8th Annual Emirates Cardiac Society Conference

ACC Middle East Conference 2017

DUBAI

OCTOBER 19 – 21, 2017

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FOURIER

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

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NO DISCLOSURES

Slides adapted from MS Sabatine, for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session

Late-Breaking Clinical Trial, March 17, 2017

ACC Middle East Conference 2017

Background:

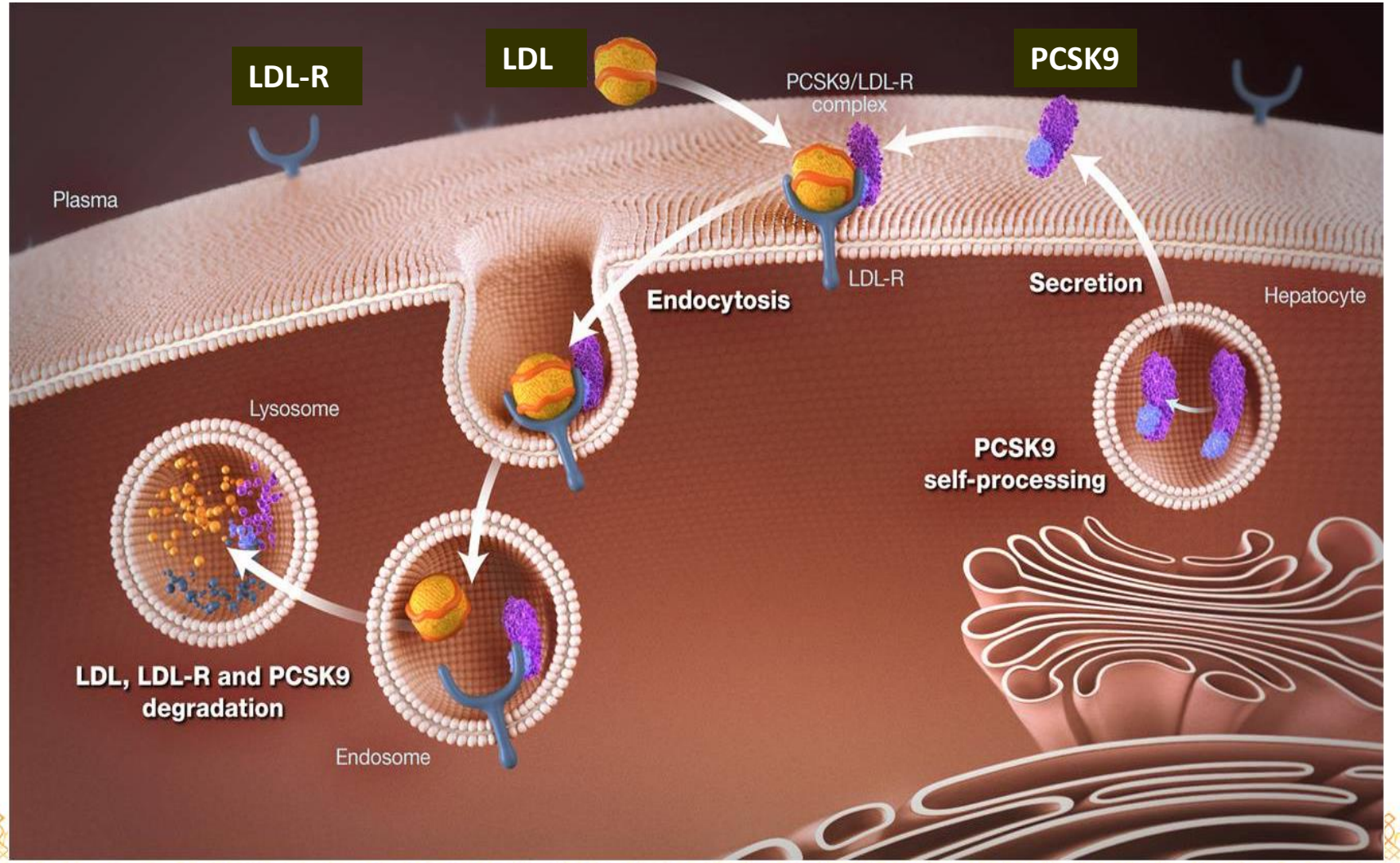
Proprotein convertase subtilisin/kexin Type 9 (PCSK9)

- Chaperones LDL-R to destruction → ↑ circulating LDL-C
- Loss-of-function genetic variants → ↑ LDL-R → ↓ LDL-C & ↓ risk of MI

Evolocumab

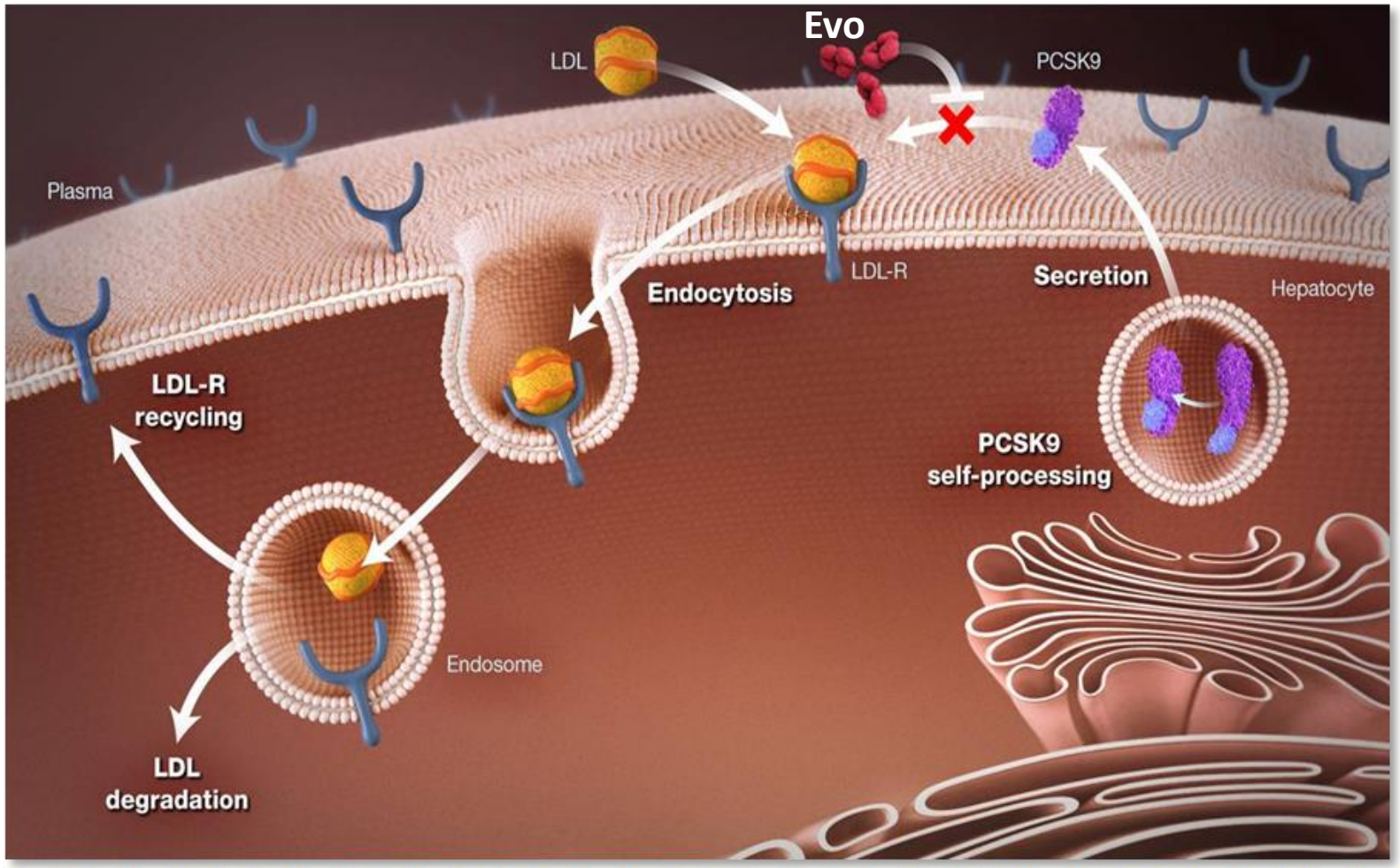
- Fully human, Anti-PCSK mAb
- ~ 60 % ↓ LDL-C
- Safe well tolerated in Ph 2 & 3 studies
- Exploratory data suggests ↓ CV events

Background:



Sever P & Mackay J. Br J Cardiol 2014;21:91-3
Giugliano RP, et al. Lancet 2012;380:2007-17
Sabatine MS, et al. NEJM 2015;372:1500-9

Background:



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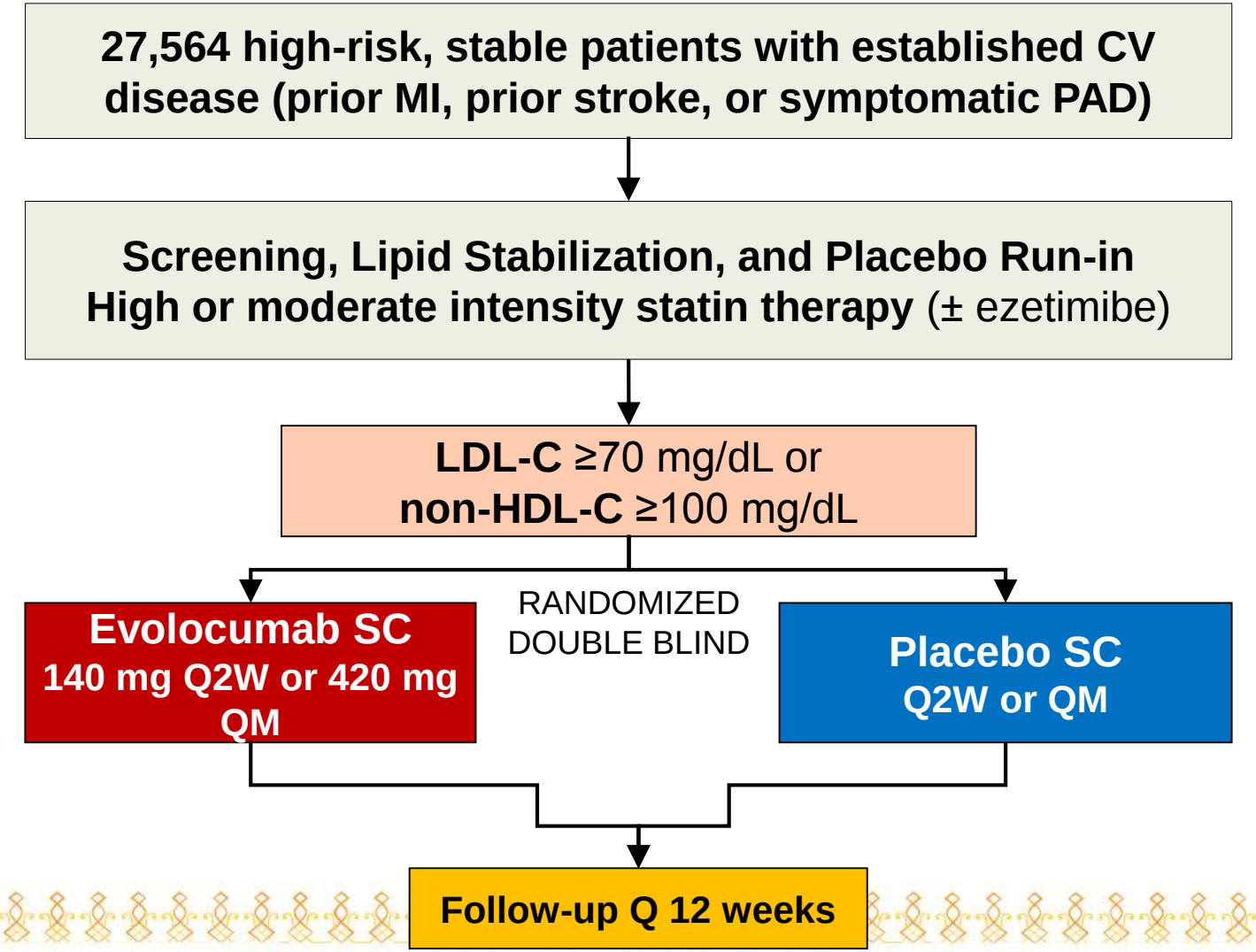
Objectives: FOURIER TRIAL

In patients with established cardiovascular disease on statin therapy:

- **Test whether the addition of evolocumab reduces the incidence of major cardiovascular events**
- **Examine the long-term safety & tolerability of evolocumab**
- **Investigate the efficacy and safety of achieving unprecedented low levels of LDL-C**

Trial Design



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

Endpoints

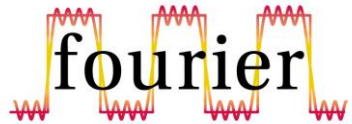
- **Efficacy**
  - **Primary: *CV death, MI, stroke, hosp. for UA, or coronary revasc***
  - **Key secondary: *CV death, MI or stroke***

- **Safety**
  - **AEs/SAEs**
  - **Events of interest incl. muscle-related, new-onset diabetes, neurocognitive**
  - **Development of anti-evolocumab Ab (binding and neutralizing)**

- **TIMI Clinical Events Committee (CEC)**
  - **Adjudicated all efficacy endpoints & new-onset diabetes**
  - **Members unaware of treatment assignment & lipid levels**

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

Trial Organizaton



Executive Committee

Marc S. Sabatine (Co-Chair)
Terje R. Pedersen (Co-Chair)
Robert P. Giugliano
Anthony C. Keech
Peter S. Sever

TIMI Study Group

Stephen D. Wiviott (CEC Chair)
Cheryl Lowe
Leah Zahn
Marc P. Bonaca (Safety Chair)
Polly Fish (Director of Ops)
Tim Abrahamsen
Sabina Murphy (Director of Stats)
Kelly Im (Assoc Dir Stats)
Julia Kuder
Estella Kanevsky

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Steering Committee & National Lead Investigators

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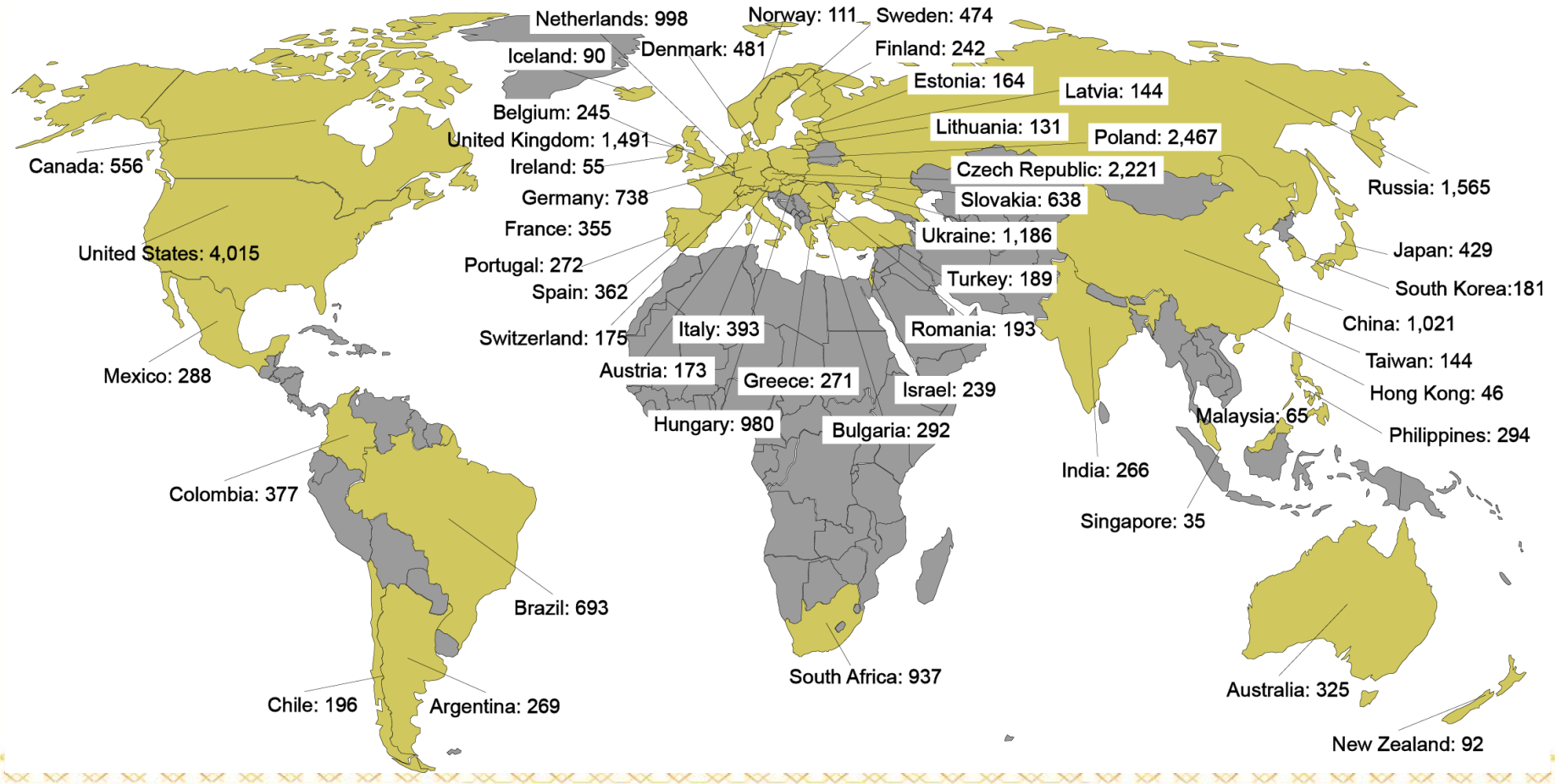
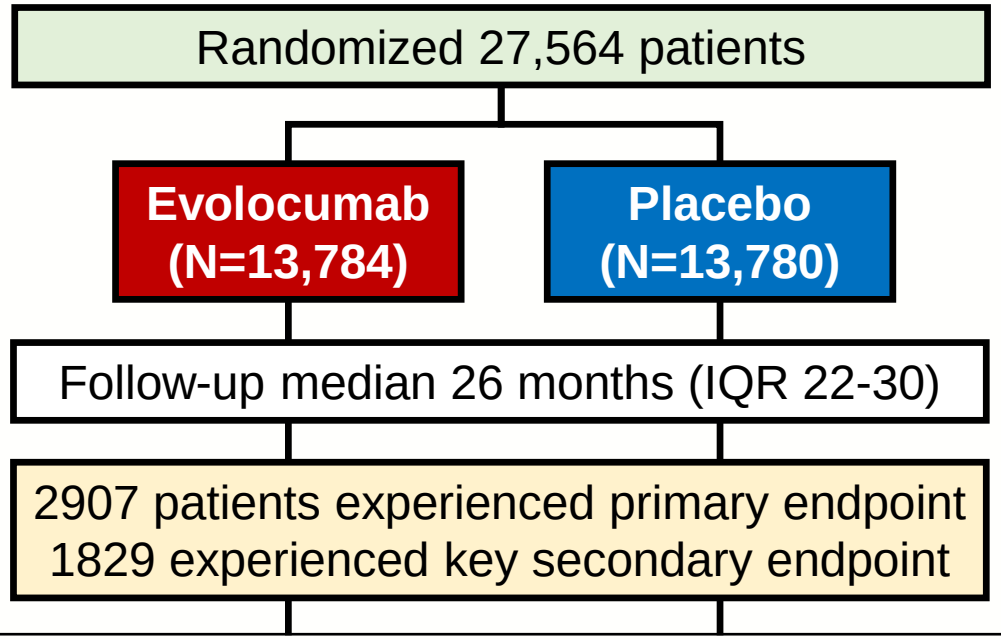
Ukraine
Oleg Kraydashenko
United Kingdom
P. Sever & D. Connolly
United States
Robert P. Giugliano

Global Enrollment

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



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

Baseline Characteristics

Characteristic	Value
Age, years, mean (SD)	**63 (9)**
Male sex (%)	**75**
Type of cardiovascular disease (%)	
Myocardial infarction	**81**
Stroke (non-hemorrhagic)	**19**
Symptomatic PAD	**13**
Cardiovascular risk factor (%)	
Hypertension	**80**
Diabetes mellitus	**37**
Current cigarette use	**28**

Median time from most recent event ~3 yrs

Pooled data; no differences between treatment arms

Lipid Lowering Therapy & Lipid Levels at Baseline

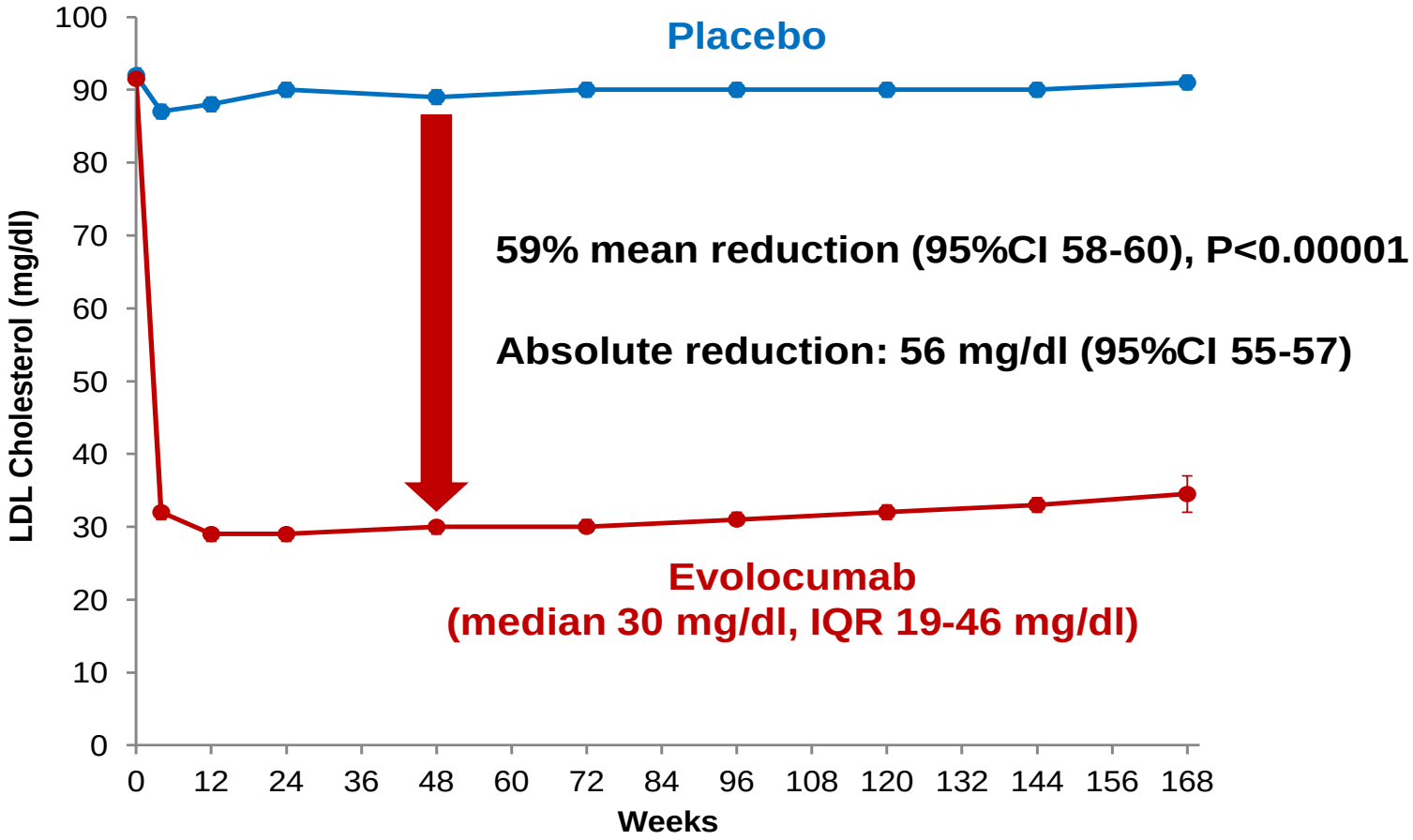
Characteristic	Value
Statin use (%)*	
High-intensity	**69**
Moderate-intensity	**30**
Ezetimibe use (%)	**5**
Median lipid measures (IQR) – mg/dL	
LDL-C	**92 (80-109)**
Total cholesterol	**168 (151-189)**
HDL-C	**44 (37-53)**

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

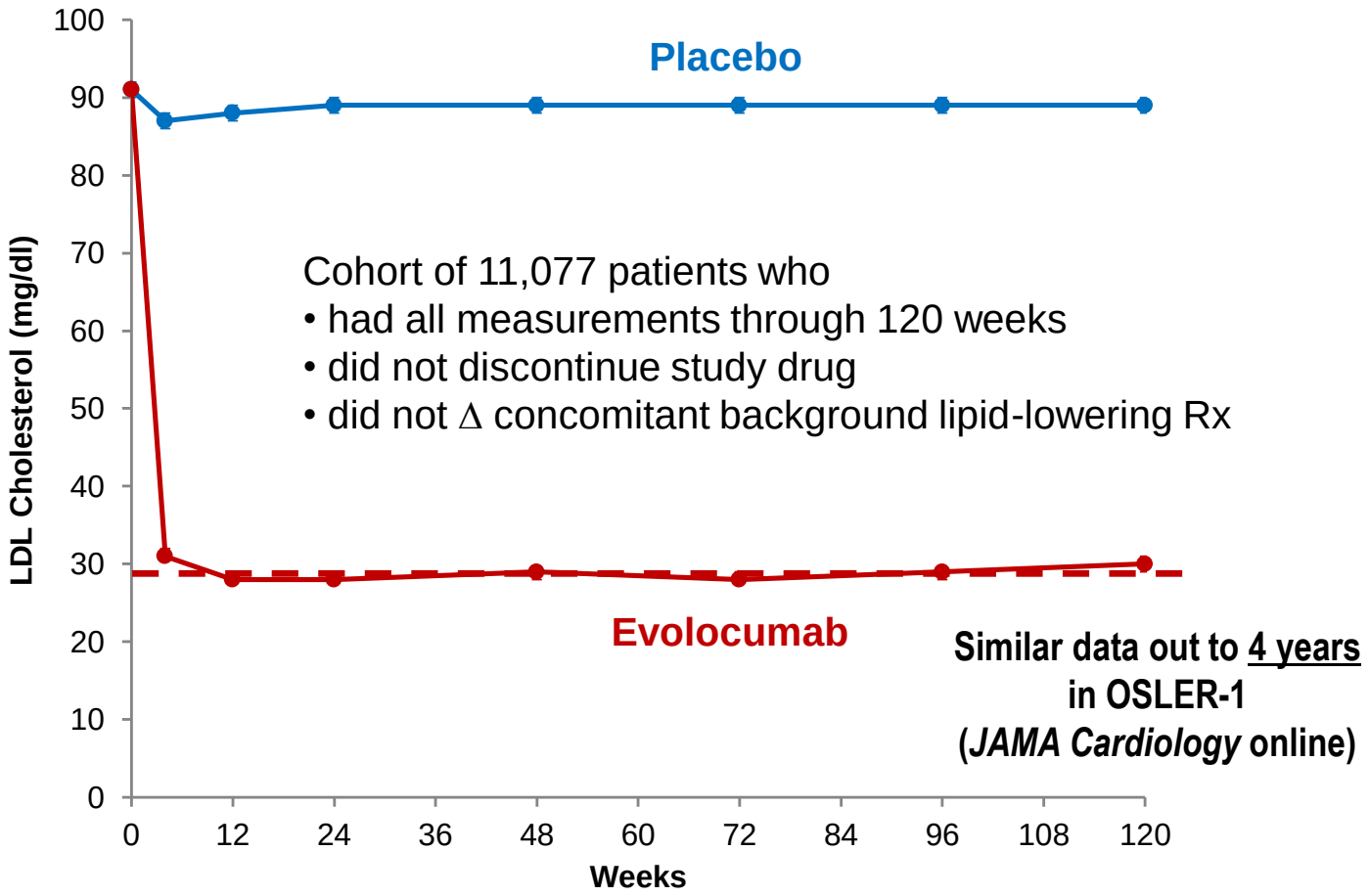
Pooled data; no differences between treatment arms

LDL Cholesterol

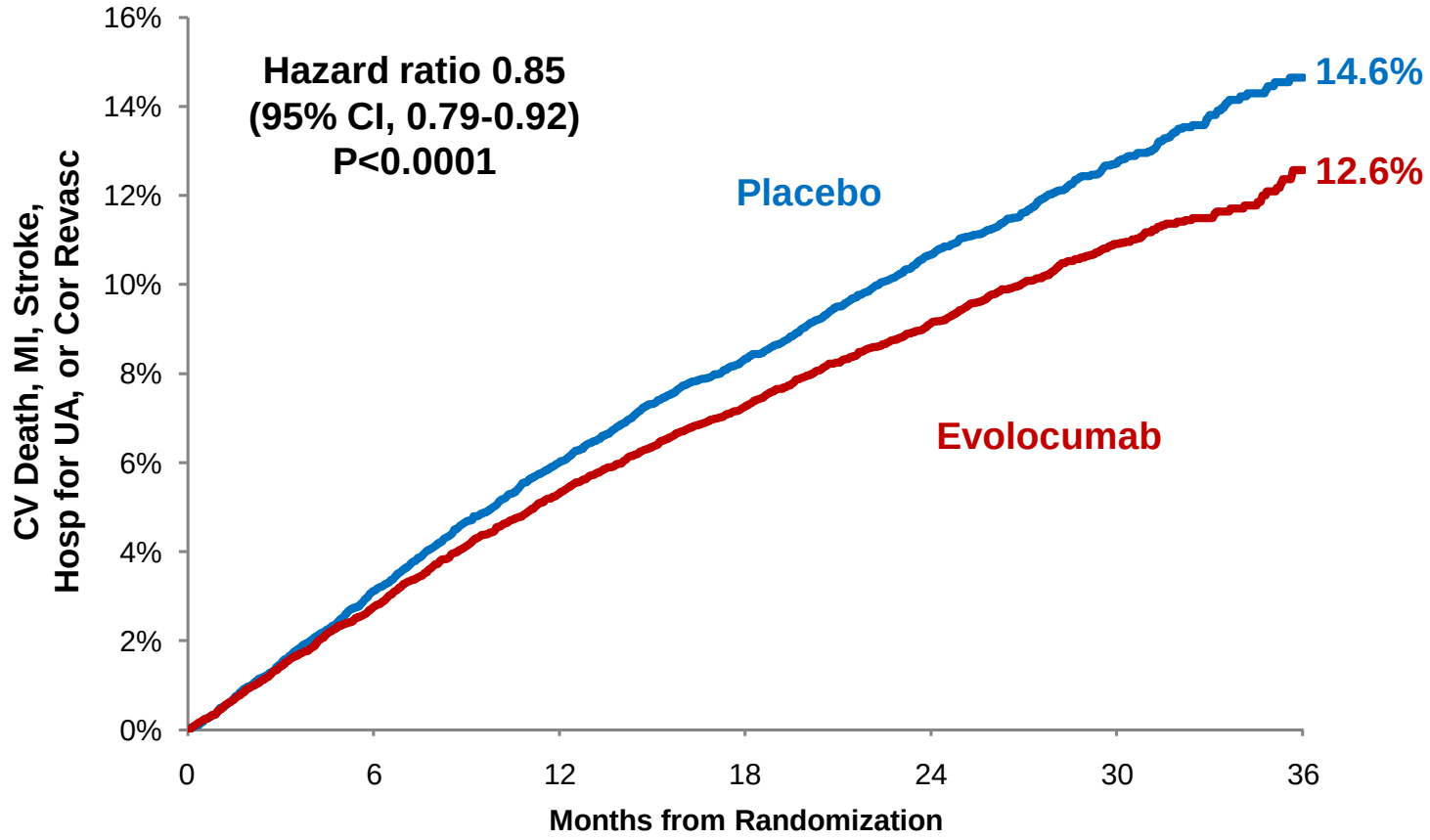
Low-Density Lipoprotein (LDL) Cholesterol Levels over Time.

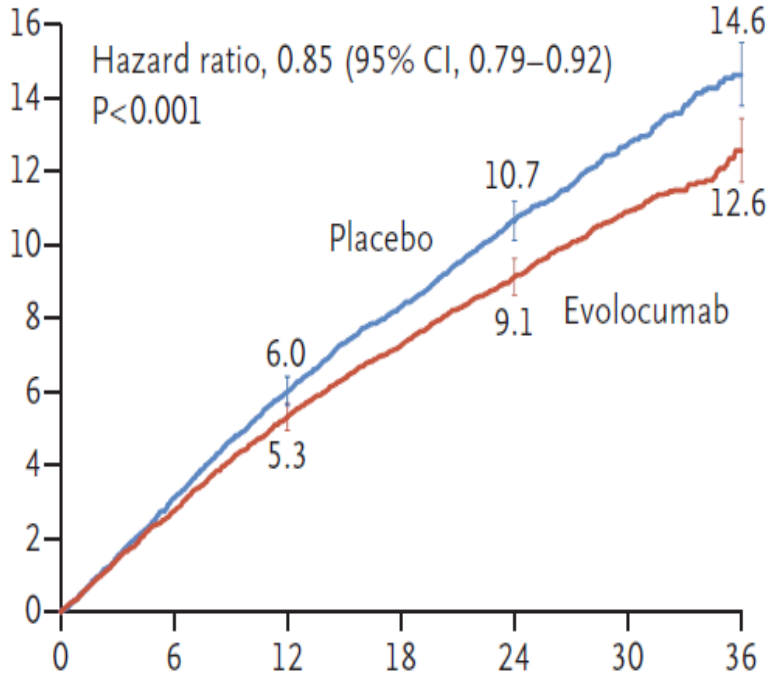


LDL Cholesterol



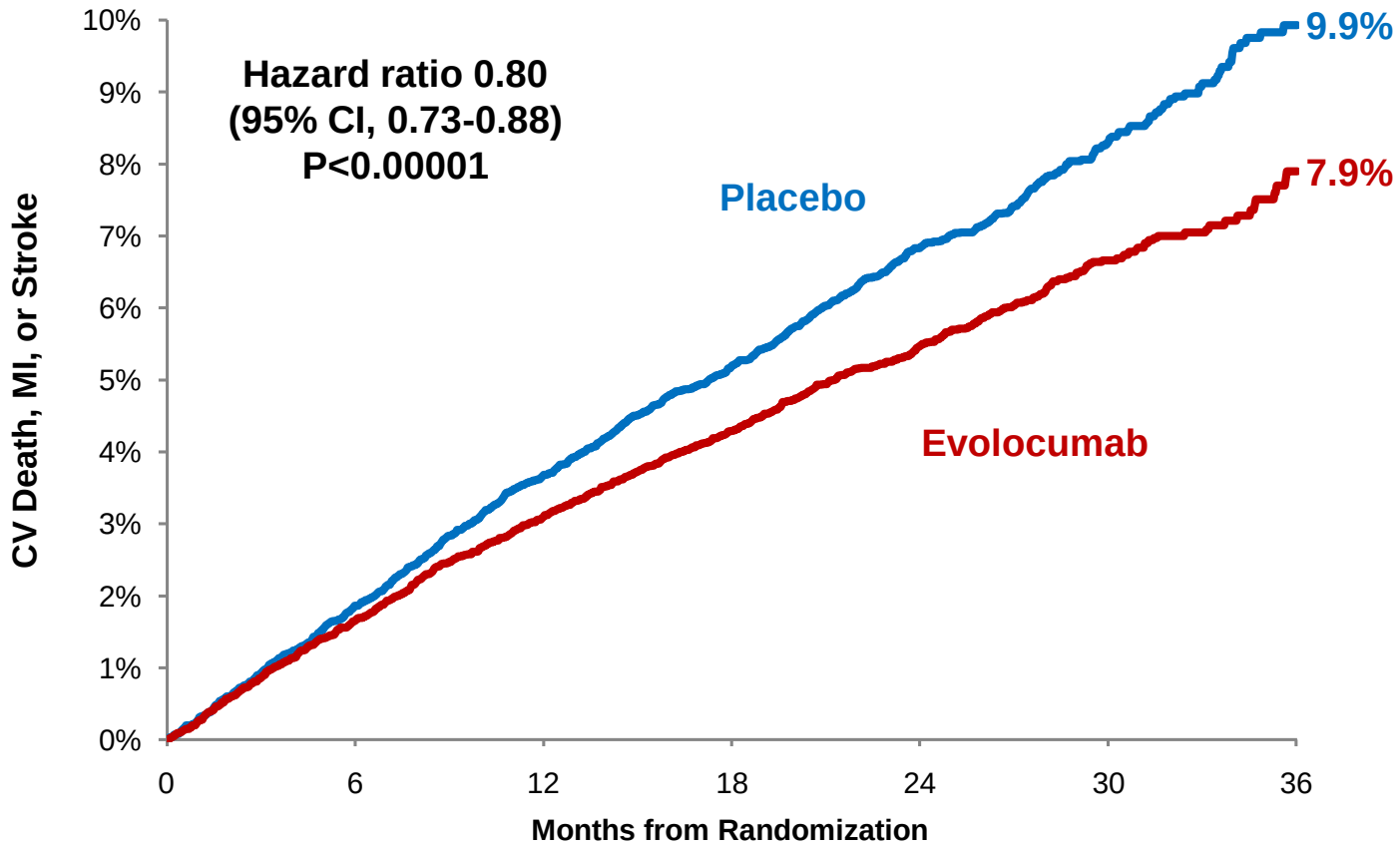
Primary Endpoint

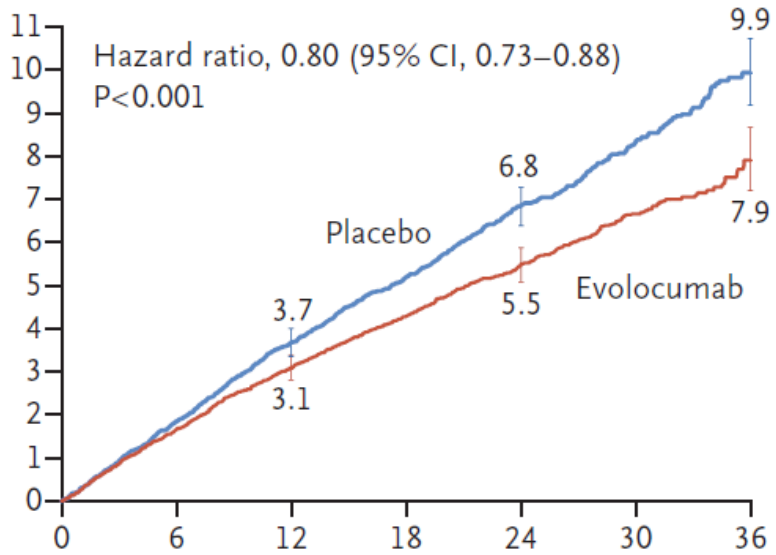




Cumulative Incidence of Cardiovascular Events.

Key Secondary Endpoint





Cumulative Incidence of Cardiovascular Events.

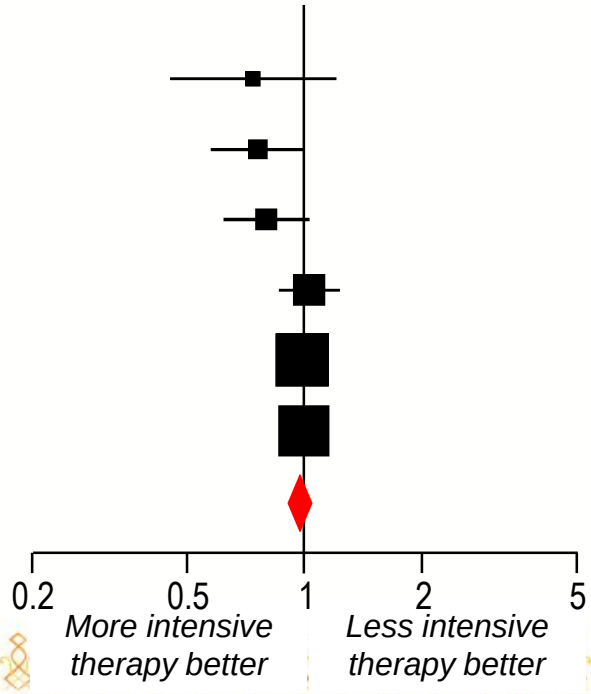
Types of CV Outcomes

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
CV death, MI, or stroke	**7.9**	**9.9**	**0.80 (0.73-0.88)**
Cardiovascular death	2.5	2.4	1.05 (0.88-1.25)
Death due to acute MI	0.26	0.32	0.84 (0.49-1.42)
Death due to stroke	0.29	0.30	0.94 (0.58-1.54)
Other CV death	1.9	1.8	1.10 (0.90-1.35)
MI	**4.4**	**6.3**	**0.73 (0.65-0.82)**
Stroke	**2.2**	**2.6**	**0.79 (0.66-0.95)**

More Intensive LDL-C Lowering & CV Death

No clear benefit on 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)**



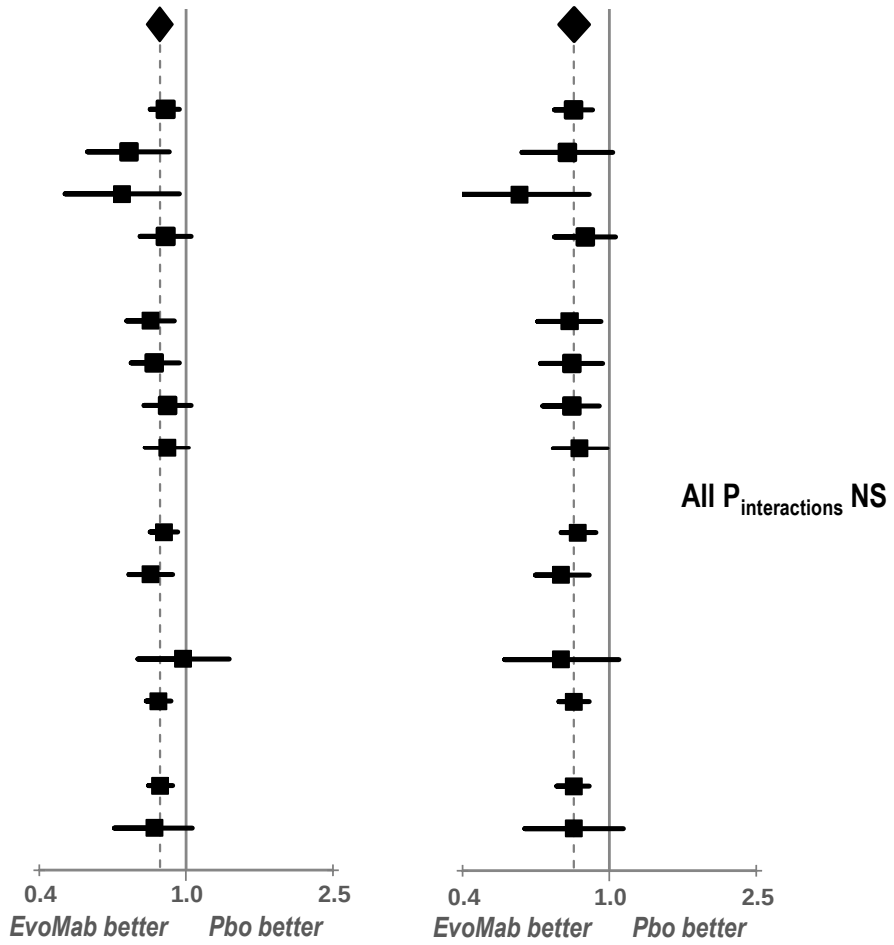
NEJM 2004;350:1495-504
JAMA 2004;292:1307-16
NEJM 2005;352:1425-35
JAMA 2005;294:2437-45
Lancet 2010;376:1658-69
NEJM 2015;372:2387-97

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)

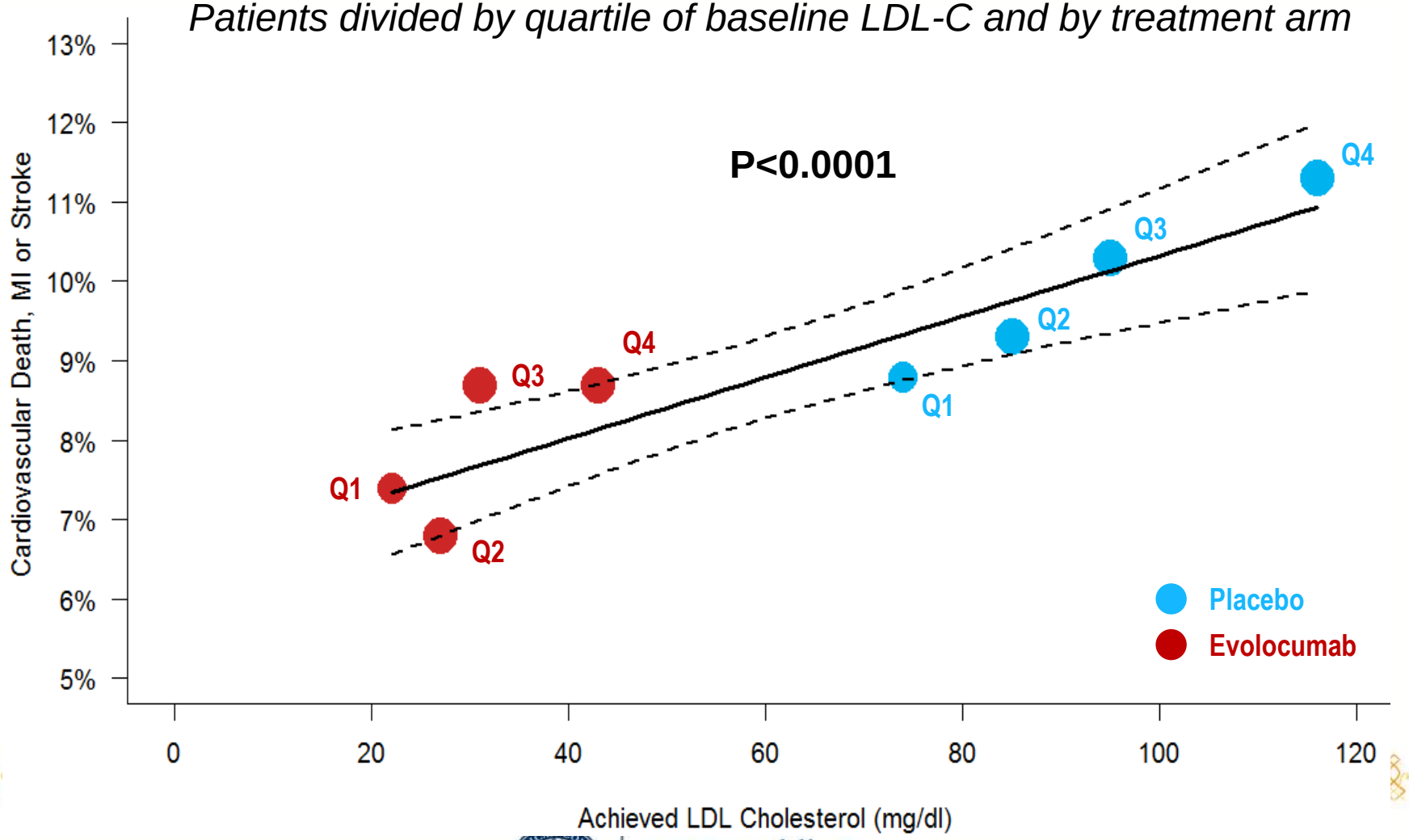
Key Subgroups

Subgroup	Patients
Overall	*27564*
Type of disease	
MI alone	19113
Stroke alone	3366
PAD alone	1505
Polyvascular disease	3563
Baseline LDL-C	
Q1 (<80 mg/dl)	6961
Q2 (80-<92 mg/dl)	6886
Q3 (92-109 mg/dl)	6887
Q4 (>109 mg/dl)	6829
Baseline statin intensity	
High	19103
Not high	8461
Ezetimibe	
Yes	1440
No	26124
Initial Dosing Regimen	
Every 2 weeks	24774
Monthly	2790

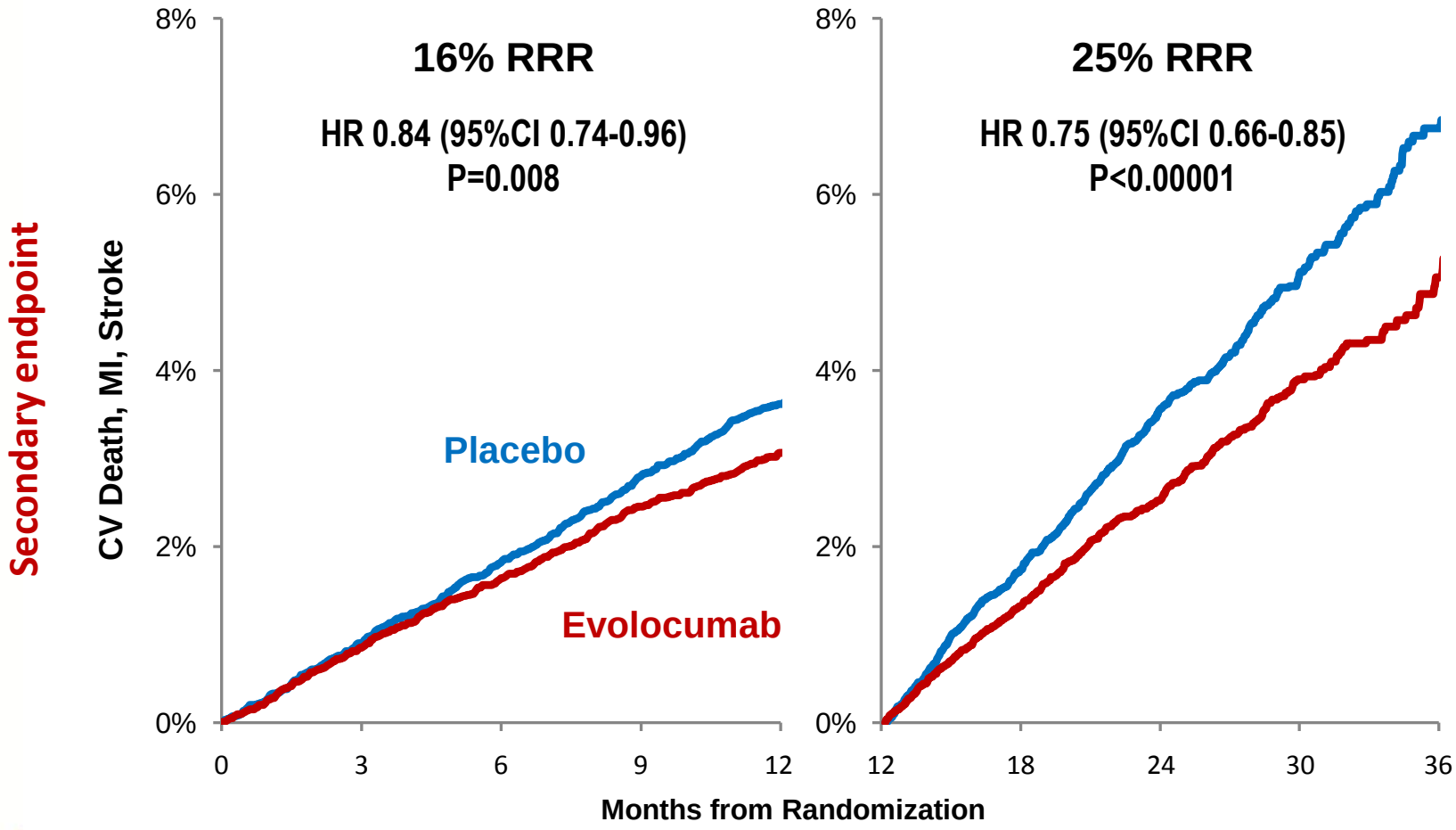


Lower LDL-C Is Better

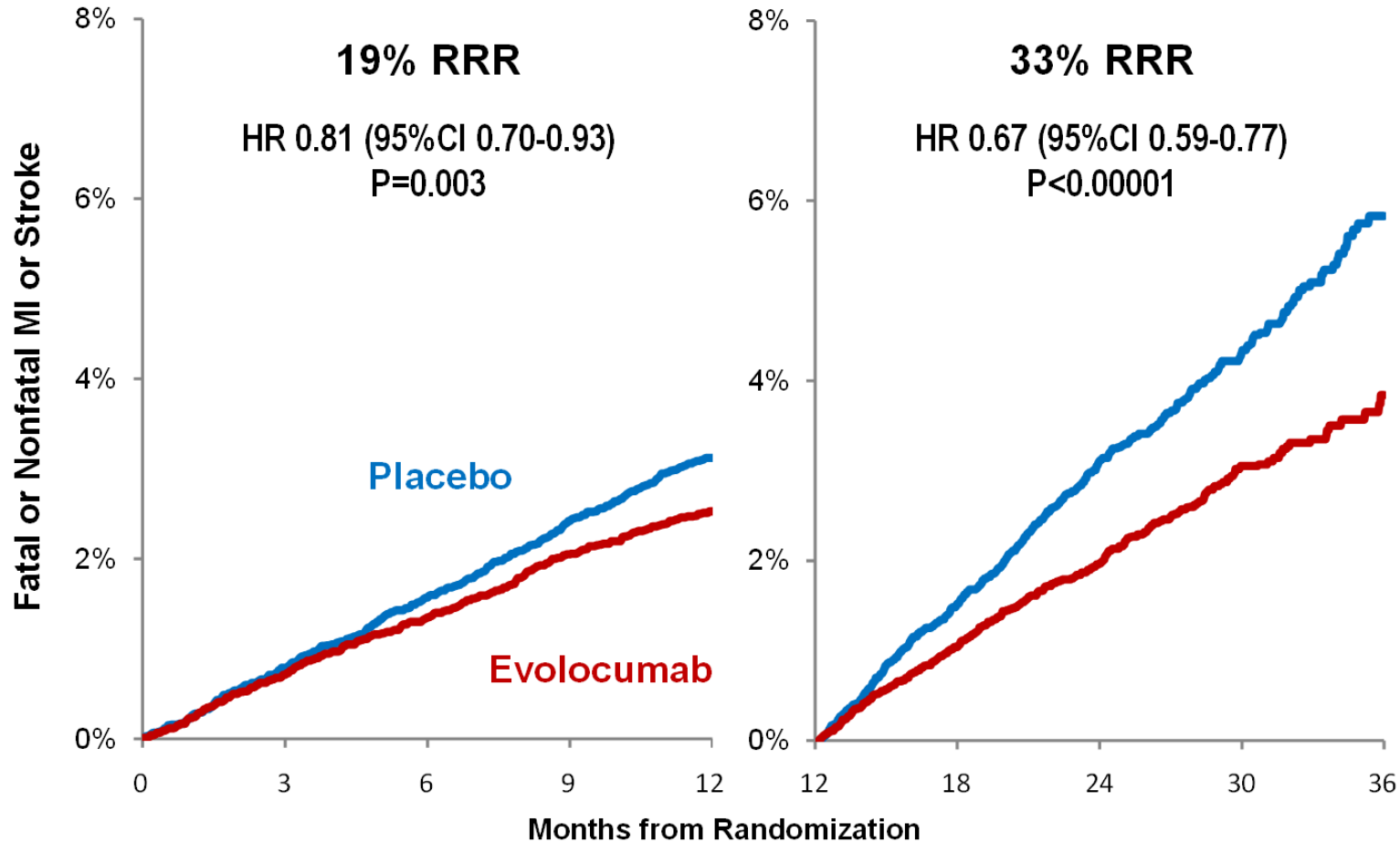
Patients divided by quartile of baseline LDL-C and by treatment arm



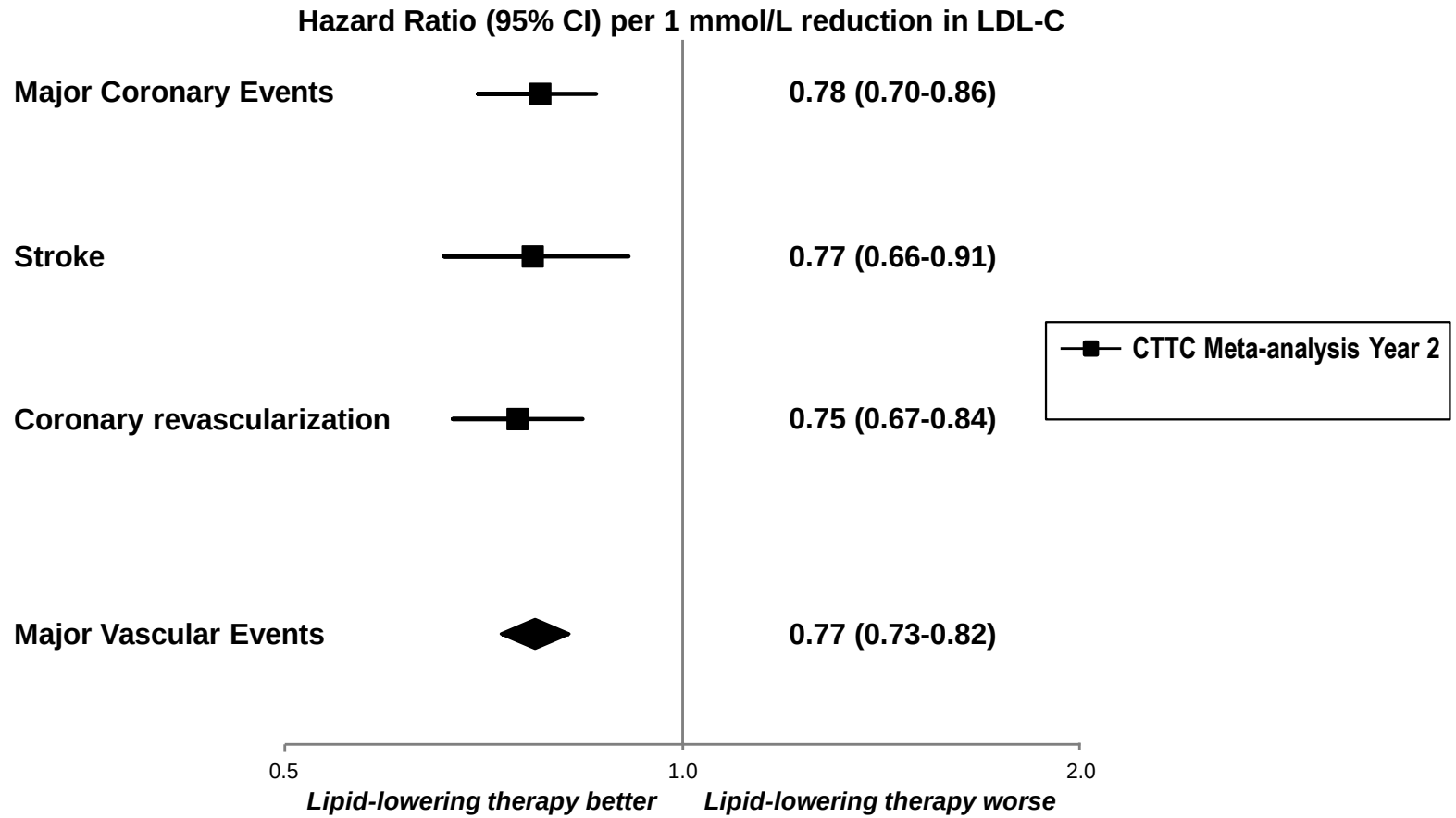
Landmark Analysis



Fatal or Nonfatal MI or Stroke

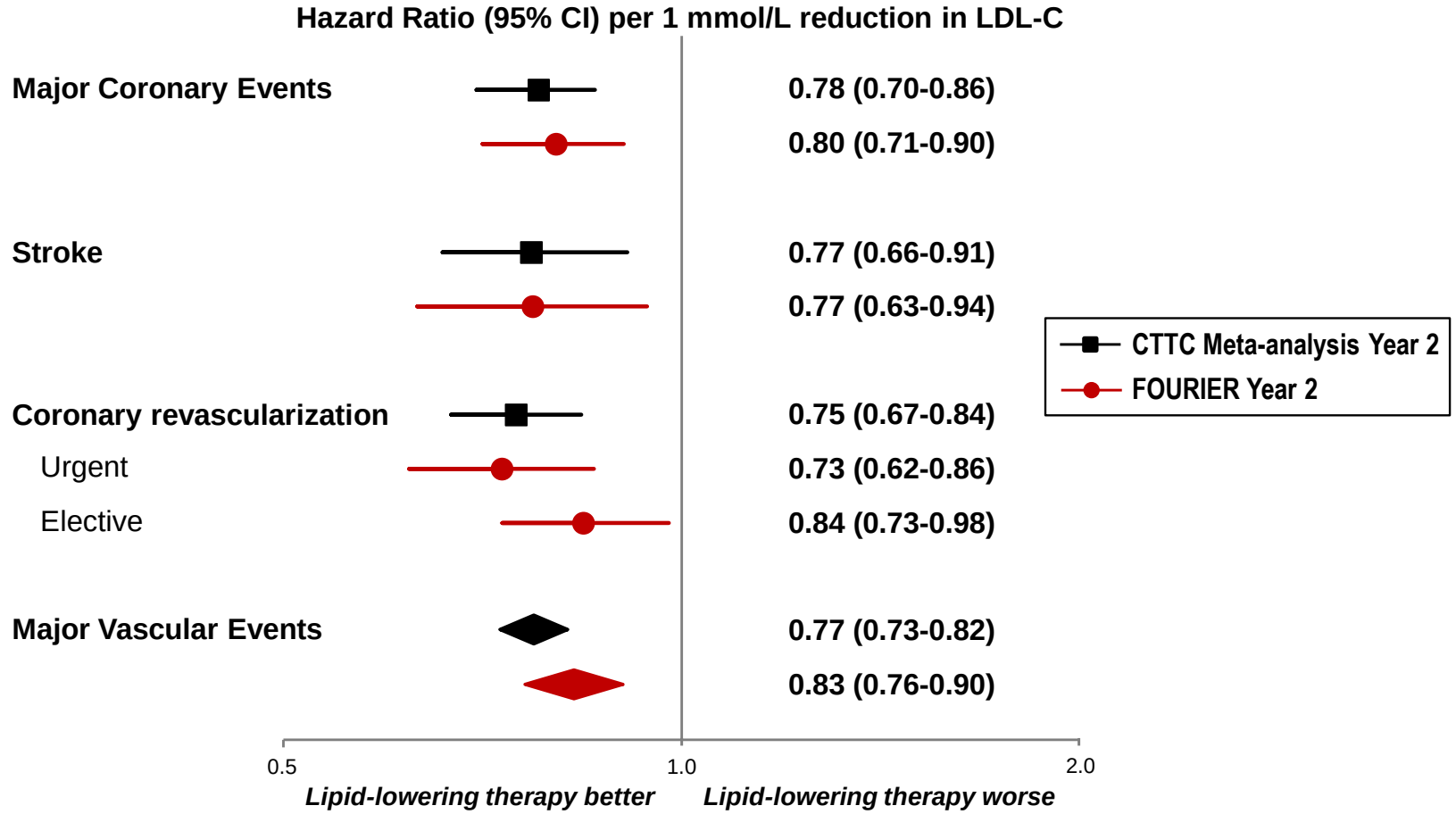


Comparison to Cholesterol Treatment Trialists Collaboration



CTTC data from *Lancet* 2010;376:1670-81

Comparison to Cholesterol Treatment Trialists Collaboration



CTTC data from *Lancet* 2010;376:1670-81

Safety

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

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

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

Conclusions:

In patients with known cardiovascular disease:

1. PCSK9 inhibition with evolocumab significantly & safely ↓ major cardiovascular events when added to statin therapy

2. Benefit was achieved with lowering LDL cholesterol well below current targets

Additional Details

fourier

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

ACC Middle East Conference 2017

Article available at www.nejm.org
Slides available at www.TIMI.org

ARS Question 1

In meta-analyses, a 40 mg/dL reduction in LDL-C decreases major CV events by:

- A. 10%
- B. 23%
- C. 30%
- D. 36%

In meta-analyses, a 40 mg/dL reduction in LDL-C decreases major CV events by:

- A. 10%
- **B. 23%**
- C. 30%
- D. 36%

ARS Question 2

Which statement is true about the PCSK9 protein?

- A. The protein is produced in the LDL particle
- B. Overactivity mutations lead to low LDL levels in the blood
- C. Binding of PCSK9 to LDL receptors causes receptor degradation
- D. Genetic mutations of PCSK9 have not been found

Which statement is true about the PCSK9 protein?

- A. The protein is produced in the LDL particle
- B. Overactivity mutations lead to low LDL levels in the blood
- **C. Binding of PCSK9 to LDL receptors causes receptor degradation**
- D. Genetic mutations of PCSK9 have not been found

Is there incremental risk reduction from add-on therapy to optimal statin use?

- ***Completed trials:***

  ACCORD: T2DM; statin vs statin + fenofibrate

  AIM HIGH and HPS 2 THRIVE: statin vs ER niacin or ERN/ laropiprant

- ***Trials in progress:*** IMPROVE IT: Post ACS; statin vs statin + ezetimibe

  CETPi + statin vs statin (REVEAL, ACCELERATE)

  EPA omega-3 + statin vs statin (REDUCE IT)

  Anti-PCSK9 + statin vs statin (ODYSSEY, FOURIER)

Background : Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)

- 9th member of family of secretory serine proteases; involved specifically in degradation of LDL Receptor
- Loss of function mutations are associated with lifelong low LDL-C levels and decreased risk of cardiovascular disease
- Gain of function mutations are associated with lifelong high LDL-C levels and increased risk of cardiovascular disease

Inclusion criteria: FOURIER TRIAL

- **Clinical ASCVD and at least 1 major risk factor**

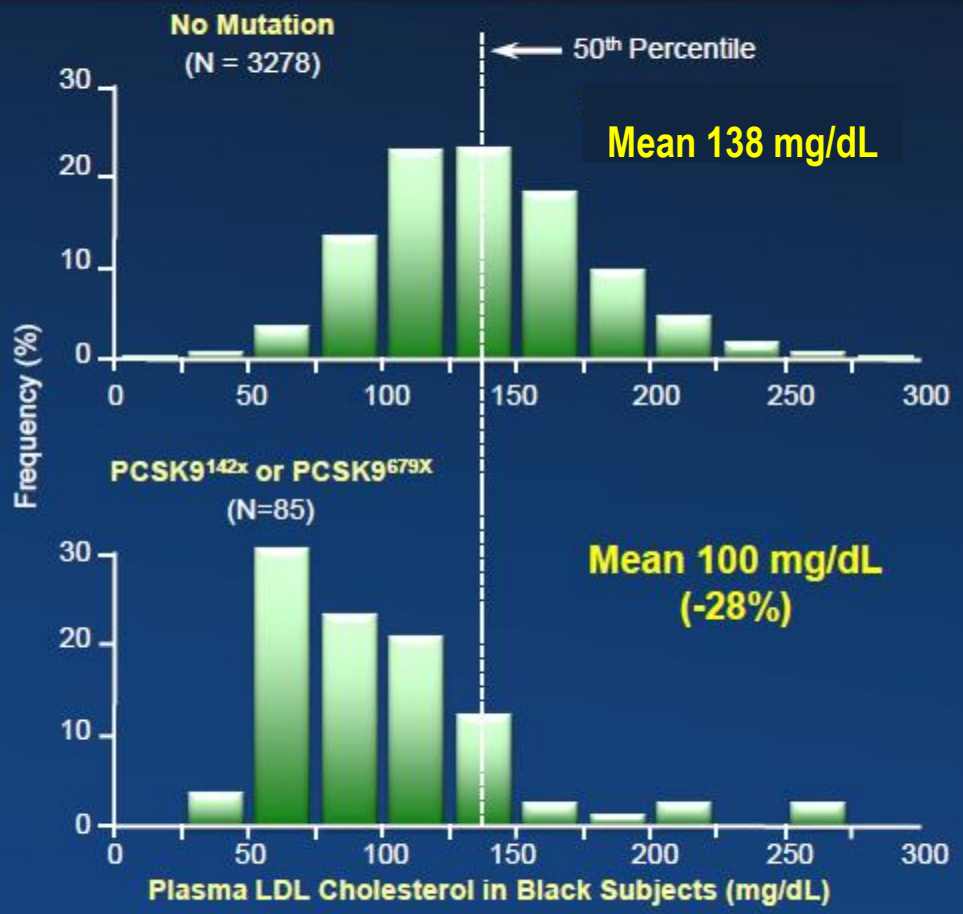
(age > 65 years, prior MI or non-hemorrhagic stroke, current cigarette smoking, symptomatic PAD with prior MI or stroke)

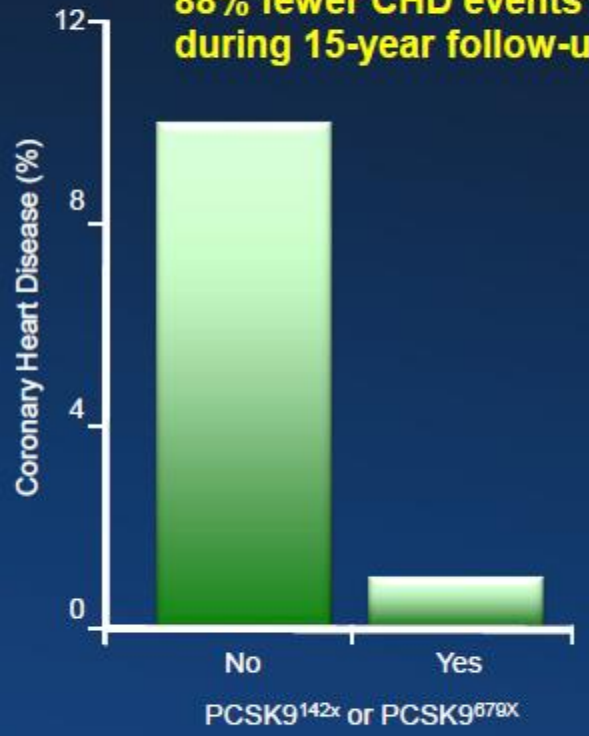
OR

- **2 minor risk factors**

(history of non-MI-related coronary revascularization, residual coronary artery disease with $40% stenosis in >2 large vessels, HDL-C <40 mg/dL for men and <50 mg/dL for women, hs-CRP >2 mg/L, or metabolic syndrome)

Loss-of-Function PCSK9 Mutations in AA Are Associated with Low LDL-C and Low Prevalence of CHD Events





Cohen JC. *NEJM*. 2006;354:1264-1267.

Mutations were associated with a 28 percent reduction in mean LDL cholesterol and an 88 percent reduction in the risk of CHD