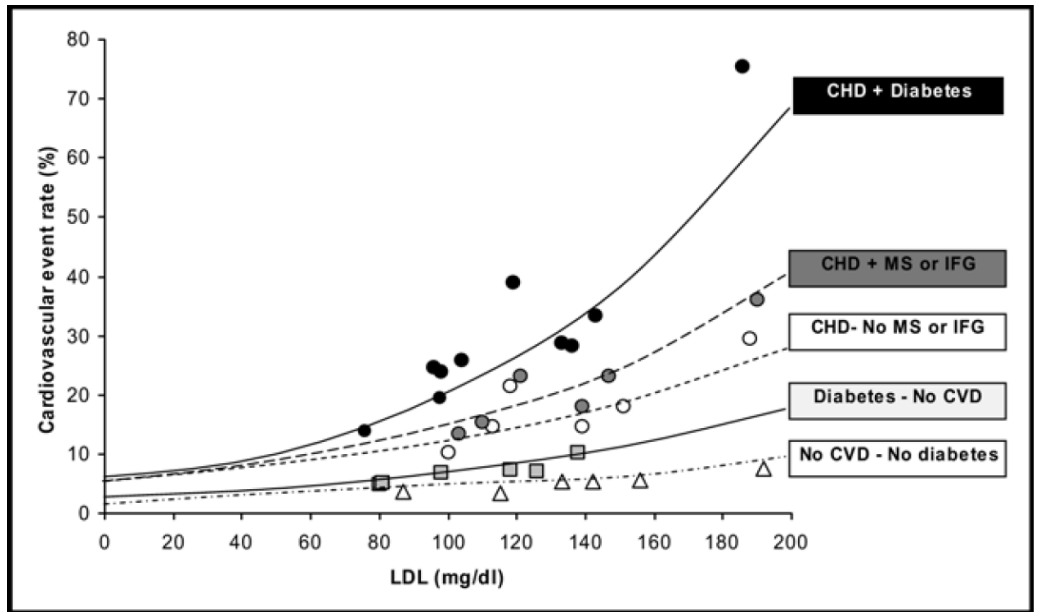
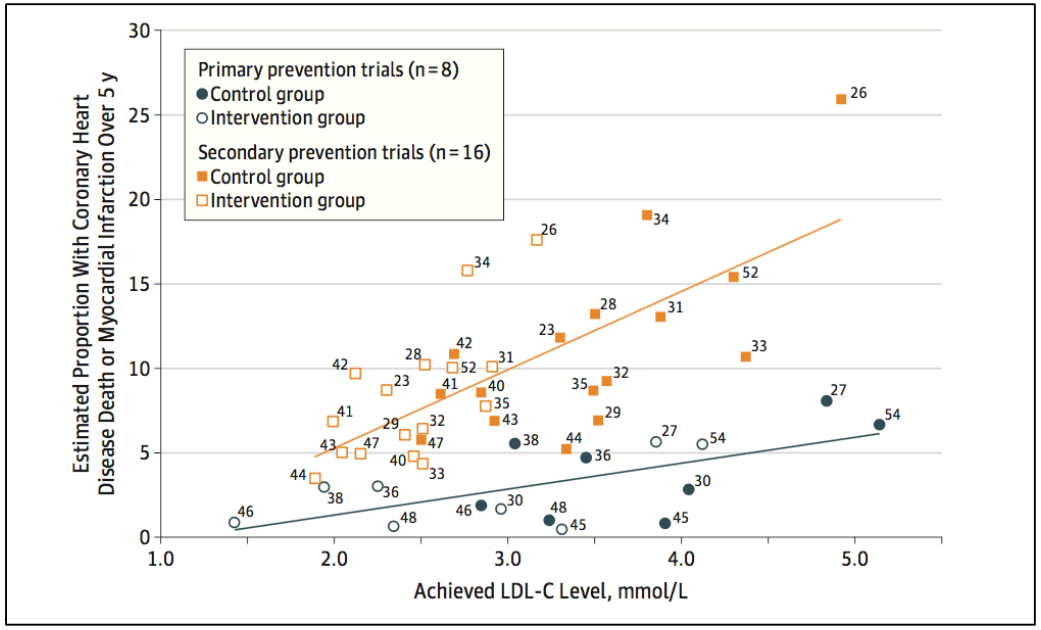
Triple Trouble : treatment of dyslipidemia with PCSK-9 Inhibitors in patients with diabetes and previous acute coronary syndrome

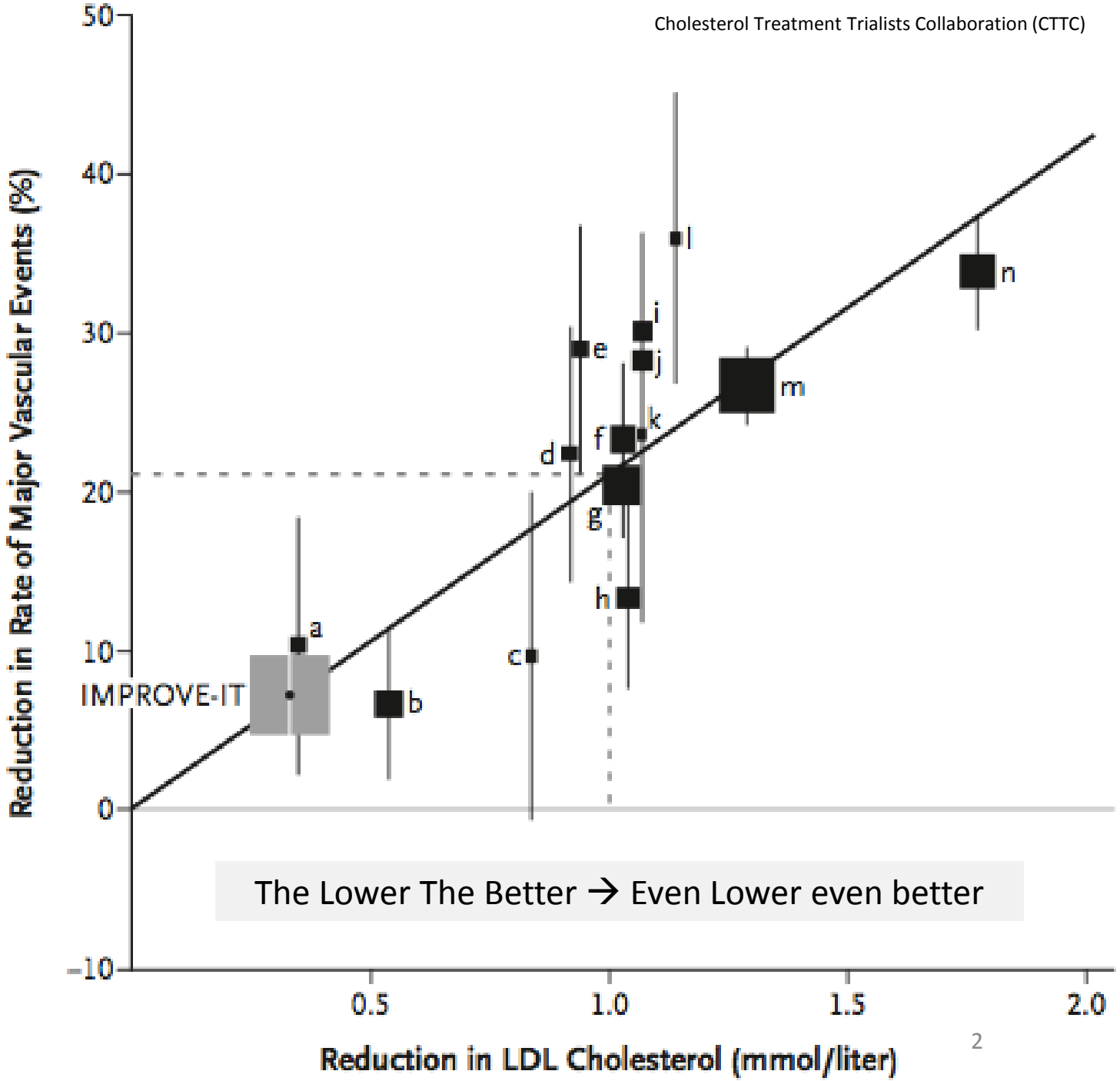
Gian Piero Perna

Department of Cardiovascular Diseases

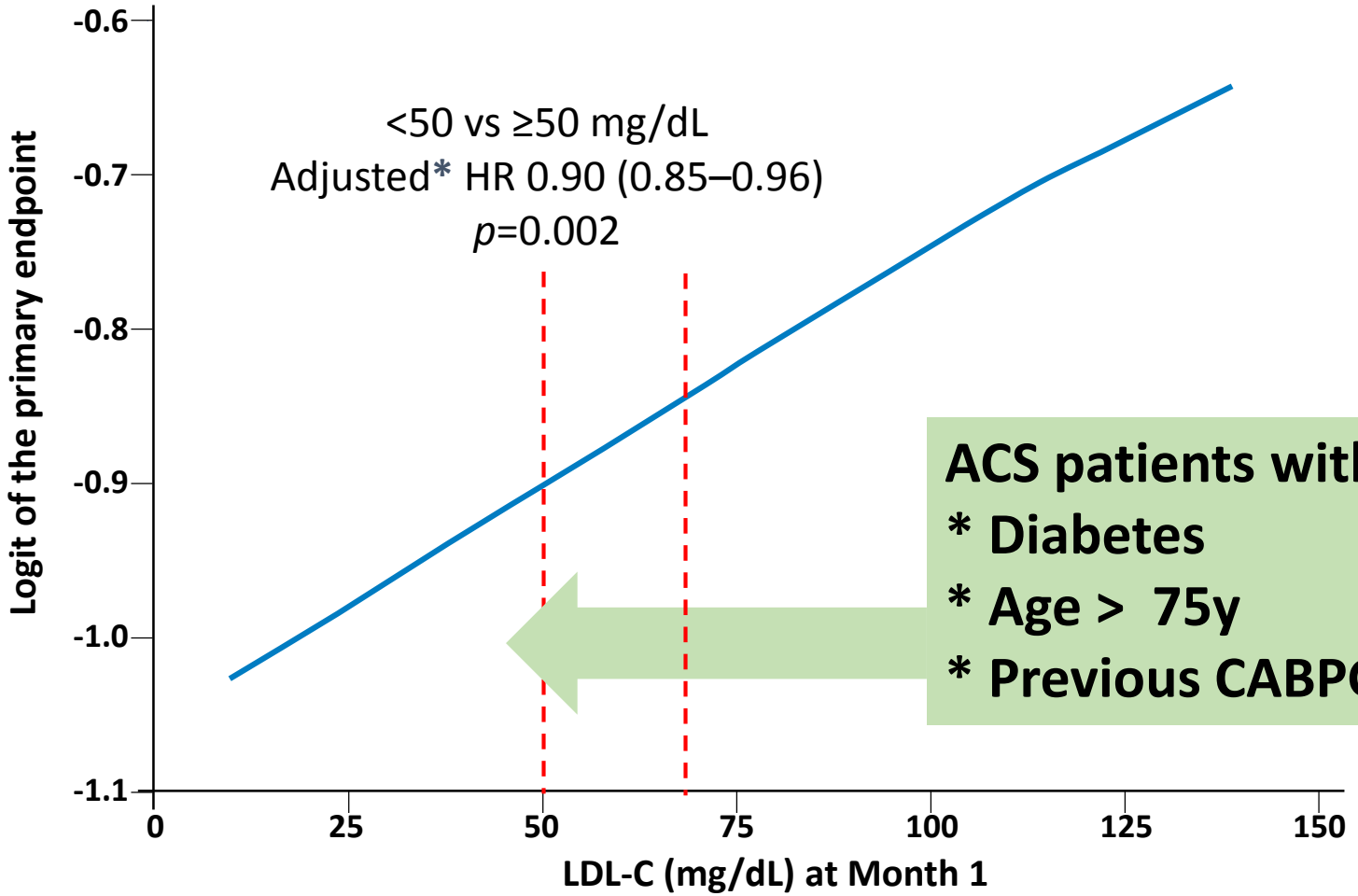




Cholesterol Treatment Trialists Collaboration (CTTC)



Reduction of LDL-C below vs above 50 mg/dL reduces CV risk by a further 10%



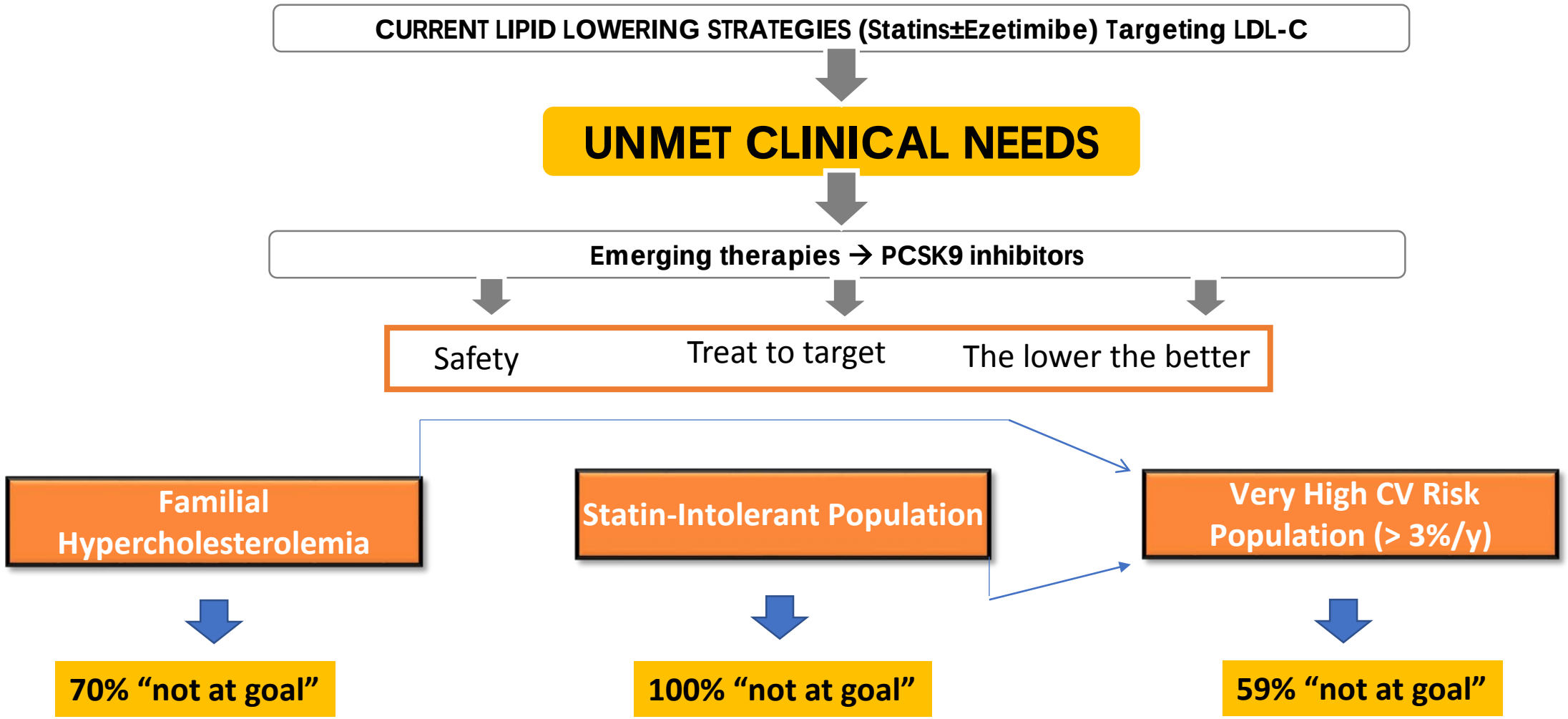
ACS patients with
*** Diabetes**
*** Age > 75y**
*** Previous CABPG**

Risk Indicators
CHF
HTN
Age≥75
DM
Prior Stroke
Prior CABG
PAD
eGFR<60
Current Smoking

**Model covariates: age, BMI, sex, race, region, Hx diabetes, current smoker, Hx hypertension, Hx MI, Hx PCI*
BMI, body mass index; HR, hazard ratio; Hx, family history of; MI, myocardial infarction; PCI, percutaneous coronary intervention.

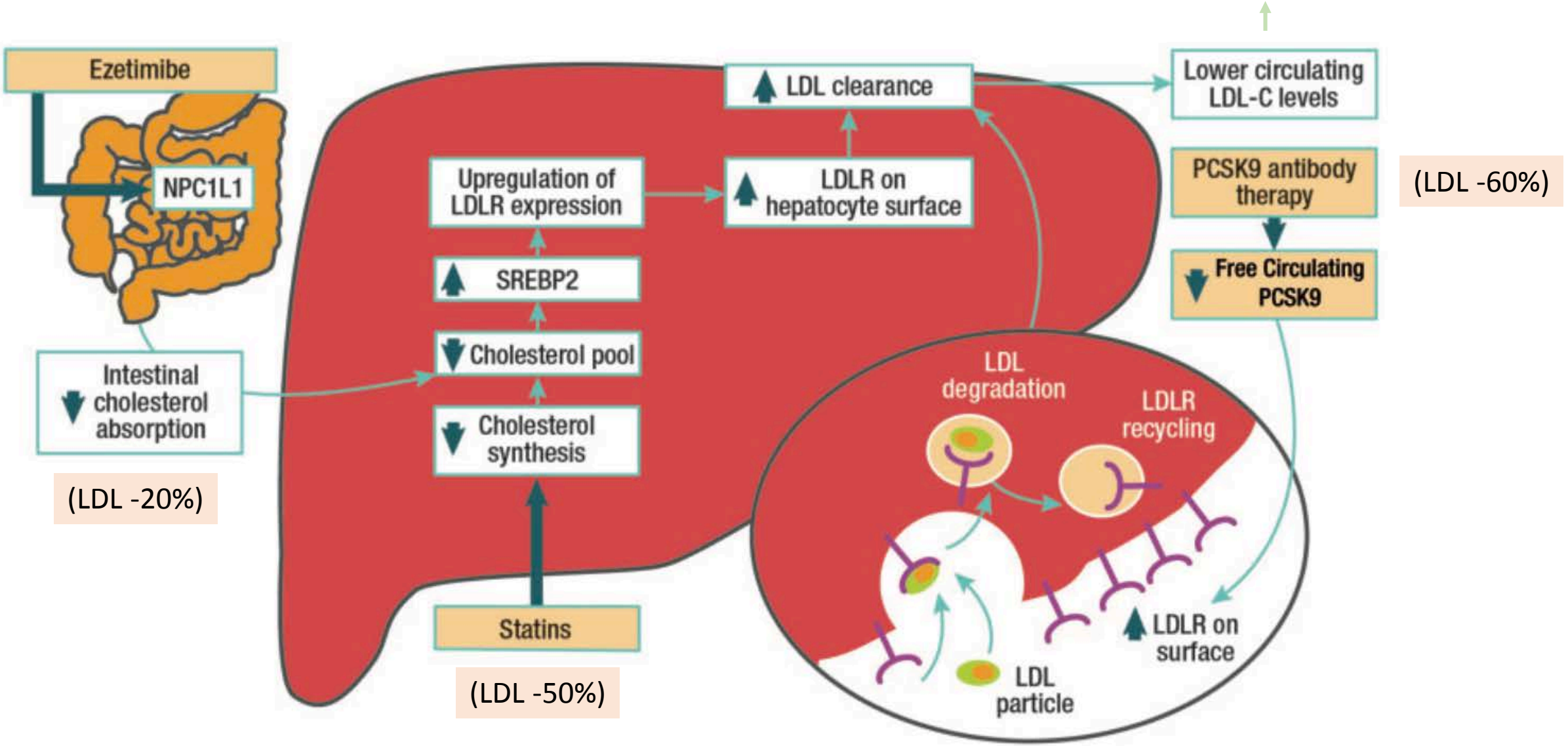
Guigliano RP, et al. Presented at European Society of Cardiology, London, 2015.

“Real Word” Populations with an Unmet Need for LDL-C Lowering



The mode of action are complementary . The effects are additives

LDL – 130%

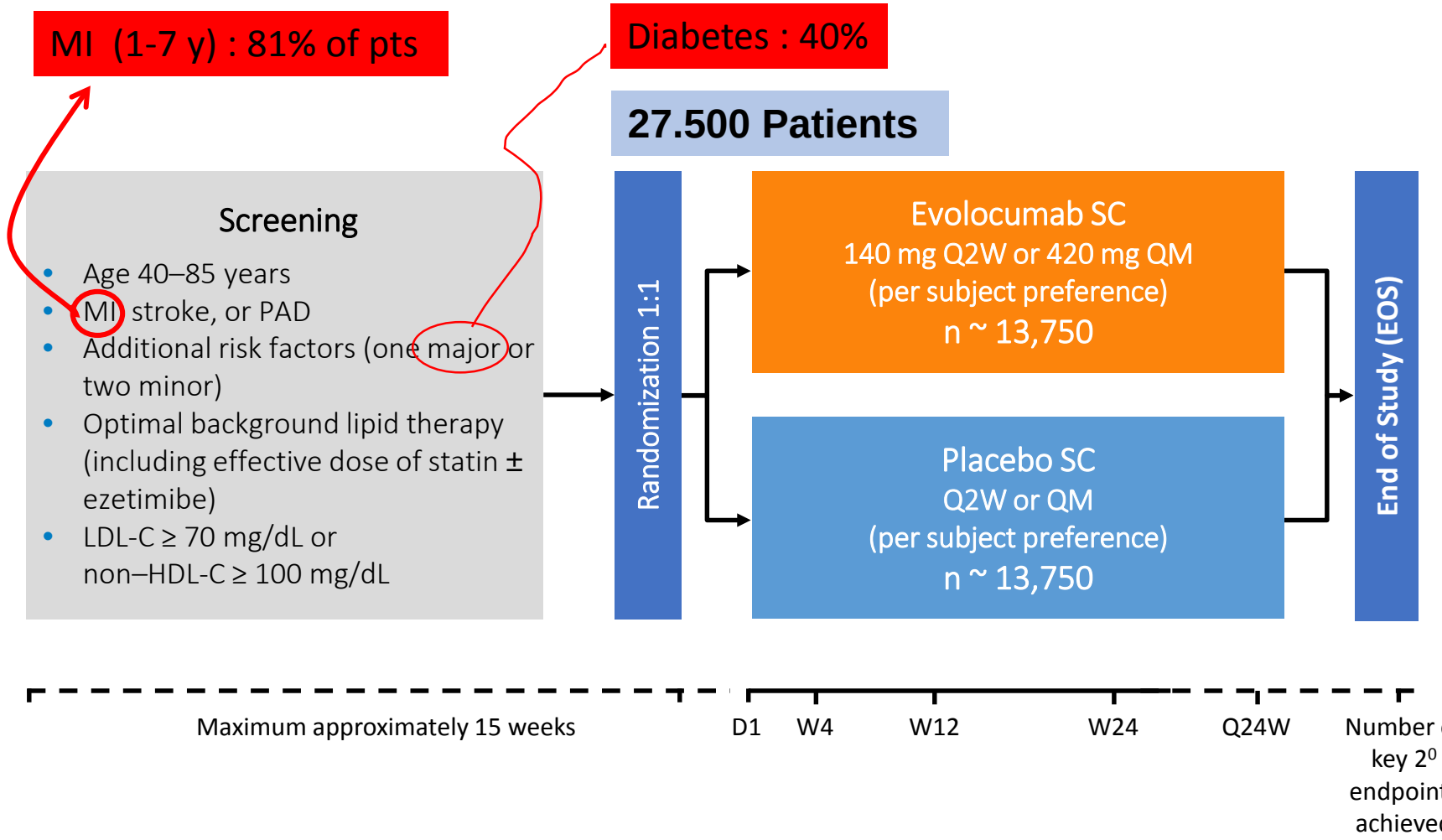


ODYSSEY OUTCOMES & FOURIER Study Designs

	ALIROCUMAB ODYSSEY OUTCOMES	EVOLOCUMAB FOURIER
Patient population	Patients with recent **ACS** on <u>maximally tolerated statin</u> ± other LLT **LDL-C** ≥70 mg/dL or **non-HDL-C** ≥100 mg/dL or **apolipoprotein B** ≥80 mg/dL) 18.000 pts (9000 vs 9000)	27.500 Patients with **MI**, **stroke**, or **PAD** and **additional risk factors** (1 major or 2 minor) + on <u>optimal background lipid therapy</u> (effective statin dose ± ezetimibe) **LDL-C** ≥70 mg/dL or **non-HDL-C** ≥100 mg/dL
Primary End Point	Time to Coronary Heart Disease death, non-fatal myocardial infarction, ischemic stroke, Unstable Angina requiring hospitalization	Time to Cardiovascular Death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for Unstable Angina or coronary revascularization
LDL-C reduction	**Treat-to-target approach** Patient started on 75Q2W (~50% LDL-C reduction) up- titration to 150Q2W if LDL-C≥50 mg/dL	**Lower-the-better approach with one dose fits all** Patients on 140Q2W/420QM ≥60% LDL-C reduction
Management of Low LDL-C	**With down-titration** from 150Q2W to 75Q2W if 2 consecutive LDL-C <25mg/dL, or from 75Q2W to placebo if 2 consecutive LDL- C <15 mg/dL	**No down-titration or switch to placebo** if low LDL-C level
Baseline LDL-C	86.5mg/dL (median)	91.5mg/dL (median)
Mean Exposure to Study Drug and Follow-up	**Mean 3 years** 2-to-5 years follow-up	**Mean 2 years** 1-to-3.5 years follow-up

[8] Sabatine, et al. *Am Heart J*. 2016;173:94-101.; Schwartz GG, et al. *Am Heart J*. 2014;168:682-689.e1.

Evolocumab Outcomes Trial: Study Design Overview



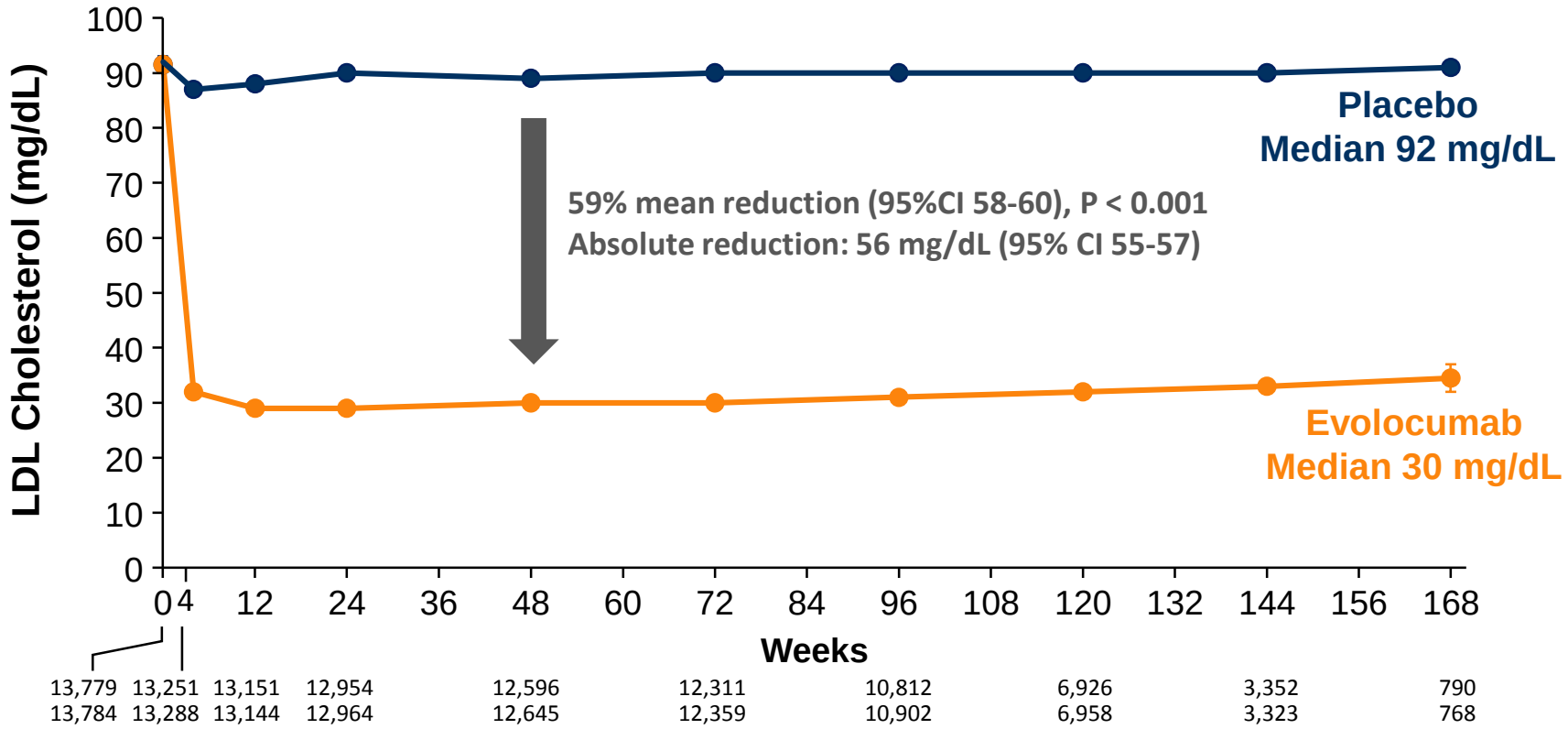
1630 events
RRR ≥ 15%

PRIMARY END-POINT:
CV Death, MI, Stroke, Hosp. or UA, or Coronary Revascularization
SECONDARY END-POINT:
CV death, MI, Stroke
CTTC END-POINT :
Coronary and Vascular Events

D = day; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery disease; Q2W = every 2 weeks; Q24W = every 24 weeks; QM = every month; SC = subcutaneous; W = week.

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

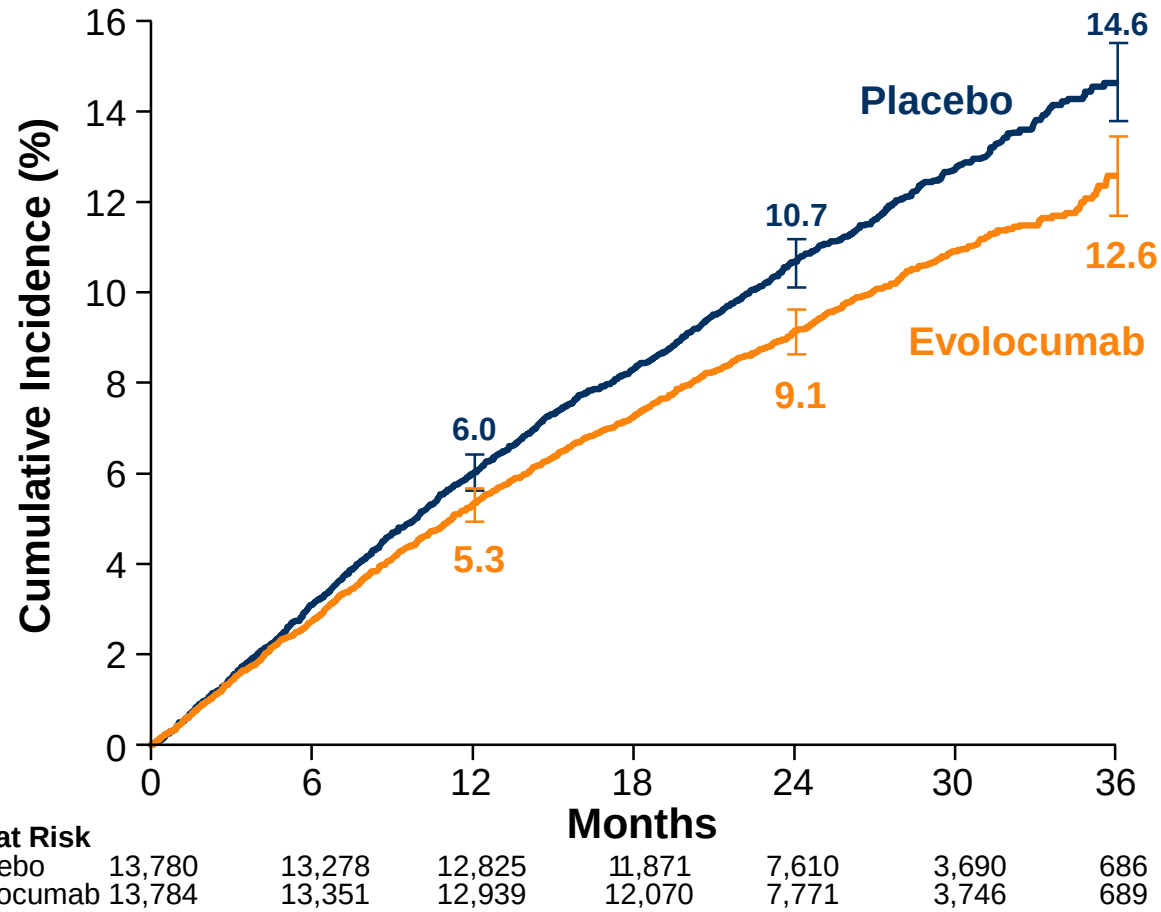
Median LDL-C Levels Over Time: All Patients



LDL-C was significantly reduced in the evolocumab group (median: 30 mg/dL) including 42% who achieved levels ≤ 25 mg/dL vs < 0.1% in the placebo group

Data shown are median values with 95% confidence intervals in the two arms; ITT.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Primary Endpoint: Composite of CV Death, MI, Stroke, Hospitalization for UA, or Coronary Revascularization



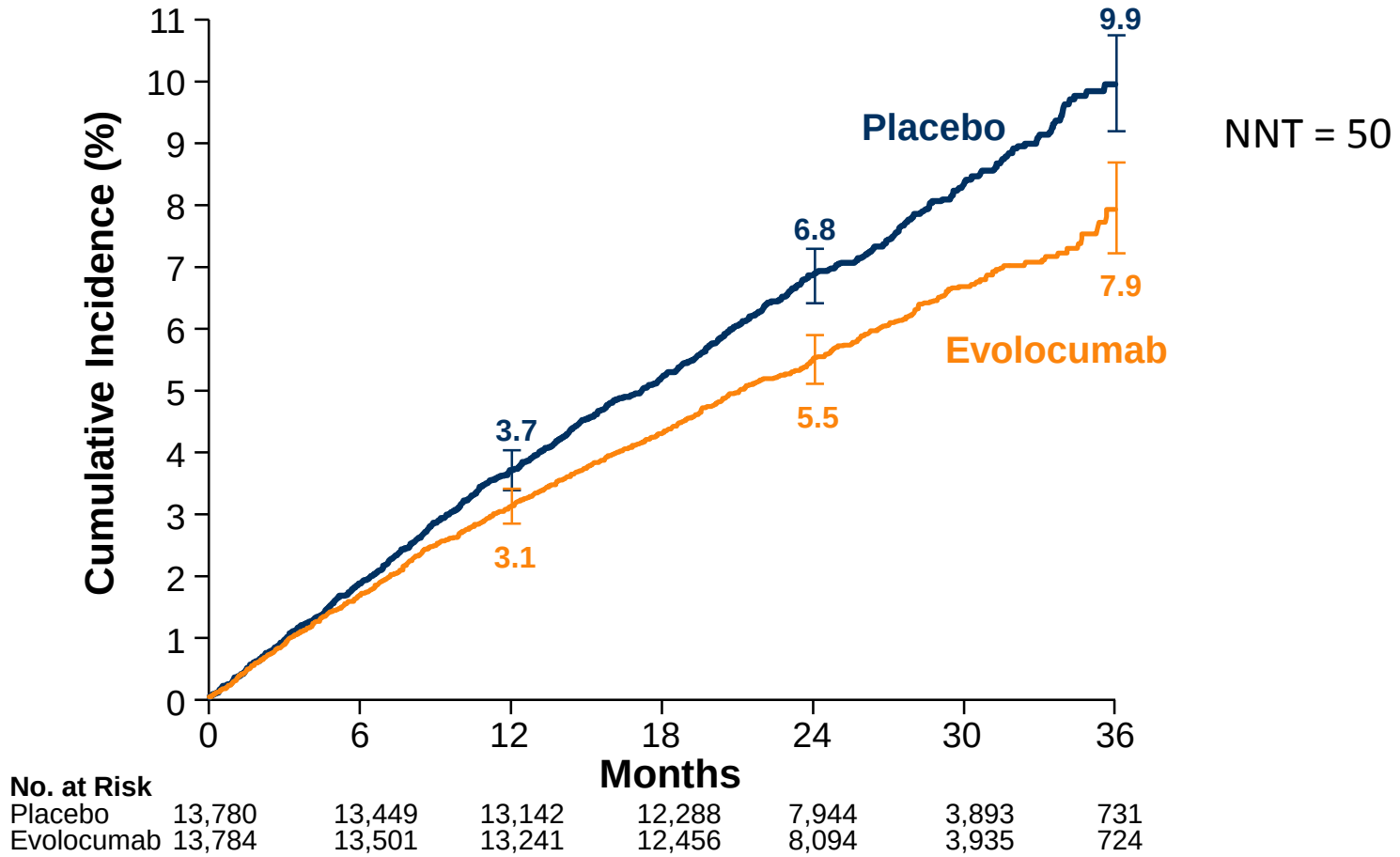
NNT : 50

HR 0.85 (95% CI 0.79 to 0.92); *P* < 0.001

CV = Cardiovascular; MI = Myocardial infarction; UA = Unstable angina; HR = Hazard ratio

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

Key Secondary Endpoint:
Composite of CV Death, MI, or Stroke



NNT = 50

HR 0.80 (95% CI 0.73 to 0.88); *P* < 0.001

CV = Cardiovascular; MI = Myocardial infarction; HR = Hazard ratio

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

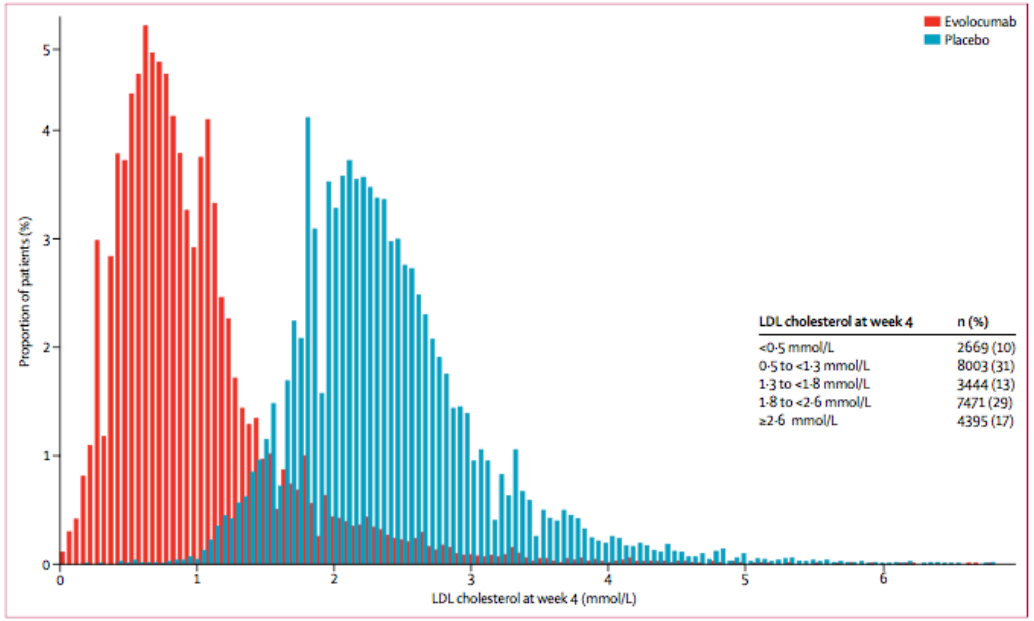
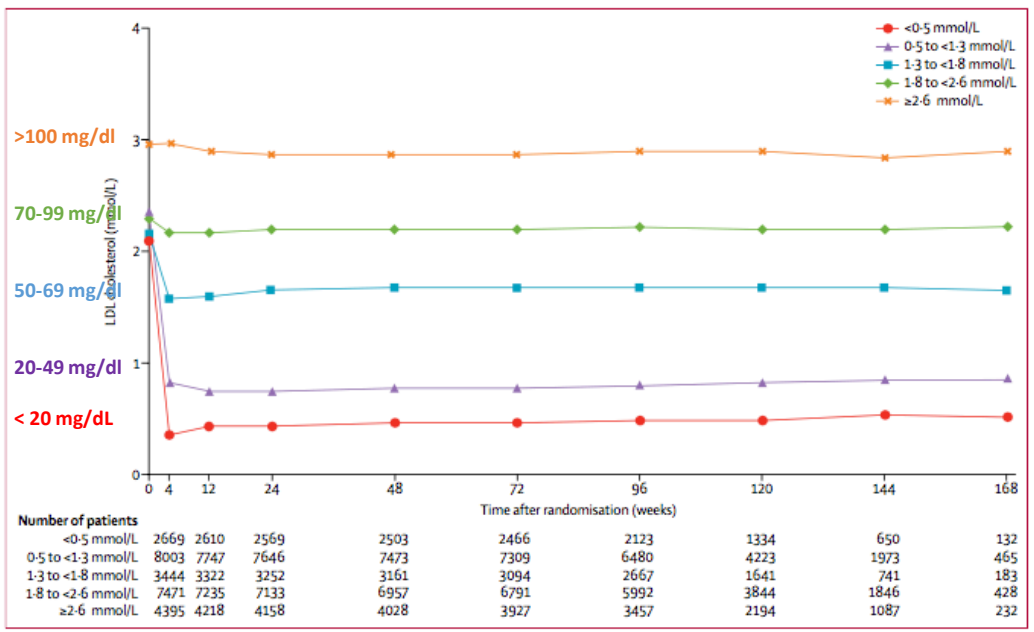
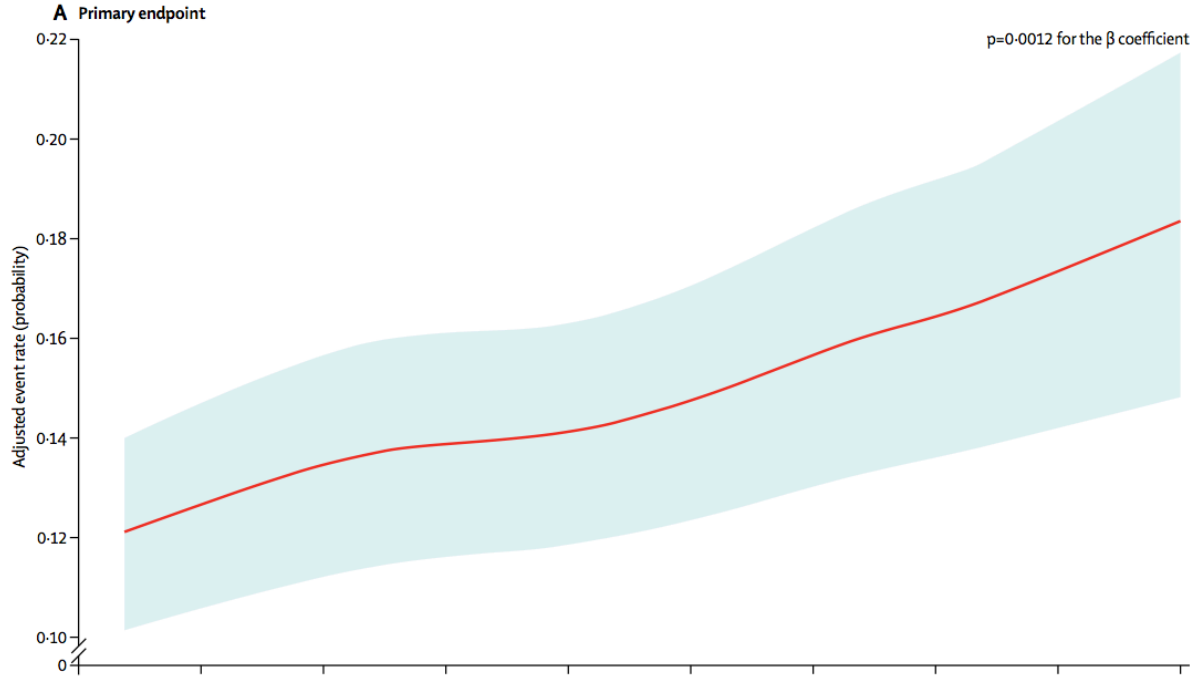
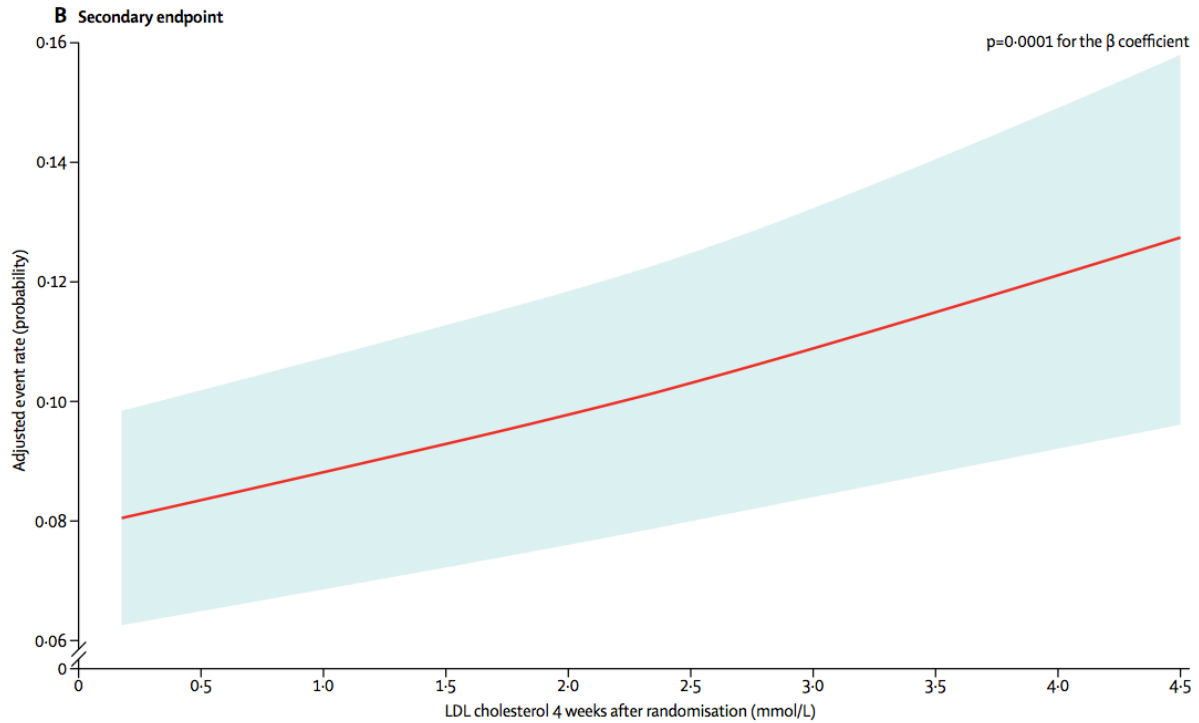


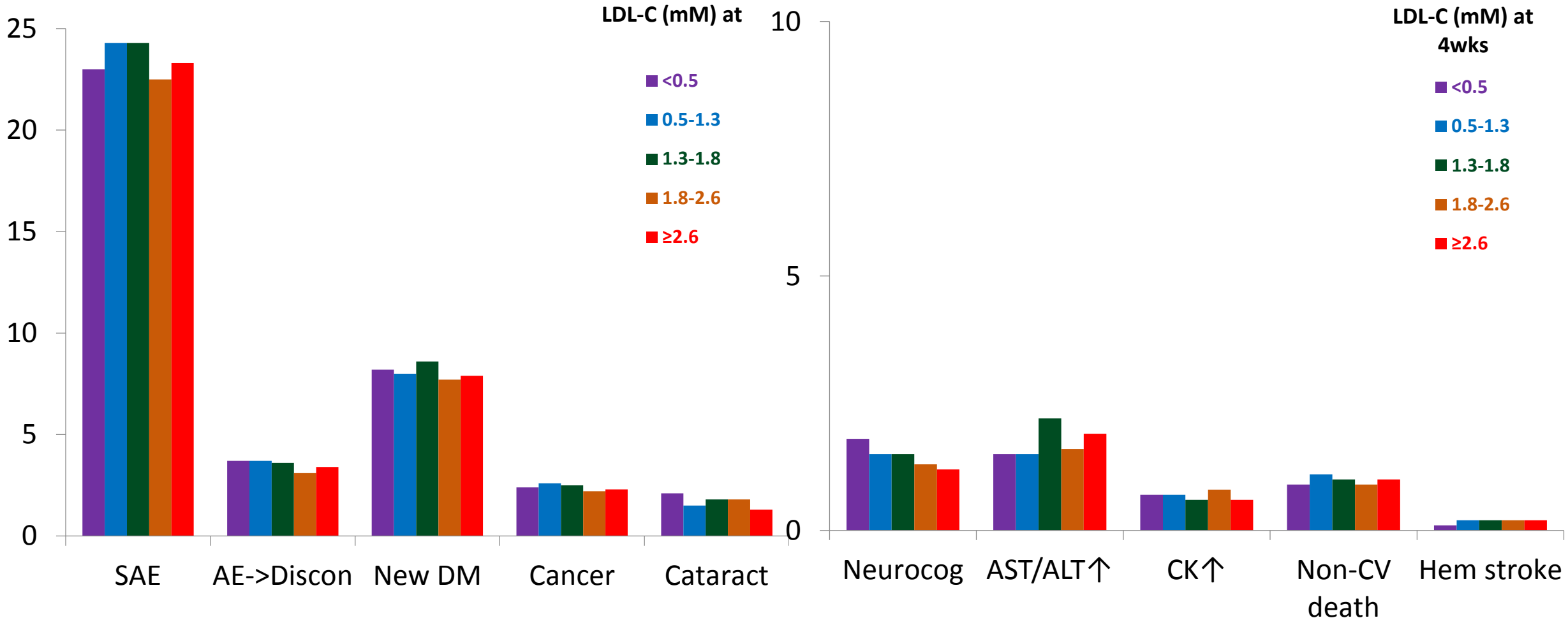
Figure 1: **Distribution of achieved LDL-cholesterol concentrations at 4 weeks in patients who did not have a primary efficacy or prespecified safety event before the study**
Red bars are evolocumab (median 0·8 mmol/L, IQR 0·5–1·2). Blue bars are placebo (median 2·2 mmol/L, IQR 1·9–2·7).







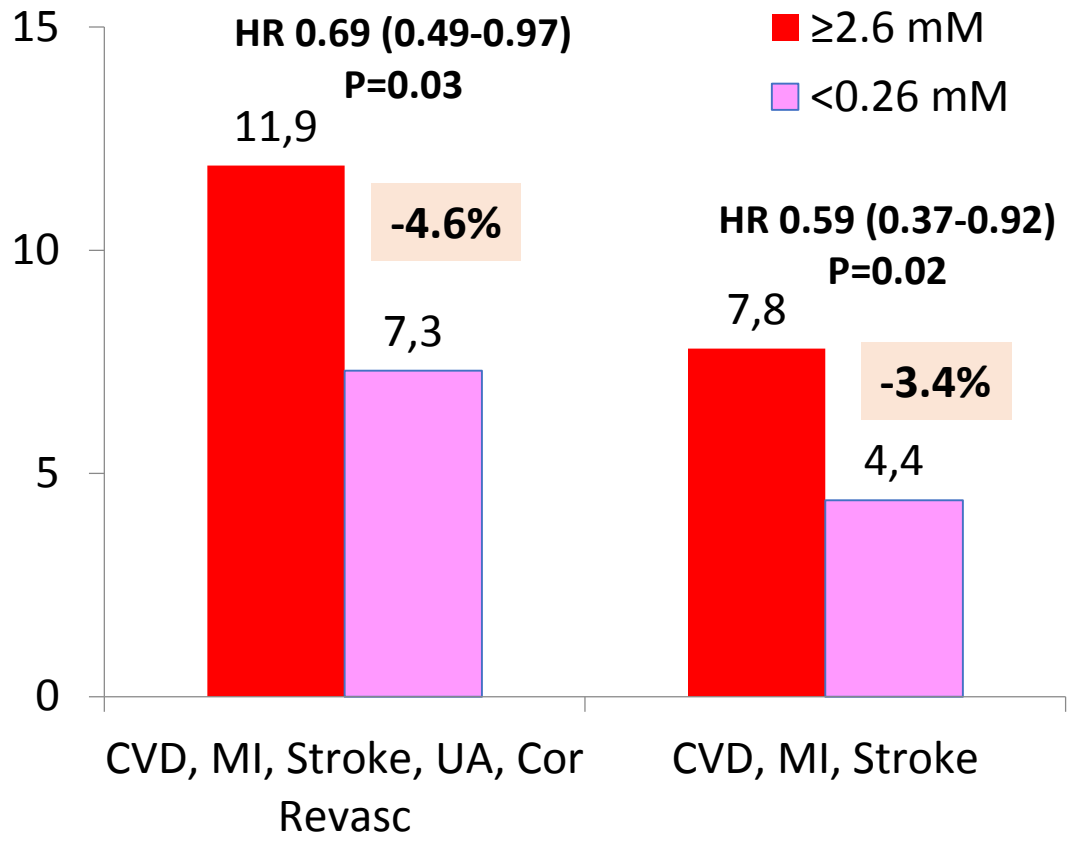
Safety


LDL-C (mM) at
<0.5
0.5-1.3
1.3-1.8
1.8-2.6
≥2.6
25
20
15
10
5
0
SAE
AE->Discon
New DM
Cancer
Cataract
LDL-C (mM) at 4wks
<0.5
0.5-1.3
1.3-1.8
1.8-2.6
≥2.6
10
5
0
Neurocog
AST/ALT↑
CK↑
Non-CV death
Hem stroke

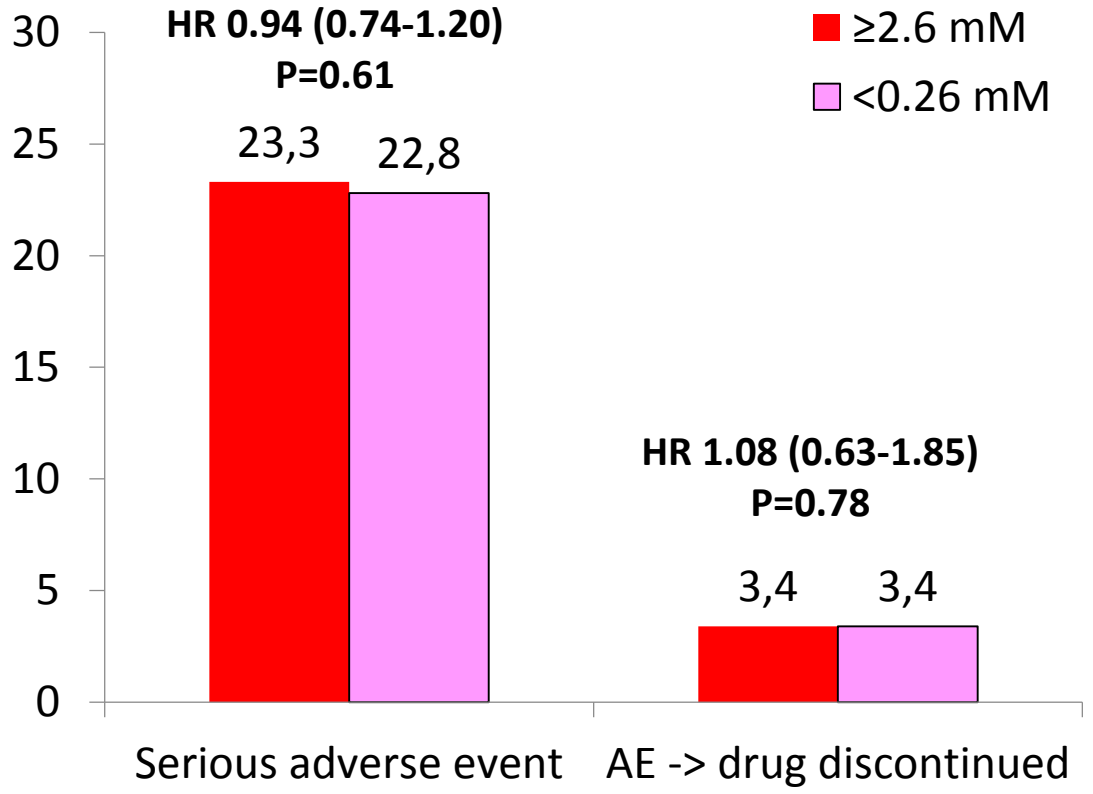
Exploratory Analysis Pts with LDL-C <0.26 mM (<10 mg/dL) at 4 wks

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

Cardiovascular Efficacy



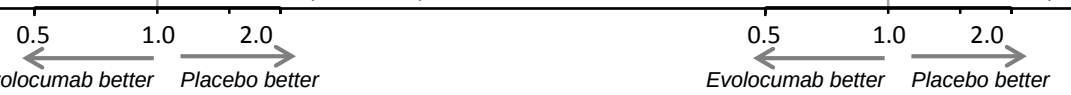
Safety



Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017

Primary and secondary composite endpoint results were consistent across all key subgroups

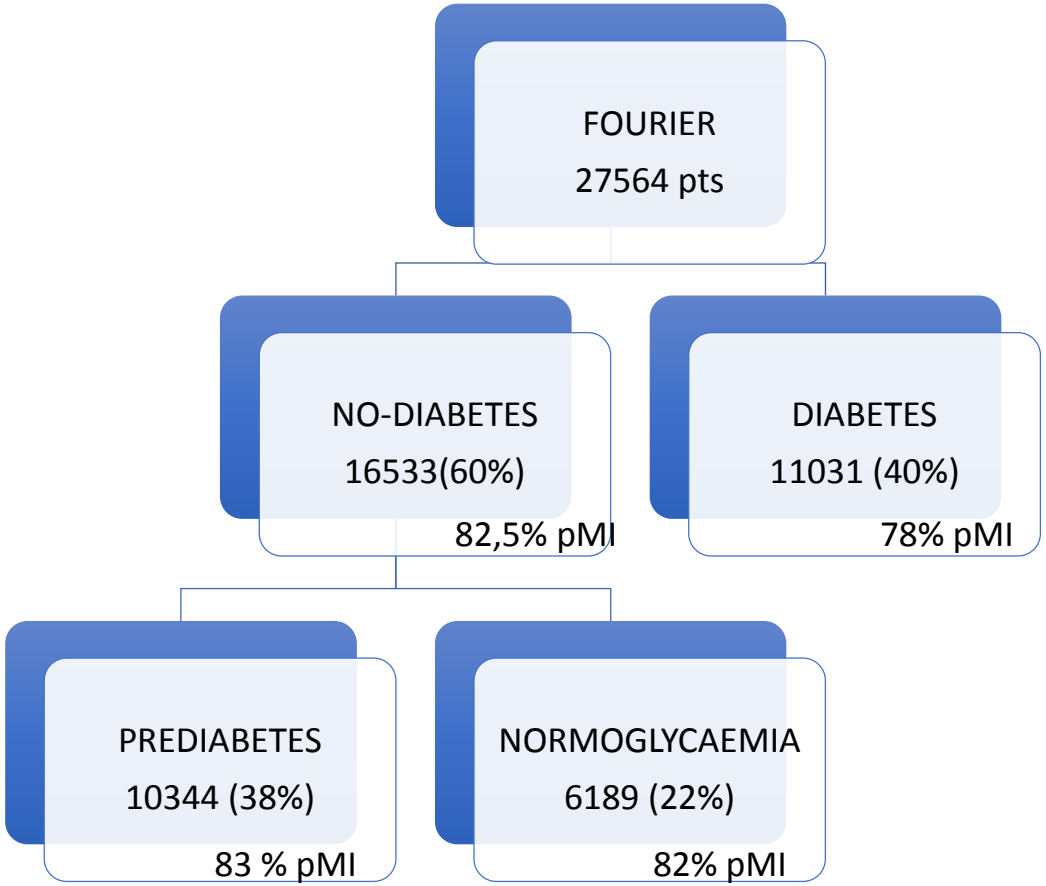
	Patients	PRIMARY ENDPOINT: 3-yr KM rate (%) Evo	Pbo	HR (95% CI)	HR (95% CI)	$P_{interaction}$	KEY SECONDARY ENDPOINT: 3-yr KM rate (%) Evo	Pbo	HR (95% CI)	HR (95% CI)	$P_{interaction}$
OVERALL	27564	12.6	14.6		0.85 (0.79-0.92)		7.9	9.9		0.80 (0.73-0.88)	
Age						0.9					0.79
<65	15310	12.6	14.6		0.86 (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)	



Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664
(Supplementary Figure S5)

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

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



1. EFFICACY of Evolocumab in pts with and without Diabetes

↓ LDL

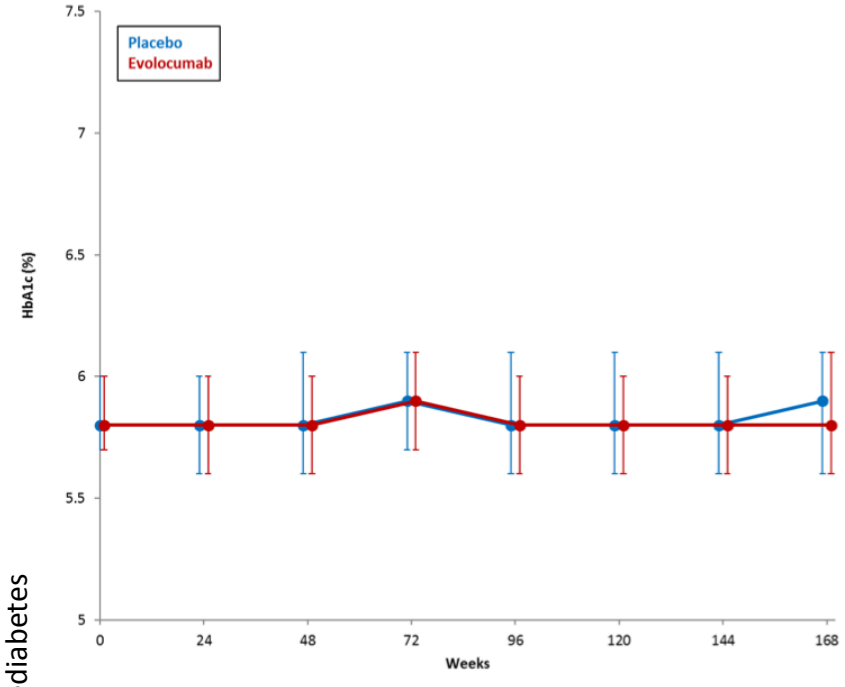
↓ CV Events

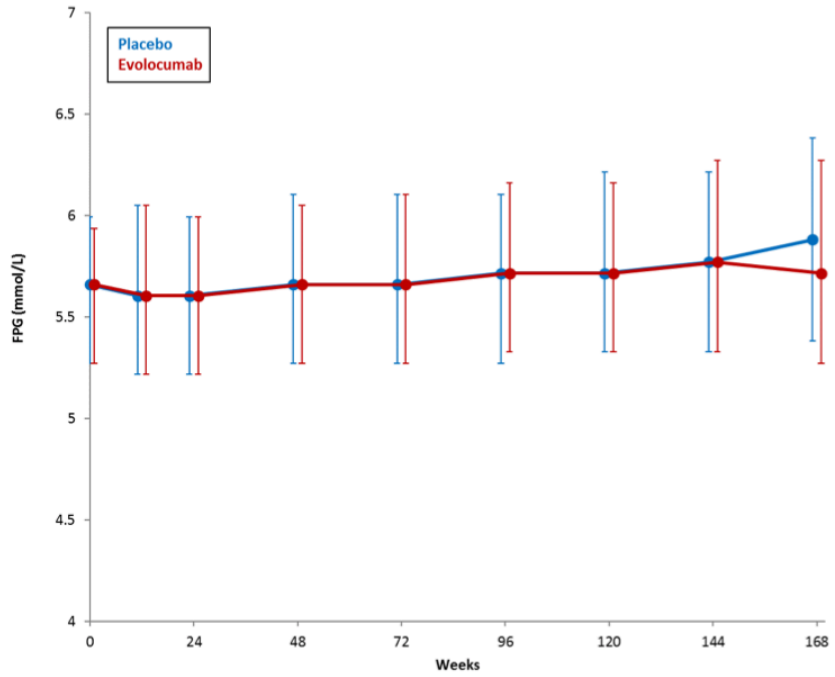
2. SAFETY of Evolocumab

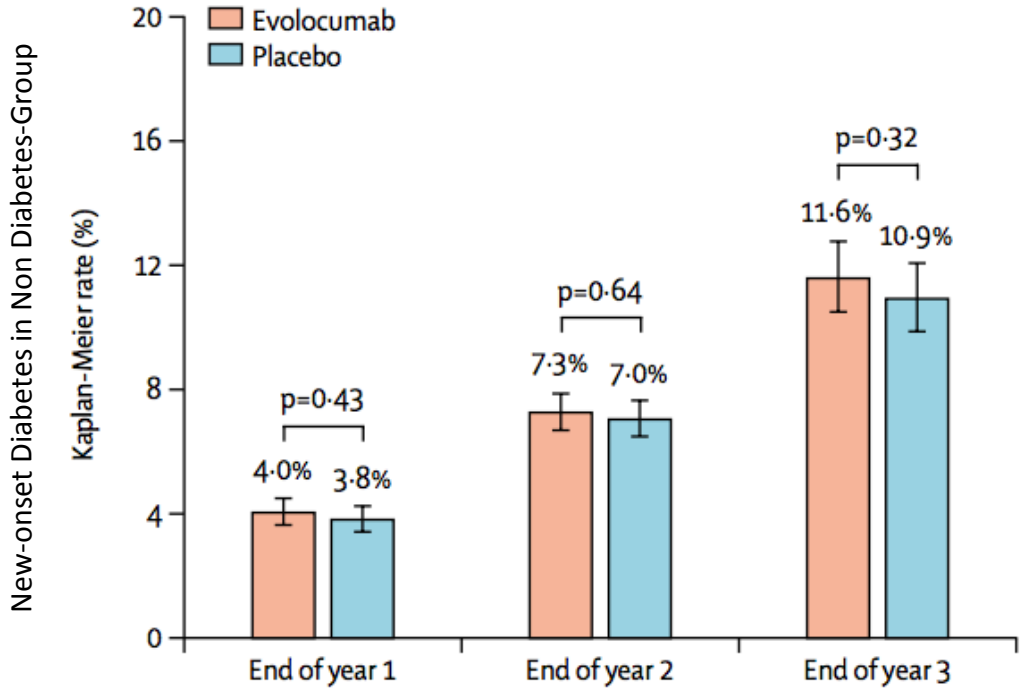
Glycaemia, HbA_{1c}

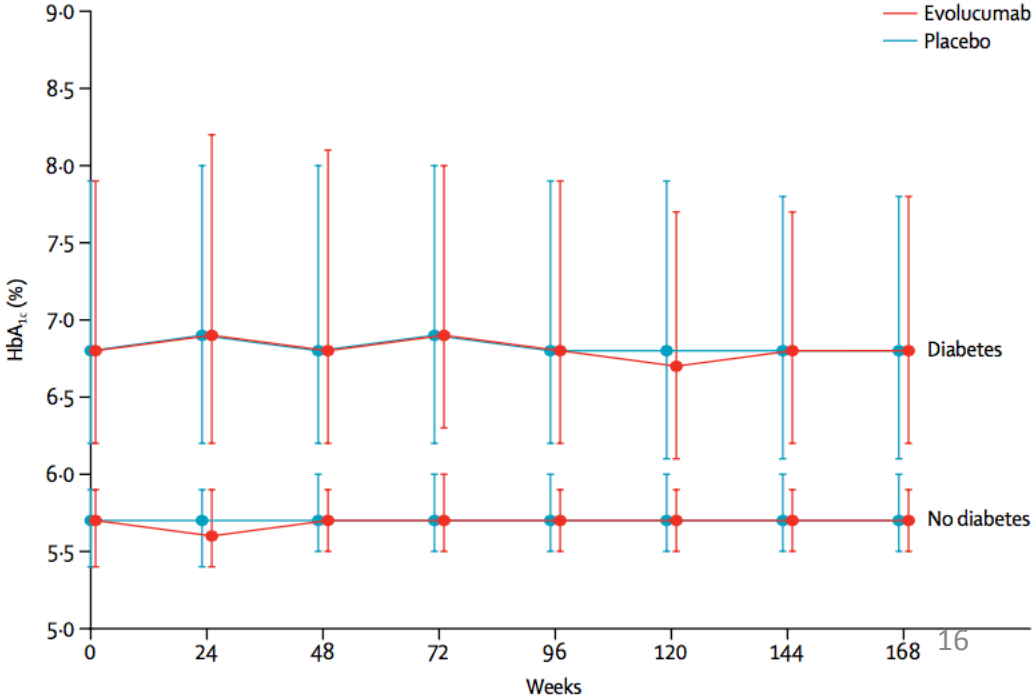
New-onset Diabetes

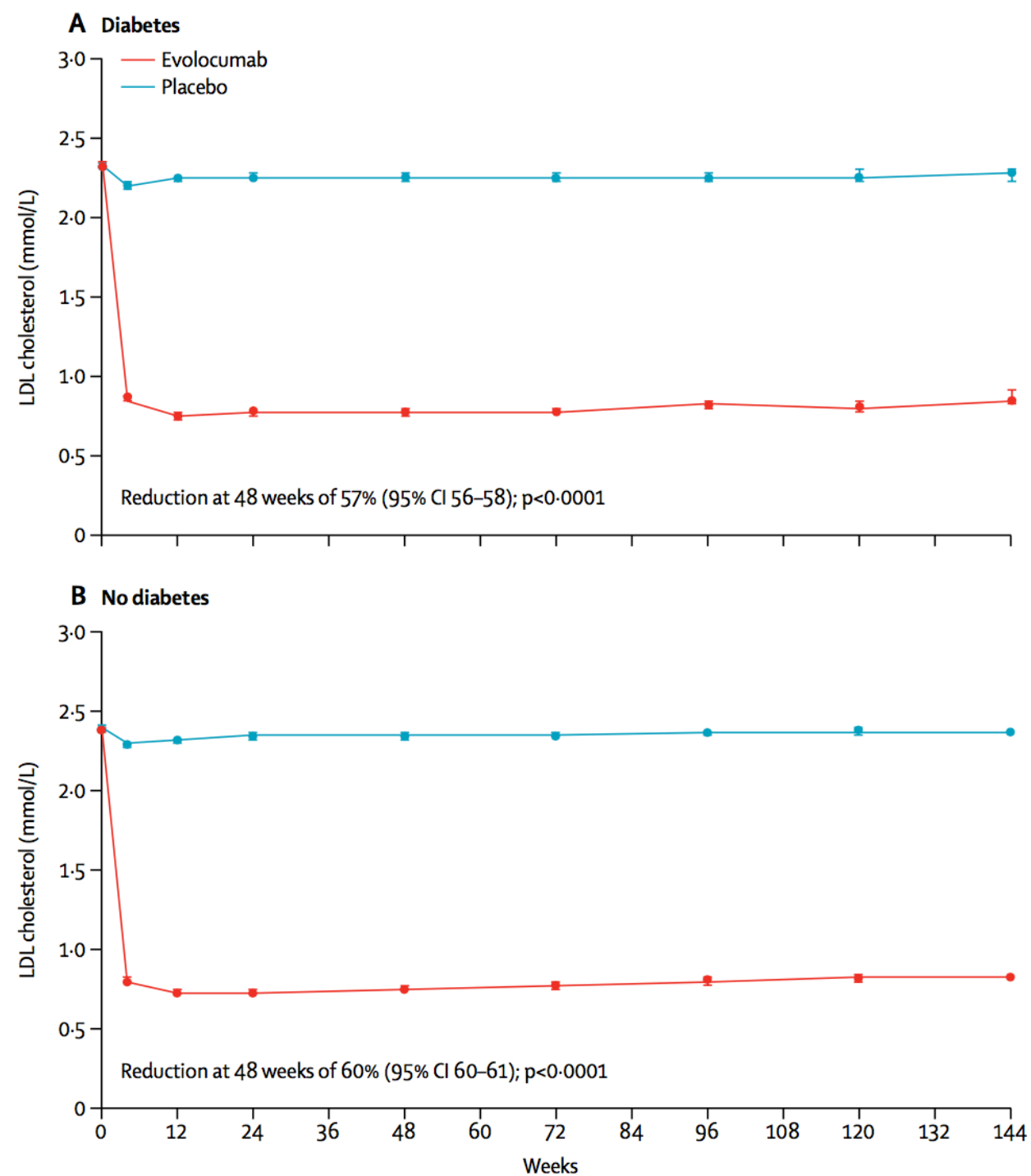
Prediabetes

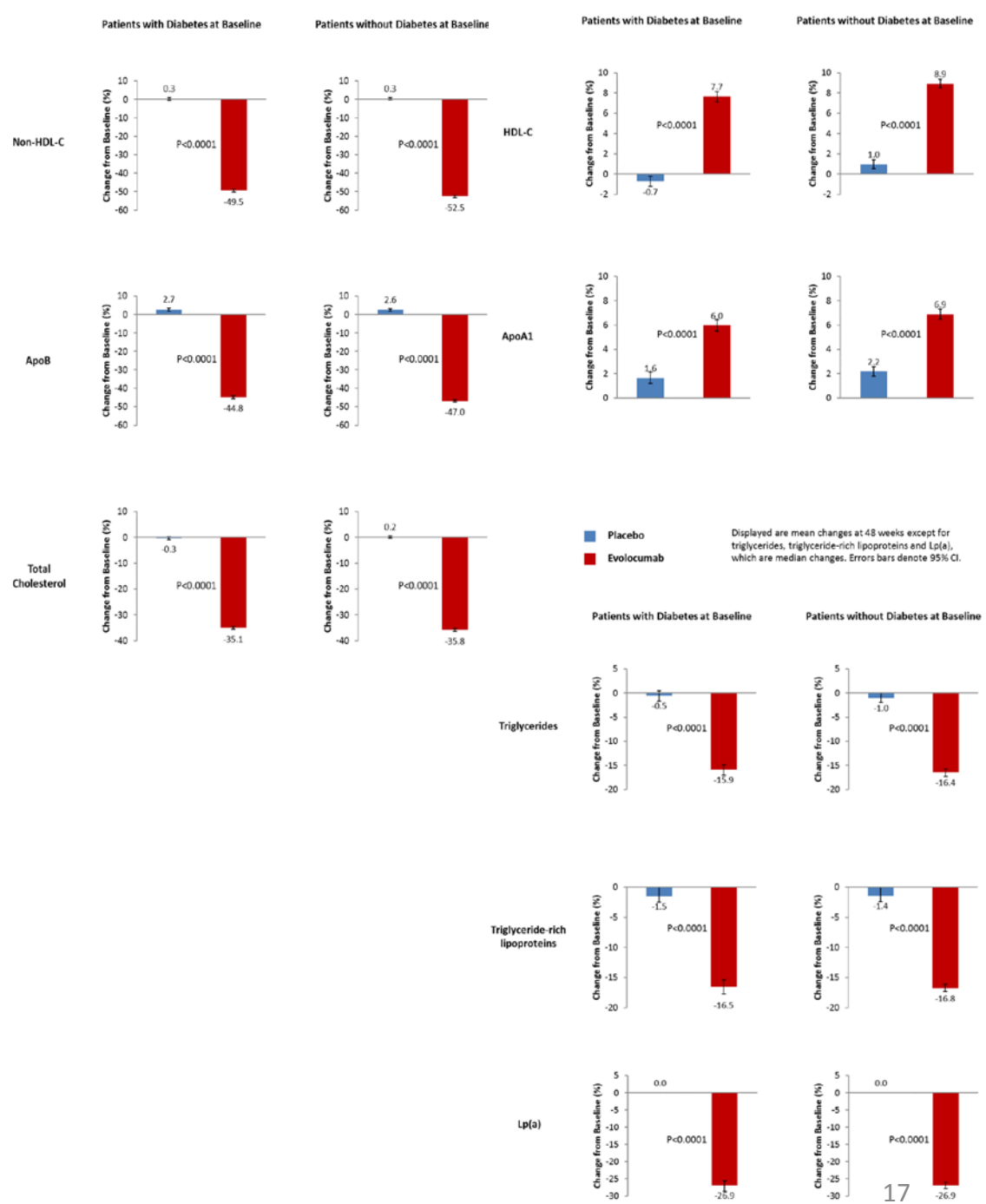




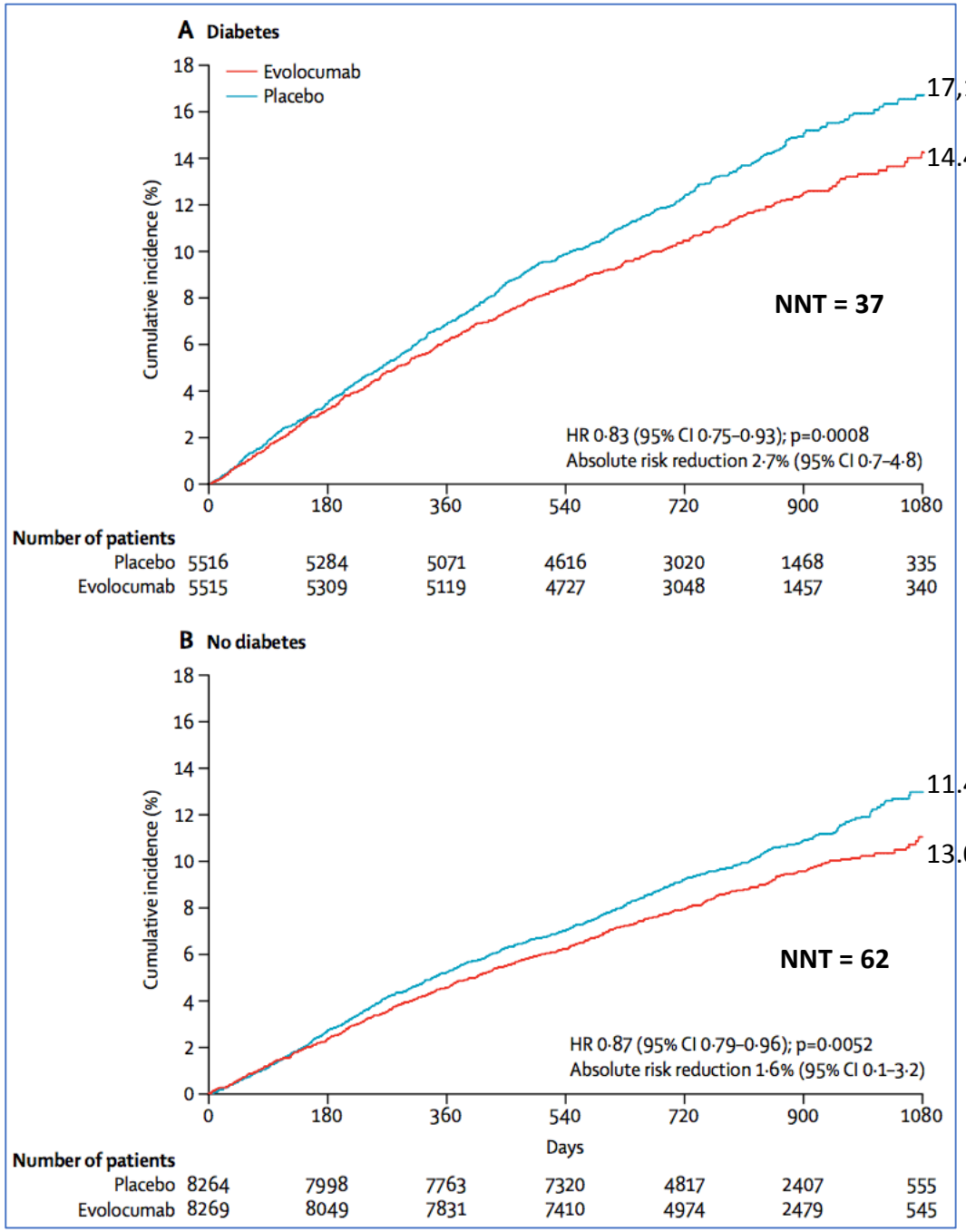





A Diabetes
Evolocumab
Placebo
LDL cholesterol (mmol/L)
3·0
2·5
2·0
1·5
1·0
0·5
0
Reduction at 48 weeks of 57% (95% CI 56–58); p<0·0001
B No diabetes
LDL cholesterol (mmol/L)
Reduction at 48 weeks of 60% (95% CI 60–61); p<0·0001
0
12
24
36
48
60
72
84
96
108
120
132
144
Weeks


Patients with Diabetes at Baseline
Patients without Diabetes at Baseline
Patients with Diabetes at Baseline
Patients without Diabetes at Baseline
Non-HDL-C
HDL-C
ApoB
ApoA1
Total Cholesterol
Triglycerides
Triglyceride-rich lipoproteins
Lp(a)
Change from Baseline (%)
P<0.0001
0.3
-49.5
0.3
-52.5
-0.7
7.7
1.0
8.9
2.7
-44.8
2.6
-47.0
1.6
6.0
2.2
6.9
-0.3
-35.1
0.2
-35.8
-0.5
-15.9
-1.0
-16.4
-1.5
-16.5
-1.4
-16.8
0.0
-26.9
-26.9
Placebo
Evolocumab
Displayed are mean changes at 48 weeks except for triglycerides, triglyceride-rich lipoproteins and Lp(a), which are median changes. Errors bars denote 95% CI.

Primary End-point



CV Death :

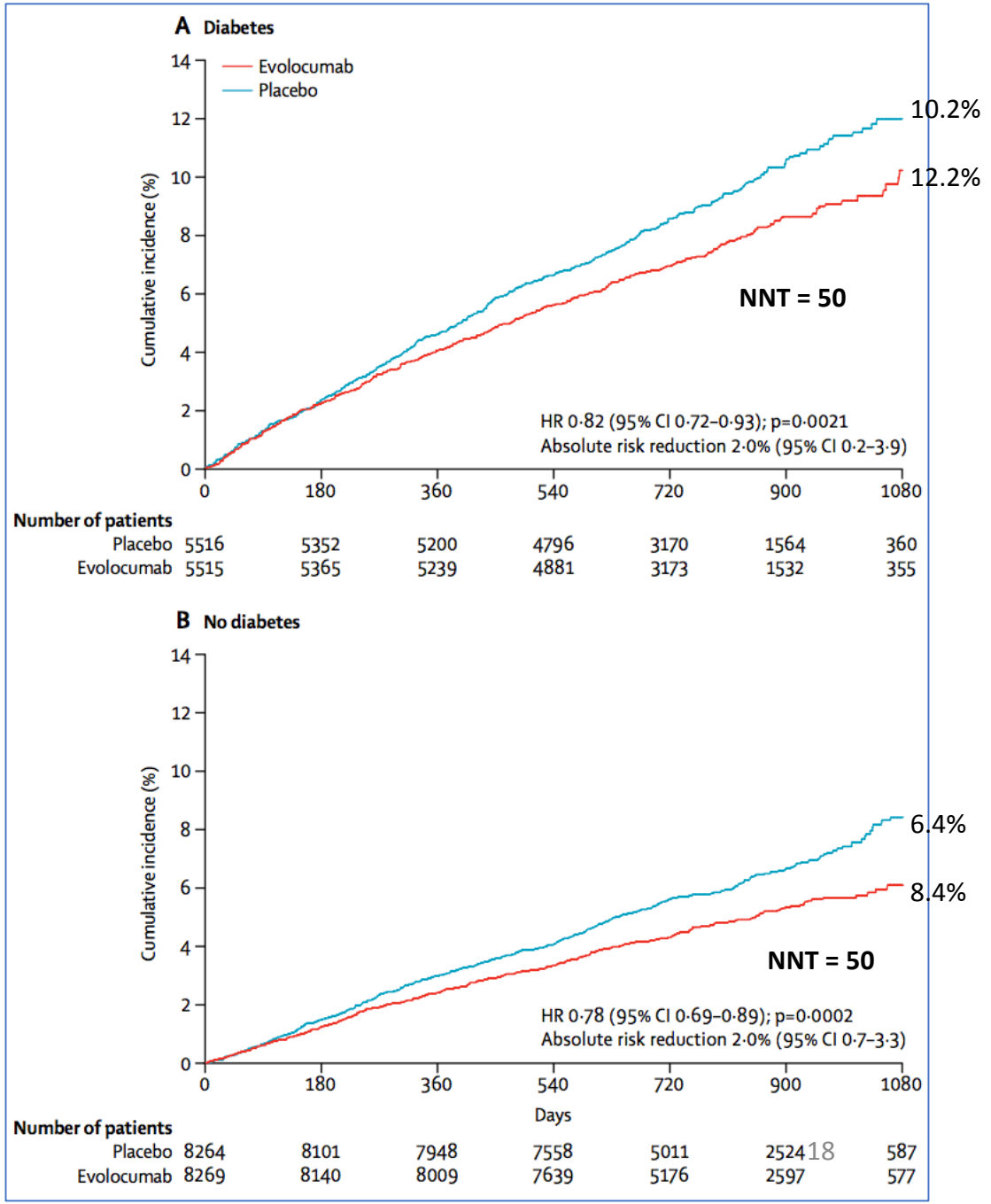
3.6%

3.5%

1.8%

1.7%

Key Secondary End-point

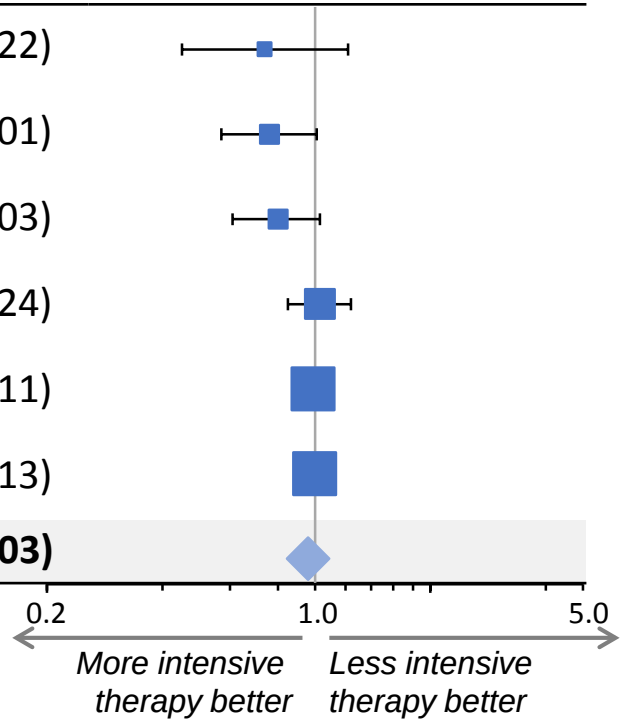


CV – Mortality in FOURIER

Mean Follow-up : 2.2y
Optimal Medical Therapy
Mortality Low Rate
Event-drive Trial

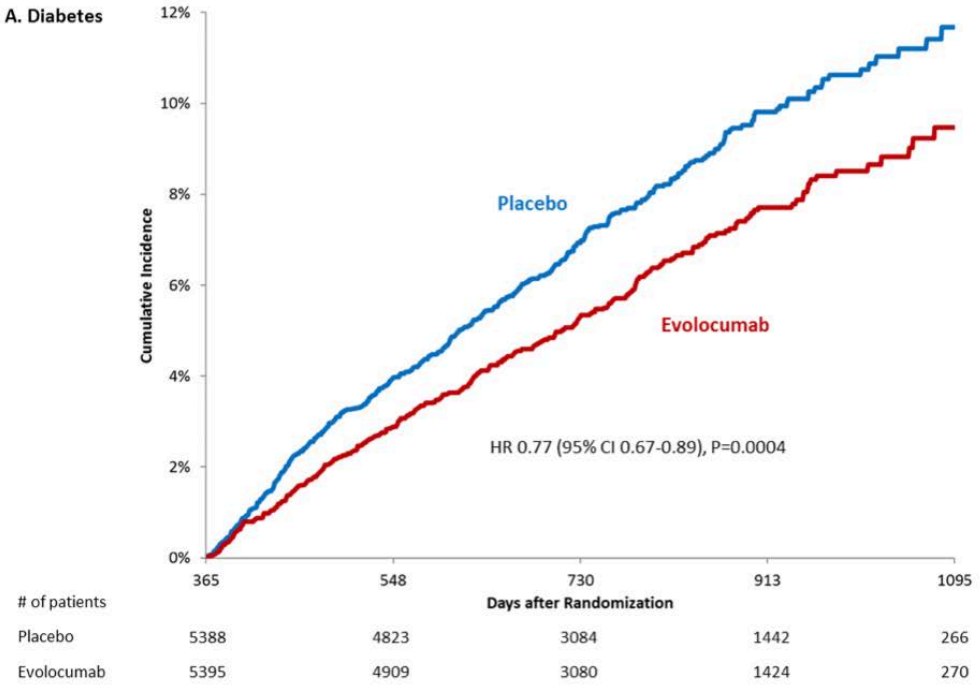
CV mortality

Trial	Year	# of CV Deaths: More Intensive Rx Arm	# of CV Deaths: 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)**

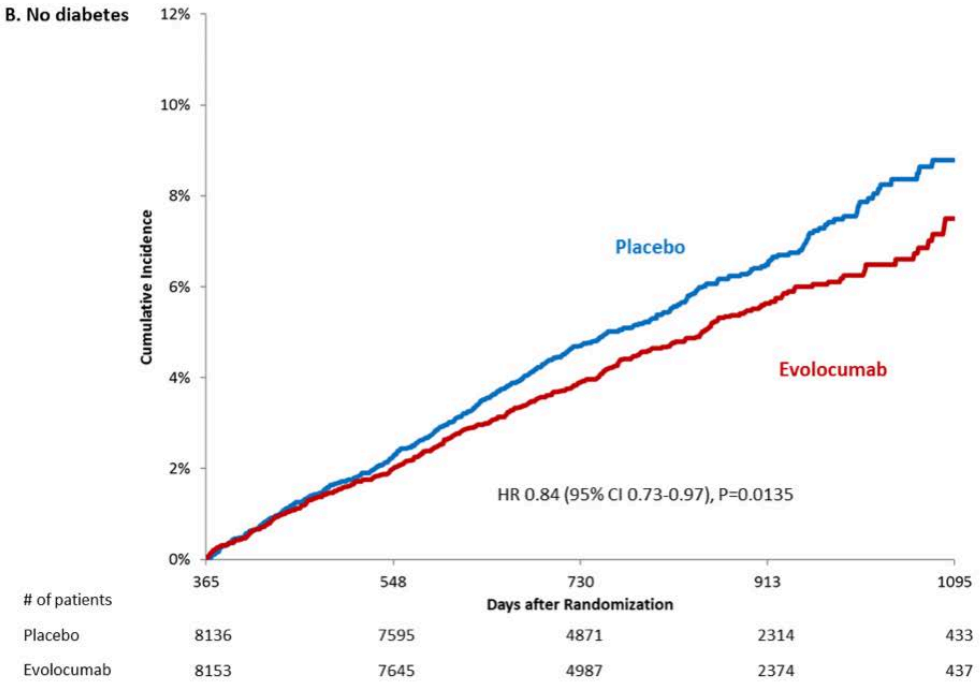


1. Cannon CP, et al. *NEJM*. 2004;350:1495-1504. 2. de Lemos JA, *JAMA* 2004;292:1307-1316. 3. LaRosa JC, et al. *NEJM*. 2005;352:1425-1435. 4. Pederson TR, et al. *JAMA*. 2005; 294:2437-2445. 5. Search Collaborative Group. *Lancet* 2010; 376: 1658–69. 6. Cannon CP, et al. *NEJM*. 2015;372:2387-2397. 7. Sabatine MS, et al. American College of Cardiology – 66th Annual Scientific
Session Late-Breaking Clinical Trial. Washington, D.C. March 17, 2017.

First Primary End-Point



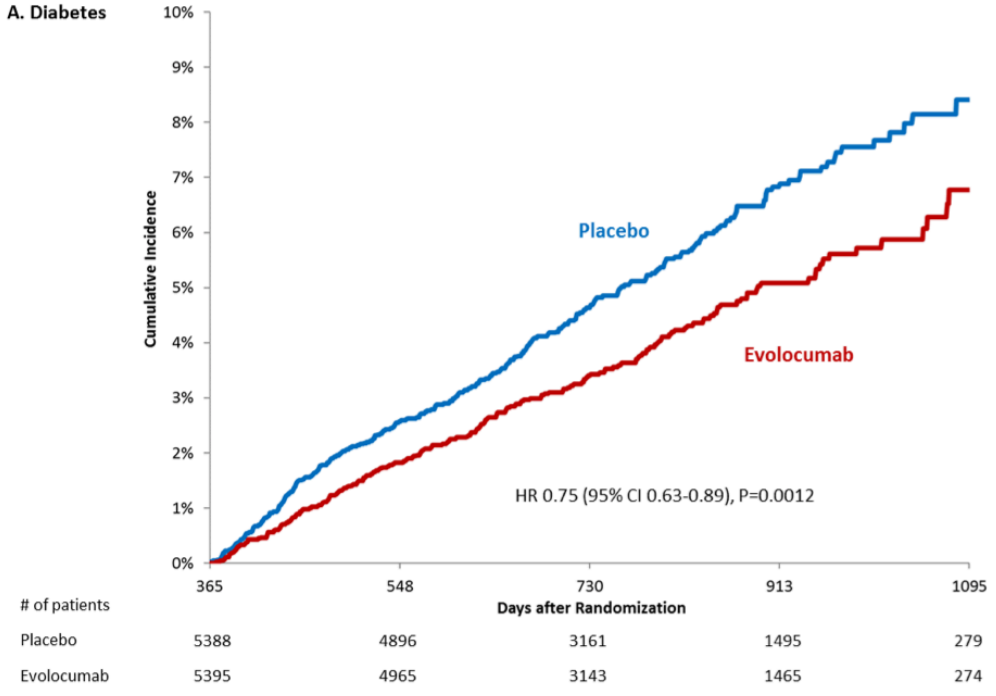
# of patients					
Placebo	5388	4823	3084	1442	266
Evolocumab	5395	4909	3080	1424	270



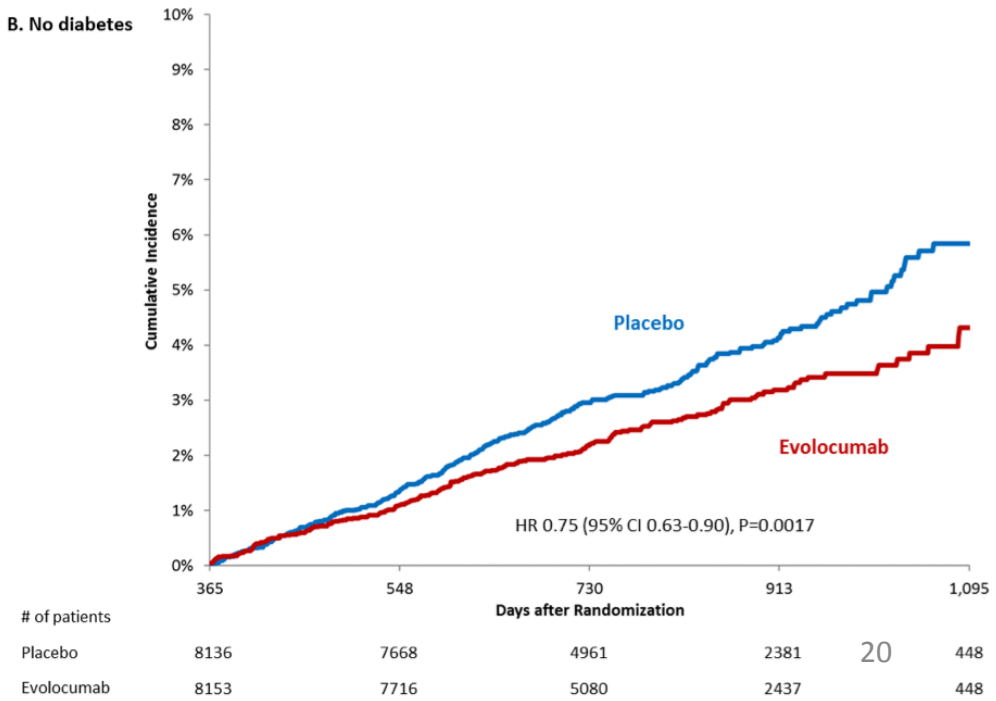
# of patients					
Placebo	8136	7595	4871	2314	433
Evolocumab	8153	7645	4987	2374	437

Landmark Analyses

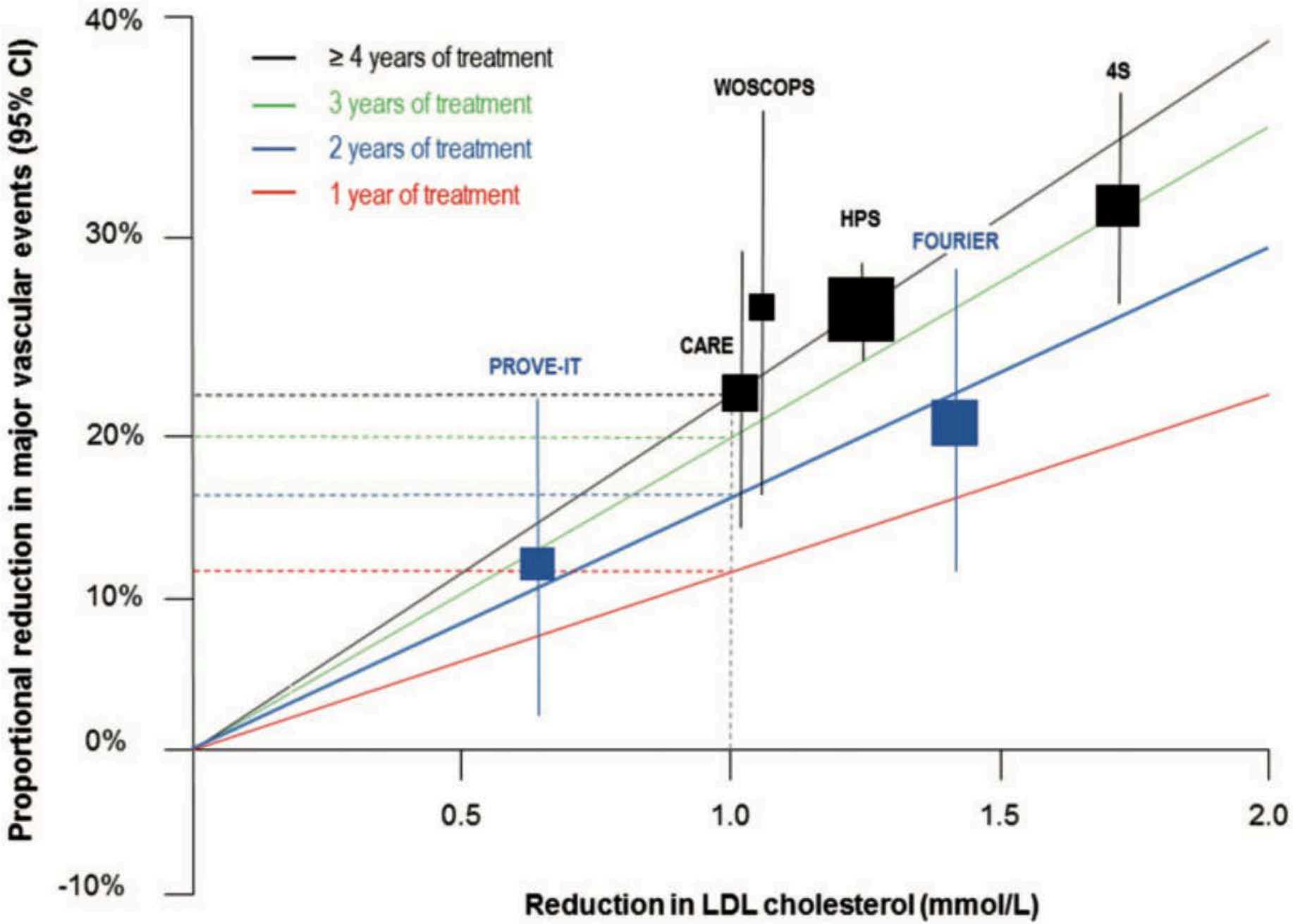
Key Secondary End-Point



# of patients					
Placebo	5388	4896	3161	1495	279
Evolocumab	5395	4965	3143	1465	274



# of patients					
Placebo	8136	7668	4961	2381	448
Evolocumab	8153	7716	5080	2437	448


40%
30%
20%
10%
0%
-10%
Proportional reduction in major vascular events (95% CI)
≥ 4 years of treatment
3 years of treatment
2 years of treatment
1 year of treatment
WOSCOPS
4S
HPS
FOURIER
CARE
PROVE-IT
0.5
1.0
1.5
2.0
Reduction in LDL cholesterol (mmol/L)

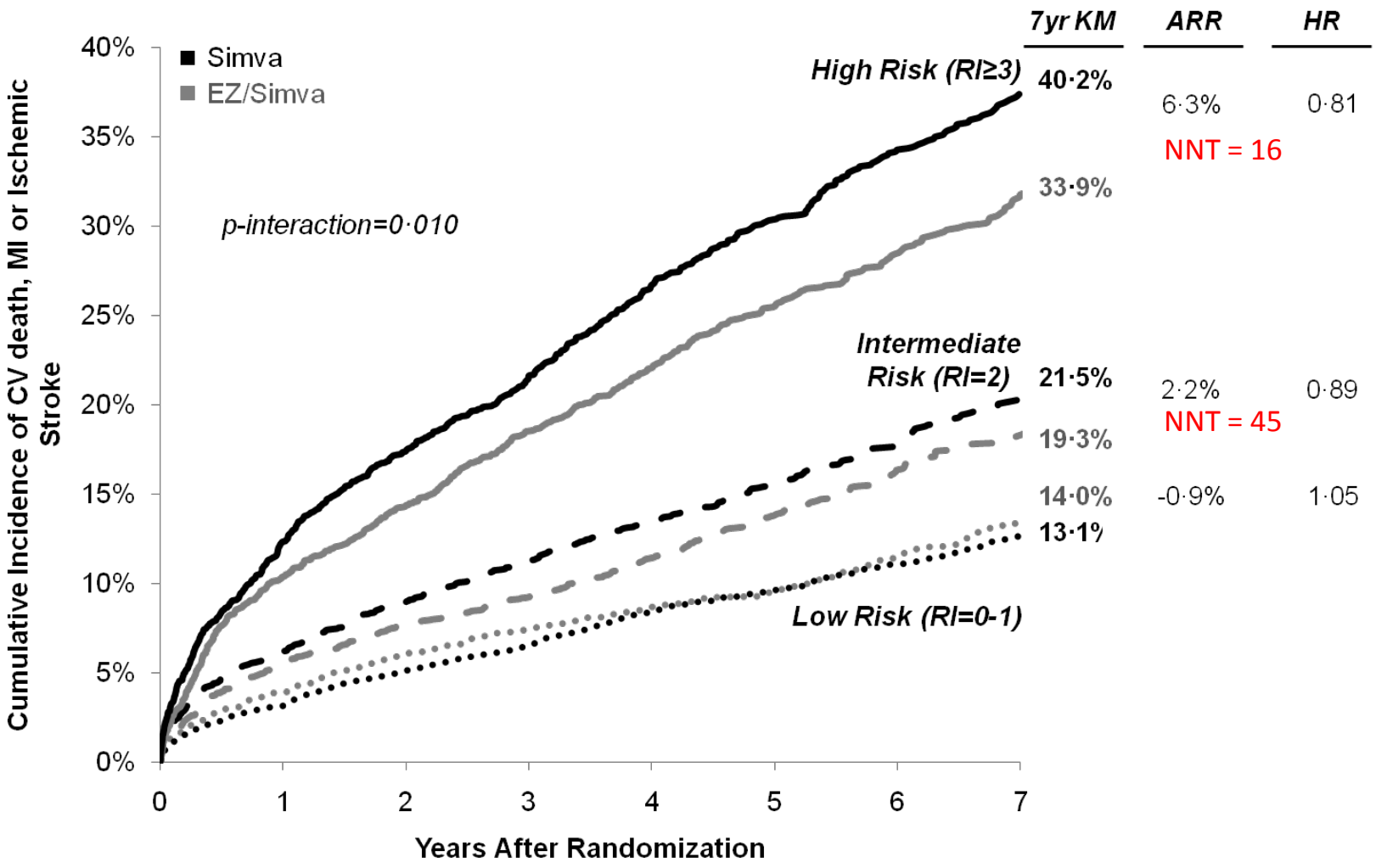
Conclusion - 1

- Among patients with previous/recent ACS the presence of diabetes, but not prediabetes, was independently associated with a substantially increased risk of cardiovascular morbidity and mortality , despite statin therapy
- PCSK9-I lowered LDL cholesterol and significantly reduced cardiovascular risk with similar efficacy in patients with and without diabetes. However, because of their heightened baseline risk of cardiovascular events, patients with diabetes tended to have a greater absolute risk reduction with PCSK9-I treatment
- Recent guidelines have recommended identifying people with diabetes and established atherosclerotic cardiovascular disease as having an extreme risk requiring more intensive treatment to achieve lower LDL goals (< 55 mg/dl)
- PCSK9-I added to statins are safe , and did not increase the risk of new-onset diabetes, nor did it worsen glycaemia and HbA_{1c}

Conclusion - 2

- The use of PCSK-9 Inhibitors in patients with diabetes and recent or previous ACS might be particularly attractive from a cost- effectiveness standpoint (NNT 60 → 32)
- In patients with recent ACS , CV-event risk > 3%/y and LDL-C > 140 mg/dl a PCSK-9I may be considered
- Risk stratification and individualization of therapy among patients with recent or previous ACS are emerging as growing needs in the context of the increasing number of “intensive” therapies
- The “Risk-Score” strategy offers an opportunity to select candidates with the potential for the greatest absolute gains

Effects of ezetimibe by TRAP 2P risk score in IMPROVE-IT



Risk Indicators	CHADS
CHF	C
HTN	H
Age≥75	A
DM	D
Prior Stroke	S
Prior CABG	
PAD	
eGFR<60	
Current Smoking	

Bohula EA et al. (2016)