8th CHALLENGES in CARDIOLOGY

Application of PCSK9 Inhibitors in the clinical practice

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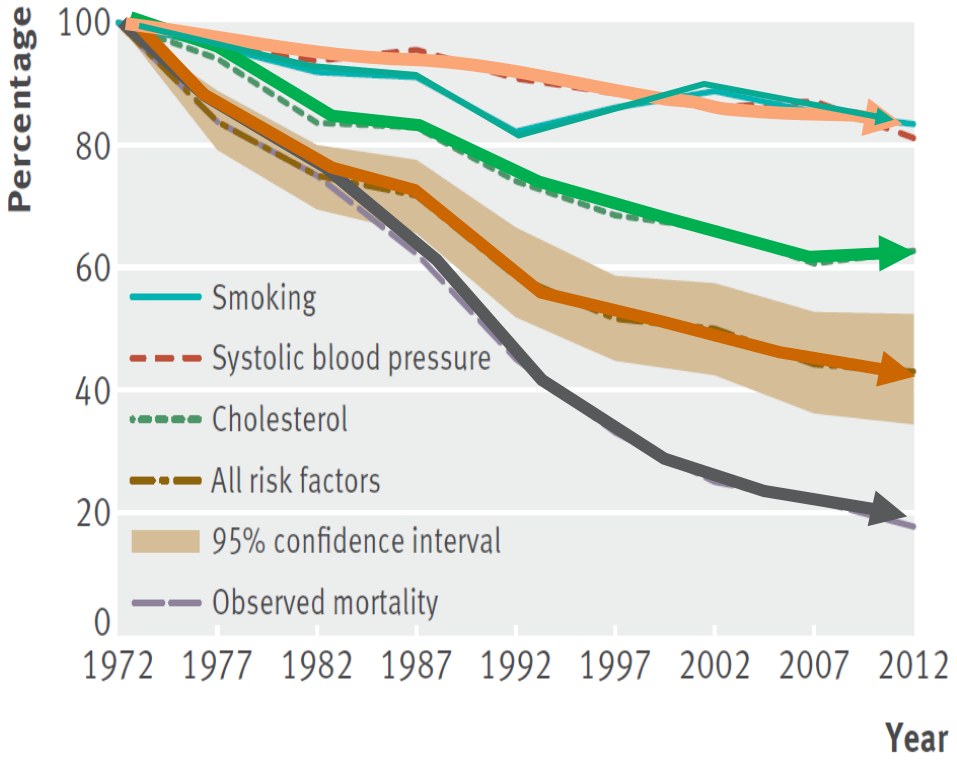
Conflicts of interest

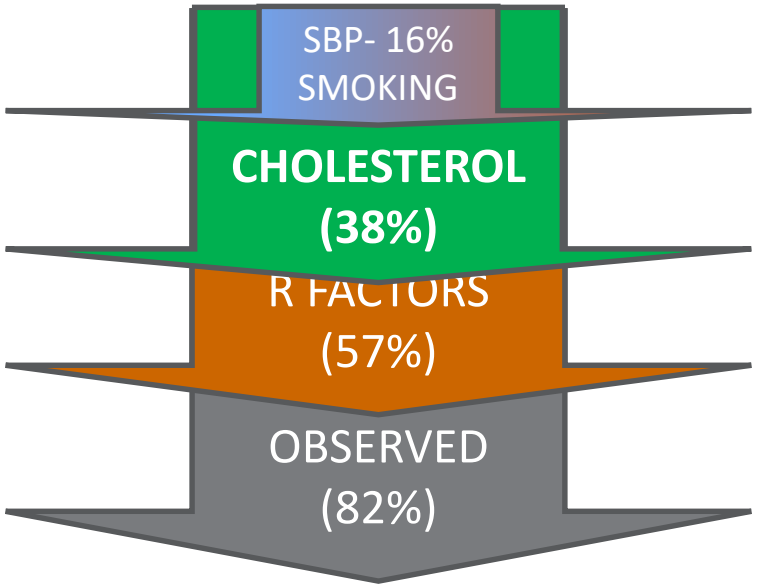
Speaker/consultant for:

AstraZeneca; Bayer Schering Pharma; Boehringer Ingelheim Pharmaceuticals GmbH; Bristol-Myers Squibb; Daiichi Sankyo Europe GmbH; Ferrer International SA; Menarini Group Farma; Novartis AG; Pfizer; Recordati Pharma; Roche Pharma; Sanofi-Aventis; Servier Laboratories; Takeda Pharmaceuticals GmbH

CHD mortality & Risk Factor reduction

40 yr population based study in Finland





Observed and predicted reduction in coronary heart disease mortality 1969-2012 in men (age 35-64 years)

BMJ 2016;352:i721
http://dx.doi.org/10.1136/bmj.i721

LDL-c is the main factor associated with the declining incidence of CAD

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Trends in Modifiable Risk Factors are Associated With Declining Incidence of Hospitalized and Non-Hospitalized Acute Coronary Heart Disease in a Population

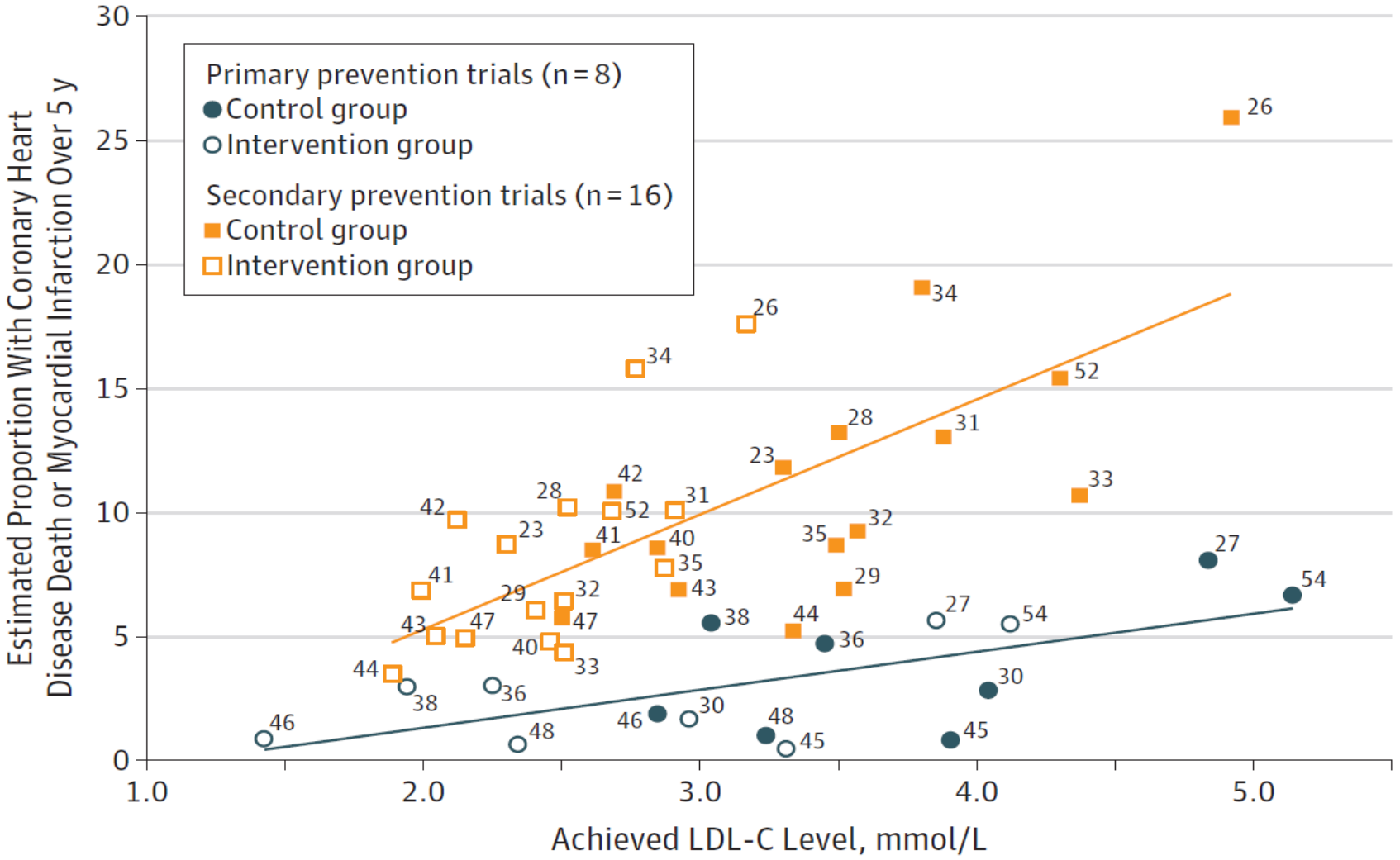
Jan Mannsverk, Tom Wilsgaard, Ellisiv B. Mathiesen, Maja-Lisa Løchen, Knut Rasmussen, Dag S. Thelle, Inger Njølstad, Laila Arnesdatter Hopstock and Kaare Harald Bønaa

1994 to 2010. The age-and sex-adjusted incidence of total coronary heart disease decreased by 3% (95% confidence interval 2.0% to 4.0%, P<0.001) each year. This decline was driven by decreases in out-hospital sudden death and hospitalized ST-elevation myocardial infarction. Changes in coronary risk factors accounted for 66% (95% confidence interval 48 to 97, P<0.001) of the decline in total coronary heart disease. Favorable changes in cholesterol contributed 32% to the decline, whereas blood pressure, smoking, and physical activity each contributed 14%, 13%, and 9%, respectively.

Mannsverk J, et al.
Circulation 2016;133(1):74-81.

Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions

A Systematic Review and Meta-analysis



Silverman MG, et al. JAMA 2016;316:1289-97

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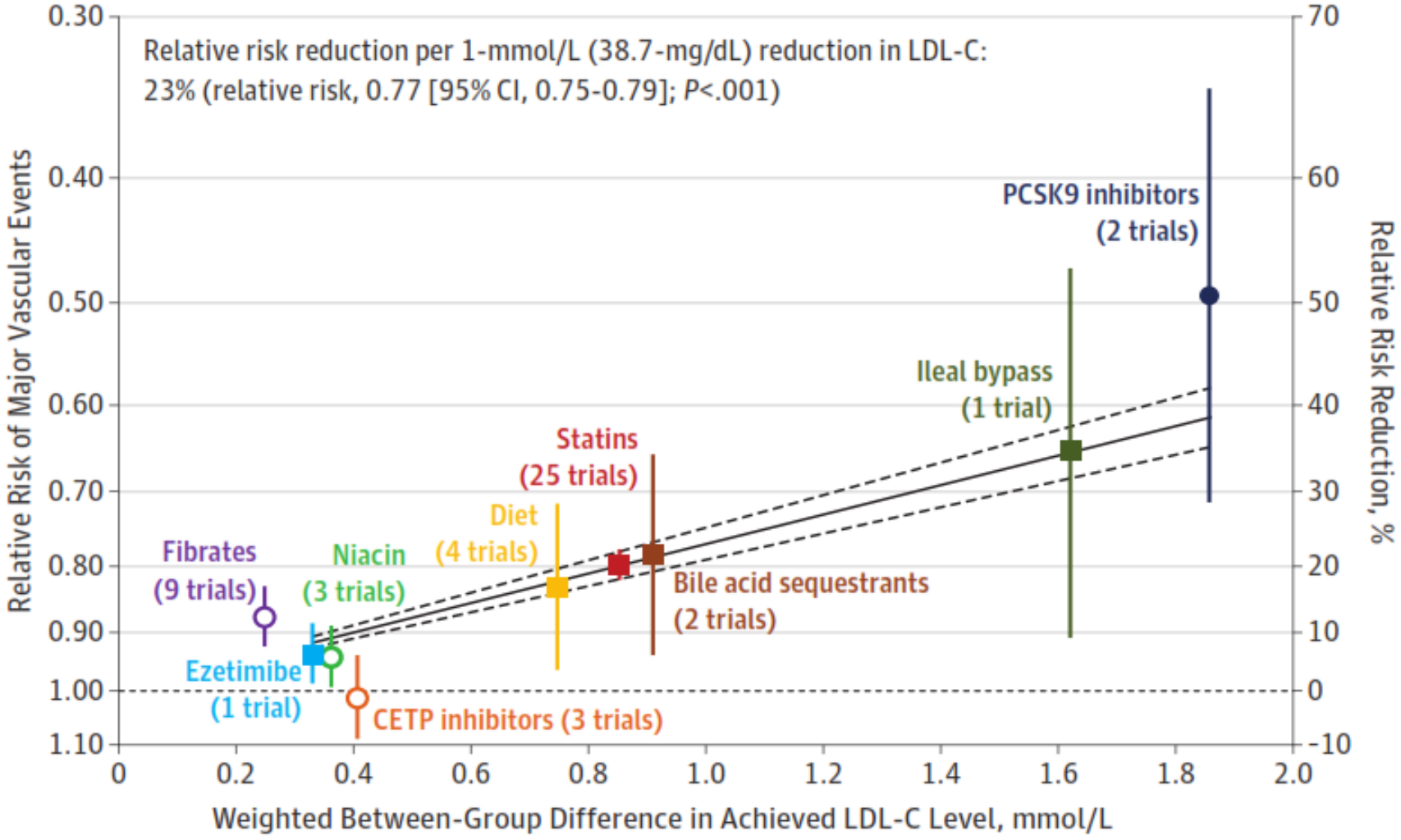
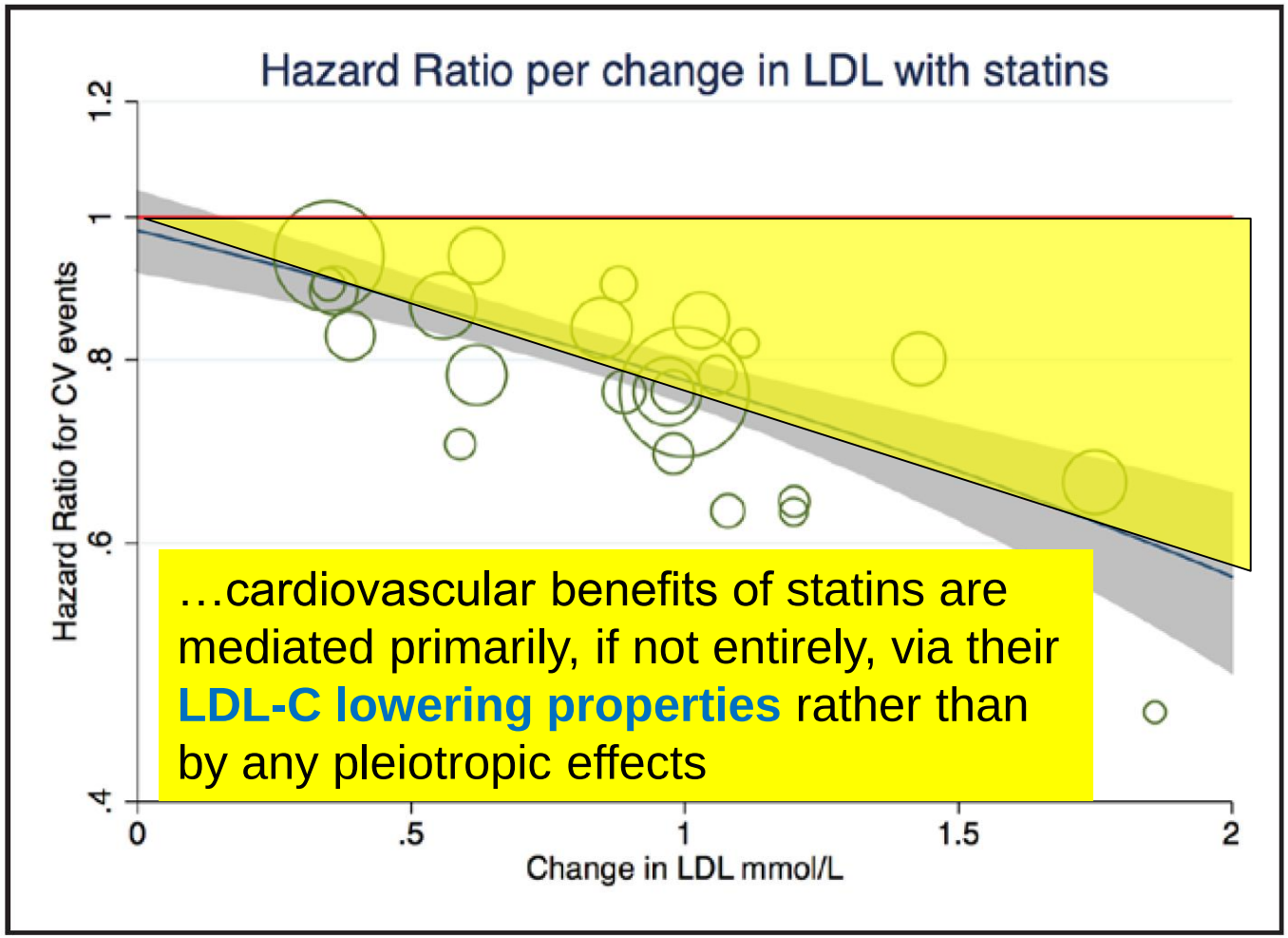


Silverman MG, et al. JAMA 2016;316:1289-97

Evaluation of the Pleiotropic Effects of Statins

A Reanalysis of the Randomized Trial Evidence Using Egger Regression



Arterioscler Thromb Vasc Biol 2018 Jan;38(1):262-65
doi: 10.1161/ATVBAHA.117.310052

ASCVD Risk Categories & LDL-c Treatment Goals

Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH – History of premature ASCVD (<55 male, <65 female)	**<55**	**<80**	**<70**
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – DM or stage 3 or 4 CKD with 1 or more risk factor(s) – HeFH	**<70**	**<100**	**<80**
High risk	– ≥2 risk factors and 10-year risk 10%-20% – DM or stage 3 or 4 CKD with no other risk factors	**<100**	**<130**	**<90**
Moderate risk	≤2 risk factors and 10-year risk <10%	**<100**	**<130**	**<90**
Low risk	0 risk factors	**<130**	**<160**	**NR**

Abbreviations: ACS, acute coronary syndrome; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not recommended.

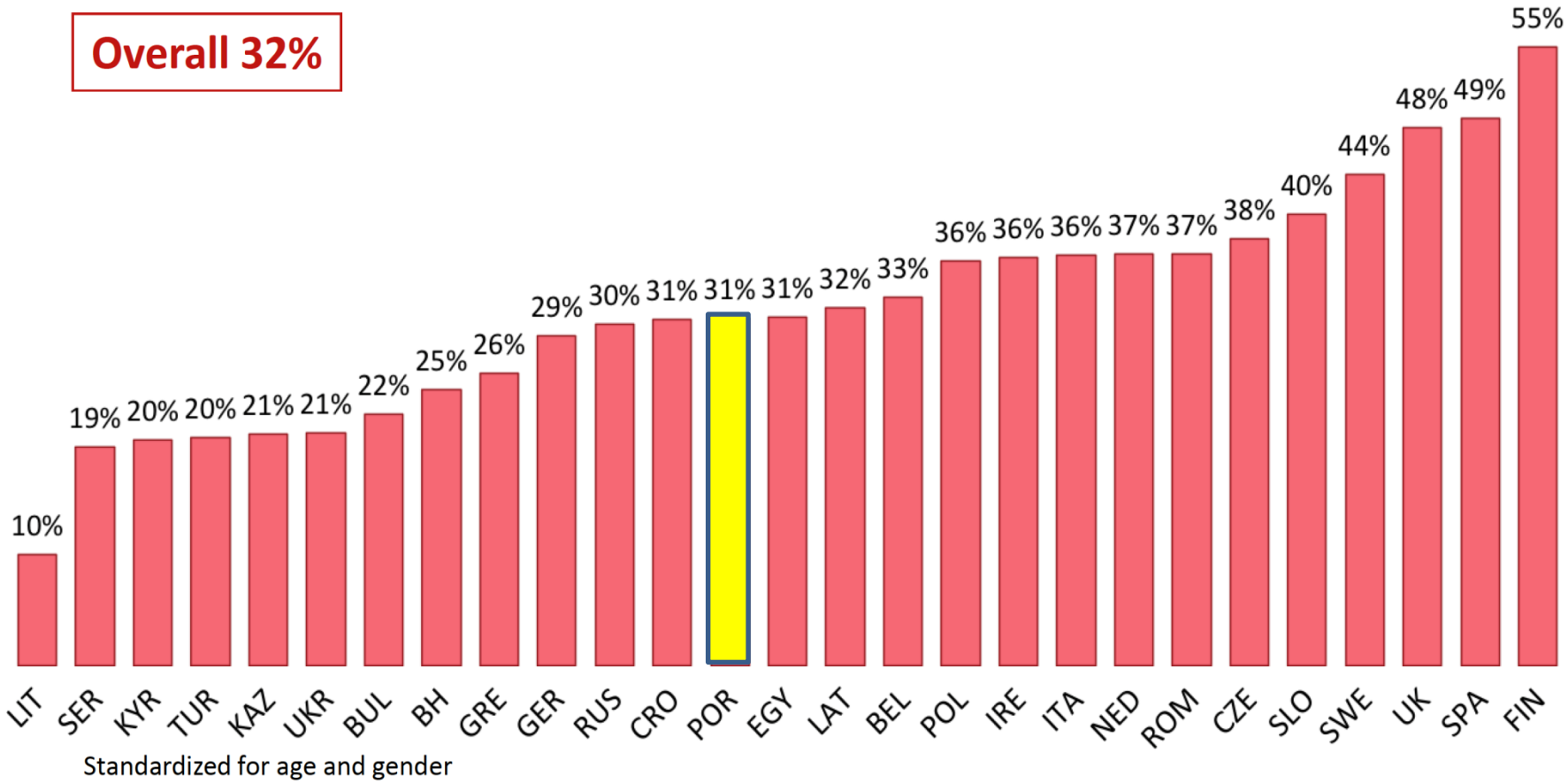
Barter PJ, et al. J Intern Med. 2006;259:247-258; Boekholdt SM, et al. J Am Coll Cardiol. 2014;64(5):485-494; Brunzell JD, et al. Diabetes Care. 2008;31:811-822; Cannon CP, et al. N Engl J Med. 2015;372(25):2387-2397; Grundy SM, et al. Circulation. 2004;110:227-239; Heart Protection Study Collaborative Group. Lancet. 2002;360:7-22; Jellinger P, Handelsman Y, Rosenblit P, et al. Endocr Practice. 2017;23(4):479-497; Lloyd-Jones DM, et al. Am J Cardiol. 2004;94:20-24; McClelland RL, et al. J Am Coll Cardiol. 2015;66(15):1643-1653; NHLBI. NIH Publication No. 02-5215. 2002; Ridker PM, J Am Coll Cardiol. 2005;45:1644-1648; Ridker PM, et al. JAMA. 2007;297(6):611-619; Sever PS, et al. Lancet. 2003;361:1149-1158; Shepherd J, et al. Lancet. 2002;360:1623-1630; Smith SC Jr, et al. Circulation. 2006;113:2363-2372; Stevens RJ, et al. Clin Sci. 2001;101(6):671-679; Stone NJ. Am J Med. 1996;101:4A40S-48S; Weiner DE, et al. J Am Soc Nephrol. 2004;15(5):1307-1315.

EUROASPIRE V

EUROASPIRE V

LDL-cholesterol <1.8 mmol/L (70 mg/dL) in patients on lipid-lowering drugs

ESC European Society of Cardiology



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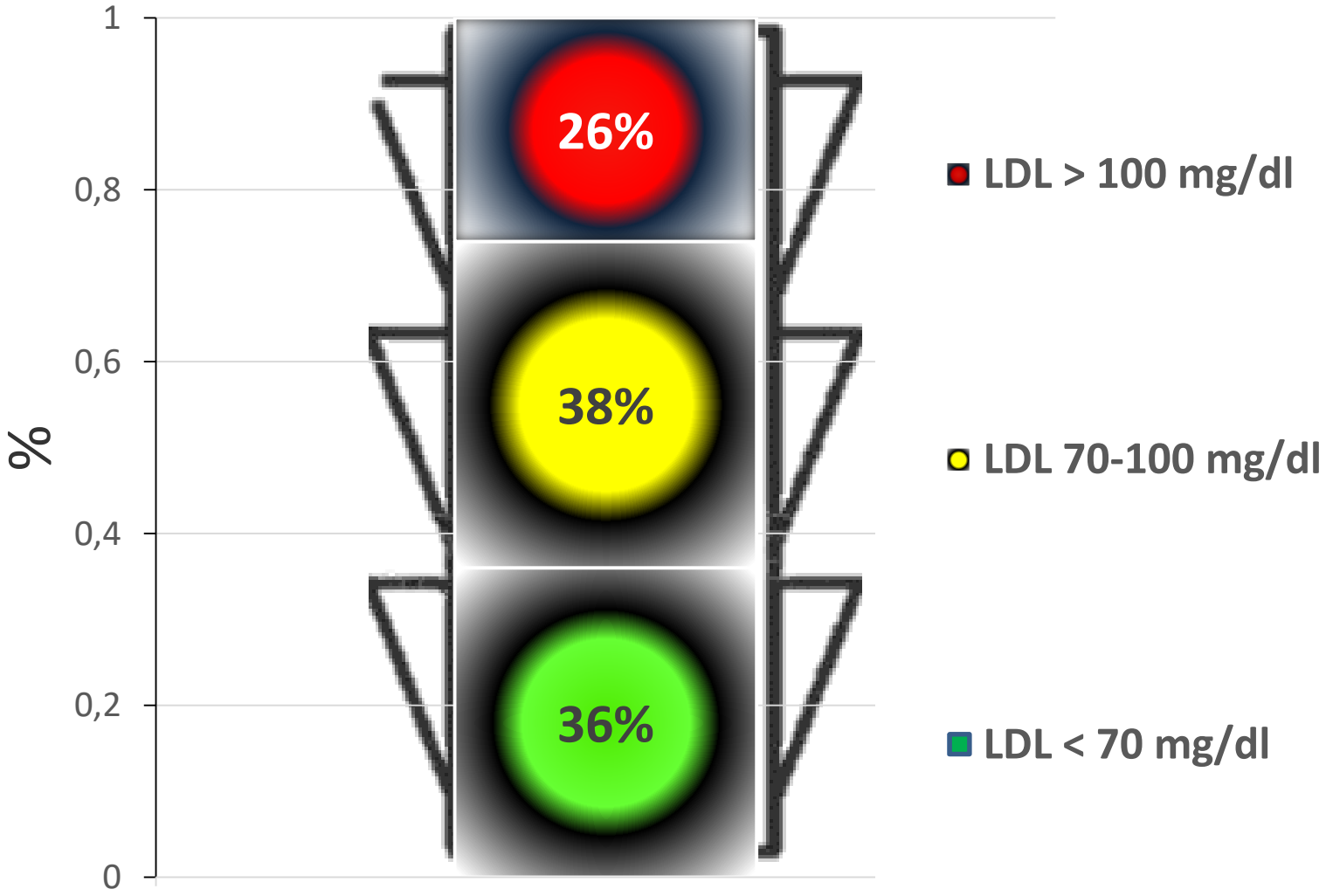
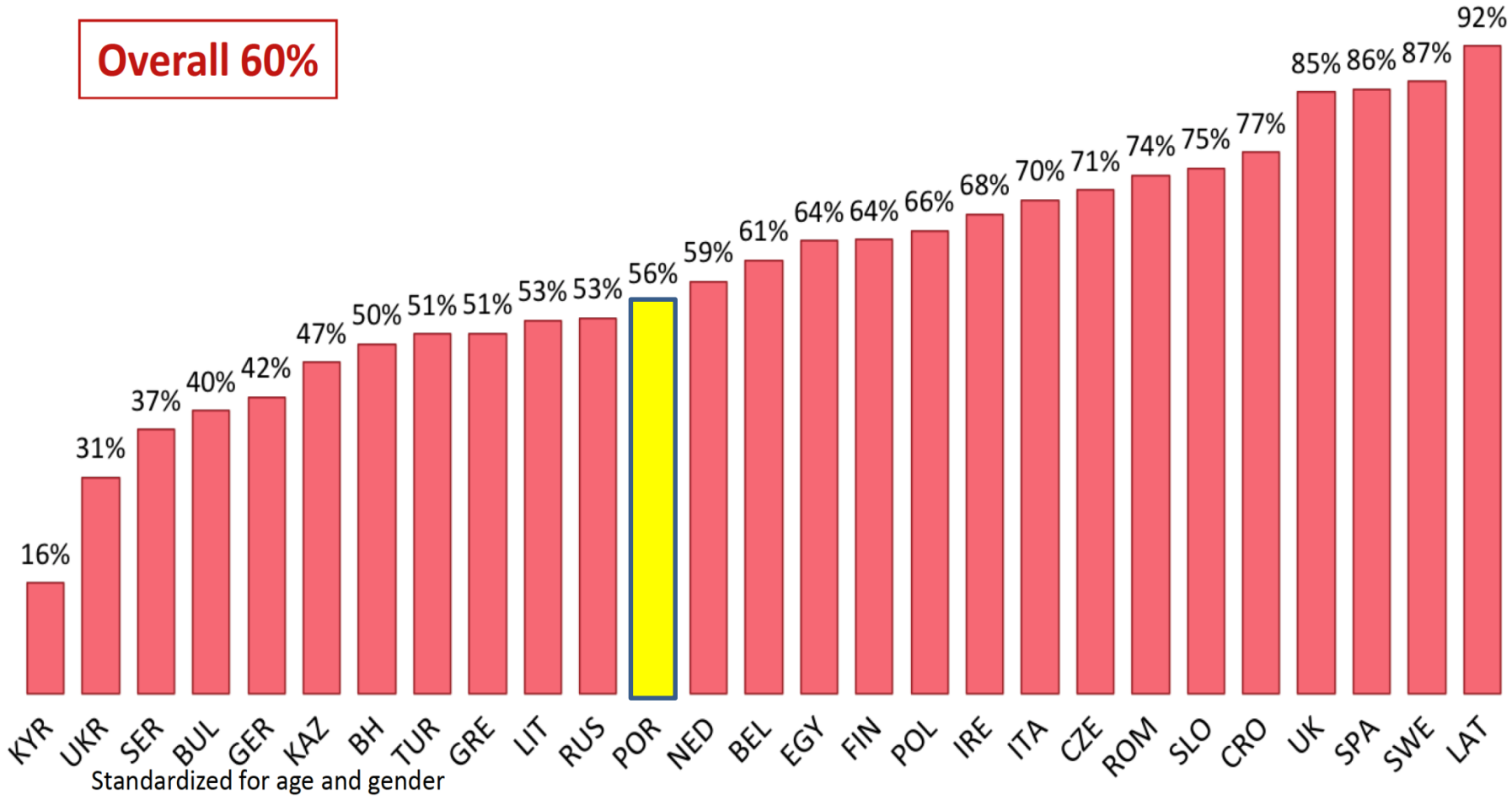


EUROASPIRE V

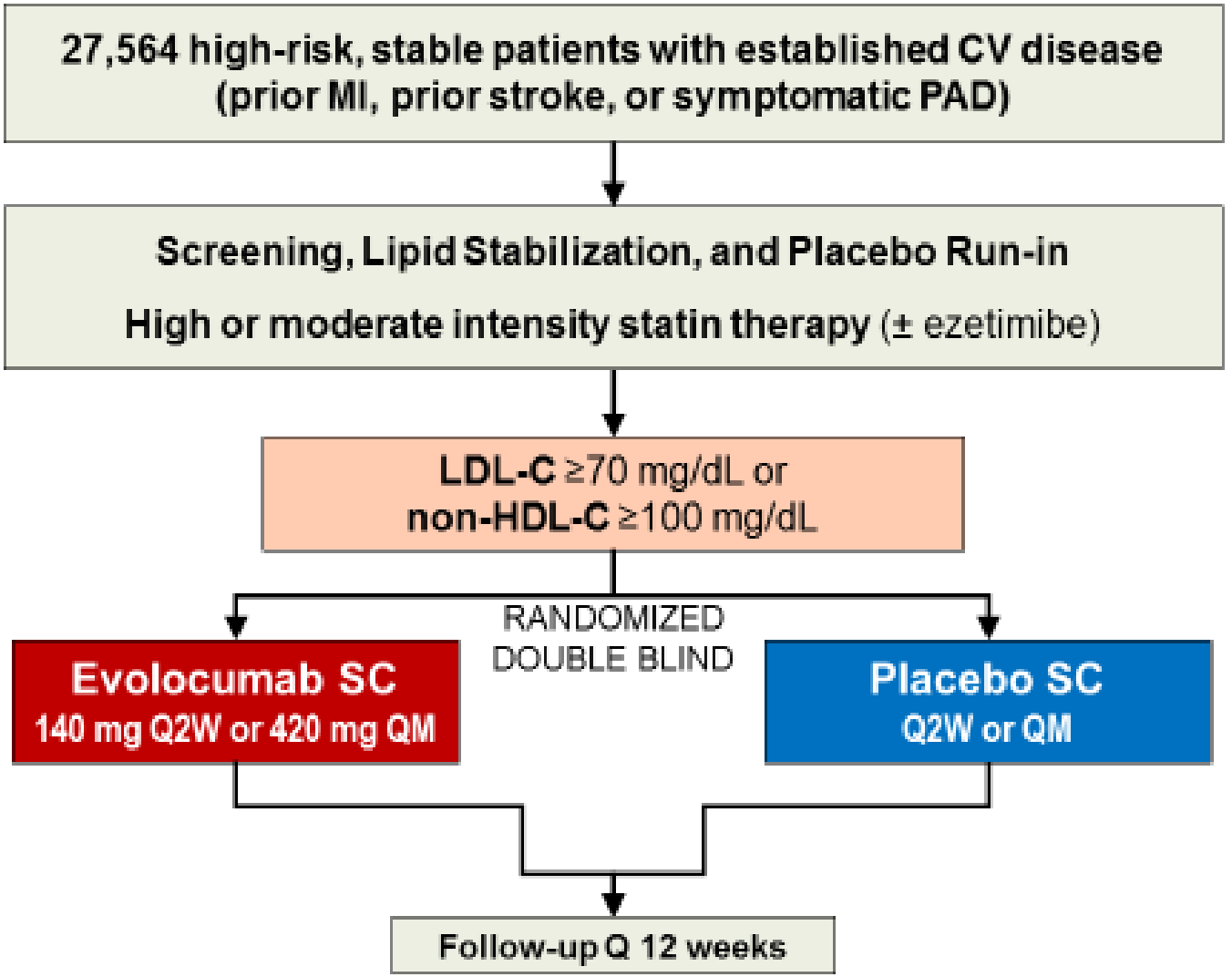
EUROASPIRE V

Use of high intensity LLD in patients on statins, combination therapy or PCSK9 inhibitors

ESC European Society of Cardiology



Trial Design



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

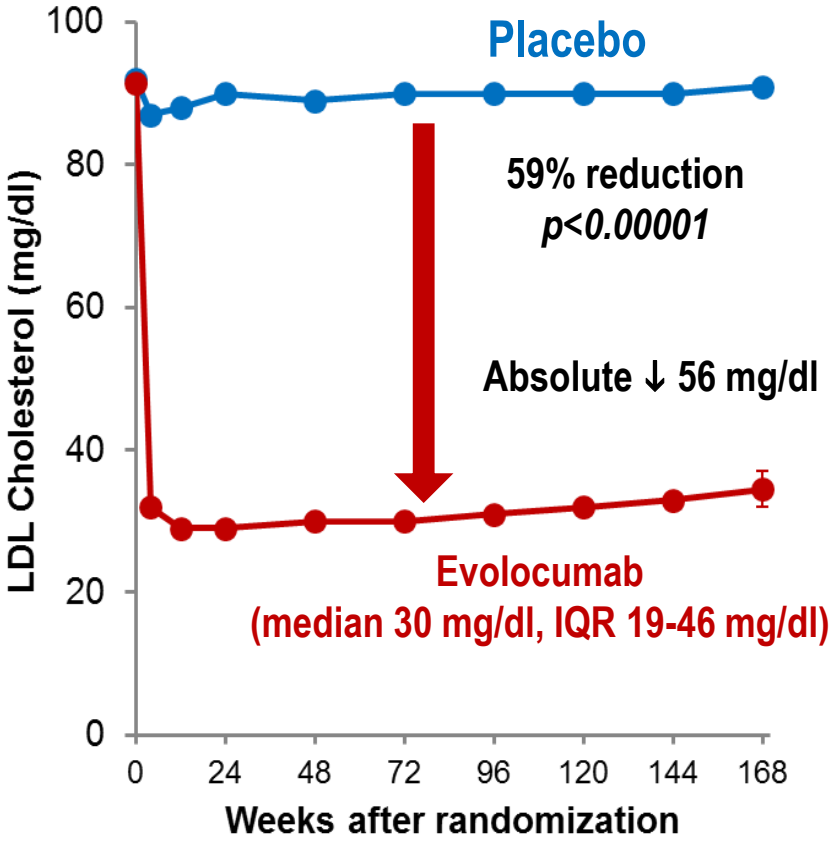
FOURIER
Baseline characteristics

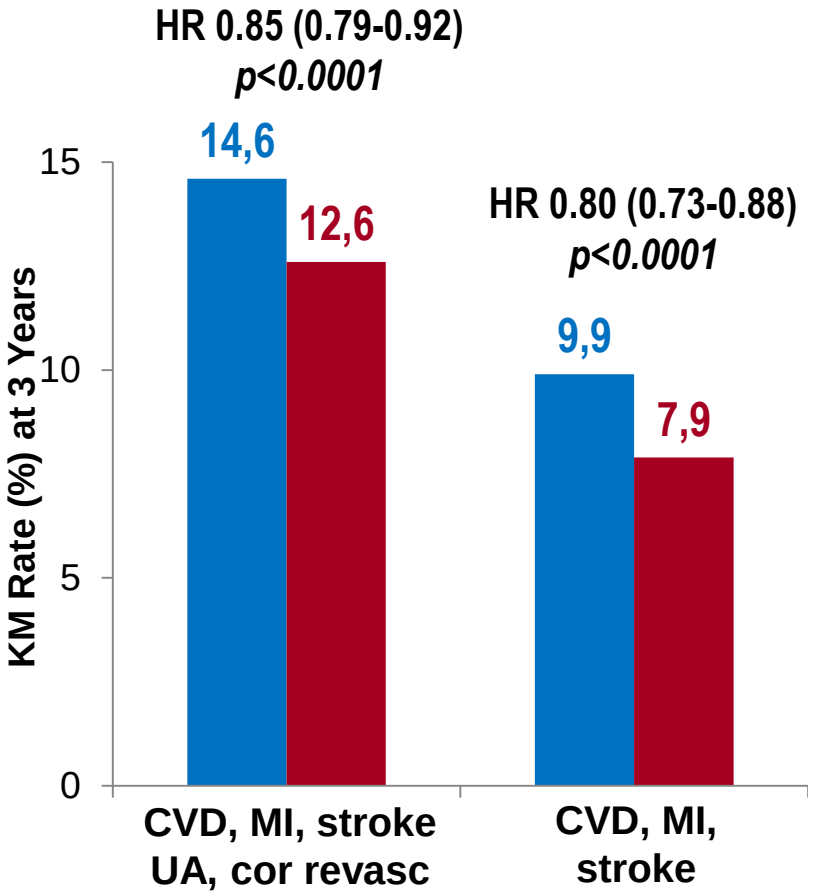
Characteristics	Evolocumab (N = 13,784)	Placebo (N = 13,780)
Demographics		
Age – y (SD)	62.5 (9.1)	62.5 (8.9)
Male sex – n (%)	10,397 (75.4)	10,398 (75.5)
White race* – n (%)	11,748 (85.2)	11,710 (85.0)
Weight – kg (SD)	85.0 (17.3)	85.5 (17.4)
Region		
North America	2,287 (16.6)	2,284 (16.6)
Europe	8,666 (62.9)	8,669 (62.9)
PORTUGAL	272 (1.0)	
Latin America	913 (6.6)	910 (6.6)
Asia Pacific and South Africa	1,918 (13.9)	1,917 (13.9)

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

Summary of Effects of PCSK9i Evolocumab

- ↓ LDL-C by 59% down to a median of 30 mg/dl
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated





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

Safety
Events by LCL-c Level

Table 3. Adverse Events and Laboratory Test Results.

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

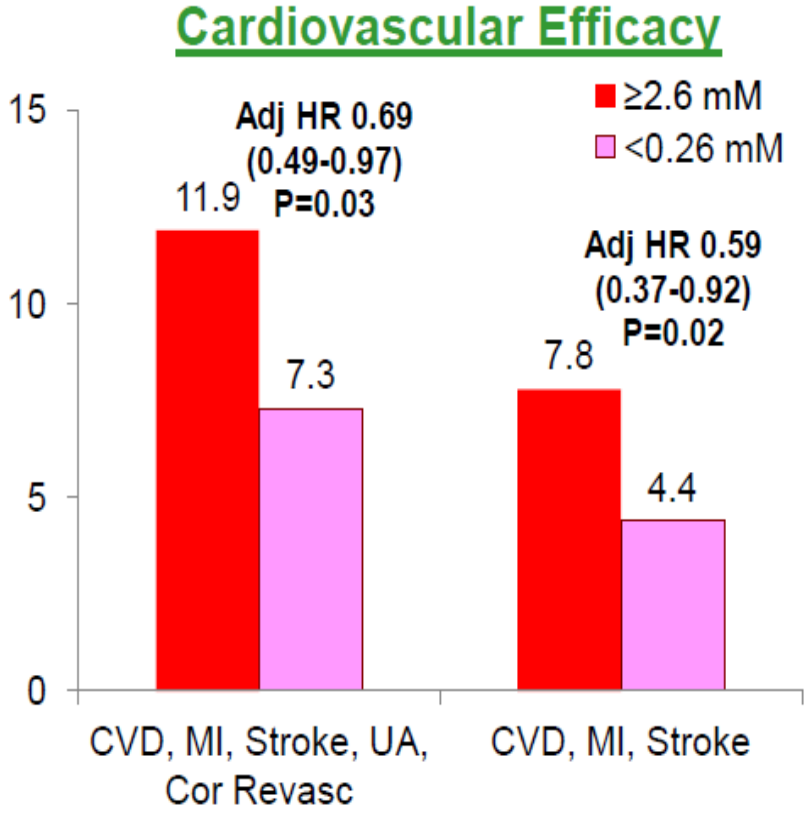
* The between-group difference was nominally significant ($P<0.001$).
† The total numbers of patients were 8337 in the evolocumab group and 8339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.

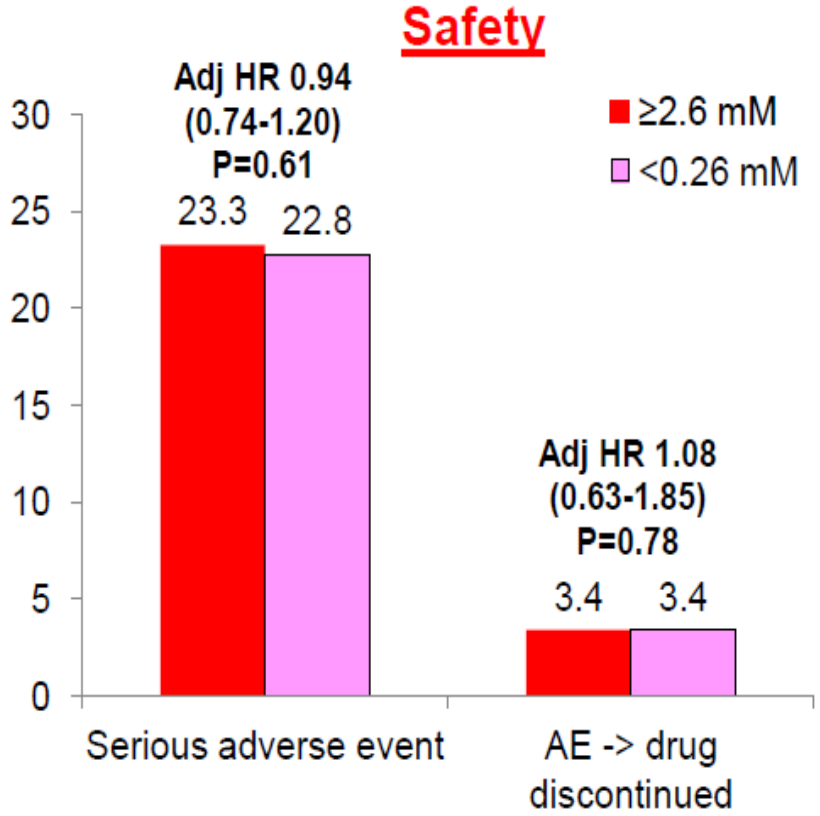
Sabatine MS et al. NEJM 2017;376:1713-22

How much can be LDL-c reduced?

Exploratory Analysis Pts with LDL-C <0.26 mM (<10 mg/dL) at 4 wks

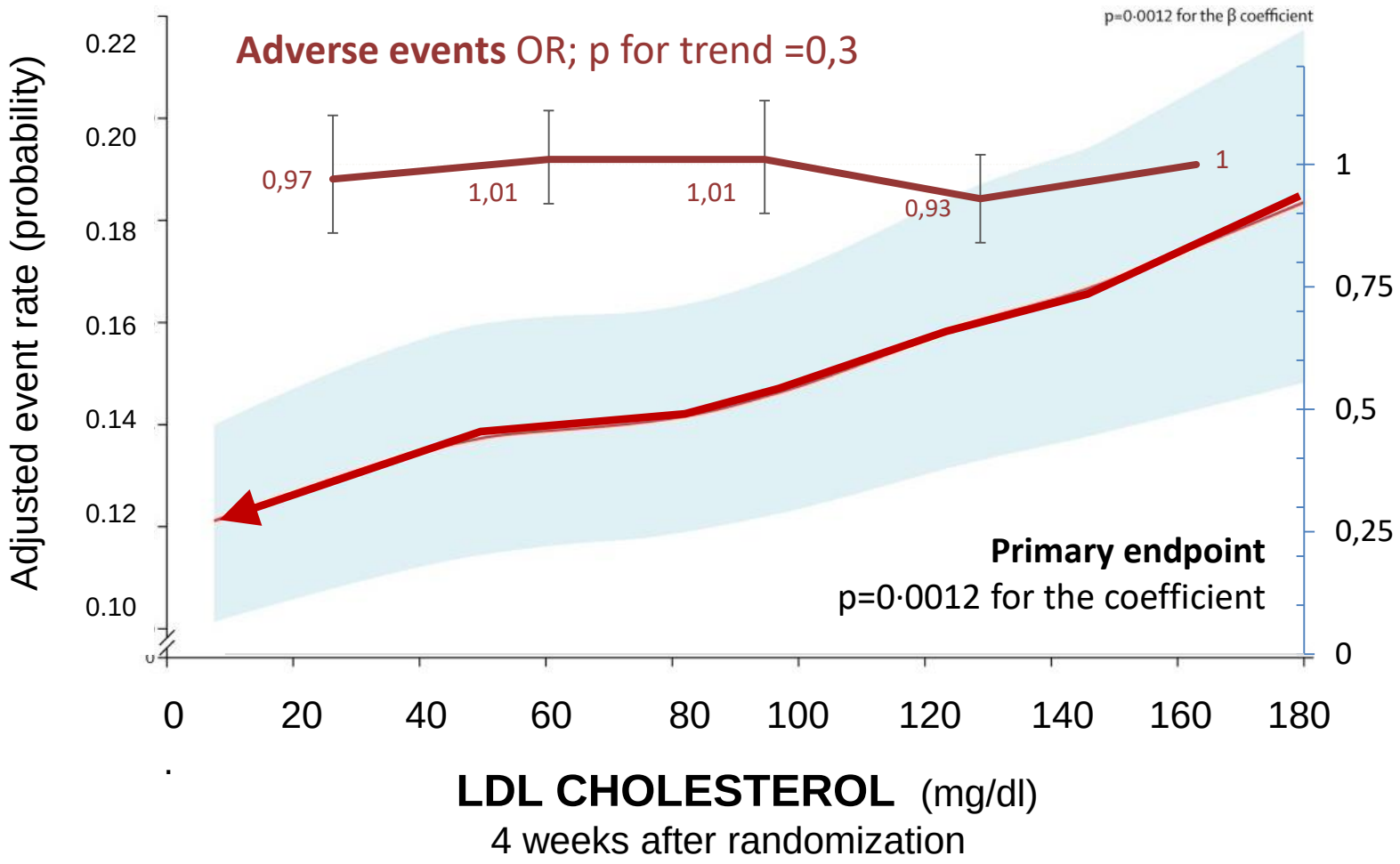
N=504: Median [IQR] LDL-C 0.18 [0.13-0.23] mM = 7 [5-9] mg/dL





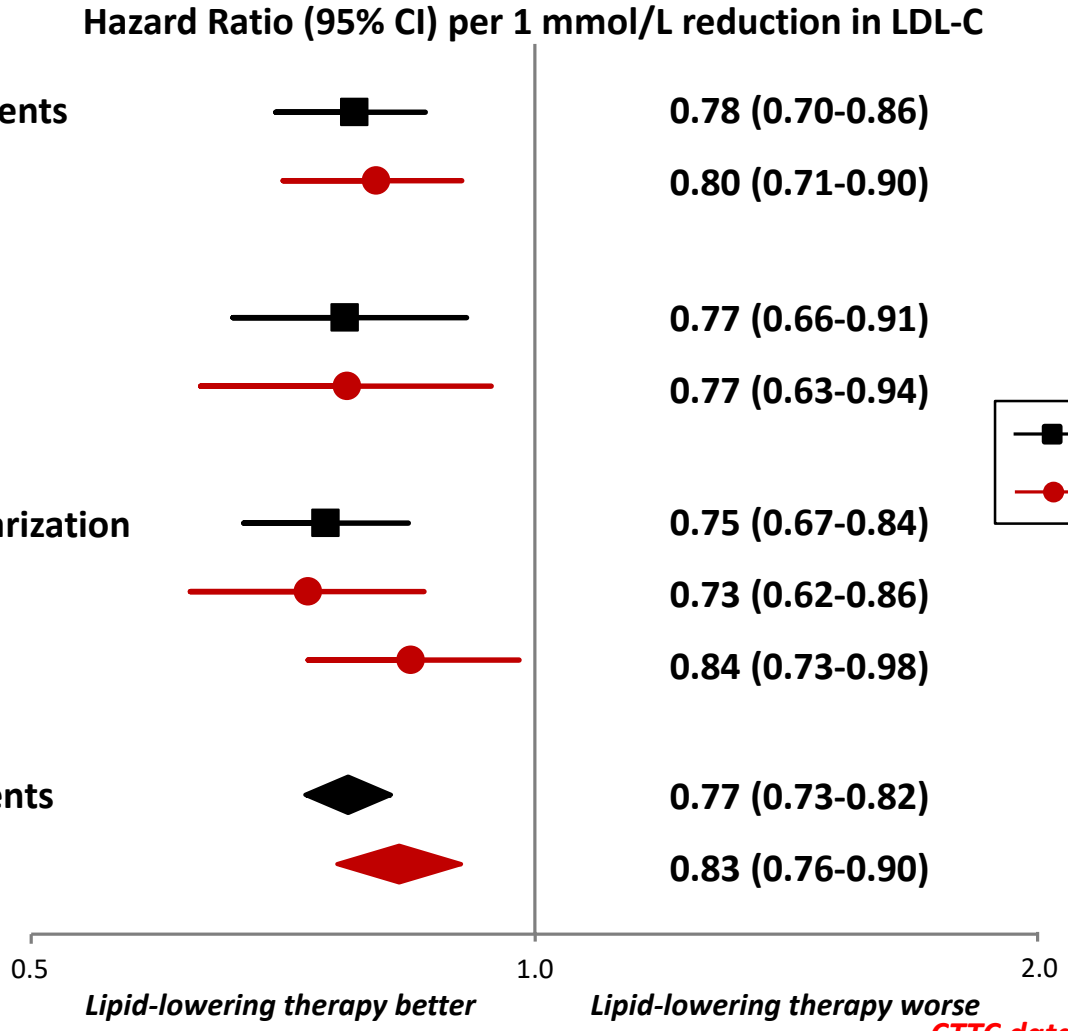
Giugliano RP, et al.
Lancet 2017 Oct 28;390(10106):1962-71

Very low LDL levels & Evolocumab
FOURIER Trial



Giugliano RP, et al.
Lancet 2017 Oct 28;390(10106):1962-71

Comparison to Cholesterol Treatment Trialists Collaboration



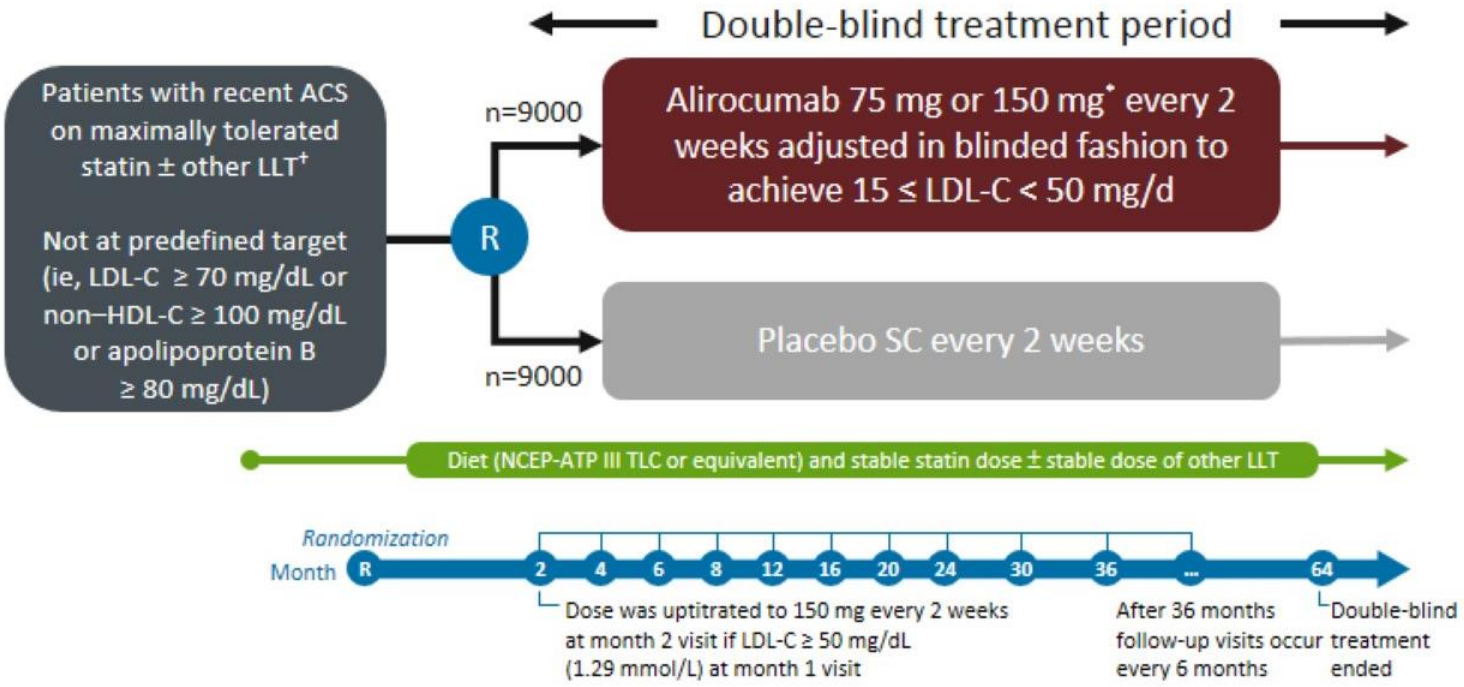
An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

CTTC data from Lancet 2010;376:1670-81

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

ODYSSEY OUTCOMES: Study Design

A randomized, double-blind, placebo-controlled study

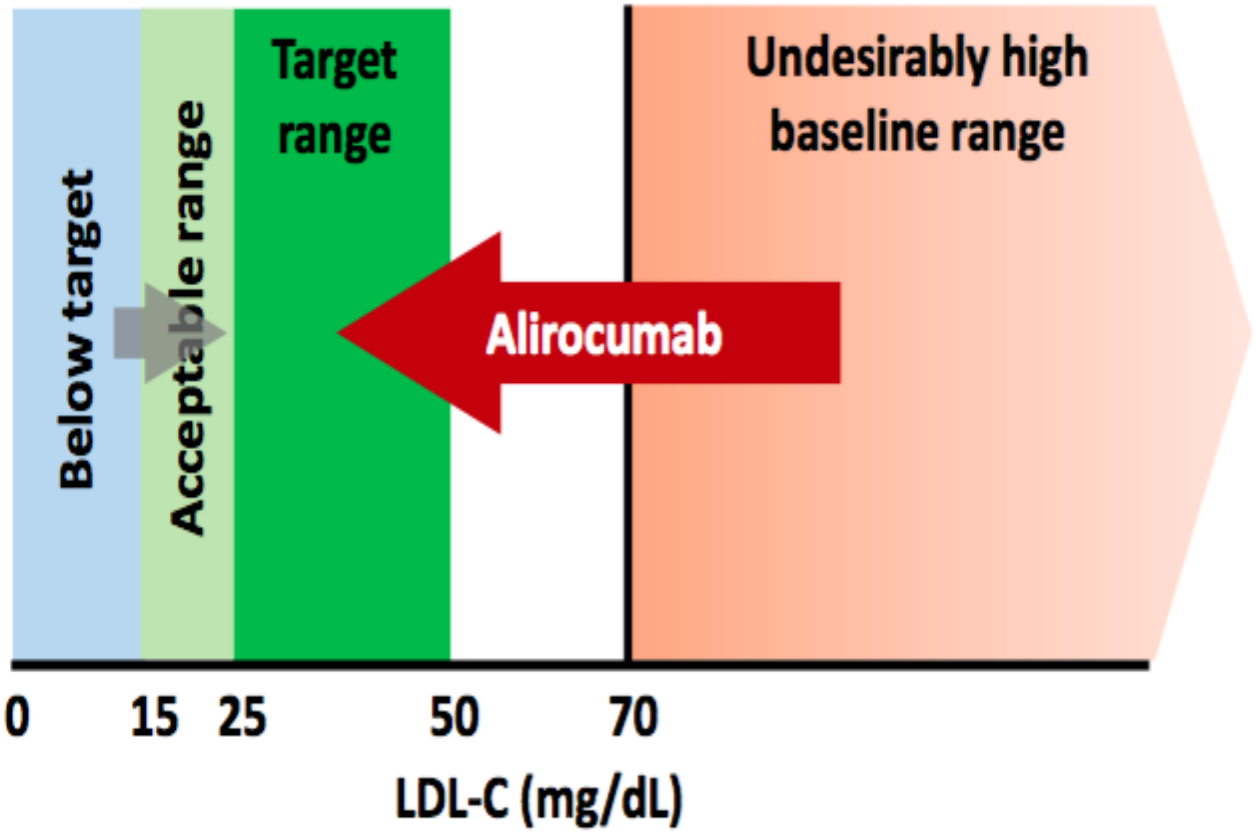


*Dose titrated up to 150 mg every 2 weeks at month 2 if LDL-C ≥50 mg/dL (1.29 mmol/L) at month 1 visit.
†Atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg OR maximally tolerated dose of statin (can be 0 mg).
If LDL-C < 25 mg/dL on any 2 consecutive measurements on alirocumab 150 mg, the dose is reduced to 75 mg.
If LDL-C < 15 mg/dL on 2 consecutive measurements with alirocumab 75 mg, active treatment is discontinued at the next study visit and substituted with placebo.
Schwartz GG, et al. *Am Heart J*. 2014;168:682-689.e1; ClinicalTrials.gov. NCT01663402.

Schawartz GG, et al. Am Heart J 2014;168:682-89.e1

A Target Range for LDL-C

We attempted to maximize the number of patients in the target range and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W) or blindly switching to placebo.



Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

ODYSSEY OUTCOMES

Main Secondary Efficacy Endpoints:
Hierarchical Testing

ODYSSEY OUTCOMES

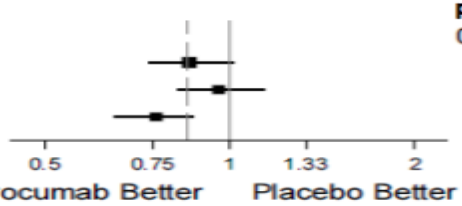
Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
CHD event	**1199 (12.7)**	**1349 (14.3)**	**0.88 (0.81, 0.95)**	**0.001**
Major CHD event	**793 (8.4)**	**899 (9.5)**	**0.88 (0.80, 0.96)**	**0.006**
CV event	**1301 (13.7)**	**1474 (15.6)**	**0.87 (0.81, 0.94)**	**0.0003**
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***

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
MACE	**903 (9.5)**	**1052 (11.1)**	**0.85 (0.78, 0.93)**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
Non-fatal MI	**626 (6.6)**	**722 (7.6)**	0.86 (0.77, 0.96)	0.006
Ischemic stroke	**111 (1.2)**	**152 (1.6)**	0.73 (0.57, 0.93)	0.01
Unstable angina	**37 (0.4)**	**60 (0.6)**	0.61 (0.41, 0.92)	0.02

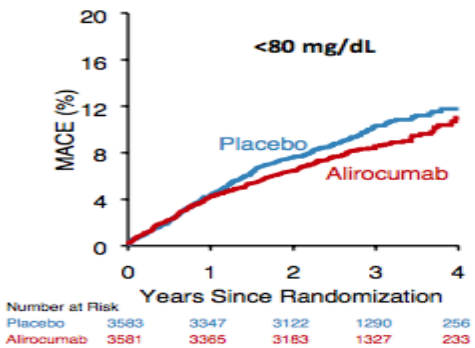
"..choose the right patient…
..more than just point out LDL-c level…"

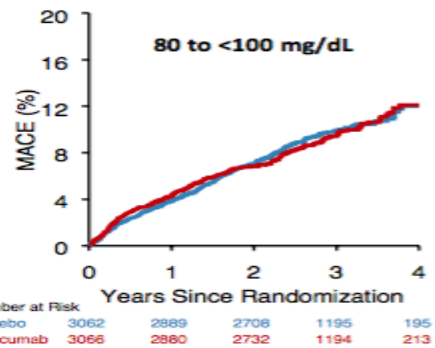
Primary Efficacy in Main Prespecified Subgroups

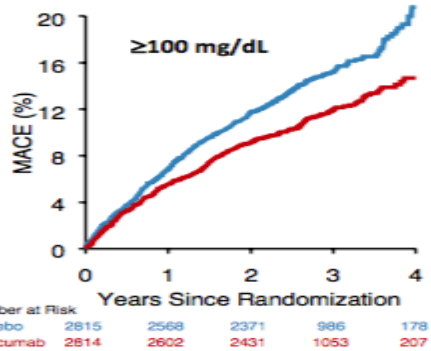
Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	



*P-values for interaction





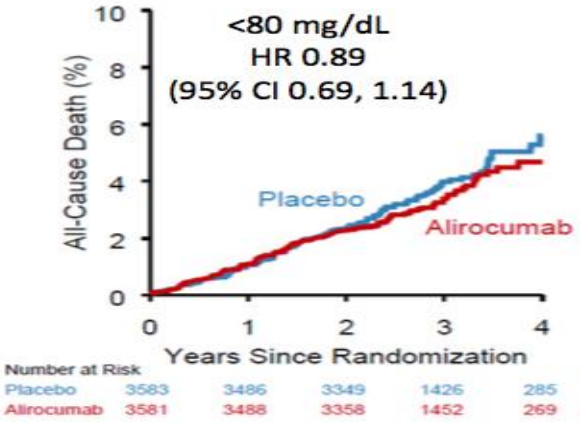


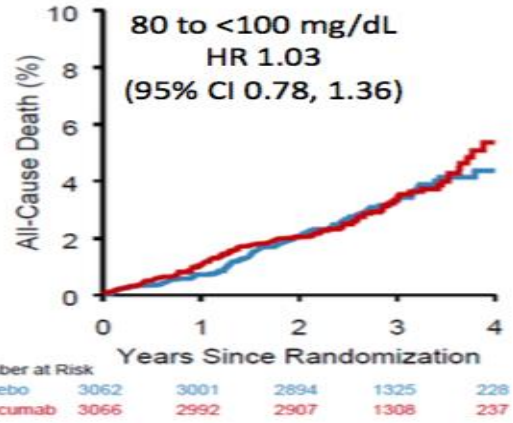
NNT 29 vs 63

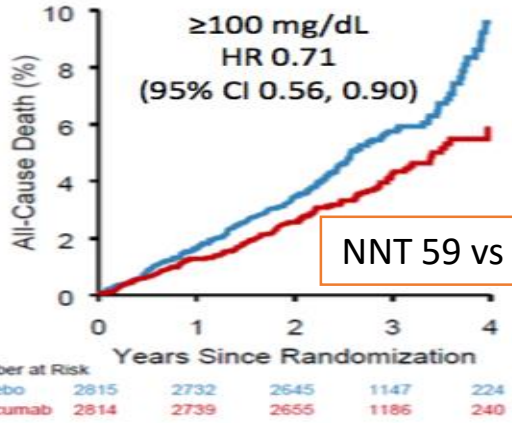
ODYSSEY OUTCOMES

Post Hoc Analysis: All-Cause Death by Baseline LDL-C Subgroups

ARR* 1.7% $P_{interaction}$=0.12



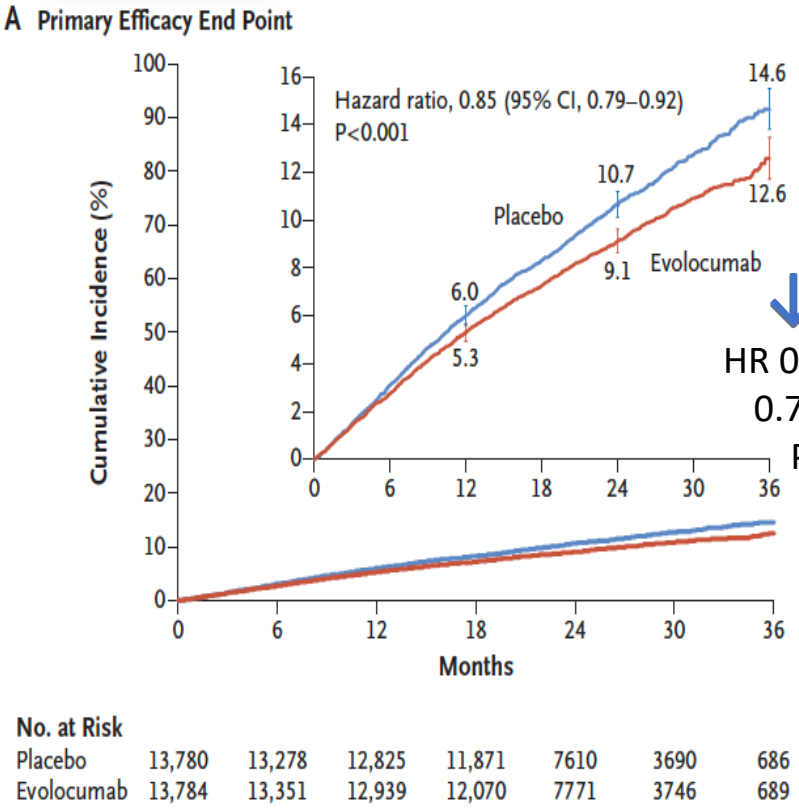




NNT 59 vs 167

Clinical benefits in RCT actually begin at LDL-c level > 70 mg/dL

fourier



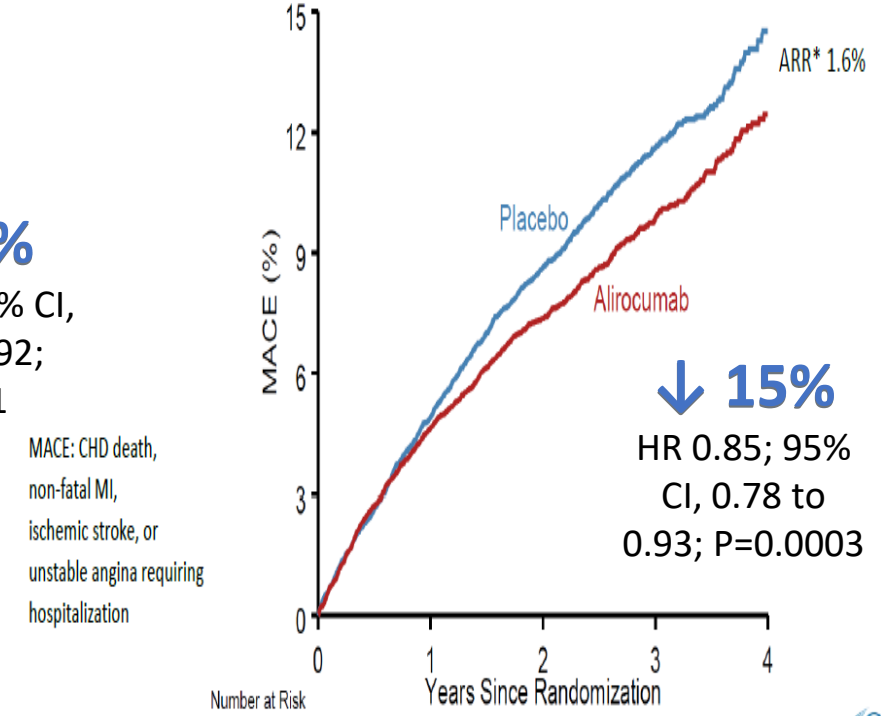
↓ 15%

HR 0.85; 95% CI, 0.79 to 0.92; P<0.001

Sabatine MS, et al.
N Engl J Med 2017;376:1713-22

Primary Efficacy Endpoint: MACE

ODYSSEY OUTCOMES



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

*Based on cumulative incidence

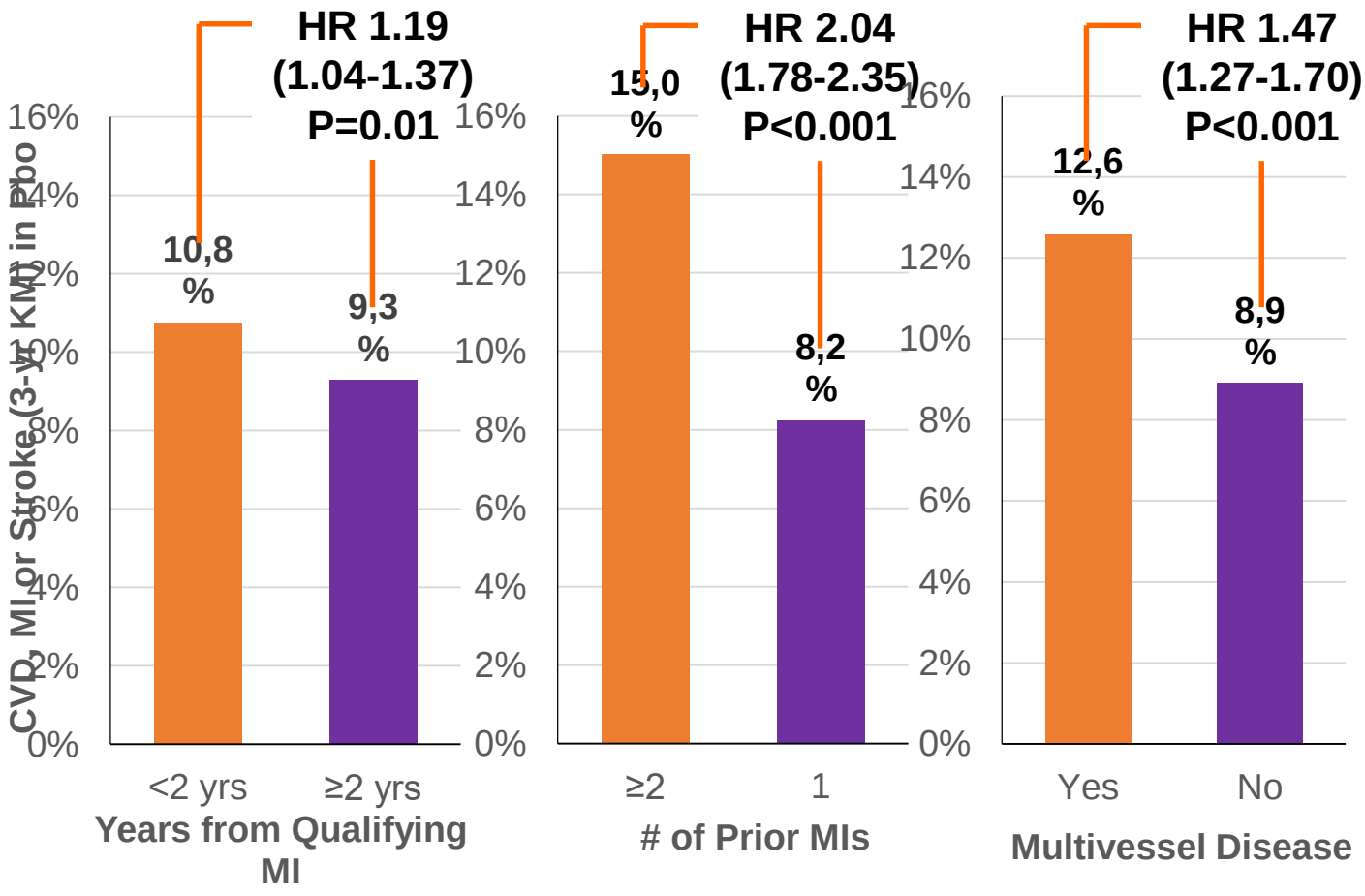
↓ 15%

HR 0.85; 95% CI, 0.78 to 0.93; P=0.0003

ODYSSEY OUTCOMES

Giugliano RP
ACC Meeting 2018 Orlando, FLO)

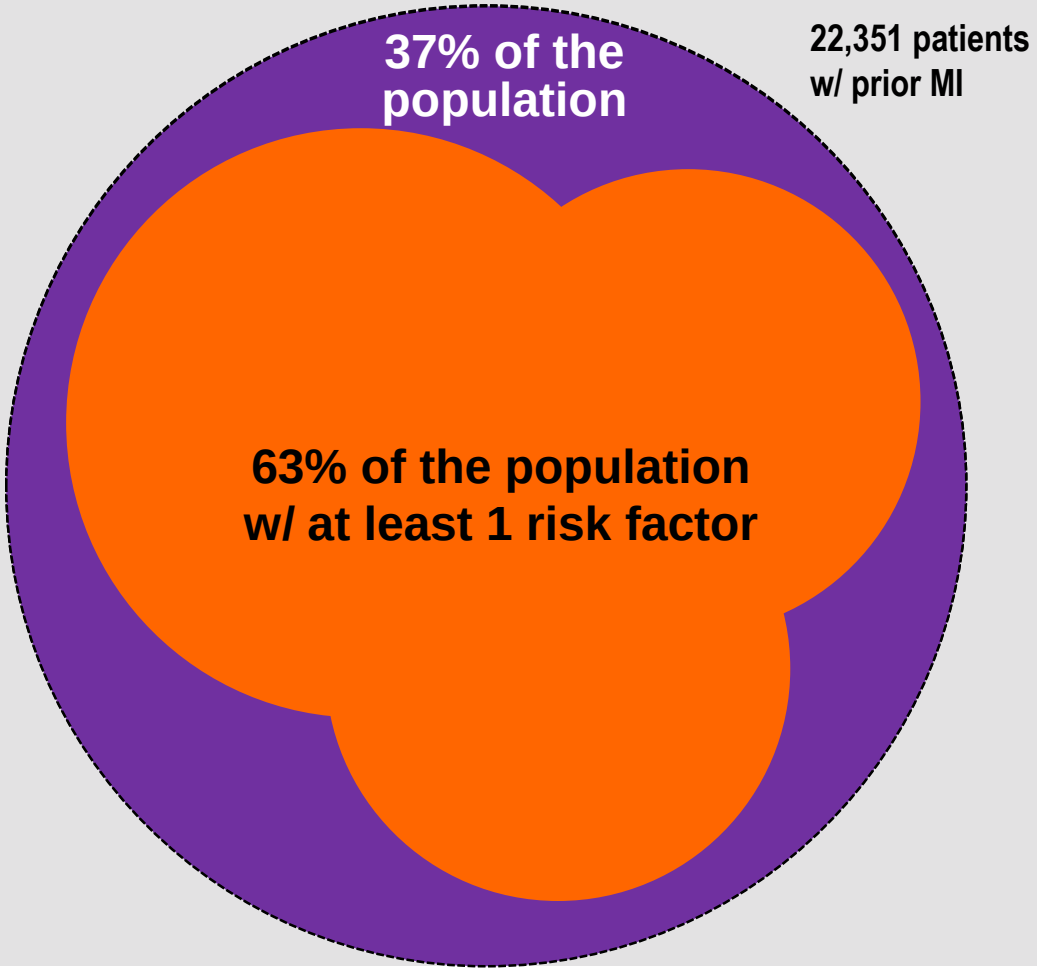
Risk of CV Death, MI or Stroke with Each Risk Factor



Analyses in placebo arm

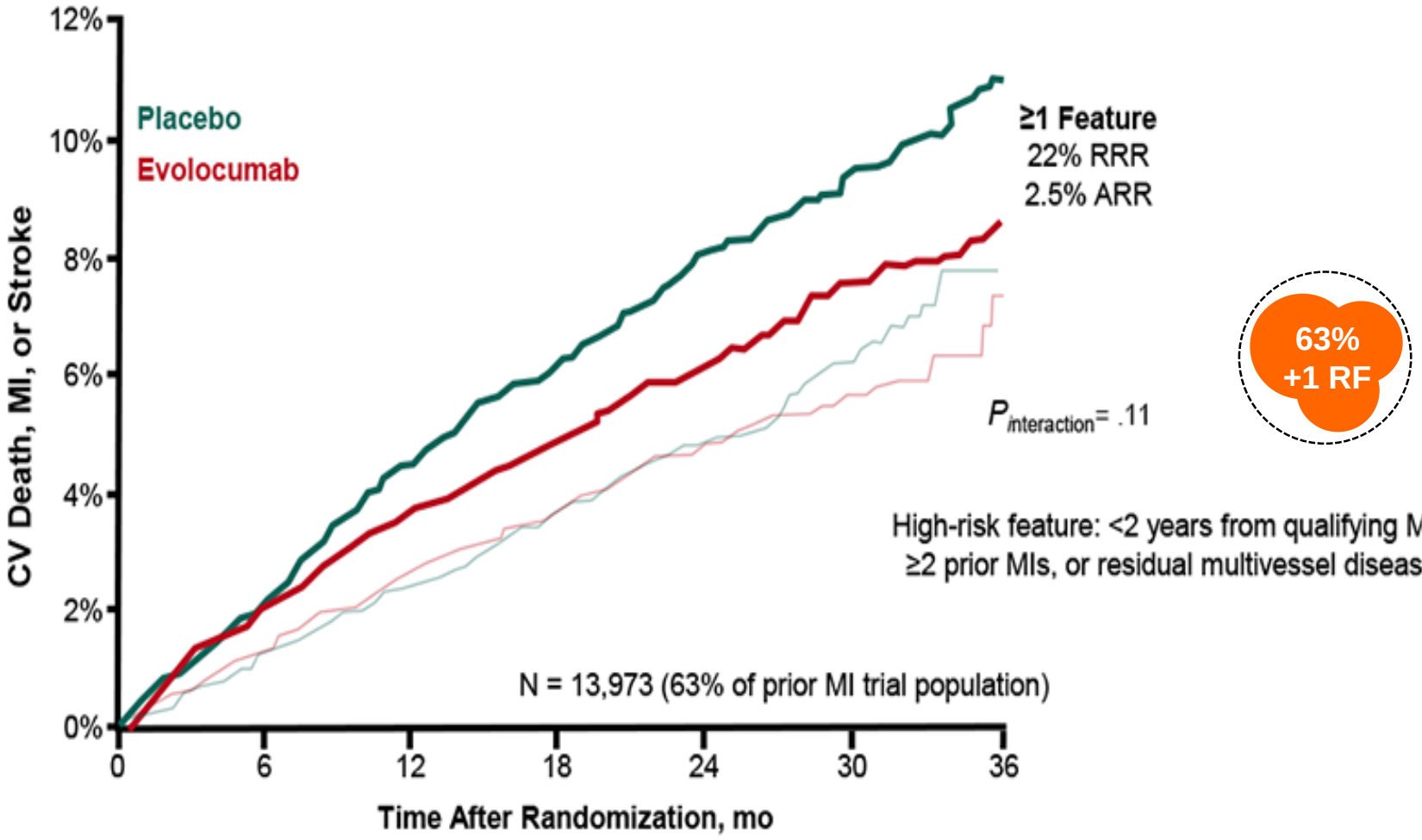
Sabatine MS, et al. Circulation 2018 Apr 6.
doi: 10.1161/CIRCULATIONAHA.118.034309. [Epub ahead of print]

OVERLAP BETWEEN FACTORS



Sabatine MS, et al. Circulation 2018

Benefit of EvoMab based on Number of High-Risk MI Features



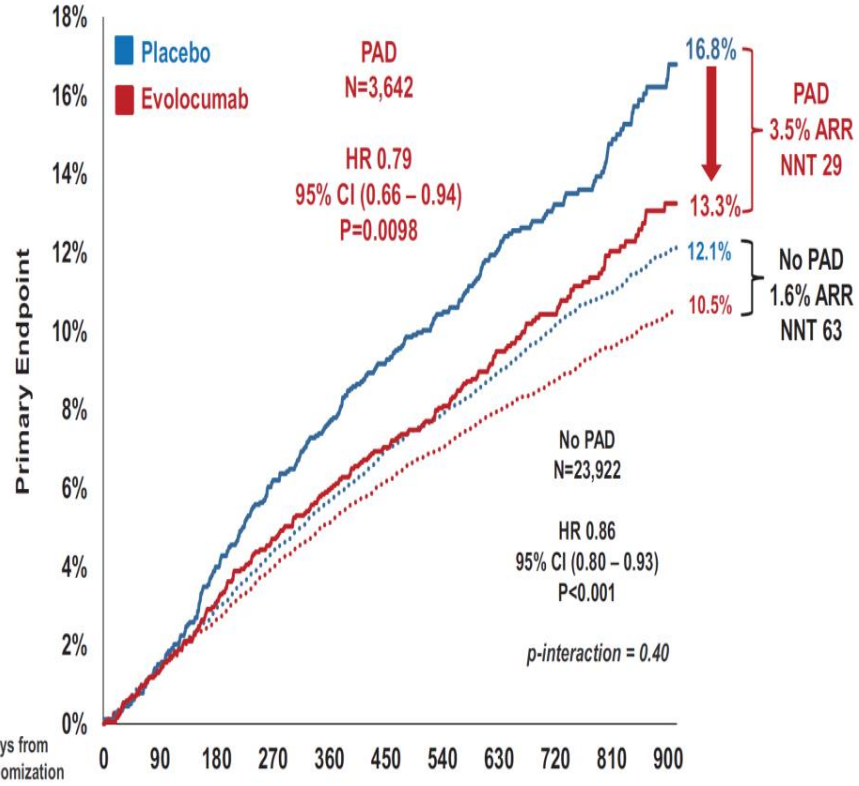
Sabatine MS, et al.
AHA Sessions Nov 2017 (Anaheim, CAL)

Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease

Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)

A

Primary Endpoint in Patients with and without PAD

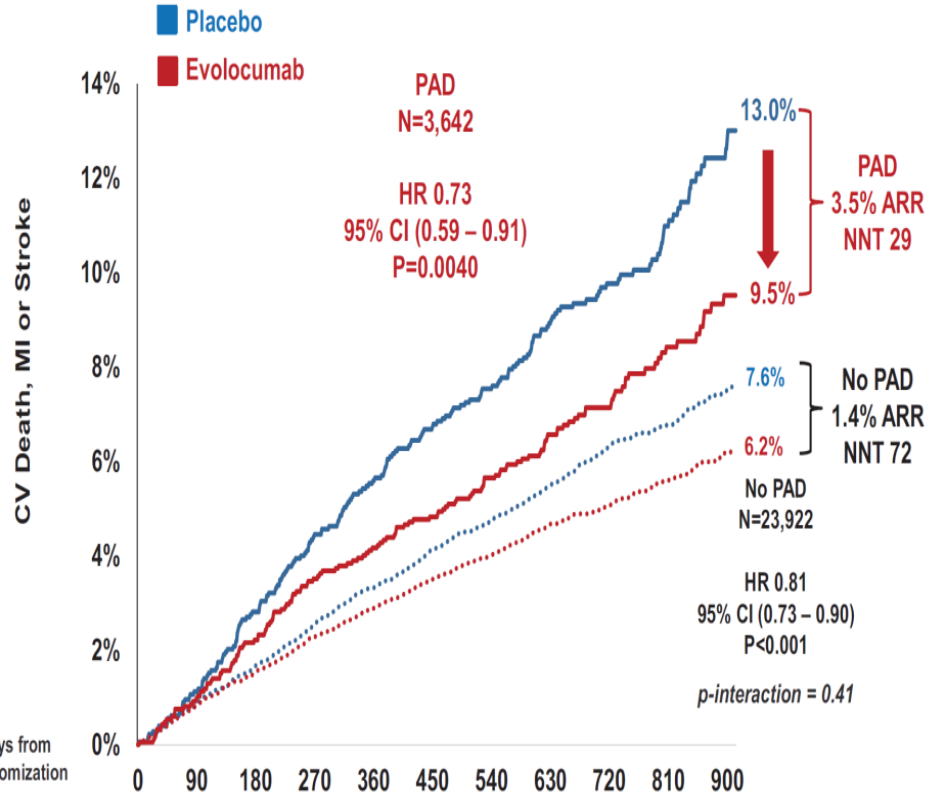


Number at risk

Placebo PAD	1784	1749	1700	1654	1617	1588	1536	1281	973	695	432
Evolocumab PAD	1858	1827	1790	1753	1726	1701	1651	1378	1050	749	460
Placebo no PAD	11996	11793	11582	11390	11217	11039	10400	8759	6864	5173	3443
Evolocumab no PAD	11926	11736	11568	11384	11224	11081	10486	8807	6972	5242	3476

B

CV Death, MI or Stroke in Patients with and without PAD

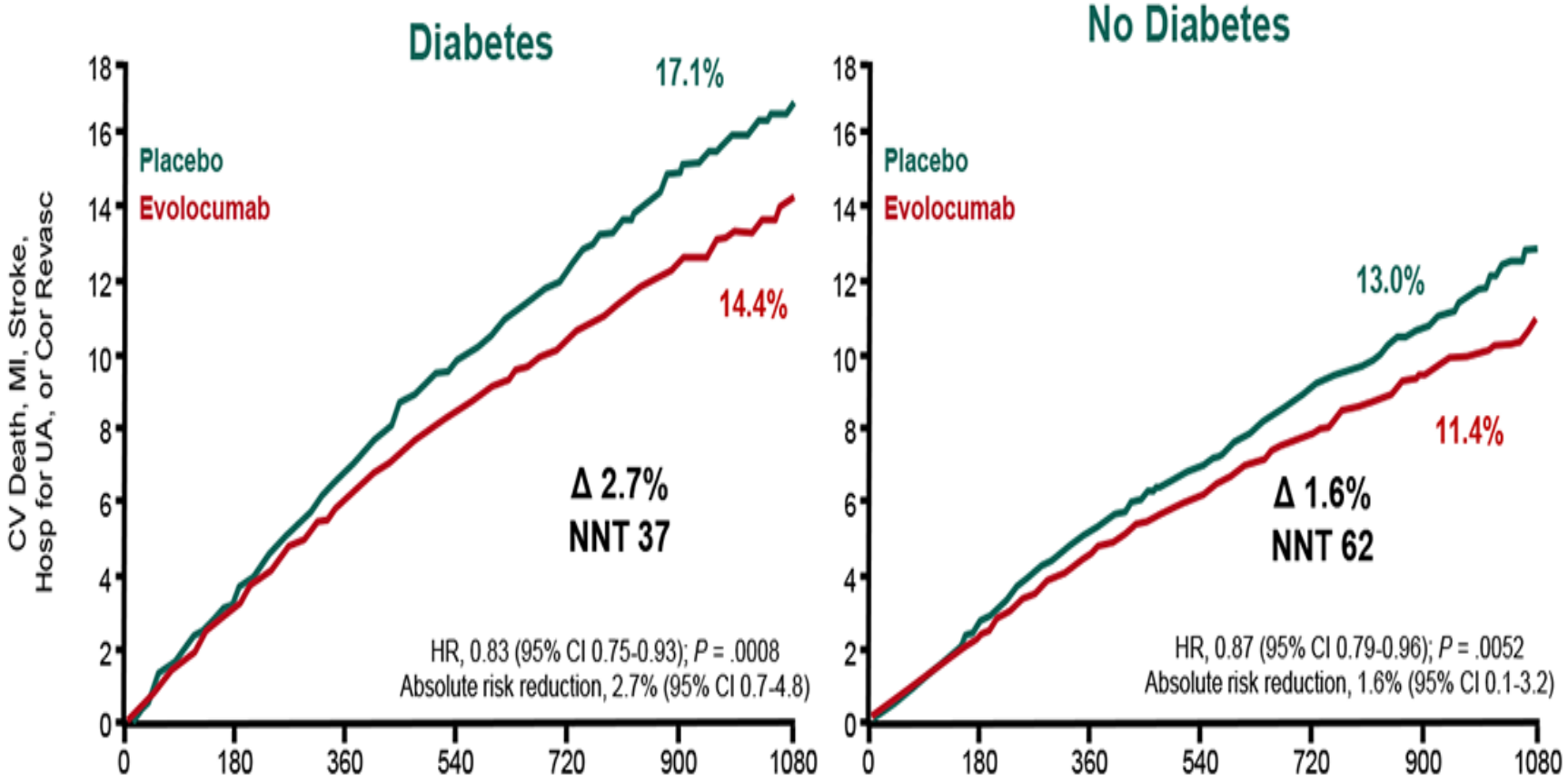


Number at risk

Placebo PAD	1784	1756	1721	1685	1654	1632	1587	1332	1014	729	452
Evolocumab PAD	1858	1834	1806	1774	1758	1740	1692	1427	1091	779	480
Placebo no PAD	11996	11861	11732	11606	11494	11375	10767	9099	7167	5429	3636
Evolocumab no PAD	11926	11802	11699	11583	11490	11397	10828	9138	7258	5474	3649

Bonaca MP, et al. Circulation 2018;137:338–50

FOURIER Prespecified Analysis: Effect of Evolocumab on Cardiovascular Events in Patients With and Without Diabetes

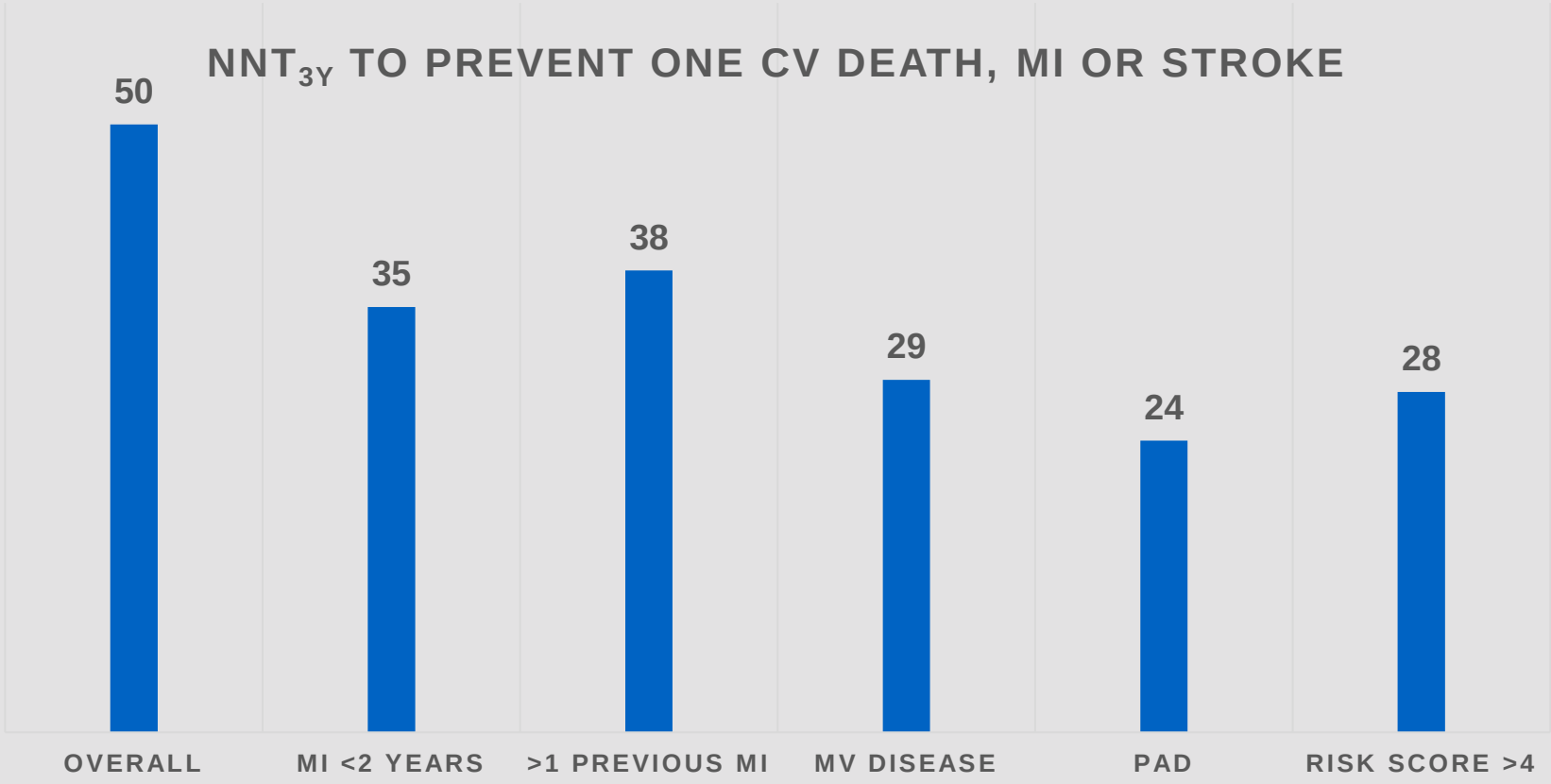


Study design: In this prespecified analysis of FOURIER, the efficacy and safety of evolocumab by diabetes status and the effect of evolocumab on glycemia and risk of developing diabetes was investigated. At study baseline, 11,031 patients had diabetes and 16,533 did not have diabetes.

Sabatine MS, et al.

Lancet Diabetes Endocrinol 2017;5:941-50

RISK STRATIFICATION AND MAGNITUDE OF BENEFIT OF EVOLOCUMAB



High-risk patients w/ ASCVD demonstrate a pattern of greater ARR in major CV events with Evolocumab

Risk indicators are Chronic Heart Failure, Hypertension, Age ≥ 75, Diabetes Mellitus, Prior Stroke, Prior CABG, PAD, eGFR < 60, Smoking, Prior MI;

Sabatine MS, et al. NEJM. 2017; doi: 10.1056/NEJMoa1615664; Bonaca MP et al. AHA – Late Breaking Science. Anaheim, CAL. Nov 13, 2017; Bohula EA et al. AHA – Anaheim, CAL. Nov 14, 2017; Sabatine MS et al. AHA – Late Breaking Science. Anaheim, CAL. Nov 13, 2017

ESC European Society of Cardiology

European Heart Journal (2018) **39**, 1131–1143
doi:10.1093/eurheartj/ehx549

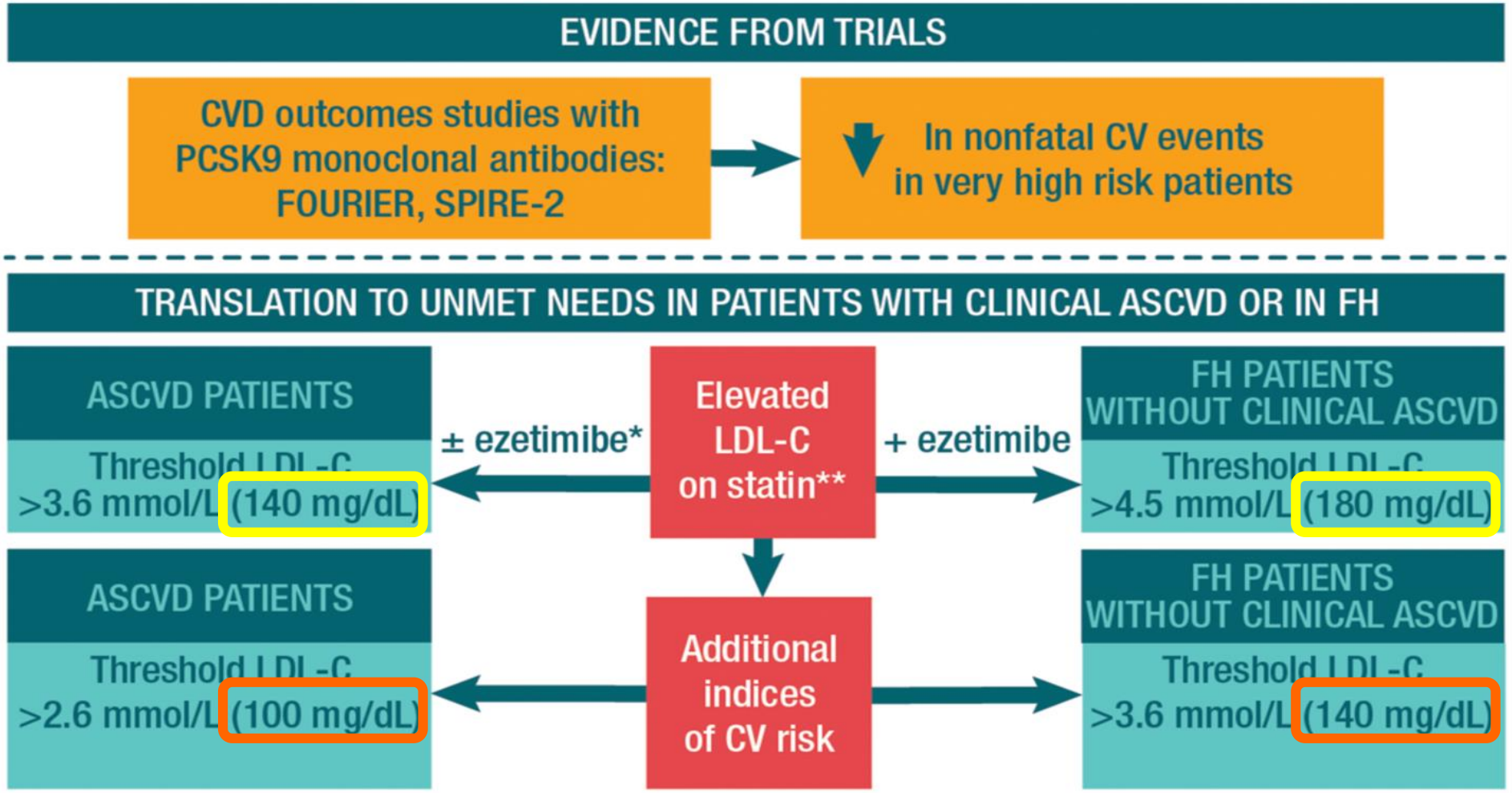
CURRENT OPINION
Lipids

2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia

Ulf Landmesser[1]*†, M. John Chapman[2†], Jane K. Stock[3], Pierre Amarenco[4], Jill J.F. Belch[5], Jan Borén[6], Michel Farnier[7], Brian A. Ference[8], Stephan Gielen[9], Ian Graham[10], Diederick E. Grobbee[11], G. Kees Hovingh[12], Thomas F. Lüscher[13], Massimo F. Piepoli[14], Kausik K. Ray[15], Erik S. Stroes[12], Olov Wiklund[16], Stephan Windecker[17], Jose Luis Zamorano[18], Fausto Pinto[19], Lale Tokgözoğlu[20], Jeroen J. Bax[21], and Alberico L. Catapano[22]

Landmesser U, et al
Eur Heart J 2018 Apr 7;39(14):1131-43

2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia

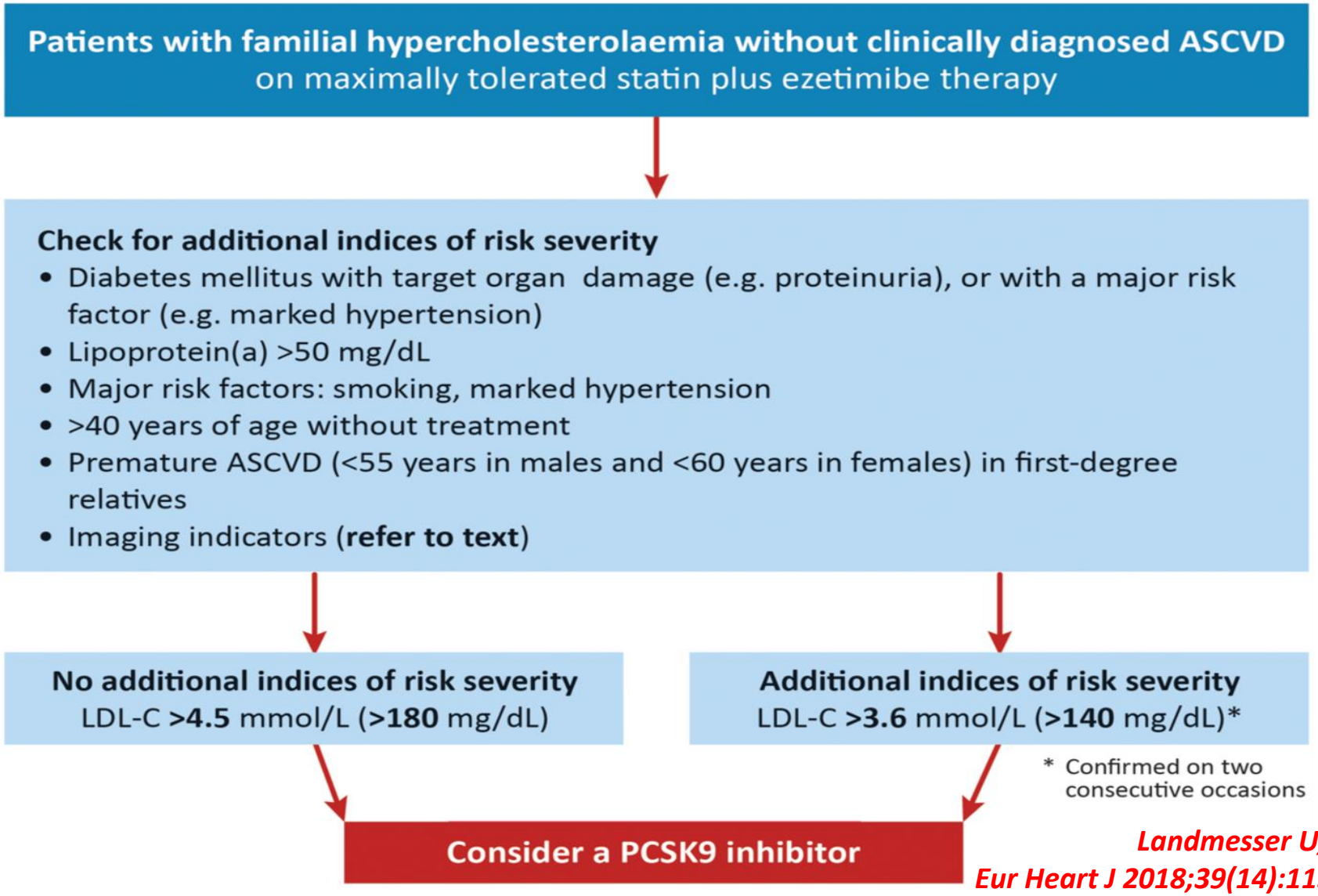


* According to clinical judgement and local guidance
** On maximally tolerated statin therapy

ASCVD atherosclerotic cardiovascular disease
FH familial hypercholesterolaemia

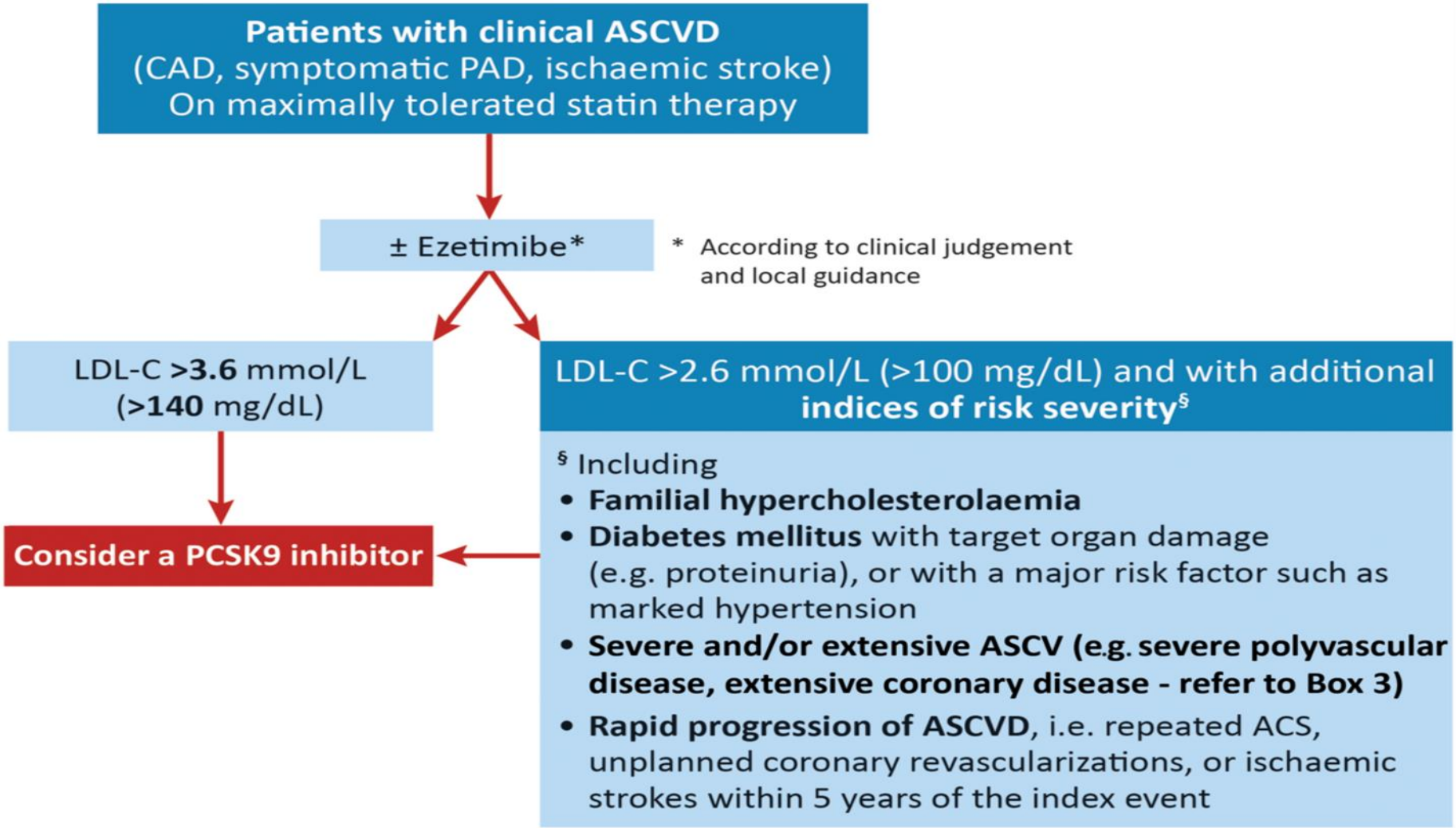
Landmesser U, et al Eur Heart J 2018;39:1131-43

2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia



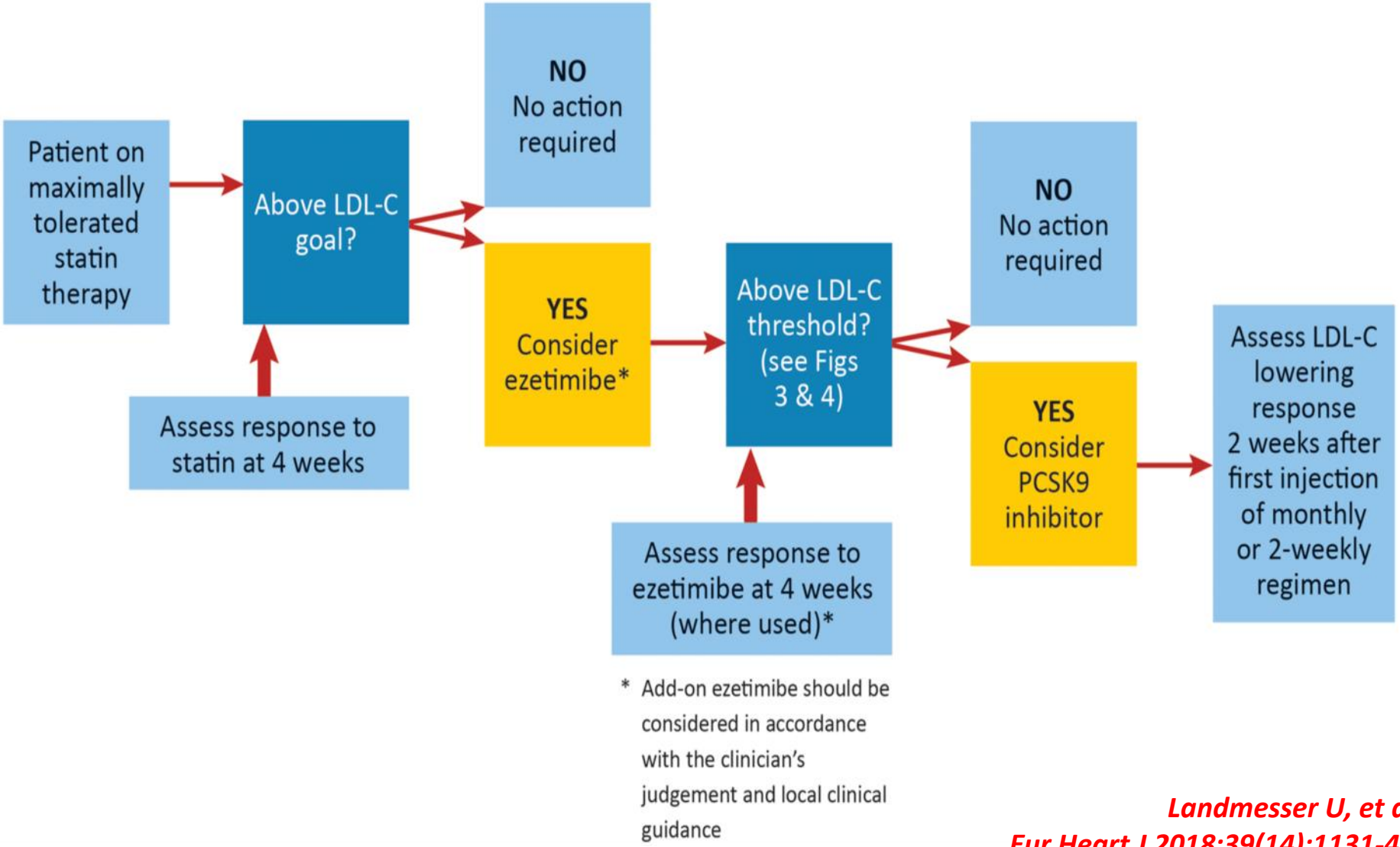
Landmesser U, et al
Eur Heart J 2018;39(14):1131-43

2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia



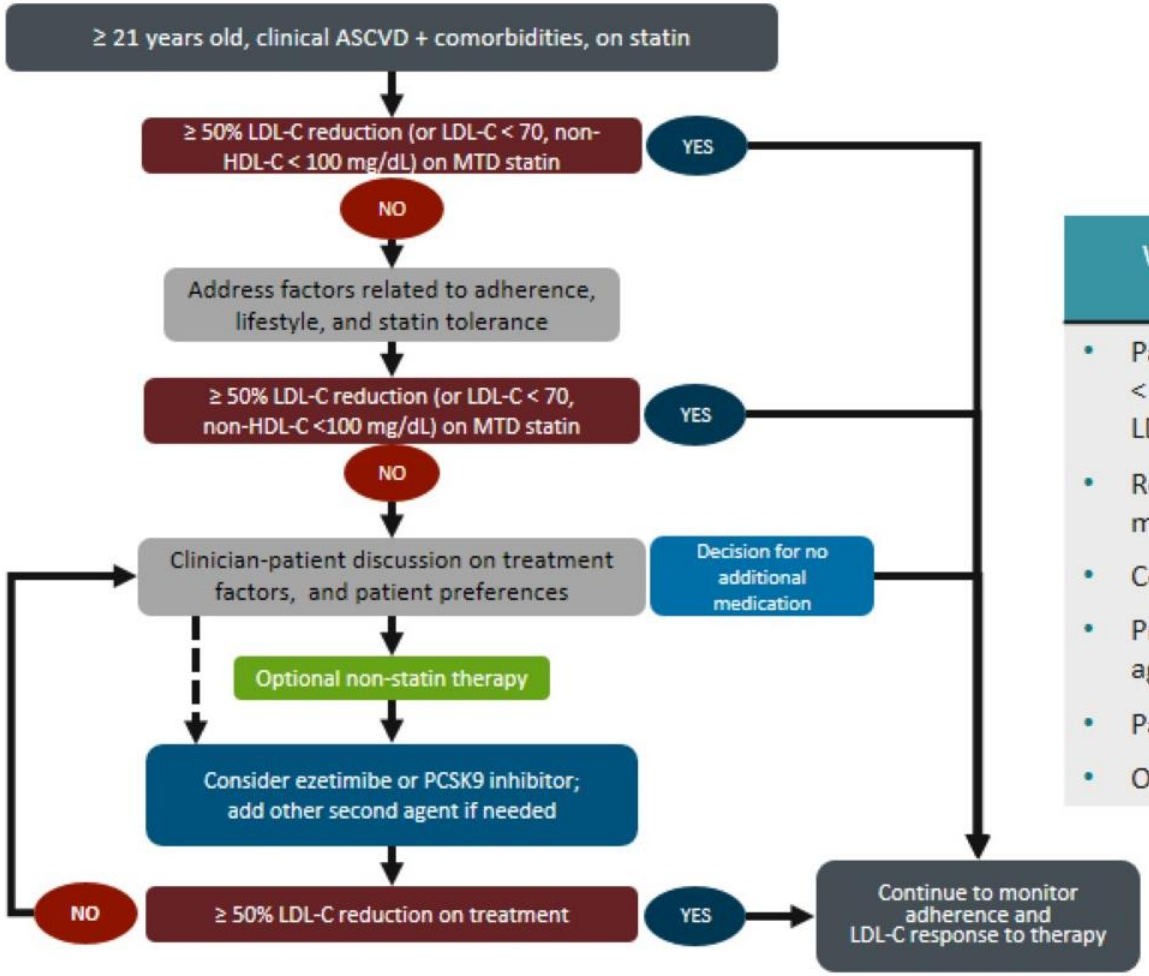
Landmesser U, et al
Eur Heart J 2018;39(14):1131-43

2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia



Landmesser U, et al
Eur Heart J 2018;39(14):1131-43

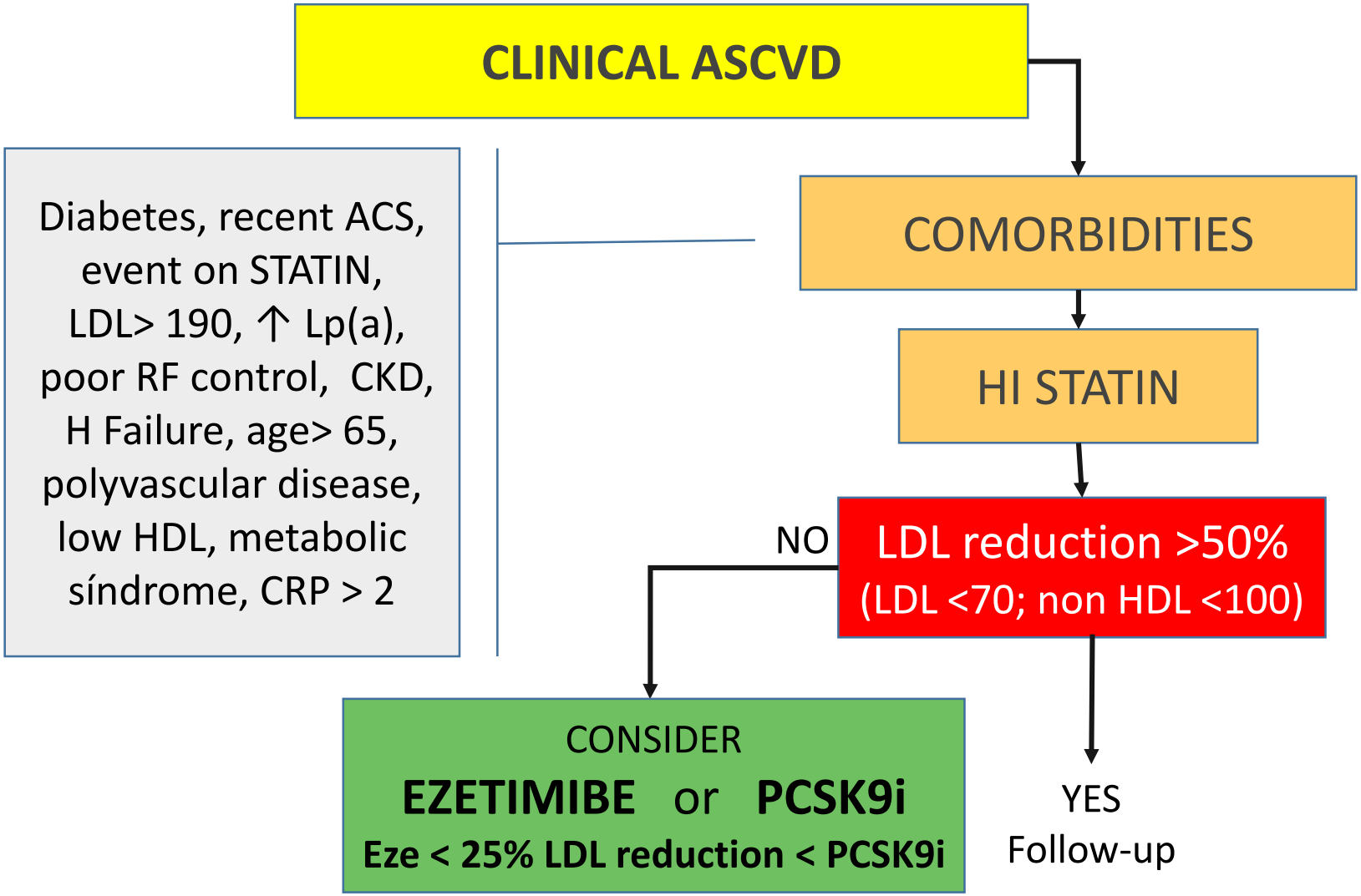
2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway: Nonstatin Therapies for ASCVD



When to Choose Ezetimibe?	When to Choose PCSK9 Inhibitor?
• Patients requiring < 25% additional LDL-C lowering • Recent ACS < 3 months • Cost considerations • Preference of oral agent • Patient preference • Other risk factors	• Patients requiring > 25% additional LDL-C lowering • Cost-benefit considerations should be discussed • Administration, dosing schedule, and storage should be discussed

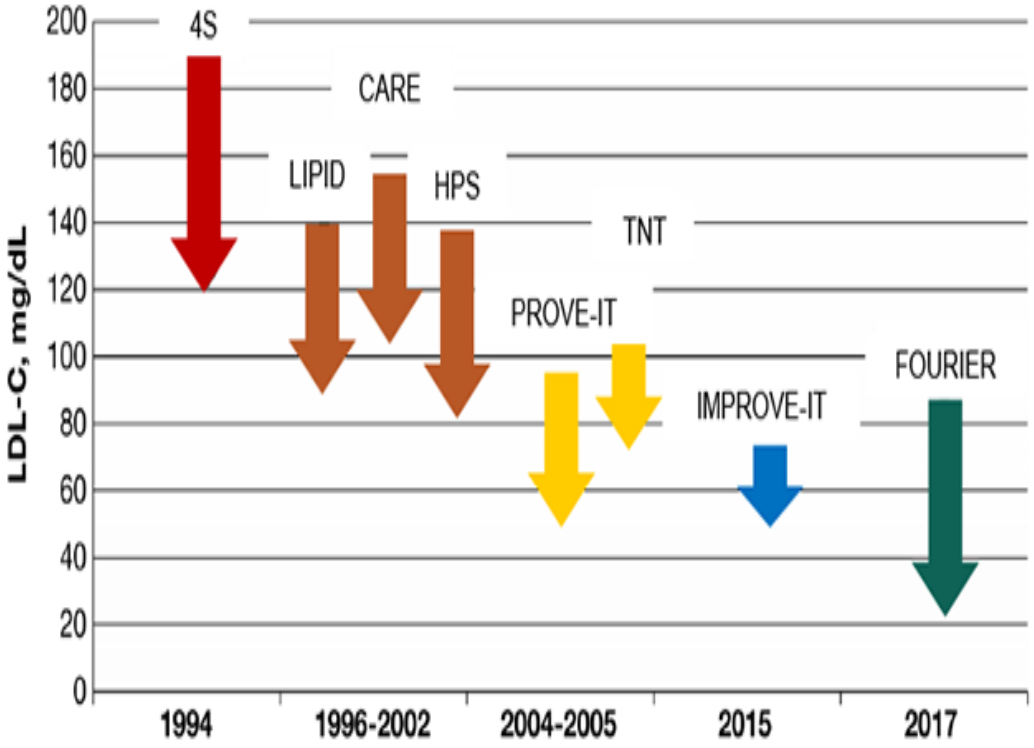
J Am Coll Cardiol 2017 Oct 3;70(14):1785-822

2017 Focused update 2016 ACC Expert Consensus Decision Pathway on The Role of Non-Statin Therapies in the Management of Atherosclerotic Cardiovascular Disease Risk



J Am Coll Cardiol 2017 Oct 3;70(14):1785-822

LDL-C Levels for Optimal CV Risk Reduction: What We Know Now



High is bad

Average is not good

Lower is better

Even lower is even better

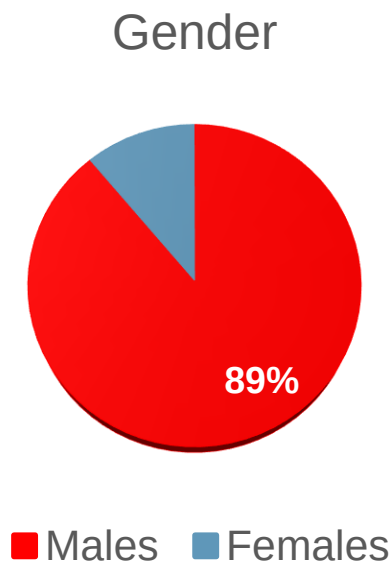
Lowest is best

Box 4 Gaps in knowledge concerning proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy

- Inter-individual variability in low-density lipoprotein cholesterol (LDL-C) lowering response to alirocumab and evolocumab
- Dedicated trials in patients with recent (<1 month) cardiovascular events
- Impact of PCSK9 inhibition in patients with chronic kidney disease (not requiring dialysis)
- Long-term efficacy and safety of PCSK9 inhibitors in clinical use
- Long-term safety of very low LDL-C levels
- Long-term impact of PCSK9 inhibition on disability and cardiovascular mortality
- Long-term evaluation of risk for type 2 diabetes
- Impact of sustained and marked LDL-C lowering to very low levels on plaque composition and stability
- Long-term impact of reduction in elevated lipoprotein(a) with PCSK9 inhibition
- Cost-effectiveness of PCSK9 inhibition added to maximally tolerated statin with or without ezetimibe therapy.

Clinical experience with Evolocumab (HRyC)

70 patients on Evolocumab
Cardiology: 55 patients

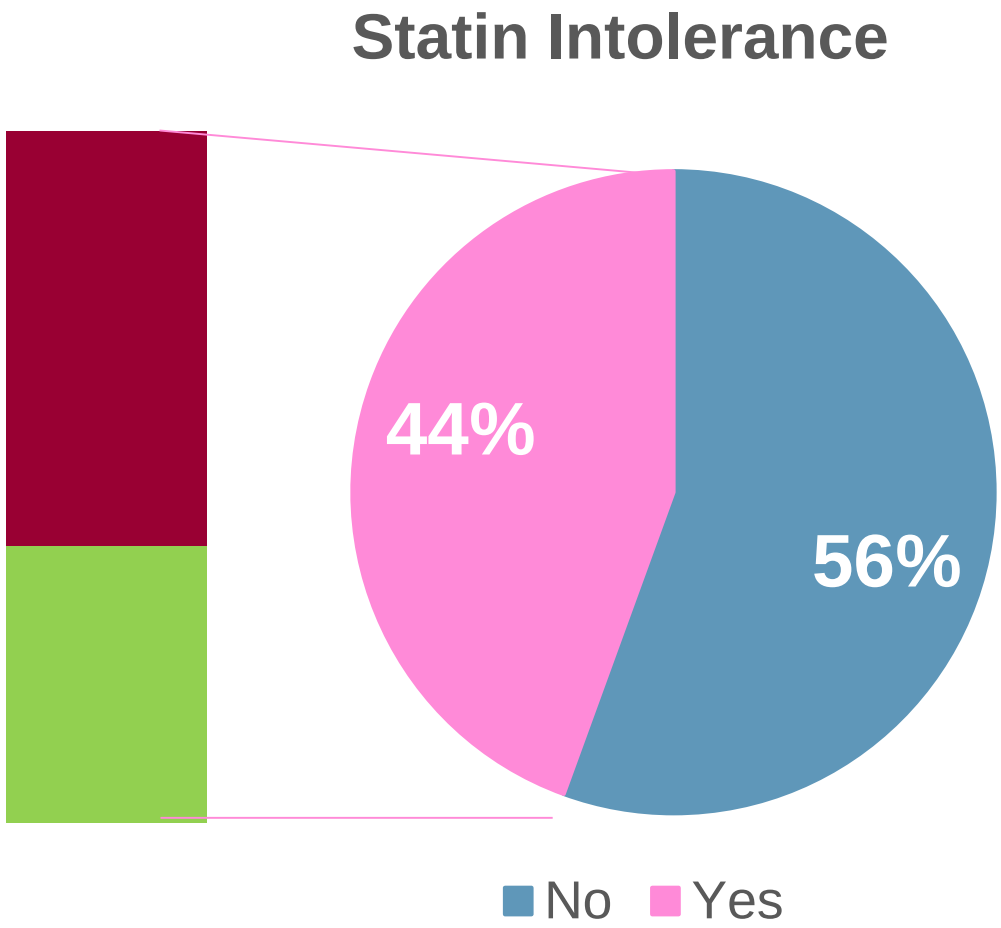


Prior MI	100%
Stroke	27%
Peripheral Artery Disease	9%

Indications for PCSK9i

Total Intolerance 60%

Partial Intolerance 40%



Results on Lipids

	Baseline (mg/dl)	4-6 months (mg/dl)
Total Cholesterol	205	116
LDL-c	134	50
HDL-c	46	46
Triglycerides	123	113

RetOSS

Retrospective Observational Study in Spain

RetOSS-Cardio Study

Vivencio Barrios
National Study Coordinator

Evolocumab Studies in clinical practice in Spain

- International Studies

- Evolocumab
  - Diabetes Mellitus
  - Pediatric
  - VIH
  - FH (Ho-He)
  - CVD established (IM, Stroke, PAD)
- Observational Studies
  - 296 Registry
  - DA VINCI Study

- Local Studies

- ✓ RETOSS-IMU (Int Med Units)
- ✓ RETOSS-ENDO
- ✓ **RETOSS-CARDIO**
- RETOSS-NEFRO (Oct-2018)

Local Studies Initial Deadlines

	RETOSS-IMU	RETOSS-Endo	RETOSS-Cardio
FP In	31-mar-17	15-sep-17	15-oct-17
FP Out	29-dic-17	15-mar-18	16-abr-18
Final	15-mar-18	21-sep-18	24-oct-18
Report	2018	2019	2019
Publication			
Centers	21	21	50
Patients	150	150	250

RetOSS CARDIO
Retrospective Observational Study in Spain

Objectives

Primary Endpoint:

- ✓ To describe main clinical characteristics (LDL-c levels and **HF status (IMU)**, **DM (Endo), CAD (Cardio), CKD (Nefro)**, before start evolocumab treatment) of patients with Hypercholesterolemia attending in Internal medicine, Cardiac, Endo and Nefro Units in Spain.

Secondary Endpoints:

- ✓ To describe and analyze full clinical characteristics of patients with hypercholesterolemia (first patients selected in Spain)
- ✓ To describe clinical management of patients with initial treatment with evolocumab.

RetOSS CARDIO
Retrospective Observational Study in Spain

Subject Inclusion Criteria

Inclusion Criteria

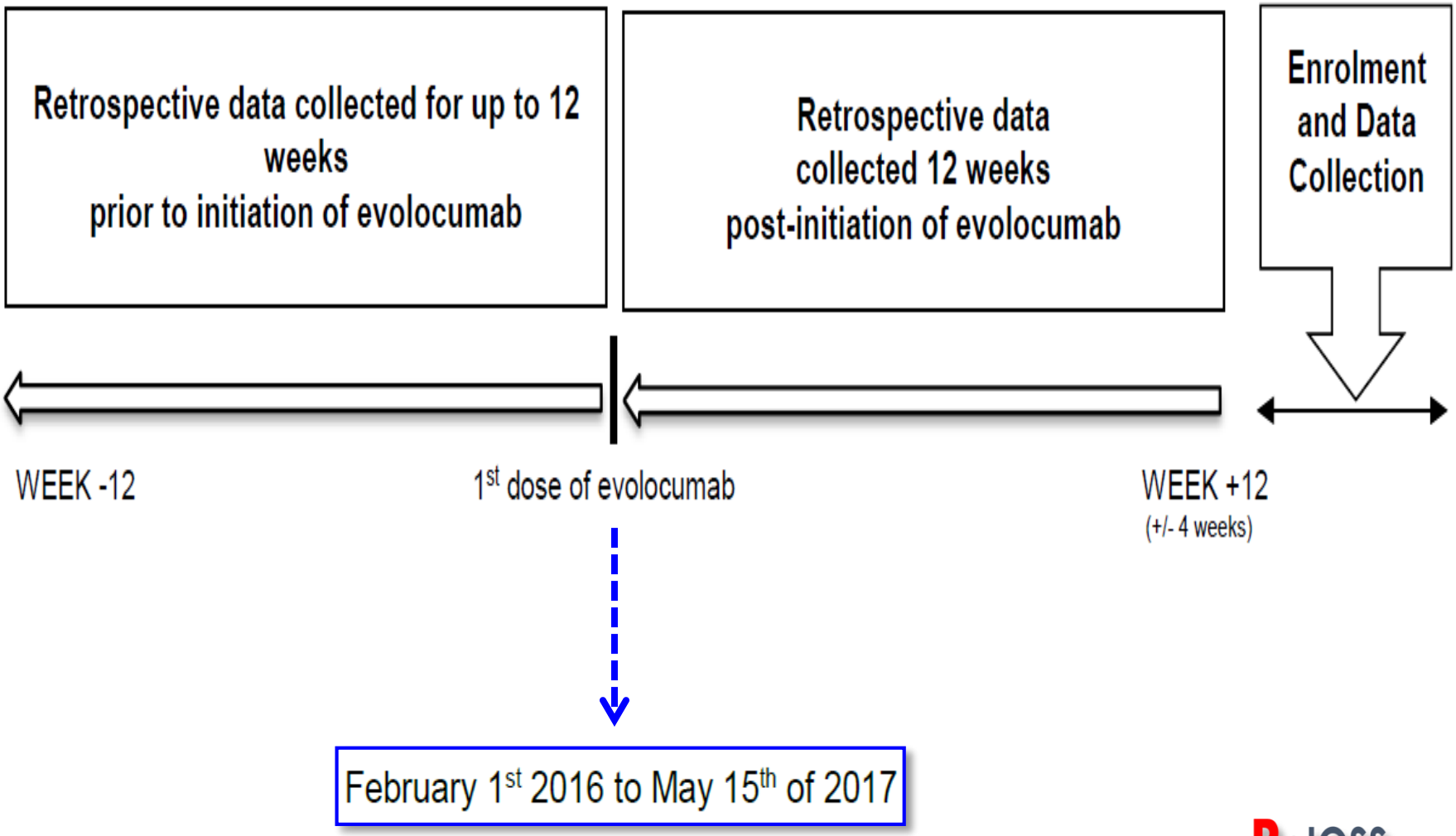
- ✓ ≥18 years at the time of evolocumab initiation
- ✓ Provided informed consent form
- ✓ Initiated on evolocumab from 01-Feb-16 to 15-May-17
- ✓ Received at least one dose of evolocumab
- ✓ At least one LDL-C measurement within the 12W prior to initiation of evolocumab

Exclusion Criteria

- × Enrolled in a study with a PCSK9 inhibitor within 12W prior to initiation of evolocumab
- × Received a PCSK9 inhibitor within 12W prior to initiation of evolocumab
- × Enrolled in a clinical study during the retrospective observational period

RetOSS CARDIO
Retrospective Observational Study in Spain

Study Design



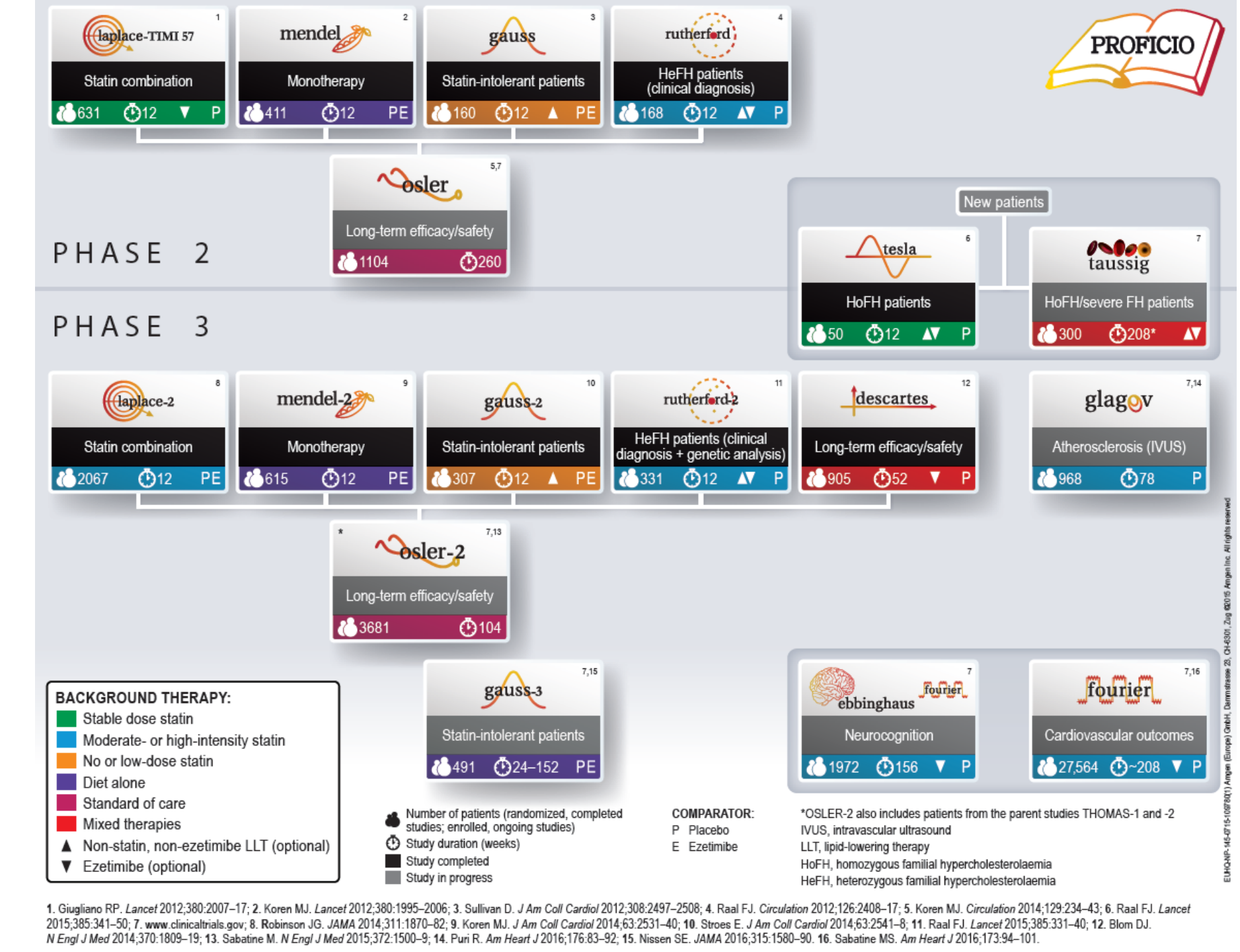
RetOSS CARDIO
Retrospective Observational Study in Spain

EVOLOCUMAB: INDICAÇÕES

Doença cardiovascular aterosclerótica estabelecida

- **Evolocumab é indicado em adultos com doença cardiovascular aterosclerótica estabelecida (enfarte do miocárdio, acidente vascular cerebral ou doença arterial periférica), para redução do risco cardiovascular através da diminuição dos valores de LDL-C, como um complemento de correção para outros fatores de risco:**
  - **em combinação com a dose máxima tolerada de uma estatina, com ou sem outras terapêuticas antidislipidémicas ou,**
  - **isolado ou em combinação com outras terapêuticas antidislipidémicas em doentes intolerantes a estatinas ou para os quais as estatinas são contraindicadas.**

Evolocumab, Resumo das Características do Medicamento, Amgen, 2018.

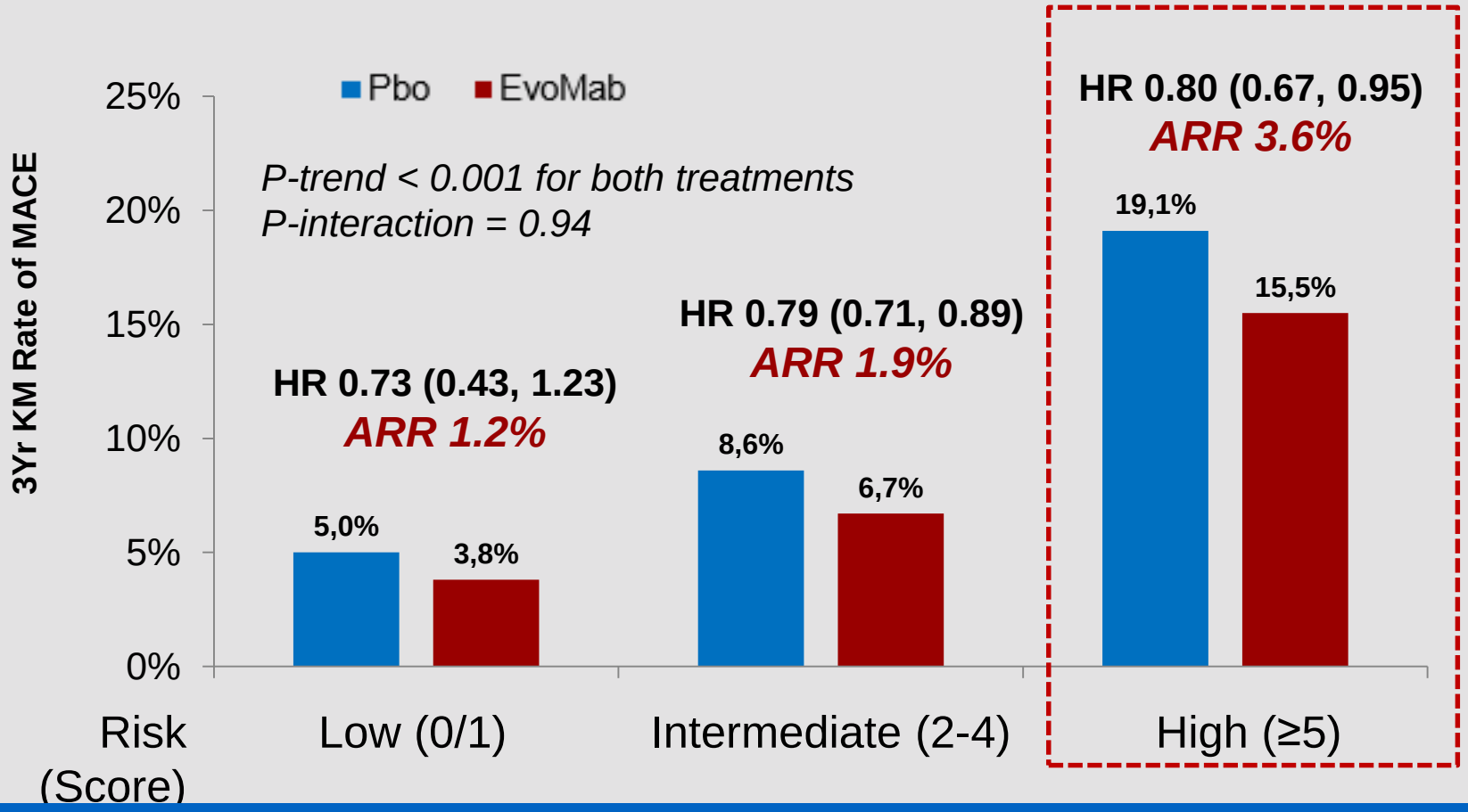


1. Giugliano RP. *Lancet* 2012;380:2007–17; **2**. Koren MJ. *Lancet* 2012;380:1995–2006; **3**. Sullivan D. *J Am Coll Cardiol* 2012;308:2497–2508; **4**. Raal FJ. *Circulation* 2012;126:2408–17; **5**. Koren MJ. *Circulation* 2014;129:234–43; **6**. Raal FJ. *Lancet* 2015;385:341–50; **7**. www.clinicaltrials.gov; **8**. Robinson JG. *JAMA* 2014;311:1870–82; **9**. Koren MJ. *J Am Coll Cardiol* 2014;63:2531–40; **10**. Stroes E. *J Am Coll Cardiol* 2014;63:2541–8; **11**. Raal FJ. *Lancet* 2015;385:331–40; **12**. Blom DJ. *N Engl J Med* 2014;370:1809–19; **13**. Sabatine M. *N Engl J Med* 2015;372:1500–9; **14**. Puri R. *Am Heart J* 2016;176:83–92; **15**. Nissen SE. *JAMA* 2016;315:1580–90. **16**. Sabatine MS. *Am Heart J* 2016;173:94–101.

" One of the side-effects is shortness of cash. "

RESULTS

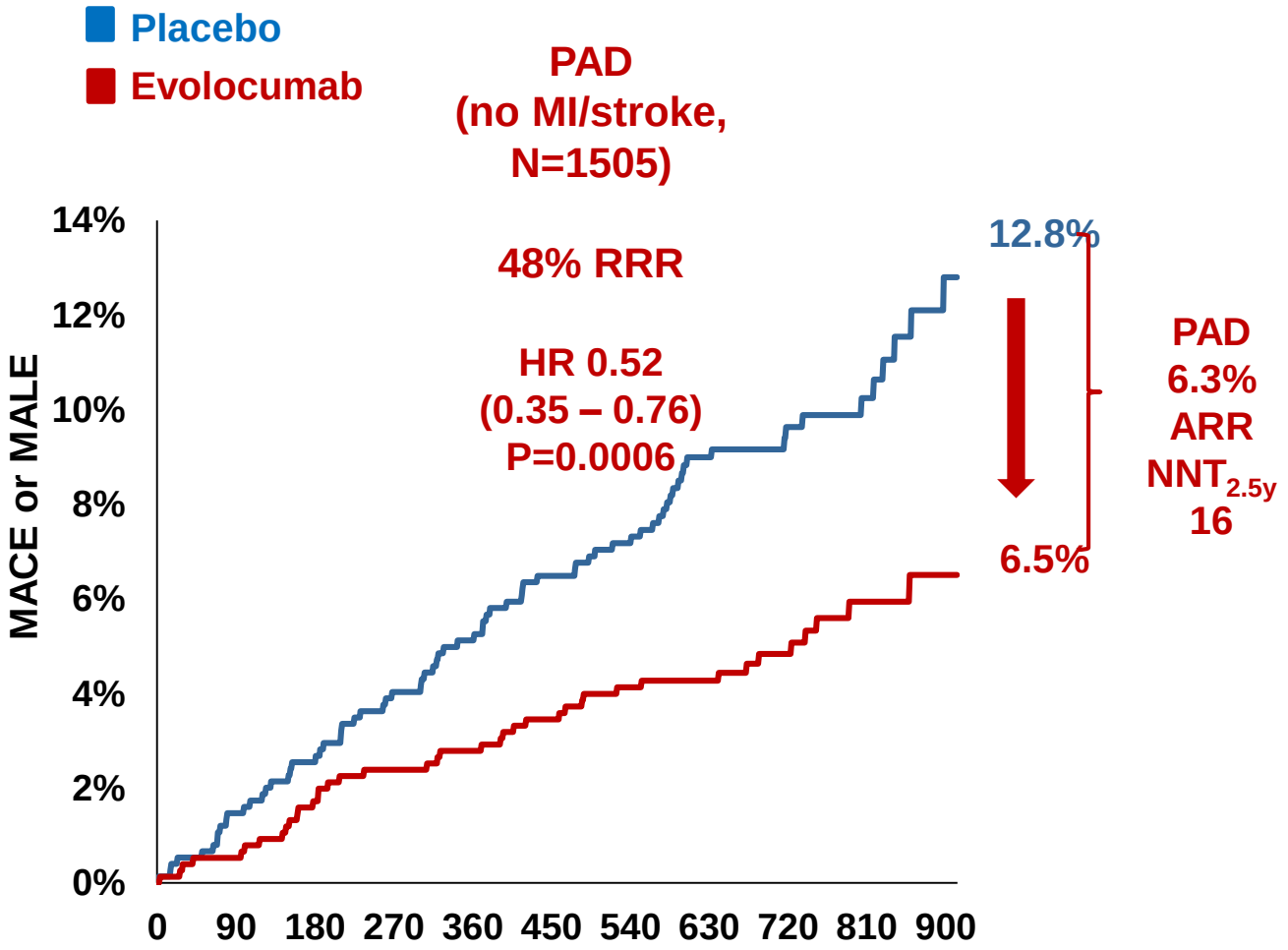
MACE BY RISK CATEGORY & RANDOMIZED TREATMENT



High-risk patients showed a ARR of 3.6% for MACE, translating in a NNT_{3y} of 28

Bohula EA, *et al*. Atherothrombotic Risk Stratification and Magnitude of Benefit of Evolocumab in FOURIER. Presented in: American Heart Association; Novembro 11-15, 2017

MACE or MALE in Patients with PAD and no MI or Stroke



Bonaca MP, et al.
Circulation 2018 Jan 23;137(4):338-50

Defining patients considered for treatment with a proprotein convertase subtilisin/kexin type 9 inhibitor

On the basis of currently available evidence, this Task Force recommends that a PCSK9 inhibitor should be considered in the following patient groups.

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

Landmesser U, et al
Eur Heart J 2018;39(14):1131-43

ODYSSEY OUTCOMES and FOURIER Demographics: Patient Histories

	ODYSSEY OUTCOMES[a] (n=18,312)	FOURIER[b] (n=27,564)
Age (mean)	58.6	62.5
Male, %	74.8	75.4
Hypertension, %	63.3	80.0
Diabetes, %	28.9	33.9
Current smoker, %	23.9	28.2
History of MI, %	100% ACS (mean time from index event 3.6 months, 75% <4 months) including 35% prior CAD + 20% with recurrent event	81.1 (31% MI < 1 y)
History of stroke, %	2.9	19.3
History of PAD, %	3.7	13.2

a. Goodman SG, et al. ACC 2017. Abstract 10269.
b. Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.

ODYSSEY OUTCOMES and FOURIER Demographics: LLTs and Lipids

	ODYSSEY OUTCOMES[a] (n=18,312)	FOURIER[b] (n=27,564)
LLTs		
High-intensity stain, %	89.5	69.2
Moderate-/low-intensity statin, %	7.8	30.7
Ezetimibe, %	2.9	5.1
Lipid parameters		
Median LDL-C, mg/dL	86.5	91.5
Total cholesterol, mg/dL	160.0	167.0
HDL-C, mg/dL	42.5	44.0
Triglycerides, mg/dL	129.2	133.0

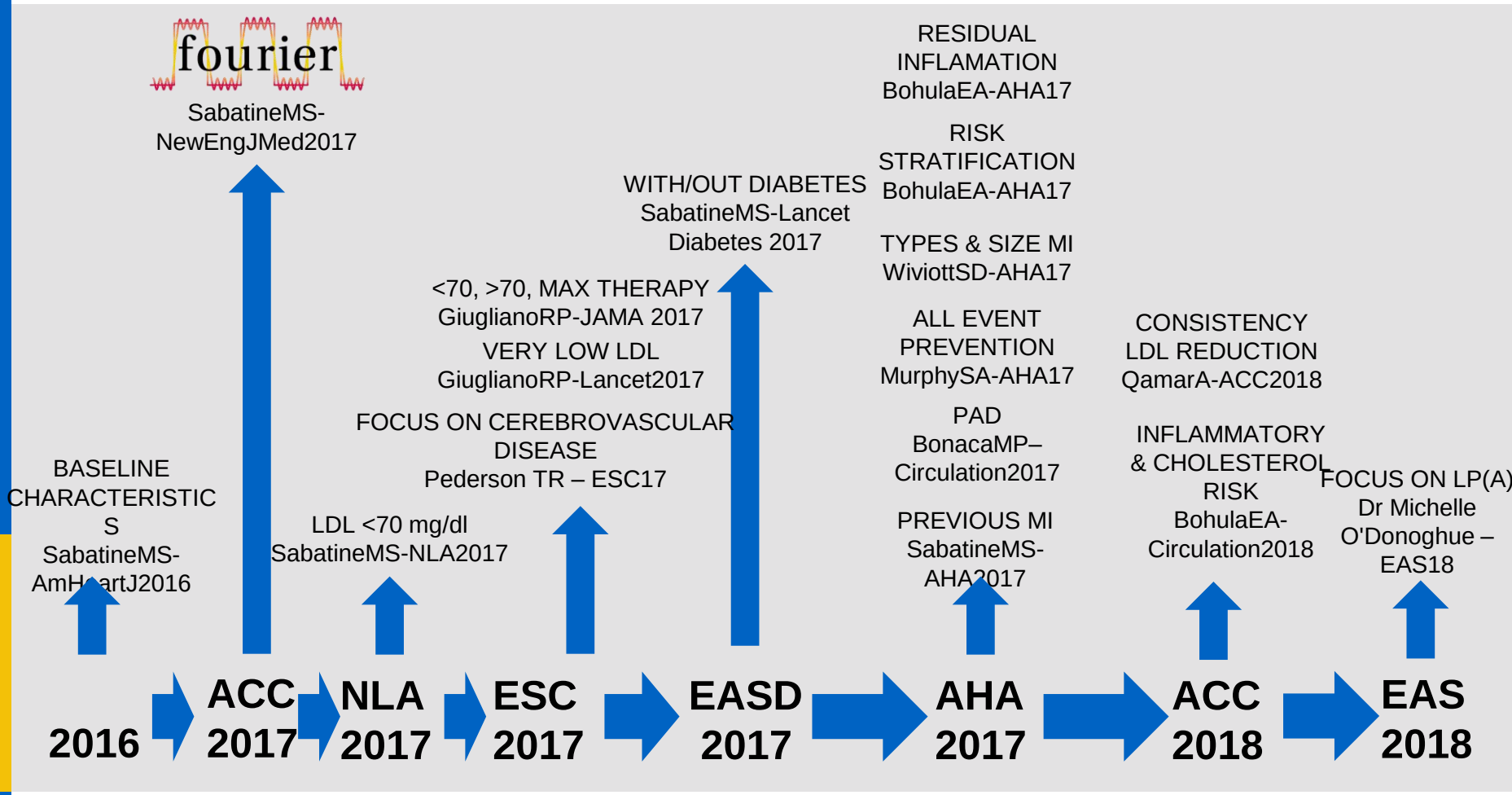
Reprinted from *Am Heart J.*, Rationale and design of the Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk trial. 94-101. Copyright 2017, with permission from Elsevier

a. Goodman SG, et al. ACC 2017. Abstract 10269.

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

THE LOWER THE BETTER

FOURIER



EVOLOCUMAB: INDICAÇÕES

Hipercolesterolemia e dislipidemia mista

- **Evolocumab é indicado em adultos com hipercolesterolemia primária (familiar heterozigótica e não familiar) ou na dislipidemia mista, como um complemento da dieta:**
  - **em combinação com uma estatina ou uma estatina com outras terapêuticas antidislipidémicas em doentes incapazes de atingir os valores objetivo de LDL-C com a dose máxima tolerada de estatina ou,**
  - **isolado ou em combinação com outras terapêuticas antidislipidémicas em doentes intolerantes a estatinas ou nos quais as estatinas estejam contraindicadas.**

Hipercolesterolemia familiar homozigótica

- **Evolocumab é indicado em adultos e adolescentes com idade igual ou superior a 12 anos com hipercolesterolemia familiar homozigótica em combinação com outras terapêuticas antidislipidémicas.**

O efeito de Evolocumab na morbilidade e mortalidade cardiovasculares ainda não foi determinado.

Evolocumab, Resumo das Características do Medicamento, Amgen, 2018.

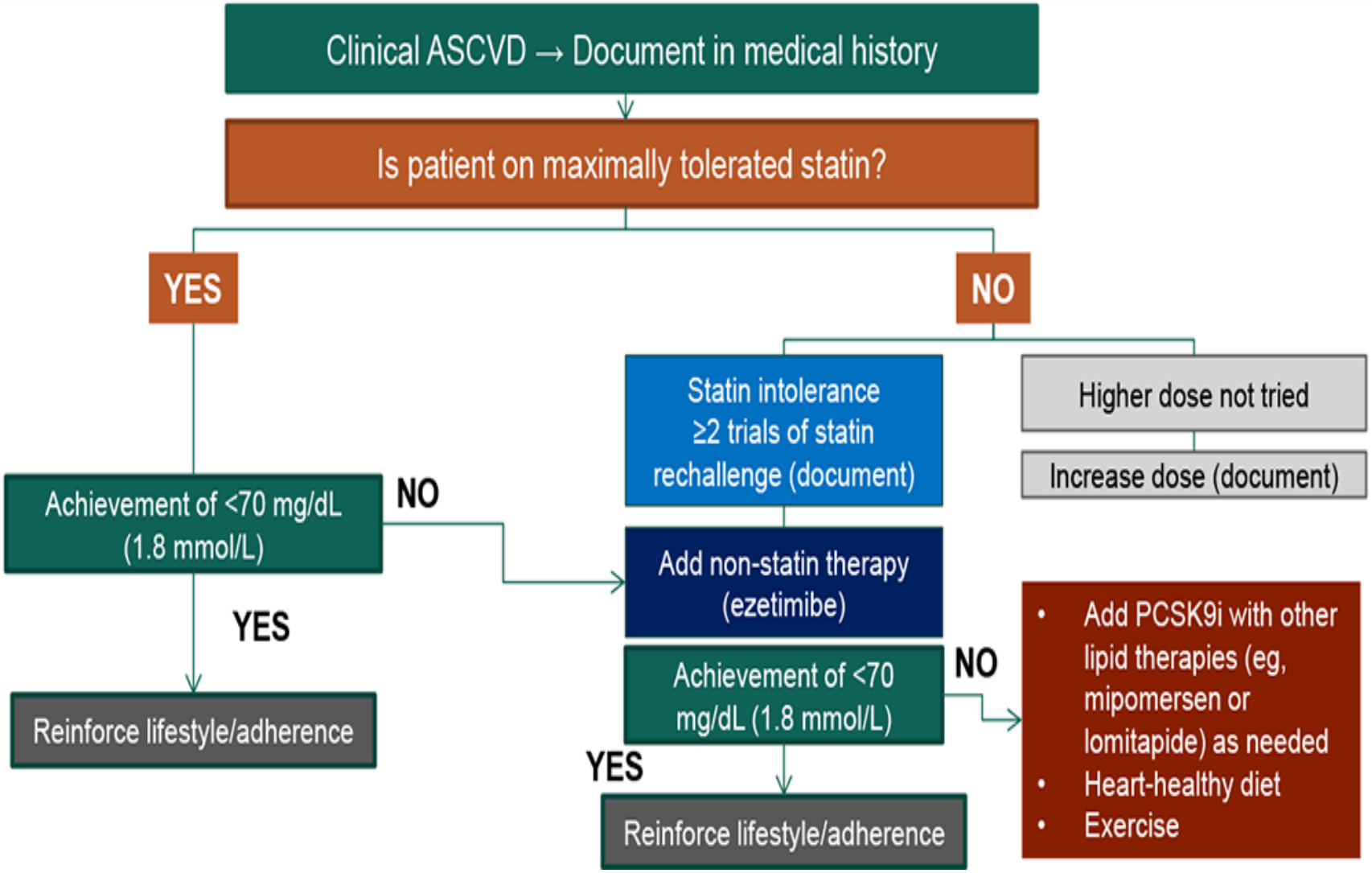
EVOLOCUMAB: INDICAÇÕES

Doença cardiovascular aterosclerótica estabelecida

- **Evolocumab é indicado em adultos com doença cardiovascular aterosclerótica estabelecida (enfarte do miocárdio, acidente vascular cerebral ou doença arterial periférica), para redução do risco cardiovascular através da diminuição dos valores de LDL-C, como um complemento de correção para outros fatores de risco:**
  - **em combinação com a dose máxima tolerada de uma estatina, com ou sem outras terapêuticas antidislipidémicas ou,**
  - **isolado ou em combinação com outras terapêuticas antidislipidémicas em doentes intolerantes a estatinas ou para os quais as estatinas são contraindicadas.**

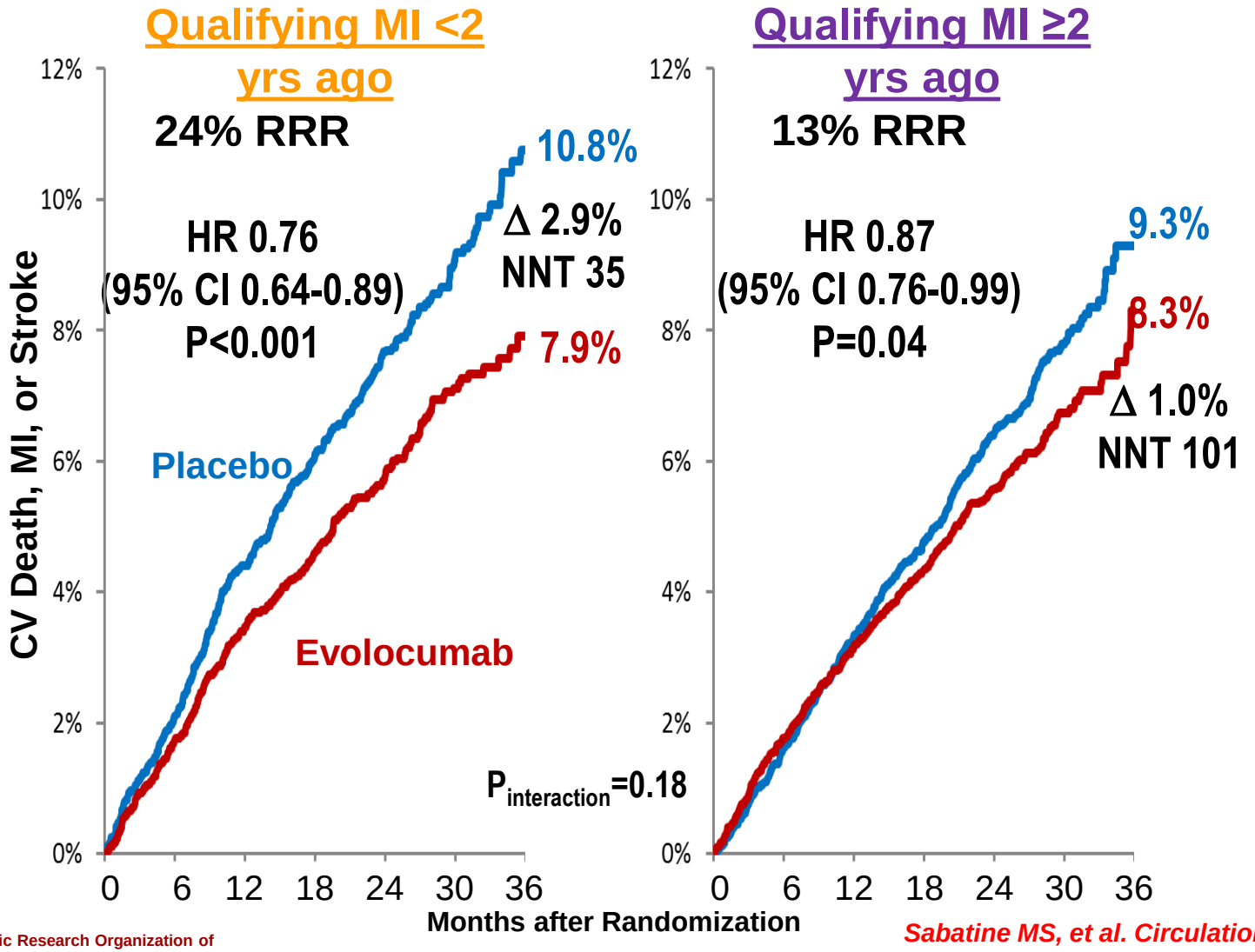
Evolocumab, Resumo das Características do Medicamento, Amgen, 2018.

Stepwise Approach for Treatment of Clinical ASCVD



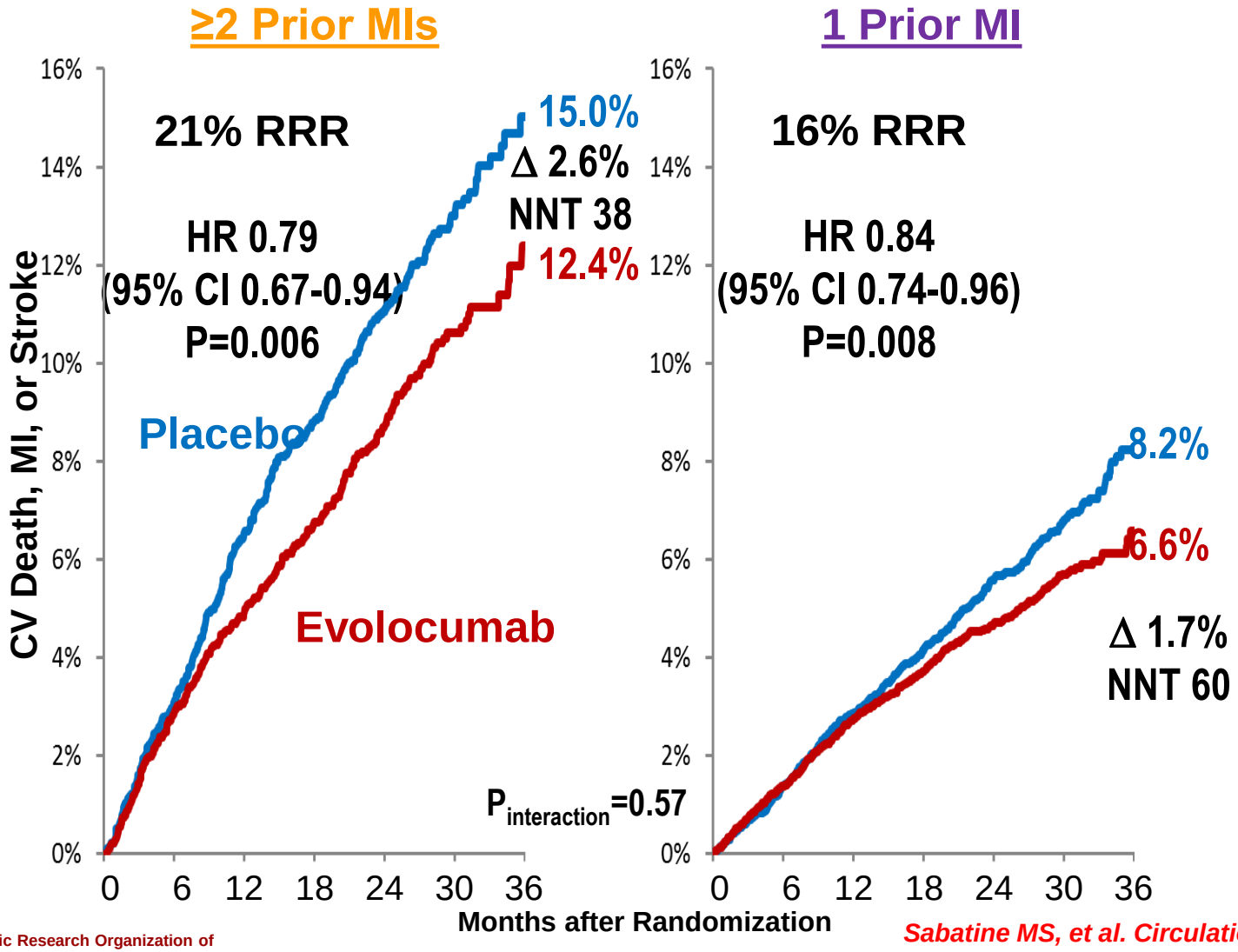
Saeed A, et al. J Clin Lipidol 2017;11:596-99
Lloyd-Jones DM, et al. J Am Coll Cardiol 2016;68:92-125

Benefit of EvoMab Based on Time from Qualifying MI



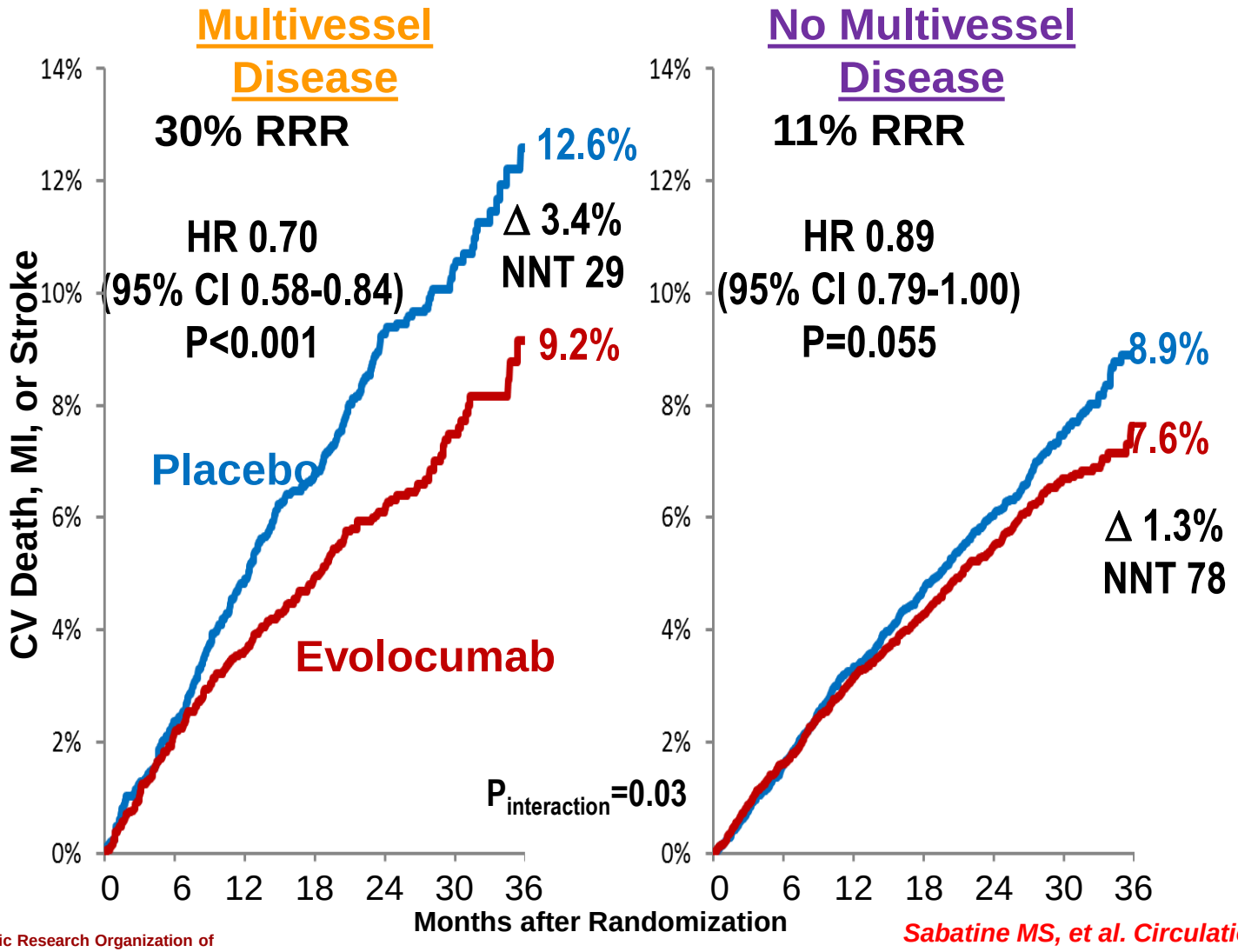
Sabatine MS, et al. Circulation 2018 Apr 6.
doi: 10.1161/CIRCULATIONAHA.118.034309 [Epub ahead of print]

Benefit of EvoMab Based on # of Prior MIs



Sabatine MS, et al. Circulation 2018 Apr 6.
doi: 10.1161/CIRCULATIONAHA.118.034309 [Epub ahead of print]

Benefit of EvoMab Based on Multivessel Disease



Sabatine MS, et al. Circulation 2018 Apr 6.
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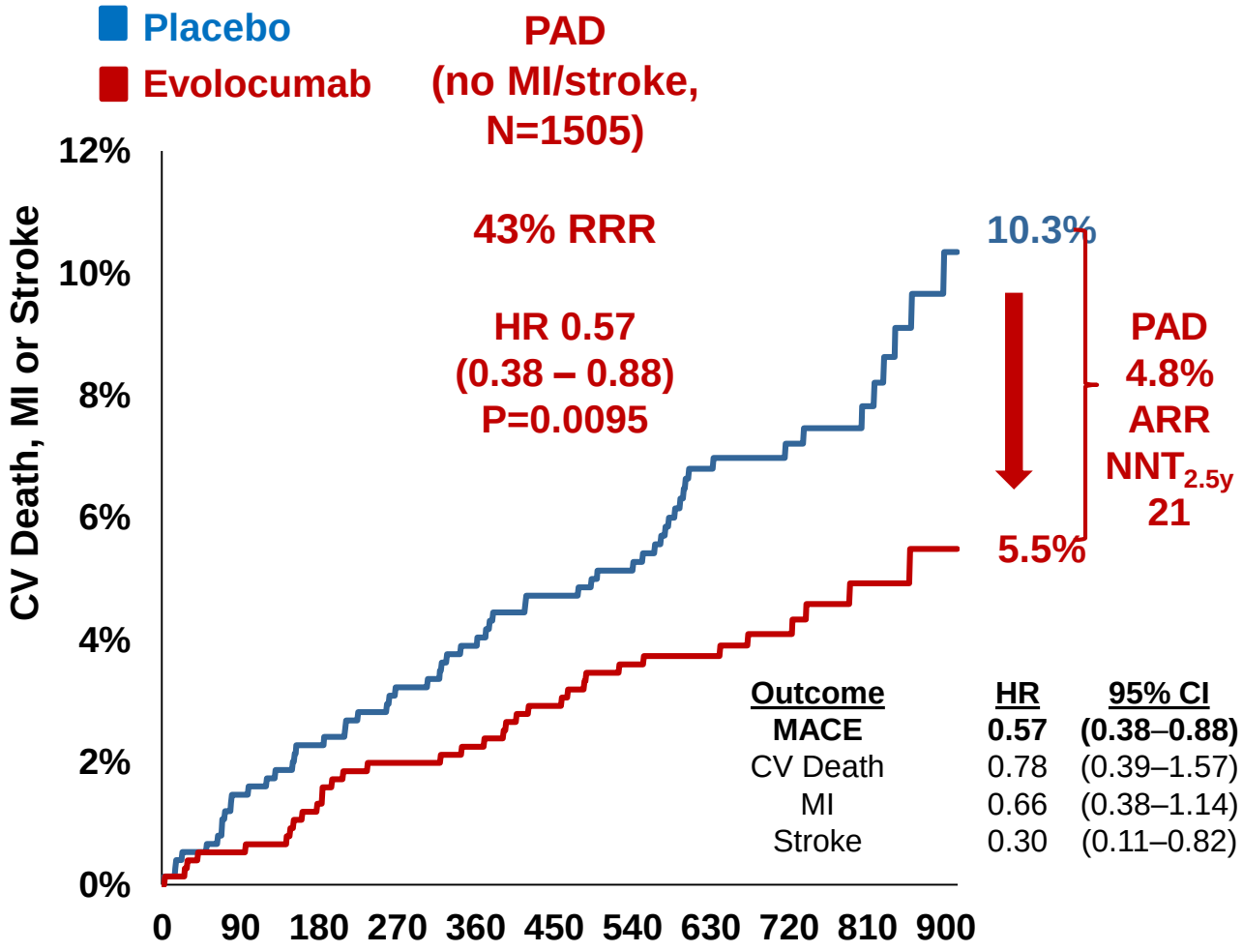
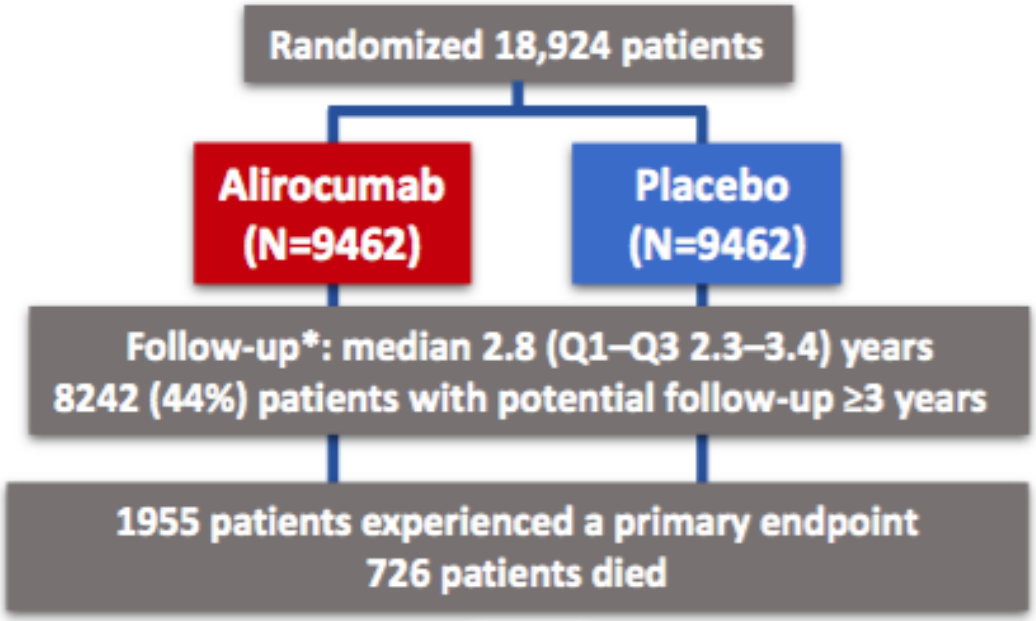
CV Death, MI or Stroke in Patients with PAD and no MI or Stroke



Bonaca MP, et al.
Circulation 2018 Jan 23;137(4):338-50

Odyssey Cardiovascular outcomes

18,924 pts with ACS without adequate LDL control despite optimal lipid-lowering treatment



• Premature treatment discontinuation	1343 (14.2%)	1496 (15.8%)
• Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)	730 (7.7%)	Not applicable
• Patients lost to follow-up (vital status)	14	9

ODYSSEY OUTCOMES

Comparación diseños de los estudios Odyssey Outcomes, Fourier y Spire 2

Design feature	ODYSSEY Outcomes	FOURIER	SPIRE-2 (terminated)
Patient population	Post ACS, 2-4-52 weeks from index event (median 2,6 months)	Stable ASCVD, i.e. MI, stroke or PAD (median ~3 years from index event)	High risk primary prevention or CVD
No. of patients	18,924	27,564	10,621
Age, years	58 (median)	63 (mean)	63 (mean)
Women	25%	25%	35%
LDL-C entry criteria mg/dl (mmol/L)	≥70 (1.8)	≥70 (1.8)	≥100 (2.6)
Baseline LDL-C mg/dl (mmol/L)	87 (2.3)	92 (2.4)	133 (3.3)
High intensity statin	89%	69%	73%
No statin	<1%	-	17%
Ezetimibe	3%	5%	13%
PCSK9 inhibitor dose regimen	Alirocumab 75 or 150 mg every 2 weeks, titrated to target LDL-C (25-50 mg/dl)	Evolocumab 140 mg every 2 weeks or 420 mg every 4 weeks	Bococizumab 150 mg every 2 weeks, down titrated if LDL-C <10 mg/dl
Duration of follow-up, yr	2.8 (44% with ≥3 years)	2.2	1
Primary endpoint	4-point: CHD death, MI, ischaemic stroke, unstable angina requiring hospitalisation	5-point: CV death, MI, stroke, hospitalisation for unstable angina, coronary revascularisation	4-point: CV death, MI, stroke, urgent revascularisation

Comparación resultados de los estudios Odyssey Outcomes, Fourier y Spire 2

Design feature	ODYSSEY Outcomes	FOURIER	SPIRE-2 (terminated)
Absolute change in LDL-C (mg/dl)	54 at 12 months, 48 at 4 years	56	62
% change in LDL-C	61%	59%	52%
Relative reduction in primary endpoint	15% (0.85, 0.78-0.93)	15% (0.85, 079-0.92)	21% (0.79, 065-0.97)
MI	14%	27%	24%
Stroke	27%	21%	34%
Unstable angina	39%	1%	5%
CVD death	12% (NS)	5% increase (NS)	18% (NS)
All-cause death	**15% (*P=0.026)**	4% increase (NS)	9% (NS)

2016 ESC/EAS Guidelines for the Management of Dyslipidemias

Risk Category	Definition	LDL-C Goal
Very high	• Documented CVD • T2D with target organ damage or a major risk factor • 10-year risk ≥ 10% for fatal CVD	< 70 mg/dL Or ≥ 50% reduction if LDL-C 70-135 mg/dL
High	• Cholesterol > 310 mg/dL or BP ≥ 180/110 mmHg • Most people with T2D • Moderate CKD • 10-year risk ≥ 5% for fatal CVD	< 100 mg/dL Or ≥ 50% reduction if LDL-C 100-200 mg/dL
Moderate	10-year risk ≥ 1% - < 5% for fatal CVD	< 115 mg/dL
Low	10-year risk < 1% for fatal CVD	< 115 mg/dL

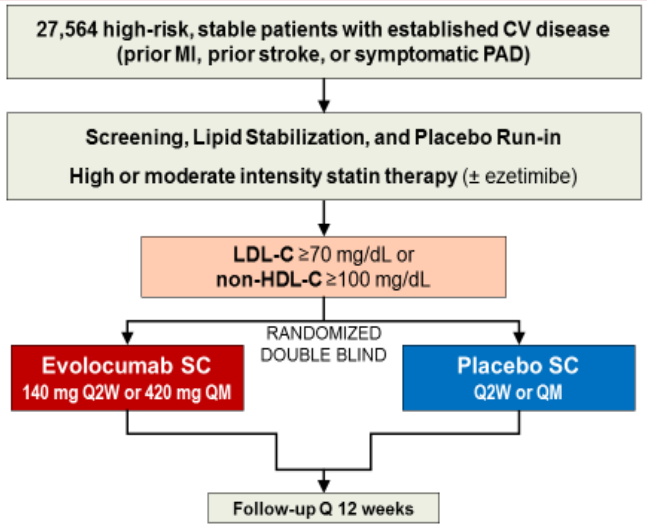
Catapano AL, et al. *Eur Heart J.* 2016;37:2999-3058.

2017 AACE Guidelines for the Management of Dyslipidemia

Risk Category	Risk Factors/10-Year Risk	Treatment Goals		
		LDL-C, mg/dL	Non-HDL-C, mg/dL	Apo B, mg/dL
Extreme risk	• Progressive ASCVD including unstable angina in patients after achieving an LDL-C < 70 mg/dL • Established clinical cardiovascular disease in patients with DM, CKD ¾, or HeF • History of premature ASCVD (< 55 male, < 65 female)	< 55	< 80	< 70
Very high risk	• Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk > 20% • Diabetes or CKD ¾ with 1 or more risk factor(s) • HeFH	< 70	< 100	< 80

Jellinger PS, et al. *Endocr Pract*. 2017;23:1-87.

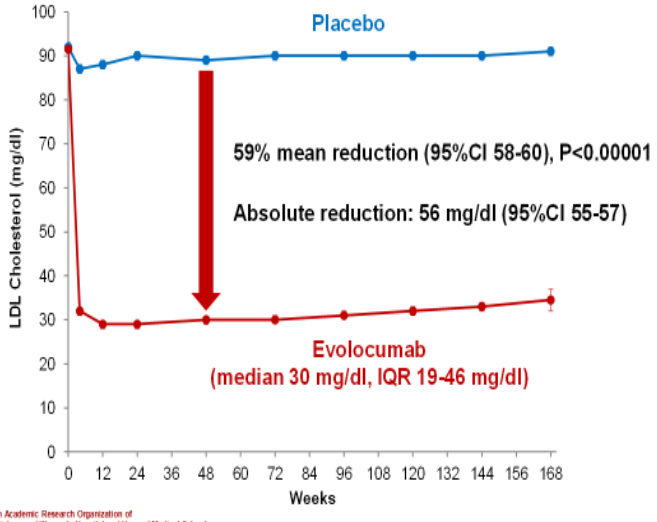
Trial Design



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

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

LDL Cholesterol



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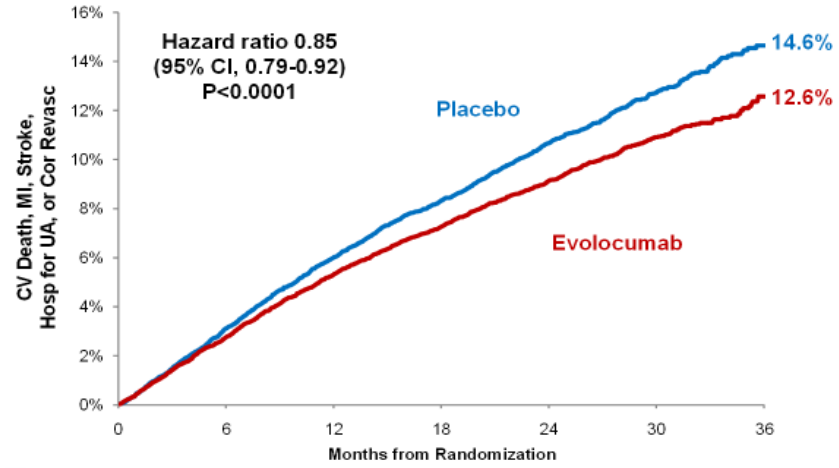
Primary Endpoint



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Summary for Evolocumab

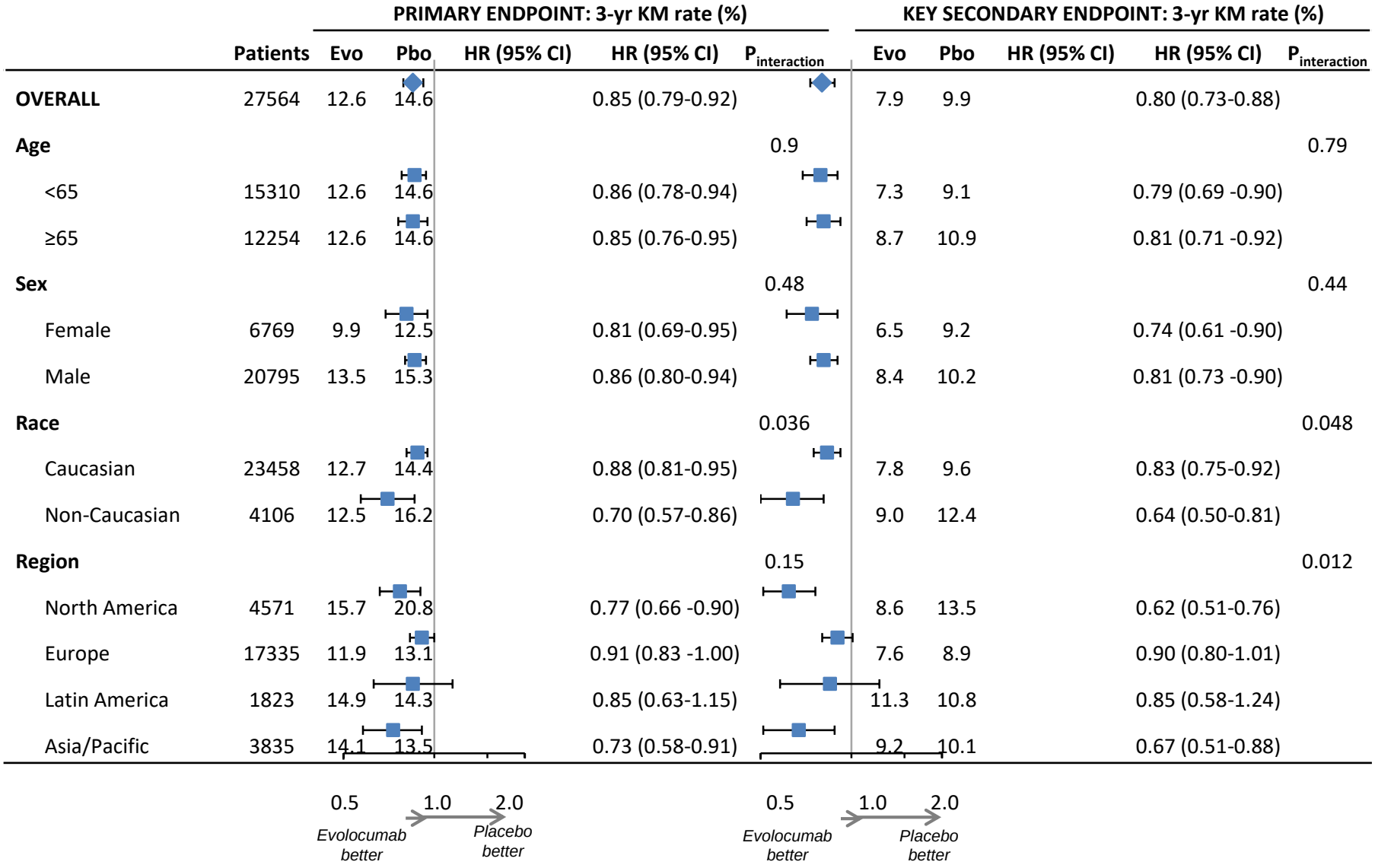
- **↓ LDL-C by 59%**
  - Consistent throughout duration of trial
  - Median achieved LDL-C of 30 mg/dl (IQR 19-46 mg/dl)
- **↓ CV outcomes in patients already on statin therapy**
  - 15% ↓ broad primary endpoint; 20% ↓ CV death, MI, or stroke
  - Consistent benefit, incl. in those on high-intensity statin, low LDL-C
  - 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**
  - Similar rates of AEs, incl DM & neurocog events w/ EvoMab & pbo
  - Rates of EvoMab discontinuation low and no greater than pbo
  - No neutralizing antibodies developed

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

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

Evolocumab Outcomes Trial:

Subgrupos

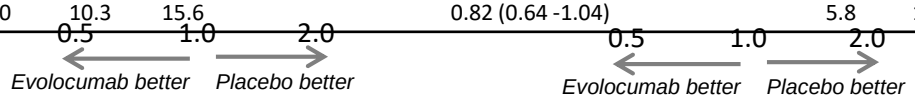


		PRIMARY ENDPOINT: 3-yr KM rate (%)					KEY SECONDARY ENDPOINT: 3-yr KM rate (%)				
	Patients	Evo	Pbo	HR (95% CI)	HR (95% CI)	$P_{interaction}$	Evo	Pbo	HR (95% CI)	HR (95% CI)	$P_{interaction}$
OVERALL	27564	12.6	14.6		0.85 (0.79-0.92)		7.9	9.9		0.80 (0.73-0.88)	
Age						0.9					0.79
<65	15310	12.6	14.6		0.86 (0.78-0.94)		7.3	9.1		0.79 (0.69 -0.90)	
≥65	12254	12.6	14.6		0.85 (0.76-0.95)		8.7	10.9		0.81 (0.71 -0.92)	
Sex						0.48					0.44
Female	6769	9.9	12.5		0.81 (0.69-0.95)		6.5	9.2		0.74 (0.61 -0.90)	
Male	20795	13.5	15.3		0.86 (0.80-0.94)		8.4	10.2		0.81 (0.73 -0.90)	
Race						0.036					0.048
Caucasian	23458	12.7	14.4		0.88 (0.81-0.95)		7.8	9.6		0.83 (0.75-0.92)	
Non-Caucasian	4106	12.5	16.2		0.70 (0.57-0.86)		9.0	12.4		0.64 (0.50-0.81)	
Region						0.15					0.012
North America	4571	15.7	20.8		0.77 (0.66 -0.90)		8.6	13.5		0.62 (0.51-0.76)	
Europe	17335	11.9	13.1		0.91 (0.83 -1.00)		7.6	8.9		0.90 (0.80-1.01)	
Latin America	1823	14.9	14.3		0.85 (0.63-1.15)		11.3	10.8		0.85 (0.58-1.24)	
Asia/Pacific	3835	14.1	13.5		0.73 (0.58-0.91)		9.2	10.1		0.67 (0.51-0.88)	

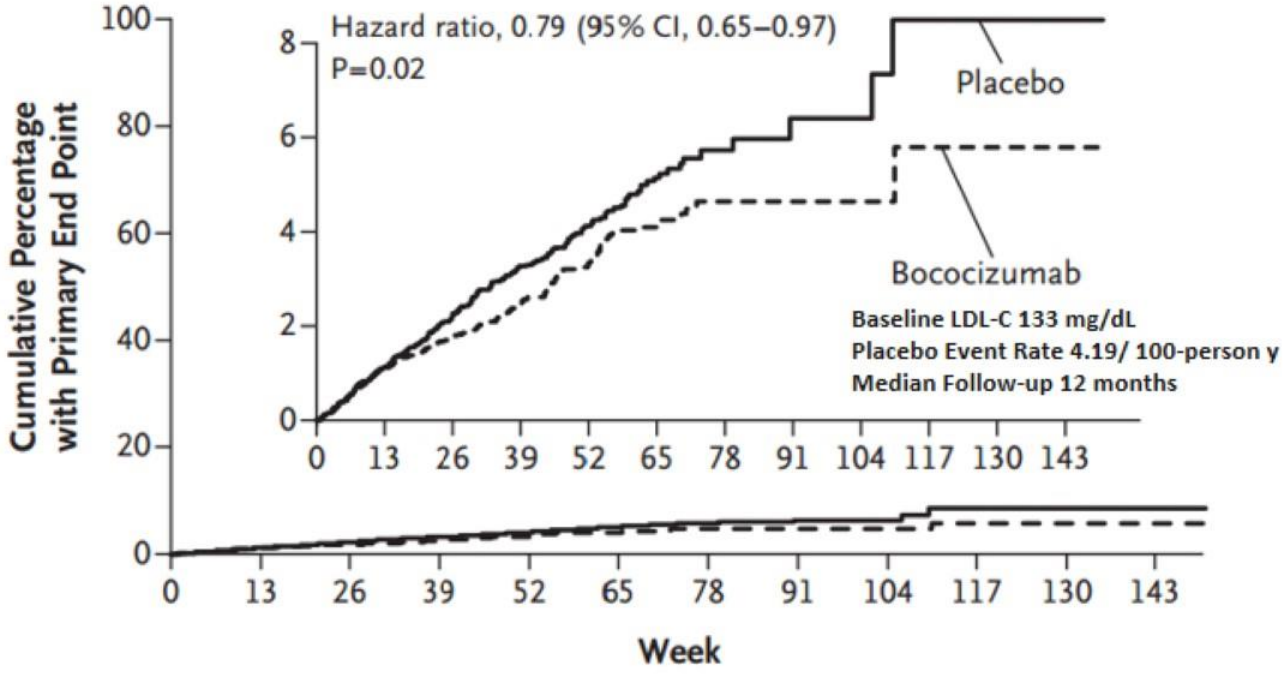
Evolocumab Outcomes Trial: fourier

Subgrupos

		PRIMARY ENDPOINT: 3-yr KM rate (%)					KEY SECONDARY ENDPOINT: 3-yr KM rate (%)				
	Patients	Evo	Pbo	HR (95% CI)	HR (95% CI)	$P_{interaction}$	Evo	Pbo	HR (95% CI)	HR (95% CI)	$P_{interaction}$
OVERALL	27564	12.6	14.6		0.85 (0.79-0.92)		7.9	9.9		0.80 (0.73-0.88)	
Type of disease						0.19					0.38
MI alone	19113	11.7	13.9		0.88 (0.80-0.96)		6.5	8.7		0.80 (0.71 -0.90)	
Stroke alone	3366	9.1	11.7		0.70 (0.54-0.90)		8.0	9.6		0.77 (0.58 -1.02)	
PAD alone	1505	9.4	12.6		0.67 (0.47-0.96)		5.5	10.3		0.57 (0.38-0.88)	
Polyvasculardisease	3563	21.5	21.5		0.88 (0.75-1.03)		16.0	16.7		0.86 (0.71-1.04)	
Baseline LDL-C						0.69					0.96
Q1 (<80 mg/dL)	6961	11.0	13.6		0.80 (0.69 -0.93)		7.4	8.8		0.78 (0.64-0.95)	
Q2 (80 -<92 mg/dL)	6886	11.4	14.4		0.82 (0.71 -0.96)		6.8	9.3		0.79 (0.65-0.96)	
Q3 (92 -109 mg/dL)	6887	13.6	14.3		0.89 (0.77 -1.03)		8.7	10.3		0.79 (0.66-0.94)	
Q4 (>109 mg/dL)	6829	14.2	16.2		0.89 (0.77-1.02)		8.7	11.3		0.83 (0.70-0.99)	
Baseline statin intensity						0.97					0.33
High	19103	12.7	14.7		0.87 (0.80-0.95)		8.0	9.8		0.82 (0.74 -0.92)	
Not High	8461	12.9	14.8		0.80 (0.70-0.92)		8.0	10.6		0.74 (0.63 -0.88)	
Ezetimibe						0.26					0.76
Yes	1440	16.1	17.0		0.98 (0.74-1.31)		9.4	13.0		0.74 (0.52-1.06)	
No	26124	12.4	14.5		0.84 (0.78-0.91)		7.8	9.7		0.80 (0.73-0.88)	
Initial Dosing Regimen						0.83					0.89
Every 2 weeks	24774	12.7	14.6		0.85 (0.79 -0.92)		8.0	10.0		0.80 (0.72-0.88)	
Monthly	2790	10.3	15.6		0.82 (0.64 -1.04)		5.8	10.9		0.80 (0.59-1.09)	



The SPIRE-2 Cardiovascular Outcomes Trial: Baseline LDL-C ≥ 100 mg/dL Primary Prespecified Endpoint*

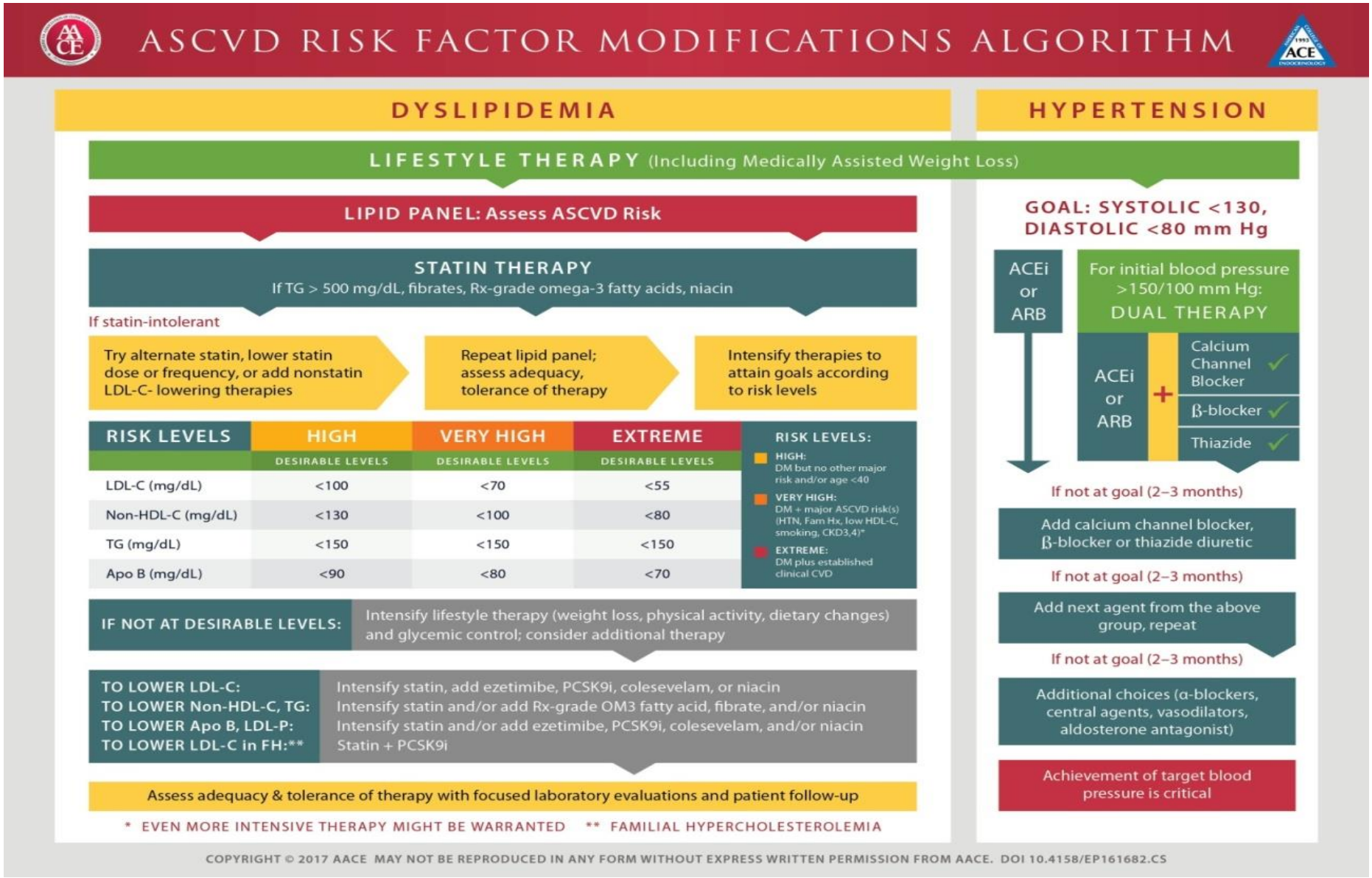


No. at Risk

Placebo	5309	5220	5130	4214	2319	1174	419	216	116	49	14	4
Bococizumab	5312	5223	5161	4250	2346	1202	431	221	118	49	13	2

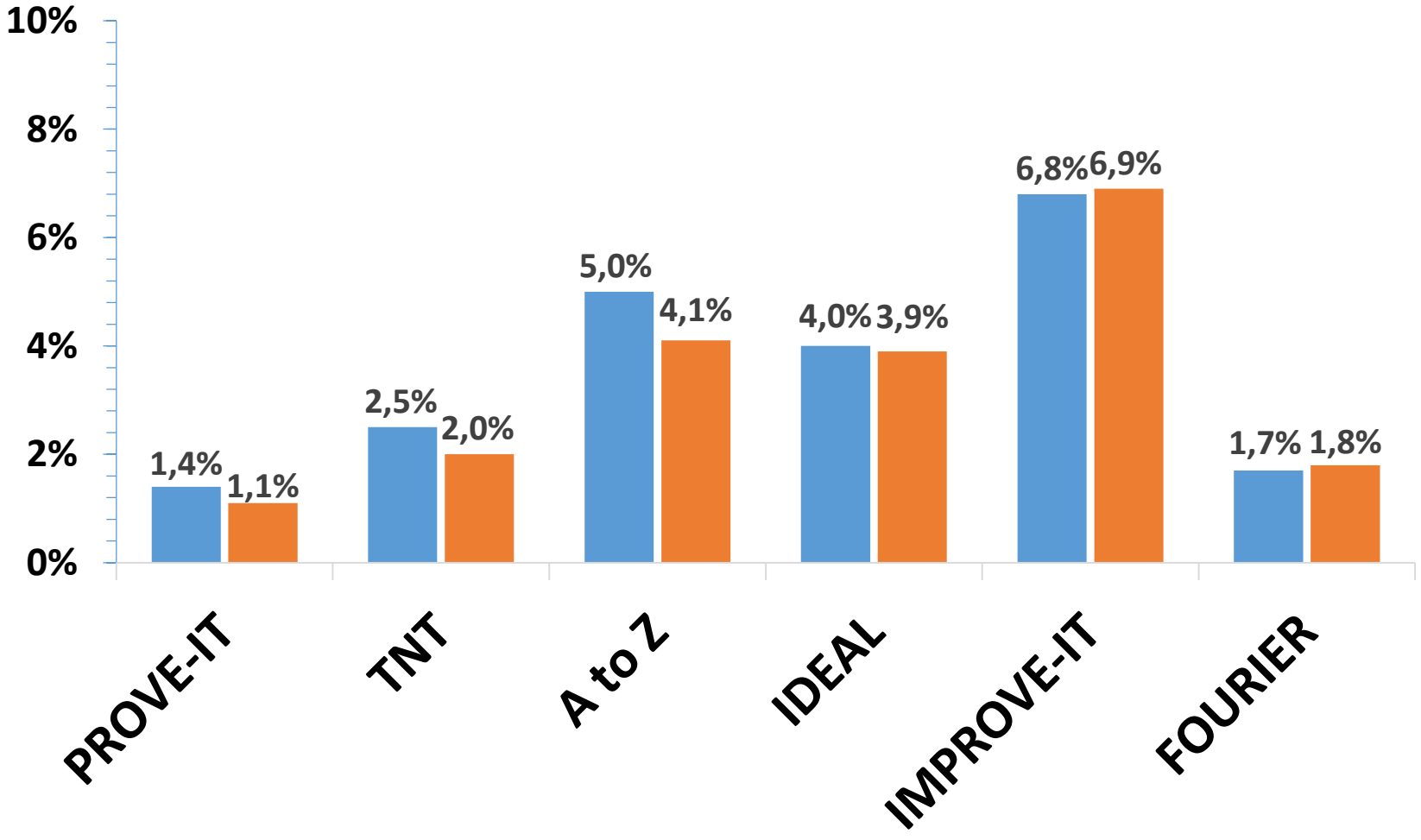
*Nonfatal MI, nonfatal stroke, hospitalization for UA requiring urgent revascularization, or CV death.

Consenso AACE/ACE 2017



Consenso para el tratamiento de la diabetes tipo 2 de la American Association of Clinical Endocrinologists (AACE) y del American College of Endocrinology (ACE) – 2017

Mortalidad CV en estudios con estatinas de Prevención 2ª



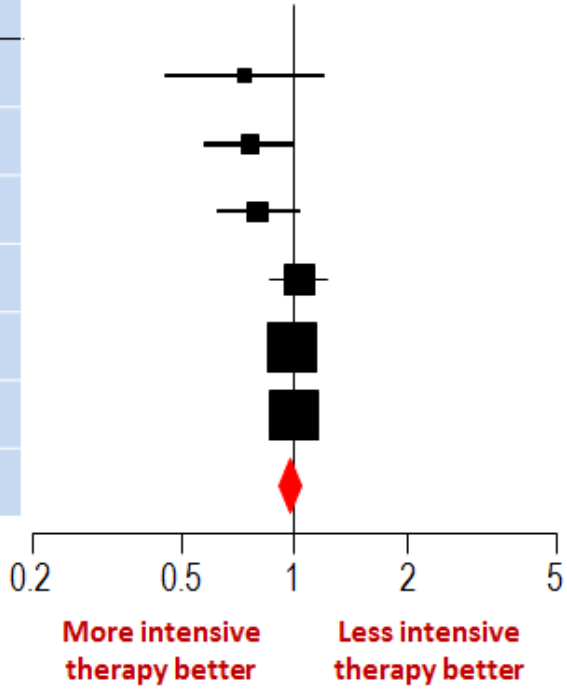
Cannon S, et al. N Engl J Med 2004;350:1495-504.
La Rosa, et al. N Engl J Med 2005;352:1425-35.

Lemos, et al. JAMA. 2004;292:1307-13165,4
Pedersen, et al. JAMA. 2005;294:2437-2445
Cannon, et al. N Engl J Med 2015;372:2387-97

More Intensive LDL-C Lowering & CV Death

No clear benefit on CV mortality

		# of CV Deaths		
Trial	**Year**	**More Intensive Rx Arm**	**Less Intensive Rx Arm**	**HR (95% CI)**
PROVE-IT TIMI 22	2004	27	36	0.74 (0.45-1.22)
A2Z	2004	86	111	0.76 (0.57-1.01)
TNT	2005	101	127	0.80 (0.61-1.03)
IDEAL	2005	223	218	1.03 (0.85-1.24)
SEARCH	2010	565	572	0.99 (0.88-1.11)
IMPROVE-IT	2015	538	537	1.00 (0.89-1.13)
Summary		**1540**	**1601**	**0.96 (0.90-1.03)**



NEJM 2004;350:1495-504
JAMA 2004;292:1307-16
NEJM 2005;352:1425-35
JAMA 2005;294:2437-45
Lancet 2010;376:1658-69
NEJM 2015;372:2387-97

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