ACC Latin America Conference 2017

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GLOBAL EXPERTS, LOCAL LEARNING

ACC Latin America Conference 2017

Current Role of PCSK9 Inhibitors

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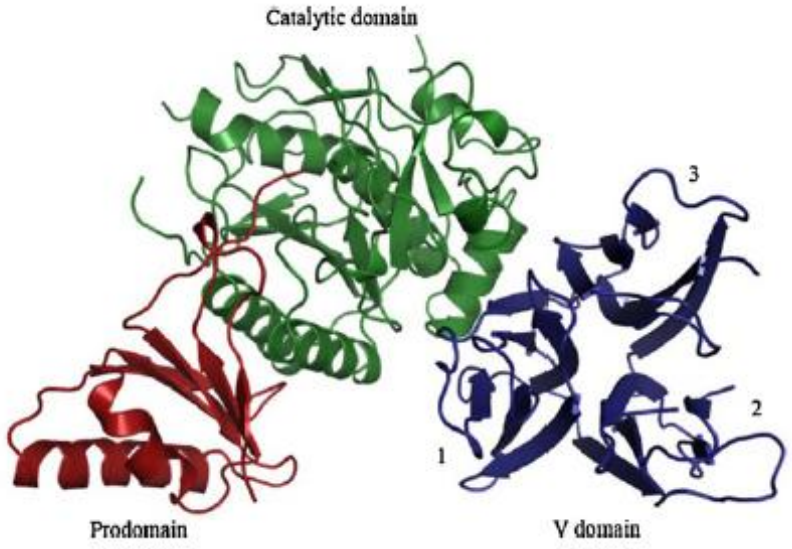
Proprotein Convertase Subtilisin-Kexin Type 9

- Secreted serine protease
- Targets the LDL-receptor for degradation
  - May also influence Apo B synthesis and TG secretion
- Gain of function mutation → higher LDL-C
- Loss of function mutation → lower LDL-C



Lambert et al. Atherosclerosis 2009;203:1–7
Soutar AK. Curr Op Lipidol 2011;22:192–196

FDA Approval August 2015

Alirocumab (Praluent)

- Adjunct to diet and maximally tolerated statin to treat adults with HeFH or clinical ASCVD who need more LDL-C reduction

Alirocumab Dose

- Initiate 75 mg SQ every 2 weeks
- May ↑ dose to 150 mg every 2 weeks

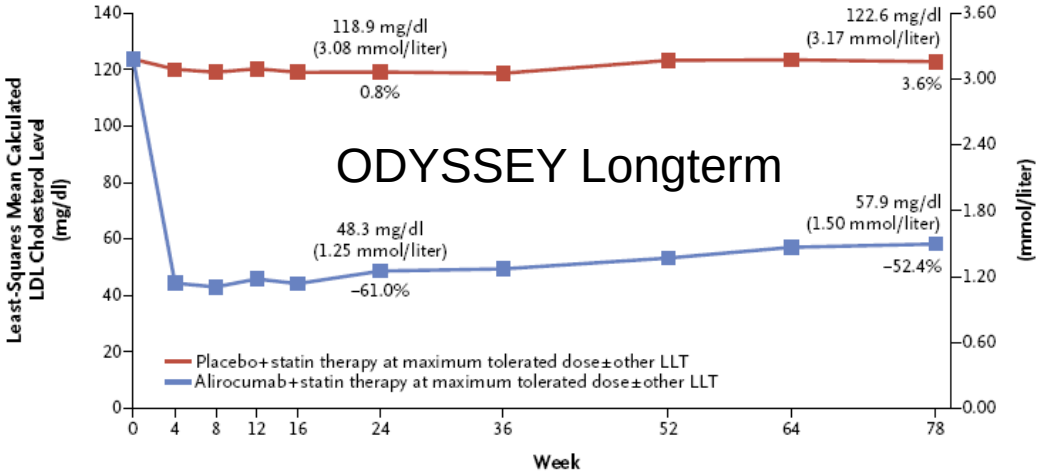
Evolocumab (Repatha)

- Adjunct to diet and maximally tolerated statin to treat adults with HeFH or clinical ASCVD who need more LDL-C reduction
- Adjunct to diet and other LDL-lowering Rx (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who need more LDL-C reduction

Evolocumab Dose

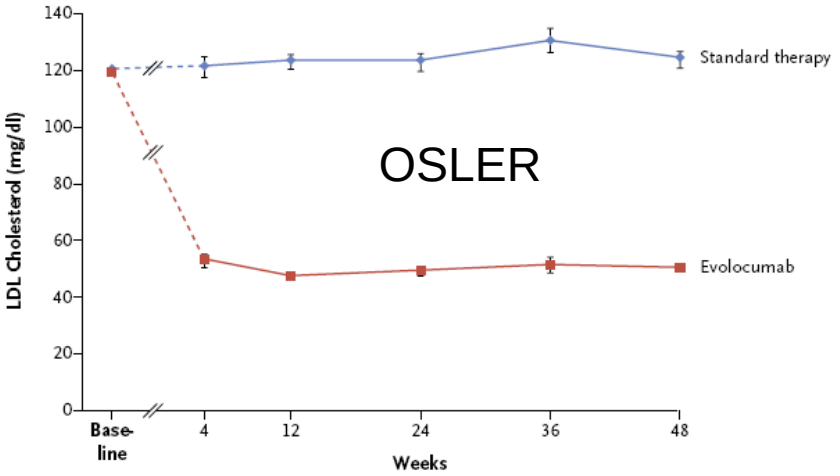
- ASCVD or HeFH
  140 mg SQ every 2 weeks or
  420 mg SQ monthly
- HoFH
  420 mg SQ monthly

LDL-C Effects on Statin Background



Alirocumab

No. of Patients with Data Available									
Placebo	780	754	747	746	716	708	694	676	659
Alirocumab	1530	1473	1458	1436	1412	1386	1359	1349	1324



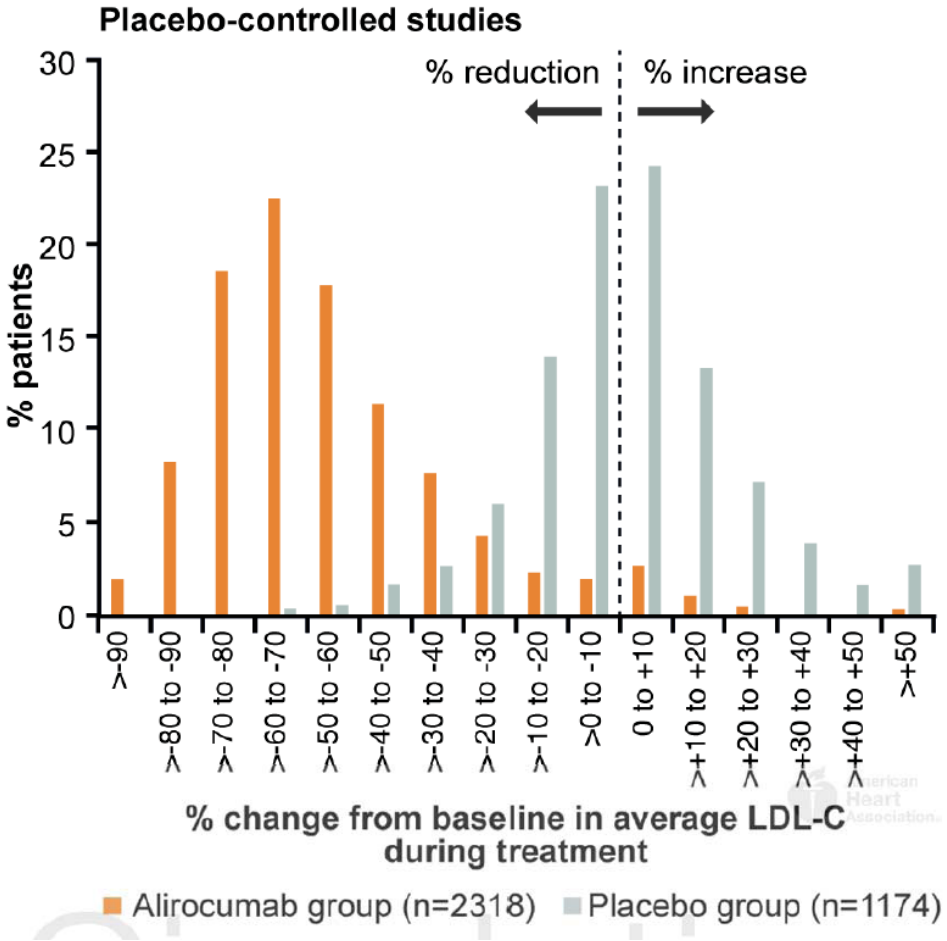
Evolocumab

No. at Risk						
Standard therapy	1489	394	1388	1376	402	1219
Evolocumab	2976	864	2871	2828	841	2508
Absolute reduction (mg/dl)		60.4	73.4	70.4	72.7	70.5
Percentage reduction		45.3	60.9	58.8	54.0	58.4
P value		<0.001	<0.001	<0.001	<0.001	<0.001

Sabatine et al. NEJM 2015;372:1500-9
Robinson et al. NEJM 2015;372:1489-99

Heterogeneity of Response to PCSK9 Inhibition

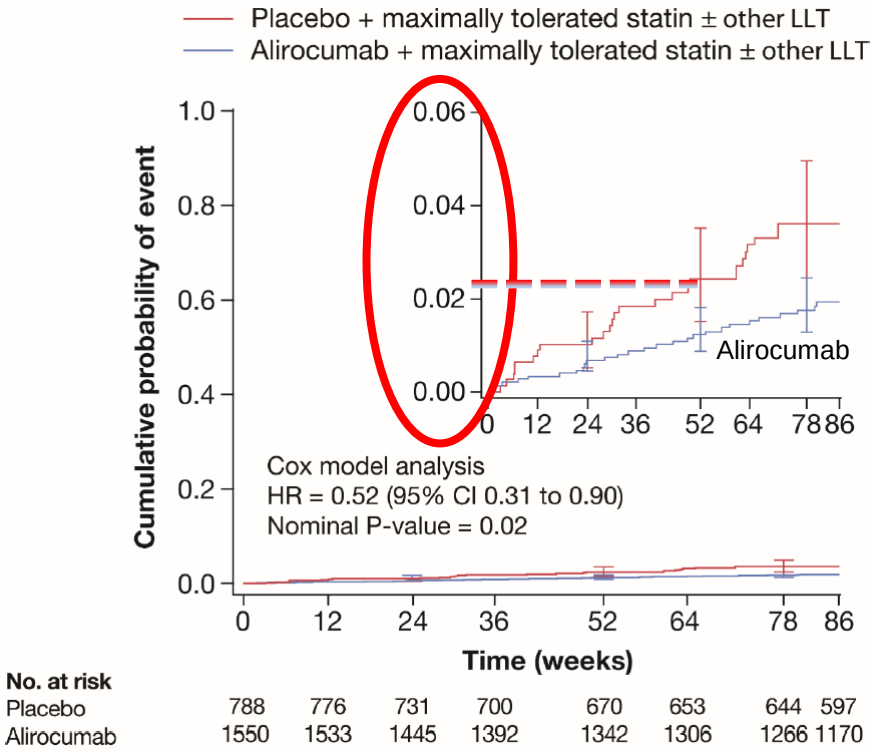
- Pooled data from 10 trials in the Phase 3 ODYSSEY Program
- Treatment for 24-104 weeks
- 52% of alirocumab treated individuals achieved LDL-C <50 mg/dL in placebo-controlled studies



Ray et al. Circulation 2016;134:1931-1943

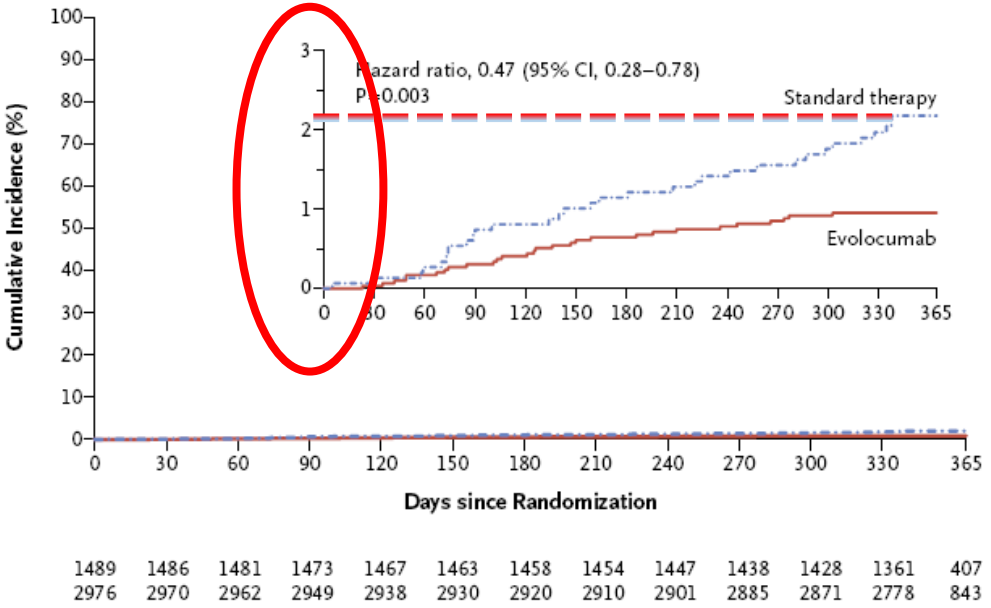
Post-hoc Data on CV Outcomes

Robinson et al. NEJM 2015;372:1489-99
Sabatine et al. NEJM 2015;372:1500-9



ODYSSEY Longterm (Alirocumab)
HR = 0.52 (95% CI 0.31-0.90)

OSLER (Evolocumab)
HR 0.47 (95% CI 0.28-0.78)

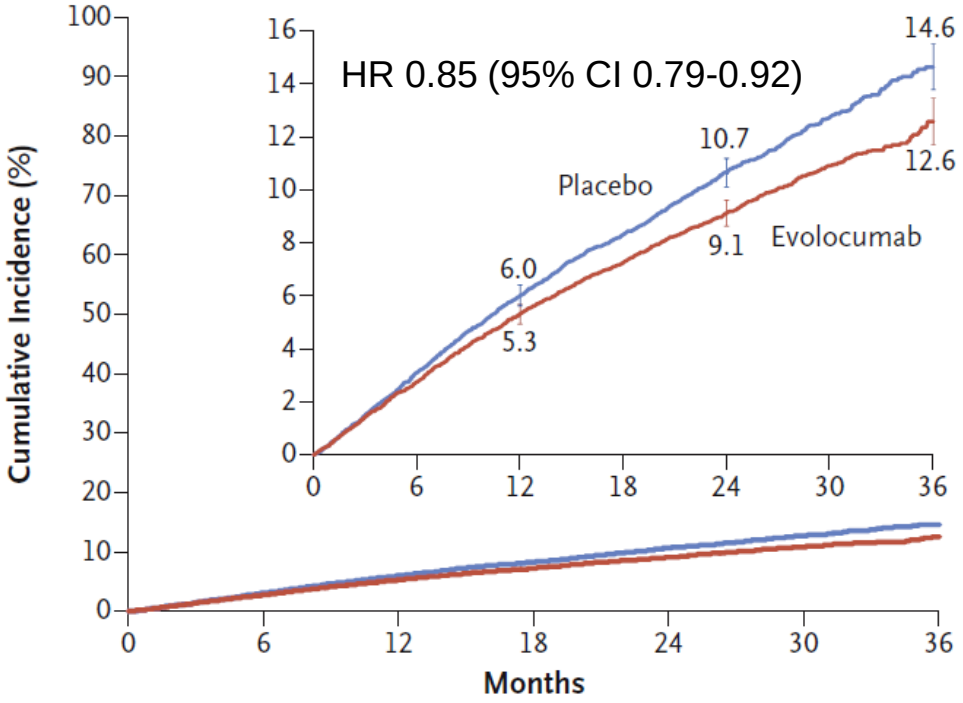


FOURIER Trial

- N=27,564
  - ASCVD
  - LDL-C ≥ 70 mg/dL* on statin therapy
- Median F/U 2.2 years
- Evolocumab vs placebo
- LDL-C reduction 59% (90 --> 30 mg/dL)

- 1º EP: CV death, MI, stroke, hospitalization for UA, or coronary revascularization
- 2º EP: CV death, MI, or stroke

FOURIER Primary Endpoint



No. at Risk							
Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolocumab	13,784	13,351	12,939	12,070	7771	3746	689

*1.8 mmol/L

Sabatine et al. NEJM 2017;376:1713-1722

FOURIER Adverse Events

Outcome	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Adverse events — no. of patients (%)		
Any	10,664 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)
Injection-site reaction*	296 (2.1)	219 (1.6)
Allergic reaction	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)

Sabatine et al. NEJM 2017;376:1713-1722

Cost

Listed price in US: ≈ $14,000 / year

Primary Endpoint

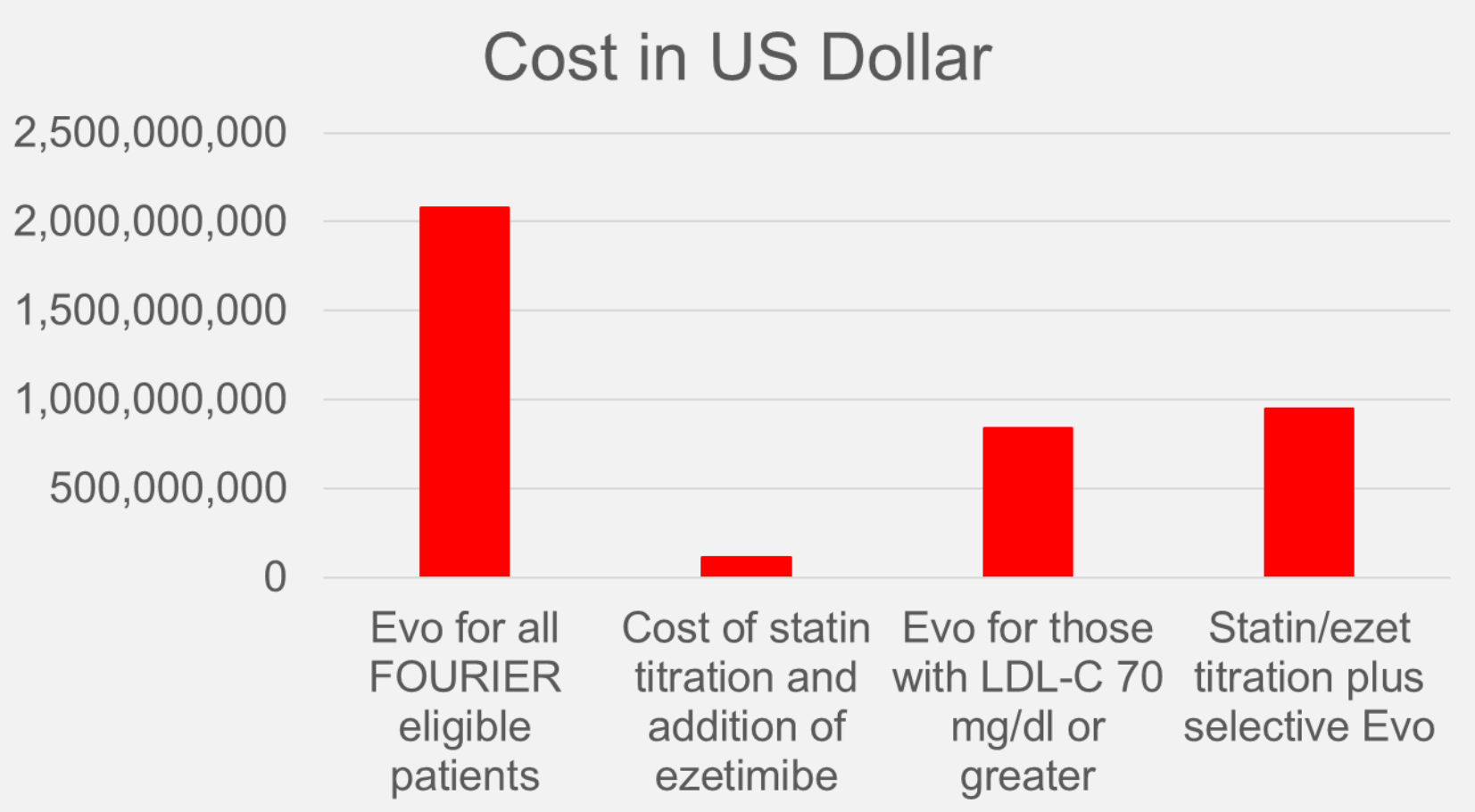
- Absolute RR 1.5% → NNT 74 (for 2 years)
- Cost for 2 years of treatment to prevent 1 event: $ 2,072,000

Secondary Endpoint

- Absolute RR 1.3% → NNT 77 (for 2 years)
- Cost for 2 years of treatment to prevent 1 event: $ 2,156,000

Sabatine et al. NEJM 2017;376:1713-1722

Applying FOURIER to the VA Population



Virani et al. Circulation 2017, May; Epub ahead of print

Take Home Points

- PCSK9 Inhibitors are powerful LDL-C lowering agents.
  - Response to PCSK9-inhibition is heterogeneous
- Evolocumab reduced events in the FOURIER trial and there was no major safety signal
  - Event reduction less robust than estimated from the pooled post-hoc analyses
  - Follow-up was very short
- PCSK9 inhibitors are expensive
  - Intensification of statin and addition of ezetimibe can reduce the need for PCSK9 inhibition and significantly reduce costs

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Muchas gracias por su atención!

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