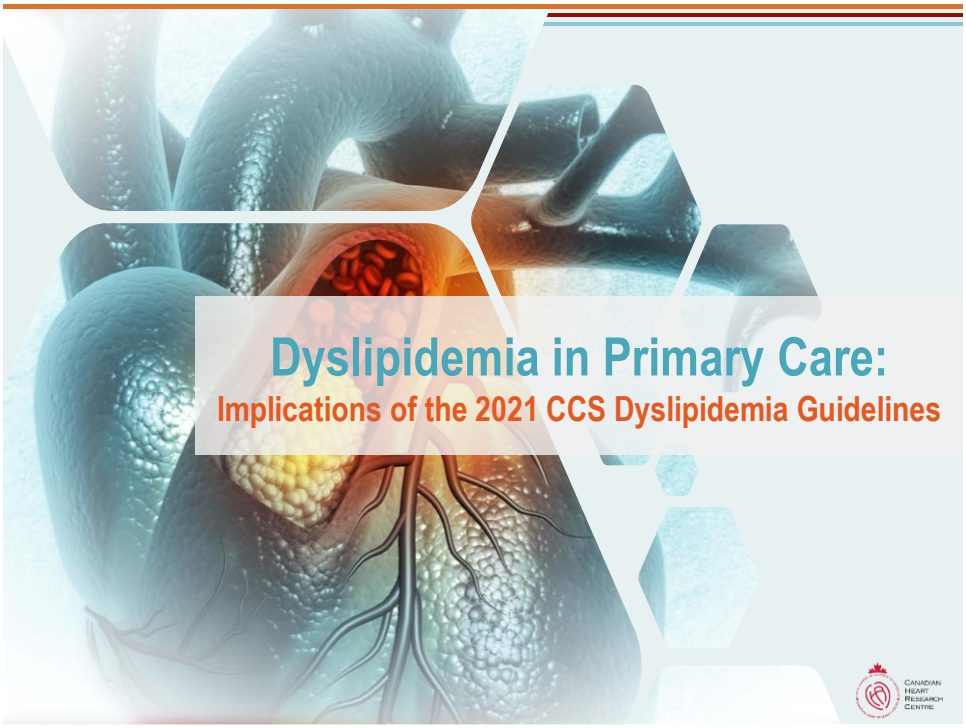


1

Learning Objectives

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

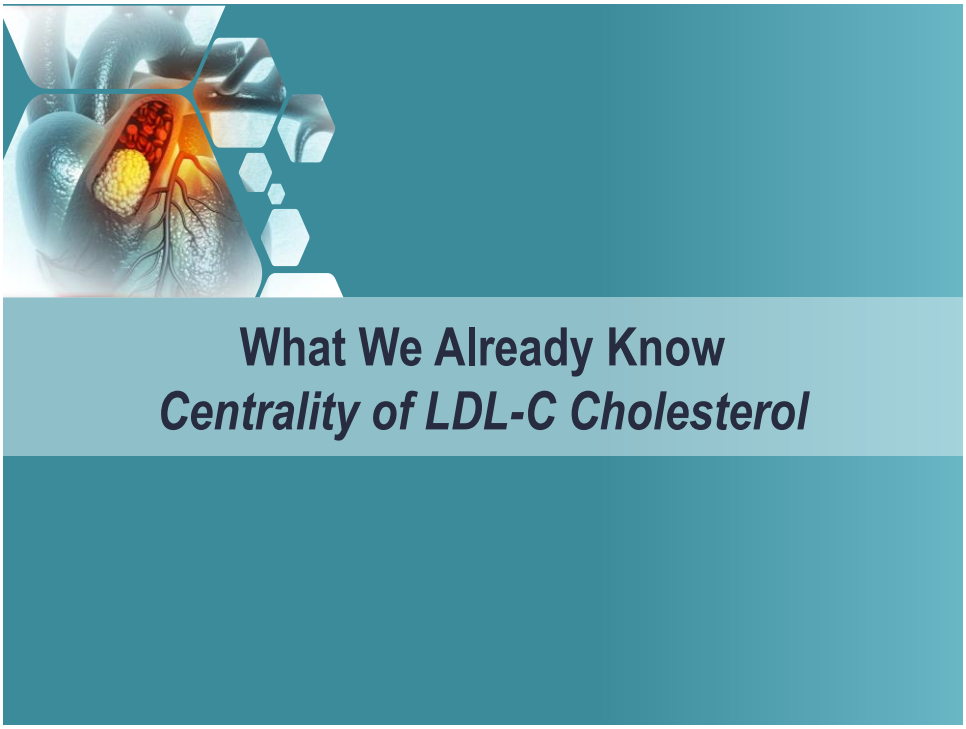
01 Explain the key updates to the 2021 CCS Dyslipidemia Guidelines for primary and secondary prevention

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

Canadian Heart Research Centre

2



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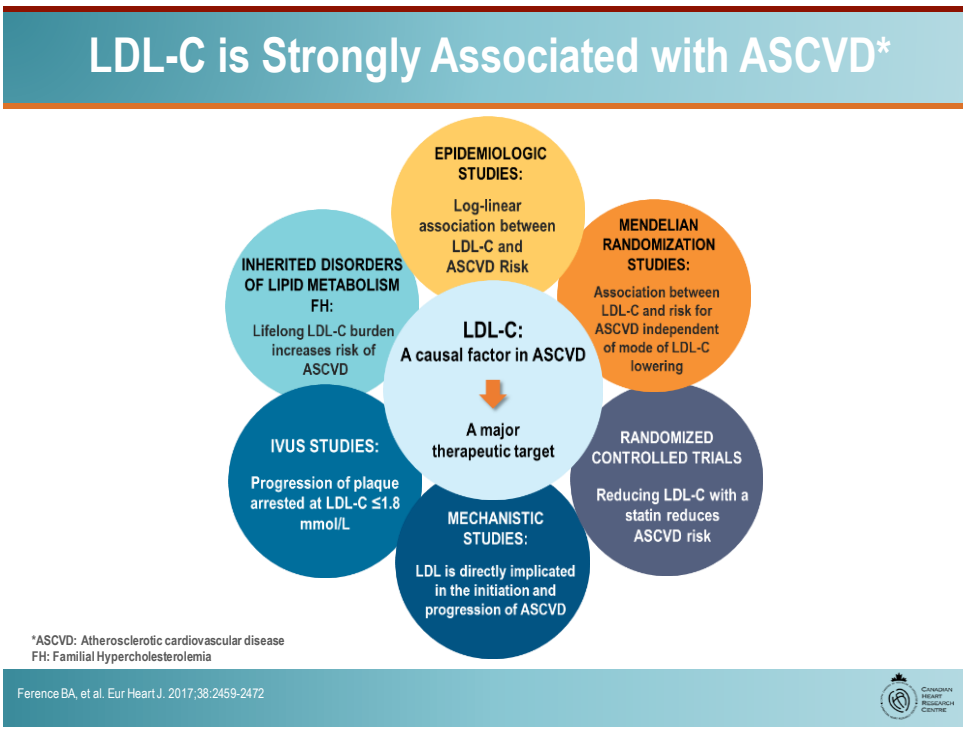


4

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

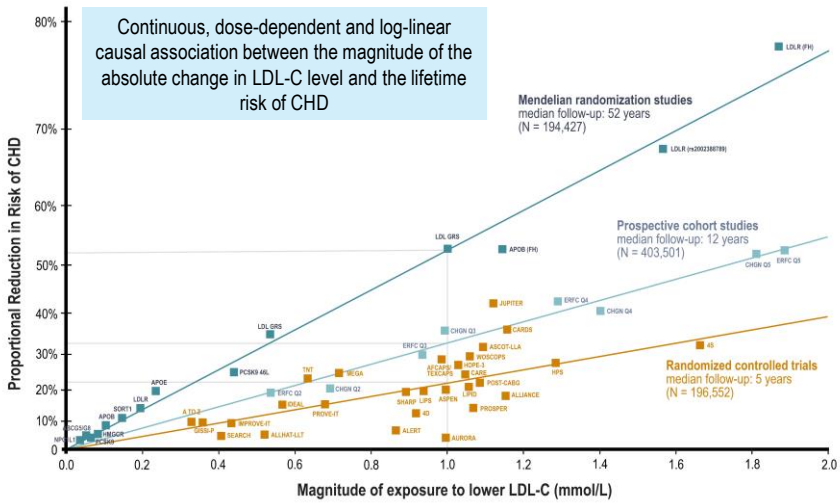
LDL-C reduction remains the main focus in guidelines

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,

5

LDL-C is Strongly and Directly Associated with the Risk of ASCVD Events



Adapted from Ference BA et al. Eur Heart J. 2017 Apr 24. doi: 10.1093/eurheartj/ehx144.

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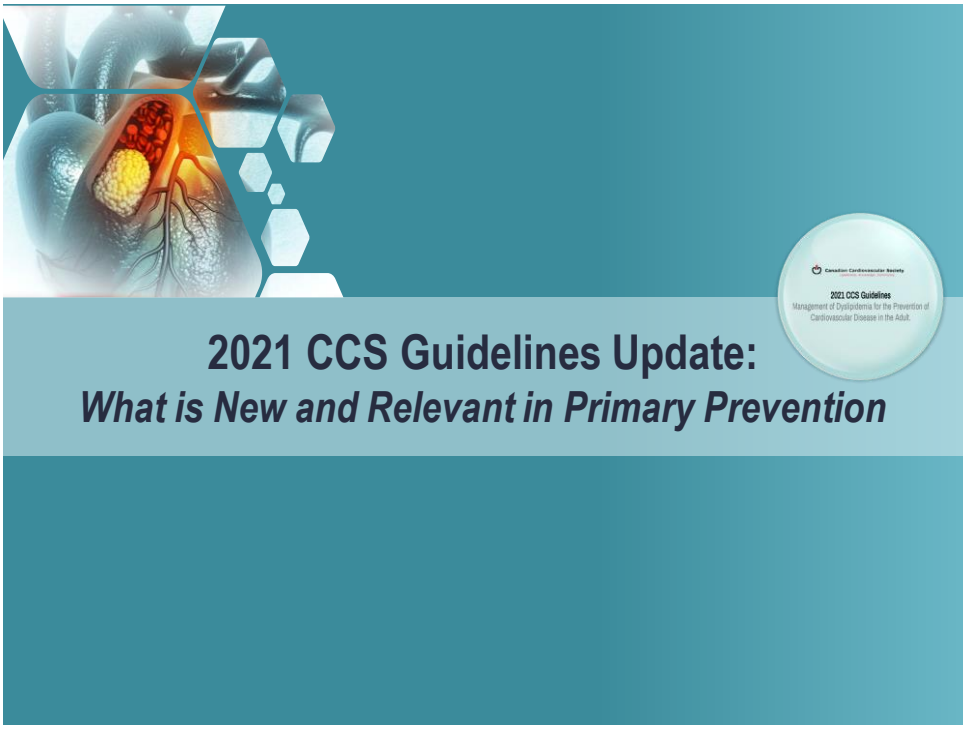


7

Screening Recommendations for Primary Prevention Patients

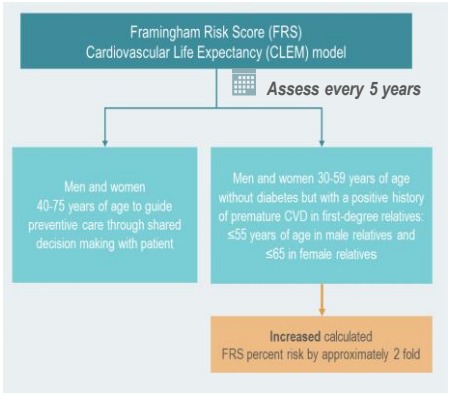
Who to Screen for Dyslipidemia in Adults at Risk

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 patient with any of the following conditions, regardless of age:

- Clinical evidence of atherosclerosis
- Abdominal aortic aneurysm (AAA)
- Diabetes mellitus
- Arterial hypertension
- Current cigarette smoking
- Stigmata of dyslipidemia (corneal arcus, xanthelasma, xanthoma)
- Family history of premature CVD†
- Family history of dyslipidemia
- Chronic kidney disease (eGFR ≤60 ml/min/1.73 m^2 or ACR ≥3 mg/mmol)
- Obesity (BMI ≥30 kg/m^2)
- Inflammatory diseases (RA, SLE, PsA, AS, IBD)
- HIV infection
- Erectile dysfunction
- COPD
- History of hypertensive disorder of pregnancy



*Adapted from the 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 erythematosus; 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

8

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 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

9

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)*

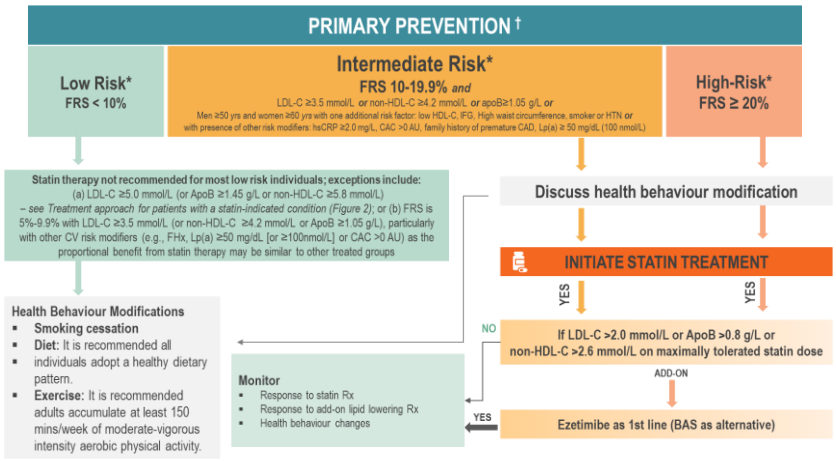
Practical Tip:

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.

10

Treatment Approach for Primary Prevention Patients (Without a Statin Indicated Condition)



- **Calculate Framingham risk score to guide whether statin therapy is recommended.**
- **Health behaviour changes remain the cornerstone of disease prevention.**

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

11

NEW Non-HDL-C vs. ApoB: Which is Preferred 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†
- *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*

- **It is recommended 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)*

†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

12

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'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;76(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. Erikhman B, Anuurad E, Berglund L. Lipoprotein (a): impactby 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

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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/ccjm.85a.17097

14

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**
- **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.**
  - ***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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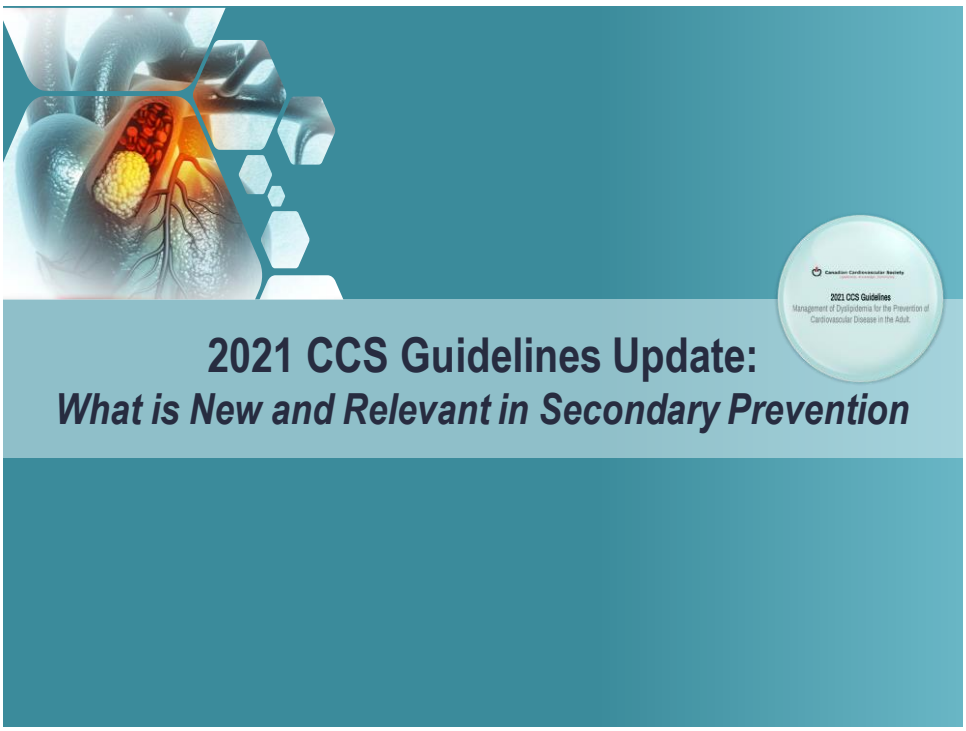
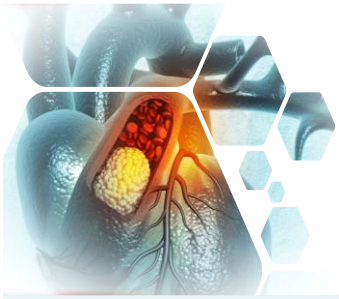


2021 CCS Guidelines Update:
What is New and Relevant in Secondary Prevention

16



The Most Appropriate Lipid/Lipoprotein Threshold for the Intensification of Therapy in the Management of Dyslipidemia

17

NEW

Introducing Treatment Thresholds…..

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

18

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:

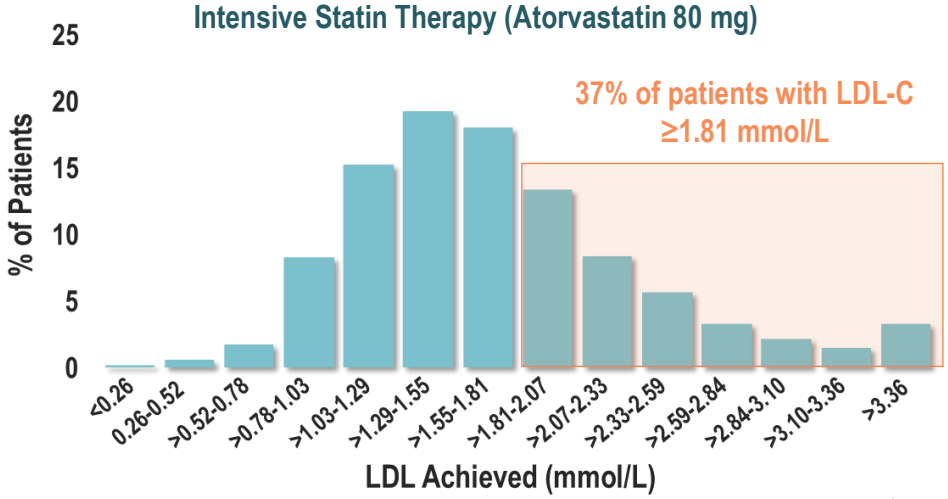
Every **1 mmol/L** reduction in LDL-C → **23%** reduction in risk of major coronary events

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
Cholesterol Treatment Trialists' (CTT) Collaborators. Lancet 2012;380:581-590

19

BUT … Not Everyone on an Intensive Statin Reaches LDL-C Threshold

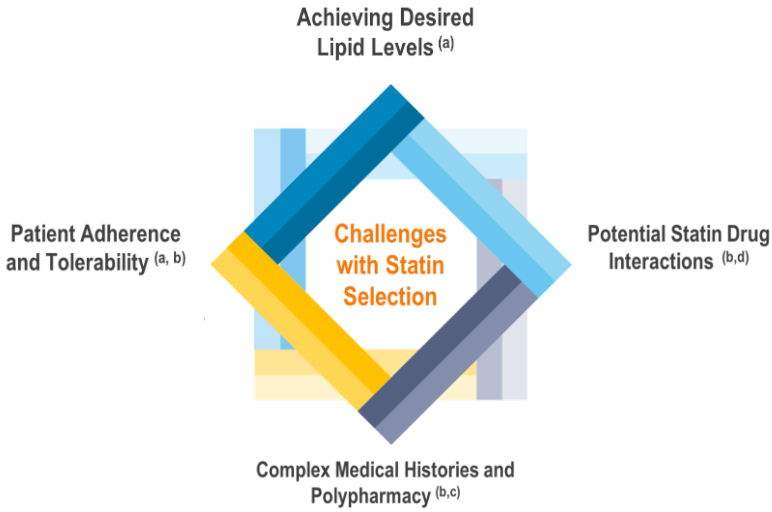
Distribution of 4-month LDL-C levels Among Patients Treated with Intensive Statin Therapy (Atorvastatin 80 mg)



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

20

Multiple Challenges with Statin Selection



a. Ansell BJ. J Manag Care Pharm. 2008; 14 (suppl S-b): 29-S15;
b. Meade LT. US Pharm. 2007; 32:66-71;
c. Vogeli C, et al. J Gen Intern Med. 2007; 22(suppl 3): 391-395;
d. Ito M, et al. J Clin Lipidol. 2014;8:69-76

21

Adverse Effects Reported with Statin Therapy

Mach F, et al. Eur Heart J 2018; 39:2526-39

22

Impact of Statin-Associated Muscle Symptoms (SAMS)

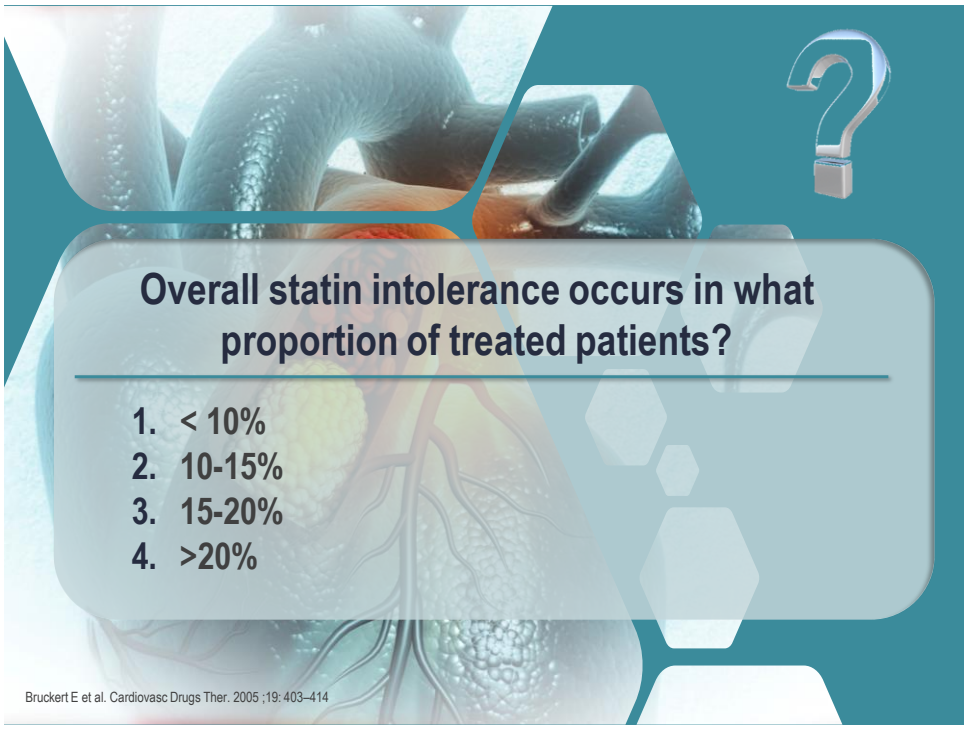
Consequences of Low Statin Adherence: Increased CV Risk

Proportion of days covered with statin therapy (%)	Hazard ratio (95% CI) Primary Prevention	Hazard ratio (95% CI) Secondary Prevention
<10	1 (reference)	1 (reference)
10-19	1.35 (1.22-1.50)	1.28 (1.18-1.39)
50-59	0.77 (0.67-0.88)	0.69 (0.63-0.76)
>90	0.55 (0.49-0.61)	0.49 (0.46-0.53)

- **75% of patients discontinue statin within 2 years**
- **SAMS is the prevailing reason in ~60% of patients**

Chodick G et al. Clin Ther 2008;30:2167-79.
Cohen J et al. Clin Lipidol 2012;6:208-15
Shalev. Arch. Int Med 2009

23



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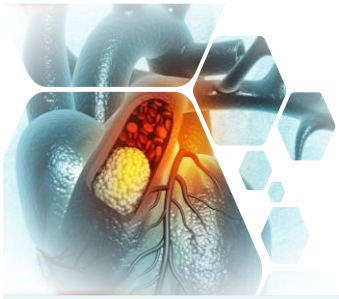

The Role of Non-Statin Therapies to Reduce ASCVD Events

25

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/m^2

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/1.73m^2

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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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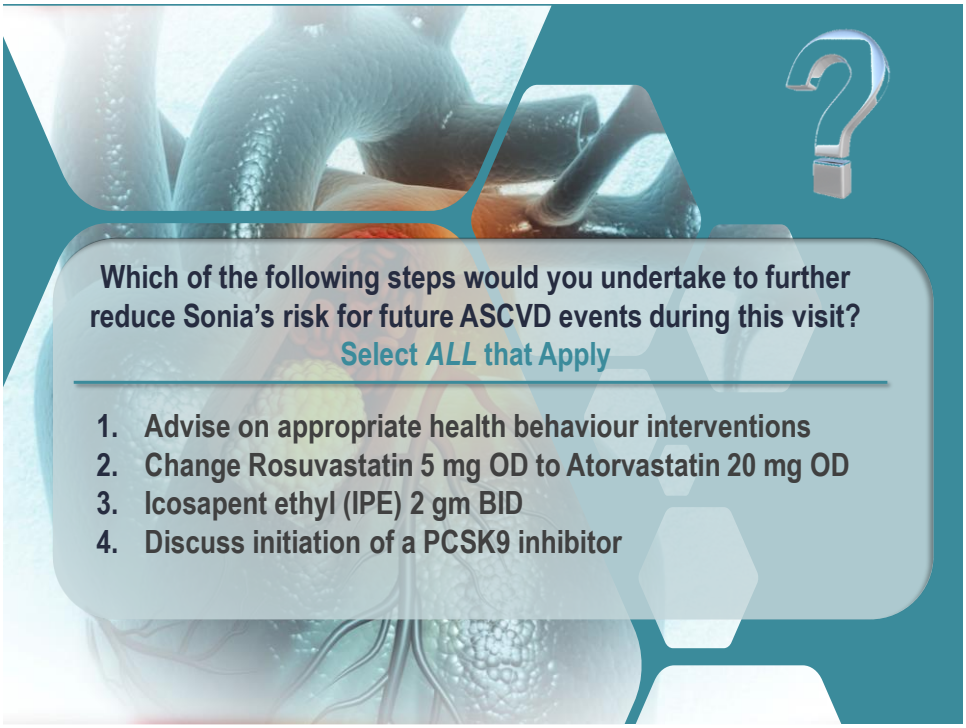

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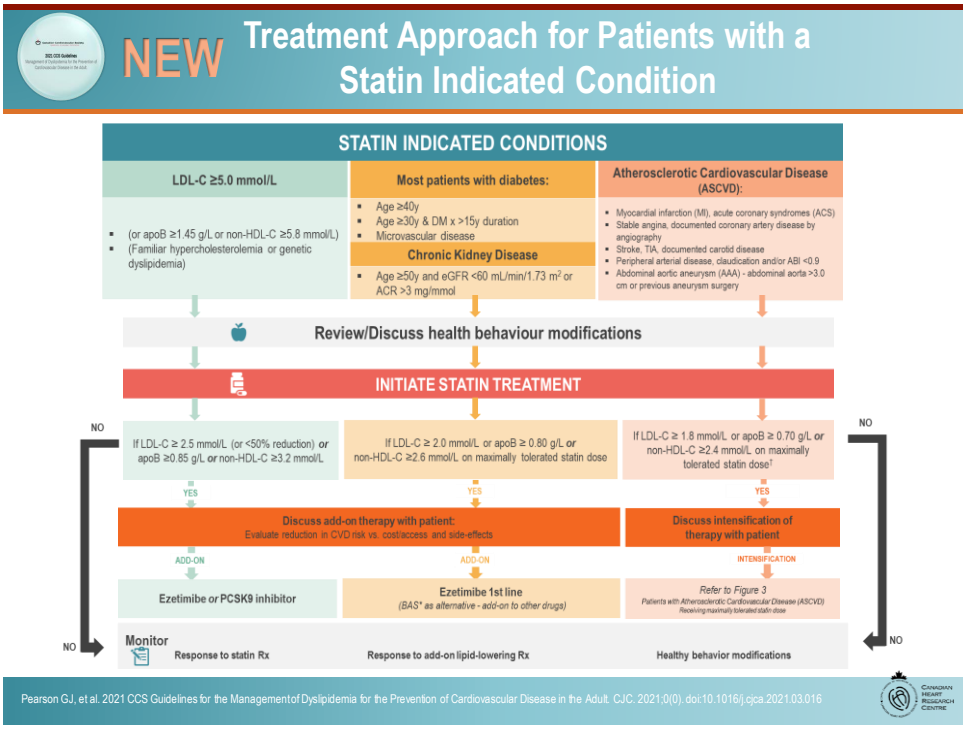

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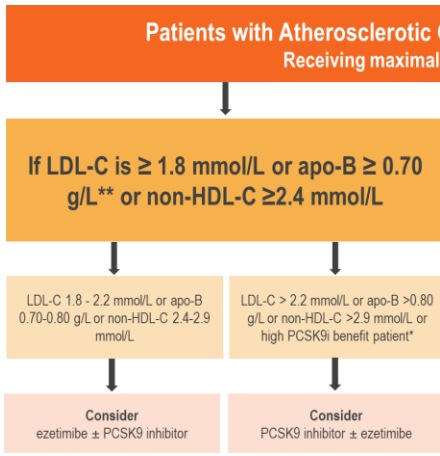
NEW Treatment Intensification Approach for Patients with Atherosclerotic Cardiovascular Disease (ASCVD)



* Patients shown to derive the largest benefit from intensification of statin therapy with a PCSK9 inhibitor therapy are identified in table 3 (next slide)
** At low levels of LDL-C or non-HDL-C, measurement of apoB is more accurate with other markers.

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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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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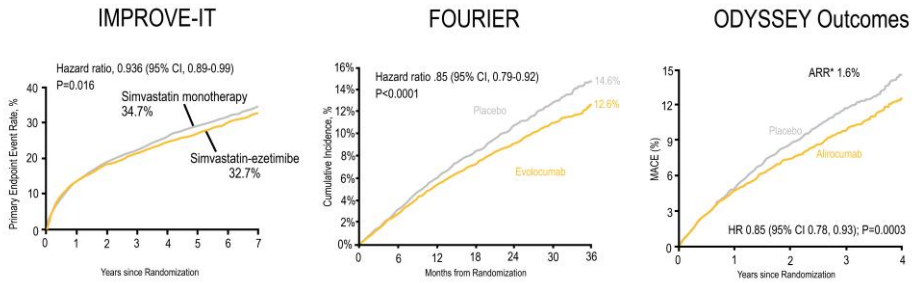
Non-Statin Strategies to Further Reduce LDL-C



- Adding ezetimibe to statin therapy provides and 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 ± 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
Sebatine 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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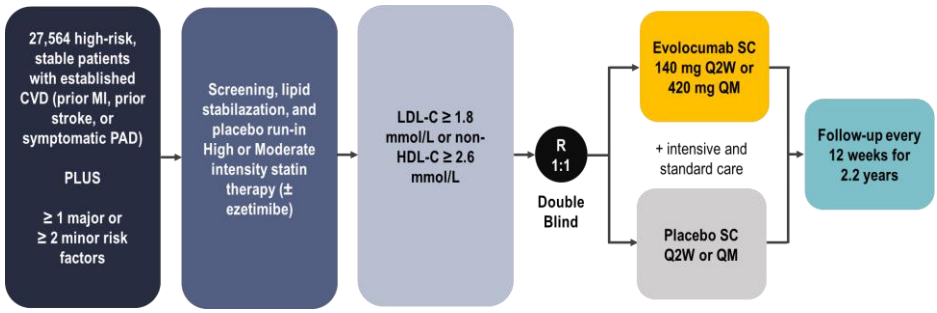
FOURIER Outcomes Trial
Evolocumab



- Primary Efficacy Endpoint: composite of CV death, MI, stroke, hospitalization for UA, or coronary revascularization
- Secondary Efficacy Endpoint: composite of CV death, MI, stroke

Sebatine MS, et al. N Engl J Med. 2017;376:1713-1722

34

ODYSSEY Outcomes Study
Alirocumab

- **18,924 patients with ACS within prior year, not stable ASCVD**
- **2 to 16 weeks optimized atorvastatin/rosuvastatin**
  - If LDL-C ≥ 1.8 mmol/L, non-HDL-C ≥ 2.6 mmol/L, or apoB ≥ 0.8 g/L patients were randomized to:
    - Alirocumab 75 mg every two weeks or placebo
- **Titration target: 0.6 to 1.3 mmol/L**
  - If LDL-C ≥ 1.3 mmol/L → alirocumab uptitrated to 150 mg every 2 weeks
  - If LDL-C < 0.4 mmol/L → switched to placebo
- **Median follow-up 2.8 years**
  - On-treatment LDL-C: alirocumab 1.4 mmol/L vs. placebo 2.6 mmol/L

Schwartz GG, et al. N Engl J Med. 2018;379:2097-2107

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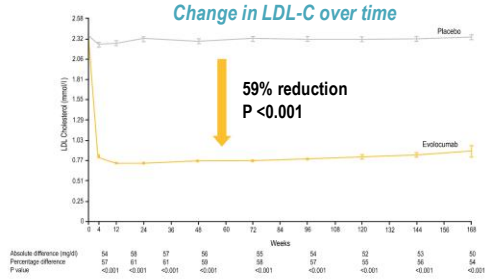
PCSK9 Inhibitors are Efficient at Lowering LDL-C

FOURIER: Evolocumab[a]

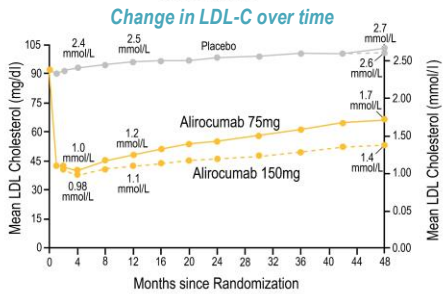
Change in LDL-C over time



↓ LDL-C by 59%

ODYSSEY Outcomes: Alirocumab[b]

Change in LDL-C over time



↓ LDL-C by 55%

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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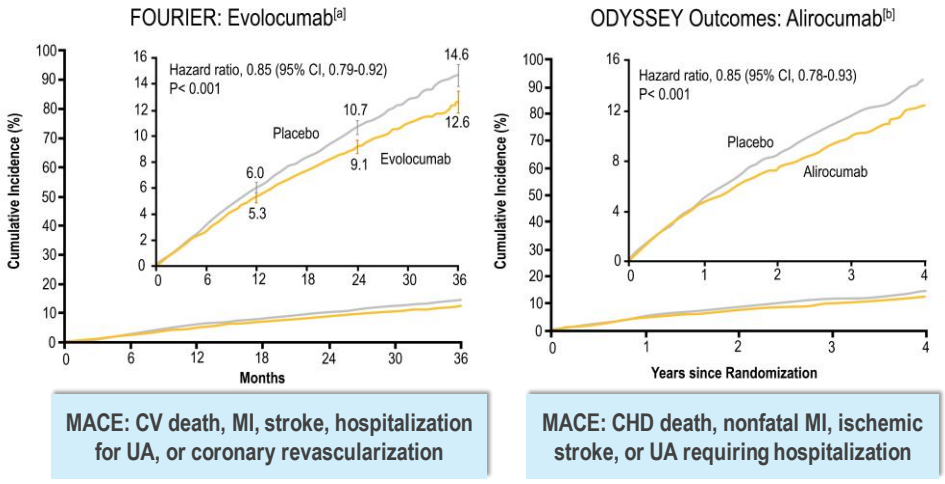
PCSK9 Inhibitors Reduce CV Events



MACE: CV death, MI, stroke, hospitalization for UA, or coronary revascularization

MACE: CHD death, nonfatal MI, ischemic stroke, or UA requiring hospitalization

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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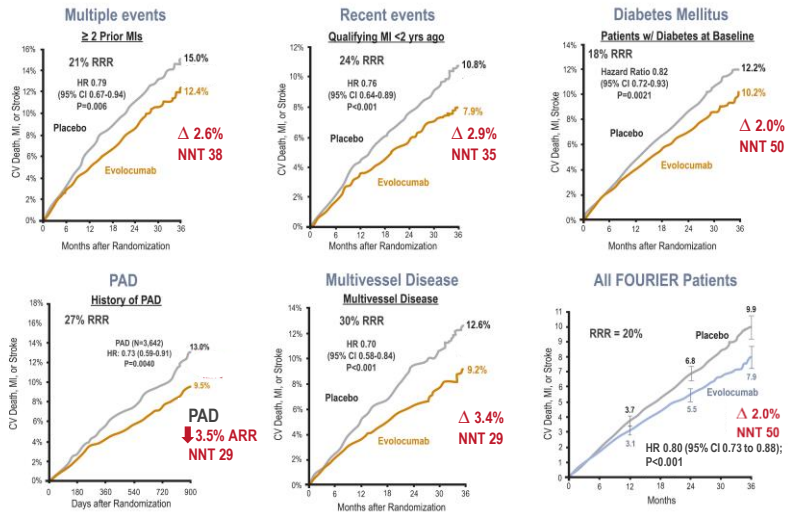
FOURIER Trial
Multiple High-Risk Patient Population Sub-Analysis



Sabatine MS, et al . AHA 2017 Poster

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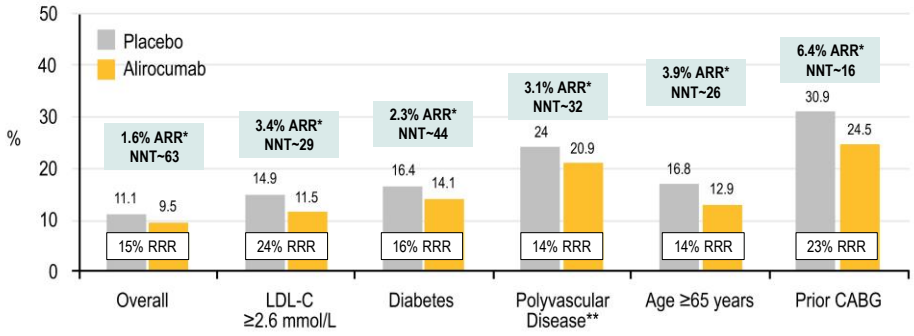
Benefit of Alirocumab in High-Risk Patients

CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization*



*Based on cumulative incidence or 3-year KM estimates

**CAD + PAD ± CeVD

Adapted from Schwartz et al N Engl J Med 2018;379:2097-107; Ray et al Lancet Diabetes Endocrinol 2019;2019;7:618-28; Jukema et al J Am Coll Cardiol 2019;74:1167-76; Sinnaeve et al Eur Heart J 2020;41:2248-58; Goodman et al J Am Coll Cardiol 2019;74:1177–86

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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 ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) on maximally tolerated statin dose is recommended. If ezetimibe is used initially and LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) PCSK9 inhibitor therapy is recommended.
(Strong recommendation; High Quality Evidence).

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.cjca.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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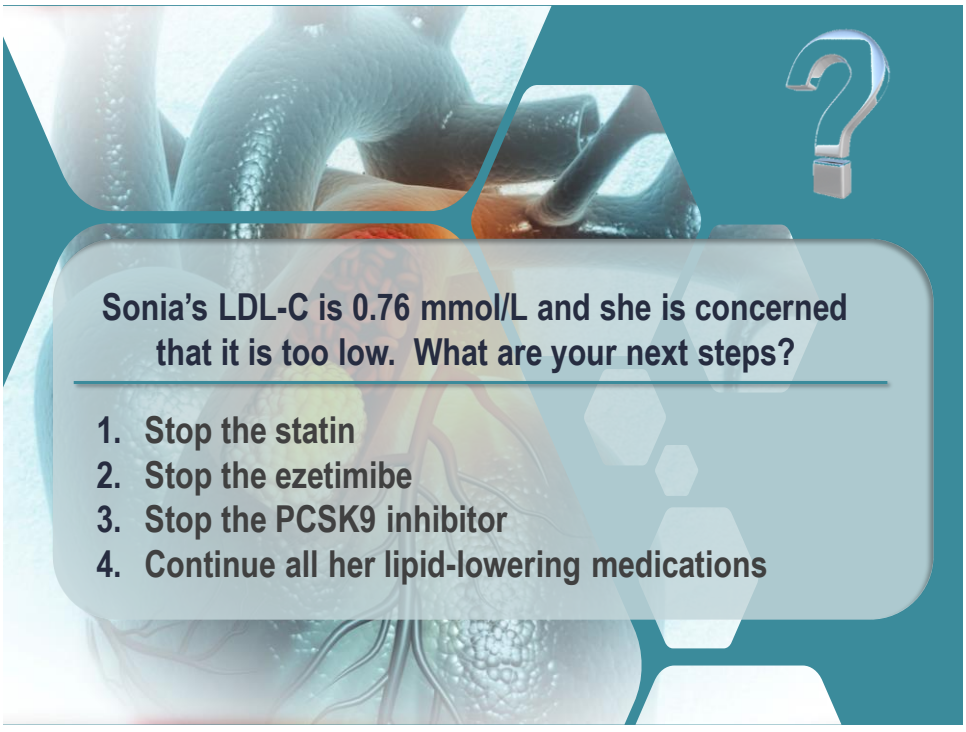
Case

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 in now too low**

41



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PCSK9 Inhibitors are Safe

FOURIER: Evolocumab[a]

Outcome	Evolocumab (N = 13,769)	Placebo (N = 13, 756)
Adverse events-no. of patients, %		
Any	77.4	77.4
Serious	24.8	24.7
Thought to be related to the study agent and leading to discontinuation of study regimen	1.6	1.5
Injection-site reaction	2.1	1.6
Allergic reaction	3.1	2.9
Muscle-related event	5.0	4.8
Rhabdomyolysis	0.1	0.1
Cataract	1.7	1.8
Adjucated case of new-onset diabetes	8.1	7.7
Neurocognitive event	1.6	1.5

ODYSSEY Outcomes: Alirocumab[b]

Variable	Alirocumab (N = 9,451)	Placebo (N = 9,443)
Adverse events-no. of patients, %		
Any adverse event	75.8	77.1
Serious adverse event	23.3	24.9
Adverse event that led to death	1.9	2.4
Adverse event that led to discontinuation of the trial regimen	3.6	3.4
Local injection-site reaction	3.8	2.1
General allergic reaction	7.9	7.8
Diabetes worsening or diabetic complication among patients with diabetes at baseline, %	18.8	21.2
New onset diabetes among patients without diabetes at baseline, %	9.6	10.1
Neurocognitive disorder	1.5	1.8
Hepatic disorder	5.3	5.7
Cataracts	1.3	1.4
Hemorrhagic stroke, adjudicated	<0.1	0.2

a. Sebatine 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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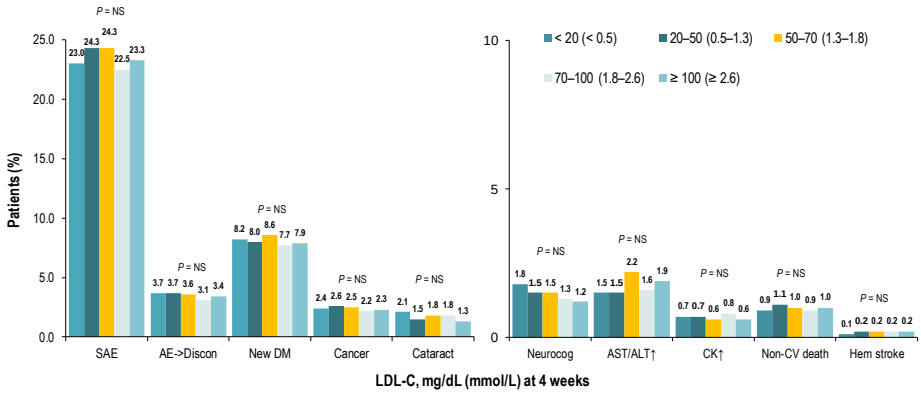
In the FOURIER Trial, Even at Very Low LDL-C < 0.5 mmol/L Safety Parameters Were Similar Across Achieved LDL-C Levels

Safety Events by Achieved LDL-C Concentration 4 Weeks After Randomization



- A secondary analysis of 25,982 patients from the FOURIER trial explored the association between LDL-C concentration at 4 weeks and prespecified safety events over a median of 2.2 years of follow-up

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CV, cardiovascular; Discon, discontinued; DM, diabetes mellitus; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk; Hem, hemorrhagic; LDL-C, low-density lipoprotein cholesterol; Neurocog, neurocognitive; NS, not significant; serious adverse event.
Giugliano RP, et al. Lancet. 2017;390:1962-1971.

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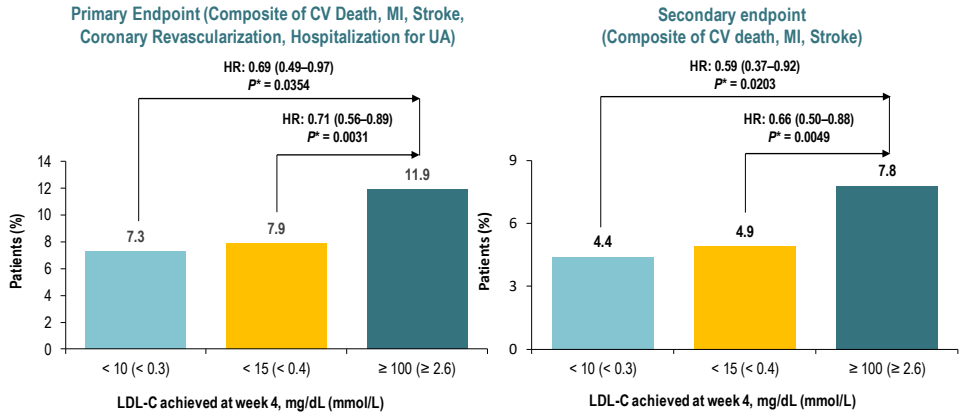
Achievement of Ultra-low LDL-C Levels in FOURIER Further Reduced the Risk of Major CV Events



Major CV events progressively declined with lower achieved LDL-C at week 4

*P value compared with the group achieving an LDL-C ≥ 100 mg/dL (≥ 2.6 mmol/L) at 4 weeks.
CV, cardiovascular; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; UA, unstable angina.
Giugliano RP, et al. Lancet. 2017;390:1962-1971.

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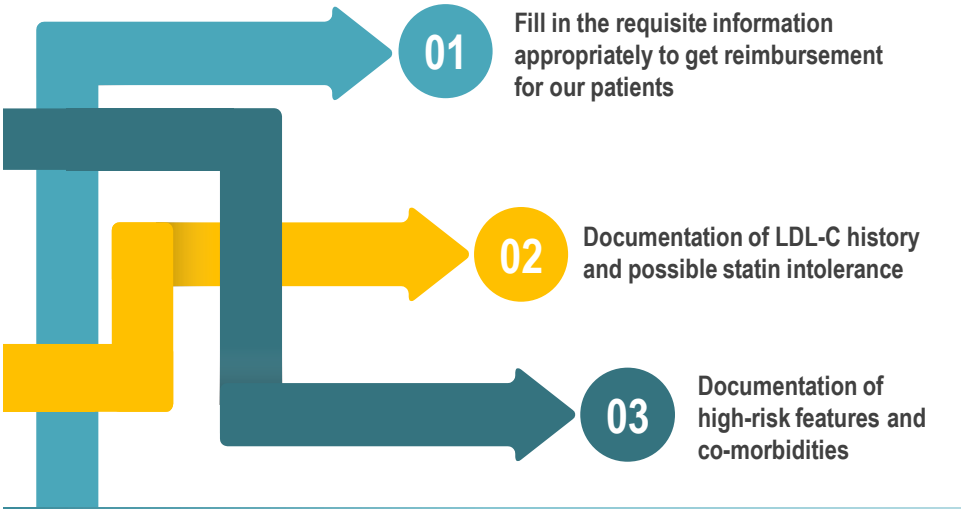
Overcoming Access Barriers to PCSK9 Inhibitors



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

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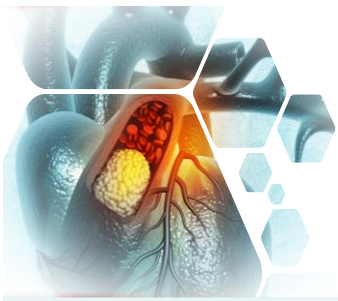

Secondary Prevention Patients Shown to Derive the Largest Benefit from Intensification of Statin Therapy with the Addition of a PCSK9 Inhibitor

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Case

Frank

History

- Frank is a 51-year-old construction site supervisor
- **Frank's History**
  - MI (4 months ago required LAD stent)
  - MI 5 years ago (RCA stent)
  - Hypertension
  - Prediabetes
  - High Cholesterol
- **Family History of pre-mature CAD**
  - Father had an MI at the age of 54 requiring CABG surgery
  - Brother had an MI at the age of 47

Current Medications

- Aspirin 81 mg OD
- Ticagrelor 90 mg BID
- Losartan 25 mg OD
- Metoprolol 25 mg OD
- Rosuvastatin 40 mg OD
- **Diet and Exercise:**
  - Frank adheres to a strict diet and runs on a treadmill at least for 30 minutes a day

49

Case

Frank

Physical Exam

- **Blood Pressure:** 140/92 mmHg
- **Waist Circumference:** 97 cm
- **BMI:** 32 kg/m^2

Current Labs

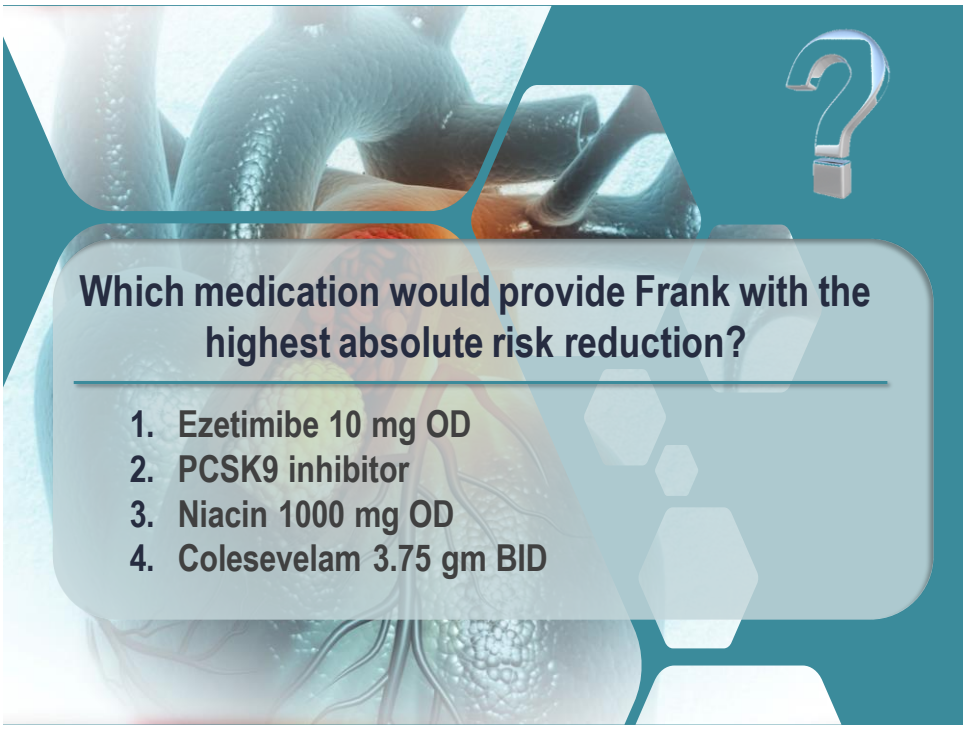
- **TC:** 3.8 mmol/L
- **Triglycerides:** 1.01 mmol/L
- **HDL-C:** 1.1 mmol/L
- **LDL-C:** 1.9 mmol/L
- **A1C:** 6.3%
- **Lp(a): 150 mg/dL**
- **Hs-CRP:** 3 mg/dL

50

DISCUSSION

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

51



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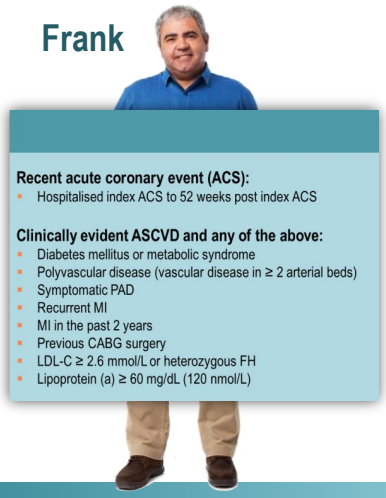
NEW

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



Intensification of lipid-lowering therapy with a PCSK9 inhibitor (evolocumab or alirocumab) – with or without the addition of ezetimibe – for secondary CV prevention patients shown to derive the largest benefit from PSCK9 inhibitor therapy in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) is recommended on maximally tolerated statin dose.

(Strong Recommendation; Moderate-Quality Evidence)

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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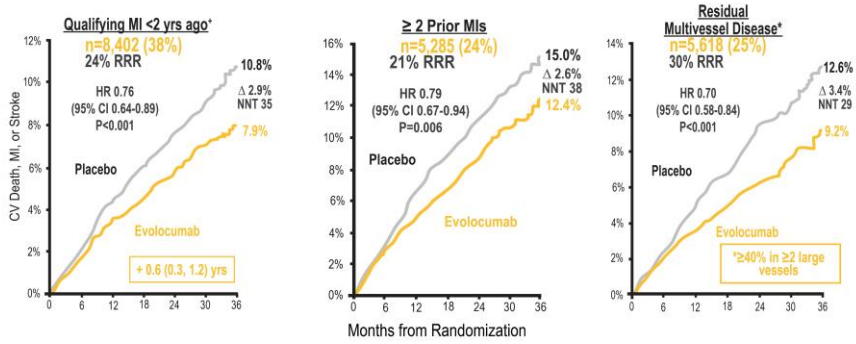
Benefit of Evolocumab in High-Risk MI Subgroups

N=22,351 with Prior MI → median ~3 (1, 7) yrs ago



MI patients with ≥1 High-Risk Feature:
Estimated $ARR_{5\ years}$=5% or $NNT_{5\ years}$~20

Sabatine et al Circulation 2018;138:756-66

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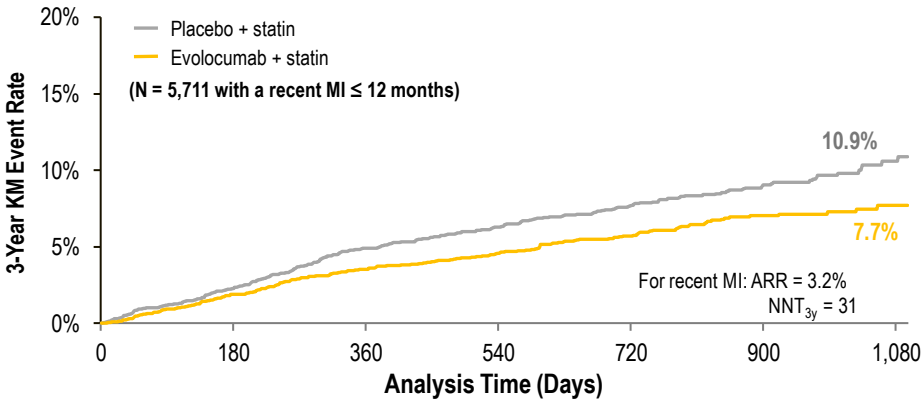
In a FOURIER Sub Analysis, Patients Treated with Evolocumab within 1 Year of Their Most Recent MI, Demonstrated a 25% Risk Reduction

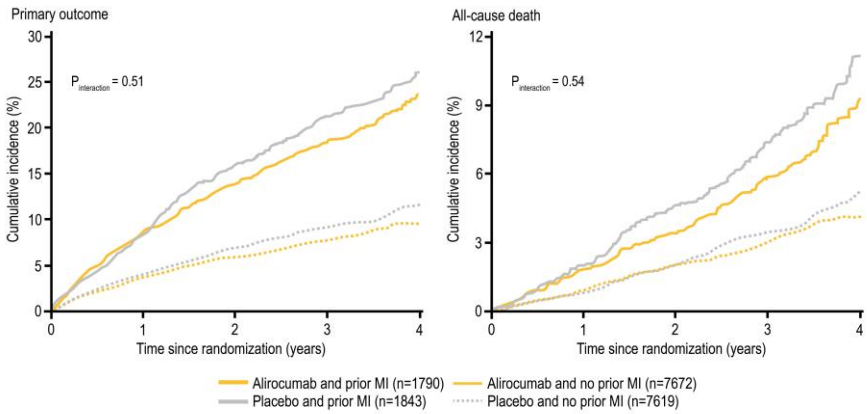
Key Secondary Endpoint (Composite of CV Death, MI, or Stroke)



Remote MI is > 12 months; ARR = 1.3%. Patients received statin background therapy with 77% in the recent MI group and 69% in the remote MI group on high-intensity statins.
ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; KM = Kaplan-Meier; MI = myocardial infarction.
Gencer B, et al. JAMA Cardiol. 2020 doi: 10.1001/jamacardio.2020.0882.

55

In an Odyssey Sub-Analysis, Patients with Recent ACS, a Previous History of MI were Associated with Greater CV Risk and Greater Absolute Risk Reduction with Alirocumab Treatment.



Chern-En Chiang et al. J Am Coll Cardiol 2021; 77:8-8.

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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 ARRs 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 ± 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

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Q&A and DISCUSSION

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BACK-UP SLIDES

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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/ccjm.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				
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

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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

for LDL-C lowering in response to therapy are defined by percentage responses

THRESHOLD

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

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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.cjca.2021.03.016

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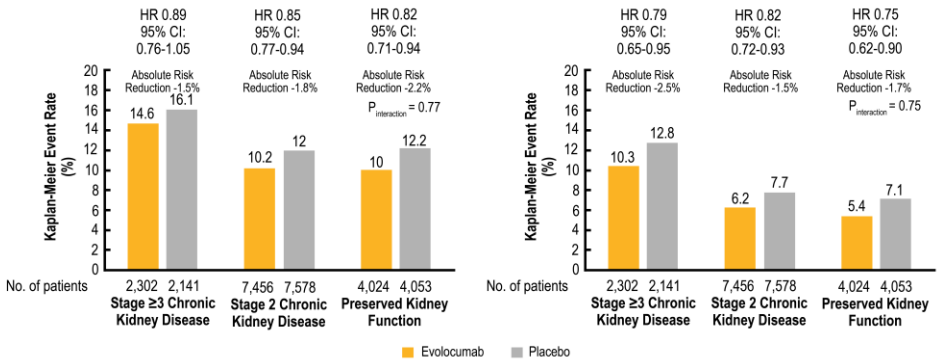
FOURIER Trial

Efficacy of Evolocumab in Patients with CKD



Kaplan-Meier event rates at 30 months are provided according to treatment group with placebo in grey and evolocumab in orange

Chaytan DM, et al. J AM Coll Cardiol. 2019:73:2961-2970

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