

1

Presenter Disclosure

Presenter - [presenter name]

Relationships with financial sponsors:

- Grants/Research Support:
- Speakers Bureau/Honoraria:
- Consulting Fees:
- Patents:
- Other:



2

Disclosure of Financial Support

This program has received financial support from Amgen Canada in the form of an educational grant.

This program has received in-kind support from Amgen Canada in the form of logistical support.

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[Presenter] has received [payment/funding, etc.] from [organization supporting this program AND/OR organization whose product(s) are being discussed in this program].

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3

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- The Canadian Heart Research Centre (CHRC) assesses conflict of interest with its instructors, planners, managers and other individuals who are in a position to control the content of CME activities. All relevant conflicts of interest that are identified are thoroughly vetted by the CHRC for fair balance, scientific objectivity of studies utilized in this program, and patient care recommendations. The CHRC is committed to providing its learners with high quality CME activities and related materials that promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest.
- The speaker had provided a full disclosure in advance of the program. The scientific content of the program is evidence based and all content related to pharmacotherapy is within product label. The program has been peer reviewed and is nationally accredited by the College of Family Physicians of Canada.
- [Presenter] has provided his disclosure information at the start of this presentation.



4

Program Development

This program was planned by the Canadian Heart Research Centre, a not-for-profit academic organization to achieve scientific integrity, objectivity, and balance.



This program has received an educational grant and in-kind support from Amgen Canada



5

Learning Objectives

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

- 01** Recognize the centrality of LDL-C and its cumulative exposure to increased risk of ASCVD events
- 02** Evaluate the limitations of current lipid lowering agents and assess recommendations for lipid lowering agents beyond, or in addition to, statin therapy for high-risk patient
- 03** Identify those patients who would benefit from additional therapy beyond statins to reduce CV risk
- 04** Explain the latest clinical data for PCSK9 inhibitors and use effective strategies to integrate the data into clinical care to reduce the risk for CV events
- 05** Appropriately apply best guideline practice recommendations into routine clinical practice based on specific patient characteristics

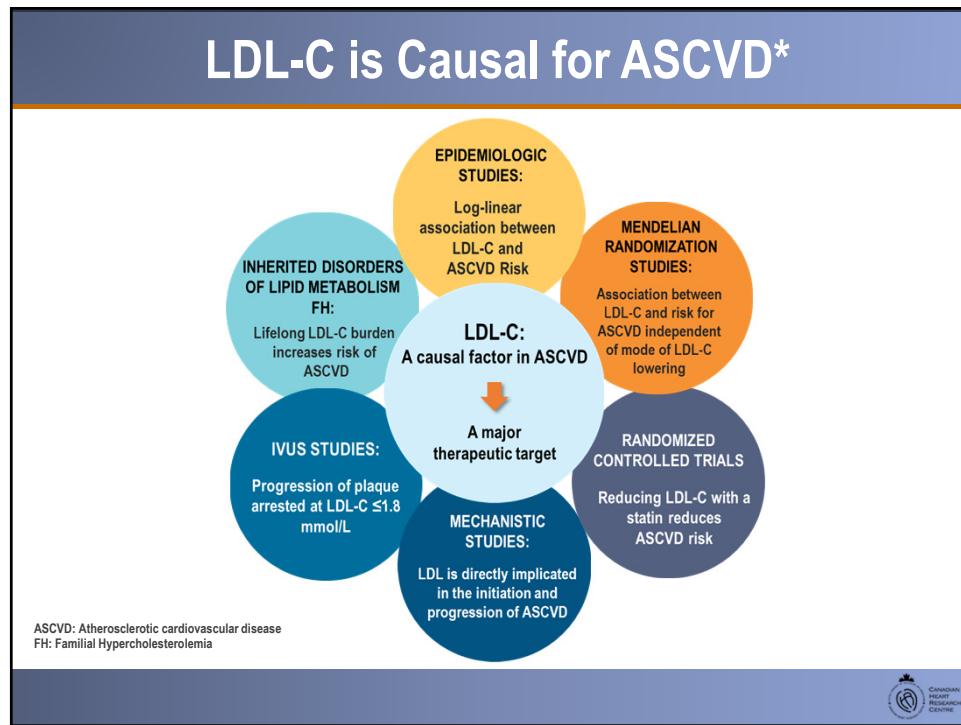
ASCVD: Atherosclerotic cardiovascular disease



6

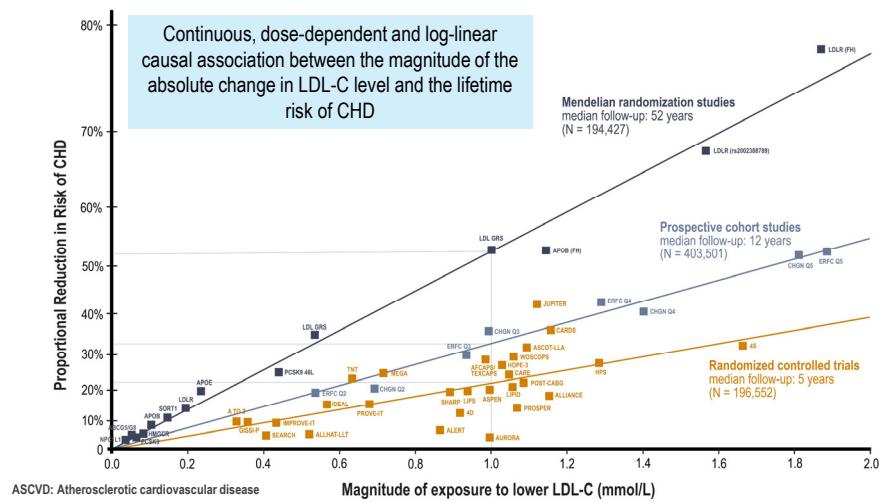


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8

Circulating LDL-C is Strongly Associated with an Increase in the Risk of ASCVD Events

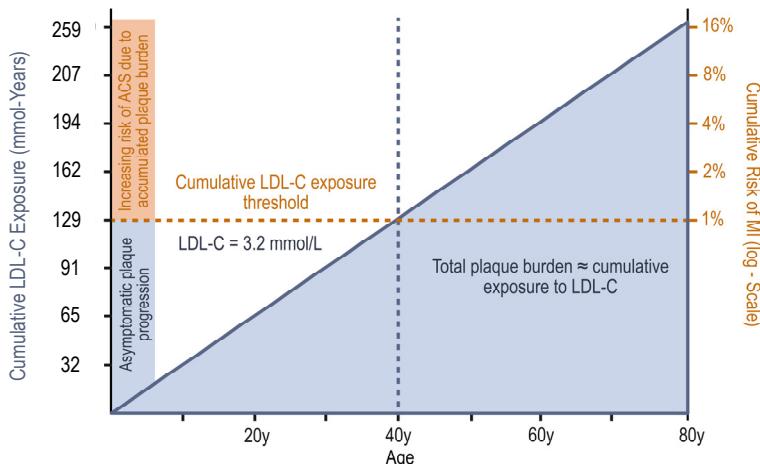


Adapted from Ference BA et al. Eur Heart J. 2017 Apr 24; doi: 10.1093/euroheartj/ehx144.



9

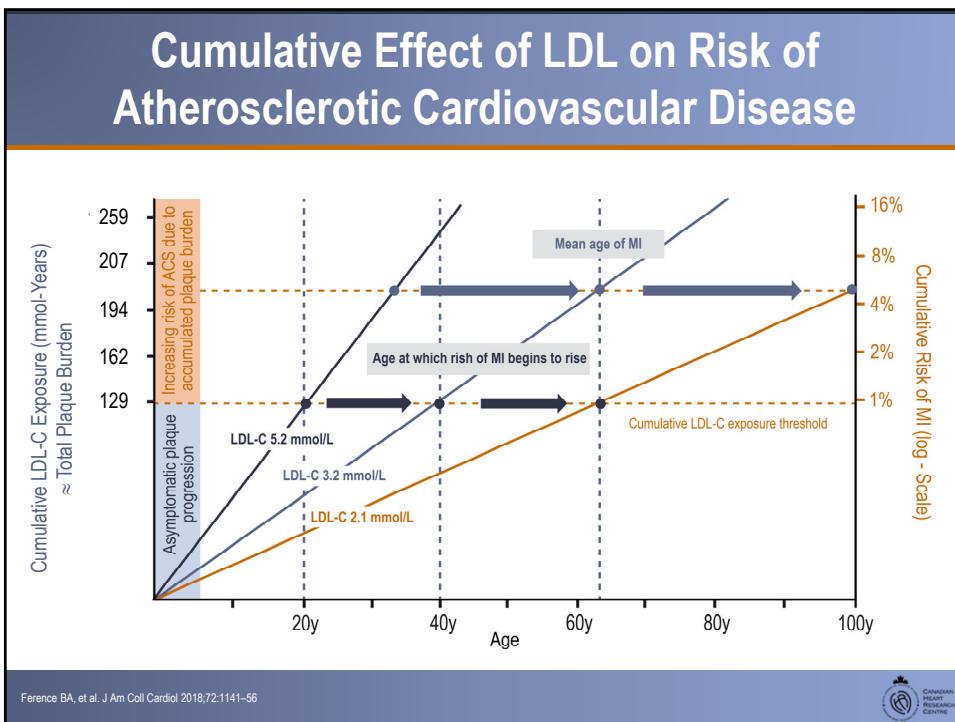
Effect of Cumulative Exposure to LDL on Plaque Burden and Risk of Cardiovascular Disease



Ference BA, et al. J Am Coll Cardiol 2018;72:1141-56



10



11



12

2016 CCS Lipid Guidelines Recommend: Targeting Lower LDL-C to Lower the Risk for CV Events

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TREATMENT TARGETS:

- LDL-C consistently <2.0 mmol/L or >50% reduction
- Consider <1.8 mmol/L in patients with clinical atherosclerosis
- Apo B ≤0.80 g/L or non-HDL-C ≤2.6 mmol/L can be considered as alternative treatment targets

STATIN INDICATED CONDITIONS
(those who will benefit the most):

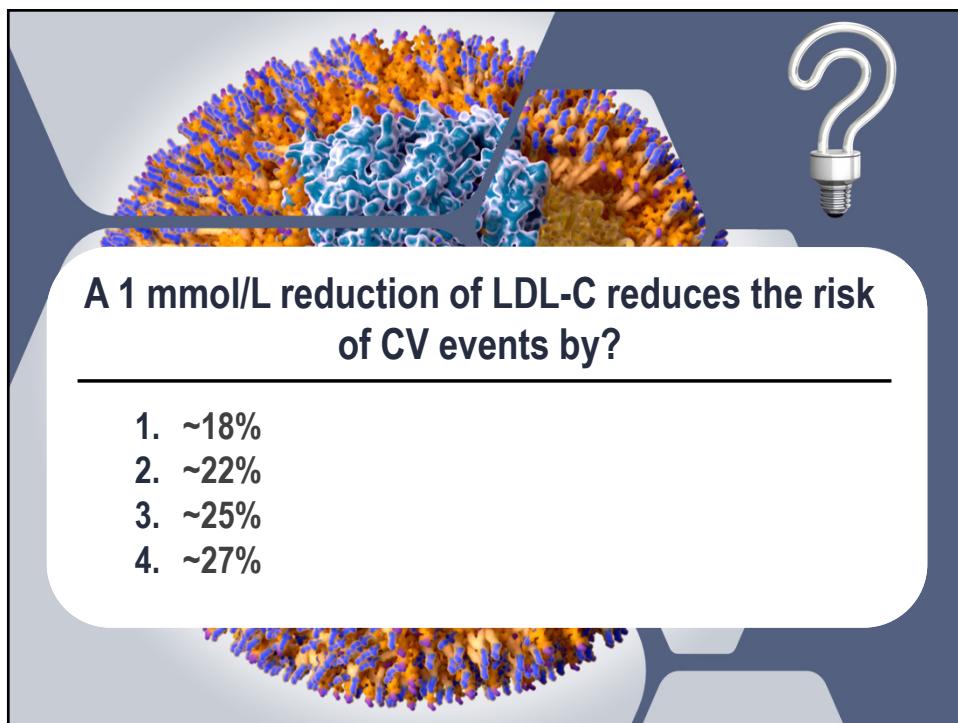
- Clinical atherosclerosis*
- Abdominal aortic aneurysm
- Most diabetes mellitus
- CKD (age >50 years)
- LDL-C ≥5.0 mmol/L

*Clinical atherosclerosis, i.e., previous MI, or coronary revascularization by PCI or CABG surgery, other arterial revascularization procedures, angina pectoris, cerebrovascular disease including TIA, or peripheral arterial disease (claudication and/or ABI <0.9)
ABI, ankle brachial index; Apo B, apolipoprotein B; CABG, coronary artery bypass graft surgery; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Anderson TJ et al. 2016;32:1263-1282

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13



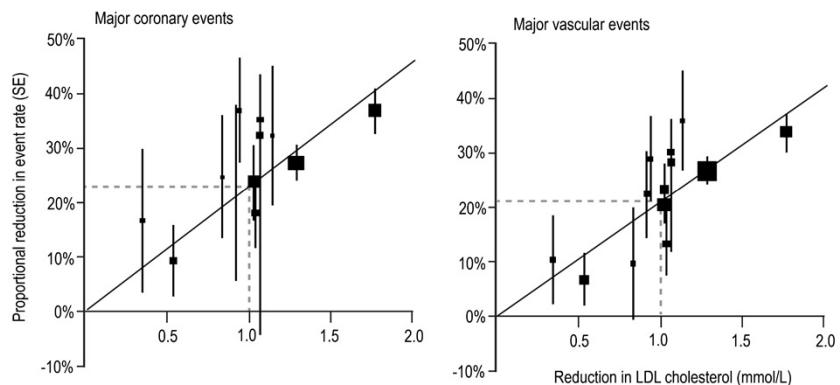
A 1 mmol/L reduction of LDL-C reduces the risk of CV events by?

1. ~18%
2. ~22%
3. ~25%
4. ~27%

14

Lessons from Statin Trials

Meta-analysis of statin trials:
1 mmol/L reduction of LDL-C = ~22% reduction in the risk of CV events



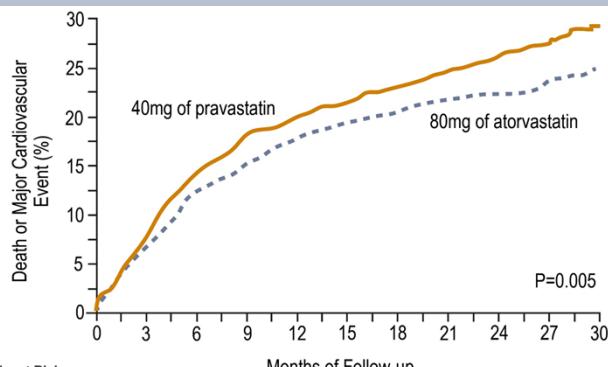
Chen et al. Can J Cardiol. 2019; 35:884-891.



15

PROVE-IT TRIAL: Lessons from Statin Trials

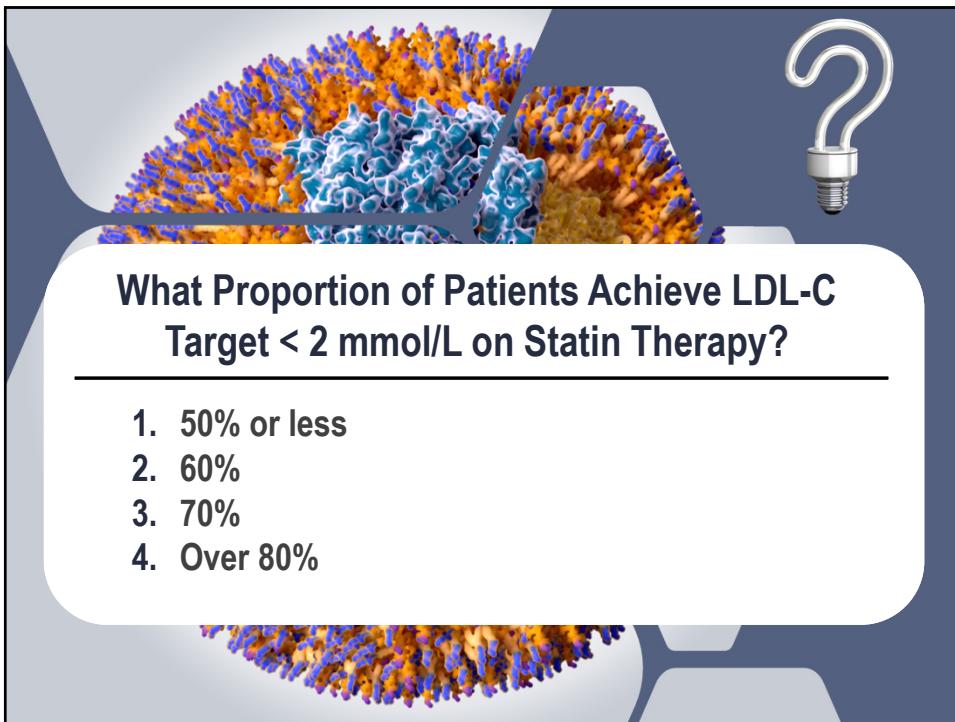
High intensity statin therapy provides greater protection against CV events than moderate intensity statin therapy.



Baigent C, et al. Lancet. 2005; 366:1267-1278;
 Cannon CP et al. N Engl J Med. 2004; 350:1495-1504



16



What Proportion of Patients Achieve LDL-C Target < 2 mmol/L on Statin Therapy?

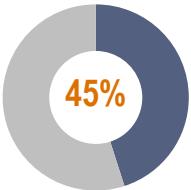
1. 50% or less
2. 60%
3. 70%
4. Over 80%

17

Many High-Risk Canadian Patients Treated with Statins Are Not at LDL-C Goal

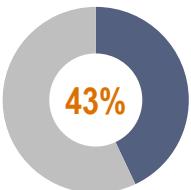
DYSIS¹
Canadian high-risk patients are NOT at LDL-C target^{1*} (< 2.0 mmol/L)

- 88% of patients received a 'potent' statin with suboptimal dose
- 14% of patients received additional lipid-lowering agent



DM-SCAN²
Canadian patients with diabetes are NOT at LDL-C target[†] (≤ 2.0 mmol/L)

- 82% of patients were on a lipid-lowering agent



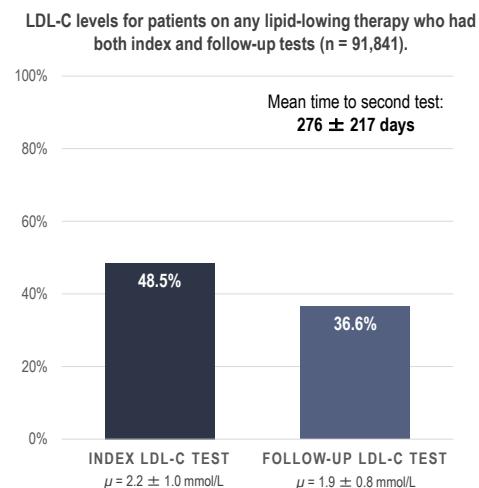
*High risk = coronary artery disease, peripheral arterial disease, cerebrovascular disease, diabetes mellitus or Framingham 10-year risk score $\geq 20\%$.
DYSI Study – 2,436 patients, 1913 high risk patients.
[†]N = 5,069

1. Goodman SG et al. on behalf of the DYSIS Canadian Investigators. Can J Cardiol. 2010;26:e330-e335.
2. Leiter LA et al. on behalf of the DM-SCAN investigators. Can J Diabetes. 2013;37:82-89.

18

Treatment and LDL-C Management in Patients Diagnosed with Clinical Atherosclerotic Cardiovascular Disease in Alberta

- Among patients on statin/non-statin therapy, n=91,841 had an index & follow-up LDL-C test.
- 48.5% of these patients were **not achieving** LDL-C <2.0 mmol/L at the index test (left);
- 36.6% were **not achieving** LDL-C <2.0 mmol/L or 50% reduction at follow-up (right).



Chen et al. Can J Cardiol. 2019; 35:884-891.



19

Treatment and LDL-C Management in Patients Diagnosed with Clinical Atherosclerotic Cardiovascular Disease in Alberta



60.2%
(n=87,048)

60.2% of patients on statin/non-statin therapy (n=144,607) were adherent (PDC \geq 0.8).

PDC, proportion of days covered

Chen et al. Can J Cardiol. 2019; 35:884-891.



20

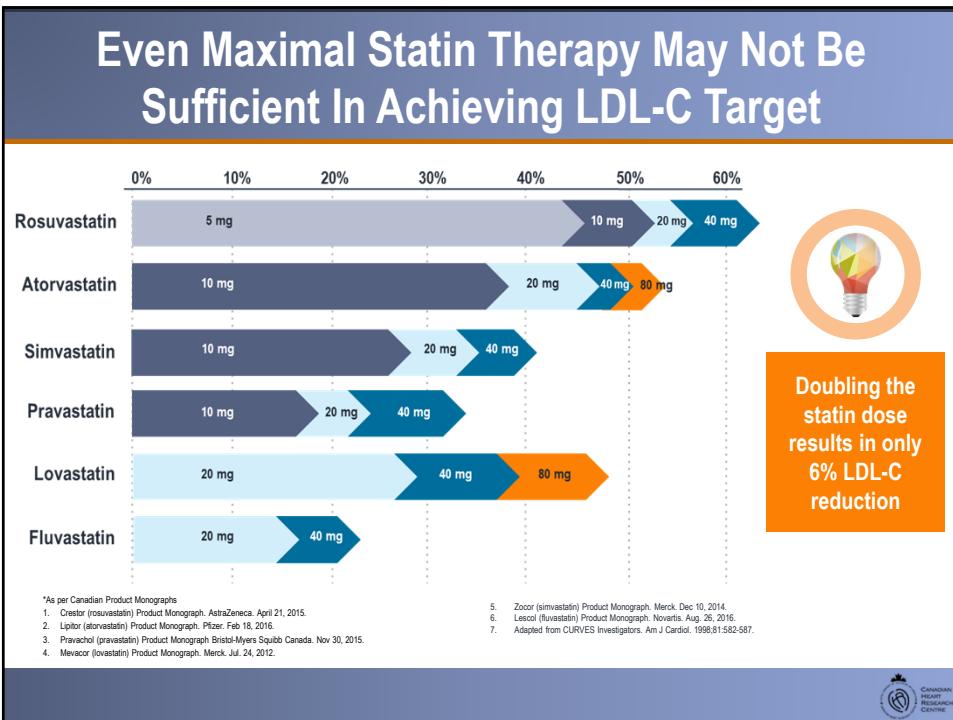


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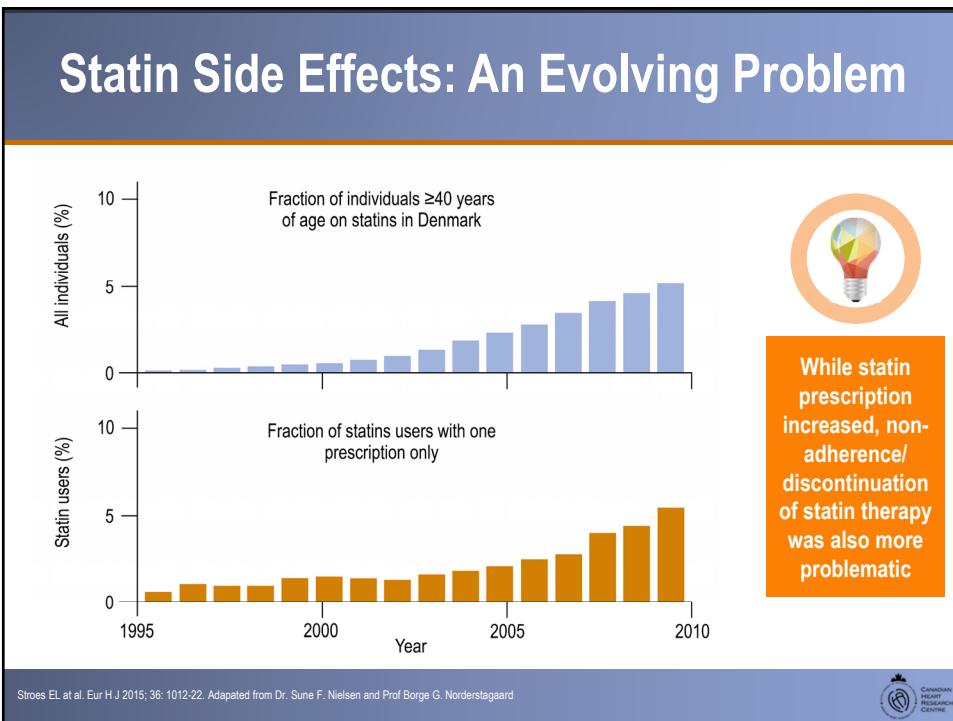
If The Statin Dose Is Doubled, LDL-C Will Be Reduced By An Additional?

- 1. 6%
- 2. 10%
- 3. 12%
- 4. 15%
- 5. Depending on the statin

22



23



24

Multiple Challenges with Statin Selection

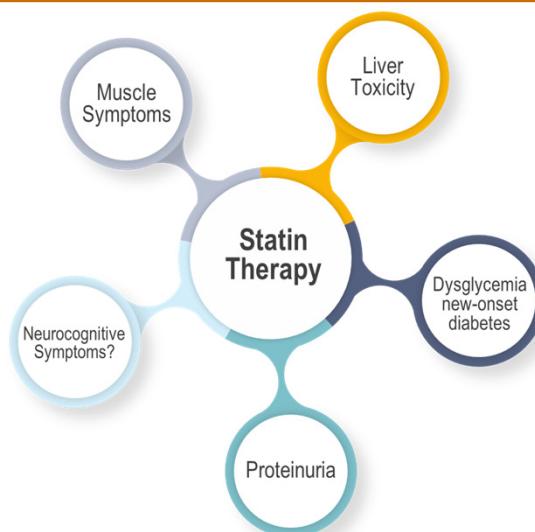


a: Ansell BJ. J Manag Care Pharm. 2008; 14 (suppl S-b): 29-S15.
 b: Mead L. US Pharm. 2007; 32:65-71.
 c: Vogel C, et al. J Gen Intern Med. 2007; 22(suppl 3): 391-395.
 d: Ito M, et al. J Clin Lipidol. 2014;8:69-76.



25

Adverse Effects Reported with Statin Therapy



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



26

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



27

In patients with statin associated side effects, what proportion occur within the first six months?

1. 30%
2. 65%
3. 78%
4. 90%

28

Overall statin intolerance occurs in what proportion of treated patients?

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

29

Statin-Associated Muscle Symptoms vs. Statin Intolerance

Muscle-Related Side Effects
Statin Intolerance

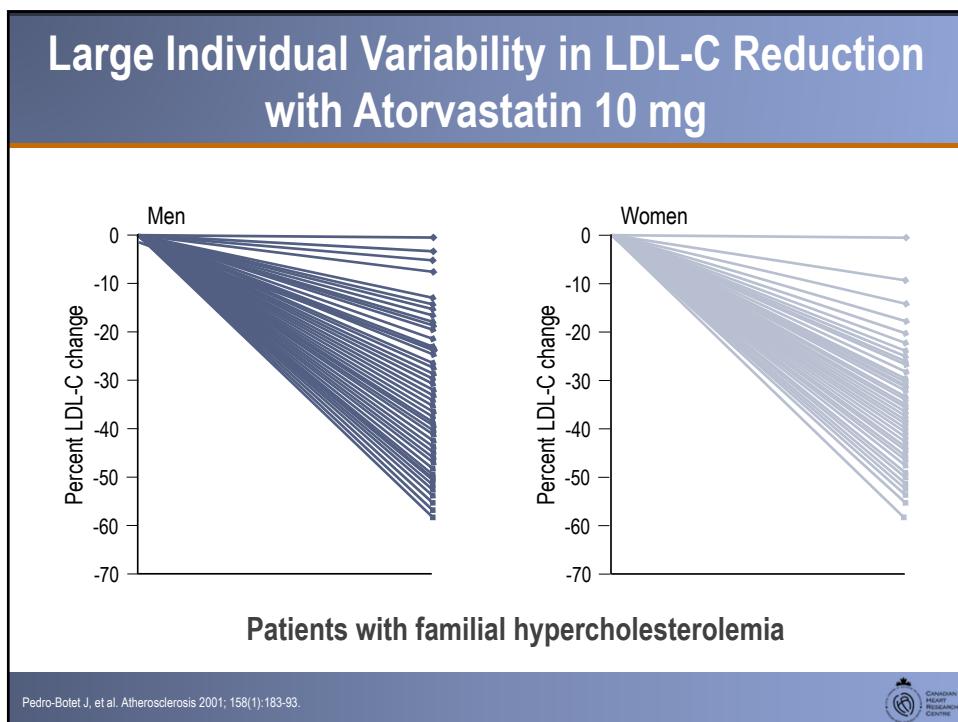
- 90% of all cases appear within the first 6 months after treatment initiation or dose up-titration
- Muscle aches (myalgia), weakness, stiffness and cramps
- Myopathy (myositis): accompanied with CK 10 x ULN
 - Patients with normal CK may also have symptoms of myopathy with statin therapy
- Rhabdomyolysis: CK >50 x ULN, myoglobinemia, myoglobinuria-induced acute renal failure; resulting in skeletal muscle injury; 10% risk of death*

- Occurs in 10% to 15% of patients
- Defined by NLA* as the inability to tolerate at least 2 statins (one at lowest daily dose and one at any daily dose) due to symptoms or abnormal labs – temporarily related to statin treatment
 - Complete intolerance – intolerant to any statin at any dose
 - Partial intolerance – intolerant to some statins and some doses
- Could result from: Muscle symptoms, headache, sleep disorders, dyspepsia, nausea, rash, alopecia, erectile dysfunction, gynecomastia, and/or arthritis

* NLA –National Lipid Association

* Death from hyperkalemia-induced arrhythmia or disseminated intravascular coagulation
Bainach M, et al. Arch Med Sci. 2015;11:1-23

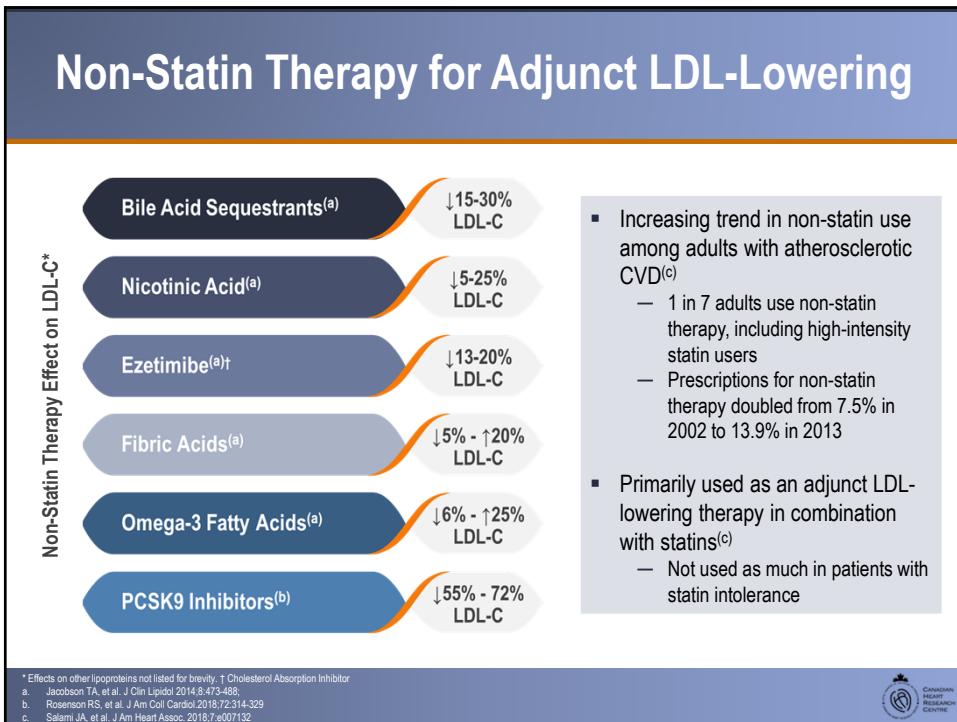
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33

2016 CCS Lipid Guidelines Recommend: Beyond Statin Drugs for ASCVD Prevention

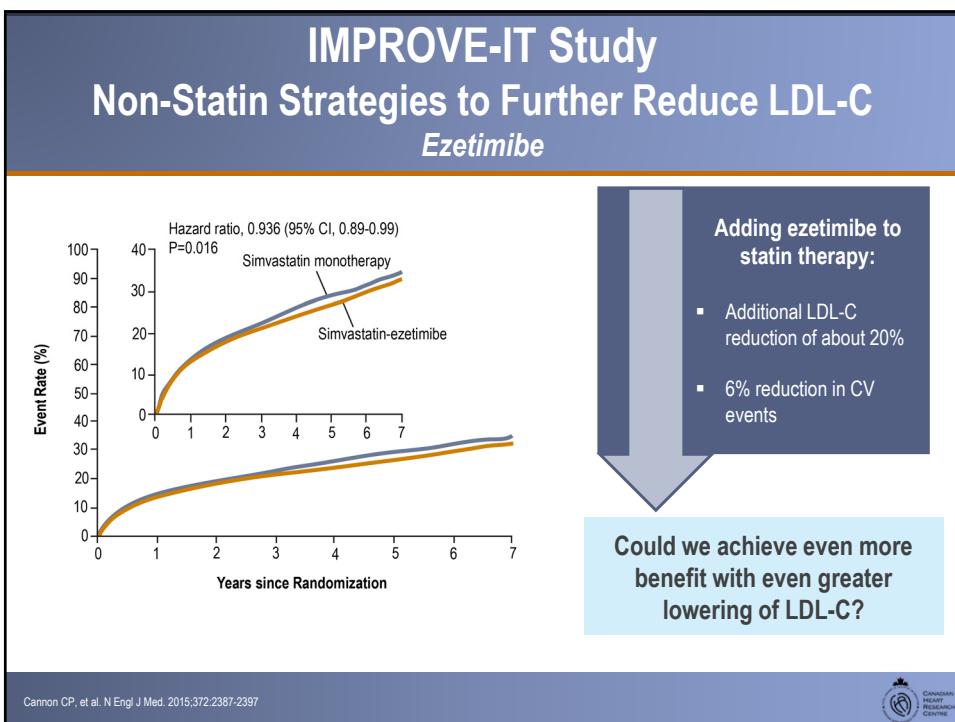
 Canadian Cardiovascular Society
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1. We recommend ezetimibe as second-line therapy to lower LDL-C in patients with clinical cardiovascular disease if targets are not reached on maximally tolerated statin therapy. (*Strong Recommendation, High Quality evidence*)
2. We recommend that niacin not be added to statin therapy for CVD prevention in patients who have achieved LDL-C targets. (*Strong Recommendation, High Quality Evidence*)
3. We do not recommend the addition of fibrates to statin therapy for CVD event prevention in patients who have achieved LDL-C targets. (*Strong recommendation, High Quality evidence*). *Values and preferences:* In sub-group analysis, patients with elevated triglycerides and low HDL-C may benefit from fibrate therapy.

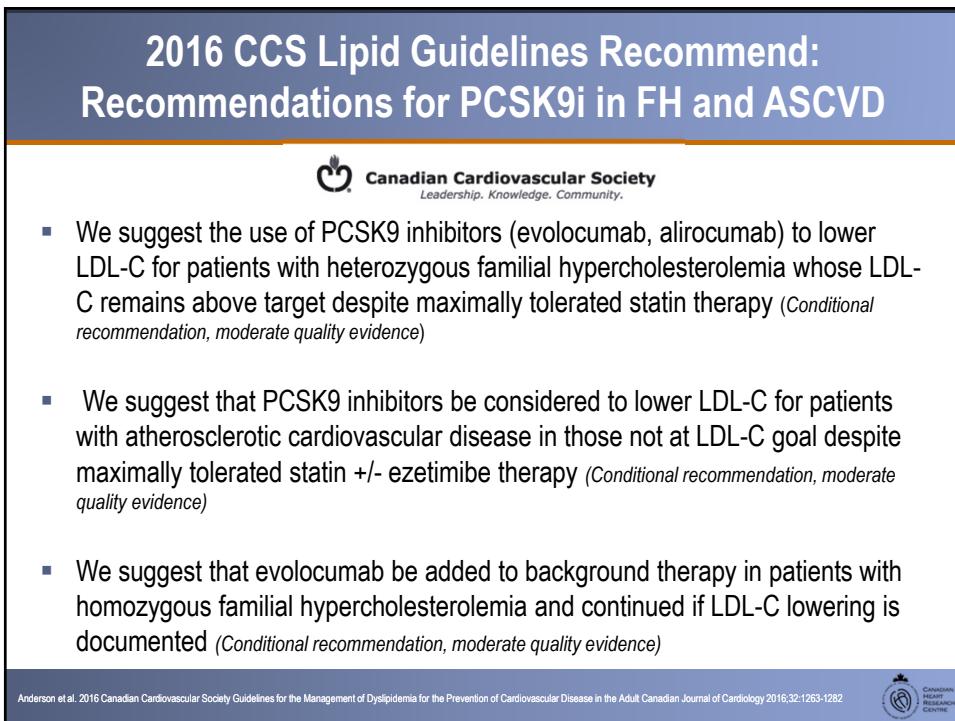
Anderson et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult Canadian Journal of Cardiology 2016;32:1263-1282

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34



35



36

Adding a PCSK9 Inhibitor to statin therapy further reduces LDL-C by?

1. 35-45%
2. 50-60%
3. 65%
4. 70%

37

Non-Statin Strategies to Further Reduce LDL-C PCSK9 Inhibitors

PCSK9 inhibitors further reduce LDL-C by an average of 50 to 60%

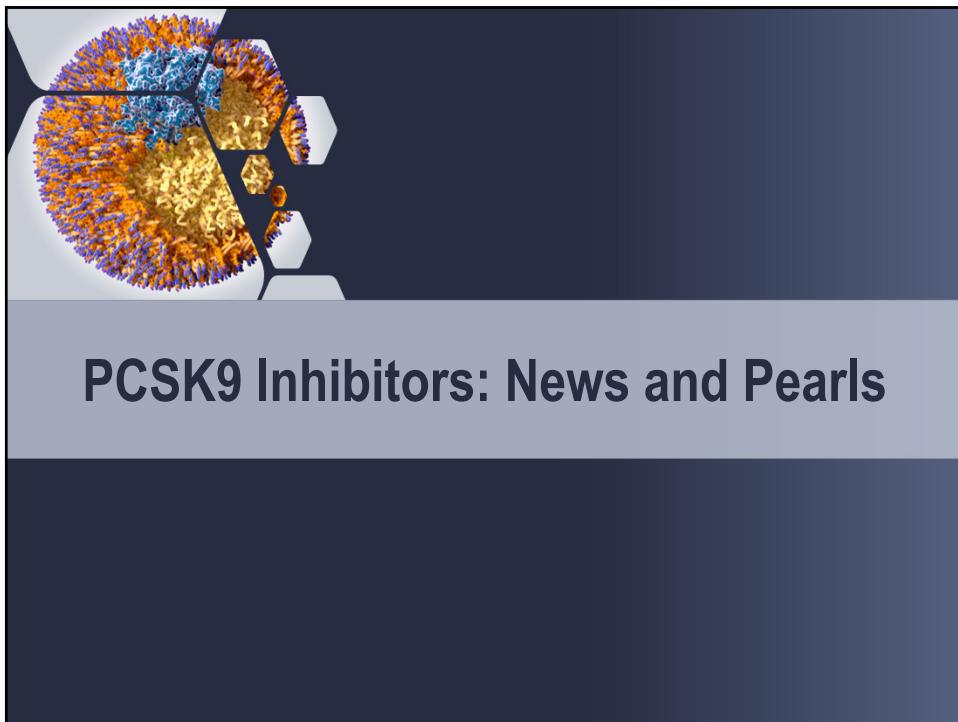
- Further reduce the risk of CV events
- CV benefits are proportional to the absolute reduction in LDL-C and the duration of treatment
- Greatest benefit reported in patients with additional high-risk factors such as recent MI, polyvascular disease, prior CV events



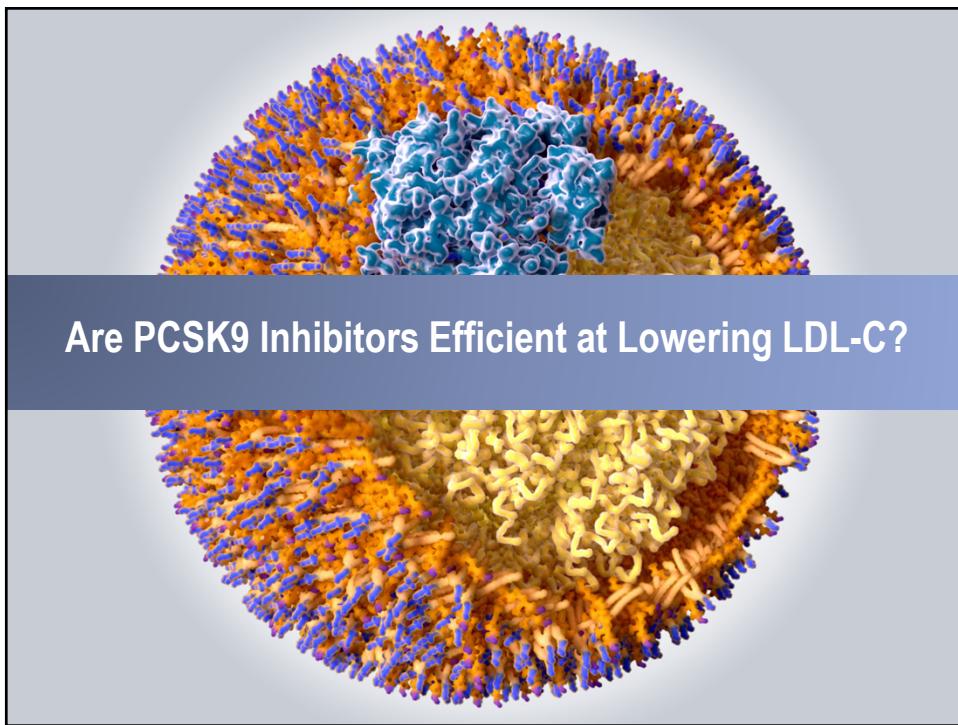
The real challenge now is to identify which patients would benefit most from PCSK9 inhibitors

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

38



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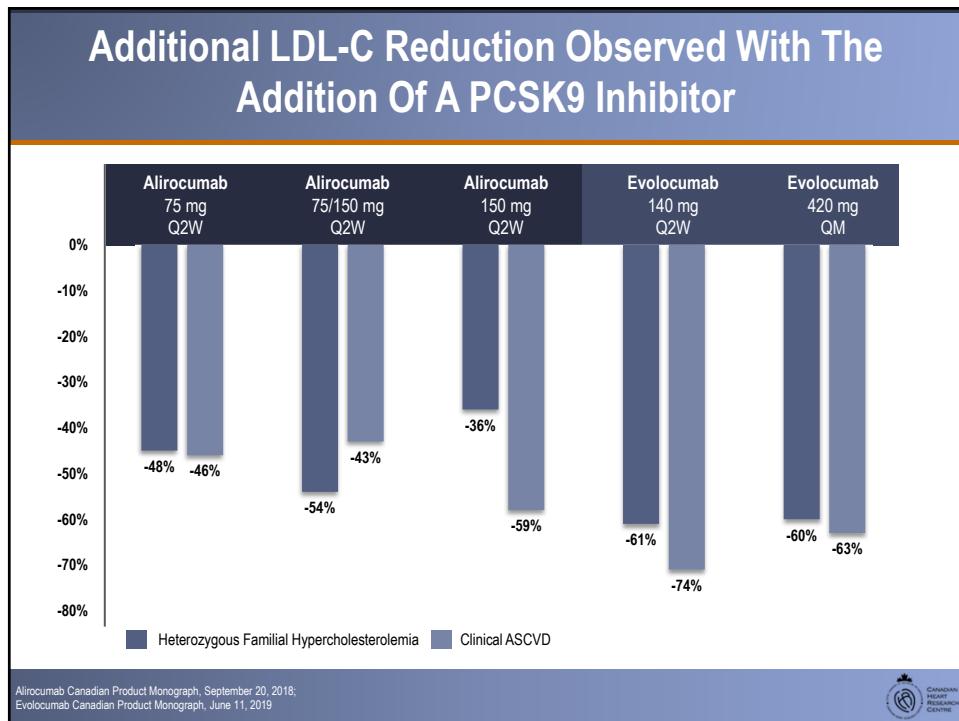


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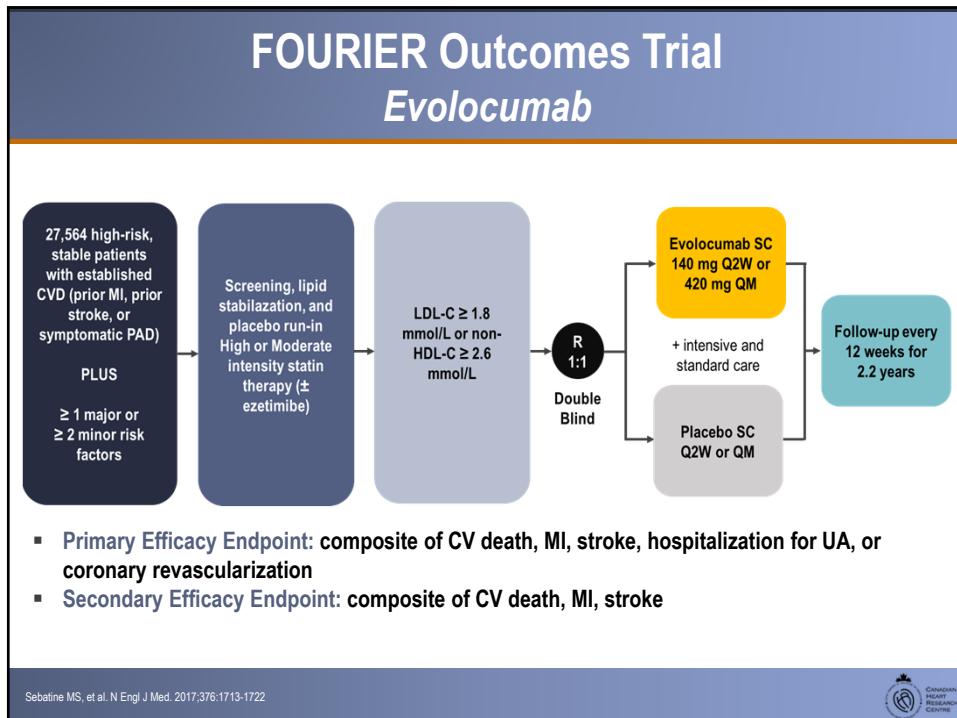
Can LDL-C Lowering be Achieved Safely and Effectively with PCSK9 Inhibitors?

1. Only if ezetimibe is used as well
2. Only if ezetimibe is not used
3. Only if maximal statin therapy is not used
4. Only in statin intolerant patients
5. None of the above

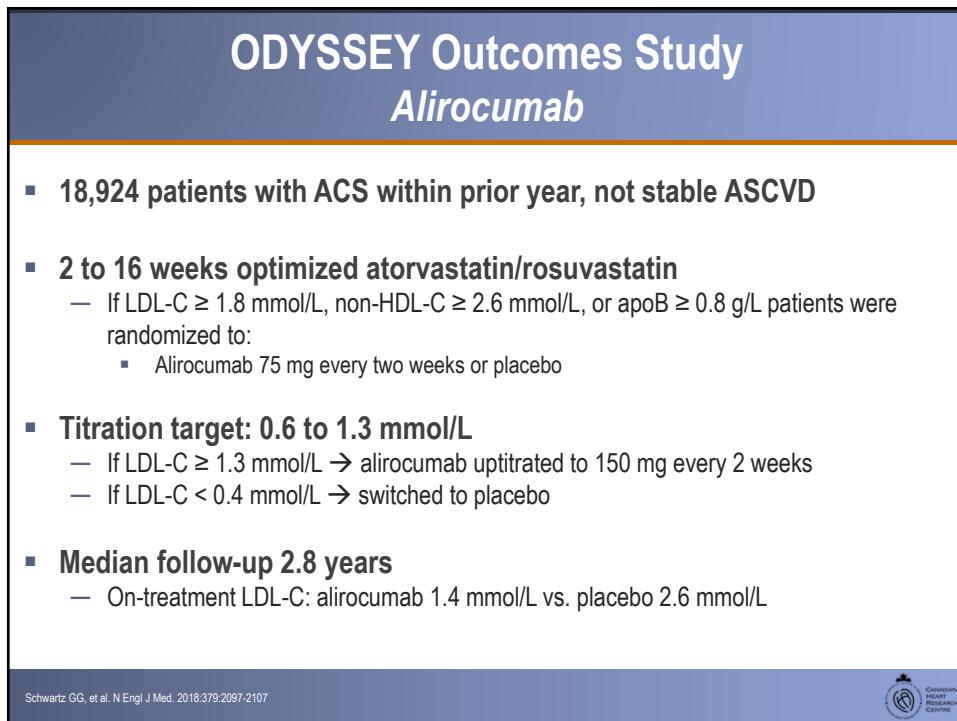
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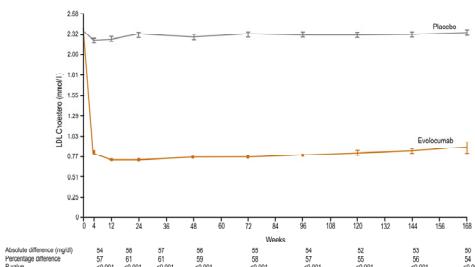
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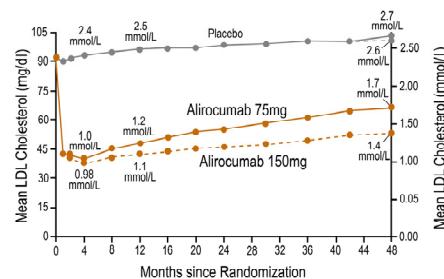
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PCSK9 Inhibitors are Efficient at Lowering LDL-C

FOURIER:
Evolocumab^[a]



ODYSSEY Outcomes:
Alirocumab^[b]



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

b. Schwartz GG, et al. N Engl J Med. 2019;380:2097-2107



45

Guideline Oriented Approach to Lipid lowering in Canada (GOAL)

- The GOAL Program is an ongoing real-world designed and coordinated by the Canadian Heart Research Centre
- The GOAL Program is evaluating the management of patients at high-risk, defined as those with clinical atherosclerotic cardiovascular disease, and an LDL-C >2.0 mmol/L despite maximal tolerated statin therapy
- The program incorporates a mechanism to support decision making and choice of therapy in order to assist physicians in achieving the Canadian Cardiovascular Society guideline-recommended LDL-C targets in high risk patients.

The interactive program has 3 distinct components:

- Capture of data as reported by the physician based on LDL-C lowering strategies at each visit.
- Feedback on potential opportunities for LDL-C lowering based on CCS guidelines.
- Identification of challenges and reasons faced by physicians (continuation of the care gap).



46

Real World Data GOAL: Baseline Lipid Profile and Management

N = 2,024

Lab Values	Median (25 th , 75 th percentiles) mmol/L
Total cholesterol	5.2 (4.4, 6.2)
Low Density Lipoprotein (LDL)-C	3.0 (2.4, 3.9)
High Density Lipoprotein (HDL)-C	1.2 (1.0, 1.5)
Non-HDL-C	3.8 (3.1, 4.9)
Triglycerides	1.6 (1.2, 2.4)

Therapy	%
Atorvastatin (10/20/40/80 mg)	28 (4/5/8/11)
Rosuvastatin (5/10/20/40 mg)	40 (5/11/12/12)
Pravastatin (10/20/40 mg)	5 (1/2/2)
Simvastatin (5/10/20/40/80 mg)	3 (<1/<1/<1/<1)
Fluvastatin (20/40 mg)	1 (<1/1)
Lovastatin (20/40 mg)	<1 (<1/<1)
No statin	24
Ezetimibe	25
Bile Acid Sequestrant	5
Fibrate	3
Niacin	<1

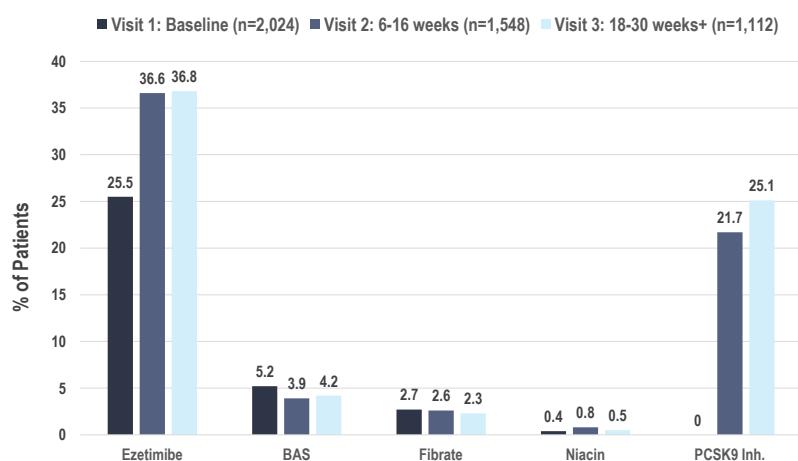


April 4, 2019 - data cut CHRC file



47

Real World Data GOAL: Additional Lipid Modifying Therapy



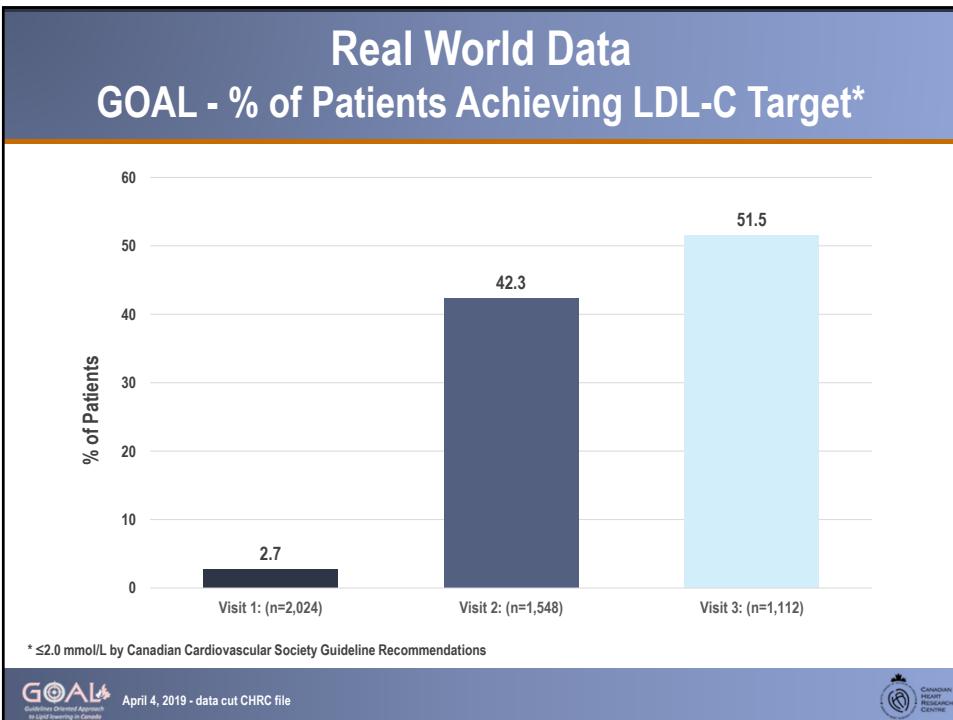
* ≥6 weeks post Visit 2



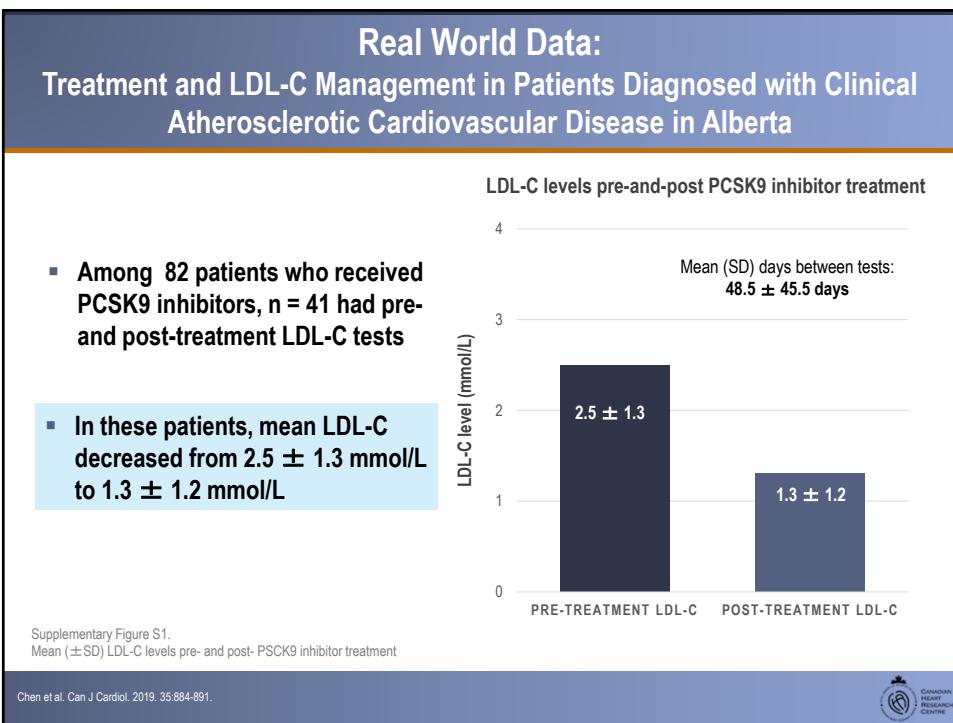
April 4, 2019 - data cut CHRC file



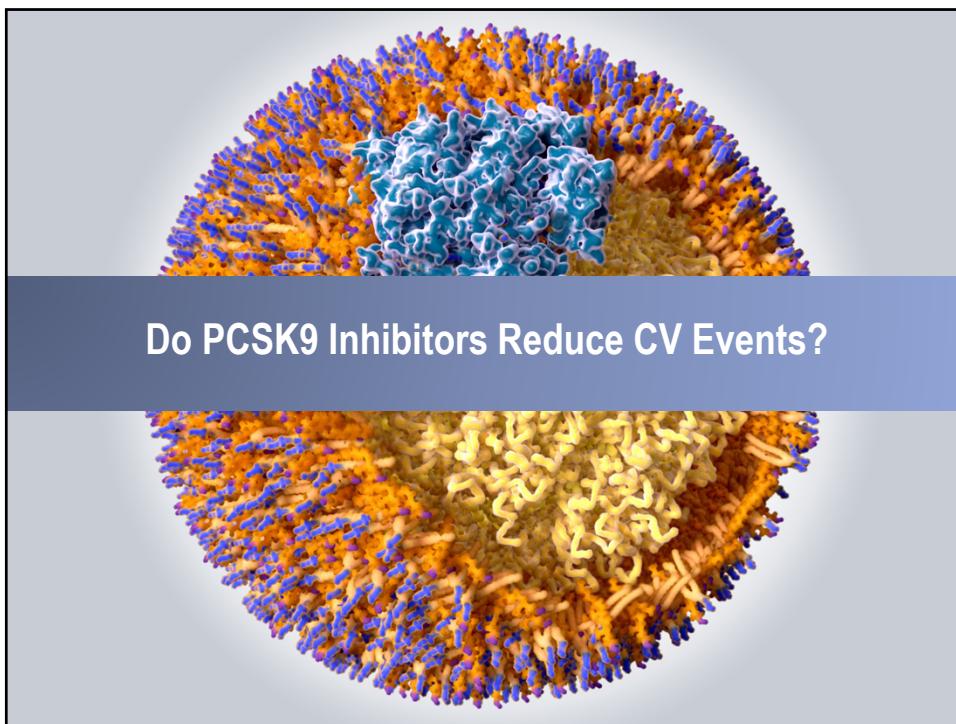
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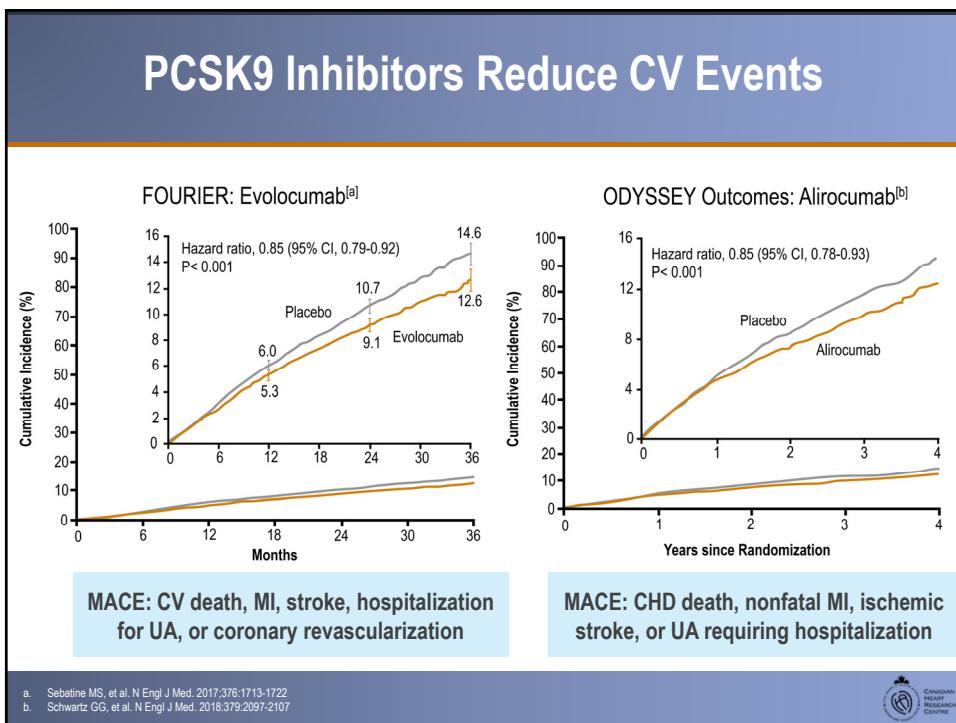
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50



51



52



53

A 3D molecular model of a PCSK9 protein complex, with a thought bubble containing a question mark above it. The thought bubble contains the text "With Respect to Safety of PCSK9 Inhibitors, Which is True?" followed by a list of four statements.

**With Respect to Safety of PCSK9 Inhibitors,
Which is True?**

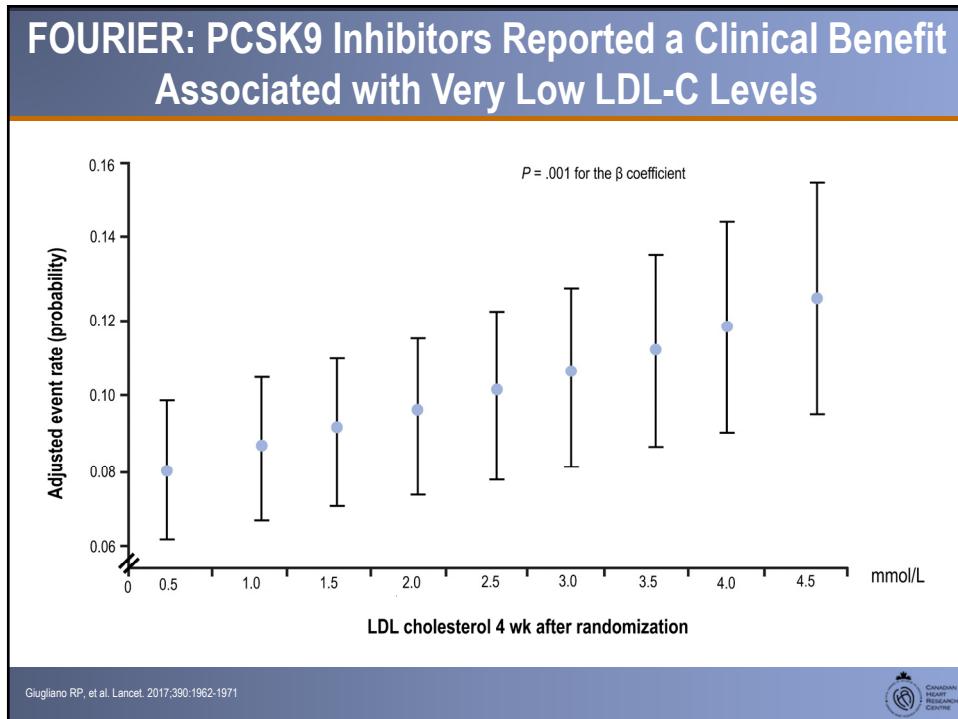
1. There is concern about neuro-cognitive AE
2. There is concern about myalgia
3. No significant adverse events have been demonstrated
4. The use of vitamin D supplementation is recommended

54

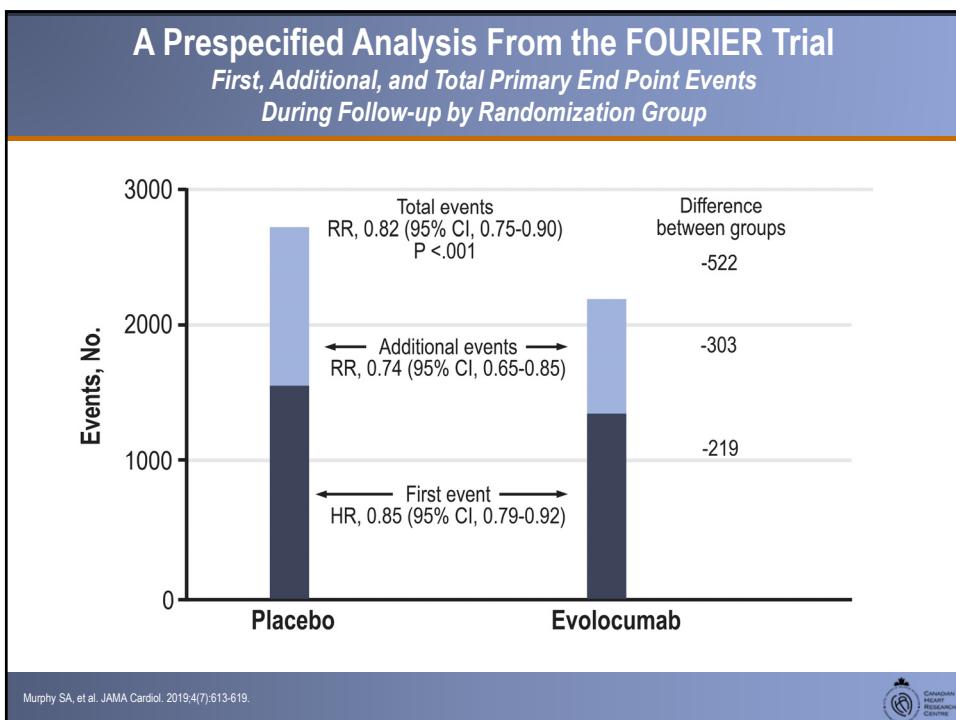
PCSK9 Inhibitors are Safe					
FOURIER: Evolocumab ^(a)		ODYSSEY Outcomes: Alirocumab ^(b)			
Outcome	Evolocumab (N = 13,769)	Placebo (N = 13,756)	Variable	Alirocumab (N = 9,451)	Placebo (N = 9,443)
Adverse events-no. of patients, %					
Any	77.4	77.4	Any adverse event	75.8	77.1
Serious	24.8	24.7	Serious 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. 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.

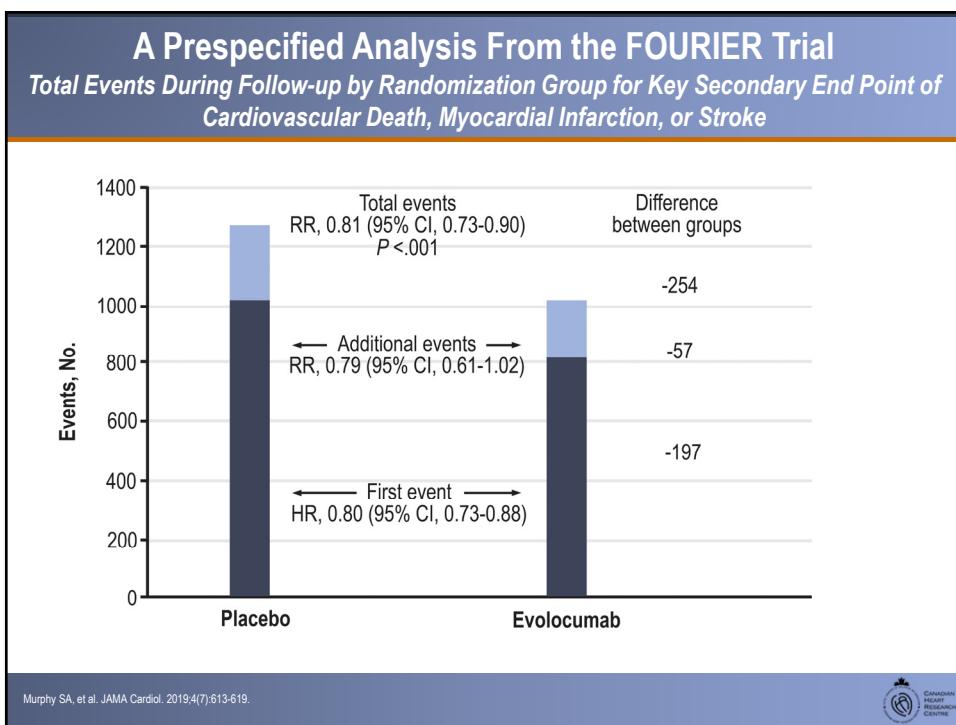
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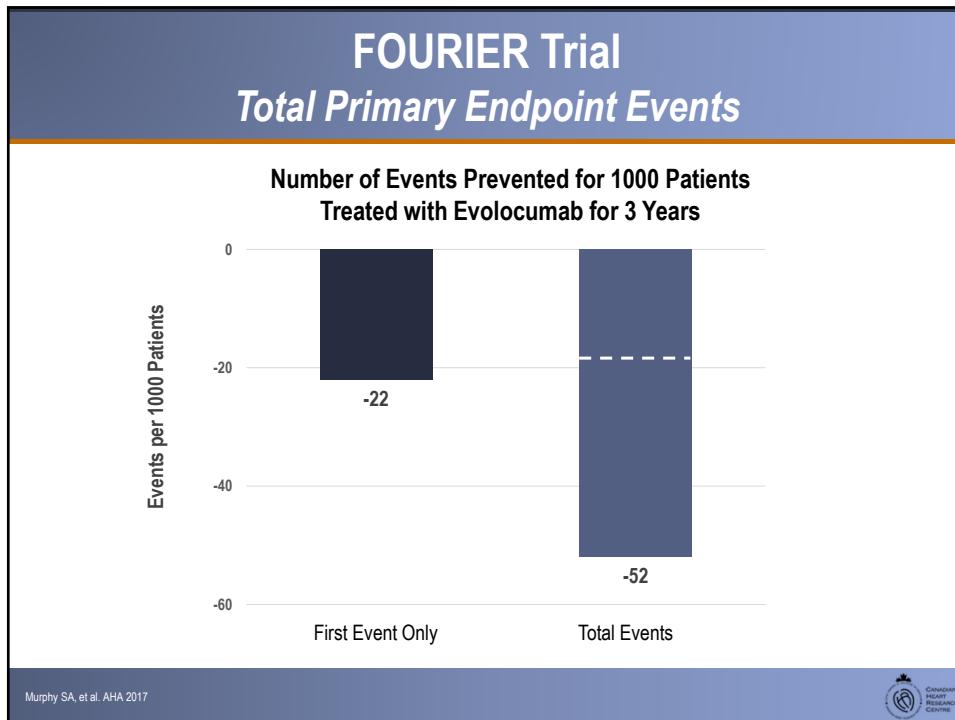
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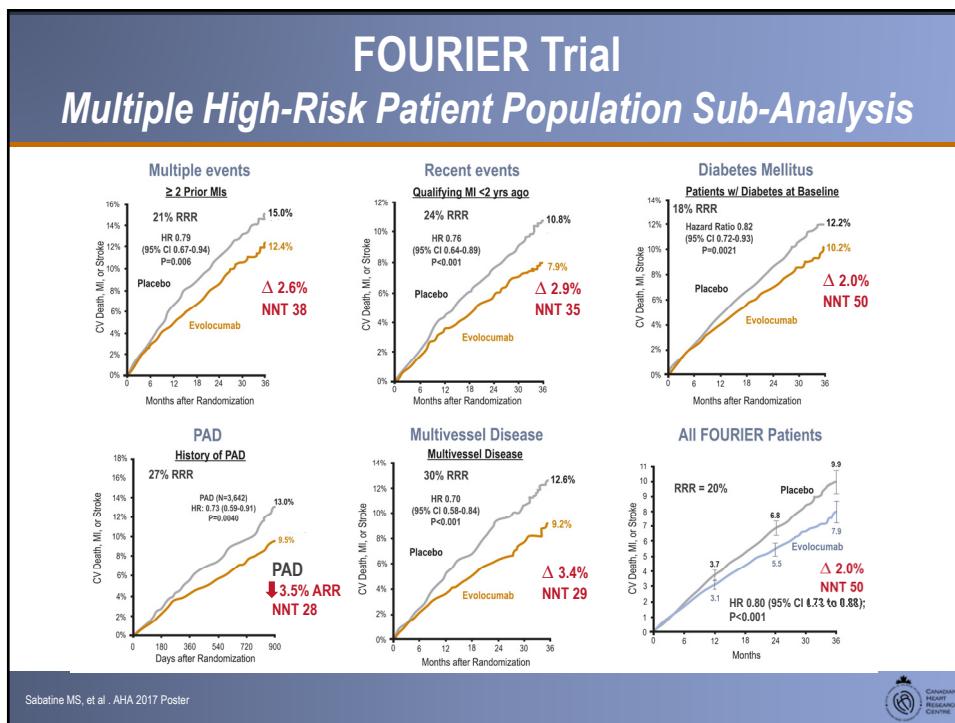
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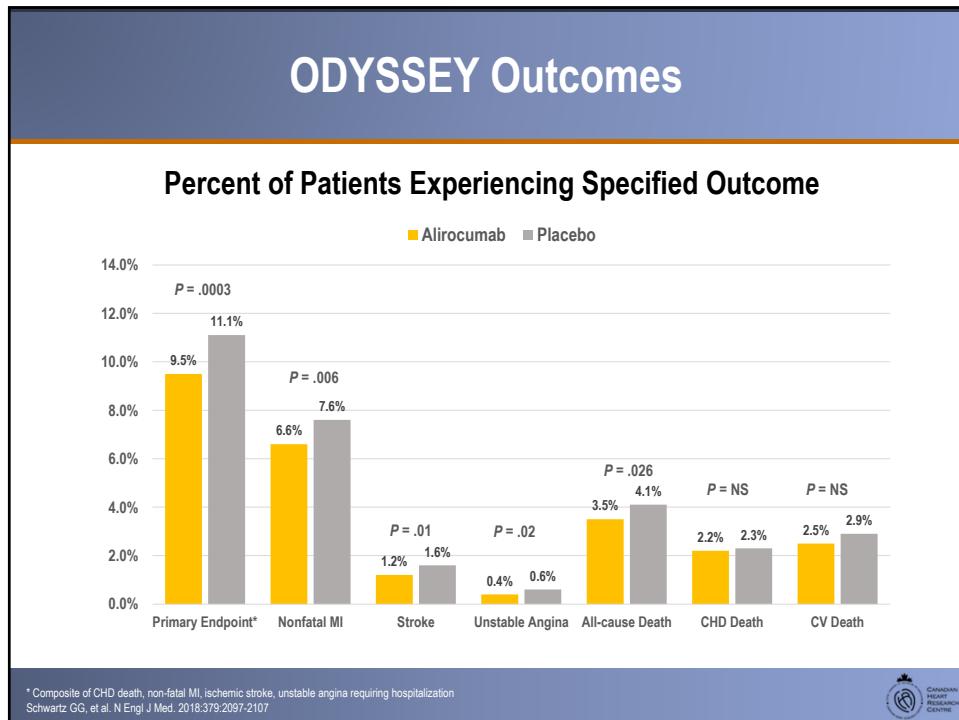
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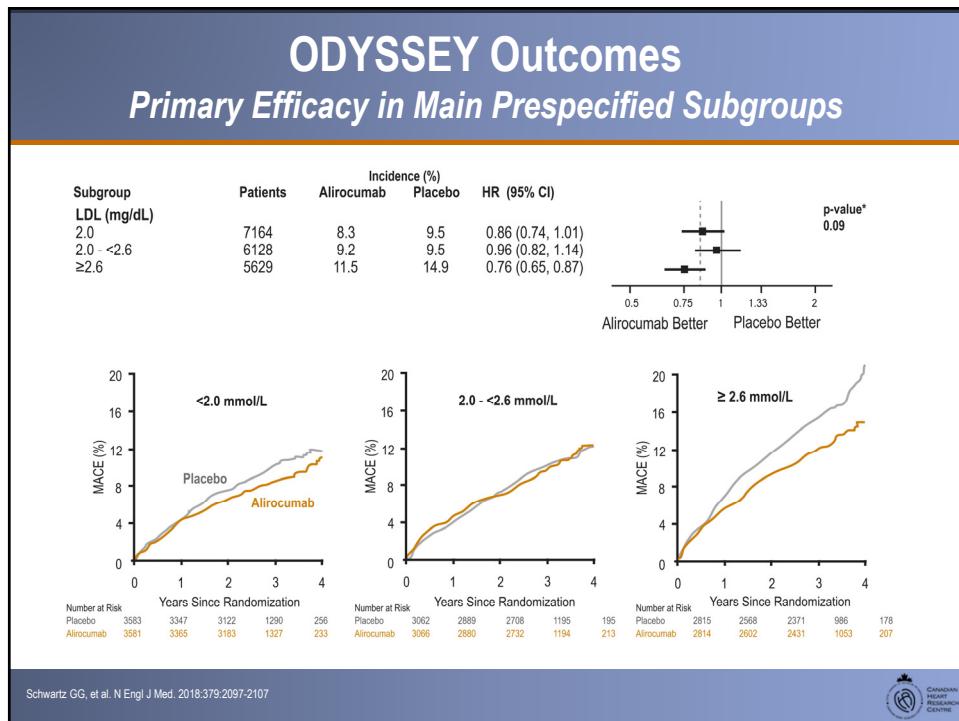
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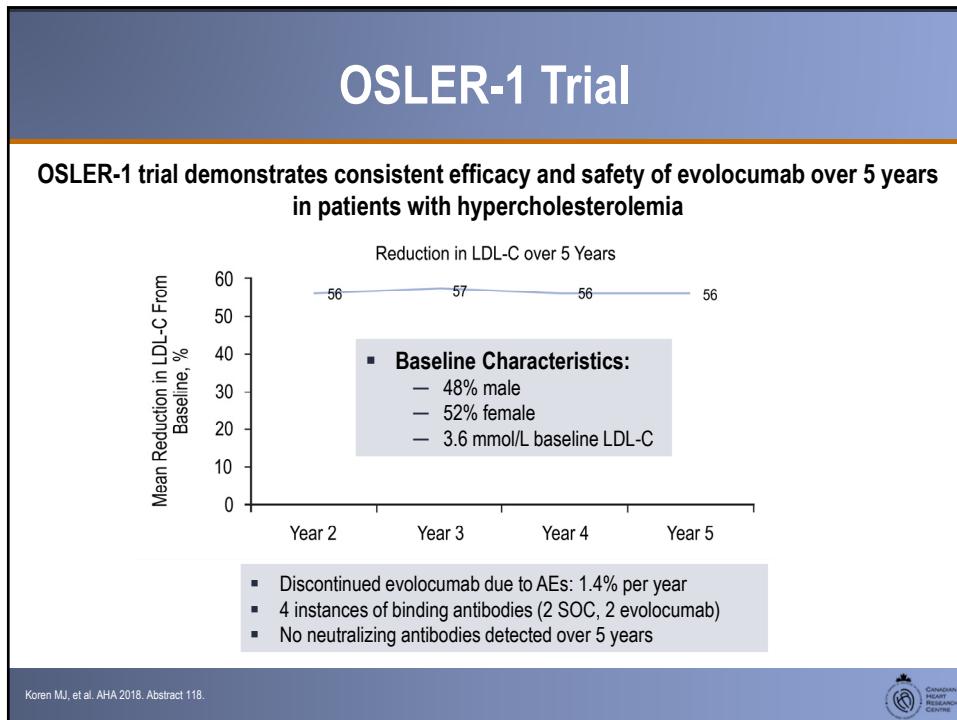
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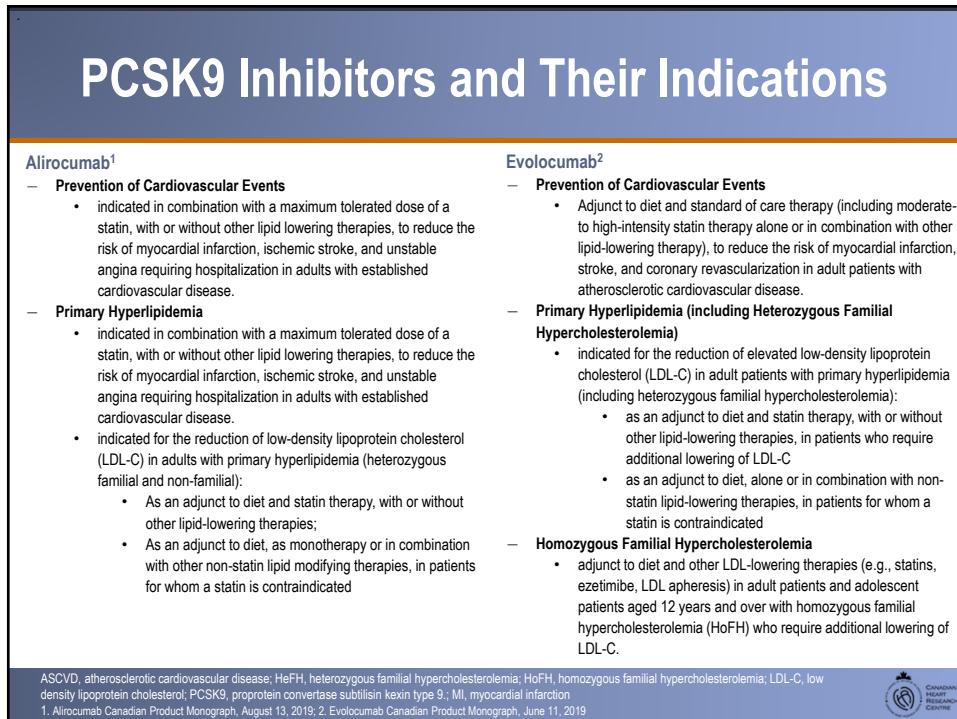
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62



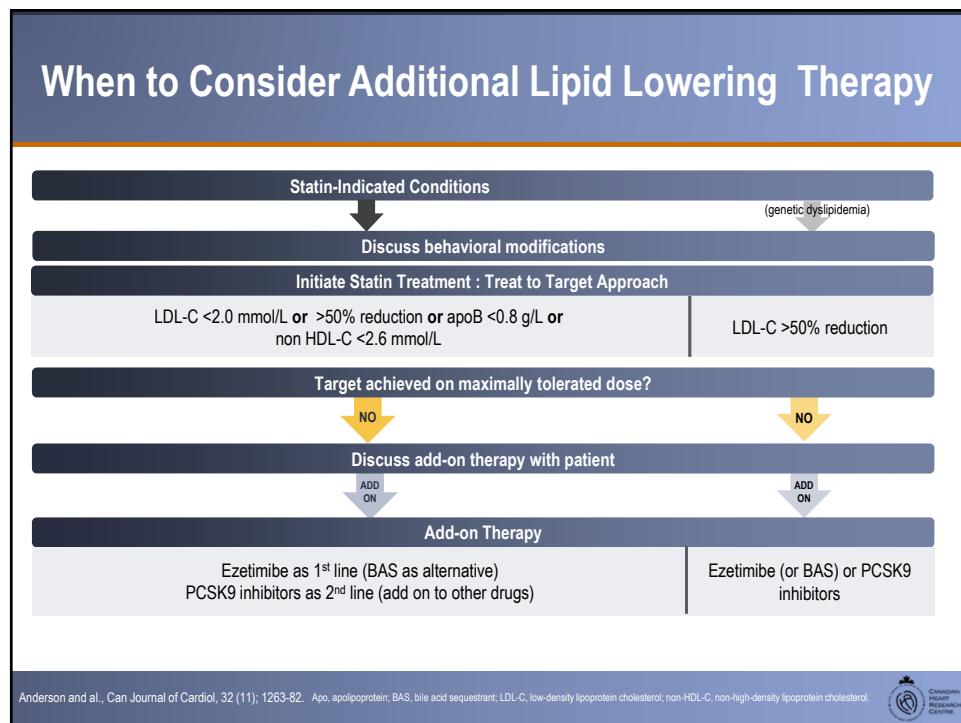
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64



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66

When to Consider Additional Lipid Lowering Therapy

- **LDL-C<15-20% away from target:**
 - addition of ezetimibe is likely to achieve target
- **LDL-C> 20% away from target:**
 - no add-on drug other than a PCSK9 inhibitor is likely to achieve target
- **Use clinician judgement and patient-centered approach when adding non-statin therapy (i.e. ezetimibe first, PCSK9 inhibitors, both).**

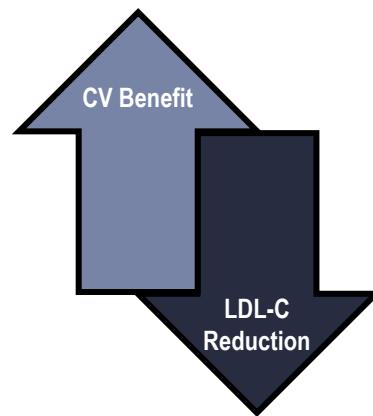
Anderson and al., Can Journal of Cardiol, 32 (11); 1263-82. Apo, apolipoprotein; BAS, bile acid sequestrant; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.



67

Re-Evaluating LDL-C Targets

- The lower the LDL-C achieved, the greater the reduction in CV risk
- Clinicians need to start re-evaluating LDL-C targets for patients with known ASCVD and other risk factors
 - Need to reduce LDL-C levels < 1.0 mmol/L where the data show there is a CV benefit at these levels



68

DISCUSSION

Which patients do you believe benefit most from PCSK9 Inhibition?



69

Identifying which Patient Will Benefit most from PCSK9 Inhibition

Need to look beyond whether a patient has established CVD or not

Important to identify risk enhancers to identify patients that would derive the greatest absolute benefit from PCSK9 inhibitors

Recent event?

Greater burden of atherosclerosis?
i.e. multiple events

Additional co-morbidities like diabetes?

70

DISCUSSION

Which patients do you believe would benefit most from “Lowest is Best Strategy”?



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71

Who will Benefit most from “Lowest is Best” Strategy

Study	ARR, %
FOURIER^(a)	
Patient with > 2 MIs	2.6
Patients with multivessel disease	3.4
Patients with PAD	3.5
Patients with recent MI (<2 y ago)	2.9
ODYSSEY^(b)	
Patient with LDL > 2.6 mmol/L	3.4
Patient with high Lp(a)	2.3
IMPROVE-IT^(c)	
TIMI 2P high-risk	6.3
Patients with CABG	8.8

a. Murphy SA, et al. The FOURIER Trial. AHA Scientific Sessions 2017

b. ODYSSEY; Bays H, et al. J Am Heart Assoc. 2017;6:e005639

c. IMPROVE-IT; Cannon C, et al. N Engl J Med. 2015;372:2387-2397

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72

PCSK9 Inhibitors – Cost and Access

■ **Private Coverage:**

- Alirocumab and Evolocumab are covered for > 90% of patients with ASCVD and FH

■ **Access Options:**

- Alirocumab and Evolocumab are supported by Patient support programs, My Praluent and RepathaREADY
- These patient support programs will help secure reimbursement, offer patient counselling, treatment information and manage renewals / adherence.
- Co-Pay options are also provided by these patient support programs

www.formulary.health.gov.on.ca/formulary
www.health.gov.on.ca/en/pro/programs/drugs/drug_stat_repatha.pdf

* Ontario Provincial Reimbursement Criteria for HeFH used as the example



73

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



74

Summary

- Despite best-evidence-based treatment, high-risk and very high risk patients continue to experience CVD events
- Failure to attain guideline-recommended LDL-C goals is an important component of this residual CVD risk
- Additional LDL-C lowering options are needed to address this unmet clinical need
- 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

