8° WORKSHOP NAZIONALE CISAI
Prevenzione e gestione delle co-morbidità associate all'infezione da HIV
Perugia, 31 marzo 2017

Inibitori del PCSK9: possibile ruolo nei pazienti HIV-positivi

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DICHIARAZIONE CONFLITTO DI INTERESSI

Il Prof. **Marcello Arca** dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Kowa - Pfizer – Regeneron – Sanofi – ISIS – Aegerion

AstraZeneca – MSD – Roche – Genzyme – Abbott - Mediolanum

Sigma Tau – Boheringer - Menarini - Chiesi

Agenda

- Infezione da HIV, dislipidemia e rischio CV
- PCSK9, metabolismo lipidico e infezione da HIV
- La farmacologia degli anti-PCSK9
- I trials clinici con gli anti-PCSK9
- La sicurezza degli anti-PCSK9

Increased Acute Myocardial Infarction Rates and Cardiovascular Risk Factors among Patients with Human Immunodeficiency Virus Disease

Health care system-based cohort study using a large data registry with 3,851 HIV and 1,044,589 non-HIV patients

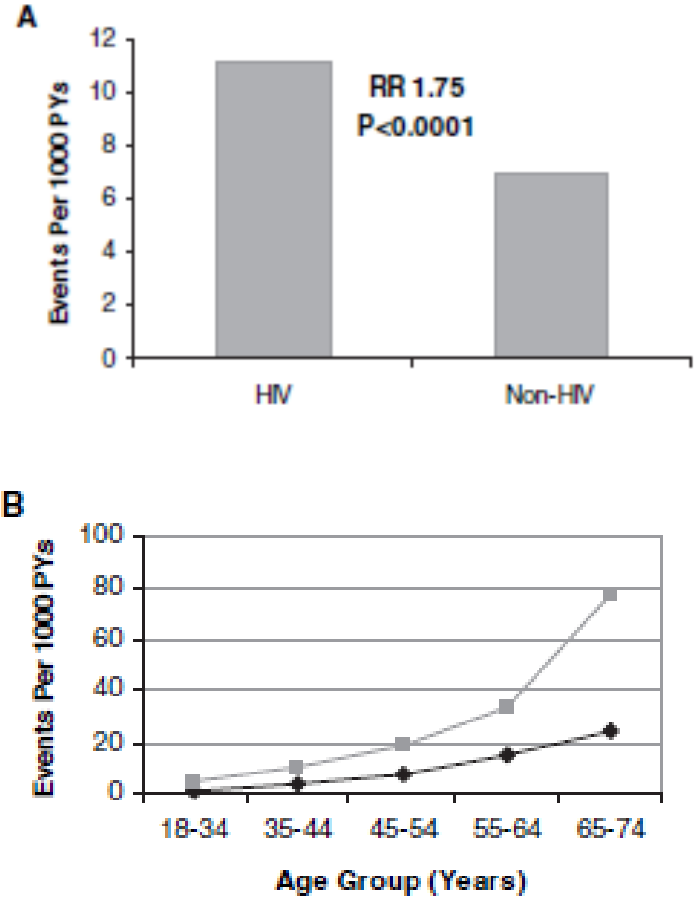


TABLE 2. Cardiac risk factors in HIV and non-HIV cohorts

	HIV (n = 3,851)		Non-HIV (n = 1,044,589)	
	n	Proportion	n	Proportion
Hypertension	818	21.2[a]	165,665	15.9
Females	211	18.0[a]	80,619	13.1
Males	607	22.7[a]	85,046	19.9
Diabetes	443	11.5[a]	68,565	6.6
Females	145	12.4[a]	34,096	5.5
Males	298	11.1[a]	34,469	8.1
Dyslipidemia	896	23.3[a]	184,291	17.6
Females	262	22.4[a]	92,411	15.0
Males	634	23.7[a]	91,880	21.5

HIV cohort includes all patients diagnosed with HIV disease by ICD code. Non-HIV cohort includes all patients not diagnosed with HIV disease by ICD code. ICD codes used were 401 and all subtypes for hypertension, 250 and all subtypes for diabetes, and 272 and all subtypes for dyslipidemia.

[a] Statistically significant comparison of HIV and non-HIV proportions, with χ^2 ($P < 0.0001$).

J Clin Endocrinol Metab 92: 2506–2512, 2007

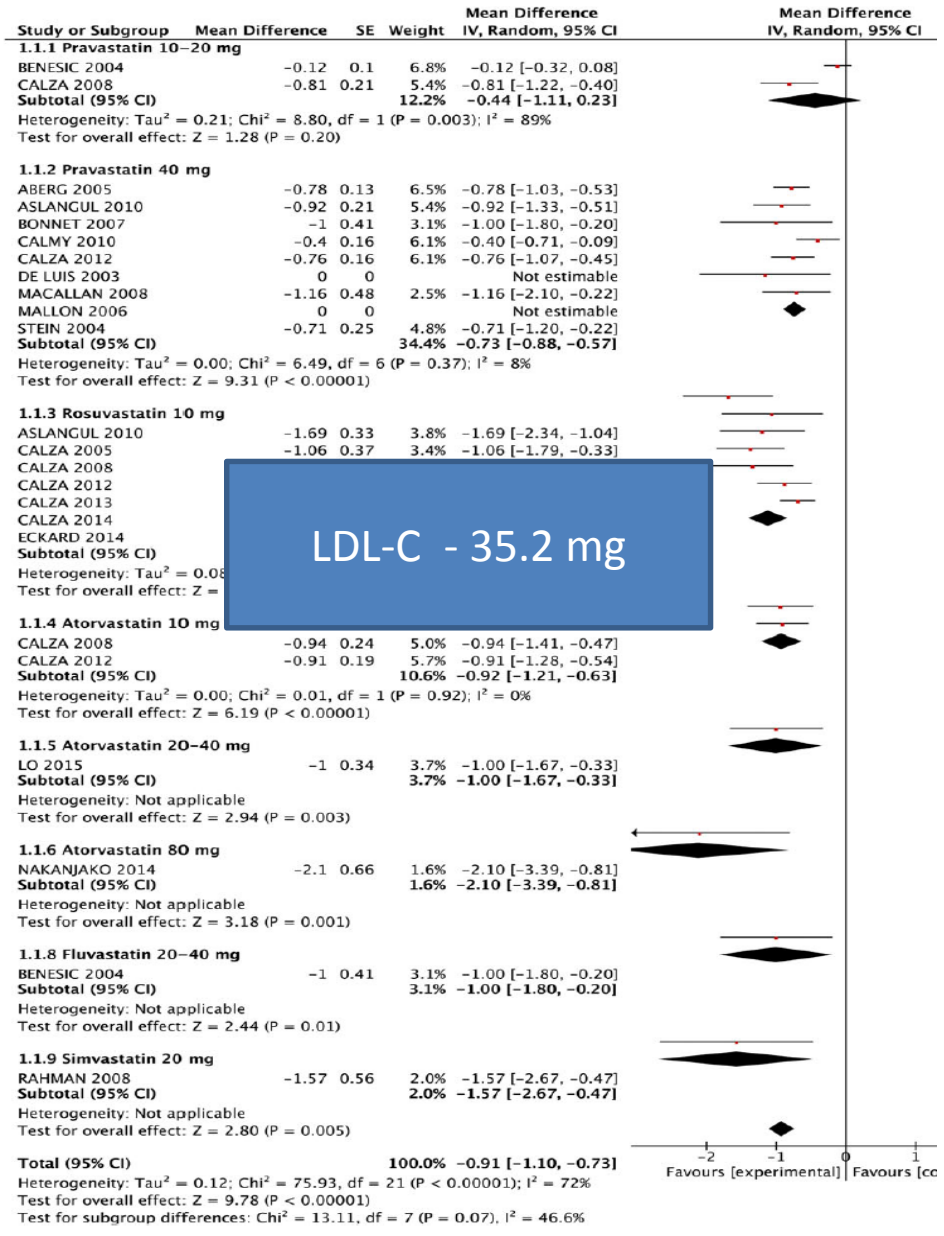
Comparative safety and efficacy of statins for primary prevention in human immunodeficiency virus-positive patients: a systematic review and meta-analysis

European Heart Journal (2016) **37**, 3600–3609
doi:10.1093/eurheartj/ehv734

Table 1 Baseline features of enrolled patients

	Median	Interquartile range
Age (years, min–max value)	44.1	36.3–56.0
Female gender	21.0	13.2–25.5
Body mass index	23.9	23.3–25.1
Cuacasian ethnicity	91.0	84.5–96.5
Men having sex with men	41.1	33.8–47.7
Intravenous drug user (previous or current)	33.0	24.8–44.0
Hypertension	10.0	8.0–23.0
Smoke	46.5	45.0–52.3
Diabetes	0.0	0.0–0.0
HBV infection	3.6	2.9–4.2
HCV infection	21.4	17.9–21.9
Lenght of follow-up (weeks)	12	12–36
Total cholesterol (mmol/L)	6.8	6.3–7.1
LDL (mmol/L)	4.2	3.6–4.5
HDL (mmol/L)	1.2	1.1–1.3
Triglycerides (mmol/L)	3.0	2.6–3.3

Values are expressed as percentage unless specified.
HBV, hepatitis B virus; HCV, hepatitis C virus.



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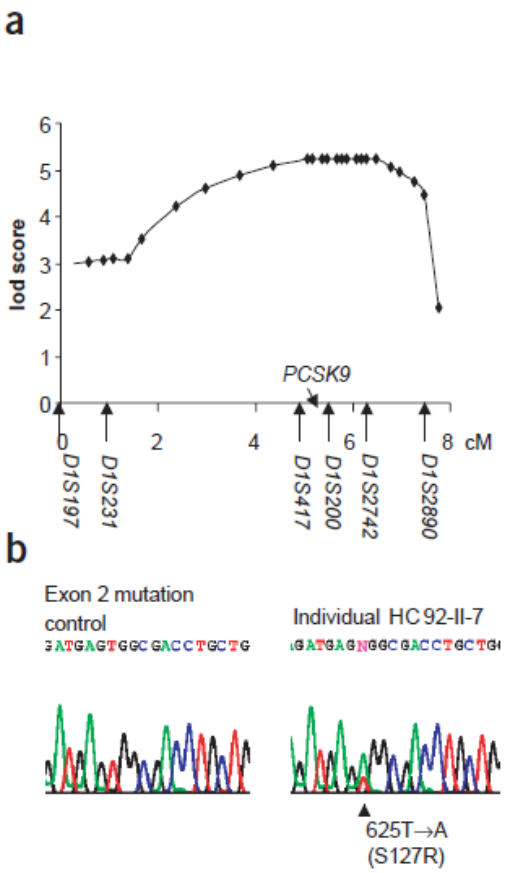
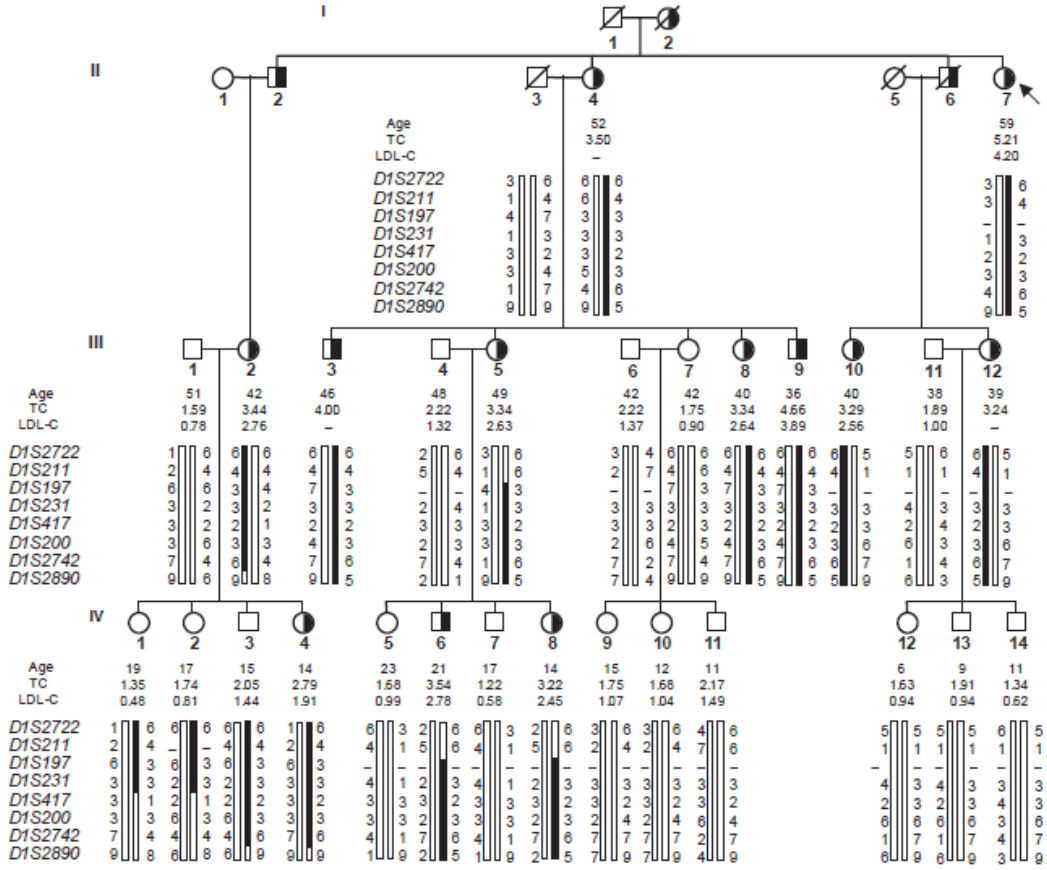
Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

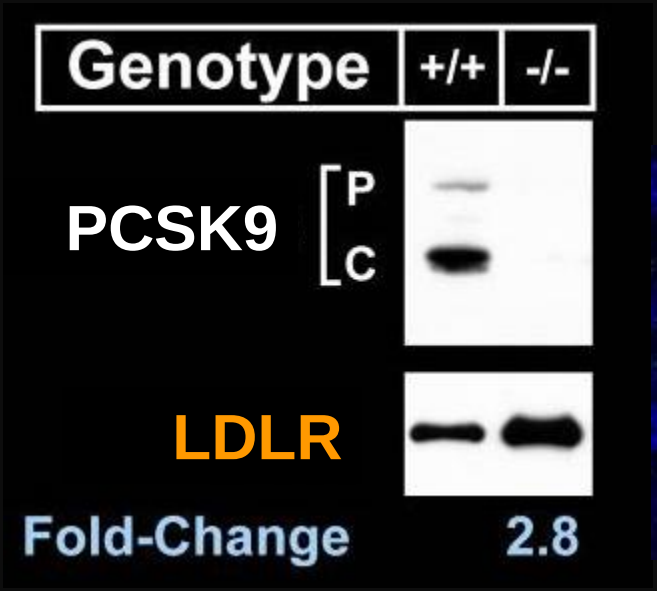
VOLUME 34 | NUMBER 2 | JUNE 2003 NATURE GENETICS

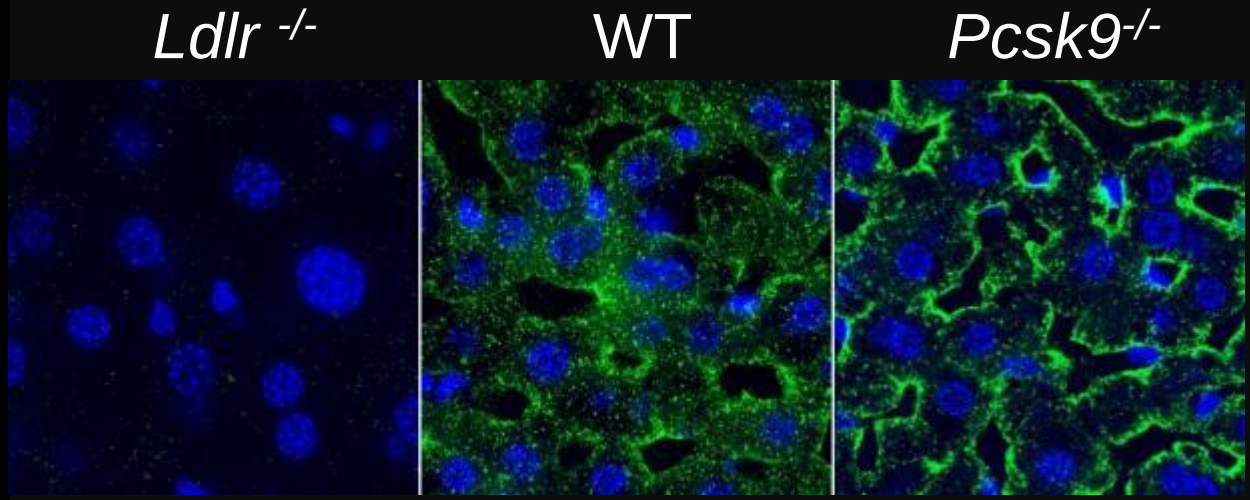
Marianne Abifadel[1,2], Mathilde Varret[1], Jean-Pierre Rabès[1,3], Delphine Allard[1], Khadija Ouguerram[4], Martine Devillers[1], Corinne Cruaud[5], Suzanne Benjannet[6], Louise Wickham[6], Danièle Erlich[1], Aurélie Derré[1], Ludovic Villéger[1], Michel Farnier[7], Isabel Beucler[8], Eric Bruckert[9], Jean Chambaz[10], Bernard Chanu[11], Jean-Michel Lecerf[12], Gerald Luc[12], Philippe Moulin[13], Jean Weissenbach[5], Annick Prat[6], Michel Krempf[4], Claudine Junien[1,3], Nabil G Seidah[6] & Catherine Boileau[1,3]





LDLR Protein Levels are Increased in Livers of Mice with No PCSK9

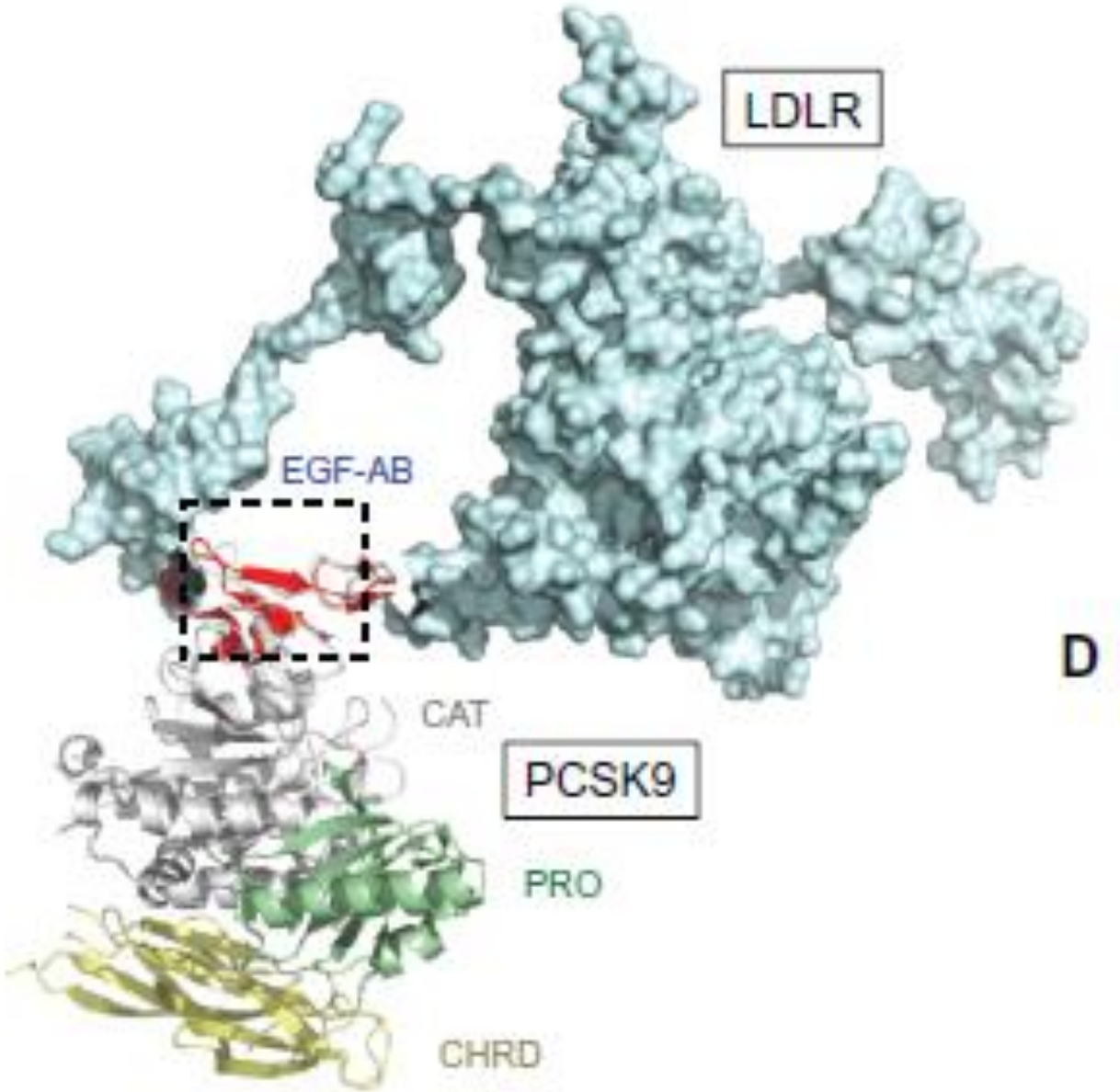




P and C denote the proprotein and cleaved forms of PCSK9

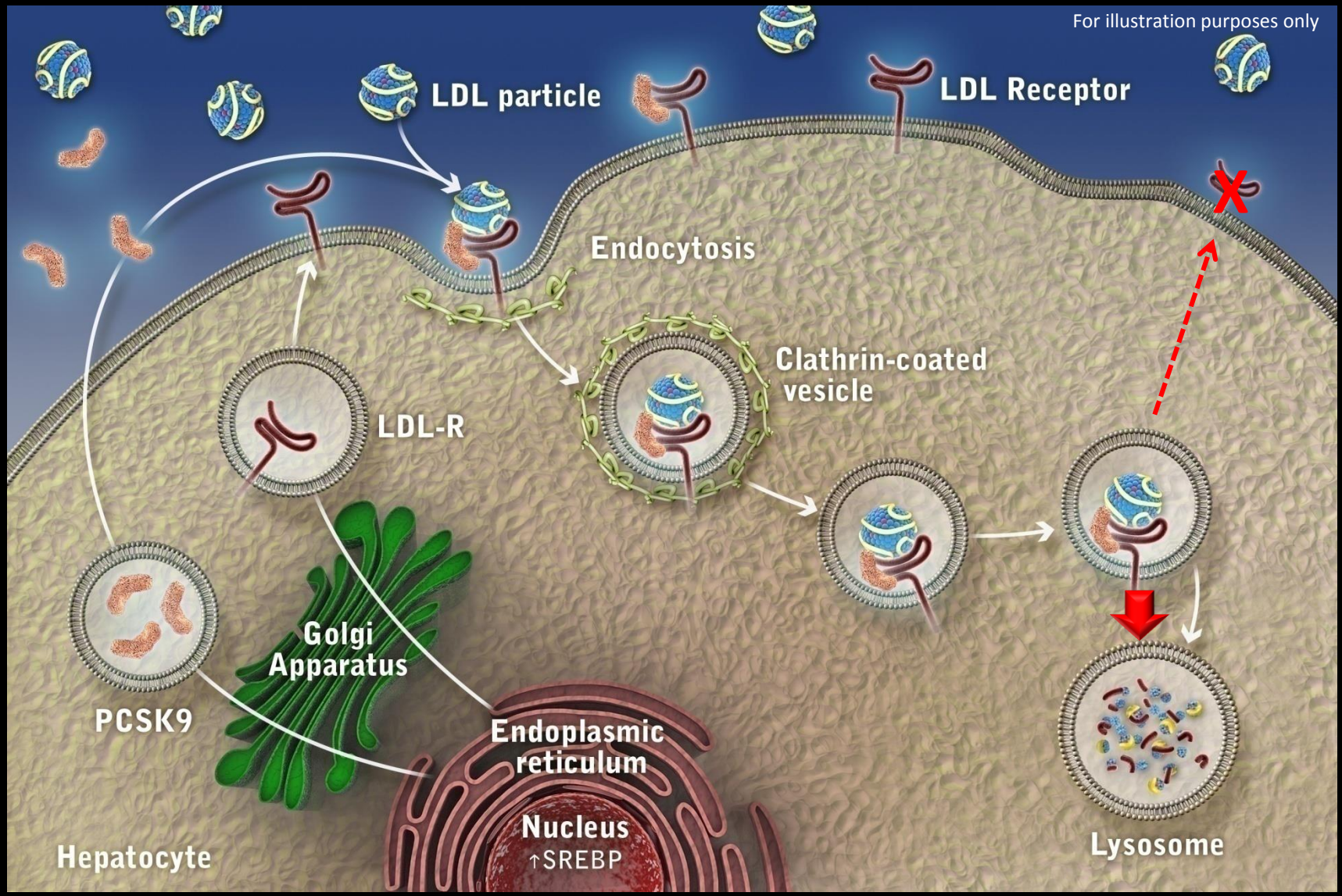
Rashid S et al. PNAS 2005; 102: 5374-9

PCSK9:LDLR binding interface



Drug Design, Development and Therapy 2013:7 1135

Il Ruolo di PCSK9 nella Regolazione dell'Espressione del Recettore per le LDL



HIV and Hepatitis C–coinfected Patients Have Lower LDL-C despite higher PCSK9: an apparent "PCSK9–Lipid Paradox"

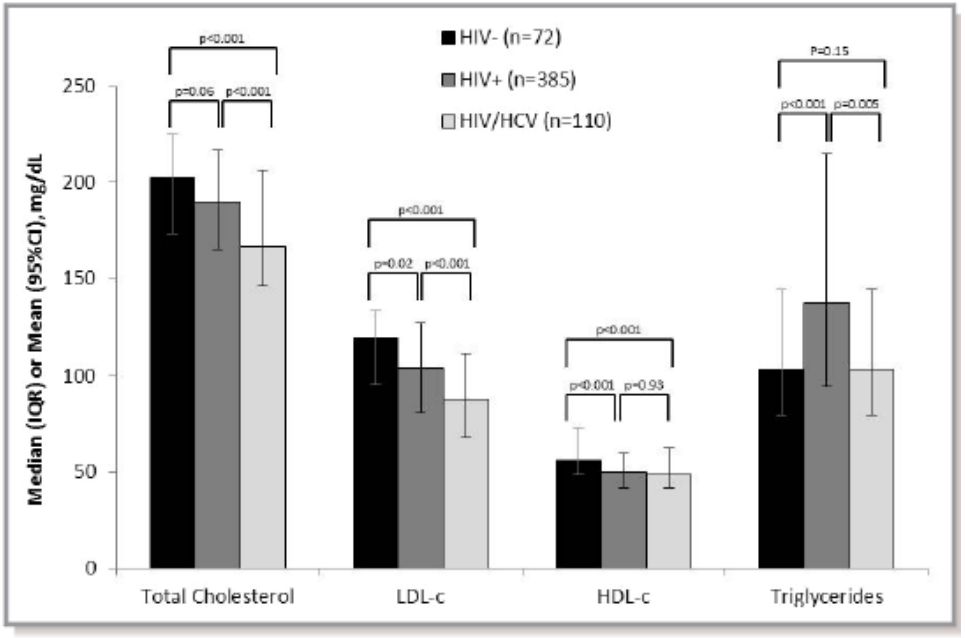
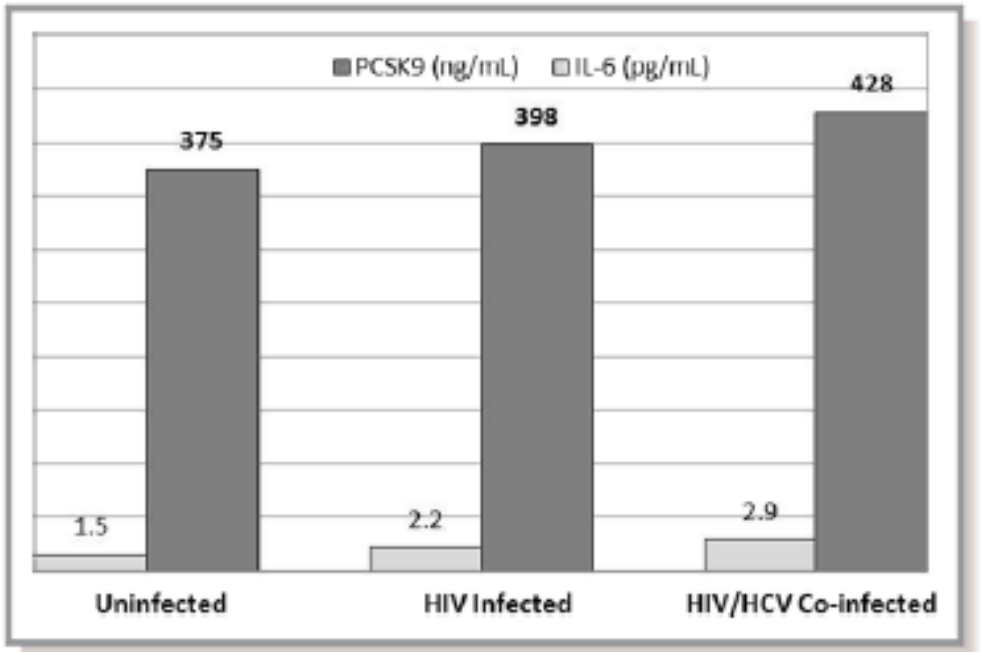


Table 2. HIV Characteristics in Monoinfected and HCV-Coinfected Individuals

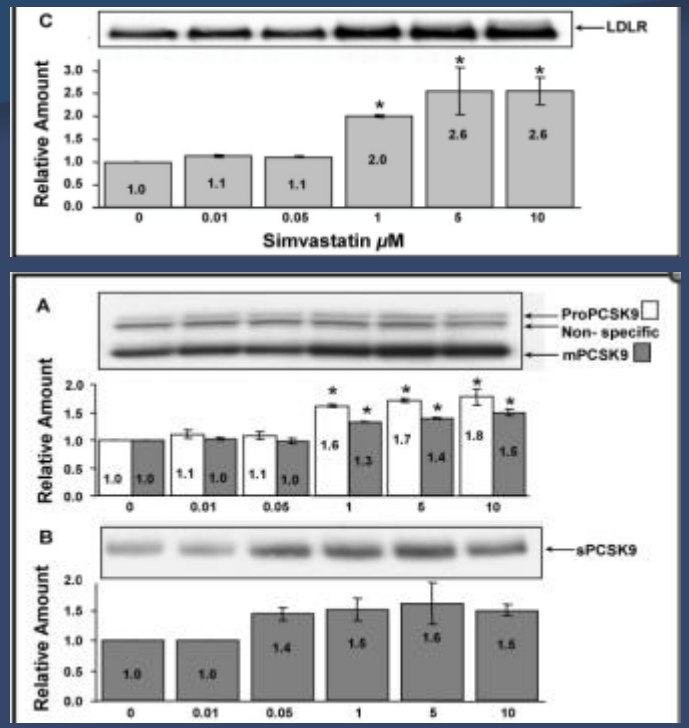
	HIV Infected (n=385)	HIV/HCV Coinfected (n=110)	*P* Value
HIV duration, y	15 (7–21)	15 (9–20)	0.87
HIV viral load, copies/mL	75 (40–860)	75 (40–1450)	0.07
Current CD4 count, cells/mm^3	533 (357–739)	516 (303–701)	0.32
Nadir CD4 count, cells/mm^3	239 (100–399)	227 (93–365)	0.67
Off current ART	111 (28.8)	40 (45.5)	<0.001
Opportunistic infection	199 (51.7)	63 (57.3)	<0.001
Off ART, viral load <75 copies	19 (4.9)	13 (11.8)	0.002
Off ART, viral load >75 copies	92 (23.9)	37 (33.6)	
On ART, viral load >75 copies	41 (10.7)	14 (12.7)	
On ART, viral load <75 copies	233 (60.5)	46 (41.8)	

All values expressed as median (IQR) or N (%): number (percentage). ART indicates antiretroviral therapy; HCV, hepatitis C virus.



J Am Heart Assoc 2016; 5:e002683

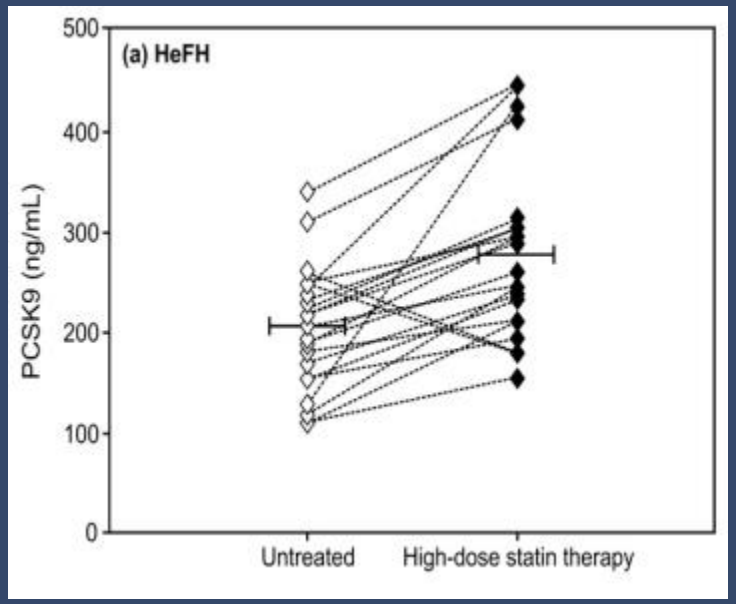
Parallel regulation of LDLR and PCSK9



Cholesterol deficiency results in upregulation of LDLR

Mayne J. et al. Lipid Health & Dis, 2008; 7(22)

Statins increase LDLR and PCSK9 levels in HepG2 treated with statins.



Raal F. et al, JAHA, 2013; 2(2):e000028

Statins increase serum PCSK9 levels in heterozygous FH patients.

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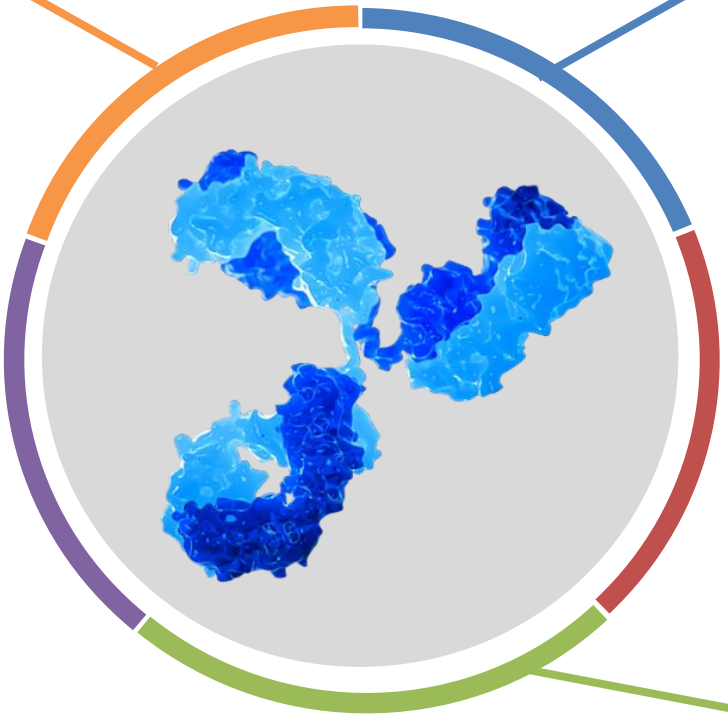
Alirocumab Is a Fully Human IgG1 Monoclonal Antibody (mAb) That Inhibits the Binding of PCSK9 to LDLR[1]

Half-life of 17–20 days[a] allows for 2-week dosing via subcutaneous dosing[1]

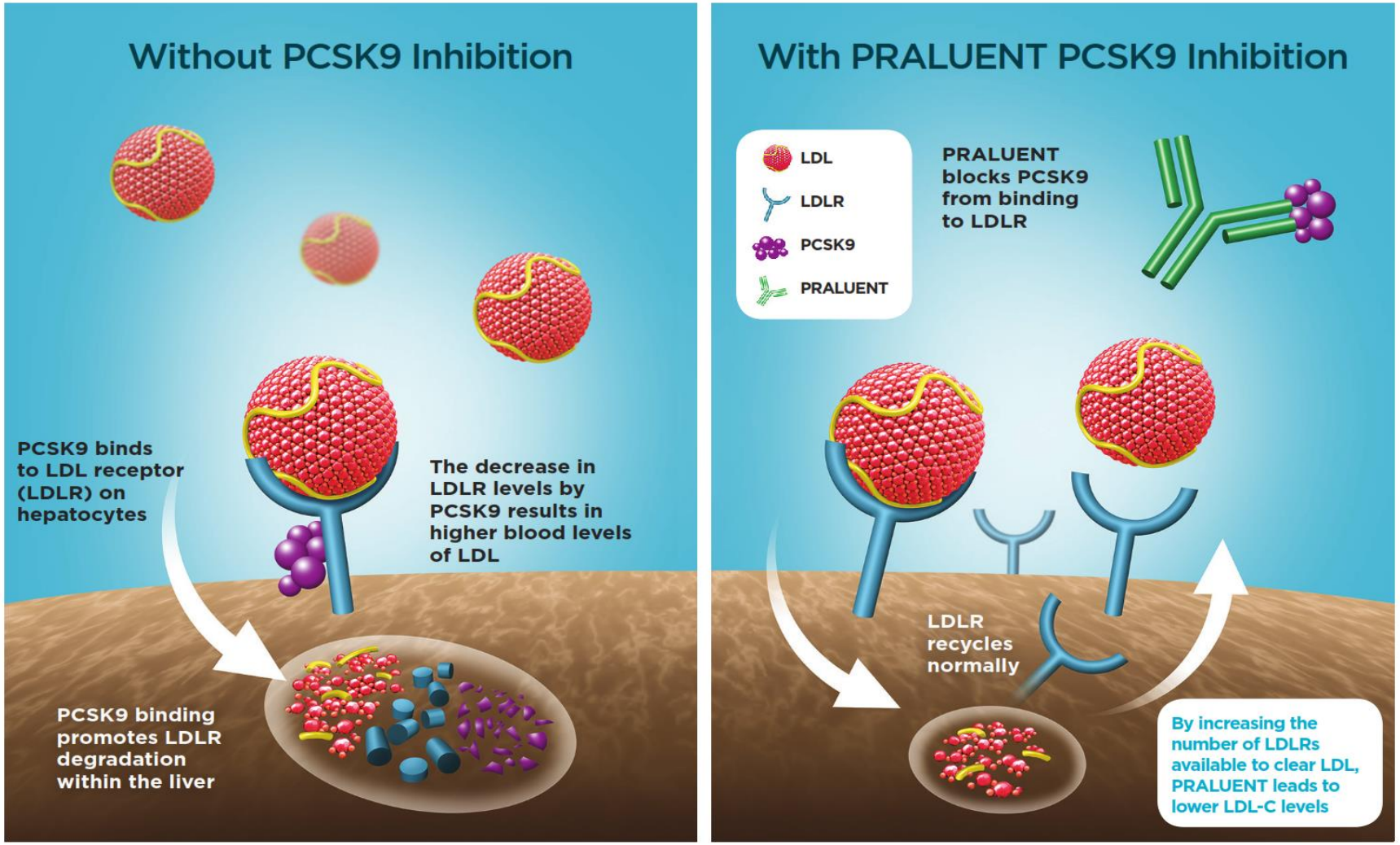
Binds with high affinity and specificity to PCSK9[1]



Like most therapeutic mAbs, alirocumab is an IgG1 molecule[1,2]

LDLR=low-density lipoprotein receptor; IgG1=immunoglobulin G1; PCSK9=proprotein convertase subtilisin/kexin type 9.
[a]Median apparent half-life at steady state is impacted by concomitant use of statin therapy.
1. PRALUENT European SmPC Sanofi/Regeneron Pharmaceuticals 2016; 2. Wang W, et al. *Clin Pharmacol Ther*. 2008;84(5):548-558.

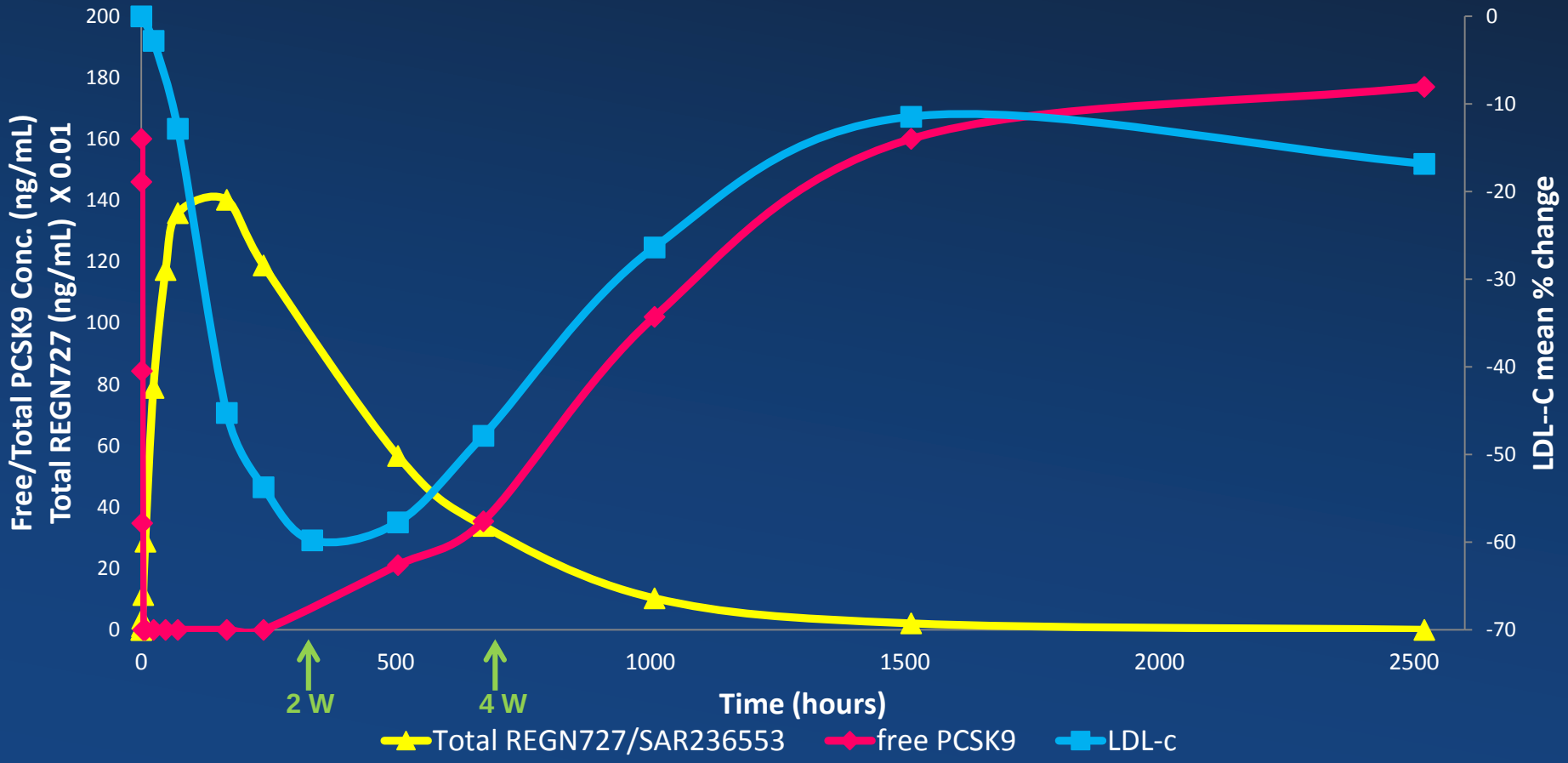
PCSK9 Physiology and Inhibition by PRALUENT® (alirocumab)[1]



1. PRALUENT European SmPC Sanofi/Regeneron Pharmaceuticals 2016.

Alirocumab : relationship between mAb levels, PCSK9 and LDL-C

Free PCSK9, Total REGN727/SAR236553 Concentration and Mean % Change LDL-C vs Time



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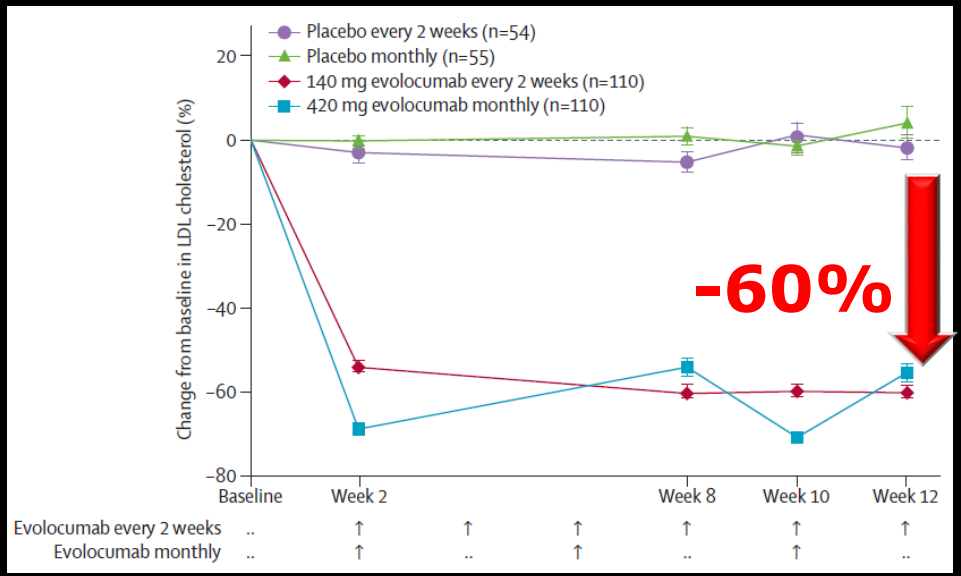
PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial

Frederick J Raal, Evan A Stein, Robert Dufour, Traci Turner, Fernando Civeira, Lesley Burgess, Gisle Langslet, Russell Scott, Anders G Olsson, David Sullivan, G Kees Hovingh, Bertrand Cariou, Ioanna Gouni-Berthold, Ransi Somaratne, Ian Bridges, Rob Scott, Scott M Wasserman, Daniel Gaudet, for the RUTHERFORD-2 Investigators*

- **329 patients** with heterozygous familial hypercholesterolaemia
- **LDL-C≥ 100 mg/dl**
- **Evolocumab** 140 mg every 2 weeks
- **Evolocumab** 420 mg monthly

Mean % change from baseline in LDL-C



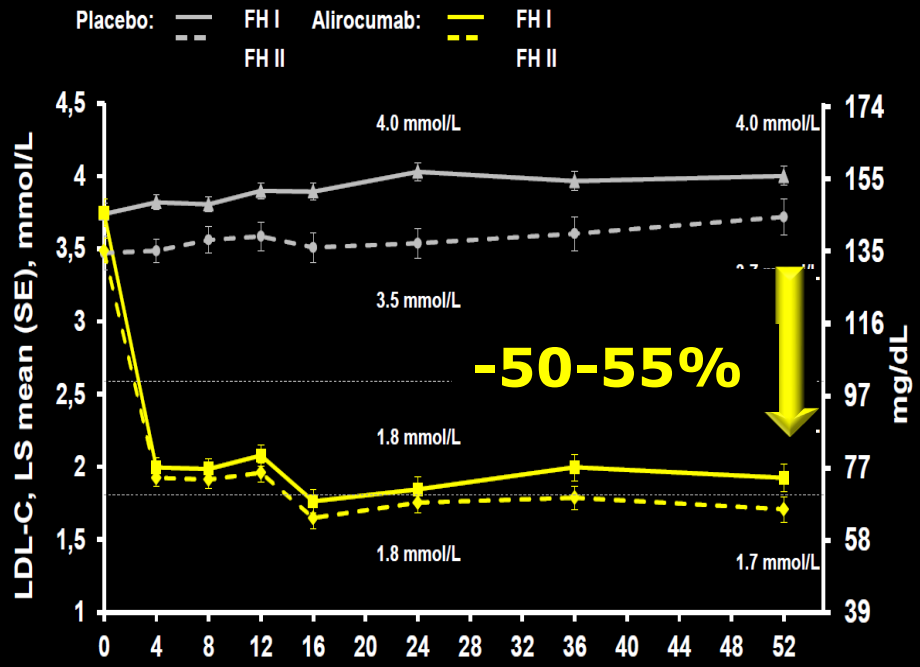
The Lancet, 385:331-340, 2015

Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolaemia (heFH) not adequately controlled with current lipid-lowering therapy: Results of ODYSSEY FH I and FH II studies

J.J.P. Kastelein, HN.Ginsberg, G Langslet, G.K Hovingh, R. Ceska, R. Dufour, D. Blom, F. Civeira, M. Krempf, M.Farnier

- **486 (FH I) e 249 (FH II) patients** with heterozygous familial hypercholesterolaemia
- **LDL-C≥ 100 mg/dl o ≥ 70 mg/dl se CVD**
- **Alirocumab** 75 mg every 2 weeks
- **Alirocumab** 150 mg every two weeks*

Achieved LDL-C Over Time on Background of Maximally-Tolerated Statin ±Other LLT

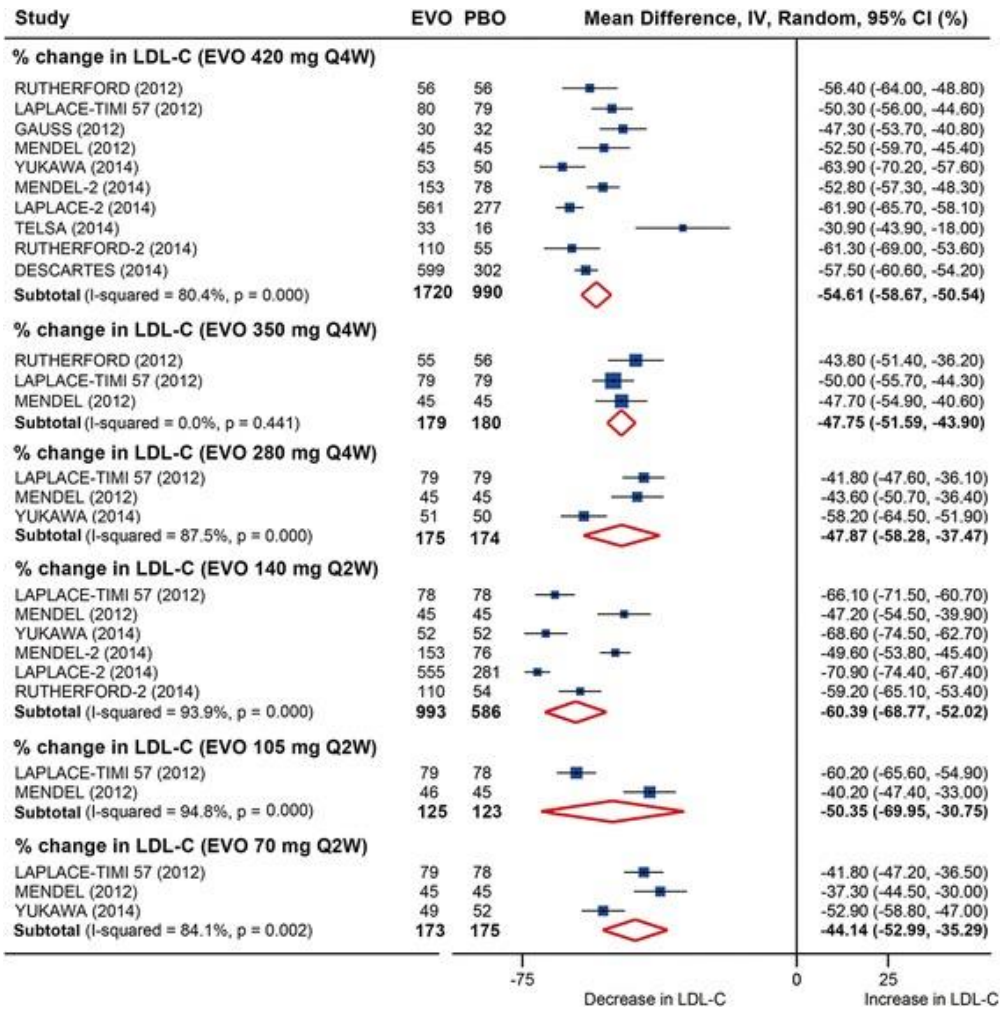


* If LDL-C>70 mg/dl at 8 weeks

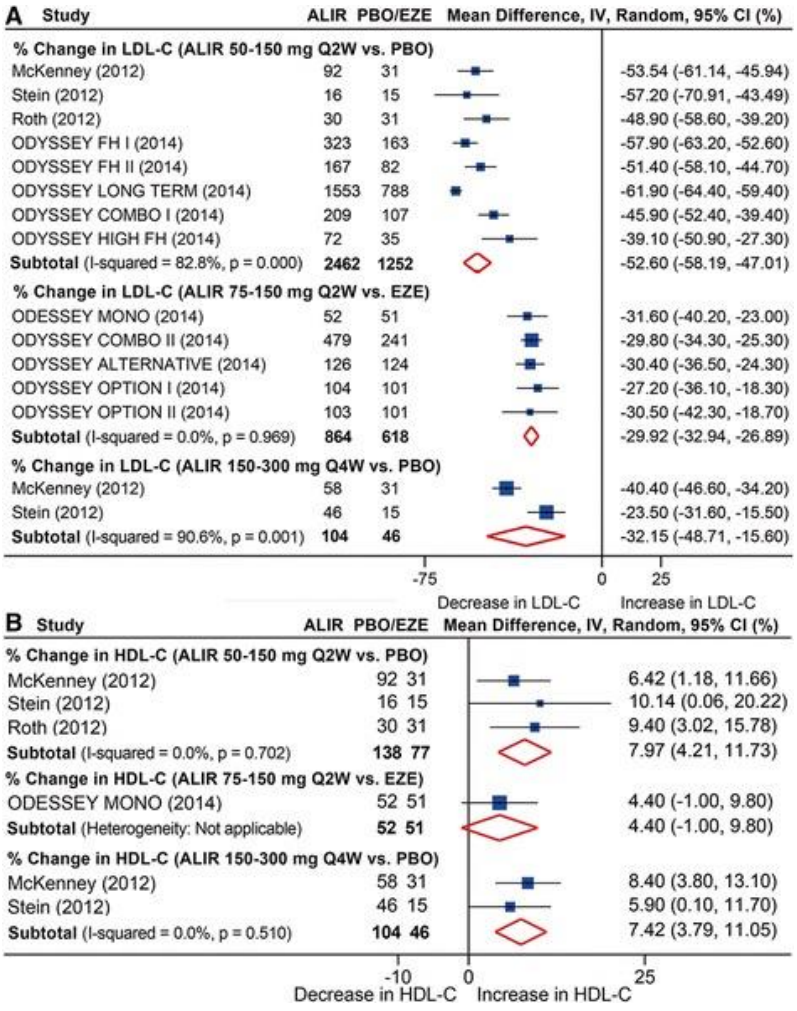
Presented ESC 2014, Barcelona

Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials

Evolocumab

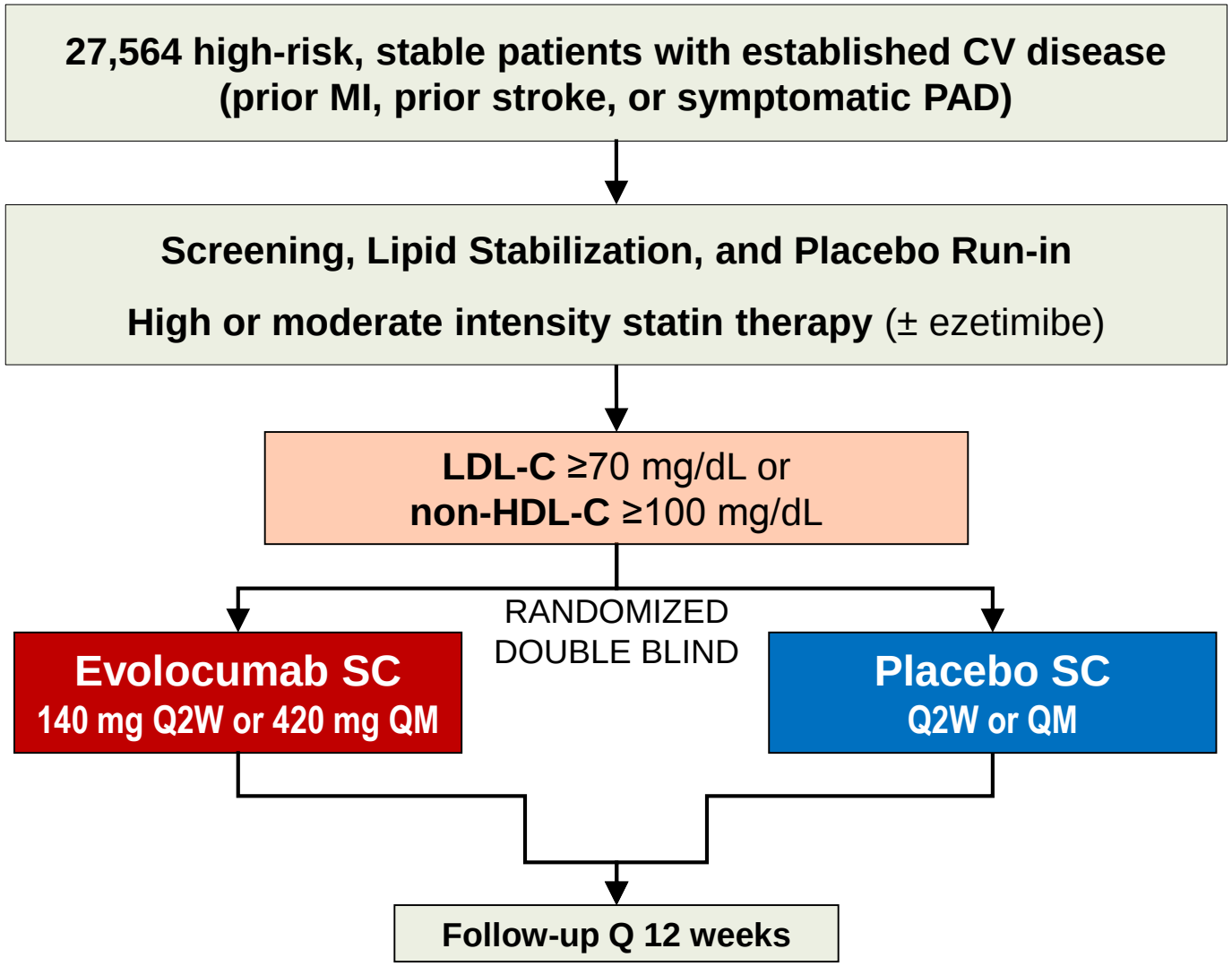


Alirocumab



Zhang et al. BMC Medicine 2015; 13:123

Trial Design



Sabatine MS et al. *Am Heart J* 2016;173:94-101

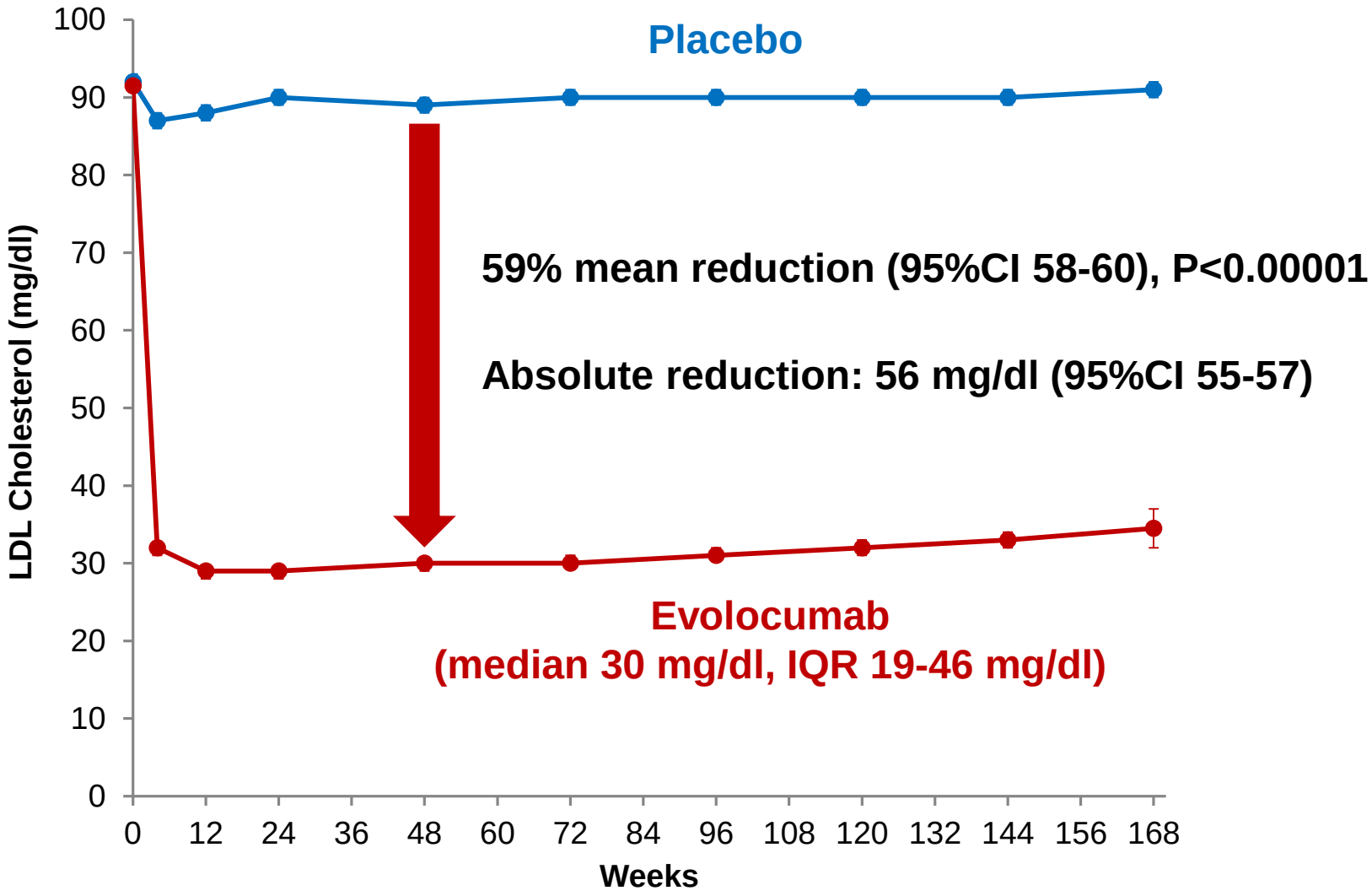
Baseline Characteristics

Characteristic	Value
Age, years, mean (SD)	**63 (9)**
Male sex (%)	**75**
Type of cardiovascular disease (%)	
Myocardial infarction	**81**
Stroke (non-hemorrhagic)	**19**
Symptomatic PAD	**13**
Cardiovascular risk factor (%)	
Hypertension	**80**
Diabetes mellitus	**37**
Current cigarette use	**28**

Median time from most recent event ~3 yrs

Pooled data; no differences between treatment arms

LDL Cholesterol



Types of CV Outcomes

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
CVD, MI, stroke, UA, or revasc	**12.6**	**14.6**	**0.85 (0.79-0.92)**
CV death, MI, or stroke	**7.9**	**9.9**	**0.80 (0.73-0.88)**
Cardiovascular death	**2.5**	**2.4**	**1.05 (0.88-1.25)**
MI	**4.4**	**6.3**	**0.73 (0.65-0.82)**
Stroke	**2.2**	**2.6**	**0.79 (0.66-0.95)**
Hosp for unstable angina	**2.2**	**2.3**	**0.99 (0.82-1.18)**
Coronary revasc	**7.0**	**9.2**	**0.78 (0.71-0.86)**
Urgent	3.7	5.4	0.73 (0.64-0.83)
Elective	3.9	4.6	0.83 (0.73-0.95)
Death from any cause	**4.8**	**4.3**	**1.04 (0.91-1.19)**

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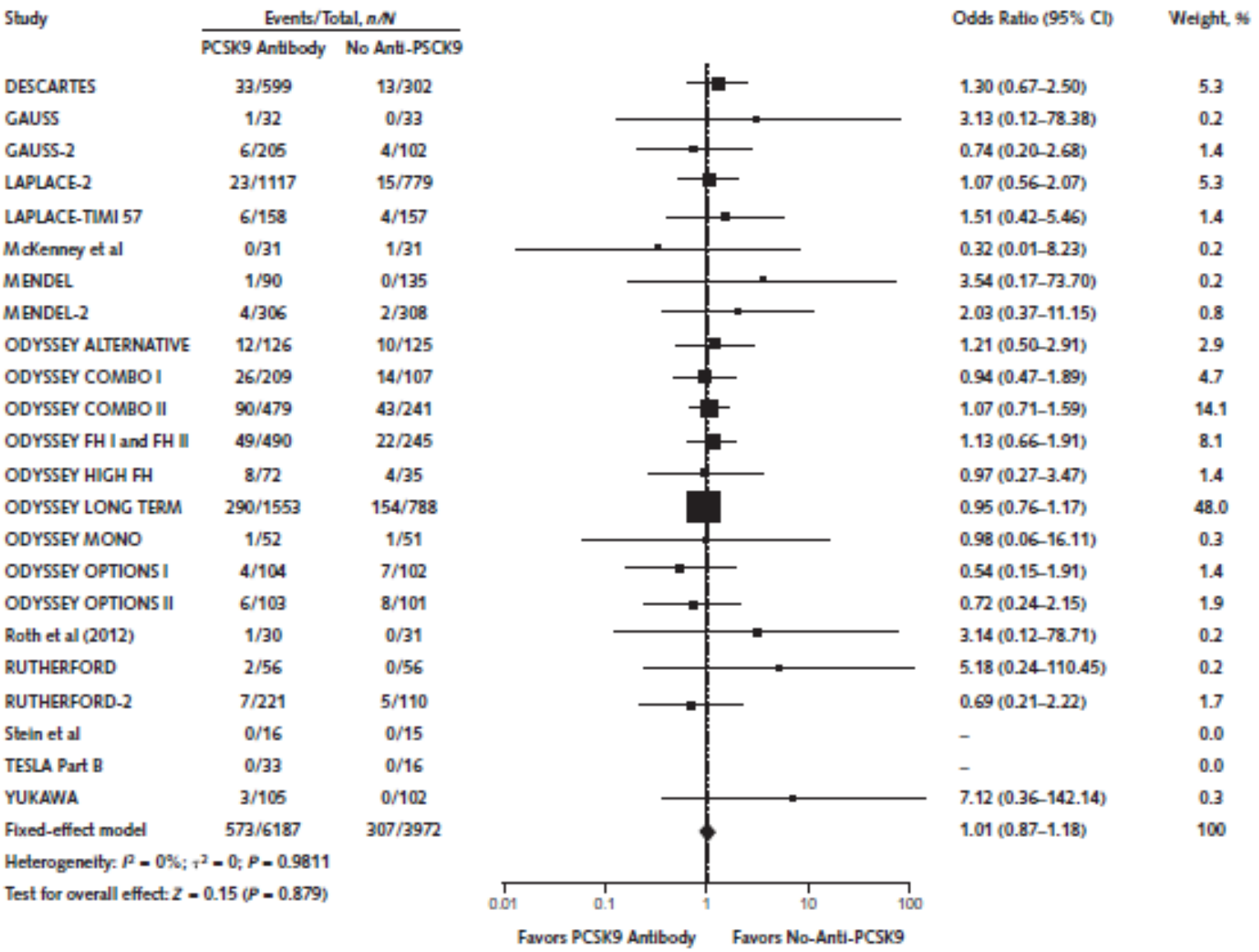
Incidence of seriuos adverse events in iPCSK9 trials: a metanalysis



Ann Intern Med. **doi:10.7326/M14-2957**

Adverse Events of Interest and Laboratory Measures in the Safety Population*

Adverse Events, n (%)	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Injection-site reaction**	296 (2.1)	219 (1.6)
Allergic reactions	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 - n/total n (%)		
Aminotransferase >3x ULN	240/13,543 (1.8)	242/13,523 (1.8)
Creatinine kinase >5x ULN	95/13,543 (0.7)	99/13,523 (0.7)

*Safety evaluations included all randomized patients who received at least one dose of study treatment and for whom post-dose data are available. **The between-group difference was nominally significant (P<0.001). †HR 1.05 (95% CI 0.94-1.17); denominators of 8337 (evolocumab) and 8339 (placebo) because patients with prevalent diabetes at the start of the trial were excluded.

- **Incidence of neurocognitive events, cataracts, and new-onset diabetes were similar between the two arms**
- **Post-baseline anti-evolocumab antibodies were detected in 0.3%, with no neutralizing antibodies detected**

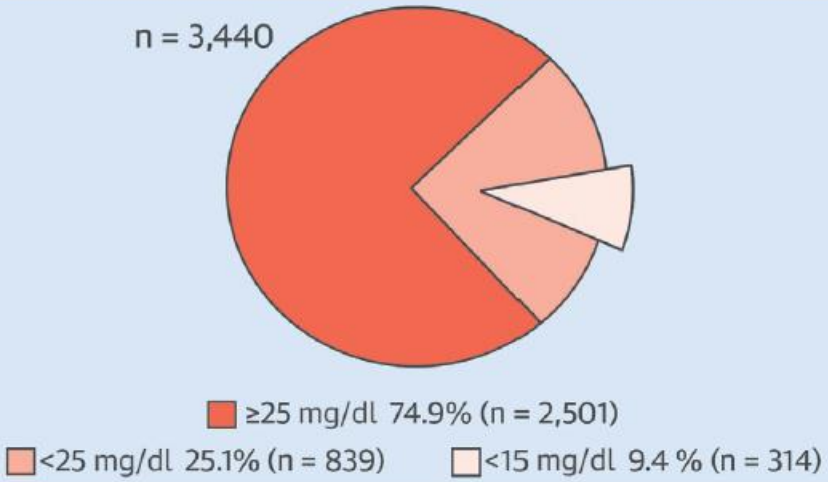
ULN = Upper Limit of Normal

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

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

Pooled Data From Randomized Trials

LDL-C Achieved With Alirocumab Treatment



Duration of Exposure to LDL-C <25 mg/dl

Factors Associated With LDL-C <25 mg/dl

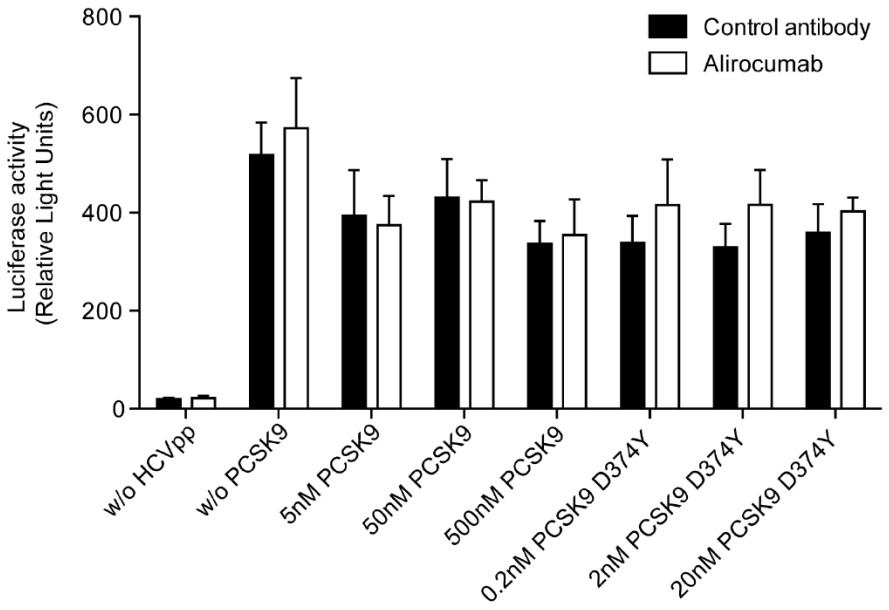
- Lower baseline LDL-C and Lp(a)
- Higher triglycerides, lower HDL-C
- Being male and older, with a lower BMI
- Not having HeFH
- Having cardiovascular disease
- Having type 2 diabetes and higher HbA1c
- Use of 150 mg Q2W alirocumab dose and baseline LDL-C <160 mg/dl

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.

Alirocumab, a Therapeutic Human Antibody to PCSK9, Does Not Affect CD81 Levels or Hepatitis C Virus Entry and Replication into Hepatocytes



Effect of soluble PCSK9, gain-of-function PCSK9 D374Y and alirocumab on HCVpp entry.
Huh-7 cells were incubated for 6 hours with the indicated concentrations of wild-type PCSK9 or the gain-of-function PCSK9 D374Y mutant and alirocumab (monoclonal antibody to PCSK9) or isotype control monoclonal antibody (n = 3 replicates per treatment). Cells were then infected with HCVpp, incubated for 48–72 hours and intracellular luciferase activity was measured.

Table 1. Patients with post-baseline positive HCV test according to baseline status—data from alirocumab Phase 3 placebo- and ezetimibe-controlled trials.

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo (n = 1174)	Alirocumab (n = 2318)	Ezetimibe (n = 618)	Alirocumab (n = 864)
Baseline status—negative*/missing				
Positive RNA	0/966	0/1930	0/316	0/351
Confirmed positive ab with negative RNA	2/966 (0.2%)	2/1930 (0.1%)	0/316	0/351

*Antibody (ab) test negative or ab test positive and reflexive RNA test negative.

PLOS ONE DOI:10.1371/journal.pone.0154498 April 26, 2016

Conclusioni

- Gli Ab anti-PCSK9 consentono di ottenere una riduzione del 50-60% della C-LDL nei pazienti a alto rischio *resistenti* alla terapia convenzionale
- La terapia con gli Ab anti-PCSK9 in aggiunta alla terapia convenzionale è in grado di determinare una significativa riduzione *incrementale* nel rischio di eventi CV maggiori
- Sebbene gli studi sono stati di breve durata, non sono stati osservati EA di particolare rilievo associati all'uso di Ab anti-PCSK9
- Il pinao di sviluppo di questi farmaci dovrà prevedere la valutazione della loro efficacia anche in altre popolazioni (CKD, DM, HIV etc)