"How Low Should You Go: Lipid Management in the PCSK9 Era"

ACCE, Meet-the-Expert

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Duality of Interests

– ***Consultant/Advisory Boards***
- Merck
- Regeneron/Sanofi aventis

– ***Grants/Research Fellowships***
- Ionis Pharmaceuticals
- UniQure

– ***Medical Education***
- CMHC
- HealthTeamWorks
- Medscape
- Medical Education Resources
- MedIntelligence
- VOX Media

The FDA's History of Cholesterol Lowering Drugs: The First Statin

- February 1987 – EMDAC discussed approvability of lovastatin
- Based in part on the CPPT, bile-acid resins, such as cholestyramine, were the drugs of choice for isolated hypercholesterolemia
- Clinicians were desperate for new options to reduce CVD risk
- "I think our recommendation is to approve this drug (lovastatin) and hope that it does as much as we think it might, but that it should be used carefully."

  - Dr. Frederick Singer, EMDAC Chairman, 19 Feb 1987

The FDA's History of Cholesterol Lowering Drugs

- 1994 – Scandinavian Simvastatin Survival Study (4S)
- Multiple cardiovascular outcomes trials (CVOTs) investigating the benefits of statins followed.
- For statins, ~40 mg/dL reduction in LDL-C reduced the risk for major CVD events by ~22%.

Cholesterol Treatment Trialists' Collaboration. *Lancet* 376:1670, 2010

Surrogate Endpoints

- What is a surrogate?
  - "….a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of therapy."
- Use depends on the evidence that a drug's effect on the surrogate predicts clinical benefit.
  - *Known* to predict benefit → "traditional" or "full" approval
  - *Reasonably likely* to predict benefit → accelerated approval
- Risk Factor ≠ Surrogate Endpoint

Accelerated Approval Proposed Rule, 57 FR 13235 (15 April 1992)

Controversy

- Until 2015 the last first-in-class drug to lower LDL-C in a broad population was Zetia (ezetimibe) in 2002
- ENHANCE (2008)[1]: addition of ezetimibe to simvastatin was not shown to reduce progression of atherosclerosis as measured by carotid intima-media thickness among patients with heterozygous familial hypercholesterolemia
- SEAS (2008)[2]: ezetimibe/simvastatin vs. placebo among patients with asymptomatic aortic stenosis
  - No evidence of reducing risk of a composite endpoint of CVD events
  - Raised cancer-related safety concern

[1] Kastelein JJP, et al *NEJM* 358:1431, 2008; [2] Rossebø AB, et al *NEJM* 359:1343, 2008

More Controversy

- Drug Safety Communications in 2009
  - ENHANCE did not change the FDA's position that "an elevated LDL cholesterol is a risk factor for ASCVD and that lowering LDL-C reduces the risk for CVD[1]
  - SEAS: "FDA believed it is unlikely that Vytorin [ezetimibe/simvastatin] or Zetia [ezetimibe] increased the risk of cancer or cancer-related death."[2]
- Despite FDA's conclusions, the lack of CVD outcomes data for ezetimibe remained highly controversial.
- Approval based on a surrogate endpoint always leaves uncertainty regarding true clinical benefit.
  - And this creates challenges when safety concerns arise.

[1] 08 Jan 2009 FDA Drug Safety Comm; [2] 22 Dec 2009 FDA Drug Safety Comm.

Even More Controversy

- The ezetimibe IMPROVE-IT trial has been completed.[1]
- Adding ezetimibe to simvastatin in the setting of acute coronary syndrome led to a statistically significant reduction in the risk of CVD events expected based on the degree of LDL-C lowering achieved.
  - Indications for ezetimibe failed to follow – 2016.
- Increasing emphasis on using therapies that have proven clinical benefit, not just specific biomarker targets?
  - 2013 ACC/AHA Guideline on Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults
  - Controversy acknowledged

[1] Cannon CP, et al. *NEJM 372:2387*, 2015

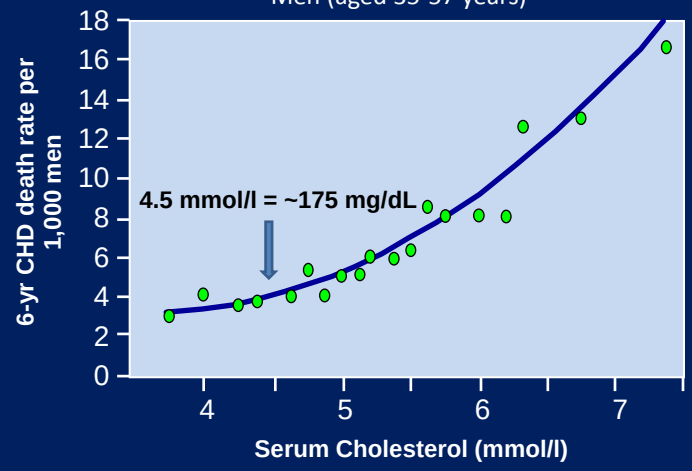
But Surrogates Can Fail

- Off-target adverse effects that are unexpected can occur.
- Sometimes the causal relationship is wrong.
  - Example: Despite ~25% reduction in LDL-C and ~70% increase in HDL-C, torcetrapib increased risk of CVD events by 25% and increased risk of all-cause mortality by 58%.[1]

[1] Barter PJ, et al. *NEJM* 357:2109, 2007

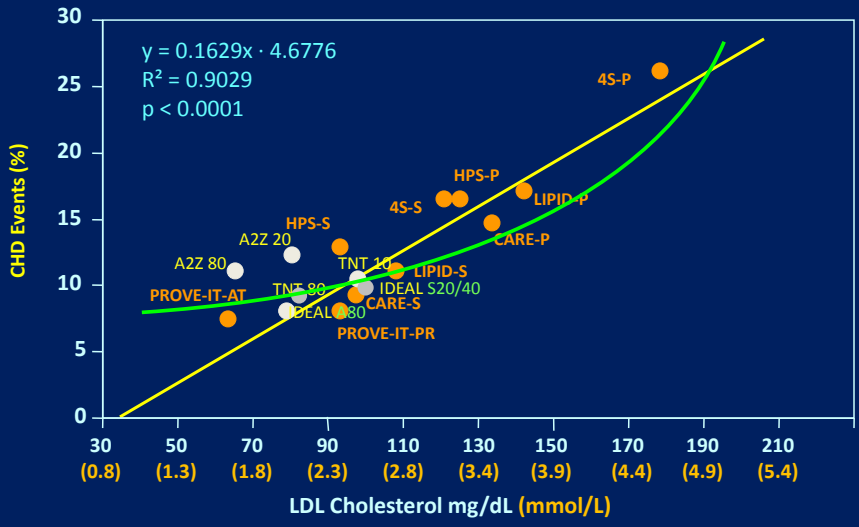
Established Epidemiologic Association Between Cholesterol and CVD

MRFIT: Age-Adjusted CHD Death Rate and Serum Cholesterol in 361,662 US Men (aged 35-57 years)



Martin MJ et al: *Lancet* 2:933, 1986

CHD Event Rates in Secondary Prevention and ACS Trials



Adapted from O'Keefe, J. et al., *JACC* 43:2142, 2004

Are we still in the surrogate age?

Articles from PM360

Panel backs approval of alirocumab, biologic injectable lipid-lowering drug

BY ELIZABETH MECHCATIE in FDA Advisory Committee Meeting on June 10th, 2015

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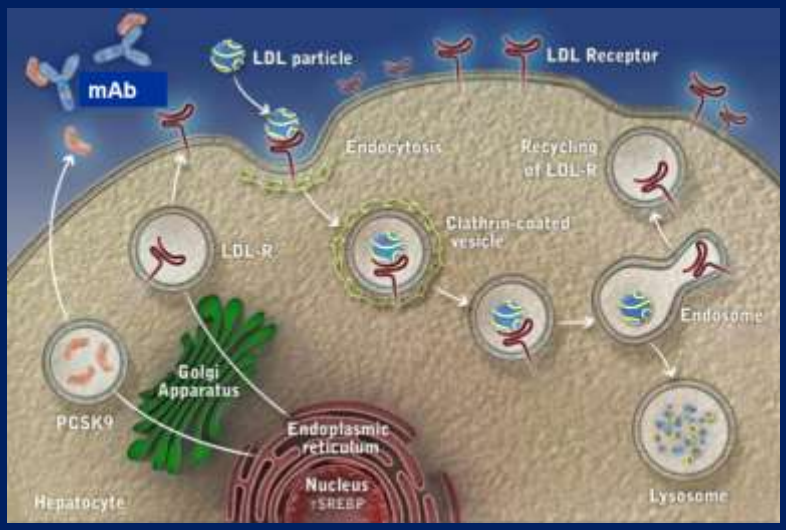
AT AN FDA ADVISORY COMMITTEE MEETING

GAITHERSBURG, MD. (FRONTLINE MEDICAL NEWS) – The majority of a Food and Drug Administration Advisory panel has supported the approval of alirocumab, a biologic lipid-lowering drug injected subcutaneously twice a month, as a long-term treatment for hypercholesterolemia, but support for the different patient populations included in the proposed indication varied.

Over 20 years, the FDA has accepted reductions in LDL cholesterol as a surrogate for CV risk reduction to support approval of lipid-lowering drugs, but once approved, CV outcomes trials are not required. One of the panelists voting against approval was Dr. Peter Wilson , professor of medicine and public health, Emory University, who said that cardiovascular outcomes data were needed to support approval. "I no longer think we are in an LDL-surrogate era," he noted.

How PCSK9 Monoclonal Antibodies Restore LDL Receptor Function



Stein EA. PCSK9 Forum.

Now who are the candidates for PCSK9 inhibitor therapy?

Patient Populations with an Unmet Need for Additional LDL-C Lowering

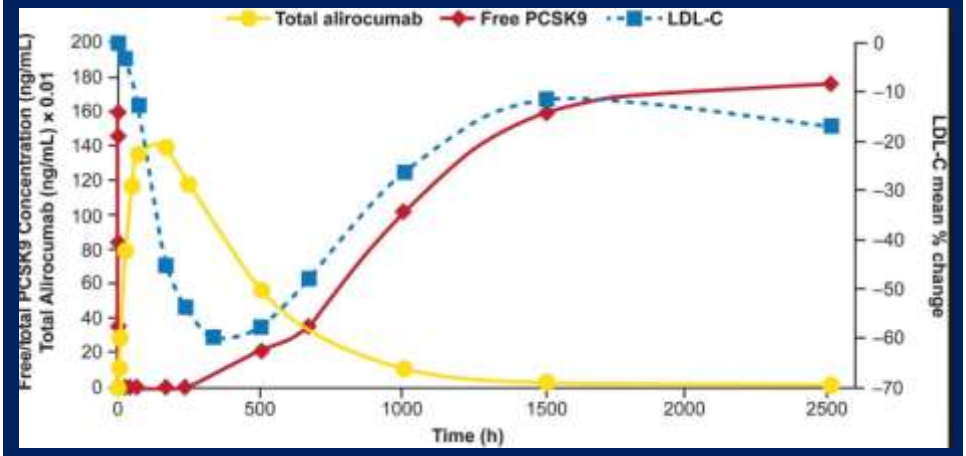
FH Population	High / Very High CV Risk Population	Statin-Intolerant Population
• Genetic disorder • High risk of early CHD • HeFH prevalence 1:200 to 1:250[1,2] • Untreated LDL-C of 200-400 mg/dL[3]	• Previous MI / stroke / CVD or multiple CV risk factors incl. T2DM • Difficult to achieve LDL-C goals, despite current therapies[5]	• 10-15% on high-intensity statins show intolerance[6] • Many discontinue due to muscle pain and/or weakness
79% with HeFH not at goal (<100 mg/dL)[4]	**• 20% with CHD not at goal (<100 mg/dL)** **• 59% at very high CV risk not at goal (<70 mg/dL)**	**Nearly all patients who need considerable LDL-C reductions will not reach goal**

[1] Nordestgaard et al. *Eur Heart J* 2013;34:3478-90. [2] Sjouke et al. *Eur Heart J* (in press).
[3] 2011 ESC/EAS Guidelines for the management of dyslipidaemias. [4] Pijlman et al. *Atherosclerosis* 2010;209:189-94.
[5] Virani et al. *Am Heart J* 2011;161:1140-6. [6] Arca et al. *Diabetes Metab Syndr Obes* 2011;4:155-66.

Expected Dose Response to the PCSK9 Inhibitors

Drug	Dosage	% LDL-C Lowering
Alirocumab	75 mg every 2 wks.	45%
	150 mg every 2 wks.	60%
Evolocumab	140 mg every 2 wks.	60%
	420 mg every 2 wks	60%

Pharmacokinetics of Alirocumab: Effect on Free PCSK9 and LDL-C



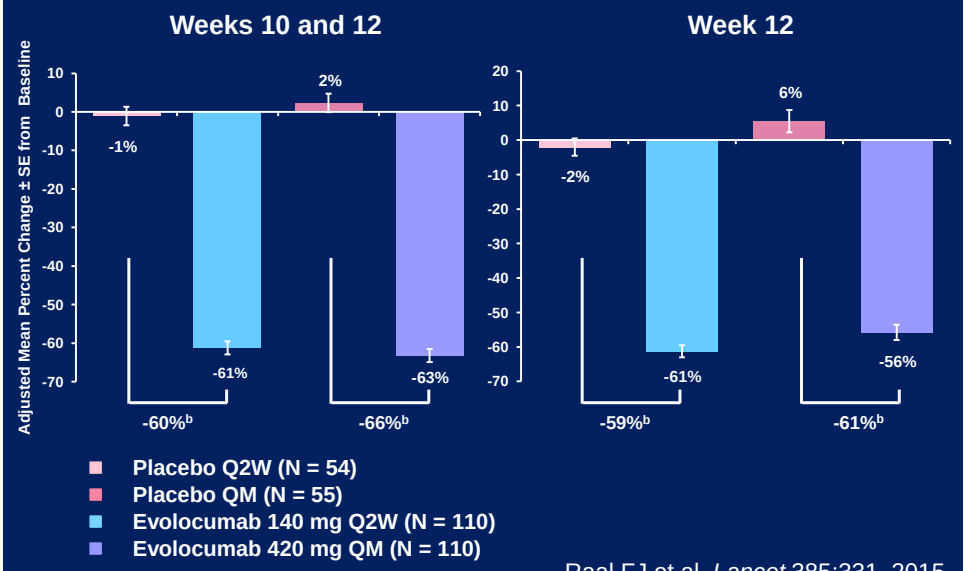
Shimada YJ & Cannon CP, *Eur Heart J.* May, 2014

- FL is a 72 year old woman with FH, CIMT thickening and LDL-C 560 mg/dL in 2008 now taking
  - Rosuvastatin 40 mg daily
  - Colesevelam 1875 mg bid
  - Ezetimibe 10 mg daily
  - Fenofibrate 145 mg daily
- Labs on 3/17/15
  - Cholesterol 195 mg/dL
  - TG 75 mg/dL
  - HDL-C 67 mg/dL
  - LDL-C 113 mg/dL
  - Lipoprotein (a) 18 mg/dL

Let's begin by setting a LDL-C target or goal

(not precluded by the 2013 ACC/AHA Cholesterol Guideline, just not evidence-based).

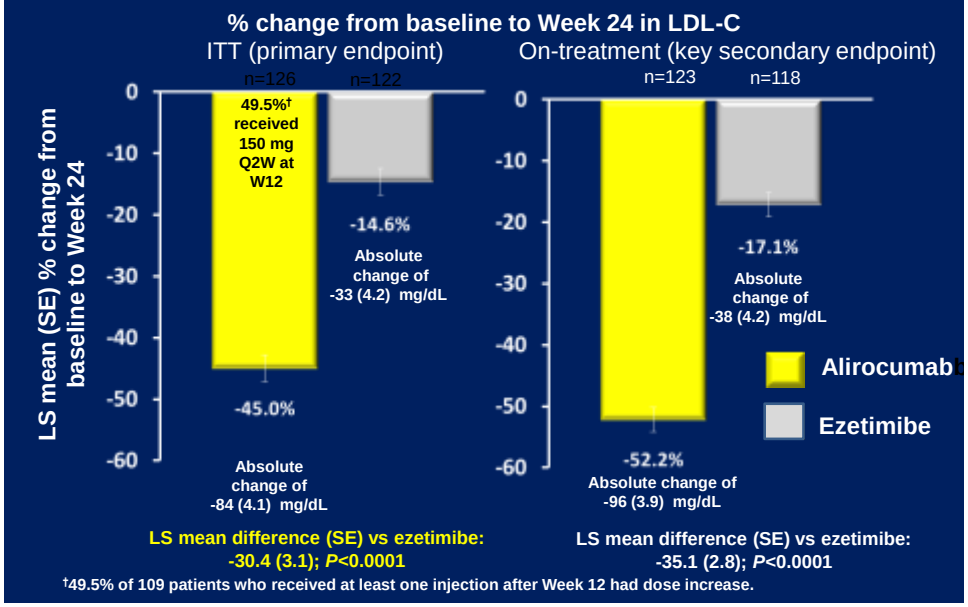
RUTHERFORD-2: Mean % Change in LDL-C[a] from Baseline to the Mean of Weeks 10 and 12, and Week 12 Alone



Raal FJ et al, *Lancet* 385:331, 2015

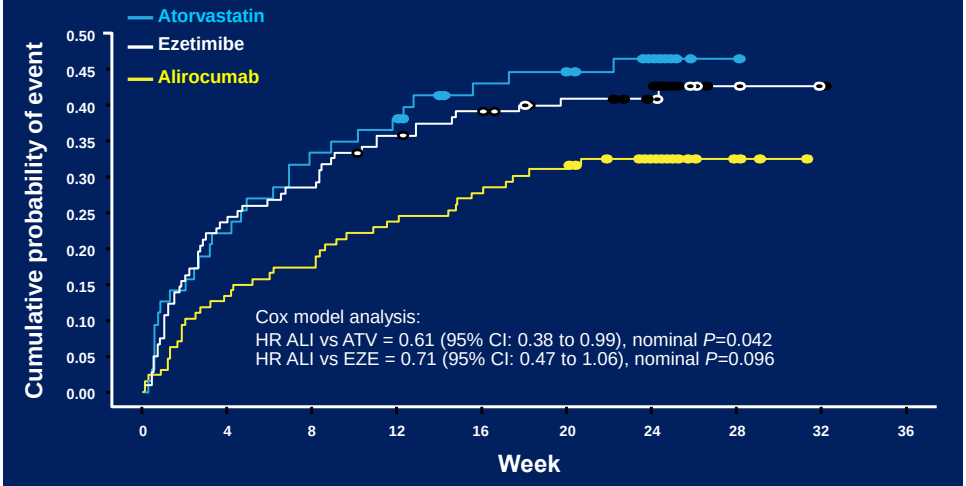
- VK is a 69 year old woman S/P AMI with combined hyperlipidemia, HTN, prediabetes and intolerant to multiple statins, fibrates and bile acid sequestrants taking
  - Ezetimibe 10 mg daily
  - Omega-3 fatty acids 930 mg bid
- Labs on 5/15/15
  - Cholesterol 254 mg/dL
  - TG 192 mg/dL
  - HDL-C 58 mg/dL
  - LDL-C 158 mg/dL
  - Lipoprotein (a) 14 mg/dL
  - HbA1c – 5.8%

Alirocumab Significantly Reduced LDL-C from Baseline to Week 24 vs. Ezetimibe



†49.5% of 109 patients who received at least one injection after Week 12 had dose increase.

Fewer Skeletal Muscle AEs with Alirocumab than with Atorvastatin

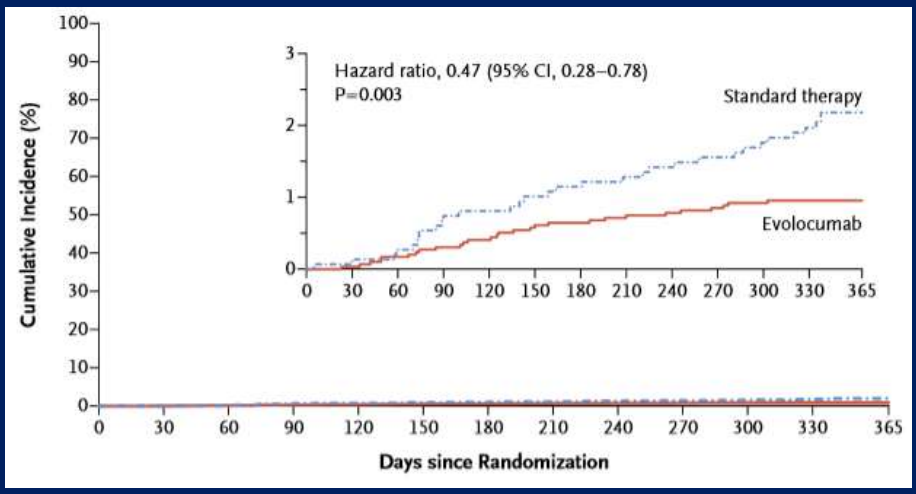


PCSK9 Inhibitors: Efficacy in Other Lipid Parameters

Parameter	Range of Mean Changes with PCSK9 Inhibitors
Apo B	-32% to -53%
Non-HDL-C	-37% to -52%
Lipoprotein(a)	-17% to -30%
Triglycerides	-6% to -26%
HDL-C	+3% to +9%
Apo A-1	+2% to +7%

But do PCSK9 inhibitors reduced ASCVD events?

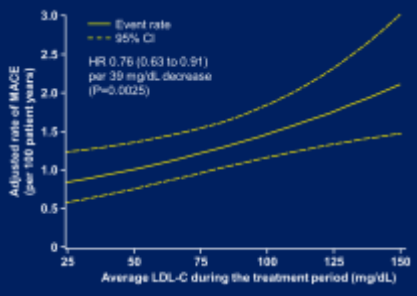
OSLER-1 & OSLER-2: Cumulative Incidence of CVD Events



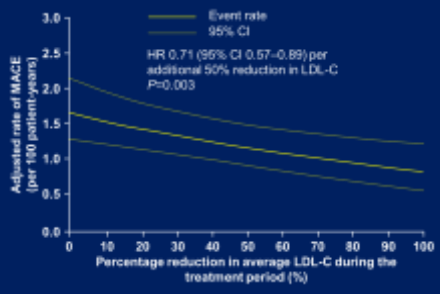
Sabatine MS et al, *NEJM* 372:1500, 2015

Emerging Evidence from ODYSSEY Program

Continuous relationship between lower on-treatment LDL-C levels and lower CV risk[1]



Direct relationship between greater LDL-C % reduction from baseline and lower ASCVD event rates[2]



Adjusted MACE rate by average LDL-C (absolute or % reduction from baseline) during treatment period.
Multivariate analysis adjusted on baseline characteristics; pool of Phase 3 ODYSSEY trials.
HR were calculated for each 39 mg/dL difference or 50% reduction in LDL-C.
1. Cannon CP et al., oral presentation [session 913], ACC 2016. 2. Ray KK et al. poster 1124M-05, ACC 2016.

PCSK9 Phase 3 Trials for CVD Events Reduction

(Statin Treated)

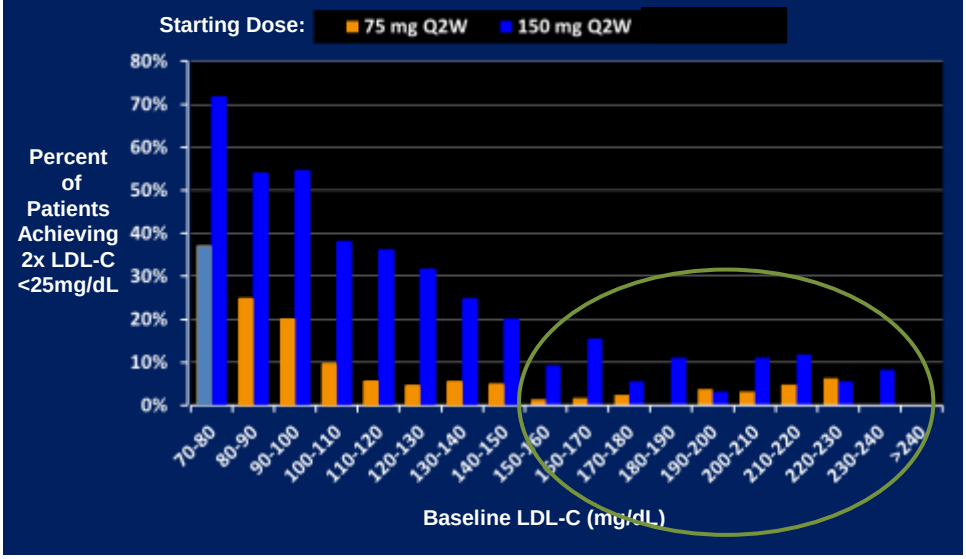
Trial	Drug	LDL-C Criterion	Sample Size	Completion Date
FOURIER	Evolocumab	≥ 70 mg/dL	27,500	Jan 2018
ODYSSEY Outcomes	Alirocumab	≥ 70 mg/dL	18,000	Jan 2018
SPIRE-1	Bococizumab	≥ 70 mg/dL	17,000	June 2018
SPIRE-2	Bococizumab	≥ 100 mg/dL	9,000	Jan 2018

Can LDL-C be Too Low?

- Abetalipoproteinemia & homozygous hypobetalipoproteinemia
  - Autosomal recessive
    - MTP and/or apo B gene mutations
  - Absent apo B-containing lipoproteins
    - Chylomicrons, VLDL, LDL
  - Neurological and ophthalmological sequela prevented by fat-soluble vitamins
  - Malabsorption prevented by low fat diet + essential fatty acids
  - Hepatic steatosis and AST/ALT elevations
    - No fibrosis
  - No ASCVD

Lee J & Hegele RA, *J Inherit Metab Dis* 37:333, 2014

Baseline LDL-C and Starting Dose Predict LDL-C<25



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TEAEs of Interest in Patients with 2 Consecutive LDL-C < 25mg/dL (0.6 mmol/L)

% of patients All patients on background of maximally tolerated statin ± other lipid-lowering therapy	Alirocumab* (N=1550)	Alirocumab* with 2 consecutive LDL-C <25mg/dL (<0.6 mmol/L) (N=575)	Placebo (N=788)
Summary of AE – no. of patients (%)			
Any adverse event	1255 (81.0)	435 (75.7)	650 (82.5)
Serious adverse event	290 (18.7)	98 (17.0)	154 (19.5)
Adverse event leading to death	8 (0.5)	4 (0.7)	10 (1.3)
Adverse event leading to study drug discontinuation	111 (7.2)	26 (4.5)	46 (5.8)

Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)

* Alirocumab is not licensed in EU

Adapted from Robinson JG et al. N Engl J Med. 2015;372(16):1489-99

TEAEs in Both Arms Patients With 2 Consecutive LDL-C < 0.65 mmol/L (25 mg/dL)

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% (n) of patients All pts on background of maximal statin therapy ± other lipid-lowering therapy	Alirocumab* (n=1550)	Alirocumab* with 2 consecutive LDL-C <25 mg/dL (0.6 mmol/L) (n=562, 37%)	Placebo (n=788)
Infections + infestations	**48.3%** (748)	**42.3%** (243)	**48.6%** (383)
Musculoskeletal + connective tissue disorders	**30.1%** (467)	**26.1%** (150)	**30.7%** (242)
Gastrointestinal disorders	**20.5%** (318)	**16.7%** (96)	**20.6%** (162)
Nervous system disorders	**18.6%** (289)	**12.9%** (74)	**19.7%** (155)
General disorders + administration site conditions	**16.1%** (250)	**11.3%** (65)	**17.8%** (140)
Injury, poisoning, + procedural complications	**15.5%** (241)	**13.2%** (76)	**15.7%** (124)
Respiratory, thoracic, + mediastinal disorders	**11.7%** (182)	**8.9%** (51)	**12.6%** (99)
Cardiac disorders	**11.0%** (171)	**10.6%** (61)	**12.9%** (102)
Skin + subcutaneous tissue disorders	**10.1%** (156)	**8.3%** (48)	**9.4%** (74)
Metabolism + nutrition disorders	**10.2%** (158)	**9.6%** (55)	**9.3%** (73)
Vascular disorders	**8.6%** (133)	**5.4%** (31)	**10.0%** (79)
Eye disorders	**7.0%** (108)	**7.0%** (40)	**6.2%** (49)
Laboratory investigations	**6.4%** (99)	**4.3%** (25)	**5.5%** (43)
Psychiatric disorders	**6.5%** (101)	**5.2%** (30)	**8.5%** (67)
Renal + urinary disorders	**5.5%** (85)	**4.7%** (27)	**6.6%** (52)
Neoplasms, benign, malignant (incl cysts/polyps)	**3.0%** (47)	**3.8%** (22)	**4.3%** (34)
Reproductive system + breast disorders	**3.2%** (50)	**2.8%** (16)	**3.4%** (27)
Blood + lymphatic system disorders	**3.0%** (46)	**2.4%** (14)	**3.7%** (29)
Ear + labyrinth disorders	**2.4%** (37)	**1.7%** (10)	**3.9%** (31)

* Alirocumab is not licensed in EU

Adapted from J. Robinson et al *NEJM* 372:1489, 2015, Appendix

Some Final Thoughts About Reduced LDL-C

- Definition ↓ LDL-C
  - Low <40 mg/dL, 2013 ACC/AHA Cholesterol Guideline
  - Very Low <25 mg/dL
- Not uncommon when statins are used in pateints with ↑TG and LDL-C is calculated.
- CVA risk increased?
  - SPARCL, *NEJM* 355:549,
  - JUPITER, Hsia JG et all, *JACC* 57:1666, 2011
- Risk of T2DM
  - JUPITER, Everett BM et al, *Am J Card* 114:1682, 2014
  - FH – 50% ↓ risk, Besseling J, et al *JAMA* 313:1029, 2015

Using FDA-Approved PCSK9 Inhibitors in Clinical Practice

- ↓ LDL-C by 45-60%
  - On top of maximum statin ± ezetimibe therapy
- Probably reduce ASCVD events
  - But is LDL-C still a surrogate for events?
- Appear safe, but risk may need decades to prove
  - Is <40 too low?
  - Is <25 mg/dL too low?
- Appear indicated when LDL-C lowering is needed
  - FH
  - High risk patients with clinical ASCVD.
  - Statin intolerant with clinical ASCVD.