Holistic Care for the Patients with CVD 2018

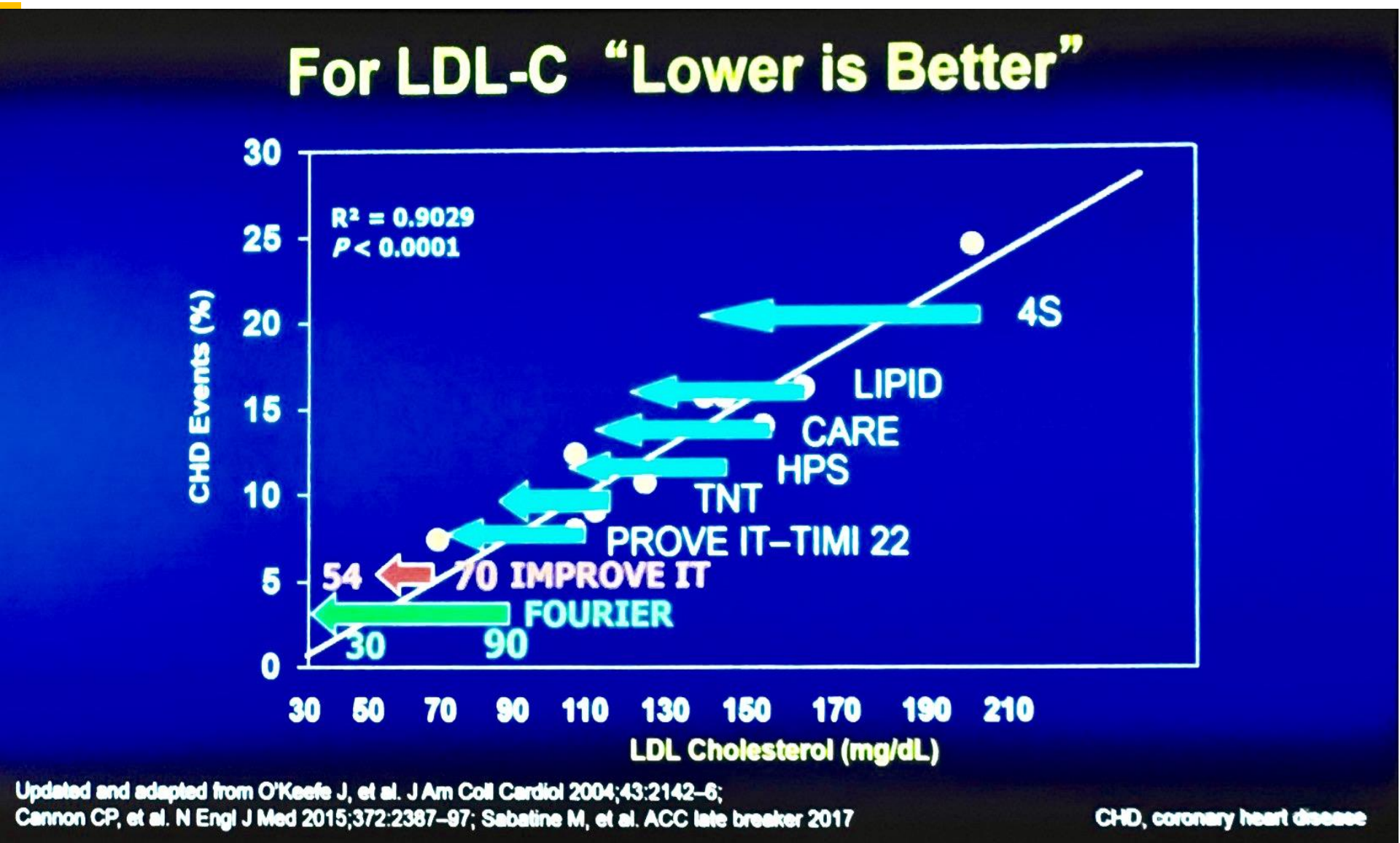
Evolocumab: A New Solution to Lower LDL-C Level

高醫大血脂生科研究中心
高雄市立大同醫院(高醫)
心臟血管內科
Chih-Sheng Chu, MD, PhD
朱志生 主治醫師

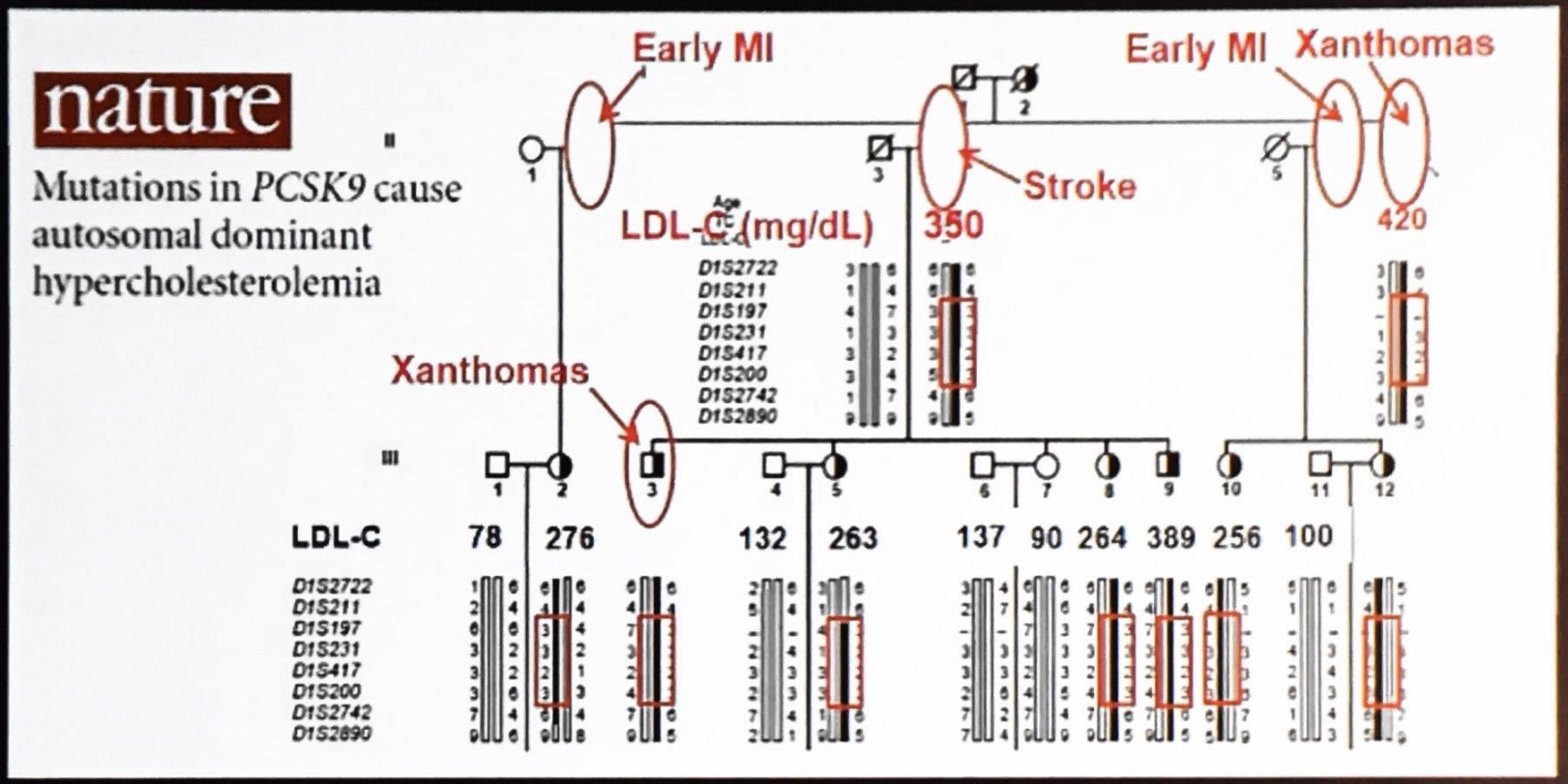
Repatha™ (evolocumab) injection 140 mg/mL

台灣血脂衛教協會
2018-04-01 (Sun)

PCSK9 inhibitor pushs the LDL-goal to 30 mg/dL



Discovery of Proprotein Convertase Subtilisin Kexin Type 9 (*PCSK9*)



PCSK9 is the third locus for autosomal dominant hypercholesterolemia (ADH): Gain-of-Function mutations in PCSK9

Abifadel M, et al. Nature Genet. 34: 154-156, 2003.

Gain-of-Function Mutations in PCSK9 Cause Familial Hypercholesterolemia*†

PCSK9 Variant	Population	Clinical/Biochemical Characteristics
D374Y[1]	British, Norwegian families, 1 Utah family	Tendon xanthomas, severe hypercholesterolemia
S127R[1]	French, South African, Norwegian families	Tendon xanthomas
R218S[2]	French families	Tendon xanthomas, arcus corneae

- Associated with:
  - High serum LDL-C[1]
  - In vitro testing in many identified mutations shows decreased levels of LDLRs[3]

*Autosomal Dominant Hypercholesterolemia

2003, two gain-of-function genetic mutations of PCSK9 in a French family was identified. This is the third autosomal dominant mutation for FH in addition to mutations in LDL-R and ApoB genes.

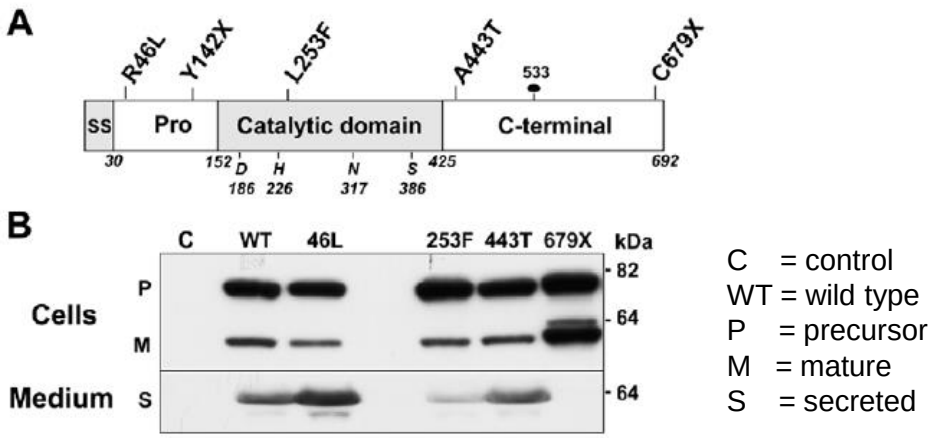
1. Abifadel M, et al. *Hum Gen*. 2009;30:520-529. **2.** Lopez D. *Biochem Biophys Acta*. 2008;1781:184-191.
3. Cameron J, et al. *Hum Mol Genet*. 2006;15:1551-1558.

†For a full list of ADH mutations, please refer to Abifadel reference.

Loss-of-Function Mutations in PCSK9 Are Associated With Decreased LDL-C

PCSK9 Variant	Population	LDL-C
R46L	ARIC[1], DHS[2]	↓ 15%[1]
Y142X or C679X	ARIC[1], DHS[2]	↓ 28%–40%[1]
R46L	CGPS[3]	↓ 11%[3]

- Heterozygous LOF mutations found in 1% to 3% of representative populations[1,3]
- Associated with
  - Lower serum LDL-C[1]



C = control
WT = wild type
P = precursor
M = mature
S = secreted

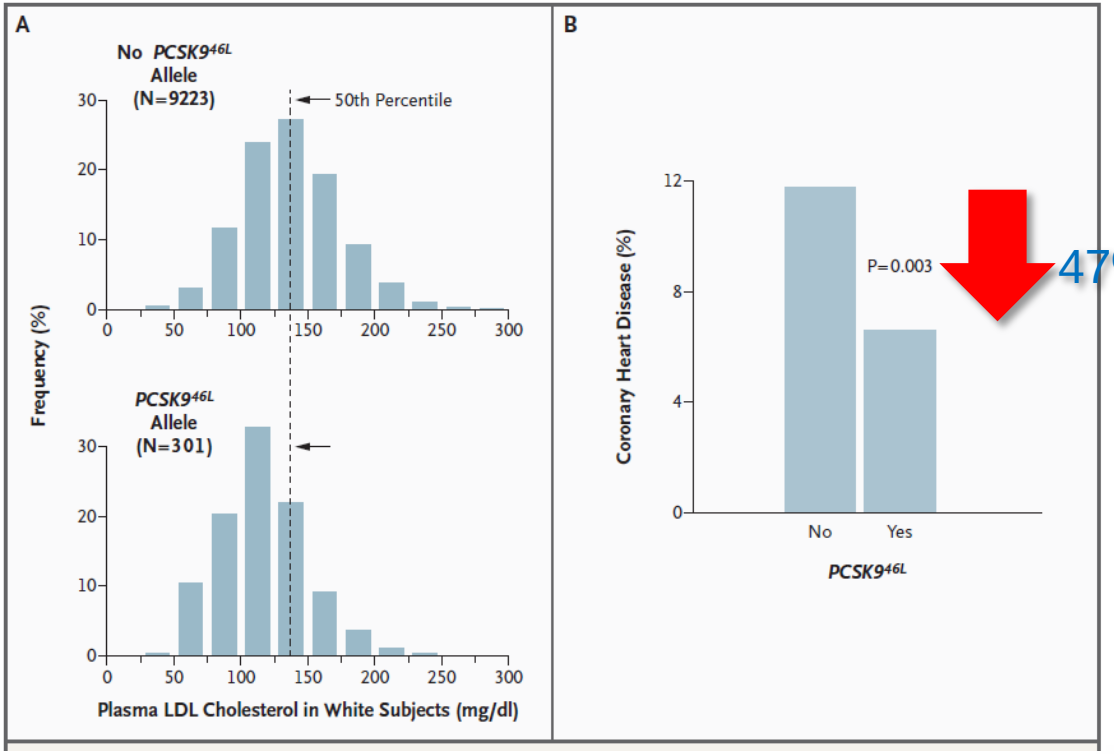
LOF = loss of function
ARIC = Atherosclerosis Risk in Communities (N ~ 4,000); DHS = Dallas Heart Study (N = 3,553);
CGPS = Copenhagen General Population Study (N = 26,013)

1. Cohen JC, et al. *N Engl J Med*. 2006;354:1264-1272. **2.** Cohen J, et al. *Nat Genet*. 2005;37:161-165
3. Benn M, et al. *J Am Coll Cardiol*. 2010;55:2833-2842. **4.** Zhao Z, et al. *Am Journal of Hum Gen*. 2006;79:514-534.

Sequence variations in PCSK9, low LDL, and protection against coronary heart disease

Incidence of CHD (myocardial infarction, fatal CHD, or coronary revascularization) over a 15-year interval in the Atherosclerosis Risk in Communities study

•Of 9524 white subjects examined, 3.2% had sequence variations in *PCSK9* with **15%** reduction in **LDL-C** and 47% reduction in the CHD risk (hazard ratio, 0.50; 95 percent confidence interval, 0.32 to 0.79; P=0.003).



Cohen, Jonathan C., et al. "Sequence variations in PCSK9, low LDL, and protection against coronary heart disease." *New England Journal of Medicine* 354.12 (2006): 1264-1272.

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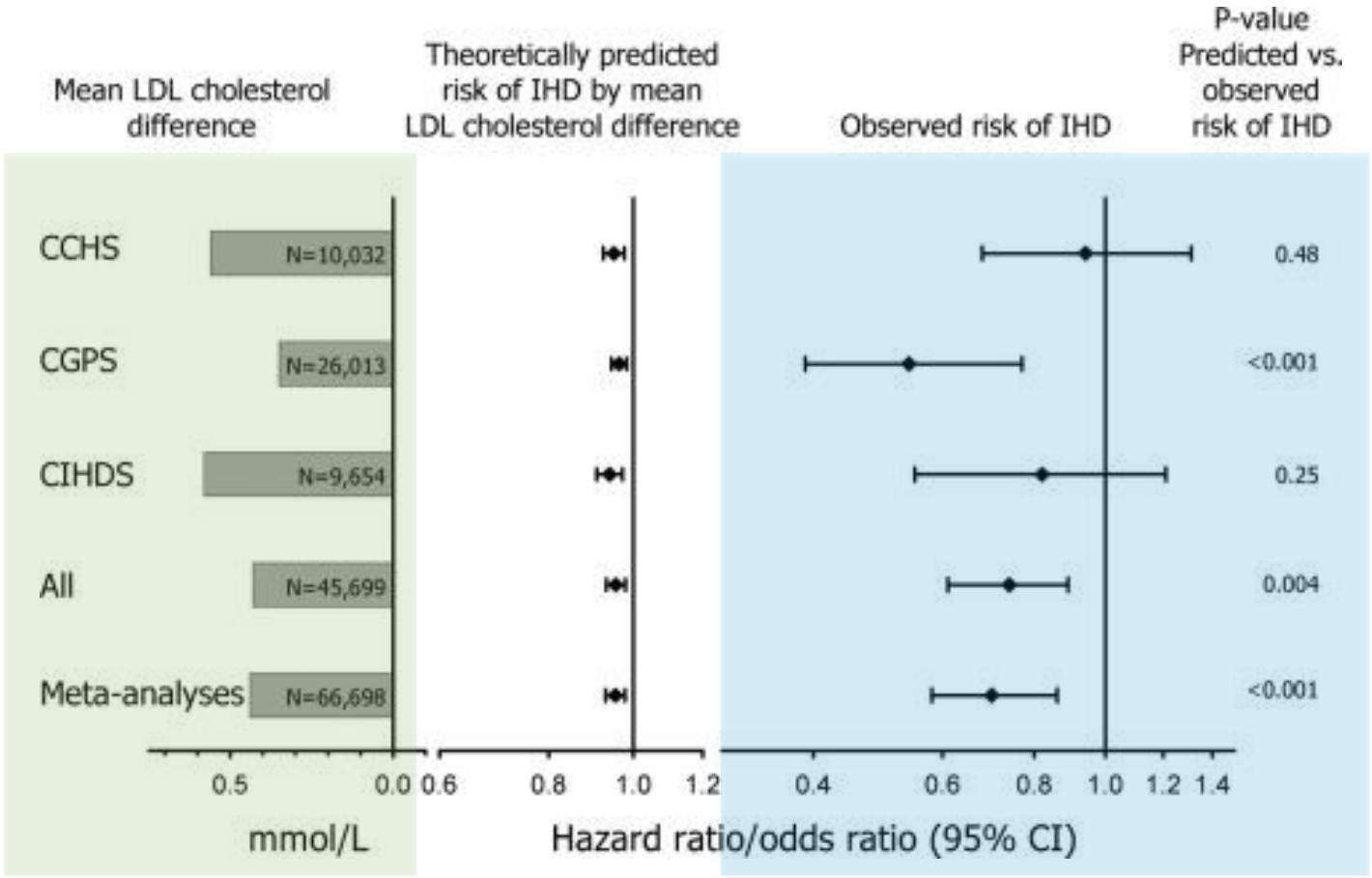
PCSK9 R46L, LDL-C and Risk of Ischemic Heart Disease
3 independent Studies and Meta-Analyses

The reduction in risk of IHD was larger than predicted by the observed reduction in LDL-C alone. This could be because genotype is a better predictor of lifelong exposure to LDL-C than LDL-C measured in adult life.



Benn, Marianne, et al. "PCSK9R46L, Low-Density Lipoprotein Cholesterol Levels, and Risk of Ischemic Heart Disease: 3 Independent Studies and Meta-Analyses." *Journal of the American College of Cardiology* 55.25 (2010): 2833-2842.

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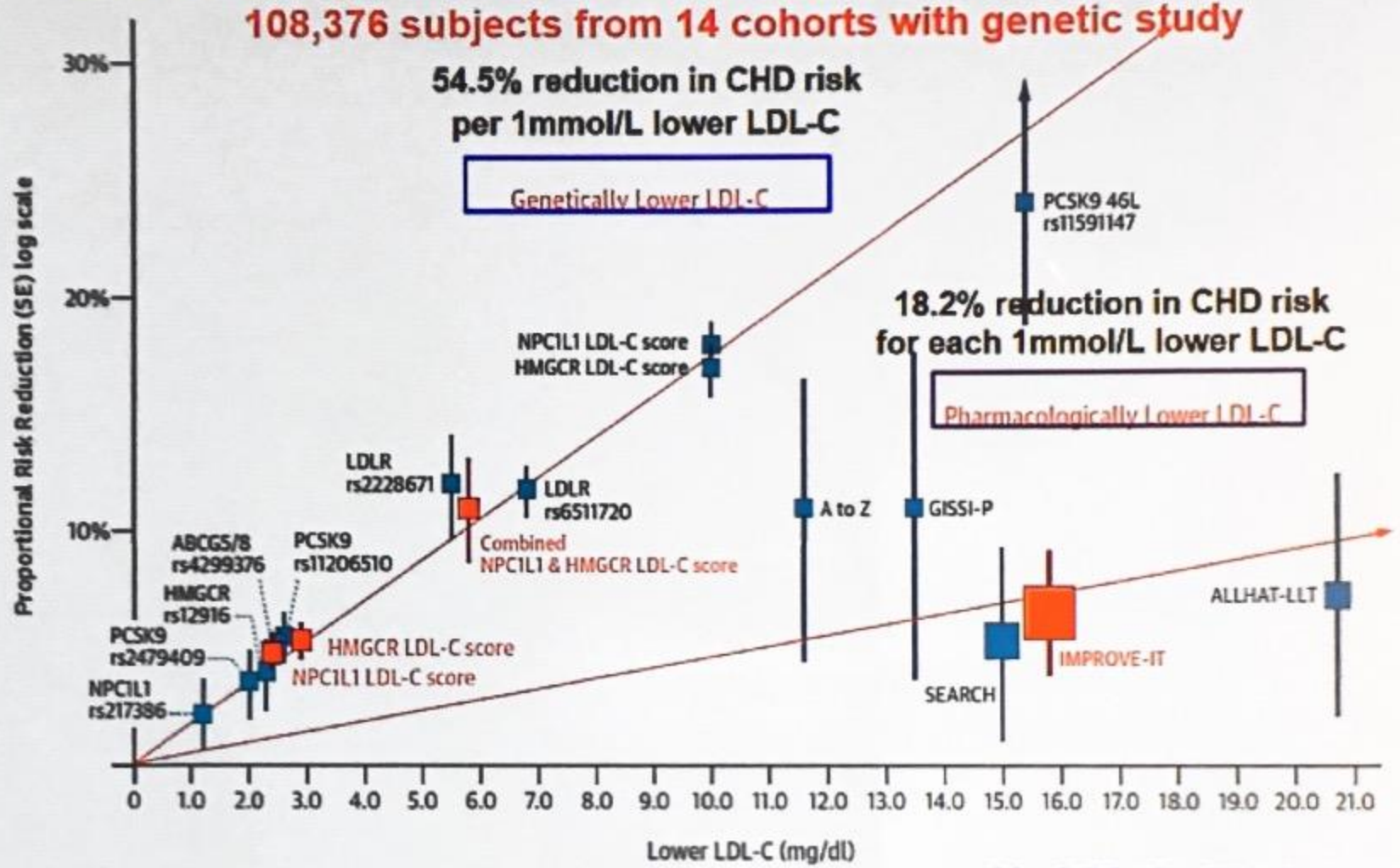
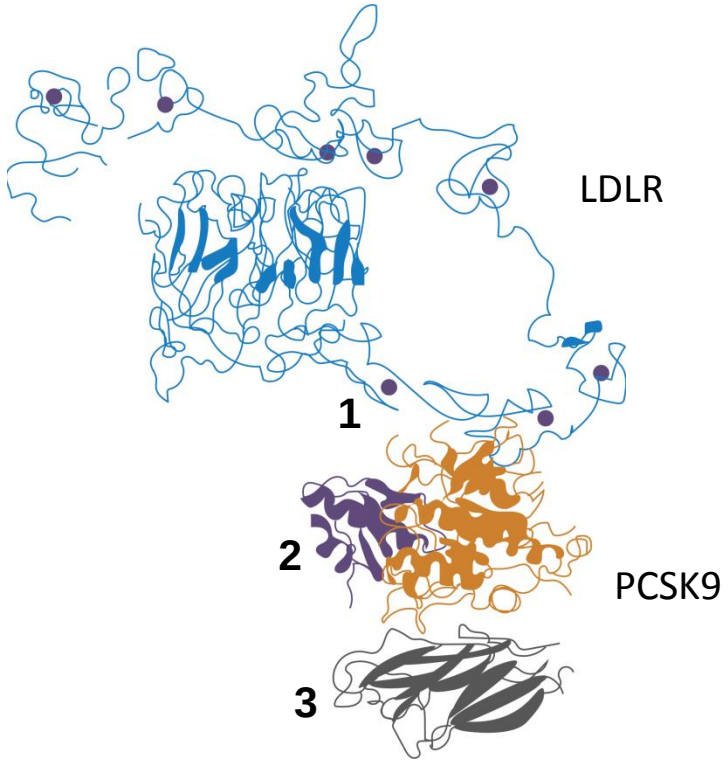
Lower LDL-C is associated with decreased CV risk



J Am Coll Cardiol. 2015 ;65:1552-61.

PCSK9 – Proprotein Convertase Subtilisin/Kexin type 9

- 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]
- 2006, Amgen first reported the crystal structure of human PCSK9 at 2.3Å resolution.

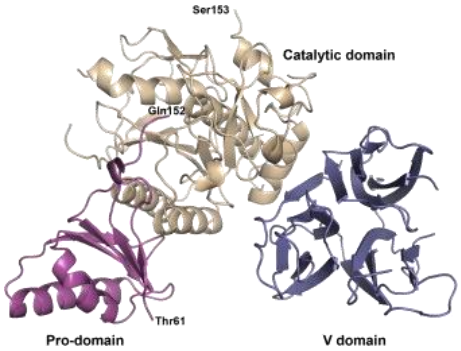


1. Catalytic domain 2. Prodomain 3. C-terminus

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.

AMGEN® Cardiovascular

The evolution of PCSK9 inhibition directed therapies



2006 Amgen first reported the crystal structure of human PCSK9 at 2.3Å resolution.

2007 PCSK9 Structure was published in journal of *Structure 15.5 (2007)*

2007 US patent WO2008109871 A8 of PCSK crystal structure was granted to Amgen.

2003

Identification of gain of function PCSK9 mutation as a cause of autosomal dominant hypercholesterolemia

2005

Role of PCSK9 in cholesterol regulation

2007

Unravelling of PCSK9 structure

Epidemiological studies o association of loss of function PCSK9 mutation and cardiovascular protection

2012

Antisense oligonucleotide pre-clinical data

Alirocumab Phase I Trial
- Stein et al.

Alirocumab Phase II Trials
- Alirocumab study 11565
- Alirocumab study 1003
- Alicorumab study 11566

Evolocumab Phase I Trial
- Dias et. Al

Evolocumab Phase II Trials
- RUTHERFORD
- LAPLACE-TIMI57
- MENDEL
- GAUSS

2014

ALN-PCS02 Phase I Trial (siRNA)

K-312 Phase I (PCSK9+CETP dual)

BMS-962476 Phase I (mimetic petide)

Bococizumab Phase II Trial

Alirocumab ODYSSEY Phase III
- ODYSSEY LONG TERM
- ODYSSEY ALTERNATIVE
- ODYSSEY HIGH FH
- ODYSSEY FH I and II
- ODYSSEY COMBO I and II
- ODYSSEY MONO

Evolocumab PROFICIO Phase III
- OSLER
- LAPLACE-2
- DESCARTES
- MENDEL-2
- RUTHERFORD-2
- GAUSS-2

2015

O-304 (AMPK & PCSK9 dual)

DS-9001 Phase I (multispecific Ab)

ATH-06 Phase I (PCSK9 vaccine)

MEDI-4166 Phase I Trial (mAb)

LY-3015014 Phase II Trial (mAb)

Alirocumab launch
- US 29-Jul-2015
- EU 31-Dec-2015

Evolocumab launch
- US 11-Sep-2015
- EU 30-Sep-2015

- Joseph, Lee, and Jennifer G. Robinson. "Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition and the future of lipid lowering therapy." *Progress in cardiovascular diseases* 58.1 (2015): 19-31.
- Piper, Derek E., et al. "The crystal structure of PCSK9: a regulator of plasma LDL-cholesterol." *Structure* 15.5 (2007): 545-552.

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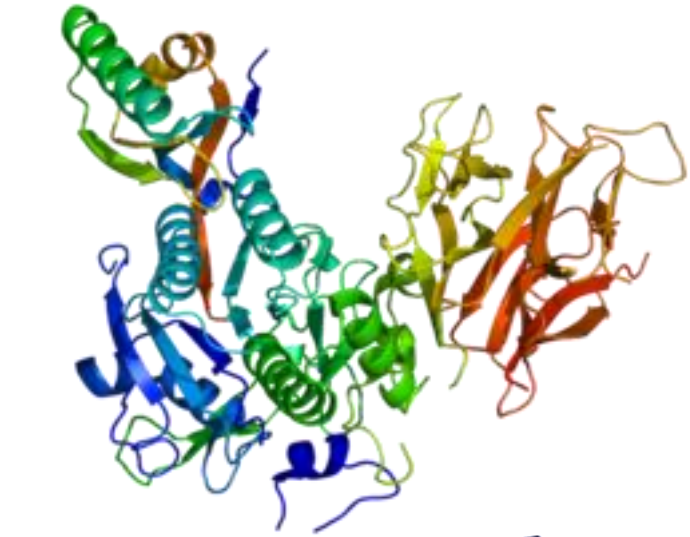
WHAT IS REPATHA® (evolocumab) 瑞百安 注射液?

- Repatha® is a human monoclonal IgG2 directed against human PCSK9.
- Repatha® binds to PCSK9 and inhibits circulating PCSK9 from binding to the low density lipoprotein (LDL) receptor (LDLR), preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface.
- By inhibiting the binding of PCSK9 to LDLR, Repatha® increases the number of LDLRs available to clear LDL from the blood, thereby lowering LDL-C levels.[1]



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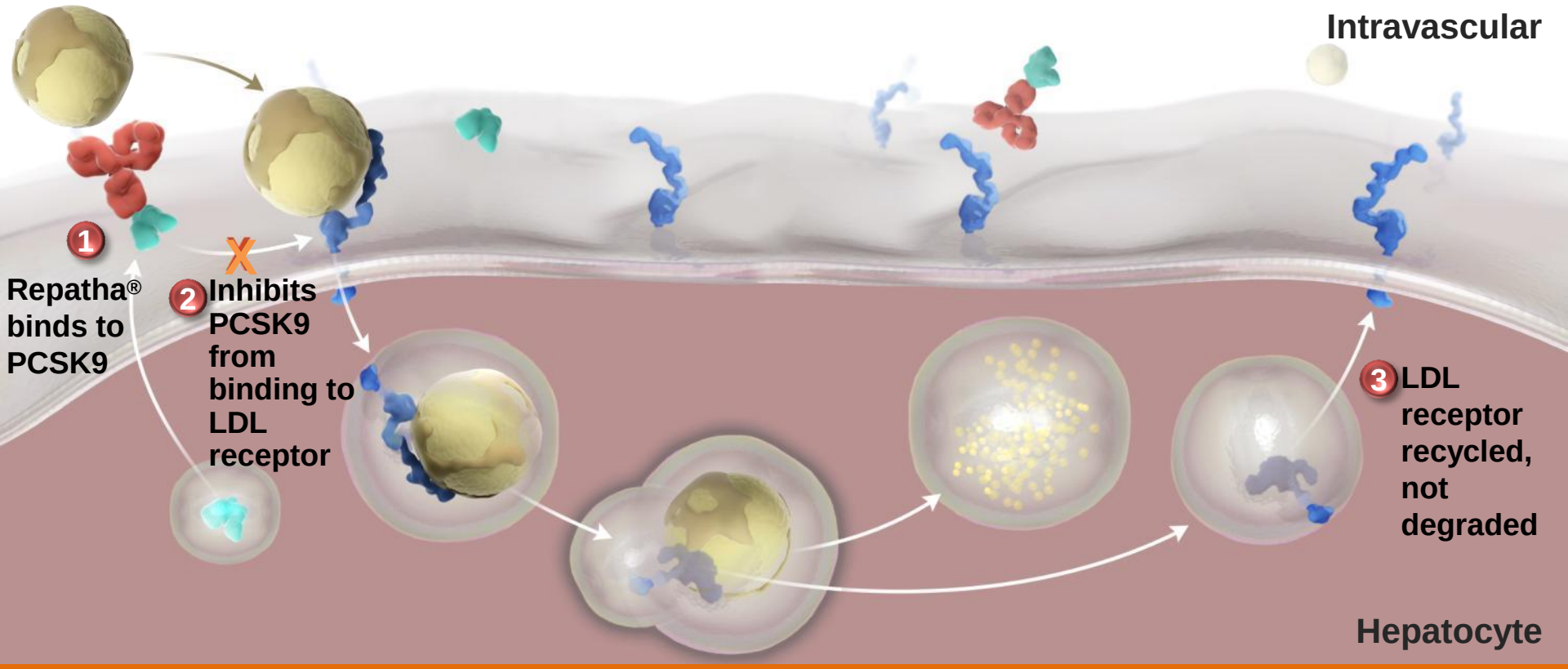
Repatha® Binds to PCSK9, Preventing PCSK9 From Binding to the LDL Receptor[1,2]



LDL receptors can recycle to hepatocyte surface to clear more plasma LDL

Repatha™ (evolocumab) injection 140 mg/mL

1. Repatha® (evolocumab) Prescribing Information, Amgen. 2. Stein AE, et al. *Drugs Future*. 2013;38:451-459.

AMGEN Cardiovascular

PCSK9 is an important new therapeutic target, with many approaches to inhibition

Type	Compound	Company
mAb	**Evolocumab (Repatha®)** AMG145	Amgen
	Alirocumab (Praluent®) REGN7272/SAR236553	Sanofi/Regeneron
	Bococizumab RN-316/PF-04950615	Pfizer/Rinat (stopped in late 2016)
	RG7652 (MPSK3169A)	Roche/Genentech (discontinued in Phase II)
	LY3015014	Eli Lilly
Adnectin	Ad. BMS-962476	BMS-Adnexus
siRNA	ALN-PCS	Alnylam Pharmaceuticals
Vaccine	AFFITOPE AT04A+adjuvant AFFITOPE AT06A+adjuvant	AFFiRiS AG
Small molecule	–	Shifa Biomedical Corp
Mimetic peptide	EGF-A peptide	Merck & Co.
	Prodomain and C-terminal domain interaction disruption	School of Medicine, University of South Carolina, USA

All except evolocumab and alirocumab currently have no marketing authorisation

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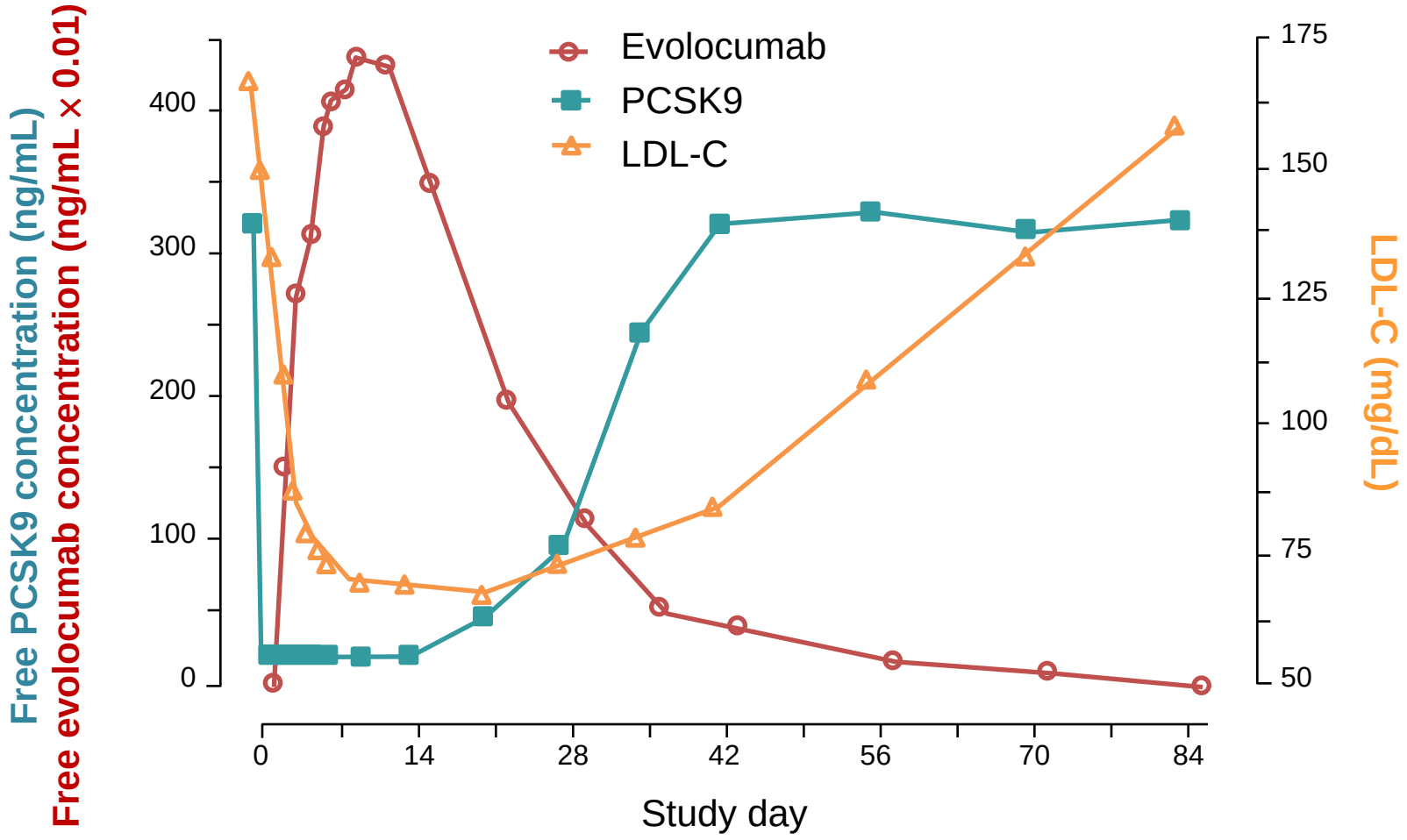
Evolocumab produces rapid suppression of PCSK9 and LDL-C levels in single dose



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

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Evolocumab is being clinically evaluated in the PROFICIO trial programme

>35,000 patients

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

✓ Completed trials

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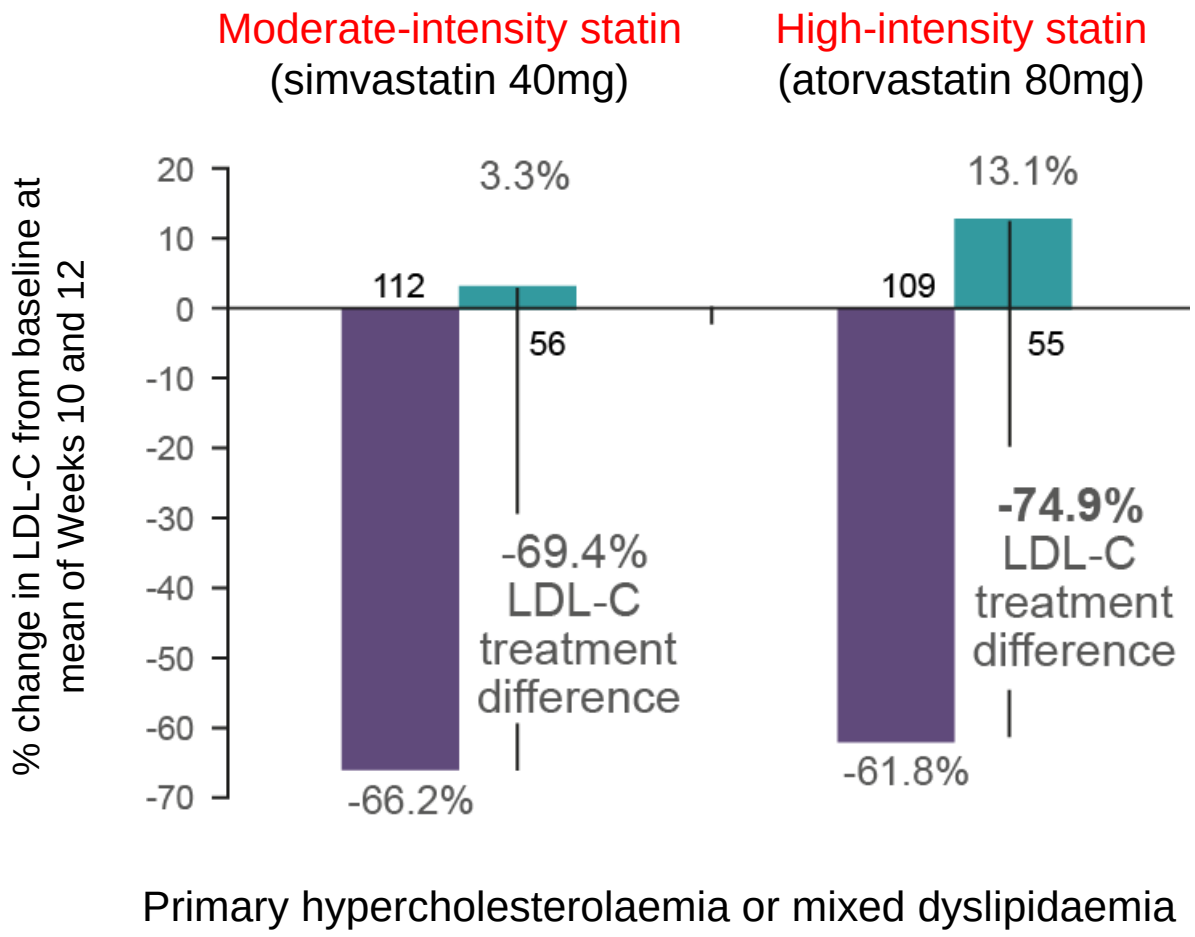
Evolocumab in combination with stain reduces LDL-C by up to 75% versus placebo



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

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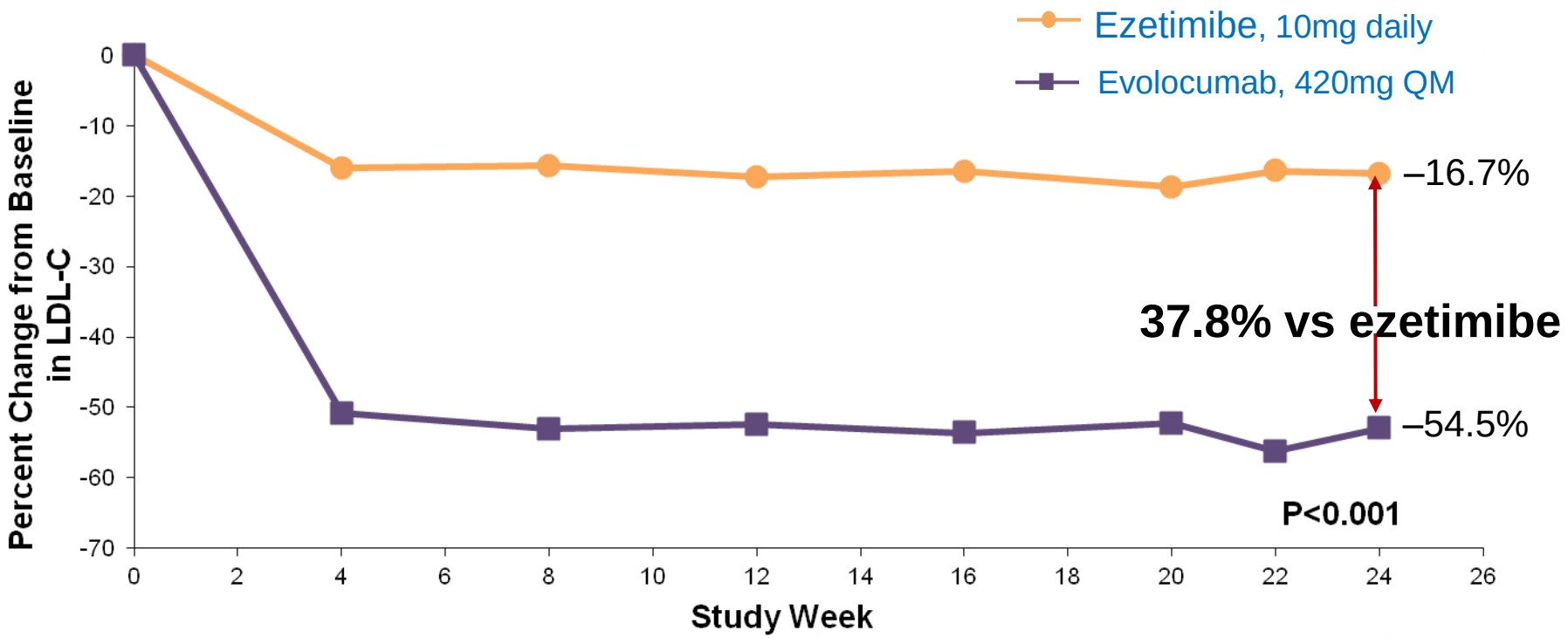
Evolocumab significantly reduces LDL-C in statin-intolerant patients in 24-week study



Ezetimibe N=73	72	70	67	67	64	60	57
Evolocumab N=145	142	142	139	137	127	127	117

Treatment difference of evolocumab vs ezetimibe was -37.8% at mean of weeks 22 and 24 (P<0.001)

Nissen et al. JAMA 2016;315:1580–90.

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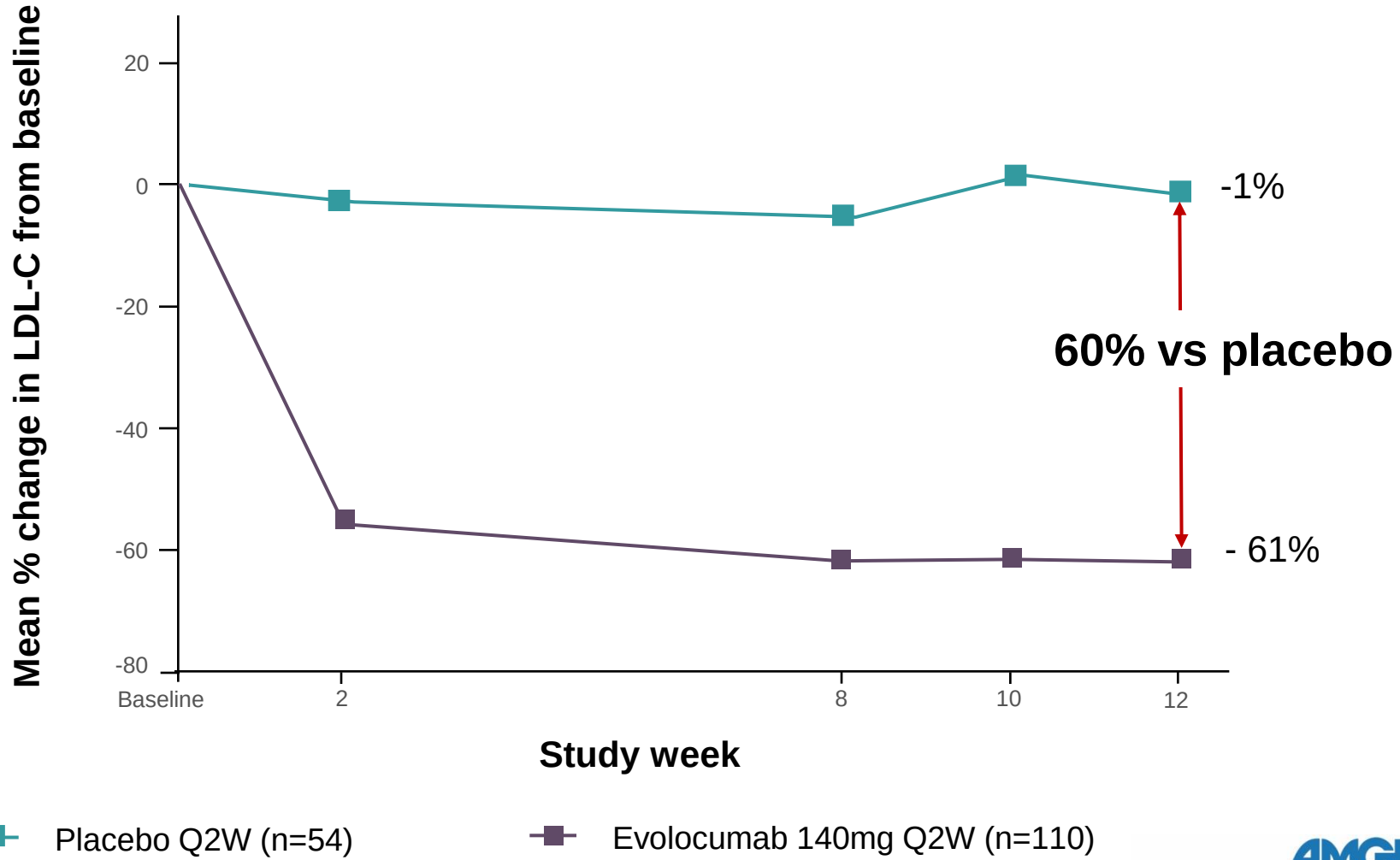
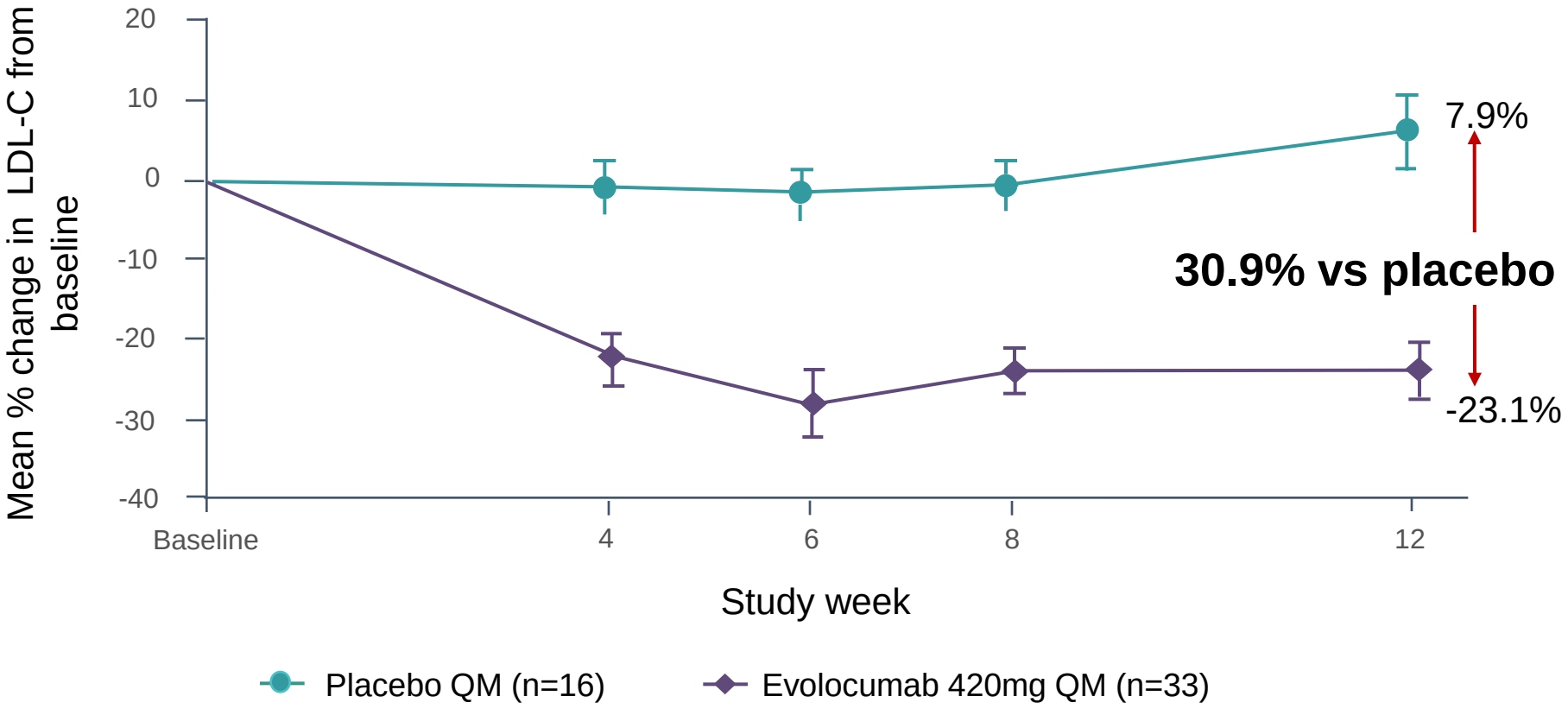
Evolocumab significantly reduces LDL-C in patients with heterozygous FH



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.

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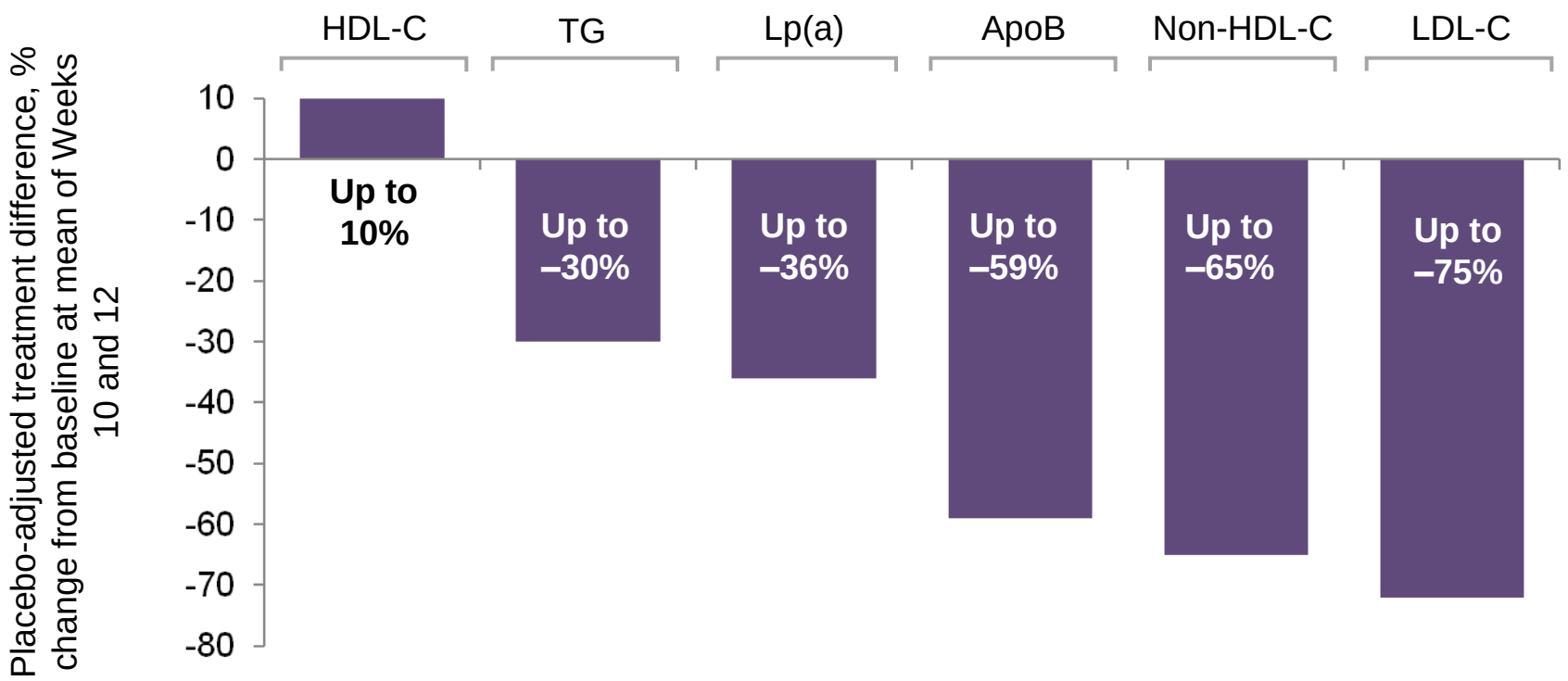
Evolocumab markedly reduces other atherogenic lipids and modestly increases HDL-C



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.

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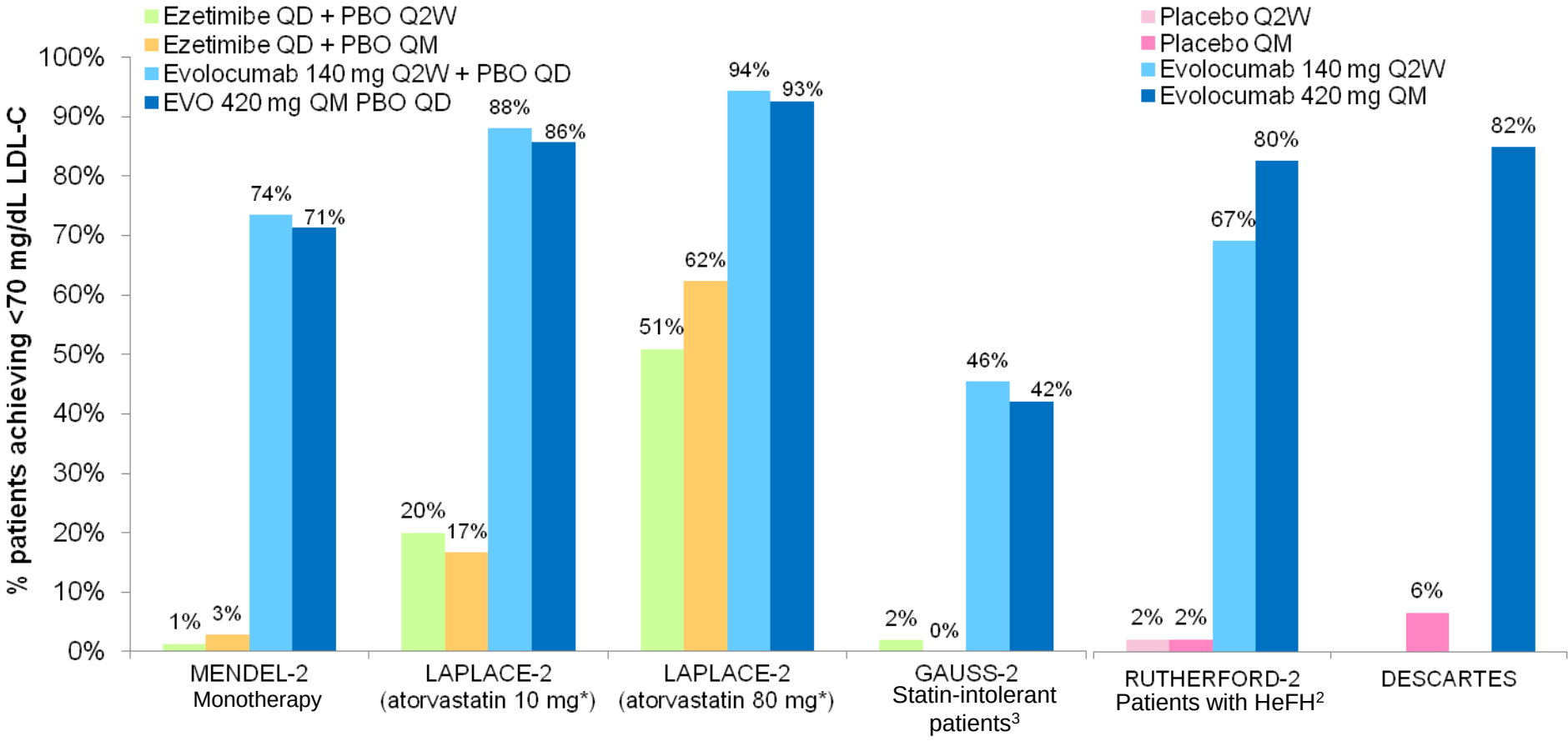
Up to 94% of evolocumab-treated patients achieved LDL-C <70mg/dL



*Only 2 statin dose groups are shown for the LAPLACE-2 study; these indicate the level of LDL-C goal fulfilment seen with moderate intensity (atorvastatin 10 mg) and high intensity (atorvastatin 80 mg) statin

Percentage of patients achieving LDL-C treatment goal of <70 mg/dL at a mean of Weeks 10 and 12; DESCARTES patients at Week 52. LAPLACE-2 patients are grouped by moderate- or high-intensity statin combination therapy.

PCSK9 CV Outcomes Trial

- FOURIER[a]
  - Estimated enrollment: 27,564 patients
- ODYSSEY Program[b]
  - Estimated enrollment: 18,600 patients
- SPIRE-1/SPIRE-2[c,d]
  - Estimated enrollment: 27,438 patients

a. ClinicalTrials.gov. NCT01764633.
b. ClinicalTrials.gov. NCT01663402.
c. ClinicalTrials.gov. NCT01975376.
d. ClinicalTrials.gov. NCT01975389.

WASHINGTON, DC
SATURDAY
MARCH 18, 2017

ACC.17 Daily
66TH ANNUAL SCIENTIFIC SESSION & EXPO

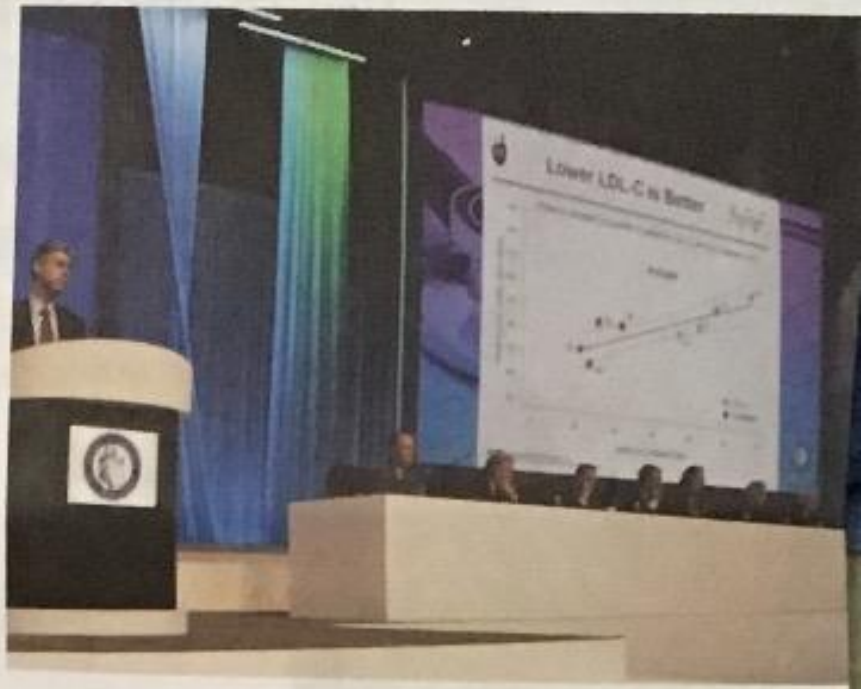
& MA
INCLUDED
INSIDE

FOURIER: Evolocumab Significantly Reduces Risk of CV Events

The addition of evolocumab, a PCSK9 inhibitor, to statin therapy over several years significantly reduced cardiovascular morbidity and mortality in patients with clinically evident atherosclerotic cardiovascular disease, according to results from the FOURIER trial presented yesterday during the joint *ACC/Journal of the American College of Cardiology* Late-Breaking Clinical Trial session and simultaneously published in the *New England Journal of Medicine*.

Between February 2013 and June 2015, the study enrolled 27,564 patients with cardiovascular disease and on a moderate- to high-intensity statin regimen at 1,272 sites in 49 countries. Most patients (81 percent) had a history of heart attack, 19 percent had suffered an ischemic stroke and 13 percent had symptomatic peripheral artery disease. The median baseline LDL cholesterol (LDL-C) was 92 mg/dL. To be included, patients had to have an LDL-C ≥70 mg/dL or a non–high density lipoprotein cholesterol ≥100 mg/dL and be on optimized statin therapy. Patients who had had an acute heart attack or stroke within the previous four weeks and those with advanced heart failure, uncontrolled heart rhythm disorders, upcoming cardiac surgery and end-stage kidney disease were excluded.

See **FOURIER**, page 4



SURTAVI: TAVR Non-Inferior to SAVR in Patients With Intermediate-Surgical Risk

Transcatheter aortic valve replacement (TAVR) was found to be non-inferior to surgical aortic valve replacement (SAVR) for the primary composite endpoint of all-cause mortality and disabling stroke at 24 months in patients with symptomatic, severe aortic stenosis who had an intermediate level of operative risk (STS score of 3 percent or higher), according to the results of the SURTAVI trial presented yesterday during the joint *ACC/Journal of the American College of Cardiology* Late-Breaking Clinical Trial session and

SPIRE 1 and SPIRE 2: Safety and CV Event Efficacy of Bococizumab in High-Risk Patients

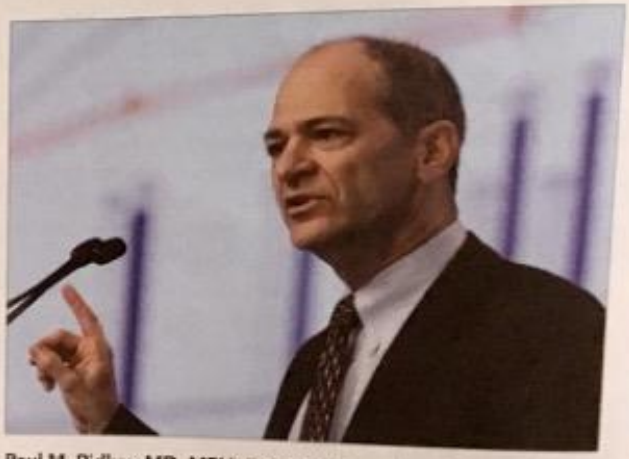
The SPIRE development program of the humanized PCSK9 inhibitor bococizumab has shown that the development of antidrug antibodies in 15 – 20 percent of patients attenuated the substantial reduction in LDL cholesterol (LDL-C) and that in terms of cardiovascular outcomes there was benefit in patients with a baseline LDL-C >100 mg/dL but not for a baseline LDL-C <100 mg/dL.

The results of the multinational trials were presented yesterday by **Paul M. Ridker, MD, MPH, FACC**, during the joint ACC/*Journal of the American College of Cardiology* Late-Breaking Clinical Trial session and simultaneously published in the *New England Journal of Medicine*. The cardiovascular outcomes studies, SPIRE-1 and SPIRE-2, were stopped prematurely in November 2016 after the lipid-lowering trial results led the sponsor to discontinue the drug's development.

Lipid-lowering results were reported for 4,449 high-risk patients (mean age 61 years, 42 percent women, LDL-C 122 mg/dL) who were treated with maximally tolerated doses of a statin (86 percent on high-intensity statin) and bococizumab 150 mg subcutaneously every two weeks or placebo. The 54.2 percent reduction in LDL-C seen at 12 weeks with bococizumab was attenuated to 43 percent at 52 weeks – and in the 16 percent of patients who developed antibodies this attenuation was greater at 31 percent. The attenuation in LDL-C reduction was greater with higher antibody levels. Further, the reductions in LDL-C were highly variable within patients, regardless of antibody status. In the lipid-lowering studies, there was a similar rate of major adverse cardiovascular events with bococizumab and placebo at 2.5 percent and 2.7 percent, respectively.

In the SPIRE-1 outcomes study of 16,817 patients with an LDL-C >70 mg/dL, at seven months there was no difference in the primary endpoint of non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina requiring urgent revascularization or cardiovascular death. However, in the SPIRE-2 study of 10,621 patients with an LDL-C >100 mg/dL, at 12 months there was a 21 percent reduction in the primary endpoint. Analyses of the combined results for SPIRE-1 and SPIRE-2 revealed that a larger reduction in LDL-C and a longer duration of treatment were both associated with significantly better outcomes.

> "In addition to supporting the general hypothesis that PCSK9 inhibitors can lower cardiovascular event rates, **differences in this medication class between fully human and humanized therapeutic monoclonal antibodies** may be important to consider."
>
> *Paul M. Ridker, MD, MPH, FACC*

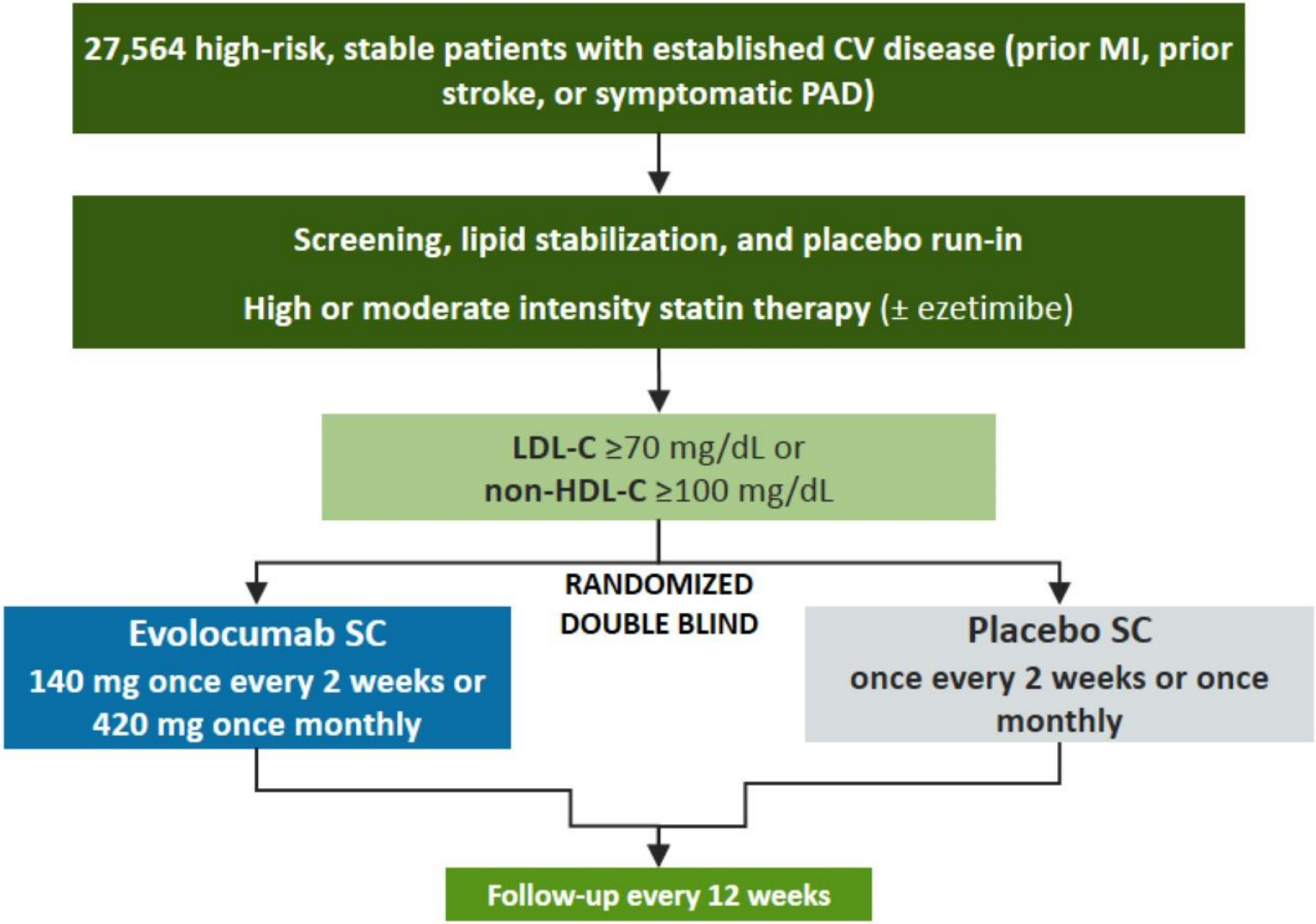


Paul M. Ridker, MD, MPH, FACC, gave results of the SPIRE 1 and SPIRE 2 trials during the first Late-Breaking Clinical Trial session.

The investigators stated that the clinical benefits were greater and statistically significant in subgroup analyses in patients who had and sustained greater absolute and proportionate reductions in LDL-C and that this is consistent with the "lower is better for longer" hypothesis. They also state their data support the use of PCSK9 inhibitors on top of aggressive statin therapy in selected patients.

"In addition to supporting the general hypothesis that PCSK9 inhibitors can lower cardiovascular event rates, differences in this medication class between fully human and humanized therapeutic monoclonal antibodies may be important to consider," Ridker said. "We believe genetic analyses could be very helpful to determine who does and does not develop antidrug antibodies to bococizumab."

FOURIER Trial Design

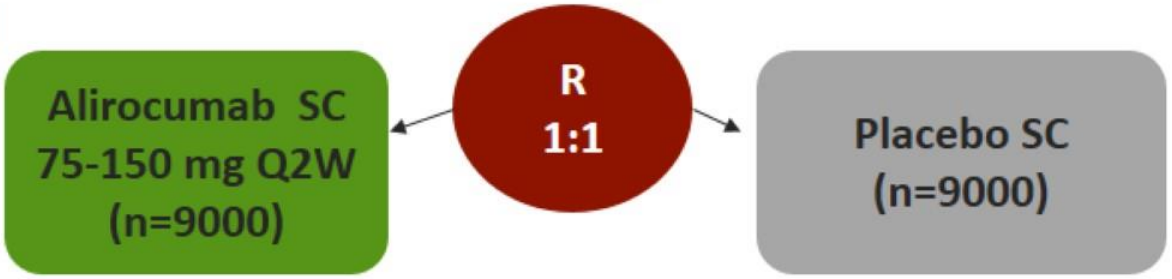


Sabatine MS, et al. *Am Heart J.* 2016;173:94-101.

ODYSSEY Outcomes:
Phase 3 Post-ACS With Alirocumab

N = 18,000 patients, age > 40 y, 4-52-wk post ACS

- On evidence-based medical therapy
- LDL-C > 70 mg/dL
- 64 months randomized treatment period and 2 month follow-up period

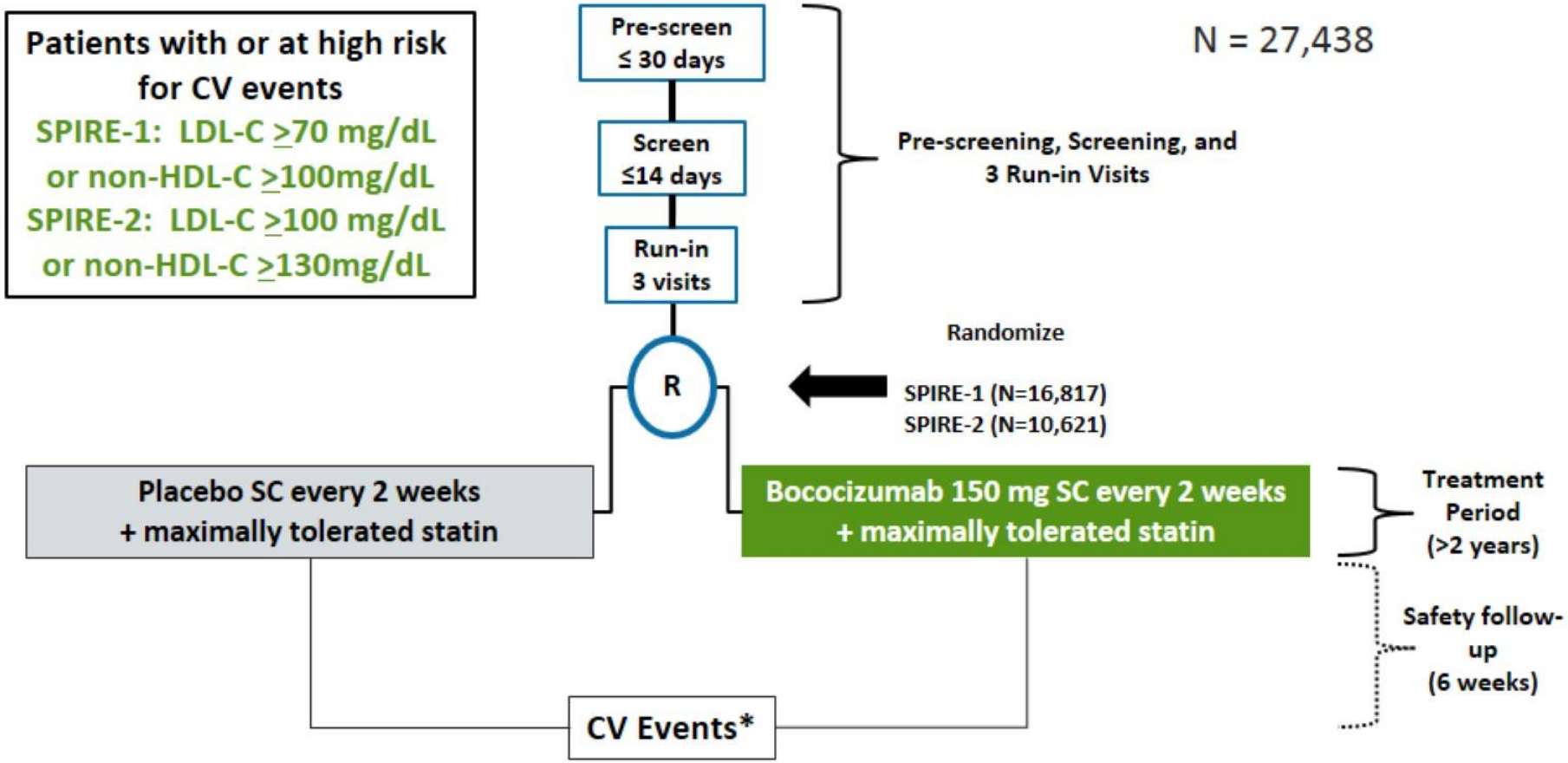


Primary end point: CHD death, nonfatal MI or stroke, or UA requiring hospitalization

Secondary end point: Any CHD event, major CHD event, any CV event; composite of all-cause mortality, nonfatal MI, or stroke; all-cause mortalilty

ClinicalTrials.gov. NCT01663402.

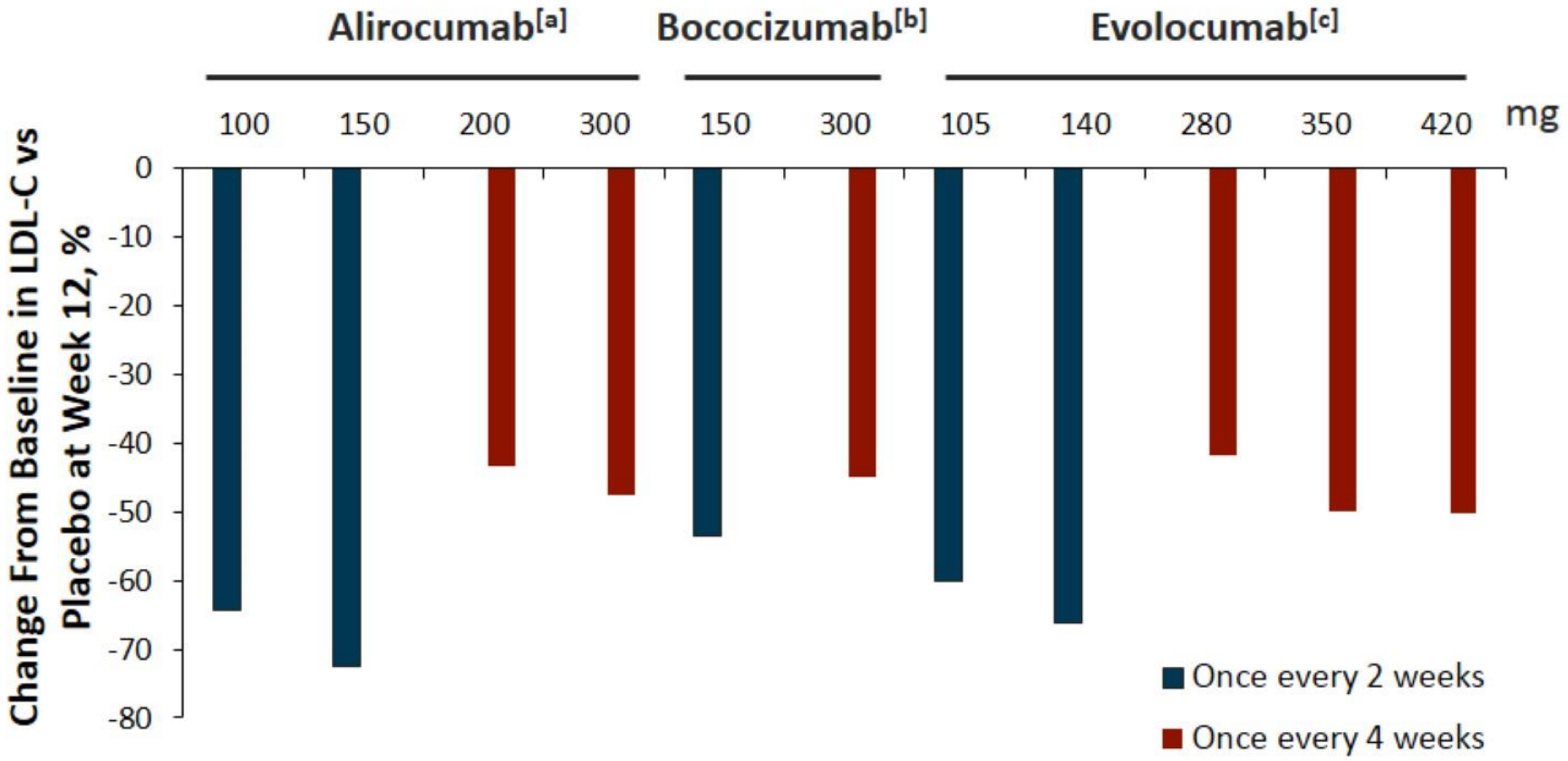
The SPIRE-1 and SPIRE-2 CV Outcome Trials



*Nonfatal MI, nonfatal stroke, hospitalization for UA requiring urgent revascularization, or CV death

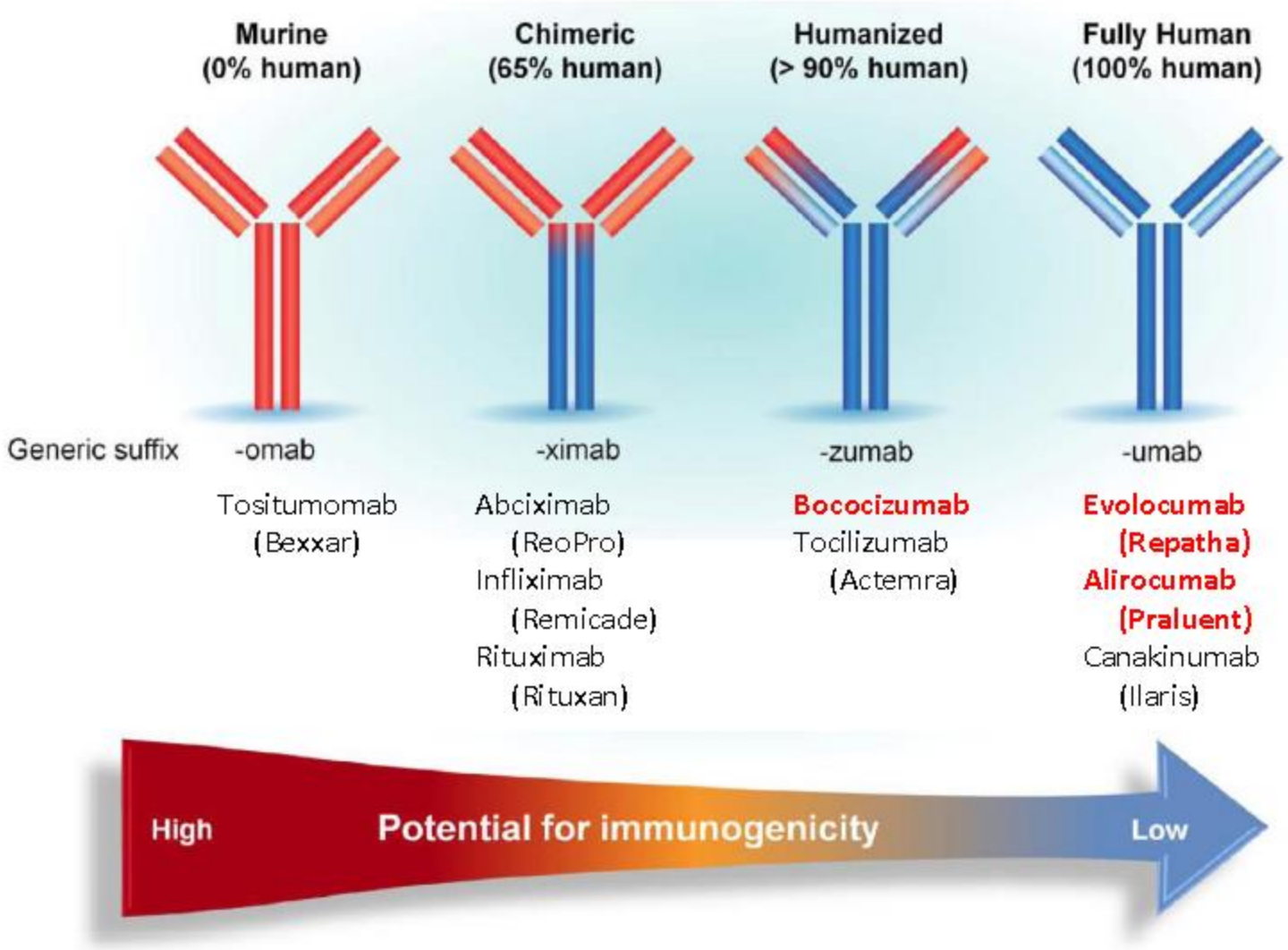
Ridker PM, et al. *New Engl J Med.* 2017. [Epub ahead of print]

PCSK9 Inhibition in Patients With Hypercholesterolemia Receiving Statin Therapy



a. McKenney JM, et al. *J Am Coll Cardiol*. 2012;59:2344-2353.
b. Ballantyne CM, et al. *J Am Coll Cardiol*. 2014;63:A1374.
c. Giugliano RP, et al. *Lancet*. 2012;380:2007-2017.

Evolution and Humanization of Therapeutic Monoclonal Antibodies



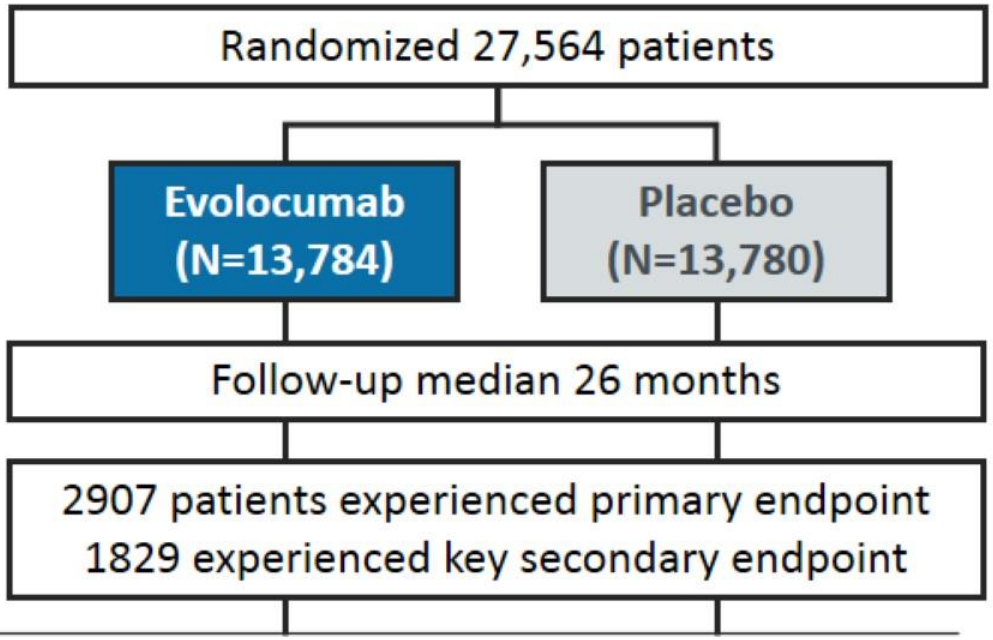
Adapted from Foltz IN, Karow M, Wasserman SM. Circulation 2013; 127:2222-2230.

FOURIER Endpoints

- Efficacy
  - Primary: CV death, MI, stroke, hosp. for UA, or coronary revascularization
  - Key secondary: CV death, MI, or stroke
- Safety
  - AEs/SAEs
  - Events of interest
    - Muscle-related
    - New-onset diabetes
    - Neurocognitive
  - Development of anti-evolocumab antibodies (binding and neutralizing)

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

FOURIER Follow-Up



Premature perm. drug discontinuation	**5.6%/yr**	**5.8%/yr**
Withdrew consent	**0.29%/yr**	**0.35%/yr**
Lost to follow-up	**5 patients**	**13 patients**

Ascertainment for primary endpoint was complete for 99.5% of potential patient-years of follow up

Sabatine MS. ACC congress 2017.
Sabatine MS, et al. *N Engl J Med.* 2017. [Epub ahead of print]

FOURIER: Baseline Characteristics

Characteristic (N=27,564)	Value
Age, years, mean	63
Male sex (%)	75
Type of CV disease (%)	
MI	81
Stroke (non-hemorrhagic)	19
Symptomatic PAD	13
CV risk factor (%)	
Hypertension	80
DM	37

Median time from most recent event ~3 yrs

Pooled data; no differences between treatment arms

Sabatine MS, et al. *N Engl J Med.* 2017. [Epub ahead of print]

FOURIER: Lipid-Lowering Therapy and Lipid Levels at Baseline

Characteristic (N=27,564)	Value
Statin use*	%
High intensity	69
Moderate intensity	30
Ezetimibe use (%)	5
Median lipid measures	mg/dL (IQR)
LDL-C	92 (80-109)
Total cholesterol	168 (151-188)
HDL-C	44 (37-53)
Triglycerides	133 (100-183)

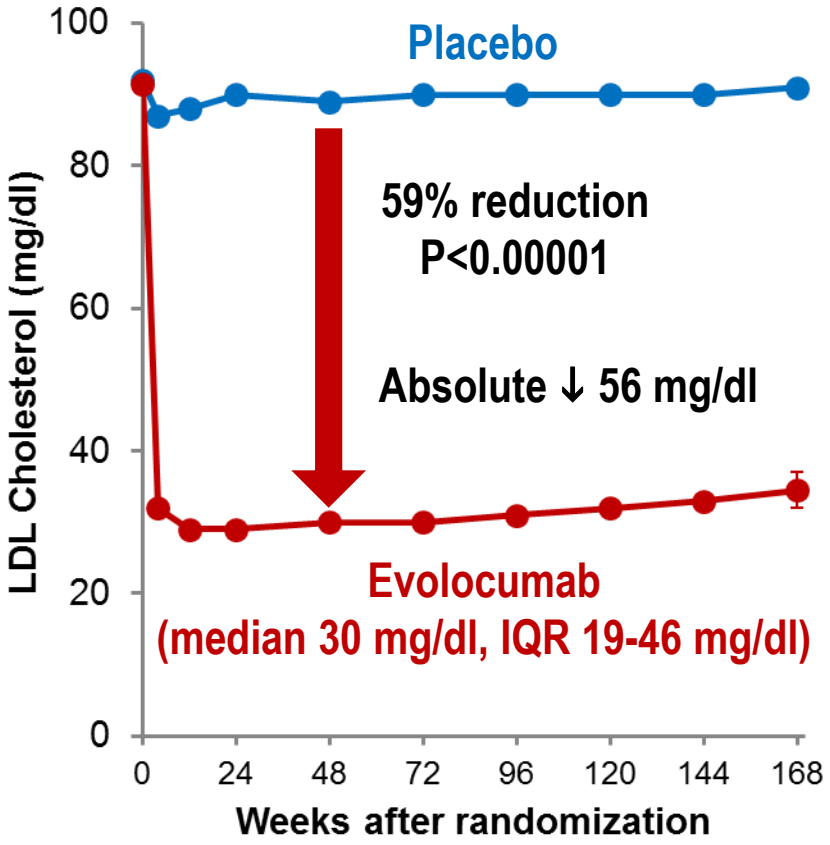
Pooled data; no differences between treatment arms

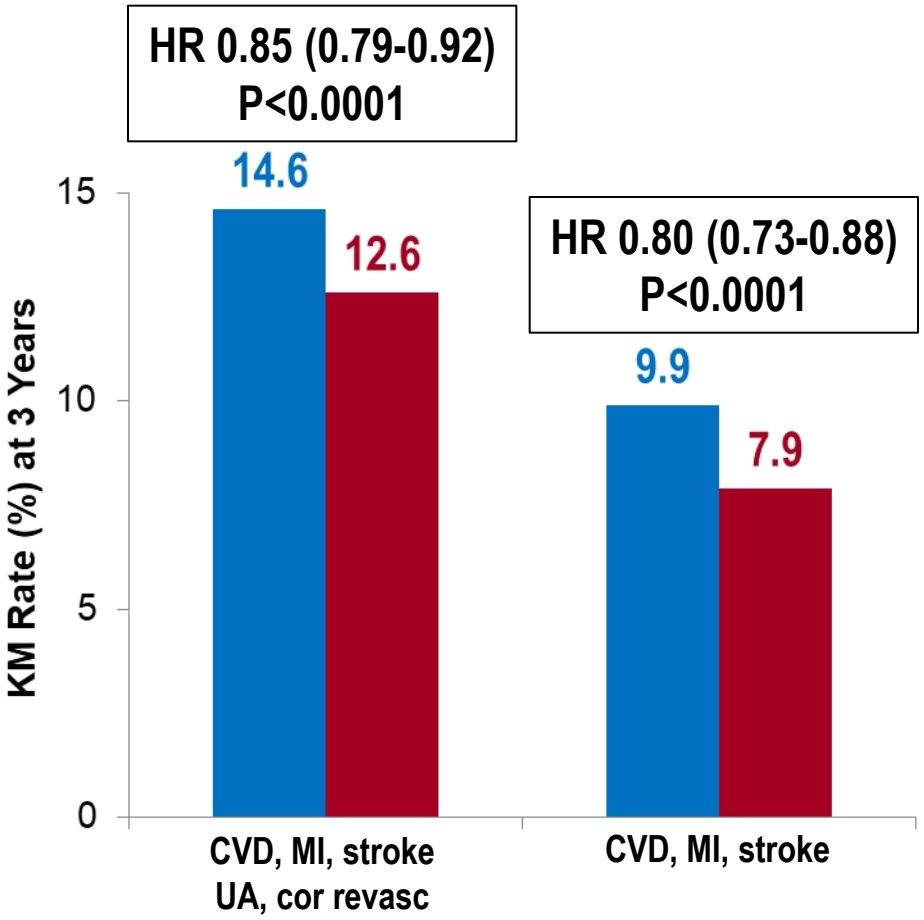
*Per protocol, patients were to be on atorvastatin ≥20 mg/d or equivalent.
1% were on low intensity or intensity data were missing.
Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines.

Sabatine MS, et al. *N Engl J Med.* 2017. [Epub ahead of print]

Summary of Effects of PCSK9i Evolocumab

- ↓ LDL-C by 59%
- ↓ First CV outcomes in patients on statin
- Safe and well-tolerated





Sabatine MS et al. *NEJM* 2017;376:1713-22

FOURIER: Main CV Outcomes (cont)

Endpoint (% number of patients)	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
CV death, MI, stroke, UA, or revascularization	9.8	11.3	0.85 (0.79, 0.92)
CV death, MI, or stroke	5.9	7.4	0.80 (0.73, 0.88)
CV death	1.8	1.7	1.05 (0.88, 1.25)
MI	3.4	4.6	0.73 (0.65, 0.82)
Hospitalization for UA	1.7	1.7	0.99 (0.82, 1.18)
Coronary revascularization	5.5	7.0	0.78 (0.71, 0.86)
Death from any cause	3.2	3.1	1.04 (0.91, 1.19)

Sabatine MS, et al. *N Engl J Med.* 2017. [Epub ahead of print]

FOURIER: Safety

N=27,564

	Evolocumab	Placebo
AEs (%)		
Any	77.4	77.4
Serious	24.8	24.7
Allergic reaction	3.1	2.9
Injection-site reaction	2.1	1.6
Muscle-related	5.0	4.8
Diabetes (new-onset)	8.1	7.7
Neurocognitive	1.6	1.5
Laboratory results (%)		
Binding antibodies	0.3	n/a
Neutralizing antibodies	none	n/a

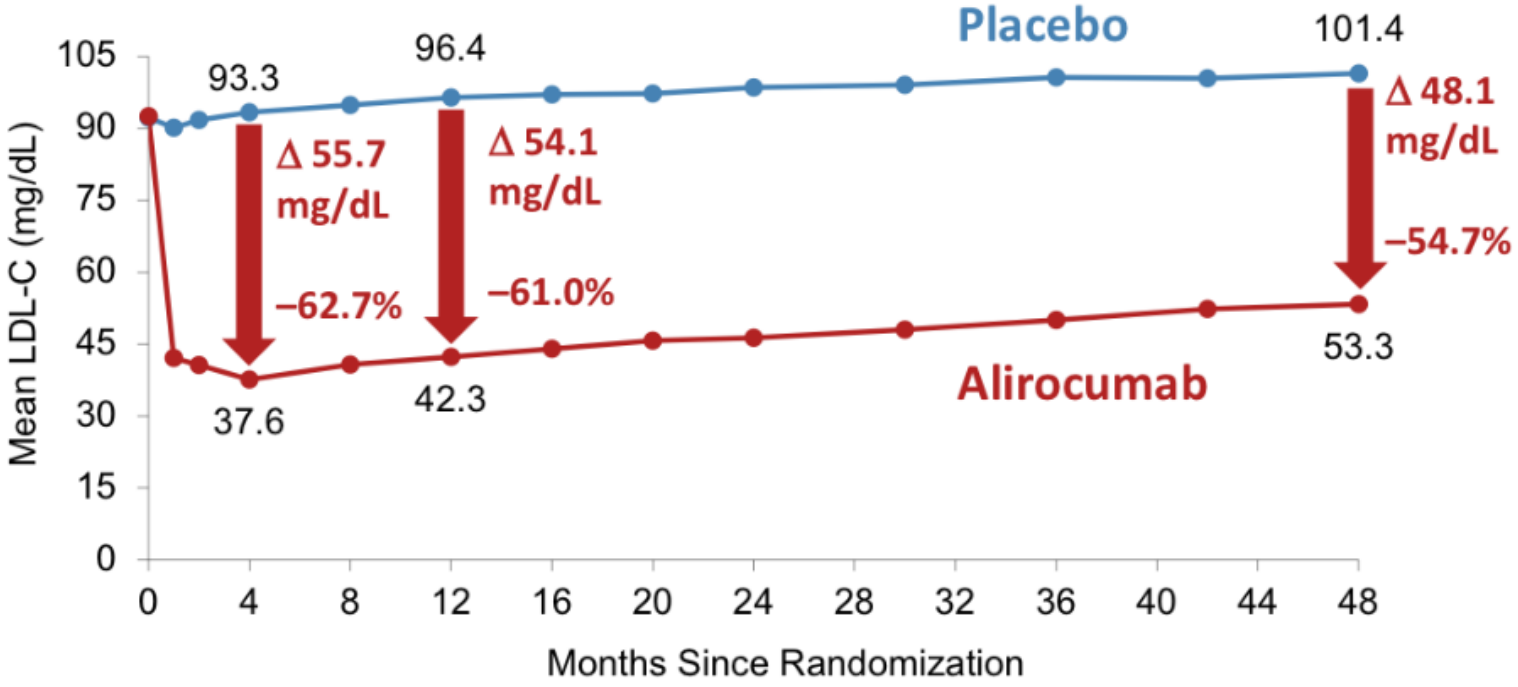
Sabatine MS, et al. *N Engl J Med.* 2017. [Epub ahead of print]

Summary of FOURIER

- Reduction of LDL-C by 59%
  - Consistent throughout duration of trial
  - Median achieved LDL-C of 30 mg/dL
- Reduction of CV events in patients already on statin therapy
  - 15% reduction of primary endpoint
  - 20% reduction of CV death, MI, or stroke
  - 25% reduction in CV death, MI, or stroke after 1st year
  - Long-term benefits consistent w/ statins per mmol/L ↓ LDL-C
- Safe and well-tolerated
  - No increase of AEs, including DM and neurocognitive events
  - No neutralizing antibodies developed

Sabatine MS, et al. *N Engl J Med.* 2017. [Epub ahead of print]

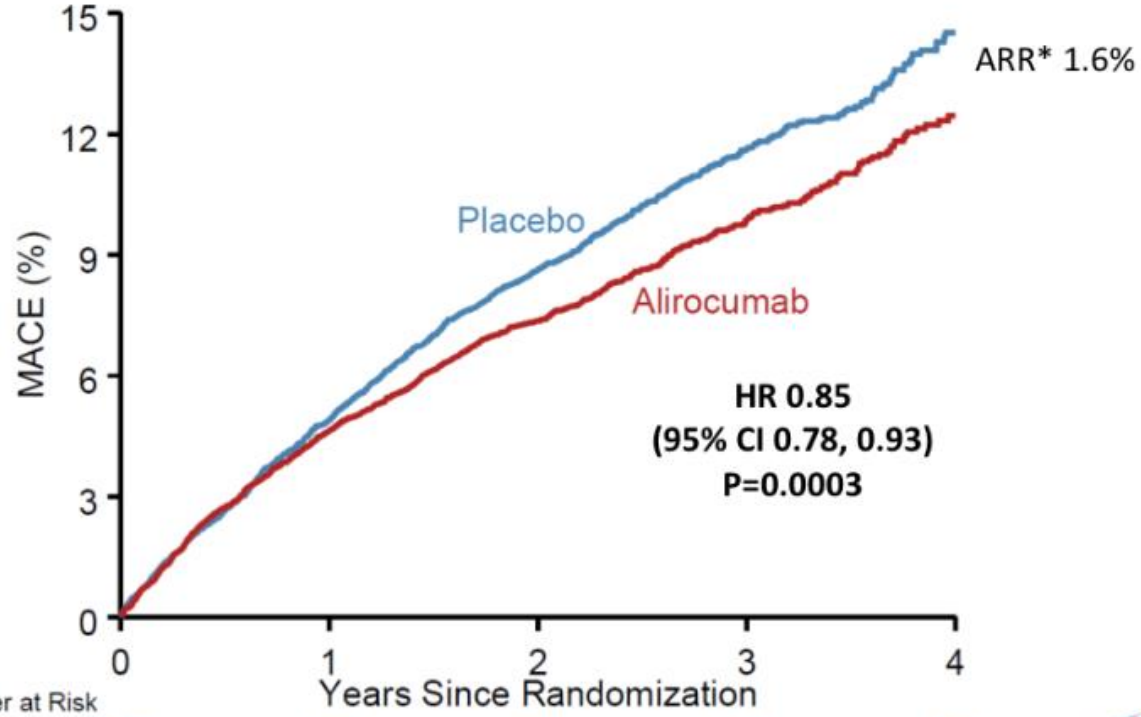
LDL-C: On-Treatment Analysis



Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
Approximately 75% of months of active treatment were at the 75 mg dose

ODYSSEY OUTCOMES

Primary Efficacy Endpoint: MACE



MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

*Based on cumulative incidence

ODYSSEY OUTCOMES

Subgroup analysis from Fourier CV outcome trials – AHA 2017 Highlight

- FOURIER total event
- FOURIER MI subgroup analysis (LBT)
- FOURIER MI type and size sub-analysis
- FOURIER risk score
- FOURIER PAD subgroup analysis (LBT)

LBT= Late-breaking trial

Patients with Peripheral Artery Disease

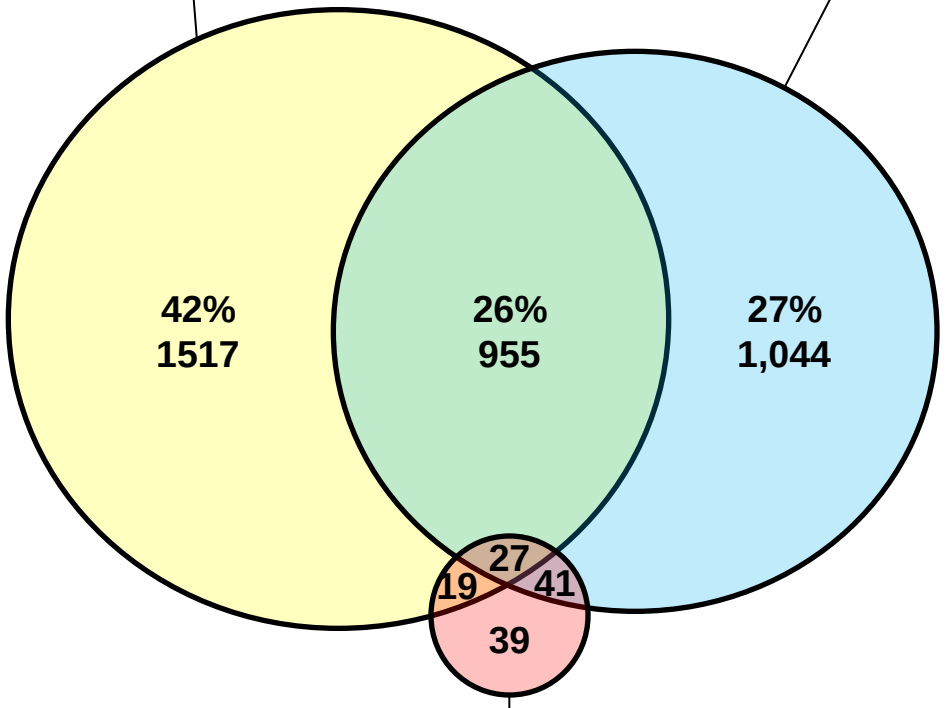
27,564
Patients with Atherosclerosis Randomized

3,642
Patients with Symptomatic Lower Extremity Peripheral Artery Disease

1,505
Patients with Symptomatic Lower Extremity Peripheral Artery Disease and no prior MI or Stroke

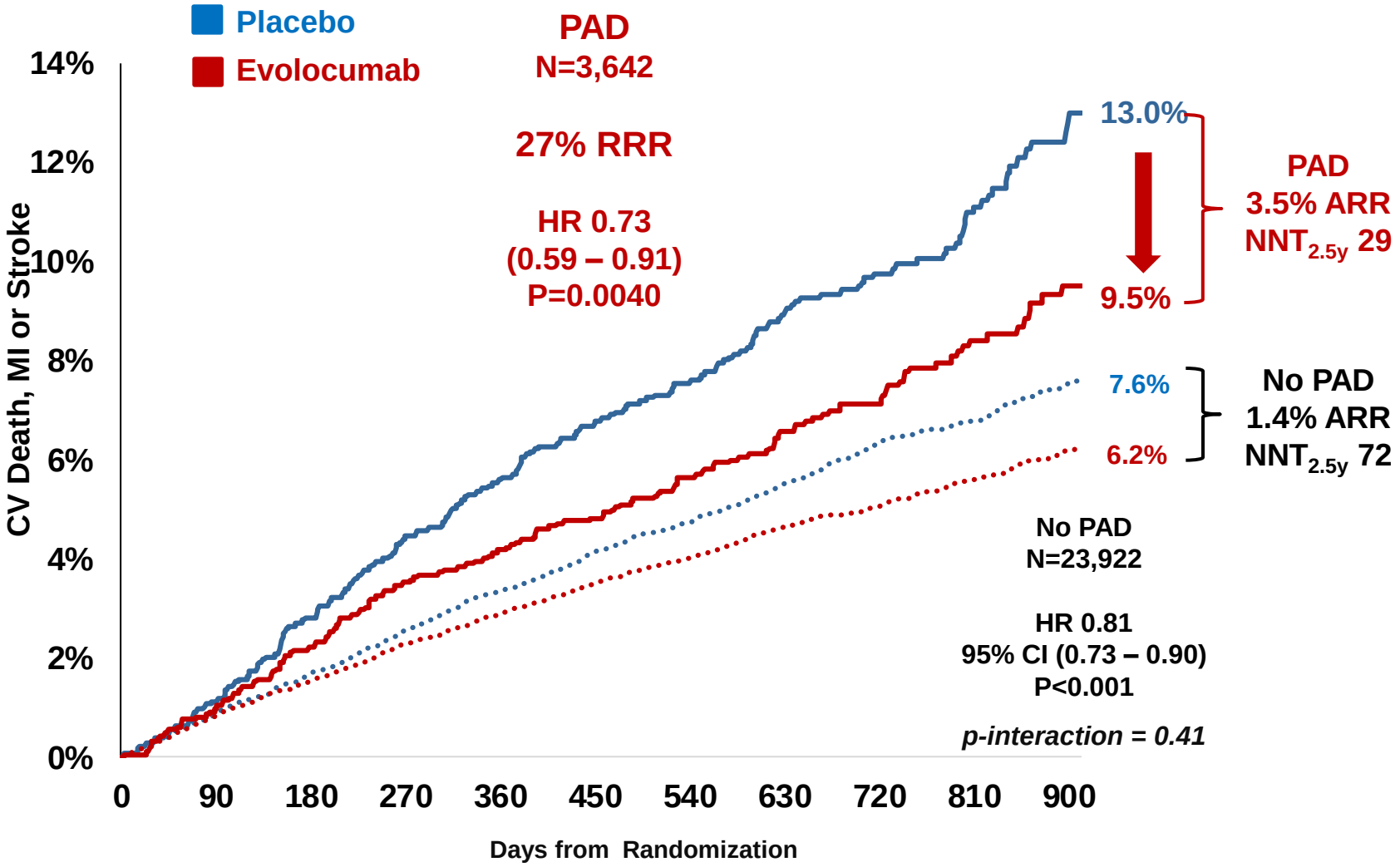
69%
Intermittent Claudication & ABI < 0.85 at Baseline

57%
Peripheral Revascularization (Median 3.7 years prior)

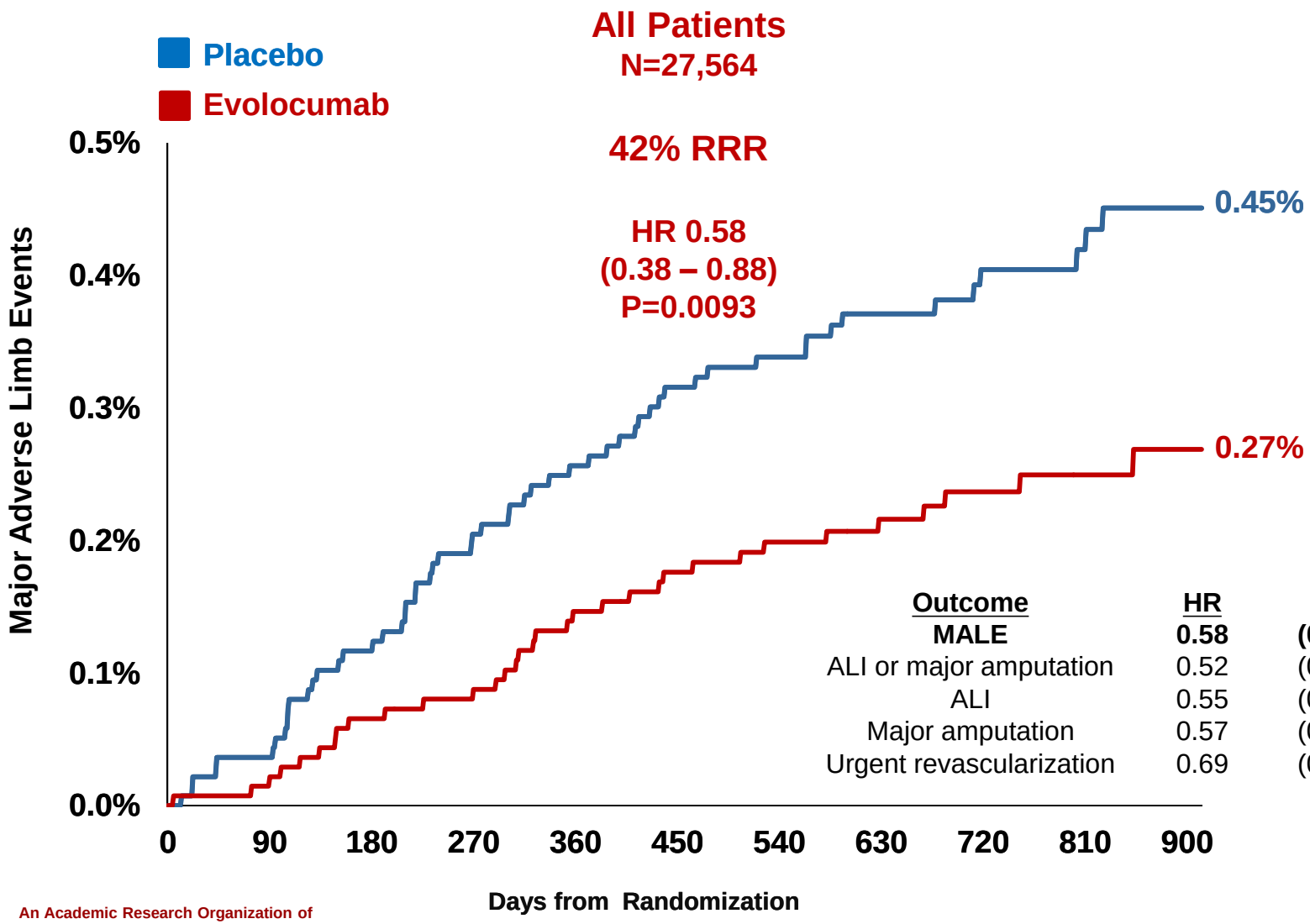


4%
Amputation for Ischemia

CV Death, MI or Stroke in Patients with and without Peripheral Artery Disease



Major Adverse Limb Events

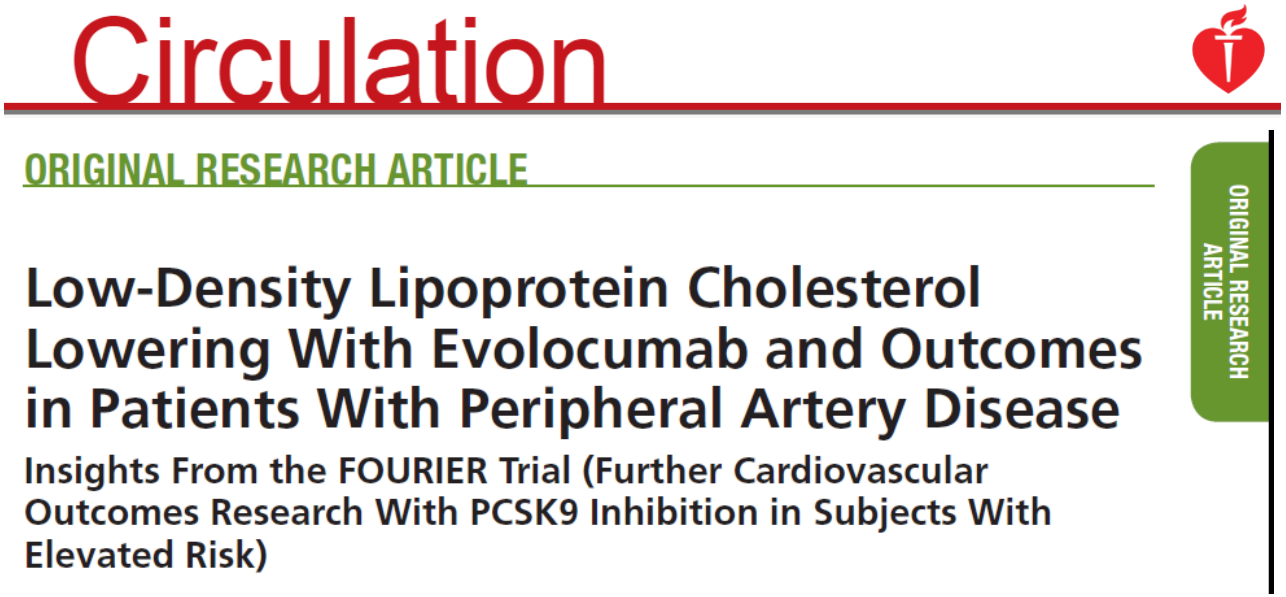


Outcome	HR	95% CI
MALE	**0.58**	**(0.38–0.88)**
ALI or major amputation	0.52	(0.31–0.89)
ALI	0.55	(0.31–0.97)
Major amputation	0.57	(0.17–1.95)
Urgent revascularization	0.69	(0.38–1.26)

Conclusion

LDL-C reduction to very low levels should be considered in patients with PAD, regardless of history of MI or stroke, to reduce the risk of MACE and MALE

For more information see simultaneous publication in:



EBBINGHAUS:

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

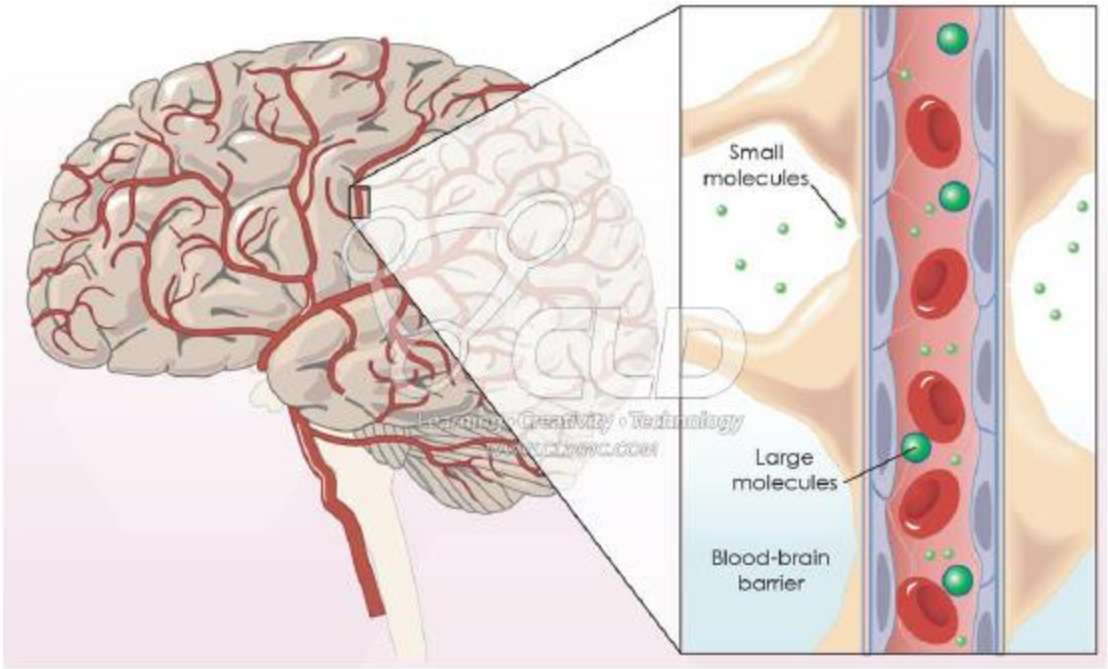
RP Giugliano, F Mach, K Zavitz, AC Keech, TR Pedersen,
MS Sabatine, P Sever, C Kurtz, N Honarpour, BR Ott,
on behalf of the EBBINGHAUS Investigators

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

Cognition and PCSK9 Inhibitors

Brain synthesizes cholesterol locally



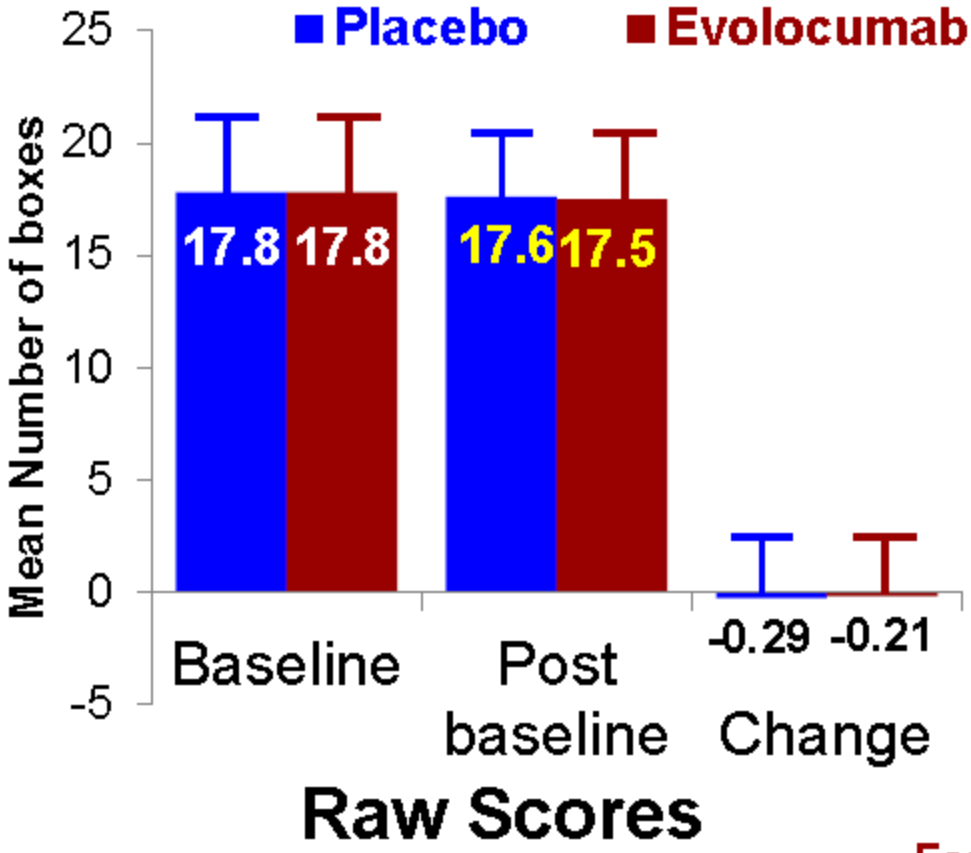
mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier

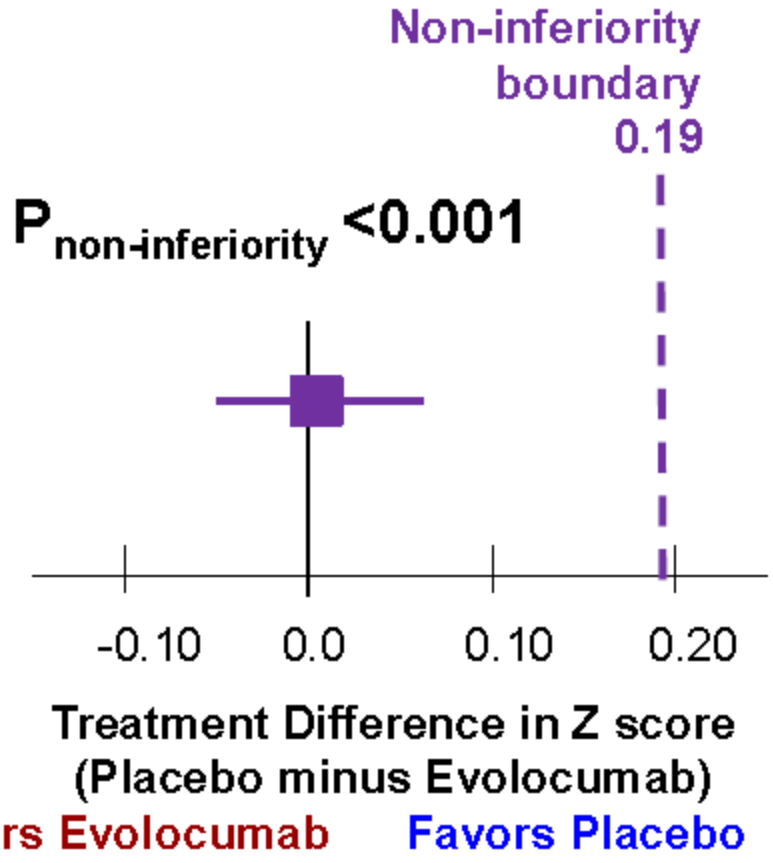
Nevertheless meta-analysis* of adverse events from 6 trials in 9581 pts suggested an increased risk with PCSK9 inhibitors: HR 2.3 [1.1, 4.9]

- Event rates low (<1%)
- Unadjudicated, diverse AE terms reported
- Not correlated with LDL-C achieved

*Lipinski MJ, et al. *Eur Heart J*. 2016;37(6):536-545.

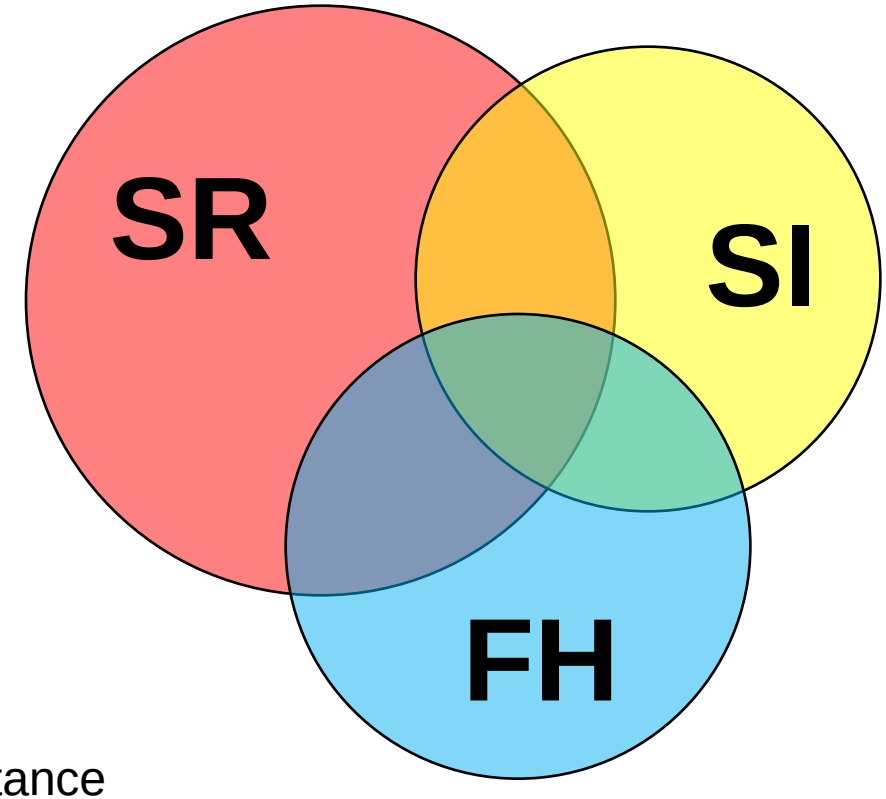
Primary Endpoint
Spatial Working Memory Strategy Index





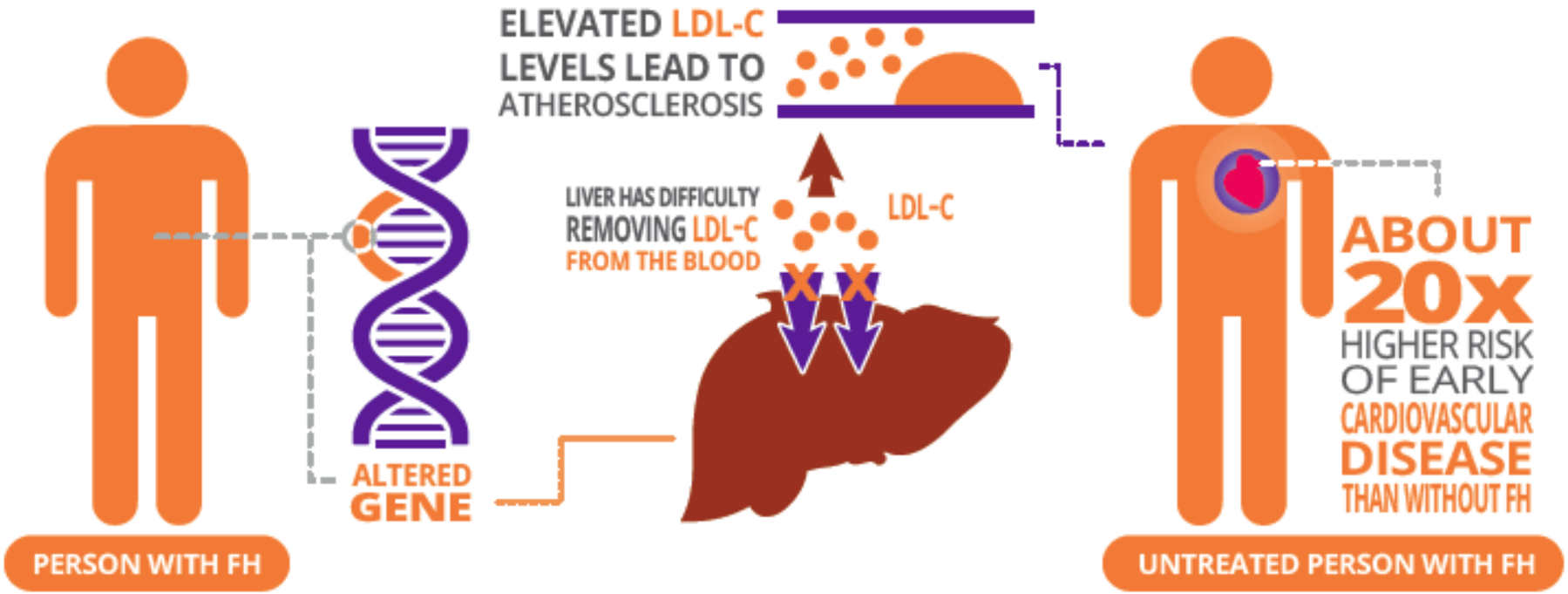
P_{NI} is from fixed estimate

Who should take PCSK9i?



SR = statin resistance
SI = statin intolerance
FH = Familial hypercholesterolemia

Familial Hypercholesterolemia



FH can be caused by mutations in 4 known genes

FH is typically caused by mutations in LDLR, ApoB, PCSK9, LDLRAP1 or other as yet other unidentified genes[1]

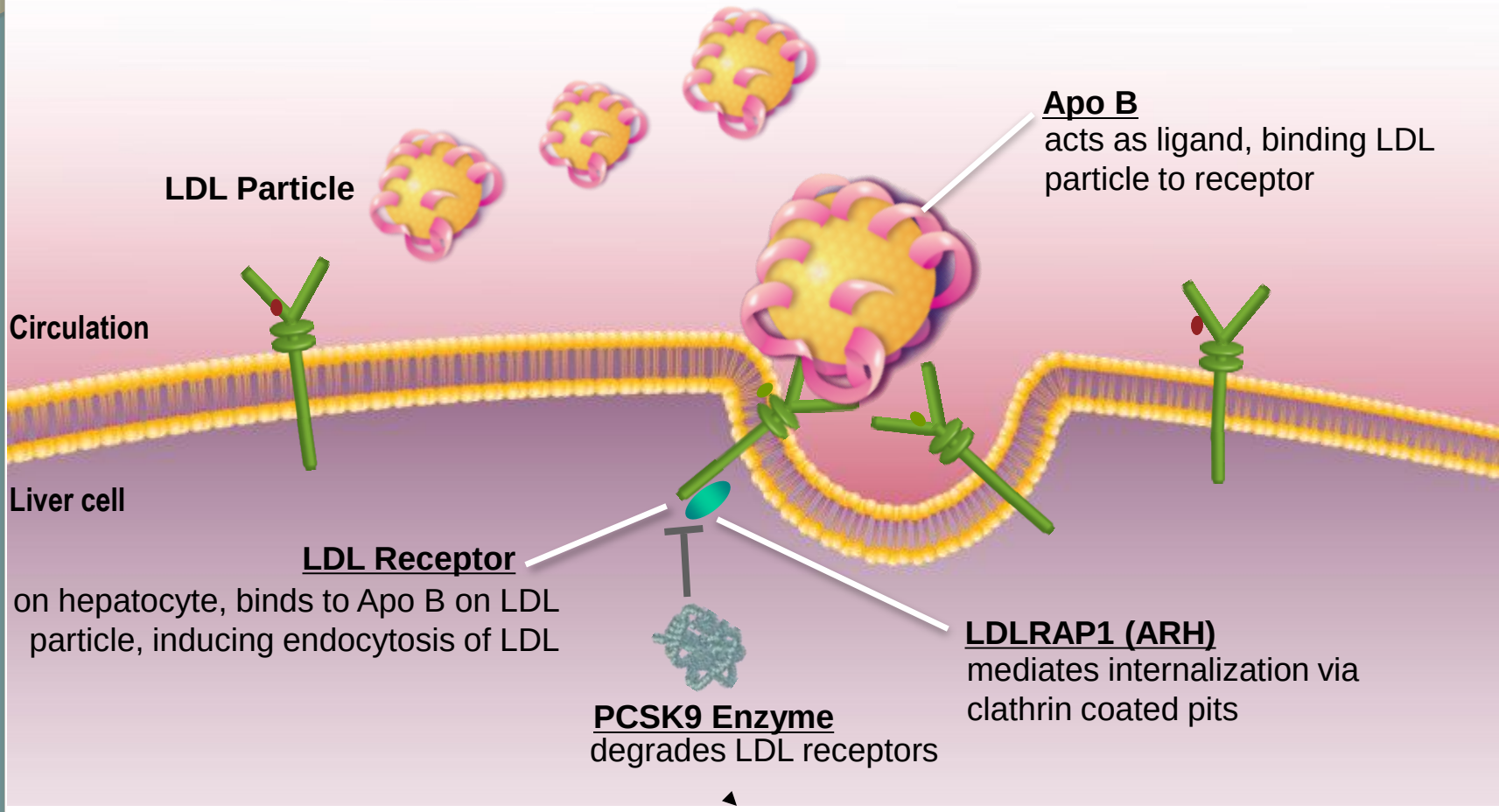
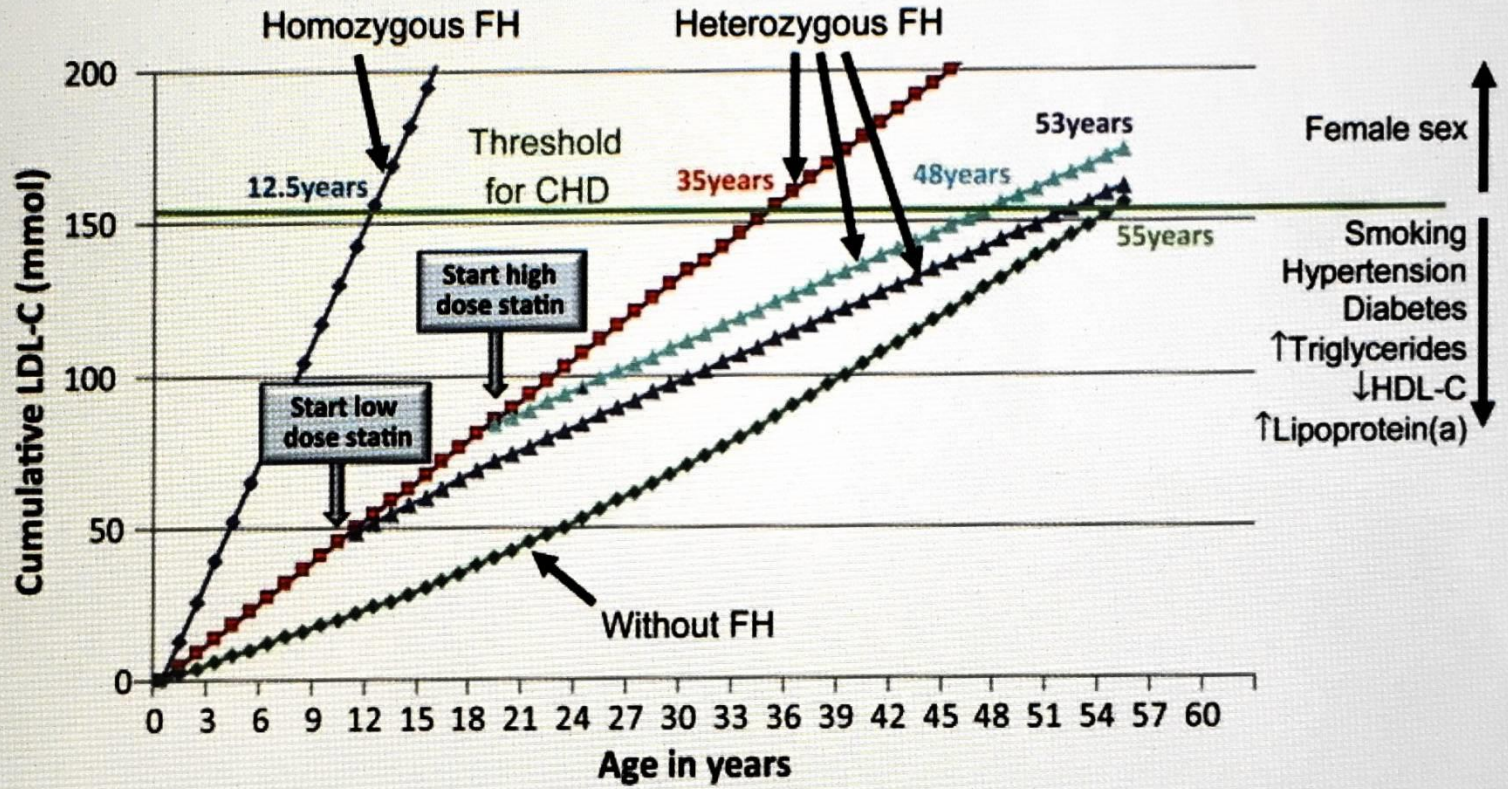


Image reproduced from http://www.dls.ym.edu.tw/ol_biology2/ultranet/Endocytosis.html.

1. De Castro-Oros I, et al. *Appl Clin Genet.* 2010;3:53-64.

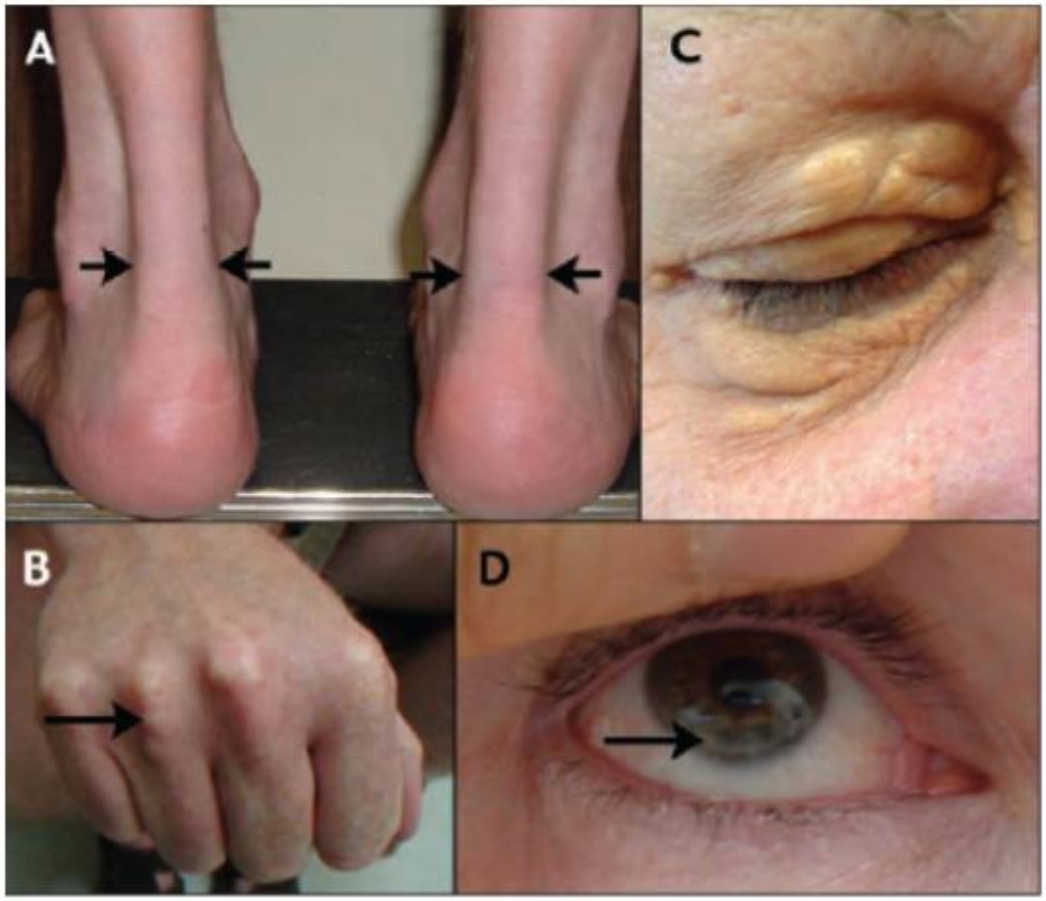
LDL-C Burden in Individuals With/Without FH as a Function of the Age of Initiation of Statin Therapy



Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273

European Heart Journal

Physical Examination



A: Lateral borders of thickened Achilles' tendons are shown with arrows.
B: Tendinous xanthomas in the extensor tendons of the hands.
C: Cholesterol deposits in the eyelids.
D: Arcus cornealis results from cholesterol infiltration around the corneal rim (arrow).

台灣FH建議診斷標準

評估項目		分數
家族史		
一等親有早發性冠狀動脈或血管疾病 一等親之LDL-C 值> 160mg/dL	或者	1
一等親出現Xanthoma 且/或Corneal arcus 18 歲以下之一等親LDL-C 值> 130 mg/dL	或者	2
臨床病史		
患者出現早發性*冠狀動脈疾病		2
患者出現早發性*腦血管或周邊血管疾病		1
理學檢查		
皮膚或肌腱黃色瘤(Xanthoma)		6
角膜環(Corneal arcus) [45 歲前]		4
LDL-C 值 (mg/dL)		
> 330		8
250 - 329		5
190 - 249		3
155 - 189		1
基因檢測		
LDL-R/ ApoB-100/ PCSK9 功能性基因突變		8

[FH 診斷結果]

確定是 **(Definite FH) > 8** 分

極可能是**(Probable FH) 6 - 8** 分

可能是 **(Possible FH) 3 - 5** 分

*早發性: 男性< *45* 歲，女性< *55* 歲

<PROFILE>

AGE: 37

GENDER: FEMALE

FH: POSITIVE

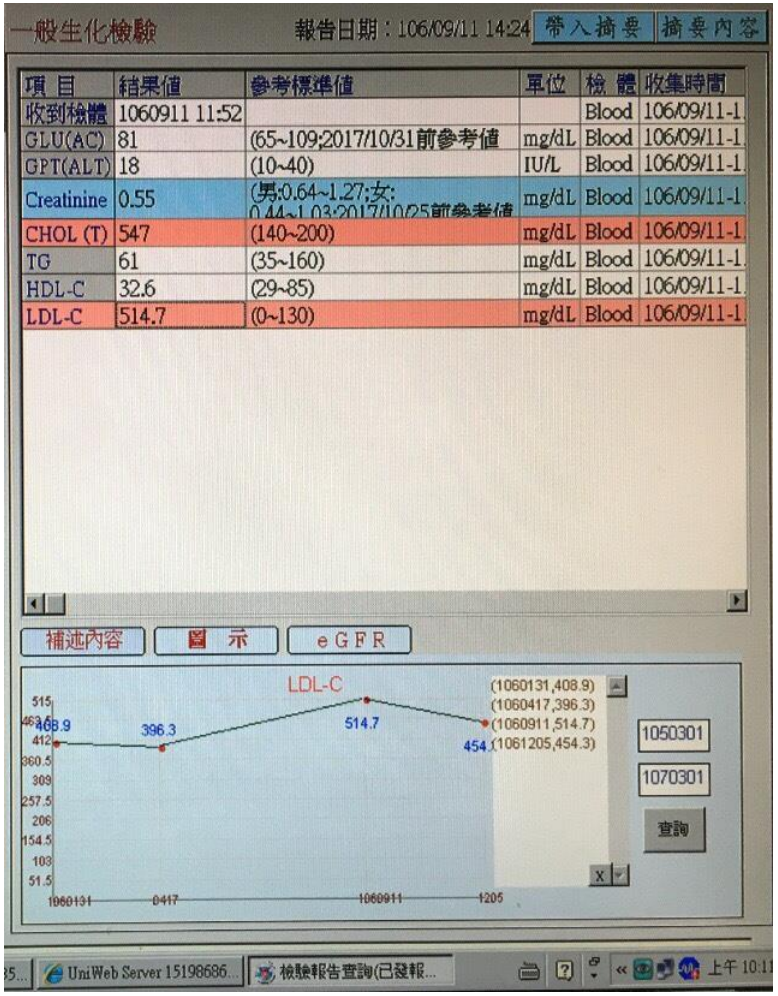
ELDERLY SISTER DIE FROM MI ATTACK AT THE AGE OF 35

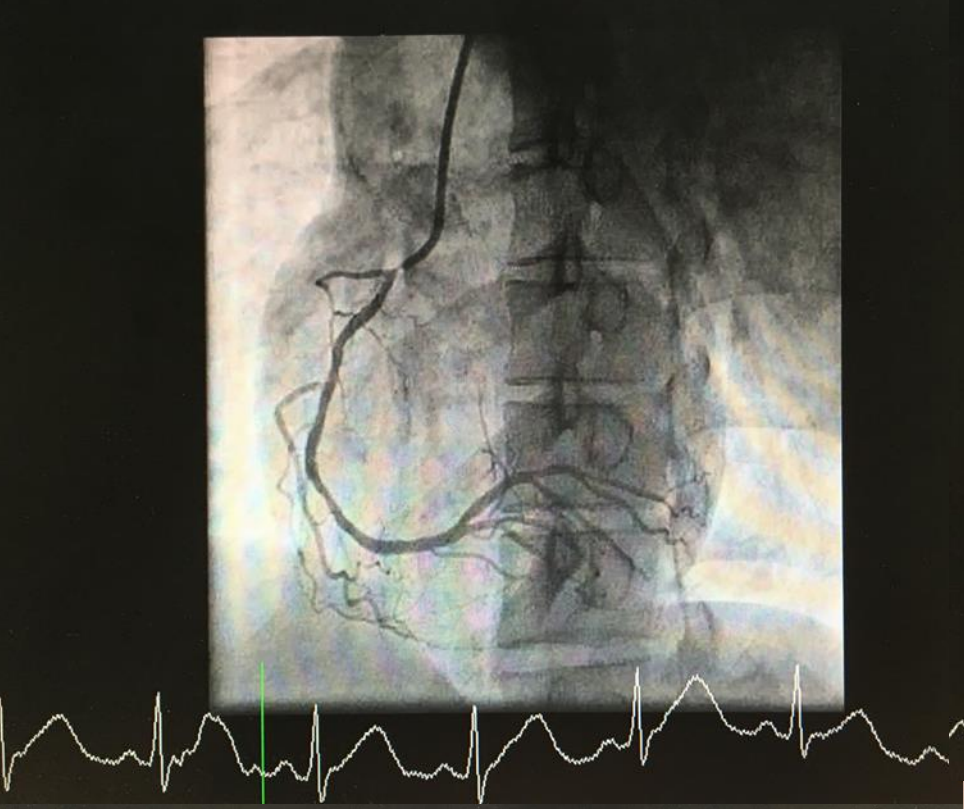
STRONG POSITIVE TREADMILL TEST

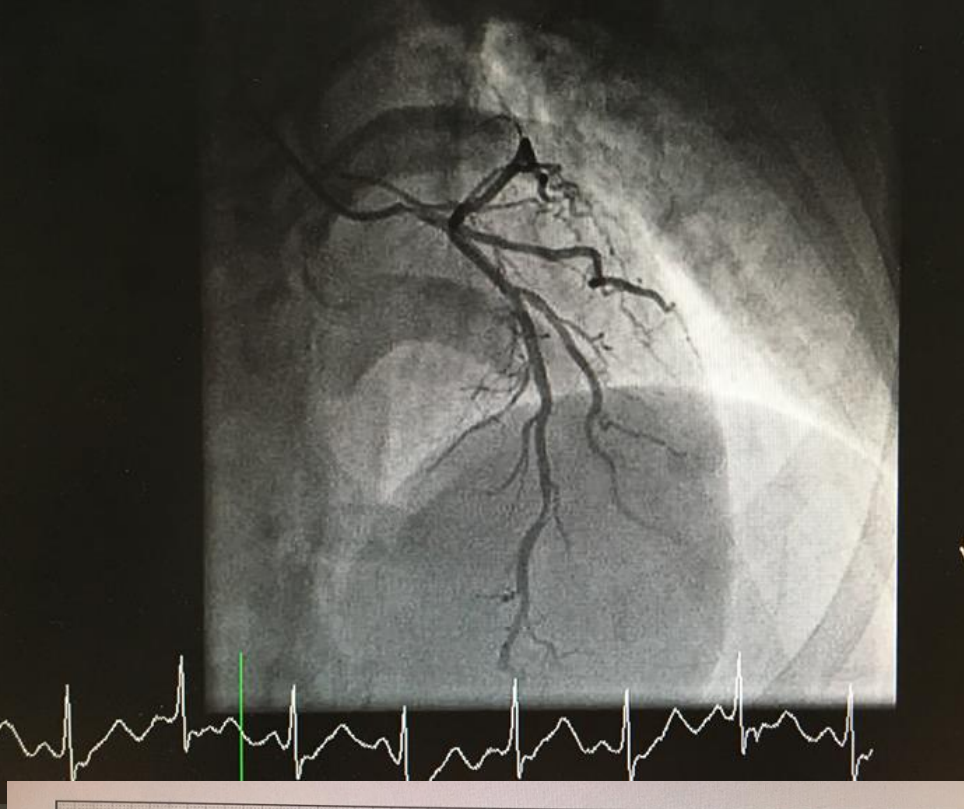
CAG: LT MAIN + 3-V-D, RCA OS LESION

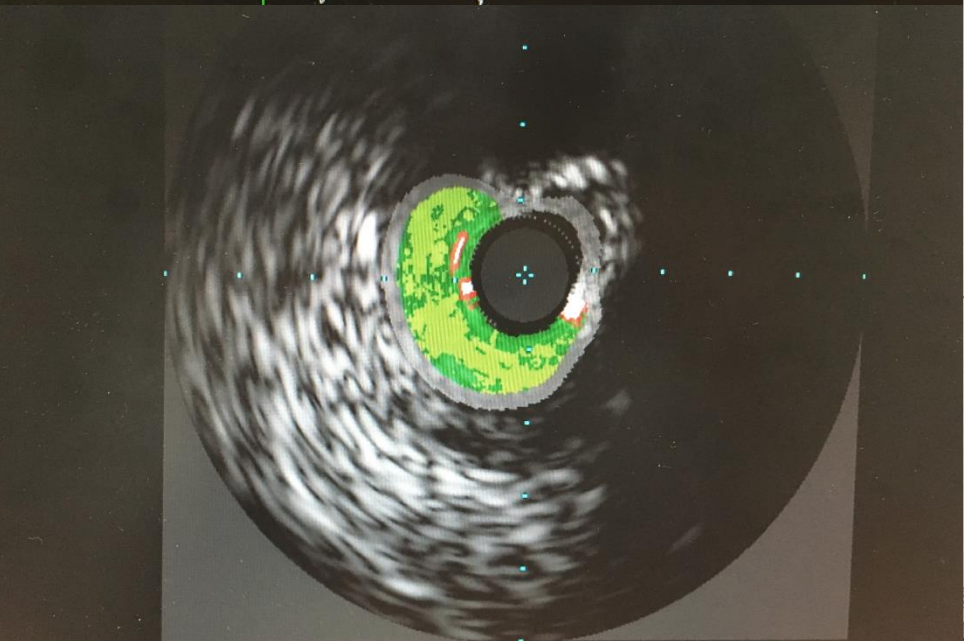
S/P PCI X 2 DES STENTS UNDER IABP SUPPORT

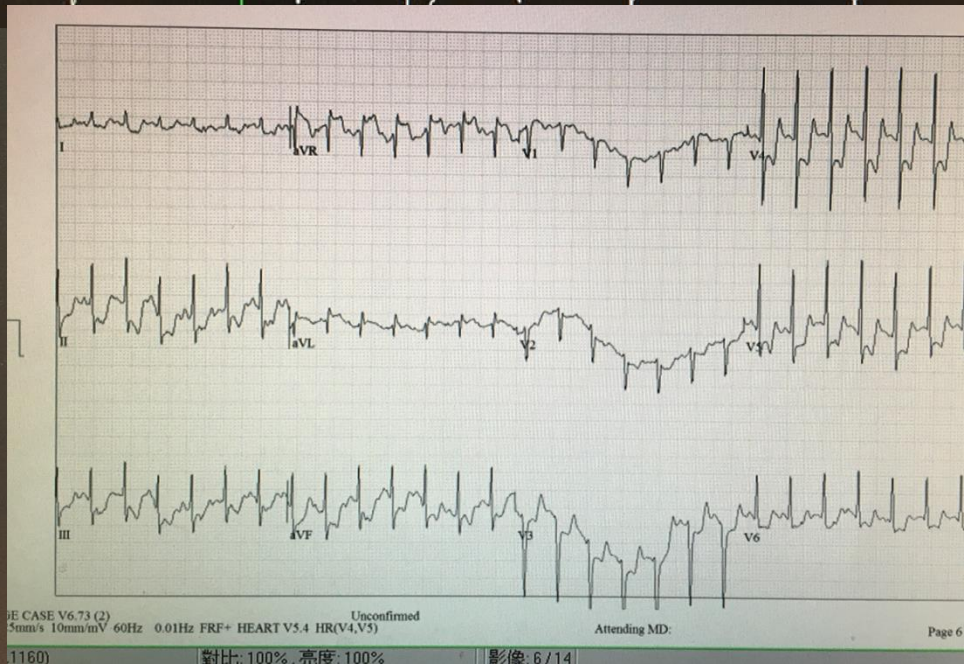
PENDING PCSK9 INHIBITOR THERAPY





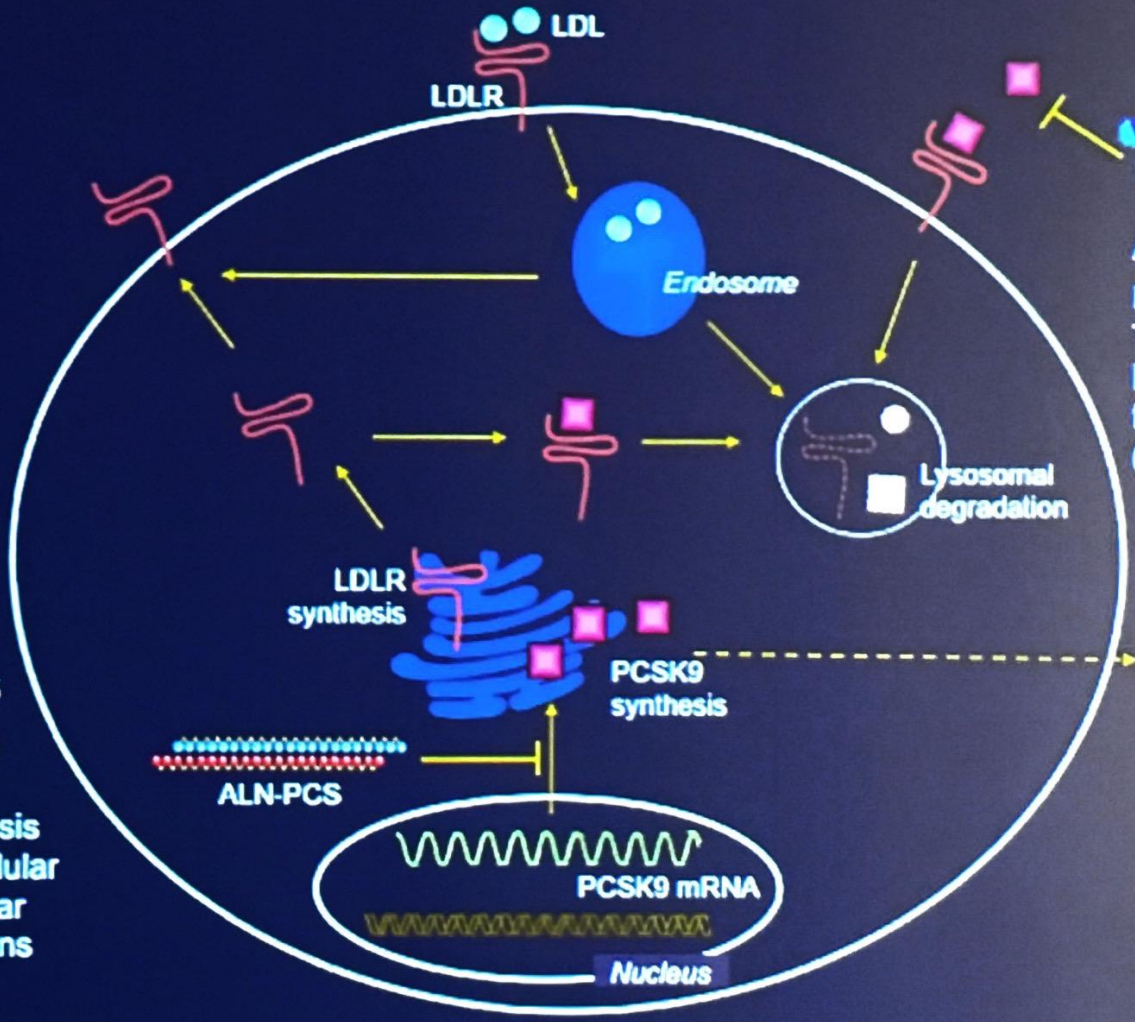





I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
E CASE V6.73 (2)
Unconfirmed
5mm/s 10mm/mV 60Hz 0.01Hz FRF+ HEART V5.4 HR(V4,V5)
Attending MD:
Page 6
1160)
對比: 100% 亮度: 100%
影像: 6 / 14

修訂後給付規定
2.6.4. Evolocumab（如 Repatha）：(107/3/1) 1.限符合下列各項條件之患者使用： (1)確診為同合子家族性膽固醇血症之患者：依中華民國血脂及動脈硬化學會「臺灣血脂異常防治共識節錄—家族性高膽固醇血症之診斷與治療」之「台灣 FH 建議診斷標準」評分總和超過 8 分，且經遺傳基因檢測或符合以下三種臨床徵狀： I.皮膚/肌腱黃色瘤、角膜環 II. 未經藥物治療之 LDL-C＞330 mg/dL 且/或 TC＞500mg/dL III. 父母有高膽固醇血症（未經藥物治療之 TC＞250mg/dL）或早發性冠心病 (2)經使用最高忍受劑量之 statin+ezetimibe 合併治療 6 個月，LDL-C 仍高於 130mg/dL 者，使用本藥品作為輔助療法。 2.需經事前審查核准使用，每次申請之療程 以 6 個月為限。 3.使用後需每 6 個月評估一次 LDL-C，若 LDL-C 連續二次未較治療前降低 18%以上，則不予同意再使用。 4.限每個月使用 1 次，每次最多使用 3 支。

Alternative Approaches to Reducing PCSK9



Anti-PCSK9 mAbs
Transiently block PCSK9 binding to LDL receptor (LDLR)

PCSK9 synthesis inhibitors
Durably block PCSK9 synthesis and all intracellular and extracellular PCSK9 functions

Fitzgerald K, et al. 2015 http://www.alnylam.com/web/assets/ALN-PCSsc-Phase-1_Presentation_08302015.pdf

The contribution of each step:

- AHA 2013 new guideline: 4 statin-benefit groups & high-intensity statin concepts
- Improve-It: non-statin therapy offer further CV benefit, e.g. Ezetamibe in combination with statin, LDL-C goal down to 55 mg/dL for post-ACS patients to reduce MACE
- PCSK9i: Repatha push LDL-C to new therapeutic low, 30 mg/dL, threshold, LDL-C principle became LDL-C fact; “The lower, the best”
- Spire-I & II: less immunogenicity & full human monoclonal antibody count.

Take Home Massages

- PSCK9i push LDL-C to 30 mg/dL on top of maximally tolerated statin +/- ezetamibe to achieve the new milestone of LDL-C lowering and open the new chapter for clinical ASCVD patients care.
- EBM of PCSK9i for several CV outcomes trials (CVOT) are accumulating, potentially fill the unmet need in residual CV risk reduction by tailoring it into personalized lipid lowering strategy,
- AHA 2017 highlights of Repatha subgroup analysis after the major Fourier CVOT deeply explored the potential PCSK9i-benefit group, including prior MI & PAD, with regard to MACE and MALE rates.

Take Home Massages

- FH should be clearly identified since they have high & premature CV mortality and now PCSK9i might restore them back to better life.

- The obstacle of PCSK9i use would be injection, dosing frequency, cost & reimbursement issues. The new chapter is opening and will be surprising.


AMERICAN COLLEGE OF CARDIOLOGY
ACC.17
66th Annual Scientific Session & Expo
Thanks for your attention!!