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**Presenter - [presenter name]**

### Relationships with financial sponsors:

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



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## Disclosure of Financial Support

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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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## Mitigating Potential Bias

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- [Presenter] has provided his disclosure information at the start of this presentation.



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## 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



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## 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

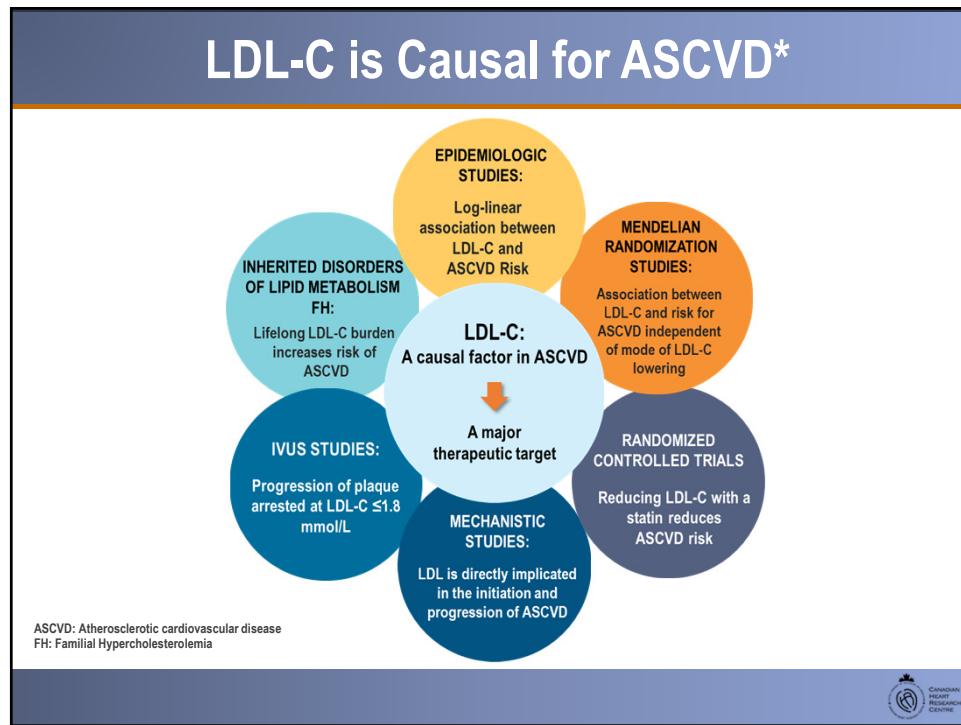
ASCVD: Atherosclerotic cardiovascular disease



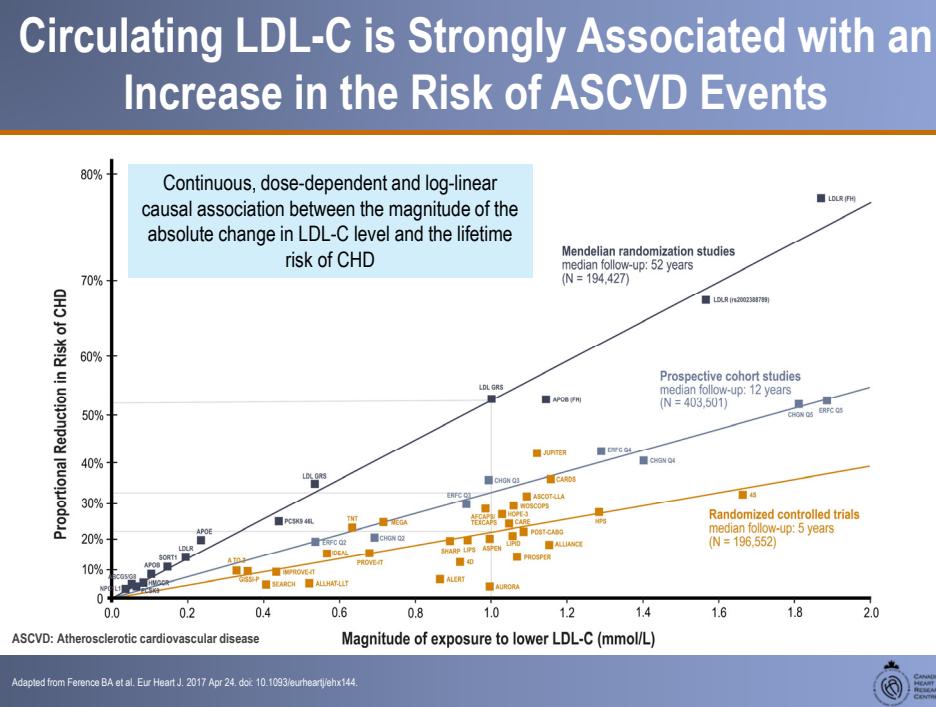
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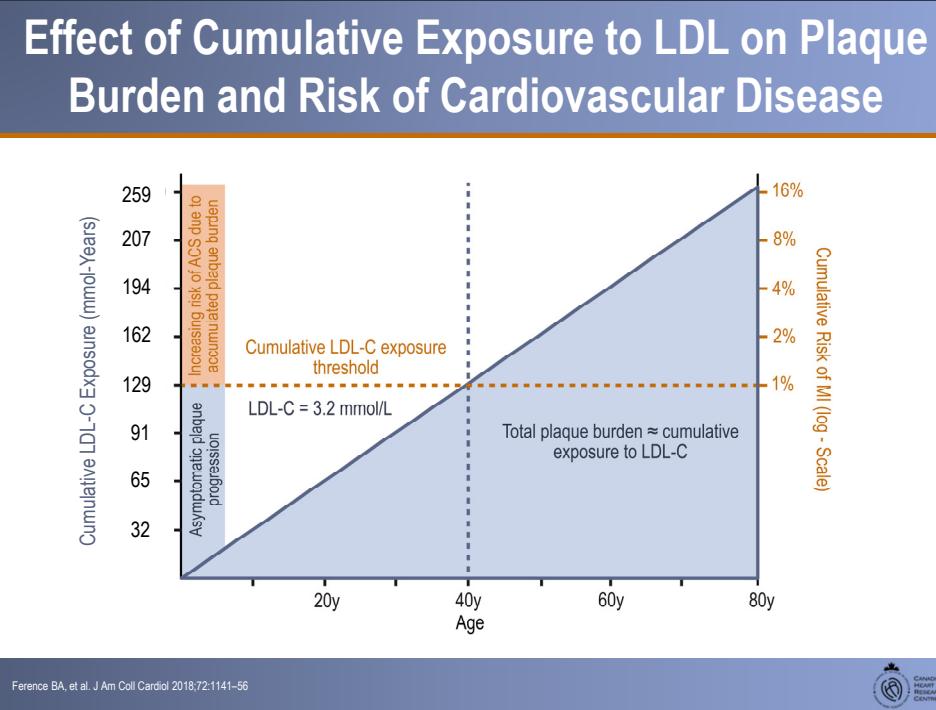
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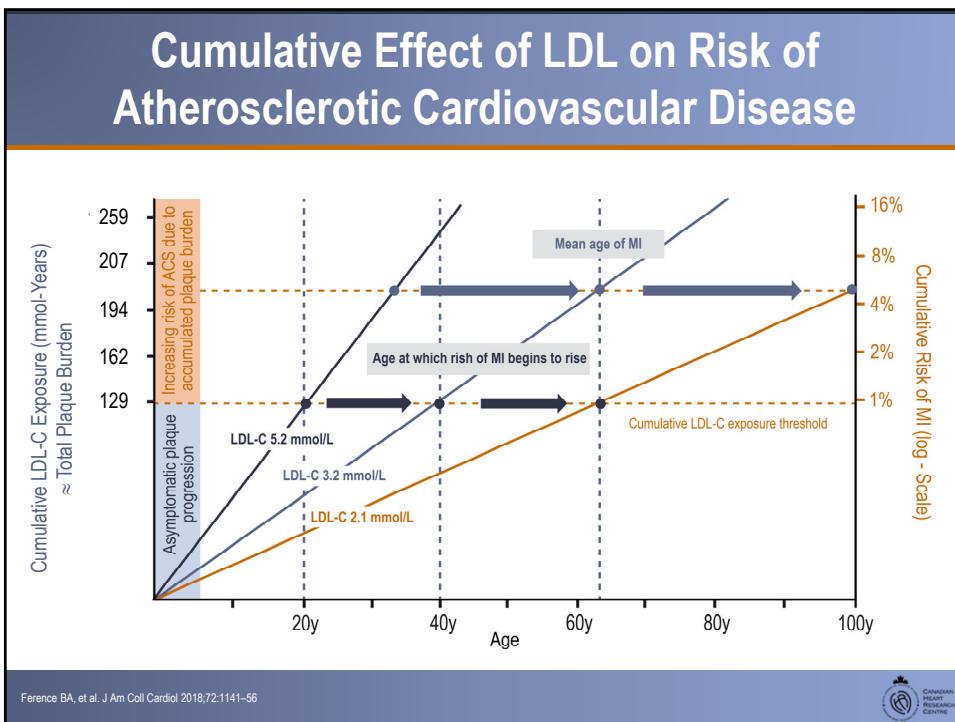
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## 2016 CCS Lipid Guidelines Recommend: Targeting Lower LDL-C to Lower the Risk for CV Events



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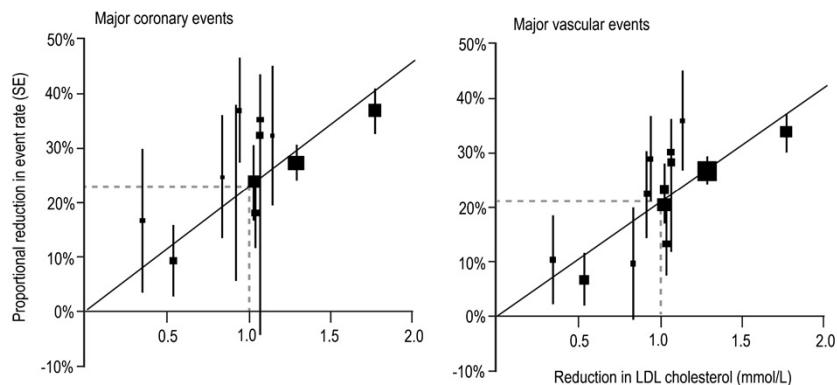
**A 1 mmol/L reduction of LDL-C reduces the risk of CV events by?**

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

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## Lessons from Statin Trials

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



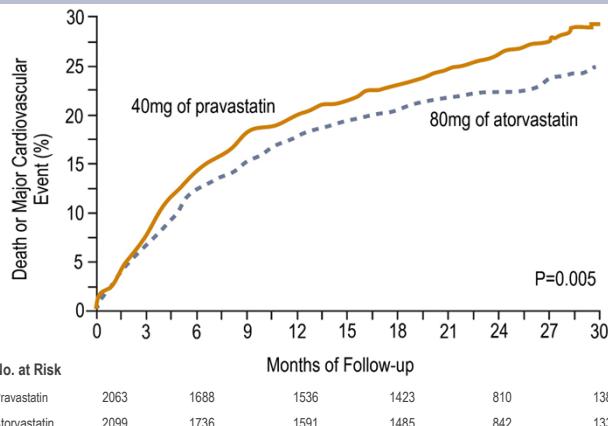
Chen et al. Can J Cardiol. 2019; 35:884-891.



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## 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



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

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

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

**DYSIS<sup>1</sup>**  
**Canadian high-risk patients are NOT at LDL-C target<sup>1\*</sup> (< 2.0 mmol/L)**

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

**DM-SCAN<sup>2</sup>**  
**Canadian patients with diabetes are NOT at LDL-C target<sup>†</sup> ( $\leq 2.0$  mmol/L)**

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

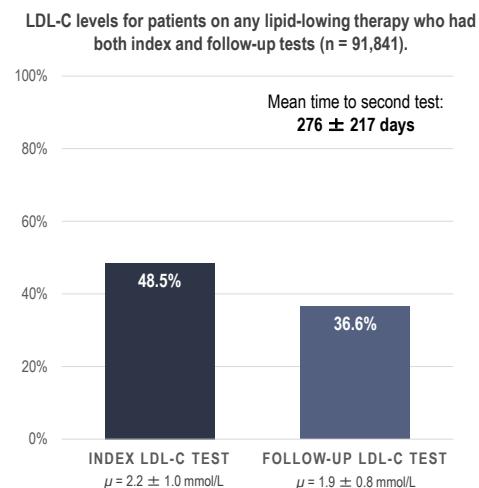
\*High risk = coronary artery disease, peripheral arterial disease, cerebrovascular disease, diabetes mellitus or Framingham 10-year risk score  $\geq 20\%$ .  
DYSI Study – 2,436 patients, 1913 high risk patients.  
<sup>1</sup>N = 5,069

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.

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## 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.



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## 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.



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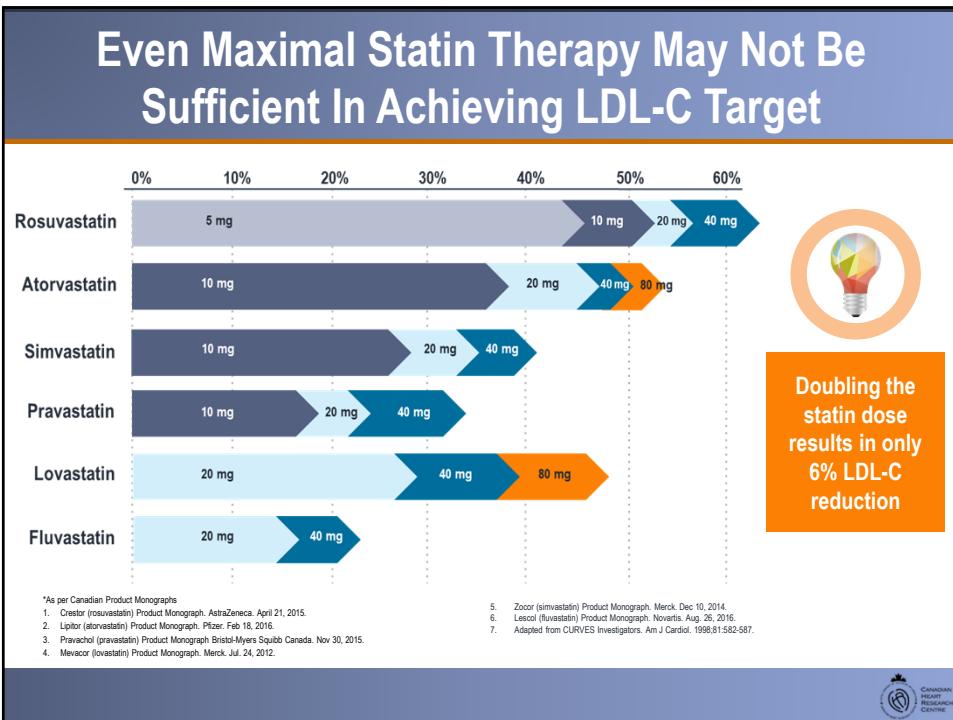
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If The Statin Dose Is Doubled, LDL-C Will Be Reduced By An Additional?

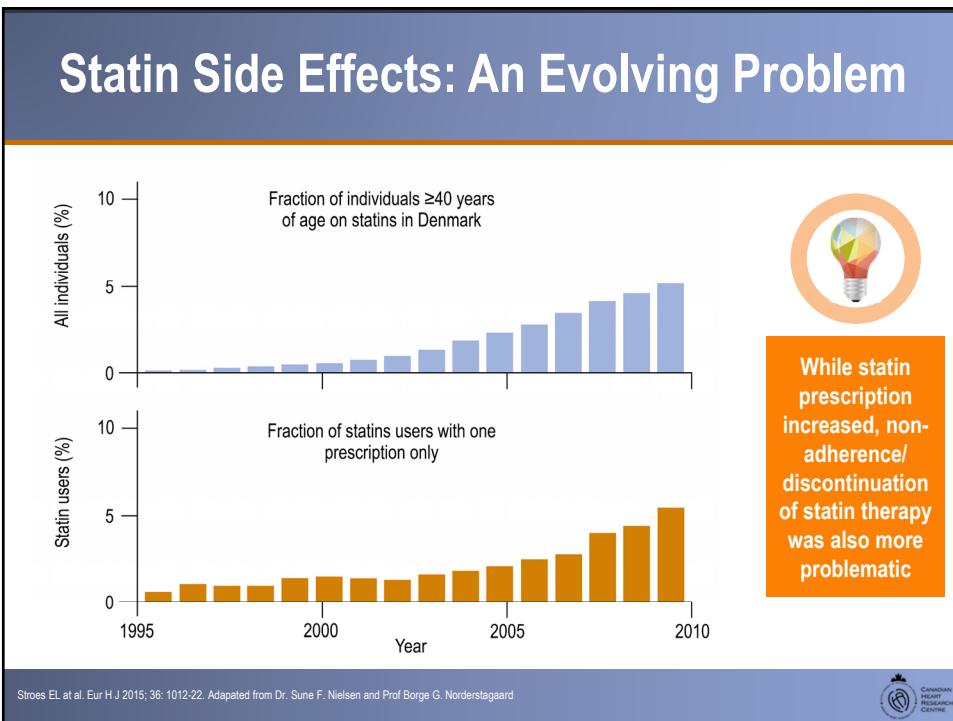
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- 1. 6%
- 2. 10%
- 3. 12%
- 4. 15%
- 5. Depending on the statin

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## Multiple Challenges with Statin Selection

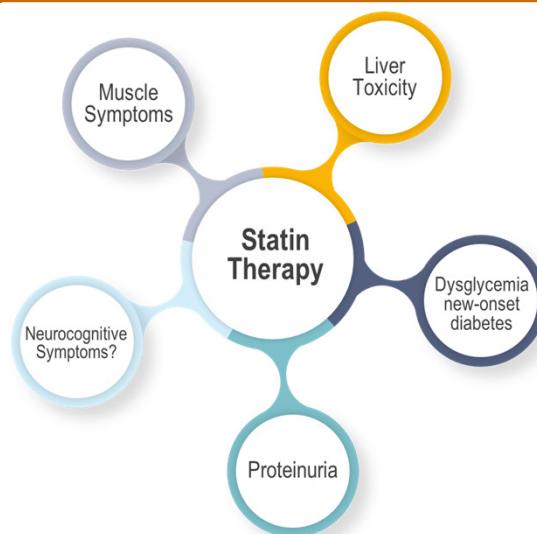


a: Ansell BJ. J Manag Care Pharm. 2008; 14 (suppl S-b): 29-S15.  
 b: Mead L. US Pharm. 2007; 32:65-71.  
 c: Vogel C, et al. J Gen Intern Med. 2007; 22(suppl 3): 391-395.  
 d: Ito M, et al. J Clin Lipidol. 2014;8:69-76.



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## Adverse Effects Reported with Statin Therapy



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



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## 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



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

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

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**Overall statin intolerance occurs in what proportion of treated patients?**

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

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### Statin-Associated Muscle Symptoms vs. Statin Intolerance

Muscle-Related Side Effects
Statin Intolerance

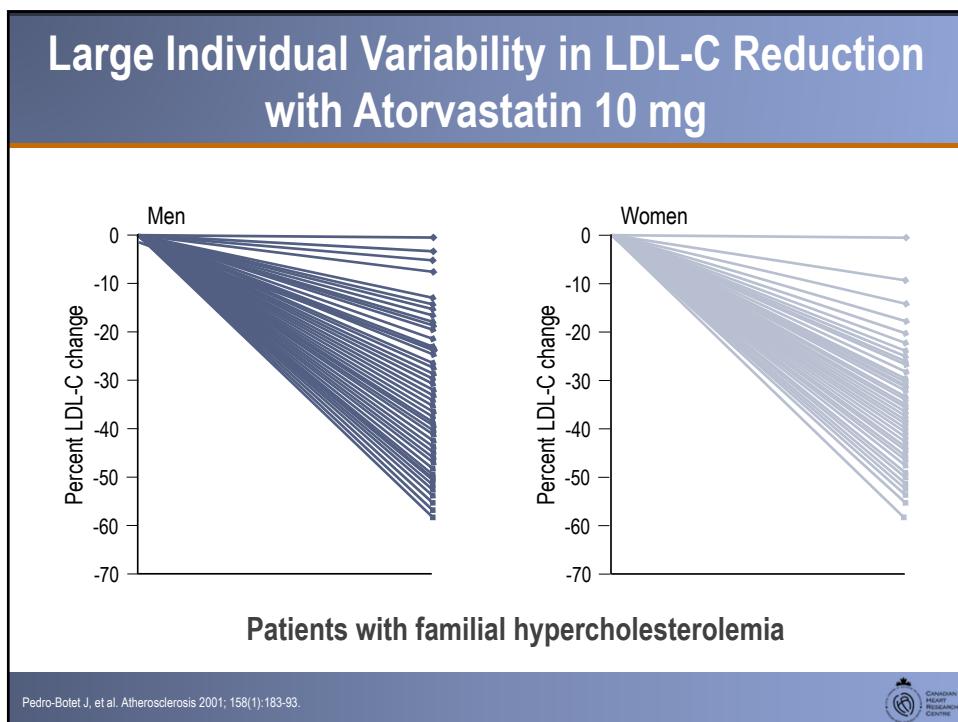
- 90% of all cases appear within the first 6 months after treatment initiation or dose up-titration
- Muscle aches (myalgia), weakness, stiffness and cramps
- Myopathy (myositis): accompanied with CK 10 x ULN
  - Patients with normal CK may also have symptoms of myopathy with statin therapy
- Rhabdomyolysis: 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

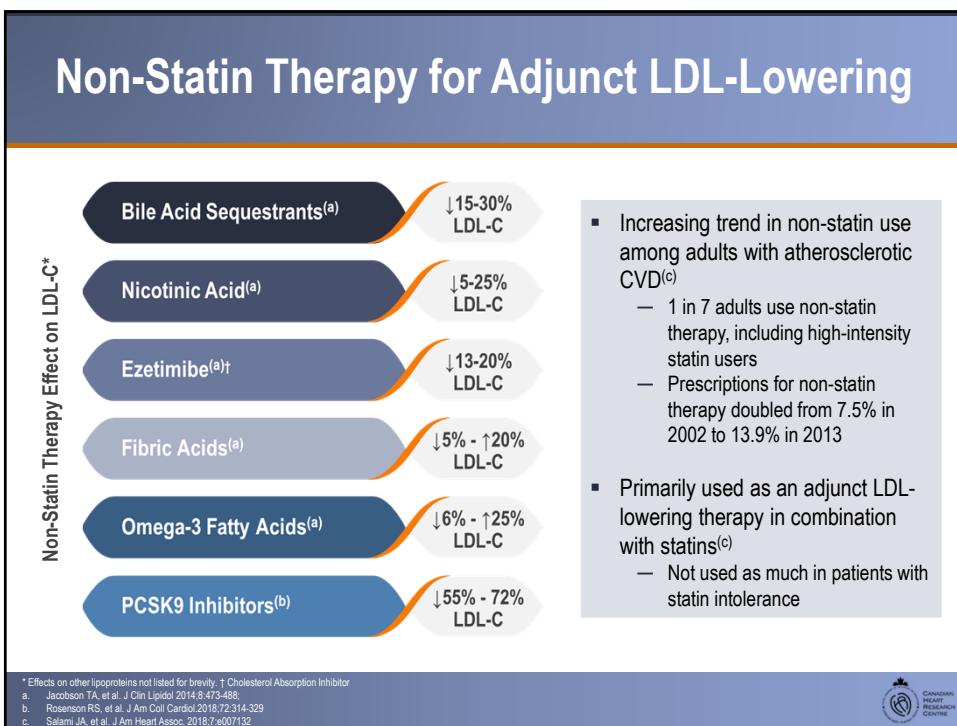
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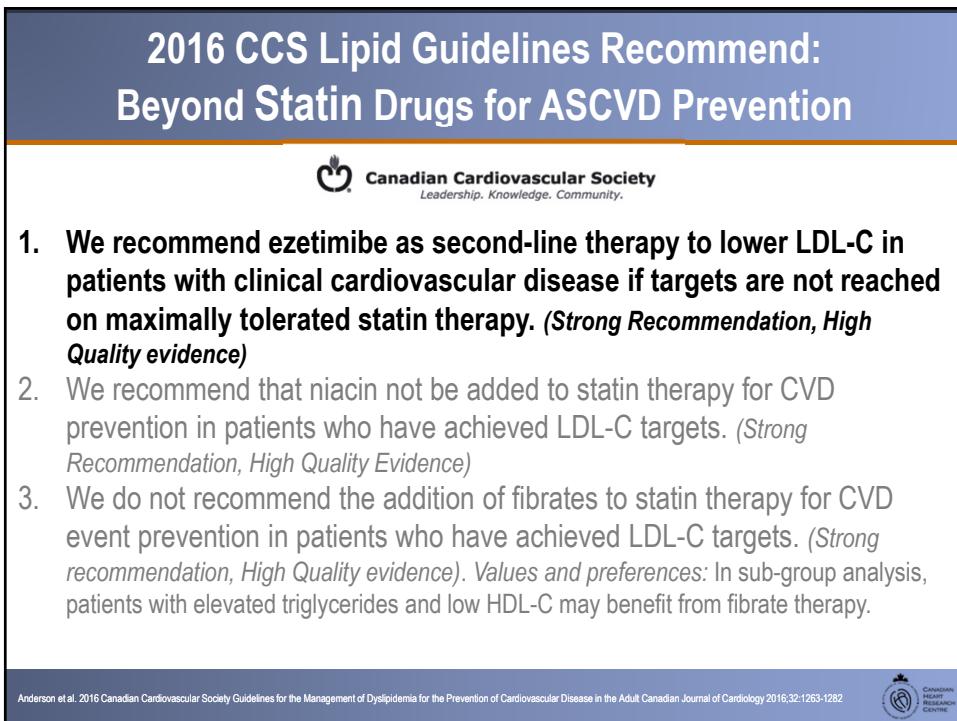
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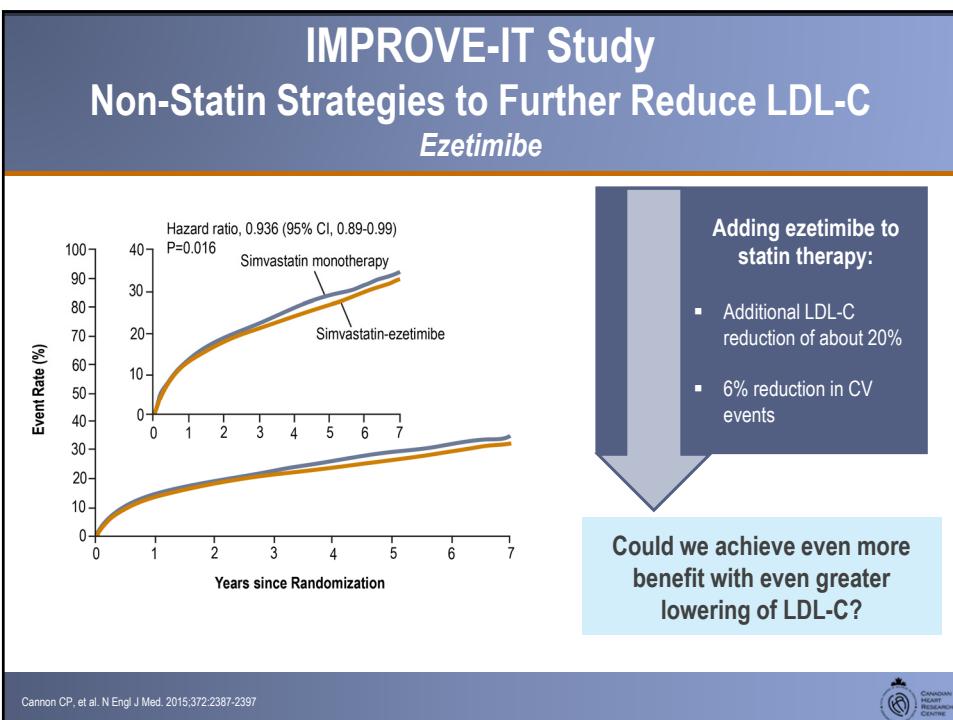
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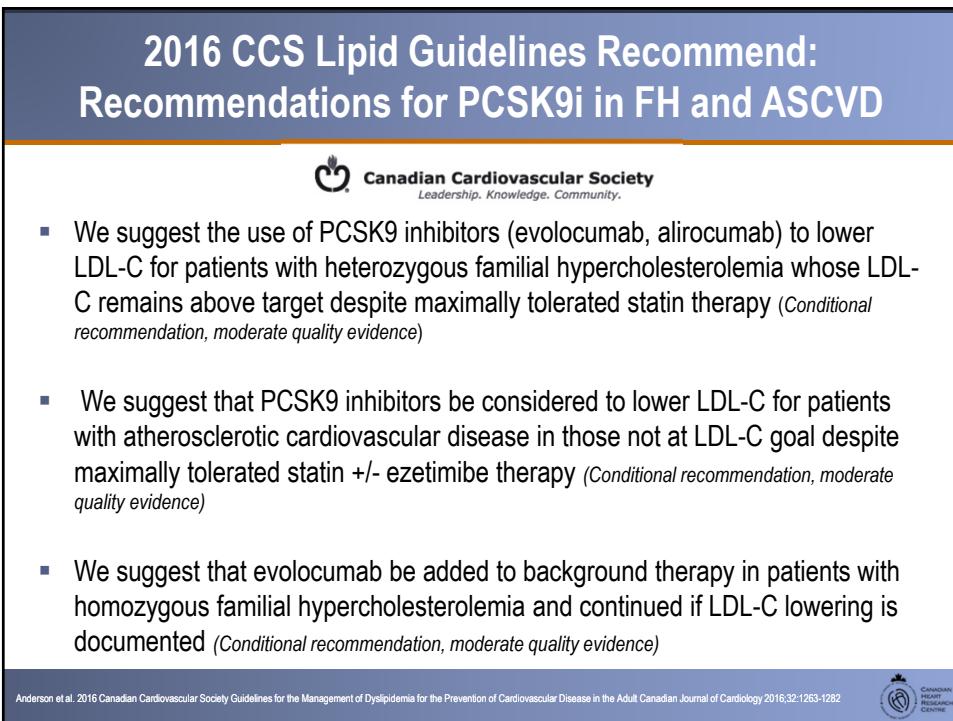
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**Adding a PCSK9 Inhibitor to statin therapy further reduces LDL-C by?**

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

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## 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



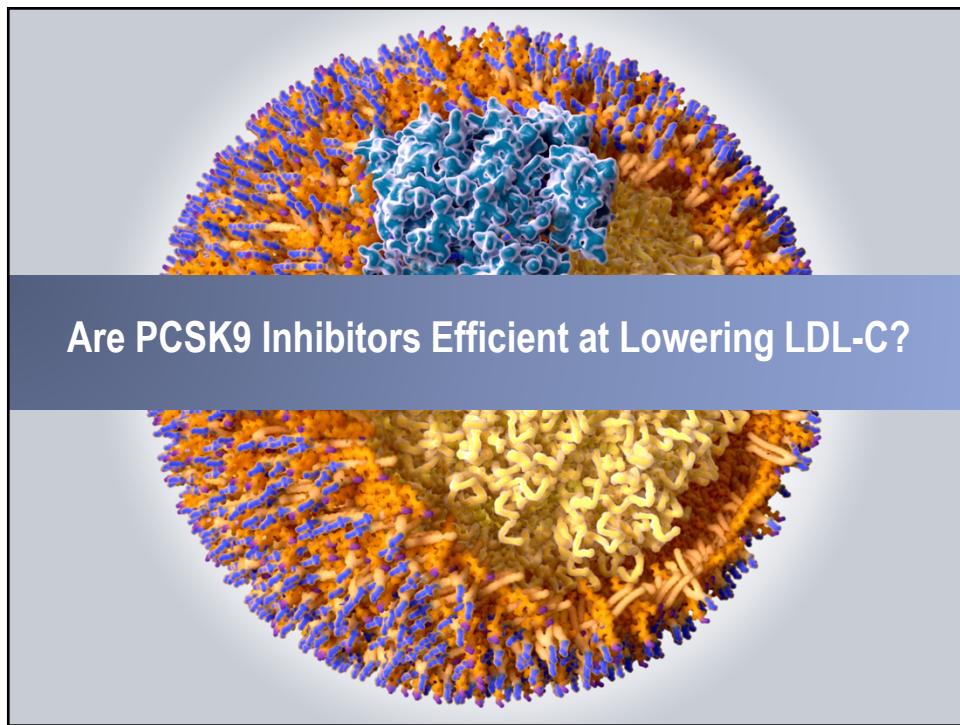
The real challenge now is to identify which patients would benefit most from PCSK9 inhibitors

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

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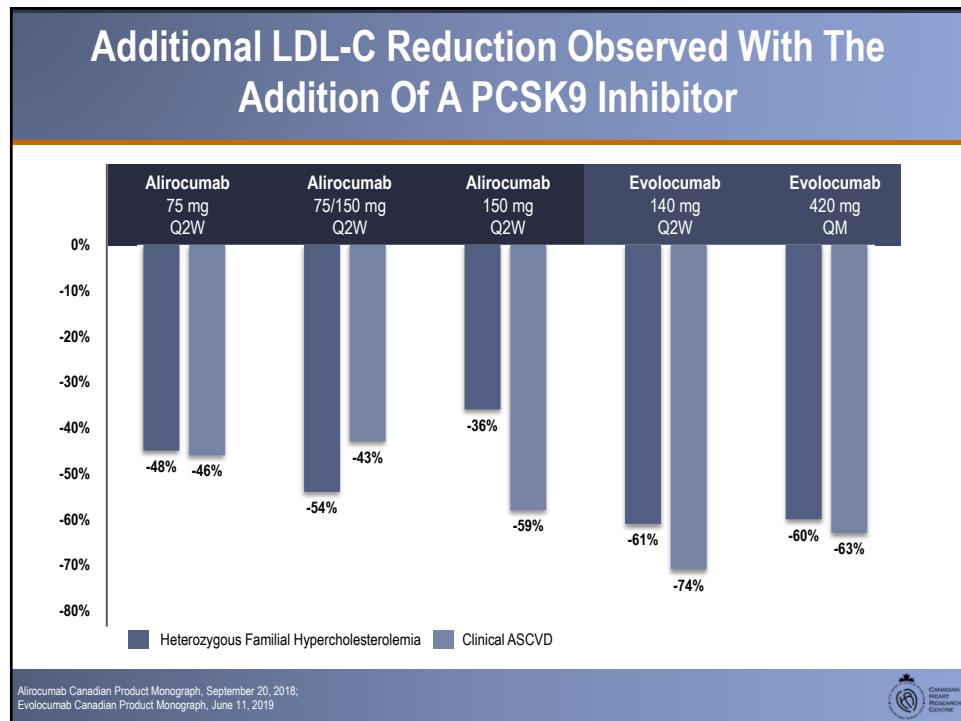
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**Can LDL-C Lowering be Achieved Safely and Effectively with PCSK9 Inhibitors?**

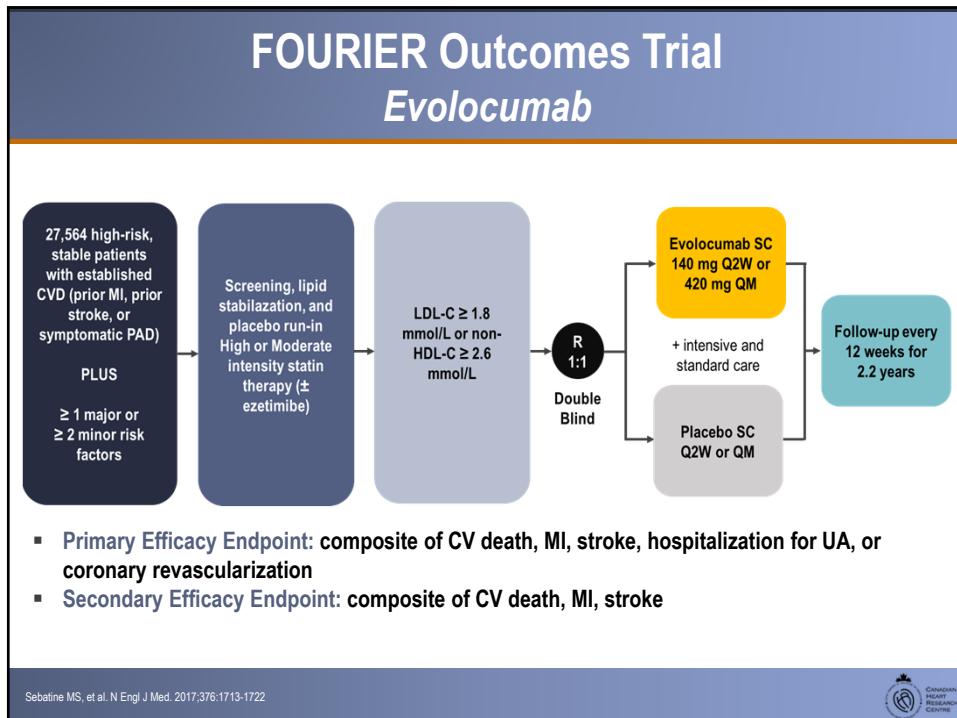
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1. Only if ezetimibe is used as well
2. Only if ezetimibe is not used
3. Only if maximal statin therapy is not used
4. Only in statin intolerant patients
5. None of the above

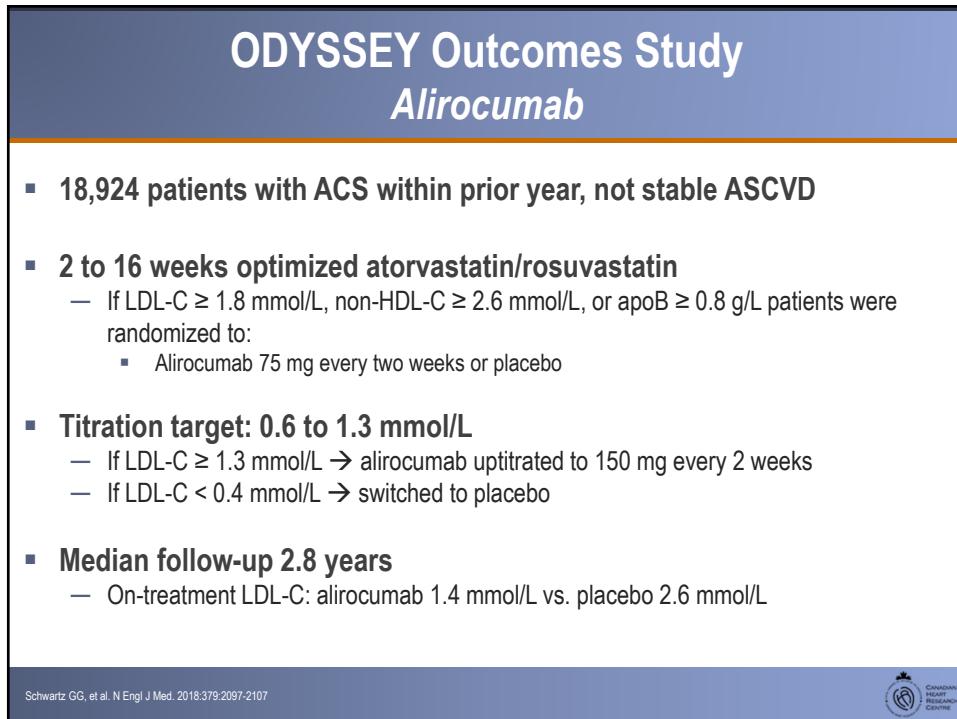
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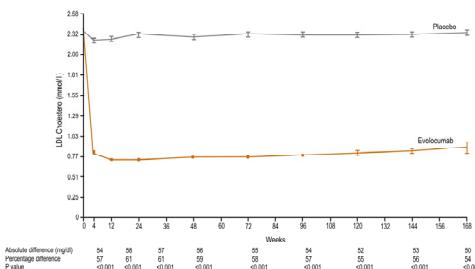
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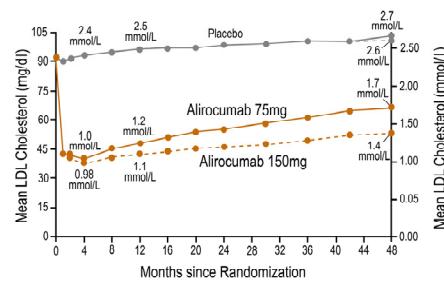
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## PCSK9 Inhibitors are Efficient at Lowering LDL-C

FOURIER:  
Evolocumab<sup>[a]</sup>



ODYSSEY Outcomes:  
Alirocumab<sup>[b]</sup>



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

b. Schwartz GG, et al. N Engl J Med. 2017;379:2097-2107



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## 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).



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## Real World Data

### GOAL: Baseline Lipid Profile and Management

**N = 2,024**

Lab Values	Median (25 <sup>th</sup> , 75 <sup>th</sup> 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)
<b>No statin</b>	<b>24</b>
Ezetimibe	25
Bile Acid Sequestrant	5
Fibrate	3
Niacin	<1



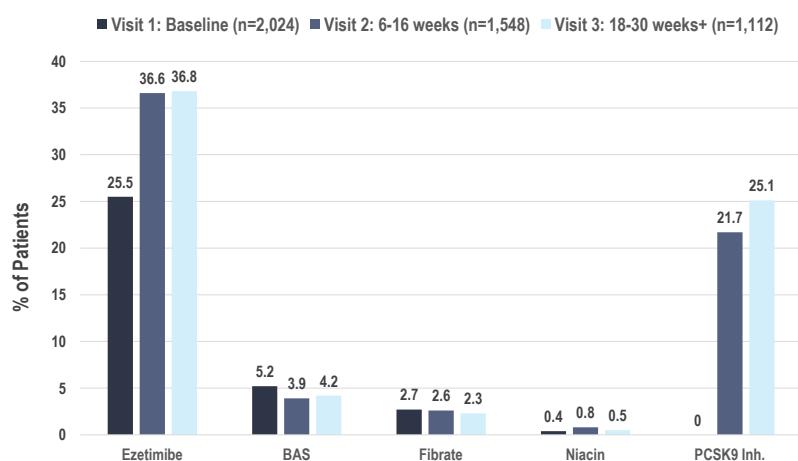
April 4, 2019 - data cut CHRC file



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## Real World Data

### GOAL: Additional Lipid Modifying Therapy



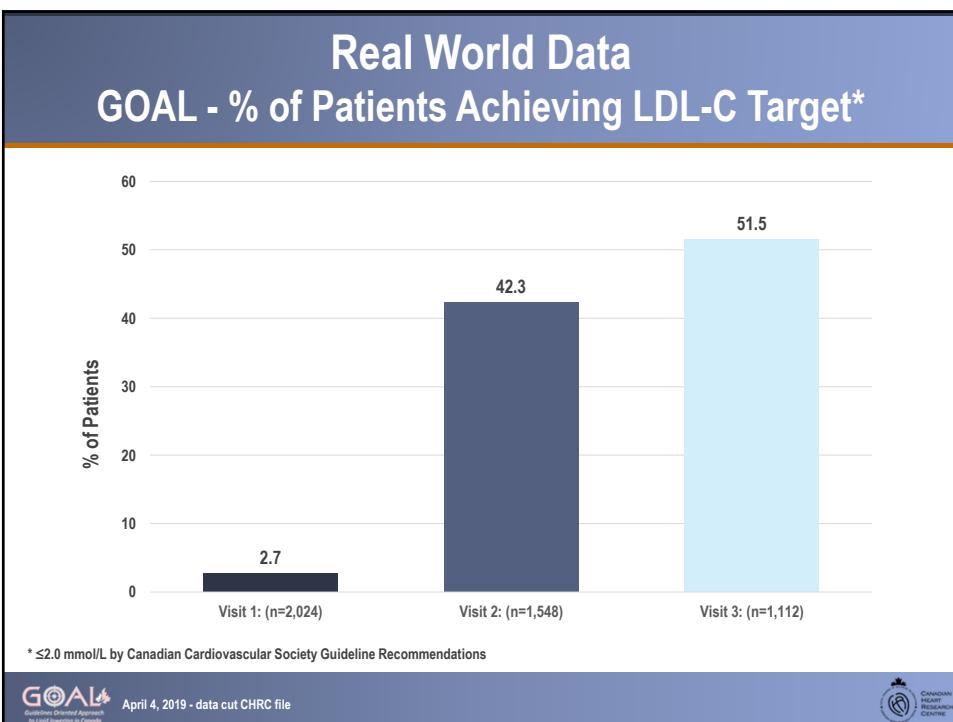
\* ≥6 weeks post Visit 2



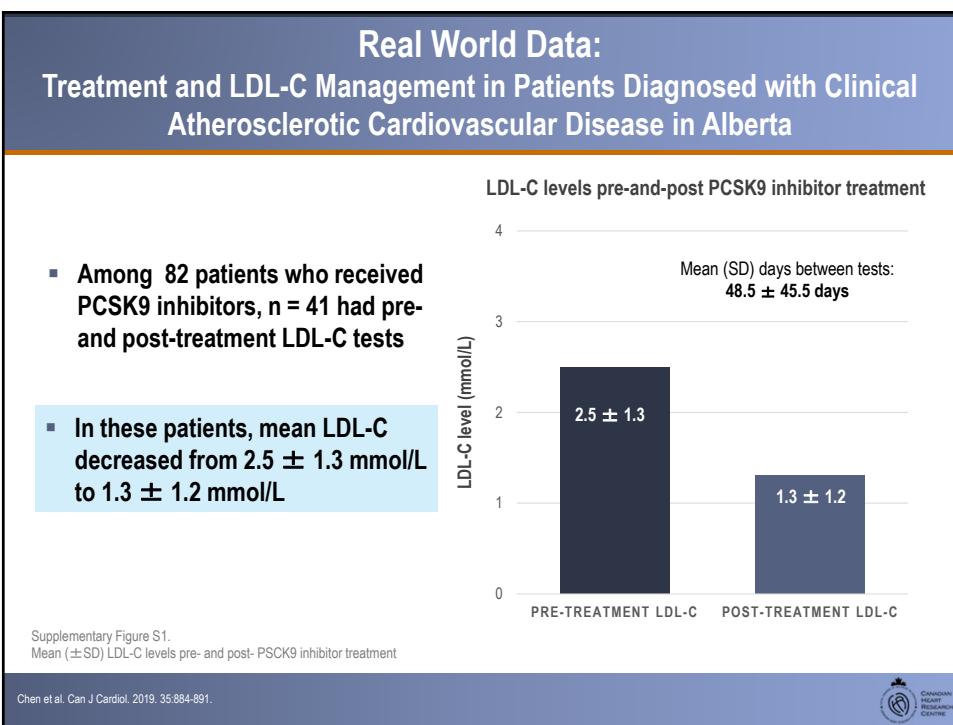
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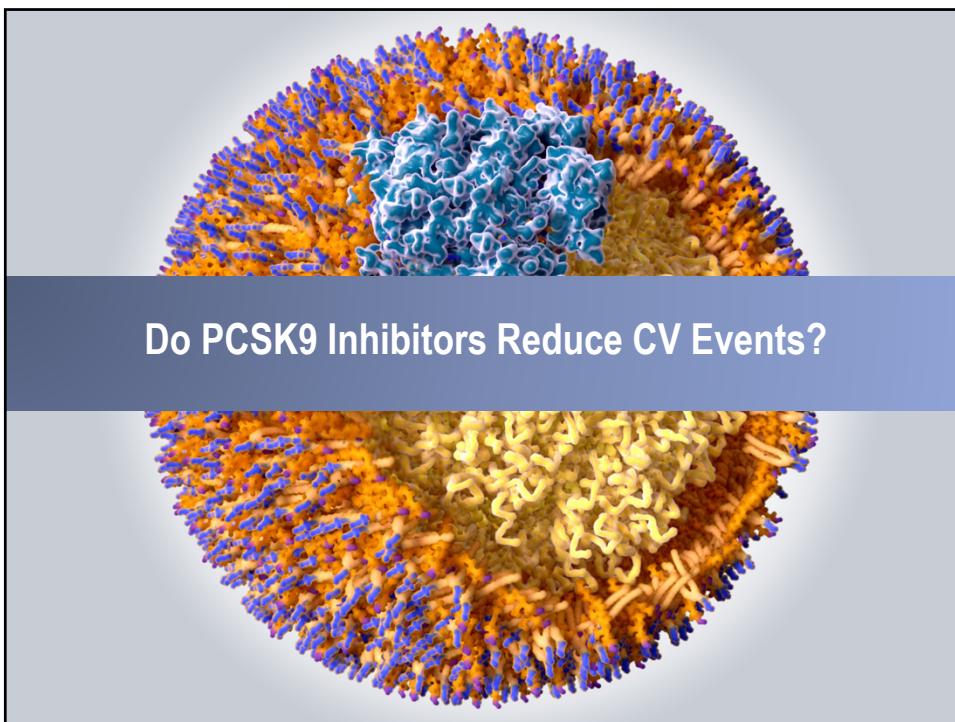
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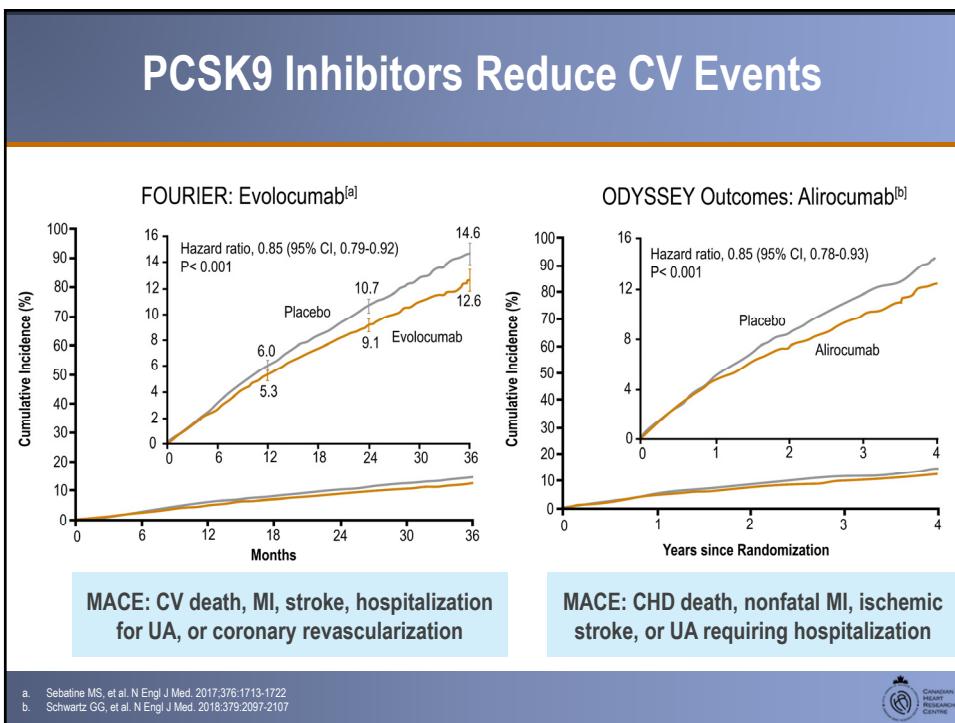
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**With Respect to Safety of PCSK9 Inhibitors,  
Which is True?**

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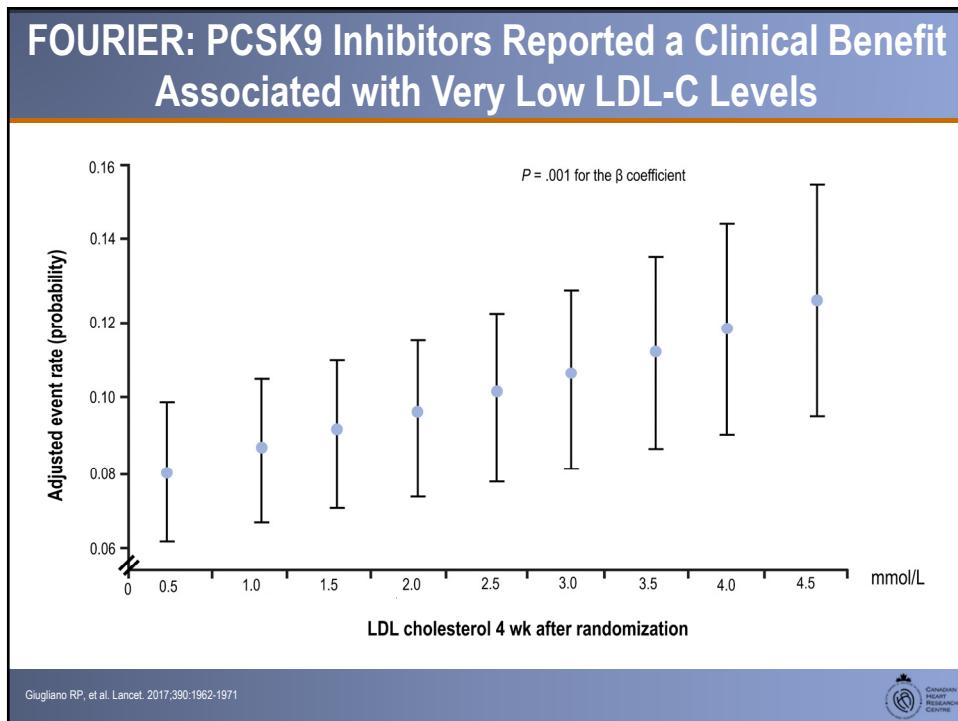
1. There is concern about neuro-cognitive AE
2. There is concern about myalgia
3. No significant adverse events have been demonstrated
4. The use of vitamin D supplementation is recommended

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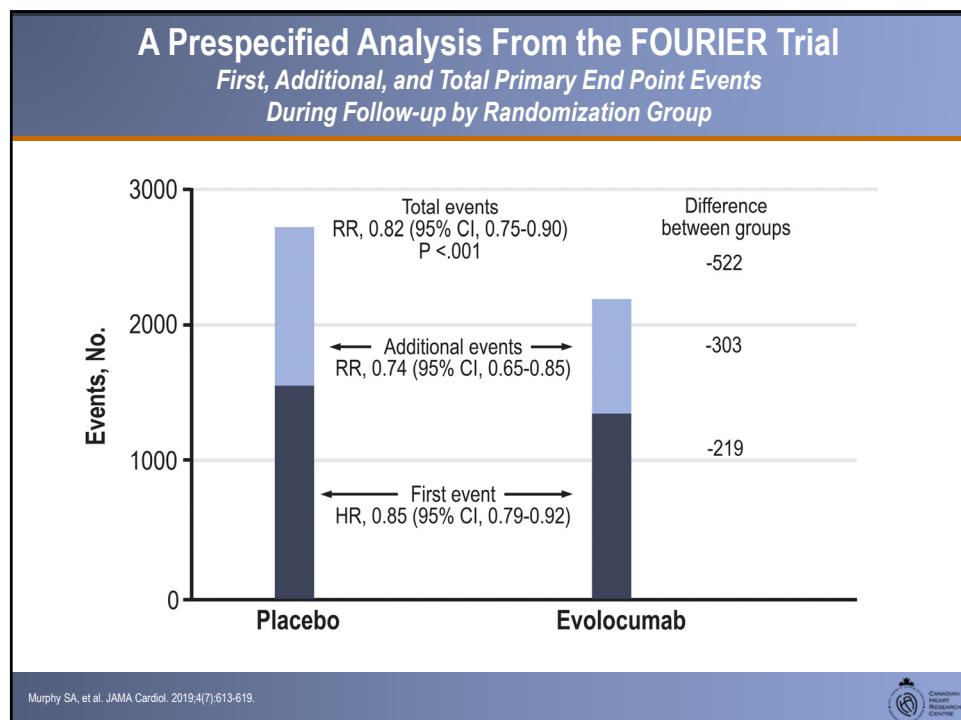
PCSK9 Inhibitors are Safe					
FOURIER: Evolocumab <sup>(a)</sup>		ODYSSEY Outcomes: Alirocumab <sup>(b)</sup>			
Outcome	Evolocumab (N = 13,769)	Placebo (N = 13,756)	Variable	Alirocumab (N = 9,451)	Placebo (N = 9,443)
Adverse events-no. of patients, %					
Any	77.4	77.4	Any adverse event	75.8	77.1
Serious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

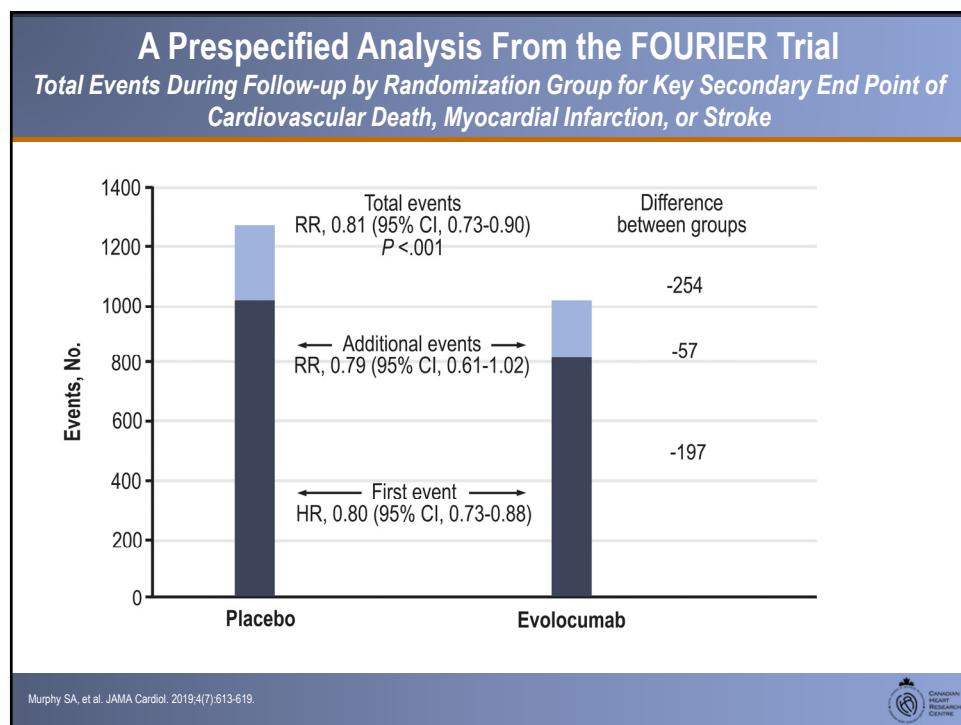
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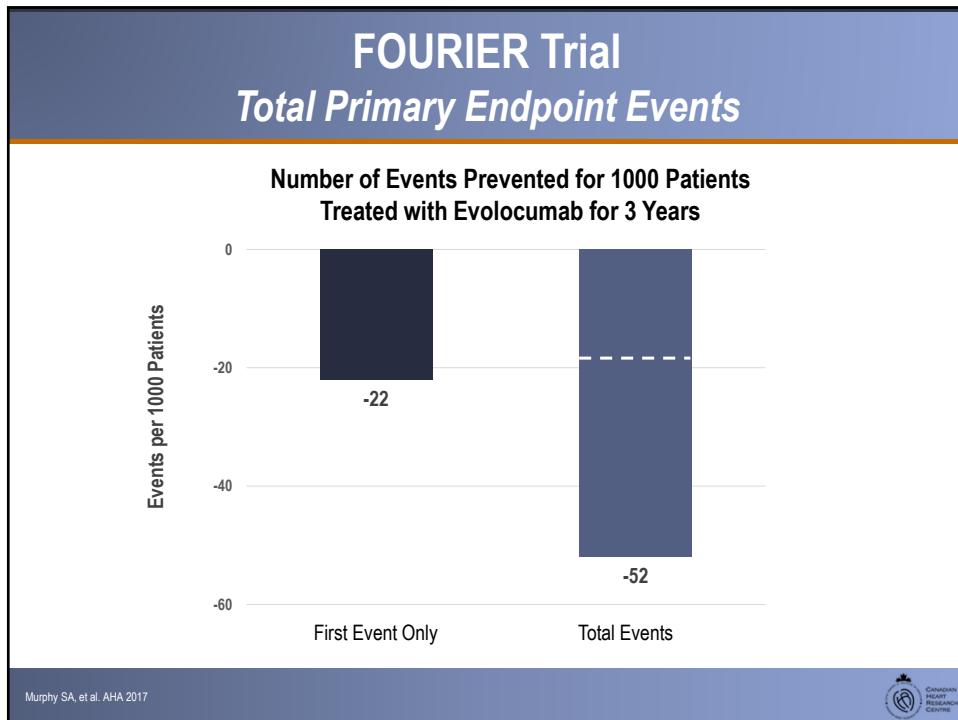
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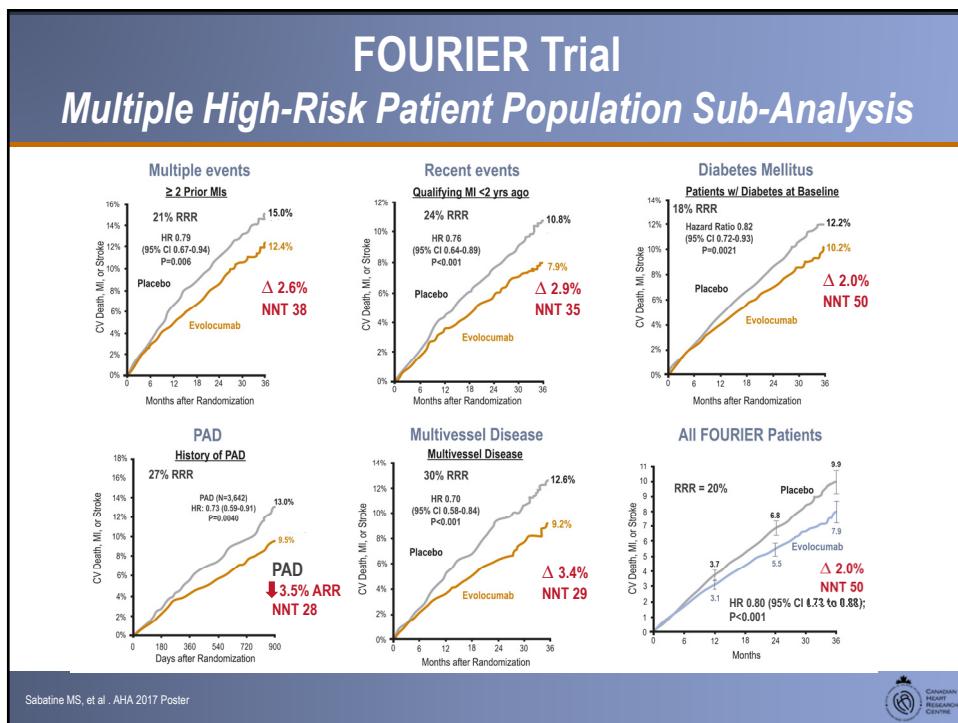
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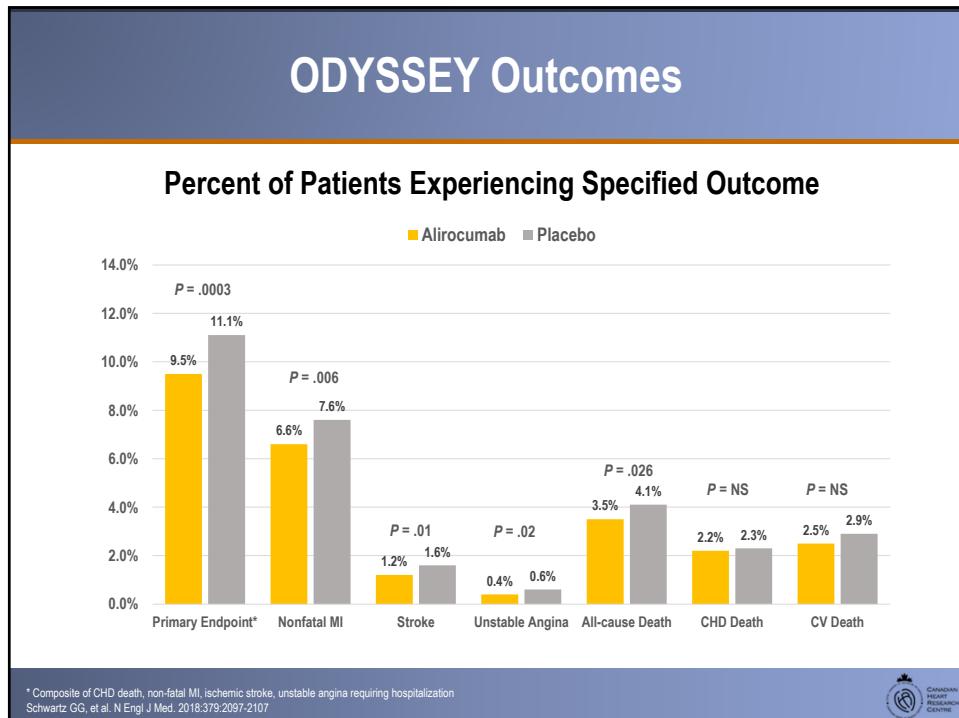
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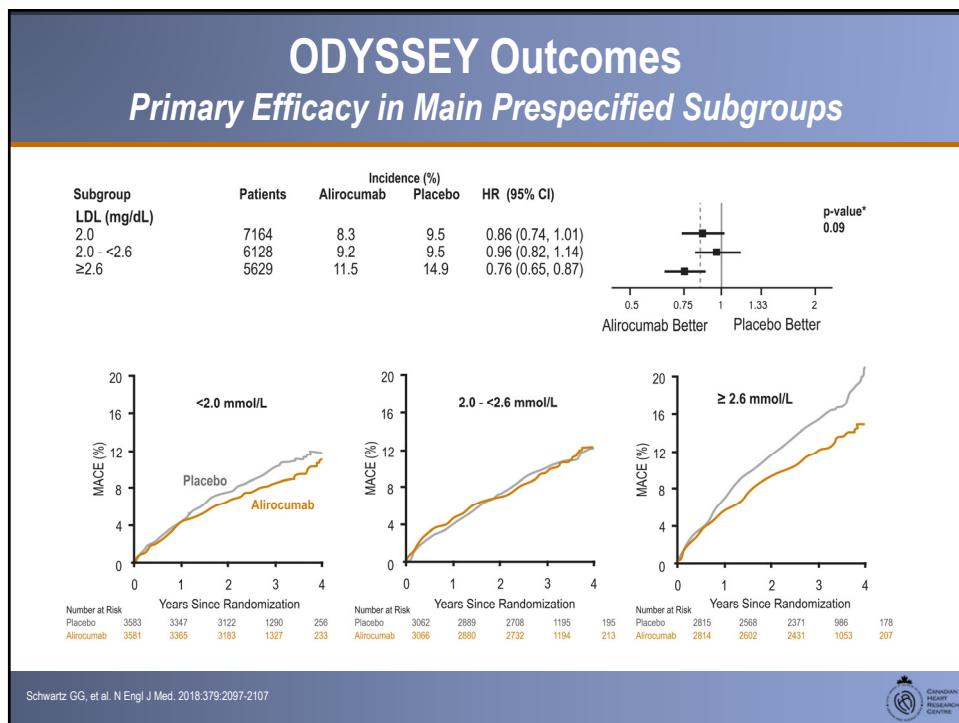
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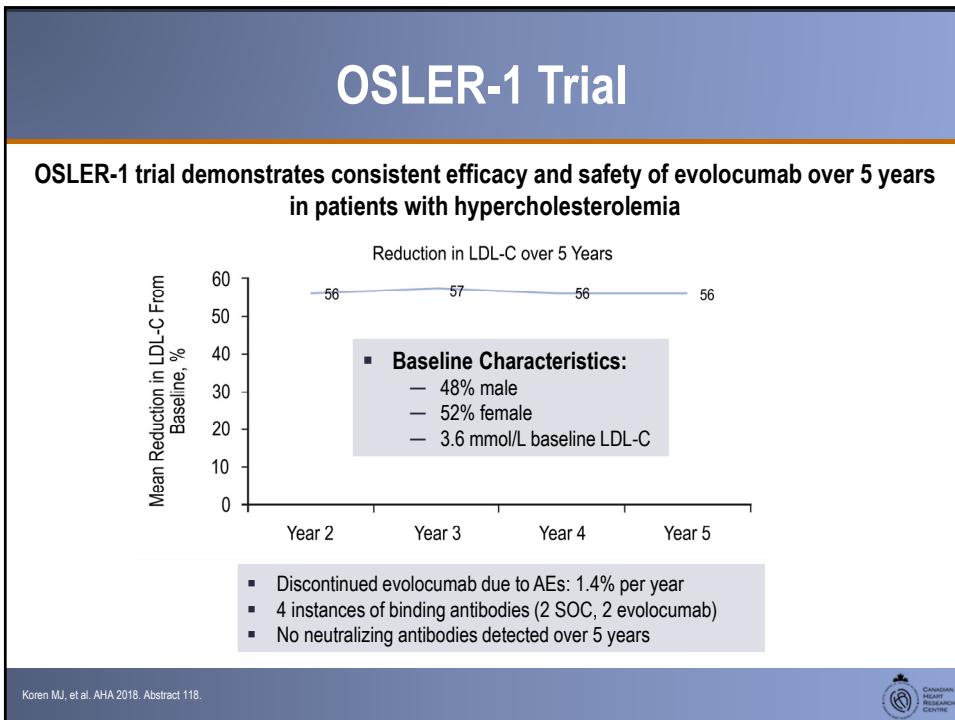
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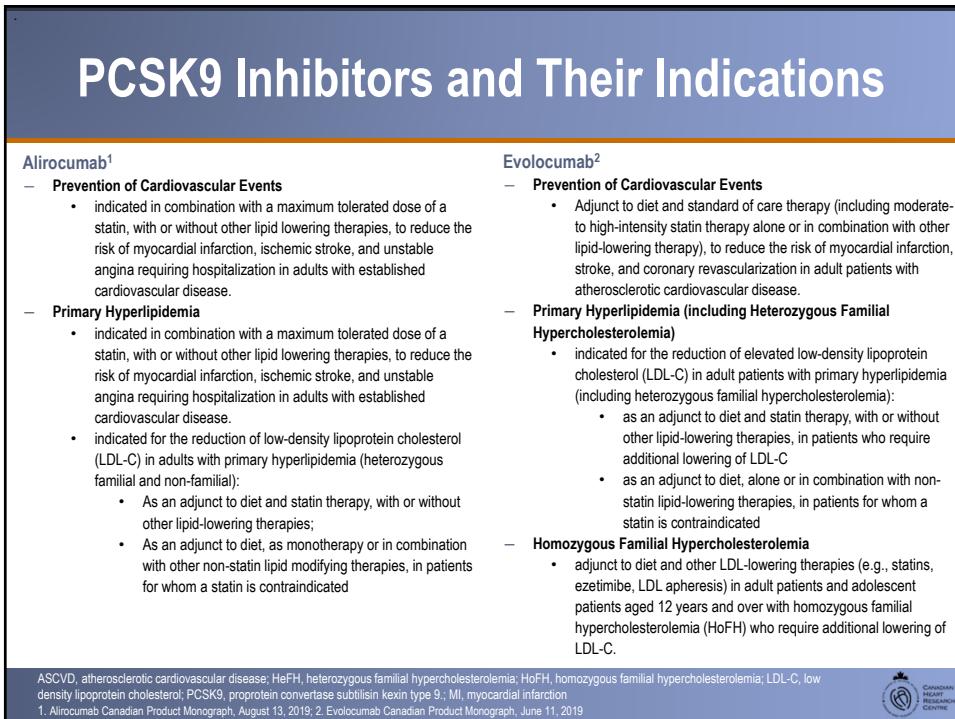
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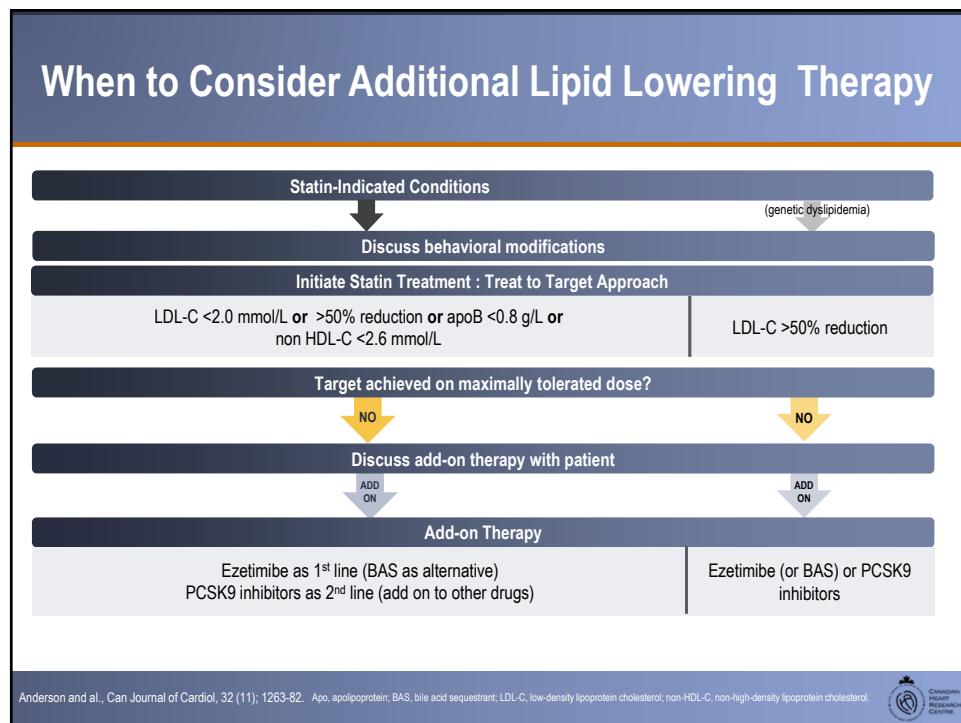
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## When to Consider Additional Lipid Lowering Therapy

- **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).**

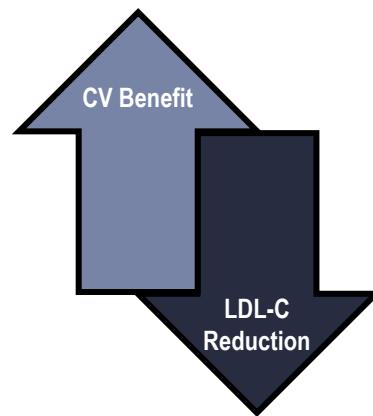
Anderson and al., Can Journal of Cardiol, 32 (11); 1263-82. Apo, apolipoprotein; BAS, bile acid sequestrant; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.



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## 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



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# DISCUSSION

**Which patients do you believe benefit most from PCSK9 Inhibition?**



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## 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?

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# DISCUSSION

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



CANADIAN  
HEART  
RESEARCH  
CENTRE

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## Who will Benefit most from “Lowest is Best” Strategy

Study	ARR, %
<b>FOURIER<sup>(a)</sup></b>	
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
<b>ODYSSEY<sup>(b)</sup></b>	
Patient with LDL > 2.6 mmol/L	3.4
Patient with high Lp(a)	2.3
<b>IMPROVE-IT<sup>(c)</sup></b>	
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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## 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](http://www.formulary.health.gov.on.ca/formulary)  
[www.health.gov.on.ca/en/pro/programs/drugs/dnug\\_stat/\\_repatha.pdf](http://www.health.gov.on.ca/en/pro/programs/drugs/dnug_stat/_repatha.pdf)

\* Ontario Provincial Reimbursement Criteria for HeFH used as the example



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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



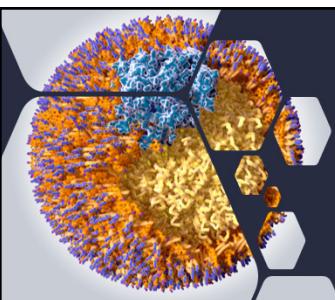
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## Summary

- 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



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### Clinicians' Corner: Additional benefit of PCSK9 inhibition in high-risk patients after myocardial infarction

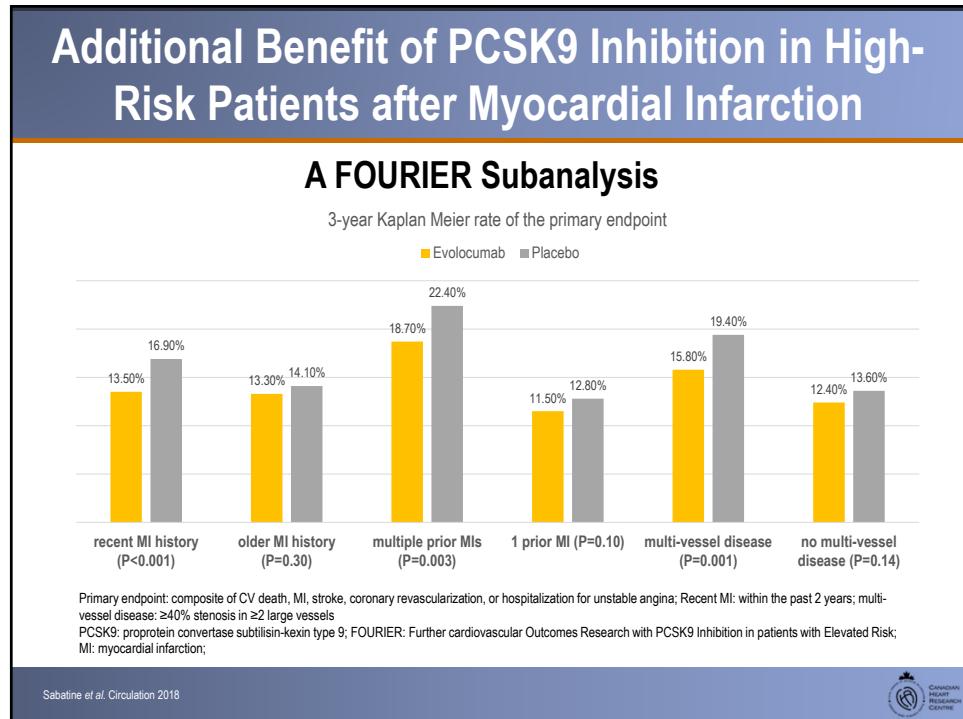
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**In the FOURIER trial, which of the following subgroups of patients with prior myocardial infarction (MI) had the greatest relative risk reduction?**

---

1. Qualifying MI >2 years ago
2. Multivessel Disease
3. 1 prior MI
4. Universal MI Type 2

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# DISCUSSION

## What are the implications for clinical practice?



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# Summary

## ▪ **Patients**

- (1) closer to their most recent MI,
- (2) with multiple prior MIs, or
- (3) with multivessel disease

**are at 34-90% ↑ risk for major vascular events**

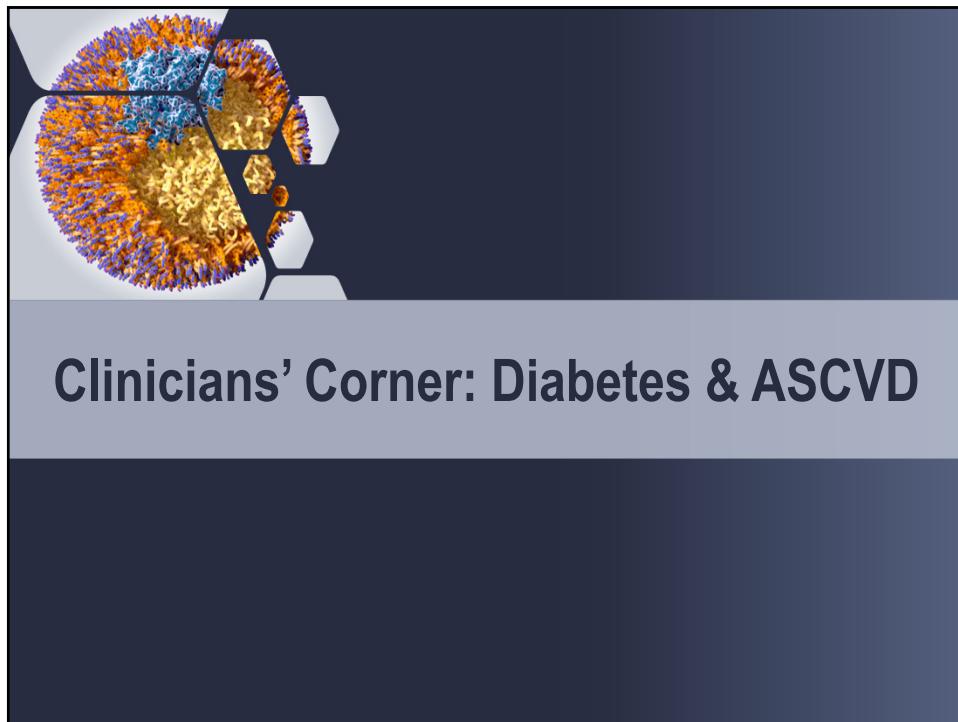
## ▪ **These patients experience substantial:**

- relative risk reductions (21-30%) and
- absolute risk reductions (2.6-3.4% over 3 years) with intensive LDL-C lowering with PCSK9i

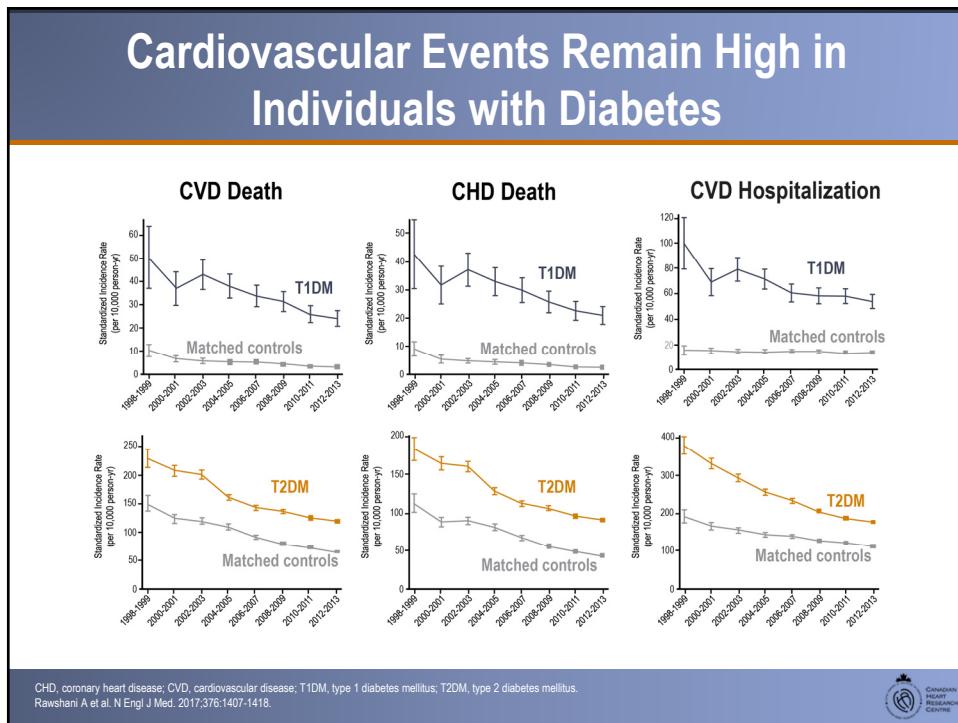
**These readily ascertainable clinical features offer one approach to tailoring therapy**

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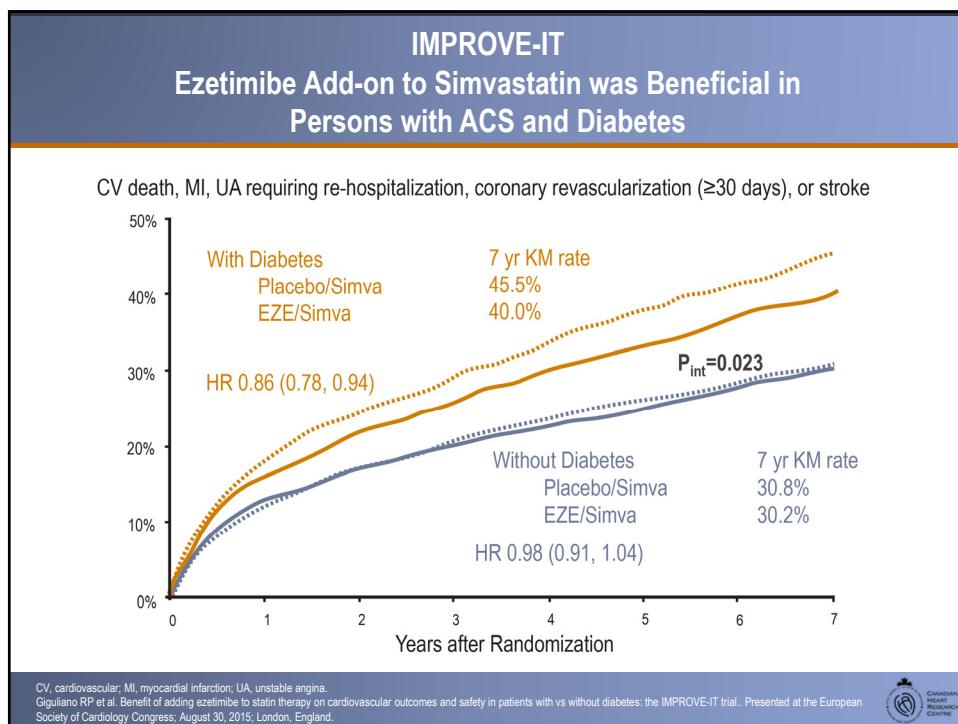
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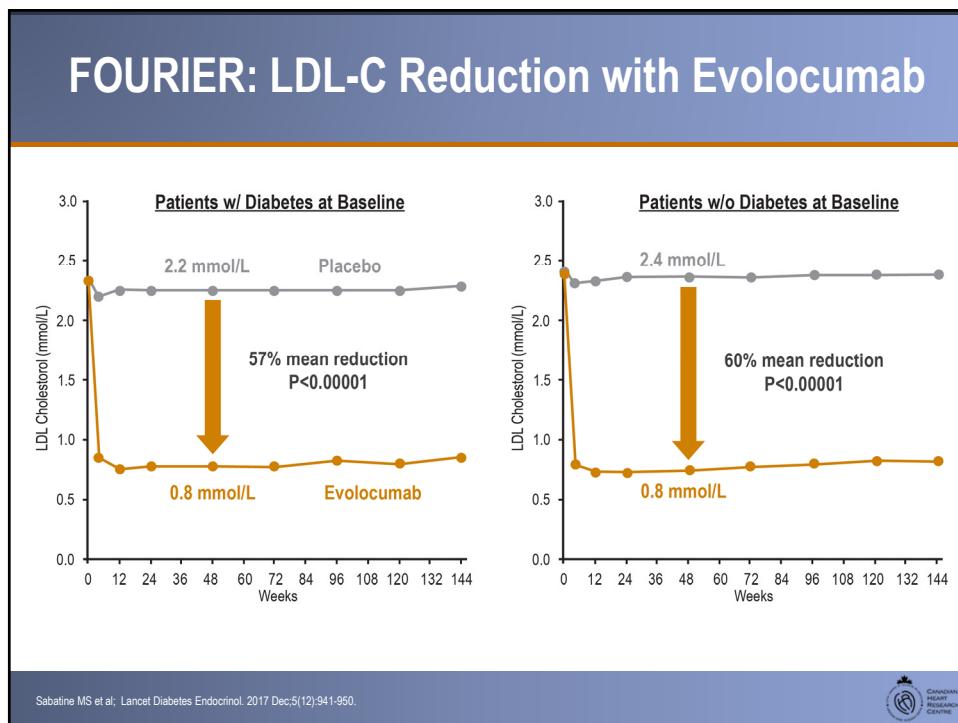
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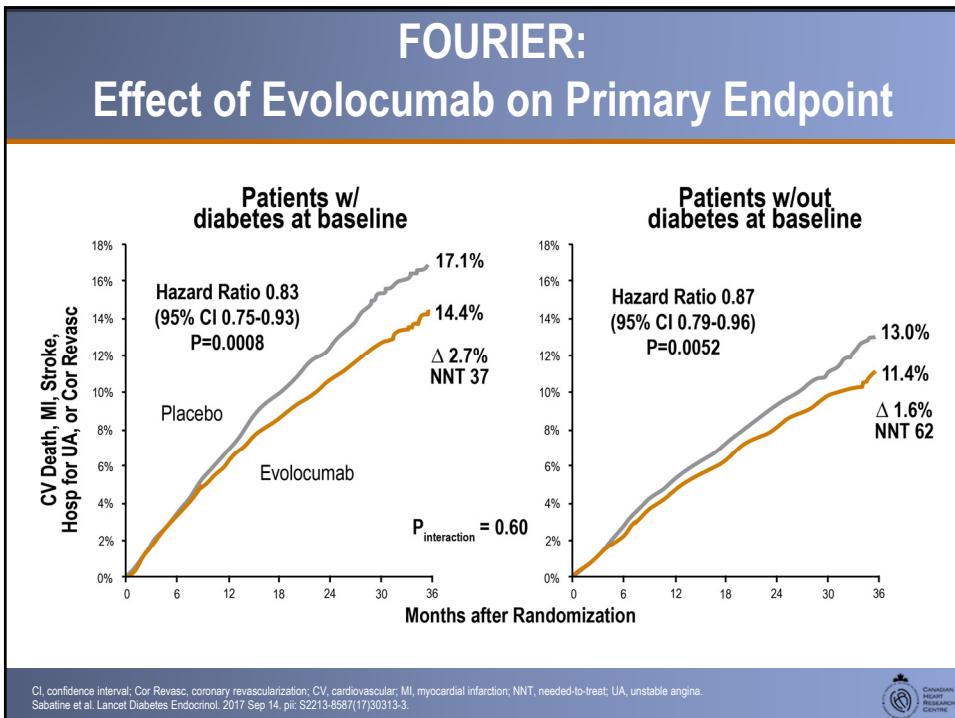
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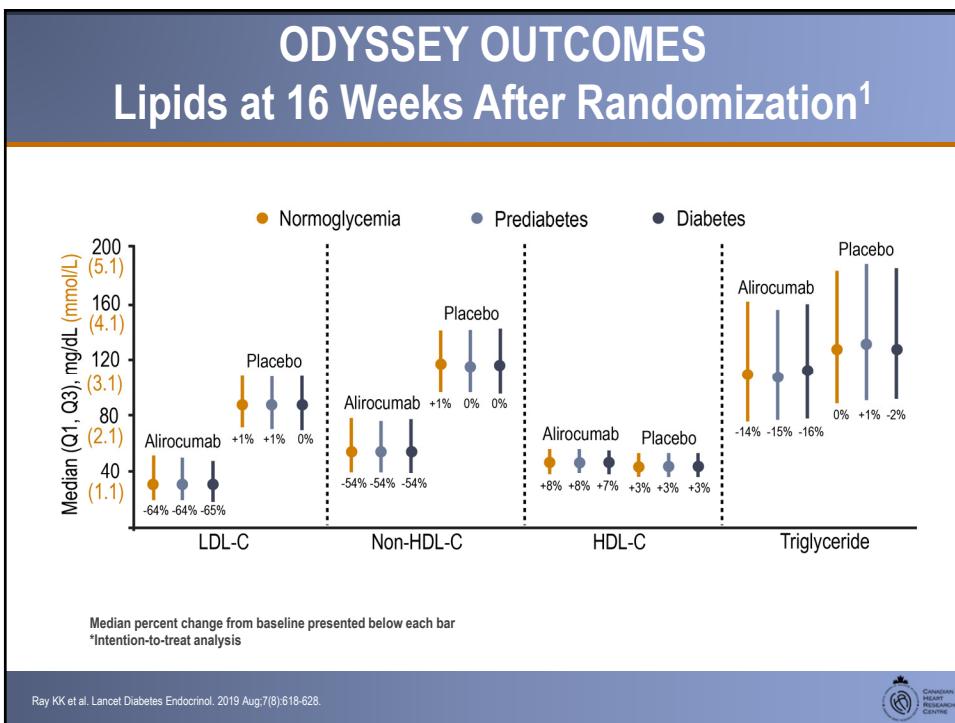
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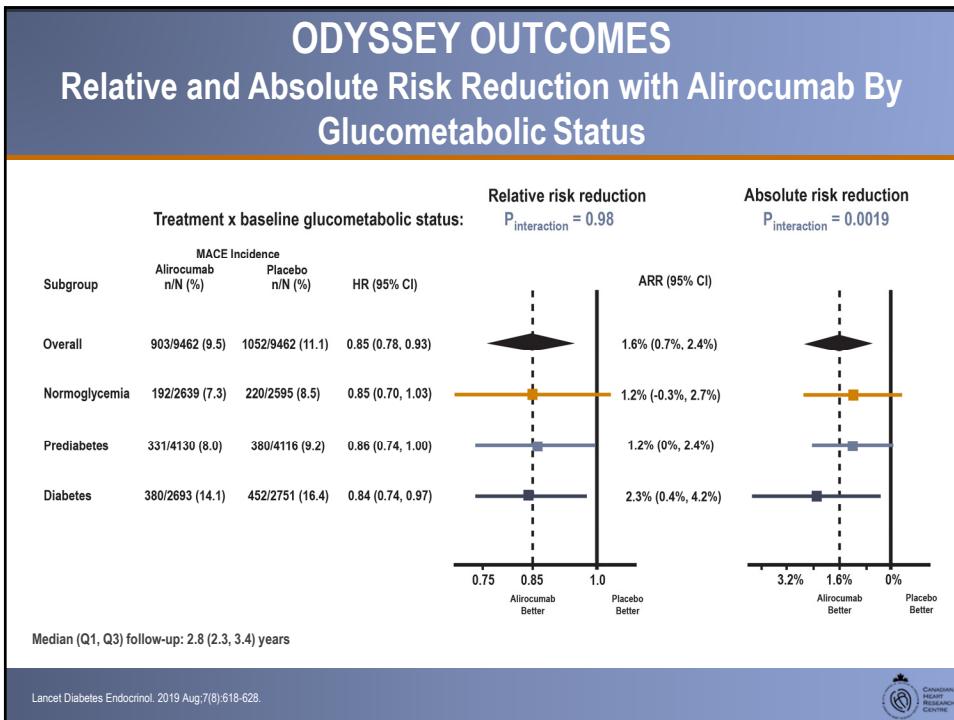
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**Recommendations for Lipid Management in Diabetes**

- For people with diabetes with indications for lipid-lowering therapy, treatment should be initiated with a statin<sup>1</sup> to achieve LDL-C consistently <2.0 mmol/L<sup>2</sup> or >50% reduction of LDL-C from baseline<sup>3</sup>.
  - Alternative targets and respective goals are apo B <0.8 g/L and non-HDL-C <2.6 mmol/L<sup>4</sup>.

1 [Grade A, Level 1]  
 2 [Grade C, Level 3]  
 3 [Grade D, Consensus]  
 4 [Grade C, Level 3]

Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325

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## Summary

- Statin monotherapy may not achieve targets in all patients
- Previous add-ons to statin are suboptimal
- PCSK9 inhibitors appear to have similar efficacy and safety in individuals with and without diabetes (with greater absolute risk reduction) and with no apparent adverse effects on glycemia

