AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS | AMERICAN COLLEGE OF ENDOCRINOLOGY

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

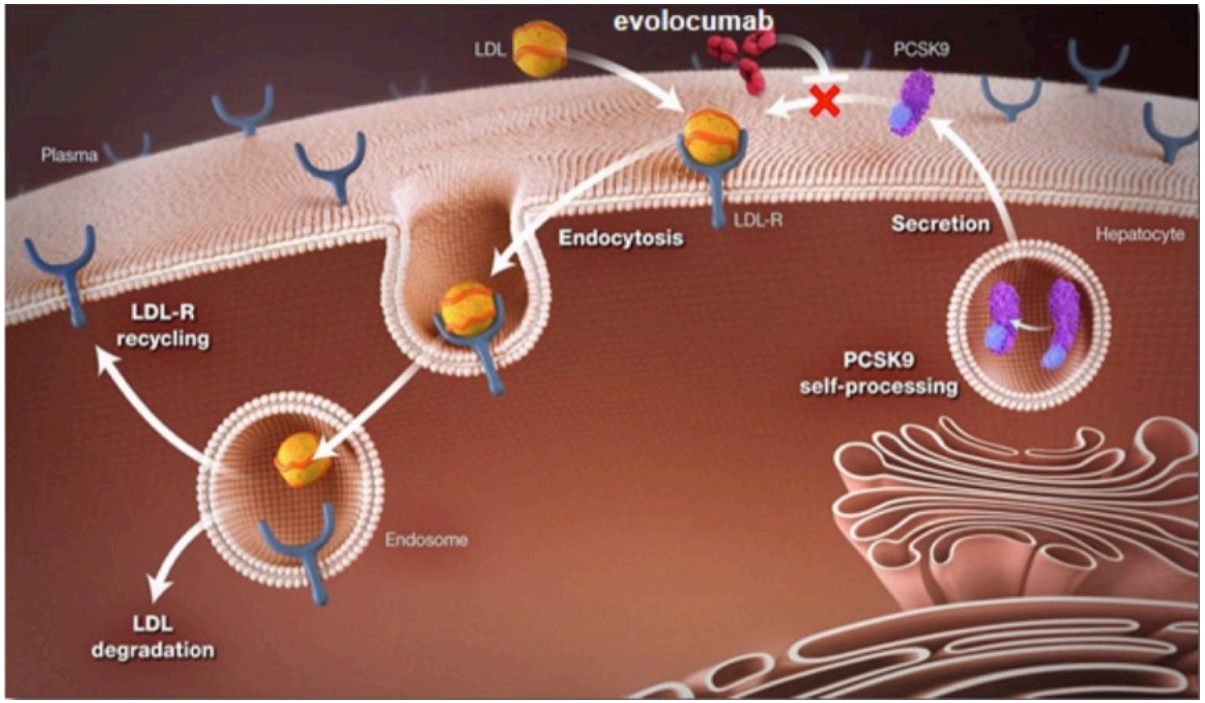
LIPID RESOURCE CENTER | LIPIDS.AACE.COM

Introduction

- What are proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and how do they work?
- Which patients are candidates for PCSK9 inhibitor therapy?
- What is the expected response to PCSK9 inhibitor therapy?
- What major clinical trials have shaped what we know about PCSK9 inhibitor therapy?
- Do PCSK9 inhibitors reduce atherosclerotic cardiovascular disease events?
- How do PCSK9 inhibitors work in individuals with diabetes?
- What are the controversies in using PCSK9 inhibitors?

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)

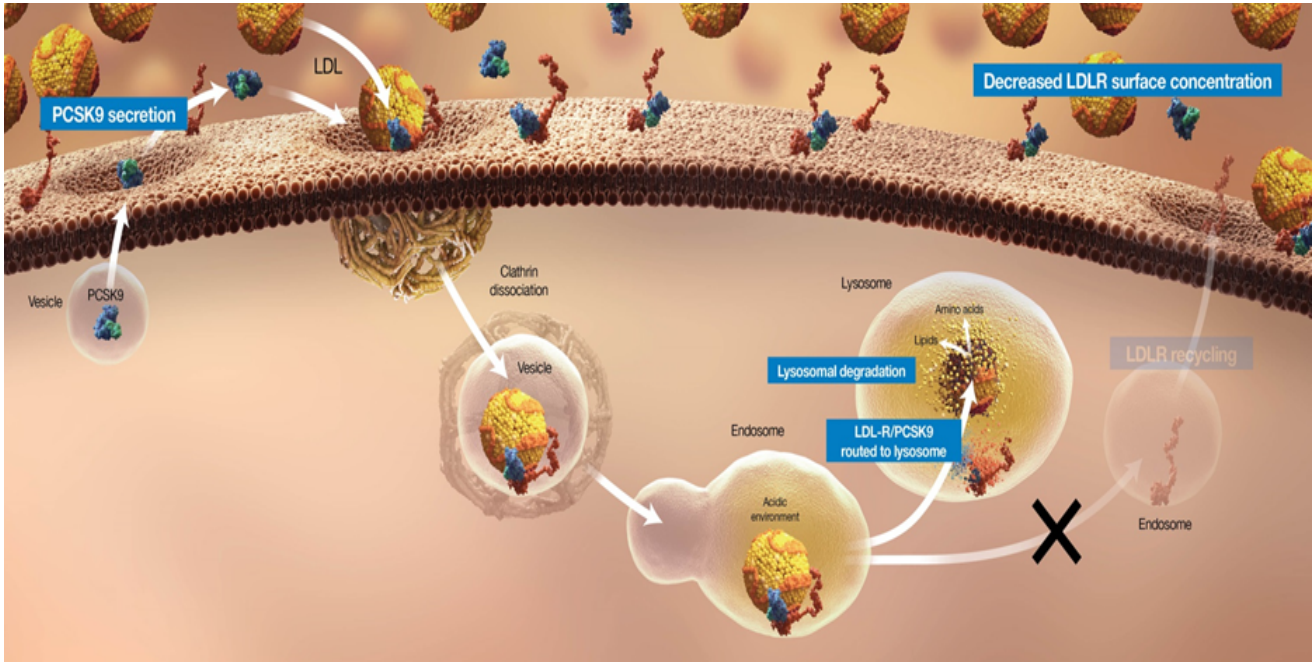
- Binds to LDL-R, targets LDL-R for lysosomal degradation in cells[1,2]
- Loss-of-function genetics variants → ↑ LDL-R → ↓ LDL-C and ↓ risk of MI[1-3]



1. Lagace TA. *Curr Opin Lipidol.* (2014) 25:387-93.
2. Server P & Mackay J. *BR J Cardiol.* (2014) 21:91-3.
3. Giugliano R, et al. *Lancet.* (2012) 380:2007-17.
4. Sabatine MS, et al. *NEJM.* (2015) 372:1500-9.

LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; LDL-R=low-density lipoprotein receptor; MI=myocardial infarction; PCSK9=proprotein convertase subtilisin/kexin type 9.

PCSK9 Regulates LDL-R Surface Expression by Targeting for Lysosomal Degradation



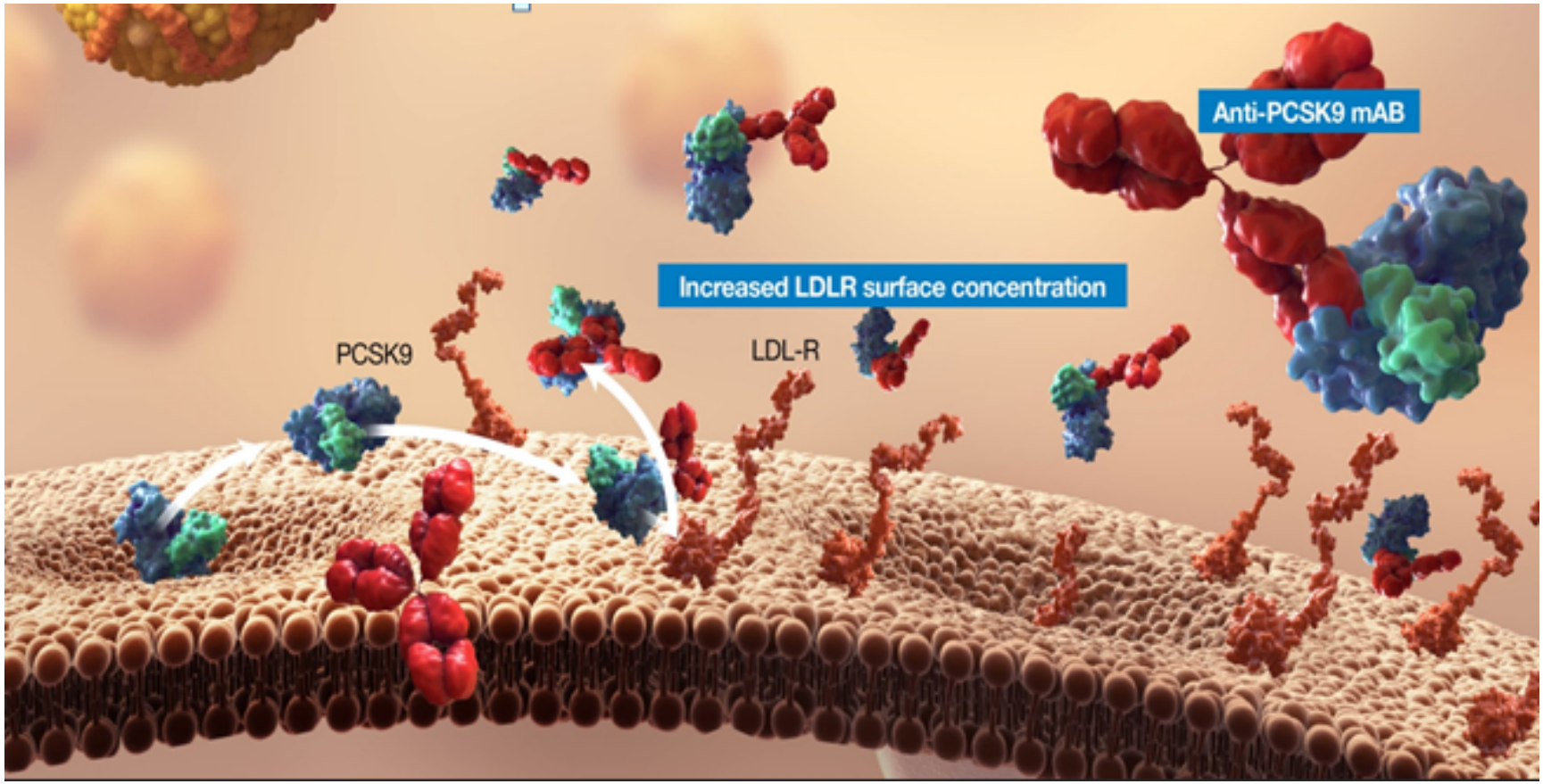
PCSK9 is a pro-protein produced in hepatocytes. It binds to the LDL-R and is internalized within the endosome.

The complex is then routed to the lysosome for degradation, thereby preventing LDL-R recycling back to the hepatocyte surface.

LDL=low-density lipoprotein; LDL-R=low-density lipoprotein receptor; PCSK9=proprotein convertase subtilisin/kexin type 9.

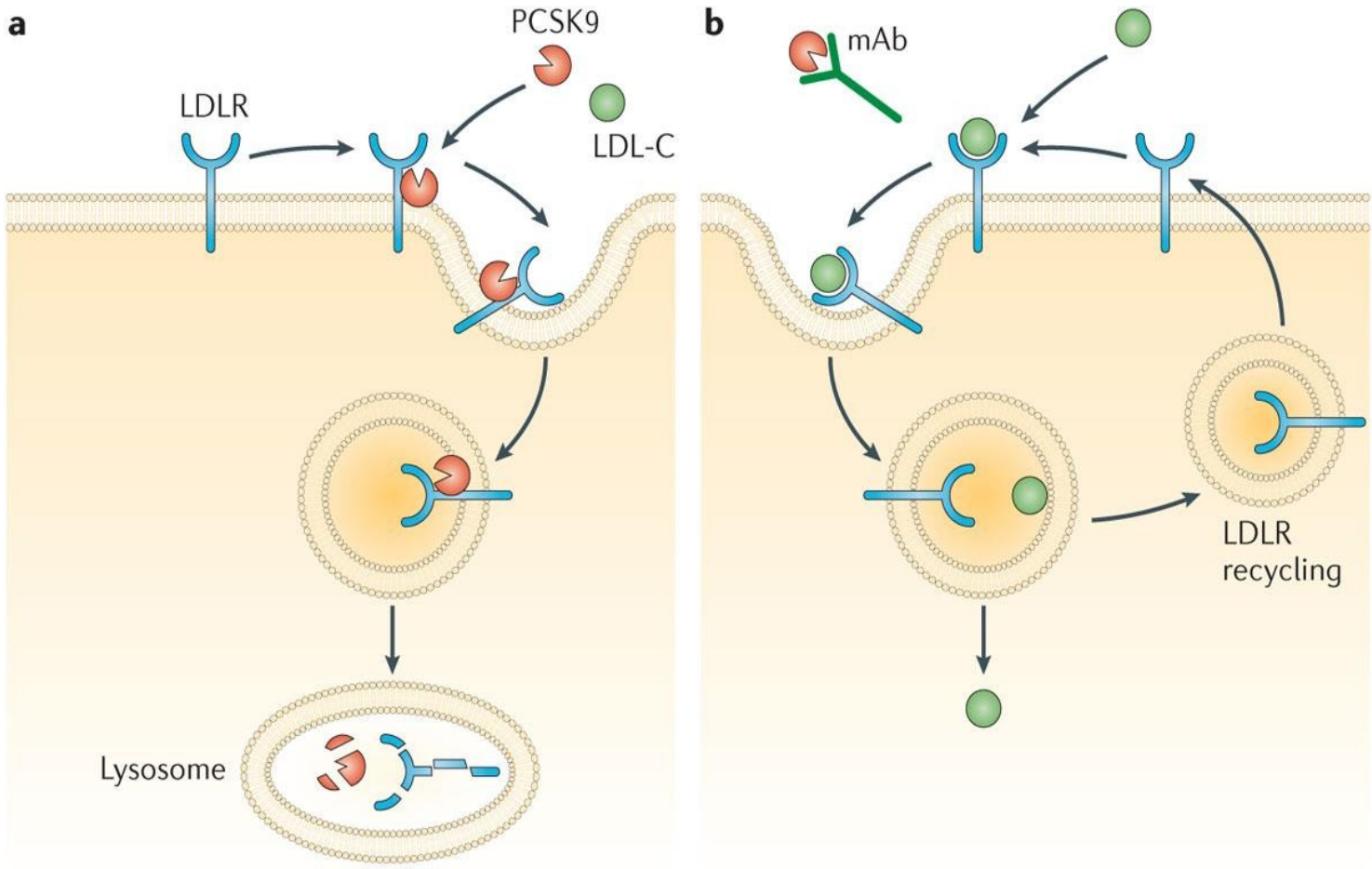
1. Horton JD, et al. *J Lipid Research.* (2009) 50:S172-S177.
2. Qian Ywetal, et al. *J Lipid Research.* (2007) 48:1488-1498.
3. Zhang DW, et al. *J Biol Chem.* (2007) 282:18602-18612.

PCSK9 Blockade Lowers LDL-C Levels By Increasing LDL Receptors on Cell Surface



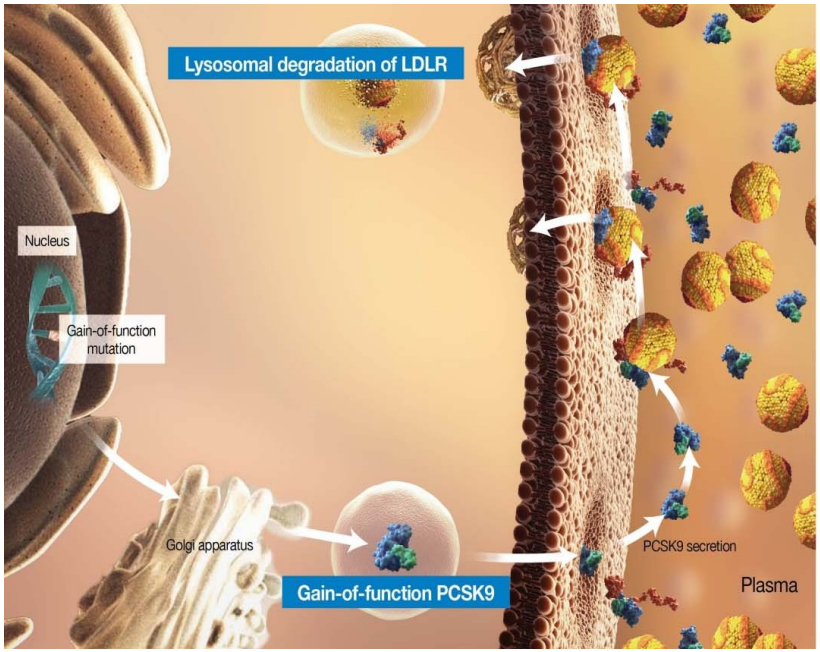
LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; LDL-R=low-density lipoprotein receptor; mAb=monoclonal antibody; PCSK9=proprotein convertase subtilisin/kexin type 9.
Chan JC, et al. *PNAS.* (2009) 106:9820-9825.

PCSK9 Inhibition Prevents LDL-R Degradation

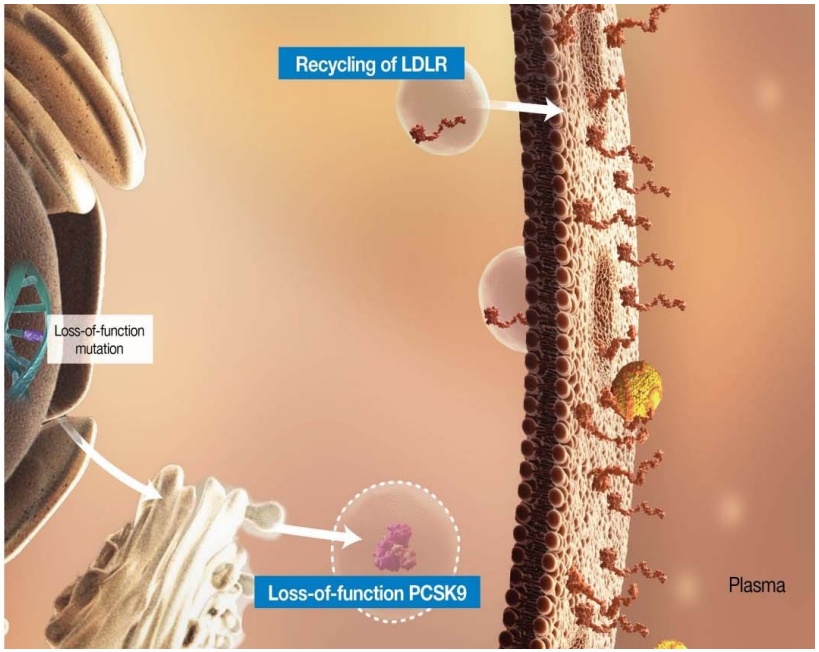


LDL-C=low-density lipoprotein cholesterol; LDL-R=low-density lipoprotein receptor; mAb=monoclonal antibody; PCSK9=proprotein convertase subtilisin/kexin type 9. Mullard A. *Nature Reviews Drug Discovery. (*2012) 11:817-819.

Genetic Variants of PCSK9 Demonstrate Its Role in Managing LDL-C Levels



Genetic mutations with PCSK9 gain-of-function: Less LDL-R, more LDL-C



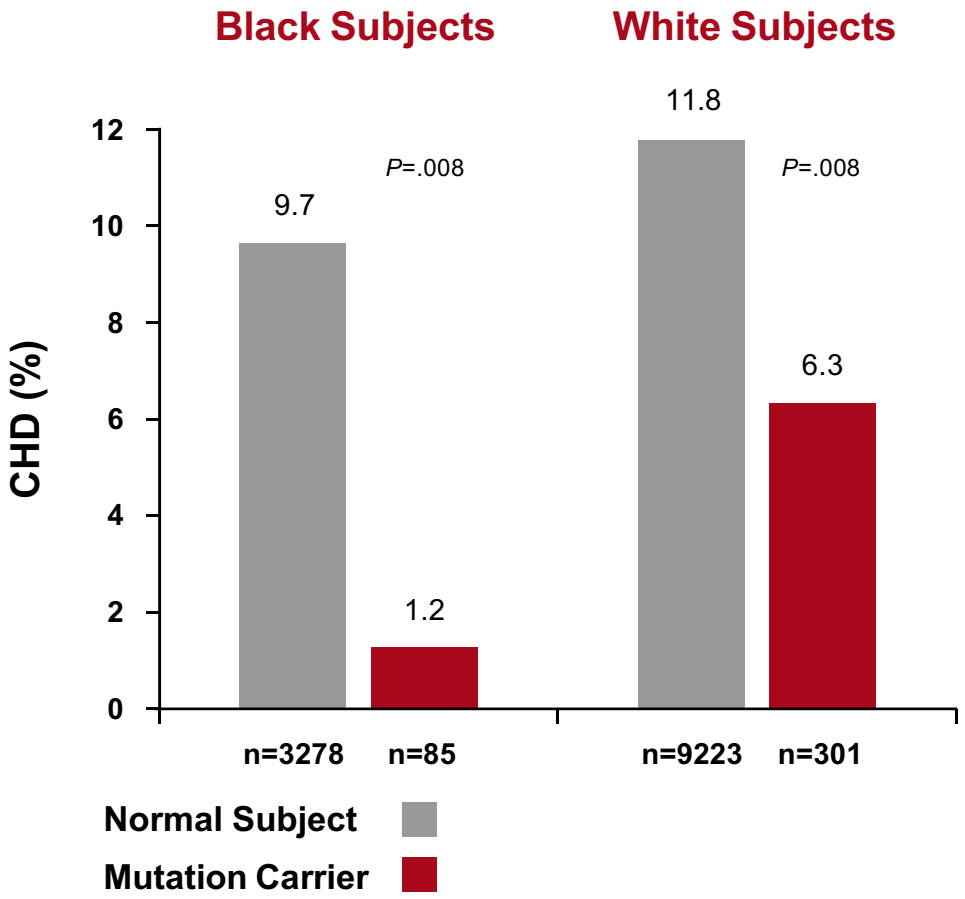
Genetic mutations with PCSK9 loss-of-function: More LDL-R, less LDL-C

LDL-C=low-density lipoprotein cholesterol; LDL-R=low-density lipoprotein receptor; PCSK9=proprotein convertase subtilisin/kexin type 9.

1. Qian Y, et al. *J Lipid Research.* (2007) 48:1488-1498.
2. Zhang D, et al. *J Biol Chem.* (2007) 282:18602-18612.

PCSK9 Loss-of-Function Mutations Resulted in Low LDL-C Levels and Reduced CHD Rates

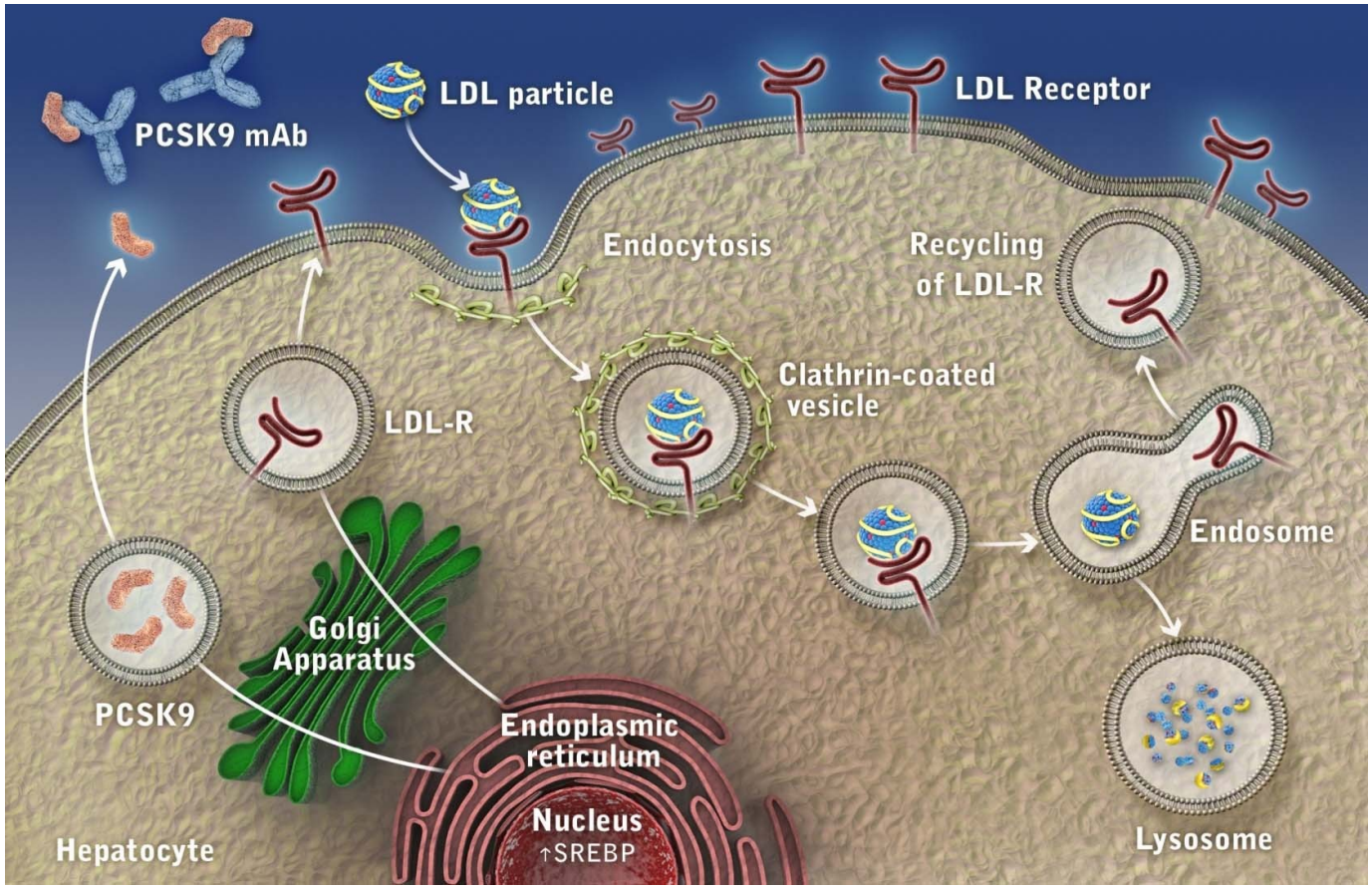
- Wild-type PCSK9 degrades LDL receptors.[1,2]
- Loss-of-function mutations increase hepatic LDL receptor expression, reducing LDL-C levels by 15%-40%.[2,3]
- CHD was reduced by 47% to 88% in PCSK9 loss-of-function mutation carriers compared with normal individuals.[3]



1. Peterson A, et al. *J Lipid Res. (*2008) 49(7):1595-1599.
2. Cohen J, et al. *Nature Genetics*. (2005) 37(2):161-165.
3. Cohen JC, et al. *N Engl J Med*. (2006) 354(12):1264-1272.

CHD=coronary heart disease; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9.

Impact of a PCSK9 mAb on LDL-R Expression



LDL=low-density lipoprotein; LDL-R=low-density lipoprotein receptor; mAb=monoclonal antibody;
PCSK9=proprotein convertase subtilisin/kexin type 9; SREBP=sterol regulatory-element binding protein.

1. Chan J, et al. *PNAS.* (2009) 106:9820-9825; 2. Giugliano R, et al. *Lancet.* (2012) 380:2007-17; 3. Sabatine M, et al. *NEJM.* (2015) 372:1500-9.

Lipid-Lowering Drug Therapies, Starting Doses, and Dosage Ranges

PCSK9 Inhibitors

Agent	Usual recommended starting daily dose	Dosage range	Method of administration
PCSK9 inhibitors			
Alirocumab	75 mg every 2 weeks or 300 mg every 4 weeks	75-150 mg every 2 weeks or 300 mg every 4 weeks	SQ
Evolocumab	140 mg every 2 weeks or 420 mg once monthly	Same as starting dose	SQ

Metabolic Effects:

- ↓LDL-C 48%-71%, ↓ non-HDL-C 49%-58%, ↓TC 36%-42%, ↓Apo B 42%-55% by inhibiting PCSK9 binding with LDL-Rs, increasing the number of LDL-Rs available to clear LDL, and lowering LDL-C levels

Main Considerations:

- Require subcutaneous self-injection; refrigeration generally needed
- Overall levels of adverse reactions and discontinuation very low
- Adverse reactions with significantly different rates between drug and placebo were: local injection site reactions and influenza
- The most common adverse reactions had similar rates for drug vs placebo and were not likely caused by the PCSK9 inhibitor. These were:
  - Alirocumab: nasopharyngitis, influenza, urinary tract infections, diarrhea, bronchitis, and myalgia
  - Evolocumab: nasopharyngitis, back pain, and upper respiratory tract infection

Apo=apolipoprotein; HDL-C=High Density Lipoprotein-Cholesterol; LDL-C=low-density lipoprotein cholesterol; LDL-R=low-density lipoprotein receptor; PCSK9=proprotein convertase subtilisin/kexin type 9; TC=total cholesterol.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479-497.

Available PCSK9 Inhibitors

- There are currently two PCSK9 inhibitors on the market
  - Evolocumab[1]
  - Alirocumab[2]
- Current FDA indications for these agents are:
  - Evolocumab:[1]
    - To reduce the risk of MI, stroke, and coronary revascularization in adults with established CVD
    - As an adjunct to diet, alone or in combination with other lipid-lowering therapies (eg, statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce LDL-C
    - As an adjunct to diet and other LDL-lowering therapies (eg, statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional LDL-C lowering
  - Alirocumab:[2]
    - As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD who require additional LDL-C lowering

ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; FDA= Food and Drug Administration; HeFH=heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; PCSK9=proprotein convertase subtilisin/kexin type 9.

1. Repatha (evolocumab) [PI]; 2017; 2. Praluent (alirocumab) [PI] 2018.

Which Patients Are Candidates for PCSK9 Inhibitor Therapy?

AACE Recommendations: Who Should Receive PCSK9 Inhibitors To Treat Dyslipidemia?

- PCSK9 inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH.
  - The use of PCSK9 inhibitors in combination with statins is recommended to lower LDL-C in individuals with FH.
  - Clinical trial data indicate that the use of PCSK9 inhibitors can significantly lower LDL-C compared to placebo (up to 61% in individuals with HeFH and 39% in individuals with HoFH).
- PCSK9 inhibitors should be considered in individuals with clinical CVD who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy.
- The additional ASCVD benefit in very high-risk individuals with further lowering of LDL-C to <55 mg/dL utilizing statin therapy in combination with ezetimibe or a PCSK9 inhibitor forms the basis of the AACE recommendation for a new category of risk, extreme risk.
- PCSK9 inhibitors should not be used as monotherapy except in statin-intolerant individuals

AACE=American Association of Clinical Endocrinologists; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; FH=familial hypercholesterolemia; HeFH= heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; HDL-C=high density lipoprotein-cholesterol; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9. Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479-497.

2018 Guideline on the Management of Blood Cholesterol
AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA

- Consider adding a PCSK9 inhibitor* to maximally tolerated statin + ezetimibe therapy in patients with:
  - Very high ASCVD risk and LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL
  - Severe primary hypercholesterolemia and LDL-C ≥100 mg/dL
- PCSK9 inhibitor + statin therapy ↓LDL-C by 43%-64%
- Clinicians should discuss risks, benefits, and safety of PCSK9 inhibitors with patients prior to initiating therapy

*Long-term (>3 years) safety of PCSK9 inhibitors is uncertain.

AHA=American Heart Association ; ACC=American College of Cardiology; AACVPR=American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA=American Academy of Physician Assistants; ABC=Association of Black Cardiologists; ACPM=American College of Preventive Medicine; ADA=American Diabetes Association; AGS=American Geriatrics Society; APhA=American Pharmaceutical Association; ASPC=American Society for Preventive Cardiology; NLA=National Lipid Association; PCNA=Preventive Cardiovascular Nurses Association; ASCVD=atherosclerotic cardiovascular disease; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9.

Grundy SM, et al. *J Am Coll Cardiol.* 2018; Nov 8. pii:S0735-1097(18)39034-X.

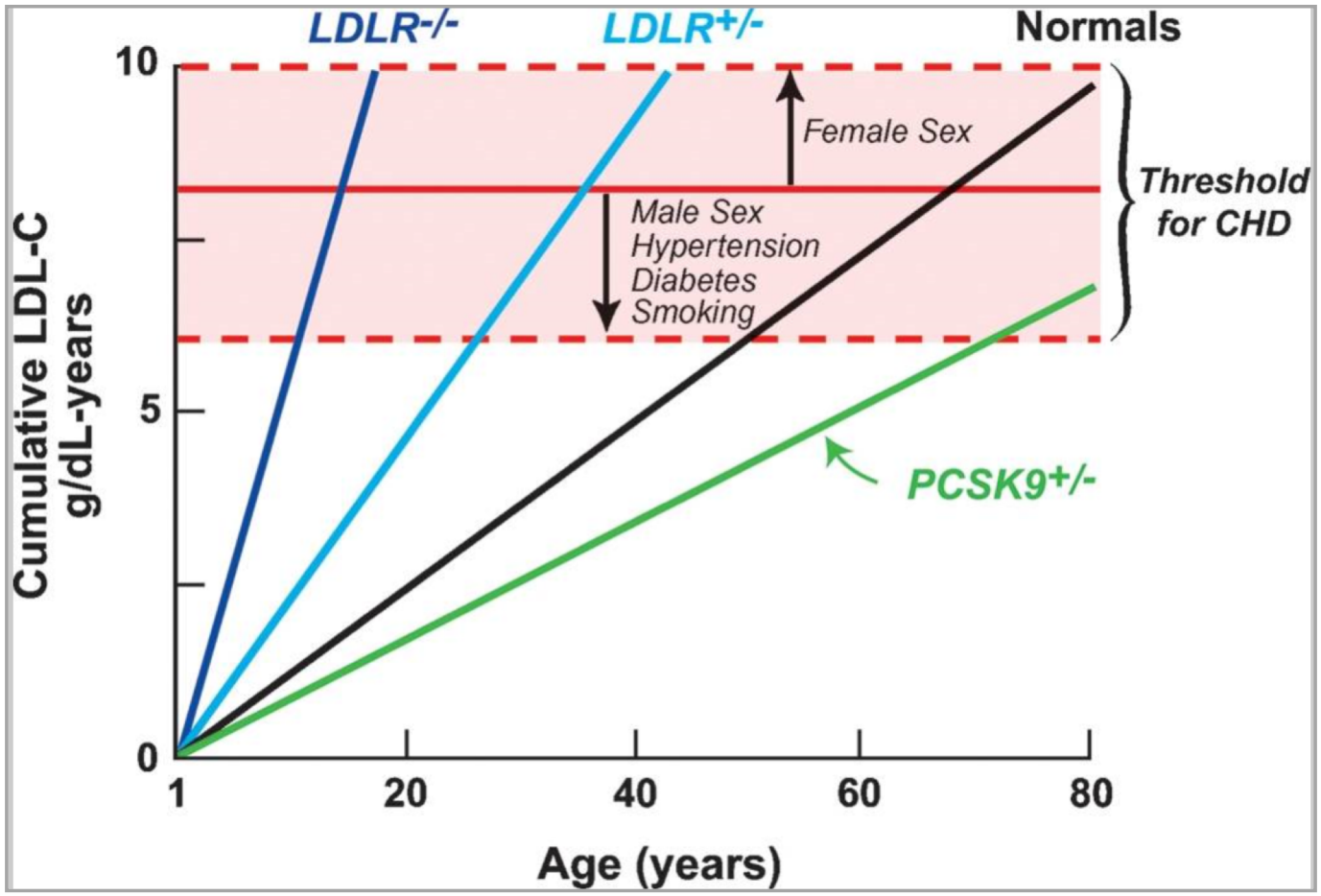
Patient Populations with an Unmet Need for Additional LDL-C Lowering

FH Population[1-4]	High / Very High CV Risk Population[5]	Statin-Intolerant Population[6,7]
• Genetic disorder • High risk of early CHD • HeFH prevalence 1:200 to 1:250 • Untreated LDL-C of 200-400 mg/dL	• Previous MI /stroke / CVD or multiple CV risk factors incl. T2D • Difficult to achieve LDL-C goals, despite current therapies	• 10-15% on high-intensity statins show intolerance • Many discontinue due to muscle pain and/or weakness
79% with HeFH not at goal (<100 mg/dL)	**•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 without further treatment**

CHD=coronary heart disease; CVD=cardiovascular disease; FH=familial hypercholesterolemia; HeFH=heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; PCSK9=proprotein convertase subtilisin/kexin type 9; T2D=type 2 diabetes.

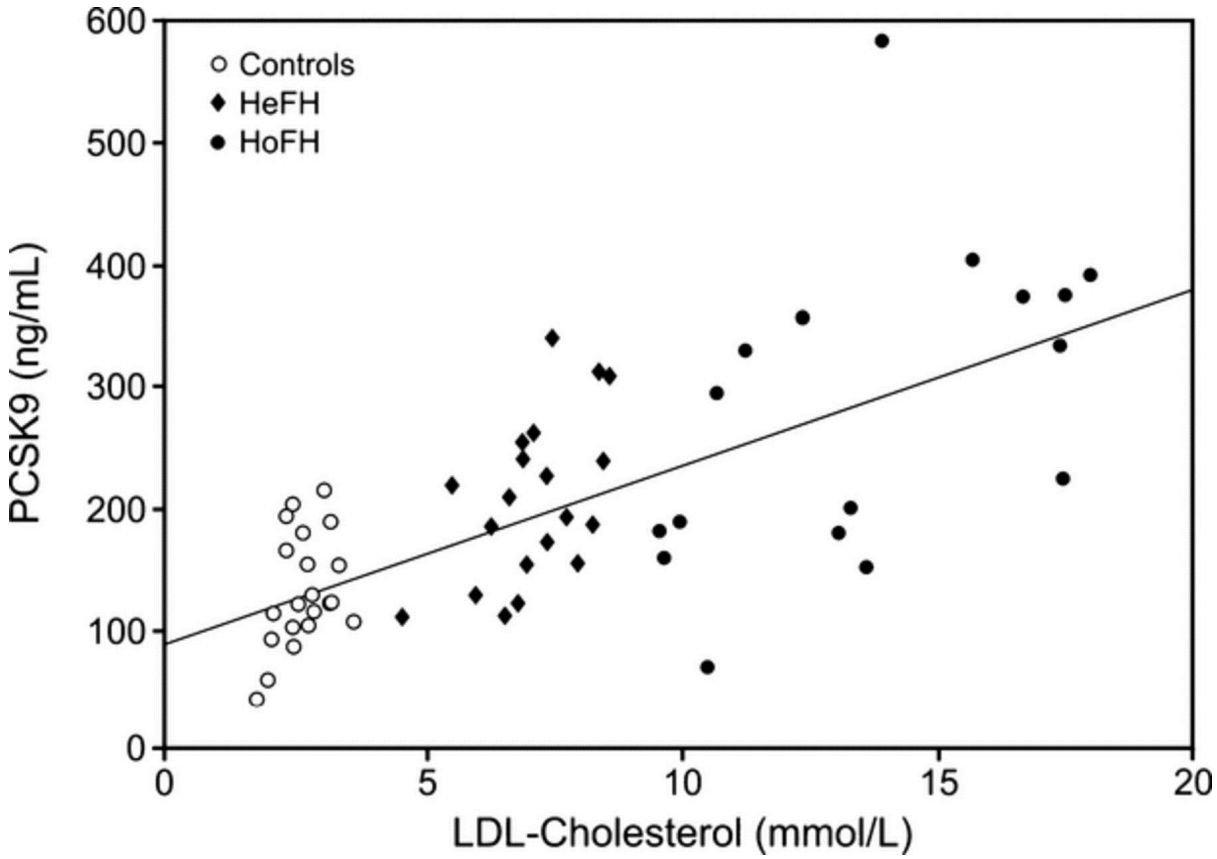
1. Nordestgaard et al. *Eur Heart J. (*2013) 34:3478-90; 2. Sjouke et al. *Eur Heart J.* (in press); 3. Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479-497; 4. Pijlman et al. *Atherosclerosis. (*2010) 209:189-94; 5. Virani et al. *Am Heart J. (*2011) 161:1140-6; 6. Arca et al. *Diabetes Metab Syndr Obes. (*2011) 4:155-66; 7. Krahenbuhl S, et al. *Drugs.* (2016) 76:1-33.

FH: Very High Cholesterol Exposure From Birth Leads To Premature CHD



CHD=coronary heart disease; FH=familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; LDL-R=low-density lipoprotein receptor; *LDL-R-/-* =FH homozygotes; *LDL-R+/-* =FH heterozygotes; PCSK9=proprotein convertase subtilisin/kexin type 9.
Horton et al. *J Lipid Res*. (2009) 50:S172-S177.

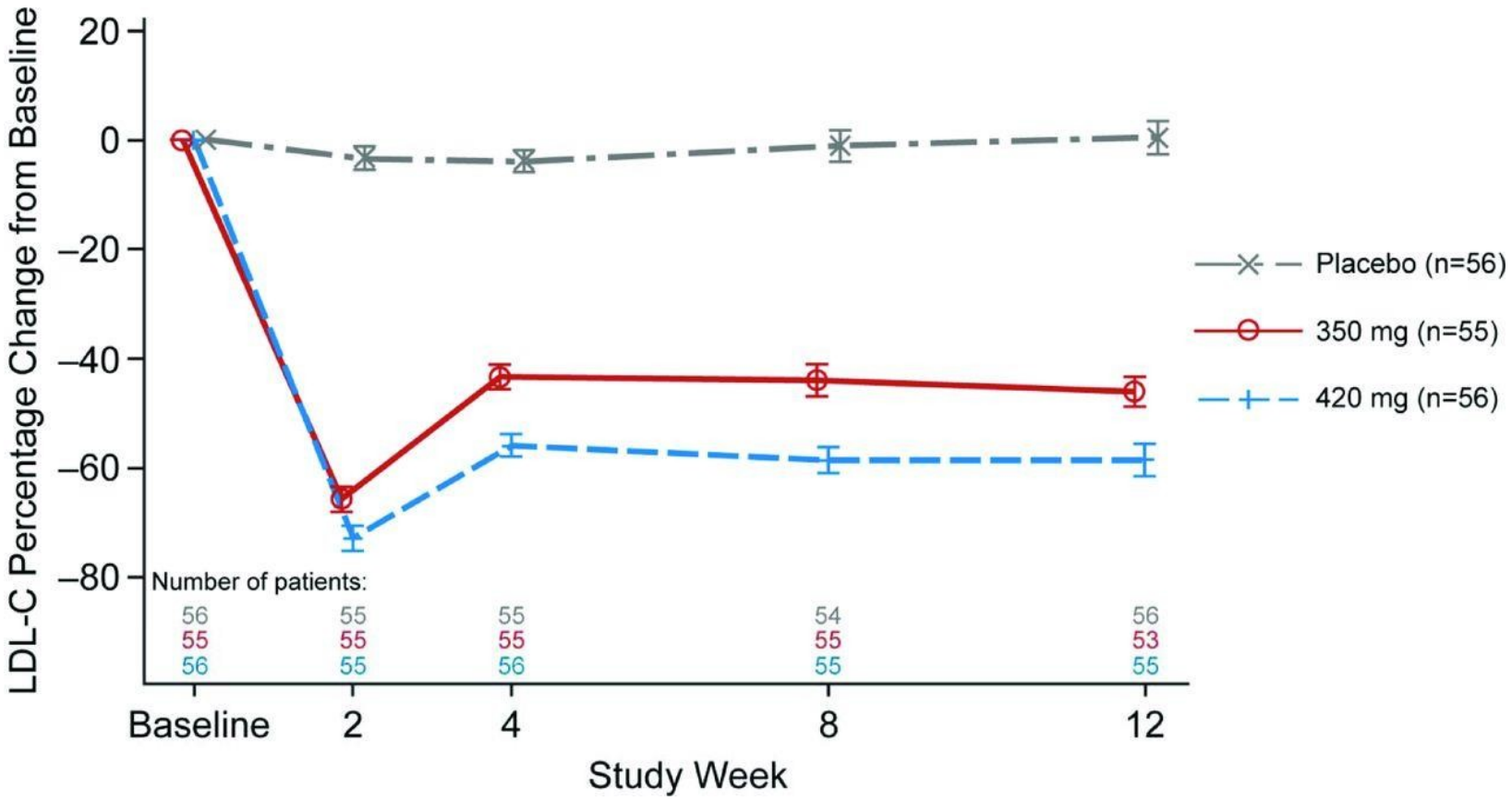
PCSK9 Levels Are Elevated in Familial Hypercholesterolemia



CHD=coronary heart disease; HeFH=heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9.

Raal F et al. *J Am Heart Assoc.* (2013) 2:e000028. doi: 10.1161/JAHA.112.000028.

PCSK9 Inhibition with Evolocumab Lowers LDL-C in HeFH Results From a Phase 2 Study

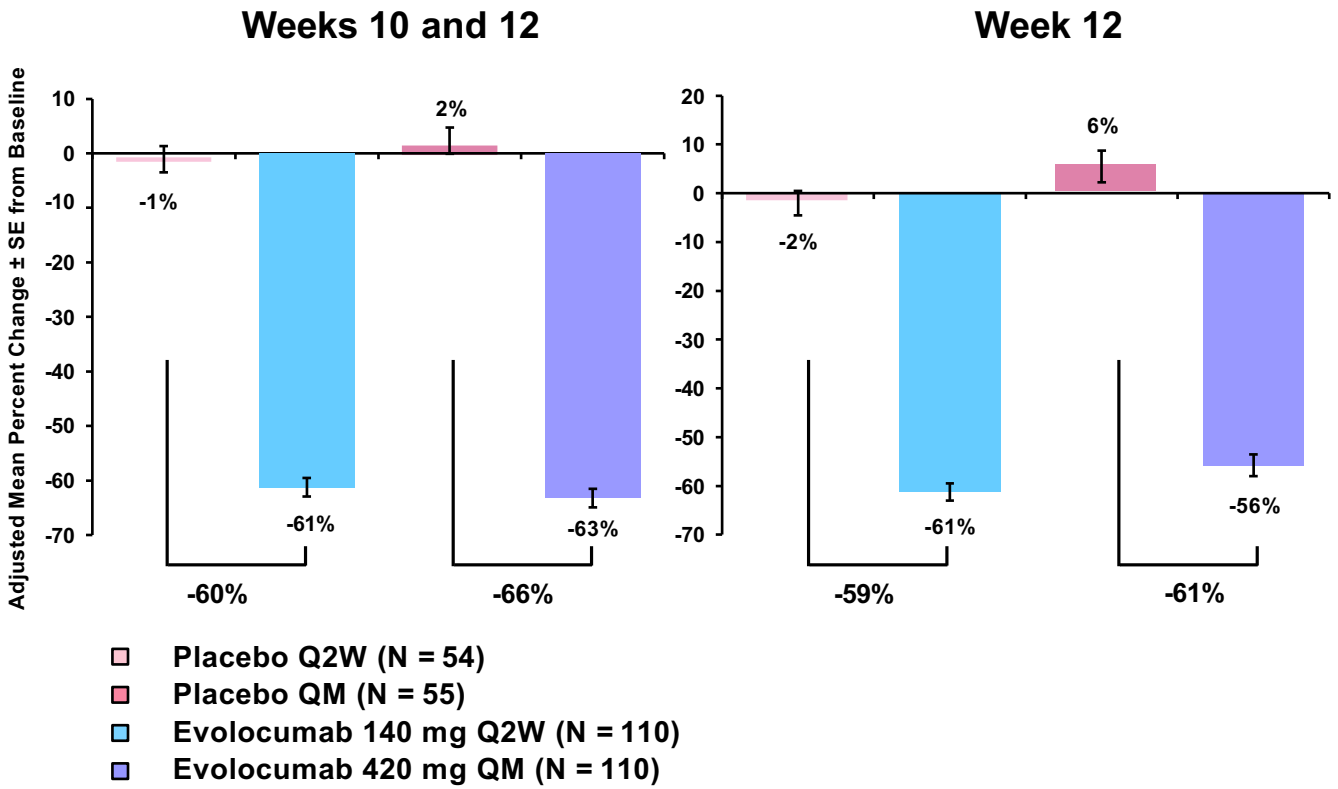


HeFH=heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9.

Raal F, et al. *Circulation.* (2012) Nov 13;126(20):2408-17. doi: 10.1161/CIRCULATIONAHA.112.144055.

RUTHERFORD-2:
PCSK9 Inhibition with Evolocumab in HeFH

Mean % change in LDL-C from baseline to the mean of weeks 10 and 12, and week 12 alone



HeFH=heterozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9; QM=every morning. Raal F, et al. *Lancet.* (2015) 385: 331–40.

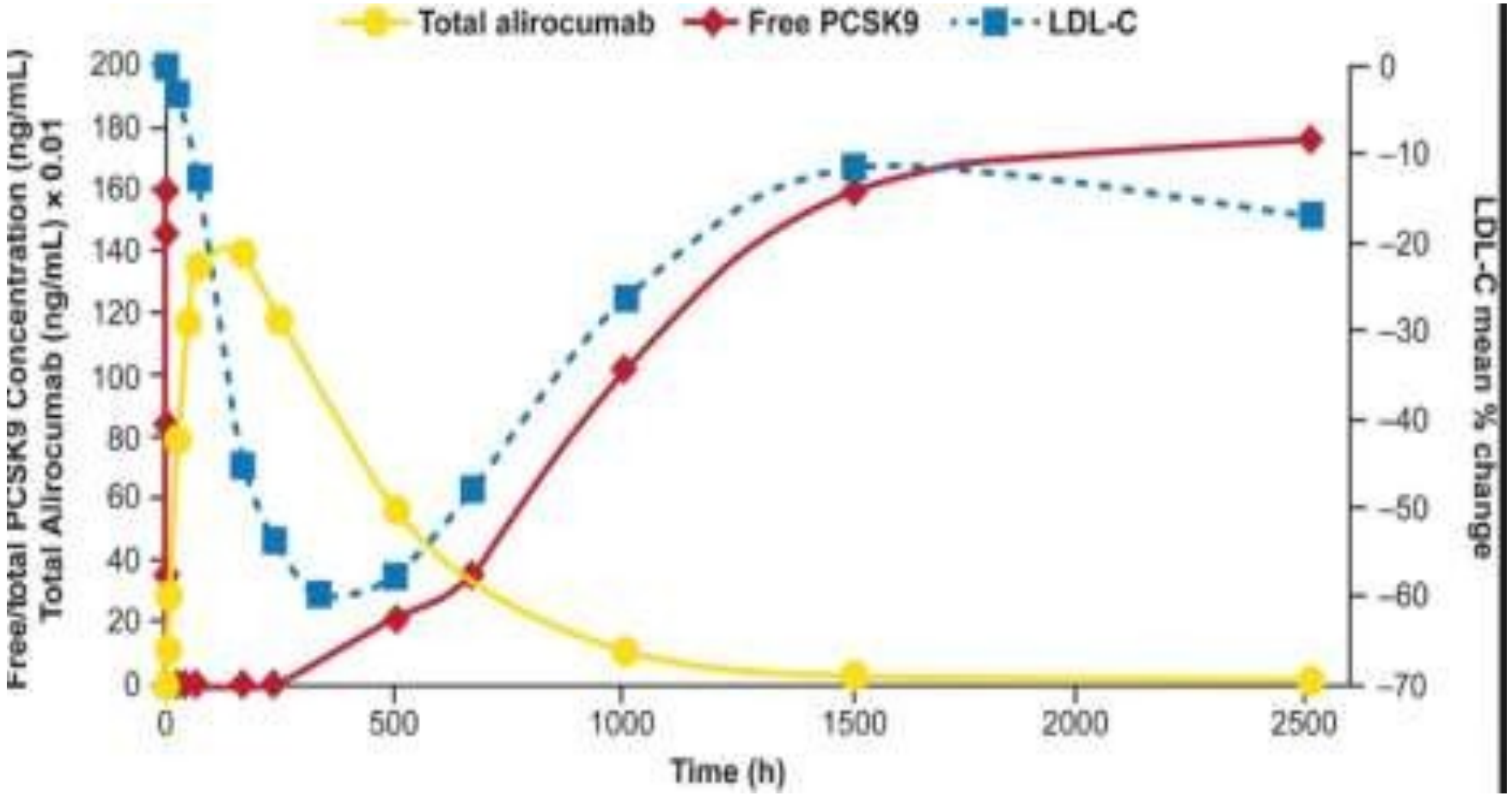
PCSK9 Inhibitors: Efficacy in Other Lipid Parameters

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%

Apo=apolipoprotein; HDL-C=high density lipoprotein-cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9.

Gaudet D, et al. *Am J Cardiol.* (2014) 114:711–715.; Raal, F, et al. *JACC.* (2014) 63:1278-1288; Sabatine M, et al. *N Engl J Med.* (2015) 372:1500-150; Schwartz GG. NEJM. November 2018. DOI: 10.1056/NEJMoa1801174

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



LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9.
Shimada Y, et al. *Eur Heart J. (*2015) Sep 21;36(36):2415-24.

What Major Clinical Trials Have Shaped What We Know About PCSK9 Inhibitor Therapy?

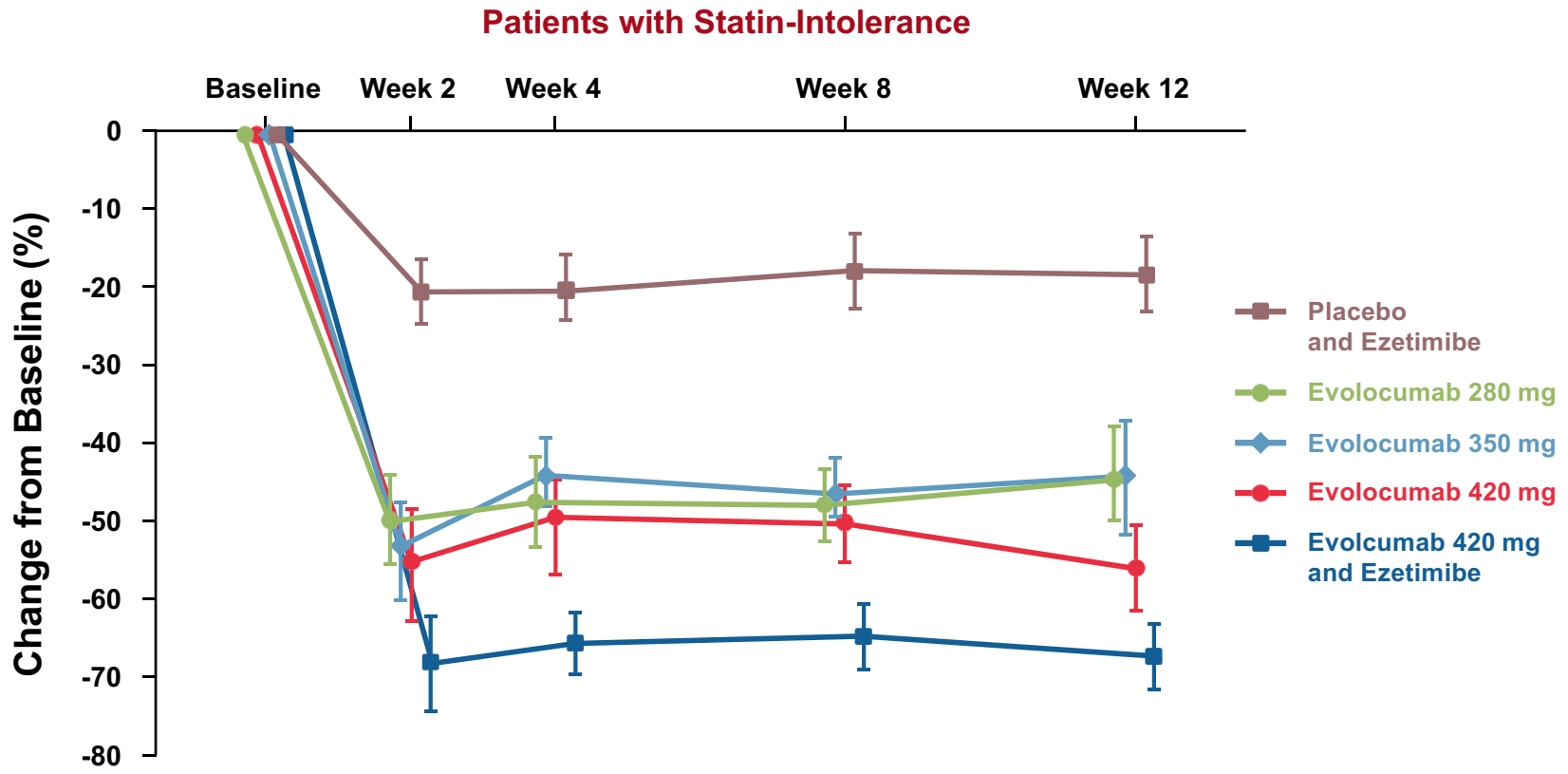
- Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects (GAUSS)
- Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels (MENDEL)
- Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER)
- The ODYSSEY clinical trial program
- Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER)
- EBBINGHAUS – PCSK9 inhibition and cognition
- The Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial
- Clinical trials on PCSK9 inhibition and Lp(a)
  - Effect of Alirocumab on Lipoprotein(a) Concentrations (a Pooled Analysis of 150 mg Every 2 Weeks Dosing from Phase 2 Trials)
  - PROFICIO (Programme to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations)

LDL-C=low-density lipoprotein cholesterol; Lp(a)=lipoprotein(a); PCSK9=proprotein convertase subtilisin/kexin type 9.

1. Koren M,, et al. *Lancet. (*2012) 380(9858):1995-2006; 2. Moriarty P, et al. *J Clin Lipidol. (*2015) 9(6): 758–769. 3. Nicholls S, et al. *JAMA.* (2016) 316:2373-2384; 4. Puri R, et al. *Am Heart J. (*2016)176:83-92; 5. Robinson J, et al. *N Eng J Med.* 2015;372:1489-1499; 6. Sabatine M, et al. *Am Heart J.* (2016) 173:94-101; 7. Sabatine M, et al. *NEJM.* (2017) 376:1713-22; 8. Sabatine M, et al. *N Engl J Med. (*2015) 372:1500-1509; 9. Schwartz et al. *AHJ.* (2014) 168(5):682-689.e1:http://dx.doi.org/10.1016/j.ahj.2014.07.028; 10. Sullivan D, et al. *JAMA*. (2012) 308(23):2497-506.

GAUSS: Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin-Intolerant Subjects

GAUSS: Effect of Evolocumab on Percentage Change in LDL-C From Baseline



GAUSS =Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9.

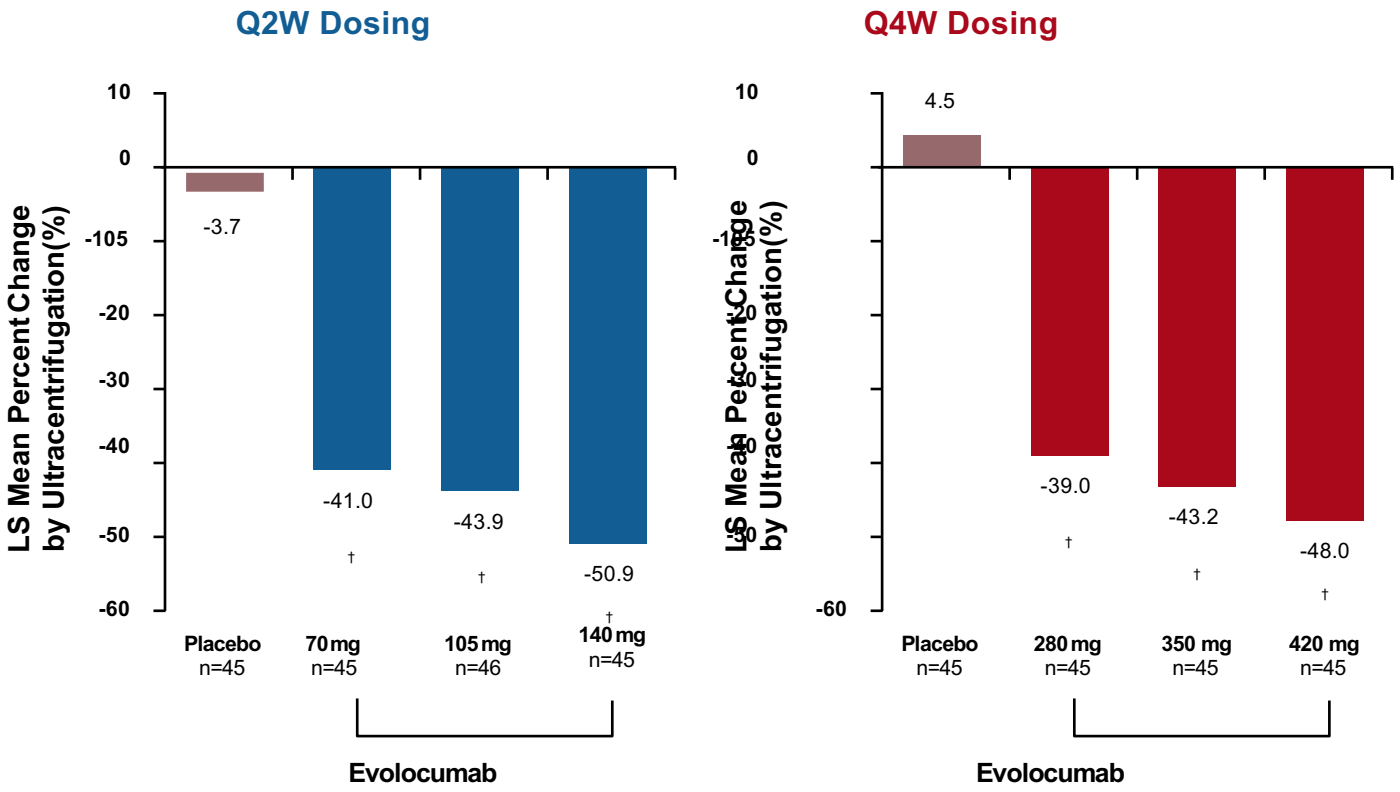
Sullivan D, et al. *JAMA*. (2012) 308(23):2497-506.

MENDEL-2: Monoclonal Antibody Against PCSK9 To Reduce Elevated LDL-C in Patients Currently Not Receiving Drug Therapy for Easing Lipid Levels-2

LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9.

MENDEL-2: Effects of Evolocumab on LDL-C at Week 12

Relative Change in LDL-C from Baseline*



*Primary endpoint; †*P*<0.001 vs placebo.

LDL-C=low-density lipoprotein cholesterol; LS=least squares; MENDEL=Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Patients Currently Not Receiving Drug Therapy For Easing Lipid Levels-2; PCSK9=proprotein convertase subtilisin/kexin type 9; Q2W=once every two weeks; Q4W=once every 4 weeks. Koren M, et al. *Lancet. (*2012) 380(9858):1995-2006.

FOURIER: Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk

PCSK9=proprotein convertase subtilisin/kexin type 9.

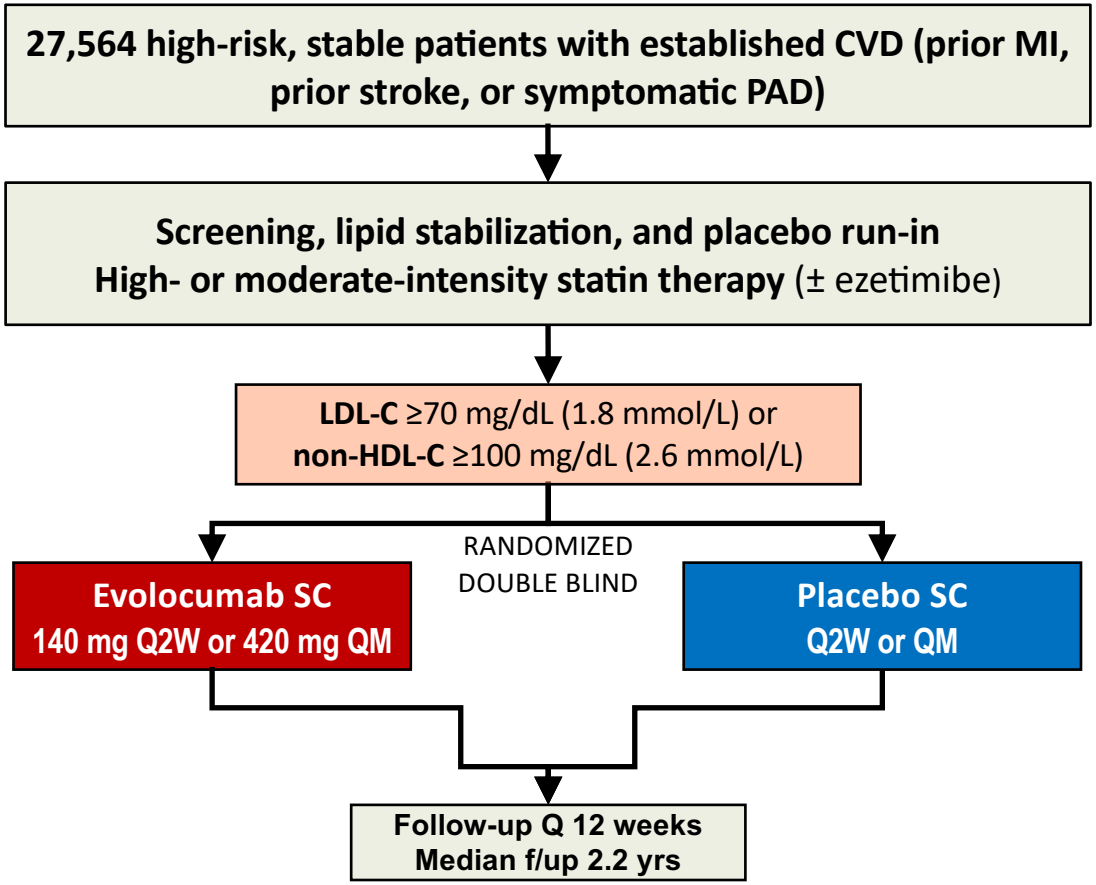
FOURIER Trial: Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk

- This randomized, double-blind, placebo-controlled trial investigated the effects of adding evolocumab to high-intensity statin therapy compared with high-intensity statins alone.
- Median patient follow-up was 2.2 years; study results included data for >27,500 individuals with clinically evident atherosclerotic disease, baseline LDL-C levels ≥70 mg/dL, and HDL-C levels ≥100 mg/dL.
- All study participants were receiving statin therapy with or without ezetimibe, and the evolocumab and placebo groups had the same baseline LDL-C (~92 mg/dL).

FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk; HDL-C=high density lipoprotein-cholesterol; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9.

Sabatine M, et al. *NEJM.* (2017) 376:1713-22.

FOURIER - Evolocumab vs Placebo



CVD=cardiovascular disease; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk; HDL-C=high density lipoprotein-cholesterol; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; PAD=peripheral artery disease; Q=dosage; Q2W=once every two weeks; QM=every morning; SC=subcutaneous.

Sabatine M, et al. *Am Heart J.* (2016) 173:94-101.

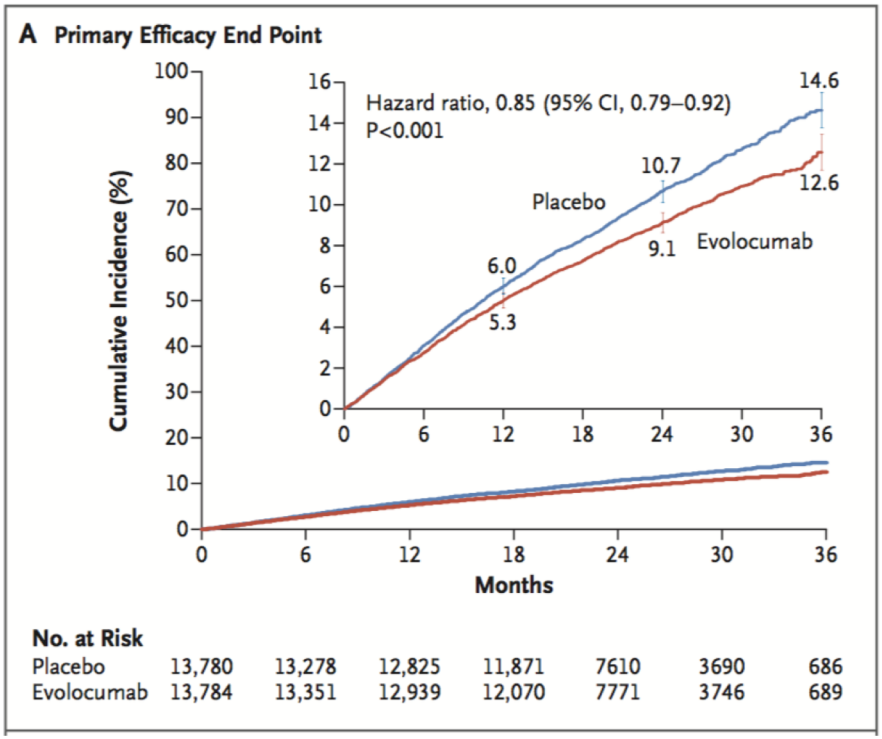
FOURIER Primary and Secondary Endpoints

- At 26 months, extremely tight lipid control with evolocumab led to a 15% decrease in risk for the primary composite endpoint and 20% decrease in risk for the secondary composite endpoint
  - Primary composite endpoint: MI, CV death, stroke, coronary revascularization, or hospitalization for unstable angina
  - Secondary composite endpoint: CV death, MI, or stroke
- Beyond the second year of follow-up, risk reduction increased to 20% for the primary endpoint and 25% for the secondary endpoint
- At 26 months, very tight lipid control reduced the risk of MI by 27%, stroke by 21%, and coronary revascularization by 22%

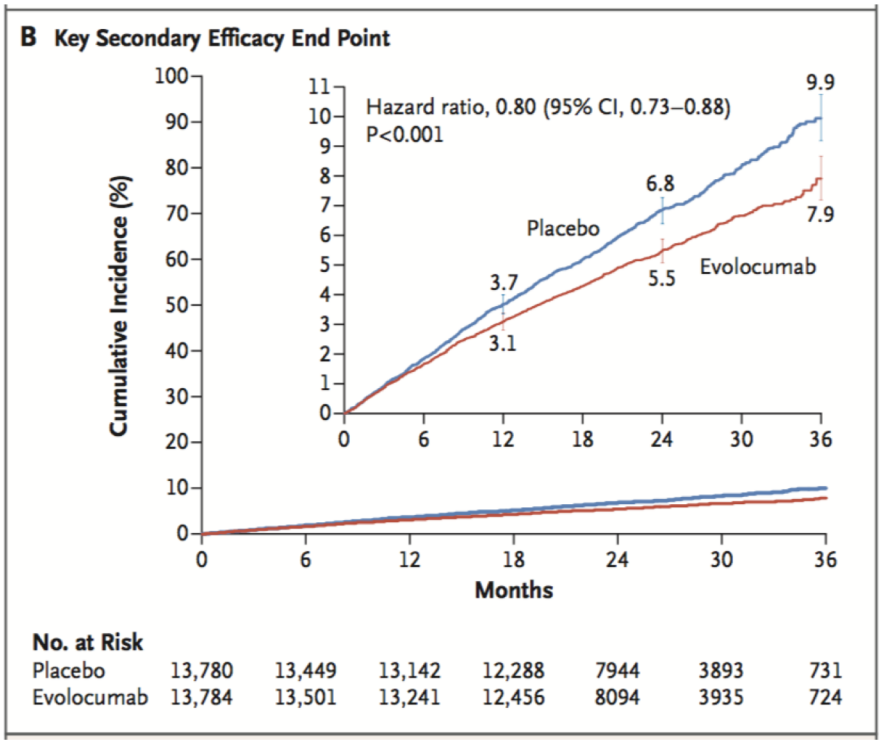
CV=cardiovascular; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; PCSK9=proprotein convertase subtilisin/kexin type 9.

Sabatine M, et al. *NEJM.* (2017) 376:1713-22.

FOURIER Evolocumab Study Endpoints



Cumulative event rates for the primary efficacy endpoint (Composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)



Cumulative rates for the key secondary efficacy endpoint (Composite of CV death, MI, or stroke)

CI=confidence interval; CV=cardiovascular; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; PCSK9=proprotein convertase subtilisin/kexin type 9. Sabatine M, et al. *NEJM.* (2017) 376:1713-22.

FOURIER Evolocumab Study Outcomes

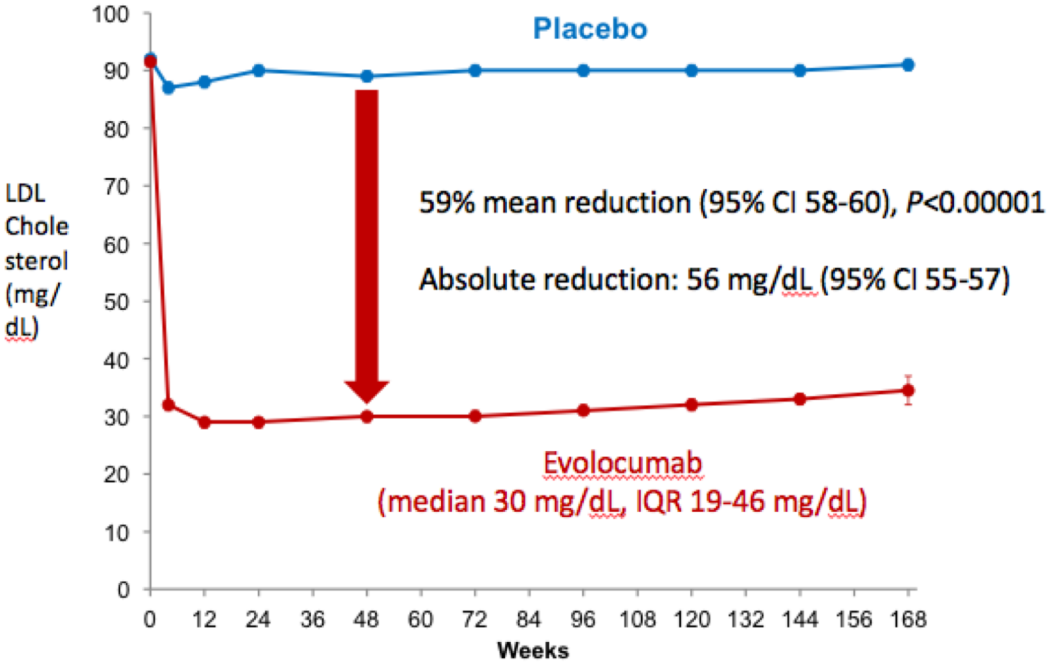
Outcome	Hazard Ratio (95% CI)	
	In first year	Beyond first year
Primary end point	0.88 (0.80-0.97)	0.81 (0.73-0.89)
Key secondary end point	0.84 (0.74-0.96)	0.75 (0.66-0.85)
Cardiovascular death	0.96 (0.74-1.25)	1.12 (0.88-1.42)
Myocardial infarction	0.80 (0.68-0.94)	0.65 (0.55-0.77)
Hospitalization for unstable angina	0.97 (0.77-1.22)	0.99 (0.75-1.30)
Stroke	0.83 (0.63-1.08)	0.76 (0.60-0.97)
Coronary revascularization	0.84 (0.74-0.96)	0.72 (0.63-0.82)

Primary endpoint: CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization

Secondary endpoint: CV death, MI, or stroke

CI=confidence interval; CV=cardiovascular; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; PCSK9=proprotein convertase subtilisin/kexin type 9.
Sabatine M, et al. *NEJM.* (2017) 376:1713-22.

FOURIER Evolocumab Study
LDL-C Levels Over Time



No. at Risk

Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768

Absolute difference (mg/dL)	54	58	57	56	55	54	52	53	50
Percentage difference	57	61	61	59	58	57	55	56	54
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

CI=confidence interval; CV=cardiovascular; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk; IQR=interquartile range; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; PCSK9=proprotein convertase subtilisin/kexin type 9.

Sabatine M, et al. *NEJM.* (2017) 376:1713-22.

ODYSSEY CLINICAL TRIAL PROGRAM

ODYSSEY OUTCOMES TRIAL

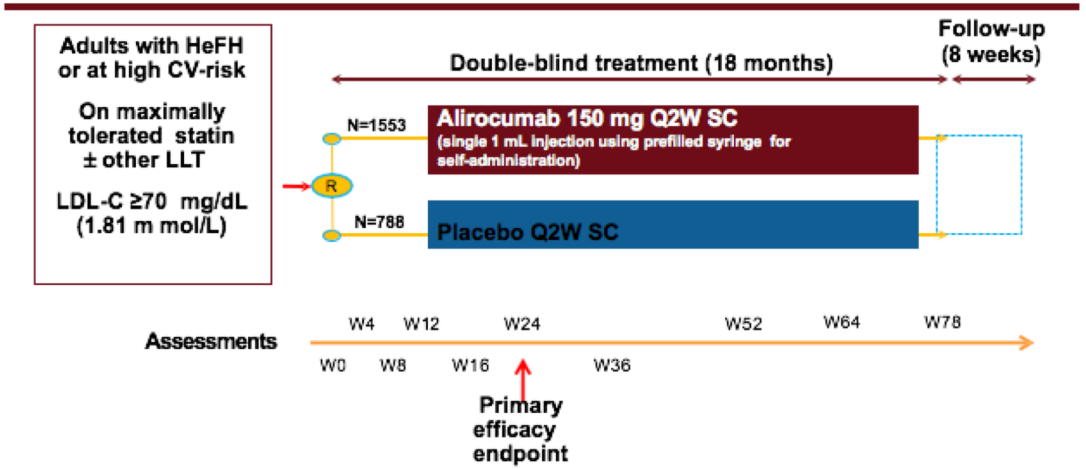
- ODYSSEY Outcomes trial was an international, multicenter, randomized, double-blind, placebo-controlled study investigating the use of alirocumab vs placebo in patients receiving statins and with inadequate lipid control
  - Inadequate lipid control defined as LDL-C≥70 mg/dL (1.81 mmol/L), non-HDL-C≥100 mg/dL (2.59 mmol/L), or apo B≥80 mg/dL
- The trial randomized 18,924 patients to receive either alirocumab or placebo
- All patients had a recent ACS event within 1 year of randomization
- Median follow-up was 34 months
- **Overall 15% reduction in MACE and all-cause death**
  - In subgroup with LDL>100 mg/dL, MACE was reduced by 24% and all-cause death by 29%
- Full ODYSSEY data were presented at the American College of Cardiology (ACC) Annual Scientific Session in Orlando, Florida, March 10, 2018, and are not yet published
  - No diabetic subgroup data is available

Apo=apolipoprotein; ACS=acute coronary syndrome; HDL-C=high density lipoprotein-cholesterol; LDL-C=low-density lipoprotein cholesterol; MACE=major adverse cardiac event.

Schwartz et al. *AHJ.* (2014) 168(5):682-689.e1:http://dx.doi.org/10.1016/j.ahj.2014.07.028.

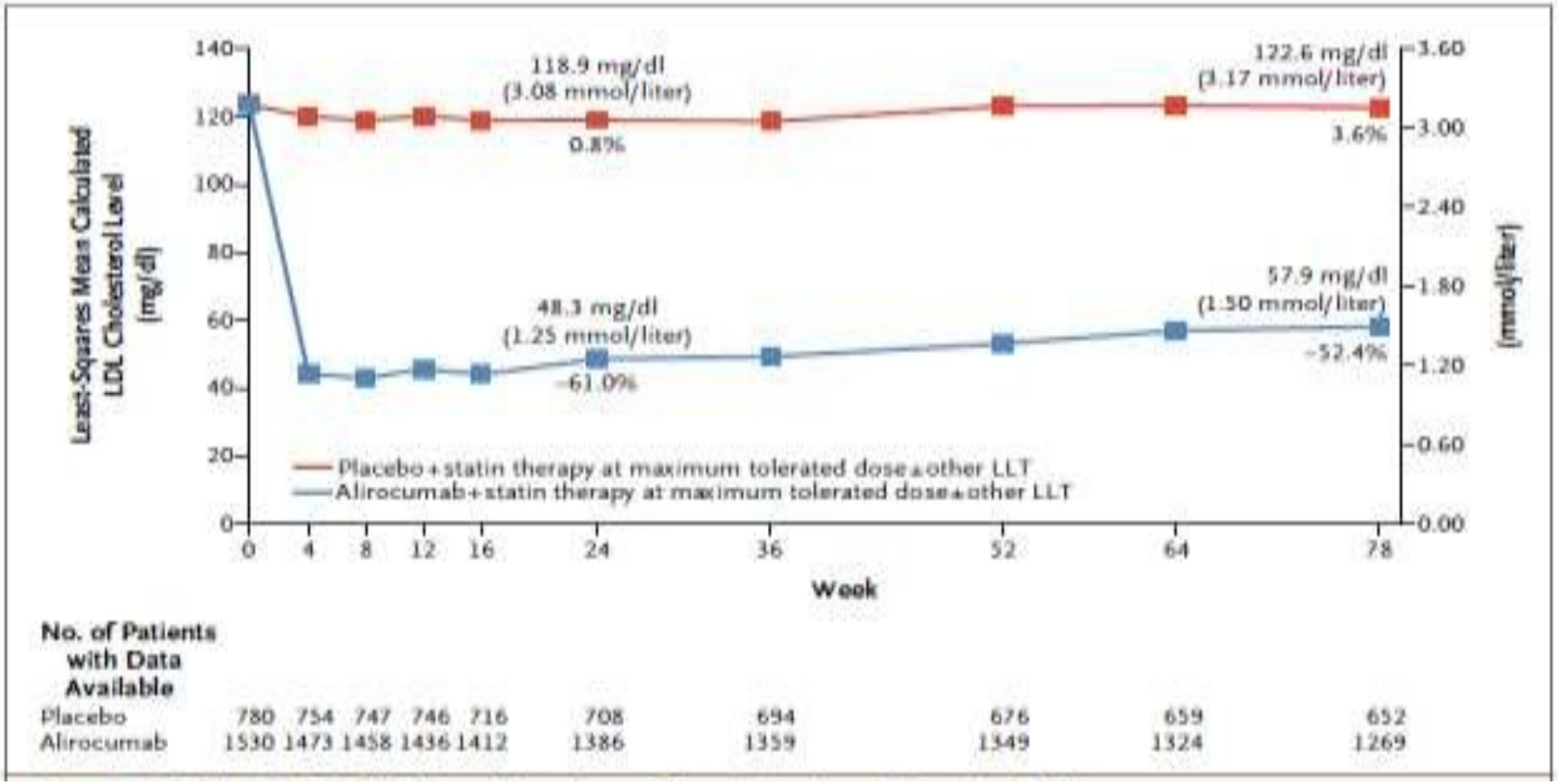
ODYSSEY LONG TERM TRIAL
Study Design

- This phase 3, randomized, double-blind, placebo-controlled, parallel-group, multinational study investigated the use of alirocumab vs placebo in individuals at high risk for CV events
  - All individuals were receiving statins and had inadequate lipid control
  - Inadequate lipid control was defined as LDL-C ≥70 mg/dL (1.81 mmol/L)
- All individuals had heterozygous FH or established CHD (or a CHD risk equivalent), and baseline LDL-C levels ≥70 mg/dL
- The trial randomized 1553 individuals to receive alirocumab and 788 to placebo
- Mean follow-up was 80.9 weeks for the alirocumab group and 80.1 weeks for the placebo group
- Mean baseline LDL-C levels were similar in the alirocumab and placebo groups (122.7±42.6 and 121.9±41.4, respectively)



CHD=coronary heart disease; CV=cardiovascular; FH=familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; LLT=lipid lowering therapy; PCSK9=proprotein convertase subtilisin/kexin type 9; SC=subcutaneous; W=week.
Robinson J, et al. *N Eng J Med. (*2015) 372:1489-1499.

ODYSSEY LONG TERM: LDL-C Reductions



LDL-C=low-density lipoprotein cholesterol; LLT=lipid lowering therapy.
Robinson J, et al. *N Eng J Med. (*2015) 372:1489-1499.

ODYSSEY LONG TERM: Treatment-Emergent Adverse Events 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)

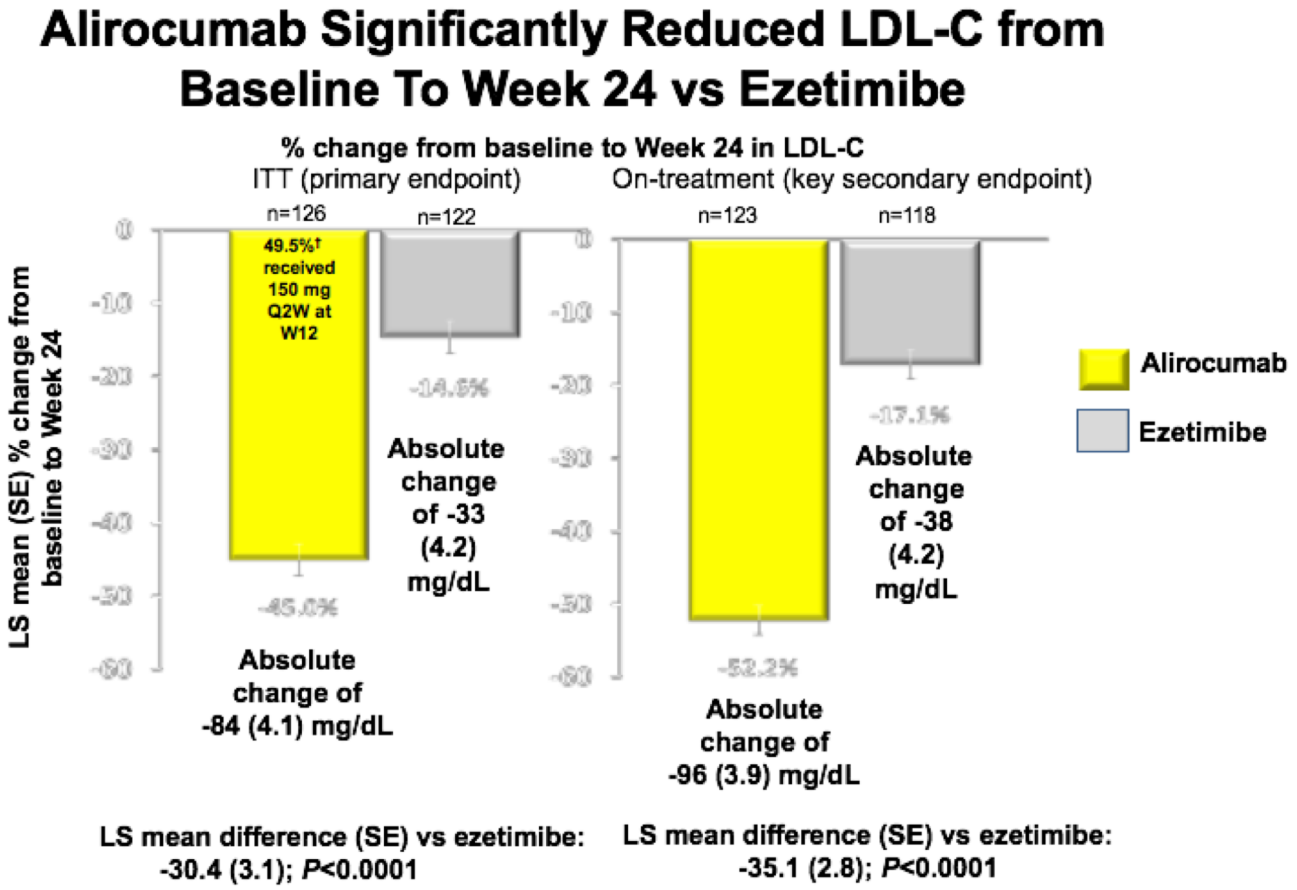
Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)

* Alirocumab is not licensed in EU

AE=adverse events; LDL-C=low-density lipoprotein cholesterol; W=week.

Robinson J, et al. *N Eng J Med.* (2015) 372:1489-1499.

ODYSSEY ALTERNATIVE TRIAL



ITT=insulin tolerance test; LDL-C=low-density lipoprotein cholesterol; LLT=lipid lowering therapy; LS=least squares; SE=standard error; W=week.
Moriarty P, et al. *J Clin Lipidol. (*2015) 9(6): 758–769.

OSLER: Open-Label Study of Long-Term Evaluation against LDL Cholesterol

LDL-C=low-density lipoprotein cholesterol.

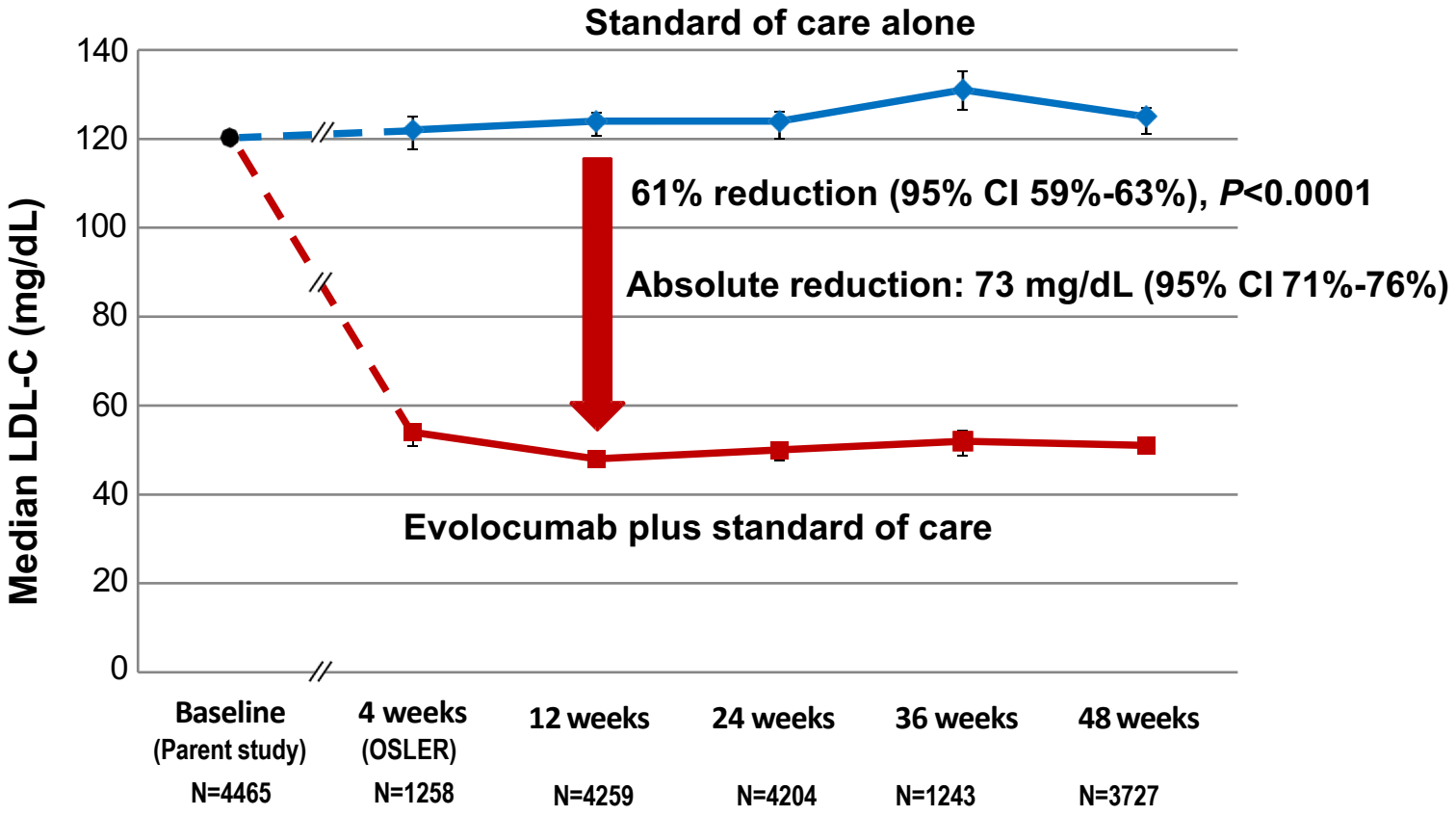
OSLER Trial Design

- OSLER-1 and OSLER-2 trials collected long-term data on safety, side-effect profile, and LDL-C reductions in patients who participated in phase 2 and phase 3 clinical trials, respectively.
- Regardless of the previous clinical trial study group, OSLER study patients were randomized to receive standard therapy or standard therapy plus evolocumab.
- The primary endpoint for both OSLER trials was the incidence of adverse events; the secondary endpoint was change in LDL-C levels.
    - The study also reported non–HDL cholesterol, total cholesterol, TGs, HDL-C, apolipoproteins A1 and B, and lipoprotein(a).
- Median patient follow-up was 11.1 months; study results included data for 4465 patients.
- Data were reported in a single pooled analysis.

HDL-C=high density lipoprotein-cholesterol; LDL-C=low density lipoprotein-cholesterol; OSLER=Open-Label Study of Long-Term Evaluation against LDL Cholesterol; TG=triglyceride.

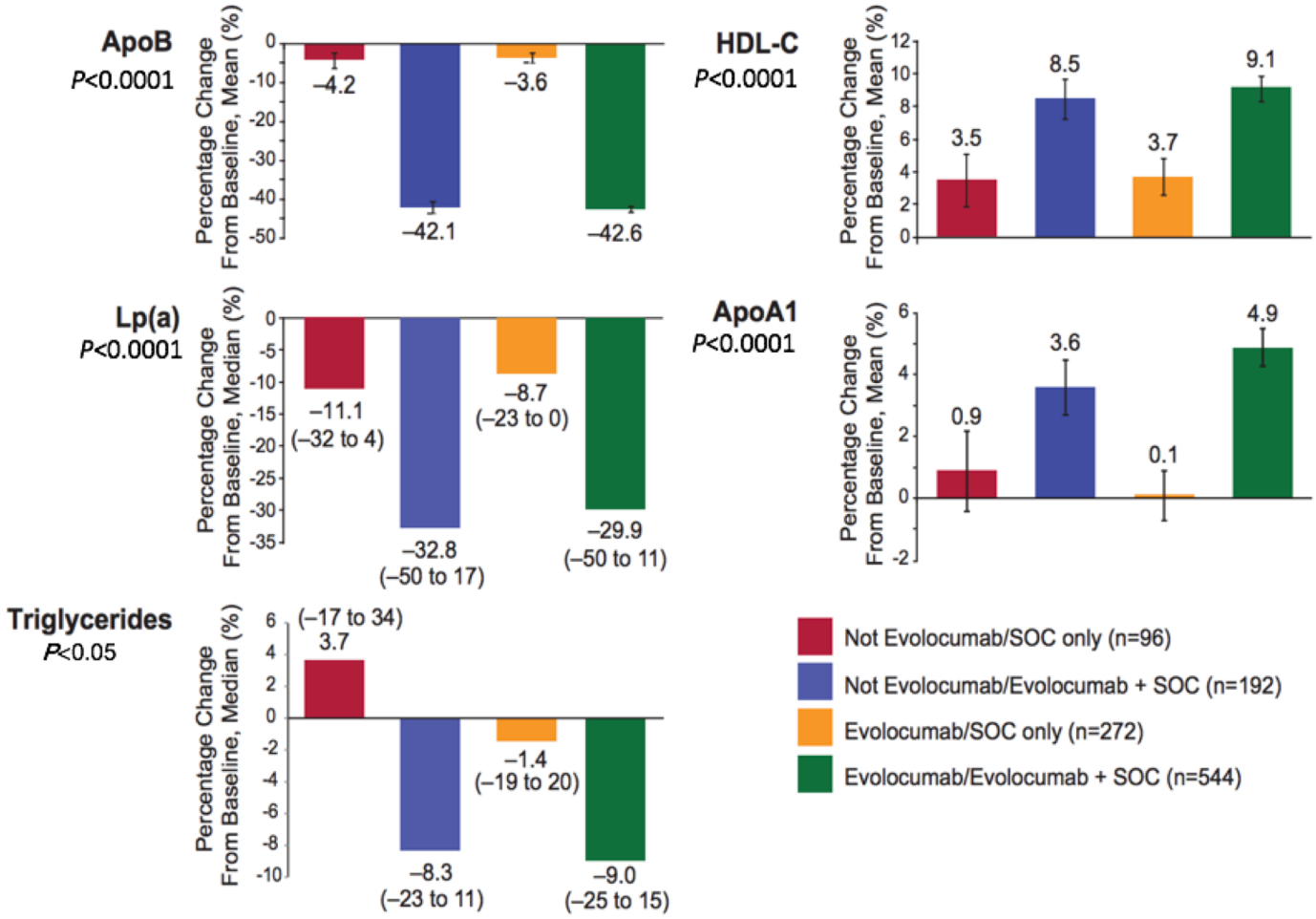
Sabatine M, et al. *N Engl J Med.* (2015) 372:1500-1509.

OSLER Trial: Effect of Evolocumab on LDL-C



CI=confidence interval; HDL-C=high density lipoprotein-cholesterol; LDL-C= low density lipoprotein-cholesterol; OSLER=Open-Label Study of Long-Term Evaluation against LDL Cholesterol.
Sabatine M, et al. *N Engl J Med.* (2015) 372:1500-1509.

OSLER: Effect of Evolocumab on Other Lipid Parameters at 1 Year



Apo=apolipoprotein; HDL-C=high density lipoprotein-cholesterol; Lp(a)=lipoprotein(a); SOC=standard of care.

Koren M, et al. *Circulation.* (2014) Jan 14;129(2):234-43.

EBBINGHAUS: Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects

EBBINGHAUS Trial Design

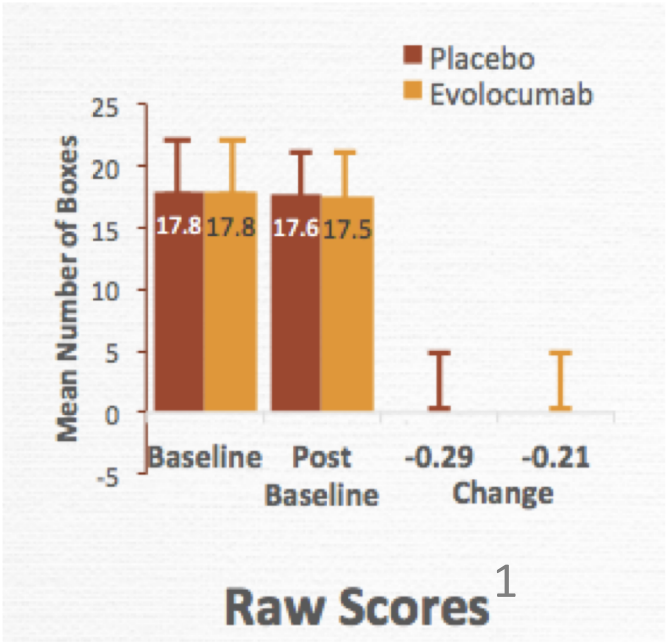
- The EBBINGHAUS trial was the first prospectively designed study to evaluate the relationship between PCSK9 inhibition and changes in cognition, including memory, attention, and reaction time.
- EBBINGHAUS was a prospective subgroup analysis of FOURIER trial participants; participants could be enrolled in EBBINGHAUS up to 12 weeks following the start of FOURIER participation; study centers were encouraged to enroll eligible participants prior to FOURIER treatment initiation.
    - Patients with dementia or a history of any cognitive dysfunction were excluded.
- The primary endpoint was the score on the spatial working memory strategy index of executive function, a principal component of the Cambridge Neuropsychological Test Automated Battery.
- 1204 patients were followed for a median of 19 months.

EBBINGHAUS=Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects; FOURIER= Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; PCSK9=proprotein convertase subtilisin/kexin type .
Giugliano R, et al. *N Engl J Med. (*2017) Aug 17;377(7):633-643.

EBBINGHAUS Study Outcomes

N=1204 patients from FOURIER Study, followed for 96 weeks[1,2]

- The mean change in the primary endpoint of executive function, as measured by the Spatial Working Memory strategy index (from the Cambridge Neuropsychological Test Automated Battery), was -0.29 with placebo and -0.21 with evolocumab (*P*<0.0001 for noninferiority)[1,3,4]
- All secondary outcomes were similar for placebo and evolocumab, including patient self-reports and investigator-reported cognitive adverse events[1,3,4]



EBBINGHAUS=Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; PCSK9=proprotein convertase subtilisin/kexin type.

1. Giugliano R, et al. *N Engl J Med. (*2017) Aug 17;377(7):633-643.
2. U.S. National Library of Medicine. EBBINGHAUS 2014. https://clinicaltrials.gov/ct2/show/NCT02207634;
3. American College of Cardiology Foundation. ACC News Story 2017. http://www.acc.org/latest-in-cardiology/articles/2017/03/13/17/44/sat-8am-ebbinghaus-cognitive-study-of-patients-enrolled-in-fourier-acc-2017?w_nav=LC;
4. American College of Cardiology. EBBINGHAUS 2017. https://challengesincardiology.com/ebbinghaus-a-cognitive-study-of-patients-enrolled-in-the-fourier-trial.

GLAGOV: Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured By Intravascular Ultrasound

GLAVOV: Study Trial Design

- GLAVOV was a multicenter, double-blind, placebo-controlled, randomized clinical trial that investigated the effects of evolocumab on the progression of coronary atherosclerosis in patients who underwent statin-treatment.
- The primary efficacy endpoint was the nominal change in PAV from baseline to week 78
- All participants were ≥18 years old and had ≥1 epicardial coronary stenosis of ≥20% on clinically indicated coronary angiography, as well as a target vessel suitable for imaging with ≤50% visual obstruction
- Participants were receiving statins for at least 4 weeks prior to enrollment and had:
  - LDL-C ≥80 mg/dL (at least 75% of the patient cohort)
  - LDL-C >60 mg/dL with 1 major or 3 minor CV risk factors (limited to 25% of patient cohort)
- The study included 968 patients, 846 of whom had evaluable imaging at the 78-week follow-up

CV=cardiovascular; GLAVOV=Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured By Intravascular Ultrasound; LDL-C=low density lipoprotein-cholesterol; PAV=premature atrial contractions; PCSK9=proprotein convertase subtilisin/kexin type 9.
Nicholls S, et al. *JAMA.* (2016) 316:2373-2384.

GLAGOV: Baseline Characteristics of Randomized Patients

Parameter*	Placebo (N = 484)	Evolocumab (N = 484)
Age, years	59.8±8.8	59.8±9.6
Men, n (%)	350 (72.3)	349 (72.1)
White, n (%)	452 (93.4)	456 (94.2)
BMI	29.5±5.0	29.4±5.0
Hypertension, n (%)	405 (83.7)	398 (82.2)
Previous PCI, n (%)	188 (38.8)	189 (39.0)
Previous MI, n (%)	171 (35.3)	169 (34.9)
Smoking, n (%)	113 (23.3)	124 (25.6)
Diabetes, n (%)	104 (21.5)	98 (20.2)
Baseline statin use,* n (%)	476 (98.3)	478 (98.8)
High intensity†, n (%)	290 (59.9)	280 (57.9)
Moderate intensity, n (%)	185 (38.2)	196 (40.5)
Low intensity, n (%)	1 (0.2)	2 (0.4)
Baseline ezetimibe use,* n (%)	9 (2.1)	9 (2.1)
Baseline medications		
Anti-platelet therapy, n (%)	465 (96.1)	454 (93.8)
Beta-blocker, n (%)	370 (76.4)	362 (74.8)
ACE inhibitor, n (%)	264 (54.5)	260 (53.7)
ARB, n (%)	92 (19.0)	87 (18.0)

Age and BMI expressed as mean ± standard deviation. *Baseline statin and ezetimibe use is defined as subject treated with statin or ezetimibe therapy at the end of the lipid stabilization period at randomization. †High intensity statin as defined by ACC/AHA criteria

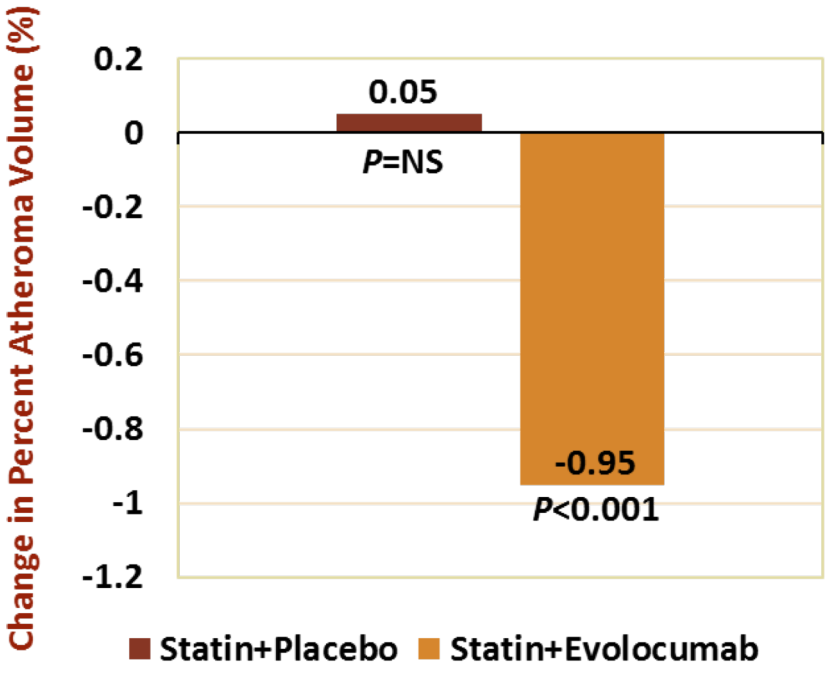
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

ARB=angiotensin receptor blockers; ACE=angiotensin-converting enzyme; BMI=body mass index; GLAVOV=Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured By Intravascular Ultrasound; MI=myocardial infarction; PCI=percutaneous coronary intervention.
Nicholls S, et al. *JAMA.* (2016) 316:2373-2384.

GLAGOV: Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured By Intravascular Ultrasound

Trial design: Individuals with CAD and elevated LDL-C on statin therapy were randomized to SQ evolocumab (n=484) vs SQ placebo (n=486).

Primary Endpoint: Percent Atheroma Volume



Results

- Nominal change in percent atheroma volume at 78 weeks: -0.95% in the evolocumab group vs 0.05% in the placebo group (*P*<0.001 for between-group comparison)
- Individuals with plaque regression: 64.3% with evolocumab vs 47.3% with placebo (*P*<0.001)
- Major adverse cardiac events: 12.2% with evolocumab vs 15.3% with placebo

Conclusions

- Among patients with angiographic evidence of CAD on chronic statin therapy, evolocumab resulted in a greater change in percent atheroma volume and a greater proportion of patients with plaque regression

CAD=coronary artery disease; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9; SQ=subcutaneous.Nicholls S, et al. *JAMA.* (2016) 316:2373-2384.

GLAGOV: Biochemical Measurements for Total Cholesterol, LDL-C, Lp(a), and hs-CRP

Parameter	Baseline		On-treatment			Absolute Change (95% CI)		
	Placebo (n = 484)	Evolocumab (n = 484)	Placebo (n = 484)	Evolocumab (n = 484)	P-Value*	Placebo (n = 484)	Evolocumab (n = 484)	P-Value*
Total cholesterol, mg/dL mean (95%CI)	166.2 (163.1 to 169.2)	166.1 (163 to 169.2)	169.1 (166.3 to 172)	108.6 (160 to 111.3)	< 0.001	1.8 (-2.0 to 5.6)	-59.0 (-62.8 to -55.2)	< 0.001
LDL-C, mg/dL† mean (95%CI)	92.4 (90 to 94.8)	92.6 (90.1 to 95.0)	93.0 (90.5 to 95.4)	36.6 (34.5 to 38.8)	< 0.001	0.2 (-2.9 to 3.4)	-56.3 (-59.4 to -53.1)	< 0.001
Lp(a), mg/dL median (IQR)	10.9 (3.9 to 50.7)	12.1 (4.6 to 57.1)	8.9 (3.9 to 48.1)	7.1 (2.5 to 46.7)	0.07	-1.0 (-2.2 to 0.2)	-7.8 (-9.0 to -6.6)	< 0.001
hs-CRP (mg/L) median (IQR)‡	1.6 (0.8 to 3.4)	1.6 (0.8 to 3.4)	1.4 (0.7 to 3.0)	1.4 (0.7 to 3.0)	0.47	-0.3 (-1.3 to 0.6)	-0.4 (-1.3 to 0.6)	0.35

Note: On-treatment laboratory parameters are the time-weighted averages (95% CIs) of all post-baseline values, and estimates are derived from an analysis of variance model with factors for treatment group and region. Baseline and time-weighted average on-treatment values and absolute changes of laboratory measures and blood pressure of patients treated with placebo or evolocumab with evaluable imaging at baseline and follow-up. Results expressed as mean (95% CI) at baseline and least-squares mean (95% CI) for on-treatment values.

*P-value for between-treatment group comparison. †When the calculated LDL-C level is less than 40 mg/dL or triglyceride level is greater than 400 mg/dL, ultracentrifugation LDL-C was determined from the same blood sample. ‡Tested using Wilcoxon rank-sum test. Final measurements are used for on-treatment values. Absolute changes are presented as least-squares means (95% CIs).

LDL-C = low-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein(a)

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

CI=confidence interval; hs-CRP=high-sensitivity C-reactive protein; GLAGOV=Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured By Intravascular Ultrasound; IQR=interquartile range; LDL-C=low-density lipoprotein cholesterol; Lp(a)=lipoprotein(a); PCSK9=proprotein convertase subtilisin/kexin type 9. Nicholls S, et al. *JAMA*. (2016) 316(22):2373-2384.

GLAGOV: Biochemical Measurements for HDL-C, TG, Apo A, and Apo B

Parameter	Baseline		On-treatment			Absolute Change (95% CI)		
	Placebo (n = 484)	Evolocumab (n = 484)	Placebo (n = 484)	Evolocumab (n = 484)	P-Value*	Placebo (n = 484)	Evolocumab (n = 484)	P-Value*
HDL-C, mg/dL mean (95%CI)	45.4 (44.2 to 46.5)	46.7 (45.5 to 47.8)	47.1 (46.0 to 48.2)	51.0 (49.8 to 52.1)	< 0.001	0.7 (-0.1 to 1.6)	3.3 (2.4 to 4.1)	< 0.001
TG, mg/dL† median (IQR)	124.5 (90.0 to 173)	117.0 (88 to 155)	130.5 (100.3 to 177.2)	105.1 (82.5 to 141.6)	< 0.001	8.1 (-0.4 to 16.6)	-10.9 (-19.4 to -2.5)	< 0.001
ApoA, mg/dL mean (95%CI)	139.5 (137.2 to 141.9)	140.5 (138.3 to 142.8)	145.4 (143.4 to 147.4)	151.6 (149.5 to 153.7)	< 0.001	3.5 (1.5 to 5.5)	8.5 (6.5 to 10.5)	< 0.001
ApoB, mg/dL mean (95%CI)	81.9 (80.1 to 83.6)	81.1 (79.3 to 82.9)	83.5 (81.8 to 85.2)	42.4 (40.8 to 44.0)	< 0.001	0.3 (-2.0 to 2.6)	-40.3 (-42.6 to 38.0)	< 0.001

Note: On-treatment laboratory parameters are the time-weighted averages (95% CIs) of all post-baseline values, and estimates are derived from an analysis of variance model with factors for treatment group and region. Baseline and time-weighted average on-treatment values and absolute changes of laboratory measures and blood pressure of patients treated with placebo or evolocumab with evaluable imaging at baseline and follow-up. Results expressed as mean (95% CI) at baseline and least-squares mean (95% CI) for on-treatment values.

*P-value for between-treatment group comparison. †Tested using Wilcoxon rank-sumtest.

HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; Apo = Apolipoprotein

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Apo=apolipoprotein; CI=confidence interval; GLAGOV=Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured By Intravascular Ultrasound; IQR=interquartile range; HDL-C=high-density lipoprotein cholesterol; Lp(a)=lipoprotein(a); PCSK9=proprotein convertase subtilisin/kexin type 9; TG=triclyceride. Nicholls S, et al. *JAMA*. (2016) 316(22):2373-2384.

GLAGOV: Biochemical Measurements for Diabetes and Blood Pressure

Fasting

Parameter	Baseline		On-treatment			Absolute Change (95% CI)		
	Placebo (n = 484)	Evolocumab (n = 484)	Placebo (n = 484)	Evolocumab (n = 484)	P-Value*	Placebo (n = 484)	Evolocumab (n = 484)	P-Value*
Glucose, mg/dL†,‡ mean (95%CI)	107.3 (104.6 to 110.1)	104.0 (101.8 to 106.2)	109.4 (106.9 to 112.0)	110.1 (107.8 to 112.3)	0.72	3.9 (1.3 to 6.5)	7.8 (5.3 to 10.4)	0.02
HbA1c, %‡ mean (95%CI)	5.9 (5.8 to 6.0)	5.8 (5.8 to 5.9)	6.0 (5.9 to 6.1)	6.0 (5.9 to 6.1)	0.85	0.2 (0.1 to 0.2)	0.2 (0.15 to 0.25)	0.09
Systolic blood pressure, mmHg mean (95%CI)	129.6 (128.2 to 131.0	131.4 (130.1 to 132.7)	131.9 (130.8 to 133.1)	131.5 (130.4 to 132.5)	0.55	0.9 (-0.7 to 2.5)	-1.3 (-2.9 to 0.4)	0.007
Diastolic blood pressure, mmHg mean (95%CI)	76.7 (75.8 to 77.6)	78.0 (77.2 to 78.9)	78.5 (77.8 to 79.2)	78.6 (77.9 to 79.2)	0.94	2.2 (1.0 to 3.3)	0.9 -0.2 to 1.99)	0.01

Note: On-treatment laboratory parameters are the time-weighted averages (95% CIs) of all post-baseline values, and estimates are derived from an analysis of variance model with factors for treatment group and region. Baseline and time-weighted average on-treatment values and absolute changes of laboratory measures and blood pressure of patients treated with placebo or evolocumab with evaluable imaging at baseline and follow-up. Results expressed as mean (95% CI) at baseline and least-squares mean (95% CI) for on-treatment values.

*P-value for between-treatment group comparison. †Tested using Wilcoxon rank-sum test. ‡Final measurements are used for on-treatment values. Absolute changes are presented as least-squares means (95% CIs)

Hb = hemoglobin

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

CI=confidence interval; GLAGOV=Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured By Intravascular Ultrasound; HbA1c=hemoglobin A1c; PCSK9=proprotein convertase subtilisin/kexin type 9.
Nicholls S, et al. *JAMA*. (2016) 316(22):2373-2384.

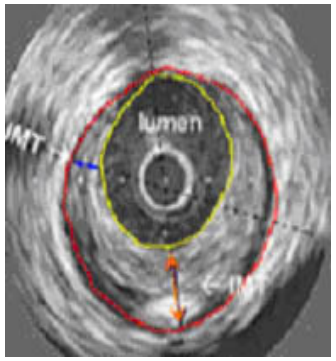
GLAGOV: Primary and Secondary Study Endpoints as Evaluated on Intravascular Ultrasonography

The *P*-value for comparison between treatments for change from baseline were generated from an analysis of covariance. Primary and secondary endpoints as evaluated on intravascular ultrasonography at baseline and 78-week follow-up with changes from baseline. Results expressed as mean (SD) and median (95% CI) for continuous variables and percentage for categorical variables at baseline and follow-up.

Parameter	Placebo (n = 423)	Evolocumab (n = 423)	Between Group Differences, Least Squares Means (95% CI)	P-value
Baseline				
Percent atheroma volume				
Mean (95% CI)	37.2 (36.4 to 38.0)	36.4 (35.6 to 37.2)	−0.76 (−1.9 to 0.4)	1.8
Median (95% CI)	37.1 (36.0 to 38.0)	36.4 (35.5 to 37.5)		
Total atheroma volume, mm^3				
Mean (95% CI)	191.4 (183.2 to 199.6)	187.0 (179.1 to 194.8)	−4.3 (−15.6 to 7.0)	.63
Median (95% CI)	175.8 (164.0 to 187.4)	174.6 (164.1 to 183.1)		
Follow-up at 78 Weeks				
Percent atheroma volume				
Mean (95% CI)	37.3 (36.5 to 38.1)	35.6 (34.8 to 36.4)	−1.7 (−2.8 to −0.6)	.002
Median (95% CI)	36.8 (35.7 to 37.8)	35.7 (34.8 to 36.5)		
Total atheroma volume, mm^3				
Mean (95% CI)	190.6 (182.5 to 198.7)	181.5 (174.1 to 188.9)	−8.9 (−19.9 to 2.0)	.23
Median (95% CI)	174.4 (164.3 to 186.6)	169.6 (160.9 to 180.7)		
Change from Baseline				***P* Value for Between Groups[a]**
Percent atheroma volume				
Least squares mean (95% CI)	0.05 (−0.32 to 0.42)	−0.95 (−1.33 to −0.58)	−1.0 (−1.8 to −0.64)	<.001
P value for change from baseline	.78	<.001		
Total atheroma volume, mm^3				
Least squares mean (95% CI)	−0.91 (−3.29 to 1.47)	−5.80 (−8.19 to −3.41)	−4.9 (−7.3 to −2.5)	<.001
P-value for change from baseline	.45	<.001		
Patients with regression, % (95% CI)				
Percent atheroma volume	47.3 (42.5 to 52.0)	64.3 (59.7 to 68.9)	17.0 (10.4 to 23.6)	<.001
Total atheroma volume	48.9 (44.2 to 53.7)	61.5 (56.8 to 66.1)	12.5 (5.9 to 19.2)	<.001

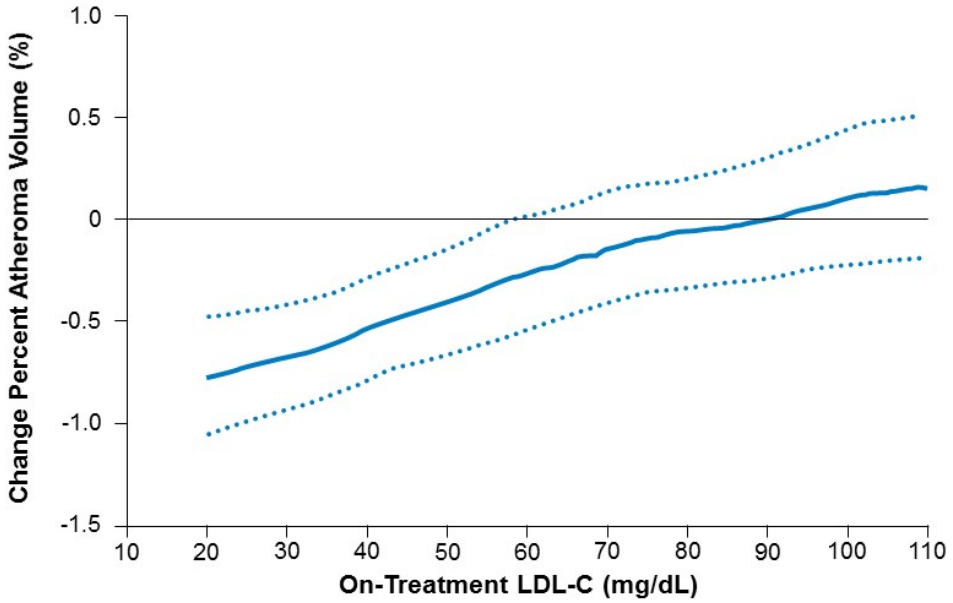
Nicholls S, et al. *JAMA*. (2016) 316(22):2373-2384.

GLAGOV: Mean On-Treatment LDL-C vs Change in Percent Atheroma Volume



Change In Percent Atheroma Volume (%)

Exploratory Analysis: Achieved LDL-C and Change in PAV in All Patients



Local regression (LOESS) curve illustrating the association (with 95% CI) between achieved LDL-C levels and change in PAV in all patients undergoing serial IVUS evaluation. PAV = percentage atheroma volume; LDL-C = low-density lipoprotein cholesterol
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016] doi: 10.1001/jama.2016.16951.

Patients with angiographic CAD were randomized to receive monthly evolocumab (420 mg; n=484) or placebo (n=484) SQ for 76 weeks, in addition to statins

Locally weighted polynomial regression (LOESS) plot demonstrates a linear continuous relationship between achieved LDL-C level and PAV progression/regression for levels of LDL-C ranging from 110 mg/dL to as low as 20 mg/dL

CAD=coronary artery disease; GLAGOV=Global Assessment of Plaque Regression with a PCSK9 Antibody; LDL-C=low-density lipoprotein cholesterol; PAV=premature atrial contractions; PCSK9=proprotein convertase subtilisin/kexin type 9; SQ=subcutaneous. Nicholls S, et al. *JAMA*. (2016) 316(22):2373-2384.

Evolocumab Effect on Atheroma Volume in Patients with T2D Treated with Statins at 78-Week Follow-Up: GLAGOV Randomized Clinical Trial

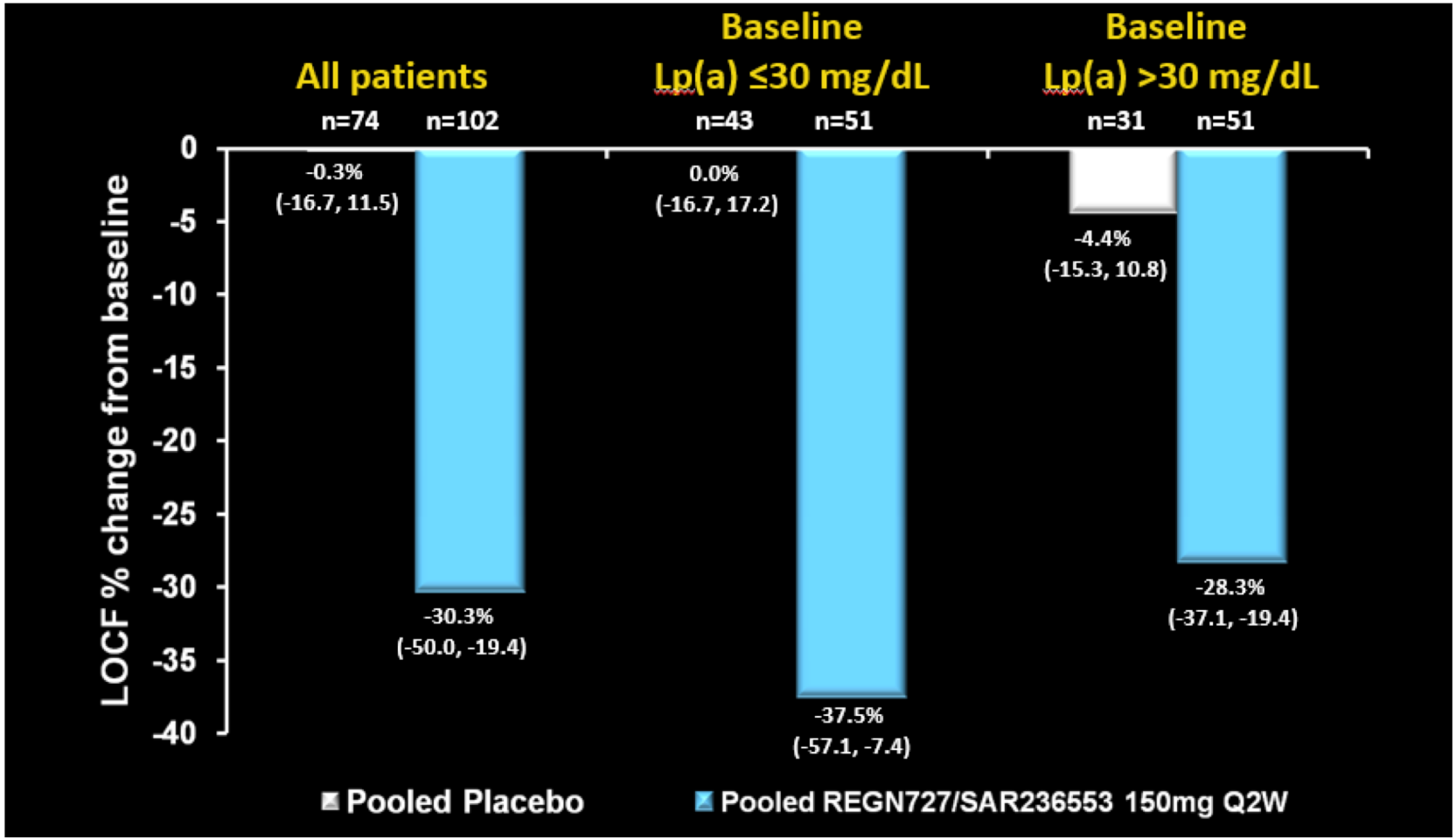
Subgroup	No.		Change in PAV, Mean (95% CI), %		Treatment Difference (95% CI)	Favors Evolocumab	Favors Placebo	*P* Value for Interaction
	Placebo	Evolocumab	Placebo	Evolocumab				
Type 2 diabetes mellitus								
Yes	87	88	0.43 (-4.90 to 5.77)	-0.85 (-5.70 to 3.99)	-1.32 (-2.10 to -0.54)			.39
No	336	335	0.04 (-5.66 to 5.75)	-0.78 (-6.54 to 4.97)	-0.93 (-1.34 to -0.51)			

CI=confidence interval; PAV= premature atrial contractions; PCSK9=proprotein convertase subtilisin/kexin type 9; T2D=type 2 diabetes.

Nicholls S, et al. *JAMA*. (2016) 316(22):2373-2384.

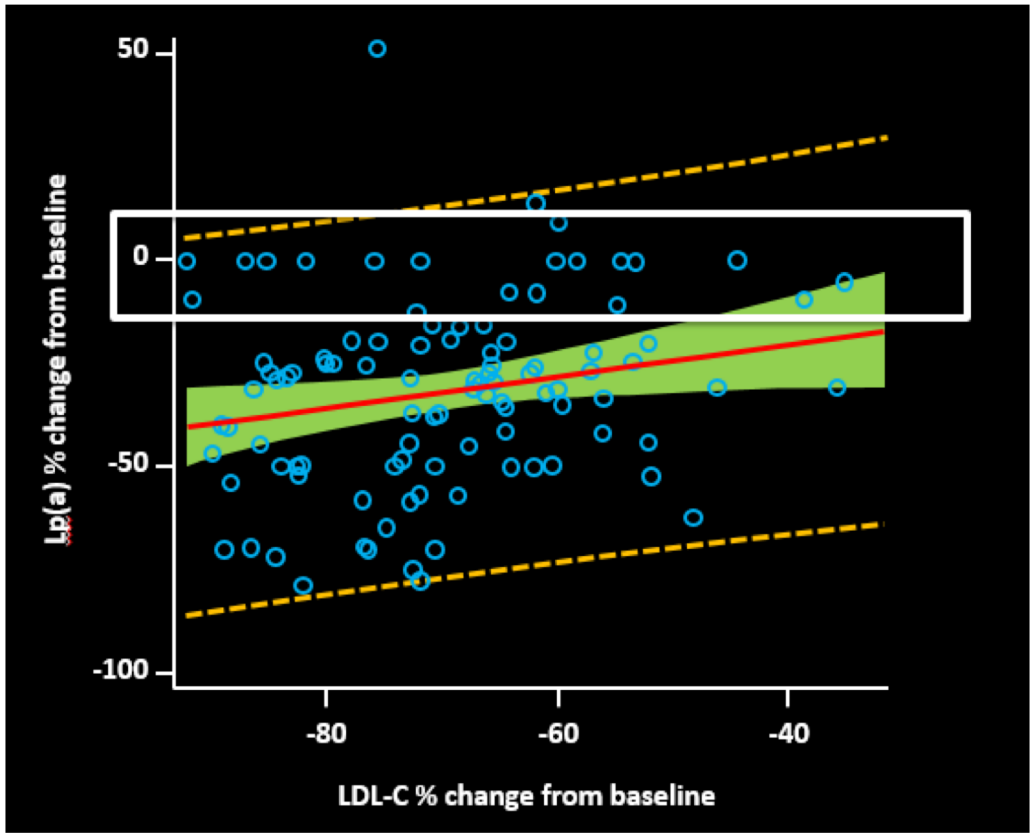
Impact of PCSK9 Inhibitors on Lp(a) Levels

Effect of Alirocumab on Lp(a) levels 150 mg Q2W on Lp(a)



LOCF=last observation carried forward ; Lp(a)= lipoprotein(a); Q2W=once every two weeks.
Gaudet D, et al. *Am J Cardiol. (*2014) 114:711–715.

Lp(a) Change From Baseline (%) vs LDL-C Change From Baseline in Alirocumab Treatment Group

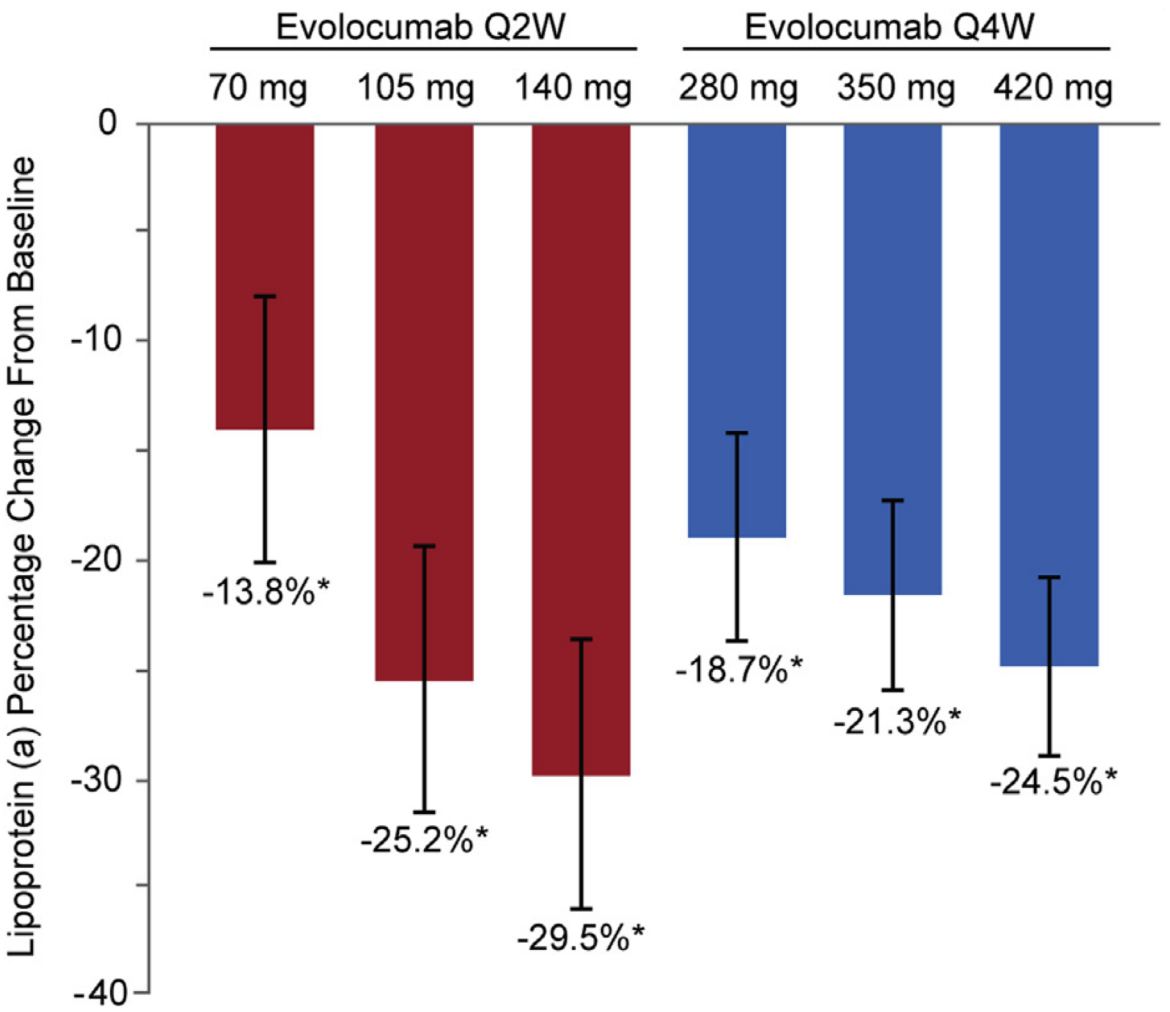


R-square: 0.0463
Spearman's correlation coefficient: 0.2236
***P*=0.0298**

Individual measurements **Fit** **95% confidence limits** **95% prediction limits**

LDL-C= low-density lipoprotein cholesterol; Lp(a)= lipoprotein(a).
Gaudet D, et al. *Am J Cardiol. (*2014) 114:711–715.

Reduction in Lipoprotein(a) with Evolocumab

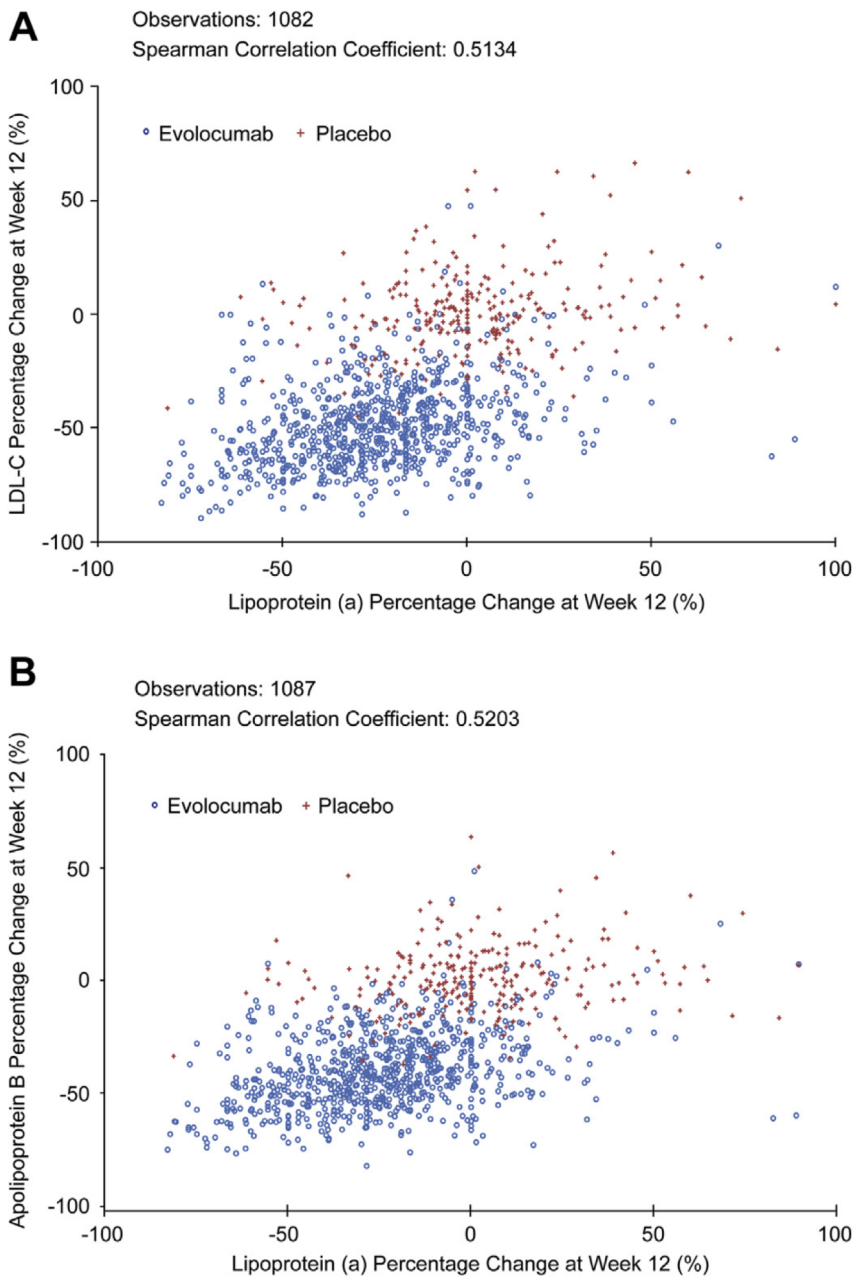


Q2W=once every two weeks; Q4W=once every 4 weeks.
Raal, F, et al. *JACC.* (2014) 63:1278-1288.

Correlation Between Lp(a) and LDL-C Changes Induced By Evolocumab

Pooled analysis of 1359 individuals at 12 weeks:

- A. Correlation of Lp(a) percentage reductions with LDL-C percentage change
- B. Correlation of Lp(a) percentage reductions with apolipoprotein B percentage change



LDL-C= low-density lipoprotein cholesterol; Lp(a)= lipoprotein(a).
Raal, F, et al. *JACC.* (2014) 63:1278-1288.

Do PCSK9 Inhibitors Reduce ASCVD Events?

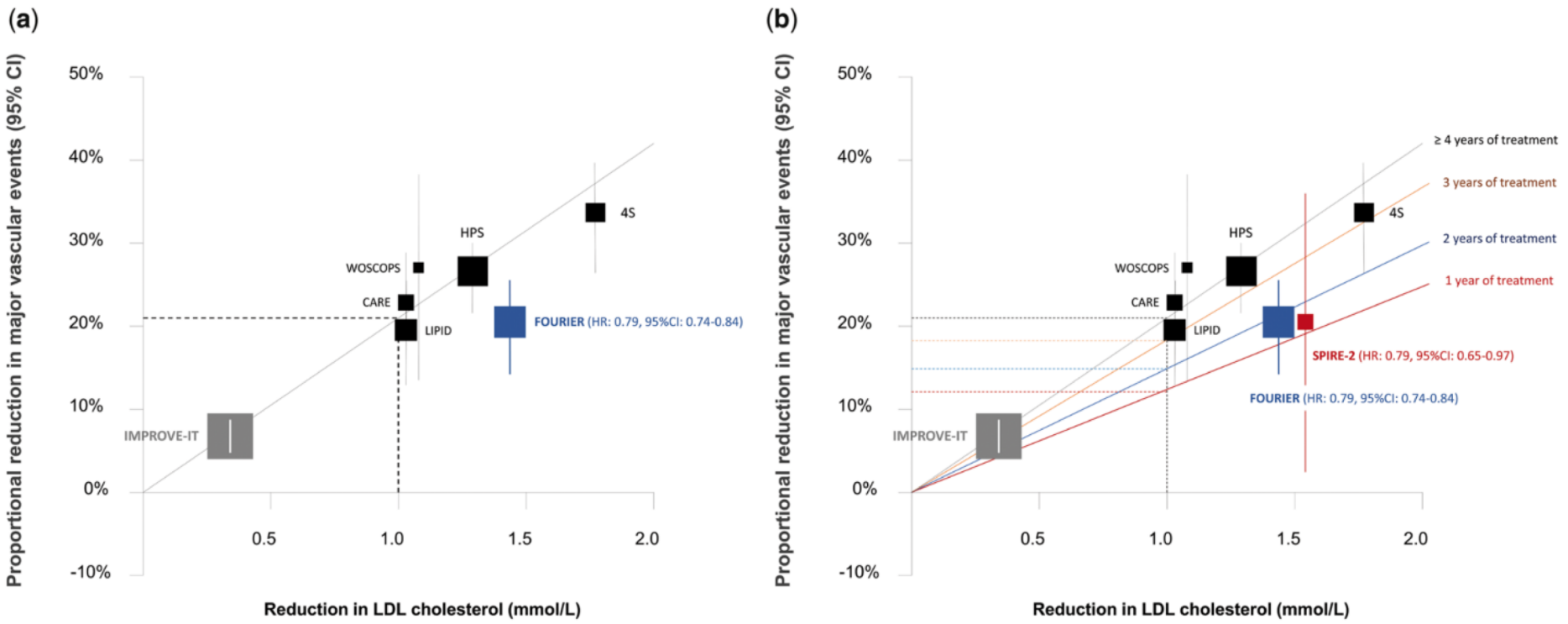
AACE: ASCVD Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – DM or stage 3 or 4 CKD with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10%-20% – DM or stage 3 or 4 CKD with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

AACE=American Association of Clinical Endocrinologists; ACS=acute coronary syndrome; apo=apolipoprotein; ASCVD=atherosclerotic cardiovascular disease; CKD=chronic kidney disease; DM=diabetes mellitus; HeFH=heterozygous familial hypercholesterolemia; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; NR= not recommended.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479-497; Barter PJ, et al. *J Intern Med*. (2006) 259:247-258; Boekholdt SM, et al. *J Am Coll Cardiol*. (2014) 64(5):485-494; Brunzell JD, et al. *Diabetes Care*. (2008) 31:811-822; Cannon CP, et al. *N Engl J Med.* (2015) 372(25):2387-2397; Grundy SM, et al. *Circulation.* (2004) 110:227-239; Heart Protection Study Collaborative Group. *Lancet*. (2002) 360:7-22 Lloyd-Jones DM, et al. *Am J Cardiol*. (2004) 94:20-24; McClelland RL, et al. *J Am Coll Cardiol*. (2015) 66(15):1643-1653; NHLBI. NIH Publication No. 02-5215. (2002) Ridker PM, *J Am Coll Cardiol*. (2005)45:1644-1648; Ridker PM, et al. *JAMA*. (2007) 297(6):611-619; Sever PS, et al. *Lancet*. (2003) 361:1149-1158; Shepherd J, et al. *Lancet*. (2002) 360:1623-1630; Smith SC Jr, et al. *Circulation*. (2006) 113:2363-2372; Stevens RJ, et al. *Clin Sci*. (2001) 101(6):671-679; Stone NJ. *Am J Med*. (1996) 101:4A40S-48S; Weiner DE, et al. *J Am Soc Nephrol.* (2004) 15(5):1307-1315.

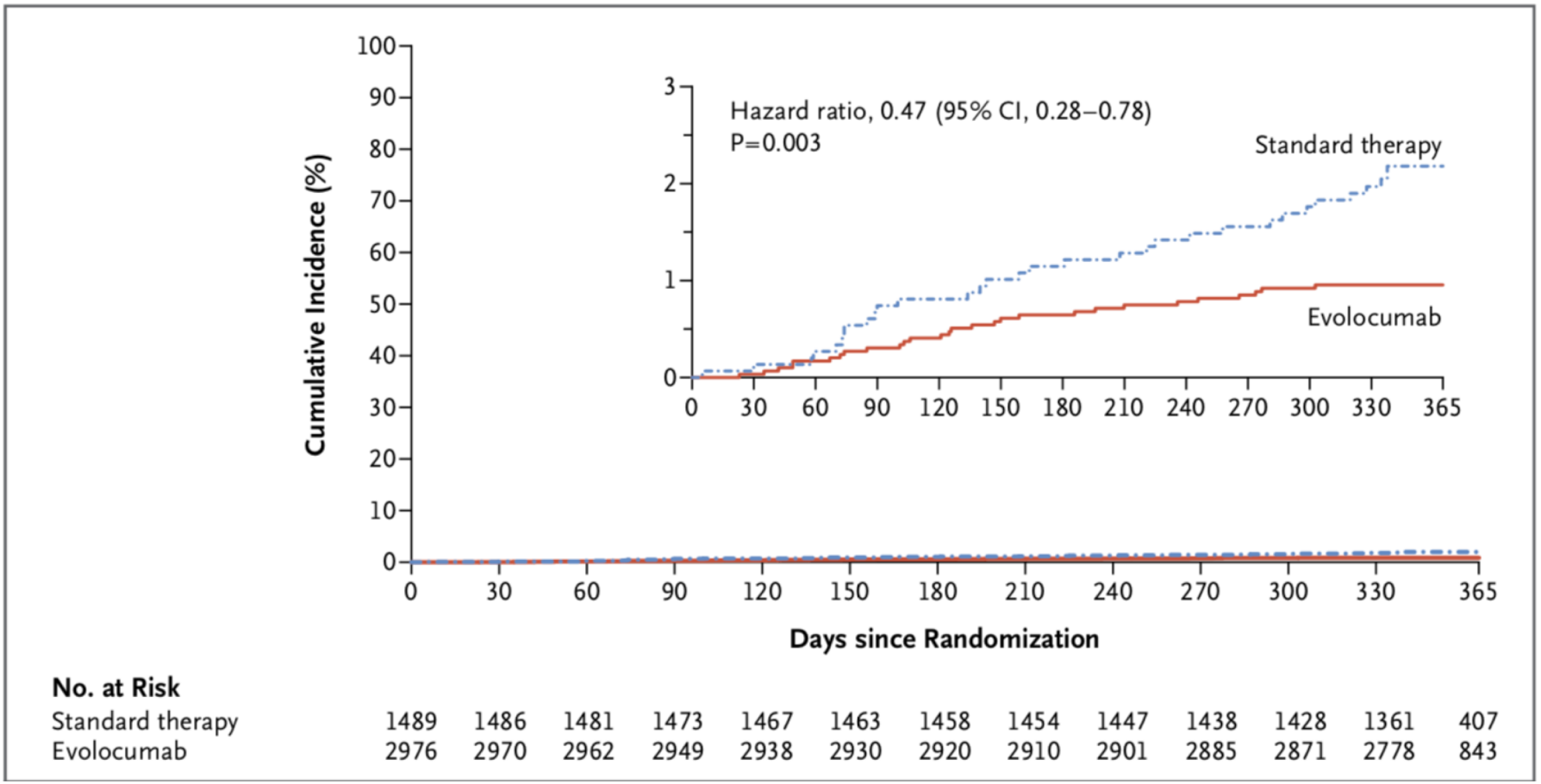
Reduction of LDL-C and CV events with PCSK9 Inhibitors and Statins: FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration



CARE=Cholesterol and Recurrent Events; CI=confidence interval; CV=cardiovascular; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; HPS=Heart-Protection Study; IMPROVE-IT: Improved Reduction of Outcomes: Vytorin Efficacy International; LDL-C=low-density lipoprotein cholesterol; LIPID=Long-term Intervention with Pravastatin in Ischemic Disease; Lp(a)=lipoprotein(a); PCSK9=proprotein convertase subtilisin/kexin type 9; WOSCOPS=West of Scotland Coronary Prevention Study.

Ference B, et al. *Eur Heart J.* (2017)38:2459–2472.

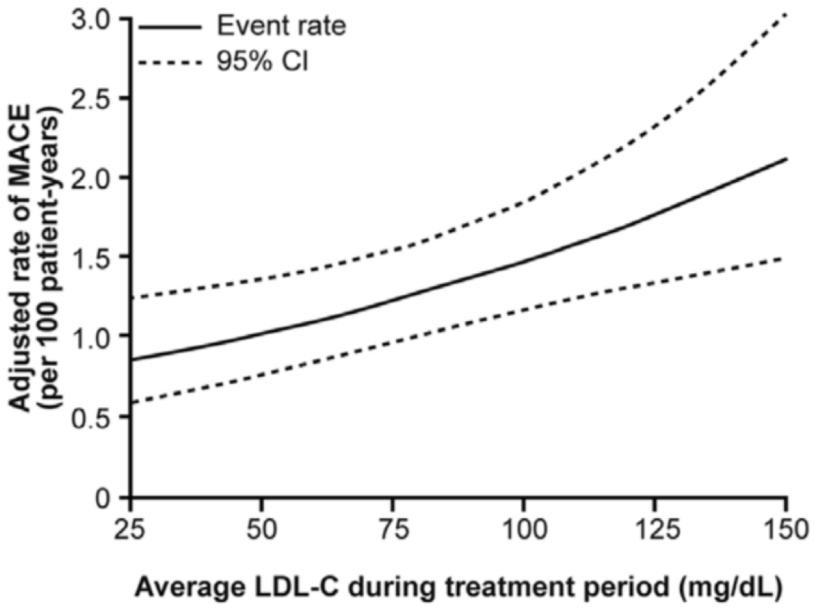
OSLER-1 and OSLER-2: Cumulative Incidence of CVD Events



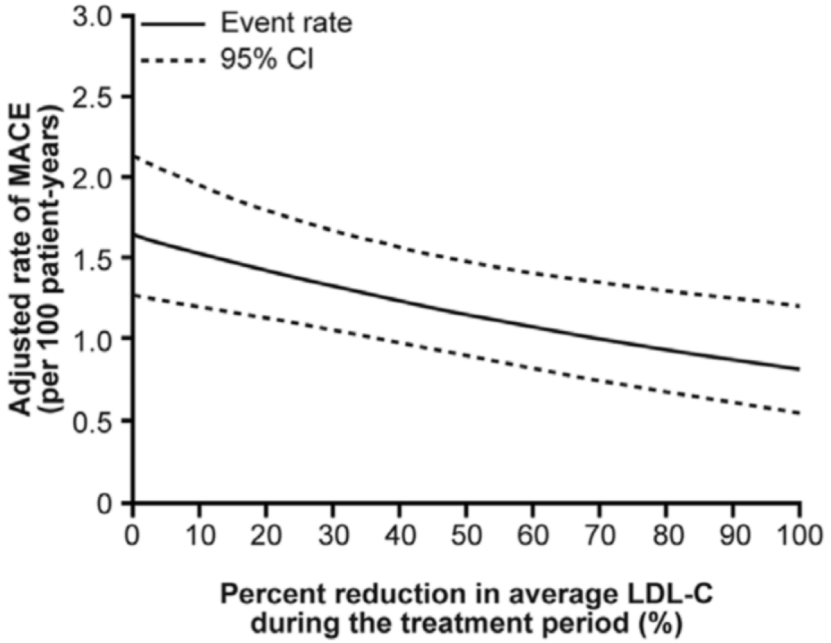
CI=confidence interval; CVD=cardiovascular disease.
Sabatine M, et al. *N Engl J Med.* (2015) 372:1500-1509.

ODYSSEY Program: Major Adverse Cardiovascular Event (MACE) Outcomes

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



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

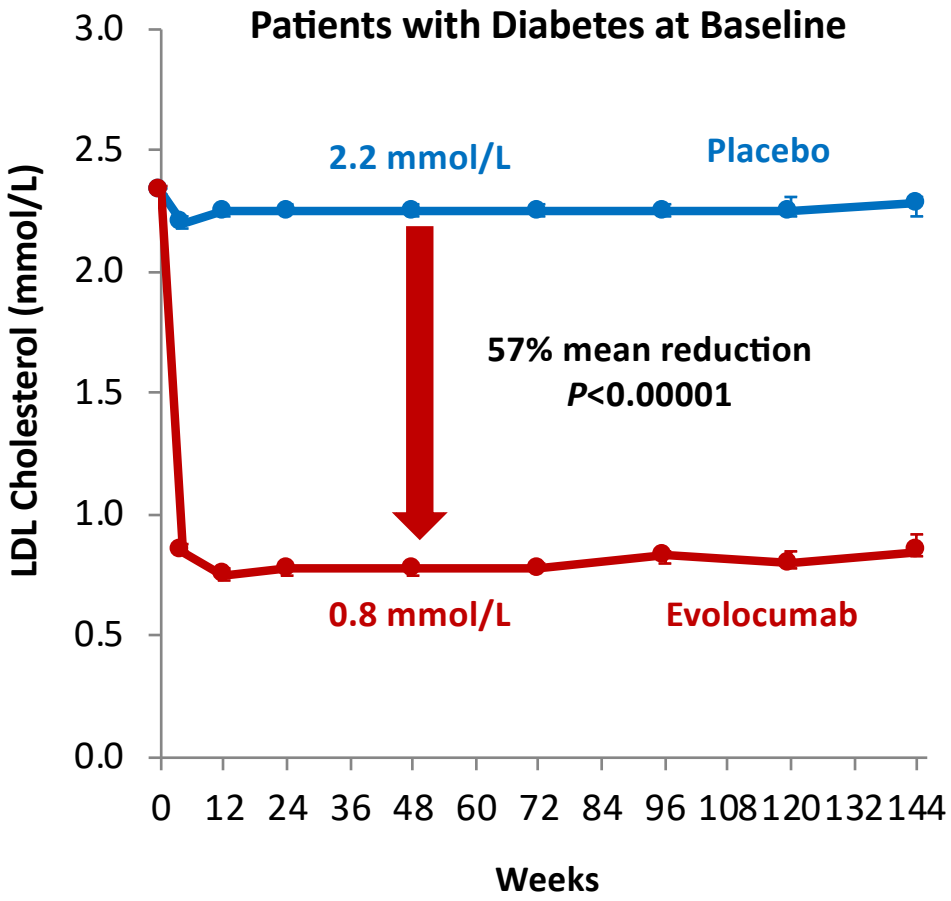


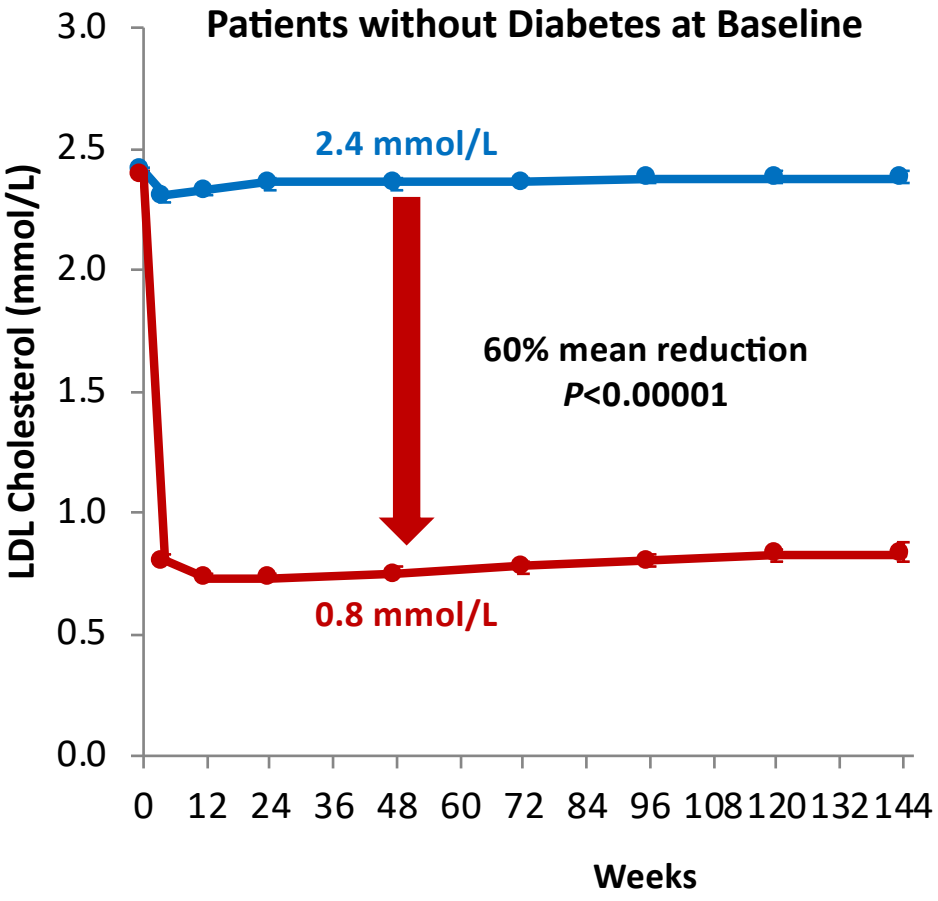
Adjusted MACE rate by average LDL-C (absolute or % reduction from baseline) during treatment period. Multivariate analysis adjusted on baseline characteristics; pool of Phase 3 ODYSSEY trials. HR were calculated for each 39 mg/dL difference or 50% reduction in LDL-C.

ACSVD=acute coronary syndrome; CI=confidence interval; CV=cardiovascular; LDL-C=low-density lipoprotein cholesterol; MACE=major adverse cardiac event. Ray K, et al. *Circulation. (*2016) 134(24):1931-1943.

PCSK9 Inhibitors and Diabetes

FOURIER- Evolocumab vs Placebo
LDL-C Reduction with Evolocumab



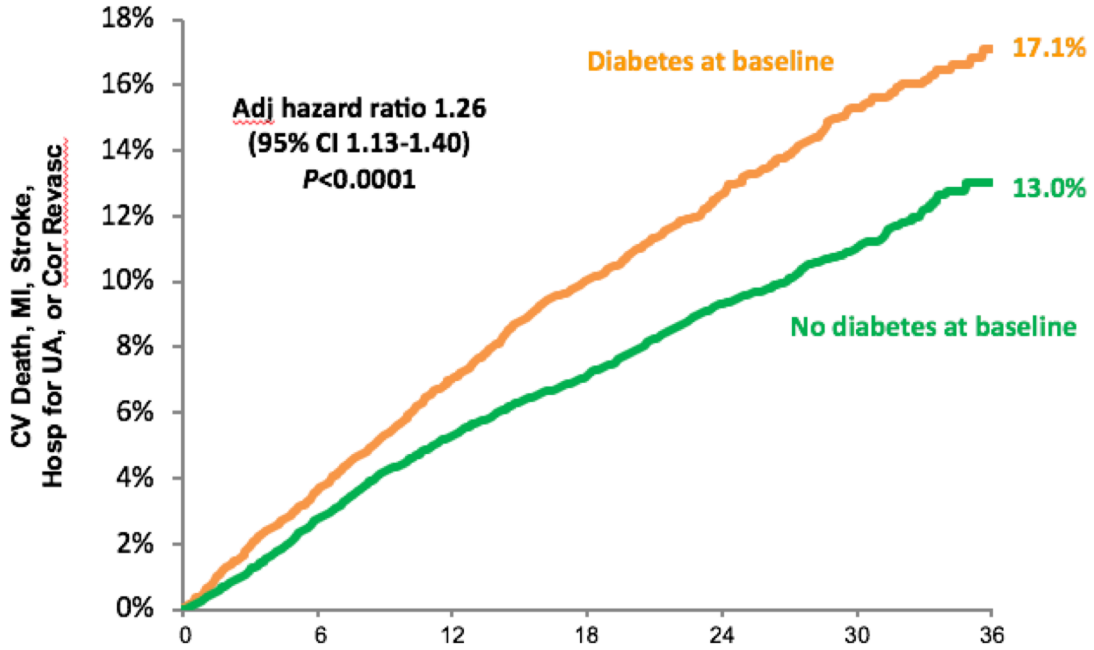


FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9.

Sabatine et al. *Lancet Diab Endocrinol.* (2017). http://dx.doi.org/10.1016/S2213-8587(17)30313-3.

FOURIER – Diabetes At Baseline vs No Diabetes At Baseline

Primary Endpoint: MI, Stroke, CV Death, UA Hospitalization, CABG, PCI



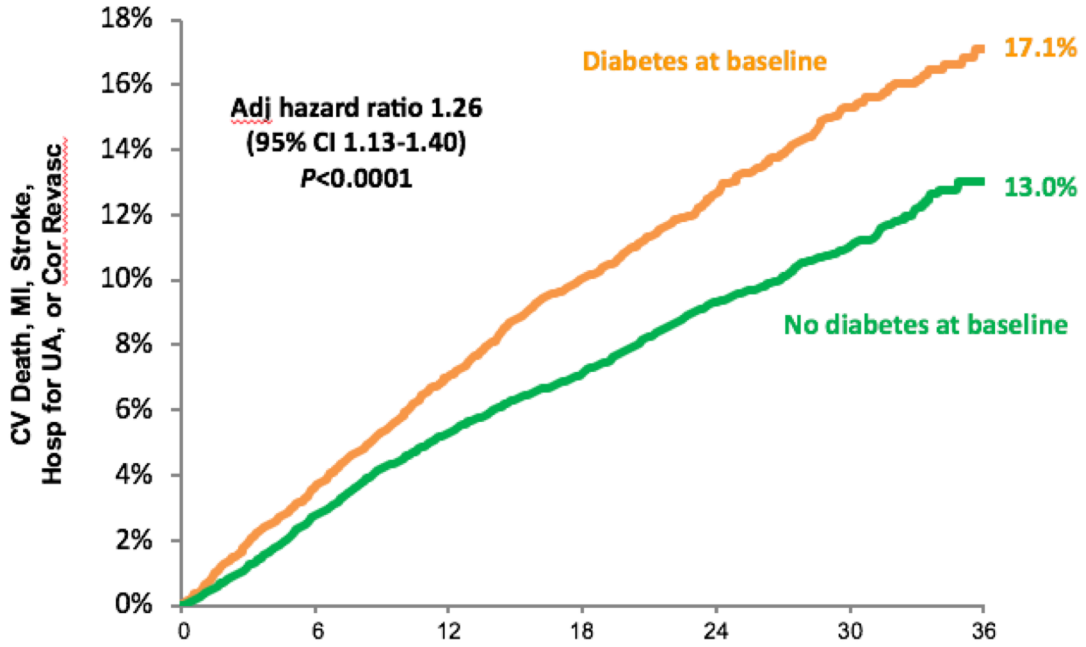
BMI=body mass index; CABG=coronary artery bypass grafting; CI=confidence interval; CV=cardiovascular; eGFR= estimated glomerular filtration rate; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; HTN=hypertension; LDL-C=low-density lipoprotein cholesterol; HF=heart failure; MI=myocardial infarction; PAD=peripheral artery disease; PCI=percutaneous coronary intervention; PCSK9=proprotein convertase subtilisin/kexin type 9; UA=unstable angina.

Sabatine et al. *Lancet Diab Endocrinol*. (2017). http://dx.doi.org/10.1016/S2213-8587(17)30313-3.

Analyses in placebo arm and adj for age, sex, BMI, race, region, history of MI, stroke, PAD, HTN, smoking, HF, eGFR, lipids, statin.

FOURIER – Diabetes At Baseline vs No Diabetes At Baseline

Primary Endpoint: MI, Stroke, CV Death, UA Hospitalization, CABG, PCI



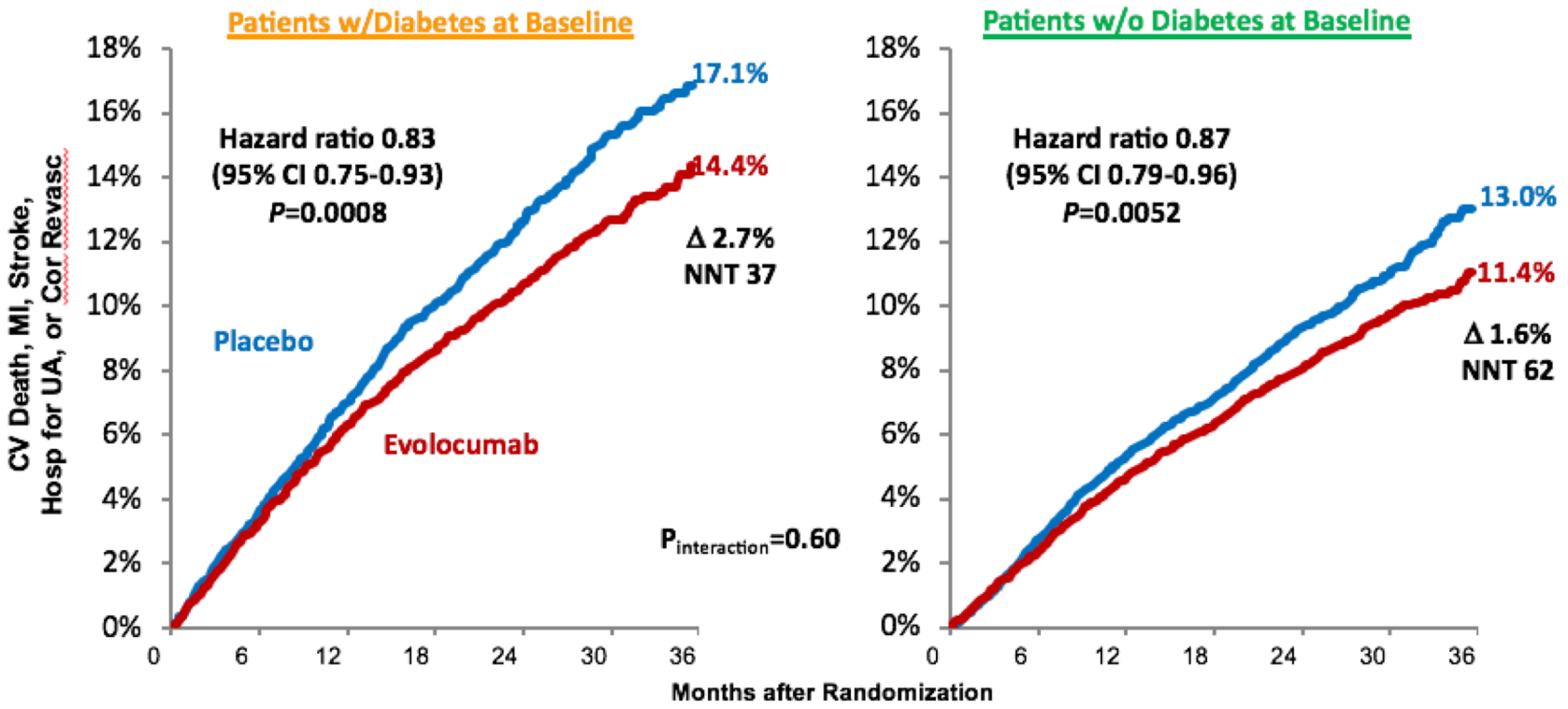
BMI=body mass index; CABG=coronary artery bypass grafting; CI=confidence interval; CV=cardiovascular; eGFR= estimated glomerular filtration rate; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; HTN=hypertension; LDL-C=low-density lipoprotein cholesterol; HF=heart failure; MI=myocardial infarction; PAD=peripheral artery disease; PCI=percutaneous coronary intervention; PCSK9=proprotein convertase subtilisin/kexin type 9; UA=unstable angina.

Sabatine et al. *Lancet Diab Endocrinol*. (2017). http://dx.doi.org/10.1016/S2213-8587(17)30313-3.

Analyses in placebo arm and adj for age, sex, BMI, race, region, history of MI, stroke, PAD, HTN, smoking, HF, eGFR, lipids, statin.

FOURIER- Evolocumab vs Placebo, Patients with and without Diabetes

Primary Endpoint: MI, Stroke, CV Death, UA Hospitalization, CABG, PCI

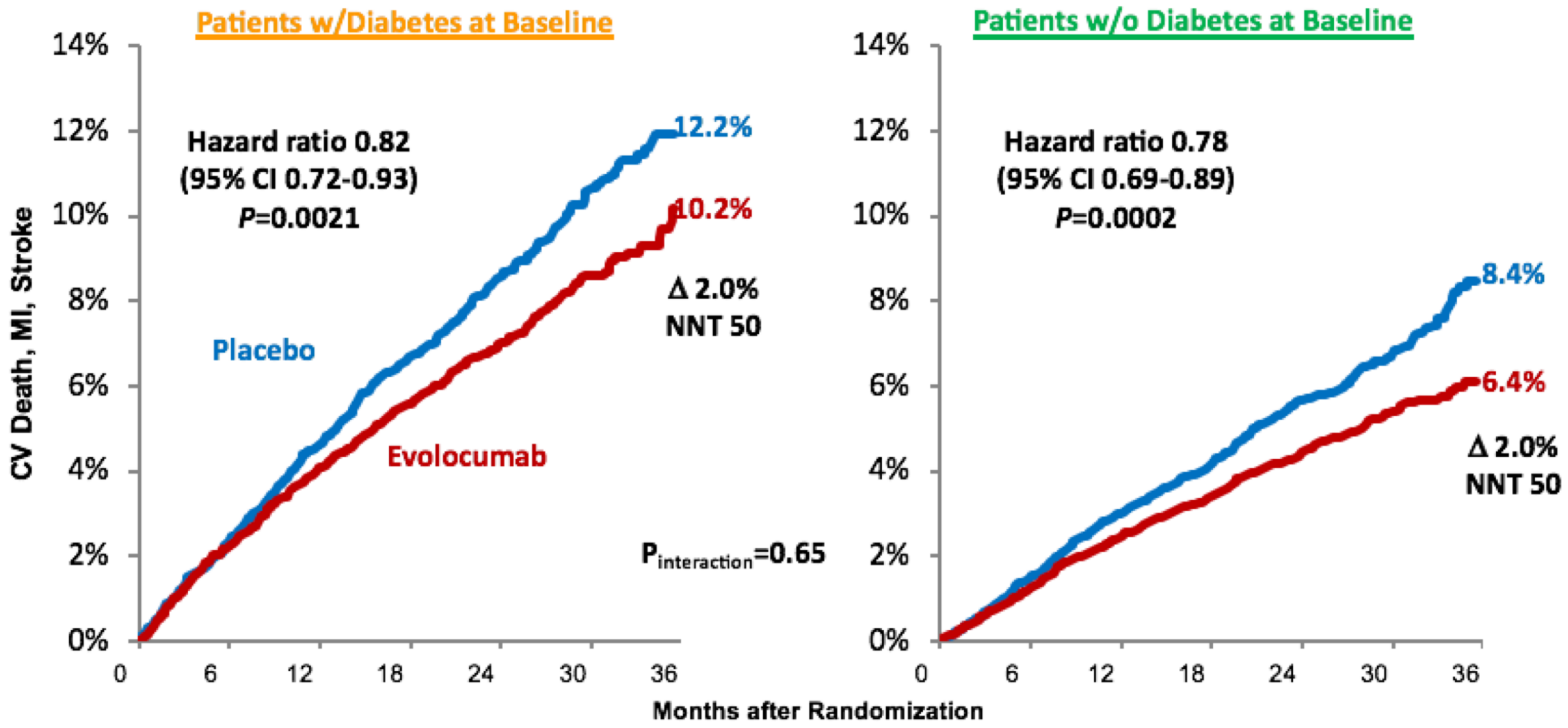


BMI=body mass index; CABG=coronary artery bypass grafting; CI=confidence interval; CV=cardiovascular; eGFR= estimated glomerular filtration rate; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; HTN=hypertension; LDL-C=low-density lipoprotein cholesterol; HF=heart failure; MI=myocardial infarction; NNT=number needed to treat; PAD=peripheral artery disease; PCI=percutaneous coronary intervention; PCSK9=proprotein convertase subtilisin/kexin type 9; UA=unstable angina.

Sabatine et al. *Lancet Diab Endocrinol.* (2017). http://dx.doi.org/10.1016/S2213-8587(17)30313-3.

FOURIER- Evolocumab vs Placebo, Patients with and without Diabetes

Secondary Endpoint: MI, Stroke, CV Death



BMI=body mass index; CI=confidence interval; CV=cardiovascular; eGFR= estimated glomerular filtration rate; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; HF=heart failure; HTN=hypertension; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; NNT=number needed to treat; PAD=peripheral artery disease; PCI=percutaneous coronary intervention; PCSK9=proprotein convertase subtilisin/kexin type 9.

Sabatine et al. *Lancet Diab Endocrinol.* (2017). http://dx.doi.org/10.1016/S2213-8587(17)30313-3.

Evolocumab: Effect on Glycemia vs Diabetes Status

At 52 weeks, no significant differences were observed in glycemic parameters in the subgroups for treatment with evolocumab vs placebo.

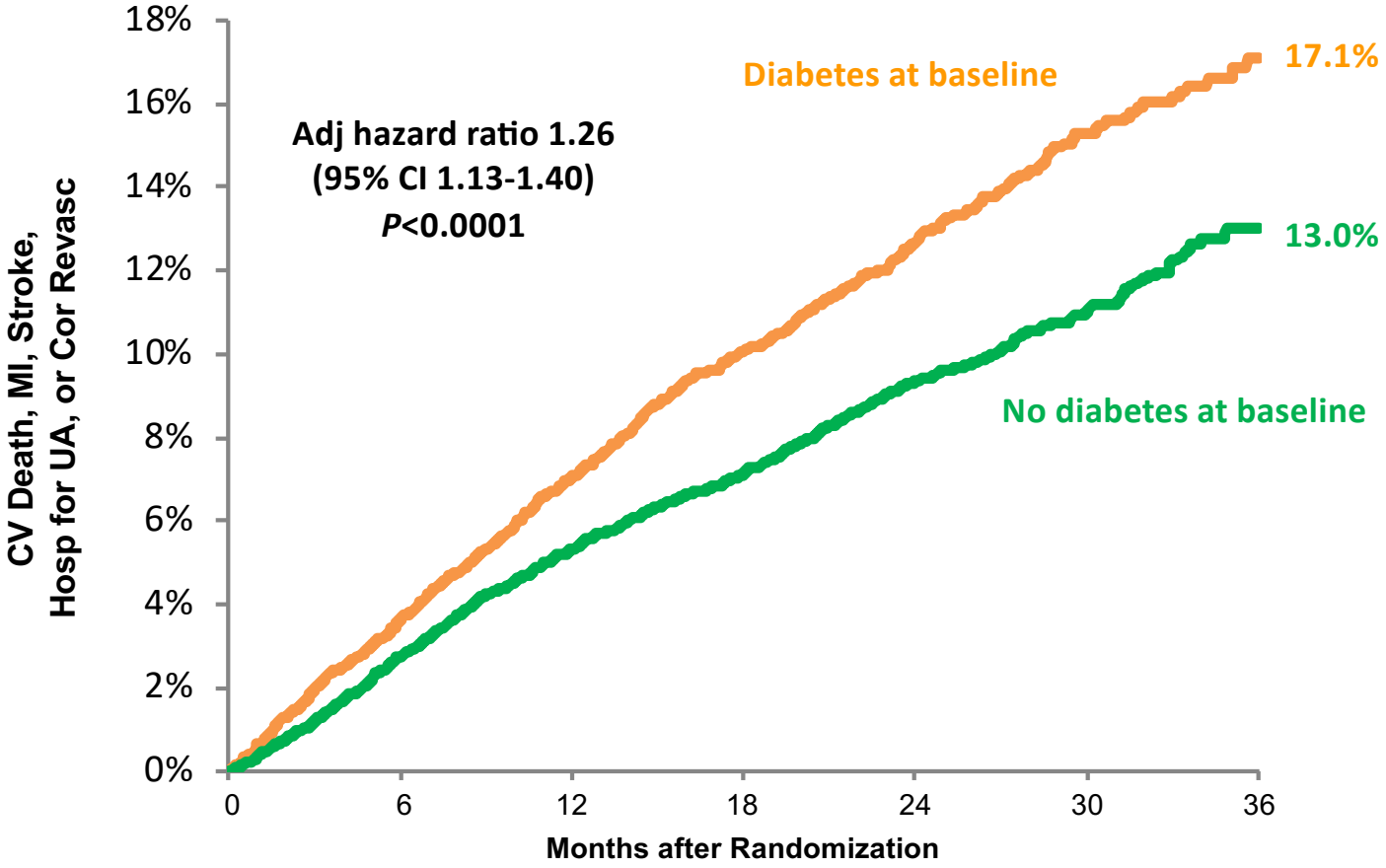
Parameter	Type 2 diabetes Placebo (n=43) vs Evolocumab (n=77)	IFG Placebo (n=99) vs Evolocumab (n=194)	Metabolic syndrome Placebo (n=107) vs Evolocumab (n=182)	No dysglycemia or metabolic syndrome Placebo (n=119) vs Evolocumab (n=274)
Glycemic parameters Treatment difference for evolocumab vs placebo, median change from baseline (SE)[a]				
A1C	0.10 (0.10)	0.00 (0.05)	0.00 (0.03)	0.00 (0.03)
FPG	-0.11 (0.21)	0.00 (0.07)	-0.06 (0.06)	0.06 (0.06)
Insulin	-7.2 (14.6)	0.0 (7.3)	0.0 (5.5)	-7.2 (5.5)
C-peptide	0.1 (0.1)	0.00 (0.04)	0.0 (0.04)	0.0 (0.03)
HOMA_%B	5.5 (5.7)	-1.3 (3.5)	-1.7 (3.9)	-2.3 (4.2)
HOMA_IR	-0.2 (0.3)	0.0 (0.1)	-0.1 (0.1)	-0.1 (0.1)

[a]Difference in median and SE calculated using Hodges-Lehmann method. *P* values were calculated using the Wilcoxon Rank Sum test. All *P* values for all glycemic parameters were non-significant (*P*>0.05). FPG=fasting plasma glucose; HOMA_%B (β cell function) & HOMA_IR (insulin resistance) calculated using the HOMA2 model; IFG=impaired fasting glucose; SE=standard error.

Blom D, et al. *Diabetes Obes Metab. (*2017) 19(1):98-107.

FOURIER – Diabetes At Baseline vs No Diabetes At Baseline

Primary Endpoint: MI, Stroke, CV Death, UA Hospitalization, CABG, PCI



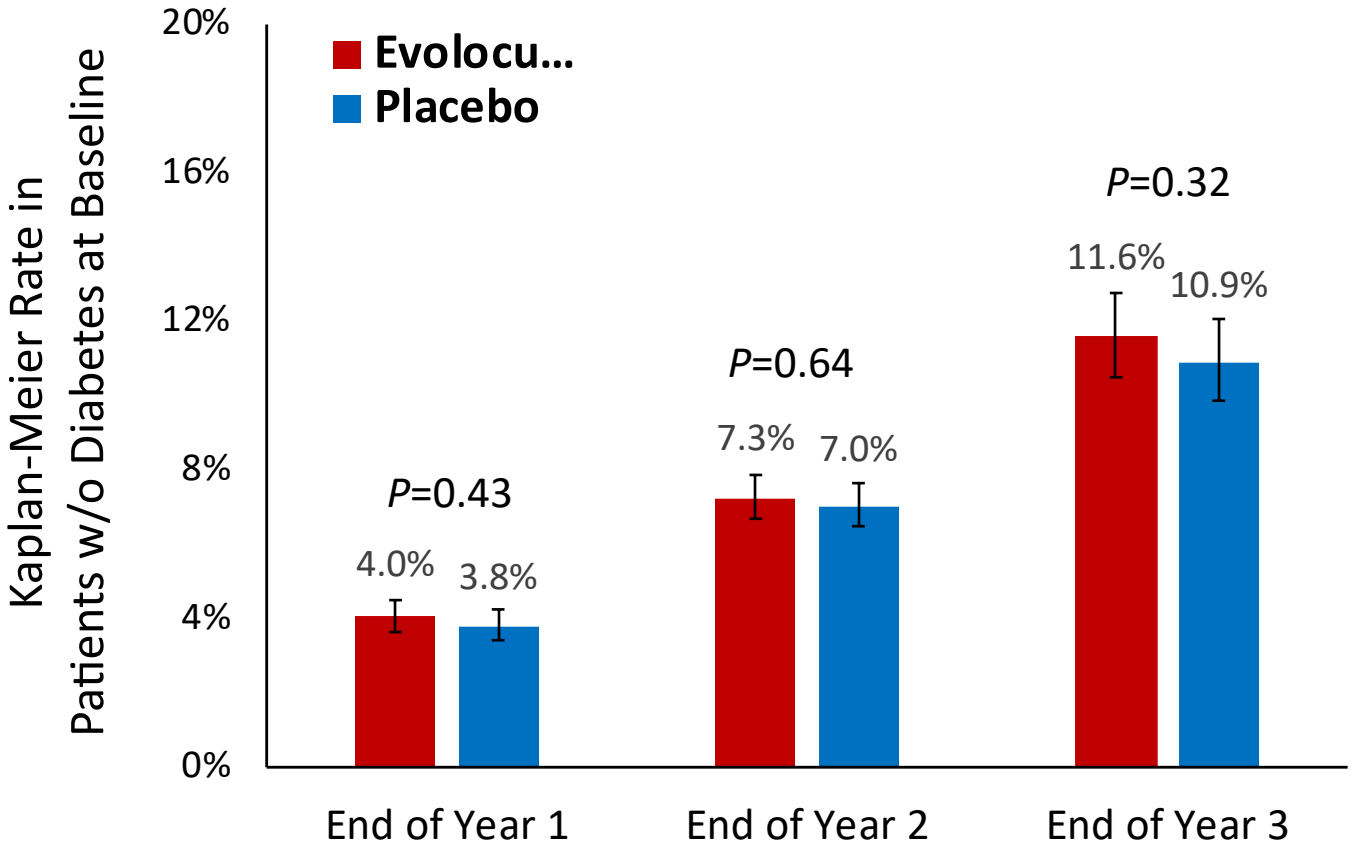
Analyses in placebo arm and adj for age, sex, BMI, race, region, history of MI, stroke, PAD, HTN, smoking, HF, eGFR, lipids, statin.

BMI=body mass index; CI=confidence interval; CV=cardiovascular; eGFR= estimated glomerular filtration rate; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; HTN=hypertension; LDL-C=low-density lipoprotein cholesterol; HF=heart failure; MI=myocardial infarction; NNT=number needed to treat; PAD=peripheral artery disease; PCI=percutaneous coronary intervention; PCSK9=proprotein convertase subtilisin/kexin type 9.

Sabatine et al. *Lancet Diab Endocrinol.* (2017). http://dx.doi.org/10.1016/S2213-8587(17)30313-3.

FOURIER – Effect of Evolocumab on Risk for New-Onset Diabetes

Use of evolocumab did not increase risk for new-onset diabetes



In all patients without diabetes at baseline (1294 incident cases in 16,510 patients):

HR 1.05
(95% CI 0.94-1.17)

In patients with prediabetes at baseline (1163 incident cases in 10,338 patients):

HR 1.00
(95% CI 0.89-1.13)

CI=confidence interval; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; HR=heart rate; PCSK9=proprotein convertase subtilisin/kexin type 9.

Sabatine et al. *Lancet Diab Endocrinol.* (2017). http://dx.doi.org/10.1016/S2213-8587(17)30313-3.

Evolocumab Individual Patient Data Meta-Analysis: Patients with Type 2 Diabetes

Evolocumab reduced atherogenic lipoproteins in patients with T2D similar to its effect on patients without T2D.

Ongoing CV trials will provide data on the effects of evolocumab on CV outcomes in patients with T2D.

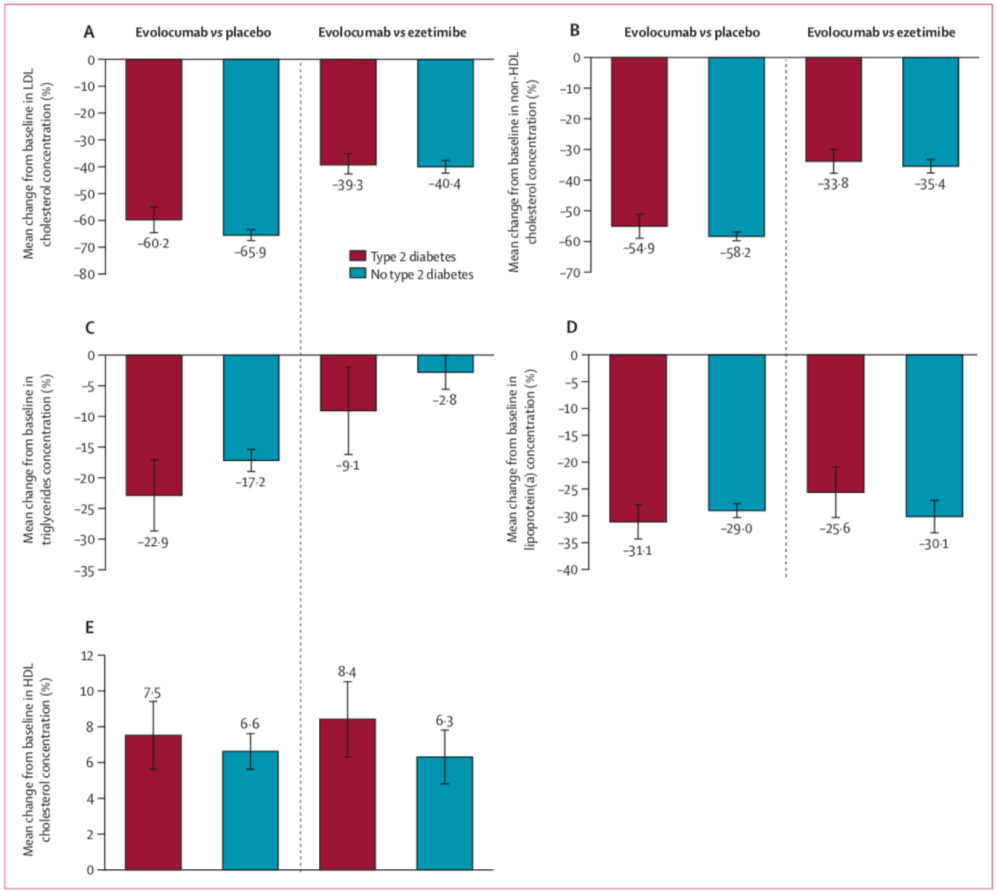


Figure 3: **Changes in lipid concentrations from baseline to 12 weeks with evolocumab relative to placebo or ezetimibe in patients with or without type 2 diabetes**
(A) LDL cholesterol. (B) Non-HDL cholesterol. (C) Triglycerides. (D) Lipoprotein(a). (E) HDL cholesterol. Error bars show SEs. For all treatment differences apart from triglycerides (evolocumab *vs* ezetimibe), p is less than 0·001 for both evolocumab versus placebo and evolocumab versus ezetimibe.

CV=cardiovascular; HDL=high-density lipoprotein; LDL=low-density lipoprotein; SE=standard error; T2D=type 2 diabetes.
Sattar N, et al. *Lancet Diabetes Endocrinol.* (2016) 4:403–10.

Evolocumab, Individual Patient Data Meta-Analysis: Patients with Type 2 Diabetes

Evolocumab reduced atherogenic lipoproteins in patients with T2D regardless of baseline insulin use, history of CV disease, A1C, or eGFR.

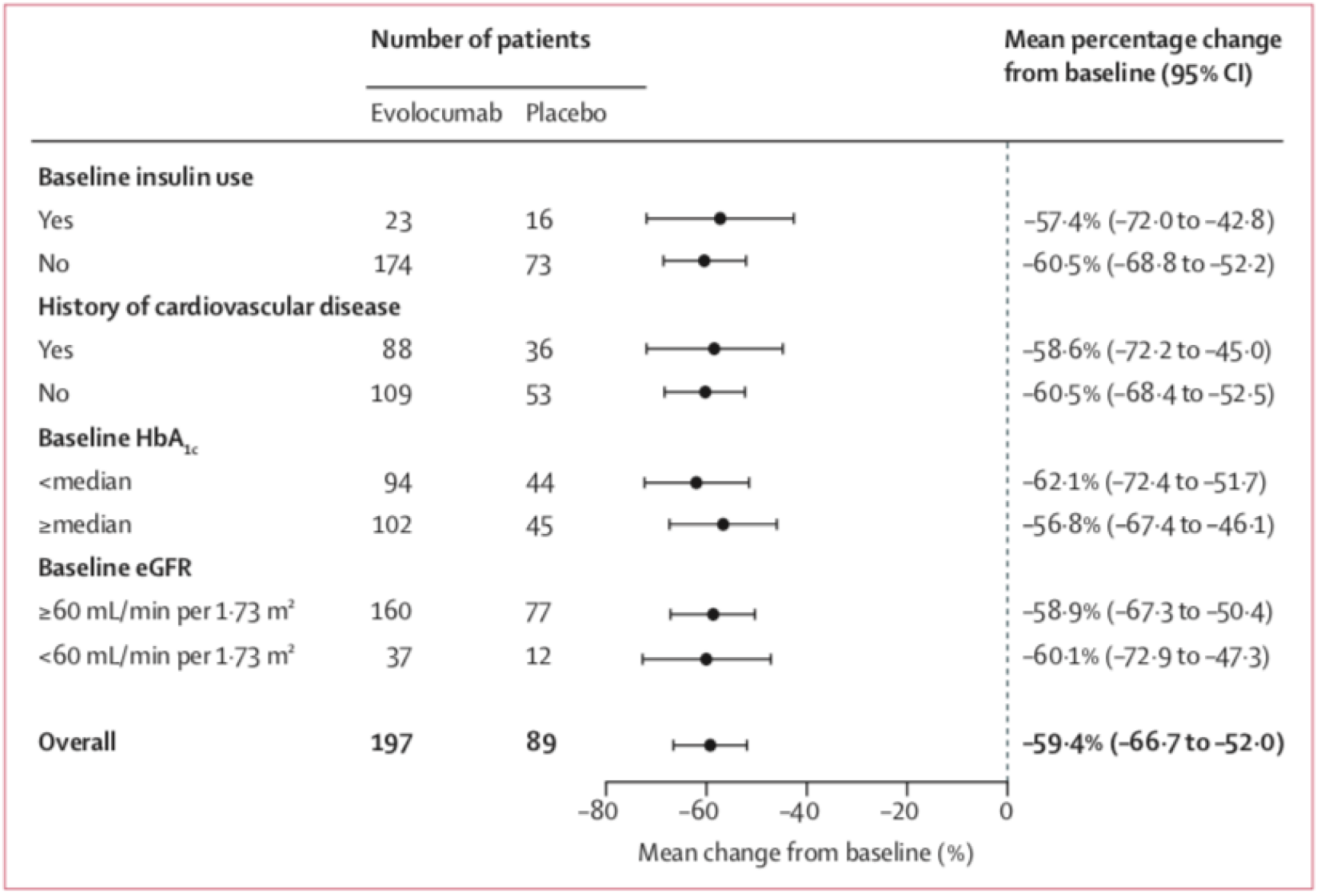


***Figure 4*: Reductions in LDL cholesterol in subgroups of patients with type 2 diabetes**
Error bars show 95% CIs. eGFR=estimated glomerular filtration rate.

CI=confidence interval; CV=cardiovascular; HbA1c=hemoglobin A1c; T2D=type 2 diabetes.
Sattar N, et al. *Lancet Diabetes Endocrinol.* (2016) 4:403–10.

Summary/Conclusion

- PCSK9 inhibitors reduce LDL cholesterol and have a favorable safety profile.
  - ↓ LDL-C by 45%-60% on top of maximum statin ± ezetimibe therapy.
- PCSK9 inhibitors are indicated for:
  - Individuals with FH.
  - High-risk individuals with clinical ASCVD.
  - Individuals with statin-intolerance and clinical ASCVD.
- PCSK9 inhibitors reduce CVD risk and also lower non-HDL-C and Lp(a).
  - May be an important tool in reducing residual risk.
- LDL-C reductions in individuals with diabetes were similar to those without diabetes
  - PCKS9 inhibitors appear to have no impact on blood glucose levels (but duration of follow up is limited).
- PCKS9 inhibitors are costly and their use should be implemented thoughtfully.

ACSVD=acute coronary syndrome; CVD=cardiovascular disease; FH=familial hypercholesterolemia; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; Lp(a)= *Lipoprotein(a)*; PCSK9=proprotein convertase subtilisin/kexin type 9.