*Norman Rockwell, Maternity waiting room, 1946*

## Gli inibitori di PCSK9 tra mito e realtà e in quali pazienti.

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Department of Medical and Surical Sciences
University of Bologna, Bologna, Italy

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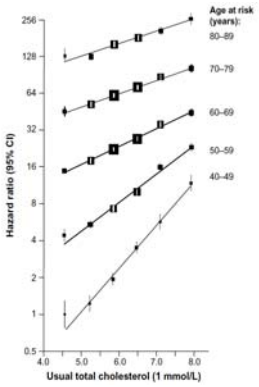



## Vascular mortality, age and cholesterol levels

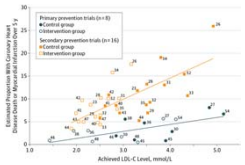

Prospective Studies Collaboration. *Lancet.* 2002;360:1903-191

2

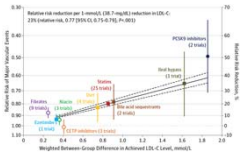
The JAMA Network

From: **Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions. A Systematic Review and Meta-analysis**

Achieved LDL-C and Major Coronary Event Rates From 24 Trials of Established Interventions That Lower LDL-C



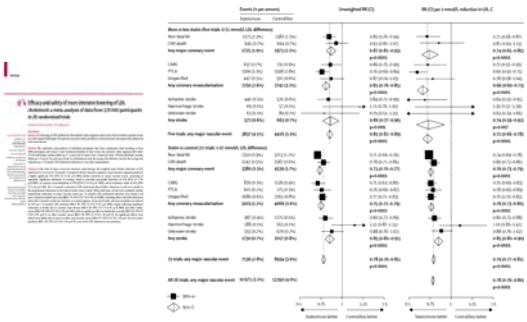

Weighted Between-Group Difference in Achieved LDL-C Level and Relative Risk for Major Vascular Events for Each type of intervention




JAMA. 2016;316(12):1289-1297. doi:10.1001/jama.2016.13985

3

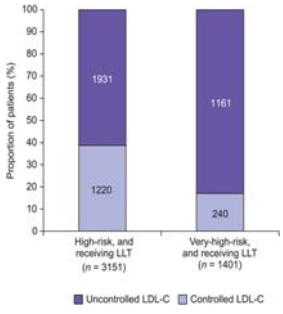
## Effects of statin treatment on each type of vascular event



Cholesterol Treatment Trialist's (CTT) Collaboration, Lancet 2010

4

Percentage of patients in the high-risk and very-high-risk groups receiving any form of lipid-lowering therapy (LLT) who have controlled and uncontrolled levels of low-density lipoprotein cholesterol (LDL-C).




Halcox J, Tubach F, Banegas J, Borghi C et al, PlosOne 2015

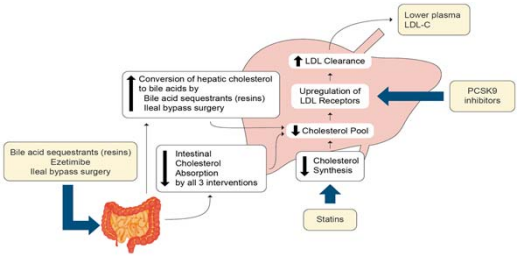
5

## Reasons for a partial LDL-C response to statins

- Poor adherence
- Individual variability in response
- Flat dose-response curve ("rule of 6")
- Counter-regolatory mechanisms

6

Low-density lipoproteins cause atherosclerotic cardiovascular disease.




Eur Heart J. 2017;38(32):2459-2472.

9

PCSK9: a convertase that coordinates LDL catabolism

Jay D. Horton,[1,6,7] Jonathan C. Cohen,[2] and Helen H. Hobbs[1,6,7,8]

Department of Internal Medicine,[6] Department of Molecular Genetics,[7] and The Howard Hughes Medical Institute,[8] University of Texas Southwestern Medical Center, Dallas, TX 75390-9046

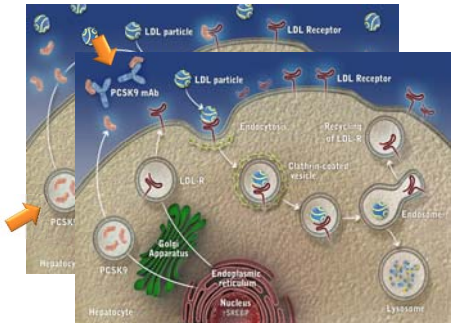
**Abstract** **The identification and characterization of proprotein convertase subtilisin-like/kexin type 9 (PCSK9) have provided new insights into LDL metabolism and the causal role of LDL in coronary heart disease (CHD). PCSK9 is a secreted protease that mediates degradation of the LDL receptor by interacting with the extracellular domain and targeting the receptor for degradation. Individuals with loss-of-function mutations in *PCSK9* have reduced plasma levels of LDL cholesterol and are protected from CHD; these observations have validated PCSK9 as a therapeutic target and suggested new approaches for the treatment and prevention of CHD.**—Horton, J. D., J. C. Cohen, and H. H. Hobbs. **PCSK9: a convertase that coordinates LDL catabolism.** *J. Lipid Res.* **2009.** 50: S172–S177.

of the proprotein convertase family, PCSK9. *PCSK9* encodes a 692 amino acid protein that is expressed predominantly in liver, intestine, and kidney (2). The protein contains a signal sequence, a prodomain (amino acids 31–152), a catalytic domain (amino acids 153–451), and a C-terminal domain (amino acids 452–692) that are rich in cysteines and histidines (**Fig. 1A**). Overexpression of PCSK9 in livers of mice markedly reduces hepatic LDL receptor (LDLR) protein (but not mRNA) levels, causing hypercholesterolemia (3). This finding suggested that the missense mutations identified by Abifadel et al. (1) conferred a gain-of-function to the mutant protein. Subsequent studies revealed that inactivation of PCSK9 in humans and mice resulted in hypocholesterolemia (3).

**Supplementary key words** low density lipoprotein receptor • proprotein convertase subtilisin-like/kexin type 9 • low density lipoprotein • hypercholesterolemia

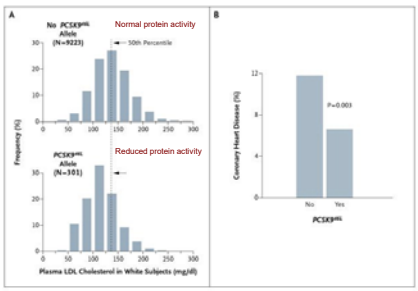
10

Effect of PCSK9 and PCSK9 antibodies on LDL-receptors




11

Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Events (Panel B) among White Subjects, According to the Absence (GoF) or Presence (LoF) of a PCSK9$^{46L}$ Allele

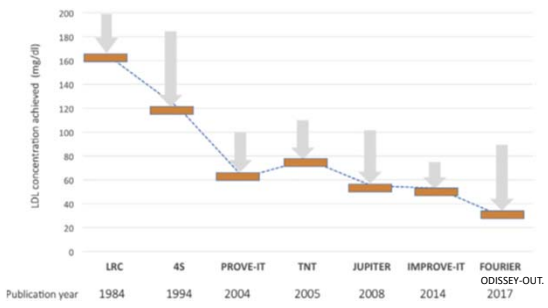



In Panel A, the distribution of plasma LDL cholesterol levels at baseline among 9223 white subjects who did not have a PCSK946L allele (top) is compared with the distribution of levels among the 301 white subjects who were either heterozygous or homozygous for this allele (reduced activity-bottom). Panel B shows the percentage of participants from these two groups who had no evidence of coronary heart disease at baseline and in whom coronary heart disease developed during the 15-year follow-up period. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

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

12

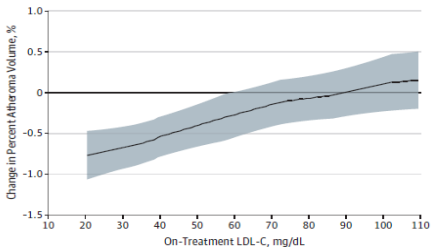
Historical perspective of LDL levels achieved in some of the major RCTs with lipid-lowering drugs




ODISSEY-OUT.

14

Post Hoc Analysis Examining the Relationship Between Achieved LDL-C Level and Change in Percent Atheroma Volume



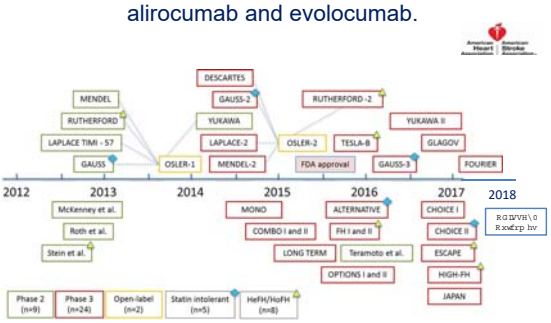

Nicholls SJ et al. JAMA. 2016 Dec 13;316(22):2373-2384

15

Clinical evidence?

16

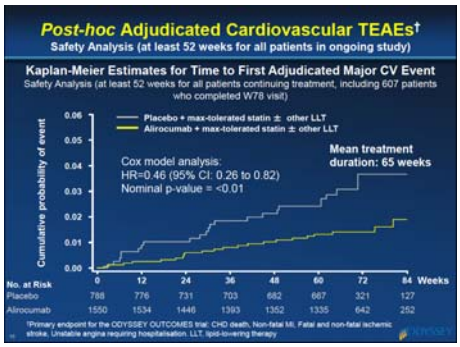
## Timeline of randomized controlled trials of alirocumab and evolocumab.




Aris Karatasakis et al. J Am Heart Assoc 2017;6:e006910

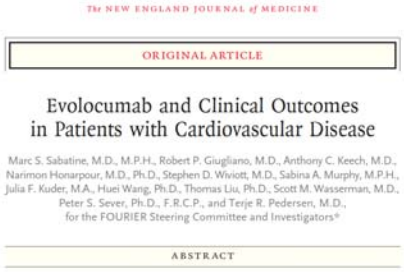
17

## ODISSEY Long-term study




Robinson JG et al, N Engl J Med 2015

19



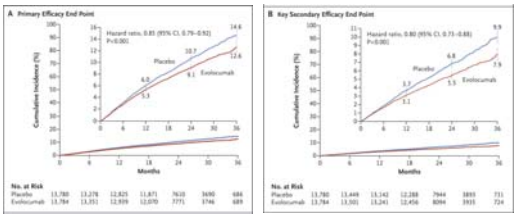

N Engl J Med 2017.
DOI: 10.1056/NEJMoa1615664

20

## Cumulative Incidence of Cardiovascular Events.

Composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization

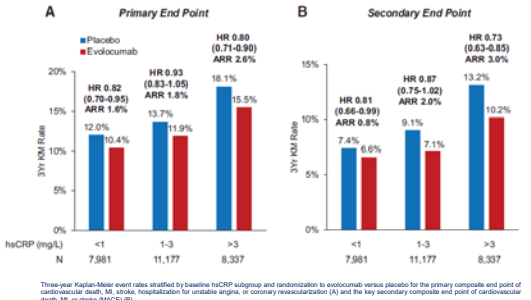
Composite of cardiovascular death, myocardial infarction, or stroke



Sabatine MS et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1615664

22

## Rate of CV events by hsCRP and randomized treatment in the FOURIER Trial

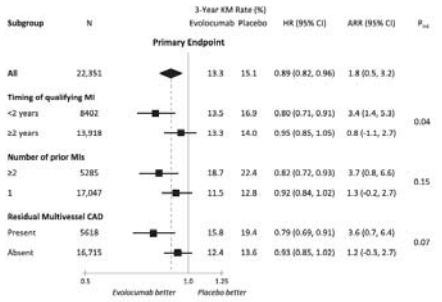



Three-year Kaplan-Meier event rates stratified by baseline hsCRP subgroup and randomization to evolocumab versus placebo for the primary composite end point of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization (A) and the key secondary composite end point of cardiovascular death, MI, or stroke (MACE) (B).

Bohula EA et Al. Circulation 2017; doi:10.1161/CIRCULATIONAHA.118.034032

23

Clinical benefit of Evolocumab by severity and extent of CAD in the FOURIER trial:
***Primary Endpoint***

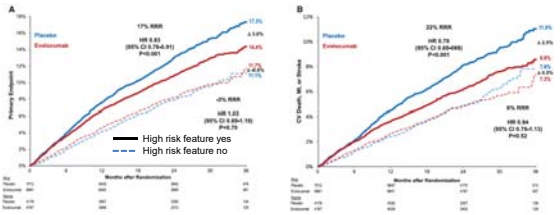



Sabatine MS et Al. Hypertension 2018; DOI: 10.1161/CIRCULATIONAHA.118.034309

24

Clinical benefit of Evolocumab by qualifying MI in the FOURIER trial in patients with at least one high risk feature or no additional high risk features

Primary end-point | Secondary end-point




Sabatine MS et Al. Hypertension 2018; DOI: 10.1161/CIRCULATIONAHA.118.034309

25

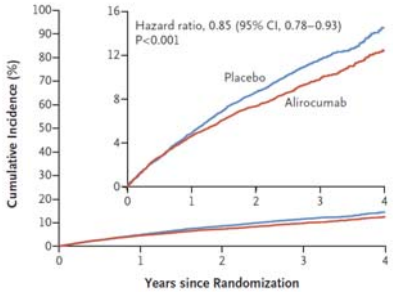

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*

N Engl J Med 2018;379:2097-107.
DOI: 10.1056/NEJMoa1801174


26

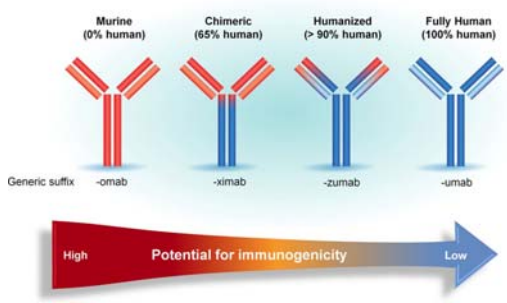
Cumulative Incidence of the Composite Primary End Point in ODYSSEY OUTCOMES trial




Schwartz GG et Al., NEJM 2018

28

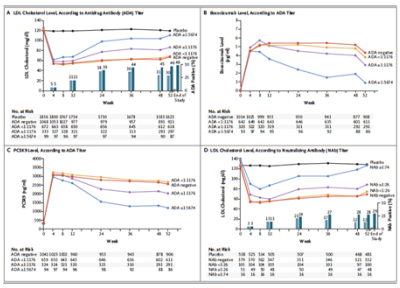
Humanization of therapeutic antibodies has reduced their immunogenicity.




Ian N. Foltz et al. Circulation. 2013;127:2222-2230

29

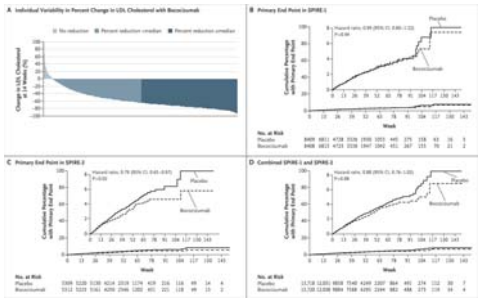
Effect of Antidrug Antibodies on the Durability of Low-Density Lipoprotein (LDL) Cholesterol Lowering and on Plasma Bococizumab and PCSK9 Levels.



Ridker PM et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1701488

30

Percent Reduction in LDL Cholesterol and the Primary End Point in SPIRE-1 and SPIRE-2.



The NEW ENGLAND JOURNAL of MEDICINE

Ridker PM et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1701488

31

Pharmacological treatment of dylipidemia

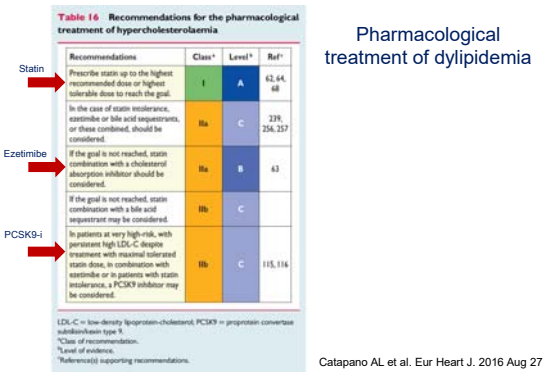



Table 16 Recommendations for the pharmacological treatment of hypercholesterolaemia

| Recommendations | Class* | Level* | Ref* |
|---|---|---|---|
| Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal. | I | A | 62, 64, 68 |
| In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered. | IIa | C | 239, 256, 257 |
| If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered. | IIa | B | 63 |
| If the goal is not reached, statin combination with a bile acid sequestrant may be considered. | IIb | C | |
| In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered. | IIb | C | 115, 116 |

LDL-C = low-density lipoprotein-cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
*Class of recommendation.
†Level of evidence.
‡Reference(s) supporting recommendations.

Catapano AL et al. Eur Heart J. 2016 Aug 27

32

## Which patients?

- FH-Homozygous
- PTS not at target with S+E
  - FH-Heterozygous
  - Previous CVD
  - High CV risk profile (no CVD)
  - ACS
- Patients intolerant to statins

33

ESC European Society of Cardiology

European Heart Journal (2017) 00, 1–13 doi:10.1093/eurheartj/ehx549

CURRENT OPINION

## 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia

Ulf Landmesser[1*†], M. John Chapman[2†], Jane K. Stock[3], Pierre Amarenco[4], Jill J.F. Belch[5], Jan Borén[6], Michel Farnier[7], Brian A. Ference[8], Stephan Gielen[9], Ian Graham[10], Diederick E. Grobbee[11], G. Kees Hovingh[12], Thomas F. Lüscher[13], Massimo F. Piepoli[14], Kausik K. Ray[15], Erik S. Stroes[12], Olov Wiklund[16], Stephan Windecker[17], Jose Luis Zamorano[18], Fausto Pinto[19], Lale Tokgözoğlu[20], Jeroen J. Bax[21], and Alberico L. Catapano[22]

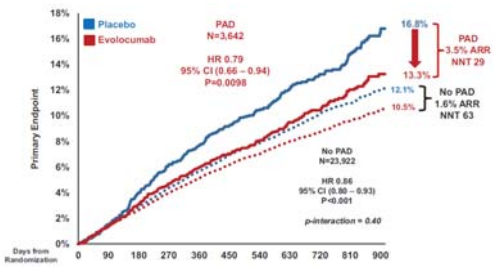
34

## Which patients?

- FH-Homozigus
- PTS not at target with S+E
  - FH-Heterozigus
  - Previous CVD
  - High CV risk profile (no CVD)
  - ACS
- Patients intolerant to statins
- PAD?

35

Primary endpoint in patients with and without PAD enrolled in the FOURIER Trial




Bonaca MP et Al., Circulation. 2017;DOI: 10.1161/CIRCULATIONAHA.117.032235

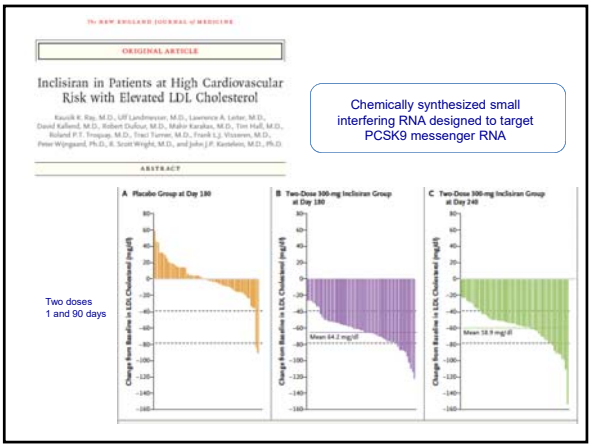
36

## Gaps in knowledge about PCSK9-inhibitor therapy

- Inter-individual variability in low-density lipoprotein cholesterol (LDL-C) lowering response to alirocumab and evolocumab
- Dedicated trials in patients with recent (<1 month) cardiovascular events
- Impact of PCSK9 inhibition in patients with chronic kidney disease (not requiring dialysis)
- Long-term efficacy and safety of PCSK9 inhibitors in clinical use
- Long-term safety of very low LDL-C levels
- Long-term impact of PCSK9 inhibition on disability and cardiovascular mortality
- Long-term evaluation of risk for type 2 diabetes
- Impact of sustained and marked LDL-C lowering to very low levels on plaque composition and stability
- Long-term impact of reduction in elevated lipoprotein(a) with PCSK9 inhibition
- Cost-effectiveness of PCSK9 inhibition added to maximally tolerated statin with or without ezetimibe therapy.

Landmesser U et al, Eur Heart J 2017

37




38


## Conclusions

- **Statins** are the drugs of choice for LDL-C reduction (RCT,GL) particularly in patients with history of CVD and Acute Coronary Syndrome (ACS).
- Not all the patients with CHD achieve a satisfactory LDL-C control with statins.
- The use of (ezetimibe) **ezetimibe+statins** is a rationale and effective approach to LLT in high risk patients and in those with ACS.
- The level of LDL-C can be further reduced by **PCSK9-inhibitors** particularly in patients with FH, high CV risk not reacing the target and statin intolerant.
- The potential use of alla these drugs and their combination has significantly extended the treatment options and the “taylored” efficacy of LLT in high-risk patients with CHD and ACS

39