03.016>

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Screening Recommendations for Primary Prevention Patients

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

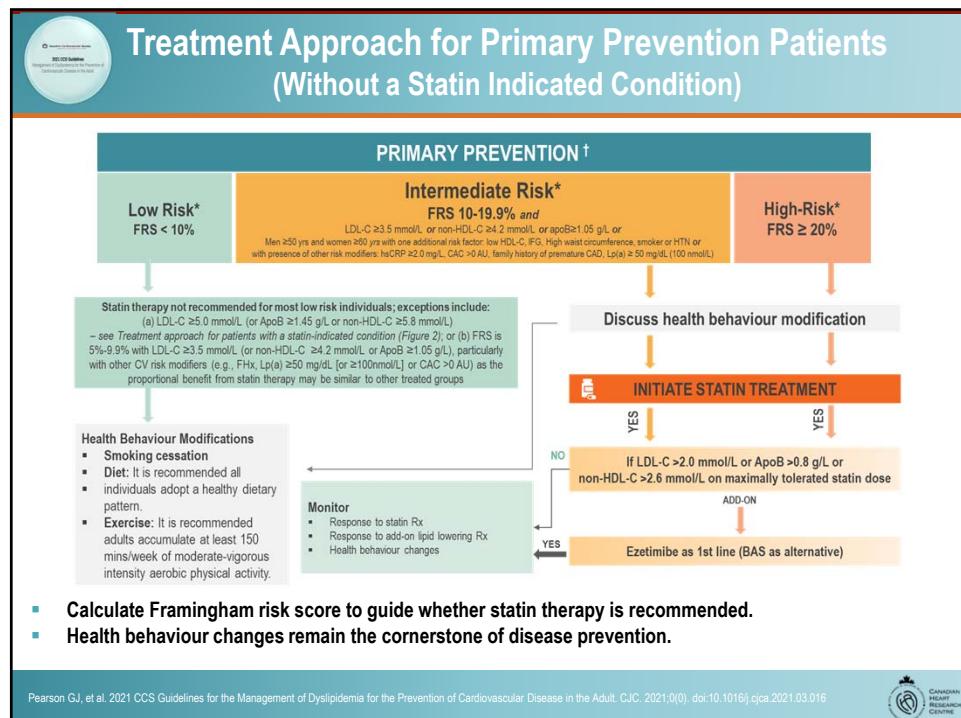
Optional

- Apolipoprotein B (ApoB)
- Urine ACR (if eGFR <60 mL/min/1.73 m², hypertension, or diabetes)

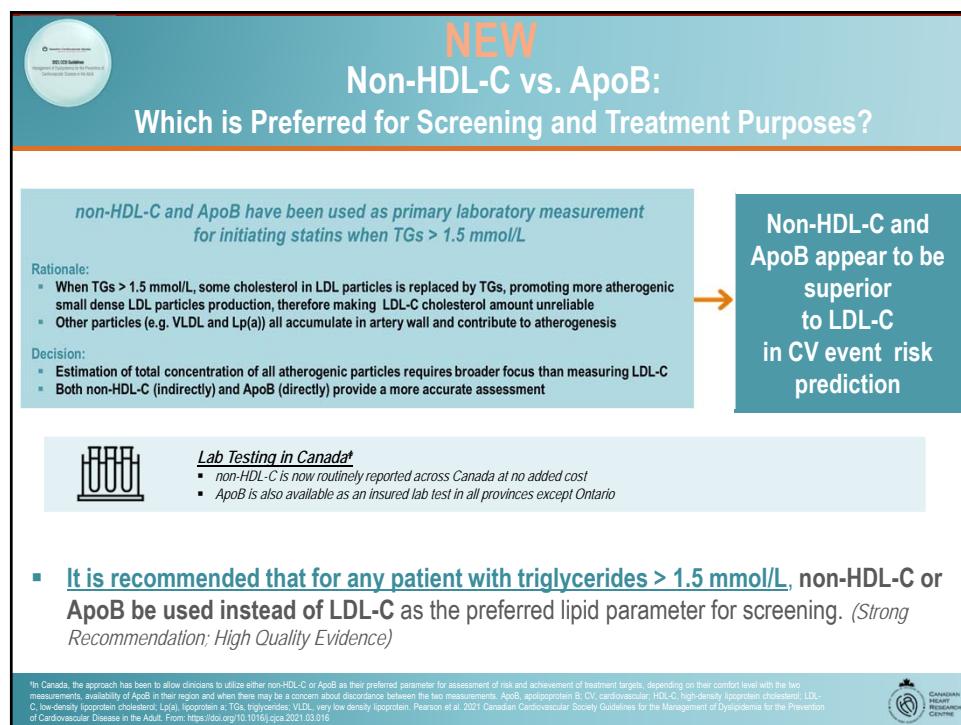
Lipids can be measured non-fasting (except if TGs >4.5 mmol/L)

Practical Tip:
Compared to fasting lipid values there will be minimal change with non-HDL-C, a slight decrease in LDL-C and small increase in triglyceride concentrations in individuals who did not fast

*Adapted from the 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult.



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NEW

Can Lp(a) Improve Risk Stratification and Dyslipidemia Management?

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

FOURIER¹ and ODYSSEY OUTCOMES² 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)

6 million Canadians have high Lp(a) - most common genetic dyslipidemia

High concentrations of Lp(a) are associated with high risk of recurrent CVD in individuals from the general population

Commonly used agents such as 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 Canada⁵

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'Donnell MJ, Faioz S, Giugliano RP, et al. Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk. Circulation. 2019;139(12):1483-92. 2. Bhatti VA, Szarek M, Alyward PE, et al. Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome. JACC. 2020;75(1):133-44. 3. Patel G, Celis A, McQueen M, Avezum SS, Ernst 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. Enthramas B, Anuradha 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, family hypercholesterolemia; LDL-C, low density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCSK9, randomized controlled trials; RFs, risk factors. Content adapted from Pernier et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia in the Adult. <https://doi.org/10.1016/j.cca.2021.07.016>

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NEW

Can Lp(a) Improve Risk Stratification and Dyslipidemia Management?

Measuring Lp(a) level once in a person's lifetime is recommended as a part of the initial lipid screening. (*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*)

1. O'Donnell MJ, Faioz S, Giugliano RP, et al. Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk. Circulation. 2019;139(12):1483-92. 2. Bhatti VA, Szarek M, Alyward PE, et al. Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome. JACC. 2020;75(1):133-44. 3. Patel G, Celis A, McQueen M, Avezum SS, Ernst 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. Enthramas B, Anuradha 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, family hypercholesterolemia; LDL-C, low density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCSK9, randomized controlled trials; RFs, risk factors. Content adapted from Pernier et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia in the Adult. <https://doi.org/10.1016/j.cca.2021.07.016>

Coronary Artery Calcium Scoring (CAC): *CAC adds to risk prediction beyond FRS*

- Coronary artery calcium testing is useful in diagnosing subclinical coronary artery disease and in predicting the risk of future cardiovascular events and death.
- Given the high negative predictive value of the test, it can also serve to reclassify risk in patients beyond traditional risk factors. *CAC adds to risk prediction beyond FRS*.
- Along with shared decision-making, elevated calcium scores can guide the initiation of statin or aspirin therapy.
- Repeat CAC testing is not recommended.

How to interpret CAC

- **CAC = 0** (true normal) has a negative predictive value in low-risk adults of 95-99% over 2-5 years, event rate of 1.5% over 10 years (not a zero rate of events).
- **CAC > 0** confirms presence of atherosclerotic plaque, and increasing scores are directly proportional to increased risk.
- **CAC > 100** is associated with high risk (>2% annual risk).
- **Even if CAC = 0**, patients with strong family history, poorly controlled risk factors, Familial Hypercholesterolemia (FH) or elevated Lp(a) still warrant consideration of treatment.

Parth P, et al; Cleveland Clinic Journal of Medicine September 2018, 85 (9) 707-716; DOI: <https://doi.org/10.3949/cjcm.85a.17097>



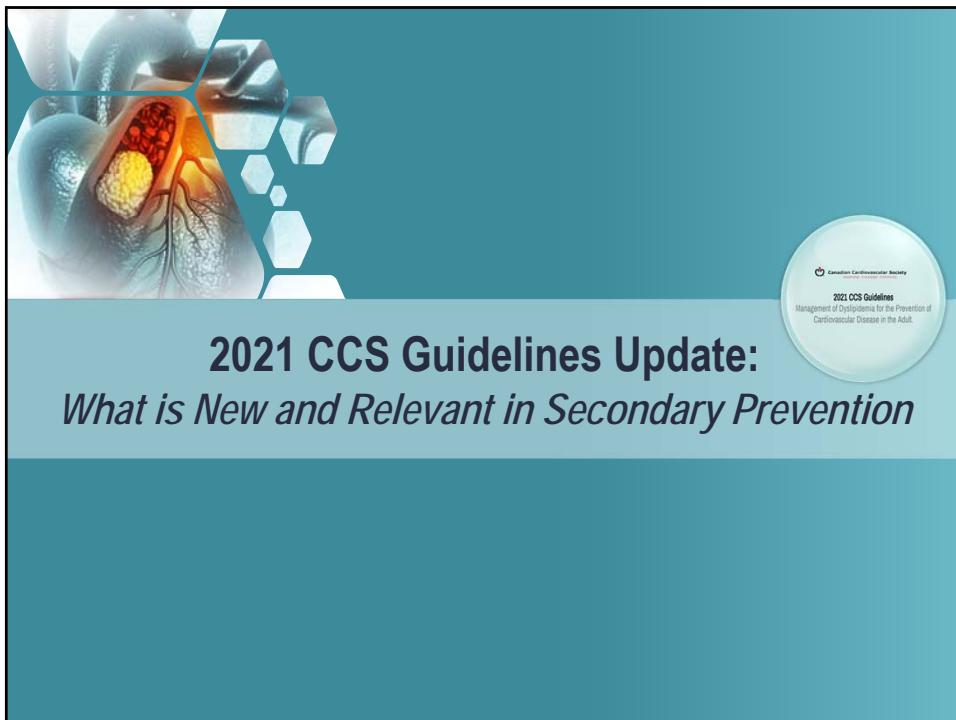
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Primary Prevention: New Key Take-Aways from the 2021 Guidelines

	Health behavior changes remain the cornerstone of disease prevention.	
	Inquire about previous HT / DM in pregnancy when assessing risk	
	<ul style="list-style-type: none">▪ Use non-HDL-C (or apoB) when TG > 1.5 mmol/L▪ Measure Lp(a) once in each patient's lifetime▪ Consider CAC in intermediate risk patients without any clear statin indication.<ul style="list-style-type: none">▪ Any score above zero is abnormal.	
	Evidence continues to show benefits of keeping low cholesterol levels throughout life, at any age, and at any level of risk.	
	Growing evidence suggests continued benefits of lipid lowering for primary prevention in older adults (>75 years)	

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>





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LDL-C ≥ 1.8 mmol/L
OR
non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L

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>

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Use High-Intensity Statins in ALL ASCVD Patients

- Use of high-intensity statin therapy in addition to appropriate health behaviour modifications for all secondary prevention CVD patients is recommended. For patients who do not tolerate a high-intensity statin, the maximally tolerated statin dose is recommended. (Strong Recommendation; High-Quality Evidence).

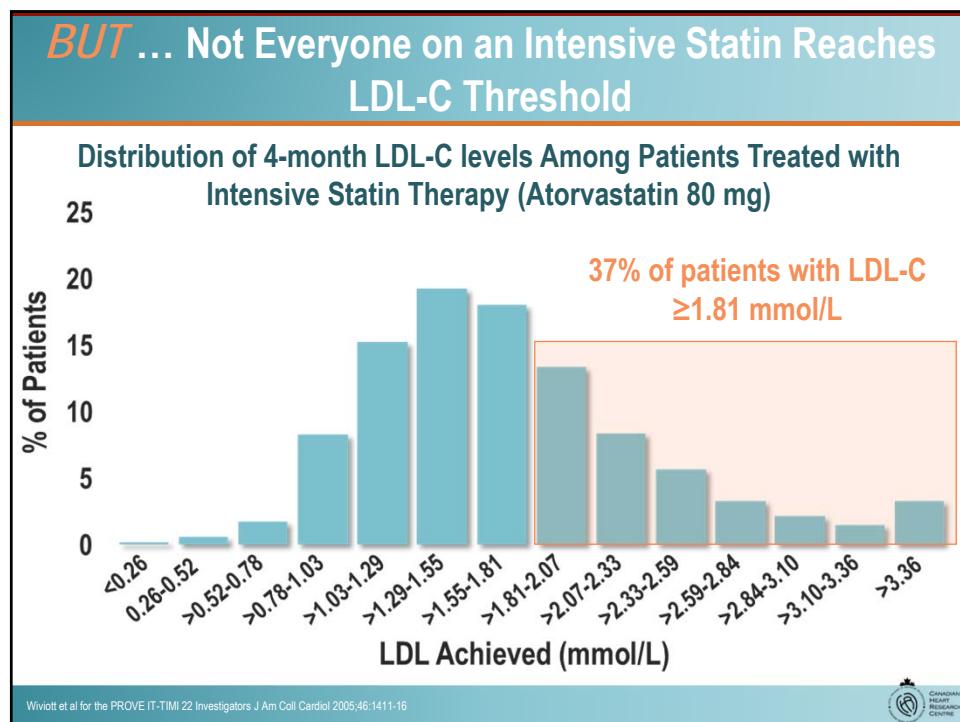
Statins are the main stay of therapy

Cholesterol Treatment Trialists' Meta-Analysis of 27 Randomized Statin Trials (n ≈ 175,000)
In patients with <10% 5-year risk of major coronary events:

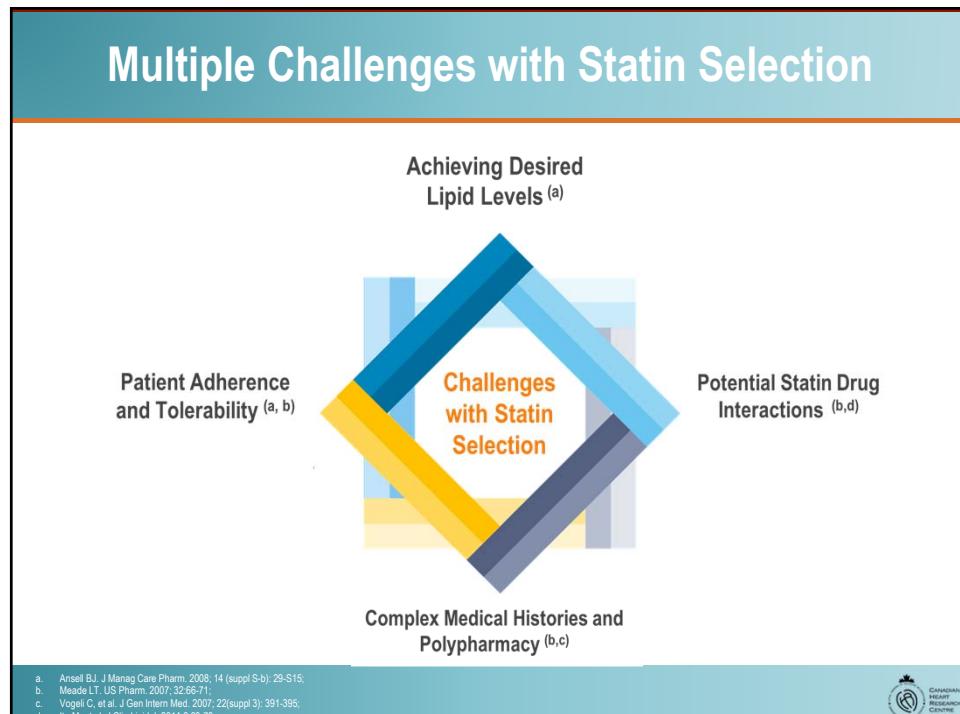
Every 1 mmol/L reduction in LDL-C \rightarrow 23% reduction in risk of major coronary events

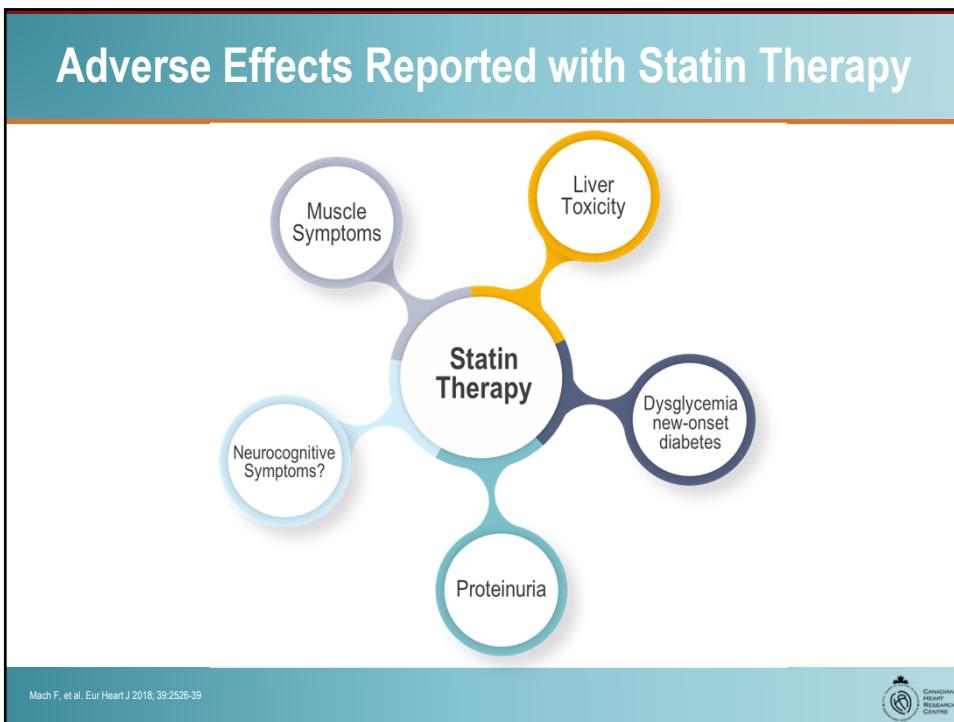
Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. From: <https://doi.org/10.1016/j.cjca.2021.03.016>

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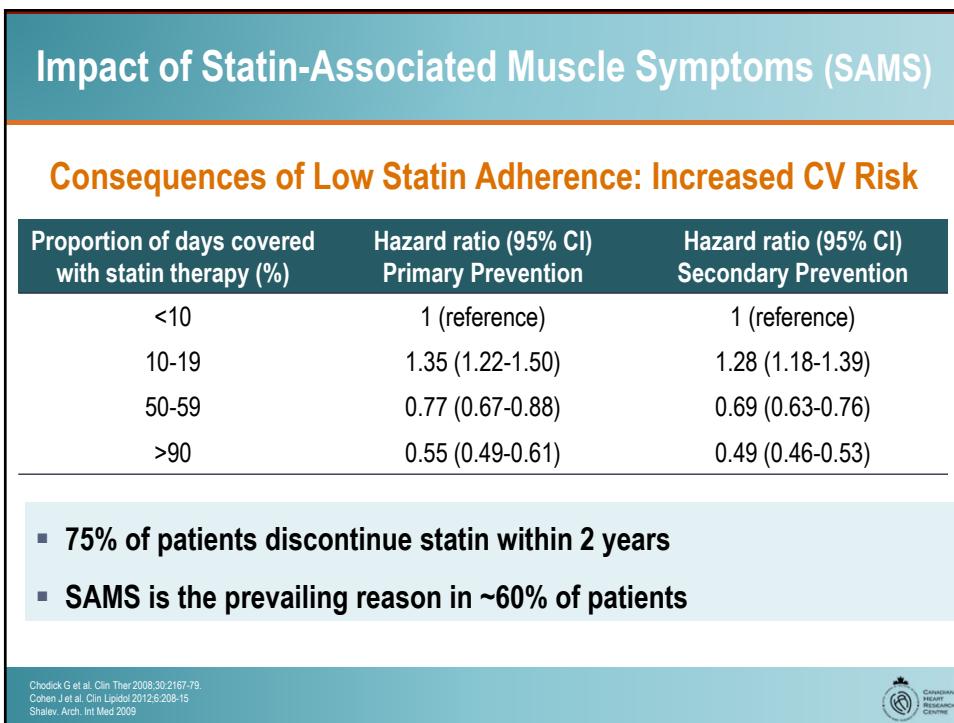


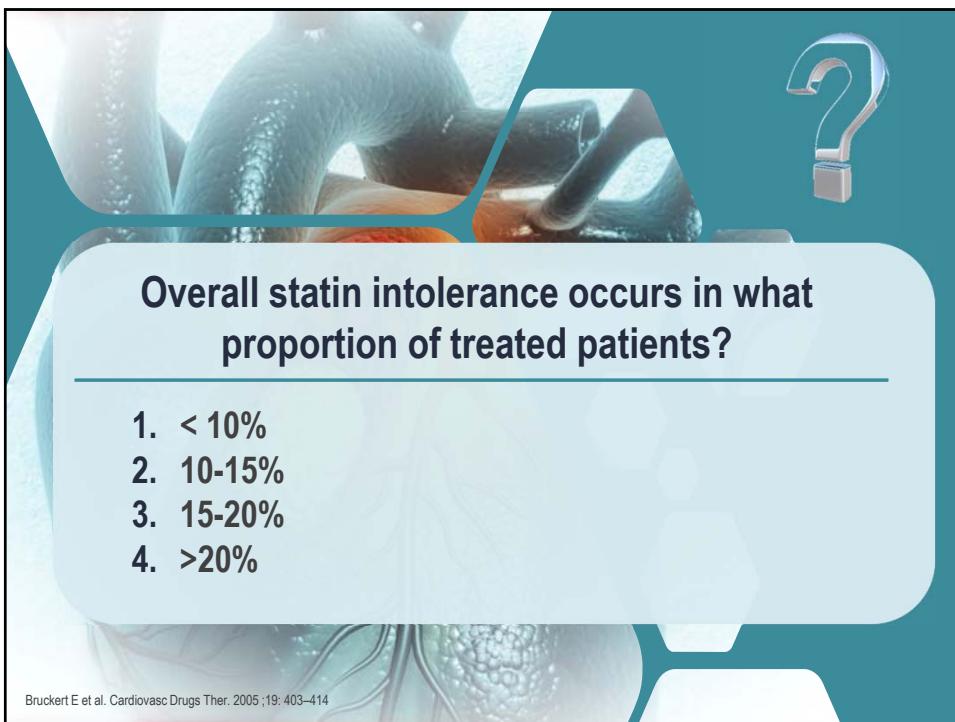
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Overall statin intolerance occurs in what proportion of treated patients?

- 1. < 10%
- 2. 10-15%
- 3. 15-20%
- 4. >20%

Bruckert E et al. Cardiovasc Drugs Ther. 2005;19: 403-414

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The Role of Non-Statin Therapies to Reduce ASCVD Events

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

Case

Sonia



History

- Sonia is a 61-year-old retired teacher
- She has a history of:
 - CAD
 - Stroke
 - HFrEF
 - Hypertension
 - CKD
 - T2DM
 - High Cholesterol
 - Statin intolerance
(reported at the previous visit)

Current Medications

- ASA 81 mg OD
- Perindopril 8 mg OD
- Carvedilol 25 mg BID
- Metformin 1 g BID
- Linagliptin 5 mg OD
- Empagliflozin 10 mg OD
- Rosuvastatin 20 mg OD *reduced* to 5 mg OD at previous visit
 - LDL-C increased from 2.0 mmol/L to 2.7 mmol/L with the reduced dose
- Ezetimibe 10 mg OD *(added during previous visit)*

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Case

Sonia



Physical Exam

- Blood Pressure: 128/75 mmHg
- Waist Circumference: 81 cm
- BMI: 32 kg/m²

Current Labs

- TC: 3.67 mmol/L
- Triglycerides: 1.16 mmol/L
- HDL-C: 0.98 mmol/L
- LDL-C: 1.96 mmol/L
- A1C: 6.7%
- Creatinine: 106.1 µmol/L
- eGFR: 50 ml/min/1.73m²

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DISCUSSION

What is Sonia's risk status?

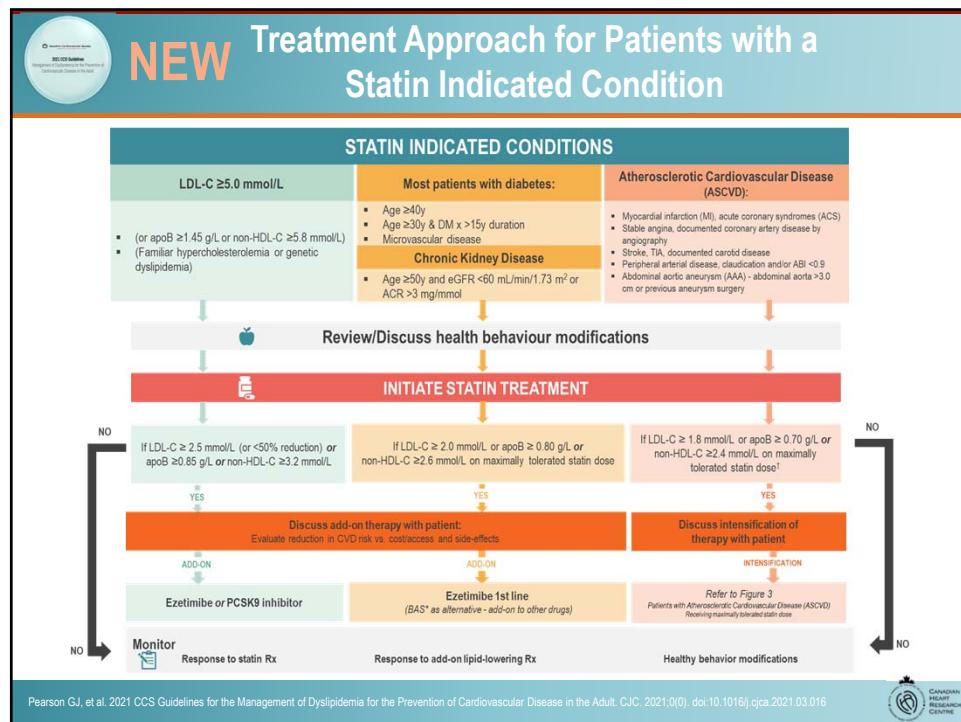
**How frequently do you manage patients with
a similar clinical profile in your practice?**



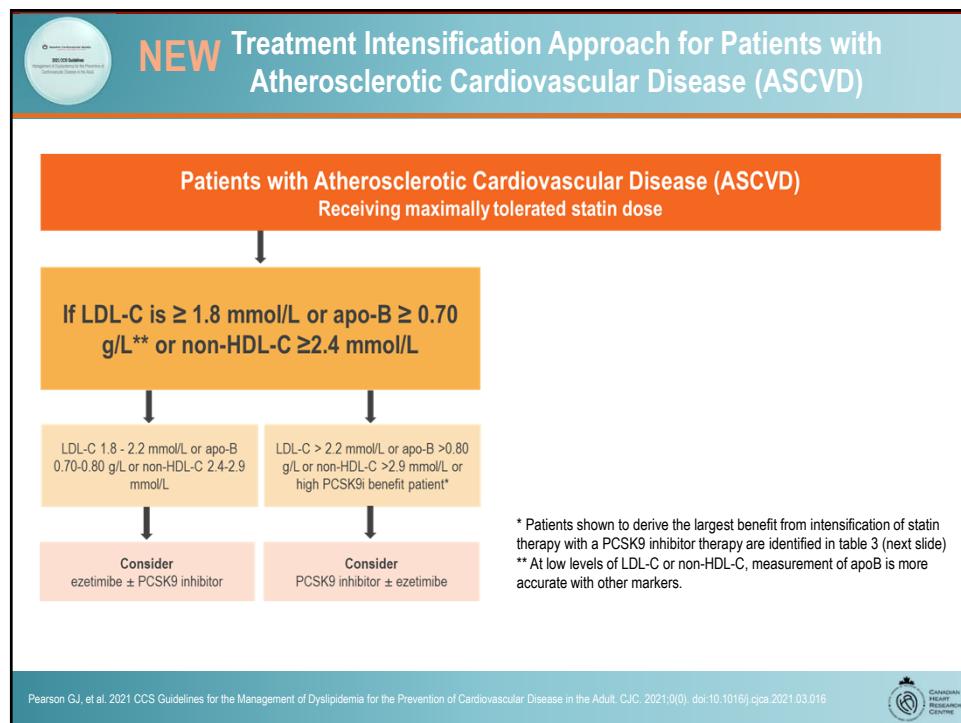
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Which of the following steps would you undertake to further reduce Sonia's risk for future ASCVD events during this visit?
Select ALL that Apply

1. Advise on appropriate health behaviour interventions
2. Change Rosuvastatin 5 mg OD to Atorvastatin 20 mg OD
3. Icosapent ethyl (IPE) 2 gm BID
4. Discuss initiation of a PCSK9 inhibitor



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NEW

Secondary Prevention Patients Shown to Derive the Largest Benefit From Intensification of Statin Therapy with the Addition of a PCSK9 Inhibitor

Recent acute coronary event (ACS):

- Hospitalised index ACS to 52 weeks post index ACS

Clinically evident ASCVD and any of the above:

- 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)

Pearson GJ, et al. 2021 CCS Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. CJC. 2021;0(0). doi:10.1016/j.cjca.2021.03.016

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Non-Statin Strategies to Further Reduce LDL-C

IMPROVE-IT

Hazard ratio, 0.936 (95% CI, 0.89-0.99)
P=0.016

Simvastatin monotherapy
34.7%

Simvastatin-ezetimibe
32.7%

Years since Randomization

FOURIER

Cumulative Incidence (%)
Hazard ratio .85 (95% CI, 0.79-0.92)
P<0.0001

Placebo
14.6%

Evolocumab
12.6%

Months from Randomization

ODYSSEY Outcomes

MACE (%)
ARR* 1.6%

Placebo
Alirocumab

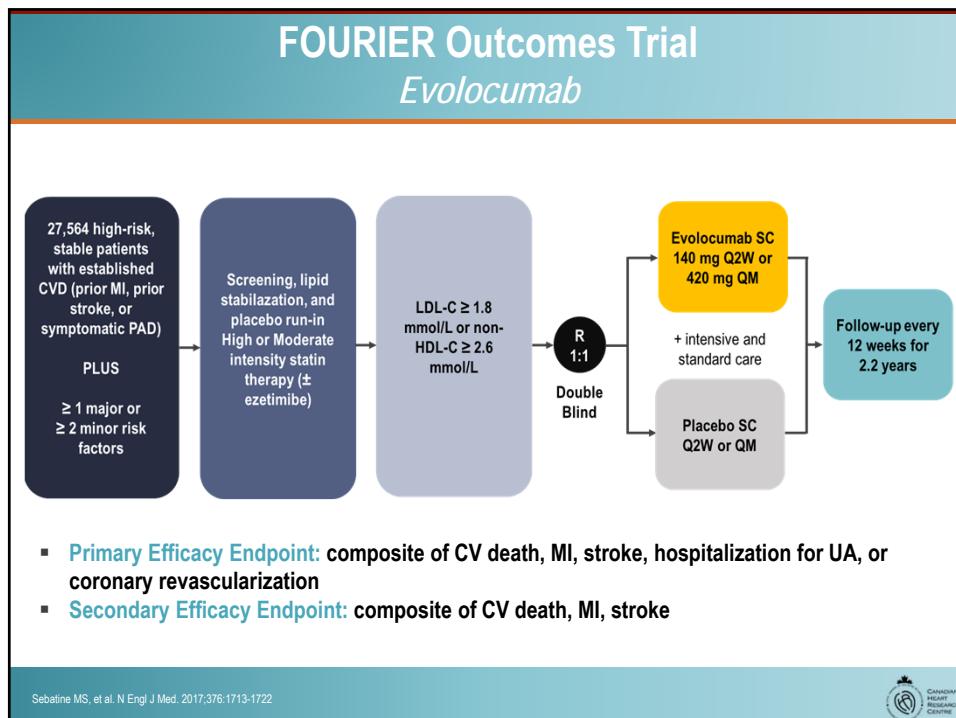
HR 0.85 (95% CI 0.78, 0.93); P=0.0003

Years since Randomization

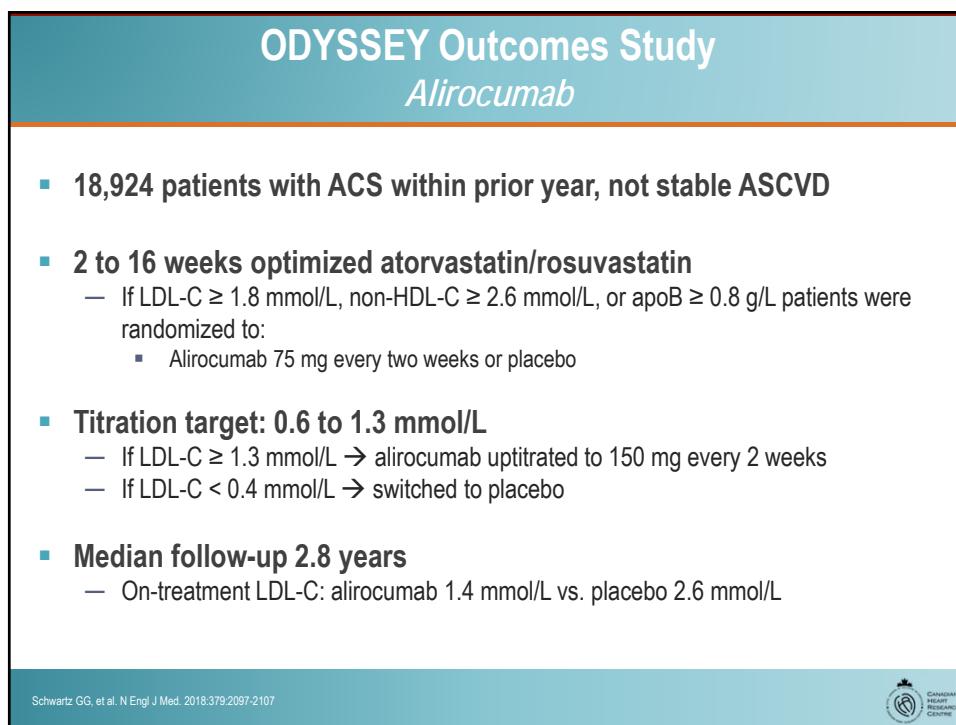
- Adding ezetimibe to statin therapy provides an additional LDL-C reduction of about 20% and 6% reduction in CV events
- The data from clinical trials with PCSK9 inhibition demonstrate efficacy and safety of LDL-C lowering by an additional 60% on top of statin \pm ezetimibe therapy resulting in further reductions in MACE. CV benefits are proportional to the absolute reduction in LDL-C and the duration of treatment

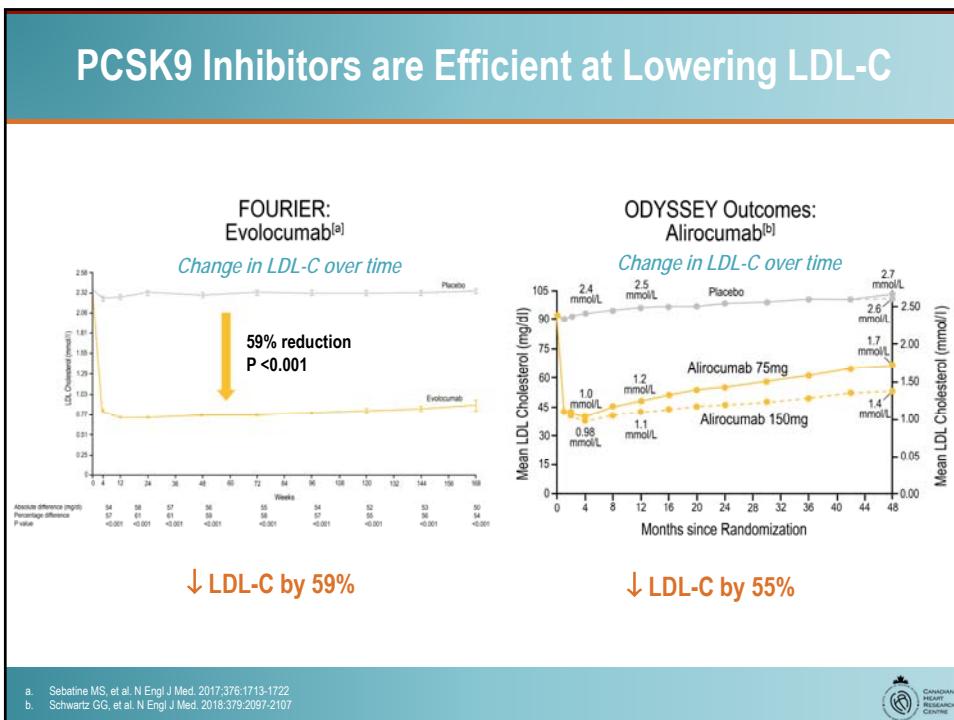
Cannon CP, et al. N Engl J Med. 2015;372:2387-2397
Sebeline MS, et al. N Engl J Med. 2017;376:1713-1722
Schwartz GG, et al. N Engl J Med. 2018;379:2097-2107

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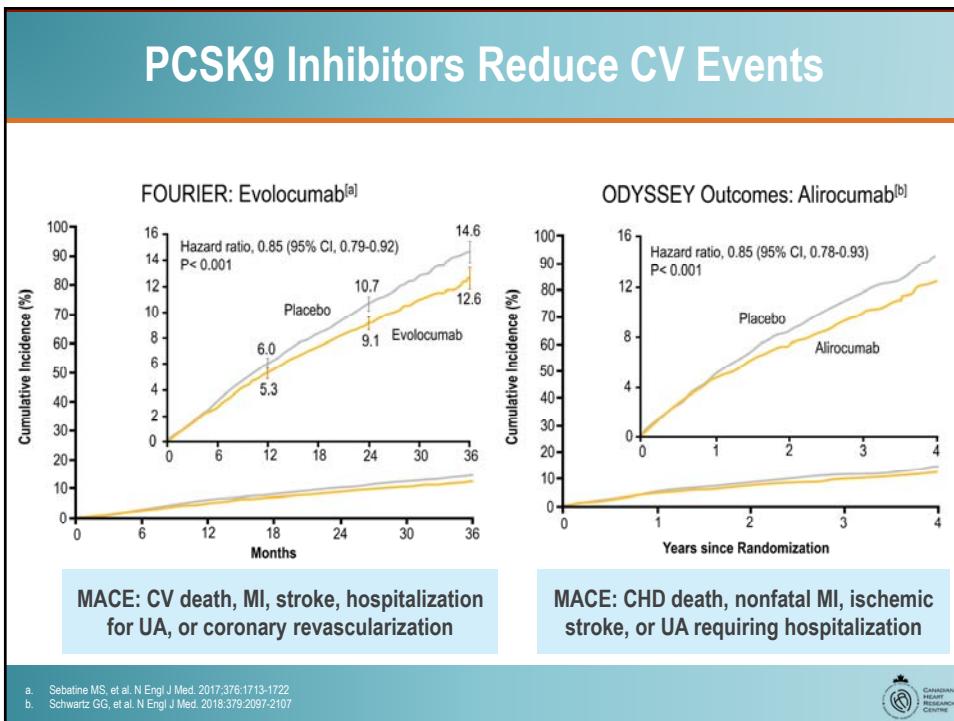


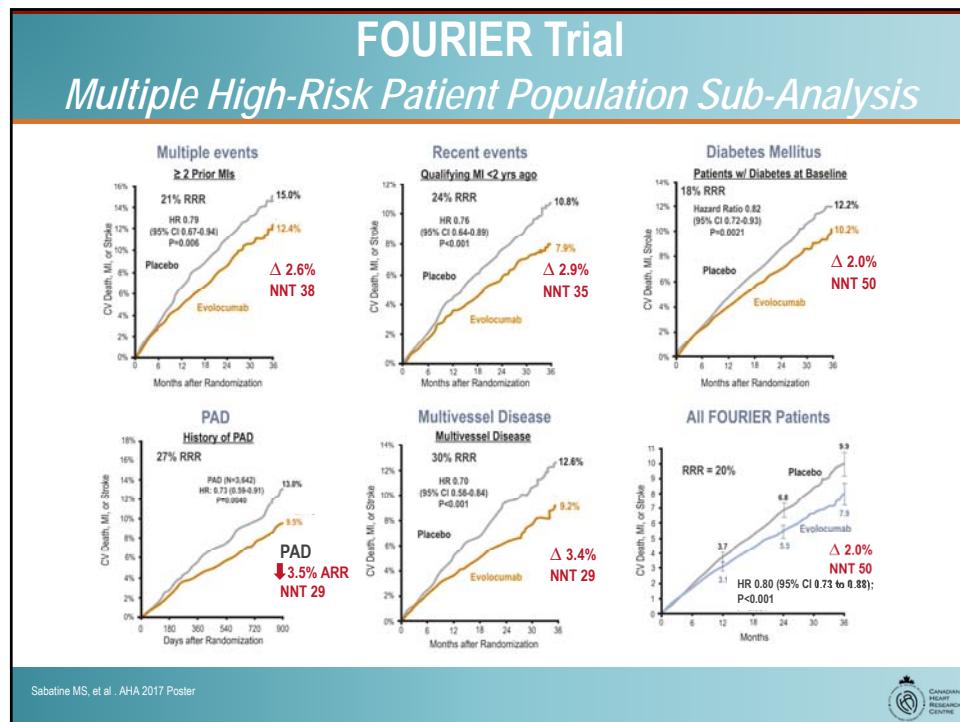
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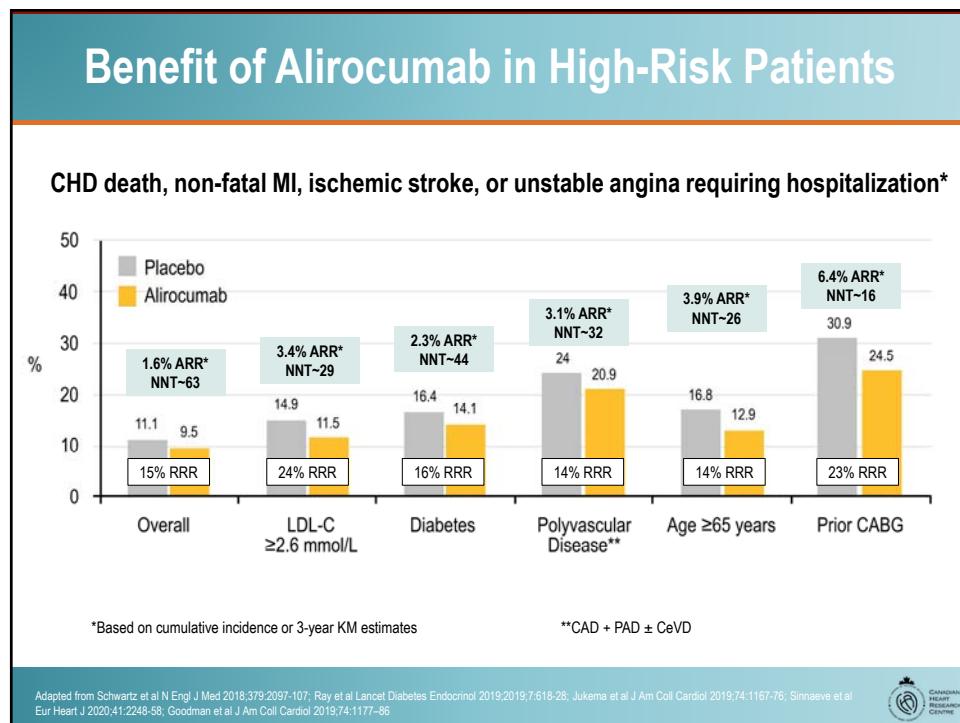


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NEW

When and How to Intensify LDL-C Lowering Therapies
Intensification of LDL-C- lowering therapy in clinical ASCVD
(in addition to maximally tolerated statins)

Sonia



Intensification of lipid-lowering therapy with ezetimibe and/or PCSK9 inhibitor therapy for all secondary prevention CVD patients in whom LDL-C remains $\geq 1.8 \text{ mmol/L}$ (or non-HDL-C $\geq 2.4 \text{ mmol/L}$ or ApoB $\geq 0.7 \text{ g/L}$) on maximally tolerated statin dose is recommended. If ezetimibe is used initially and LDL-C remains $\geq 1.8 \text{ mmol/L}$ (or non-HDL-C $\geq 2.4 \text{ mmol/L}$ or ApoB $\geq 0.7 \text{ g/L}$) PCSK9 inhibitor therapy is recommended.
(Strong recommendation; High Quality Evidence).

**Sonia is on a maximally tolerated statin dose
(Rosuvastatin 5 mg OD) &
Ezetimibe 10 mg OD**

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.cca.2021.03.016>
Wiviott et al for the PROVE IT-TIMI 22 Investigators. J Am Coll Cardiol 2005;46:1411-16

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Case

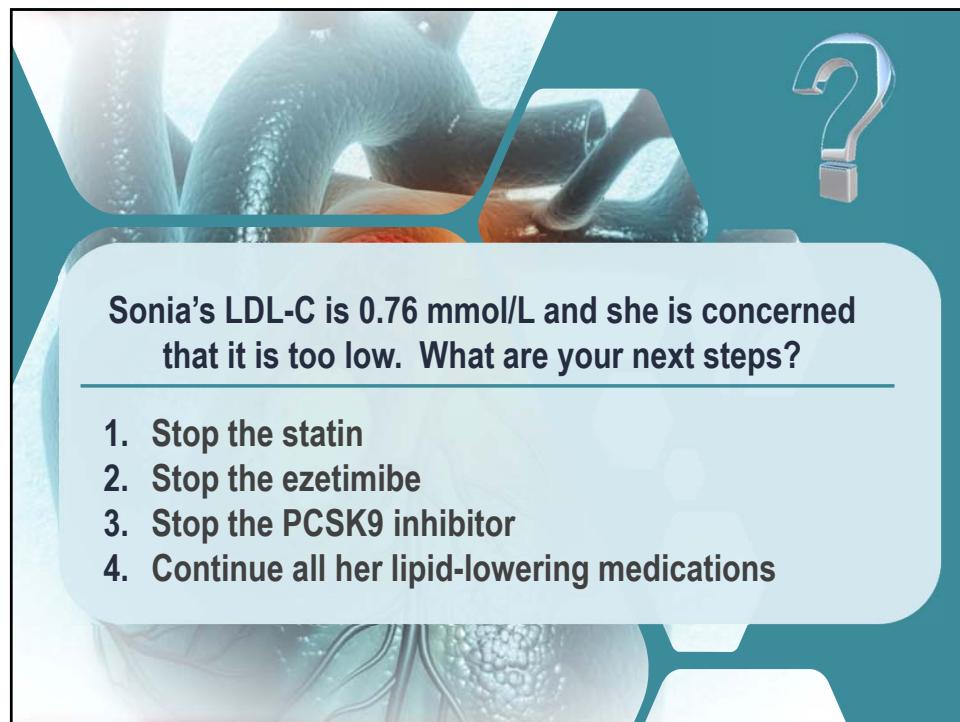
Sonia



Follow-Up Visit

- You added a PCSK9-inhibitor**
- At the two months follow-up visit, Sonia's liver and kidney function labs were stable
- Sonia's most recent LDL-C was **0.76 mmol/L**
- She is concerned that her LDL-C is now too low**

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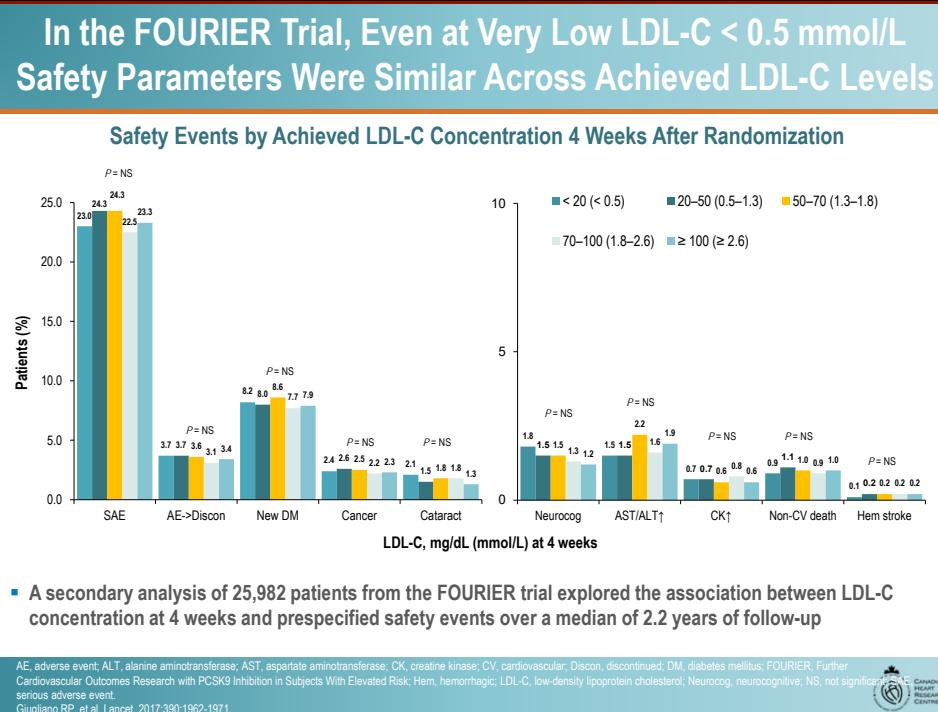


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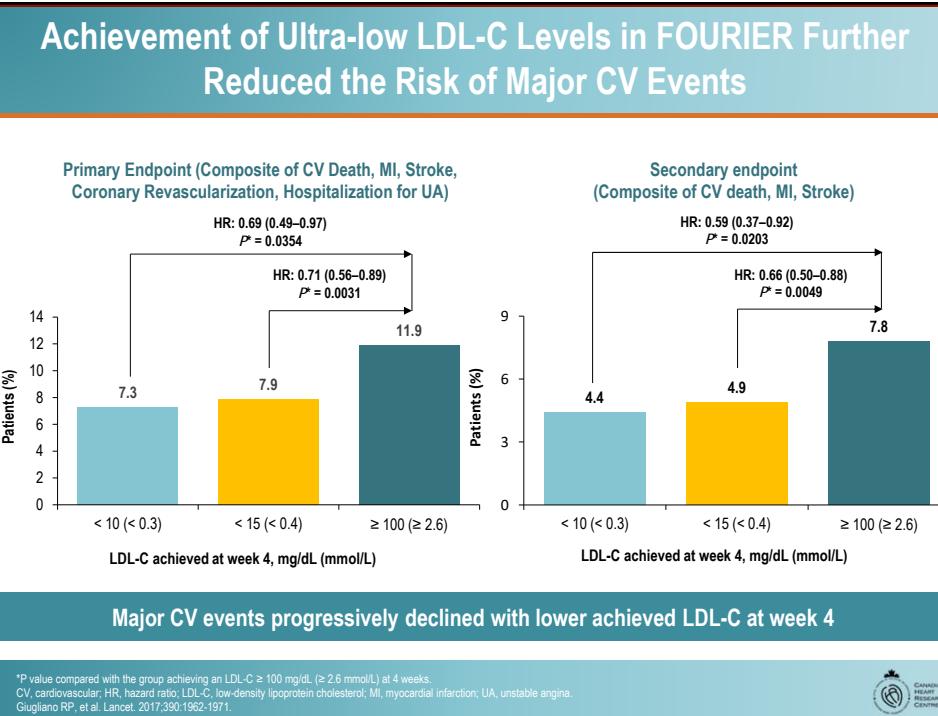
FOURIER: Evolocumab ^(a)			ODYSSEY Outcomes: Alirocumab ^(b)		
Outcome	Evolocumab (N = 13,769)	Placebo (N = 13,756)	Variable	Alirocumab (N = 9,451)	Placebo (N = 9,443)
Adverse events-no. of patients, %					
Any	77.4	77.4	Any adverse event	75.8	77.1
Serious	24.8	24.7	Serious adverse event	23.3	24.9
Thought to be related to the study agent and leading to discontinuation of study regimen	1.6	1.5	Adverse event that led to death	1.9	2.4
Injection-site reaction	2.1	1.6	Adverse event that led to discontinuation of the trial regimen	3.6	3.4
Allergic reaction	3.1	2.9	Local injection-site reaction	3.8	2.1
Muscle-related event	5.0	4.8	General allergic reaction	7.9	7.8
Rhabdomyolysis	0.1	0.1	Diabetes worsening or diabetic complication among patients with diabetes at baseline, %	18.8	21.2
Cataract	1.7	1.8	New onset diabetes among patients without diabetes at baseline, %	9.6	10.1
Adjudicated case of new-onset diabetes	8.1	7.7	Neurocognitive disorder	1.5	1.8
Neurocognitive event	1.6	1.5	Hepatic disorder	5.3	5.7
			Cataracts	1.3	1.4
			Hemorrhagic stroke, adjudicated	<0.1	0.2

a. Sabatine MS, et al. N Engl J Med. 2017;376:1713-1722.
b. Schwartz GG, et al. N Engl J Med. 2018;379:2097-2107.





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Overcoming Access Barriers to PCSK9 Inhibitors

01

Fill in the requisite information
appropriately to get reimbursement
for our patients

02

Documentation of LDL-C history
and possible statin intolerance

03

Documentation of
high-risk features and
co-morbidities

Baum SJ, et al. Clin Cardiol. 2017;40:243-254



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Strategies for Lipid Guideline Implementation

- Keep medication regimens simple and provide clear instructions to the patient.
- Promote adherence and involve family / care-giver support when applicable.
- Lower medication barriers and assess adherence often.
- Embed decision support tools into electronic medical records and use technology to identify high-risk patients not receiving appropriate therapy or meeting thresholds.
- Shared decision making and communication is critical to adherence to lifestyle and drug therapy along with follow-up lipids.
- Communicate the essential nature of a risk decision involving the evidence, patient characteristics, clinician judgment and after hearing about benefits, risks, and options, the inclusion of patient preference in shared decision-making.

Adapted from: http://accjacc.acc.org/Clinical_Document/Cholesterol_GL_Web_Supplement.pdf
Grundy SM, et al. Circulation 2019;139(25):e1082-e1143



Secondary Prevention Patients Shown to Derive the Largest Benefit from Intensification of Statin Therapy with the Addition of a PCSK9 Inhibitor

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Case

Frank

History	Current Medications
<ul style="list-style-type: none">▪ Frank is a 51-year-old construction site supervisor▪ Frank's History<ul style="list-style-type: none">• MI (4 months ago required LAD stent)• MI 5 years ago (RCA stent)• Hypertension• Prediabetes• High Cholesterol▪ Family History of pre-mature CAD<ul style="list-style-type: none">• Father had an MI at the age of 54 requiring CABG surgery• Brother had an MI at the age of 47	<ul style="list-style-type: none">▪ Aspirin 81 mg OD▪ Ticagrelor 90 mg BID▪ Losartan 25 mg OD▪ Metoprolol 25 mg OD▪ Rosuvastatin 40 mg OD <p>Diet and Exercise:</p> <ul style="list-style-type: none">• Frank adheres to a strict diet and runs on a treadmill at least for 30 minutes a day

Case

Frank



Physical Exam	Current Labs
<ul style="list-style-type: none">Blood Pressure: 140/92 mmHgWaist Circumference: 97 cmBMI: 32 kg/m²	<ul style="list-style-type: none">TC: 3.8 mmol/LTriglycerides: 1.01 mmol/LHDL-C: 1.1 mmol/LLDL-C: 1.9 mmol/LA1C: 6.3%Lp(a): 150 mg/dLHs-CRP: 3 mg/dL

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DISCUSSION

How frequently do you manage patients with a similar clinical profile in your practice?



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Which medication would provide Frank with the highest absolute risk reduction?

1. Ezetimibe 10 mg OD
2. PCSK9 inhibitor
3. Niacin 1000 mg OD
4. Colesevelam 3.75 gm BID

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NEW

Secondary Prevention Patients Shown to Derive the Largest Benefit from Intensification of Statin Therapy with the Addition of a PCSK9 Inhibitor

Frank

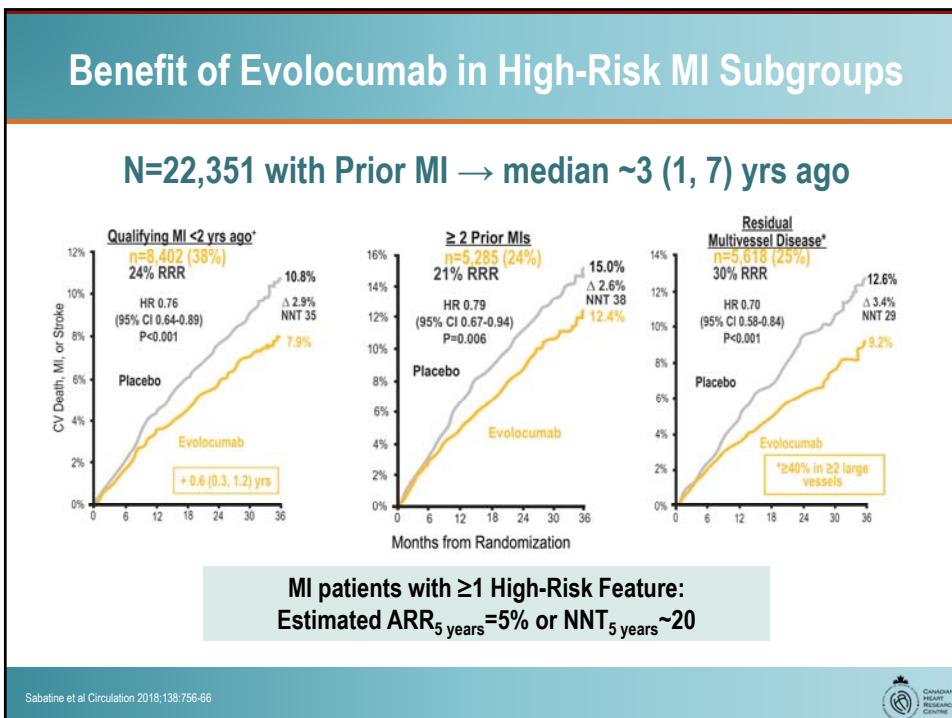
Recent acute coronary event (ACS):
• Hospitalised index ACS to 52 weeks post index ACS

Clinically evident ASCVD and any of the above:
• 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)

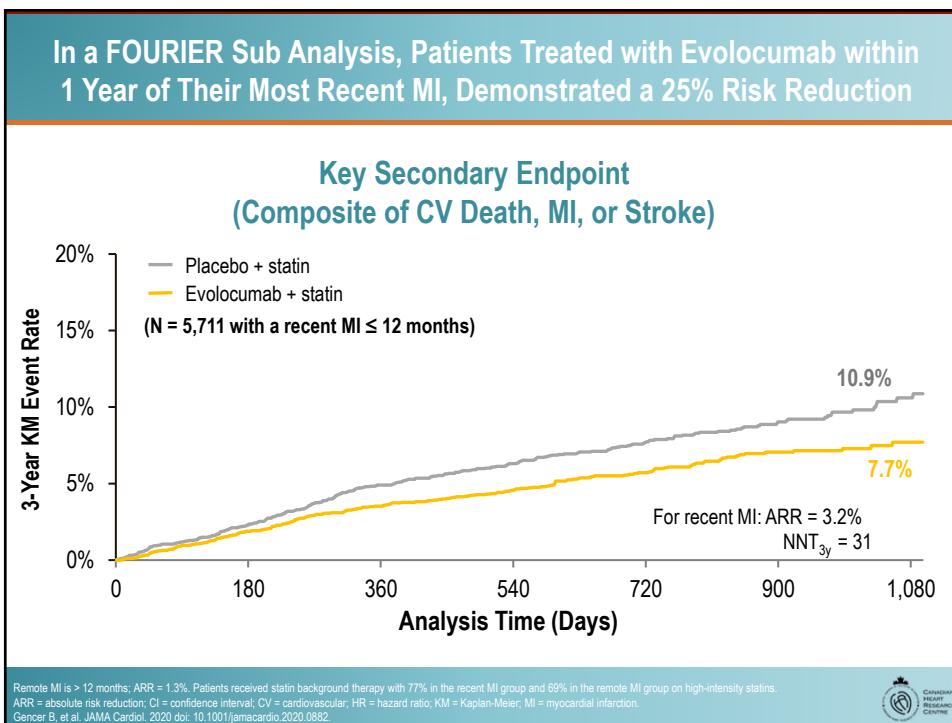
Intensification of lipid-lowering therapy with a PCSK9 inhibitor (evolocumab or alirocumab) – with or without the addition of ezetimibe – for secondary CV prevention patients shown to derive the largest benefit from PCSK9 inhibitor therapy in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) is recommended on maximally tolerated statin dose.
(Strong Recommendation: Moderate-Quality Evidence)

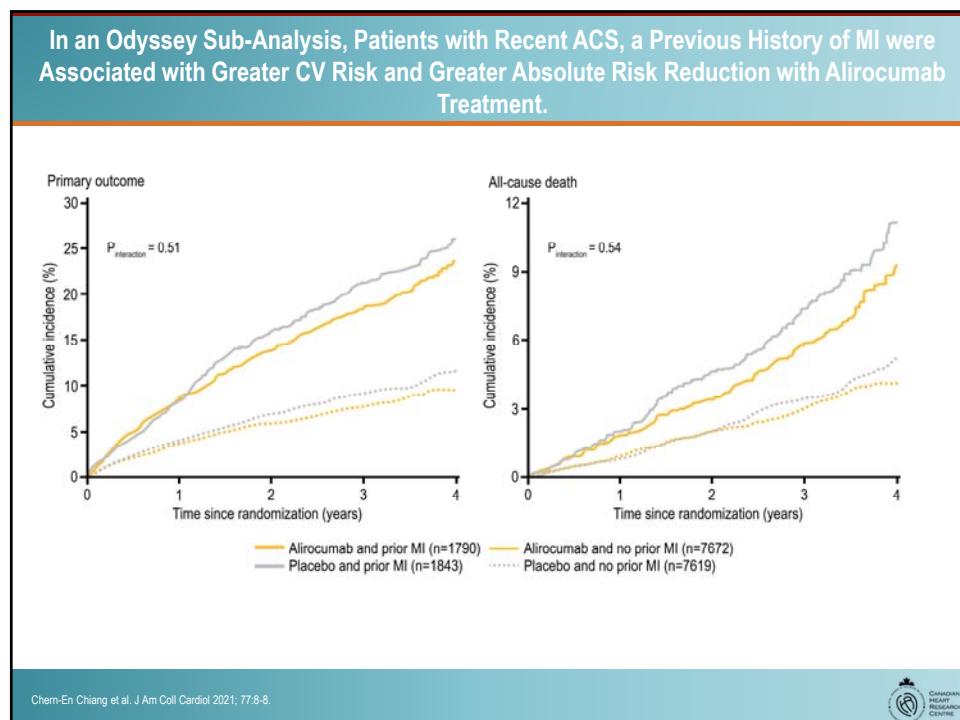
Pearson GS, et al. 2021 CCS Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. CJC. 2021;0(0). doi:10.1016/j.cjca.2021.03.016

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Case

Frank

Follow-Up Visit

- You added a PCSK9-inhibitor
- Re-emphasize the benefit of Frank's adherence to healthy lifestyle choices.
- Frank's most recent LDL-C was 0.7 mmol/L

- Patients with a recent MI are at a higher risk of CV events and show greater ARR with PCSK9 inhibitors than those with a more remote MI.
- Patients with a recent MI have a higher baseline risk and experience similar relative risk reduction with PCSK9 inhibitors.
- These findings support the overall concept in the 2021 Dyslipidemia Guidelines to aggressively lower LDL-C levels in very high-risk patients such as those with a recent MI.

ARR: Absolute Risk Reduction

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Secondary Prevention: New Key Take-Aways from the 2021 Guidelines

- LDL-C threshold of 1.8 mmol/L for intensification of lipid-lowering therapy with non-statin drugs in secondary prevention is emphasized.
- In very high-risk patients with LDL-C ≥ 1.8 mmol/L, intensification with PCSK9 Inhibitor is especially recommended with or without ezetimibe. *Table 3 (Secondary Prevention Patients Shown to Derive the Largest Benefit from Intensification of Statin Therapy with the Addition of a PCSK9 Inhibitor)* of the guidelines elaborates on the groups of very high-risk patients.
- For rest of the patients with ASCVD, ezetimibe is recommended first, unless the patient has LDL-C > 2.2 mmol/L when “it may be preferable to consider a PCSK9i as second line therapy” (i.e. after statin).
- Additional lipid-lowering therapy with ezetimibe and PCSK9i may also be considered for ASCVD patients with an LDL-C < 1.8 mmol, especially for patients considered to be at high risk for recurrent ASCVD events.
- No risk at very low LDL-C so no need for lipid-lowering therapy de-intensification (low LDL-C is safe).

Pearson GJ, et al. 2021 CCS Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. CJC. 2021;0(0). doi:10.1016/j.cjca.2021.03.016



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Program Summary

- In patients at risk for CV events, LDL-C reduction remains the top priority.
- LDL-C is the most modifiable risk factor in CV risk, and failure to attain guideline-recommended LDL-C thresholds is a key component of continued risk.
- Lower thresholds for treatment intensification have now been recommended and therefore additional LDL-C lowering options are needed.
- The data from clinical trials with PCSK9 inhibitors demonstrate efficacy and safety of LDL-C lowering by an additional 60% on top of statin \pm ezetimibe therapy resulting in further reductions in MACE.

Pearson GJ, et al. 2021 CCS Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. CJC. 2021;0(0). doi:10.1016/j.cjca.2021.03.016



Q&A and DISCUSSION



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BACK-UP SLIDES

Coronary Artery Calcium Scoring (CAC): *CAC adds to risk prediction beyond FRS*

- Coronary artery calcium testing is useful in diagnosing subclinical coronary artery disease and in predicting the risk of future cardiovascular events and death.
- Given the high negative predictive value of the test, it can also serve to reclassify risk in patients beyond traditional risk factors. *CAC adds to risk prediction beyond FRS*.
- Along with shared decision-making, elevated calcium scores can guide the initiation of statin or aspirin therapy.
- Repeat CAC testing is not recommended.

How to interpret CAC

- **CAC = 0** (true normal) has a negative predictive value in low-risk adults of 95-99% over 2-5 years, event rate of 1.5% over 10 years (not a zero rate of events).
- **CAC > 0** confirms presence of atherosclerotic plaque, and increasing scores are directly proportional to increased risk.
- **CAC > 100** is associated with high risk (>2% annual risk).
- **Even if CAC = 0**, patients with strong family history, poorly controlled risk factors, Familial Hypercholesterolemia (FH) or elevated Lp(a) still warrant consideration of treatment.

Parth P, et al; Cleveland Clinic Journal of Medicine September 2018, 85 (9) 707-716; DOI: <https://doi.org/10.3949/cccjm.85a.17097>



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CAC Impact on Risk Stratification Beyond FRS *Can Reclassify ASCVD Risk Between 7.5 – 19.9%*

Using 10-year ASCVD risk estimates plus Coronary Artery Calcium (CAC) score to guide therapy				
Patient's 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimate				
	<5%	5-7.5%	>7.5-19.9%	>20%
Using ASCVD Risk Estimate alone	Statin not recommended	Consider Statin in select groups*	Recommend Statin*	Recommend Statin*
Using ASCVD Risk Estimate alone + CAC	Statin not recommended	Statin not recommended	Statin not recommended	Recommend Statin
If CAC score = 0	Statin not recommended	Statin not recommended	Statin not recommended	Recommend Statin
If CAC score > 0	Statin not recommended	Consider for Statin	Recommend Statin	Recommend Statin
Does CAC score modify treatment plan?	X CAC not effective for this population	✓ CAC can reclassify risk up or down	✓ CAC can reclassify risk up or down	X CAC not effective for this population

* After risk discussion
Modified from: Greenland P et al JACC 2018;72(4): 434 - 47



NEW

CAC and the Decision to Treat

- **CAC screening using computed tomography imaging may be considered for asymptomatic adults ≥ 40 years and at intermediate risk (FRS 10%- 20%) for whom treatment decisions are uncertain is suggested. (Strong Recommendation, Moderate-Quality Evidence)**
- **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)
- **CAC screening may be considered for a subset of low-risk individuals > 40 years with a family history of premature ASCVD (men < 55 years; women ≤ 65 years) in addition to identifying known genetic causes of CAD such as elevated Lp(a) or FH is suggested. (Weak Recommendation; Low-Quality Evidence)**

 **Lab Testing in Canada**

- CAC testing is not uniformly available or uniformly funded in Canada at this time

ASCVd, atherosclerotic cardiovascular disease; AU, Agatston units; CAC, coronary artery calcium; CV, cardiovascular; FH, familial hypercholesterolemia; FRS, Framingham Risk Score; Lp(a), lipoprotein a; MI, myocardial infarction.
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: 

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Targets vs. Threshold Clarifying Terminology

 TARGETS	 THRESHOLD
for LDL-C lowering in response to therapy are defined by percentage responses	A specific value for LDL-C (or non-HDL-C) at or above which clinicians should consider starting or intensifying therapy

Grundy SM, et al. J Am Coll Cardiol. 2019; 73:e285-e350 

Targets vs Thresholds for Therapy

- RCTs identify thresholds of initiation of intensified lipid lowering therapy in secondary prevention.
- No direct evidence from RCTs (or other research) for any specific targets.
- No evidence for the often-quoted argument that targets rather than thresholds will result in better implementation of intensified lipid lowering therapy in secondary prevention.
- Potential detrimental effect of targets as it may lead to dose adjustment and higher LDL-C levels.
- Possible more complicated algorithm in clinical practice when chasing targets.
- Inaccuracy in calculated LDL -C for low LDL-C concentrations.

Pearson GJ, et al. 2021 CCS Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. CJC. 2021;0(0). doi:10.1016/j.cca.2021.03.016

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