FOURIER

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

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for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
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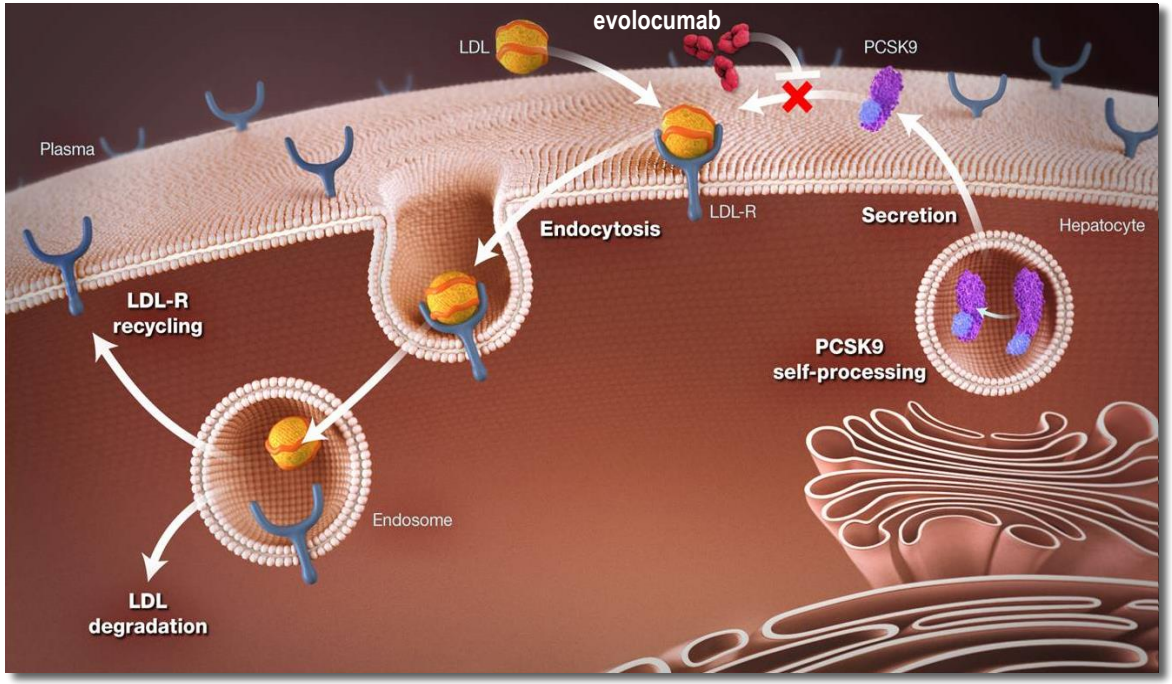
An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Background

Proprotein convertase subtilisin/kexin type 9 (PCSK9)

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



Evolocumab

- Fully human anti-PCSK9 mAb
- ~60% ↓ LDL-C
- Safe & well-tolerated in Ph 2 & 3 studies
- Exploratory data suggested ↓ CV events

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

Objectives

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 Organization

Executive Committee

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TIMI Study Group

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Independent Data Monitoring Committee

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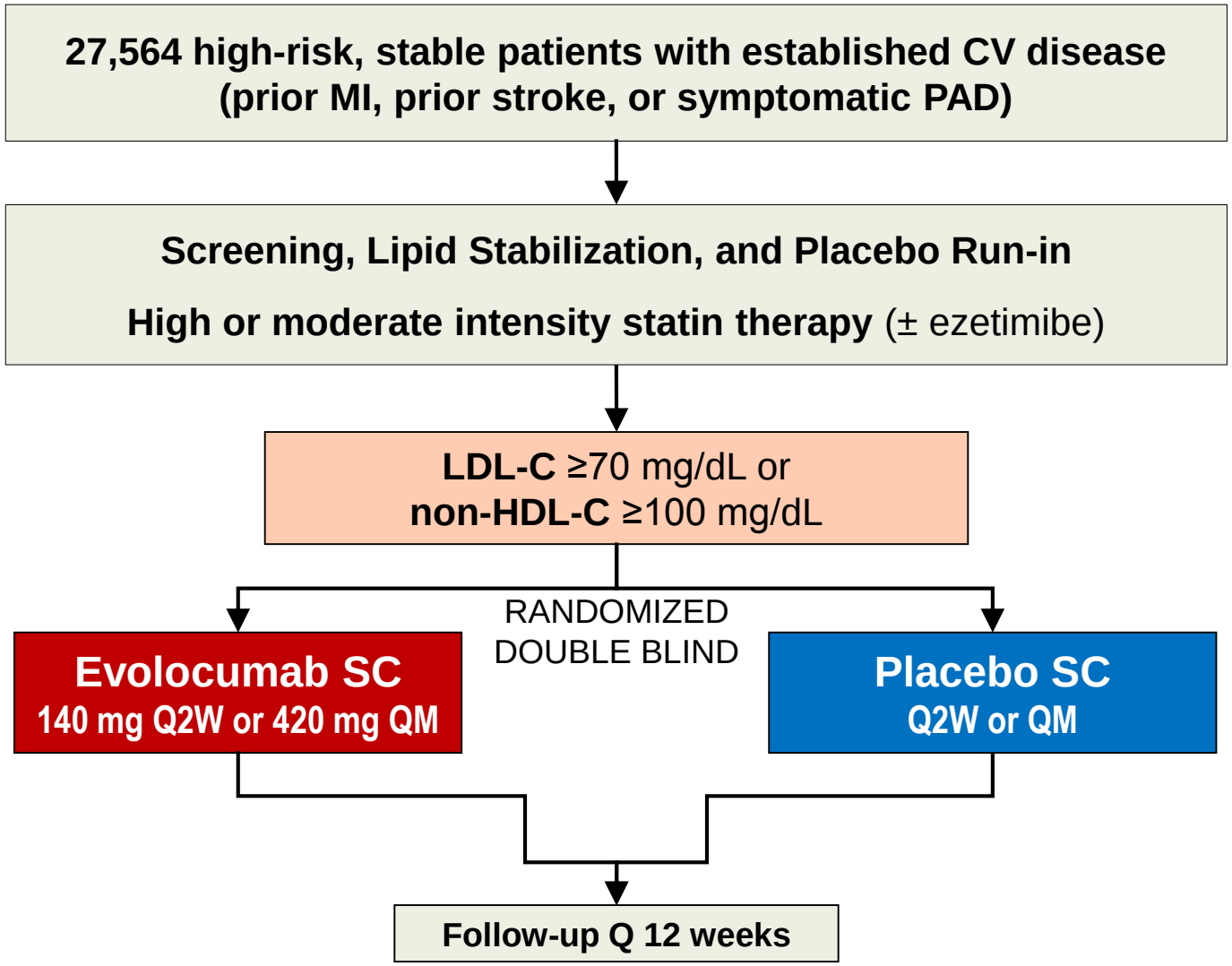
W. Virgil Brown — Barry R. Davis — John W. Newcomer
Sarah K. Wood

Lipid Monitoring Committee

John LaRosa (Chair) — Benjamin Ansell — Anders Olsson

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

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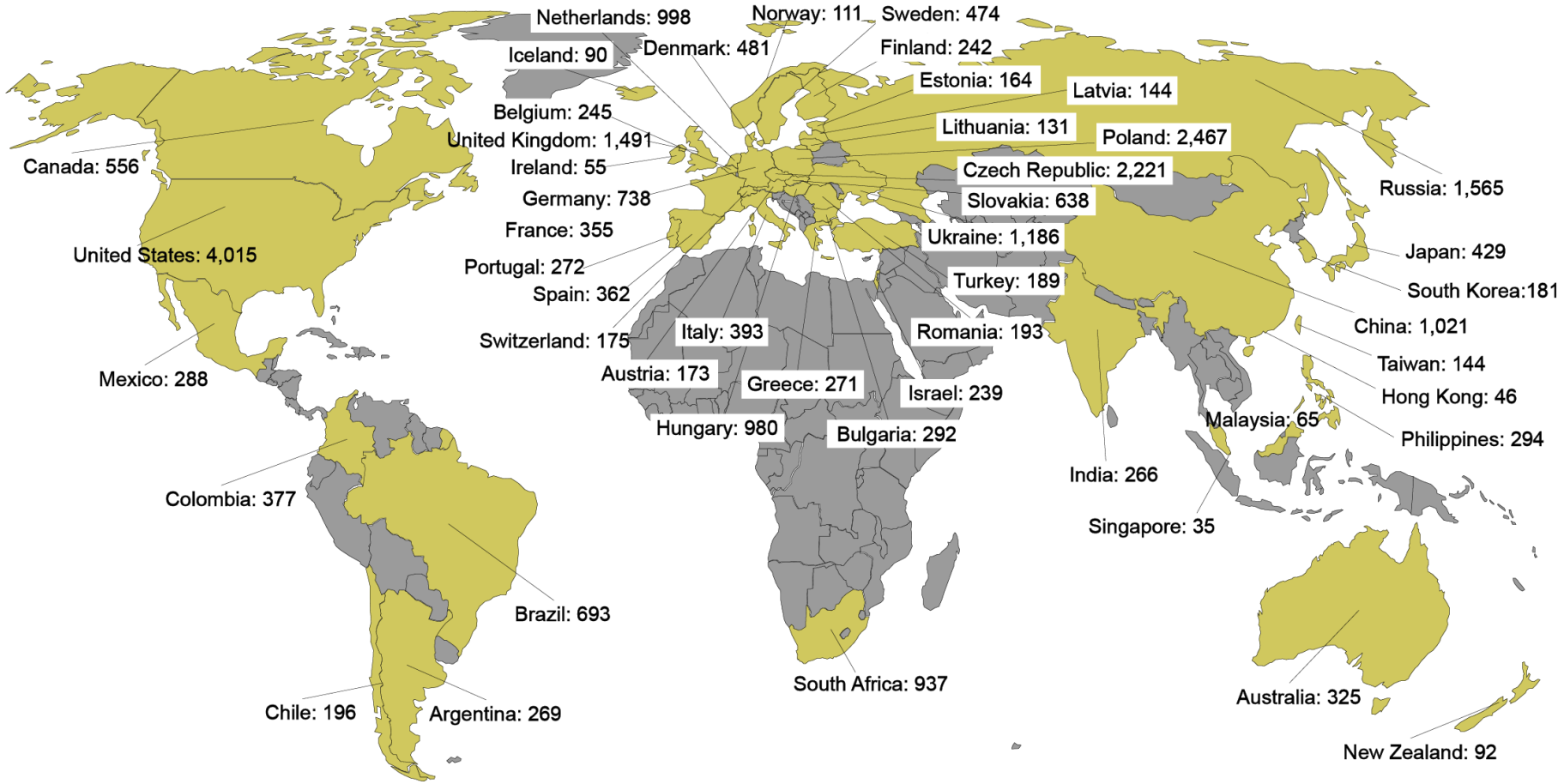
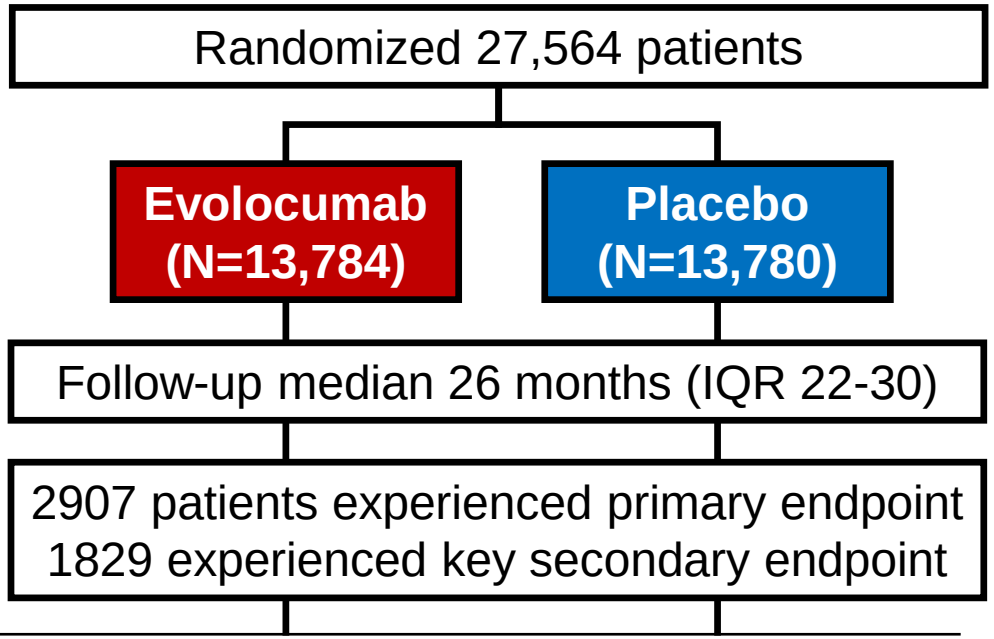
Global Enrollment

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

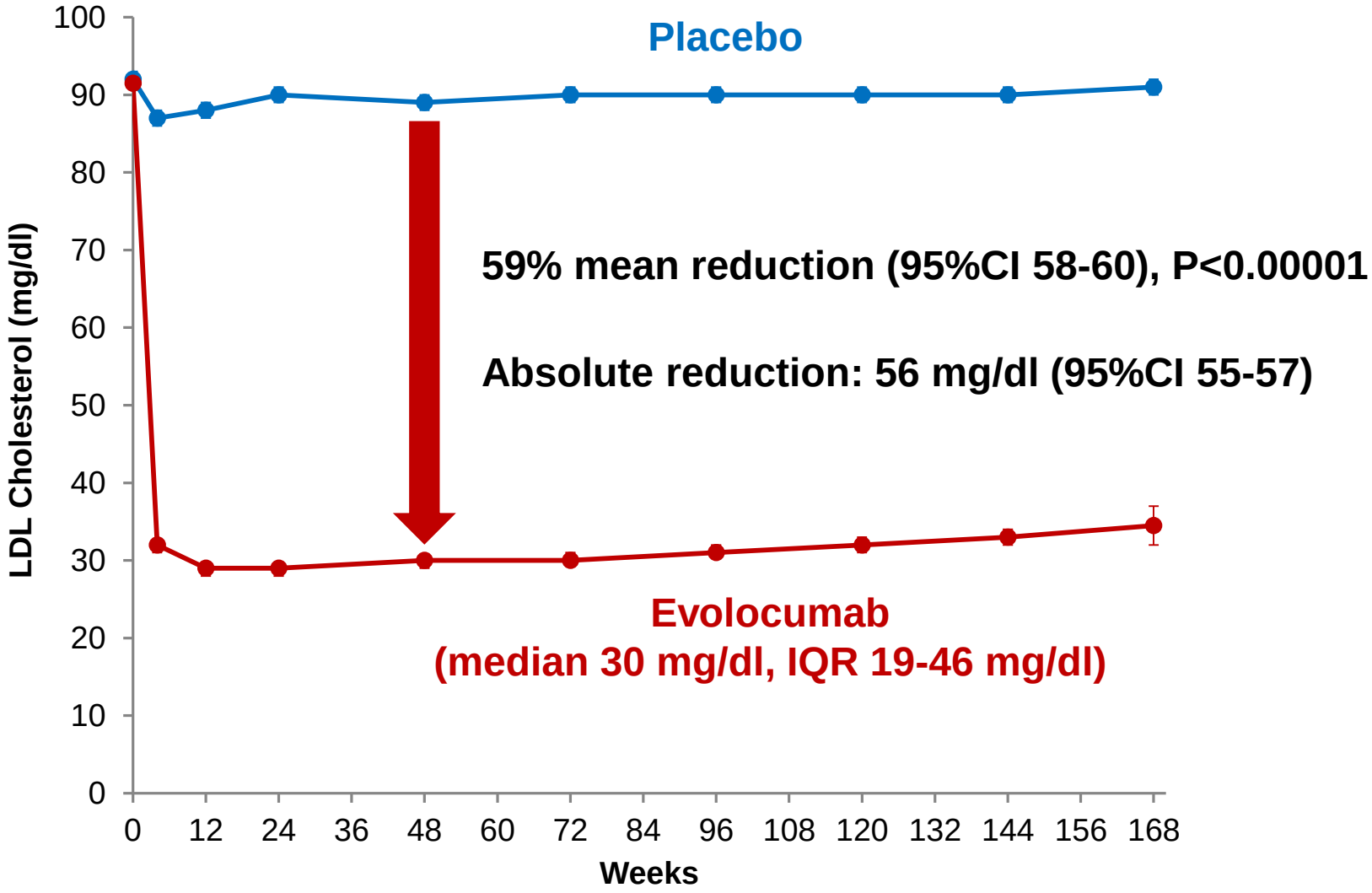
Lipid Lowering Therapy & Lipid Levels at Baseline

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)**
Triglycerides	**133 (100-182)**

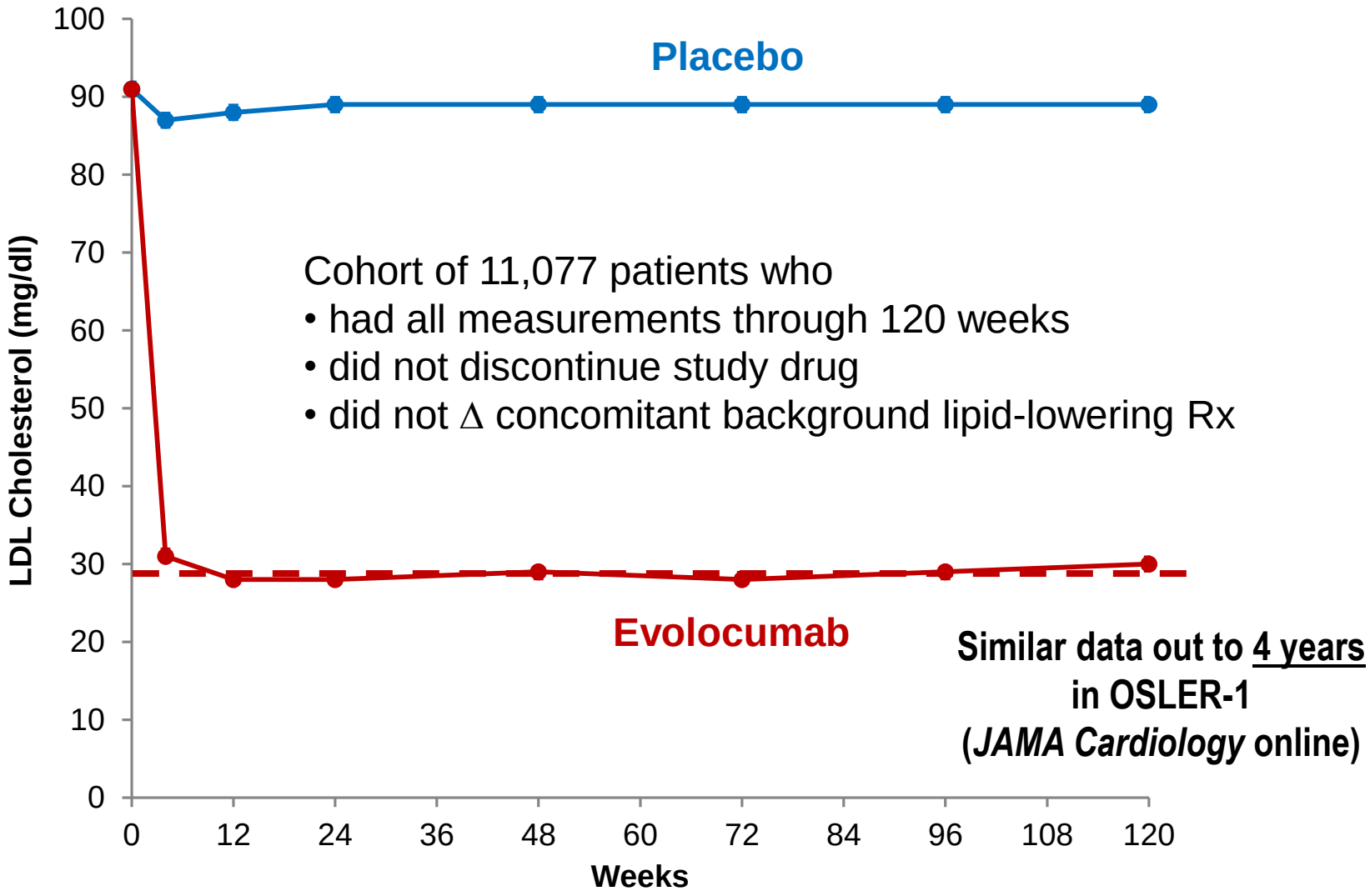
*Per protocol, patients were to be on atorva ≥20 mg/d or equivalent.
1% were on low intensity or intensity data were missing.
Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines.

Pooled data; no differences between treatment arms

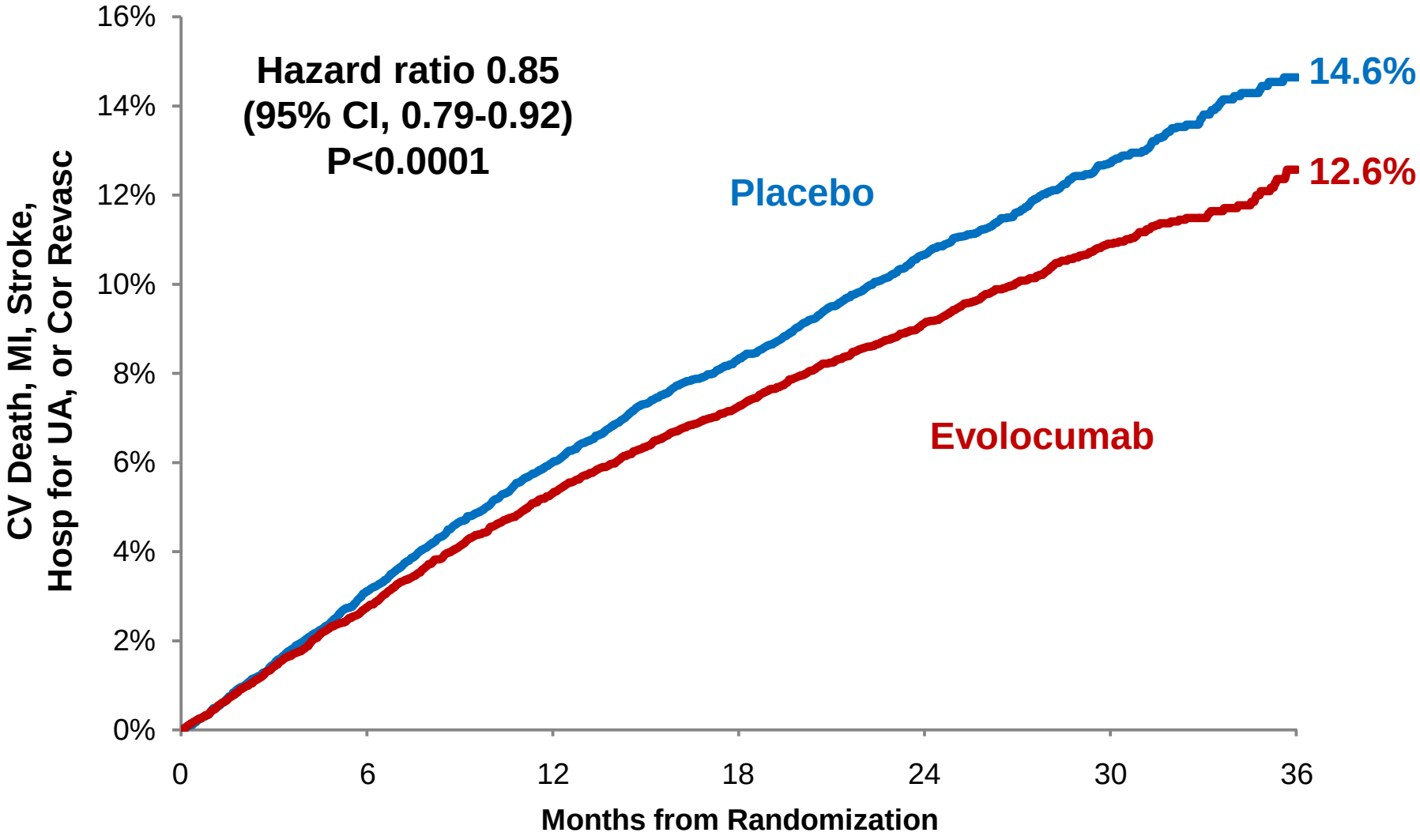
LDL Cholesterol



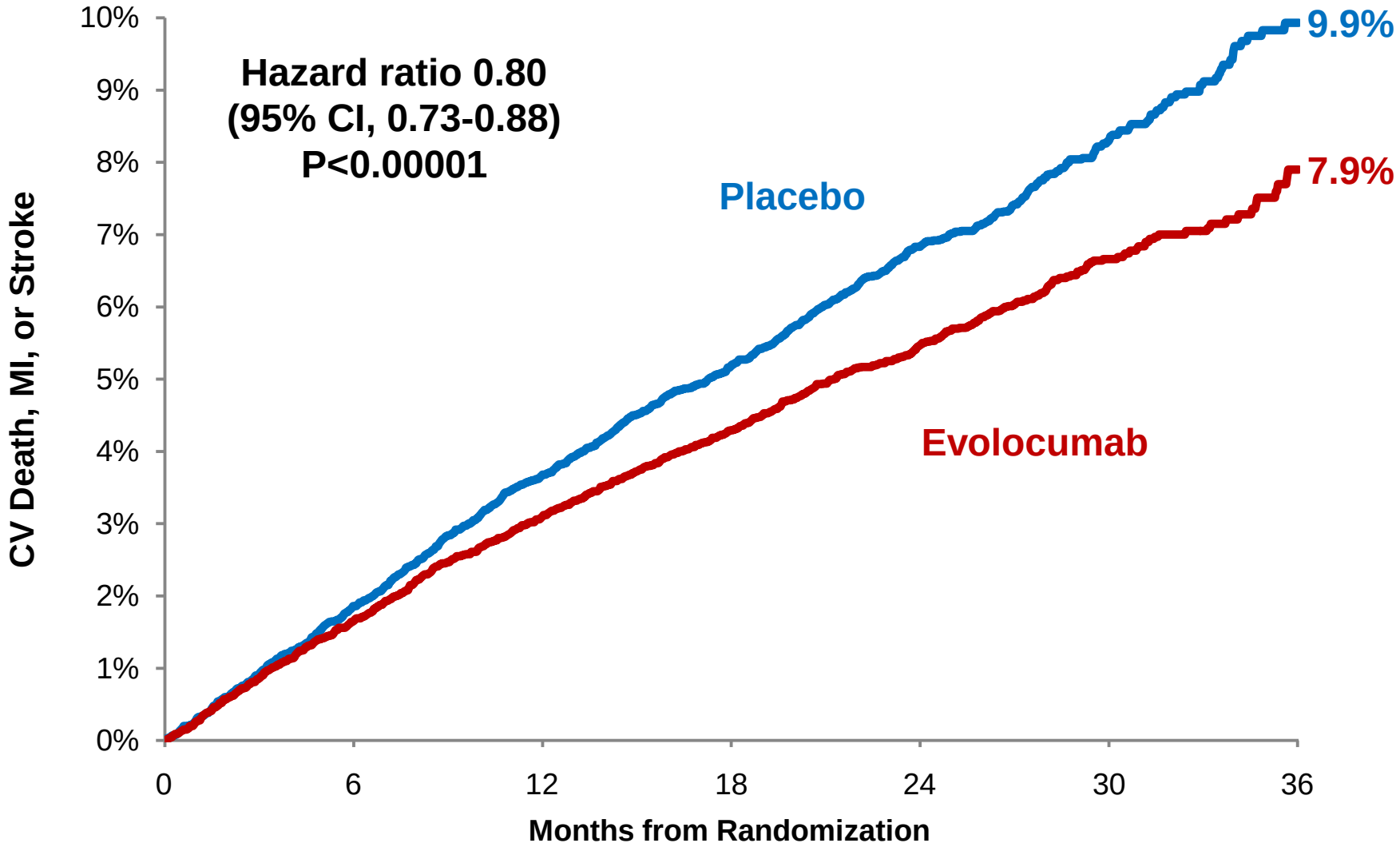
LDL Cholesterol



Primary Endpoint



Key Secondary Endpoint



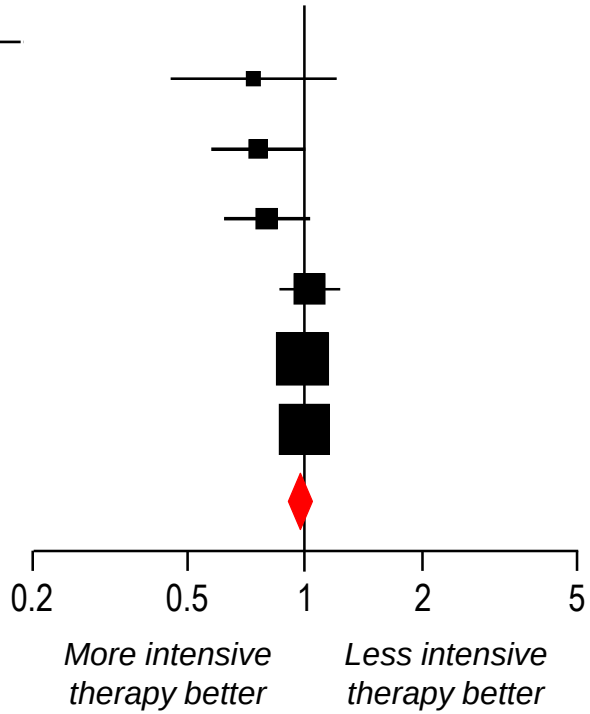
Types of CV Outcomes

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)**



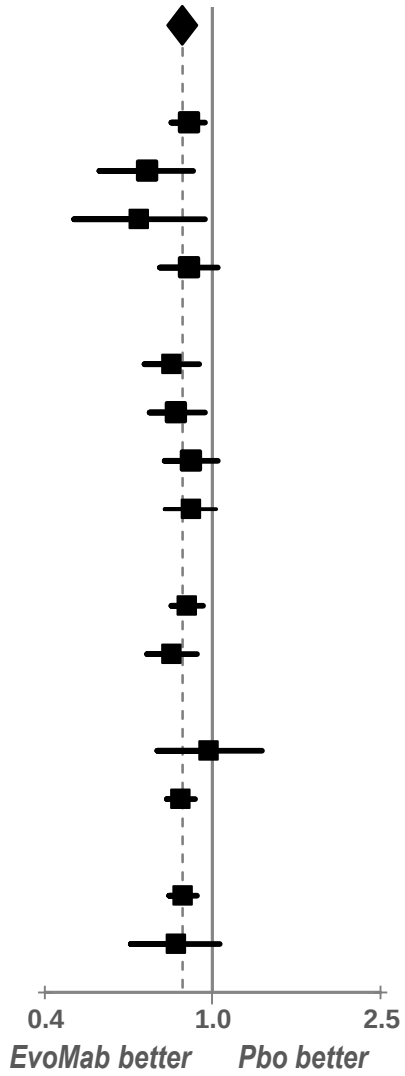
NEJM 2004;350:1495-504
JAMA 2004;292:1307-16
NEJM 2005;352:1425-35
JAMA 2005;294:2437-45
Lancet 2010;376:1658-69
NEJM 2015;372:2387-97

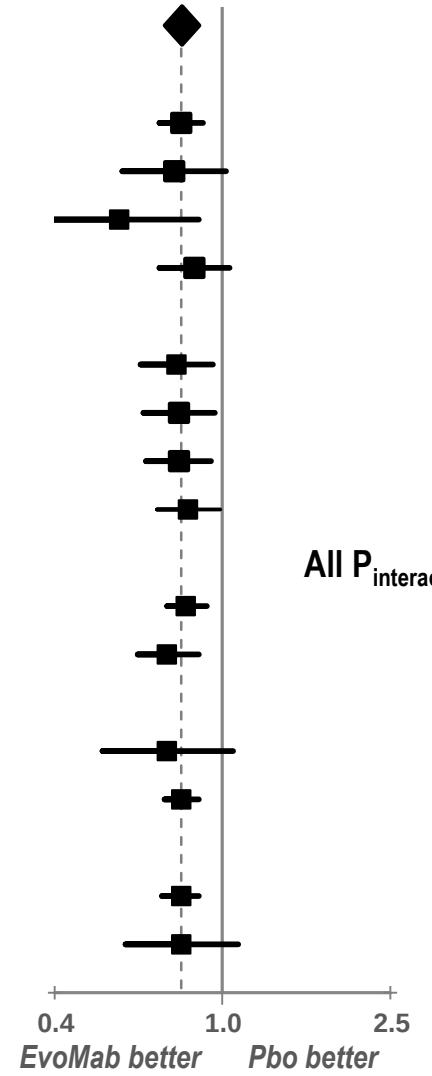
Types of CV Outcomes

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

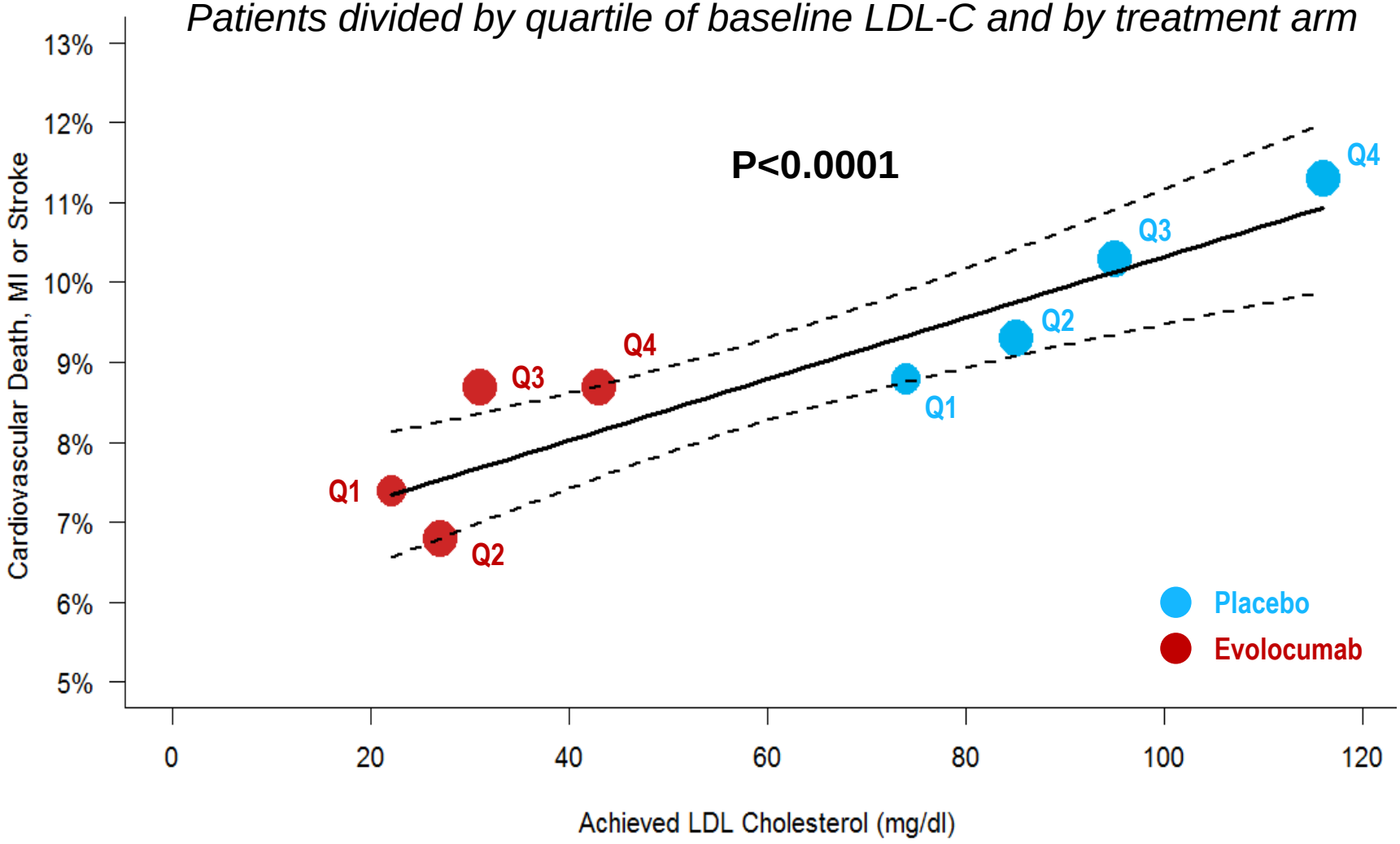




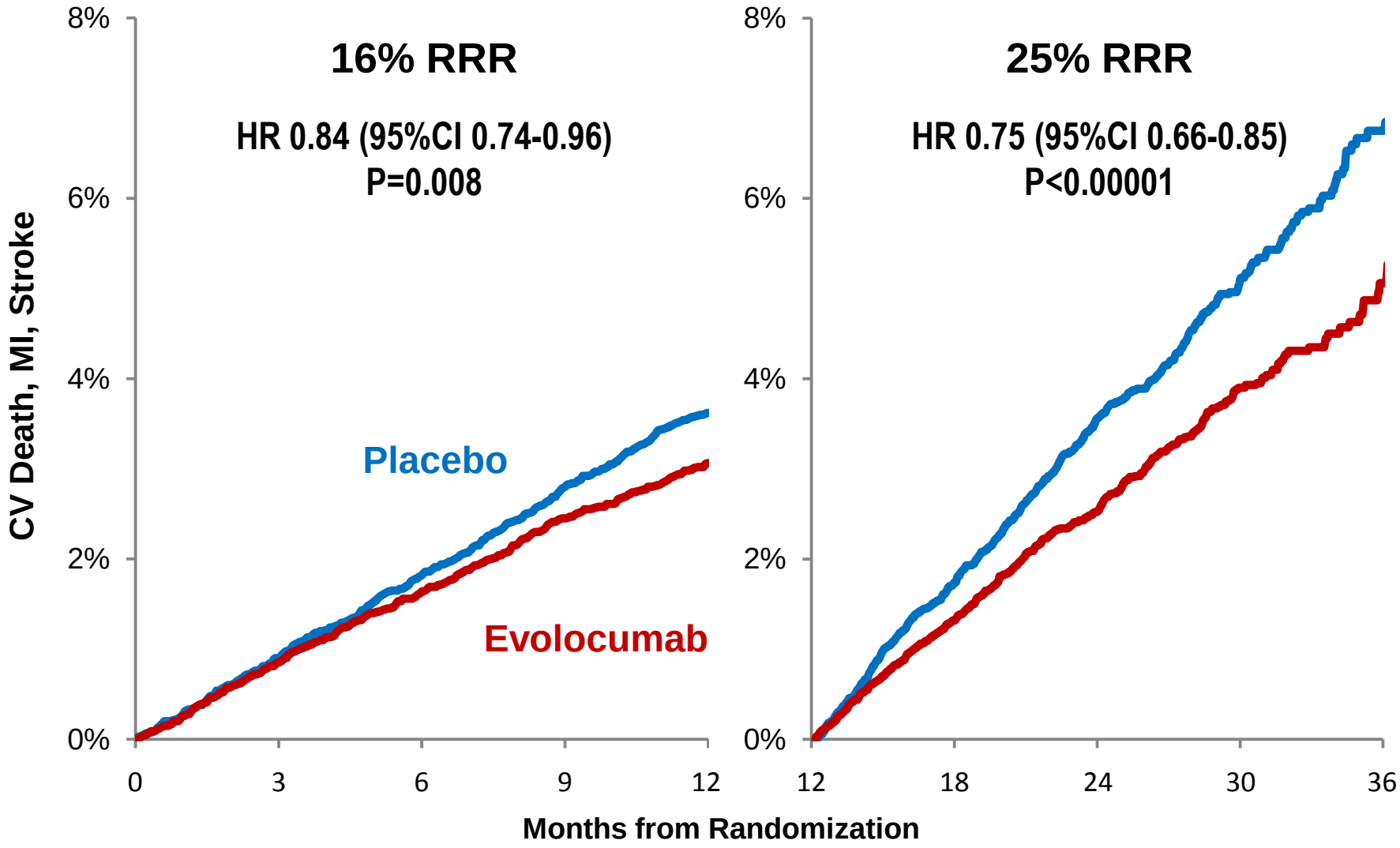
All $P_{interactions}$ NS

Lower LDL-C Is Better

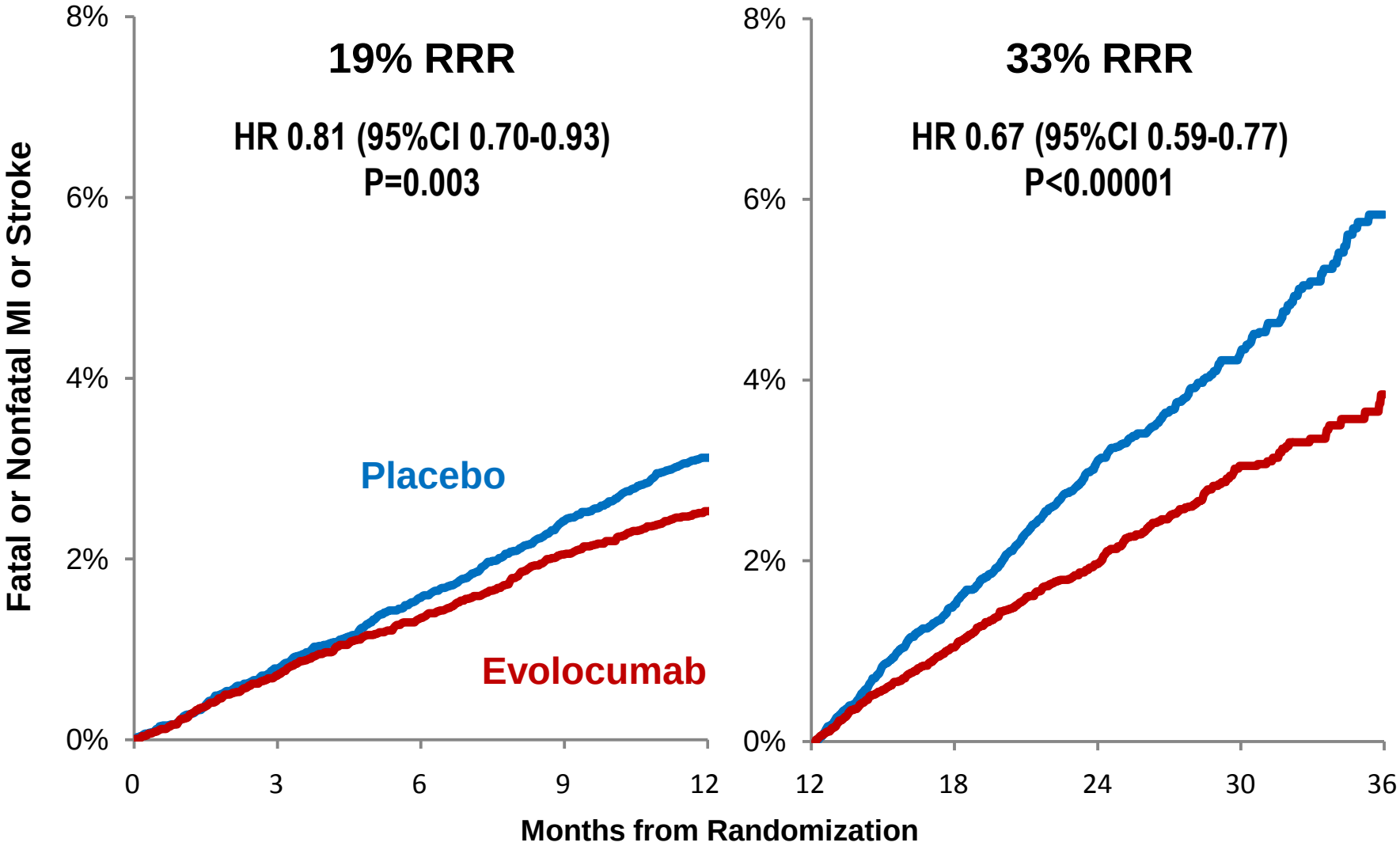
Patients divided by quartile of baseline LDL-C and by treatment arm



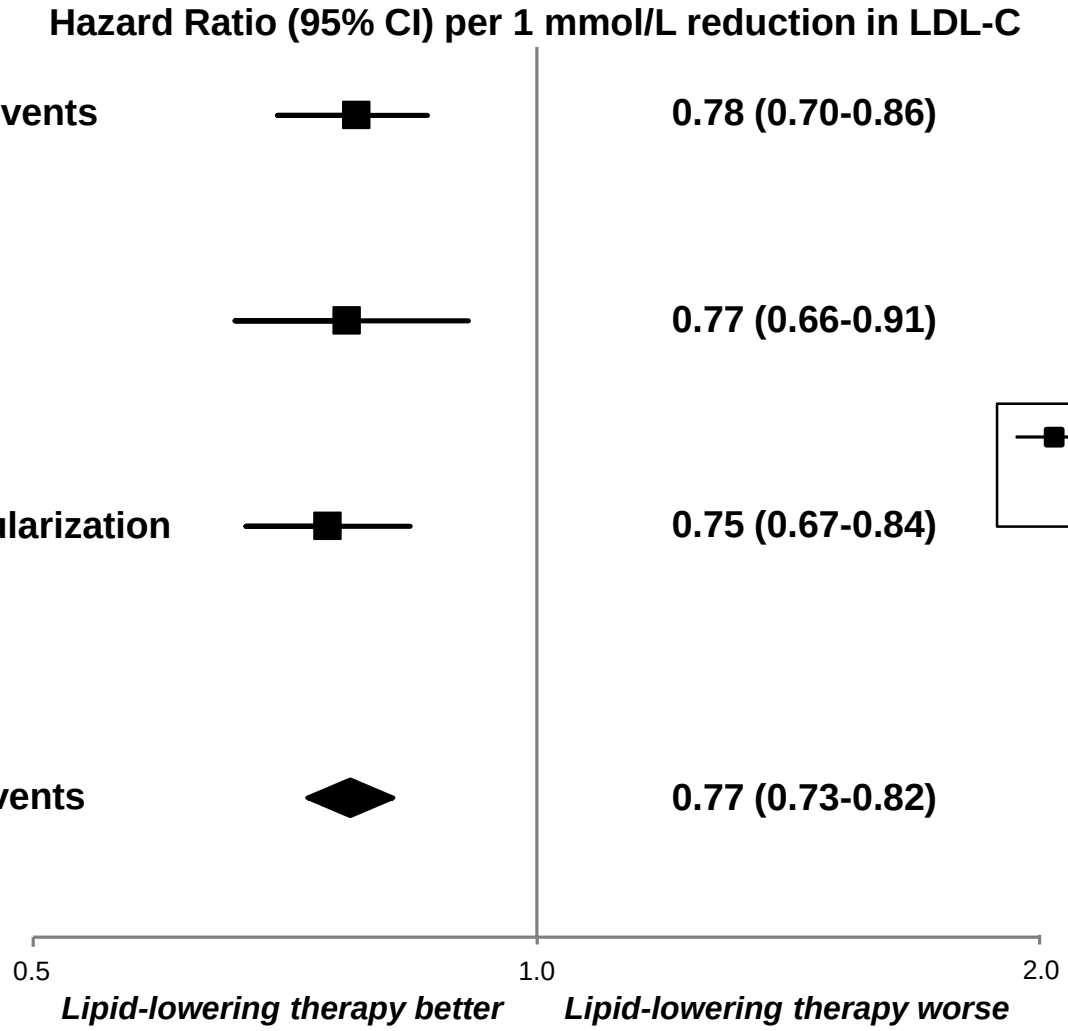
Landmark Analysis



Fatal or Nonfatal MI or Stroke

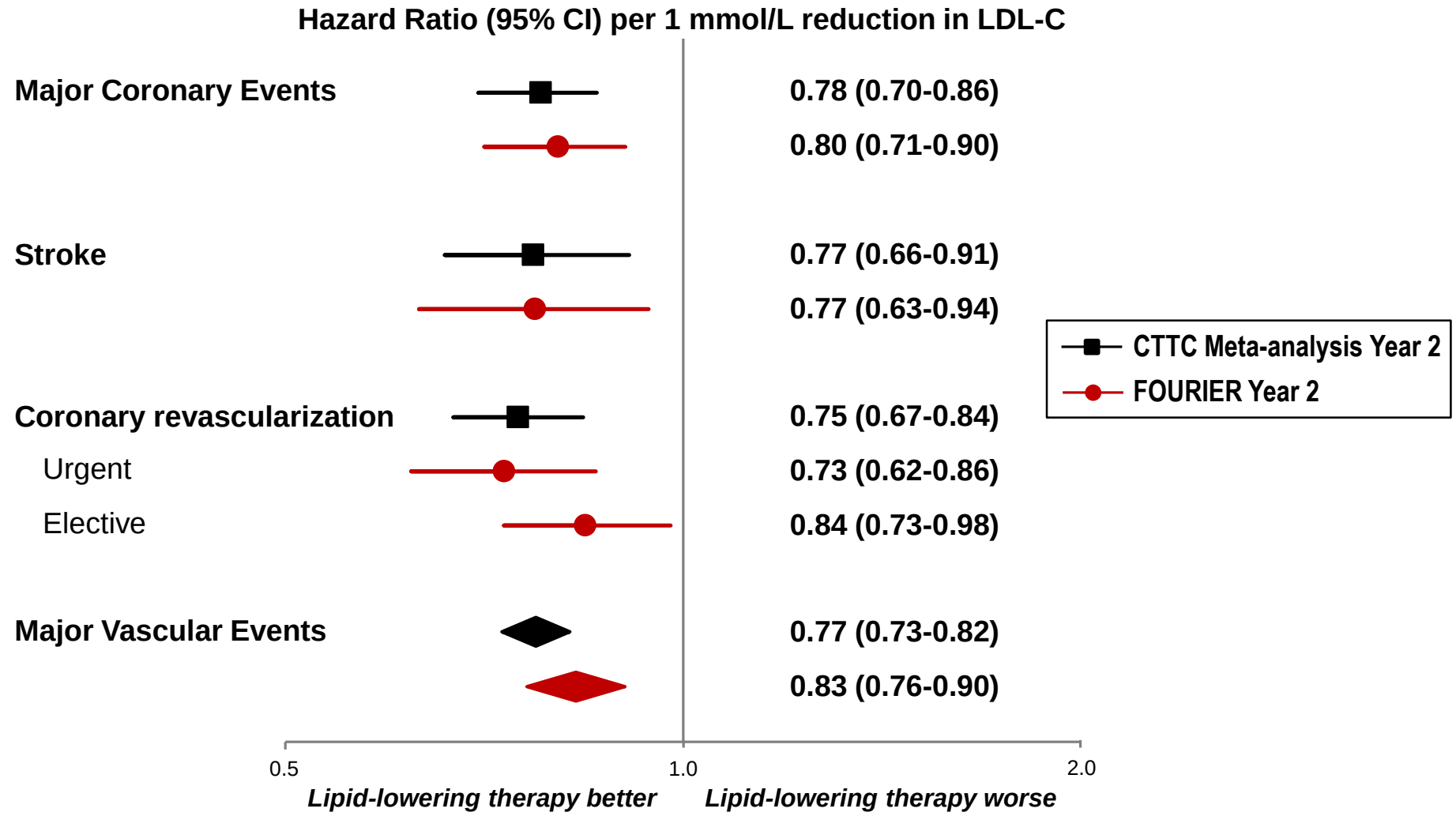


Comparison to Cholesterol Treatment Trialists Collaboration



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**

Further Details

The NEW ENGLAND JOURNAL of MEDICINE

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

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