Evolocumab : A New Solution to Lower LDL-C Level

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Outlines

- Introduction
- The development PCSK9-inhibitor
- The pharmacodynamics and pharmacokinetic of evolocumab (repatha)
- GLAGOV :coronary atherosclerotic plaque
- FOURIER/Odyssey : long-term CV outcomes
- EBBINGHAUS: neurocognitive function
- Take home message

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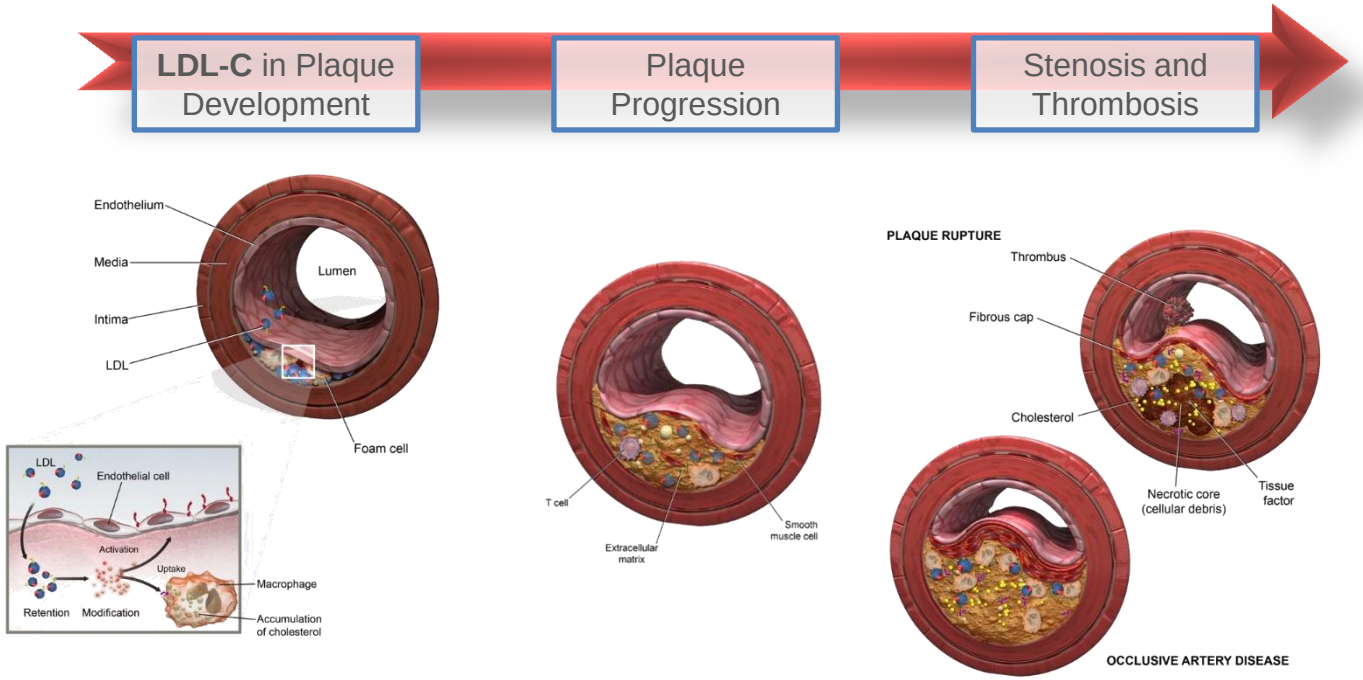
Dyslipidaemia and Atherosclerosis: Particle to Plaque



Hansson GK. *N Engl J Med*. 2005;352:1685-1695.
Rader DJ, Daugherty A. *Nature*. 2008;904-913.

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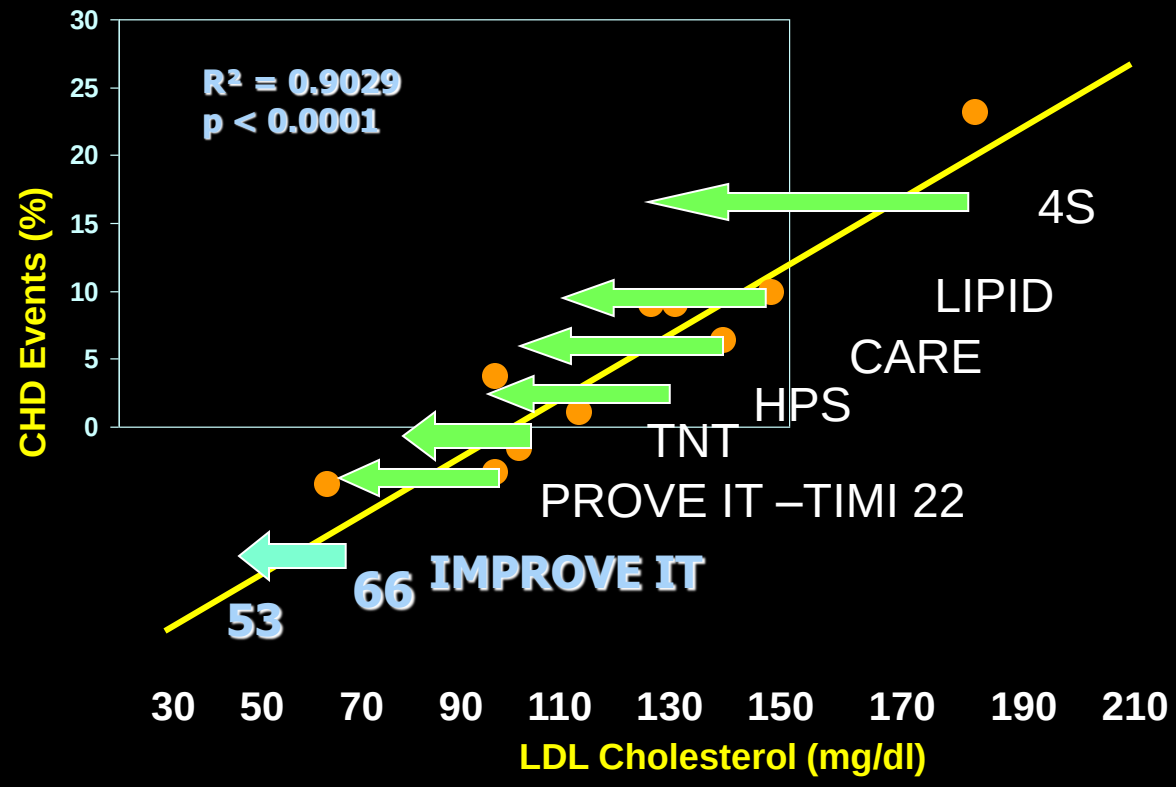
The Statin Decade: For LDL: "Lower is Better"



Adapted and Updated from O'Keefe, J. et al., *J Am Coll Cardiol* 2004;43:2142-6.

Current Guidelines: LDL-C Targets

NATIONAL LIPID ASSOCIATION

Table 2 Treatment goals for non–HDL-C, LDL-C, and Apo B in mg/dL

	Treatment goal		
Risk category	Non–HDL-C	LDL-C	Apo B*
Very high	<100	<70	<80

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Lipids LDL-C is the primary target	**Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL)** or a reduction of at least 50% if the baseline[b] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).

AMERICAN COLLEGE OF CARDIOLOGY

Patients with clinical ASCVD with comorbidities,* on statin for secondary prevention

↓

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or may consider non-HDL-C <100 mg/dL in patients with diabetes) on maximally tolerated statin†

J Clin Lipidol 2015;9:129-69; *EHJ* 2016;37:2999-3058; *JACC* 2016;68:92-105

Treatment Guideline in Taiwan (2017)

2017台灣高風險病人血脂異常臨床治療指引

疾病 / 狀態	低密度膽固醇 (LDL-C) 之目標
急性冠心症候群	< 70 mg/dL
急性冠心症候群+ 糖尿病	< 55 mg/dL 可以考慮
穩定冠狀動脈疾病	< 70 mg/dL
缺血性腦中風或暫時性腦部缺氧	< 100 mg/dL
糖尿病	<100 mg/dL
糖尿病+心血管疾病	< 70 mg/dL
慢性腎臟病(階段 3a–5, eGFR < 60)	> 100 mg/dL 時開始治療
家族性高膽固醇血症	成人: < 100 mg/dL 小孩: < 135 mg/dL 有心血管疾病: < 70 mg/dL

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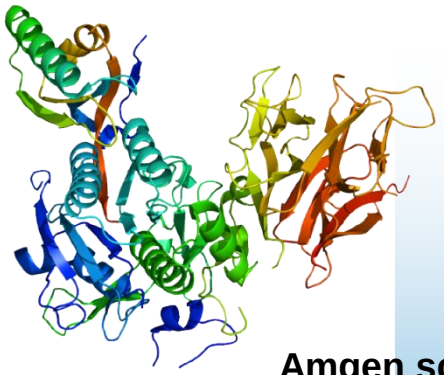
Amgen Innovation: Rapid Translation of a Genetic Discovery into a New Therapy



PCSK9 Crystal Structure

2003 — Role of PCSK9 in LDL metabolism emerges

2005 — Amgen launches PCSK9 program

2006 — Amgen scientists elucidate complete structure of PCSK9 (published 2007)

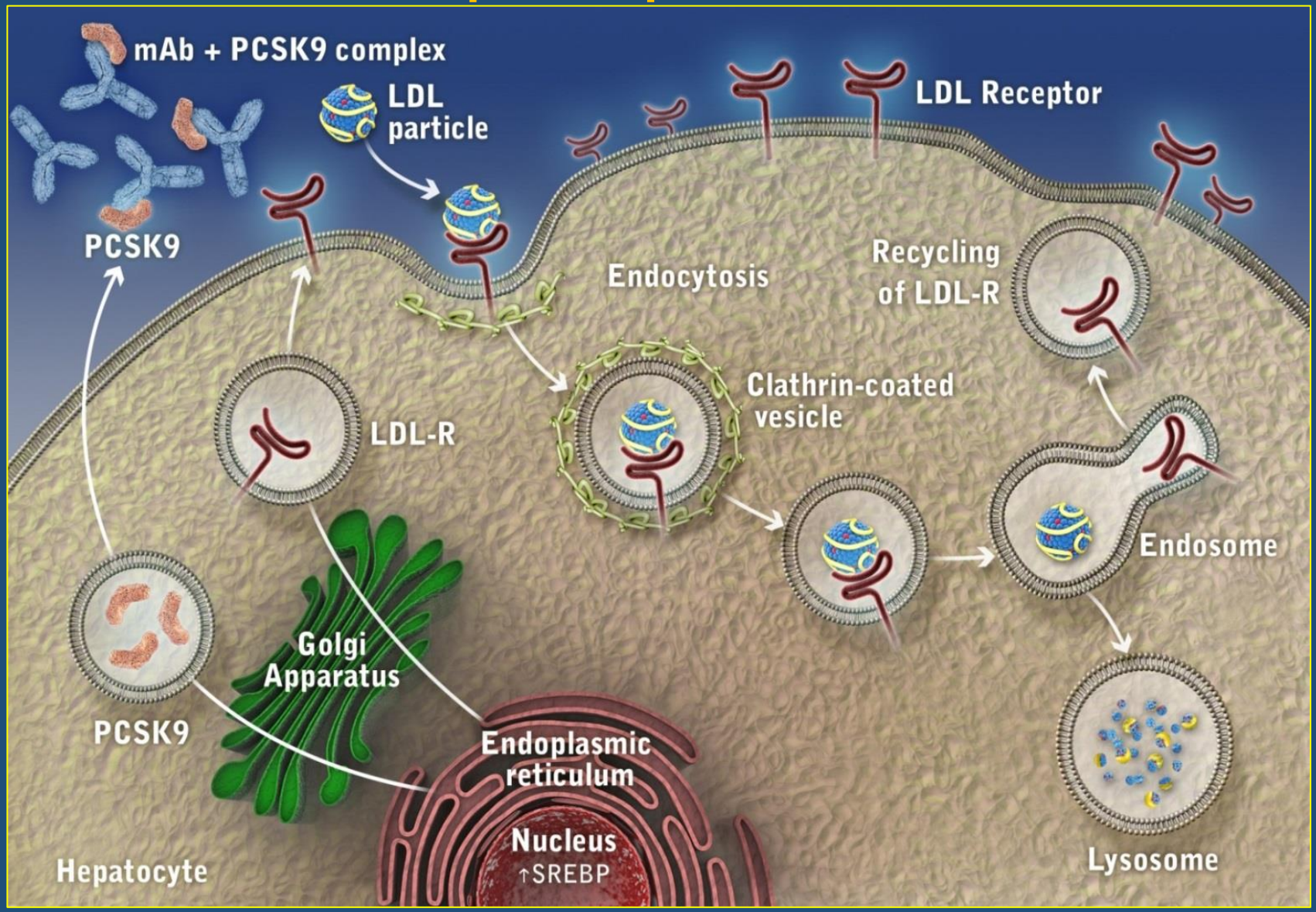
2007 — Amgen scientists file patent application to Abs that block PCSK9-LDL-R interaction and lower cholesterol *in vivo*

2009 — Evolocumab enters clinical development - first human dosed

2014 — Evolocumab is the first PCSK9 therapy filed

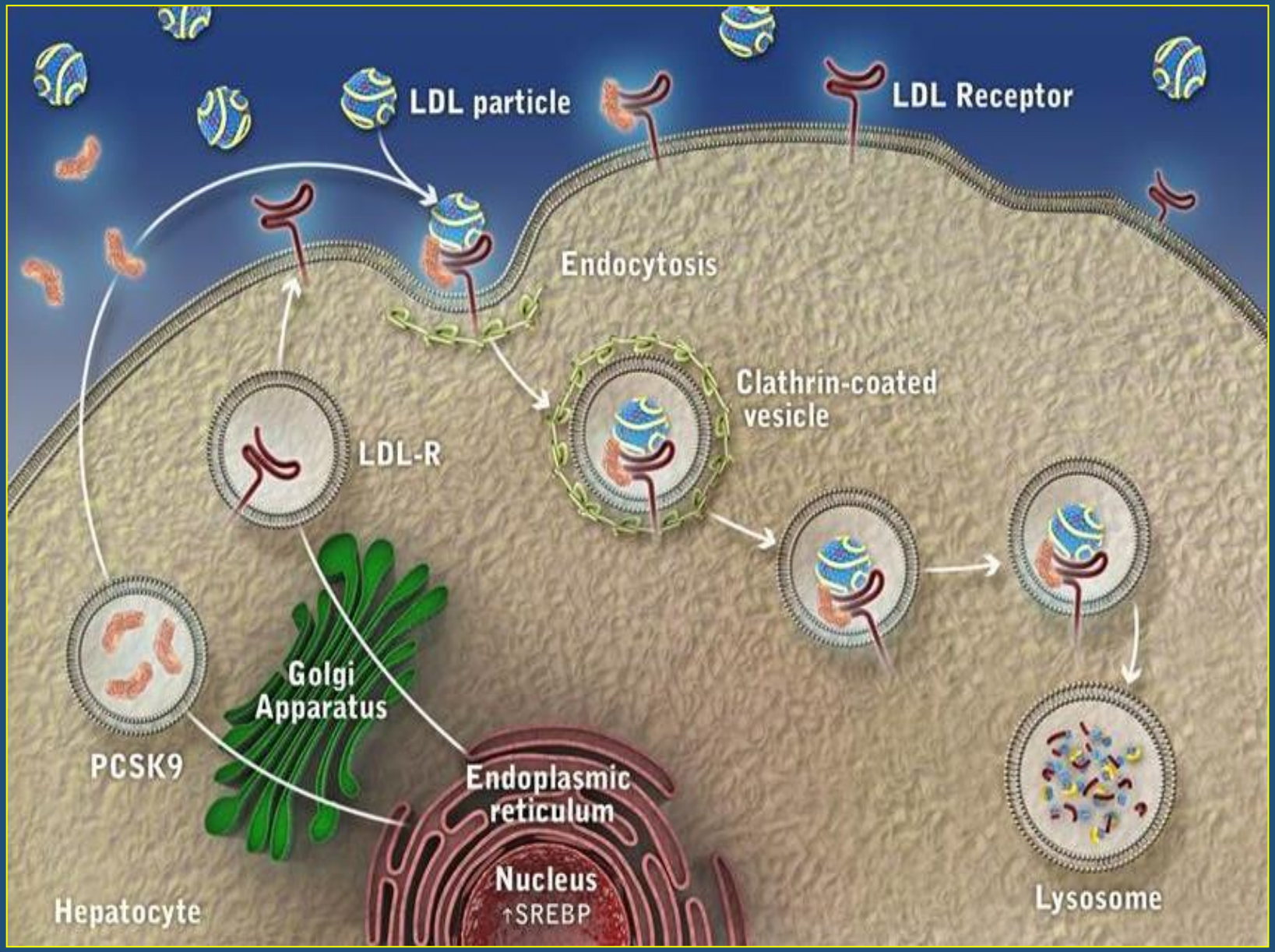
2015 — Evolocumab Approval in Europe/ US

PCSK9 Monoclonal Antibodies Inactivate PCSK9 → Increase LDL-Receptor Expression → ↓ LDL-C levels



LDL=low-density lipoprotein; LDL-R=LDL receptor; mAb=monoclonal antibody; PCSK9=proprotein convertase subtilisin/kinexin type 9; SREBP-2=sterol regulatory element-binding protein-2.; Adapted from: Catapano AL, Papadopoulos N. *Atherosclerosis* 2013;228:18–28.

Proprotein Convertase Subtilisin-like/kexin type 9 (PCSK9) Targets the LDL-Receptor for Lysosomal Degradation



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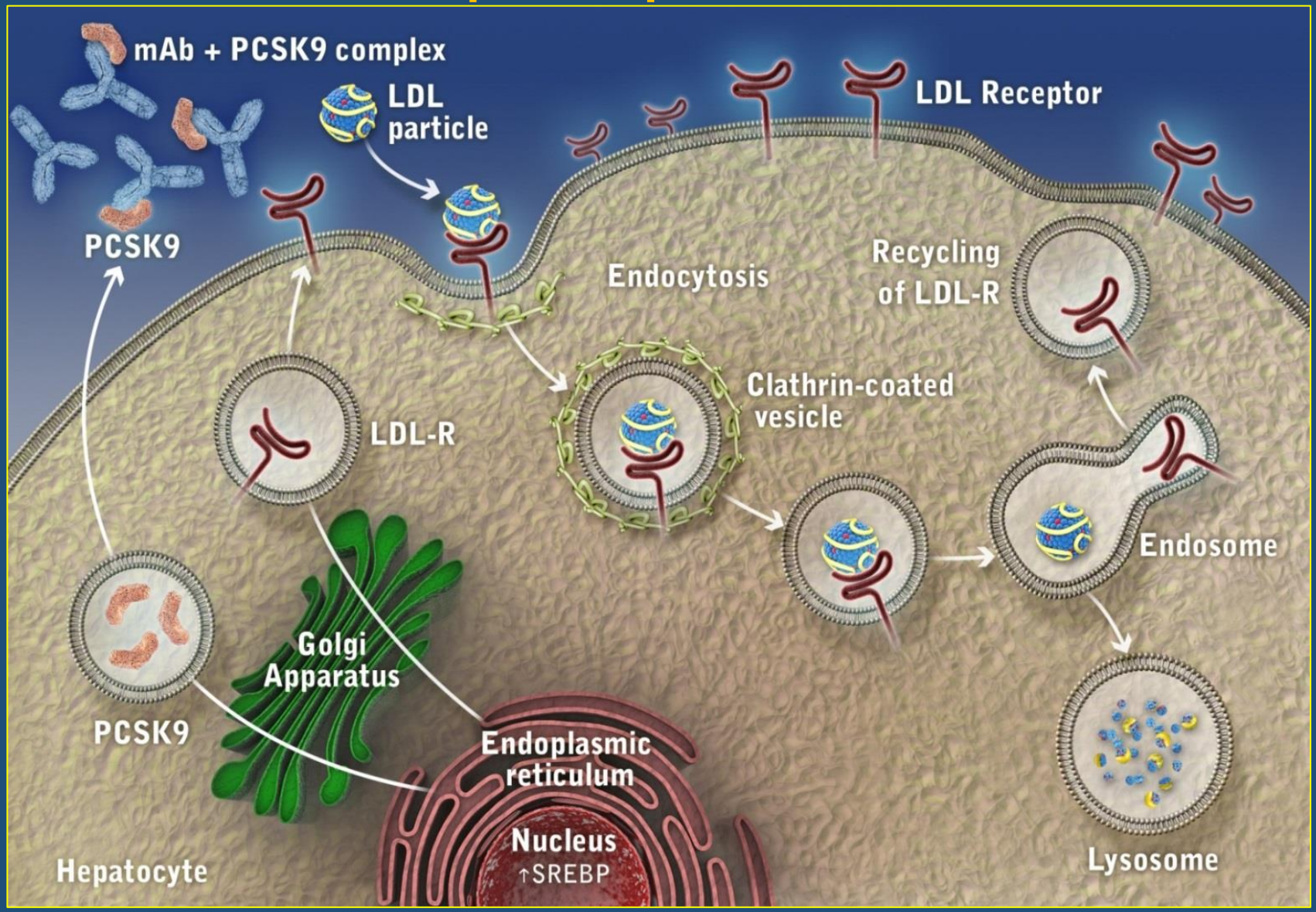
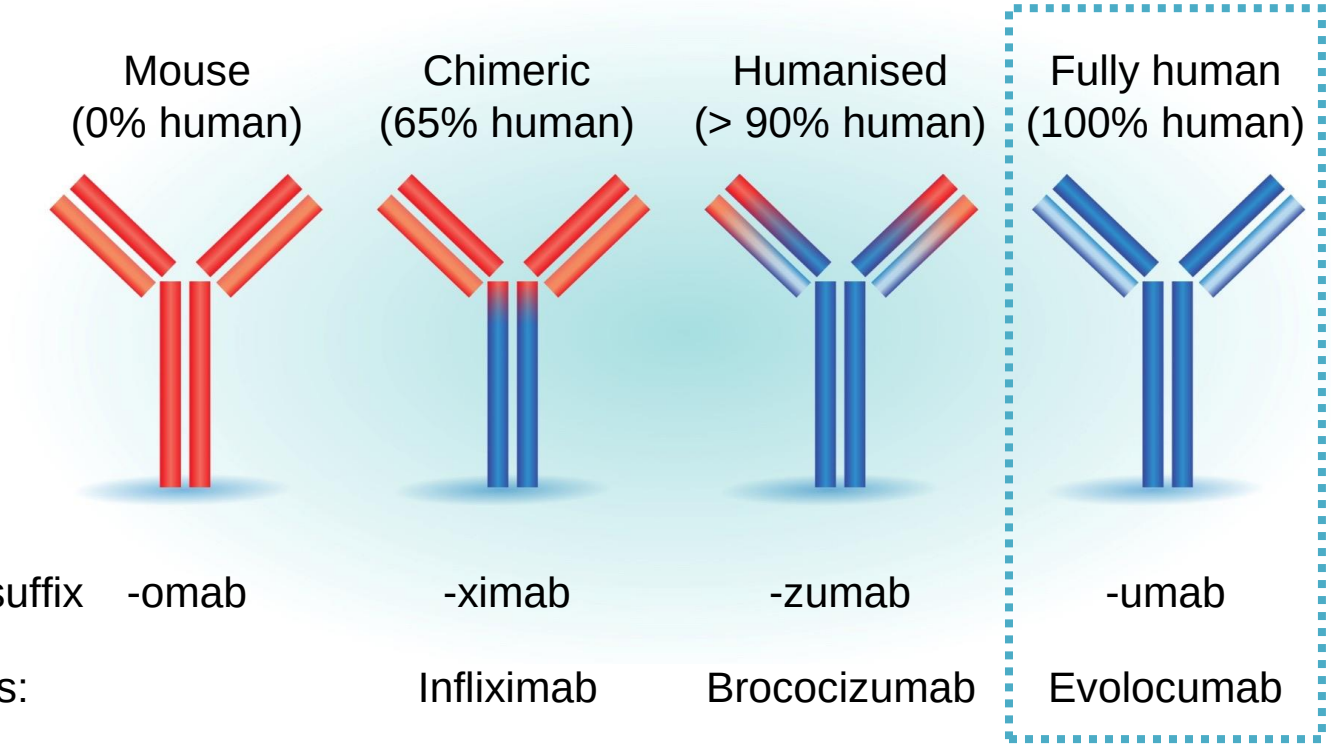
PCSK9 Monoclonal Antibodies Inactivate PCSK9 → Increase LDL-Receptor Expression → ↓ LDL-C levels



LDL=low-density lipoprotein; LDL-R=LDL receptor; mAb=monoclonal antibody; PCSK9=proprotein convertase subtilisin/kinexin type 9; SREBP-2=sterol regulatory element-binding protein-2.; Adapted from: Catapano AL, Papadopoulos N. *Atherosclerosis* 2013;228:18–28.

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

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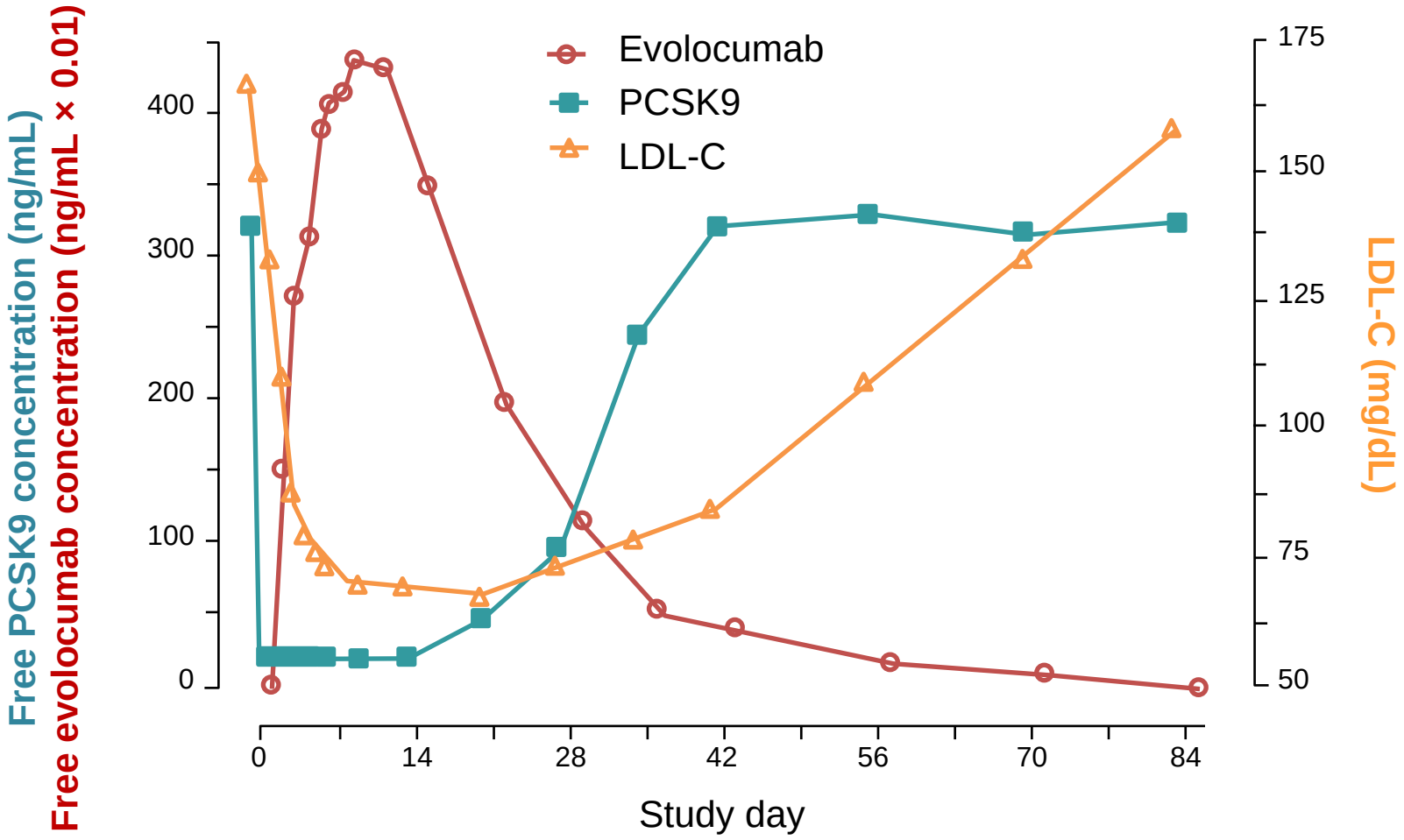
Evolocumab produces rapid suppression of PCSK9 and LDL-C levels in single dose



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

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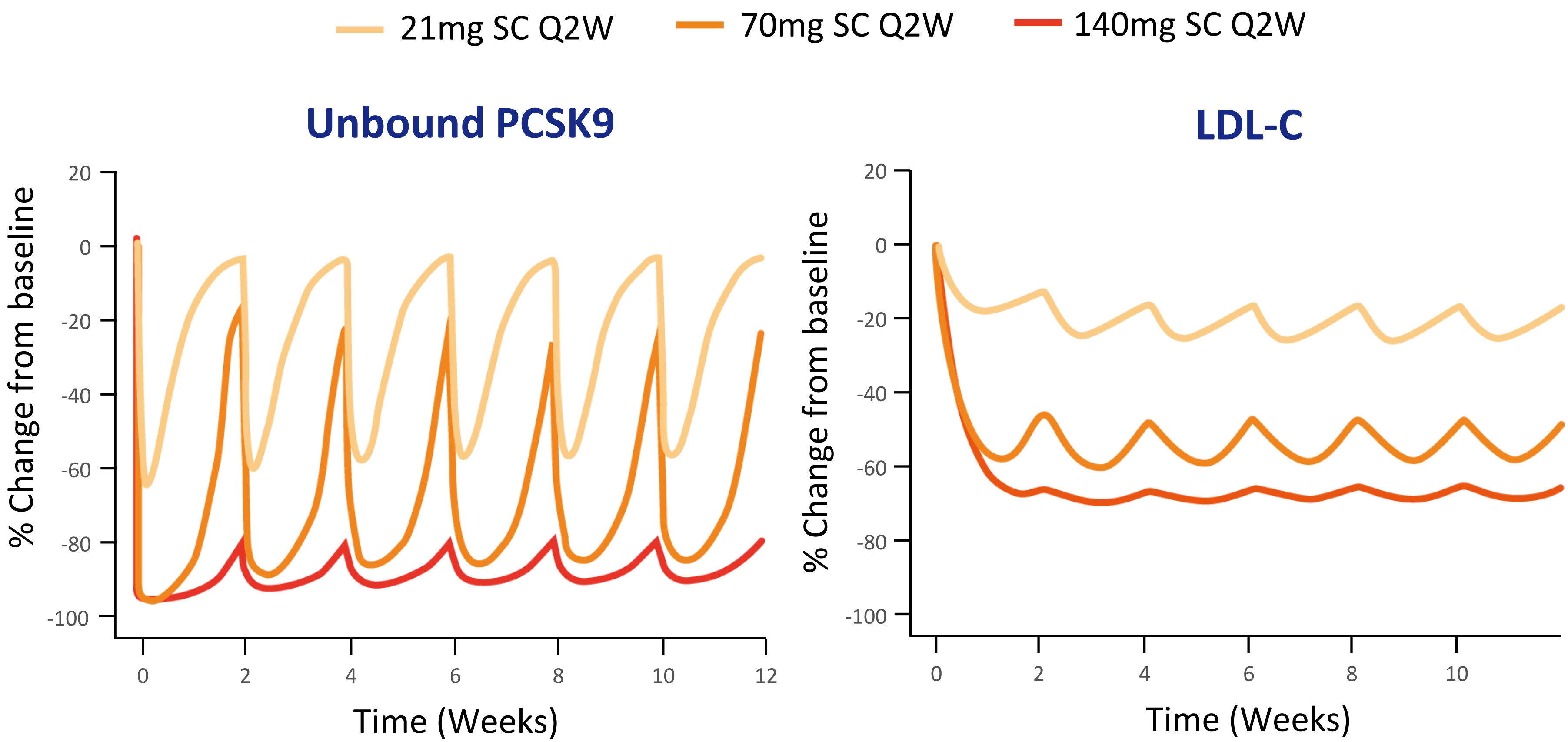
RE-TWN-Med-NP-208-2017-FEB

Sustained PCSK9 inhibition with 140mg Q2W leads to effective, stable LDL-C reduction



Data on file, Amgen Inc

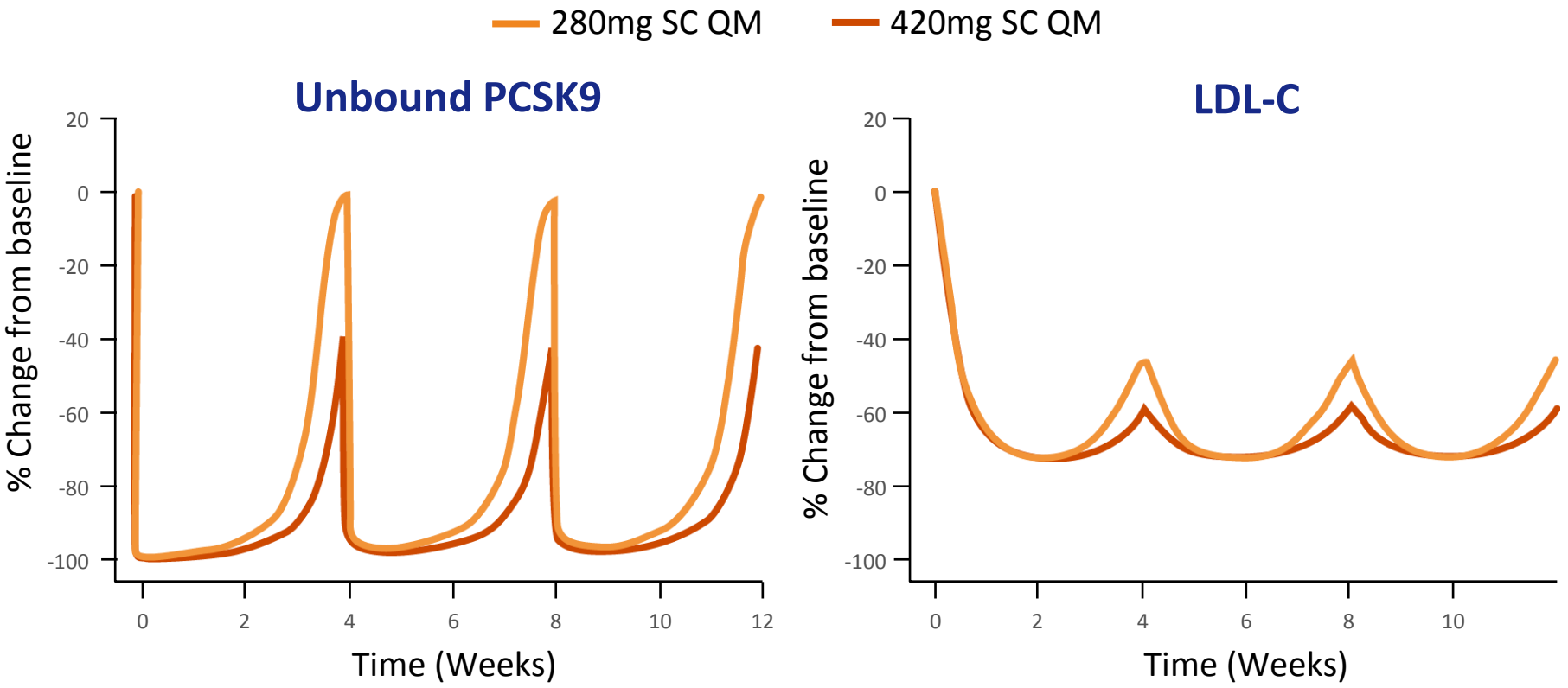
AMGEN® Cardiovascular

Repatha™ (evolocumab) injection 140 mg/mL

RE-TWN-MKT-P-234-2017-MAR

Sustained PCSK9 inhibition with 420mg QM leads to effective, stable LDL-C reduction

- Triple dose provides same inhibition for double duration



Data on file, Amgen Inc

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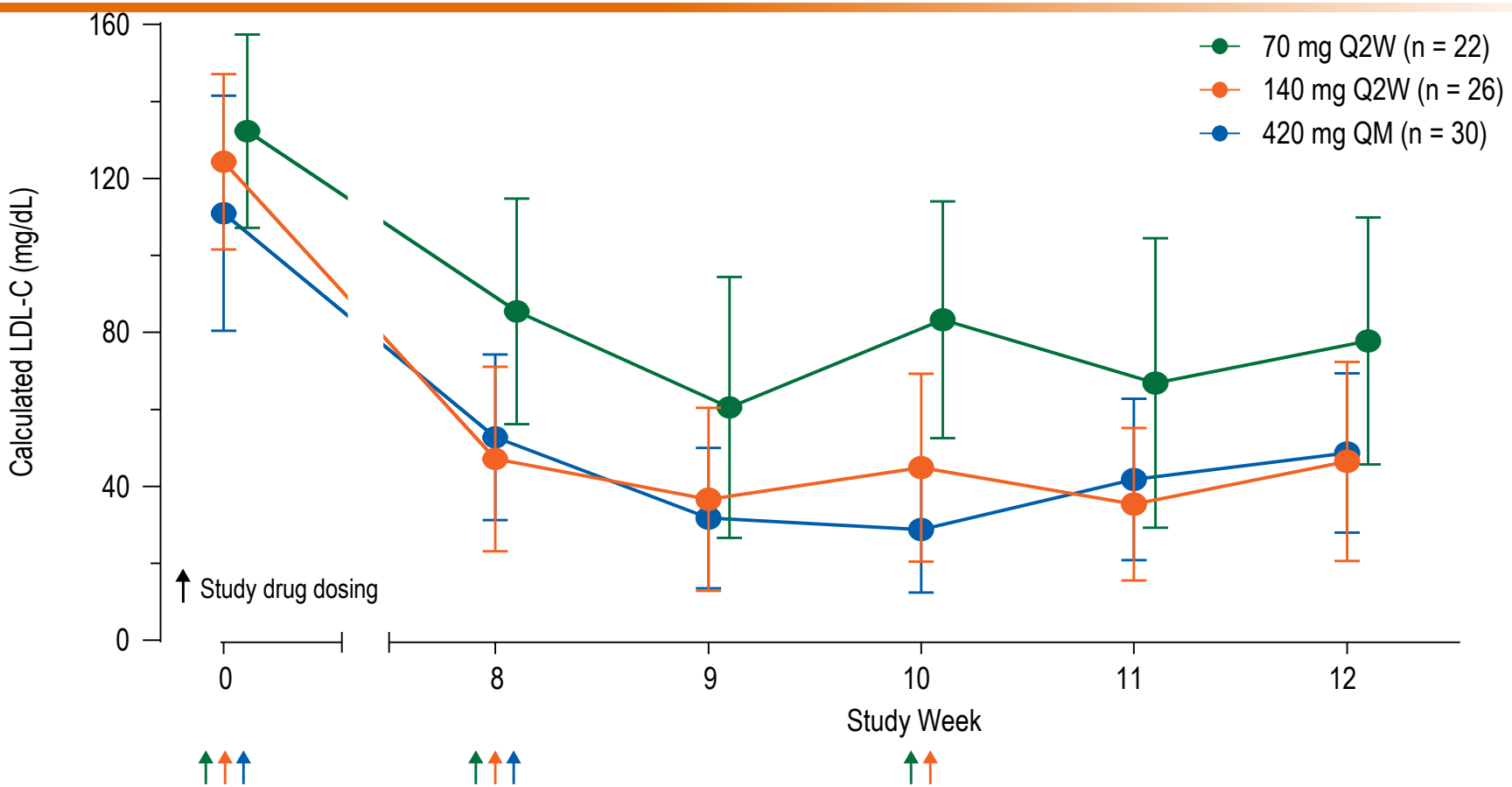
Cardiovascular

Repatha™ (evolocumab) injection 140 mg/mL

RE-TWN-MKT-P-234-2017-MAR

Time Course of Mean (± SD) Calculated LDL-C Following SC Evolocumab Q2W Dosing for a Low (70 mg) and Higher Dose (140 mg) and a Monthly 420 mg Dose Over Weeks 8–12 From Patients in the PKPD Substudy Combined PKPD Substudy Patients in MENDEL and LAPLACE-TIMI 57 Studies



- Peak LDL-C effect occurred after one week for Q2W dosing and after two weeks for QM dosing.
- Higher doses of evolocumab (140 or 420 mg) produced a greater and more sustained LDL-C response over the dosing interval compared to the lower dose (70 mg).

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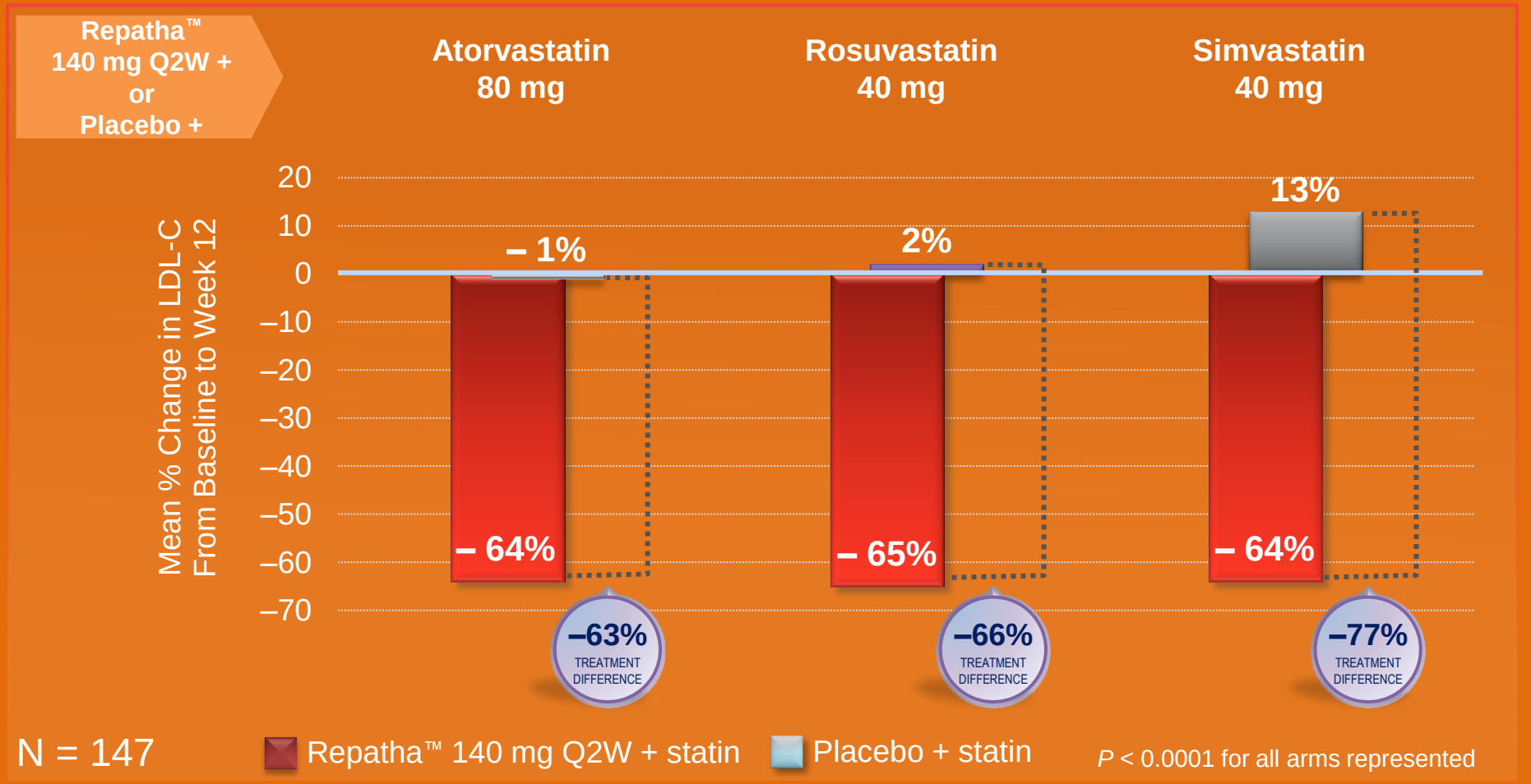
Repatha™ + a Statin Achieved Intensive LDL-C Reduction Up to 77% vs Placebo[1,2]

COMBINATION WITH STATIN THERAPY
STUDY 1



Estimates based on a multiple imputation model that accounts for treatment adherence.[1]

1. Repatha™ (evolocumab) Prescribing Information, Amgen. 2. Data on file, Amgen.

Repatha™ (evolocumab) injection 140 mg/mL

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Cardiovascular

A Robust Clinical Trial Program Demonstrates LDL-C–Lowering, Atherosclerosis Regression, and Major Cardiovascular Event Reduction

Trials included patients with hyperlipidemia on background statin therapy, HeFH patients, statin-intolerant patients, and patients with heart attack, stroke, or PAD[1-6]

2014

laplace-2 TIMI 57

Patients with hyperlipidemia on background statin therapy[4,†]

2015

rutherford-2

HeFH patients with LDL-C > 100 mg/dL despite statin ± ezetimibe[5]

2016

gauss-2

Statin-intolerant* patients with hypercholesterolemia[1]

glagov

Patients with coronary artery disease treated for LDL-C lowering[2,‡]

gauss-3

Statin-intolerant* patients with hypercholesterolemia[6]

2017

ebbinghaus

A safety substudy of Repatha® Outcomes–FOURIER[7]

Repatha Outcomes

Patients with heart attack, stroke, or PAD and LDL-C ≥ 70 mg/dL[3,‡]

* For GAUSS-2: lipid-lowering therapy was used by 33% of patients; 18% received a low-dose statin. Patients included in this study could not tolerate effective doses of ≥ 2 different statins due to muscle-related side effects.[1] For GAUSS-3: patients included in the study could not tolerate ≥ 3 statins (1 at lowest approved dose) or 2 statins (1 must be atorvastatin 10 mg).[6]

†Included statin therapy with or without ezetimibe. No additional prescription lipid-modifying drugs were allowed during the trial.[4]

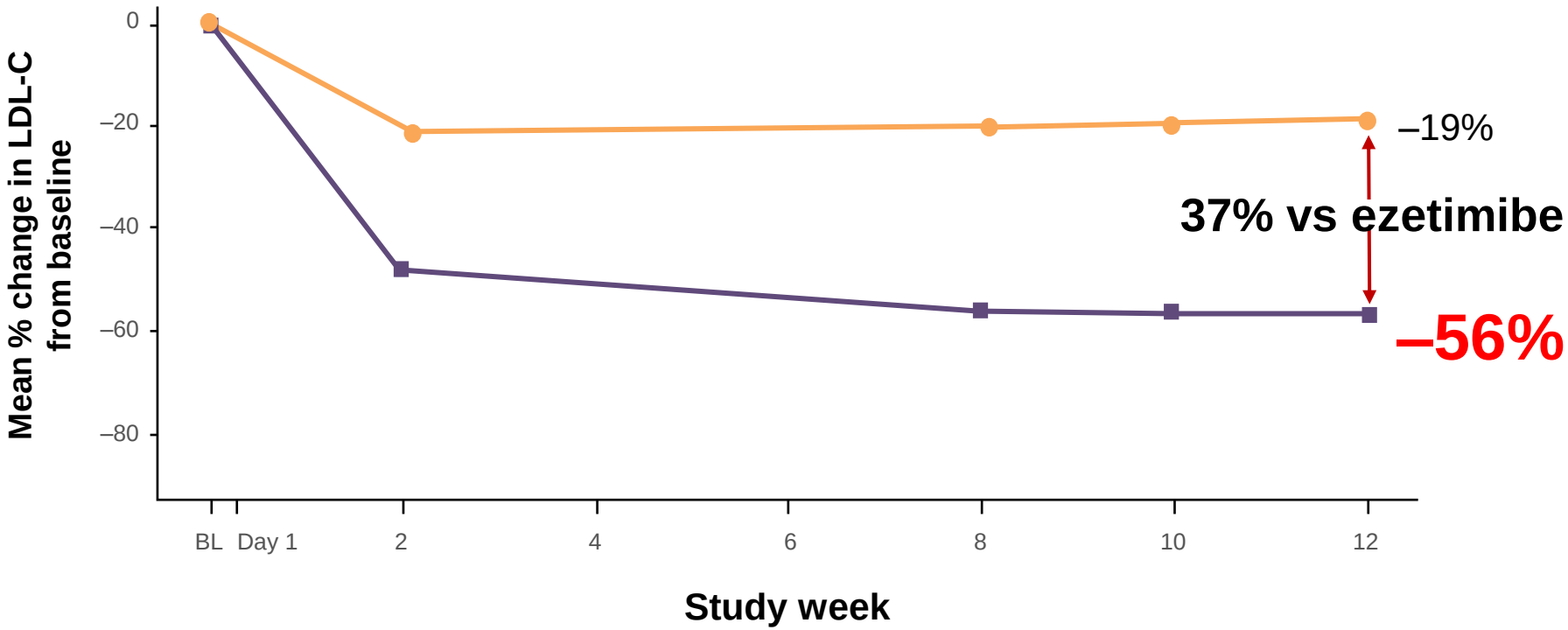
‡Repatha® or placebo was administered on top of moderate- to high-intensity statin therapy.[3,7]

1. Stroes E, et al. *J Am Coll Cardiol.* 2014;63:2541-2548; 2. Puri R, et al. *Am Heart J.* 2016;176:83-92; 3. Sabatine MS, et al. *Am Heart J.* 2016;173:94-101; 4. Robinson JG, et al. *JAMA.* 2014;311:1870-1882; 5. Raal FJ, et al. *Lancet.* 2015;385:331-340; 6. Nissen SE, et al. *JAMA.* 2016;315:1580-1590; 7. Giugliano RP, et al. *Clin Cardiol.* 2017 Feb 16. [Epub ahead of print].

Repatha® (evolocumab)

Evolocumab significantly reduces LDL-C in statin-intolerant patients in 12-week study

gauss-2



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

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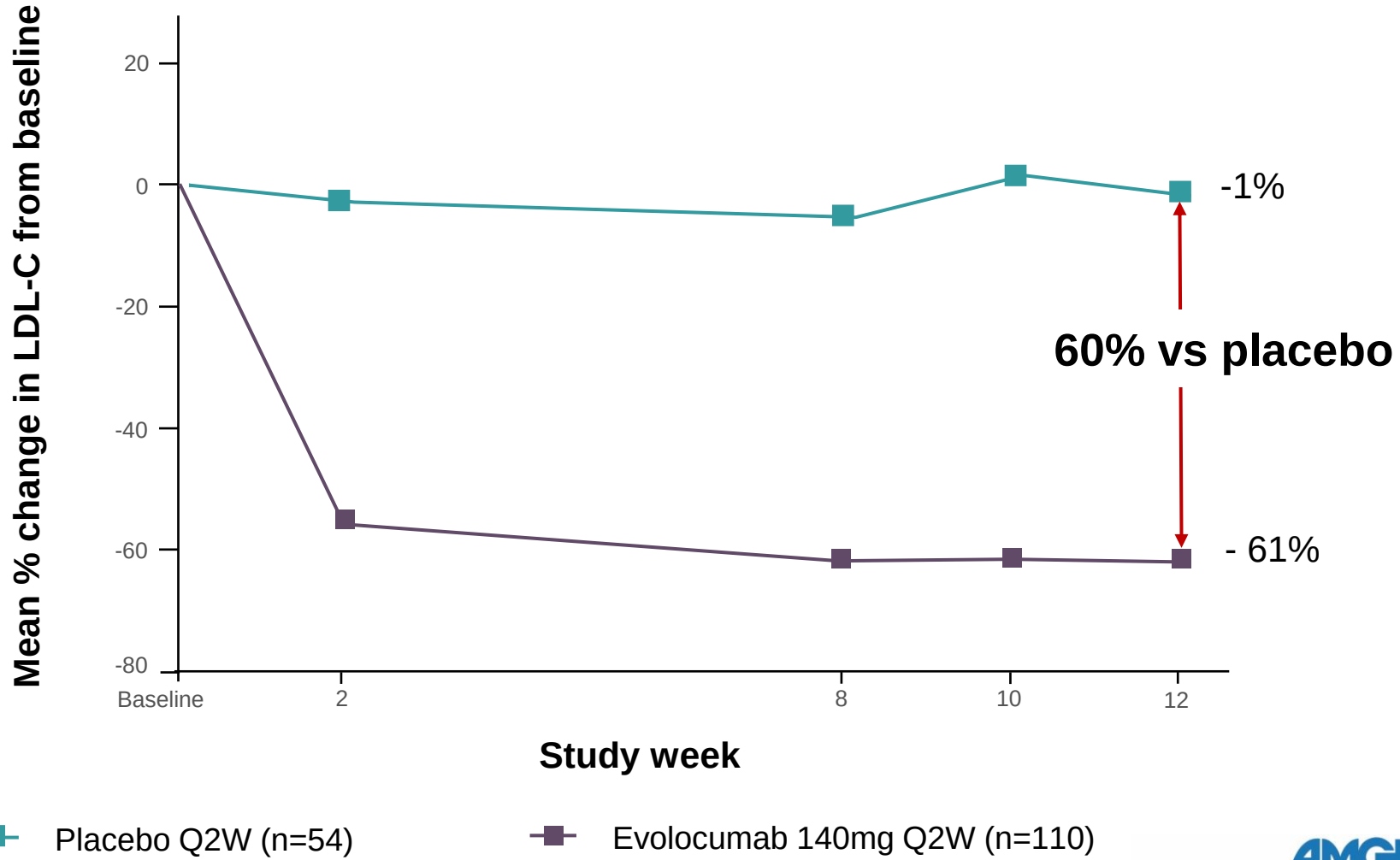
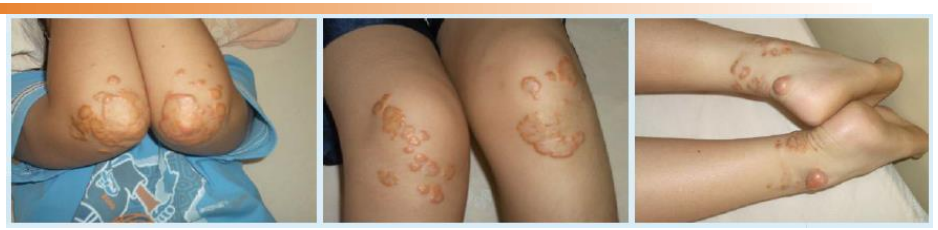
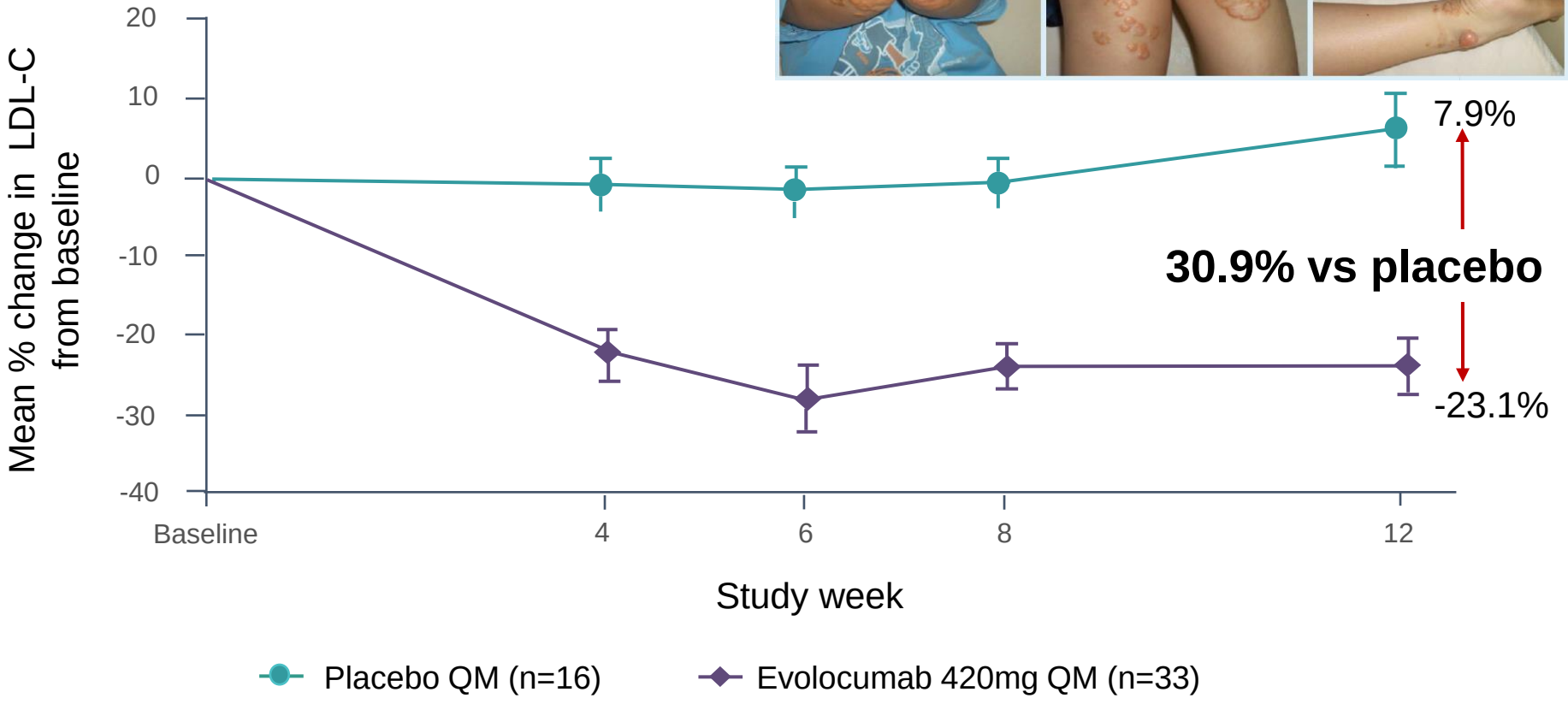
Evolocumab significantly reduces LDL-C in patients with heterozygous FH



Raal et al. Lancet 2015;385:331–340.

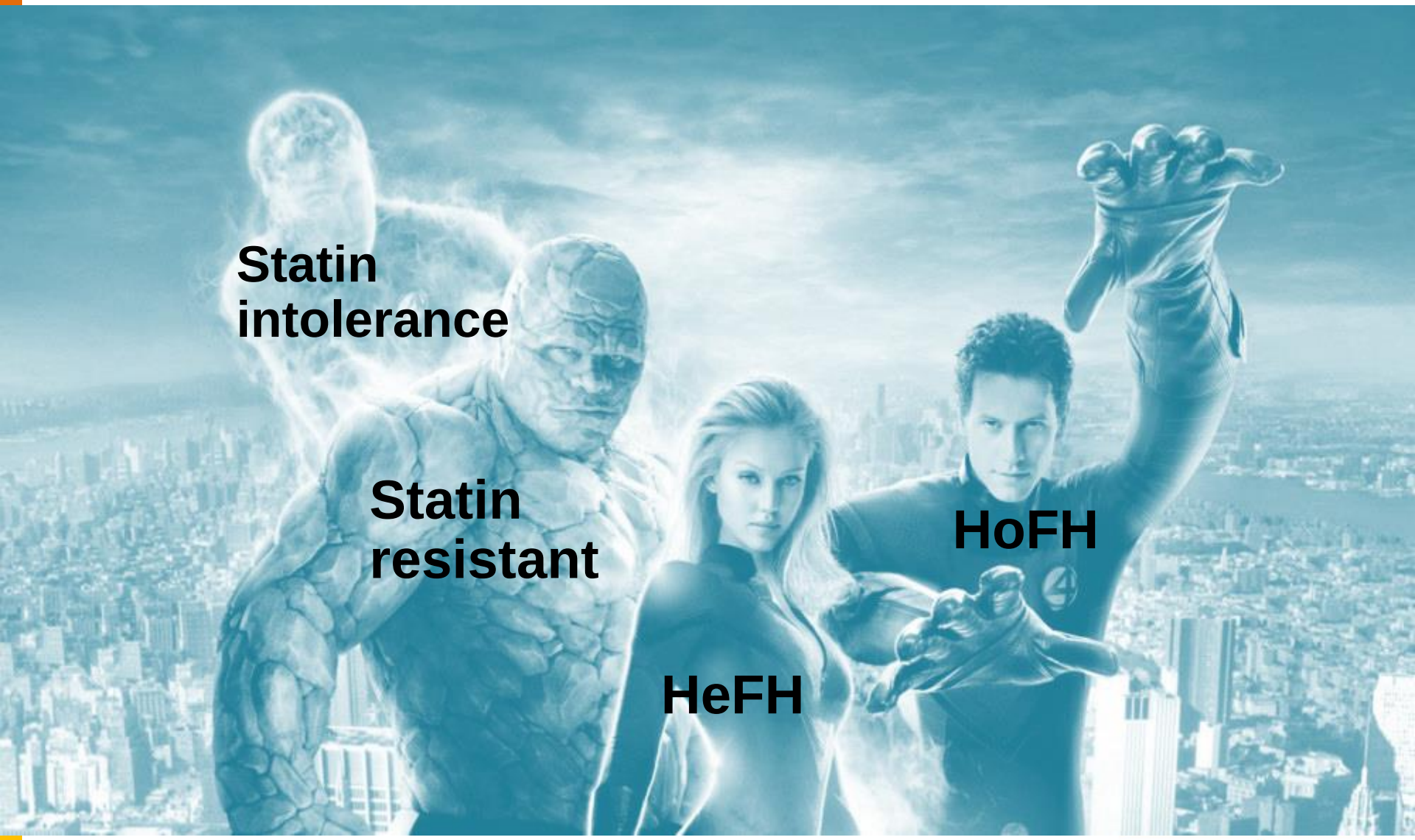
Evolocumab significantly reduces LDL-C even in patients with homozygous FH



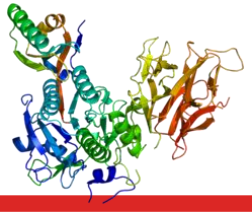


Raal et al. Lancet 2015;385:341–350.

Repatha: Place in therapy



Two licenses in Taiwan



一般適應症

異合子家族性高膽固醇血症
或動脈粥狀硬化心血管疾病

- 已接受最高耐受劑量statin
- 低密度脂蛋白膽固醇 (LDL-C) 仍無法達到目標值
- 對於這兩類成人患者，Repatha 可作為飲食外的輔助治療。

原發性高膽固醇血症
或混合型血脂異常

- statin 不耐受或禁用 statin 的原發性高膽固醇血症 (異合子家族性及非家族性) 或混合型血脂異常
- 對於此類成人患者，Repatha 可單獨使用或併用其他降血脂藥物，作為飲食外的輔助治療。

罕見疾病適應症

同合子家族性高膽固醇血症: Repatha 適用於飲食及其他降血脂療法(如: statins、ezetimibe、LDL 血漿析離術)之輔助療法，用以進一步降低LDL-C，但LDLR-negative mutation 之病人除外

*說明：所謂動脈粥狀硬化心血管疾病 包括急性冠狀動脈症候群、有心肌梗塞病史、穩定型或不穩定型心絞痛、接受過冠狀動脈或其他動脈血管再通術(revascularization)、中風、短暫性腦缺血發作，及疑似因動脈粥狀硬化引起之周邊動脈疾病等

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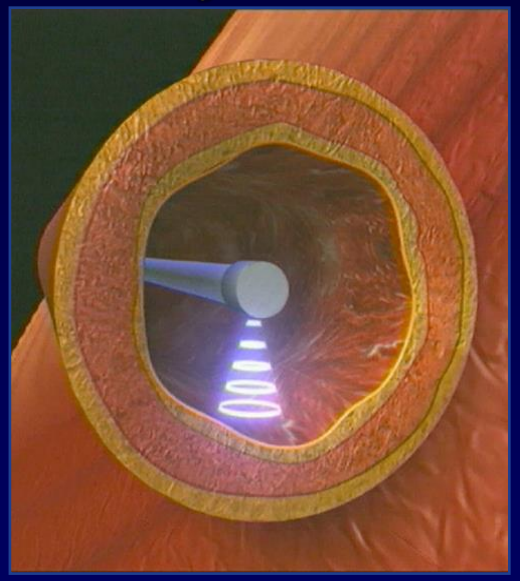
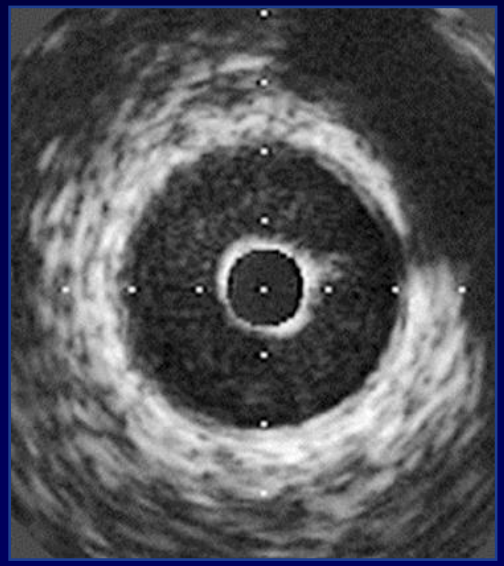
The IVUS coronary imaging technique

Rotating transducer

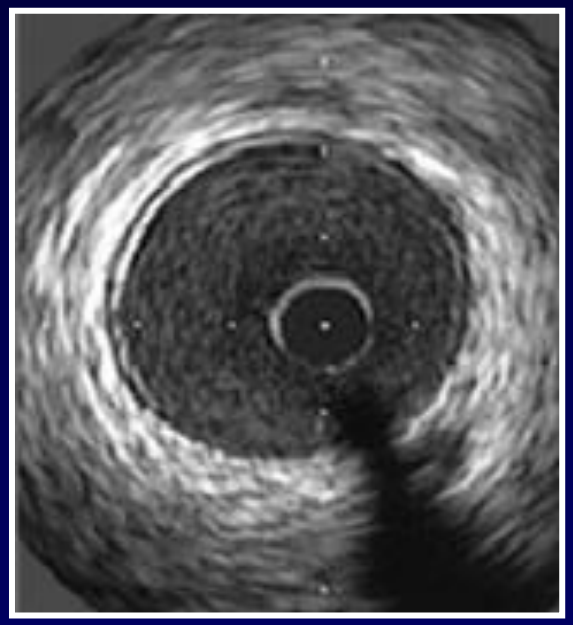


Normal coronary anatomy

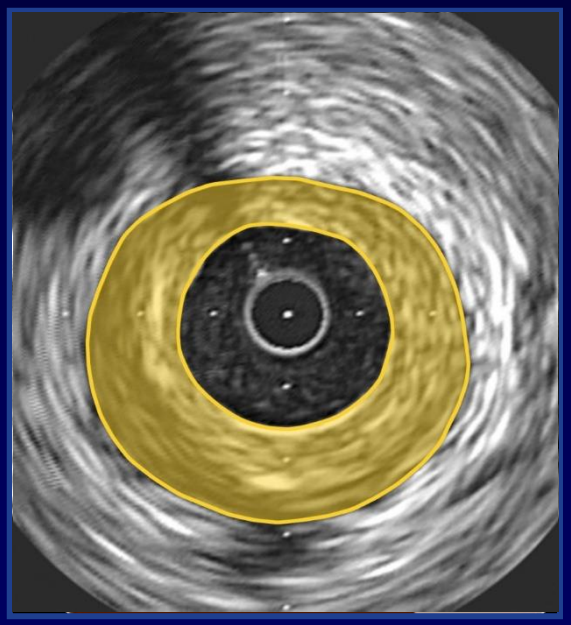


Images courtesy of Cleveland Clinic Intravascular Ultrasound Core Laboratory

IVUS: Normal and diseased anatomy



Normal Anatomy

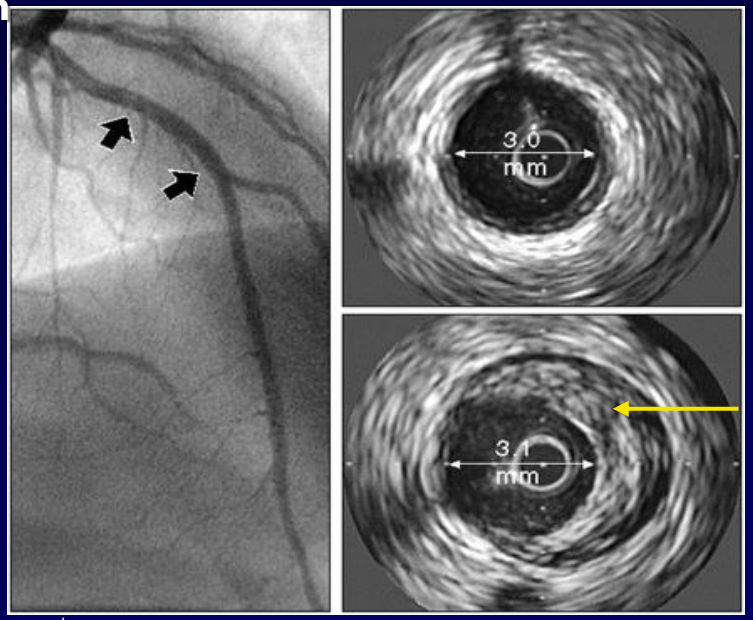


Concentric Disease

The IVUS technique can detect angiographically 'silent' atheroma

Angiogram

No evidence of disease



IVUS

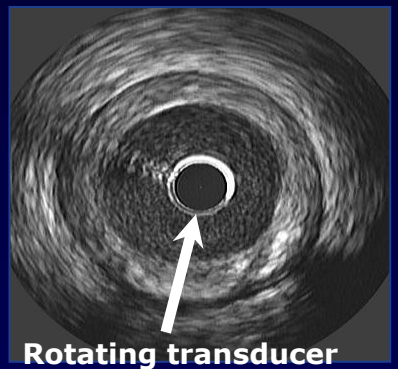
Little evidence of disease

Atheroma

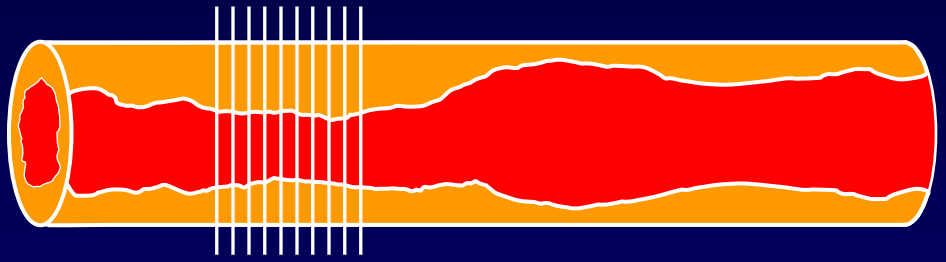
IVUS=intravascular ultrasound

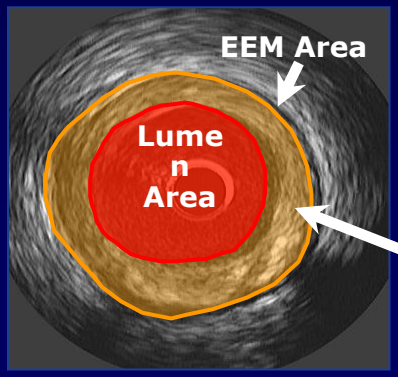
Nissen S, Yock P. *Circulation 2001*; 103: 604–616

Effects of evolocumab on intravascular ultrasound (IVUS) - derived coronary artery atheroma burden



IVUS enables measurement of the volume of atheroma within the wall of the arteries by combining a series of cross-sectional images of the vessel over a predefined length





Atheroma Area = EEM Area -Lumen Area

EEM = External Elastic Membrane

Images courtesy of Cleveland Clinic Intravascular Ultrasound Core Laboratory

1 Nissen S et al. JAMA 2006;295 (13):1556-1565

Summary of statin on coronary atherosclerosis

Study	ARTMAP	ORION	COSMOS	REVERSAL	ASTEROID	SATURN
Tx	Ros10 vs Ator20	Ros 5 vs 40/80	Ros 2.5	Ator 80 vs prava 40	Ros40	Ros40 vs Ator80
Patients	CAD	Neurological asymptomatic	Stable CAD	CAD	Statin-naive	CAD
Patient numbers	271	35	214	502	349	1039
Primary endpoint	PAV	Change in plaque morphology	TAV	TAV	PAV	PAV
Regression	✓		✓		✓	✓
Imaging	IVUS	MRI	IVUS	IVUS	IVUS	IVUS
Note	6-month	2y, too small to tell anything	76-wk open label	18-month	2y, open-label	104-wk

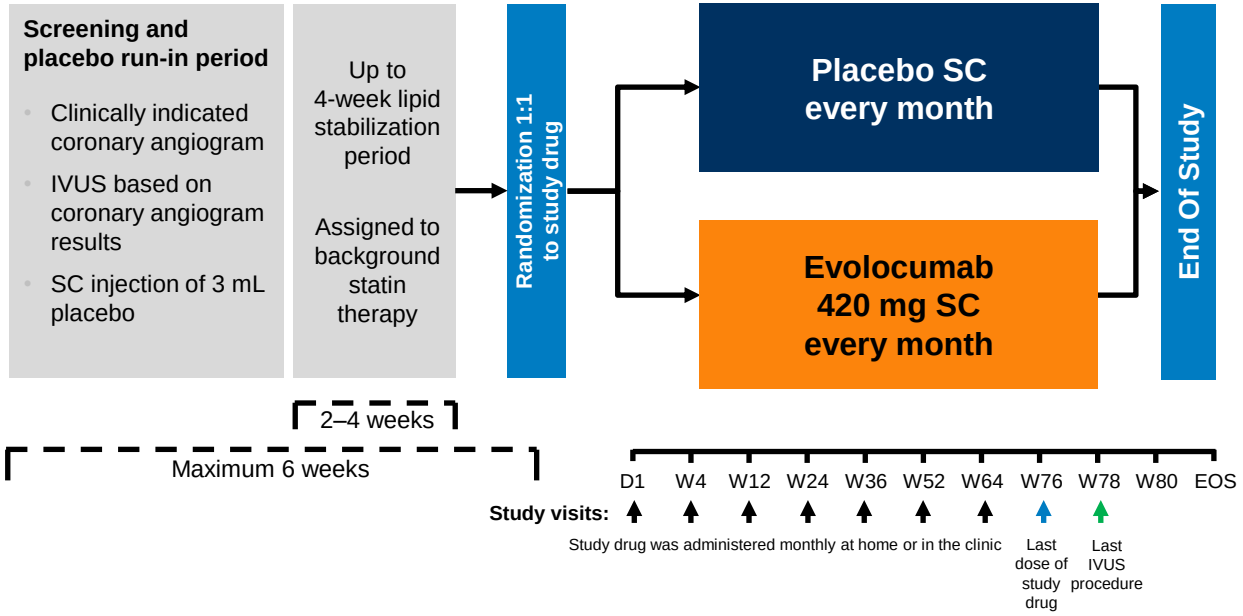
For scientific exchange purpose only

Summary of statin on coronary atherosclerosis

Study	ARTMAP	ORION	COSMOS	REVERSAL	ASTEROID	SATURN
Age	56	65.2	62.6	55.8	58.5	57.4
LDL	109 →53	148.4 (-59.9%)	140.2→82.9 (-38.6%)	150.2→78.9 (-46.3%)	130.4→60.8 (-53.2%)	120→62.6
HDL	40→47	47.3 (+10.1%)	47.1→55.2 (+19.8%)	42.3→43.1 (+2.9%)	43.1→49 (14.7%)	45.3→50.4
hs-CRP			3.36→0.93 (-18.1%)	2.8→1.8 (-36.4%)		1.7→1.1
LDL/HDL ratio			3.12→1.56		3.1→1.3	2.8→1.3(rosu) 2.8→1.5(ator)
Results	regression		regression		regression	regression
Note		too small to tell anything				TAV: favor rosuva-statin

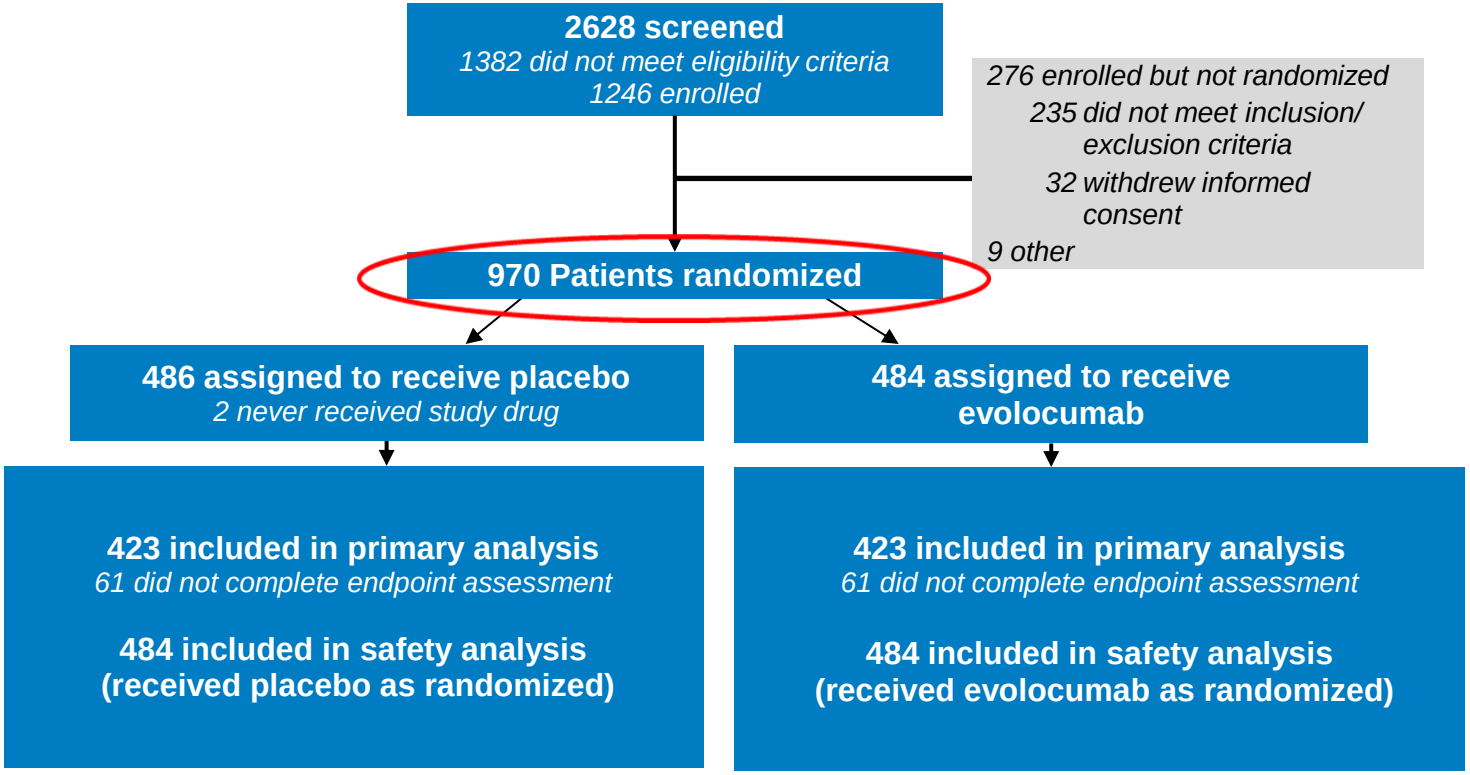
Some data adapted from high potency group

GLAGOV: Study Design



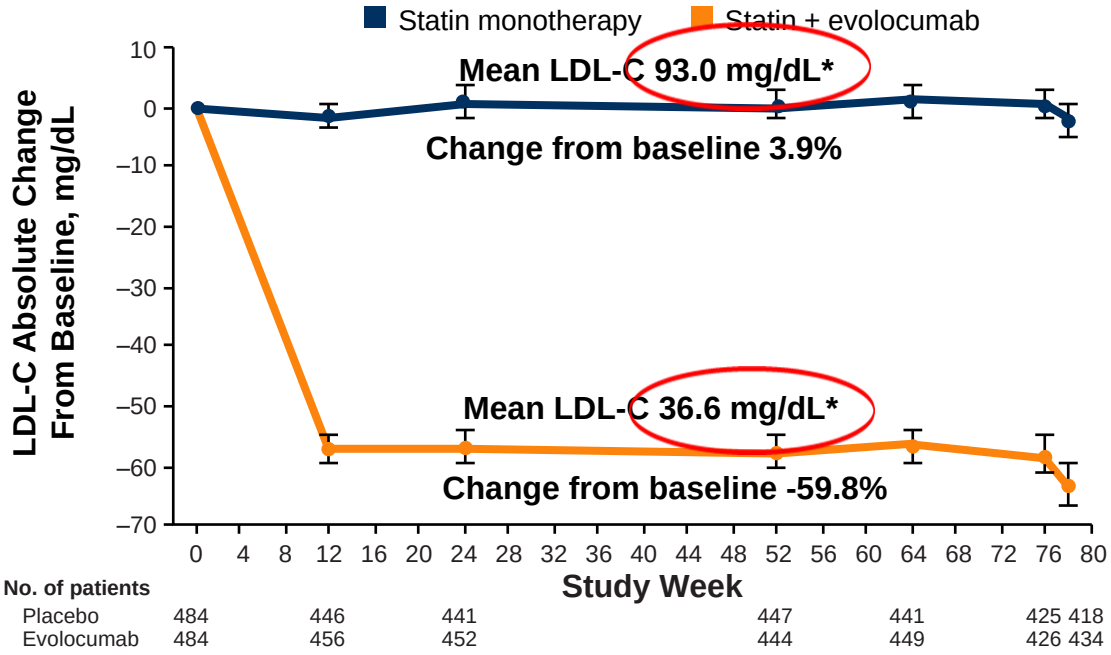
*Nominal change refers to the actual number, as opposed to percent change
D = day; IVUS = intravascular ultrasound; SC = subcutaneously; W = week.
Puri R, et al. *Am Heart J*. 2016;176:83-92.

GLAGOV: Disposition of Patients During the Study



Adapted from: Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Mean Absolute Change in LDL-C



Absolute change for evolocumab-statin group: -56.3 (-59.4 to -53.1); *P* < 0.001

Data shown are Mean (95% CI) *Time-weighted LDL-C; LDL-C = low-density lipoprotein cholesterol

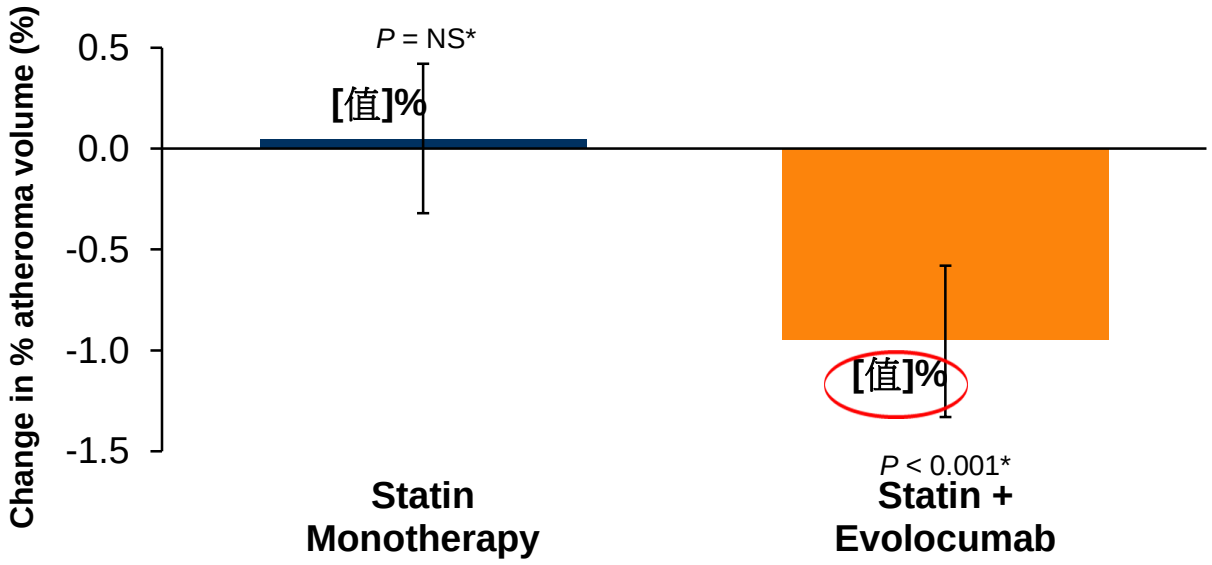
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Nissen SE, et al. *American Heart Association Scientific Sessions,* Nov 12 - 16, 2016, New Orleans, Louisiana. Oral Presentation.

AMGEN

Cardiovascular

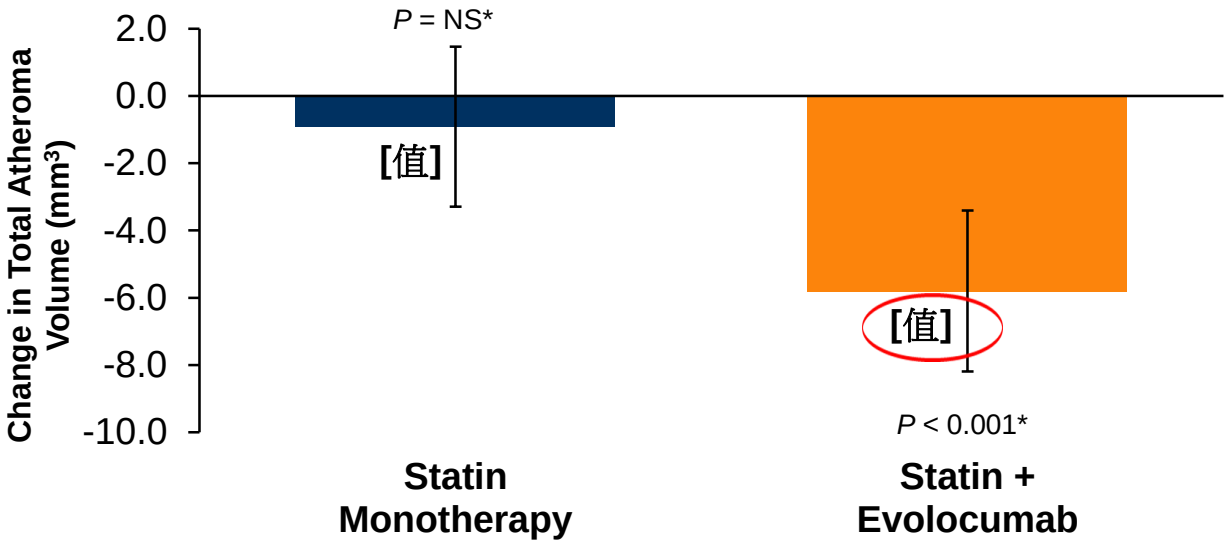
Primary Endpoint: Nominal Change in PAV From Baseline to Week 78



Difference between groups: -1.0% (-1.8 to -0.64); *P* < 0.001

Data shown are least-squares mean (95% CI). PAV = Percent Atheroma Volume
*Comparison versus baseline
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Secondary Endpoint:Nominal Change in TAV From Baseline to Week 78



Difference between groups: -4.9mm³ (-7.3 to -2.5); *P* < 0.001

Data shown are least-squares mean (95% CI). TAV = Total Atheroma Volume
*Comparison versus baseline
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Outlines

- Introduction
- The development PCSK9-inhibitor
- The pharmacodynamics and pharmacokinetic of evolocumab (repatha)
- GLAGOV :coronary atherosclerotic plaque
- FOURIER/Odyssey : long-term CV outcomes
- EBBINGHAUS: neurocognitive function
- Take home message

FOURIER

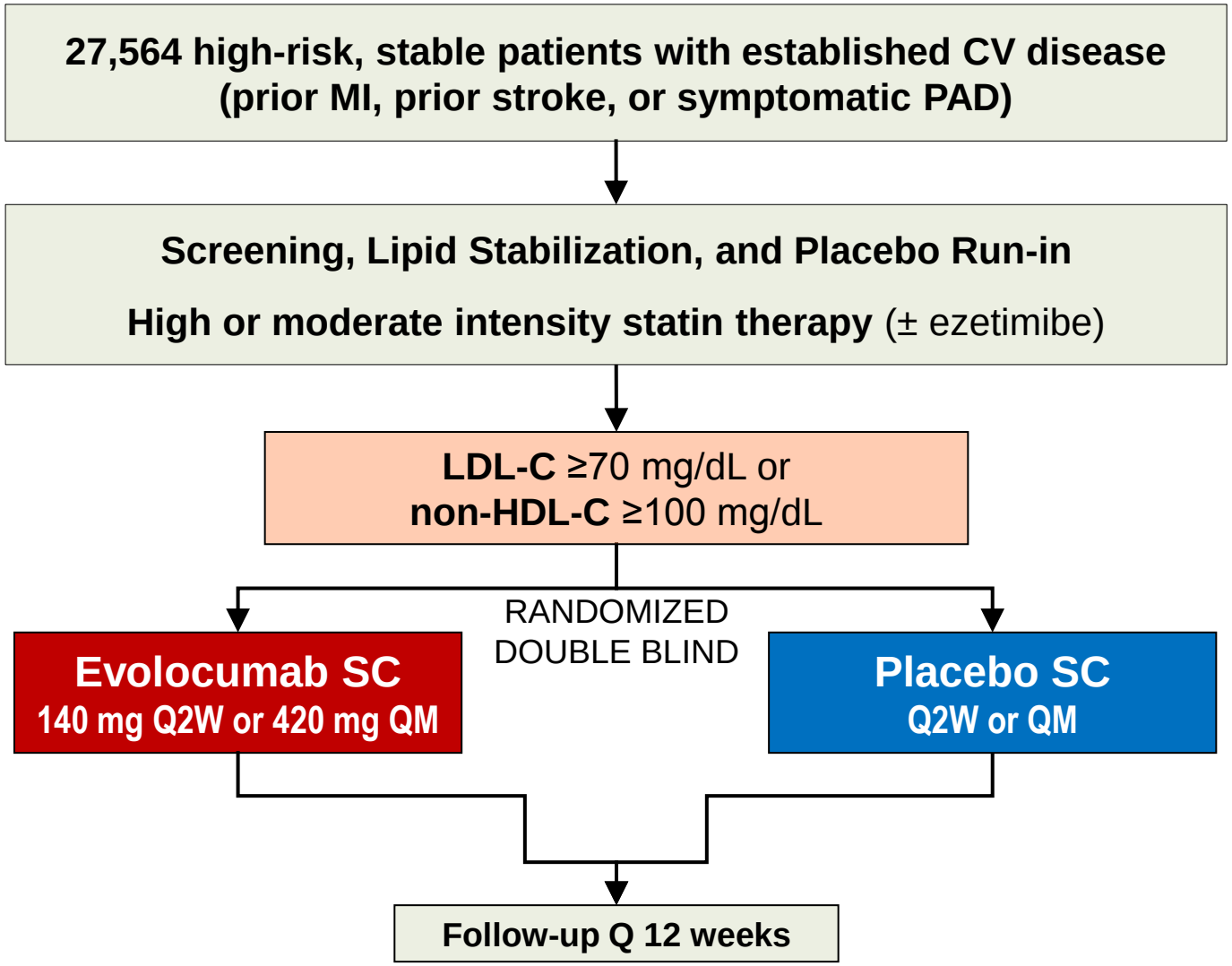
Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

MS Sabatine, RP Giugliano, AC Keech, N Honarpour,
SM Wasserman, PS Sever, and TR Pedersen,
for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 17, 2017

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Trial Design



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

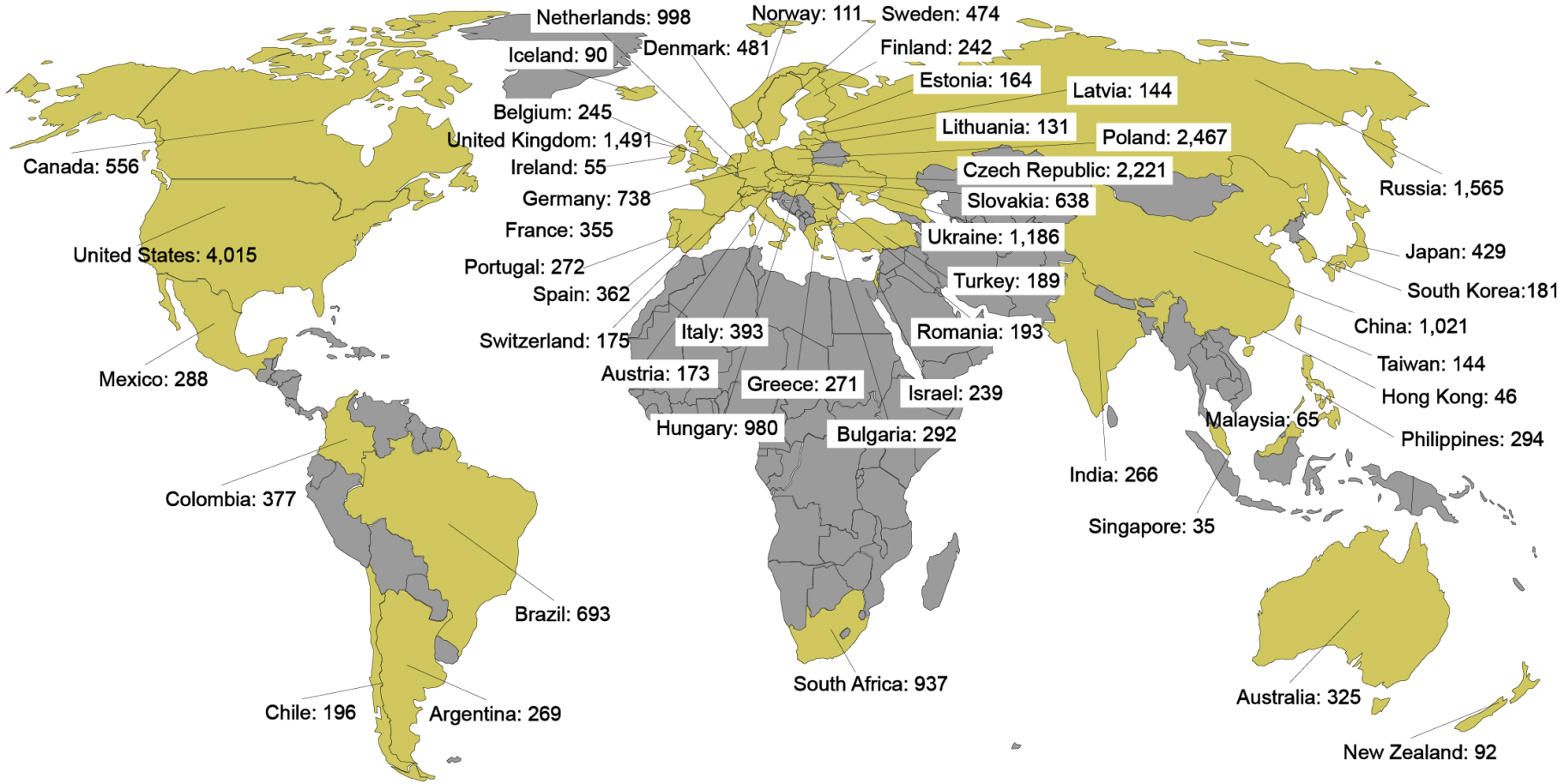
Endpoints

- **Efficacy**
  - **Primary: CV death, MI, stroke, hosp. for UA, or coronary revasc**
  - **Key secondary: CV death, MI or stroke**
- **Safety**
  - **AEs/SAEs**
  - **Events of interest incl. muscle-related, new-onset diabetes, neurocognitive**
  - **Development of anti-evolocumab Ab (binding and neutralizing)**
- **TIMI Clinical Events Committee (CEC)**
  - **Adjudicated all efficacy endpoints & new-onset diabetes**
  - **Members unaware of treatment assignment & lipid levels**

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

Global Enrollment

27,564 patients randomized at 1242 sites
in 49 countries between 2/2013 – 6/2015



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

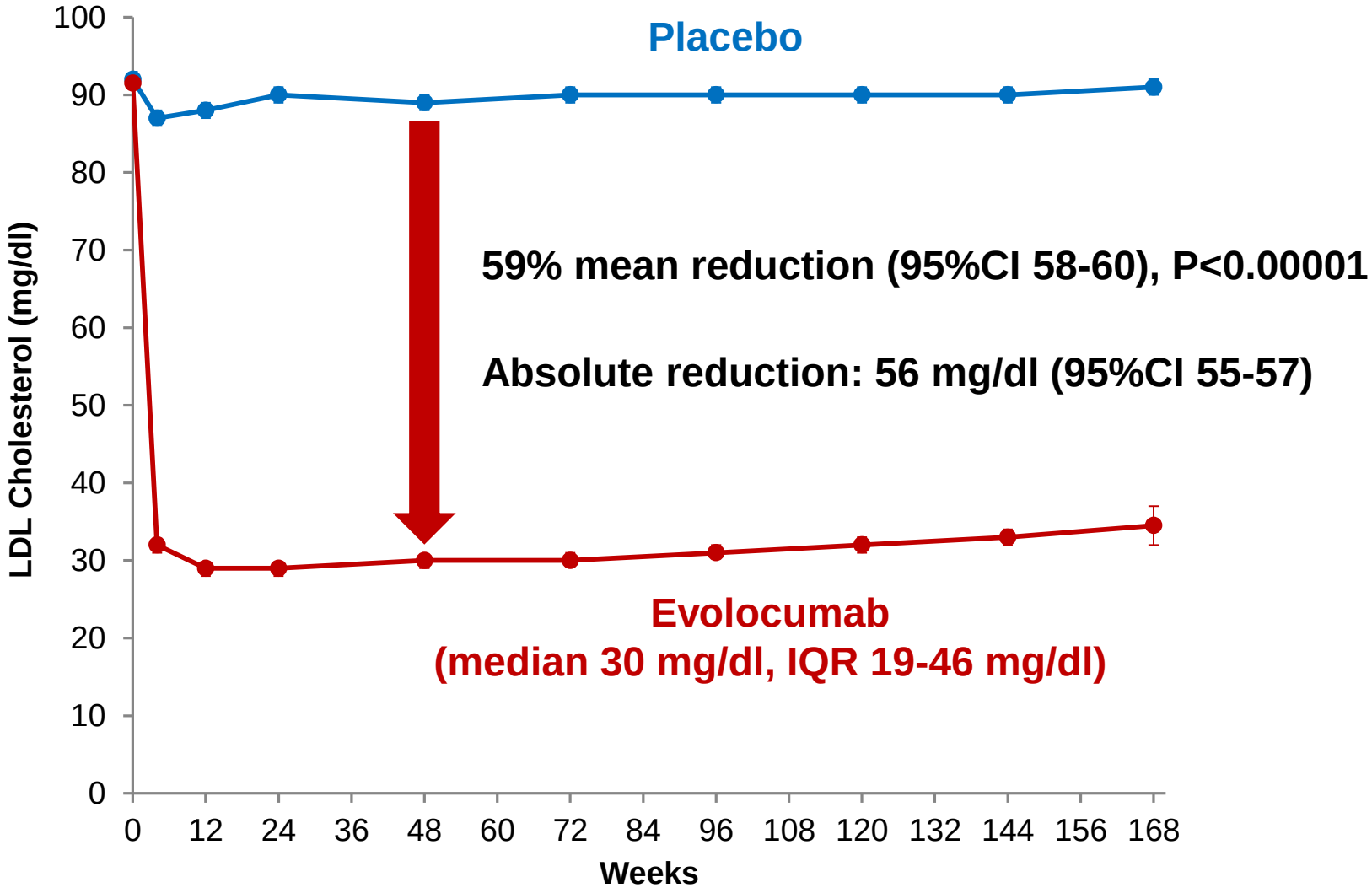
Lipid Lowering Therapy & Lipid Levels at Baseline

Characteristic	Value
Statin use (%)*	
High-intensity	**69**
Moderate-intensity	**30**
Ezetimibe use (%)	**5**
Median lipid measures (IQR) – mg/dL	
LDL-C	**92 (80-109)**
Total cholesterol	**168 (151-189)**
HDL-C	**44 (37-53)**
Triglycerides	**133 (100-182)**

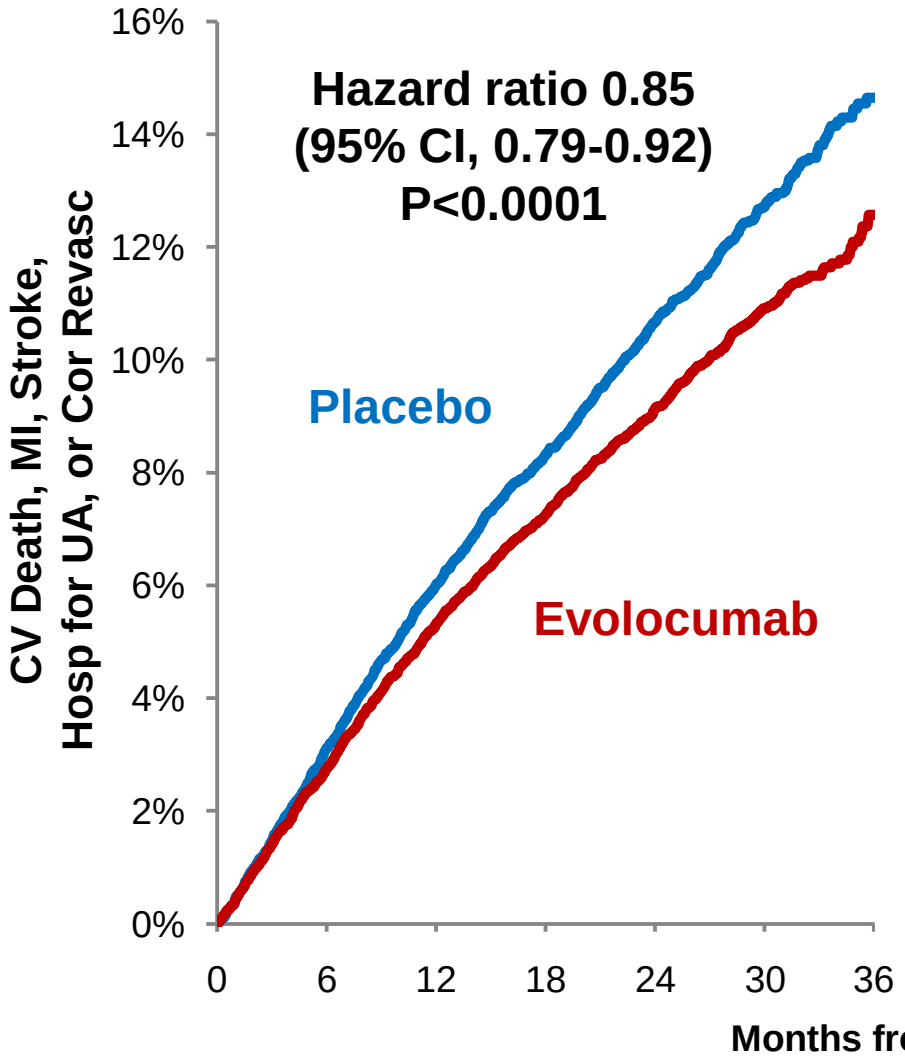
*Per protocol, patients were to be on atorva ≥20 mg/d or equivalent.
1% were on low intensity or intensity data were missing.
Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines.

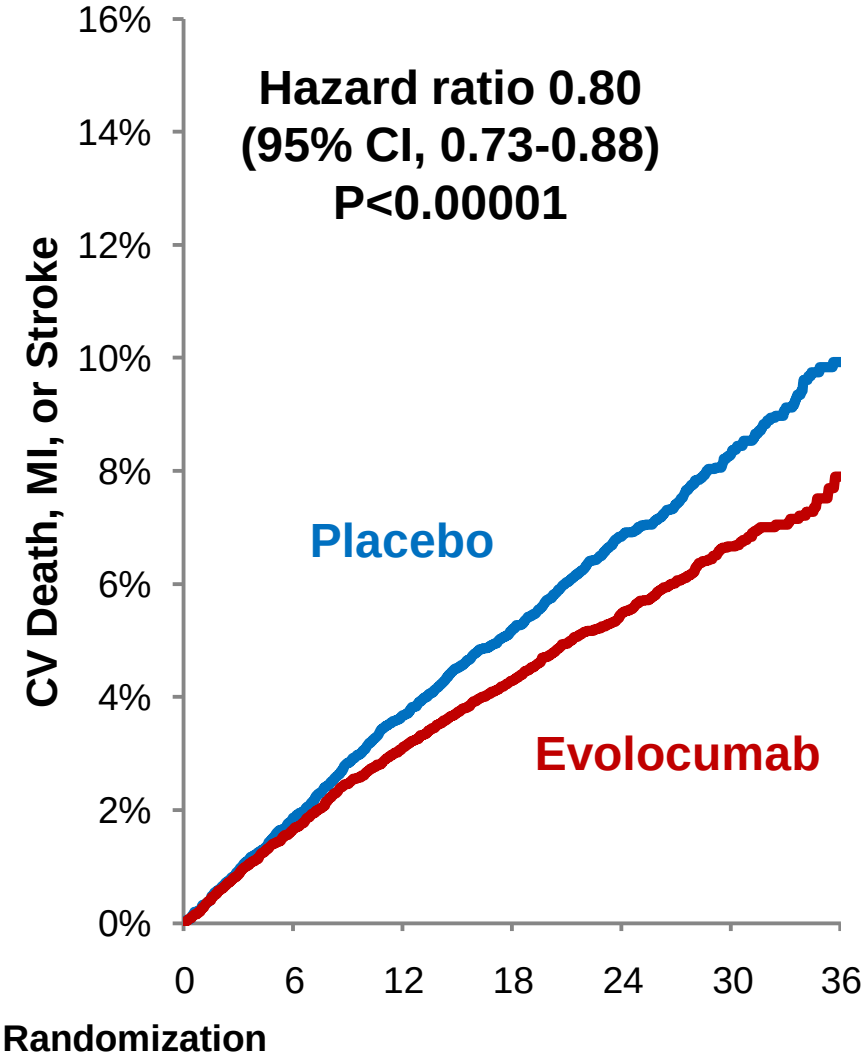
Pooled data; no differences between treatment arms

LDL Cholesterol



Primary & Key Secondary Endpoints





Sabatine MS et al. *NEJM* 2017;376:1713-1722

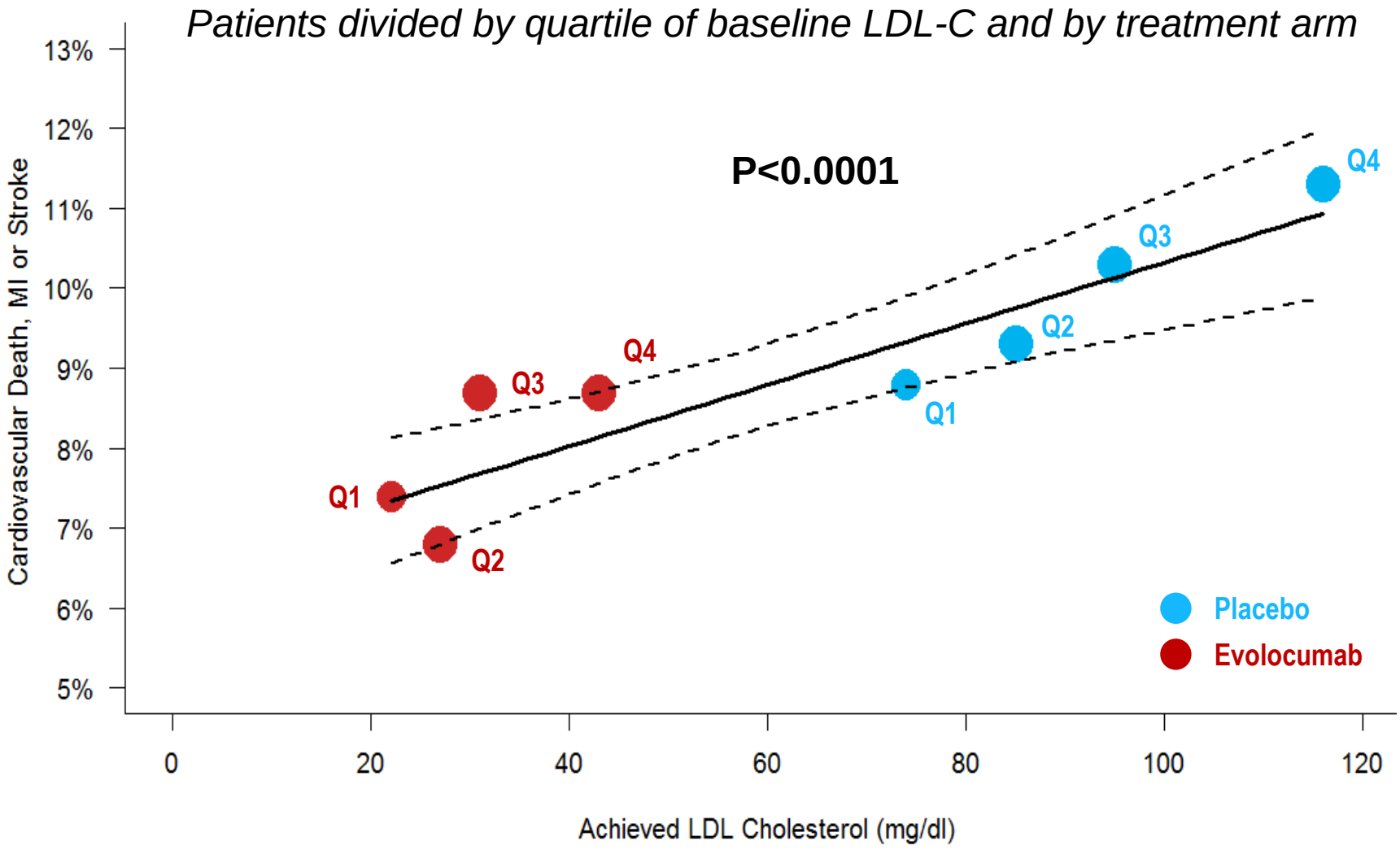
Types of CV Outcomes

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
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)**
Death due to acute MI	0.26	0.32	0.84 (0.49-1.42)
Death due to stroke	0.29	0.30	0.94 (0.58-1.54)
Other CV death	1.9	1.8	1.10 (0.90-1.35)
MI	**4.4**	**6.3**	**0.73 (0.65-0.82)**
Stroke	**2.2**	**2.6**	**0.79 (0.66-0.95)**

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)**

Lower LDL-C Is Better

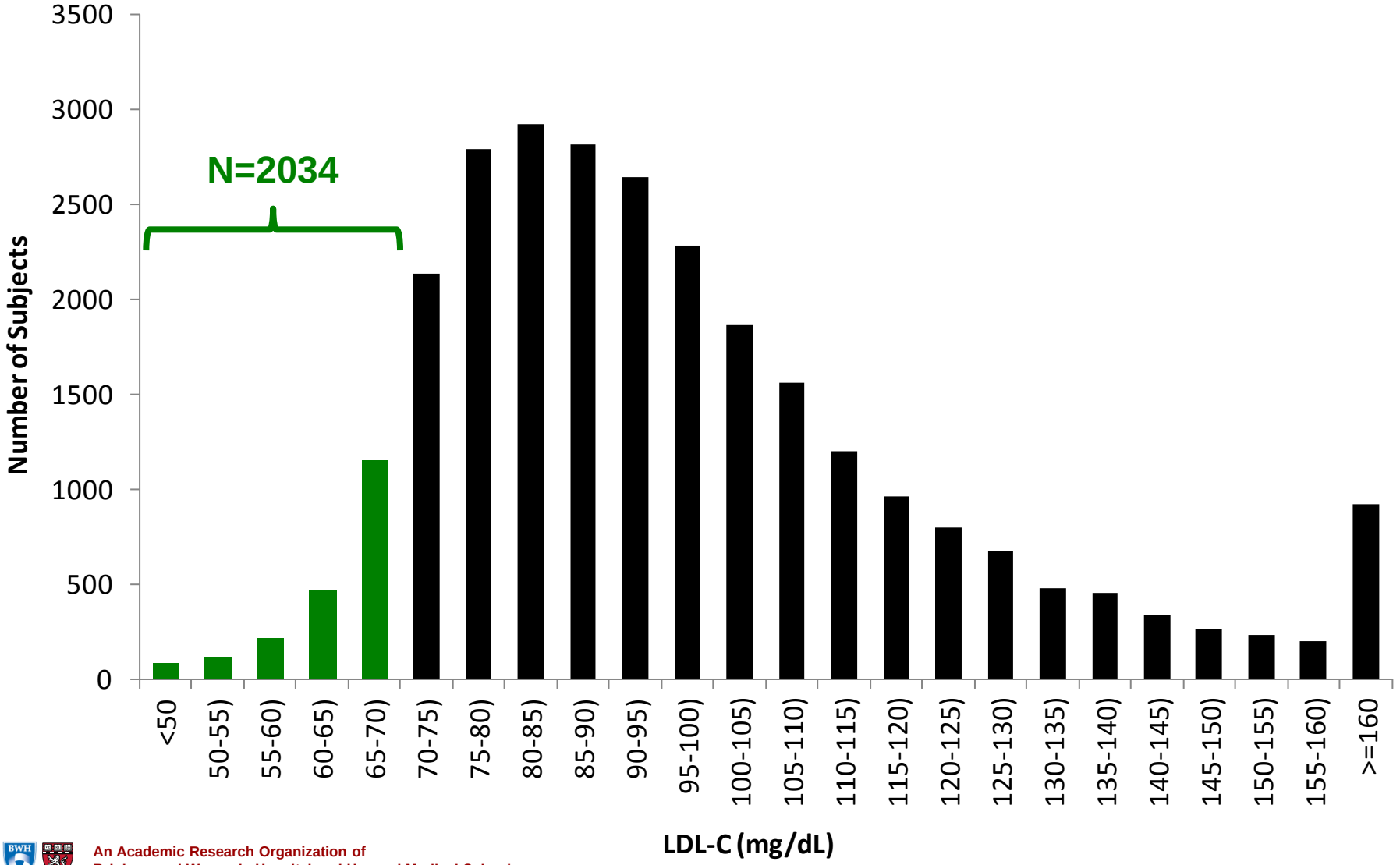


Safety

	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events (%)		
Any	77.4	77.4
Serious	24.8	24.7
Allergic reaction	3.1	2.9
Injection-site reaction	2.1	1.6
Treatment-related and led to d/c of study drug	1.6	1.5
Muscle-related	5.0	4.8
Cataract	1.7	1.8
Diabetes (new-onset)	8.1	7.7
Neurocognitive	1.6	1.5
Laboratory results (%)		
Binding Ab	0.3	n/a
Neutralizing Ab	*none*	n/a

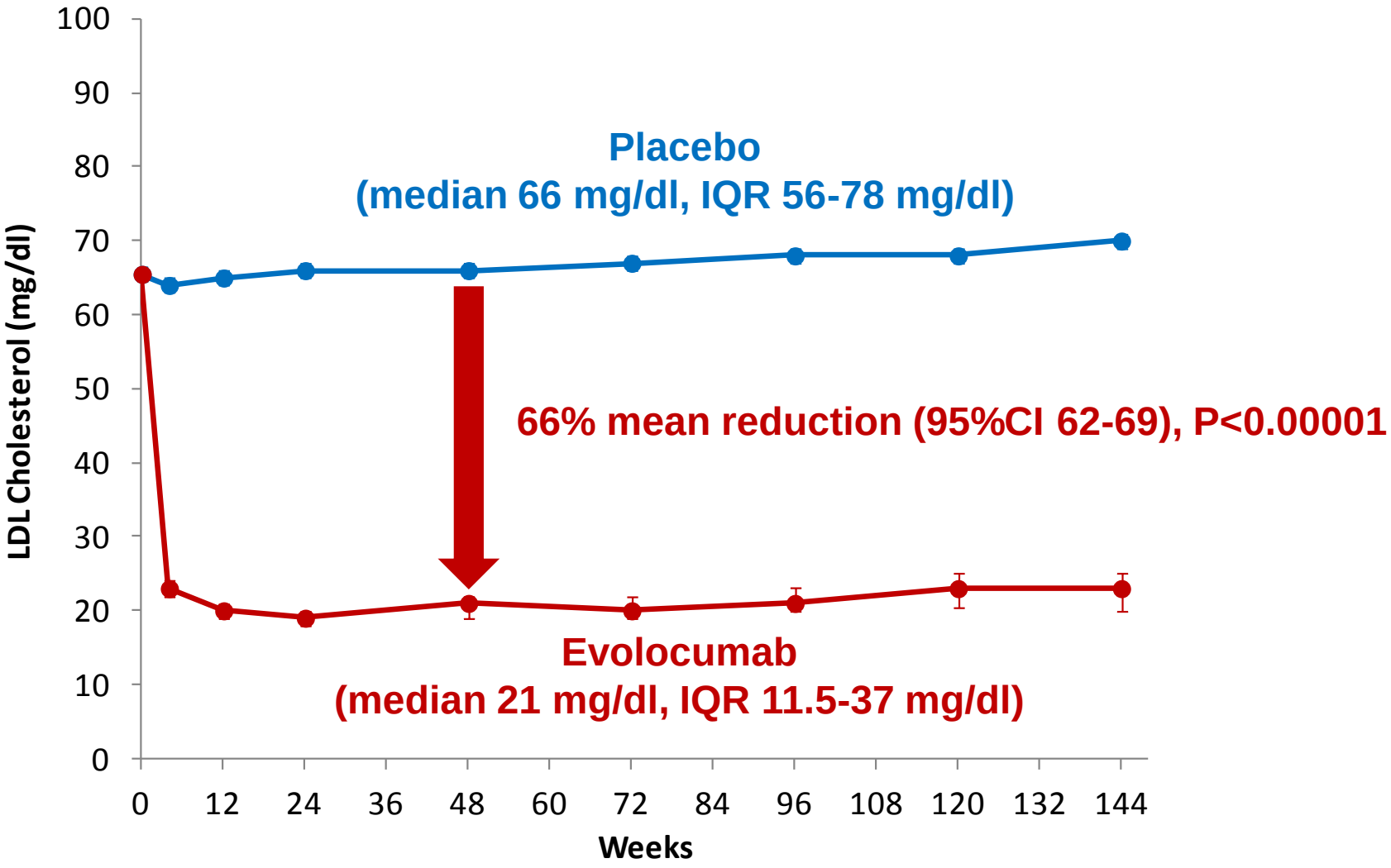
New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC

Baseline LDL-C

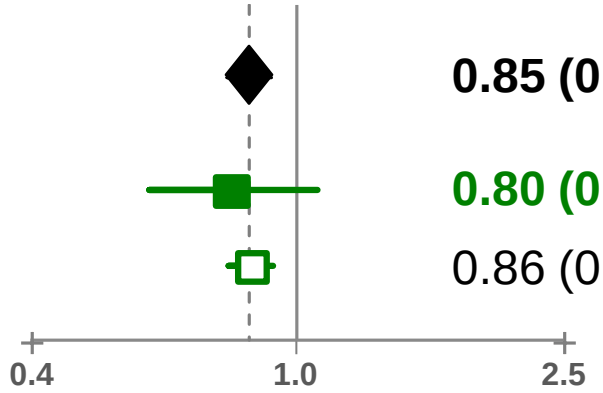


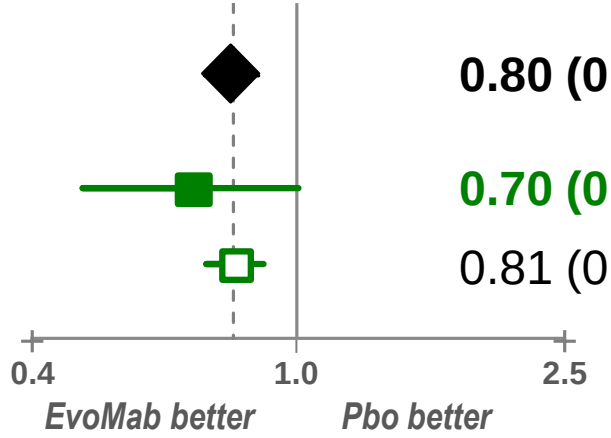
LDL Cholesterol

In patients with baseline LDL-C<70 mg/dL



Clinical Outcomes
by Baseline LDL-C





Safety

In patients with baseline LDL-C<70 mg/dL

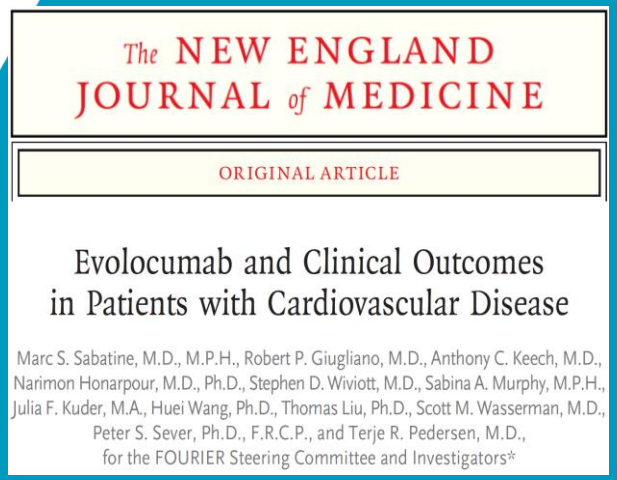
	Evolocumab (N=1030)	Placebo (N=1003)
Adverse events (%)		
Any	79.7	77.9
Serious	26.0	27.3
Allergic reaction	3.8	3.3
Injection-site reaction	2.9	1.6
Treatment-related and led to d/c of study drug	1.8	1.9
Muscle-related	4.8	6.0
Cataract	1.8	1.6
Diabetes (new-onset)	8.8	11.2
Neurocognitive	1.7	1.2
Laboratory results (%)		
ALT or AST >3× ULN	2.7	2.3
CK >5× ULN	0.9	0.9

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC.
No significant interactions between baseline LDL-C, evolocumab, and the rates of adverse events.

Odyssey CardioVascular Outcomes Trials (Odyssey CVOTs) [alirocumab]

V.S.

FOURIER study (Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) [evolocumab]


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

SANOFI REGENERON

ODYSSEY OUTCOMES & FOURIER Study Populations

	ODYSSEY OUTCOMES	FOURIER
Patient population	Recent ACS (4-52 weeks)	MI, stroke, symptomatic PAD, plus risk factors
Duration	Median 33 months 2-to-5 years follow-up	Median 26 months 1-to-3.5 years follow-up
% High-intensity statins	89.5%	69.2%

Schwartz GG. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of ODYSSEY outcomes trial. Am Heart J. 2014 Nov.

ODYSSEY OUTCOMES & FOURIER

Primary Endpoints

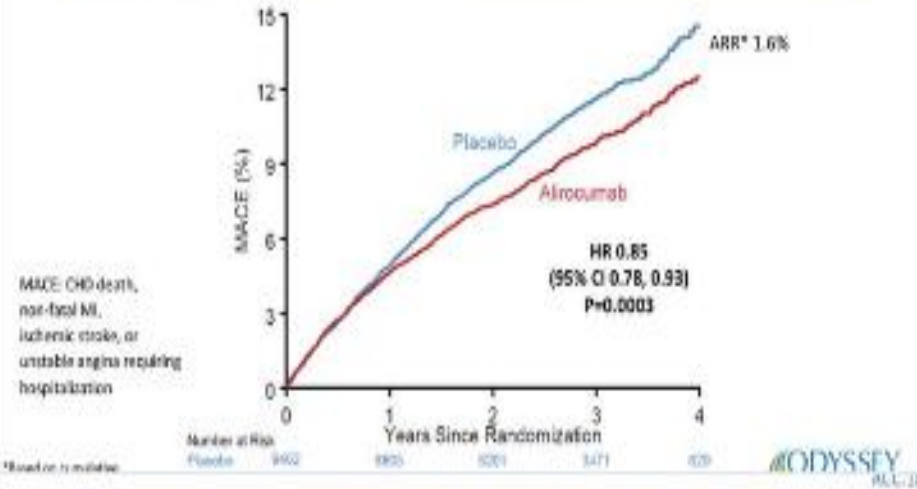
FOURIER is powered on the key secondary endpoint: composite of CV death, MI or stroke

	ODYSSEY OUTCOMES	FOURIER
CHD death	X	
CV death		X
MI	X (non-fatal)	X
Stroke	X (fatal/non-fatal)	X (ischemic or hemorraghic)
UA requiring hospitalization	X	X
Coronary revascularization		X

CHD: Coronary Heart Disease MI: Myocardial Infarction CV: Cardiovascular UA: Unstable Angina

Schwartz GG. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of ODYSSEY outcomes trial. Am Heart J. 2014 Nov.

Primary Efficacy Endpoint: MACE



ODYSSEY

Main Secondary Efficacy Endpoints: Hierarchical Testing

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
CHD event	1199 (12.7)	1349 (14.3)	**0.88 (0.81, 0.95)**	**0.001**
Major CHD event	793 (8.4)	899 (9.5)	**0.88 (0.80, 0.96)**	**0.006**
CV event	1301 (13.7)	1474 (15.6)	**0.87 (0.81, 0.94)**	**0.0003**
Death, MI, ischemic stroke	973 (10.3)	1126 (11.9)	**0.86 (0.79, 0.93)**	**0.0003**
CHD death	205 (2.2)	222 (2.3)	0.92 (0.76, 1.11)	0.38
CV death	240 (2.5)	271 (2.9)	0.88 (0.74, 1.05)	0.15
All-cause death	334 (3.5)	392 (4.1)	**0.85 (0.73, 0.98)**	**0.026***

Efficacy: Subgroup with Baseline LDL-C ≥100 mg/dL (Median Baseline LDL-C 118 mg/dL)

Endpoint, n (%)	Alirocumab (N=2814)	Placebo (N=2815)	Absolute risk reduction (%)	HR (95% CI)
MACE	324 (11.5)	420 (14.9)	3.4	**0.76** (0.65, 0.87)
CHD death	69 (2.5)	96 (3.4)	1.0	**0.72** (0.53, 0.98)
CV death	81 (2.9)	117 (4.2)	1.3	**0.69** (0.52, 0.92)
All-cause death	114 (4.1)	161 (5.7)	1.7	**0.71** (0.56, 0.90)

ODYSSEY

Conclusions

Compared with placebo in patients with recent ACS, alirocumab 75 or 150 mg subcutaneous Q2W targeting LDL-C levels 25–50 mg/dL, and allowing levels as low as 15 mg/dL:

1. Reduced MACE, MI, and ischemic stroke
2. Was associated with a lower rate of all-cause death
3. Was safe and well-tolerated over the duration of the trial

ODYSSEY

Outlines

- Introduction
- The development PCSK9-inhibitor
- The pharmacodynamics and pharmacokinetic of evolocumab (repatha)
- GLAGOV :coronary atherosclerotic plaque
- FOURIER/Odyssey : long-term CV outcomes
- EBBINGHAUS: neurocognitive function
- Take home message

EBBINGHAUS:

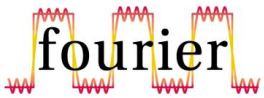
- *A Cognitive Study of Patients Enrolled in the FOURIER Trial*

RP Giugliano, F Mach, K Zavitz, AC Keech, TR Pedersen,
MS Sabatine, P Sever, C Kurtz, N Honarpour, BR Ott,
on behalf of the EBBINGHAUS Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 18, 2017

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Trial Design



RANDOMIZED
DOUBLE BLIND

Placebo SC
Q2W or QM

Evolocumab SC
140 mg Q2W or 420 mg QM

2442 patients screened for EBBINGHAUS

MAJOR EXCLUSIONS
1. Not enrolled in FOURIER
2. >12 wk FOURIER visit
3. H/O dementia, cognitive impairment or other conditions interfering with participation

1974 Enrolled (Full Analysis Pop)
Median F/U 19.8 months

Primary Analysis Cohort (N=1204)
Baseline cognitive testing on/before 1st dose of study drug and had f/u cognitive testing post dosing*

Additional 770 pts w/ baseline assessment before week 12 visit

*Cognitive tests performed at baseline; at 6, 12, 24 months; and end of study

Giugliano RP et al. *Clin Card* 2017;40:59–65

Endpoints

1. **Cambridge Neuropsychological Test Automated Battery (CANTAB) Assessments, a standardized, well-validated computer tablet-based testing platform.**
   Assessed at baseline, 6, 12, 24, 48 mos and study end.
   - **Primary:** **Spatial working memory strategy index of executive function**
   - Secondary: Spatial working memory between errors
     Paired associates learning
     Reaction time
   - Exploratory: Global score (combines above 4 tests)
2. **Patient survey of everyday cognition* at study end**
3. **Investigator report of cognitive AEs**

*Memory and executive function domains

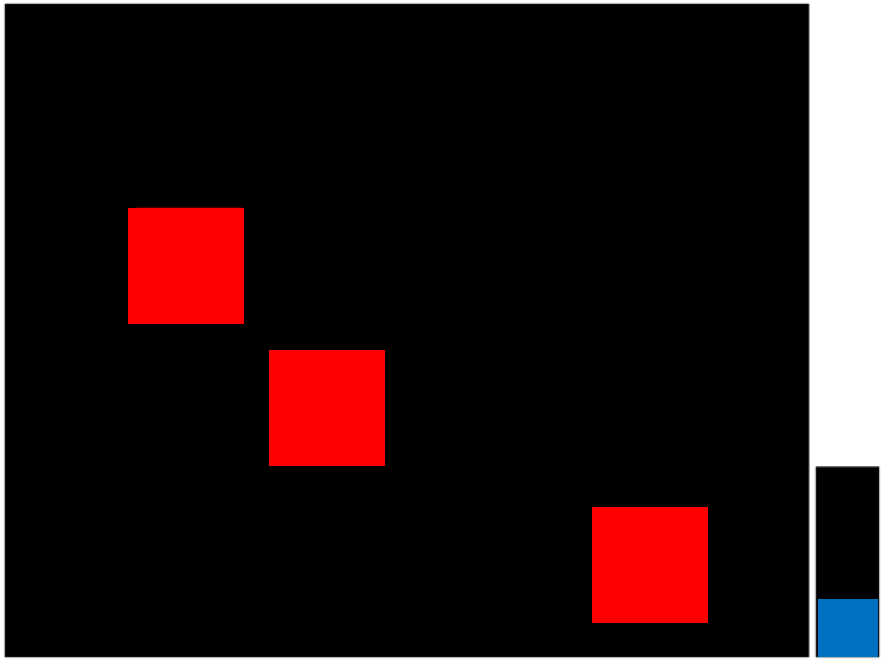
Owen 1990 PMID: 2267054; Sahakian 1988, PMID: 3382917; Owen 1996 PMID: 8714706; Kollins PMID: 21476931

Giugliano RP et al. *Clin Card* 2017;40:59-65

CANTAB - Spatial Working Memory (SWM)

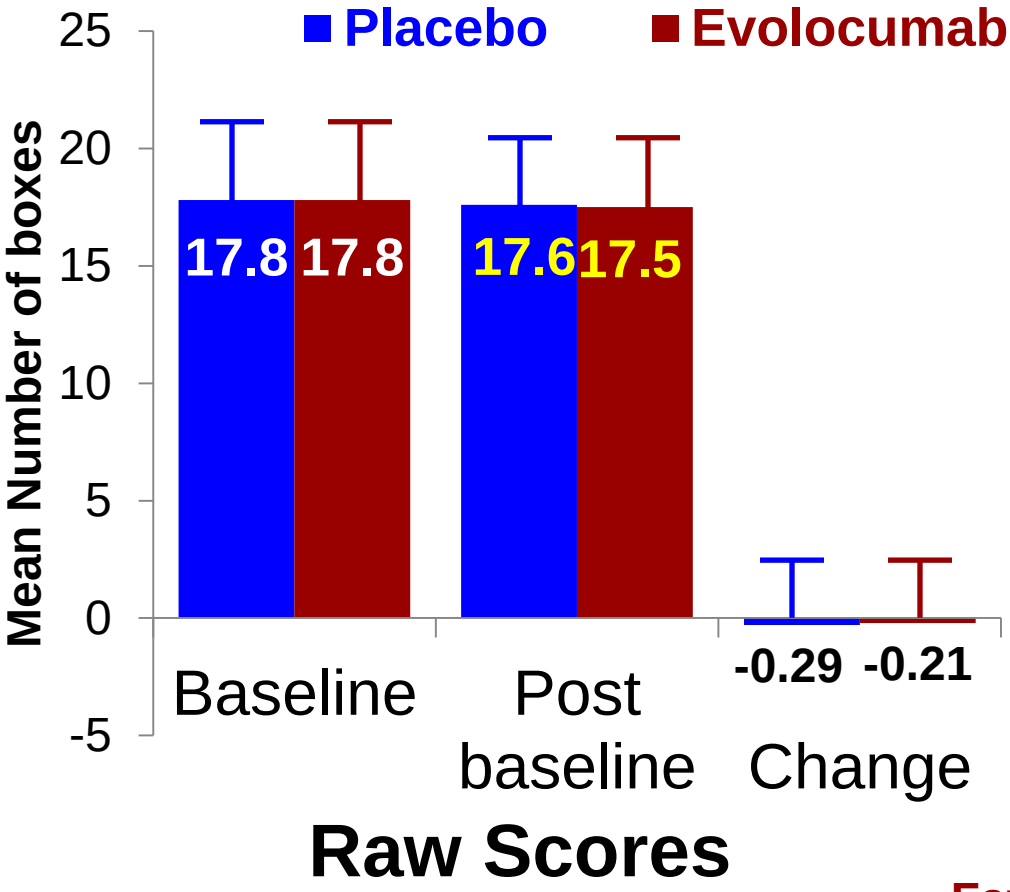
- Search for the blue token hidden within a red box
- Number of red boxes increases each round (3, 4, 6, 8).
- Critical instruction*: Do not return to a box where a blue token was found.*

SWM strategy index: = # inefficient searches started. Range 4-28.

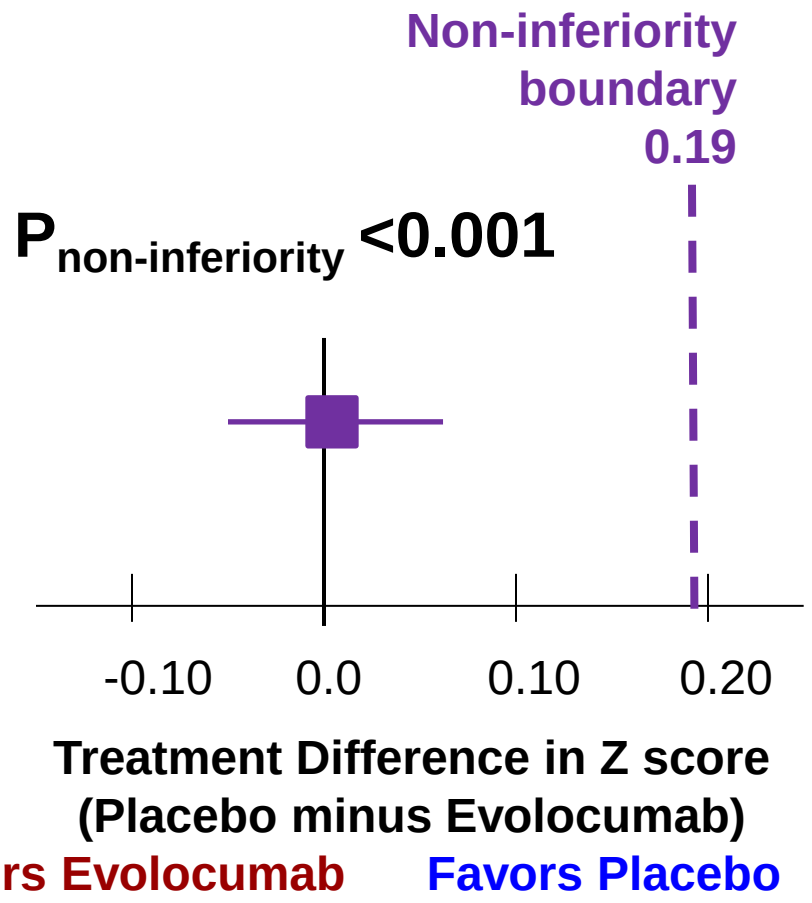


Lower scores represent better performance

Primary Endpoint
Spatial Working Memory Strategy Index

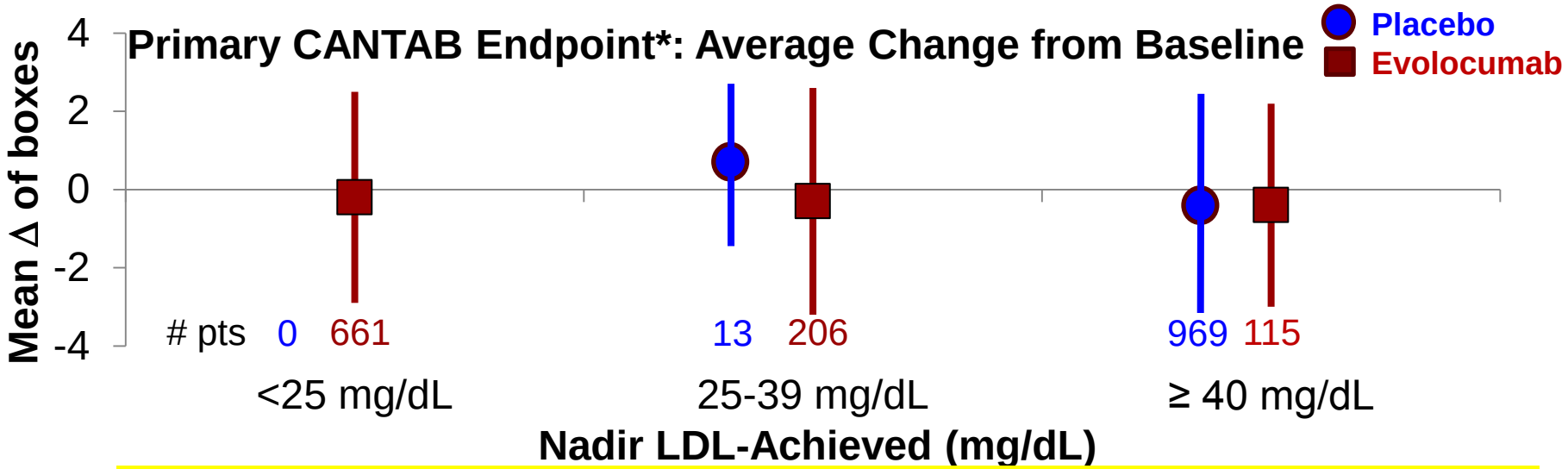


Raw Scores

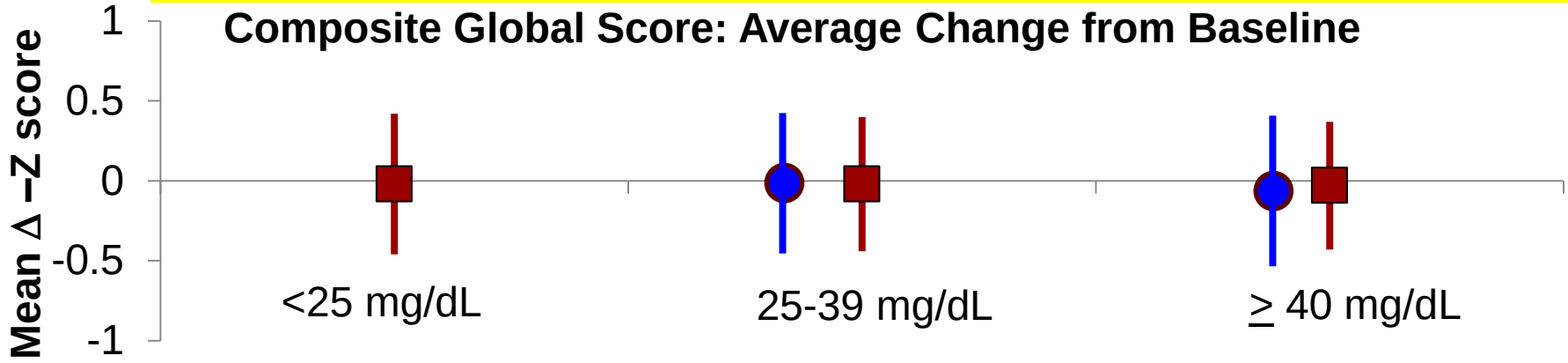


P_{NI} is from fixed estimate

Cognitive Assessments by Nadir Achieved LDL-C and Treatment (Full Pop)



P=NS across LDL values achieved and also between treatments



Negative score -> improvement
Lower scores are better

*Spatial working memory strategy index of executive function, raw score

Patient Self-Report: 23 Questions Regarding Everyday Cognition

All Patients	Placebo (N=781) Mean (SD)	Evolocumab (N=800) Mean (SD)	P-Value
Memory	1.16 (0.39)	1.17 (0.39)	0.81
Executive functioning total score	1.11 (0.32)	1.12 (0.32)	0.28
Planning	1.08 (0.31)	1.10 (0.32)	0.20
Organization	1.09 (0.32)	1.10 (0.33)	0.57
Divided attention	1.15 (0.42)	1.16 (0.41)	0.54
Total Score	**1.13 (0.33)**	**1.14 (0.33)**	**0.42**

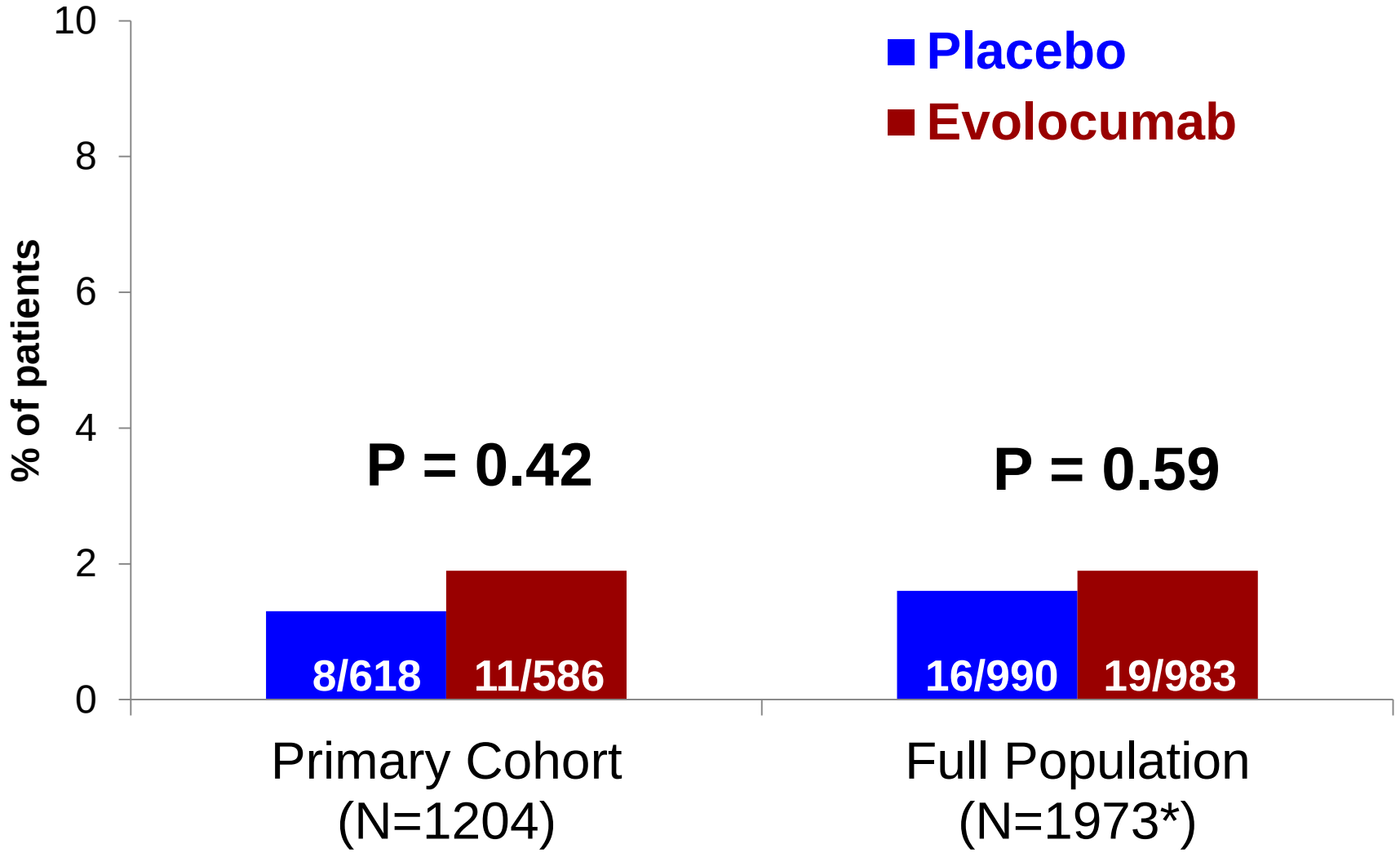
Patient self-report at end of study as compared to randomization, graded as

1. *Better or no change*
2. *Questionable / occasionally worse*
3. *Consistently a little worse*
4. *Consistently much worse*

Lower scores represent better cognition

Results shown are in the full study population

Investigator Reported Cognitive Adverse Events



Data shown are % of patients with at least 1 event

*1 patient who did not take study drug is excluded from the evolocumab group

Outlines

- Introduction
- The development PCSK9-inhibitor
- The pharmacodynamics and pharmacokinetic of evolocumab (repatha)
- GLAGOV :coronary atherosclerotic plaque
- FOURIER/Odyssey : long-term CV outcomes
- EBBINGHAUS: neurocognitive function
- Take home message

Take home message

- Lower is better !
- PCSK9-inhibitor is a novel drug to decrease LDL through the recycle of LDL receptor by binding with PCSK9
- Several phase II/III trials revealed the efficacy and safety of evolocumab (repatha) in combination therapy, monotherapy, statin intolerant, HeFH/HoFH patients
- From GLAGOV trial, addition of evolocumab in statin-treated patients, 420 mg monthly can achieve LDL-C levels averaging 36.6 mg/dL compared with 93 mg/dL for a statin alone. Produced plaque regression, mean change in PAV of -0.95% vs. +0.05% ($P < 0.001$).
- From FOURIER trial, PCSK9 inhibition with evolocumab significantly reduce major cardiovascular events and safely when added to statin therapy. The Odyssey trial showed similar results
- The EBBINGHAUS study showed that no evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL
-


Thank you for your attention!!