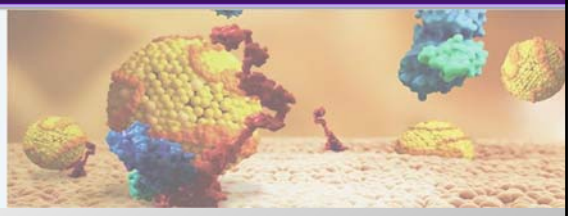
New Horizons in Dyslipidemia Management in Primary Care



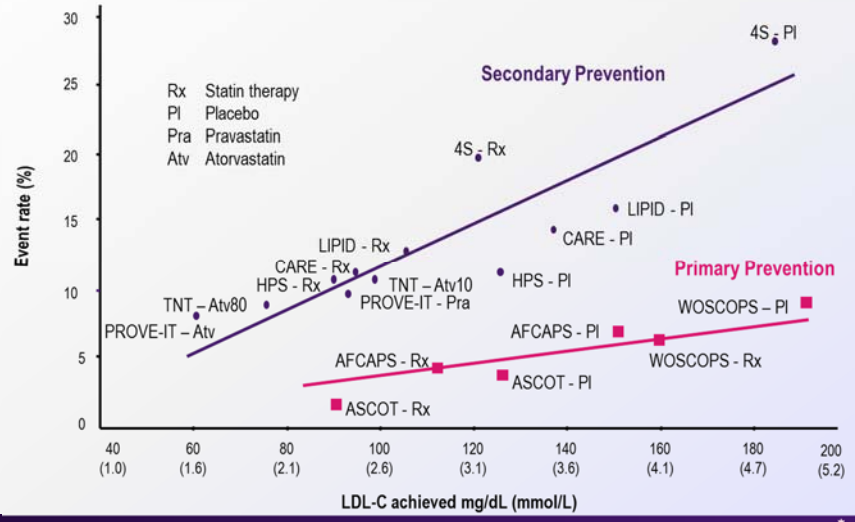
CANADIAN HEART RESEARCH CENTRE

Learning Objectives

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

01	Discuss the role of LDL-C lowering in cardiovascular risk reduction with emphasis on the results of recently completed clinical trials
02	Evaluate recommendations for lipid lowering agents beyond or in addition to statin therapy for patients with atherosclerotic cardiovascular disease
03	Explain the mechanism of action of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and apply the latest clinical data to patient management strategies
04	Apply best guideline practice recommendations into routine clinical practice based on specific patient characteristics

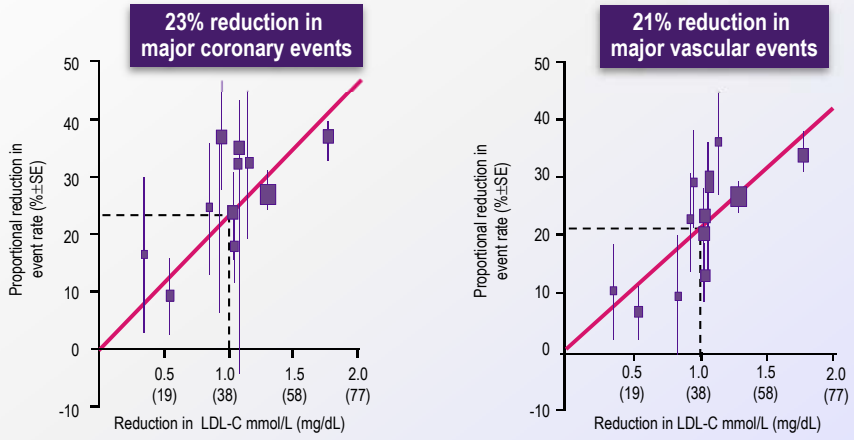
Relationship Between LDL-C and CV Event Rate



Rosenson RS. Exp Opin Emerg Drugs 2004;9(2):269-279, LaRosa JC et al. N Engl J Med 2005;352:1425-1435.

Reduction in CV Events is Proportional to LDL-C Reduction at 1 Year

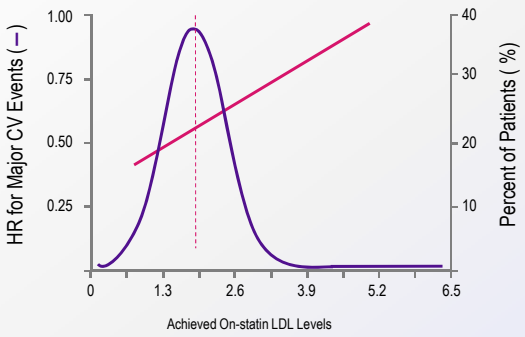
A prospective meta-analysis of data from 90,056 individuals from 14 trials of statins
A 1 mmol/L reduction in LDL-C was associated with a…



Adapted from Baigent C, et al, Cholesterol Treatment Trialists' (CTT) Collaborators. Lancet 2005;366:1267–1278.

On-Statin LDL-C Levels and Risk for Major Cardiovascular Events

There is often a need for LDL-C reduction beyond statin therapy

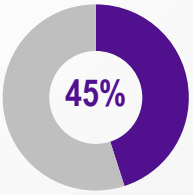


In clinical trials, even amongst those patients on a similar statin dosage, those who had the lowest LDL-C levels had the lowest CV event rates

Meta-analysis of 8 statin trials (N=38,153):
>40% did not reach LDL-C target (<1.8 mmol/L) on high dose statin

CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio.
Boekholdt SM et al. J Am Coll Cardiol. 2014;64:485-494.

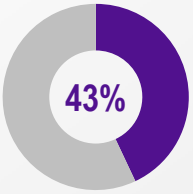
Many High-Risk Canadian Patients Treated with Statins Are Not at LDL-C Goal



DYSIS[1]

Canadian high-risk patients are NOT at LDL-C target[1*] (< 2.0 mmo/L)

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



DM-SCAN[2]

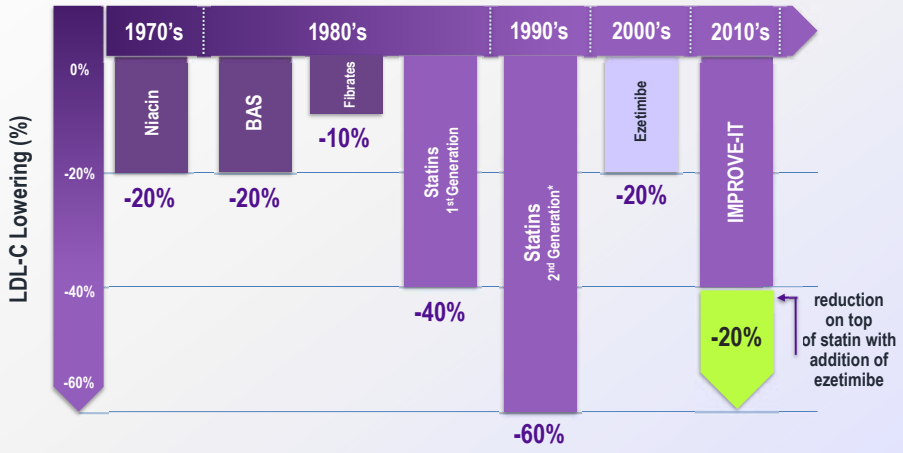
Canadian patients with diabetes are NOT at LDL-C target[†] (≤ 2.0 mmo/L)

- 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 ≥20%. DYSIS 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.

Limitations of Current Lipid-Lowering Therapies



BAS: Bile Acid Sequesterant

1. The Coronary Drug Project Research Group. JAMA. 1975;231:360-81; 2. Lipid Research Clinics Program. JAMA. 1984;251:351-64; 3. Frick MH et al. N Engl J Med. 1987;317:1237-45; Vaughan CJ, 4. Gotto AM Jr. Circulation. 2004;110:886-92; IMPROVE-IT Investigators. N Engl J Med. 2015;372:2387-97. 5. National Institute for Health and Clinical Excellence. London: National Institute for Health and Clinical Excellence, 2012.

Why is Statin Treatment Not Enough?

- Side-effects such as statin associated muscle symptoms reported in 10% to 25%
- Wide range of individual responses to statins
- Limited ability to lower LDL-C
- Real-world data from the GOAL Program showing the need beyond statin use

Bruckert et al 2005; Cohen et al 2012

Prevalence of Statin Associated Muscle Symptoms (SAMS) in PRIMO

Retrospective observational + high-dose statin

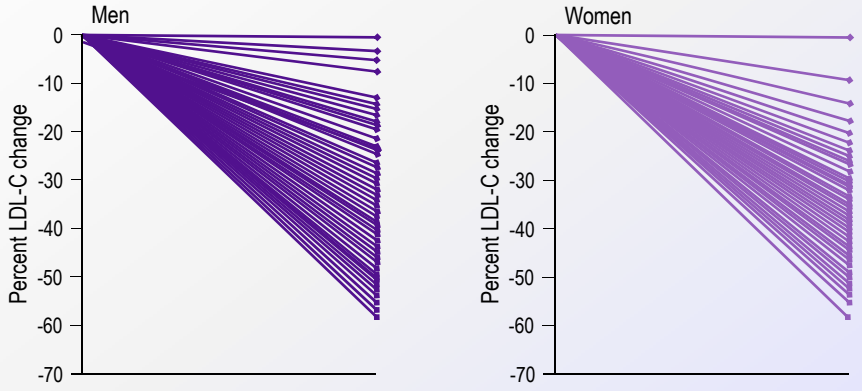
Statin	Dosage	Percentage of patients with muscular symptoms*	Odds Ratio† [95% CI]	P value‡
Pravastatin	40 mg/day	10.9%		
Atorvastatin	40–80 mg/day	14.9%	1.28 [1.02–1.60]	0.035
Simvastatin	40–80 mg/day	18.2%	1.78 [1.39–2.29]	<0.0001
Fluvastatin	80 mg/day	5.1%	0.33 [0.26–0.42]	<0.0001

*% values relative to the total number of patients with or without muscular symptoms.
† Odds ratios were calculated using pravastatin as the reference.
‡ P values were determined by Pearson's Chi-squared test.

PRIMO: Prediction of Muscular Risk in Observational conditions

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

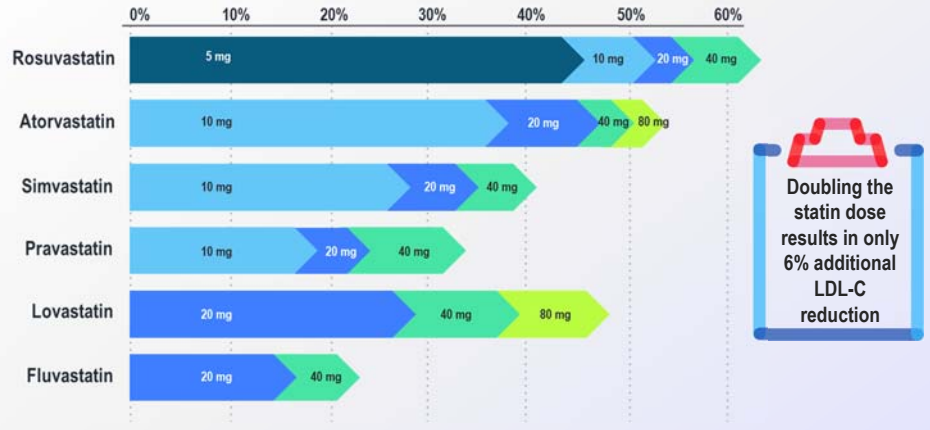
Large Individual Variability in LDL-C Reduction with Atorvastatin 10 mg



Patients with familial hypercholesterolemia

Pedro-Botet J, et al. Atherosclerosis 2001; 158(1):183-93.

Even Maximal Statin Therapy May Not Be Sufficient In Achieving LDL-C Target



*As per Canadian Product Monographs

1. Crestor (rosuvastatin) Product Monograph. AstraZeneca. April 21, 2015.
2. Lipitor (atorvastatin) Product Monograph. Pfizer. Feb 18, 2016.
3. Pravachol (pravastatin) Product Monograph Bristol-Myers Squibb Canada. Nov 30, 2015.
4. Mevacor (lovastatin) Product Monograph. Merck. Jul. 24, 2012.
5. Zocor (simvastatin) Product Monograph. Merck. Dec 10, 2014.
6. Lescol (fluvastatin) Product Monograph. Novartis. Aug. 26, 2016.
7. Adapted from CURVES Investigators. Am J Cardiol. 1998;81:582-587.

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:

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

GOAL: Co-Morbidities

Co-morbidities in high-risk patients (defined as those with clinical atherosclerotic cardiovascular disease) and LDL-C > 2.0 mmol/L despite maximal tolerate statin therapy

N = 1,571 patients

Medical History	Percent of Patients
Coronary artery disease	51%
Cerebrovascular disease	8%
Abdominal aortic aneurysm	2%
Peripheral arterial disease	9%
Diabetes	36%
Treated hypertension	61%
Chronic kidney disease	8%
Familial hypercholesterolemia	46%

GOAL March 28, 2018 - data cut CHRC file

GOAL: Lipid Profile and Management

N = 1,571 patients

Lab Values	Mean ± std	Median (IQR)
Total cholesterol (mmol/L)	5.5±1.4	5.2 (4.4, 6.2)
LDL-C (mmol/L)	3.3±1.2	3.0 (2.4, 3.9)
HDL-C (mmol/L)	1.3±0.4	1.2 (1.0, 1.5)
Non HDL-C (mmol/L)	4.1±1.5	3.8 (3.1, 4.9)

GOAL March 28, 2018 - data cut CHRC file

GOAL: Lipid Profile and Management

N = 1,571 patients

Lipid Lowering Agent	%
Atorvastatin	27.6
10 mg	4.2
20 mg	4.8
40 mg	8.0
80 mg	10.6
Rosuvastatin	39.1
10 mg	10.8
20 mg	11.0
40 mg	12.4
Simvastatin	2.9
10 mg	0.9
40 mg	1.0
80 mg	0.2
No Statin	24.6
Ezetimibe	20.3%

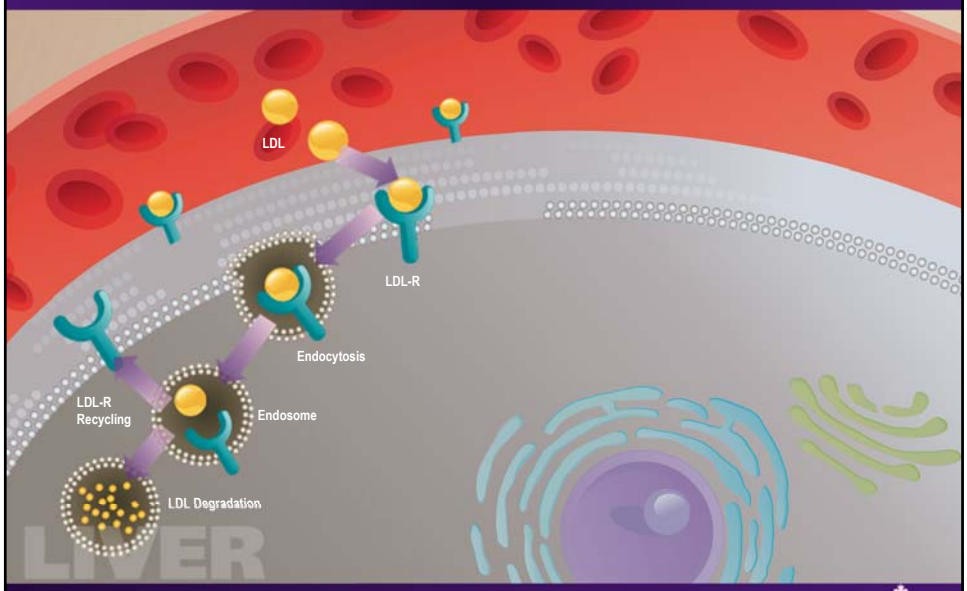
GOAL March 28, 2018 - data cut CHRC file

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

Please select from one of the available options

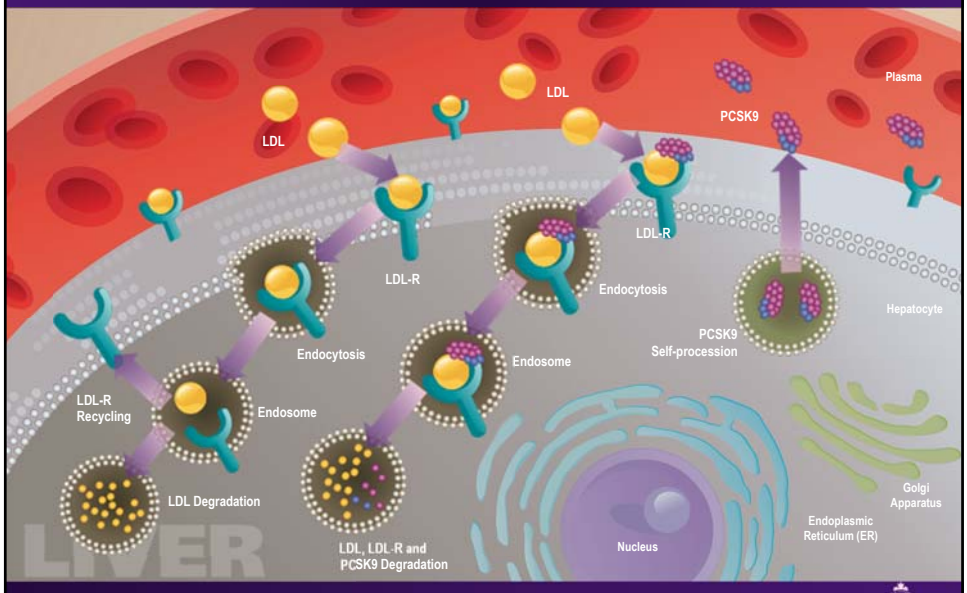
1. Only if ezetimibe is used as well
2. Only if ezetimibe is not used
3. Only if maximal statin therapy is not used
4. Only in statin intolerant patients
5. None of the above

Serum LDL-Cholesterol Binds to LDL-Receptors. Following Internalization, LDL is Degraded and the Receptor Recycled



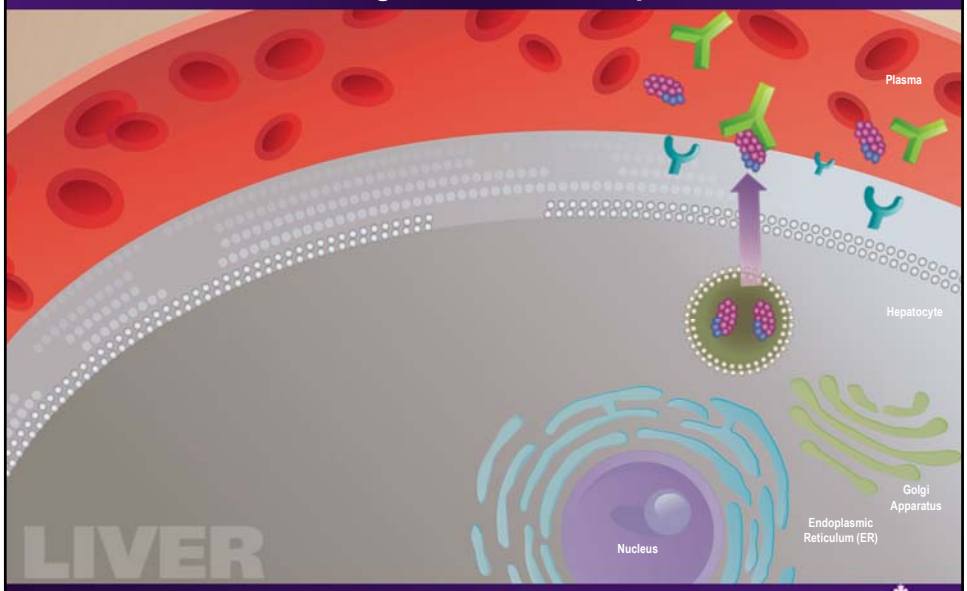
Qian YW, et al. J Lipid Res. 2007;48:1488-1498; Horton JD, et al. J Lipid Res. 2009;50(suppl):S172-S177.

In the Presence of PCSK9, the LDL-R Is Degraded and Does Not Cycle Back to Cell Surface



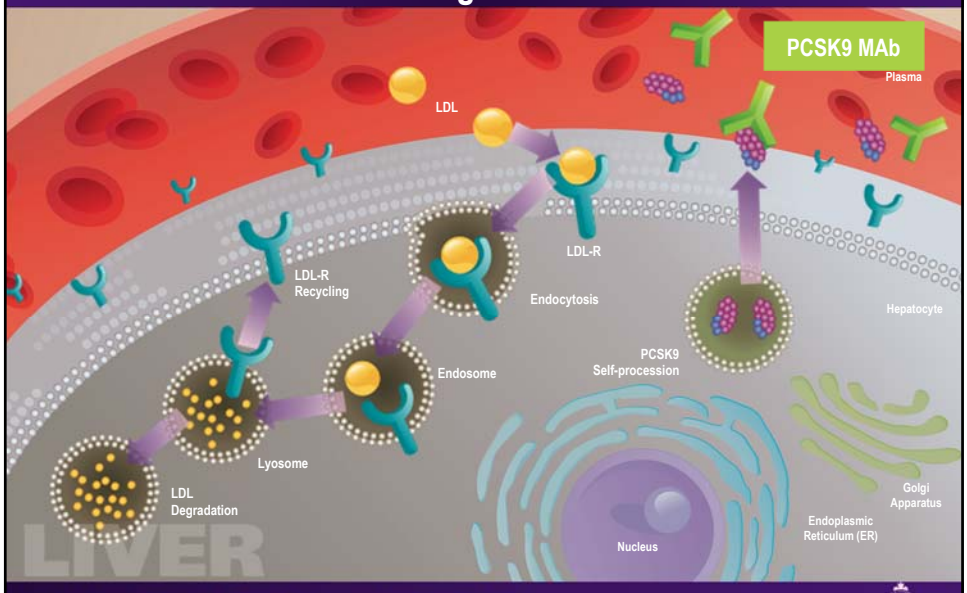
Qian YW, et al. J Lipid Res. 2007;48:1488-1498; Horton JD, et al. J Lipid Res. 2009;50(suppl):S172-S177.

Monoclonal Antibody binds to PCSK9 and inhibits Binding to the LDL-Receptor



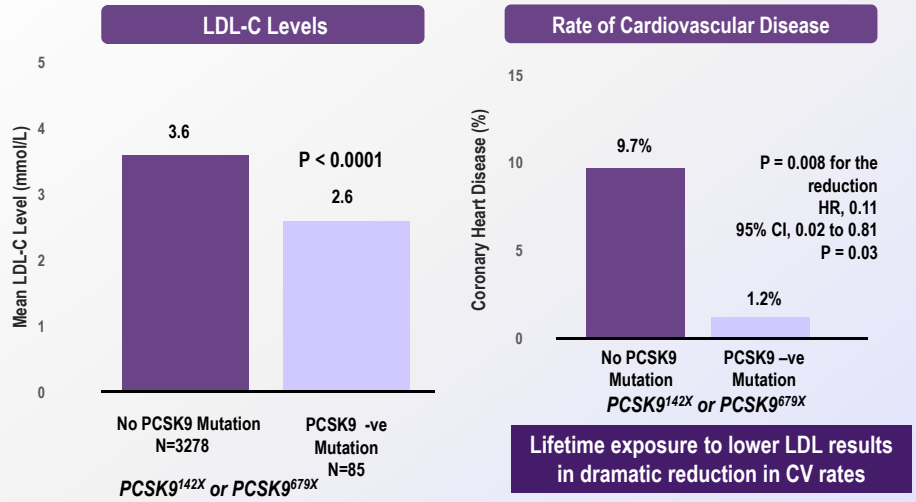
Qian YW, et al. J Lipid Res. 2007;48:1488-1498; Horton JD, et al. J Lipid Res. 2009;50(suppl):S172-S177.

Blocking PCSK9 Activity Inhibits Intracellular Degradation of LDL-R



Qian YW, et al. J Lipid Res. 2007;48:1488-1498; Horton JD, et al. J Lipid Res. 2009;50(suppl):S172-S177.

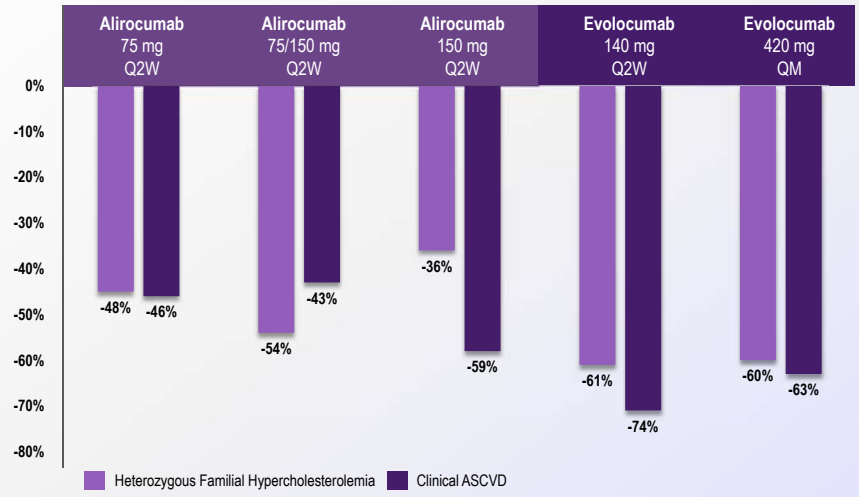
Loss-of-function Mutations for PCSK9 are Associated with Lower Serum LDL-C and Lower Incidence of CHD



Lifetime exposure to lower LDL results in dramatic reduction in CV rates

Cohen JC, et al. N Engl J Med. 2006;354:1264-1272.

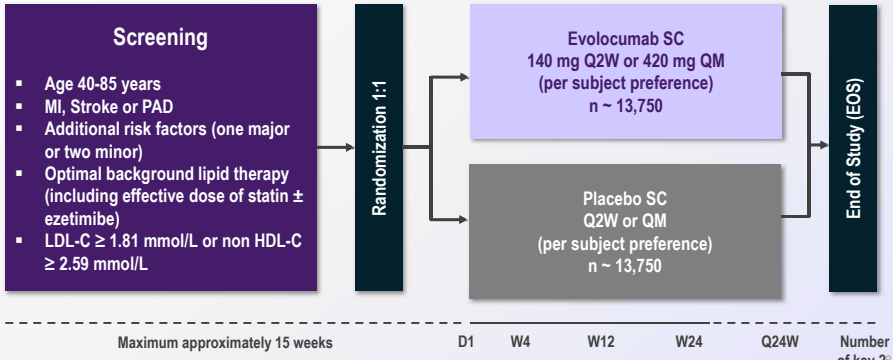
Additional LDL-C Reduction Observed With The Addition Of A PCSK9 Inhibitor



Praluent (alirocumab) Canadian Product Monograph. April 11, 2016.
Repatha™ (evolocumab) Canadian Product Monograph. June 29 2016.

Evolocumab Cardiovascular Outcomes Trial: Study Population

FOURIER: Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

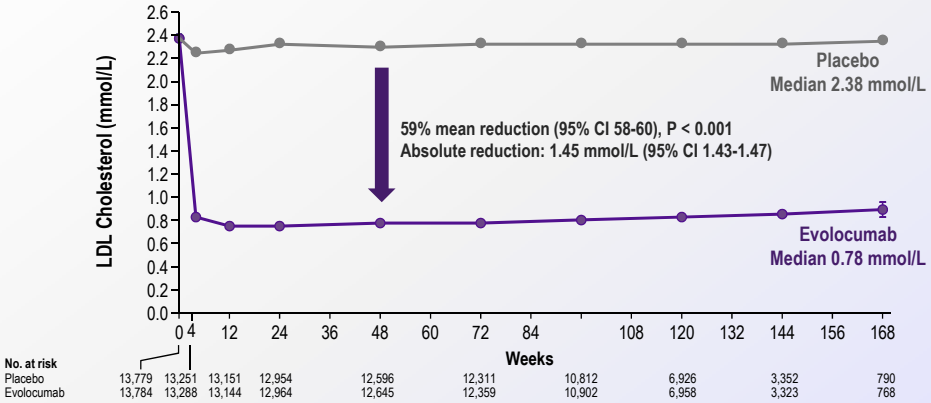


Background lipid-lowering therapy

- Patients must be on an optimized lipid-lowering regimen (moderate to high intensity statin +/- ezetimibe)
- In general, patients are not to change open-label background lipid-lowering therapies after randomization

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

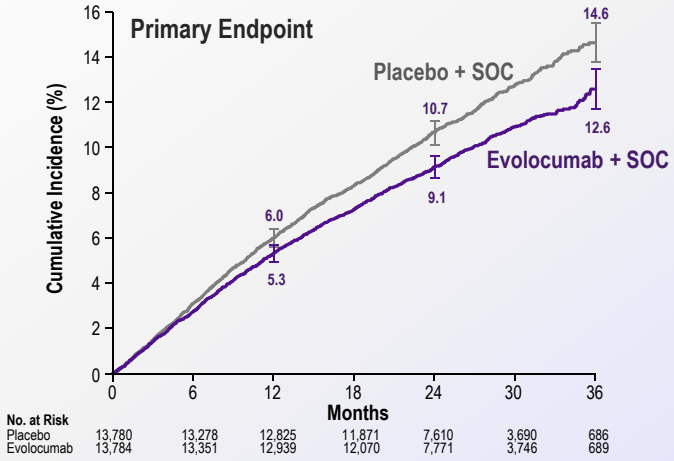
FOURIER
Median LDL-C Levels Over Time



LDL-C was significantly reduced in the evolocumab group (median: 0.78 mmol/L) including 42% who achieved levels ≤ 0.65 mmol/L vs < 0.1% in the placebo group

Data shown are median values with 95% confidence intervals in the two arms; ITT.
Sabatine MS, et al . N Engl J Med 2017; 376:1713-1722

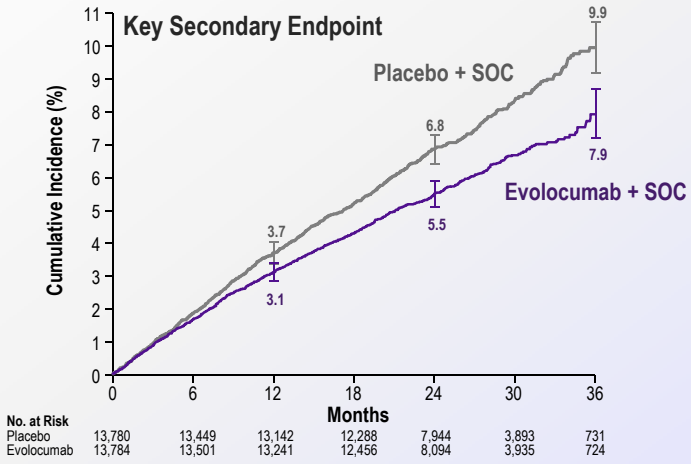
FOURIER
Composite of CV Death, MI, Stroke, Hospitalization for UA, or Coronary Revascularization



HR 0.85 (95% CI 0.79 to 0.92); *P* < 0.001

CV = Cardiovascular; MI = Myocardial infarction; UA = Unstable angina; HR = Hazard ratio; SOC = Standard of Care
Sabatine MS, et al . N Engl J Med 2017; 376:1713-1722

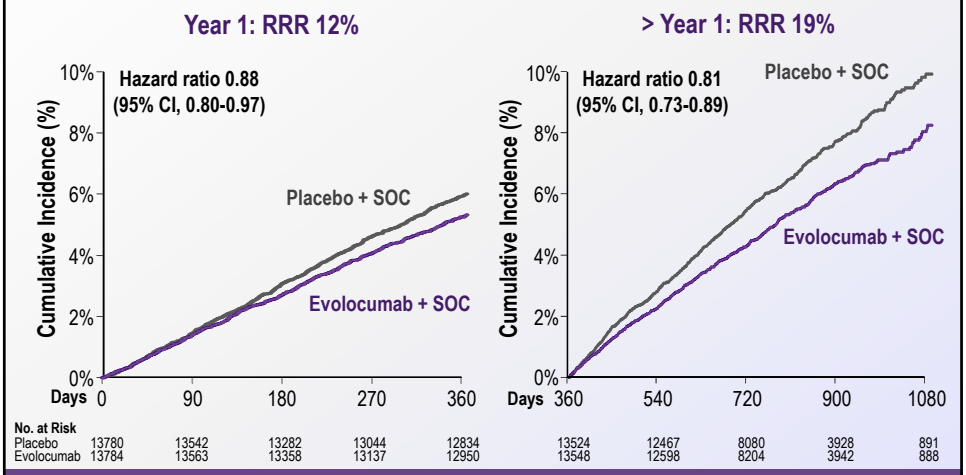
FOURIER
Composite of CV Death, MI, or Stroke



HR 0.80 (95% CI 0.73 to 0.88); *P* < 0.001

CV = Cardiovascular; MI = Myocardial infarction; UA = Unstable angina; HR = Hazard ratio ; SOC = Standard of Care
Sabatine MS, et al . N Engl J Med 2017; 376:1713-1722

FOURIER
Landmark Analysis of Primary Endpoint

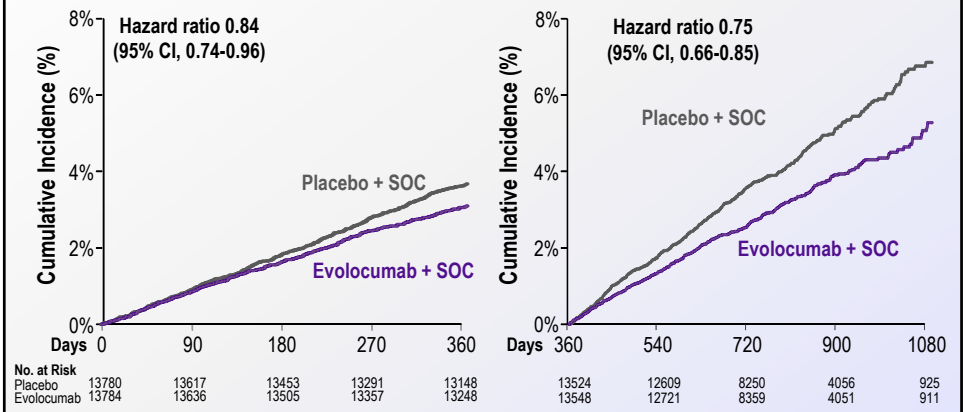


Longer duration of treatment and follow up suggests larger risk reduction

Landmark analyses were performed in which patients who were alive and in follow-up at the start of the period of interest formed the group at risk.

RRR = Relative Risk Reduction; SOC = Standard of Care
Sabatine MS, et al . N Engl J Med 2017; 376:1713-1722 (Supplementary Figure S4)

FOURIER
Landmark Analysis of Key Secondary Endpoint



Longer duration of treatment and follow up suggests larger risk reduction

Landmark analyses were performed in which patients who were alive and in follow-up at the start of the period of interest formed the group at risk.

RRR = Relative Risk Reduction; SOC = Standard of Care
Sabatine MS, et al . N Engl J Med 2017; 376:1713-1722 (Supplementary Figure S4)

FOURIER
Efficacy is consistent Across Key Subgroups for Primary and Key Secondary Endpoints

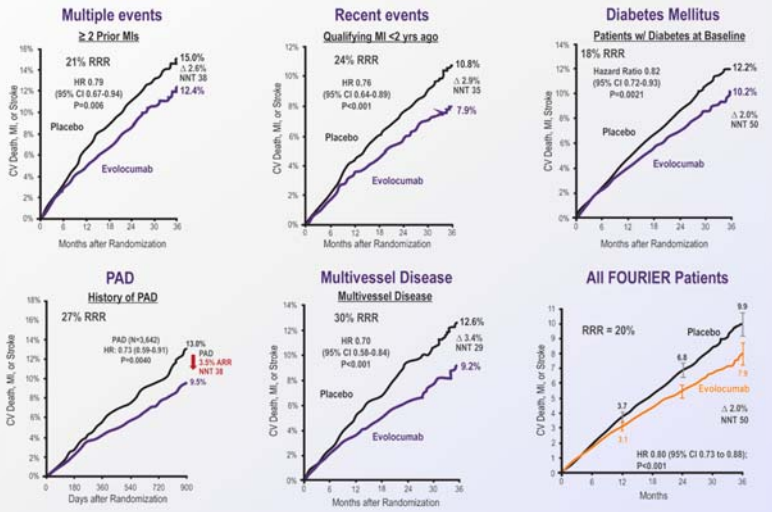
	Patients	PRIMARY ENDPOINT: Event Rate (%) Evo	Pbo	HR (95% CI)	$P_{interaction}$	KEY SECONDARY ENDPOINT: Event Rate (%) Evo	Pbo	HR (95% CI)	$P_{interaction}$
OVERALL	27564	9.8	11.3	0.85 (0.79-0.92)		5.9	7.4	0.80 (0.73-0.88)	
Type of disease					0.19				0.38
MI alone	19113	9.6	10.8	0.88 (0.80-0.96)		5.2	6.4	0.80 (0.71 -0.90)	
Stroke alone	3366	6.0	8.5	0.70 (0.54-0.90)		5.0	6.5	0.77 (0.58 -1.02)	
PAD alone	1505	6.7	9.9	0.67 (0.47-0.96)		4.5	7.8	0.57 (0.38-0.88)	
Polyvasculardisease	3563	15.5	17.4	0.88 (0.75-1.03)		11.1	12.9	0.86 (0.71-1.04)	
Baseline LDL-C					0.69				0.96
Q1 (<2.07 mmol/L)	6961	8.3	10.4	0.80 (0.69 -0.93)		5.1	6.6	0.78 (0.64-0.95)	
Q2 (2.07 -<2.4 mmol/L)	6886	9.3	11.2	0.82 (0.71 -0.96)		5.4	6.8	0.79 (0.65-0.96)	
Q3 (2.4 -2.8 mmol/L)	6887	10.2	11.3	0.89 (0.77 -1.03)		6.3	7.9	0.79 (0.66-0.94)	
Q4 (>2.8 mmol/L)	6829	11.2	12.5	0.89 (0.77-1.02)		6.9	8.2	0.83 (0.70-0.99)	
Baseline statin intensity					0.37				0.33
High	19103	10.2	11.6	0.87 (0.80-0.95)		6.1	7.4	0.82 (0.74 -0.92)	
Not High	8461	8.8	10.7	0.80 (0.70-0.92)		5.5	7.2	0.74 (0.63 -0.88)	
Ezetimibe					0.26				0.76
Yes	1440	13.4	13.6	0.98 (0.74-1.31)		7.4	9.8	0.74 (0.52-1.06)	
No	26124	9.5	11.2	0.84 (0.78-0.91)		5.8	7.2	0.80 (0.73-0.88)	
Initial Dosing Regimen					0.83				0.89
Every 2 weeks	24774	9.9	11.5	0.85 (0.79 -0.92)		6.0	7.5	0.80 (0.72-0.88)	
Monthly	2790	8.6	10.3	0.82 (0.64 -1.04)		5.2	6.4	0.80 (0.59-1.09)	

0.5 1.0 2.0 — *Evolocumab better* / *Placebo better*

Primary and secondary composite endpoint results were consistent across all key subgroups

CI: confidence interval; Evo: evolocumab; HR: hazard ratio; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; PAD: peripheral artery disease; Pbo: placebo; Q: quartile
Sabatine MS, et al . N Engl J Med 2017; 376:1713-1722

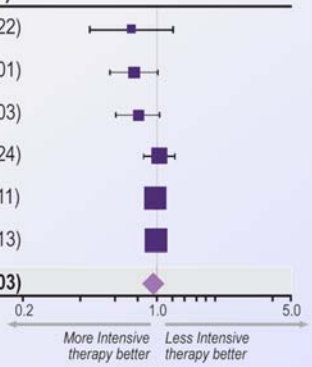
FOURIER
Multiple High-Risk Patient Population Sub-Analysis



Sabatine MS, et al . AHA 2017 Poster

More Intensive LDL-C Lowering and CV Mortality

Trial	Year	# of CV Deaths: More Intensive Rx Arm	# of CV Deaths: Less Intensive Rx Arm	HR (95% CI)
PROVE-IT TIMI 22	2004	27	36	0.74 (0.45-1.22)
A2Z	2004	86	111	0.76 (0.57-1.01)
TNT	2005	101	127	0.80 (0.61-1.03)
IDEAL	2005	223	218	1.03 (0.85-1.24)
SEARCH	2010	565	572	0.99 (0.88-1.11)
IMPROVE-IT	2015	538	537	1.00 (0.89-1.13)
SUMMARY		**1540**	**1601**	**0.96 (0.90-1.03)**



1. Cannon CP, et al. N Engl J Med. 2004;350:1495-1504. 2. de Lemos JA, JAMA 2004;292:1307-1316. 3. LaRosa JC, et al. N Engl J Med. 2005;352:1425-1435. 4. Pederson TR, et al. JAMA. 2005; 294:2437-2445. 5. Search Collaborative Group. Lancet 2010; 376: 1658–69. 6. Cannon CP, et al. N Engl J Med. 2015;372:2387-2397. 7. Sabatine MS, et al. American College of Cardiology – 66th Annual Scientific Session Late-Breaking Clinical Trial. Washington, D.C. March 17, 2017.

FOURIER

Adverse Events and Laboratory Measures in the Safety Population*

Adverse Events, n (%)	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Injection-site reaction**	296 (2.1)	219 (1.6)
Allergic reactions	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results - n/total n (%)		
Aminotransferase >3x ULN	240/13,543 (1.8)	242/13,523 (1.8)
Creatinine kinase >5x ULN	95/13,543 (0.7)	99/13,523 (0.7)

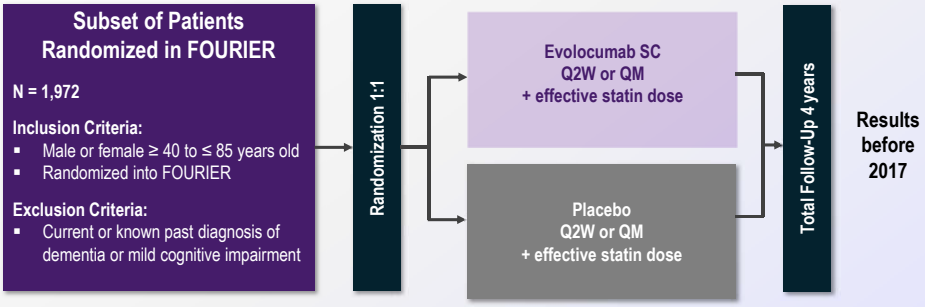
*Safety evaluations included all randomized patients who received at least one dose of study treatment and for whom post-dose data are available.
**The between-group difference was nominally significant (P<0.001). †HR 1.05 (95% CI 0.94-1.17); denominators of 8337 (evolocumab) and 8339 (placebo) because patients with prevalent diabetes at the start of the trial were excluded.

- **Incidence of neurocognitive events, cataracts, and new-onset diabetes were similar between the two arms**
- **Post-baseline anti-evolocumab antibodies were detected in 0.3%, with no neutralizing antibodies detected**

ULN = Upper Limit of Normal
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

EBBINGHAUS
Evaluating PCSK9 Binding Antibody Influence On Cognitive Health in High Cardiovascular Risk Subject

- **Purpose:** Evaluate change over time in neurocognitive testing in subjects receiving statin therapy in combination with evolocumab, compared with subjects receiving statin therapy in combination with placebo



- **Primary endpoint:** Mean change from baseline over time in Spatial Working Memory index of executive function
- **Secondary endpoints:** Mean change from baseline over time in Spatial Working Memory between-errors score, mean change from baseline over time in paired associated learning total errors adjusted, and mean change from baseline over time in reaction time median 5-choice reaction time

Q2W, every 2 weeks; QM, every month; SC, subcutaneous.
ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02207634. Accesses February 2, 2016

EBBINGHAUS
Results and Conclusions

In patients with known cardiovascular disease on background statin followed for 20 months

1. **No differences between evolocumab vs placebo**
   - A battery of cognitive tests
   - Patient-reported everyday cognition
   - Adverse cognitive events reported by MD
2. **No evidence of differences in cognitive tests by achieved nadir LDL-C, even 0.65 mmol/L**

ODYSSEY Outcomes Study Design

Post-ACS (4-52 weeks) patients[1] age ≥40 yrs (n~18,000)
with *LDL-C ≥1.81 mmol/L, or ApoB ≥ 0.8 g/L, or Non-HDL-C ≥ 2.59 mmol/L*
despite high-intensity (or maximally tolerated) statin (atorvastatin 40-80 mg or rosuvastatin 20-40 mg/daily) x ≥2 wks ± other lipid-modifying therapy (e.g., ezetimibe, fenofibrate)[2]

Randomization[3]

Alirocumab 75 mg SC Q2wks x 2 months → 150 mg SC Q2wks based upon Month 1
LDL-C ≥ 1.3 mmol/L[4] with dose titrated to maintain LDL-C in the 0.6-1.3 mmol/L target range

Placebo SC Q2wks

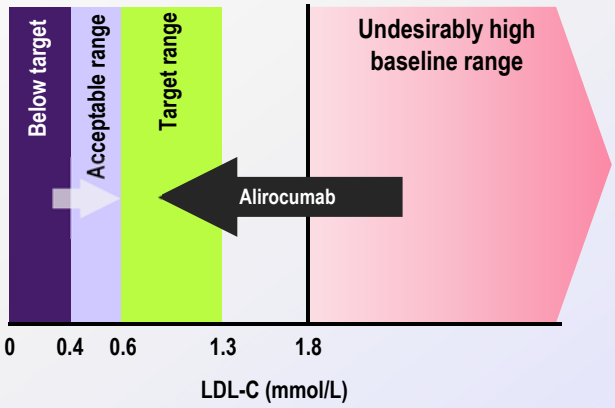
Primary Endpoint: Time to first CHD death/non-fatal MI/fatal and non-fatal ischemic stroke/unstable angina requiring hospitalization
Follow-Up: Minimum 24 months or target number of events (~1600) → estimated 11.4% rate at 4 yrs, 15% risk reduction; 90% power, 1-sided p=0.025, 1% lost

[1] Elevated troponin or CK-MB or resting ECG changes + obstructive coronary disease (new/presumed new ischemia/infarction by perfusion imaging, regional wall motion abnormality, coronary stenosis ≥70% by angiography)
[2] Key exclusion criteria: Uncontrolled hypertension; NYHA III-IV or LVEF<25%; prior hemorrhagic stroke; TG>4.52 mmol/L; hepatitis; eGFR<30 ml/min
[2] Following ≥2 wk (+ 5 days) run-in period with placebo (1 mL volume in an autoinjector) SC Q2wks
[3] Titration downwards for very low LDL

Schwartz et al Am Heart J 2014;168:682-689.e1

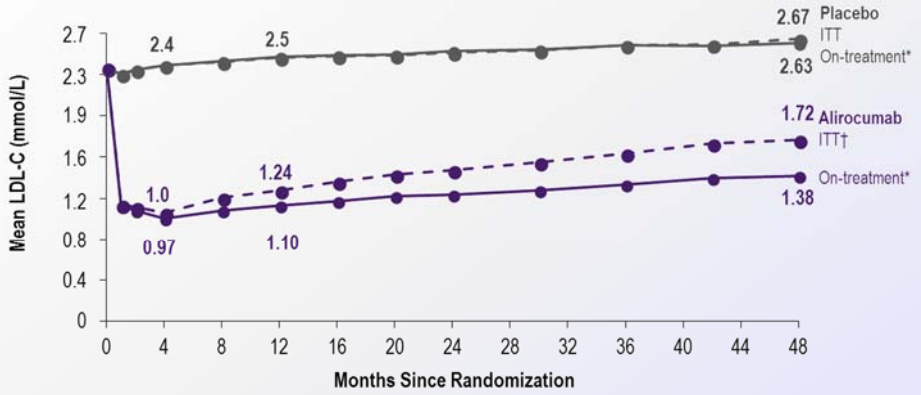
ODYSSEY Outcomes
A Target Range for LDL-C

An attempt was made to maximize the number of patients in the target range and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W) or blindly switching to placebo.



Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

ODYSSEY Outcomes
LDL-C: ITT and On-Treatment Analyses

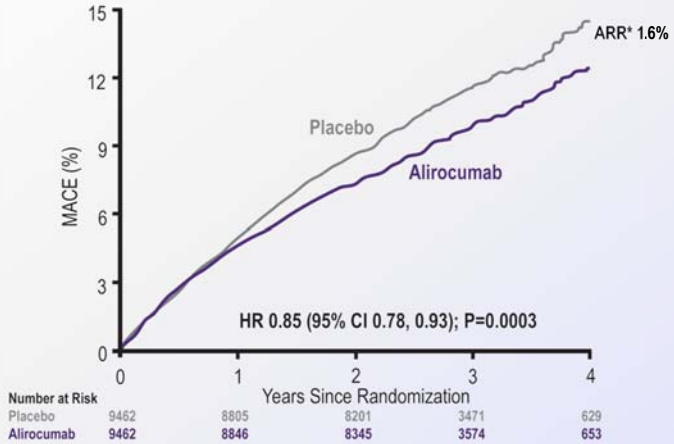


*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo

Steg G. et al; On behalf of the ODYSSEY OUTCOMES Investigators and Committees - American College of Cardiology – 67th Scientific Sessions - March 10, 2018

ODYSSEY Outcomes
Primary Efficacy Endpoint: MACE

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



*Based on cumulative incidence

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ODYSSEY Outcomes
Primary Efficacy Endpoint and Components

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
MACE	**903 (9.5)**	**1052 (11.1)**	**0.85 (0.78, 0.93)**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
Non-fatal MI	**626 (6.6)**	**722 (7.6)**	0.86 (0.77, 0.96)	0.006
Ischemic stroke	**111 (1.2)**	**152 (1.6)**	0.73 (0.57, 0.93)	0.01
Unstable angina	**37 (0.4)**	**60 (0.6)**	0.61 (0.41, 0.92)	0.02

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ODYSSEY Outcomes
Main Secondary Efficacy Endpoints - Hierarchical Testing

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
CHD event	**1199 (12.7)**	**1349 (14.3)**	**0.88 (0.81, 0.95)**	**0.001**
Major CHD event	**793 (8.4)**	**899 (9.5)**	**0.88 (0.80, 0.96)**	**0.006**
CV event	**1301 (13.7)**	**1474 (15.6)**	**0.87 (0.81, 0.94)**	**0.0003**
Death, MI, ischemic stroke	**973 (10.3)**	**1126 (11.9)**	**0.86 (0.79, 0.93)**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
CV death	**240 (2.5)**	**271 (2.9)**	0.88 (0.74, 1.05)	0.15
All-cause death	**334 (3.5)**	**392 (4.1)**	**0.85 (0.73, 0.98)**	**0.026***

***Nominal P-value**

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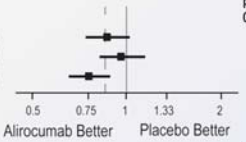
ODYSSEY Outcomes
Primary Efficacy in Main Prespecified Subgroups

Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
2.0	7164	8.3	9.5	0.86 (0.74, 1.01)	
2.0 - <2.6	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥2.6	5629	11.5	14.9	0.76 (0.65, 0.87)	



*P-values for interaction

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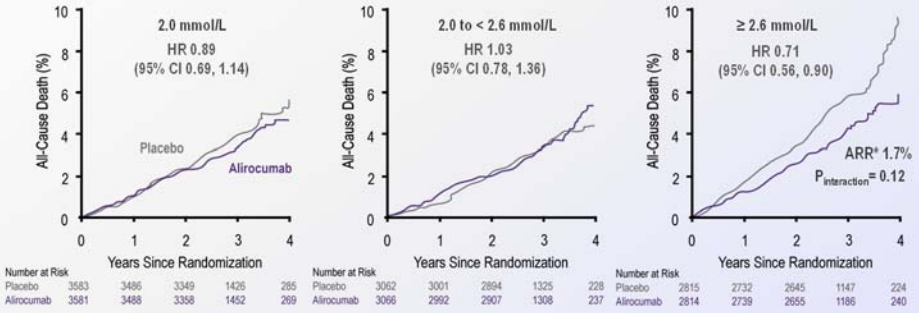
ODYSSEY Outcomes
Post Hoc Analysis: All-Cause Death by Baseline LDL-C Subgroups



*Based on cumulative incidence
ARR = Absolute Risk Reduction

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ODYSSEY Outcomes
Safety

Treatment-emergent adverse events, n (%)	Alirocumab (N=9451)	Placebo (N=9443)
Any	7165 (75.8)	7282 (77.1)
Serious	2202 (23.3)	2350 (24.9)

Laboratory value	Alirocumab	Placebo
ALT >3 × ULN, n/N (%)	212/9369 (2.3)	228/9341 (2.4)
Creatine kinase >10 × ULN, n/N (%)	46/9369 (0.5)	48/9338 (0.5)

Event	Alirocumab (N=9451)	Placebo (N=9443)
Diabetes worsening or diabetic complications: *pts w/DM at baseline*, n/N (%)	506/2688 (18.8)	583/2747 (21.2)
New onset diabetes; *pts w/o DM at baseline*, n/N (%)	648/6763 (9.6)	676/6696 (10.1)
General allergic reaction, n (%)	748 (7.9)	736 (7.8)
Hepatic disorder, n (%)	500 (5.3)	534 (5.7)
Local injection site reaction, n (%)*	360 (3.8)	203 (2.1)
Neurocognitive disorder, n (%)	143 (1.5)	167 (1.8)
Cataracts, n (%)	120 (1.3)	134 (1.4)
Hemorrhagic stroke, n (%)	9 (<0.1)	16 (0.2)

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ODYSSEY Outcomes
Conclusions

Compared with placebo in patients with recent ACS, alirocumab 75 or 150 mg subcutaneous Q2W targeting LDL-C levels 0.6-1.3 mmol/L, and allowing levels as low as 0.4 mmol/L:

1. Reduced MACE, MI, and ischemic stroke
2. Was associated with a lower rate of all-cause death
3. Was safe and well-tolerated over the duration of the trial

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

Canadian Cardiovascular Society
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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

Beyond Statin Drugs for ASCVD Prevention

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

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

Recommendations for PCSK9i in FH and ASCVD

Canadian Cardiovascular Society
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- We suggest the use of PCSK9 inhibitors (evolocumab, alirocumab) to lower LDL-C for patients with heterozygous familial hypercholesterolemia whose LDL-C remains above target despite maximally tolerated statin therapy (*Conditional recommendation, moderate quality evidence*)
- We suggest that PCSK9 inhibitors be considered to lower LDL-C for patients with atherosclerotic cardiovascular disease in those not at LDL-C goal despite maximally tolerated statin +/- ezetimibe therapy *(Conditional recommendation, moderate quality evidence)*
- We suggest that evolocumab be added to background therapy in patients with homozygous familial hypercholesterolemia and continued if LDL-C lowering is documented *(Conditional recommendation, moderate quality evidence)*

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

PCSK9 Inhibitors and Their Indications

- **Alirocumab**[1]
  - Adjunct to diet and maximally tolerated statin therapy where additional LDL-C lowering is needed in adults with
    - HeFH
    - Clinical ASCV
- **Evolocumab**[2]
  - Adjunct to diet and maximally tolerated statin therapy where additional LDL-C lowering is needed in adults with
    - HeFH
    - Clinical ASCVD
  - Adjunct to diet and other LDL-C lowering therapies in persons ≥12 years with HoFH who require additional LDL-C lowering

ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin kexin type 9.

1. Praluent Canadian Product Monograph, April 11, 2016; 2. IRepatha Canadian Product Monograph, June 29 2016;

Summary

- Despite clear guidelines and widespread use of statin therapy, almost half of high risk patients do not achieve the recommended target for LDL-C < 2.0 mmol/L
- Challenges in reaching the LDL-C target include
  - Wide range of LDL-C lowering seen in patients
  - Side effects, particularly myalgia
  - Limited efficacy of statin therapy in lowering LDL-C
- There is a need for LDL-C lowering beyond statin therapy
- 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

MACE = Major Adverse Cardiovascular Events