Case 2

Raj

LDL-C: How Low Do You Go?

ASCVD: atherosclerotic cardiovascular disease

Learning Objectives

Upon completion of this case based session, participants will be able to:

01 Apply the recent CCS Dyslipidemia guidelines to clinical practice

02 Discuss the importance of lowering LDL-C to target and selecting the appropriate therapeutic options to achieve guideline recommended targets

03 Explain the evidence and safety of achieving very low LDL-C levels

Canadian Heart Research Centre

Case 2

Raj
60 years old

Raj, a 60 year old IT executive with a good private insurance plan, presents to your office for a routine follow-up appointment post labs.

He is looking forward to retiring soon.

Case 2

Raj
60 years old

Raj's History

- Experienced NSTEMI 2 months earlier (stent x 2)
- Ex-smoker (just quit after MI)
- Hypertension
- Family history of CVD

Physical Exam

- Weight 95.3 kg
- Height 1.90 m
- BMI 27.7 kg/m^2
- BP 132/84 mmHg
- HR 70 BPM regular
- Echo preserved LV function

Case 2

Raj
60 years old

Medications

- Atorvastatin 80 mg qhs
- Aspirin 75 mg OD
- Clopidogrel 75mg OD
- Bisoprolol 5 mg OD
- Perindopril 8 mg OD

Labs

- eGFR 56 ml/min
- LDL-C 2.6 mmol/L

Case 2

Raj
60 years old

Raj is complaining of myalgias on atorvastatin 80 mg daily and wants to stop taking his statin

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

Canadian Cardiovascular Society

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

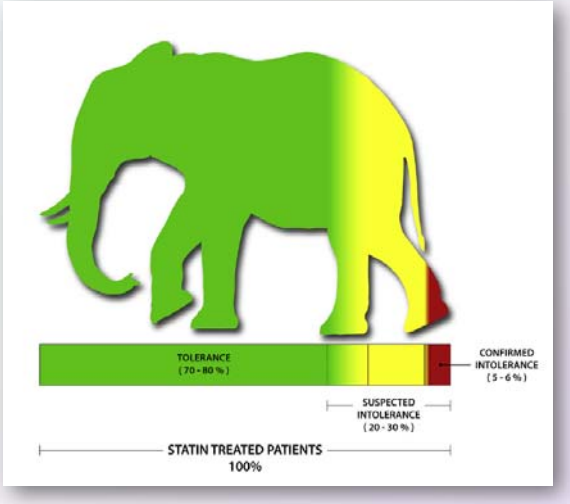
(those who will benefit the most):

- 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

Clinical Experience vs Randomized Clinical Trials: The Elephant in the Room regarding Goal-Inhibiting Statin Intolerance (GISI)



Mancini et al, DOI: http://dx.doi.org/10.1016/j.cjca.2016.01.003

Definition of Statin Intolerance

- A clinical syndrome (i.e. there is no specific test yet) defined as:
  - → Inability to use statins due to significant symptoms and/or biomarker abnormalities attributed to statin use as determined by stop and re-challenge approach
  - → Either "complete" (intolerant to any statin at any dose) or "partial" (intolerant to some statins at some doses); practically, at least 2 statins
  - → Not due to drug-drug interactions or predisposing factors (e.g. untreated hypothyroidism, febrile illness etc)

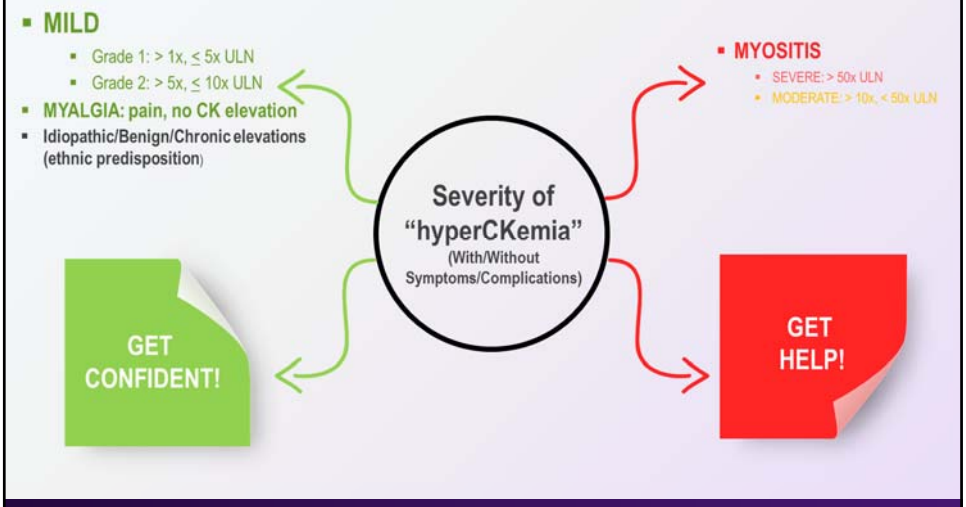
Mancini et al Can J Cardiol 2011;27:635-662

Clinical Features

- Myalgia ranging from 1% to 5% in controlled clinical trials to 11% to 29% in observational cohorts
- Increase in muscle enzymes, "hyperCKemia"
- Clinically evident myopathy with weakness and/or markedly increased serum muscle enzymes (myositis) - rare

Mancini et al Can J Cardiol 2011;27:635-662

Clinical Features



Mancini et al Can J Cardiol 2011;27:635-662

Why Bother Re-Challenging?

remained on statin 12 months after the initial statin-related discontinuation **92.2 %**

72.5 % were able to tolerate long-term (6-month follow-up) therapy with a stable dosage of statin

Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med. 2013;158: 526–534
Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. Am Heart J. 2013;166:597–603

Case 2
3 months later…

Raj
60 years old

Raj's myalgias have resolved on atorvastatin 40 mg OD and ezetimibe 10 mg OD

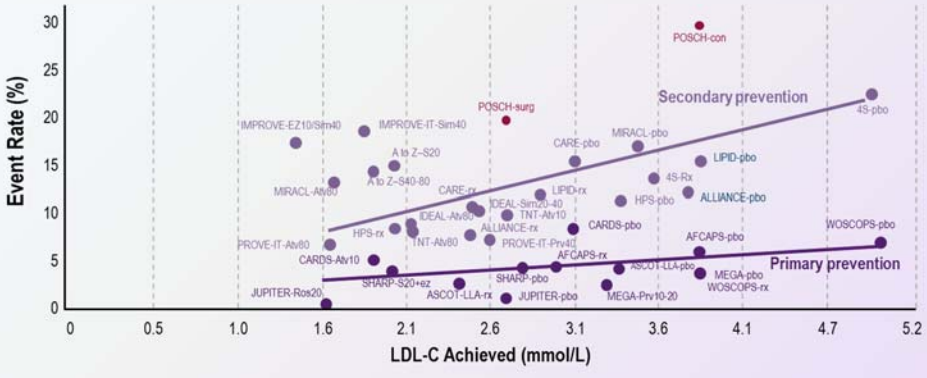
He feels very well and is looking forward to retirement

His most recent LDL-C is 2.2 mmol/L

- Initial Visit LDL-C: 2.6 mmol/L

Linear Relationship With Lowering of LDL-C and Reduced CV Events in CV Outcomes Statin Trials

Major Lipid Trials: LDL-C Levels vs. Rates of Coronary Events

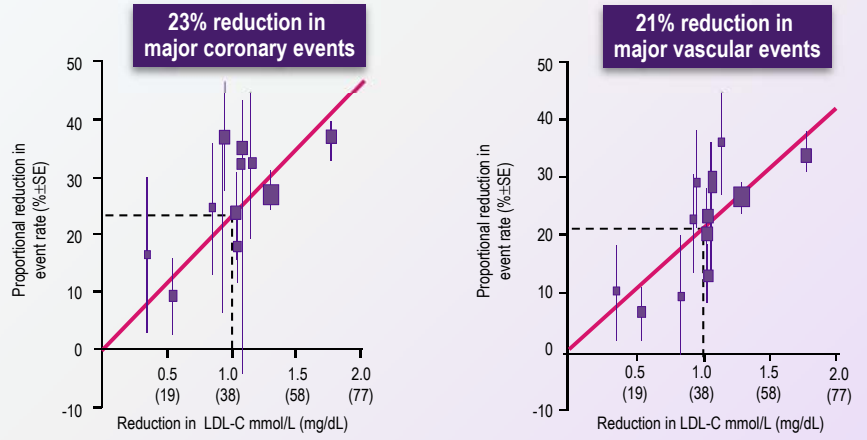


Similar associations between LDL-C lowering and reduction of major coronary events were seen in both primary prevention and secondary prevention trials

Note: Line for secondary prevention studies excludes IMPROVE-IT. IMPROVE-IT reflects 7-year rate of major coronary events (nonfatal MI or CHD) and mean LDL-C achieved at year 1.
CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol.
1. Raymond C, et al. Cleve Clin J Med. 2014;81:11-19. 2. Cannon CP, et al. N Engl J Med. 2015;372:2387-2397.

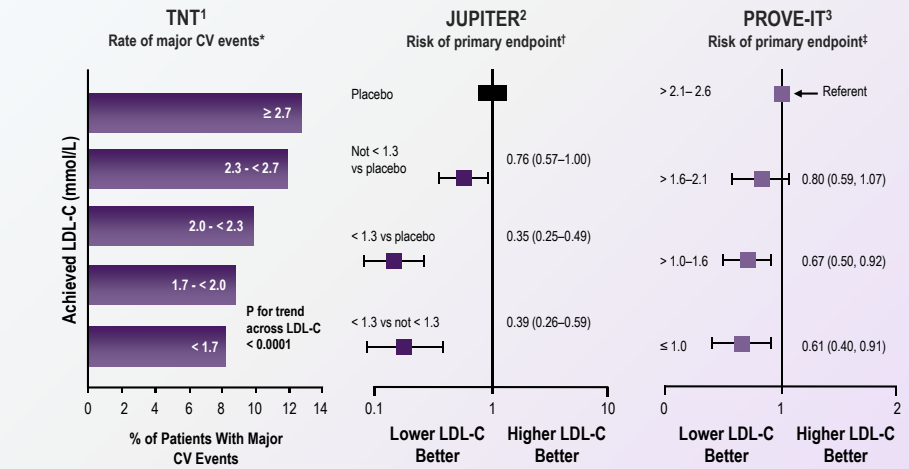
Reduction in CV Events is Proportional to LDL-C Reduction at 1 Year

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.

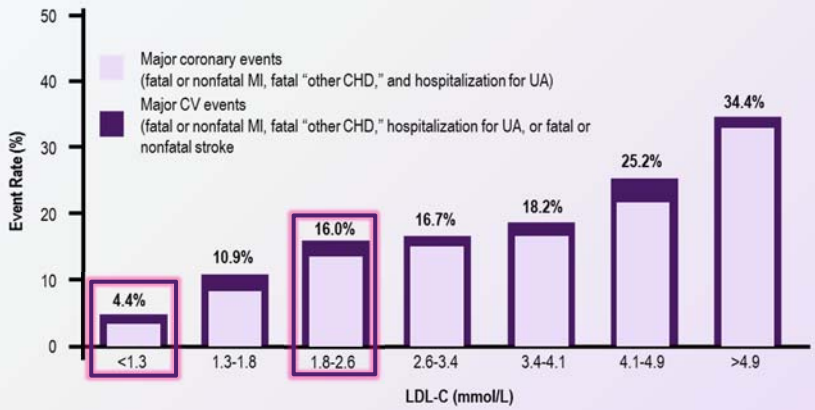
No Evidence for a Lower LDL-C Limit in Reducing Major CV Events



*Major CV events for TNT trial were defined as defined as CHD death, nonfatal non-procedured–related MI, resuscitated cardiac arrest, and fatal or nonfatal stroke.
†JUPITER primary endpoint was composite of MI, stroke, arterial revascularization, unstable angina, or confirmed death from CV causes.
‡PROVE-IT primary endpoint was composite of death, MI, stroke, revascularization and unstable angina requiring hospital admission.
CHD = coronary heart disease; CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol, MI = myocardial infarction.

1. LaRosa JC, et al. Am J Cardiol. 2007;100:747-752.
2. Hsia J, et al. J Am Coll Cardiol. 2011;57:1666-1675.
3. Wiviott et al. J Am Coll Cardiol. 2005;46:1411-1416.

Statin Trials Have Also Shown That Very Low (Vs Moderately Low) LDL-C Is Associated With Significantly Lower Risk For Major CV Events



CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; UA, unstable angina.

Boekholdt SM et al. J Am Coll Cardiol. 2014;64:485-94.

Case 2
3 months later…

Raj
60 years old

Raj is very motivated to stay healthy as he is looking to retire soon.

He has coverage for PCSK9i, so you started him on evolocumab 140 mg sc q2 during his previous visit (in addition to atorvastatin 40 mg OD).

He stopped taking his ezetimibe 10 mg OD.

Case 2
3 months later…

Raj
60 years old

Raj saw his labs online and is concerned that his LDL-C may now be "too low"

His most recent LDL-C is 1.2 mmol/L

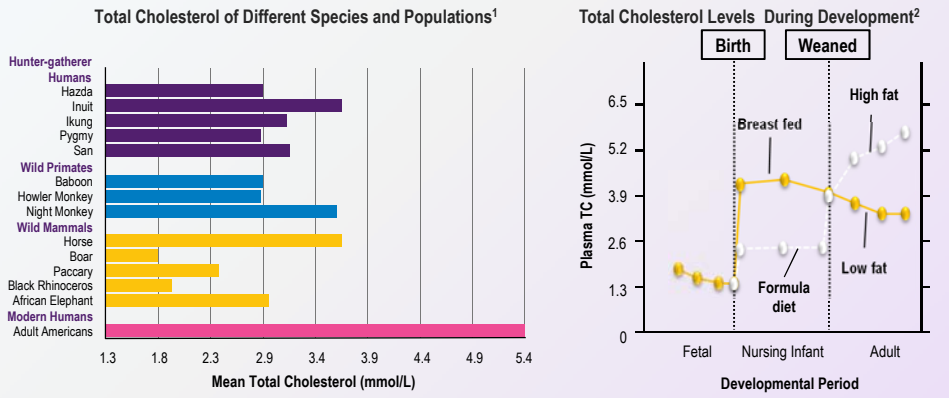
- Previous Visit LDL-C: 2.2 mmol/L
- Initial Visit LDL-C: 2.6 mmol/L

Low LDL-Cholesterol

- Cholesterol is a precursor for synthesis of steroid hormones and is an essential component of all cell membranes
- **BUT:**
  - → Enters the circulation via chylomicrons and VLDL-C, *not* LDL-C[1]
  - → Low levels of LDL-C are present in human neonates and other mammals[2]

1 Swiger & Martin Drug Saf 2015;38:519-26
2 O'Keefe et al Am J Cardiol 2017;119:565-71

Many Species Have Low Cholesterol, Even During Development



LDL-C Levels in Humans Increase With Age, Beginning at ~0.78-1.8 mmol/L as Newborns[1] and Typically Rising Above 2.6 mmol/L by Age 20[3]

LDL-C = low-density lipoprotein-cholesterol; TC = total cholesterol.

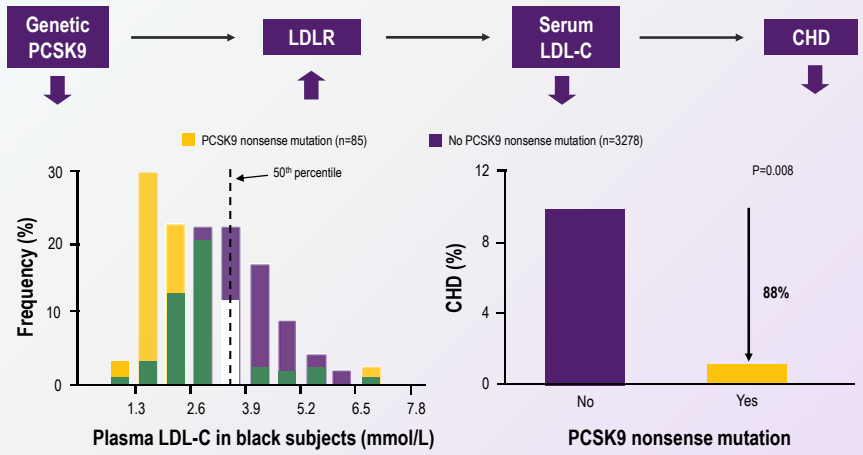
1. O'Keefe JH Jr, et al. J Am Coll Cardiol. 2004;43:2142-2146.
2. Adapted from Dietschy JM, et al. J Lipid Res. 2004;45:1375-1397.
3. Cohen JD, et al. Am J Cardiol. 2010;106:969-975.

Low LDL-Cholesterol

- Individuals with heterozygous hypobeta-lipoproteinemia have lifelong low total cholesterol and LDL-C (e.g., <1.0 mmol/L)
  - → but have overall excellent health and above average life expectancy (due to the relative absence of atherosclerosis and its complications[1]
- Loss-of function mutations of PCSK9 (with lifelong extremely low LDL-C levels)
  - → have been described in otherwise healthy individuals[2,3]

1. O'Keefe et al Am J Cardiol 2017;119:565-71;
2. Zhao et al Am J Hum Genet 2006;79:514-23;
3. Hooper et al Atherosclerosis 2007;193:445-8

Loss-of-function Variants in PCSK9, with Lifetime Low LDL-C, Are Associated With A Lower Risk of CV Events

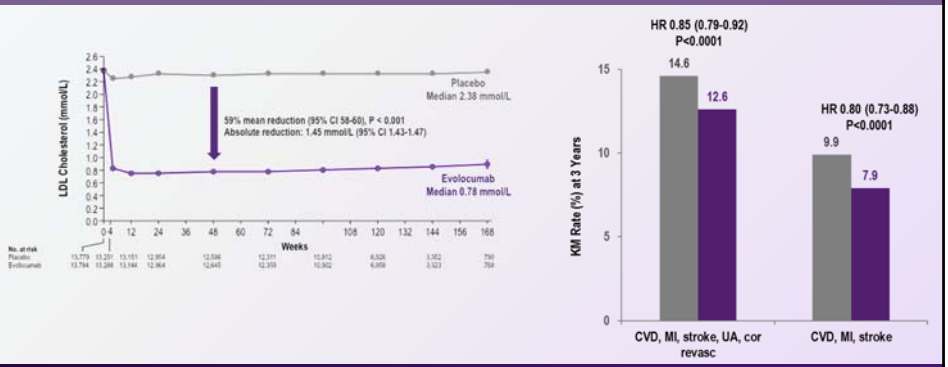


In frequency disribution of plasma LDL-C levels, green represents overlap in frequency of patients with and without PCSK9 mutations.
CHD = coronary heart disease; CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; LDL-R = low-density lipoprotein receptor; PCSK9 = proprotein convertase subtilisin–kexin type 9.

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

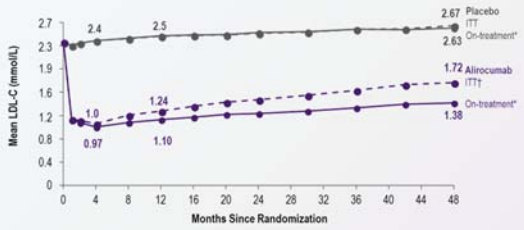
FOURIER
Median LDL-C Levels Over Time

- 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, nearly all of whom were on background statin therapy
- ↓ CV outcomes
- Safe and well-tolerated

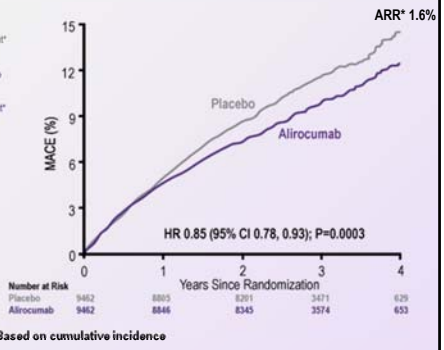


Data shown are median values with 95% confidence intervals in the two arms; ITT.
Sabatine MS, et al . N Engl J Med 2017; 376:1713-1722

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



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



*Based on cumulative incidence

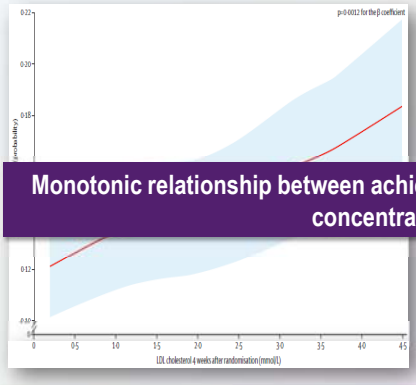
*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo

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

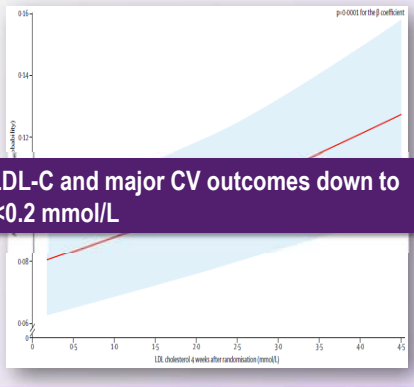
Efficacy of Achieving Very Low LDL-C Concentrations with Evolocumab

Prespecified secondary analysis of 25,982 patients from FOURIER who had an LDL-C measured at 4 weeks and had not experienced a primary endpoint event or one of the ten prespecified safety events before the week-4 visit

CVD, MI, Stroke, UA, or Revasc.



CV Death, MI or Stroke



Monotonic relationship between achieved LDL-C and major CV outcomes down to concentrations <0.2 mmol/L

Giugliano et al Lancet 2017;390:1962-71

FOURIER

Adverse Events and Laboratory Measures in the Safety Population*

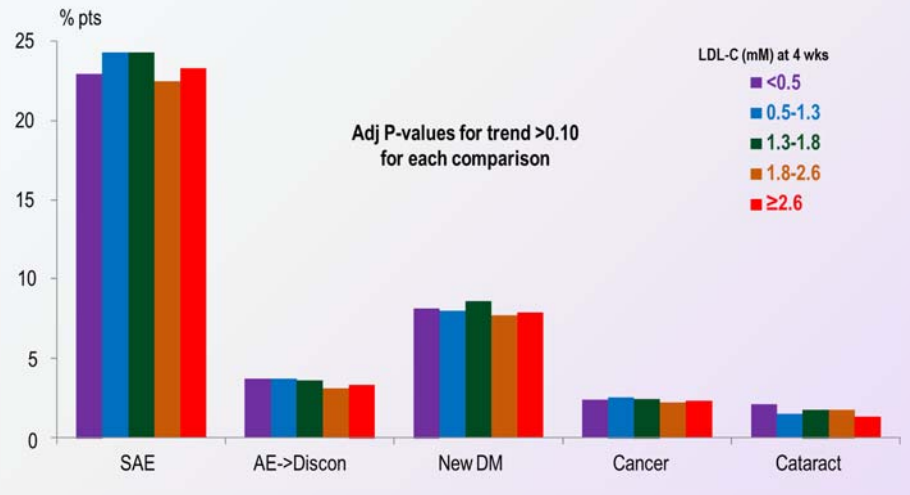
Adverse Events, n (%)	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Injection-site reaction**	296 (2.1)	219 (1.6)
Allergic reactions	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	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

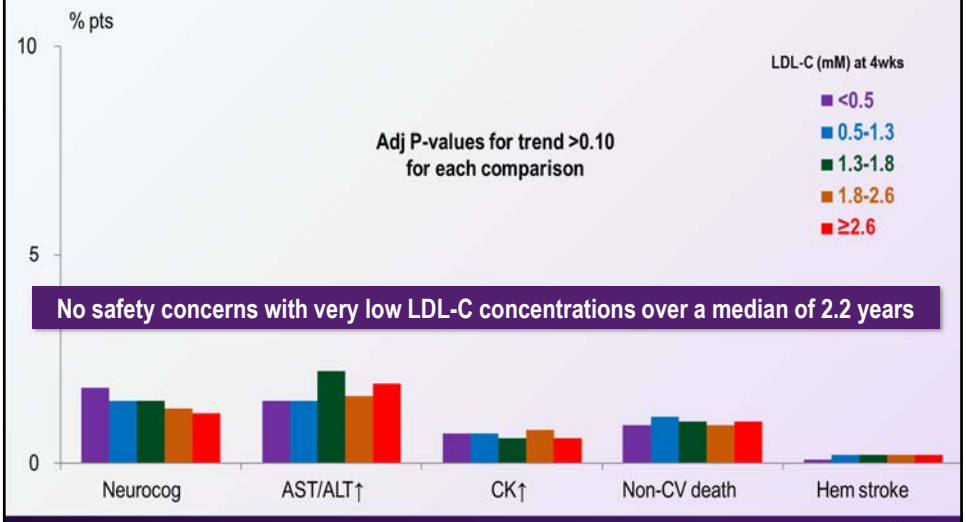
ULN = Upper Limit of Normal
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Detailed Safety Events from FOURIER Stratified by Achieved LDL-C (Part 1)



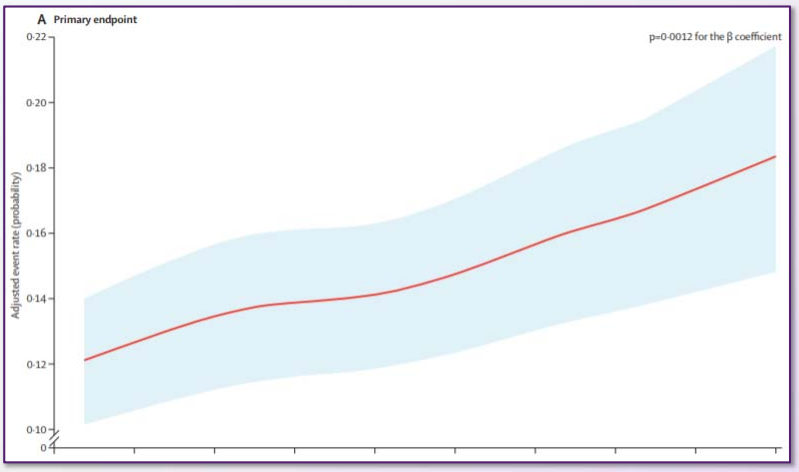
Giugliano et al Lancet 2017;390:1962-71

Detailed Safety Events from FOURIER Stratified by Achieved LDL-C (Part 2)



Giugliano et al Lancet 2017;390:1962-71

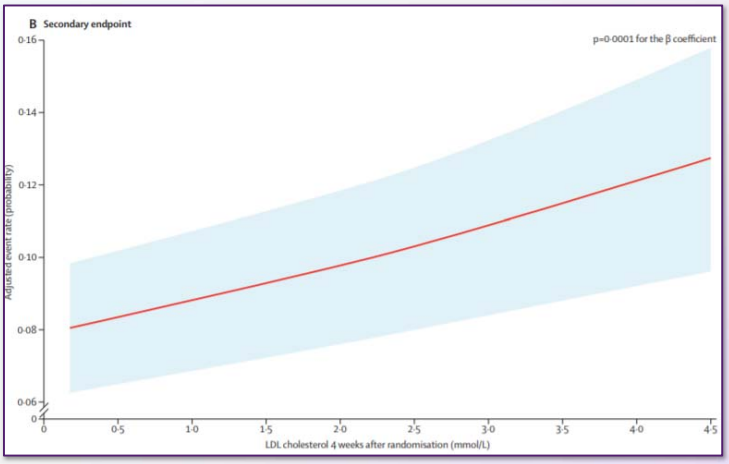
FOURIER Sub-Analyses: Relationship Between The Achieved LDL-Cholesterol Concentration at 4 Weeks and the Risk of the Primary Efficacy Composite Endpoints



The primary efficacy endpoint was a composite of cardiovascular death, myocardial infarction, stroke, coronary revascularisation, or hospital admission for unstable angina. The red line represents the adjusted probability of an event and blue areas are the 95% CIs of the regression model estimate.

Giugliano et al Lancet 2017;390:1962-71

FOURIER Sub-Analyses: Relationship Between The Achieved LDL-Cholesterol Concentration at 4 Weeks and the Risk of the Key Secondary Efficacy Composite Endpoints



The key secondary efficacy endpoint was a composite of cardiovascular death, myocardial infarction, or stroke.
The red line represents the adjusted probability of an event and blue areas are the 95% CIs of the regression model estimate.

Giugliano et al Lancet 2017;390:1962-71

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

Subset of Patients Randomized in FOURIER

N = 1,972

Inclusion Criteria:
- Male or female ≥ 40 to ≤ 85 years old
- Randomized into FOURIER

Exclusion Criteria:
- Current or known past diagnosis of dementia or mild cognitive impairment

Randomization 1:1

Evolocumab SC
Q2W or QM
+ effective statin dose

Placebo
Q2W or QM
+ effective statin dose

Total Follow-Up 4 years

Results before 2017

- **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/NCT02007634. 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
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)

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

Summary

- Evidence is emerging that very low LDL-C levels achieved with safe medications can lower residual CV risk substantially
- Adjuncts to statin monotherapy, including PCSK9 inhibitors, are important therapies that will help achieve LDL-C goals
- In clinical trials, there were no safety concerns with very low LDL-C concentrations (eg: <0.5 mmol/L) over a median of 2.2 years