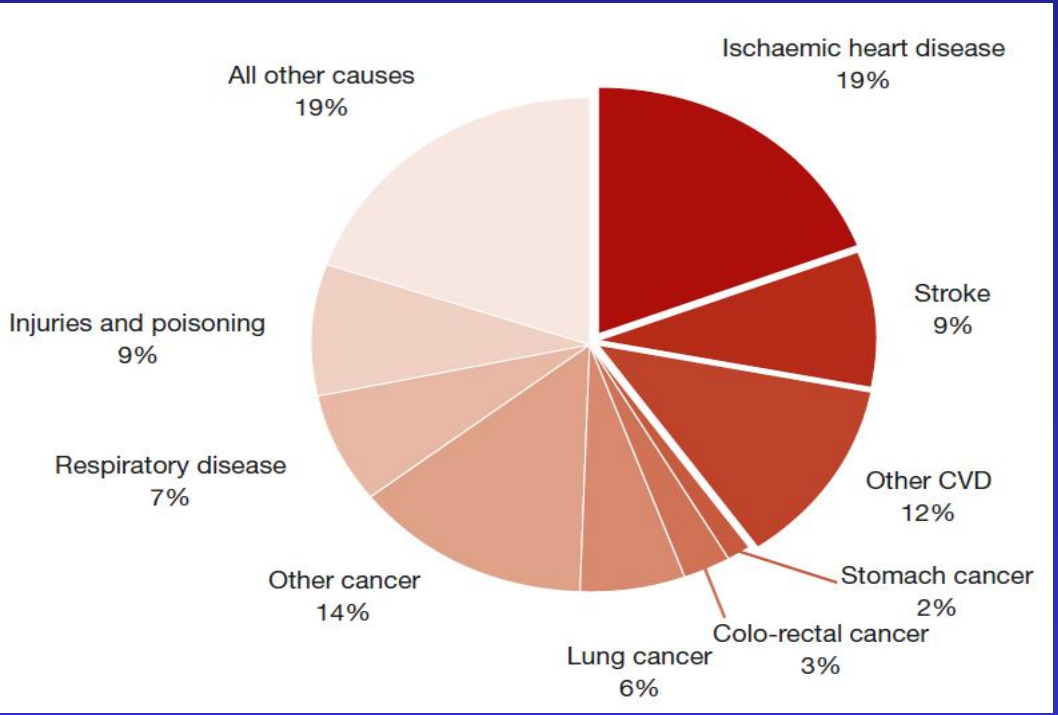
A.S.L. CN1
Azienda Sanitaria Locale
di Cuneo, Mondovì e Savigliano

PCSK9 inhibitors: from large trials to clinical practice.

Mauro Feola

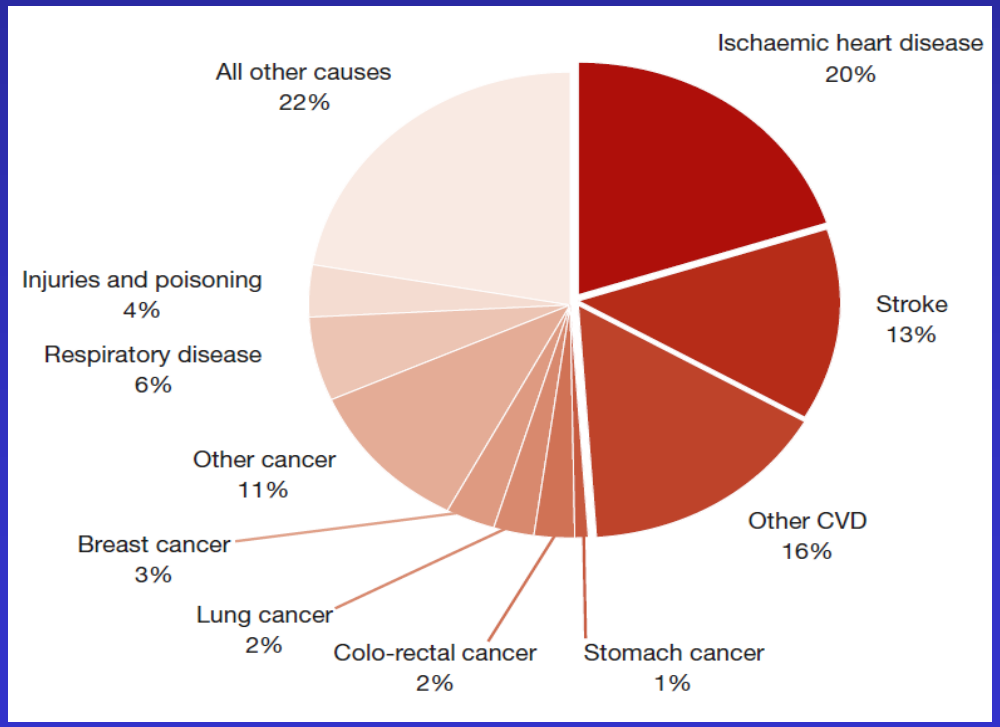
Cardiologia Ospedale di Mondovi' (CN)

Cardiovascular Disease accounts for 45% of all deaths in Europe



40% total Deaths by cause, males, Europe

49% total Deaths by cause, females, Europe



European Cardiovascular Disease Statistics – 2017 Edition

CV RISK CATEGORIES

ESC European Society of Cardiology
EAS

2019

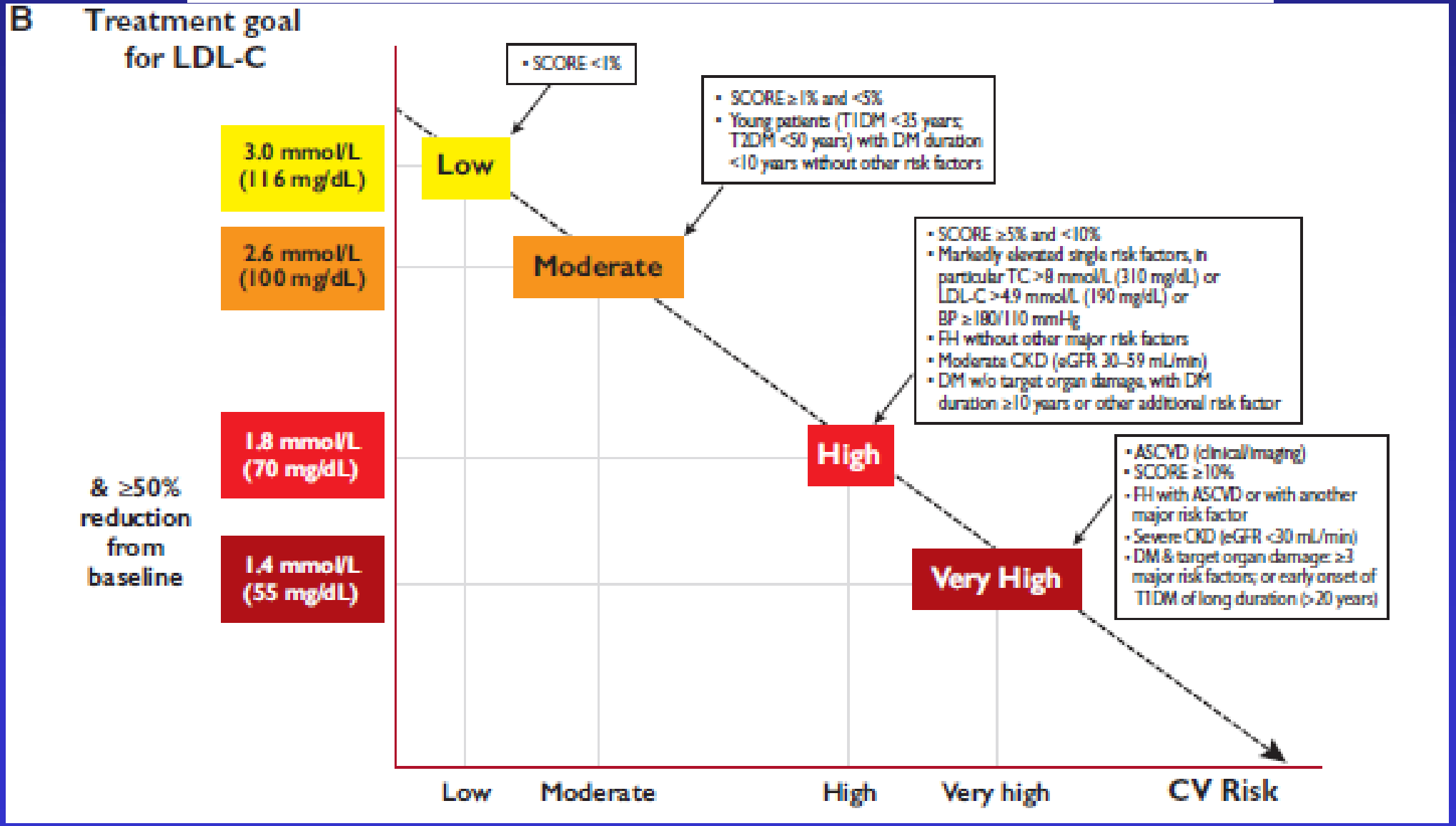
Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.

2016

Very high-risk	Subjects with any of the following: • Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia. • Severe CKD (GFR <30 mL/min/1.73 m^2). • A calculated SCORE ≥10% for 10-year risk of fatal CVD.

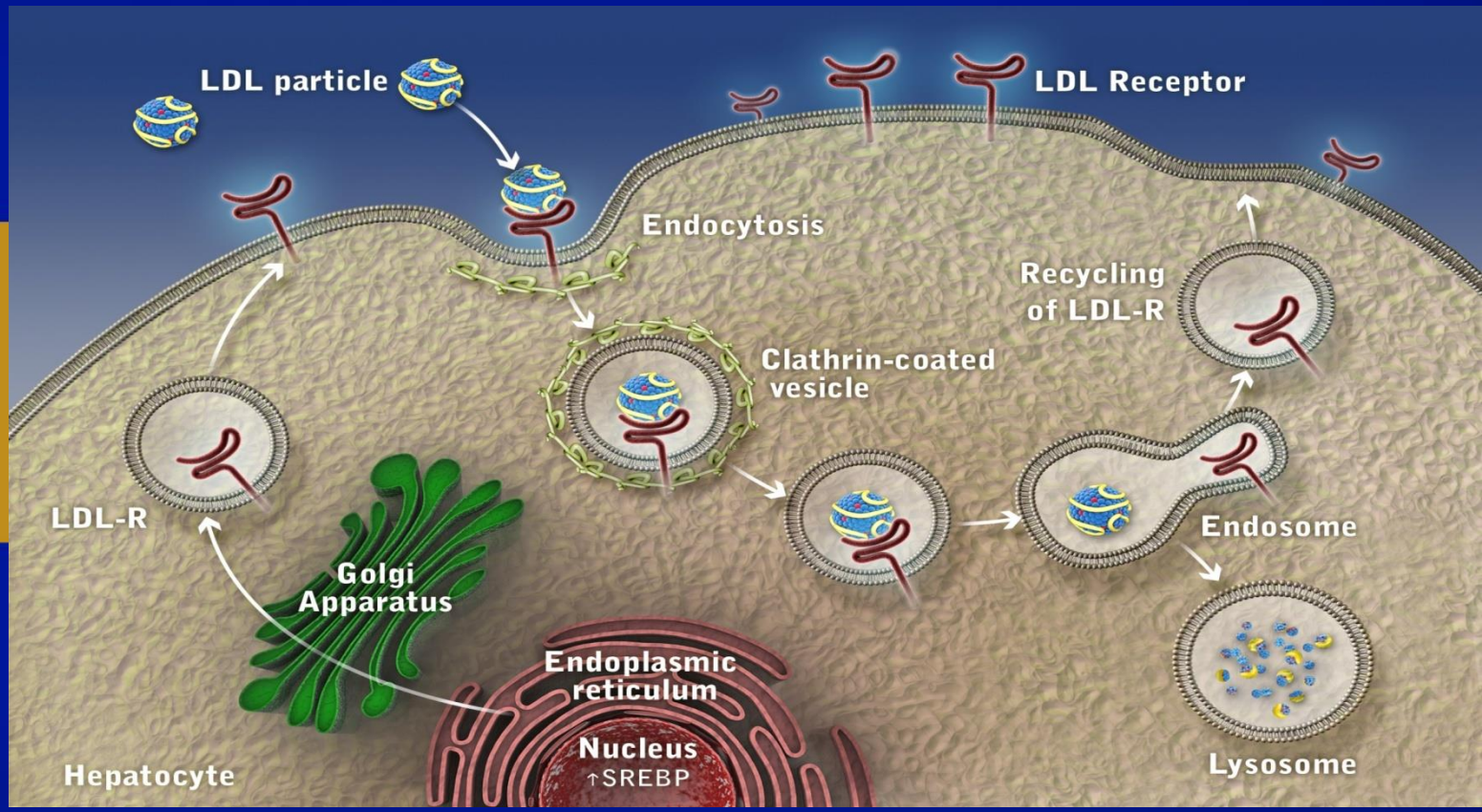
1. ASCVD definition more precise
2. DM definition more precise
   - T1DM of long duration added
3. FH with ASCVD or another risk factor added

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*



LDL Receptor Function and Life Cycle

1985 Goldstein & Brown



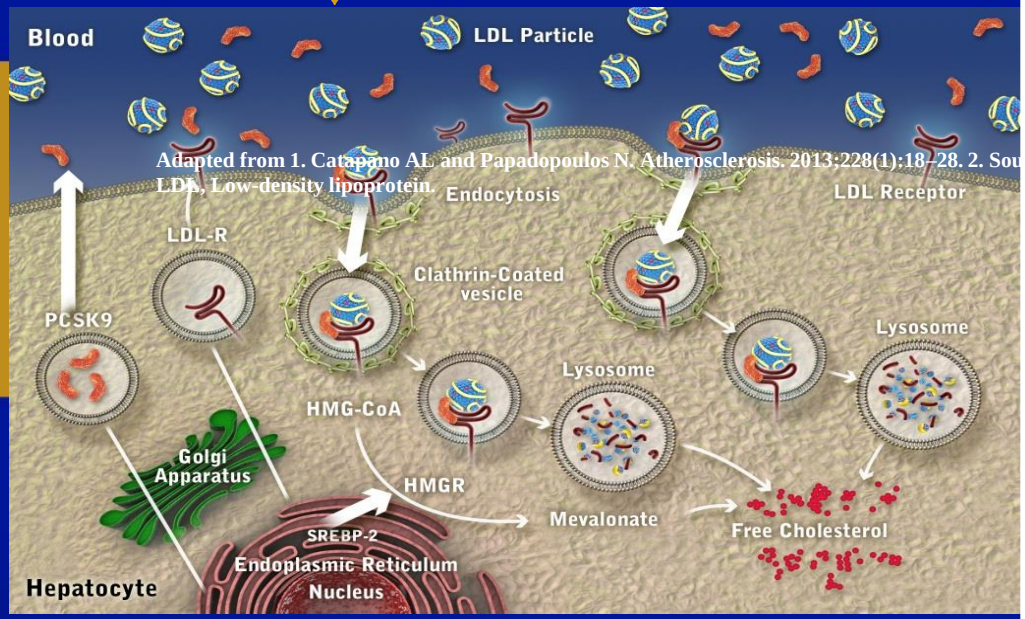
Adapted from Catapano & Papadopoulos *Atherosclerosis* 2013;228:18–28

PCSK9 mutations and effect on LDL metabolism

Gain of Function

↓LDL-R levels

↓LDL clearance



Adapted from 1. Catapano AL and Papadopoulos N. Atherosclerosis. 2013;228(1):18–28. 2. Sou
LDL, Low-density lipoprotein.

↑LDL

High risk for atherosclerosis and coronary heart disease (CHD)

Loss of Function

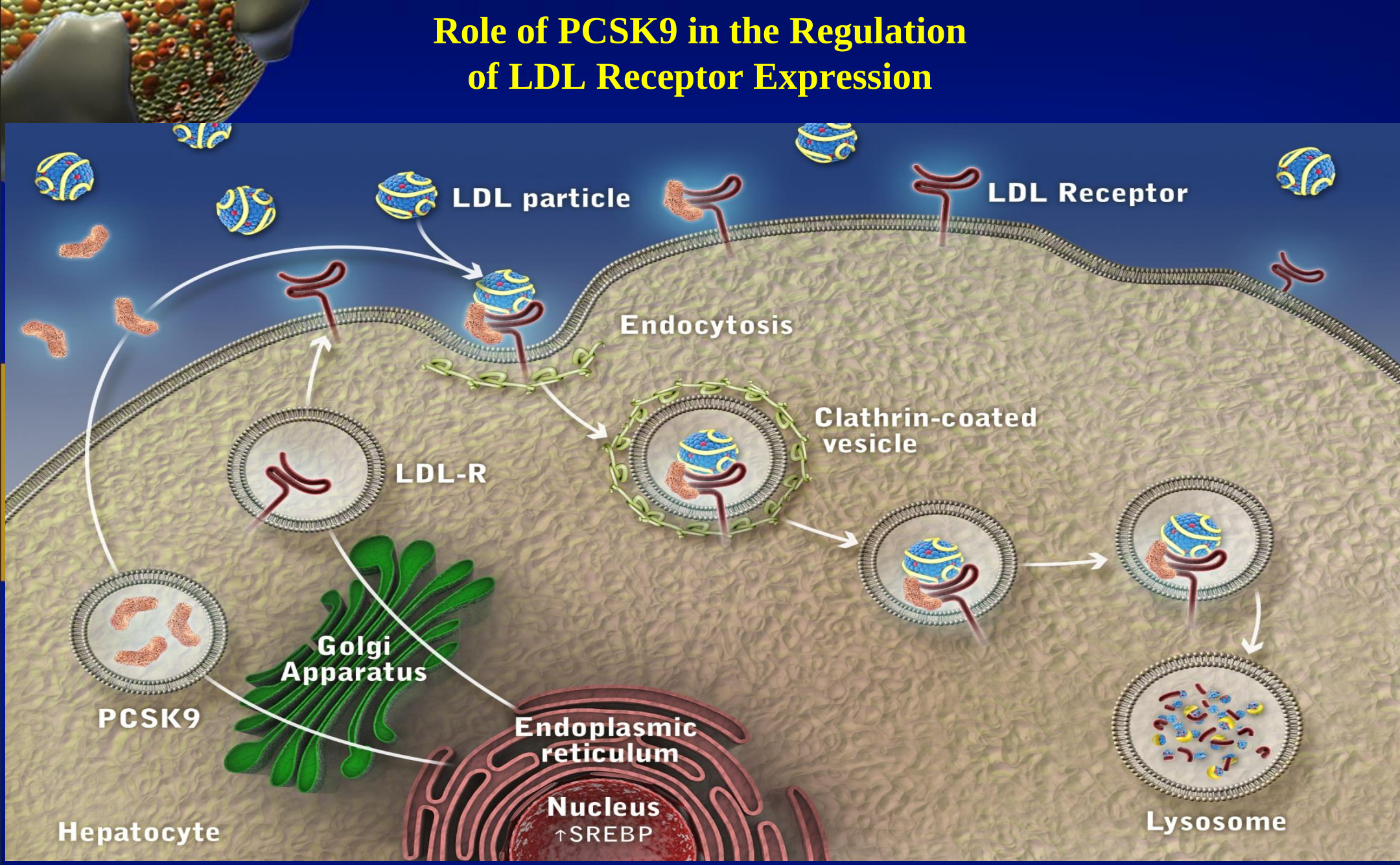
↑LDL-R levels

↑LDL clearance

↓LDL

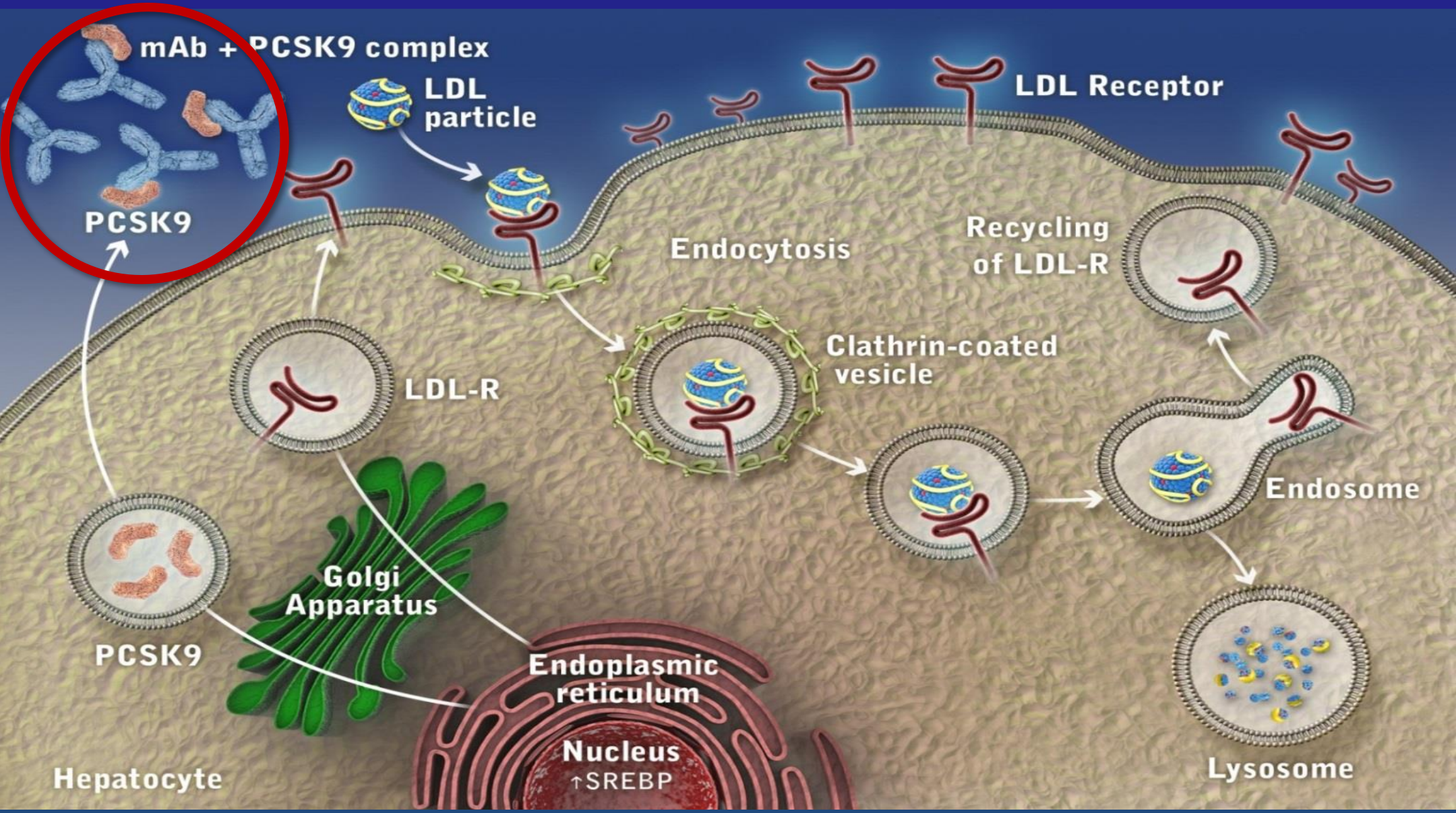
Protection from atherosclerosis and CHD

Role of PCSK9 in the Regulation of LDL Receptor Expression



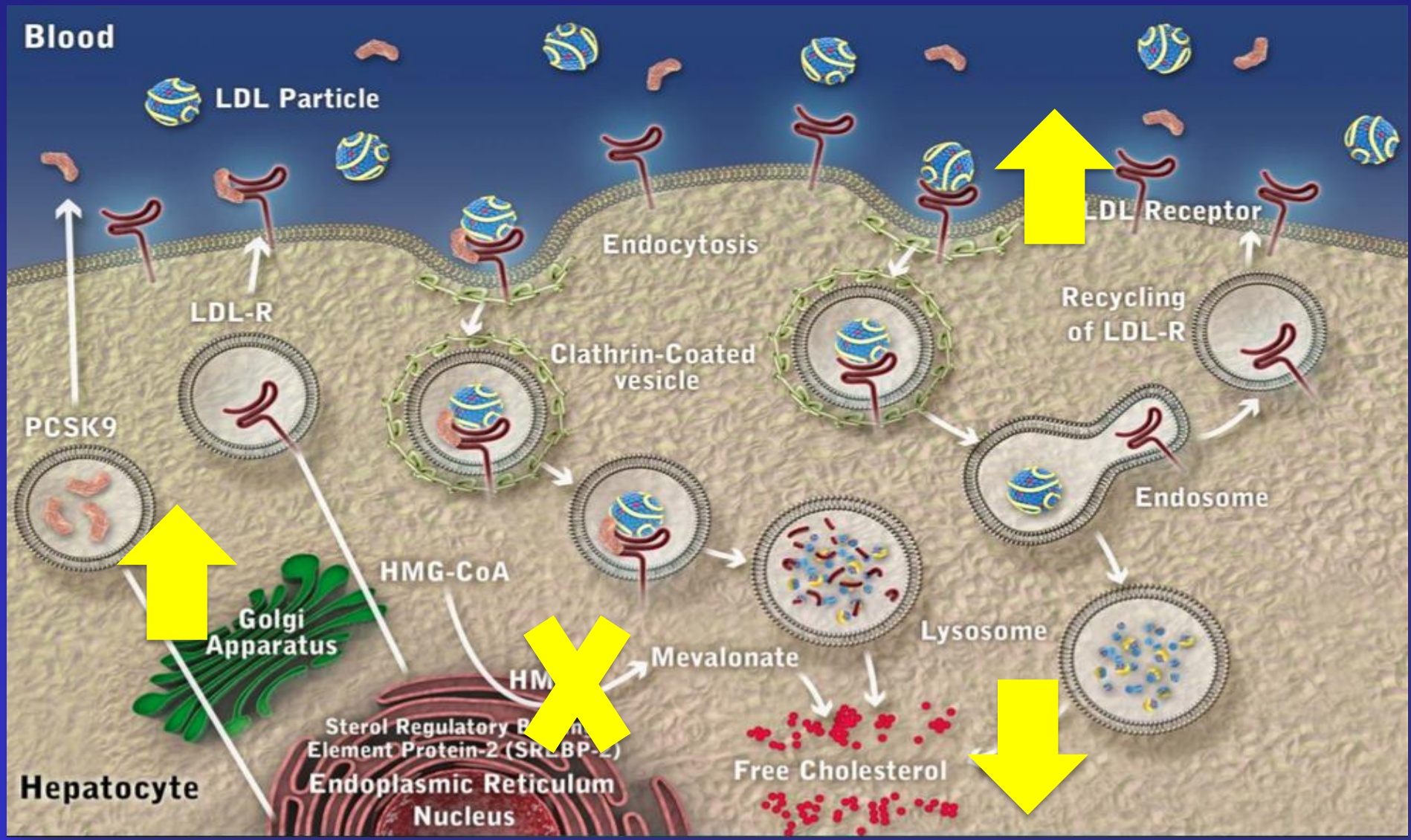
Adapted from Catapano & Papadopoulos Atherosclerosis 2013;228:18–28

Impact of a PCSK9 Monoclonal Antibody on LDL Receptor Expression



Adapted from Catapano & Papadopoulos Atherosclerosis 2013;228:18–28

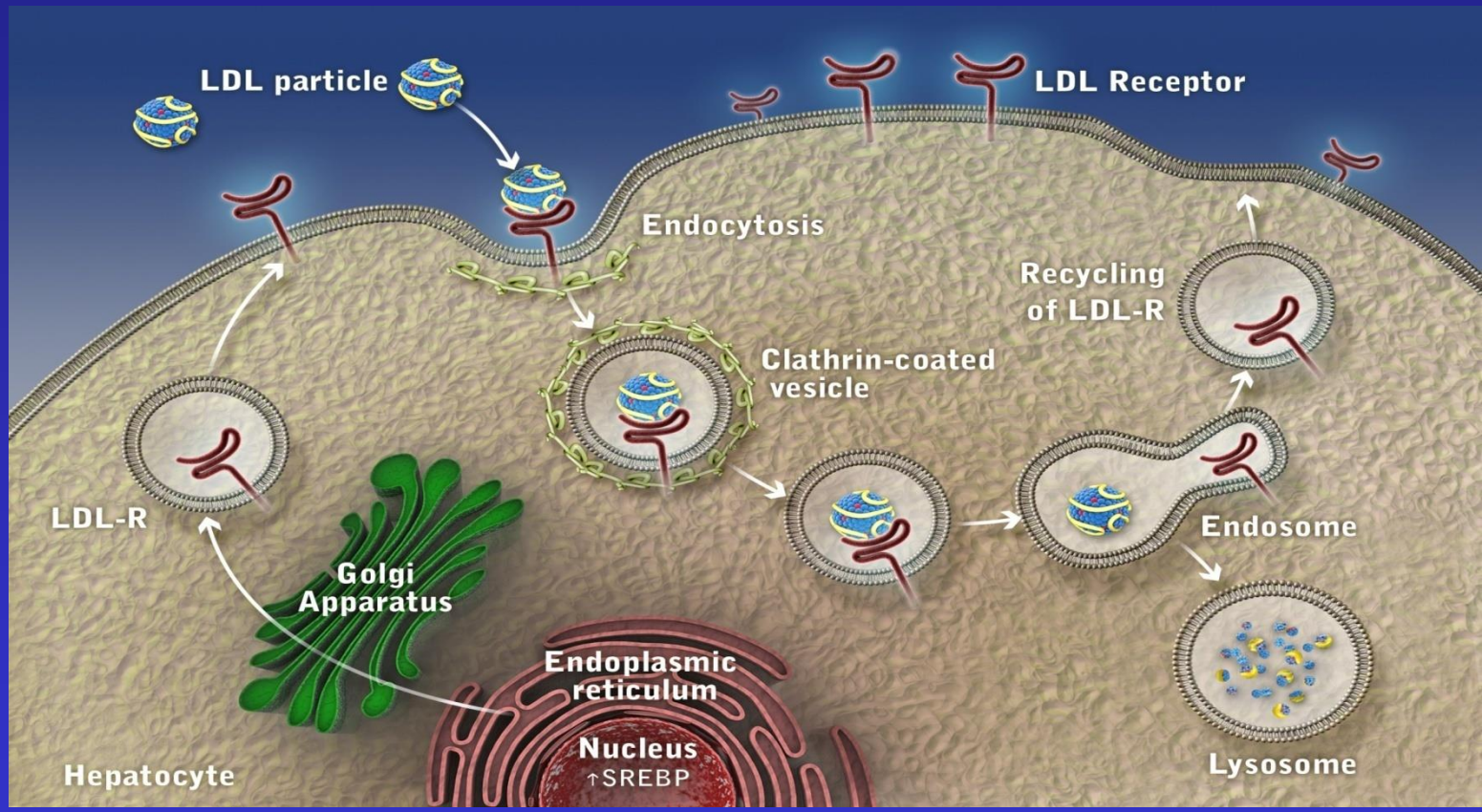
Synergic effect of PCSK9 inhibitors and statins



Adapted from Catapano & Papadopoulos Atherosclerosis 2013;228:18–28

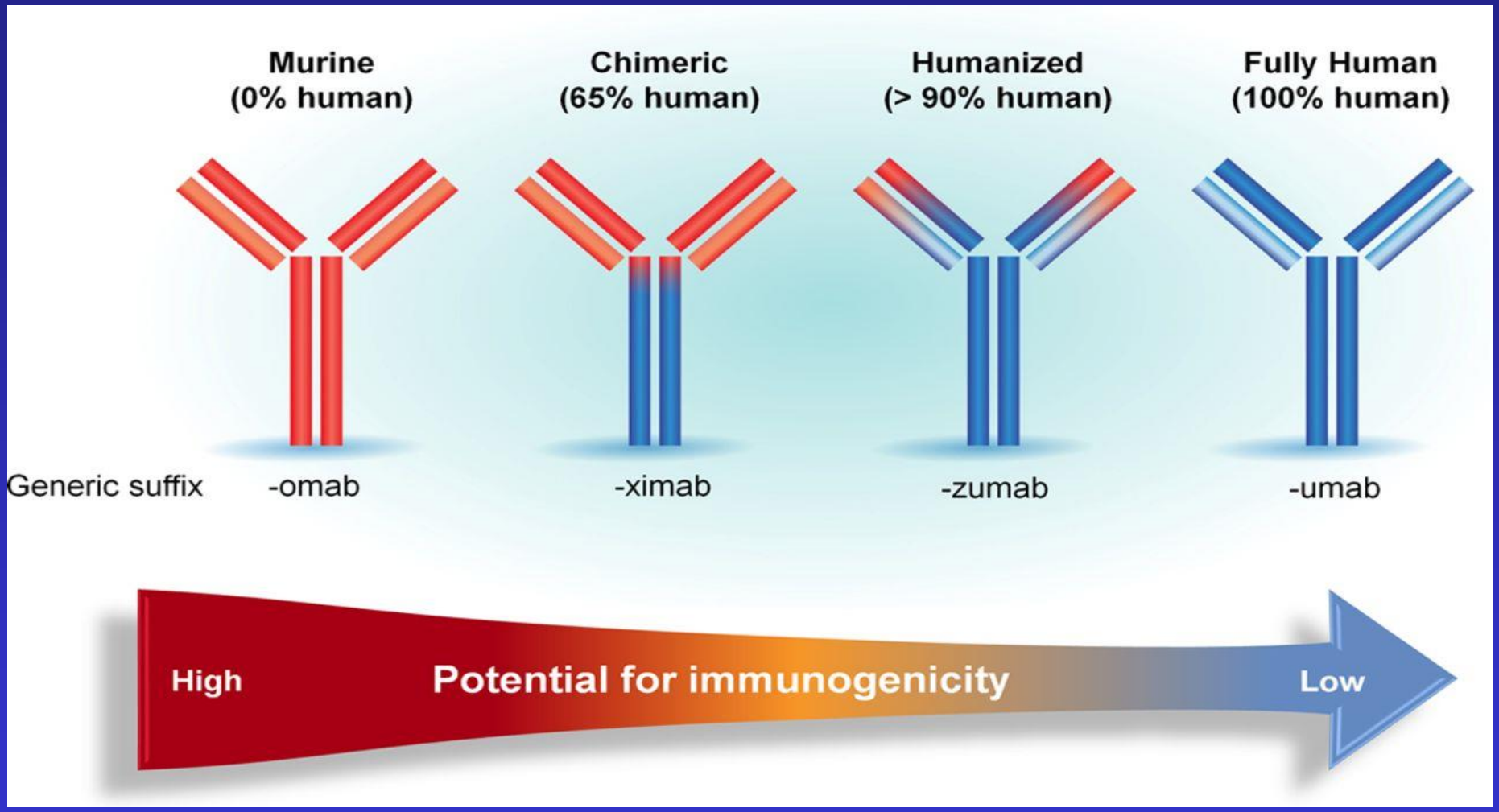
LDL Receptor Function and Life Cycle

1985 Goldstein & Brown



Adapted from Catapano & Papadopoulos *Atherosclerosis* 2013;228:18–28

Humanization of therapeutic antibodies has reduced their immunogenicity.



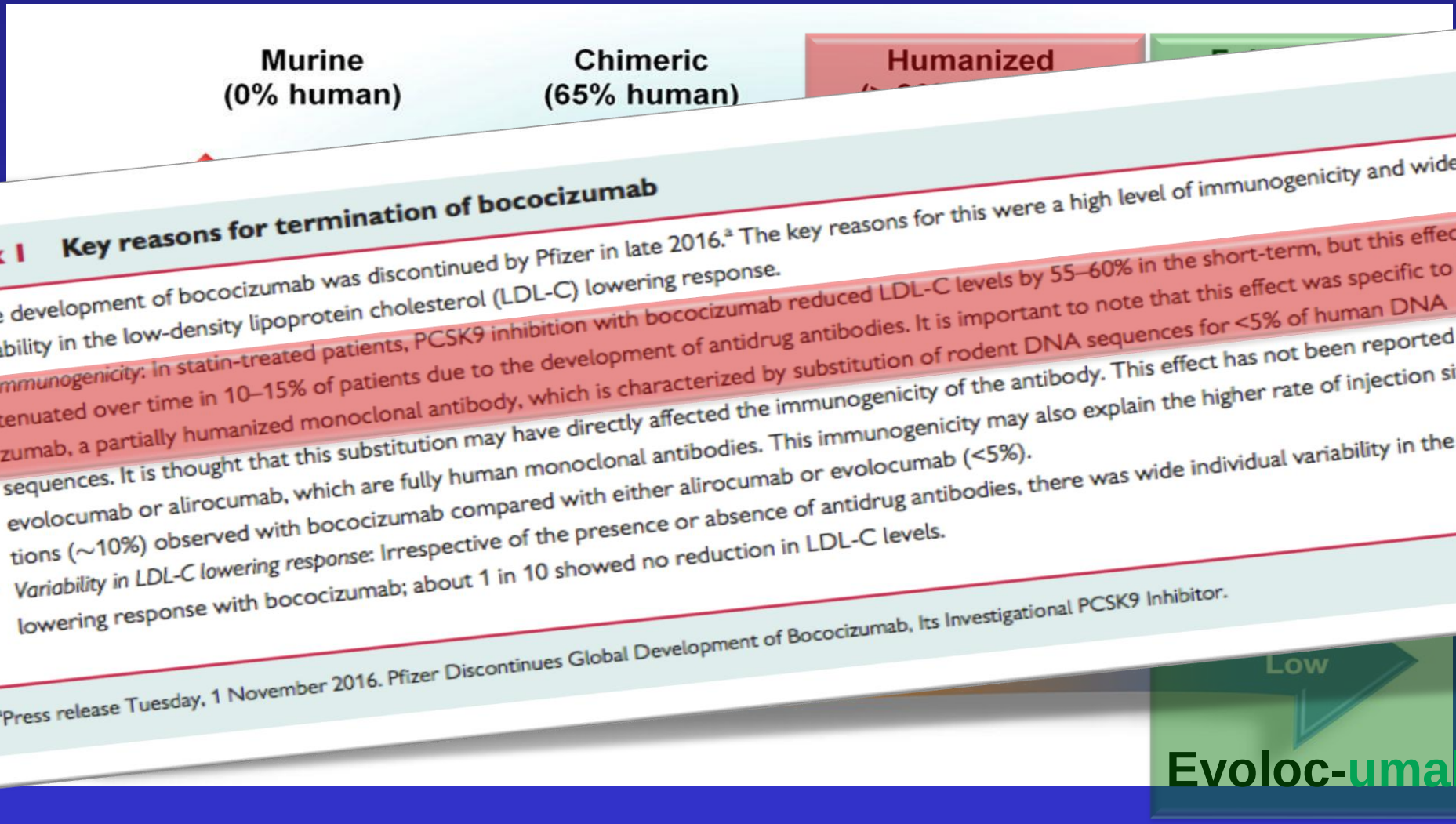
Ian N. Foltz et al. Circulation. 2013;127:2222-2230

American Heart Association.

Drugs evolution

Company	Drug (alternate name)	Phase
Sanofi/ Regeneron	Alirocumab (SAR236553/REGN72)	Approved
Amgen	Evolocumab (AMG-145)	Approved
Pfizer/ Rinat	Bococizumab (RN316/PF04950615)	Discontinued
Novartis	LGT-209	Discontinued
Genentech	MPSK3169A-RG7652	Discontinued

Drugs evolution



Box 1 Key reasons for termination of bococizumab

The development of bococizumab was discontinued by Pfizer in late 2016.[a] The key reasons for this were a high level of immunogenicity and wide variability in the low-density lipoprotein cholesterol (LDL-C) lowering response.

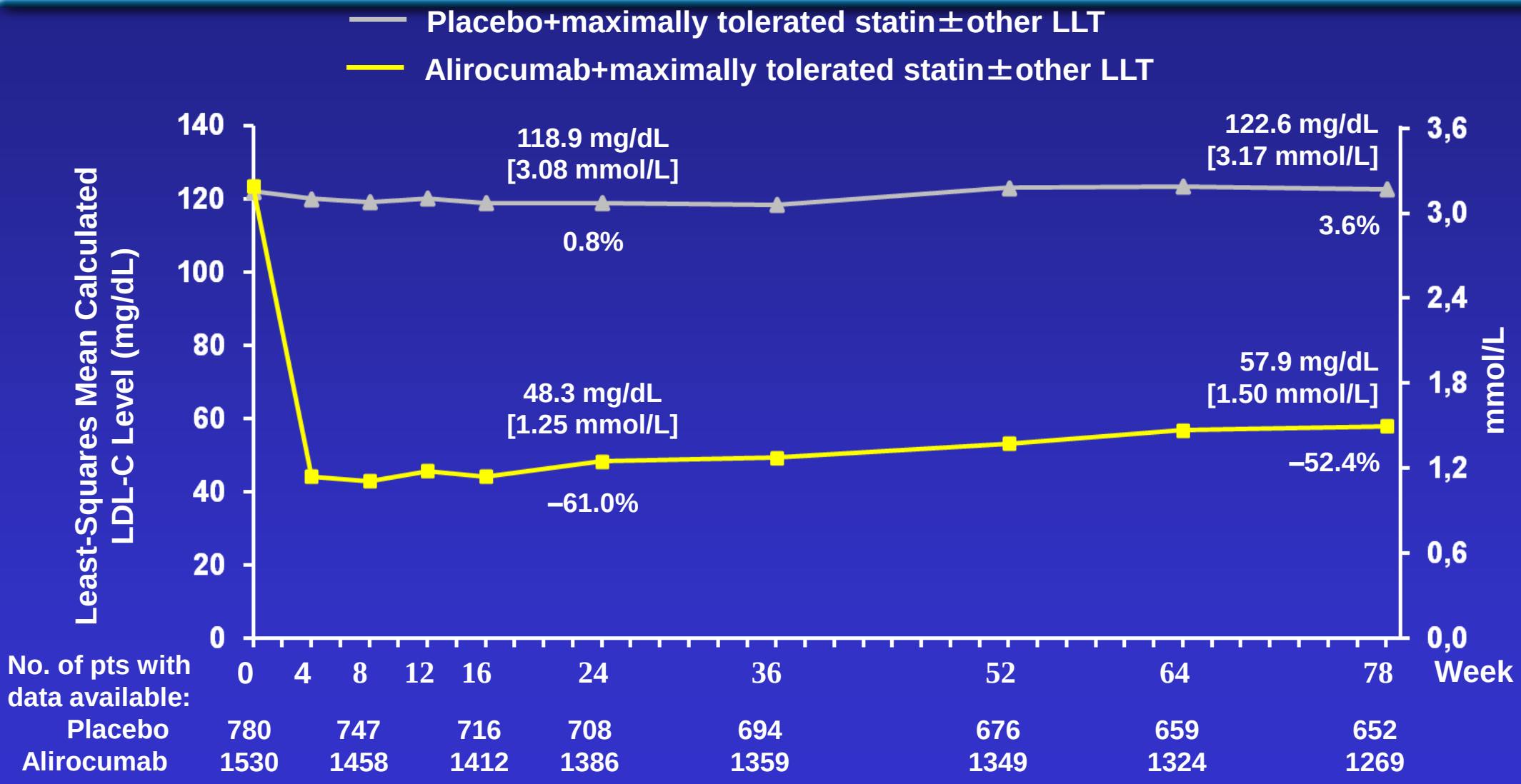
- *Immunogenicity*: In statin-treated patients, PCSK9 inhibition with bococizumab reduced LDL-C levels by 55–60% in the short-term, but this effect was attenuated over time in 10–15% of patients due to the development of antidrug antibodies. It is important to note that this effect was specific to bococizumab, a partially humanized monoclonal antibody, which is characterized by substitution of rodent DNA sequences for <5% of human DNA sequences. It is thought that this substitution may have directly affected the immunogenicity of the antibody. This effect has not been reported for either evolocumab or alirocumab, which are fully human monoclonal antibodies. This immunogenicity may also explain the higher rate of injection site reactions (~10%) observed with bococizumab compared with either alirocumab or evolocumab (<5%).
- *Variability in LDL-C lowering response*: Irrespective of the presence or absence of antidrug antibodies, there was wide individual variability in the LDL-C lowering response with bococizumab; about 1 in 10 showed no reduction in LDL-C levels.

[a]Press release Tuesday, 1 November 2016. Pfizer Discontinues Global Development of Bococizumab, Its Investigational PCSK9 Inhibitor.

Ian N. Foltz et al. Circulation. 2013;127:2222-2230; Landmesser U. et al.European Heart Journal (2017) 0, 1–13

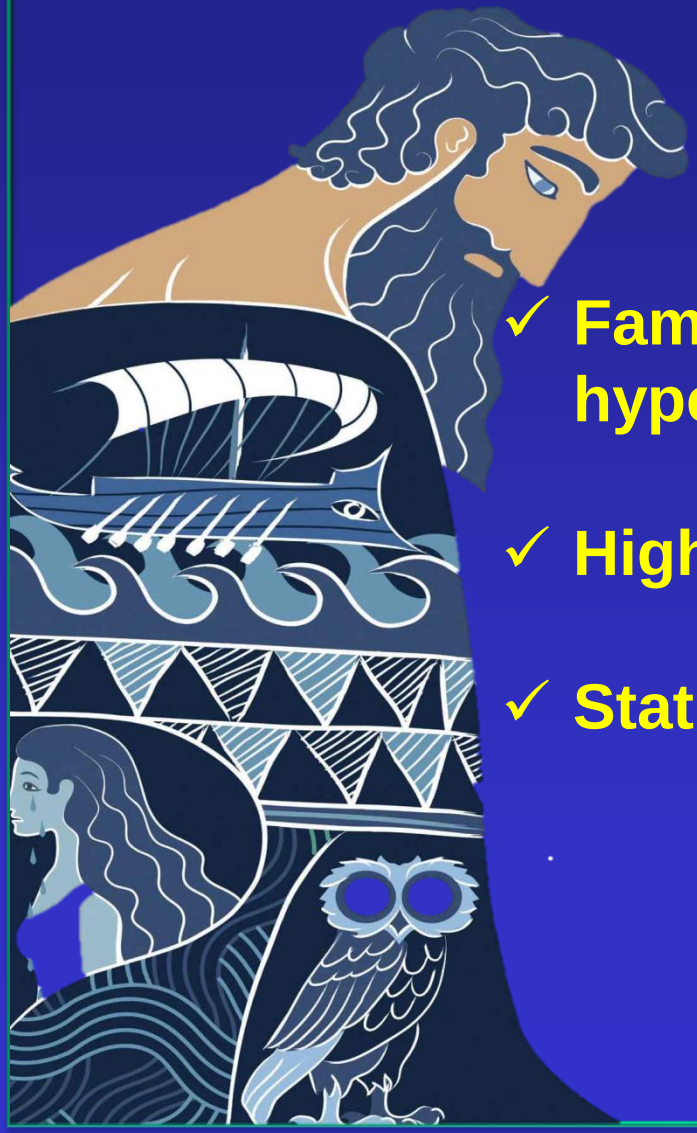
Calculated LDL-C Levels over Time

ITT Analysis



Robinson JG et al. *NEJM* 2015; 372:1489-99.

PCSK9 inhibitors: effects on hypercholesterolemia



- ✓ **Familiar hypercholesterolemia**
- ✓ **High CV risk**
- ✓ **Statins intolerant**

PCSK9 inhibitors: effects on hypercholesterolemia?

Lipid lowering

Monotherapy	Statin intolerance	High LDL-C	High LDL-C	High LDL-C	High LDL-C	FH	FH
ODYSSEY MONO[90] *n*=103 24 weeks	ODYSSEY ALTERNATIVE[91] *n*=314 24 weeks	ODYSSEY OPTIONS I[92] *n*=347 24 weeks ODYSSEY OPTIONS II[93] *n*=300 24 weeks	ODYSSEY COMBO I[94] *n*=306 52 weeks	ODYSSEY COMBO II[95] *n*=660 115 weeks	ODYSSEY CHOICE I[96] *n*=700 24 weeks	ODYSSEY FH I[97] *n*=471 78 weeks ODYSSEY FH II[98] *n*=249 52 weeks	ODYSSEY HIGH FH[99] *n*=105 78 weeks

Alirocumab ODYSSEY program

PCSK9 inhibitors: effects on hypercholesterolemia?

Lipid lowering

Monotherapy	Statin intolerance	At-target LDL-C	High LDL-C	FH
MENDEL-2[102]	GAUSS-2[103]	DESCARTES[104]	LAPLACE-2[105]	RUTHERFORD-2[106]
n=600	*n*=500	*n*=905	*n*=1,700	*n*=300
12 weeks	24 weeks	52 weeks	12 weeks	12 weeks

Evolocumab PROFICIO program

PCSK9 inhibitors: effects on hypercholesterolemia?

Vs placebo - 52,6%

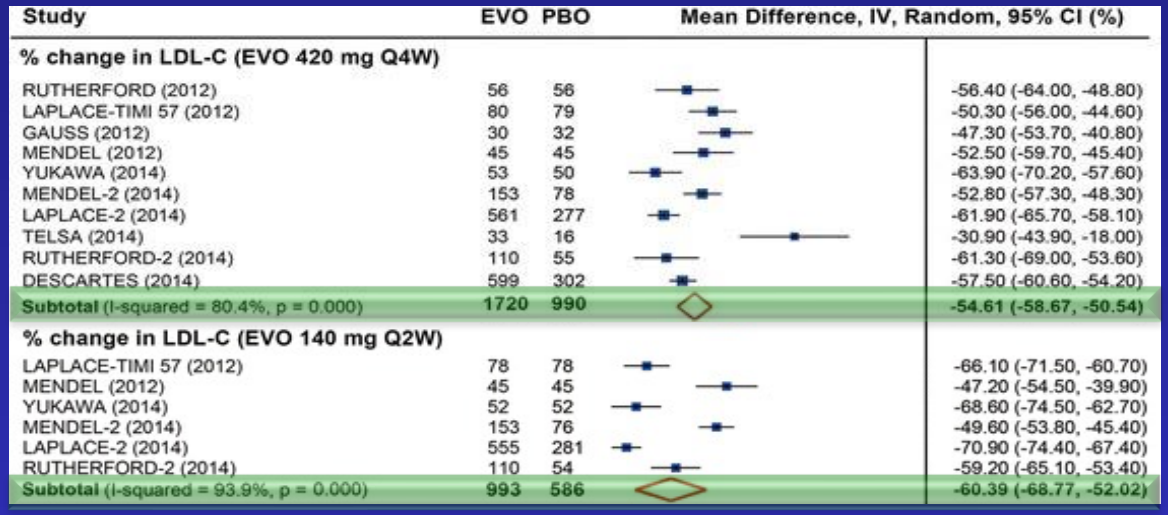
Vs ezetimibe - 29,92%

A Study	ALIR	PBO/EZE	Mean Difference, IV, Random, 95% CI (%)
% Change in LDL-C (ALIR 50-150 mg Q2W vs. PBO)			
McKenney (2012)	92	31	-53.54 (-61.14, -45.94)
Stein (2012)	16	15	-57.20 (-70.91, -43.49)
Roth (2012)	30	31	-48.90 (-58.60, -39.20)
ODYSSEY FH I (2014)	323	163	-57.90 (-63.20, -52.60)
ODYSSEY FH II (2014)	167	82	-51.40 (-58.10, -44.70)
ODYSSEY LONG TERM (2014)	1553	788	-61.90 (-64.40, -59.40)
ODYSSEY COMBO I (2014)	209	107	-45.90 (-52.40, -39.40)
ODYSSEY HIGH FH (2014)	72	35	-39.10 (-50.90, -27.30)
Subtotal (I-squared = 82.8%, p = 0.000)	**2462**	**1252**	-52.60 (-58.19, -47.01)
% Change in LDL-C (ALIR 75-150 mg Q2W vs. EZE)			
ODESSEY MONO (2014)	52	51	-31.60 (-40.20, -23.00)
ODYSSEY COMBO II (2014)	479	241	-29.80 (-34.30, -25.30)
ODYSSEY ALTERNATIVE (2014)	126	124	-30.40 (-36.50, -24.30)
ODYSSEY OPTION I (2014)	104	101	-27.20 (-36.10, -18.30)
ODYSSEY OPTION II (2014)	103	101	-30.50 (-42.30, -18.70)
Subtotal (I-squared = 0.0%, p = 0.969)	**864**	**618**	-29.92 (-32.94, -26.89)

Alirocumab ODYSSEY program

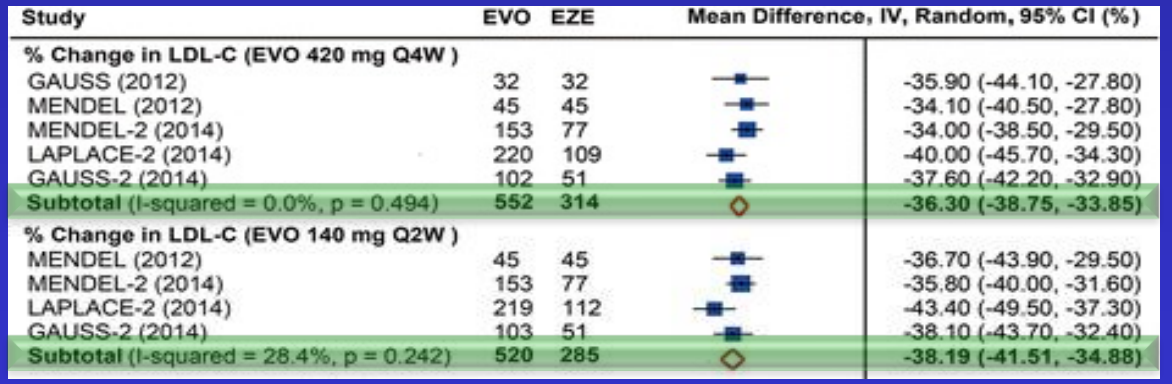
Zhang et al. BMC Medicine 2015; 13:123

PCSK9 inhibitors: effects on hypercholesterolemia?



Vs placebo
420 mg Q4W -54,61%
140 mg Q2W- 60,39%

Vs ezetimibe
420 mg Q4W -36,3%
140 mg Q2W- 38,19%

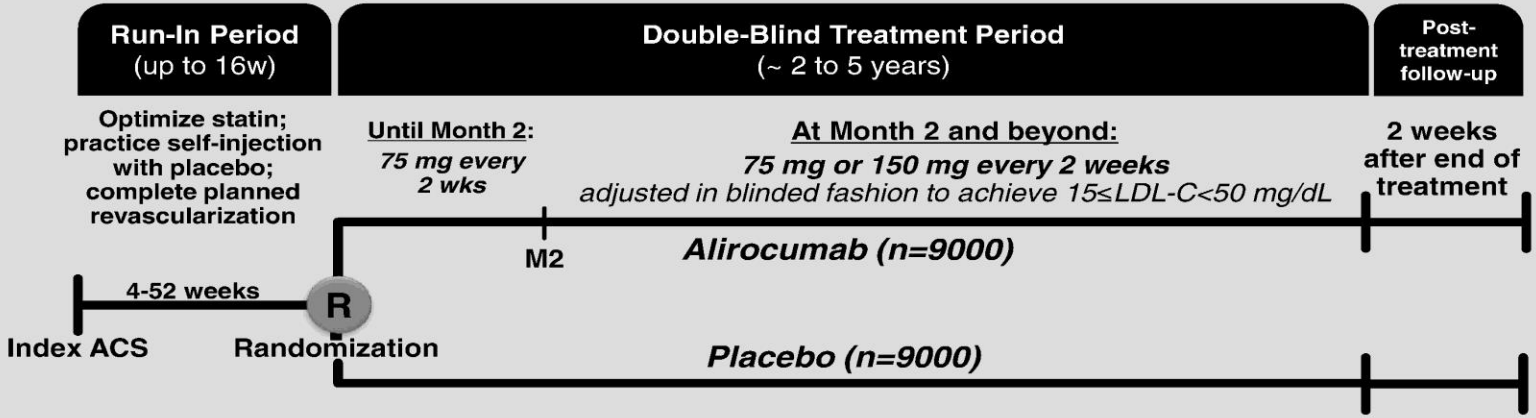


Evolocumab PROFICIO program

Zhang et al. BMC Medicine 2015; 13:123

PCSK9 inhibitors reduce CV events?

- **Patient population:**
  - Recent ACS
  - Inadequate control of atherogenic lipoproteins* despite optimal statin treatment†
- **Primary endpoint:** Composite of
  - Coronary heart disease death
  - Non-fatal myocardial infarction
  - Ischemic stroke
  - Unstable angina requiring hospitalization



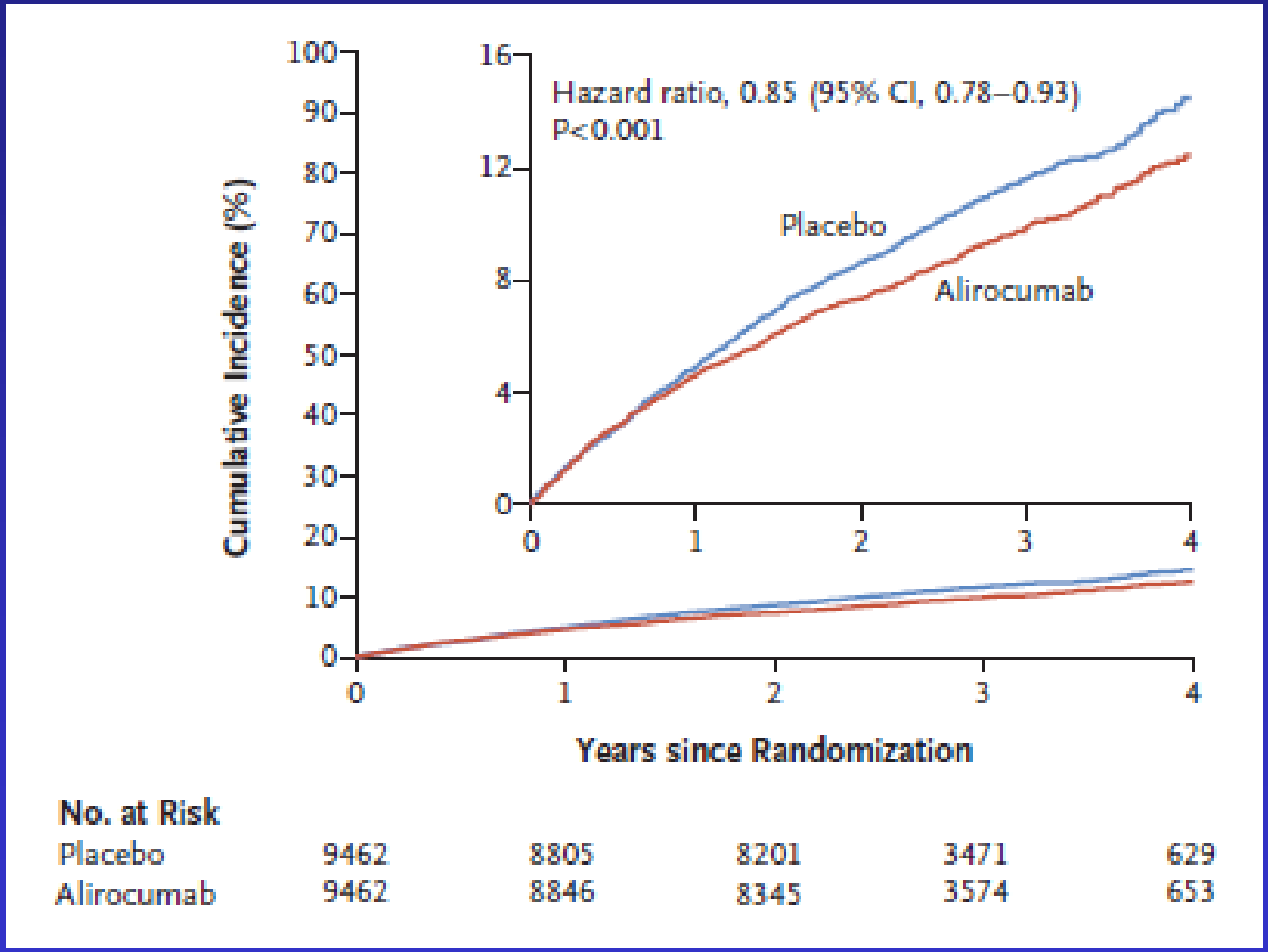
† **Optimal statin treatment:** Atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg, or maximal tolerated dose of one of these statins, with or without non-statin lipid treatments. NCEP-ATPIII therapeutic lifestyle changes or equivalent throughout study.

* **Inadequate control of atherogenic lipoproteins.** At least one of the following: 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

Alirocumab ODYSSEY outcome

Schwartz GG, et al., Am Heart J. 2014

PCSK9 inhibitors reduce CV events?

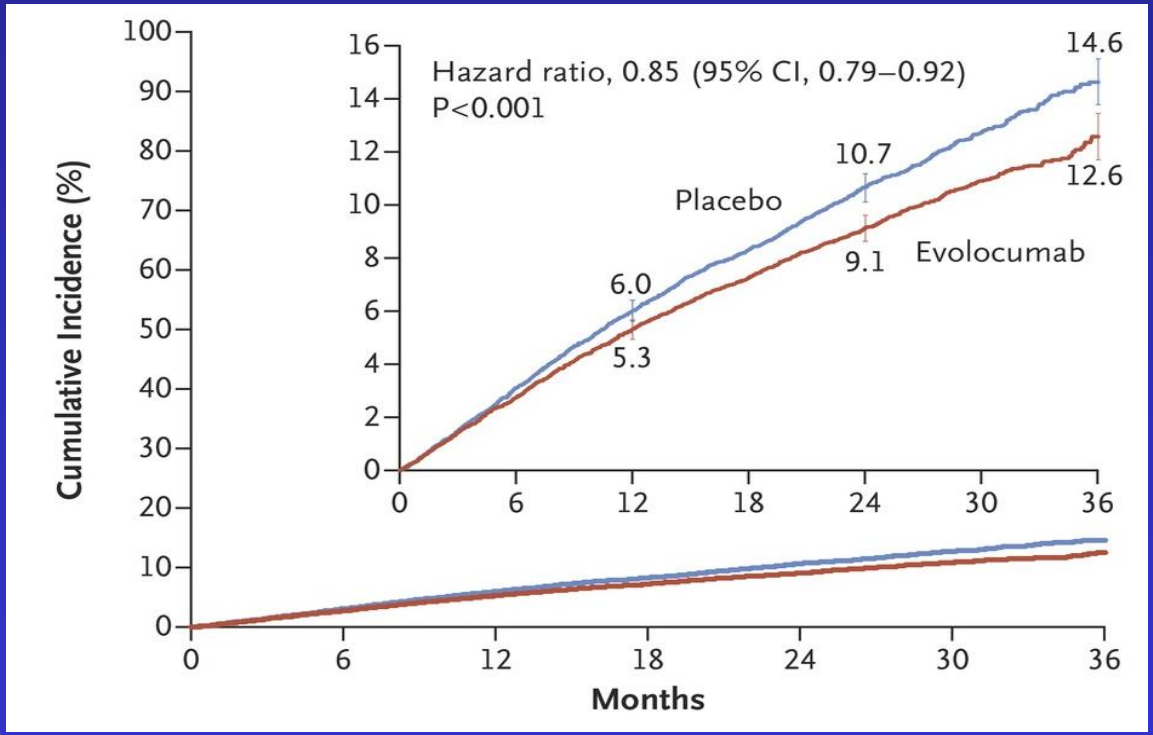


Alirocumab ODYSSEY outcome

Schwartz GG, et al., New Engl J med 2018

PCSK9 inhibitors reduce CV events?

27,564 patients with cardiovascular disease (clinically evident atherosclerotic cardiovascular disease, defined as a history of myocardial infarction, nonhemorrhagic stroke, or symptomatic peripheral artery disease) and LDL cholesterol levels of 70 mg per deciliter or higher on statin therapy were assigned to either evolocumab or placebo.



primary efficacy end point (the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization)

Evolocumab Fourier trial

Sabatine MS, et al. N Engl J Med 2017; 376:1713-1722

PCSK9 inhibitors reduce CV events?

Outcome	Evolocumab (N = 13,784)	Placebo (N = 13,780)	Hazard Ratio (95% CI)	P Value*
	no. of patients (%)			
Primary end point: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization	1344 (9.8)	1563 (11.3)	0.85 (0.79–0.92)	<0.001
Key secondary end point: cardiovascular death, myocardial infarction, or stroke	816 (5.9)	1013 (7.4)	0.80 (0.73–0.88)	<0.001
Other end points				
Cardiovascular death	251 (1.8)	240 (1.7)	1.05 (0.88–1.25)	0.62
Due to acute myocardial infarction	25 (0.18)	30 (0.22)	0.84 (0.49–1.42)	
Due to stroke	31 (0.22)	33 (0.24)	0.94 (0.58–1.54)	
Other cardiovascular death	195 (1.4)	177 (1.3)	1.10 (0.90–1.35)	
Death from any cause	444 (3.2)	426 (3.1)	1.04 (0.91–1.19)	0.54
Myocardial infarction	468 (3.4)	639 (4.6)	0.73 (0.65–0.82)	<0.001
Hospitalization for unstable angina	236 (1.7)	239 (1.7)	0.99 (0.82–1.18)	0.89
Stroke	207 (1.5)	262 (1.9)	0.79 (0.66–0.95)	0.01
Ischemic	171 (1.2)	226 (1.6)	0.75 (0.62–0.92)	
Hemorrhagic	29 (0.21)	25 (0.18)	1.16 (0.68–1.98)	
Unknown	13 (0.09)	14 (0.10)	0.93 (0.44–1.97)	
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 (0.71–0.86)	<0.001
Urgent	403 (2.9)	547 (4.0)	0.73 (0.64–0.83)	
Elective	420 (3.0)	504 (3.7)	0.83 (0.73–0.95)	
Cardiovascular death or hospitalization for worsening heart failure	402 (2.9)	408 (3.0)	0.98 (0.86–1.13)	0.82
Ischemic stroke or transient ischemic attack	229 (1.7)	295 (2.1)	0.77 (0.65–0.92)	0.003
CTTC composite end point†	1271 (9.2)	1512 (11.0)	0.83 (0.77–0.90)	<0.001

Evolocumab Fourier trial

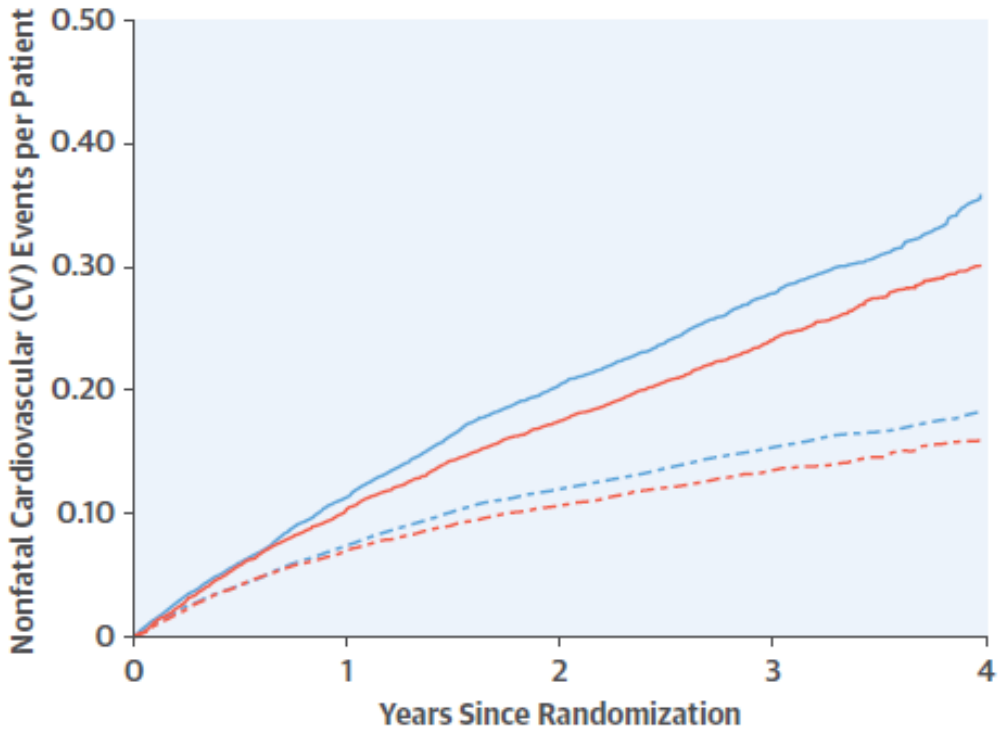
Sabatine MS, et al. N Engl J Med 2017; 376:1713-1722

Alirocumab Reduces Total Nonfatal Cardiovascular and Fatal Events

The ODYSSEY OUTCOMES Trial

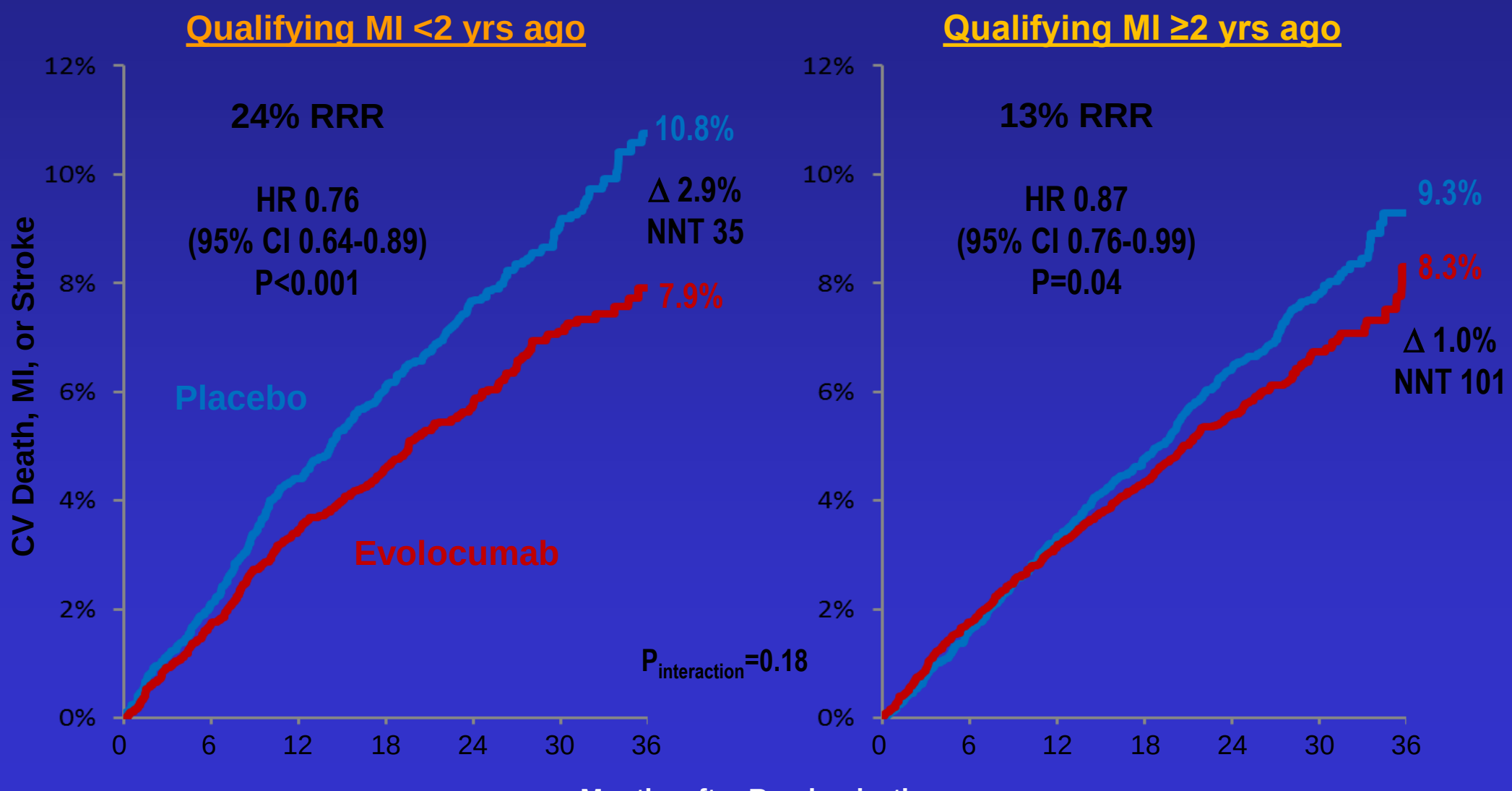
NNT (95% CI) for 4 years:

- **18 (11, 53) for total events**
- **44 (26, 129) for first events**

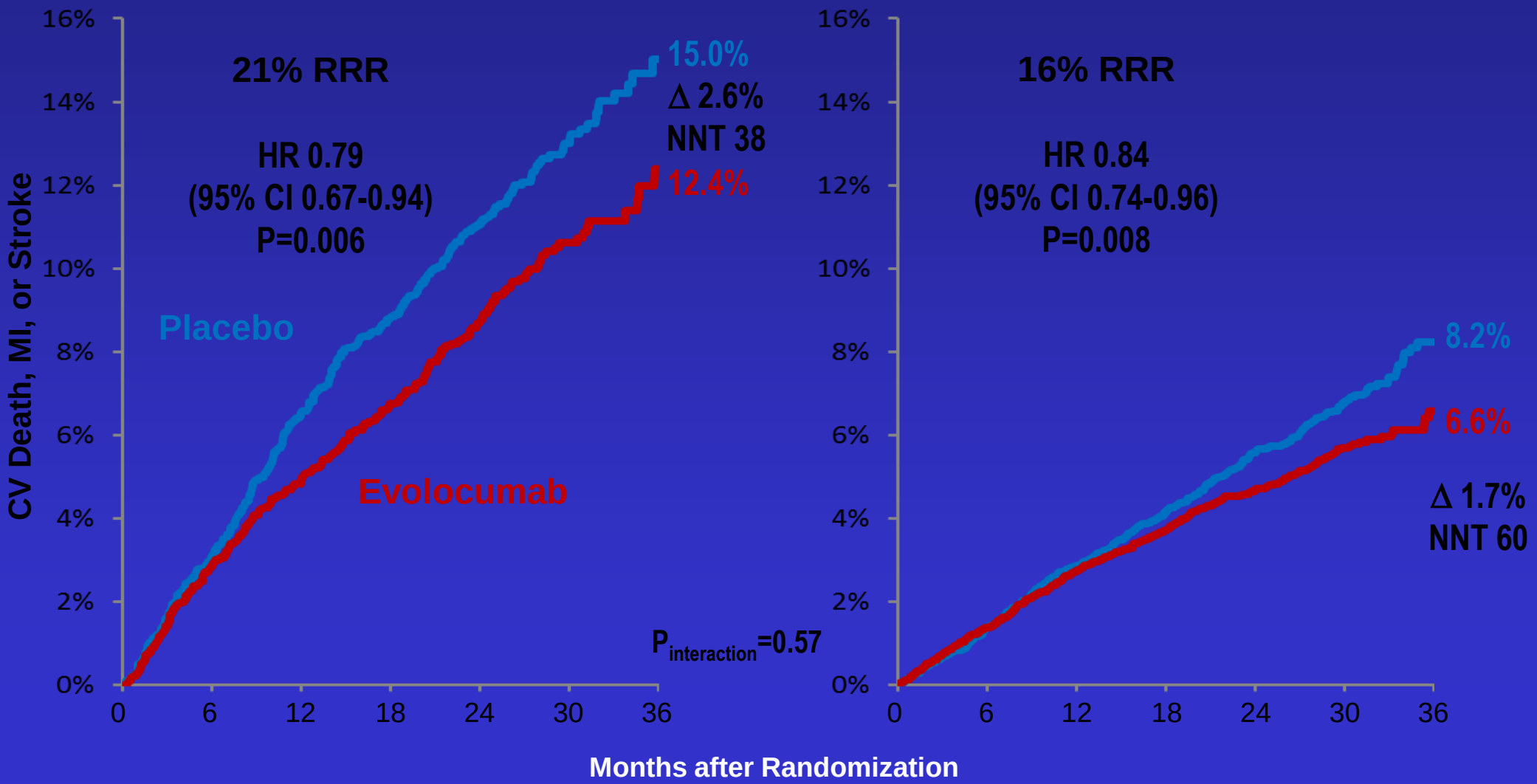


Szarek, M. et al. J Am Coll Cardiol. 2019;73(4):387-96.

Benefit of EvoMab Based on Time from Qualifying MI



Benefit of EvoMab Based on # of Prior MIs

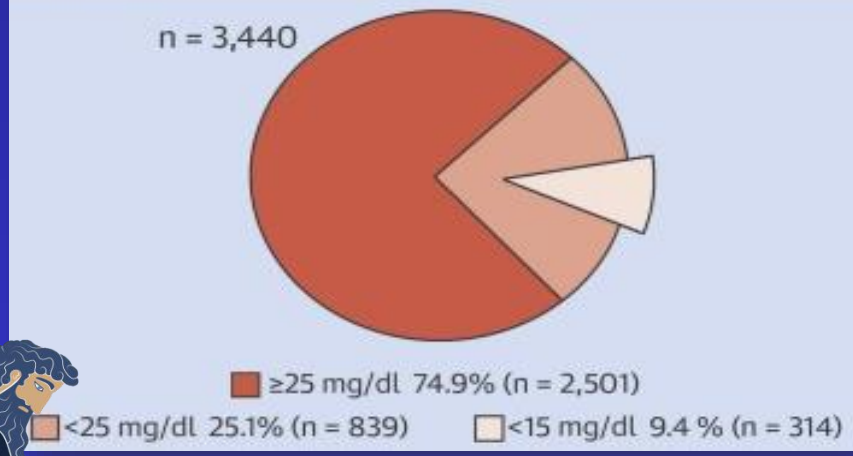


Safe profile - Alirocumab

Safety of Very Low Low-Density Lipoprotein Cholesterol Levels With Alirocumab

Pooled Data From Randomized Trials

LDL-C Achieved With Alirocumab Treatment



Adverse Events

- Overall similar AE rates including neurological and neurocognitive events in patients achieving LDL-C <25 vs. ≥25 mg/dl
- Higher rates of cataracts with LDL-C <25 vs. ≥25 mg/dl (2.6% vs. 0.8%) although no difference between overall alirocumab and control group.

Robinson J.G. et al. J Am Coll Cardiol. 2017; 69(5):471-82.

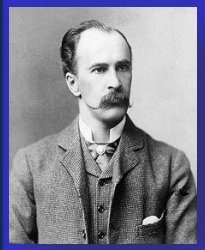
Safe Profile - Evolocumab

ORIGINAL ARTICLE

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

Table 3. Adverse Events and Laboratory Results.*

Variable	Evolocumab Group (N=2976)	Standard-Therapy Group (N=1489)
	no. (%)	
Adverse events		
Any	2060 (69.2)	965 (64.8)
Serious	222 (7.5)	111 (7.5)
Leading to discontinuation of evolocumab	71 (2.4)	NA
Muscle-related	190 (6.4)	90 (6.0)
Injection-site reaction	129 (4.3)	NA
Neurocognitive event†	27 (0.9)	4 (0.3)
Other‡		
Arthralgia	137 (4.6)	48 (3.2)
Headache	106 (3.6)	32 (2.1)
Limb pain	99 (3.3)	32 (2.1)
Fatigue	83 (2.8)	15 (1.0)
Laboratory results		
Alanine or aspartate aminotransferase >3×ULN at any visit after baseline	31 (1.0)	18 (1.2)
Creatine kinase >5×ULN at any visit after baseline	17 (0.6)	17 (1.1)



Sabatine MS et al. N Engl J Med 2015;372:1500-1509.

Safe Profile - Evolocumab

Table 3. Adverse Events and Laboratory Test Results.

Outcome	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events — no. of patients (%)		
Any	10,664 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)
Injection-site reaction*	296 (2.1)	219 (1.6)
Allergic reaction	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results — no. of patients/total no. (%)		
Aminotransferase level >3 times the upper limit of the normal range	240/13,543 (1.8)	242/13,523 (1.8)
Creatine kinase level >5 times the upper limit of the normal range	95/13,543 (0.7)	99/13,523 (0.7)

Evolocumab Fourier trial

Sabatine MS, et al. N Engl J Med 2017; 376:1713-1722

Effects of a short-term alirocumab administration on the aortic stiffness: preliminary results

Feola Mauro[1,#], Ferreri Cinzia[2], Rossi Arianna[2], Testa Marzia[1], Ruocco Gaetano[1], Francesco Tassone[3]

[1]*Cardiology Division Ospedale Regina Montis Regalis Mondovi', Italy*
[2]*School of Geriatry Università degli Studi di Torino, Torino, Italy*
[3]*Endocrinology Division Ospedale S. Croce-carle Cuneo Italy*

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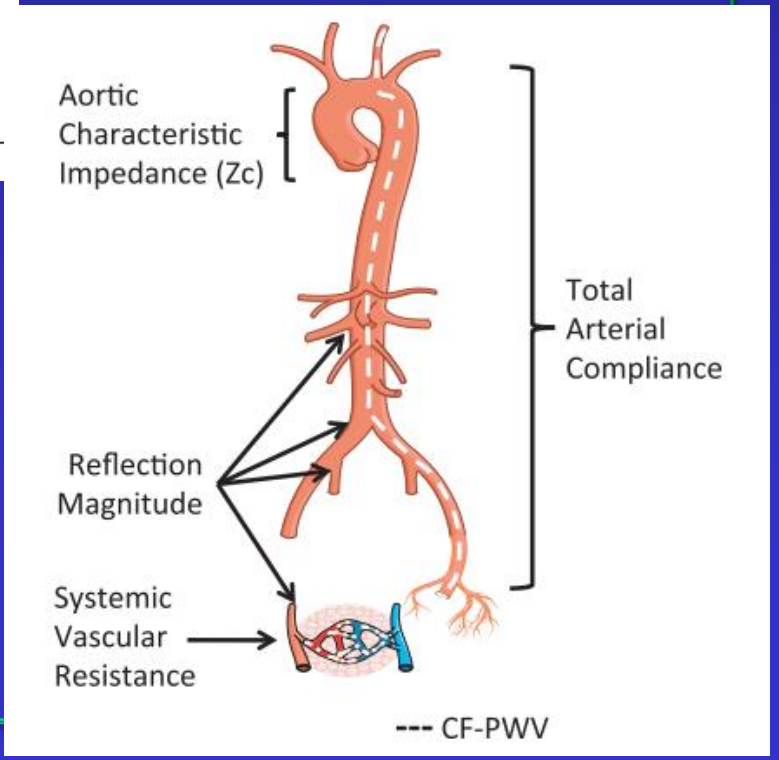
Table 1.

	Baseline	1-month	2-month	3-month	6-month
PWV, m/s	13.07 ± 2.4	12.23 ± 2.14	12.1 ± 1.73	11.1 ± 0.94	10.5 ± 1.43*
Aix7	36% ± 2%	30.3% ± 3.5%	34.3% ± 5%	34.3% ± 2.3%	34% ± 8.5%
Central PP, mmHg	59.3 ± 14.2	51.3 ± 15.9	53.3 ± 20.1	51 ± 5.2	53 ± 19.3
Central SP, mmHg	135.7 ± 28.2	129 ± 25.7	134.6 ± 30.9	118.7 ± 9.7	119.7 ± 18.1
Brachial SP, mmHg	147.7 ± 31.5	142 ± 31.5	146.8 ± 37.9	130.7 ± 14.5	131 ± 12.5
Brachial PP, mmHg	72.7 ± 16.6	65 ± 19.5	65.7 ± 26	63.7 ± 9.8	65.7 ± 22.5

PWV: pulse wave velocity; Aix75: augmentation index; PP: pulse pressure; SP = systolic pressure. *$P < 0.05$.



ESC European Society of Cardiology

European Heart Journal (2017) **0**, 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

Published 16 october 2017

- Patients with ASCVD, by definition at very high risk,[6,7] who have substantially elevated LDL-C levels despite maximally tolerated statin with or without ezetimibe therapy, and thus are considered at particularly high risk of an adverse prognosis.
- Patients with ASCVD and at very high risk who do not tolerate appropriate doses of at least three statins and thus have elevated LDL-C levels.
- Familial hypercholesterolaemia patients without clinically diagnosed ASCVD, at high or very high cardiovascular risk, and with substantially elevated LDL-C levels despite maximally tolerated statin plus ezetimibe therapy.

Landmesser U. et al.European Heart Journal (2017) 0, 1–13

ESC European Society of Cardiology
EAS

2016	2019
Pharmacological LDL-C lowering	**Pharmacological LDL-C lowering**
If the LDL goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	If the goals are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.
Pharmacological LDL-C lowering	**Pharmacological LDL-C lowering**
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.	For secondary prevention, patients at very-high risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.
	For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.
Lipid-lowering therapy in patients with ACS	**Lipid-lowering therapy in patients with ACS**
If the LDL-C target is not reached with the highest tolerated statin dose and/or ezetimibe, PCSK9 inhibitors may be considered on top of lipid-lowering therapy; or alone or in combination with ezetimibe in statin-intolerant patients or in whom a statin is contraindicated.	If the LDL-C goal is not achieved after 4 - 6 weeks despite maximal tolerated statin therapy and ezetimibe, addition of a PCSK9 inhibitor is recommended.