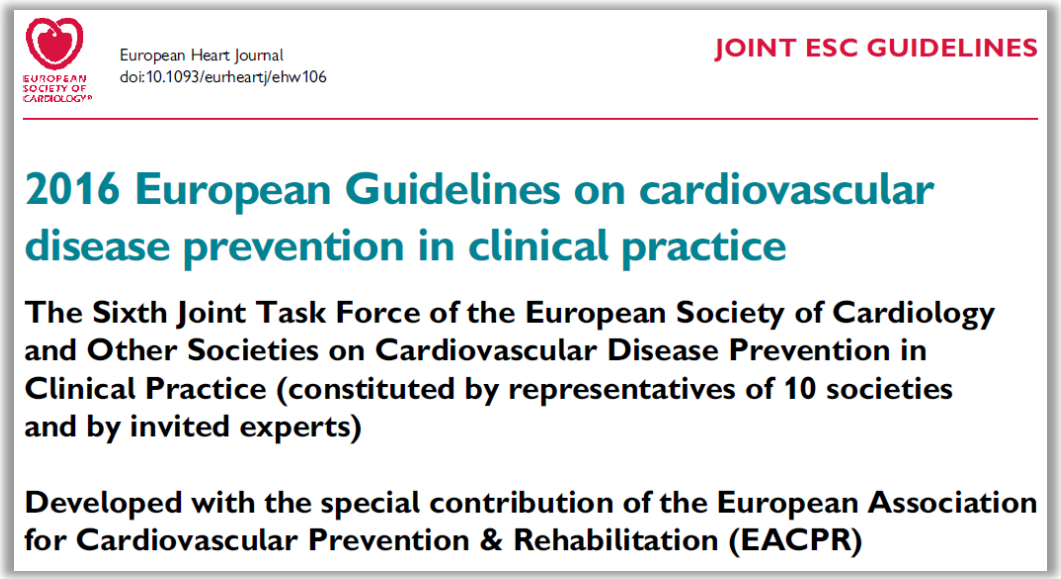
Nuove frontiere per il trattamento delle dislipidemie

Savina Nodari
Cattedra e U.O. di Cardiologia
Spedali Civili e Università degli Studi di Brescia



Lipid control for CV Prevention: key messages

- Elevated levels of plasma LDL-C are causal to atherosclerosis.
- Reduction of LDL-C decreases CV events.
- Low HDL-C is associated with increased CV risk, but manoeuvres to increase HDL-C have not been associated with a decreased CV risk.
- Lifestyle and dietary changes are recommended for all.
- **Total CV risk should guide the intensity of the intervention.**
- Total cholesterol and HDL-C are adequately measured on nonfasting samples, thus allowing non-HDL-C to be derived.

European Heart Journal
doi:10.1093/eurheartj/ehw106

JOINT ESC GUIDELINES

2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

Strategie e stima del rischio: chi può trarne beneficio?

Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes **significant** plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m2). • A calculated SCORE ≥10%.

Alcune particolari categorie di soggetti sono già di per sé ad elevato rischio cardiovascolare senza la necessità di una valutazione del rischio e devono quindi essere sottoposti immediatamente a trattamento di tutti i fattori di rischio.

Risk categories & risk factor goals and target level for CV risk factor

High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m^2). • A calculated SCORE ≥5% and <10%.
Moderate risk	SCORE is ≥1% and <5% at 10 years. Many middle-aged subjects belong to this category.
Low-risk	SCORE <1%.

2016 European Guidelines on cardiovascular disease prevention in clinical practice
2016 ESC Guidelines for the Management of Dyslipidemias

Smoking	No exposure to tobacco in any form.
Diet	Low in saturated fat with a focus on wholegrain products, vegetables, fruit and fish.
Physical activity	At least 150 minutes a week of moderate aerobic PA (30 minutes for 5 days/week) or 75 minutes a week of vigorous aerobic PA (15 minutes for 5 days/week) or a combination thereof.
Body weight	BMI 20–25 kg/m^2. Waist circumference <94 cm (men) or <80 cm (women).
Blood pressure	<140/90 mmHg[a]
Lipids[b] LDL[c] is the primary target	**Very high-risk: <1.8 mmol/L (<70 mg/dL),** or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL)[d] **High-risk: <2.6mmol/L (<100 mg/dL)**, or a reduction of at least 50% if the baseline is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) **Low to moderate risk: <3.0 mmol/L (<115 mg/dL).**
HDL-C	No target but >1.0 mmol/L (>40mg/dL) in men and >1.2 mmol/L (>45 mg/dL) in women indicate lower risk.
Triglycerides	No target but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c <7%. (<53 mmol/mol)

European Heart Journal
doi:10.1093/eurheartj/ehw272

ESC/EAS GUIDELINES

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

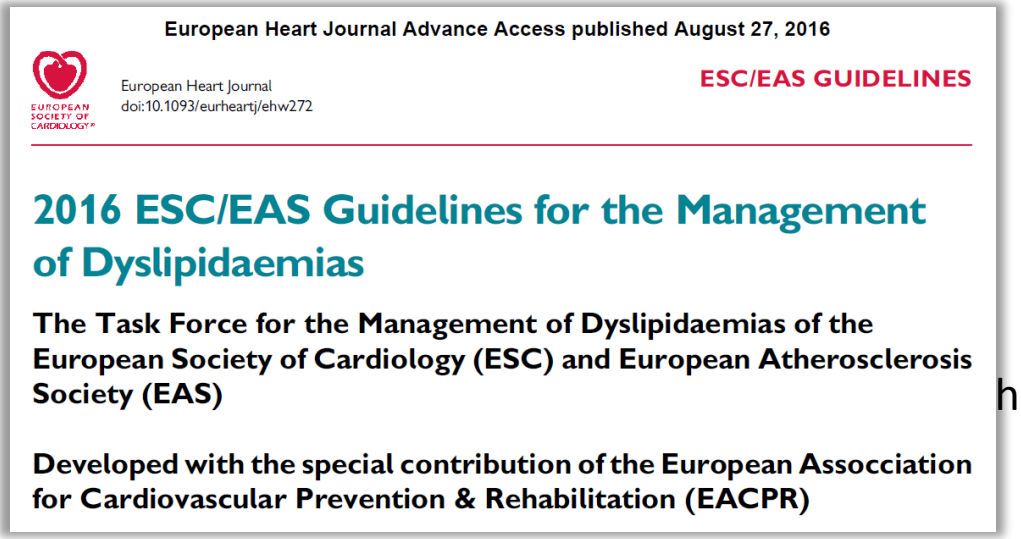
Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR)

Recommendations for Lipid Control

The evidence that reducing plasma LDL-C reduces CVD risk in high risk patients is unequivocal

Every 1.0 mmol/L reduction in LDL-C (38 mg/dl) is associated with a corresponding 20–25%reduction in CVD mortality and non-fatal MI

Recommendations[d e]	Class[a]	Level[b]
In patients at VERY HIGH CV risk, an LDL-C goal <1.8 mmol/L (<70 mg/dL), or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.[f]	I	B
In patients at HIGH CV risk, an LDL-C goal <2.6 mmol/L (<100 mg/dL), or a reduction of at least 50% if the baseline is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) is recommended.	I	B
In the remaining patients on LDL-C lowering treatment, an LDL-C goal <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C



Drugs and drugs combinations

Currently available lipid-lowering drugs:

Statins, fibrates, bile acid sequestrants (anion exchange resins), niacin (nicotinic acid), selective cholesterol absorption inhibitors (e.g. ezetimibe) and, more recently, **proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors**.

Statins should be used as the drugs of **first choice** in patients with hypercholesterolemia or combined hyperlipidaemia

Patients with dyslipidemia, particularly those with established CVD, DM or asymptomatic high-risk individuals, may not always reach treatment goals, even with the highest tolerated statin dose. Therefore, combination treatment may be needed.

It must be stressed, however, that the only combination that has evidence of clinical benefit is that of a **statin combined with ezetimibe**

Terapia con statine: problemi aperti

- Mancato raggiungimento dei valori target di colesterolo LDL nonostante l'impiego di statine ad elevata efficacia, in associazione ad ezetimibe
- Ipercolesterolemia familiare
- Intolleranza alle statine

Original scientific paper

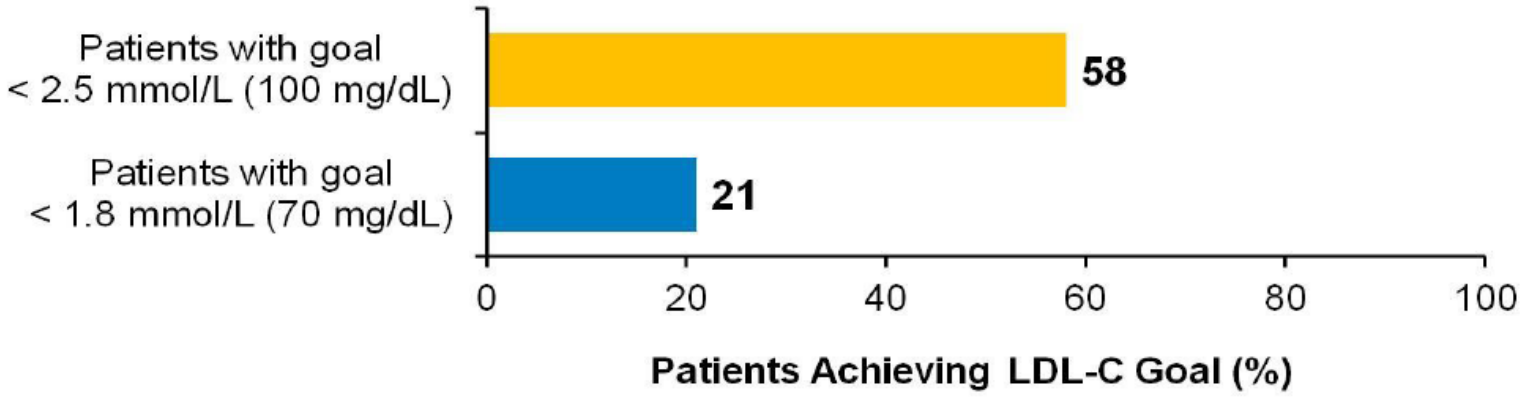
European Journal of Preventive Cardiology

European Journal of Preventive Cardiology
0(00) 1–13

DOI: 10.1177/2047487315569401
ejpc.sagepub.com
SAGE

EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries

- There is a clear need to treat high-risk patients[1]
- The majority (87%) of secondary-prevention patients now receive a statin[2]
- Issues remain in bringing patients to LDL-C goals[1,2]



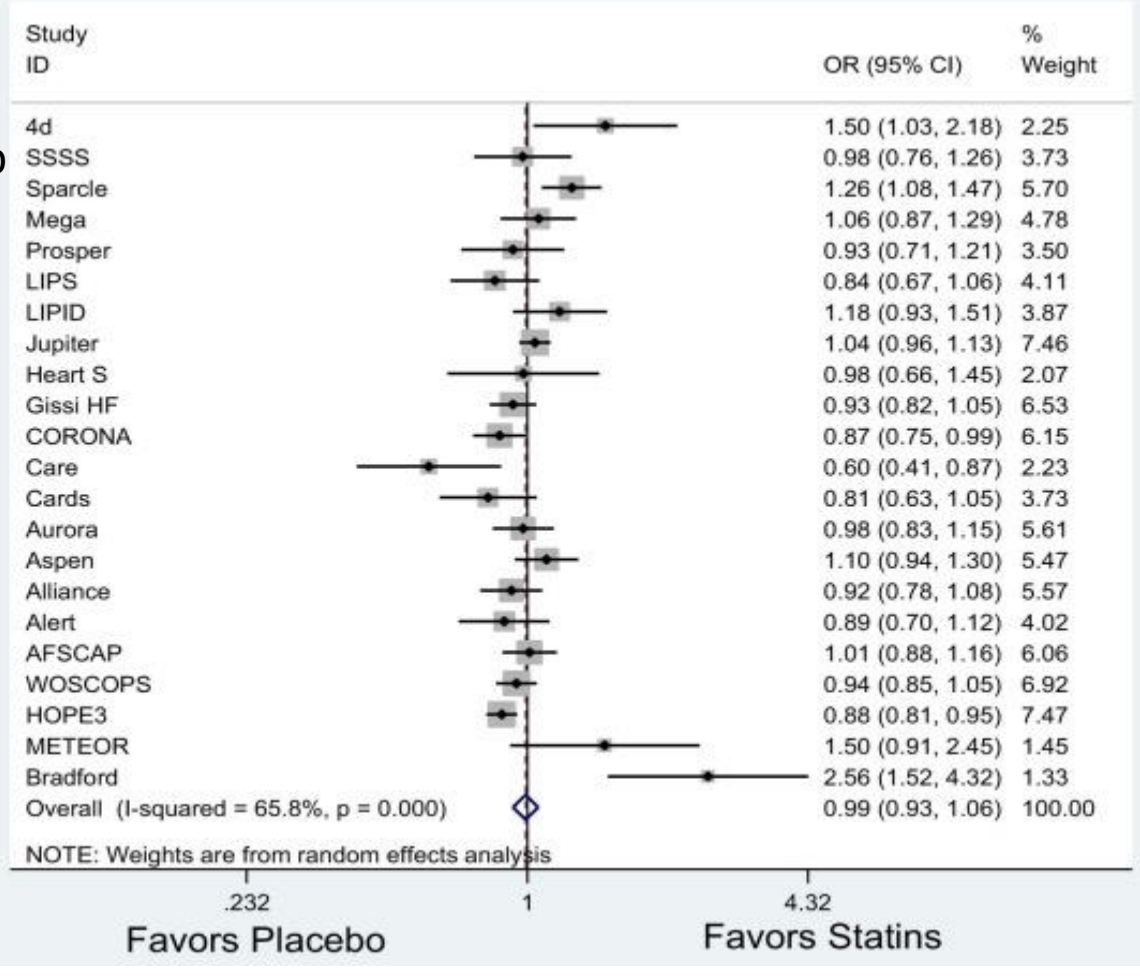
1. http://www.eas-society.org/bringing-more-patients-to-goal-is-the-guidelines-controversy-overblown.aspx [Accessed 2 July 2014];
2. http://www.escardio.org/about/press/press-releases/esc13-amsterdam/Pages/euroaspire-iv-success-challenges-secondary-prevention-CVD-europe.aspx [Accessed 2 July 2014].

Meta-analysis of Placebo-Controlled Randomized Controlled Trials on the Prevalence of Statin Intolerance

Haris Riaz, MD[a,*], Abdur Rahman Khan, MD[b], Muhammad Shahzeb Khan, MD[c], Karim Abdur Rehman, MD[a], Shehab Ahmad Redha Alansari, MD[a], Bashaer Gheyath, MD[a], Sajjad Raza, MD[d], Amr Barakat, MD[a], Faraz Khan Luni, MD[e], Haitham Ahmed, MD, MPH[f], and Richard A. Krasuski, MD[g]

Discontinuation rates of statins versus placebo

over a mean follow-up of 4.1 years, the rates of discontinuation were 13.3% (8,872 patients)for statin-treated patients and13.9% (8,898 patients) for placebo-treated patients



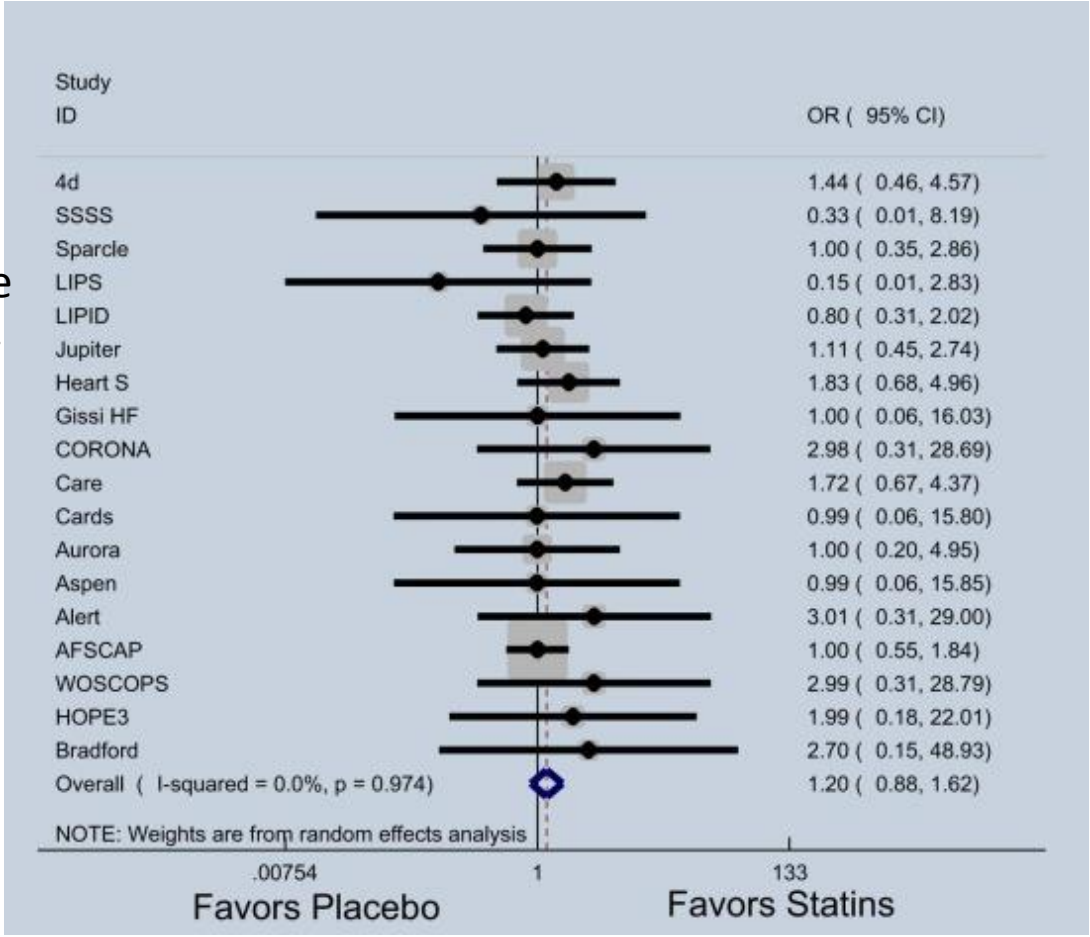
Am J Cardiol 2017;120:774–781

Meta-analysis of Placebo-Controlled Randomized Controlled Trials on the Prevalence of Statin Intolerance

Haris Riaz, MD[a,*], Abdur Rahman Khan, MD[b], Muhammad Shahzeb Khan, MD[c], Karim Abdur Rehman, MD[a], Shehab Ahmad Redha Alansari, MD[a], Bashaer Gheyath, MD[a], Sajjad Raza, MD[d], Amr Barakat, MD[a], Faraz Khan Luni, MD[e], Haitham Ahmed, MD, MPH[f], and Richard A. Krasuski, MD[g]

Rates of myopathy of statins versus placebos

The rates of myopathy were similar between the statin-treated and the placebo-treated patients (OR =1.2, 95% CI =0.88 to 1.62, p =0.25)



Am J Cardiol 2017;120:774–781

Statin Intolerance: real or not real??

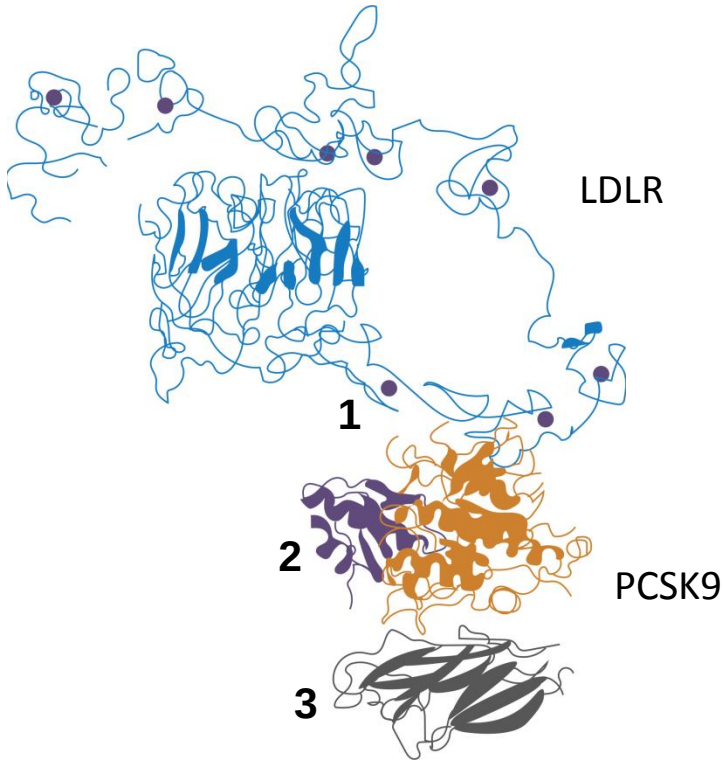
The phrase “statin side effects” yields 670,000 hits on Google (as of November 23, 2016), thereby having the tendency to shape public opinion about the adverse effects of this important class of medications

Intolleranza alle statine: criteri di eleggibilità

- Impossibilità a tollerare almeno 2 statine di cui una alla dose iniziale (rosuvastatina 5 mg/die, atorvastatina 10 mg/die, simvastatina 10 mg/die, lovastatina 20 mg/die, pravastatina 40 mg/die, fluvastatina 40 mg/die) ed una seconda statina ad una qualsiasi dose
- Associazione con uno o più eventi avversi correlati all'uso di statine confermati e non tollerabili oppure associazione con significative alterazioni dei biomarkers (CK >10v)
- Risoluzione o netto miglioramento della sintomatologia, normalizzazione o netta riduzione dei biomarkers alla sospensione/riduzione della dose di statina.
- Sintomatologia/innalzamento dei biomarkers non attribuibile ad altre cause (interazioni farmacologiche o condizioni cliniche note che possono aumentare il rischio di intolleranza alle statine)

PCSK9 (Proprotein convertase subtilisin/kexin type 9): new therapeutic target

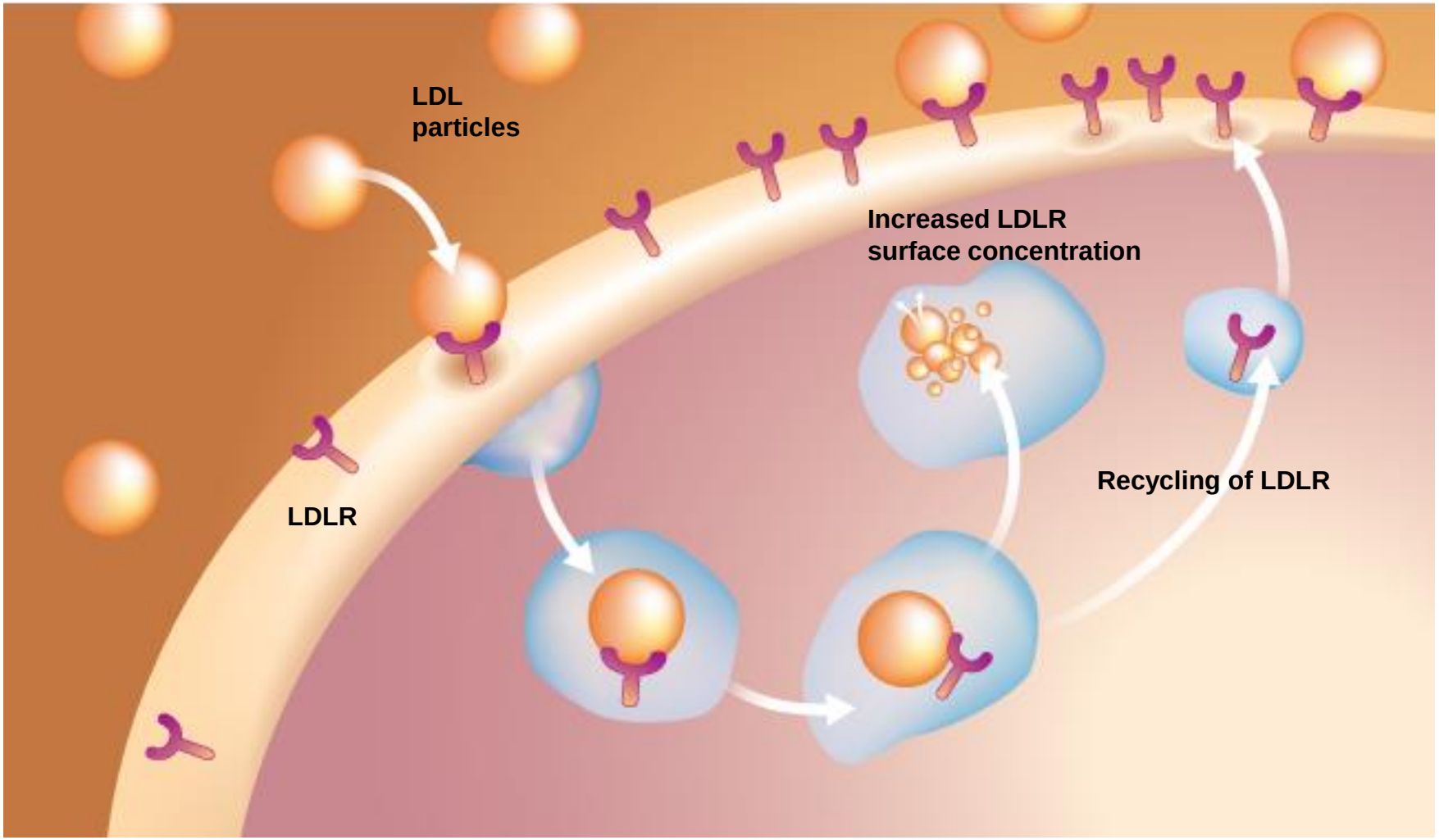
- A serine proprotein convertase[1]
- Expressed in hepatocytes, kidney mesenchymal cells, intestinal ileum and colon epithelia, CNS[2]
- Regulates hepatic LDLRs, which bind and internalise LDL particles[3]



1. Catalytic domain 2. Prodomain 3. C-terminus

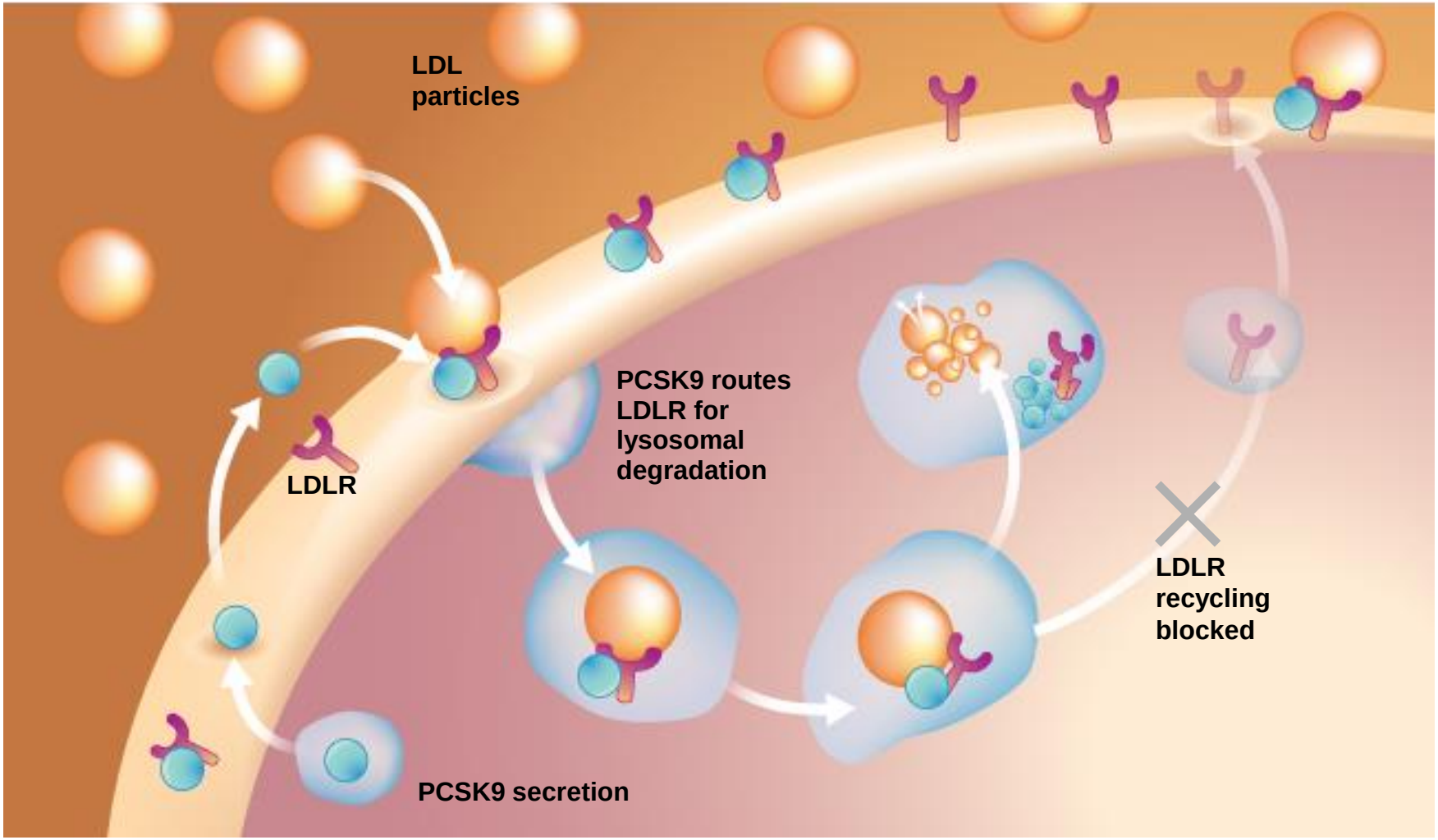
1. Abifadel et al. Hum Mutat 2009;30:520–529.
2. Seidah et al. Proc Natl Acad Sci USA 2003;100:928–933.
3. Horton et al. J Lipid Res 2009;50:S172–S177.

Plasma LDL-C is controlled by hepatic low-density lipoprotein receptor (LDLR) levels



Brown et al. Proc Natl Acad Sci USA 1979;76:3330–3337.

PCSK9 reduces LDLR recycling, thereby increasing plasma LDL-C



Horton et al. J Lipid Res 2009;50:S172–S177.

Genetic variants of PCSK9 demonstrate its importance in regulating LDL levels

PCSK9 gain of function (GOF) = **Fewer** LDLRs[1] (rare[2])

GOF variant	Population	Characteristics
D374Y	British, Norwegian families, 1 Utah family	Premature CHD, tendon xanthomas, severe hypercholesterolaemia
S127R	French, South African, Norwegian patients	Tendon xanthomas; CHD, early MI, stroke
D129G	New Zealand family	Brother died at 31 from MI; strong family history of CVD

PCSK9 loss of function (LOF) = **More** LDLRs[3] (more common[3])

LOF variant	Population	LDL-C	CHD risk
R46L	ARIC, DHS	↓ 15%	↓ 47%
Y142X or C679X	ARIC, DHS	↓ 28%–40%	↓ 88%
R46L	CGPS	↓ 11%	↓ 46%

1. Abifadel et al. Hum Mutat 2009;30:520–529. 2. Dadu et al. Nat Rev Cardiol 2014;11:563–575.
3. Benn et al. J Am Coll Cardiol 2010;55:2833–2842.

STATE-OF-THE-ART PAPER

Targeting the Proprotein Convertase Subtilisin/Kexin Type 9 for the Treatment of Dyslipidemia and Atherosclerosis

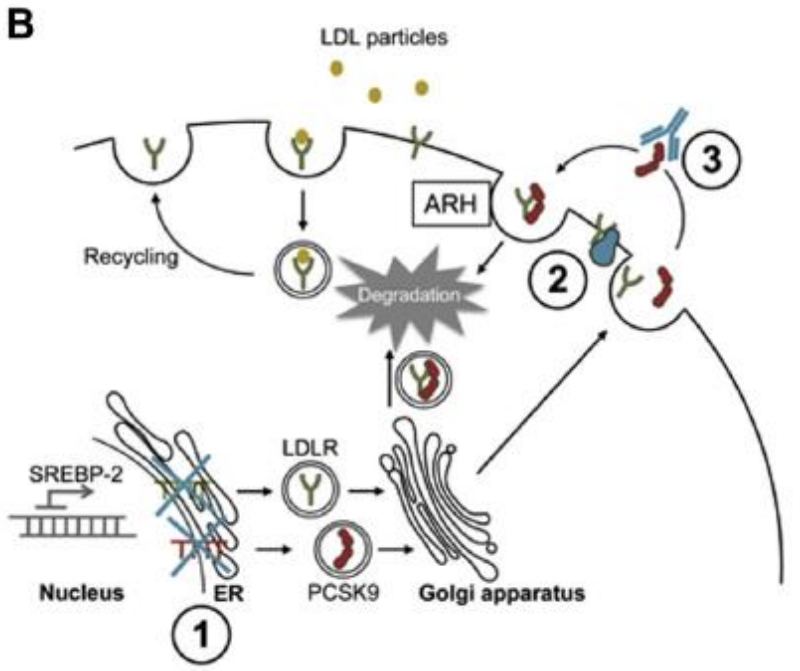
Daniel Urban, MD, Janine Pöss, MD, Michael Böhm, MD, Ulrich Laufs, MD
Homburg/Saar, Germany

Pharmacologic approaches targeting PCSK9 synthesis or function are under development

1) Antisense oligonucleotides or siRNAs inhibit PCSK9 protein expression by specifically binding PCSK9 mRNA.

2) Mimetic peptides competitively bind to the LDLR thereby preventing PCSK9-mediated degradation.

3) Monoclonal Ab inhibit PCSK9 function by specifically binding extracellular PCSK9. ARH ¼ autosomal recessive hypercholesterolemia adaptor protein



(J Am Coll Cardiol 2013;62:1401–8)

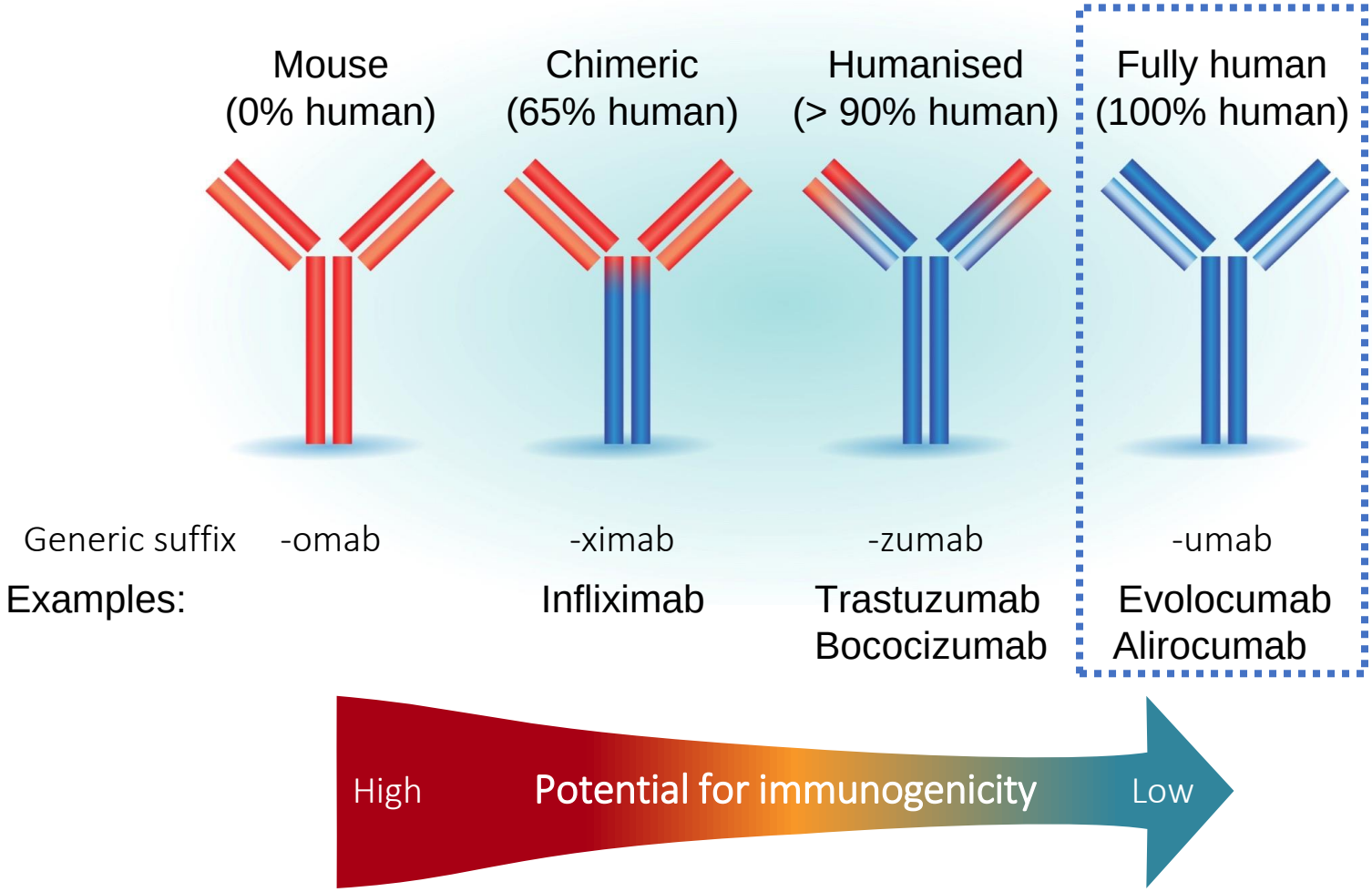
Phase III Trial with PCSK9 inhibitors

Studio	Trattamento	N. pazienti	Criteri di inclusione	Outcome	Fine dello studio
ODYSSEY (NCT01663402)	Alirocumab o placebo	18 000	Pregressa SCA C-LDL >70 mg/dl Terapia con statine ad alta efficacia	Morte cardiaca ischemica, infarto o ictus non fatali ed angina instabile che richieda ospedalizzazione	2018
FOURIER (NCT01764633)	Evolocumab o placebo	22 500	Pregresso evento CV ed elevato rischio residuo C-LDL >70 mg/dl Terapia con statine ad alta efficacia	Morte cardiaca, infarto non fatale ed ospedalizzazione per angina instabile, ictus o rivascolarizzazione coronarica	2017
SPIRE-1 (NCT01975376)	Bococizumab o placebo	12		orte CV, infarto o ictus non fatali angina instabile che richieda pedalizzazione urgente	2017
SPIRE-2 (NCT01975389)	Bococizumab o placebo	6		orte CV, infarto o ictus non fatali angina instabile che richieda pedalizzazione urgente	2017

A 52 settimane dall'inizio della terapia bocucizumab perdeva la potenza nella riduzione di LDL rispetto a quanto osservato a 12 e 24 settimane. Effetto da attribuirsi alla produzione di anticorpi naturali diretti verso il farmaco

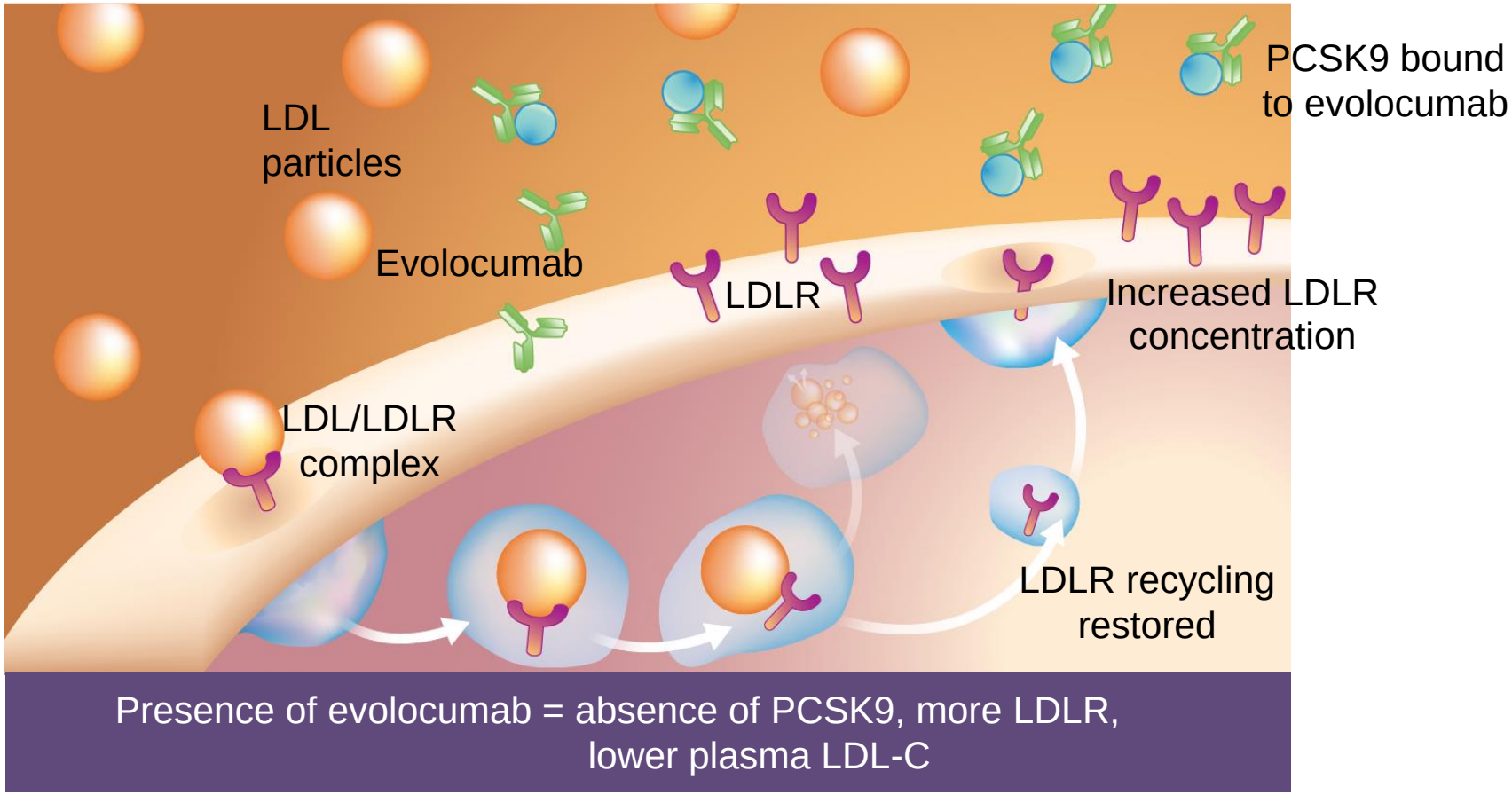
C-LDL, colesterolo LDL; CV, cardiovascolare; SCA, sindrome coronarica acuta.

Fully human antibodies are less immunogenic than those containing elements of mouse antibodies



Weiner. J Immunother 2006;29:1–9.
Yang et al. Crit Rev Oncol Hematol 2001;38:17–23.
WHO INN (International Nonproprietary Names) Working Document 05.179

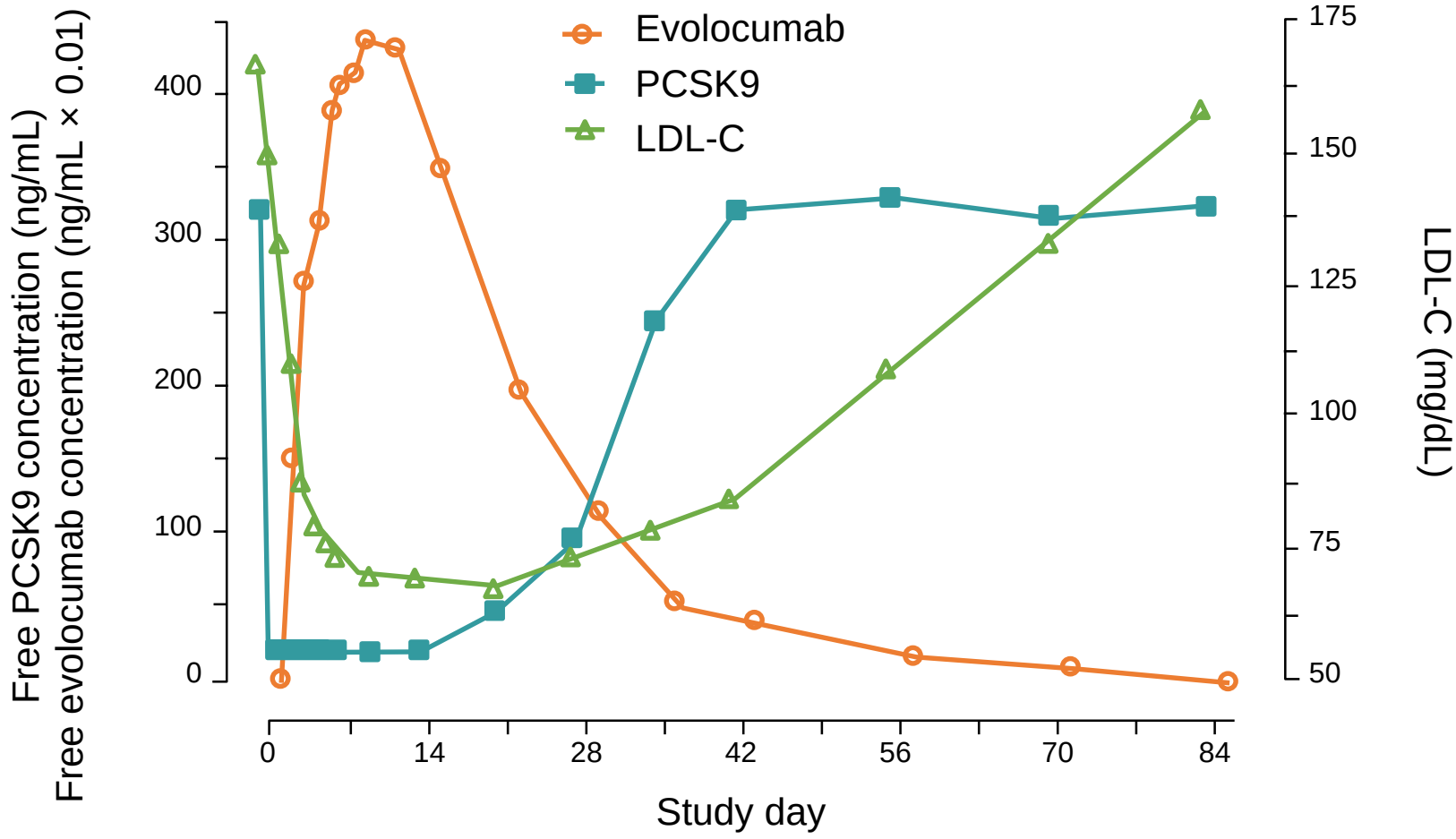
Evolocumab is a fully human monoclonal antibody that binds PCSK9



"Overdosing" is not generally seen with a blocking antibody such as evolocumab

Chan et al. Proc Nat Acad Sci USA 2009;106:9820–9825.

Evolocumab produces rapid suppression of PCSK9 and LDL-C levels



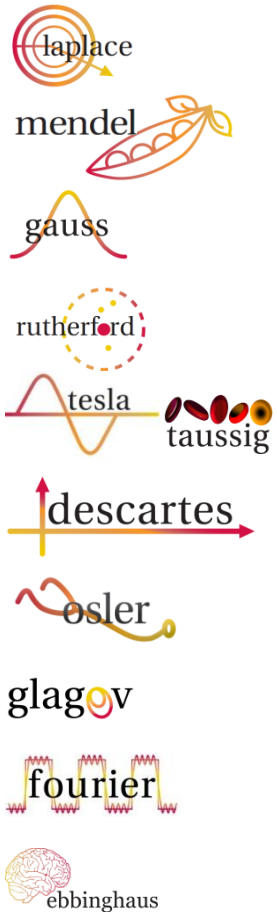
- **Evolocumab 140mg Q2W and Evolocumab 420mg QM have been shown to be clinically equivalent.[2]**

Stein et al. Drugs of the Future 2013;38:451–459.

Evolocumab is being clinically evaluated in the PROFICIO trial programme

PROFICIO

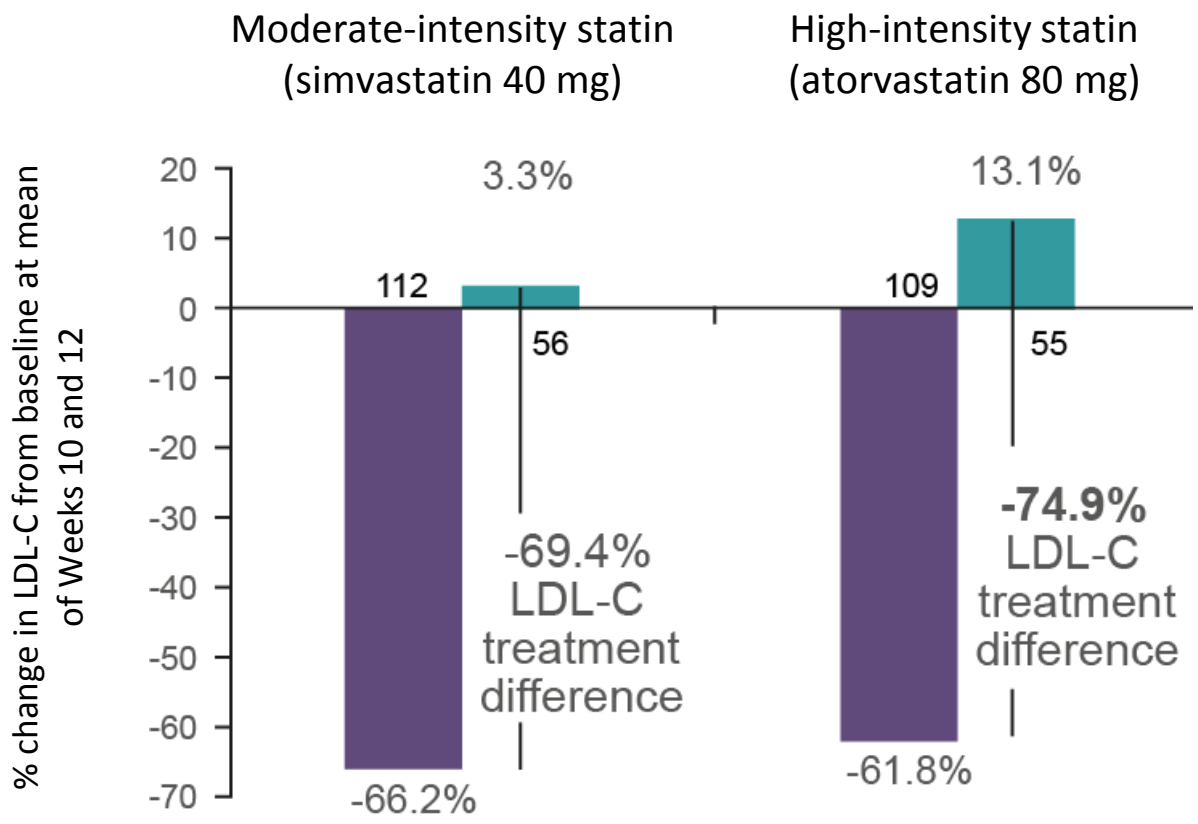
>35,000 patients



Combination therapy	Phase 2 (n=631) ✓	Phase 3 (n=2,067) ✓	
Monotherapy	Phase 2 (n=411) ✓	Phase 3 (n=615) ✓	
Statin intolerant	Phase 2 (n=160) ✓	Phase 3 (n=307) ✓	Phase 3 (n=511) ✓
HeFH	Phase 2 (n=168) ✓	Phase 3 (n=331) ✓	
HoFH/Severe FH	Phase 2/3 (n=58) ✓	Phase 2/3 (n=300) ✓	
Long-term safety and efficacy		Phase 3 (n=905) ✓	
Open-label extension	Phase 2 (n=1,324) ✓	Phase 3 (n=3,141) ✓	
Atherosclerosis		Phase 3 (n=968) ✓	
Secondary Prevention		Phase 3 (n=27,564) ✓	
Neurocognition		Phase 3 (n=1,972) ✓	

✓ Completed trials ✓ Trials with open-label extension ongoing

Evolocumab reduces LDL-C by up to 75% *versus* placebo



2,067 patients with primary hypercholesterolaemia or mixed dyslipidaemia were initially randomised to a moderate-intensity (atorvastatin 10mg, simvastatin 40mg, or rosuvastatin 5mg) or high-intensity (atorvastatin 80mg, rosuvastatin 40mg) statin. After a 4-week lipid-stabilisation period, 1,899 patients were randomised to compare evolocumab (140mg every 2 weeks or 420mg monthly) with placebo (every 2 weeks or monthly) or ezetimibe (10mg or placebo daily; atorvastatin patients only) when added to statin therapies.[1]

Primary hypercholesterolaemia or mixed dyslipidaemia

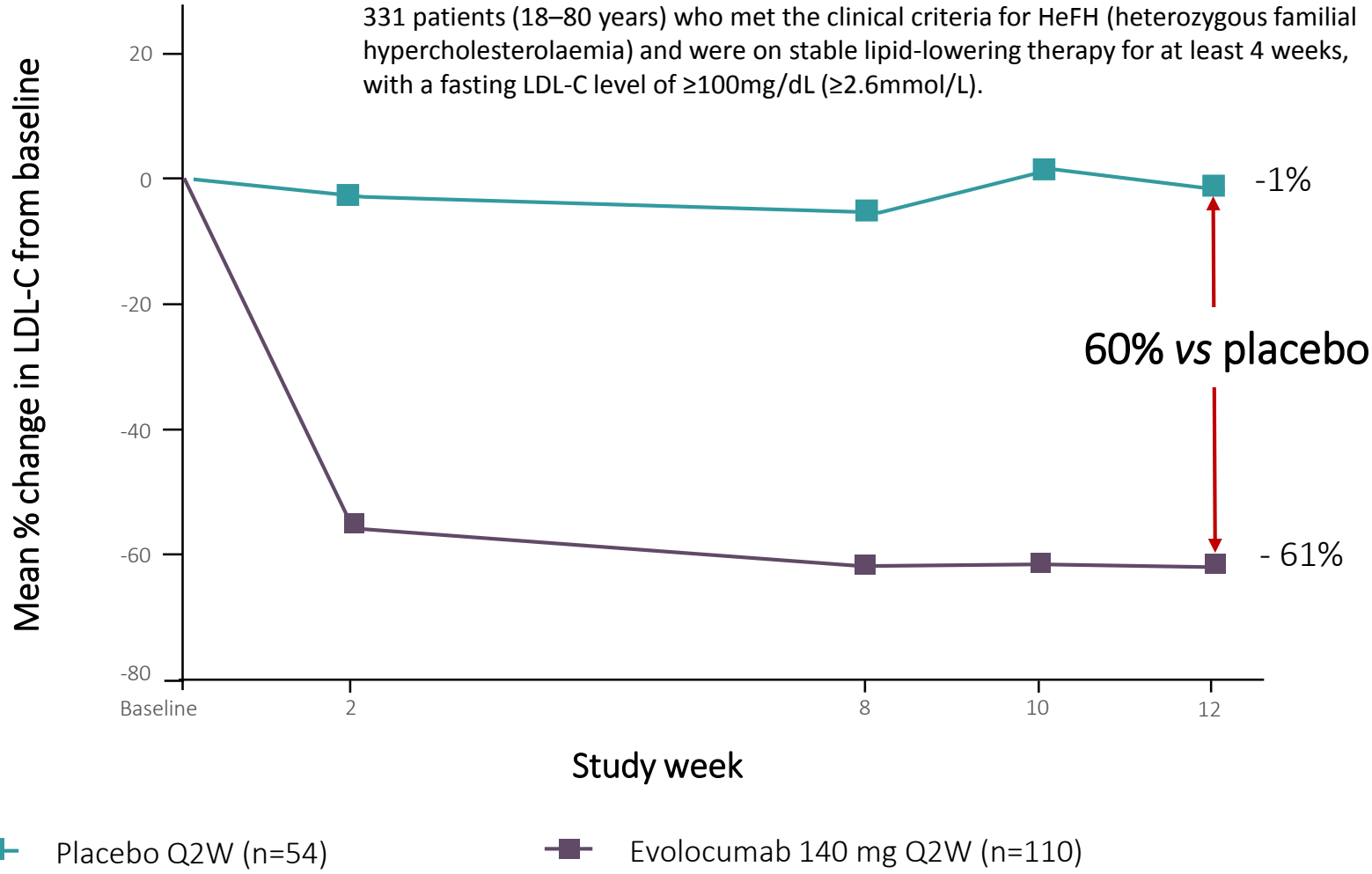
Evolocumab 140 mg Q2W

Placebo Q2W

- **Evolocumab 140mg Q2W and Evolocumab 420mg QM have been shown to be clinically equivalent.[2]**

Robinson et al. JAMA 2014;311:1870–1882.

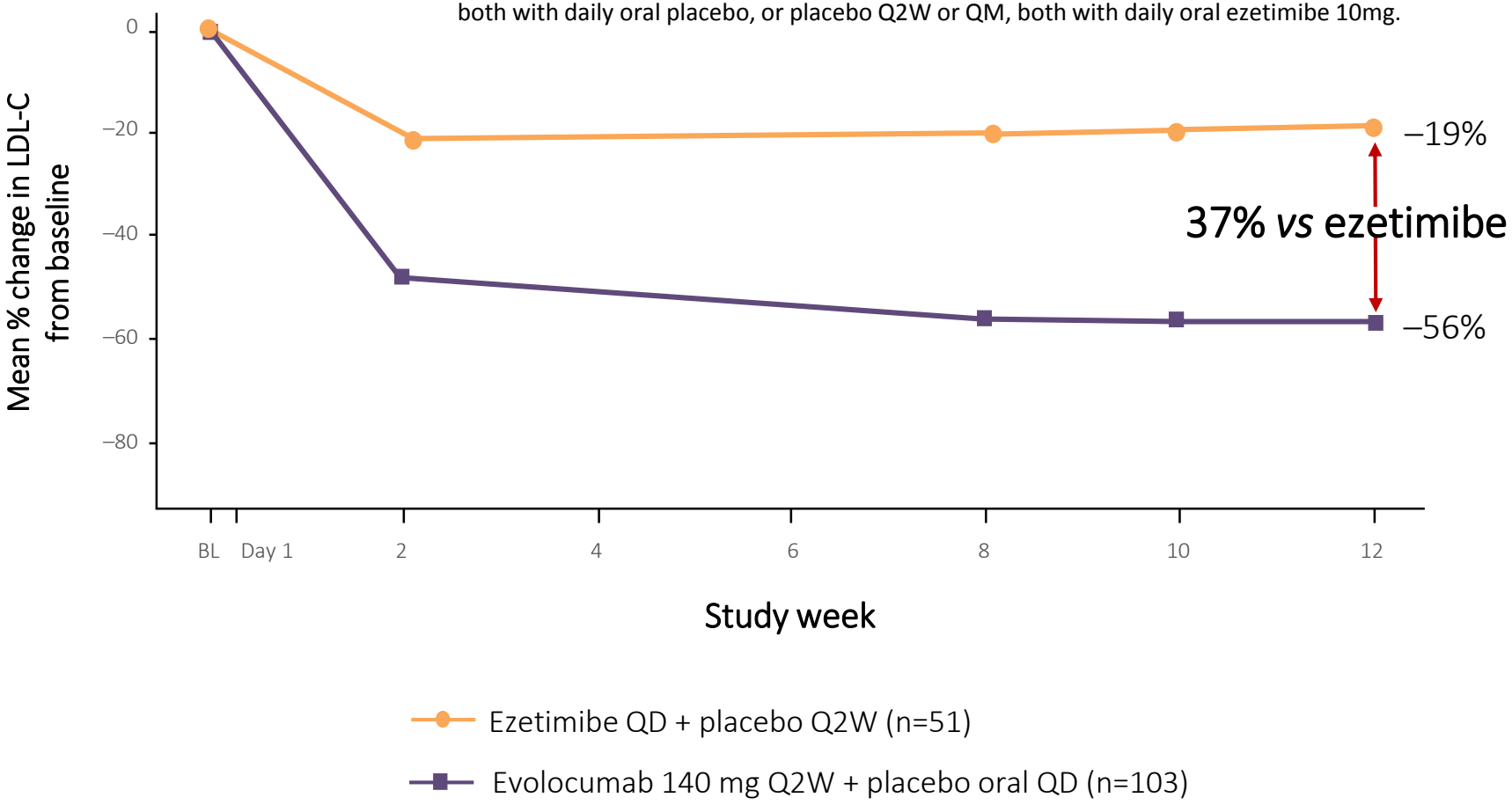
Evolocumab significantly reduces LDL-C in patients with heterozygous FH



Raal et al. Lancet 2015;385:331–340.

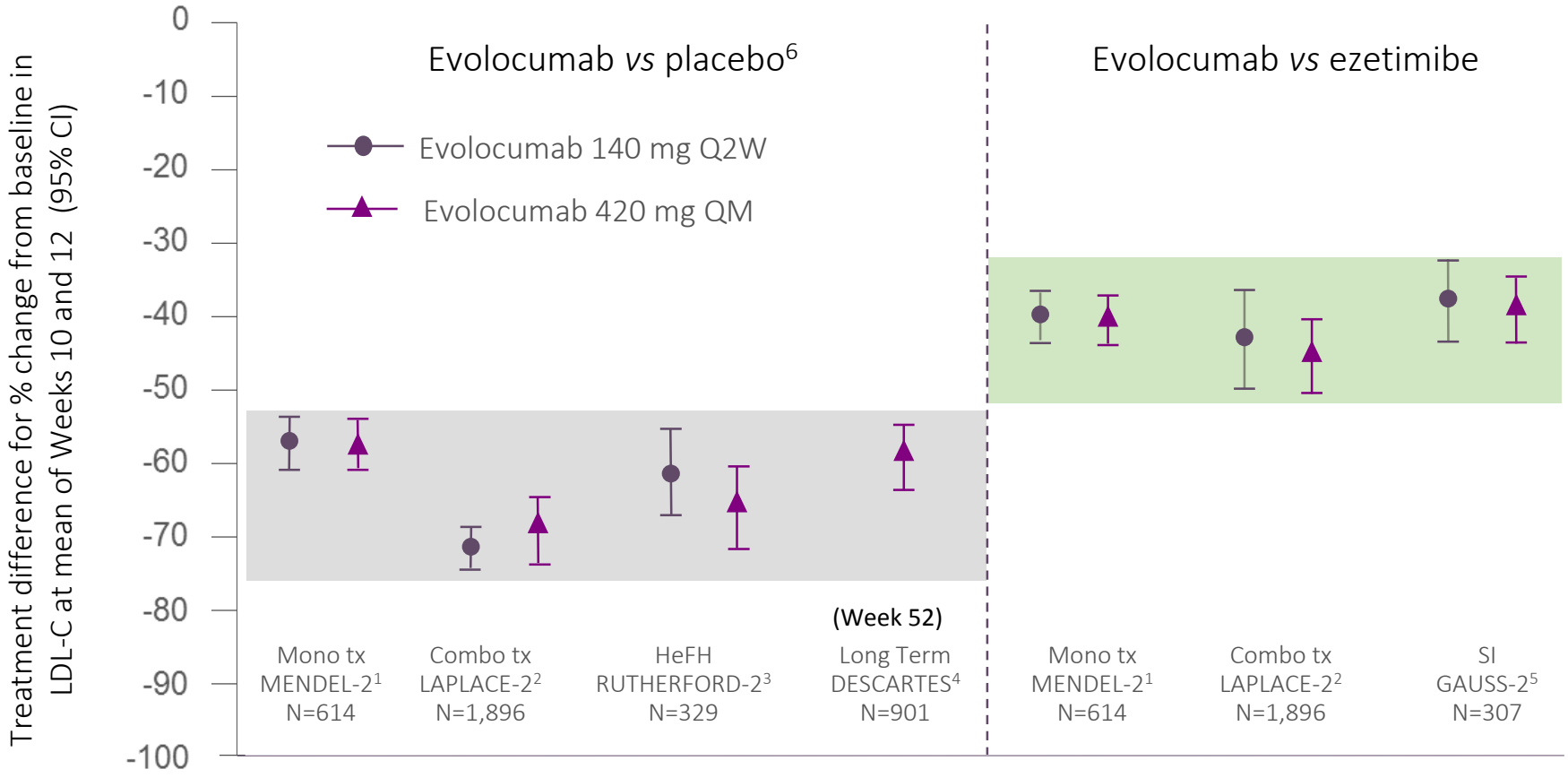
Evolocumab significantly reduces LDL-C over 12 weeks in patients unable to tolerate statins

The GAUSS-2 trial was a 12-week, double-blind, randomised, ezetimibe-controlled study in 307 hypercholesterolaemic patients who were unable to tolerate effective statin doses. Patients were randomly allocated in a 2:2:1:1 ratio to receive evolocumab 140mg Q2W or evolocumab 420mg QM, both with daily oral placebo, or placebo Q2W or QM, both with daily oral ezetimibe 10mg.



Stroes et al. J Am Coll Cardiol 2014;63:2541–2548.

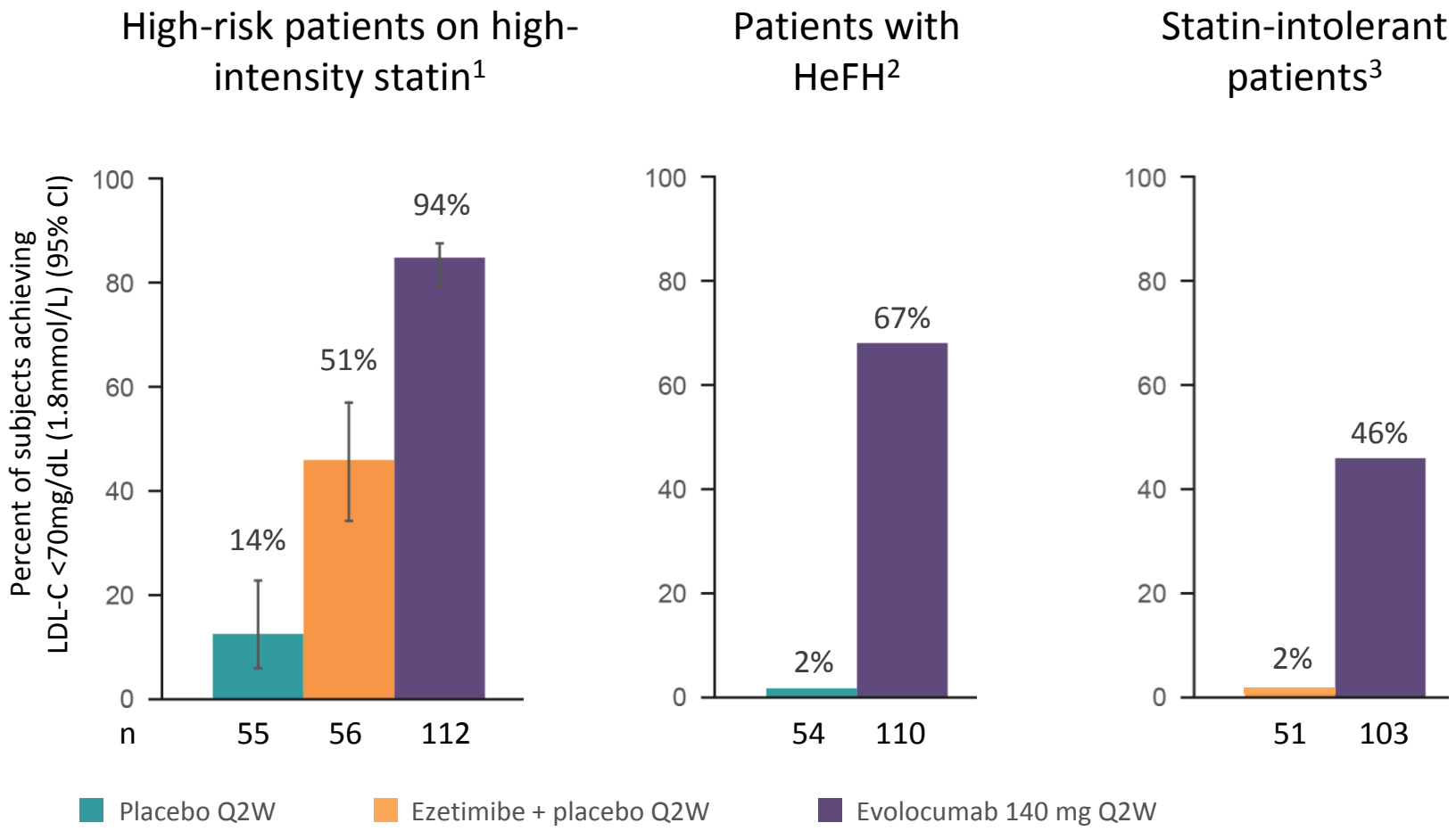
Evolocumab provides consistent LDL-C reduction across pivotal studies, therapeutic settings and doses



Across all studies of patients with primary hyperlipidaemia (heterozygous familial and non-familial) and mixed dyslipidaemia

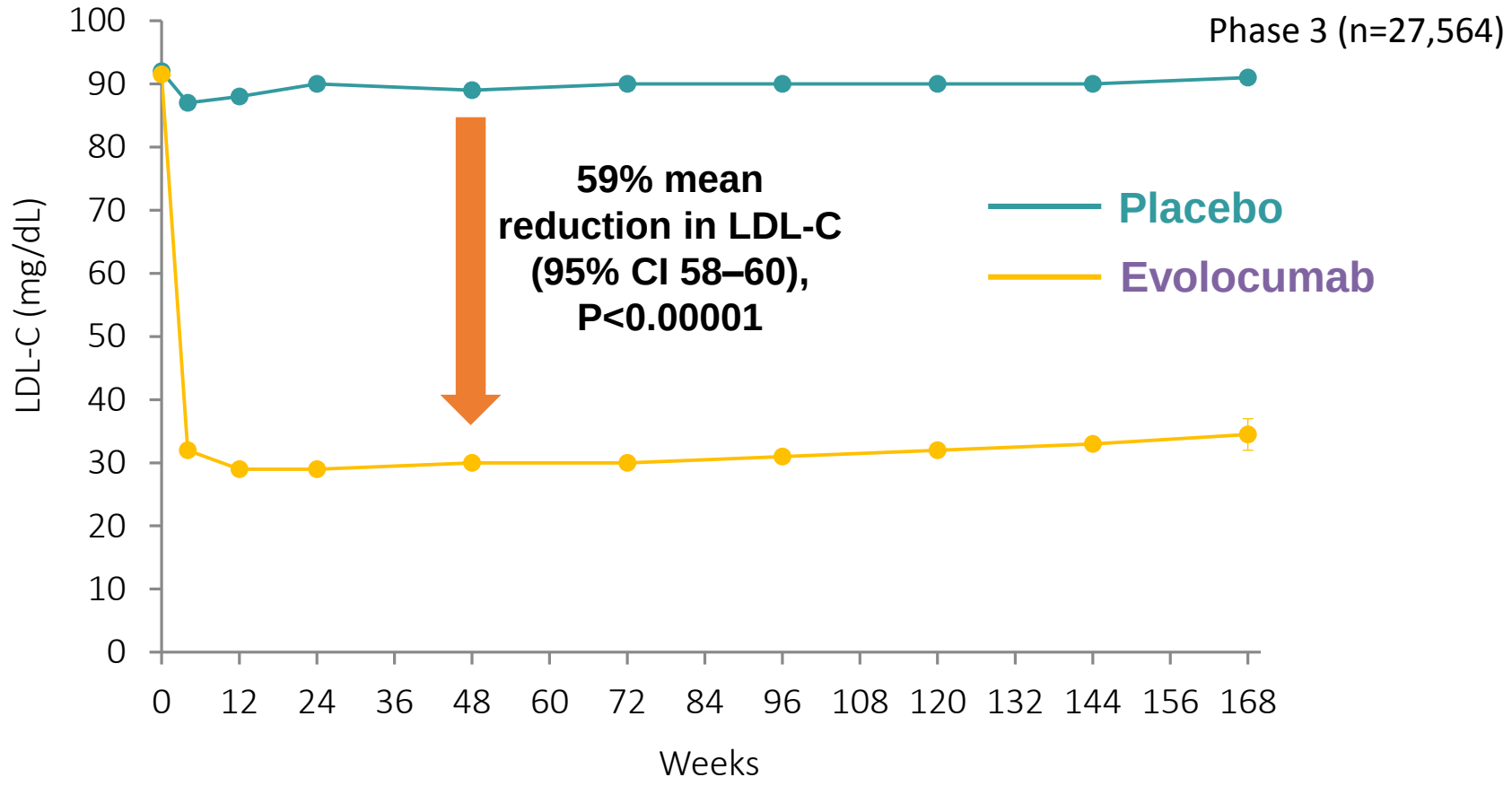
1. Koren et al. J Am Coll Cardiol 2014;63:2531–2540. 2. Robinson et al. JAMA 2014;311:1870–1882. 3. Raal et al. Lancet 2015;385:331–340. 4. Blom et al. N Engl J Med 2014;370:1809–1819.
5. Stroes et al. J Am Coll Cardiol 2014;63:2541–2548. 6. Najam et al. Clin Lipidol 2015;10:481–498.

Up to 94% of evolocumab-treated patients achieved LDL-C <70 mg/dL (1.8 mmol/L)



1. Robinson et al. JAMA 2014;311:1870–1882. 2. Raal et al. Lancet 2015;385:331–340.
3. Stroes et al. J Am Coll Cardiol 2014;63:2541–2548.

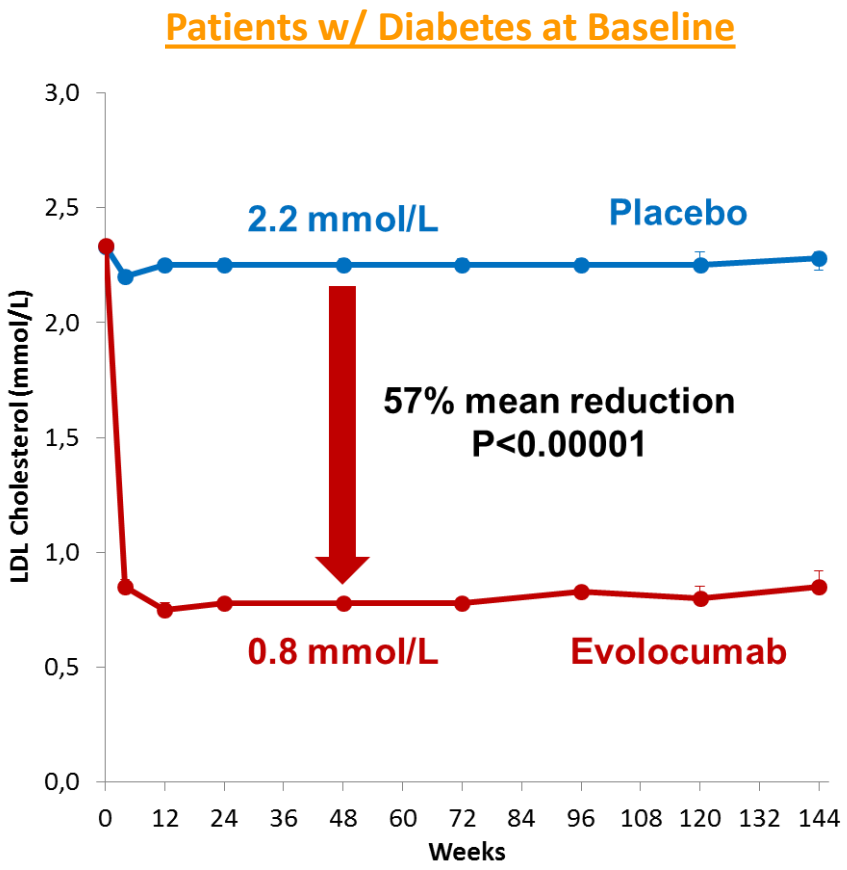
LDL-C reductions are maintained over 3 years

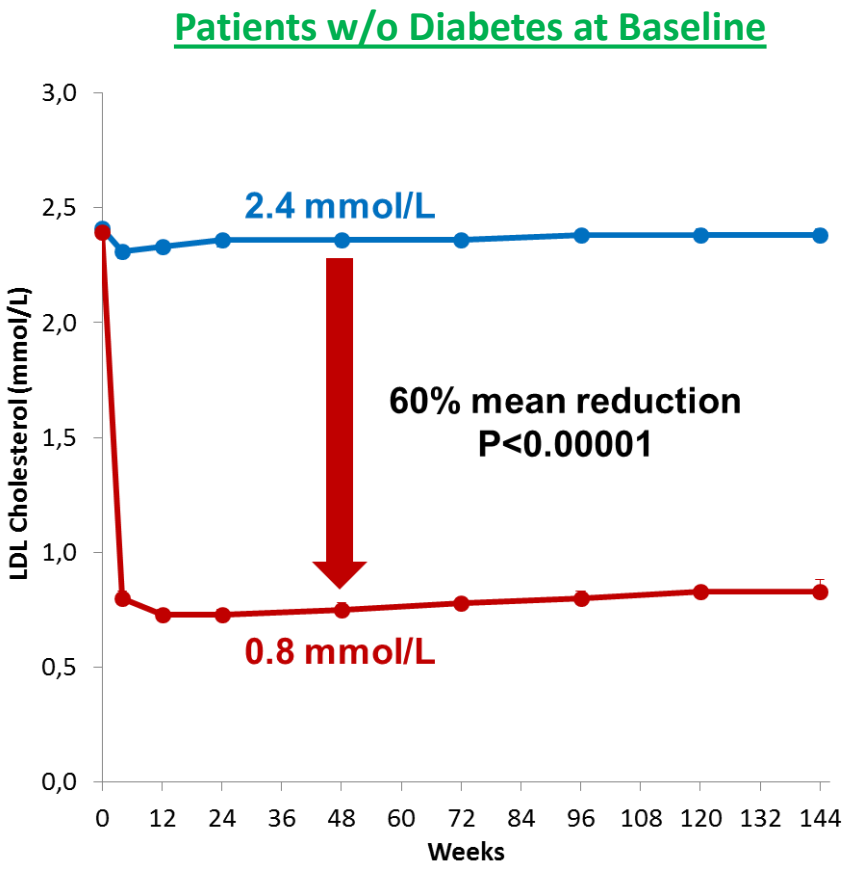


Absolute reduction in LDL-C for evolocumab vs placebo: 56 mg/dL (95% CI 55–57); 59% mean reduction

Sabatine et al. N Eng J Med 2017; doi: 10.1056/NEJMoa1615664.

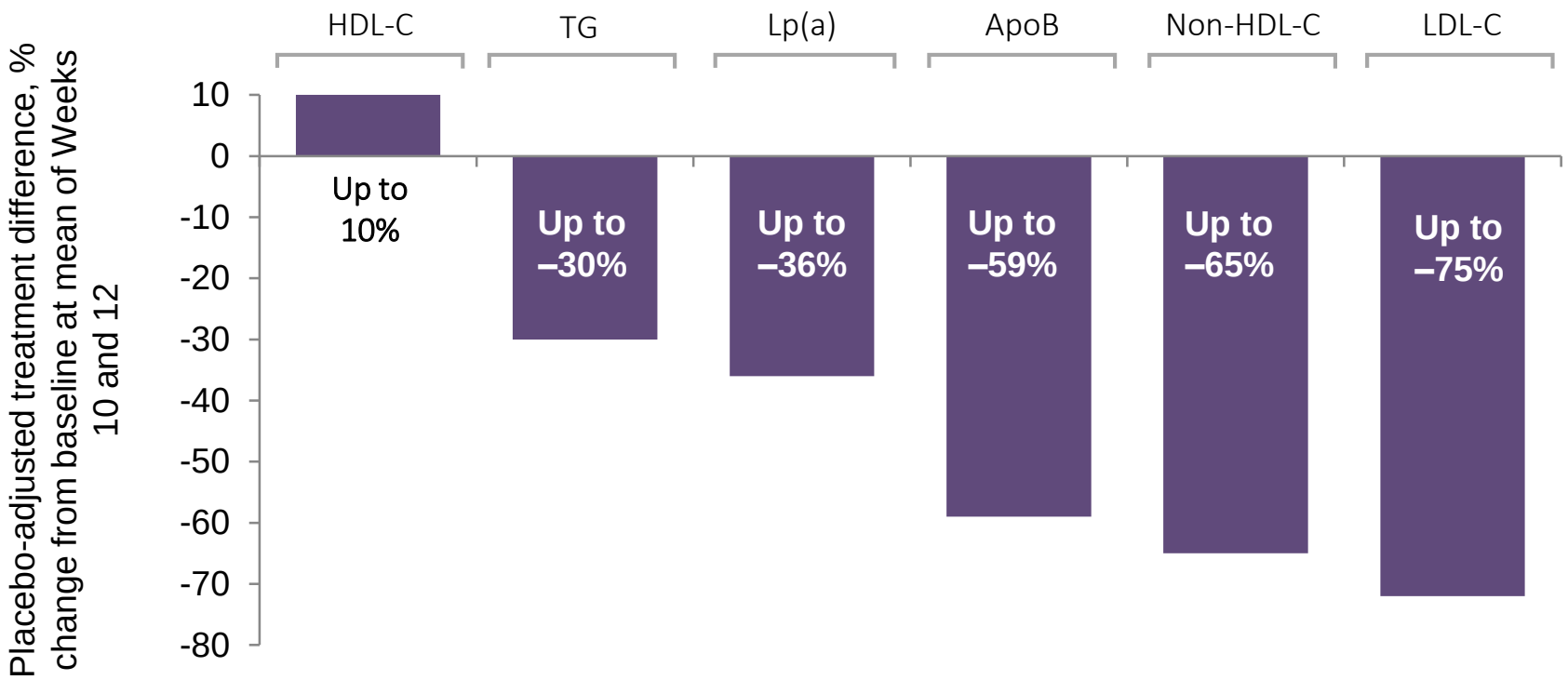
LDL-C Reduction with Evolocumab: diabetes vs no diabetes





Sabatine et al. Lancet Diabetes Endocr 2017

Evolocumab markedly reduces other atherogenic lipids and modestly increases HDL-C

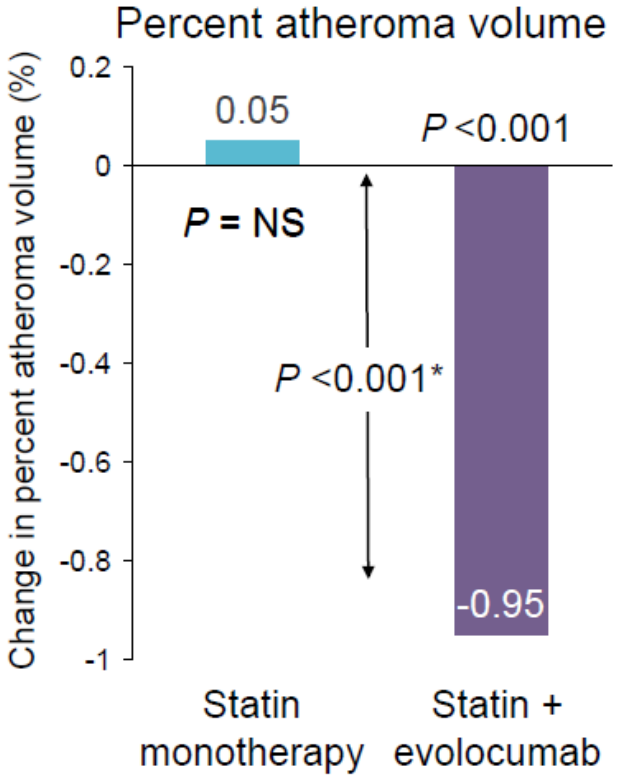


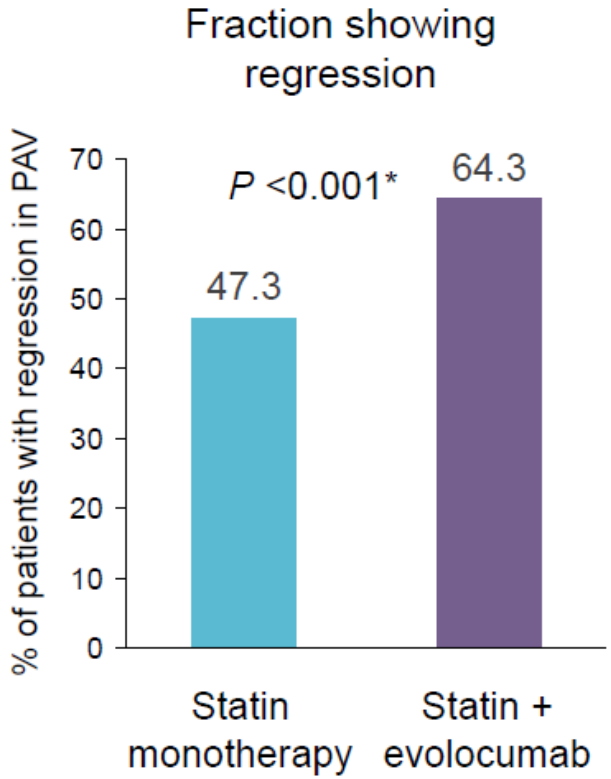
P<0.001 when compared with placebo

Data range includes the results observed in both the evolocumab Q2W and QM study arms.
Robinson et al. JAMA 2014;311:1870–1882.

Evolocumab reduced PAV and increased regression more than statins alone

GLAGOV (GLobal Assessment of plaque reGression with a PCSK9 antibOdy as measured by intraVascular ultrasound) was a study designed to evaluate the effects of evolocumab in reducing coronary atherosclerosis when administered with statins, compared with statin therapy alone, over the 78 weeks





Mean LDL-C	mg/dL	mmol/L
Statin monotherapy	93.0	2.41
Statin + evolocumab	36.6	0.95

*Between-treatment group comparison

percentage atheroma volume (PAV)

Nicholls SJ et al. JAMA 2016. doi:10.1001/jama.2016.16951

The NEW ENGLAND JOURNAL of MEDICINE

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

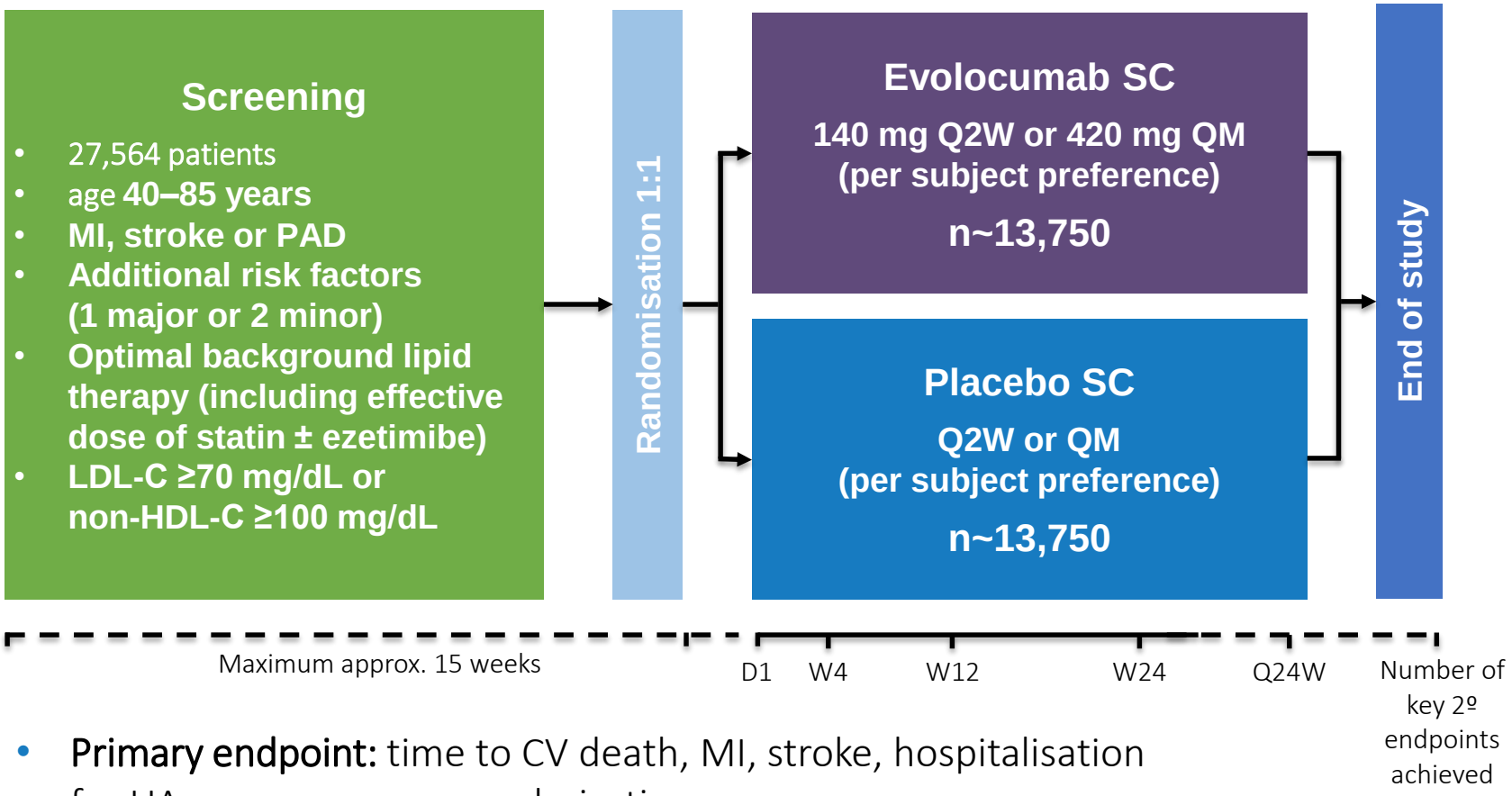
Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon 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*

- 27,564 patients with atherosclerotic cardiovascular disease and LDL chol ≥70 mg/dL receiving statin therapy.
- Randomization to evolocumab (140 mg every 2 weeks or 420 mg monthly) or 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 median duration of follow-up was 2.2 years.

N Engl J Med 2017;376:1713-22

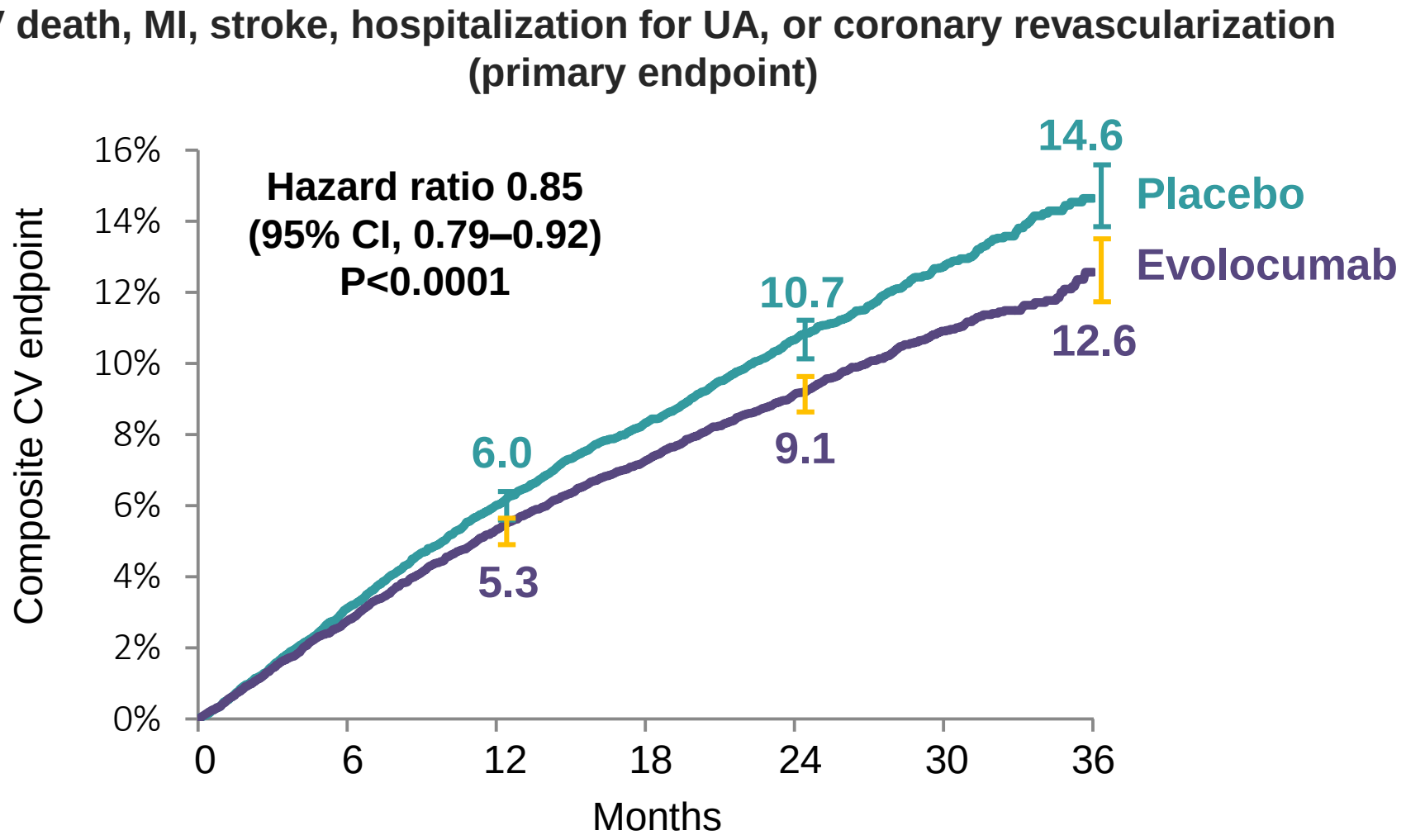
FOURIER: Study design overview



- **Primary endpoint:** time to CV death, MI, stroke, hospitalisation for UA or coronary revascularisation
- **Key secondary endpoint:** time to CV death, MI or stroke

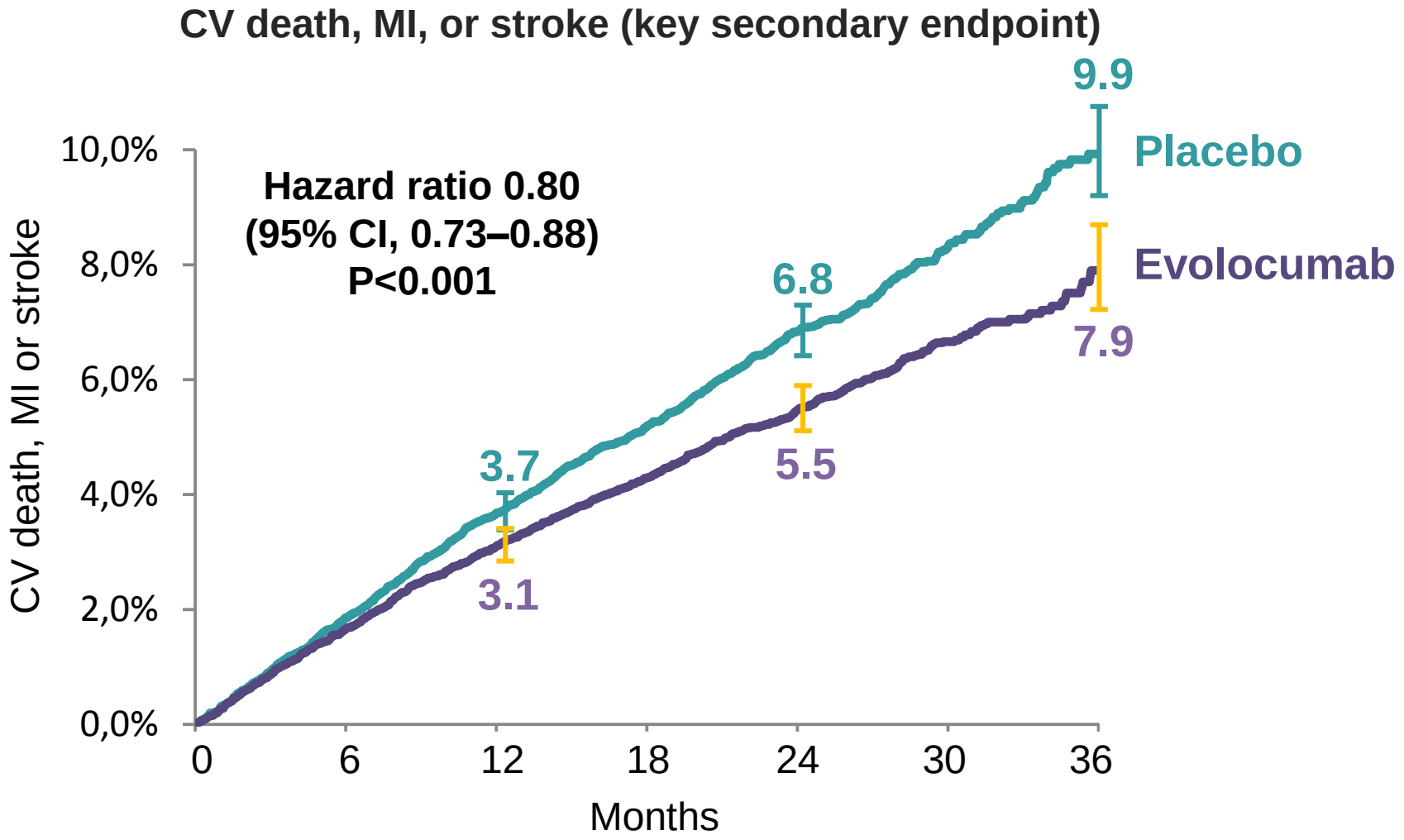
Sabatine MS, et al. Am Heart J 2016;173:94–101.

Evolocumab significantly reduces the risk of CV events compared with placebo



Sabatine et al. N Eng J Med 2017; doi: 10.1056/NEJMoa1615664.

Evolocumab significantly reduces the risk of MACE events compared with placebo

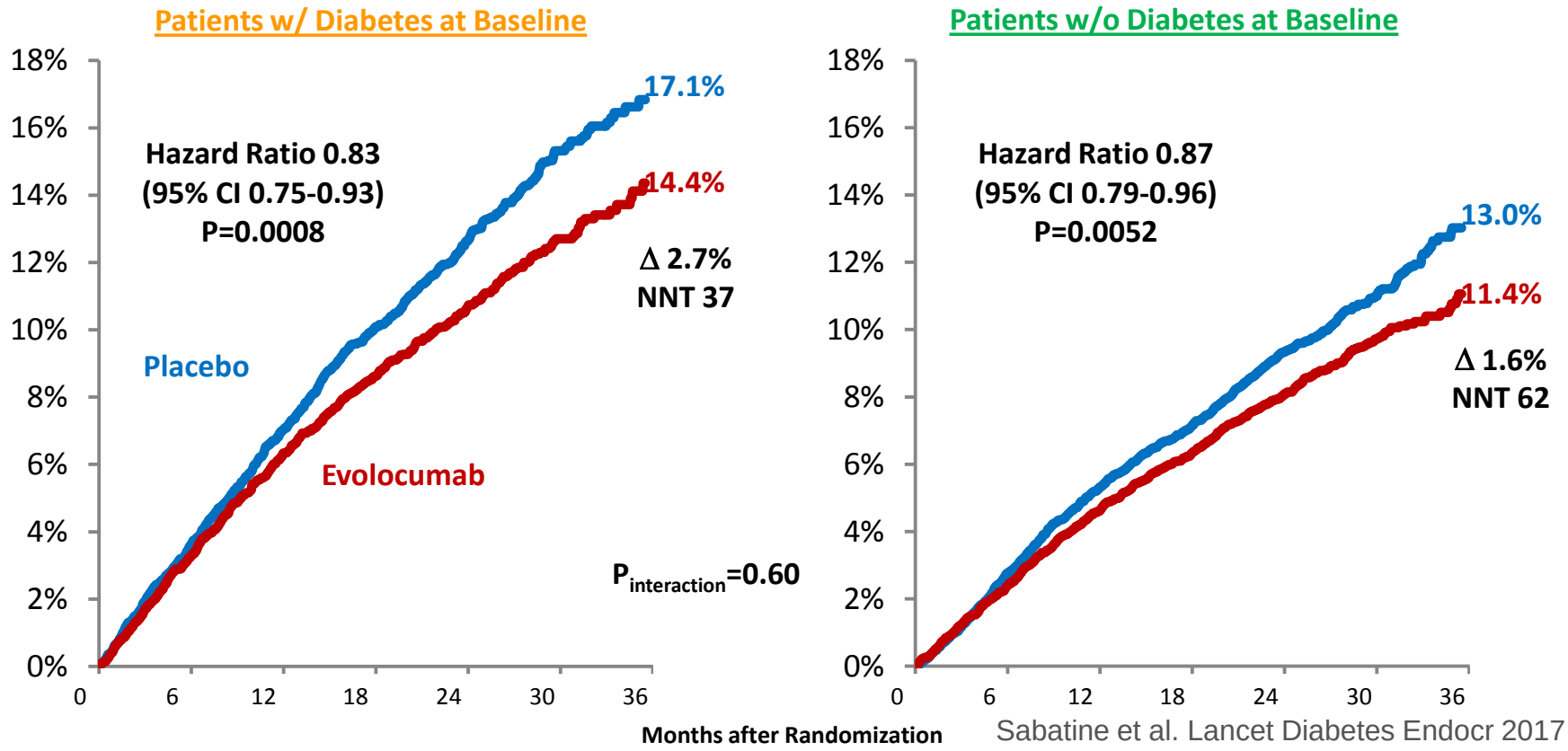


Sabatine et al. N Eng J Med 2017; doi: 10.1056/NEJMoa1615664.

Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial

Marc S Sabatine, Lawrence A Leiter, Stephen D Wiviott, Robert P Giugliano, Prakash Deedwania, Gaetano M De Ferrari, Sabina A Murphy, Julia F Kuder, Ioanna Gouni-Berthold, Basil S Lewis, Yehuda Handelsman, Armando Lira Pineda, Narimon Honarpour, Anthony C Keech, Peter S Sever, Terje R Pedersen

Effect of Evolocumab on CV death, MI, stroke, hospitalisation for UA, or coronary revascularisation (primary endpoint)

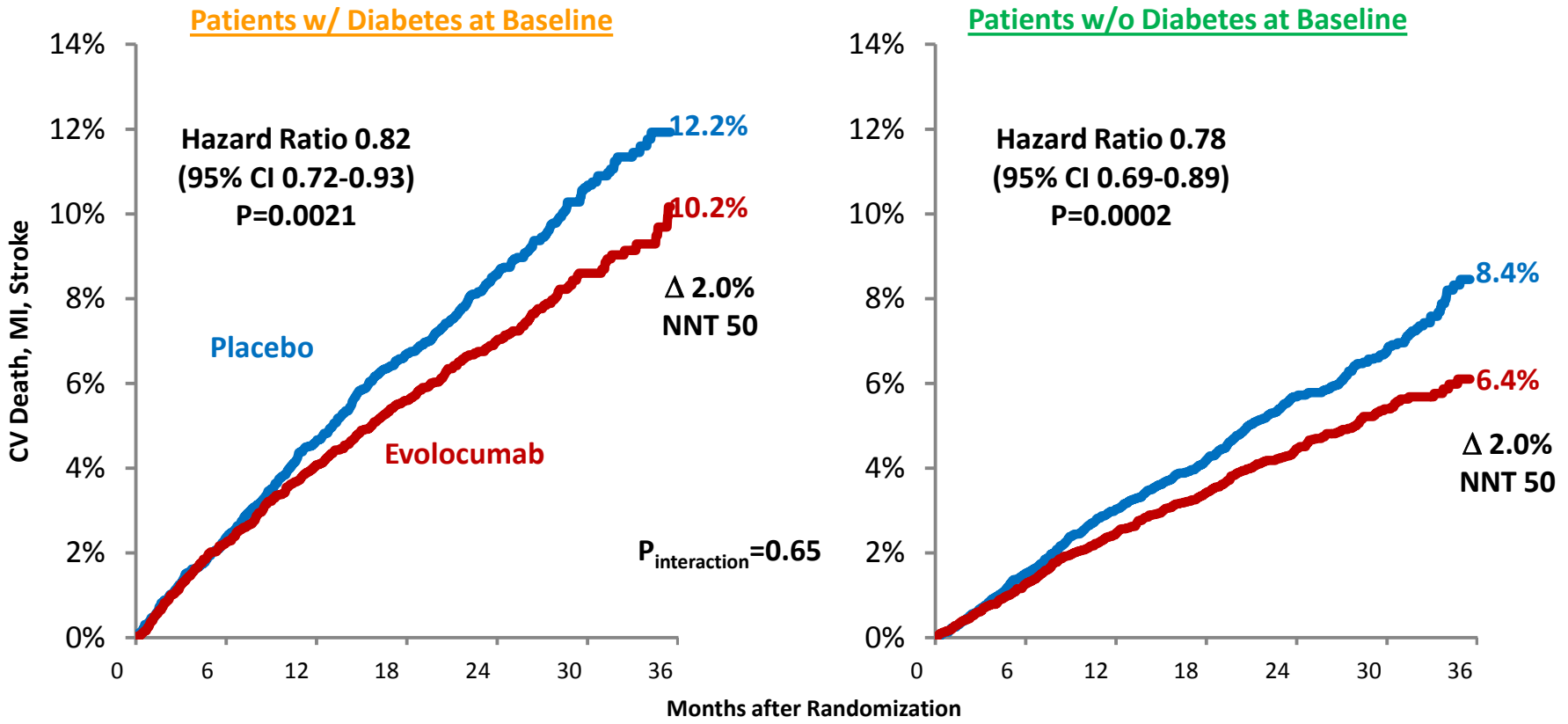


Sabatine et al. Lancet Diabetes Endocr 2017

Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial

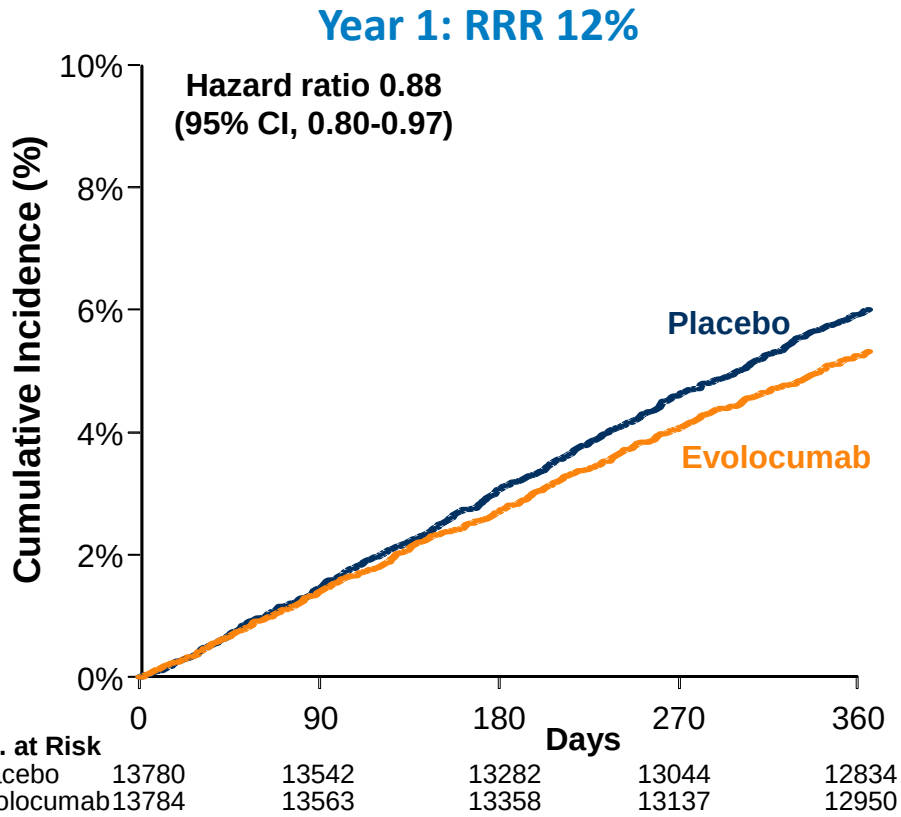
Marc S Sabatine, Lawrence A Leiter, Stephen D Wiviott, Robert P Giugliano, Prakash Deedwania, Gaetano M De Ferrari, Sabina A Murphy, Julia F Kuder, Ioanna Gouni-Berthold, Basil S Lewis, Yehuda Handelsman, Armando Lira Pineda, Narimon Honarpour, Anthony C Keech, Peter S Sever, Terje R Pedersen

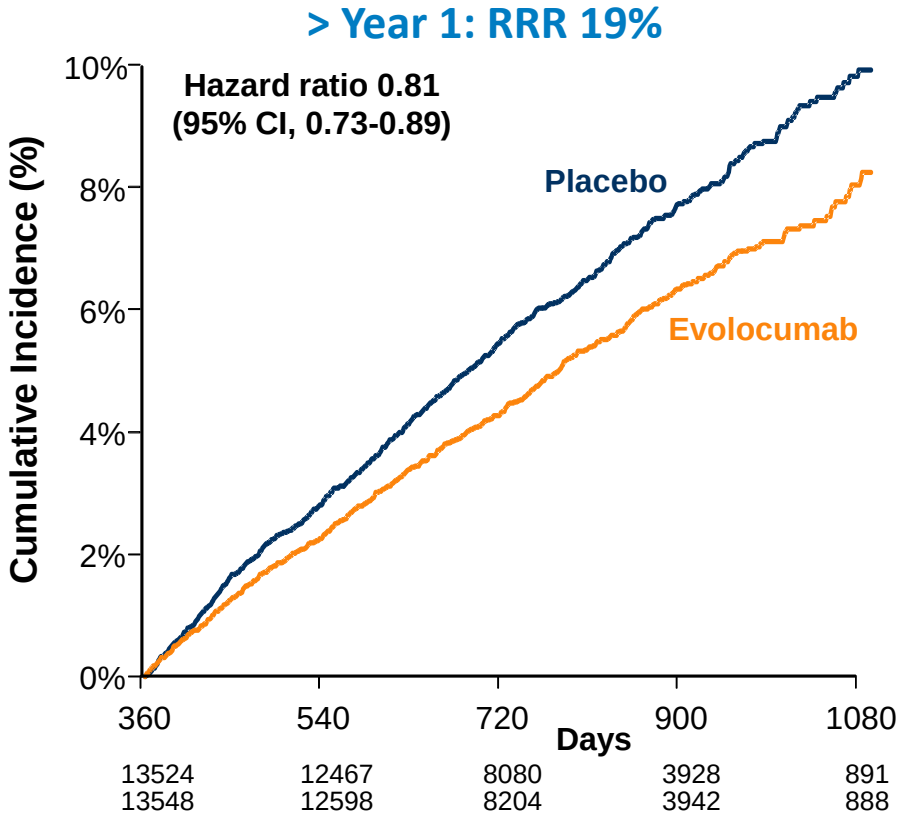
Effect of Evolocumab on CV death, MI, stroke (key secondary endpoint)



Sabatine et al. Lancet Diabetes Endocr 2017

Risk reduction with evolocumab grows over time: landmark analysis of primary endpoint



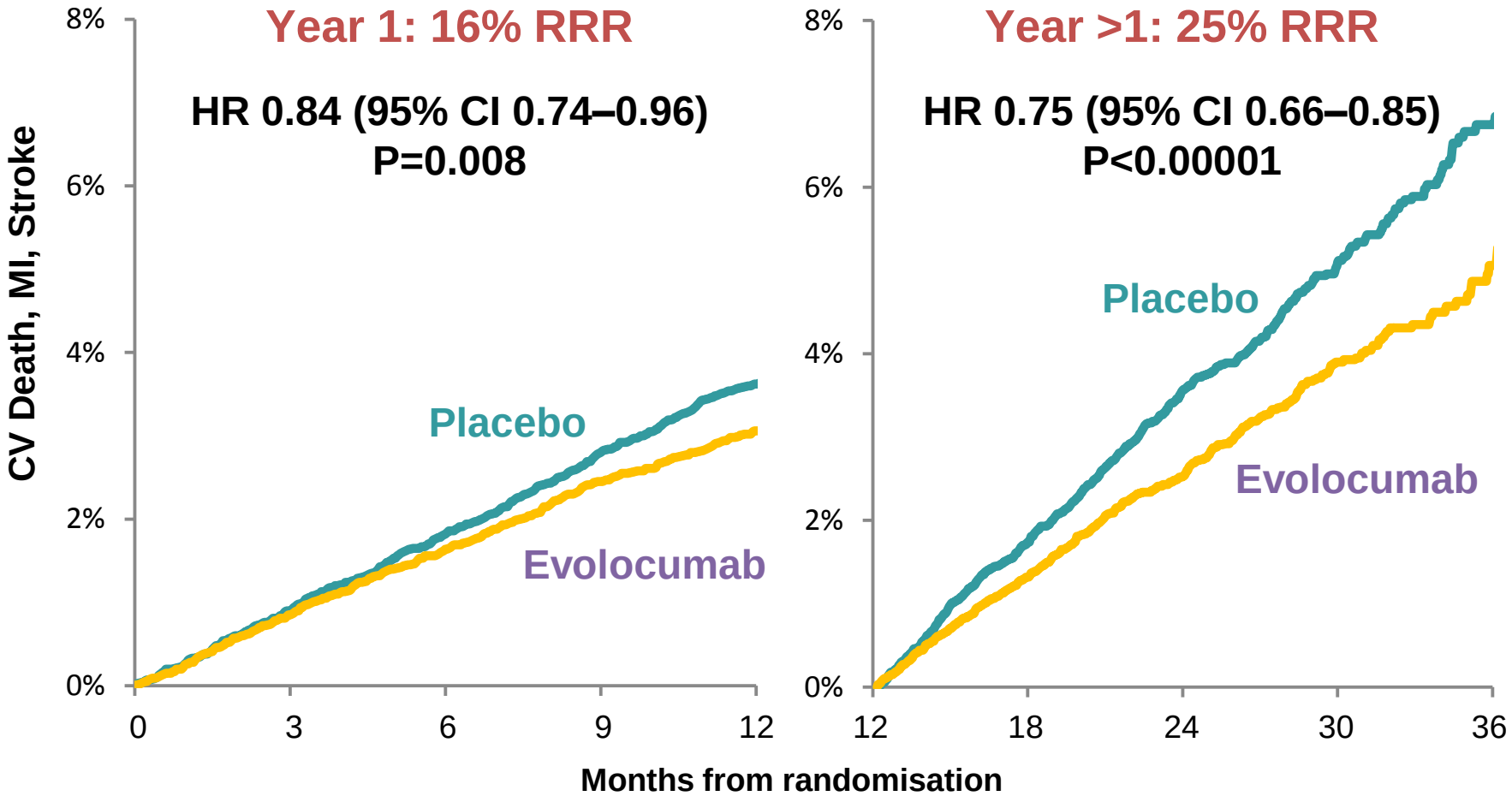


Longer duration of treatment and follow up suggests larger risk reduction

Landmark analyses were performed in which patients who were alive and in follow-up at the start of the period of interest formed the group at risk.

Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722.
(Supplementary Figure S4)

Risk reduction with evolocumab grows over time: landmark analysis of key secondary endpoint



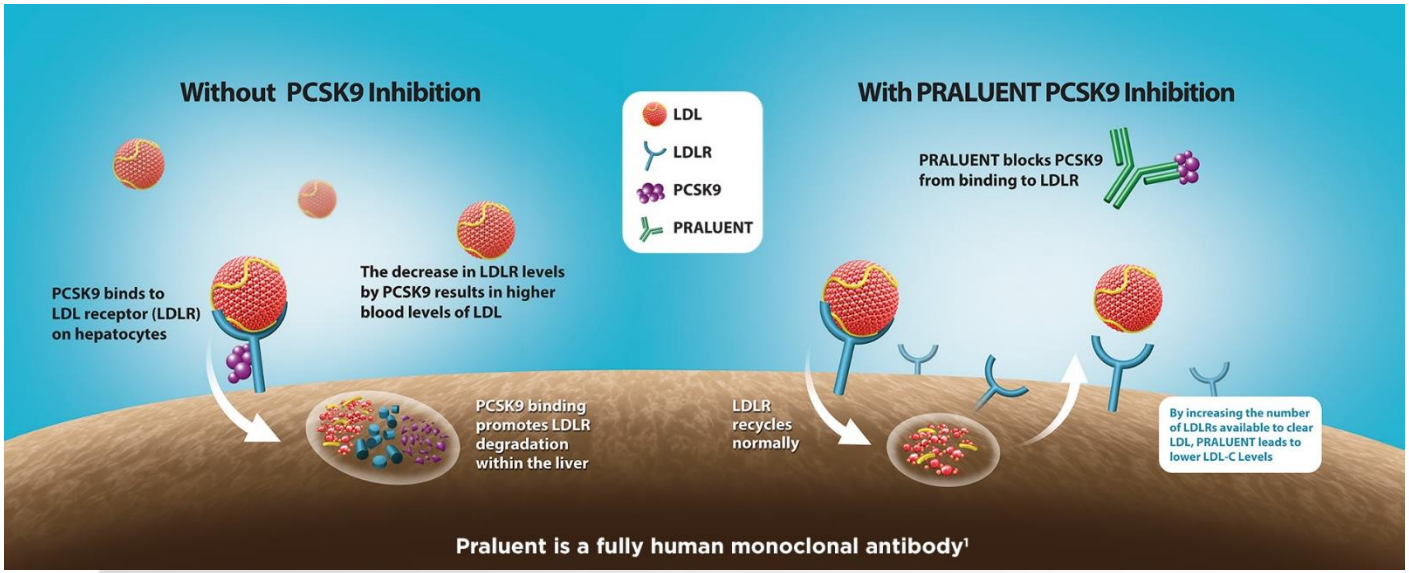
Sabatine et al. N Eng J Med 2017; doi: 10.1056/NEJMoa1615664 (Supplementary Figure S4).

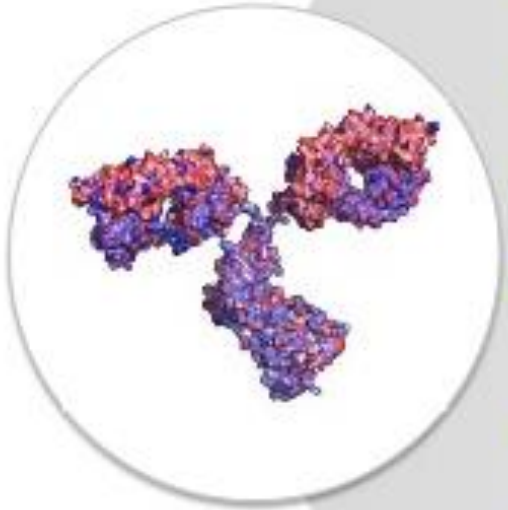
Dal 7 Febbraio 2017 Evolocumab (REPATHA) è prescrivibile e rimborsabile dal SSN in Italia con le seguenti indicazioni:

Pazienti adulti con età ≤ 80 anni:

1) **HoFH** ≥ 12 anni
2) **Prevenzione primaria:**
   - HeFH con DLCN > 8 e **C-LDL ≥ 130 mg/dL** dopo 6 mesi di terapia con statine ad alta potenza alla massima dose tollerata (atorva 40-80mg oppure rosuva 20-40mg) + ezetimibe oppure intolleranti alle statine*
3) **Prevenzione secondaria**:
   - HeFH con DLCN > 8 e **C-LDL ≥ 100 mg/dL** dopo 6 mesi di terapia con statine ad alta potenza alla massima dose tollerata (atorva 40-80mg oppure rosuva 20-40mg) + ezetimibe oppure intolleranti alle statine
   - Ipercolesterolemia non familiare e dislipidemia mista** **con C-LDL ≥ 100 mg/dL** dopo 6 mesi di terapia con statine ad alta potenza alla massima dose tollerata (atorva 40-80mg oppure rosuva 20-40mg) + ezetimibe oppure intolleranti alle statine*

Alirocumab





- Fully human monoclonal antibody against PCSK9
- Binds PCSK9 with high affinity
- Up to 70% LDL-C reduction observed in Phase 2 trial
- Being investigated in a broad Phase 3 program to lower LDL-C and to reduce the risk for CV disease
- Dosing flexibility in terms of dose, titration, and interval
- Patient friendly pen being evaluated in Phase 3

Overview of the ODYSSEY Phase 3 Program

Fourteen global Phase 3 trials including >23 500 patients across >2000 study centres

HeFH population

Add-on to max tolerated statin (± other LLT)

ODYSSEY FH I (NCT01623115; EFC12492)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=486; 18 months

ODYSSEY FH II (NCT01709500; CL1112)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=249; 18 months

ODYSSEY HIGH FH (NCT01617655; EFC12732)
LDL-C ≥160 mg/dL
n=107; 18 months

ODYSSEY OLE (NCT01954394; LTS 13463)
Open-label study for FH from EFC 12492, CL 1112, EFC 12732 or LTS 11717
n≥1000; 30 months

ODYSSEY LONG TERM (NCT01507831; LTS11717)
LDL-C ≥70 mg/dL
n=2341; 18 months

HC in high CV-risk population

Add-on to max tolerated statin (± other LLT)

ODYSSEY COMBO I (NCT01644175; EFC11568)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=316; 12 months

†ODYSSEY COMBO II (NCT01644188; EFC11569)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=720; 24 months

ODYSSEY CHOICE I (NCT01926782; CL1308)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=700; 12 months

ODYSSEY OUTCOMES (NCT01663402; EFC11570)
LDL-C ≥70 mg/dL
n=18 000; 64 months

Additional populations

ODYSSEY MONO (NCT01644474; EFC11716)
Patients on no background LLTs
LDL-C ≥100 mg/dL
n=103; 6 months

ODYSSEY ALTERNATIVE (NCT01709513; CL1119)
Patients with defined statin intolerance
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=314; 6 months

ODYSSEY CHOICE II (NCT02023879; EFC13786)
Patients not treated with a statin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=200; 6 months

ODYSSEY OPTIONS I (NCT01730040; CL1110)
Patients not at goal on moderate-dose atorvastatin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=355; 6 months

ODYSSEY OPTIONS II (NCT01730053; CL1118)
Patients not at goal on moderate-dose rosuvastatin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=305; 6 months

ODYSSEY

14 global phase 3 trials including >23,500 patients across >2,000 study centers

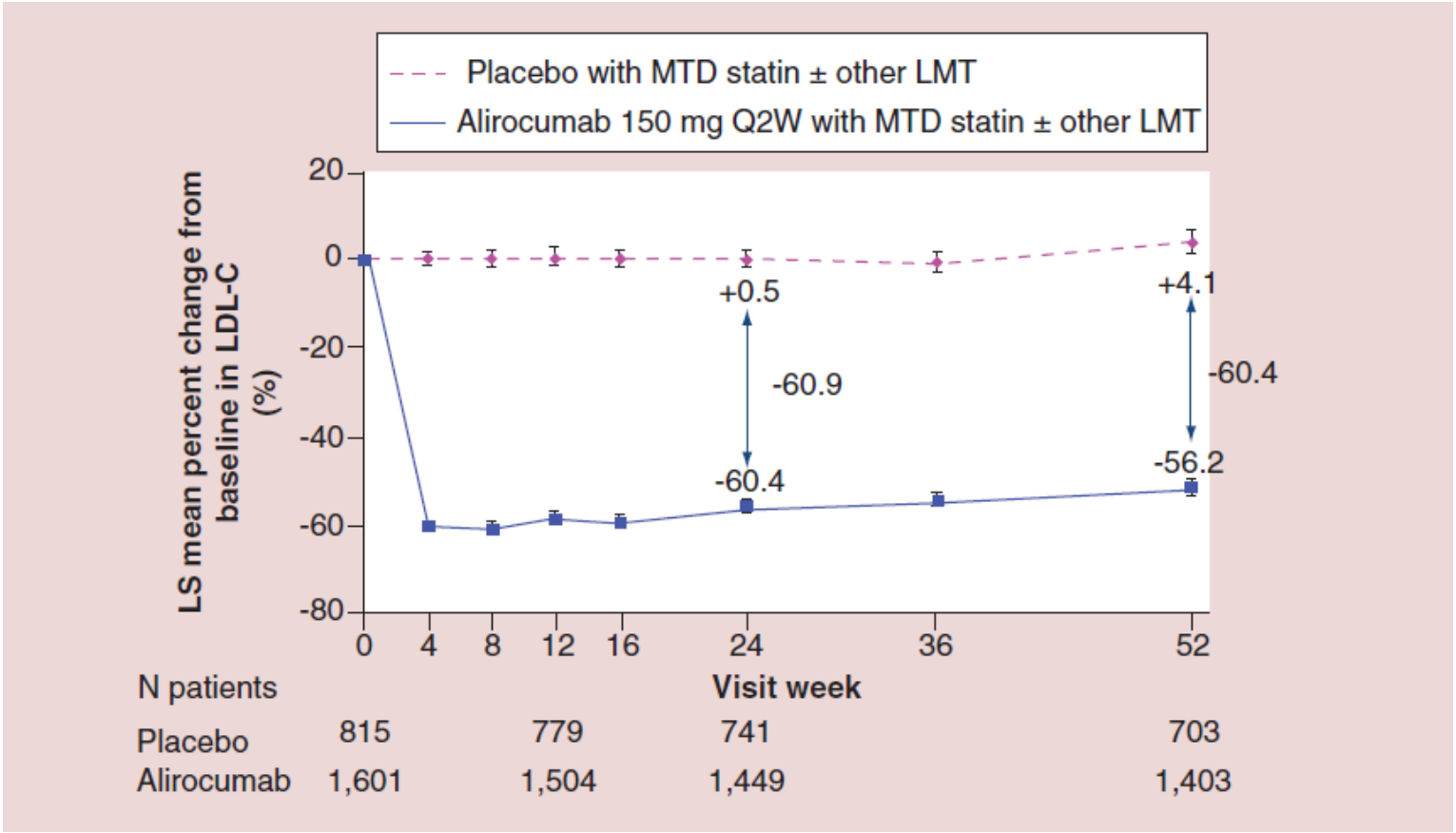
	Study	Dosing q2w	Baseline LDL-C (mg/dL)	LDL-C Change from Baseline at 24 Weeks			
				Alirocumab	Comparator		
HeFH	HIGH FH	150 mg	198	↓ **46%**	↓ 7%	placebo	On top of max statin doses
	FH I	75/150 mg[1]	145	↓ **49%**	↑ 9%	placebo	
	FH II	75/150 mg[1]	134	↓ **49%**	↑ 3%	placebo	
High CV Risk	LONG TERM	150 mg	122	↓ **61%**	↑ 1%	placebo	
	COMBO I	75/150 mg[1]	102	↓ **48%**	↓ 2%	placebo	
	COMBO II	75/150 mg[1]	108	↓ **51%**	↓ 21%	ezetimibe	
	OPTION I	75/150 mg[1]	105	↓ **44-54%**	↓ 21-23% ↓ 5% ↓ 21%	ezetimibe statin x2 statin switch	On top of regular statin doses
	OPTION II	75/150 mg[1]	111	↓ **36-51%**	↓ 11-14% ↓ 16%	ezetimibe statin switch	
Statin Intolerant	ALTERNATIVE	75/150 mg[1]	191	↓ **45%**	↓ 15%	ezetimibe	Not receiving statins
Moderate CV Risk	MONO	75/150 mg[1]	140	↓ **48%**	↓ 16%	ezetimibe	

Primary efficacy endpoint met in all 10 reported trials

ClinicalTrials.gov. ODYSSEY Phase 3 Trials. http://clinicaltrials.gov

Phase III clinical trials program

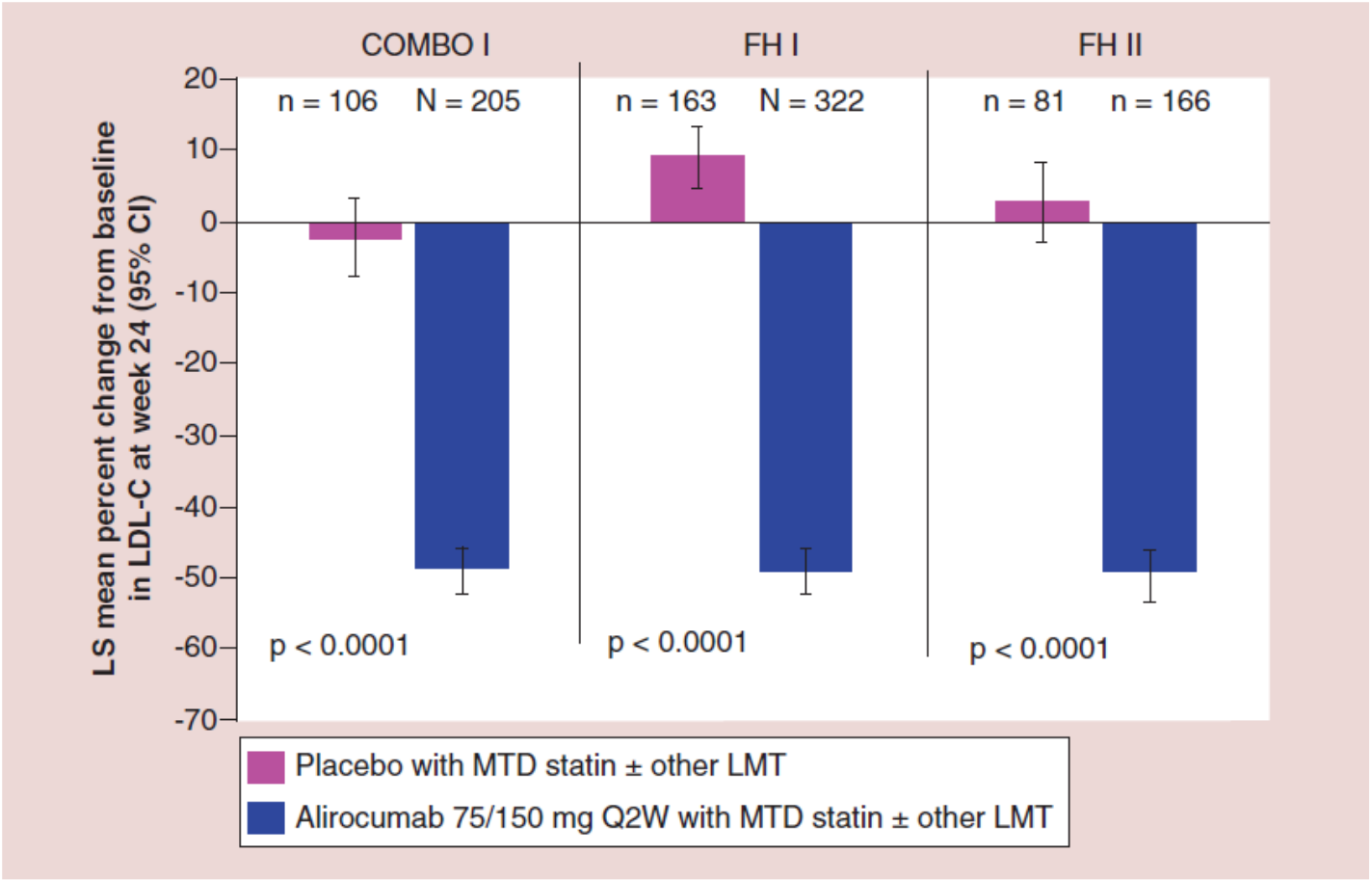
Pooled 1-year efficacy results from LONG TERM and HIGH FH studies



LDL-C: Low density lipoprotein cholesterol; LMT: Lipid-modifying therapy; LS: Least square; MTD: Maximally tolerated dose; Q2W: Every 2 weeks.

Phase III clinical trials program

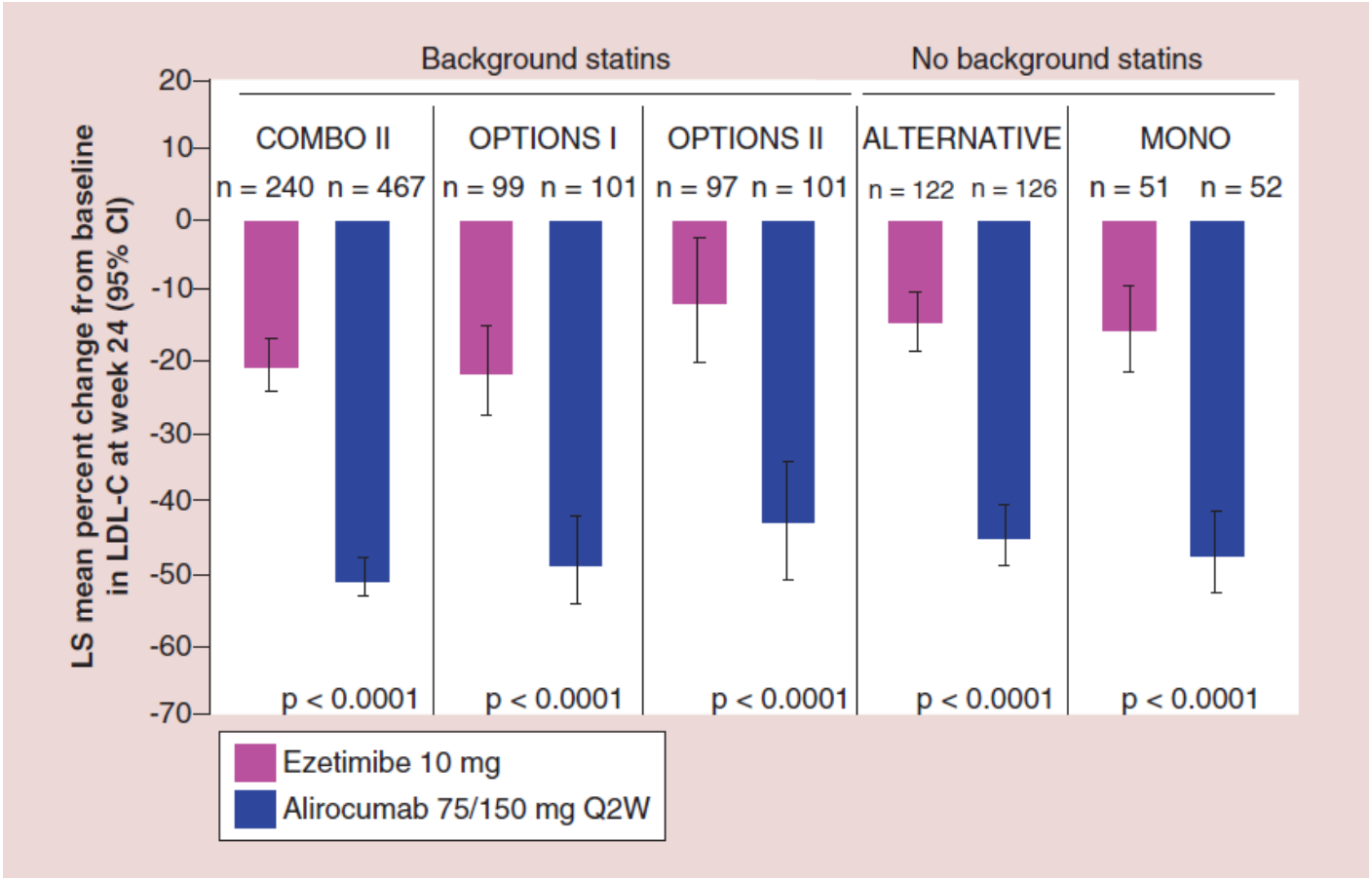
Alirocumab 75/150 mg versus placebo (with statins)



LDL-C: Low density lipoprotein cholesterol; LMT: Lipid-modifying therapy; LS: Least square; MTD: Maximally tolerated dose; Q2W: Every 2 weeks

Phase III clinical trials program

Alirocumab 75/150 mg versus ezetimibe



LDL-C: Low density lipoprotein cholesterol; LMT: Lipid-modifying therapy; LS: Least square; MTD: Maximally tolerated dose; Q2W: Every 2 weeks

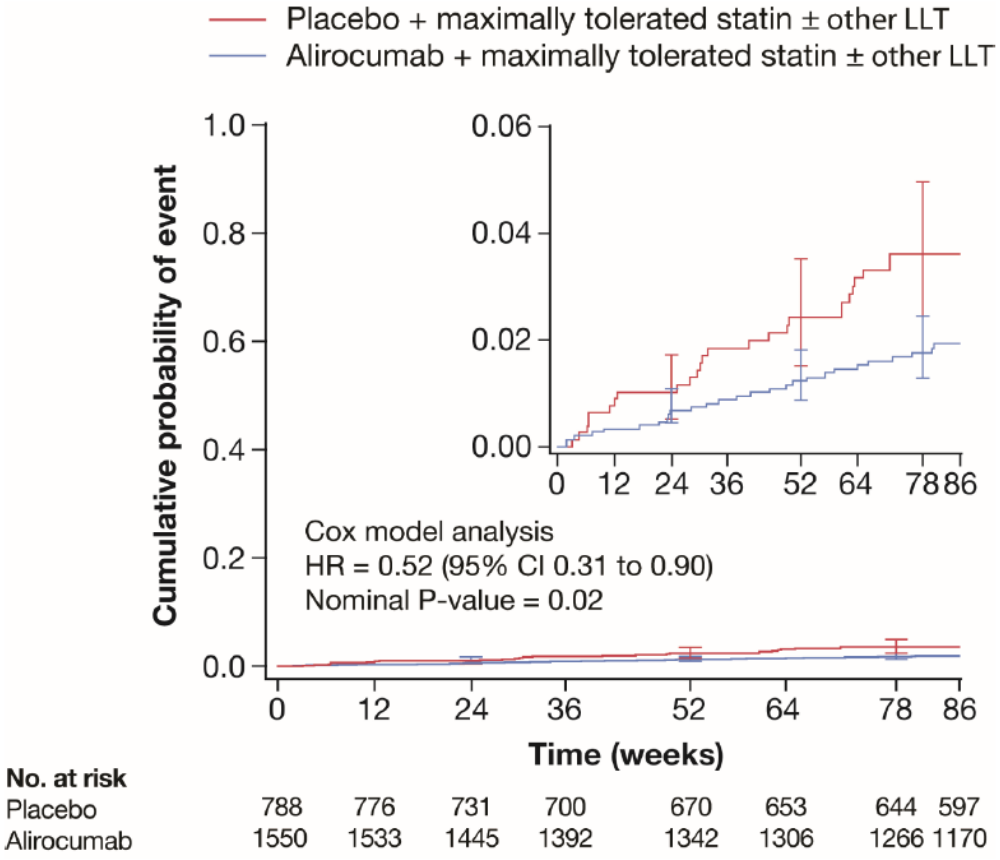
Phase III clinical trials program

ODYSSEY LONG TERM: secondary OUTCOMES endpoint

2341 patients at high risk for cardiovascular events who had LDL cholesterol levels of 70 mg/dl 1.8 mmol per liter) or more and were receiving treatment with statins at the maximum tolerated dose

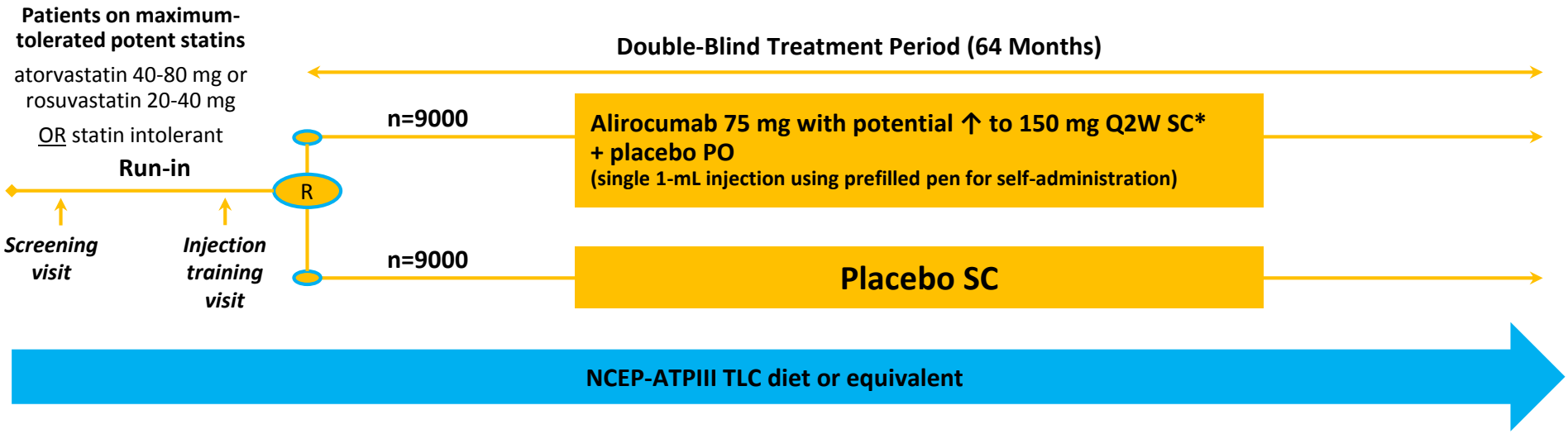
Patients were randomly assigned in a 2:1 ratio to receive alirocumab (150 mg) or placebo as a 1-ml subcutaneous injection every 2 weeks for 78 weeks

The primary efficacy end point was the percentage change in calculated LDL cholesterol level from baseline to week 24



ODYSSEY OUTCOMES – Study Design

Population	Lipid criteria at entry	Primary endpoint
• Patients 4-52 weeks post-ACS • Age ≥ 40	• LDL-C ≥70 mg/dL [≥1.81 mmol/L] OR • ApoB ≥80 mg/dL [≥0.8 mmol/L] OR • Non-HDL-C ≥100 mg/dL [≥2.59 mmol/L]	• Composite of – CHD death – Nonfatal MI – Ischemic stroke – High-risk UA requiring hospitalization



November 2015: 18,000-Patient ODYSSEY OUTCOMES Trial of alirocumab Injection Fully Enrolled

***Dose titrated up to 150mg Q2W at Month 2 if LDL-C ≥50 mg/dL(1.29 mmol/L) at Month 1 visit.**

ClinicalTrials.gov. ODYSSEY OUTCOMES Study. http://clinicaltrials.gov/ct2/show/NCT01663402. Accessed May 14, 2015.
Schwartz GG, et al. *Am Heart J*. 2014;168:682-689.e1.

Dal 6 Marzo 2017 Alirocumab (PRALUENT) è prescrivibile e rimborsabile dal SSN in Italia con le seguenti indicazioni:

- in **PREVENZIONE PRIMARIA** in pazienti di età ≥18 e ≤80 aa con ipercolesterolemia familiare eterozigote e livelli di **LDL-C ≥130 mg/dL** nonostante terapia da almeno 6 mesi con statina ad alta potenza alla massima dose tollerata + ezetimibe oppure con dimostrata intolleranza alle statine
- in **PREVENZIONE SECONDARIA** in pazienti di età ≥18 e ≤80 aa con ipercolesterolemia familiare eterozigote o ipercolesterolemia non familiare o dislipidemia mista e livelli di **LDL-C ≥100 mg/dL** nonostante terapia da almeno 6 mesi con statina ad alta potenza alla massima dose tollerata + ezetimibe oppure con dimostrata intolleranza alle statine.

L'effetto di Praluent su morbidità e mortalità cardiovascolare non è ancora stato determinato

- No responders
- Concern about AE related to very low LDL- C levels
- New onset diabetes

Need of very long term results

High costs

Conclusions

- Association between high levels of LDL cholesterol and cardiovascular events and have been widely demonstrated
- Reducing LDL cholesterol reduces CV events
- Importance of achieving target levels of LDL cholesterol (the lower the better)
- Drugs currently available may not be sufficient to reach the desired target or may cause intolerance
- Fully humanized PCSK9 inhibitors have been shown to be effective in reducing LDL-Cholesterol levels and CV events in high risk patients and have proven to be safe
- Their usefulness in homozygous familial hypercholesterolaemia and in patients with raised lipoprotein(a) concentrations is less striking
- We have to wait for real world data to confirm the results from clinical trials in terms of long term efficacy, safety and the cost-benefit ratio.

Nuove frontiere per il trattamento delle dislipidemie

Grazie per l'attenzione