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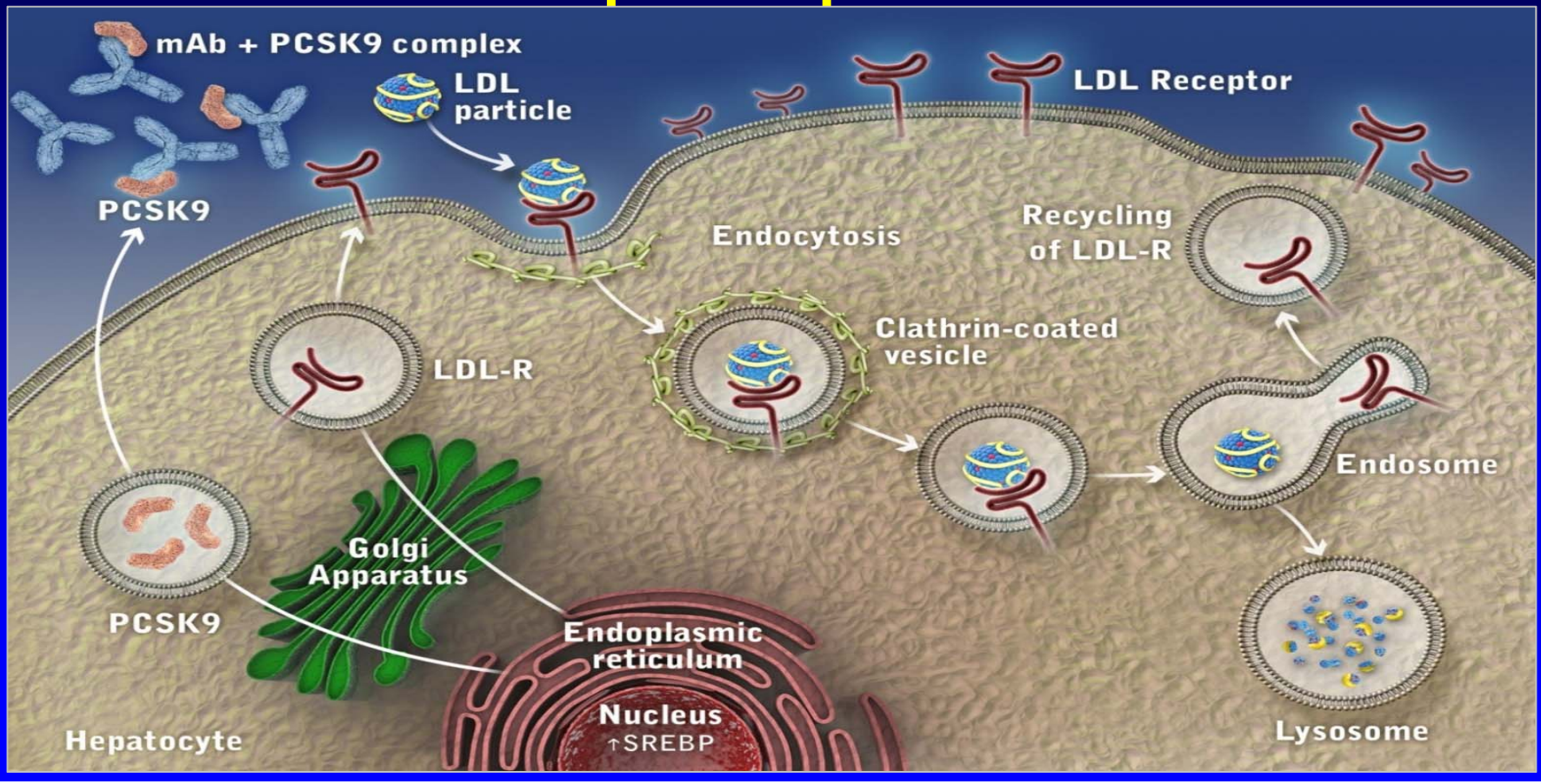
Clinical Trials of PCSK9 Inhibitors for the (Secondary) Prevention of Atherosclerotic Cardiovascular Disease (ASCVD)

Shaun Goodman

Disclosures

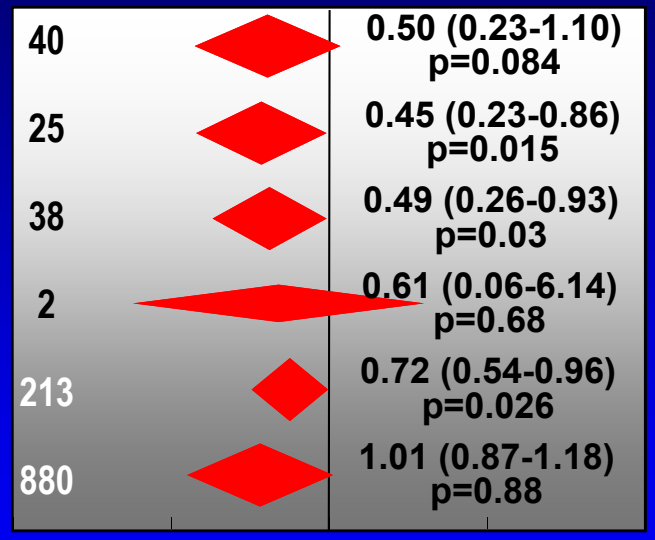
- Research grant support, speaker/consulting honoraria (no patents):
  - Amgen
    - Including Guidelines Oriented Approach to Lipid lowering (GOAL) in Canada Steering Committee member; Consultant to the Canadian Heart Research Centre (CHRC; Canadian ARO)
  - Sanofi and Regeneron
    - Including ODYSSEY Outcomes trial Executive Steering Committee member and Canadian National Coordinator; Co-Director of the Canadian VIGOUR Centre (CVC; Canadian ARO)
  - Esperion
    - CLEAR OUTCOMES Steering Committee member
  - Lilly
    - ACCELERATE and LY3015014 trials Steering Committee member
  - AstraZeneca, Bristol-Myers Squibb, HLS Therapeutics, Merck, Pfizer
- Additional relationships (research grant support, speaker/consulting honoraria) with commercial interests but not relevant to this presentation
  - *http://thecvc.ca/about-us/relationships-with-industry/*

Impact of a PCSK9 Monoclonal Antibody on LDL Receptor Expression



PCSK9 Inhibitors vs. No PCSK9 Inhibitors

24 RCTs (n=10,159)
Mean LDL-C reduction 47% (25%-70%)



[1] PCSK9i (n=6187) and [2] No PCSK9i (n=3972); except [3] (n=3289/1906) and [4] (n=2515/1379)

Navarese et al *Ann Intern Med* 2015;163:40-51

Trial Design

27,564 high-risk, stable patients with established CV disease:
Prior MI (81%), prior non-hemorrhagic stroke (19%), or symptomatic PAD (13%)

Screening, Lipid Stabilization, and Placebo Run-in

High (69%) or moderate (30%)-intensity statin therapy ± ezetimibe (5%)

LDL-C ≥1.8 mmol/L or
non-HDL-C ≥2.6 mmol/L

RANDOMIZED
DOUBLE BLIND

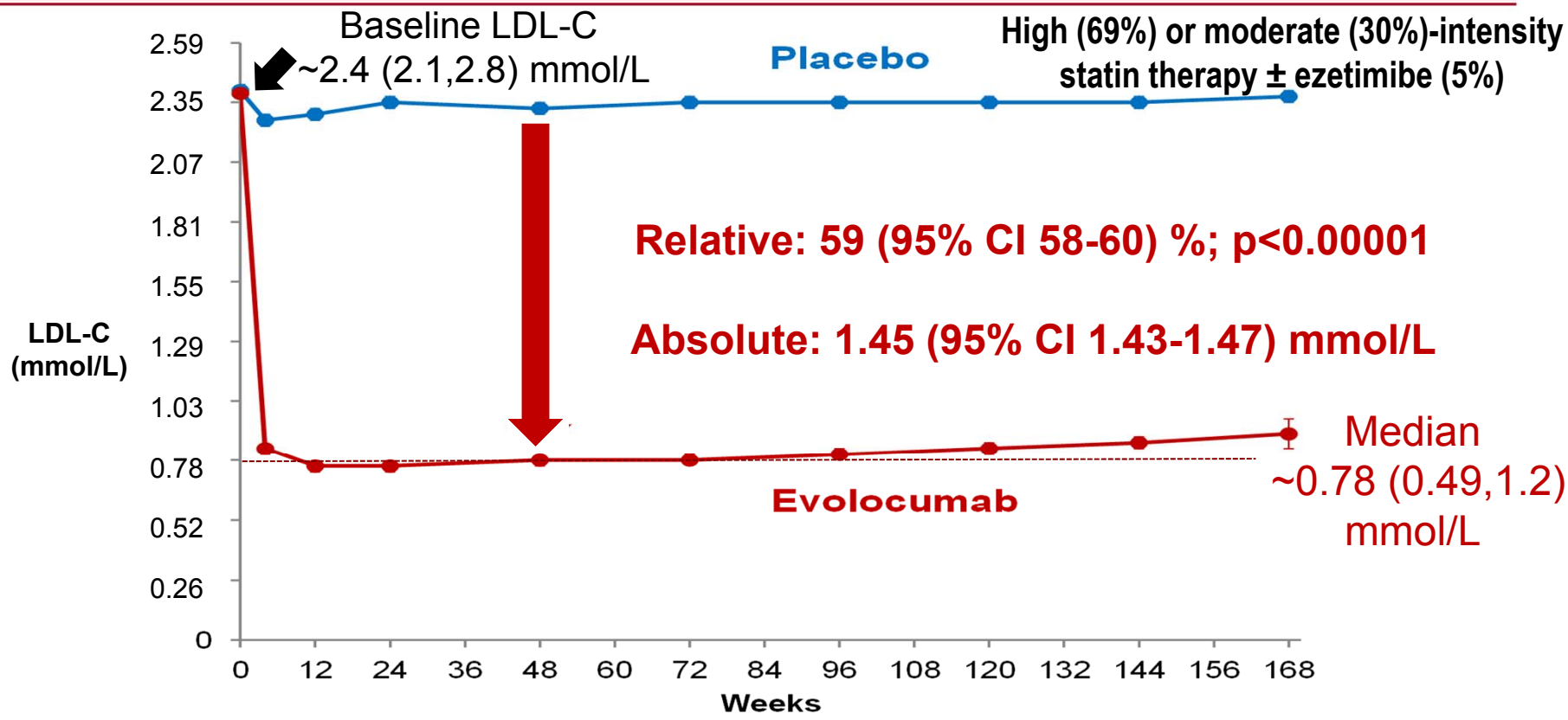
Evolocumab SC
140 mg Q2W or 420 mg Q4W

Placebo SC
Q2W or Q4W

Follow-up Q 12 weeks

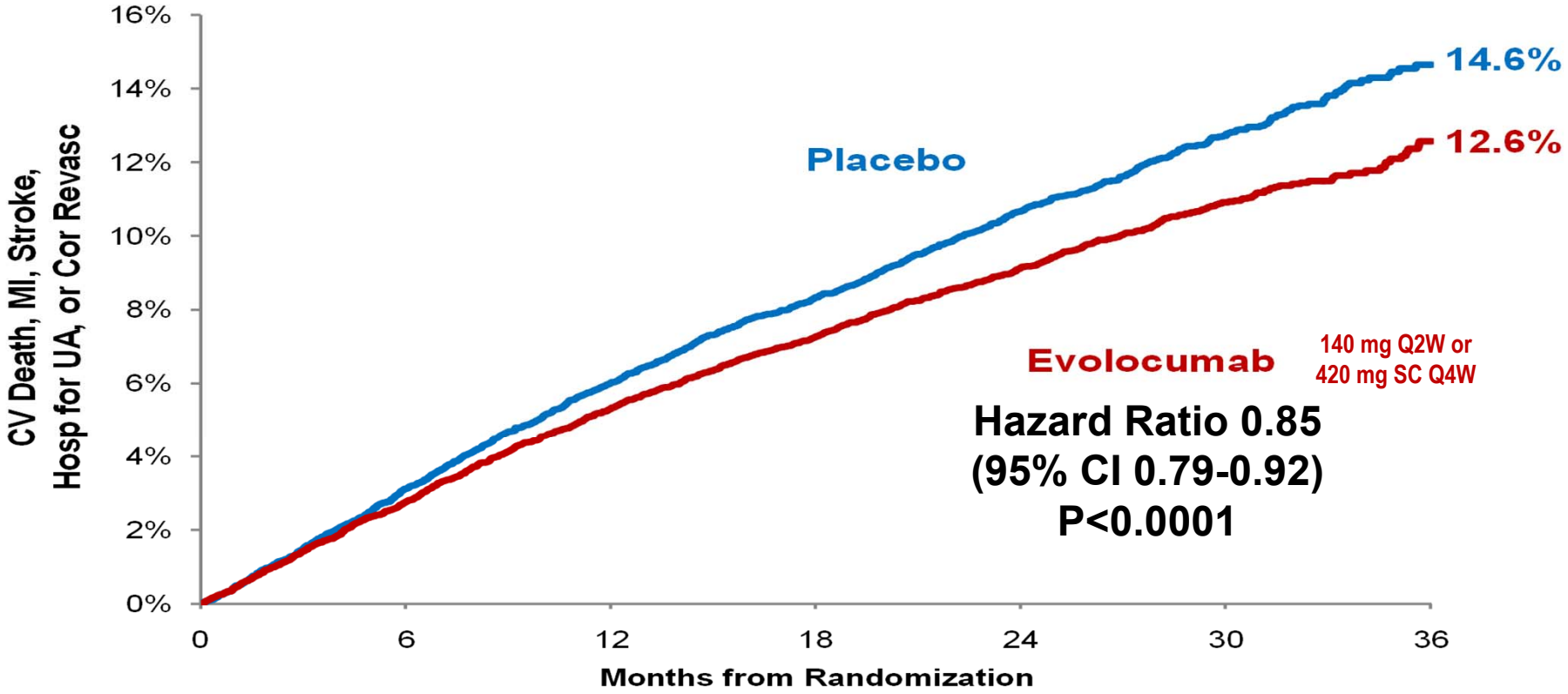
Sabatine et al *Am Heart J* **2016;173:94-101 and** *N Engl J Med* **2017;376:1713-22**

LDL Cholesterol



Sabatine et al *N Engl J Med* 2017;376:1713-22

Primary Endpoint



Sabatine et al *N Engl J Med* 2017;376:1713-22

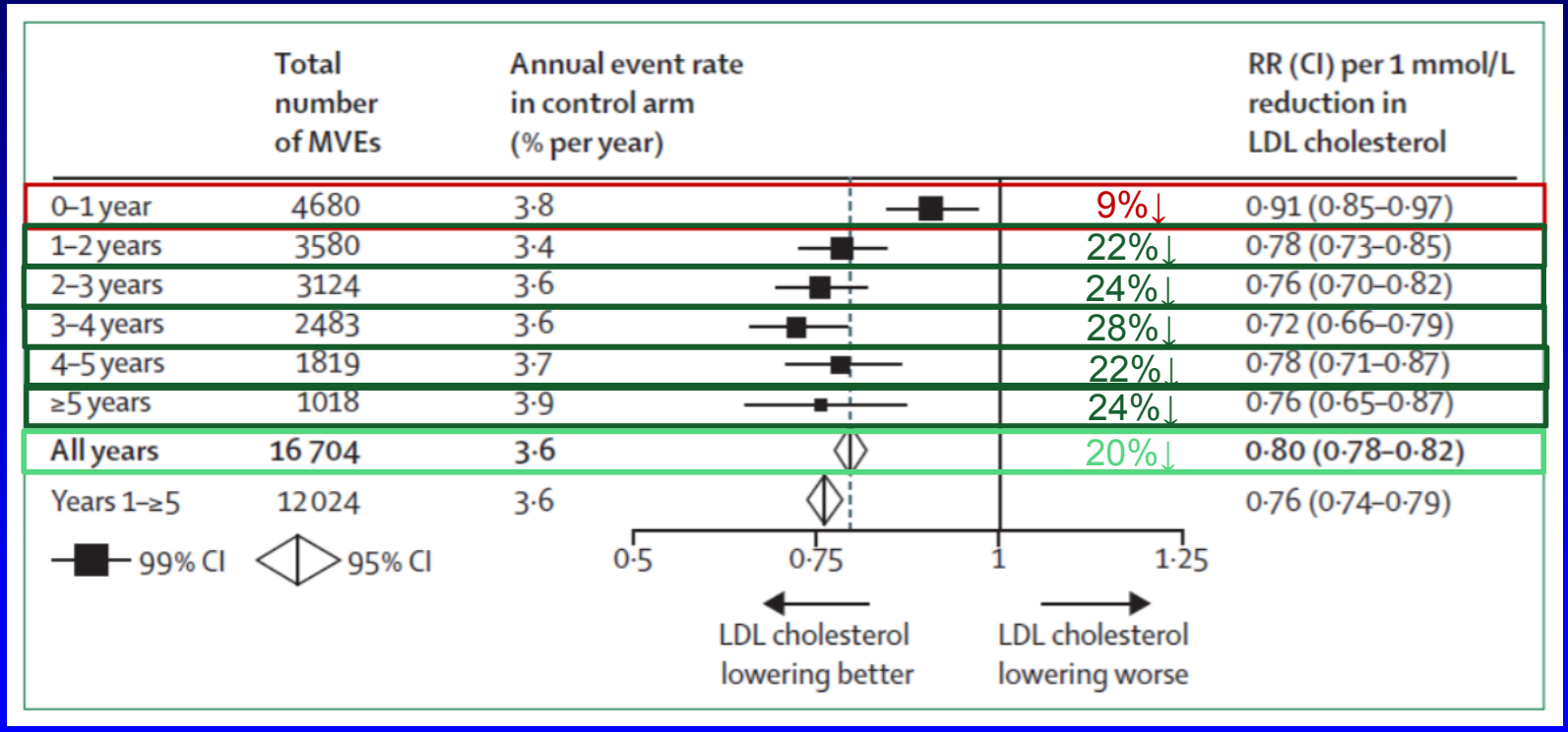
Types of CV Outcomes

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
CVD, MI, stroke, UA, or revasc	**12.6**	**14.6**	**0.85 (0.79-0.92)**
CV death, MI, or stroke	**7.9**	**9.9**	**0.80 (0.73-0.88)**
Cardiovascular death	**2.5**	**2.4**	**1.05 (0.88-1.25)**
MI	**4.4**	**6.3**	**0.73 (0.65-0.82)**
Stroke	**2.2**	**2.6**	**0.79 (0.66-0.95)**
Hosp. for unstable angina	**2.2**	**2.3**	**0.99 (0.82-1.18)**
Coronary revasc	**7.0**	**9.2**	**0.78 (0.71-0.86)**
Urgent	3.7	5.4	0.73 (0.64-0.83)
Elective	3.9	4.6	0.83 (0.73-0.95)
Death from any cause	**4.8**	**4.3**	**1.04 (0.91-1.19)**
CTTC Composite Endpoint*	**9.2**	**11.0**	**0.83 (0.77-0.90)**

*Coronary heart death (CHD), nonfatal MI, stroke, coronary revascularization

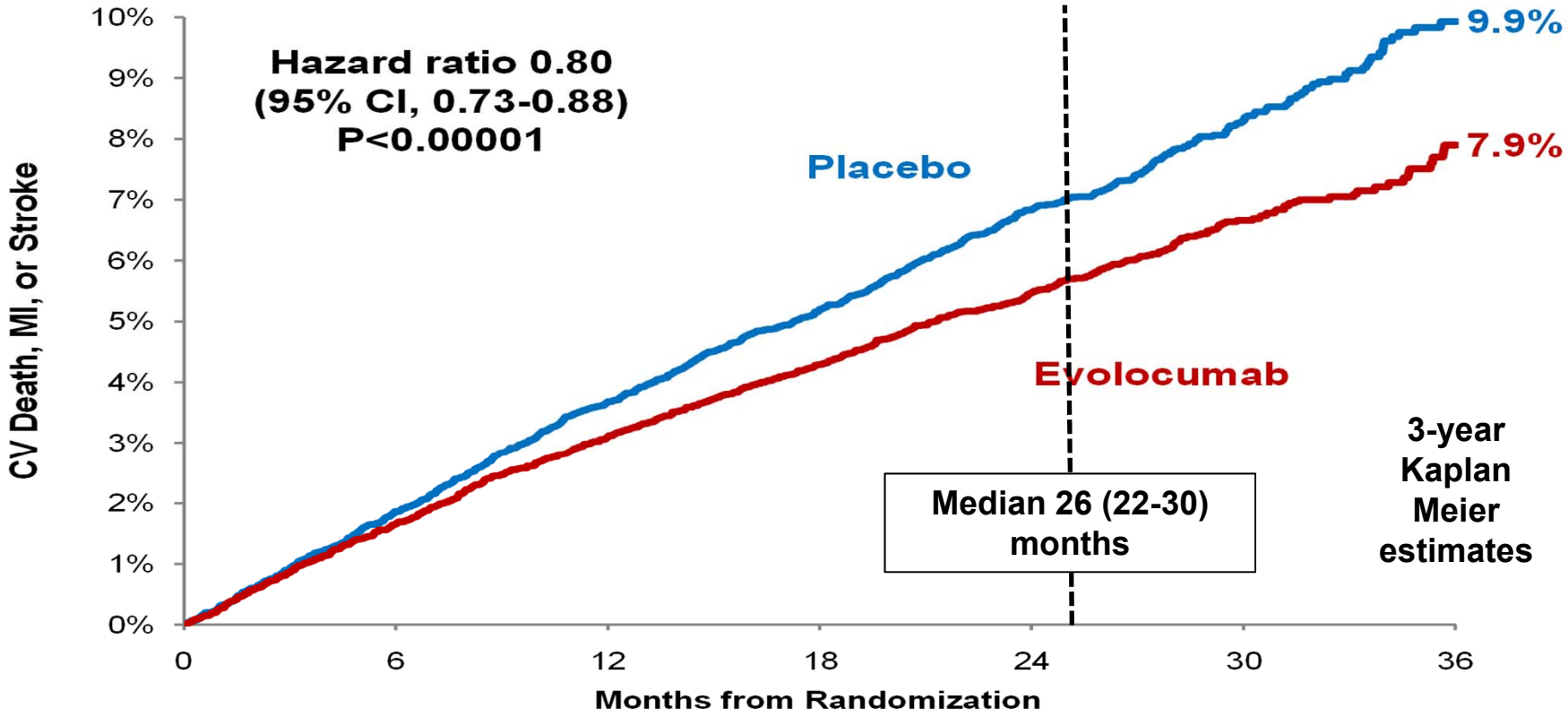
Sabatine et al *N Engl J Med* **2017;376:1713-22**

Statin Effect Size by Year of Treatment



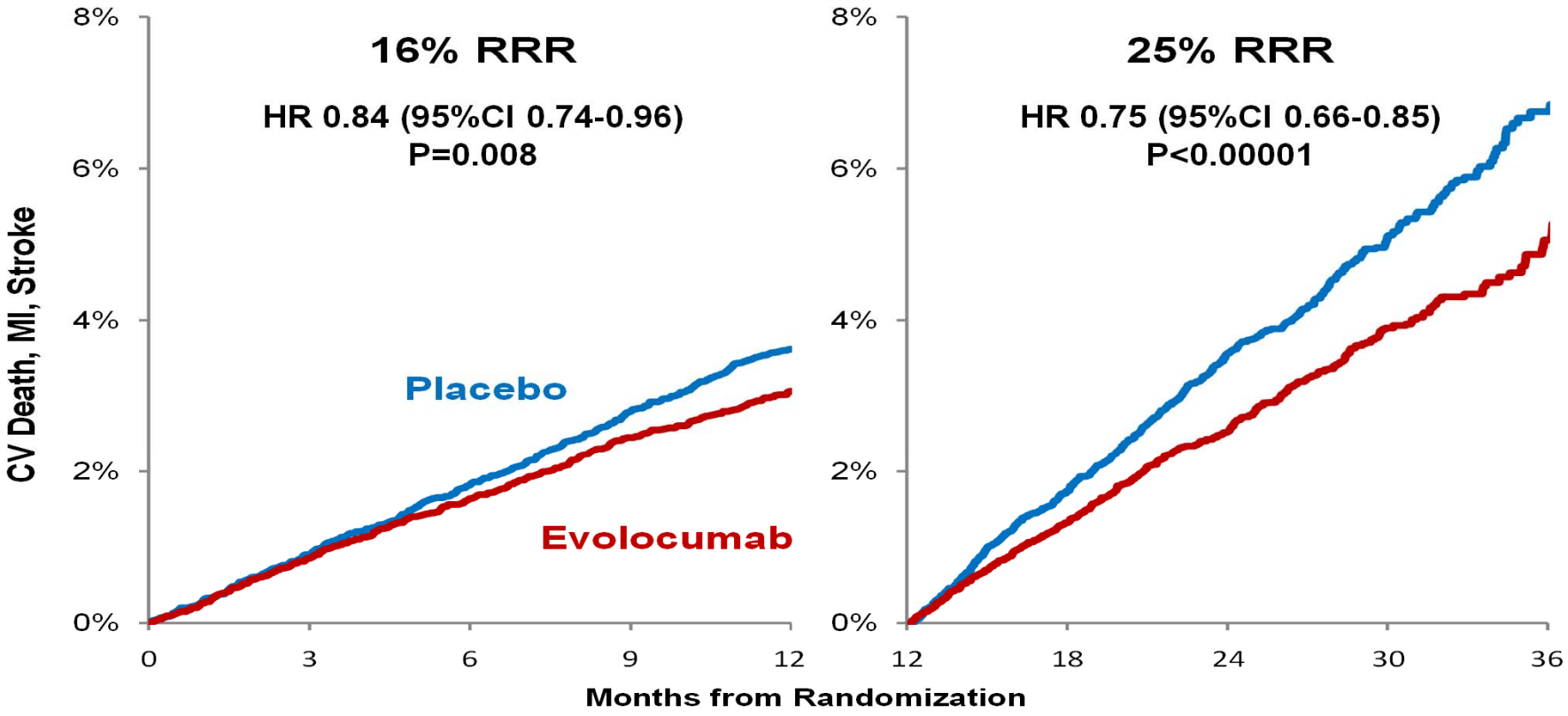
Adapted from Cholesterol Treatment Trialists' (CTT) Collaboration *Lancet* 2010;376:1670-81 (Supplementary Webappendix)

Key Secondary Endpoint



Sabatine et al *N Engl J Med* 2017;376:1713-22

Landmark Analysis: Secondary Outcome



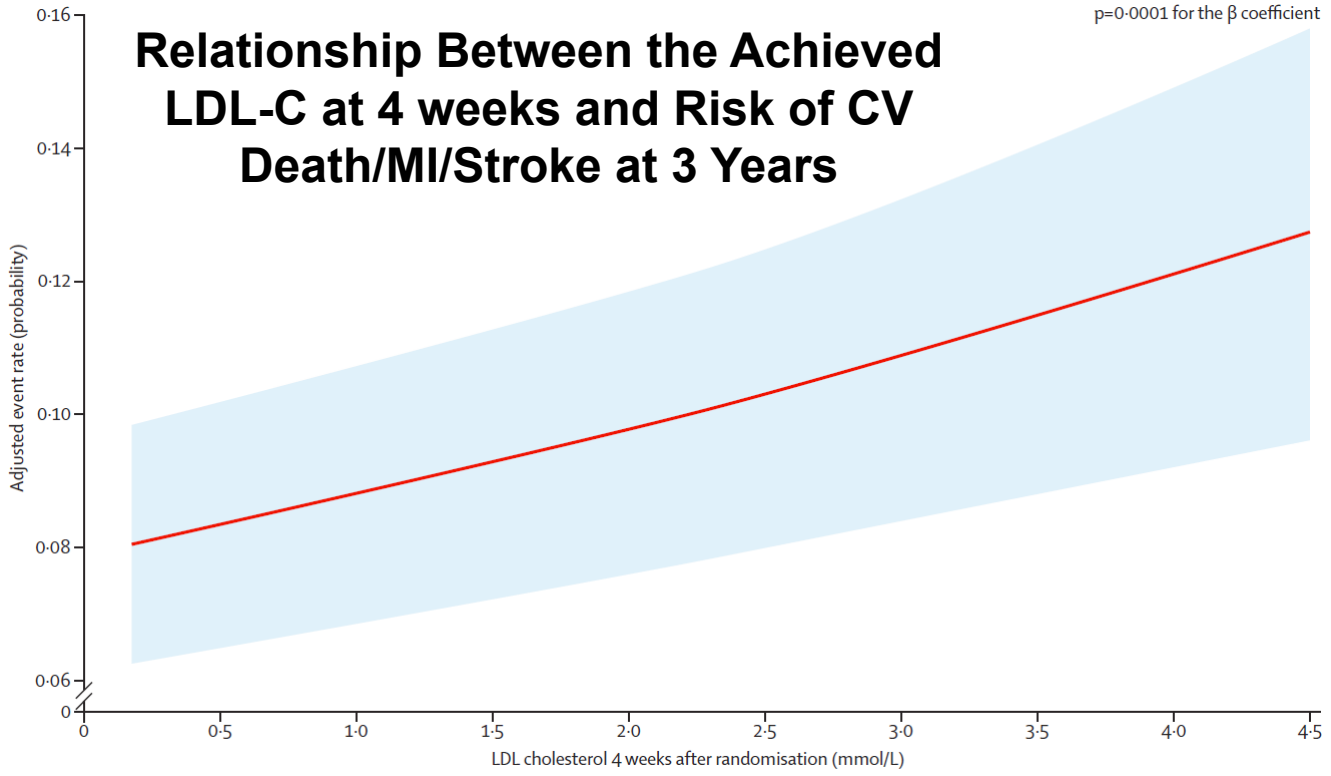
Sabatine et al *N Engl J Med* 2017;376:1713-22 (supplementary appendix)

Safety

	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events (%)		
Any	77.4	77.4
Serious	24.8	24.7
Allergic reaction	3.1	2.9
Injection-site reaction	2.1	1.6
Treatment-related and led to d/c of study drug	1.6	1.5
Muscle-related	5.0	4.8
Cataract	1.7	1.8
Diabetes (new-onset)	8.1	7.7
Neurocognitive	1.6	1.5

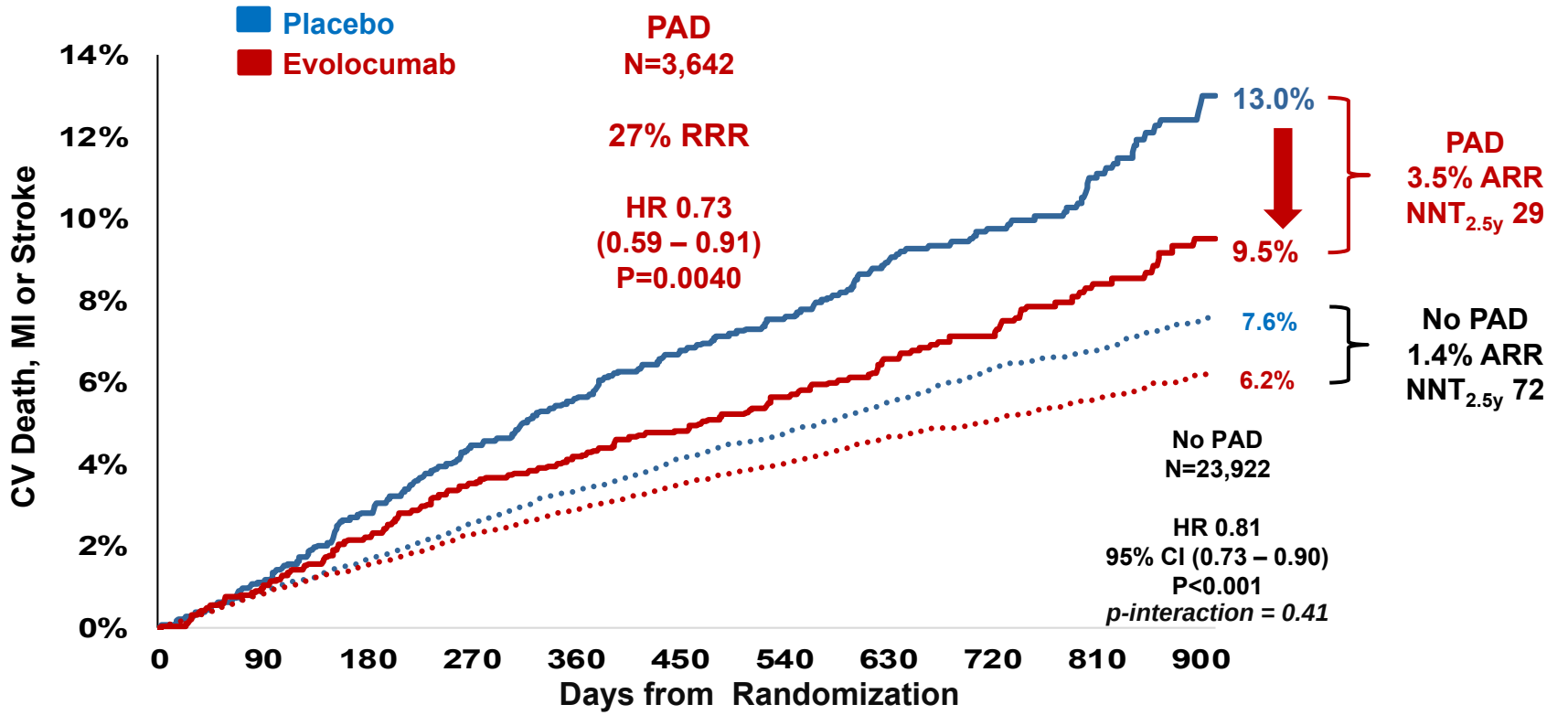
Giugliano et al *Clin Card* 2017;40:59-65 and *N Engl J Med* 2017;377:633-43

Lowest LDL-C Is Best



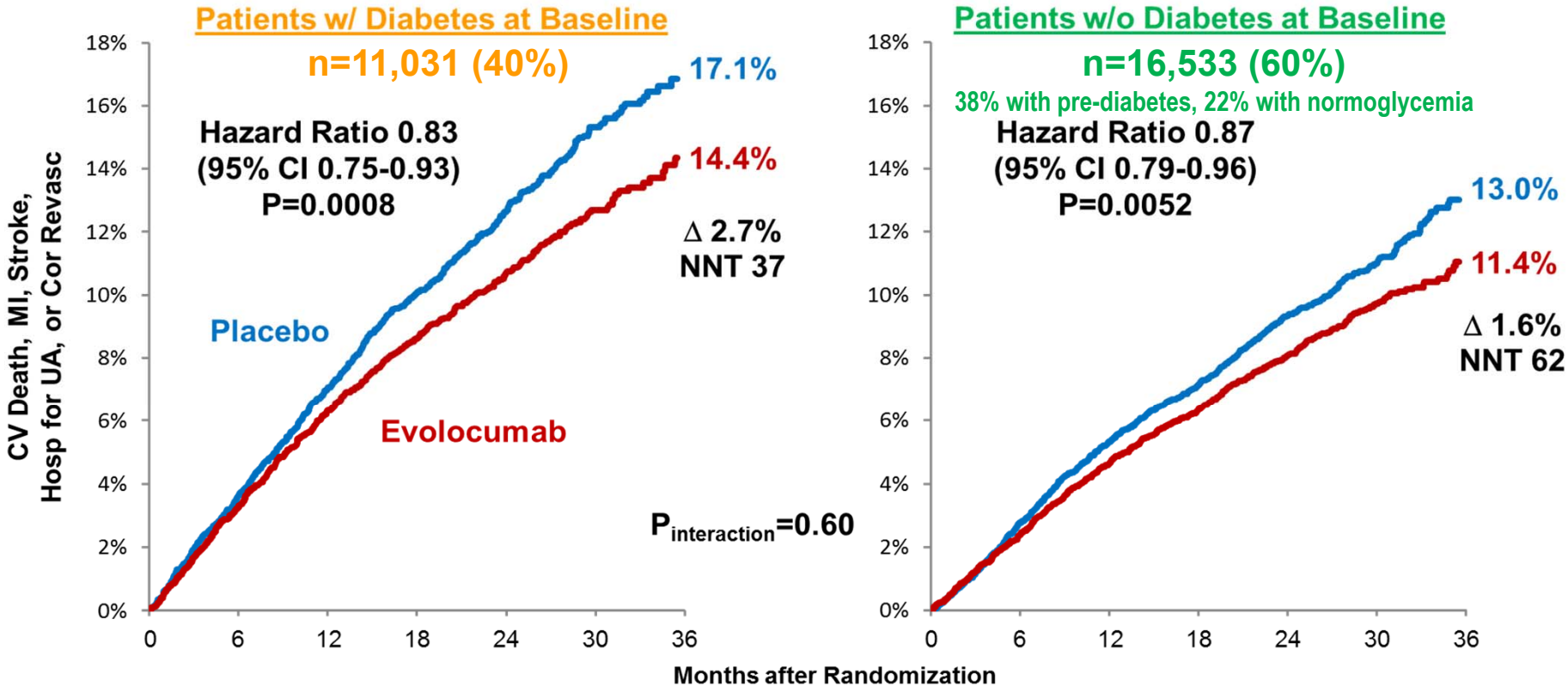
Giugliano et al *Lancet* 2017;390:1962-71

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



Bonaca et al *Circulation* 2017;137:338-50

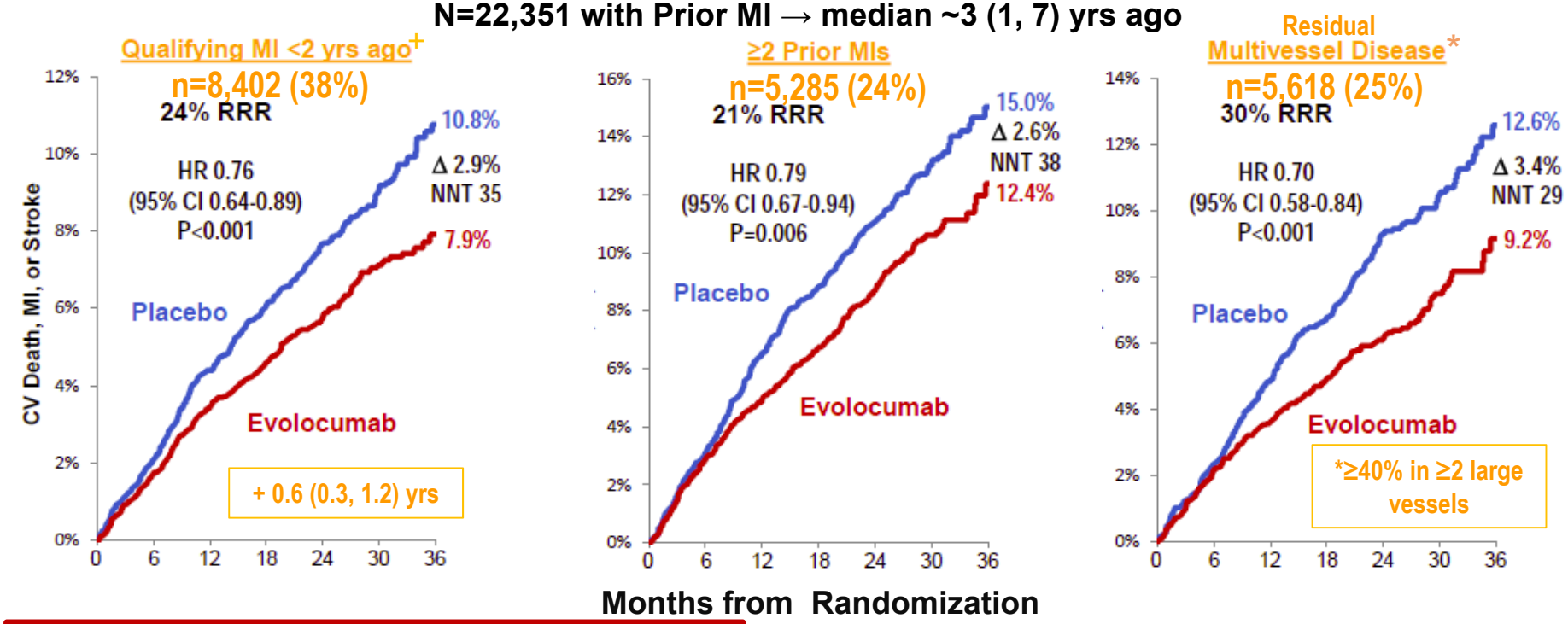
Effect of Evolocumab on Primary Endpoint



Sabatine et al *Lancet Diabetes Endocrinol* **2017:5:941-50**

Benefit of Evolocumab in High-Risk MI Subgroups

N=22,351 with Prior MI → median ~3 (1, 7) yrs ago



MI patients with ≥1 High-Risk Feature:
Estimated $ARR_{5\ years}$=5% or $NNT_{5\ years}$~20

Sabatine et al *Circulation* 2018;138:756-66

Study Hypothesis

Alirocumab vs. placebo reduces cardiovascular (CV) morbidity and mortality after recent acute coronary syndrome (ACS) in patients with elevated levels of atherogenic lipoproteins despite intensive or maximum-tolerated statin therapy

Schwartz et al *Am Heart J* 2014;168:682-689.e1
and Schwartz G et al *N Engl J Med* 2018;379:2097-107

ODYSSEY OUTCOMES

Main Inclusion Criteria

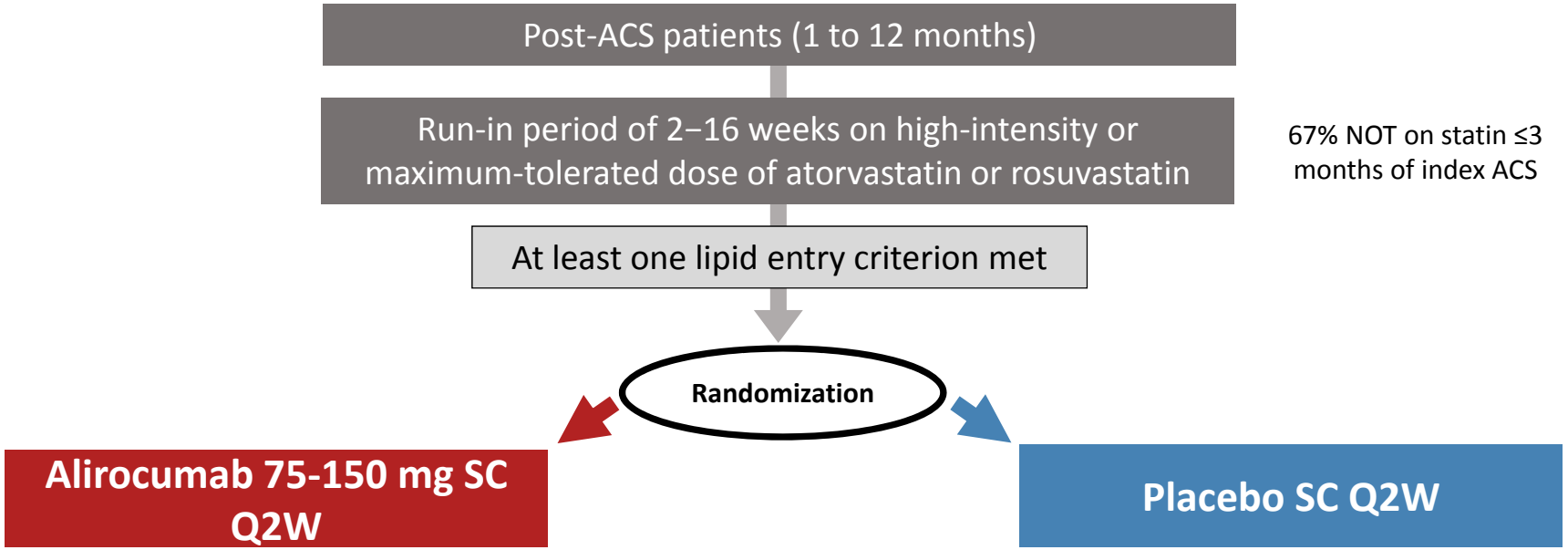
- **Age** ≥40 years
- **ACS**
  - 1 to 12 months prior to randomization
  - Acute myocardial infarction (MI) or unstable angina
- **High-intensity statin therapy***
  - Atorvastatin 40 to 80 mg daily or
  - Rosuvastatin 20 to 40 mg daily or
  - Maximum tolerated dose of one of these agents for ≥2 weeks
- **Inadequate control of lipids**
  - LDL-C ≥1.8 mmol/L or
  - Non-HDL-C ≥2.6 mmol/L or
  - Apolipoprotein B ≥0.8 mg/L

*Patients not on statins were authorized to participate if tolerability issues were present and documented

Schwartz et al *Am Heart J* 2014;168:682-689.e1
and Schwartz G et al *N Engl J Med* 2018;379:2097-107

ODYSSEY OUTCOMES

Treatment Assignment



67% NOT on statin ≤3 months of index ACS

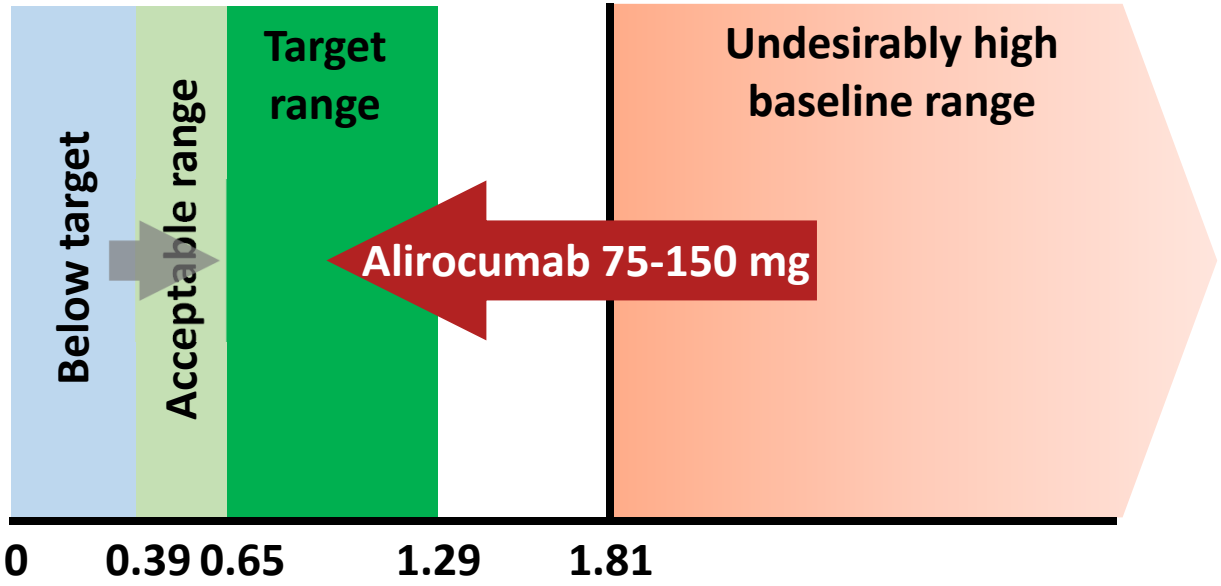
Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

Schwartz et al *Am Heart J* 2014;168:682-689.e1
and Schwartz G et al *N Engl J Med* 2018;379:2097-107

ODYSSEY OUTCOMES

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.

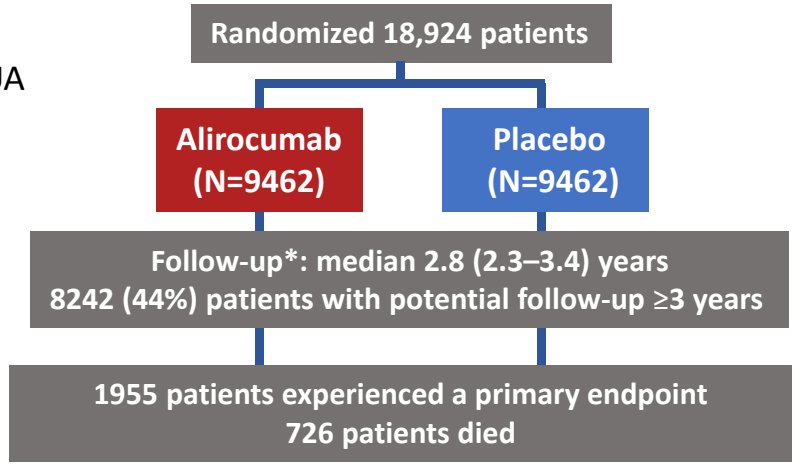


Schwartz et al *Am Heart J* 2014;168:682-689.e1
and Schwartz G et al *N Engl J Med* 2018;379:2097-107

ODYSSEY OUTCOMES

Patient Disposition

Mean 59 years
25% female
34% STEMI, 48% NSTEMI, 17% UA
Index ACS PCI or CABG 72%



Time from index ACS to randomization: 2.6 (1.7-4.4) months

*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively

• **Premature treatment discontinuation**	**1343 (14.2%)**	**1496 (15.8%)**
• **Blinded switch to placebo (2 consecutive LDL-C values <0.39 mmol/L)**	**730 (7.7%)**	**Not applicable**
• **Patients lost to follow-up (vital status)**	**14**	**9**

Schwartz G et al *N Engl J Med* 2018;379:2097-107

ODYSSEY OUTCOMES

Baseline LDL-C and Lipid-Lowering Therapy

	Alirocumab (N=9462)	Placebo (N=9462)
LDL-C,* mmol/L (Q1-Q4)	2.2 (1.9–2.7)	2.2 (1.9-2.7)
High-dose atorvastatin/rosuvastatin, n (%)	8380 (88.6)	8431 (89.1)
Low-/moderate-dose atorvastatin/rosuvastatin, n (%)	830 (8.8)	777 (8.2)
Ezetimibe, with or without statin, n (%)	269 (2.8)	285 (3.0)
No lipid-lowering therapy,[+] n (%)	87 (0.9)	91 (1.0)

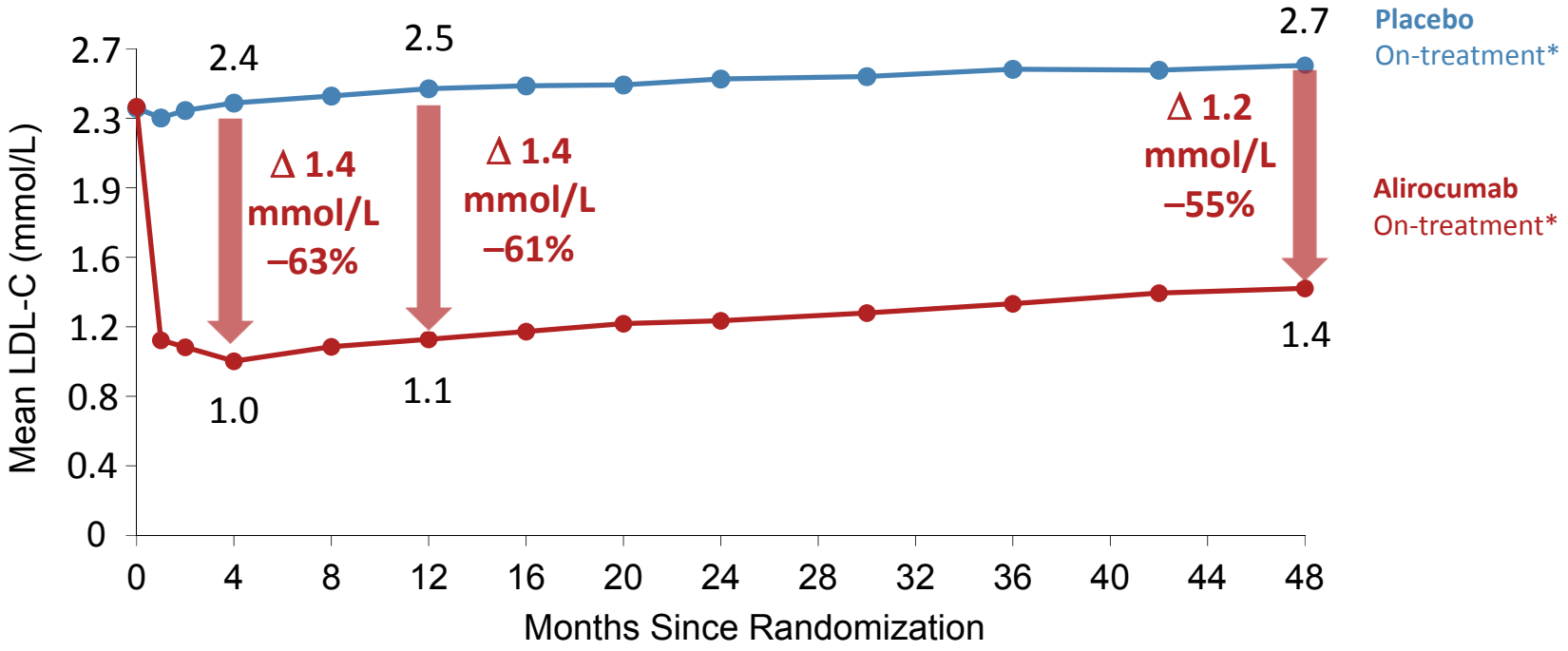
*92.1% of patients qualified on the basis of LDL-C ≥1.81 mmol/L, 7.2% non-HDL ≥1.81 mmol/L

[+]Patients not on statins authorized to participate if tolerability issues were present and documented

Schwartz G et al *N Engl J Med* 2018;379:2097-107

ODYSSEY OUTCOMES

LDL-C: On-Treatment Analysis



Exposure to the intended trial regimen (% of the total follow-up time) 90%; of total time on treatment with alirocumab 78% on 75 mg, 22% on 150 mg

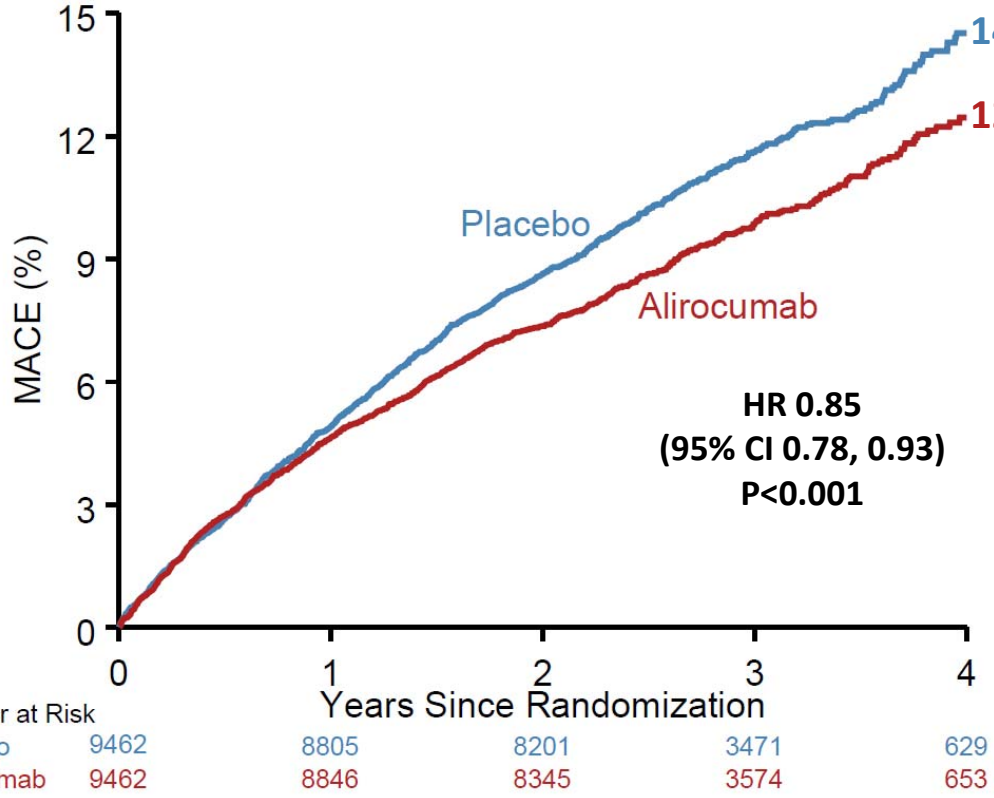
*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo

Schwartz G et al *N Engl J Med* 2018;379:2097-107

ODYSSEY OUTCOMES

Primary Efficacy Endpoint: MACE

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



ARR 2.0%*

$NNT_{4\ yrs}$ ~49 (28, 64)

*Based on 4-yr KM estimate

Schwartz G et al *N Engl J Med* 2018;379:2097-107

ODYSSEY OUTCOMES

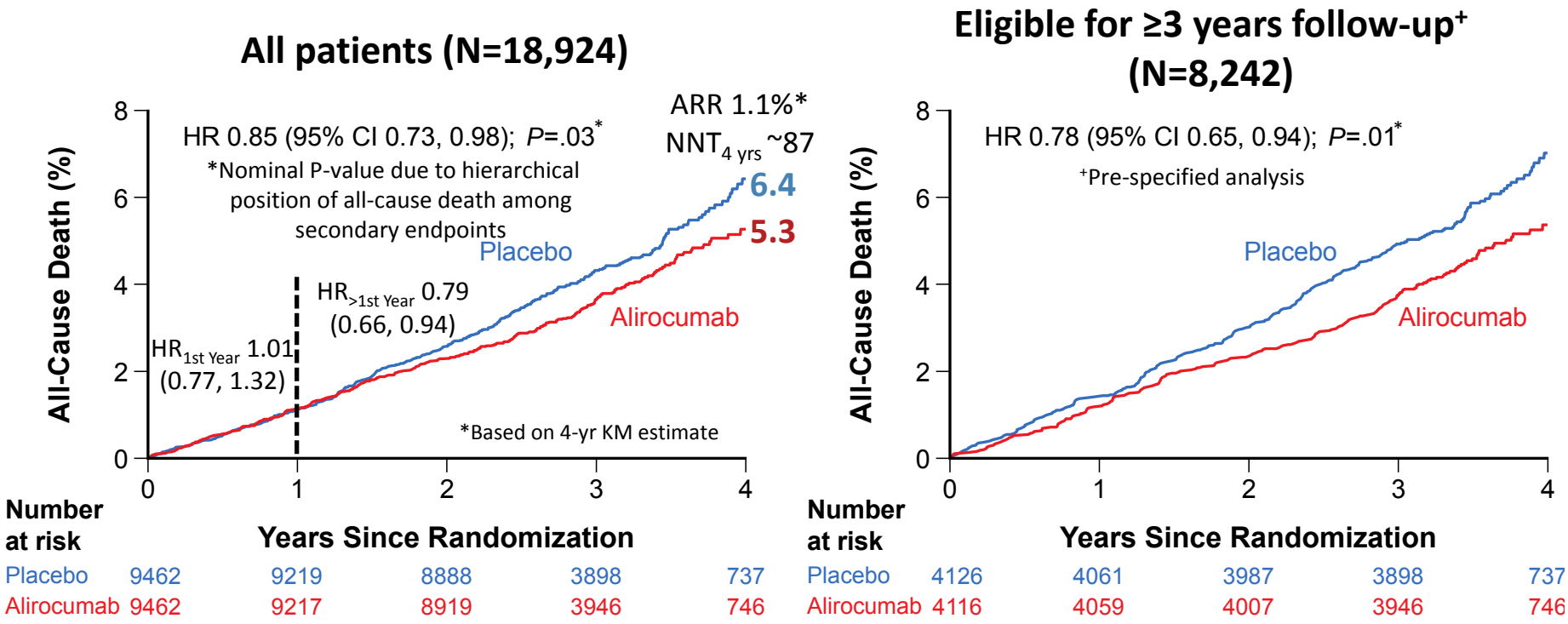
Primary Efficacy and Components

Endpoint, n (%)* *Cumulative Incidence	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

Schwartz G et al *N Engl J Med* 2018;379:2097-107

ODYSSEY OUTCOMES

All-Cause Death: All Patients



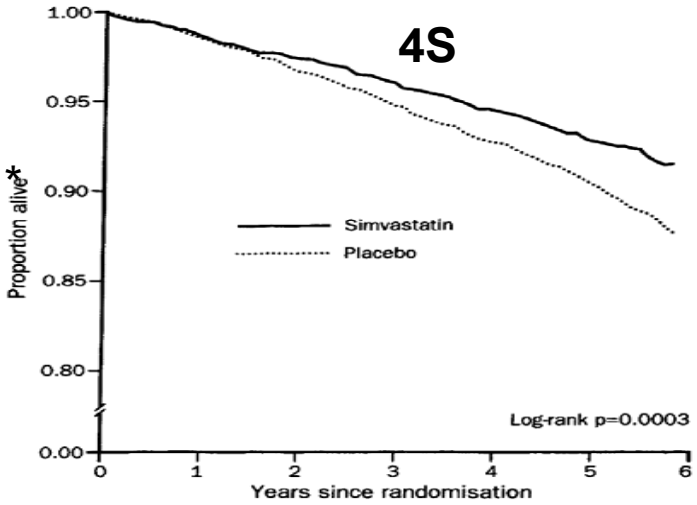
Schwartz G et al *N Engl J Med* 2018;379:2097-10
and Steg et al *Circulation* 2019;10.1161/CIRCULATIONAHA.118.038840

ODYSSEY OUTCOMES

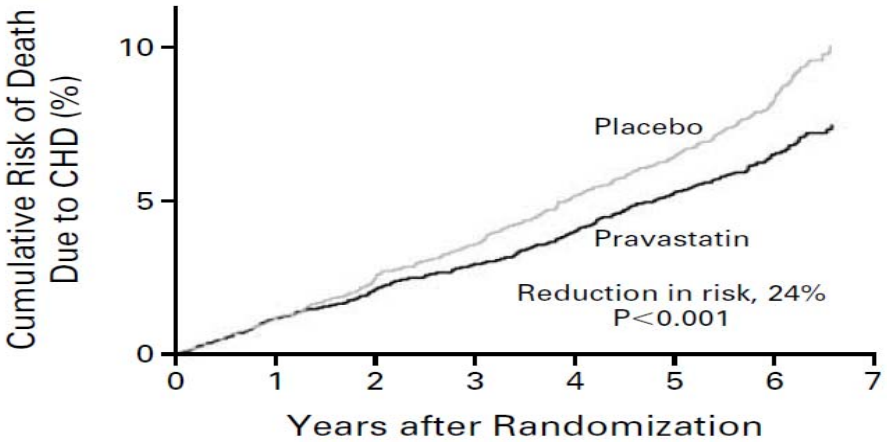
LDL-C Lowering and Mortality

Benefit on mortality was not apparent early, even in trials in which it was the primary endpoint

4S



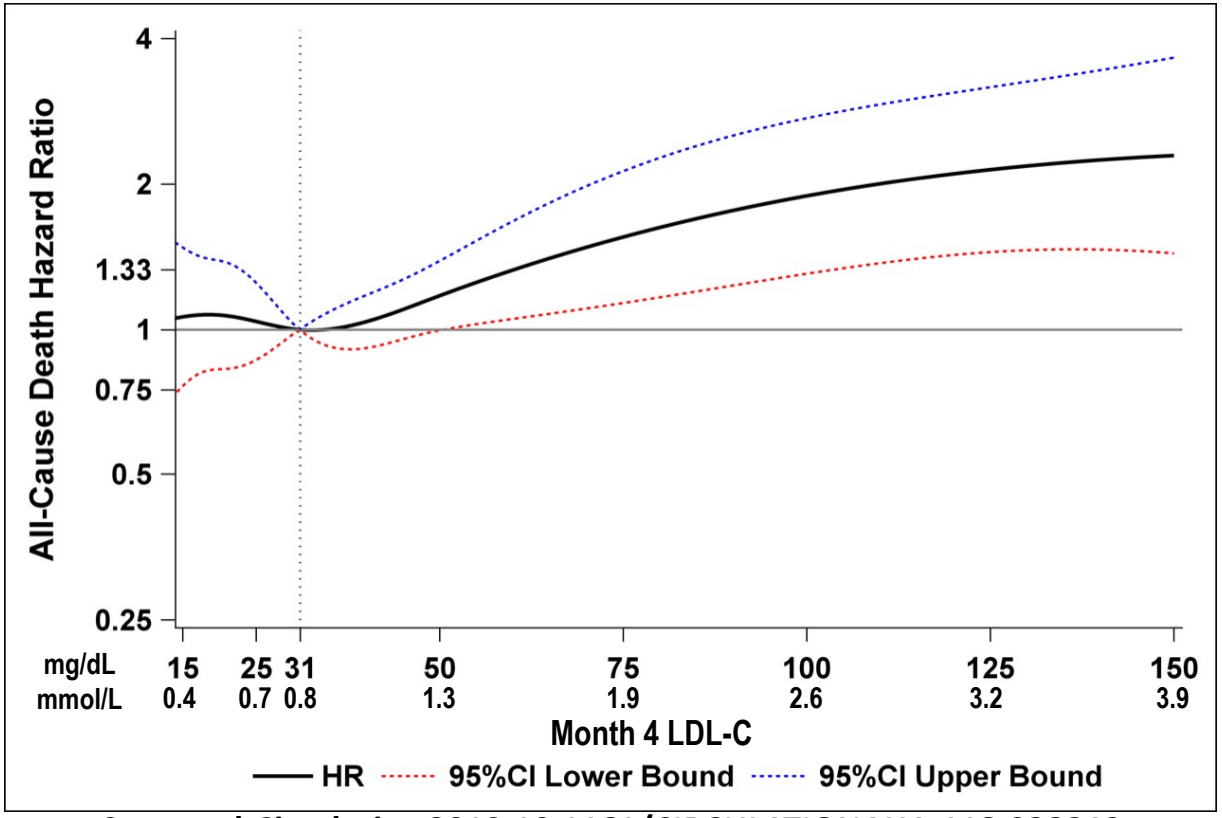
LIPID



*All-cause mortality

Scandinavian Simvastatin Survival Study Group *Lancet* **1994;344:1383-89**
The LIPID Study Group *N Engl J Med* **1998;339:1349-57**

Death According to *Achieved LDL-C* in the Alirocumab Group at Month 4



Steg et al *Circulation* 2019;10.1161/CIRCULATIONAHA.118.038840

ODYSSEY OUTCOMES

Safety

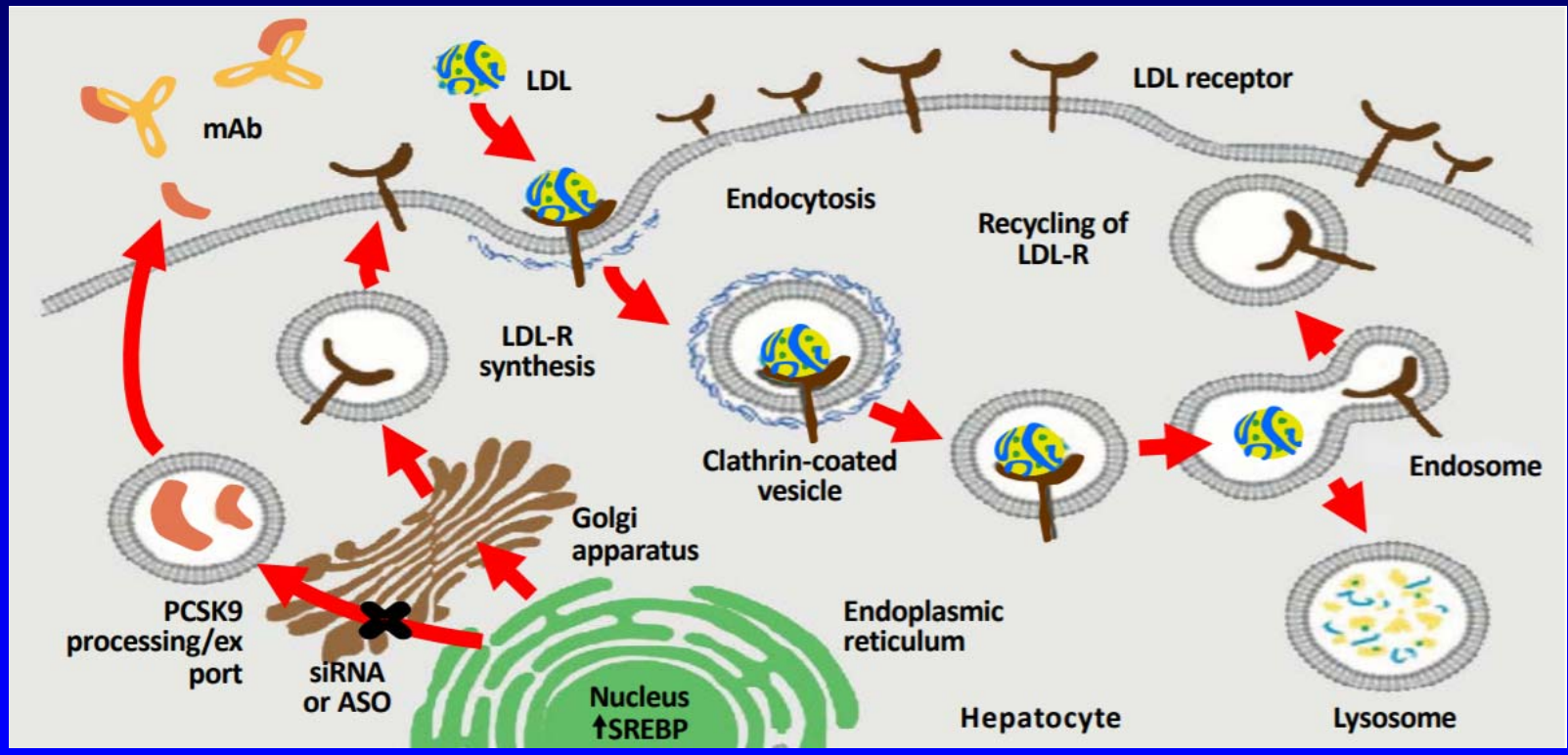
Event	Alirocumab (N=9451)	Placebo (N=9443)
Treatment-emergent adverse events	7165 (75.8)	7282 (77.1)
Serious Adverse Events (SAEs)	2202 (23.3)	2350 (24.9)
ALT >3 × ULN	212/9369 (2.3)	228/9341 (2.4)
Diabetes worsening or diabetic complications[1]	506/2688 (18.8)	583/2747 (21.2)
New onset diabetes[2]	648/6763 (9.6)	676/6696 (10.1)
General allergic reaction	748 (7.9)	736 (7.8)
Hepatic disorder	500 (5.3)	534 (5.7)
Local injection site reaction*	360 (3.8)	203 (2.1)
Neurocognitive disorder	143 (1.5)	167 (1.8)
Cataracts	120 (1.3)	134 (1.4)
Hemorrhagic stroke	9 (<0.1)	16 (0.2)

Patients *with*[1]*/without*[2] diabetes at baseline

Schwartz G et al *N Engl J Med* 2018;379:2097-107

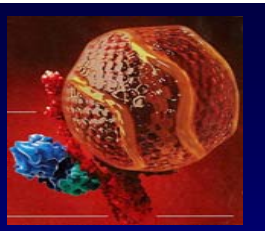
ODYSSEY OUTCOMES

Small interfering RNA (siRNA): Inhibits Translation of PCSK9



Adapted from Hovingh et al *Eur Heart J* 2013;34:962-71

Who Might Receive a PCSK9 Inhibitor?



- LDL-C ≥1.8 mmol/L (70 mg/dL) despite maximally tolerated statin ± ezetimibe AND
  - Recent ACS
  - Residual multivessel CAD (e.g., ≥40% stenoses in ≥2 vessels, prior CABG)
  - Polyvascular ASCVD (e.g., CAD + PAD)
  - Diabetes
  - LDL-C far from target (i.e., ≥2.6 mmol/L [100 mg/dL])

ASCVD=Atherosclerotic CV Disease; CAD=Coronary Artery Disease; PAD=Peripheral Artery Disease