Dilemma in Dyslipidemia management
Is there a new place for PSCK9 therapy?

BY

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February 2018

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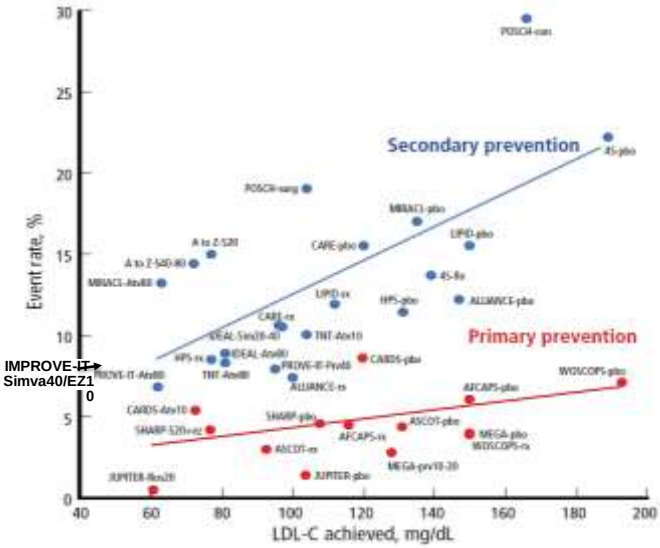
Agenda

- Limitations of Current Statin Therapies patients with ASCVD and hypercholesterolemia.
- The mechanism of action for PCSK9 inhibitors.
- Clinical Trials for PCSK9 inhibitors.

Benefits of Decreased LDL-C

LDL: Lower is Better



Raymond C, et al. *Cleve Clin J Med*. 2014;81(1):11-19.

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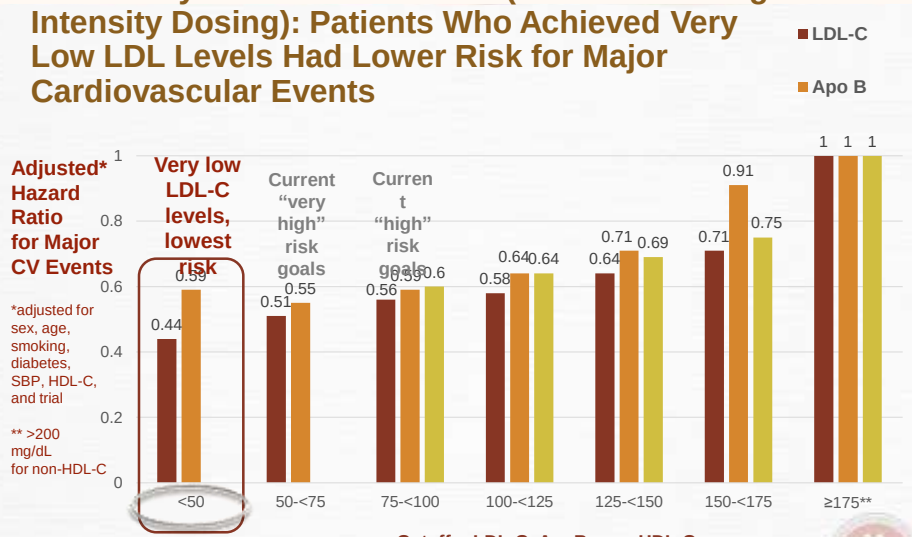
Meta-analysis of 8 Statin Trials (Moderate- to High-Intensity Dosing): Patients Who Achieved Very Low LDL Levels Had Lower Risk for Major Cardiovascular Events



Abbreviations: apo, apolipoprotein; CV, cerebrovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64(5):485-494.

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Efficacy of Intensive LDL-C Lowering in Patients With Low Baseline LDL-C

Meta-analysis of randomized controlled trials of major vascular events (coronary death, myocardial infarction, coronary revascularization, and ischemic stroke) with at least 1,000 patients and ≥2 years of more vs. less intense statin dosage (N=169,138)

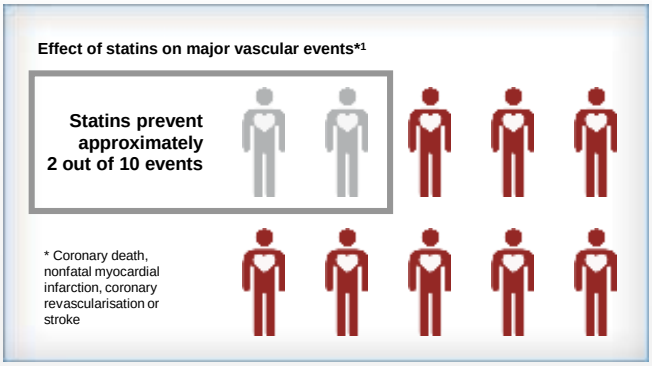
For each 39 mg/dL reduction in LDL-C:

- Individuals with baseline LDL-C **<77** mg/dL had a **29%** further reduction in major vascular events (*P*=0.007)
- Those with baseline LDL-C **<70** mg/dL had a **37%** further reduction in major vascular events (*P*=0.004)

Cholesterol Treatment Trialists' Collaboration. Lancet 2010;376:1670-1681; Jellinger P, Handelsman Y, Rosenblit P, et al. Endocr Practice. 2017;23(4):479-497.

Despite Statins Therapy, a Substantial Residual Risk Remains

A meta-analysis of 21 randomized clinical trials (n=129,526) revealed that Statin treatment prevented approximately 2 out of 10 major vascular events* (a 22% relative risk reduction, p<0.0001)1



1. Baigent C et al. Cholesterol Treatment Trialists' Collaborators. *Lancet*. 2010;376:1670-81.

Limitations of Statin Therapy

- Doubling the dose of the statin decreases the LDL level further by only 6%.
- Into… at least 2 st… erant.

Combination therapy may be necessary to address residual risk

- Lack of Adherence: 40% to 70% of patients discontinue statin therapy within one year of initiation.
- Risk of Type II diabetes, liver damage, rhabdomyolosis.

Guyton JR, et al. *J Clin Lipidol*. 2014;8(3 Suppl):S72-S81.
Rosenson RS, et al. *J Clin Lipidol*. 2014;8(3 Suppl):S58-S71.

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2016 ACC Consensus Statement on Addition of non-statin drug

Non-statins may be considered in:

- High-risk patients and failure to achieve at least a 50% reduction in LDL-C on maximally tolerated statin,
- Patients who can not take a statin or an effective dose.
- Almost all patients with Ho / He FH.

Non-statins may be considered in this order:

1. Ezetimibe – first additional medication added
2. Bile acid sequenstrants – inefficacy of/intolerance to ezetimibe
3. PCSK9 inhibitors if therapy goals are not met on maximally tolerated statin/ezetimibe therapy

Lloyd-Jones DM, et al. *J Am Coll Cardiol*. 2016;68(1):92-125.

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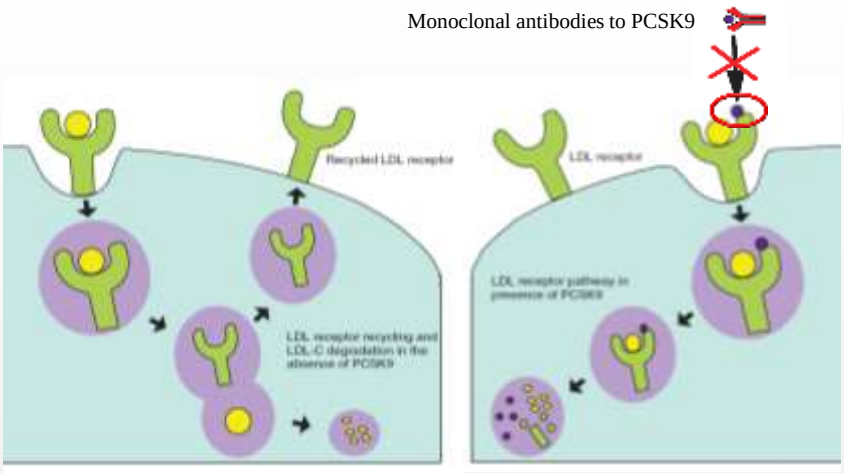
Proprotein convertase subtilisin/kexin type 9 (PCSK9)

LDL receptor pathways in hepatocytes

Monoclonal antibodies to PCSK9



PCSK 9 is synthetized in ER and its 1ry function is regulation of LDLR levels by its effect on receptor recycling.

PCSK 9 Inhibitors

PCSK 9 inhibitors are probably the most promising and the next wonder drug after statins that may save the lives of millions of people in the future.

- ***Evolocumab (Repatha®)*** *marketed by Amgen*
- ***Alirocumab (Praluent®)*** *Currently marketed by Sanofi*
- ***Bococizumab*** *Expected release around 2017-2018 by Pfizer*

Atherosclerosis Supplements. 5(3):13-16 · October 2004.

HeFH: heterozygous familial hypercholesterolemia
HoFH: homozygous familial hypercholesterolemia
ASCVD: atherosclerotic cardiovascular disease

Repatha® [package insert]. Thousand Oaks, CA: Amgen; 2015.
Images available from: https://www.repathahcp.com/

Clinical Trials For Currently Marketed

Evolocumab (Repatha®) and Alirocumab (Praluent®)

- **DESCARTES Trial**
- **ODYSSEY Long-Term Trial**
- **FOURIER Trial**
- **GLAGOV Trial**

N Eng J Med May 8, 2014

ORIGINAL ARTICLE

A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlipidemia

Dirk J. Blom, M.D., Ph.D., Tomas Hala, M.D., Michael Bolognese, M.D., Michael J. Lillestol, M.D., Phillip D. Toth, M.D., Lesley Burgess, M.B., B.Ch., M.Med., Ph.D., Richard Ceska, M.D., Ph.D., Eli Roth, M.D., Michael J. Koren, M.D., Christie M. Ballantyne, M.D., Maria Laura Monsalvo, M.D., Kate Tsirtsonis, M.Sc., Jae B. Kim, M.D., Rob Scott, M.D., Scott M. Wasserman, M.D., and Evan A. Stein, M.D., Ph.D., for the DESCARTES Investigators*

ABSTRACT

BACKGROUND

Evolocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), significantly reduced low-density lipoprotein (LDL) cholesterol levels in phase 2 studies. We conducted a phase 3 trial to evaluate the safety and efficacy of 52 weeks of treatment with evolocumab.

METHODS

We stratified patients with hyperlipidemia according to the risk categories outlined by the Adult Treatment Panel III of the National Cholesterol Education Program. On the basis of this classification, patients were started on background lipid-lowering therapy with diet alone or diet plus atorvastatin at a dose of 10 mg daily, atorvastatin at a dose of 80 mg daily, or atorvastatin at a dose of 80 mg daily plus ezetimibe at a dose of 10 mg daily, for a run-in period of 4 to 12 weeks. Patients with an LDL cholesterol level of 75 mg per deciliter (1.9 mmol per liter) or higher were then randomly assigned in a 2:1 ratio to receive either evolocumab (420 mg) or placebo

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DESCARTES trial

- 2120 patients with LDL levels >75 mg/dl were included:
- Of the 901 patients who received a study drug,
  111 received background lipid-lowering therapy with diet alone,
  383 received 10 mg of atorvastatin daily,
  218 received 80 mg of atorvastatin daily, and
  189 received 80 mg of atorvastatin plus 10 mg of ezetimibe daily.

Trial Name	Patient Population	Treatments * In addition to statin
DESCARTES[53]	Background therapy of: Diet Atorvastatin 10 mg Atorvastatin 80 mg Atorvastatin 80 + Zetia	In addition to background therapy: 1) Evolocumab 2) Placebo

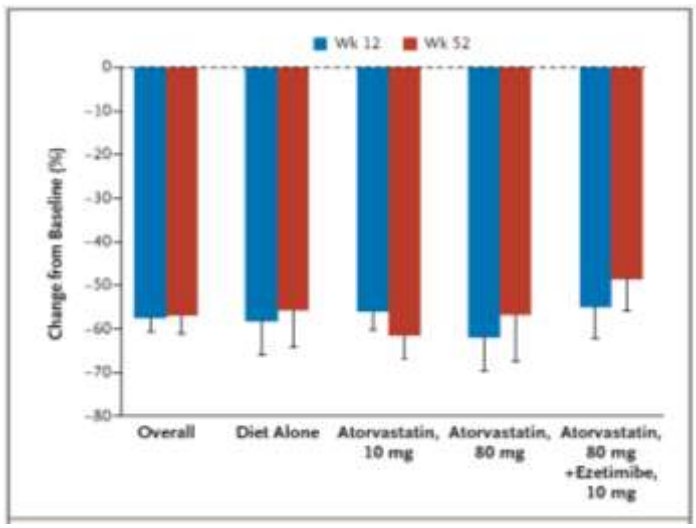
Primary: % change from baseline in LDL-C at week 52

Secondary:

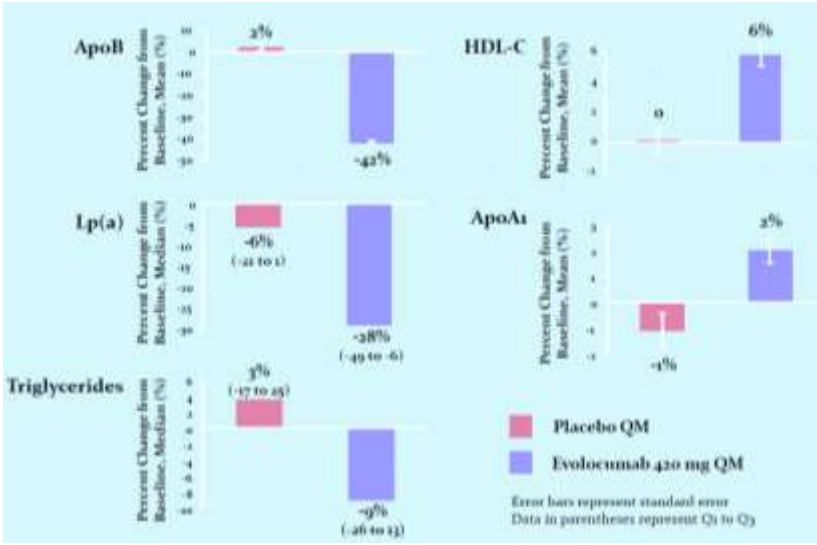
- % change from baseline in LDL C at week 12 and 52.
- % of patients with LDL-C <70 mg/dL at wk 52
- % changes from baseline for TC, HDL-C, ApoB, VLDL-C, TG, and Lp(a) at wk 52

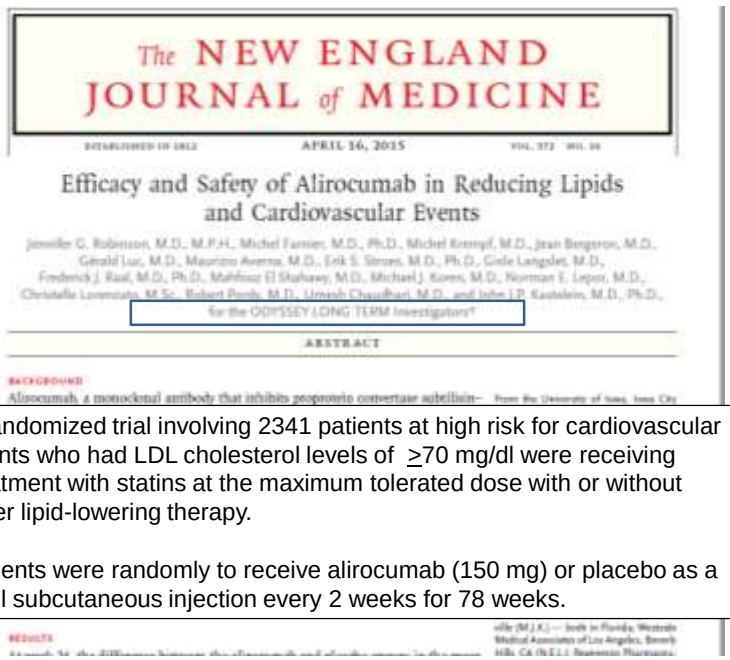
Dirk J. Blom, et al. A 52-Week Placebo-Controlled Trial N Engl J Med 370;19 May 8, 2014of

Percent Reduction from Baseline in LDL Levels in the Evolocumab Group, as Compared with Placebo Group, at Weeks 12 and 52, According to Background Lipid-Lowering Therapy.



DESCARTES: Other Lipids





The NEW ENGLAND JOURNAL of MEDICINE

APRIL 16, 2015

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

ABSTRACT

A randomized trial involving 2341 patients at high risk for cardiovascular events who had LDL cholesterol levels of ≥70 mg/dl were receiving treatment with statins at the maximum tolerated dose with or without other lipid-lowering therapy.

Patients were randomly to receive alirocumab (150 mg) or placebo as a 1-ml subcutaneous injection every 2 weeks for 78 weeks.

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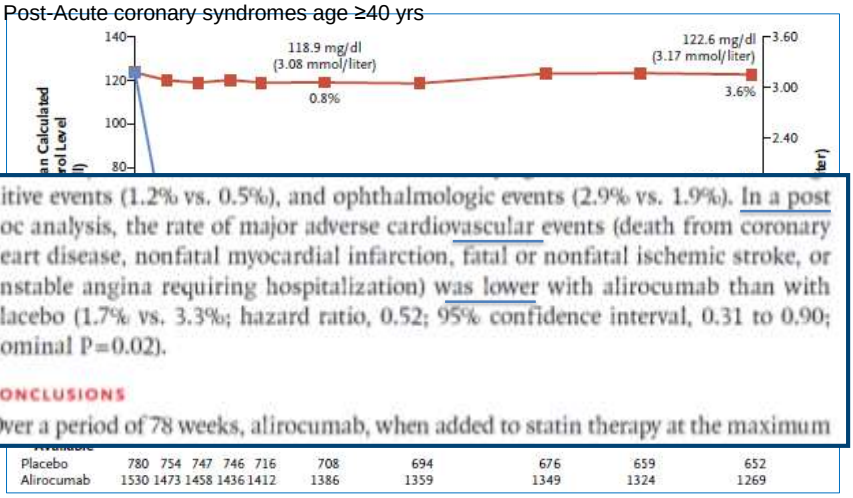
ODYSSEY Long-Term Trial (Alirocumab)

Post-Acute coronary syndromes age ≥40 yrs



nitive events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%). In a post hoc analysis, the rate of major adverse cardiovascular events (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was lower with alirocumab than with placebo (1.7% vs. 3.3%; hazard ratio, 0.52; 95% confidence interval, 0.31 to 0.90; nominal P=0.02).

CONCLUSIONS

Over a period of 78 weeks, alirocumab, when added to statin therapy at the maximum

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Robinson JG, et al. *N Engl J Med*. 2015;372(16):1489-1499. Used with permission.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 4, 2017 VOL. 376 NO. 18

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Nariman Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9) and lowers low-density lipoprotein (LDL) cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain.

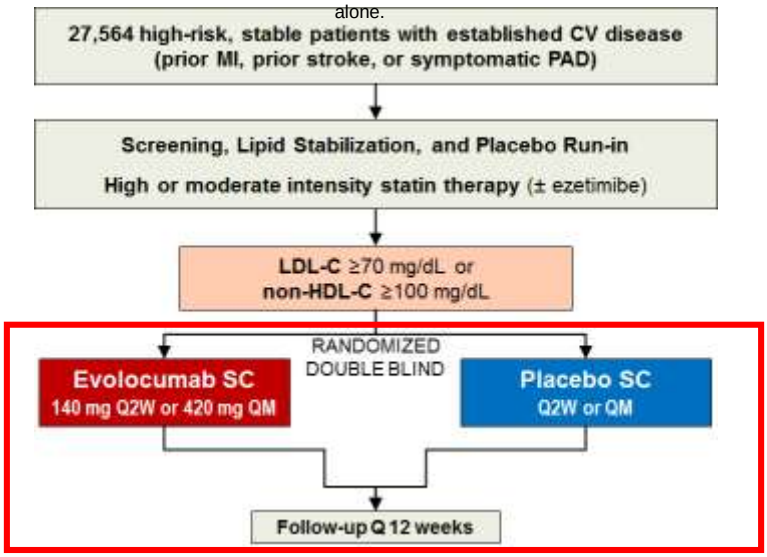
METHODS

We conducted a randomized, double-blind, placebo-controlled trial involving 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (M.S.S., R.P.G., S.D.W., S.A.M., J.F.K.); Sydney Medical School, National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney (A.C.K.); Amgen, Thousand Oaks, CA (N.H., H.W., T.L., S.M.W.); International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London (P.S.S.); and Oslo University Hospital, Ullevål and

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.



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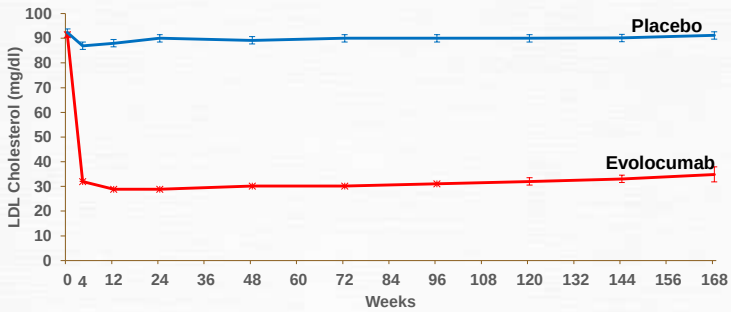
FOURIER Evolocumab Study

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

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; LDL-C, low-density lipoprotein cholesterol.

Sabatine MS, et al. *NEJM*. 2017; epub ahead of print.

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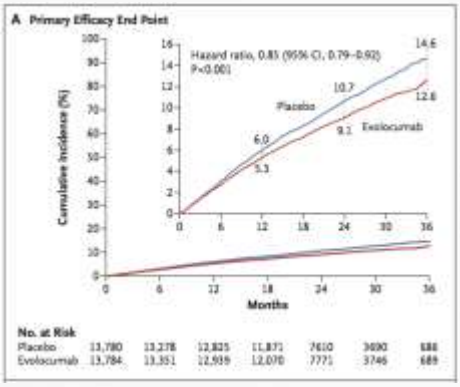
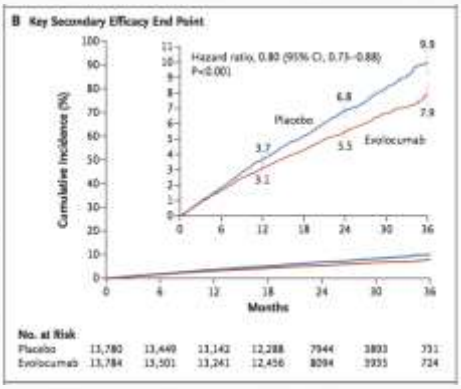
Endpoints

Primary Endpoint Major cardiovascular events, defined as the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization.
Secondary Endpoint Composite of cardiovascular death, MI, or stroke.



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



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

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; MI, myocardial infarction.

Sabatine MS, et al. *NEJM*. 2017; epub ahead of print.

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JAMA

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Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients
The GLAGOV Randomized Clinical Trial

JAMA
The Journal of the American Medical Association

SJ Nicholls and coauthors

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial

Published online November 15, 2016

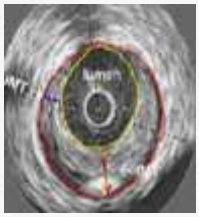
Available at jama.com and mobile.jamanetwork.com

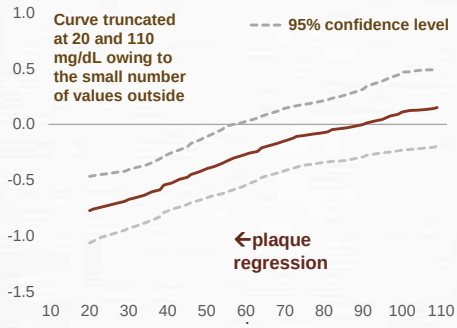
The JAMA Network

jamanetwork.com

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

The GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial (enrollment 5/2013 to 1/2015) conducted at 197 academic and community hospitals in 6 continents, enrolling 968 patients (mean age 59.8 years, 27.8% female) with CAD





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

Abbreviations: CAD, coronary artery disease; GLAGOV, Global Assessment of Plaque Regression With a PCSK9 Antibody; LDL-C, low-density lipoprotein cholesterol; SQ, subcutaneous.

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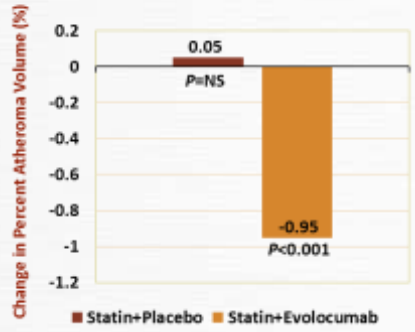
With a PCSK9 Antibody as Measured by Intravascular Ultrasound

Trial design: Patients 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)
- Patients 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, the PCSK9 inhibitor evolocumab resulted in a greater change in percent atheroma volume and a greater proportion of patients with plaque regression

Abbreviations: CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; SQ, subcutaneous.

Nicholls SJ, et al. *JAMA*. 2016;316:2373-2384.

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

PCSK9 Inhibitors

Agent	Usual recommended starting daily dosage	Dosage range	Method of administration
PCSK9 inhibitors			
Alirocumab	75 mg every 2 weeks	75-150 mg every 2 weeks	SQ
Evolocumab	140 mg every 2 weeks or 420 mg once monthly	Not applicable	SQ

Metabolic Effects:

- ↓LDL-C 48%-71%, ↓ non-HDL-C 49%-58%, ↓TC 36%-42%, ↓Apo B 42%-55% by inhibiting PCSK9 binding with LDLRs, increasing the number of LDLRs 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 with similar rates for drug vs. placebo were:
  - Alirocumab: nasopharyngitis, influenza, urinary tract infections, diarrhea, bronchitis, and myalgia
  - Evolocumab: nasopharyngitis, back pain, and upper respiratory tract infection

Abbreviations: apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; SQ, subcutaneous injection; TC, total cholesterol.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497; Praluent (alirocumab) [PI] 2015; Repatha (evolocumab) [PI]; 2016.

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Conclusions

- Statins are as effective in reducing atherosclerotic CVD risk.
- 10 to 15% of patients are Statin Intolerant and 40% to 70% of patients/year are non-adherent.
- Monoclonal antibodies to PCSK9 added to statins, inhibit LDL-receptor degradation and ↓ LDL-C by 55-60%.
- They reduce apoB, TG and TC significantly with modest increase in HDL-C.

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Conclusions

- Alirocumab and evolcumab are indicated in addition to diet and maximally tolerated statin therapy in patients with ASCVD or Homo/Heterozygous FH who require more LDL-C reduction.
- Given by S.C injections once or twice a month.
- Safety and tolerability profile have so far been excellent.

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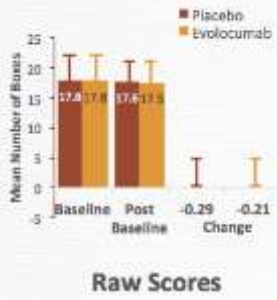
EBBINGHAUS: Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects

N=1,974 patients from FOURIER Study, followed for 96 weeks

- EBBINGHAUS is the first prospectively designed study to evaluate the relationship between PCSK9 inhibition and changes in cognition, including memory, attention, and reaction time
- 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)
- All secondary outcomes were similar for placebo and evolocumab, including patient self-reports and investigator-reported cognitive adverse events



Raw Scores

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; PCSK9, proprotein convertase subtilisin/kexin type 9.

https://clinicaltrials.gov/ct2/show/NCT02207634;
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;
https://challengesincardiology.com/ebbinghaus-a-cognitive-study-of-patients-enrolled-in-the-fourier-trial/.

PCSK9 Inhibitors cost nearly 100 times as much as generic atorvastatin 80 mg (2016)

From http://www.goodrx.com/high-cholesterol/drugs Accessed 26 Jan 2016

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

Abbreviations: 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.

Baigent C, et al. *Lancet*. 2005;366:1267-1278; 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; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497; 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.

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Genetic studies support the role of PCSK9 in affecting LDL levels

➢ Gain in function mutation:

↑ PCSK9 → ↓ LDLR → ↑ LDL-C

Causes high LDL-C levels → premature CVD.

➢ Loss of function mutations:

PCSK9 → ↑ LDLR → ↓ LDL-C

Cause low LDL-C levels → Reduced incidence of CHD,

Abifadel M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet 2003; 34: 154–6.
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