UNIVERSITY OF OTTAWA
HEART INSTITUTE
INSTITUT DE CARDIOLOGIE
DE L'UNIVERSITÉ D'OTTAWA

PCSK9 Inhibitors: Forging the New Frontier

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5th International Ottawa Heart Conference

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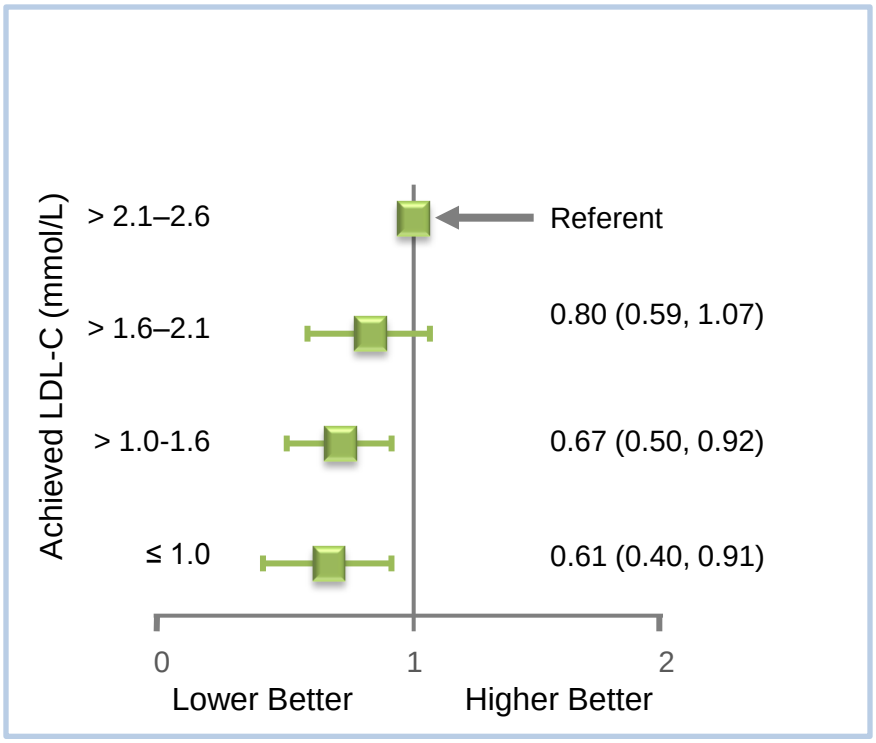
Faculty/Presenter Disclosure

- **Faculty:** Ruth McPherson

- **Relationships with commercial interests:**
  - **Grants/Research Support:** Sanofi Regeneron, Pfizer
  - **Speakers Bureau/Honoraria:** Amgen, Sanofi
  - **Consulting Fees:** None
  - **Other:** None

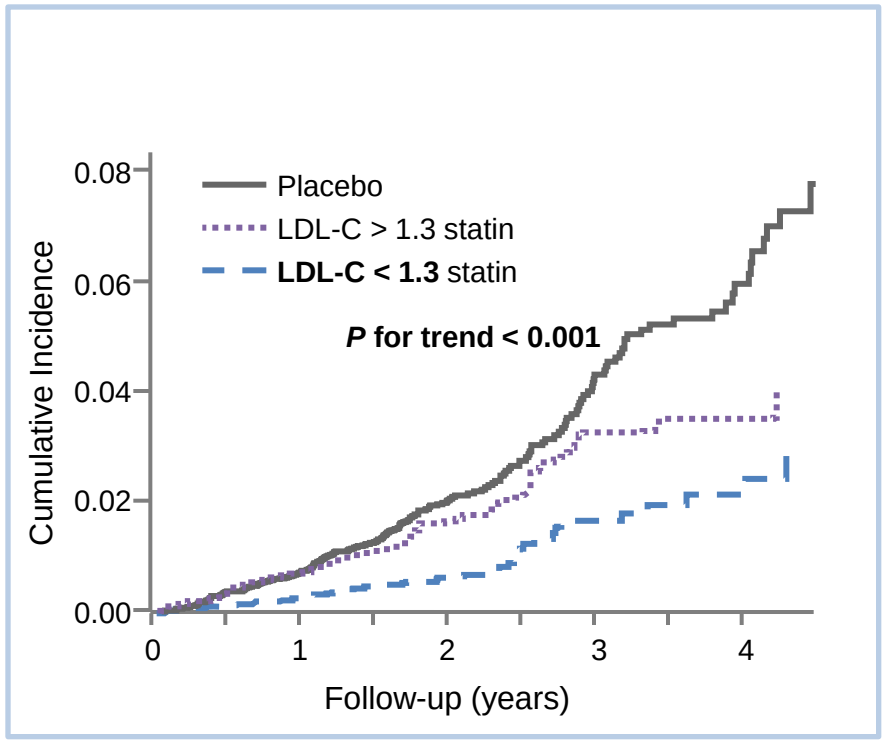
Lower is better

PROVE-IT



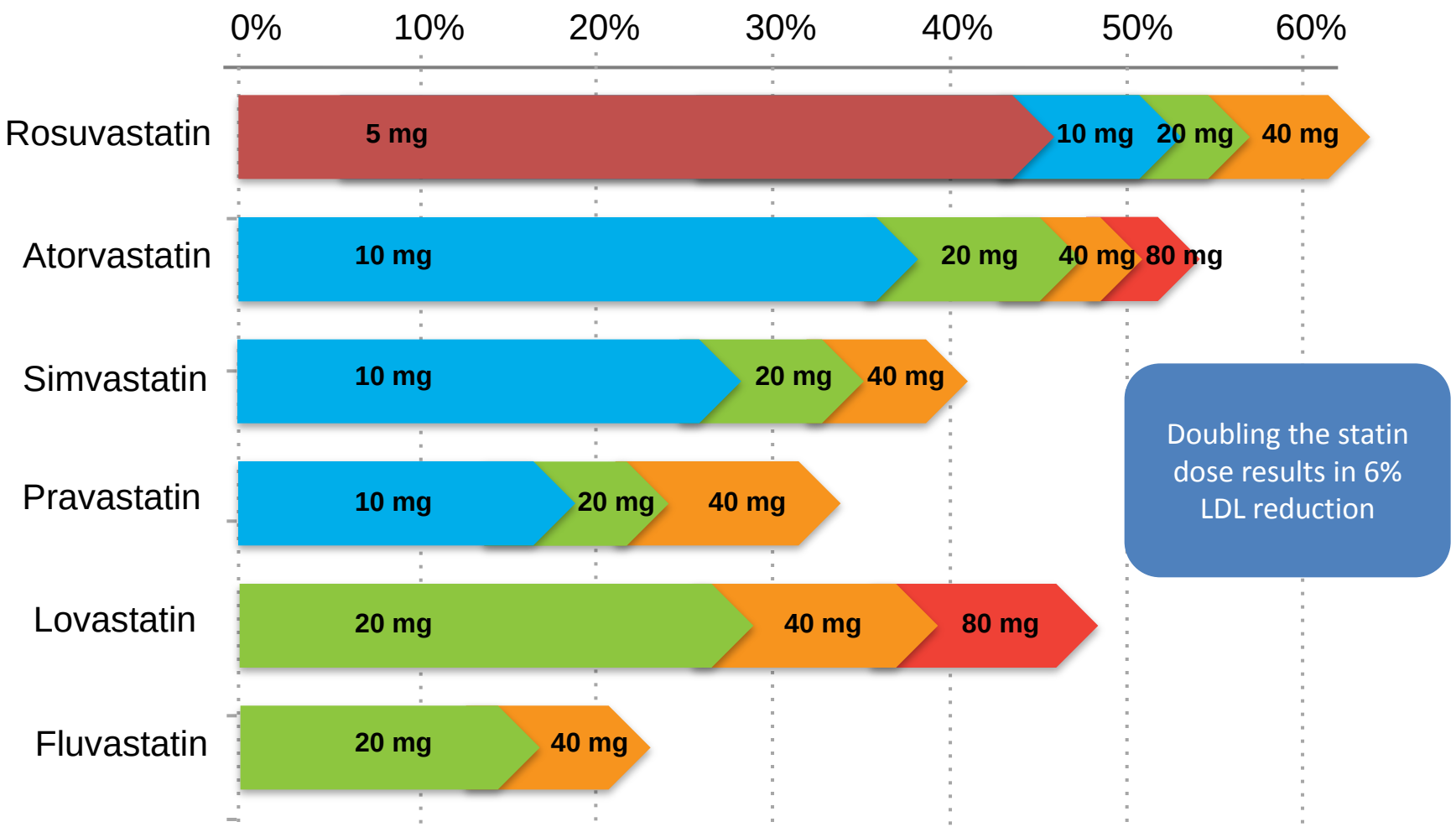
Hazard Ratio of Primary End Point Compared With Achieved LDL-C 2.1-2.6 mmol/L

JUPITER



Time to Occurrence of Major CV Events According to Treatment Group and Achieved LDL-C Concentrations

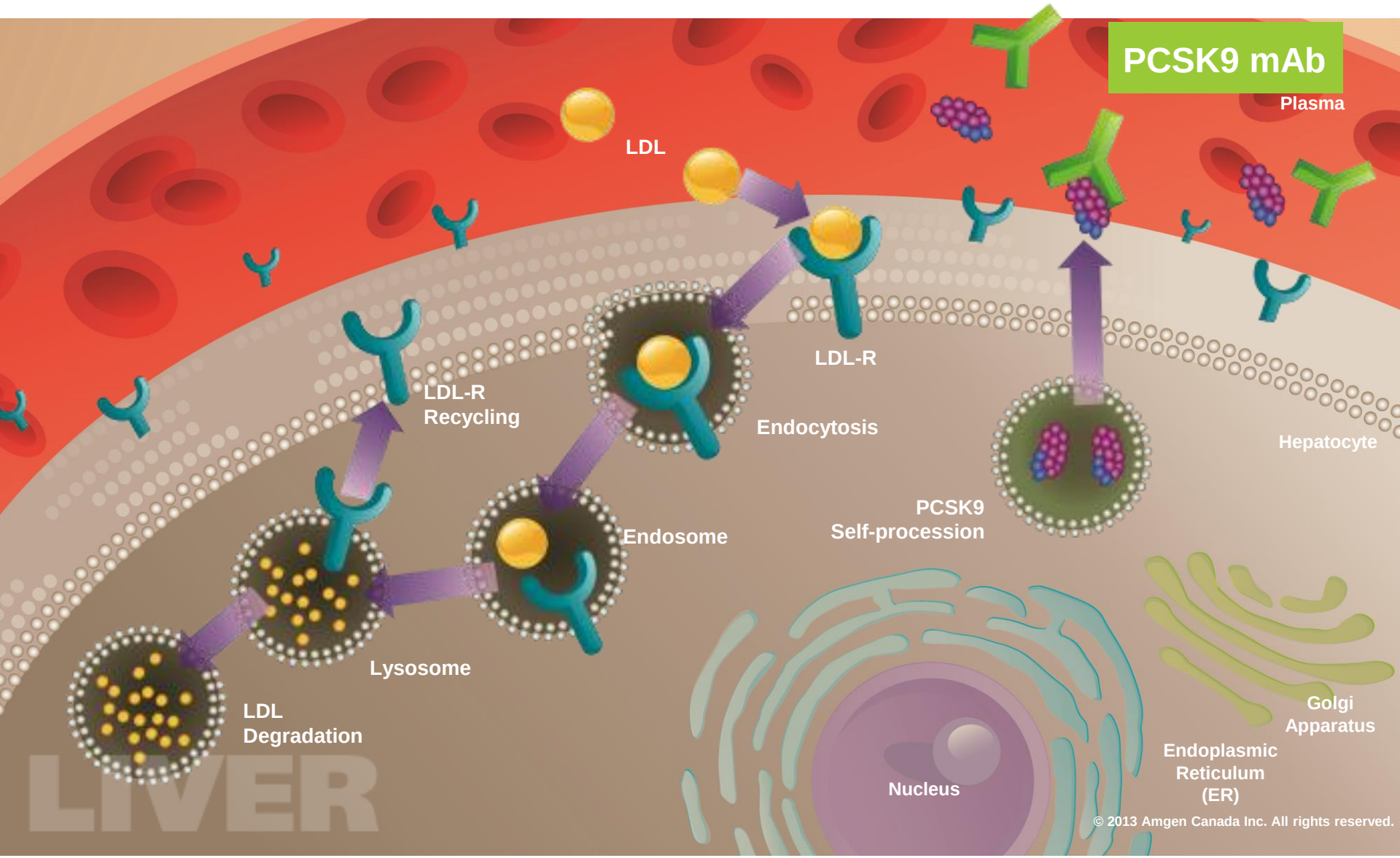
Statin Monotherapy: LDL-C ↓ 20-60%



PCSK9 Inhibitors: Targeted Therapy

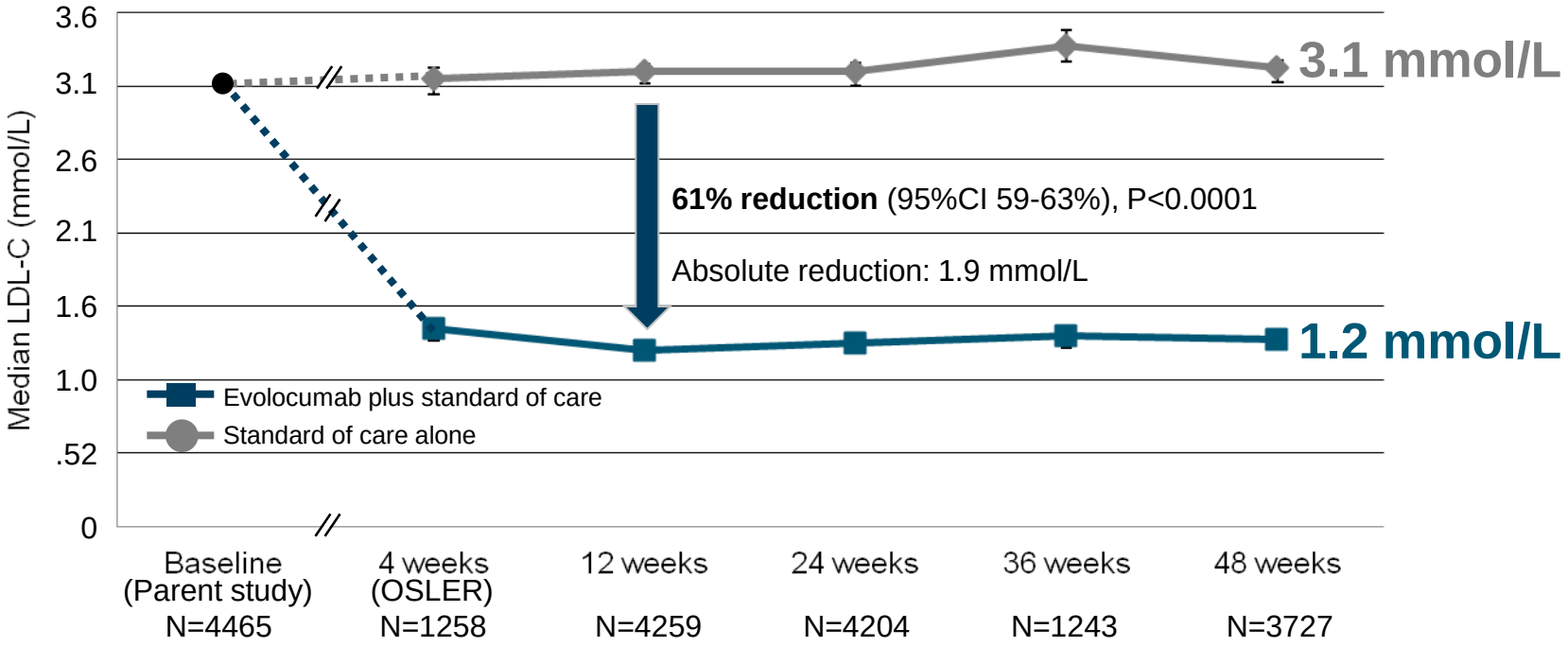
Monoclonal Antibody binds to PCSK9 and inhibits Binding to the LDL Receptor

Blocking PCSK9 Activity Inhibits Intracellular Degradation of LDL-R



Qian YW, et al. J Lipid Res. 2007;48:1488-1498; Horton JD, et al. J Lipid Res. 2009;50(suppl):S172-S177.

OSLER: Evolocumab Plus Standard of Care Achieved a 61% Reduction in LDL-C over Standard of Care at 12 Weeks



Sabatine MS, et al. N Engl J Med. 2015;372(16):1500-9.

AMGEN

The NEW ENGLAND JOURNAL of MEDICINE

GLAGOV: Objective

Objective

- To test the hypothesis that LDL-C lowering with a monthly subcutaneous injection of evolocumab 420 mg for 78 weeks will result in a significantly greater change from baseline in percentage atheroma volume (PAV) compared with placebo in subjects taking background statin therapy

Design

- A 78-week, randomized, double-blind, placebo-controlled, multicenter, phase 3 study.

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.
Puri R, et al. *Am Heart J*. 2016;176:83-92.

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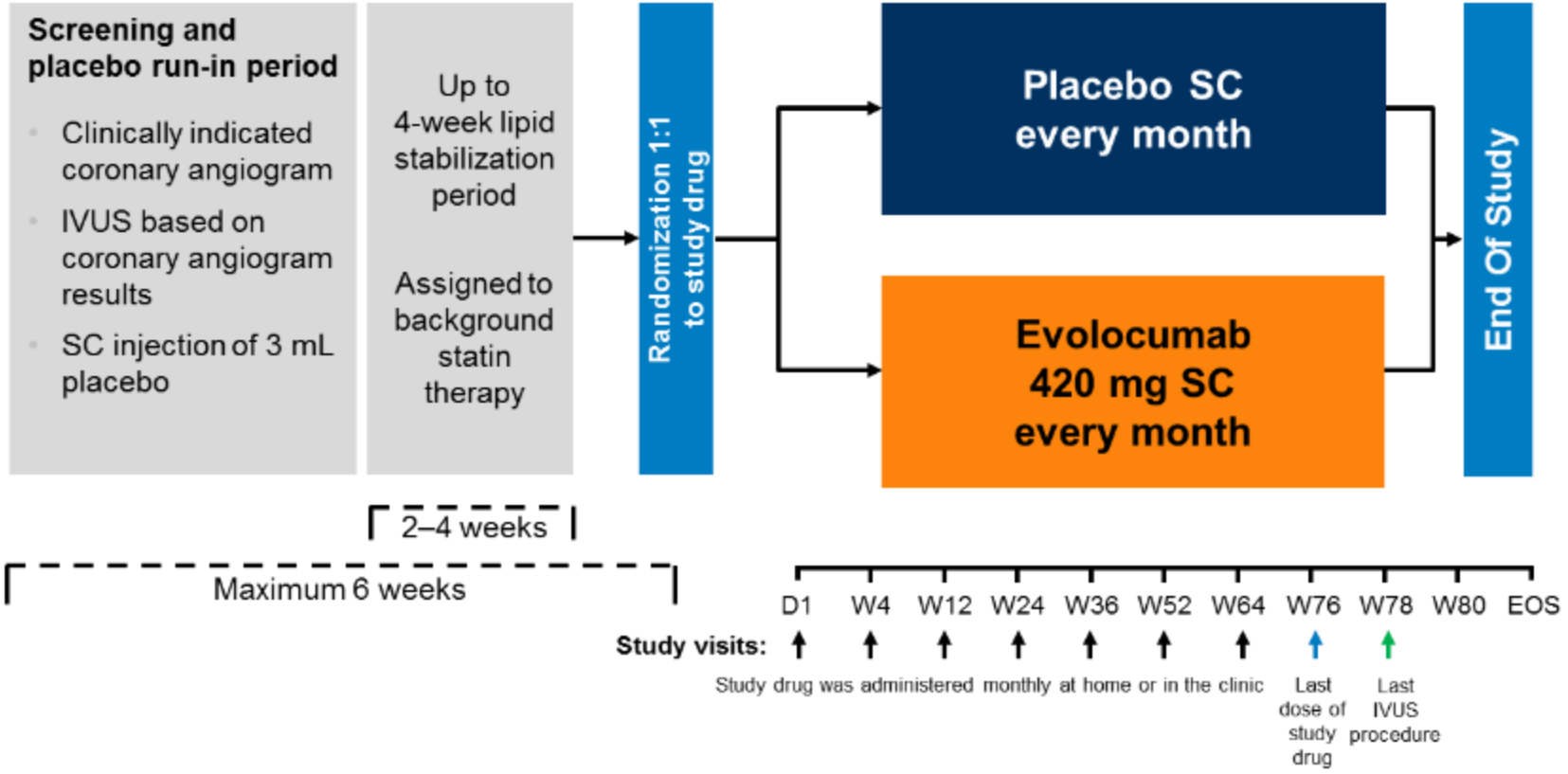
GLAGOV: Study Design



*Nominal change refers to the actual number, as opposed to percent change
D = day; IVUS = intravascular ultrasound; SC = subcutaneously; W = week.
Puri R, et al. *Am Heart J*. 2016;176:83-92.

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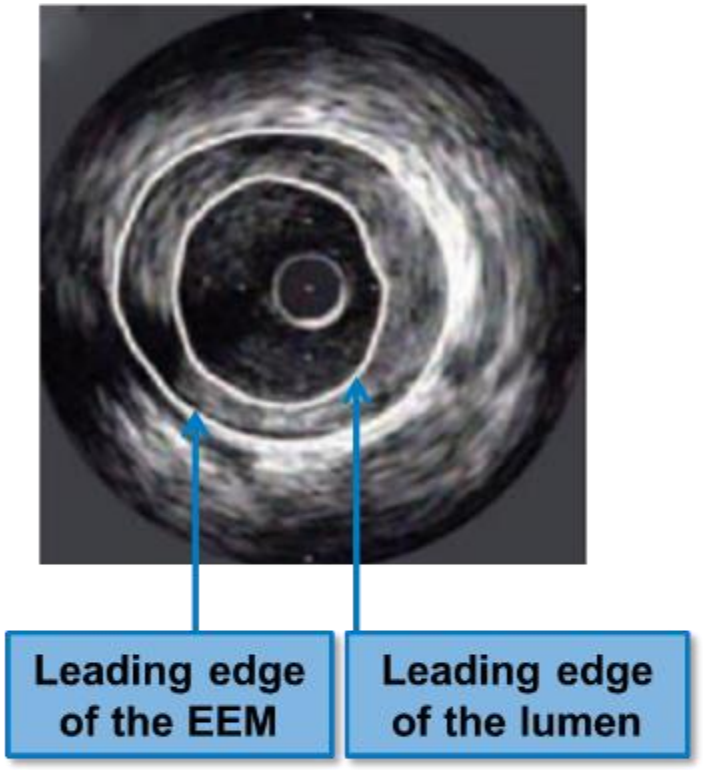
GLAGOV: Analysis of IVUS Imaging

- Plaque area is calculated as the area between the two leading edges
- Two measures of atheroma burden will be calculated for each patient
  - PAV is calculated as the proportion of the EEM volume occupied by atherosclerotic plaque

$$PAV = \frac{\Sigma(EEM_{area} - lumen_{area})}{\Sigma(EEM_{area})} \times 100$$

  - TAV is calculated as the summation of plaque areas in each measured cross-sectional image within the segment and subsequently normalized by the median number of images analyzed in the entire cohort to account for heterogeneity in segment length between subjects

$$TAV_{normalized} = \frac{\Sigma(EEM_{area} - lumen_{area})}{\text{Number of images in pullback}} \times \text{Median number of images in cohort}$$



IVUS = intravascular ultrasound; EEM = external elastic membrane; PAV = percentage atheroma volume; TAV = total atheroma volume.

Puri R, et al. *Am Heart J*. 2016;176:83-92.
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951

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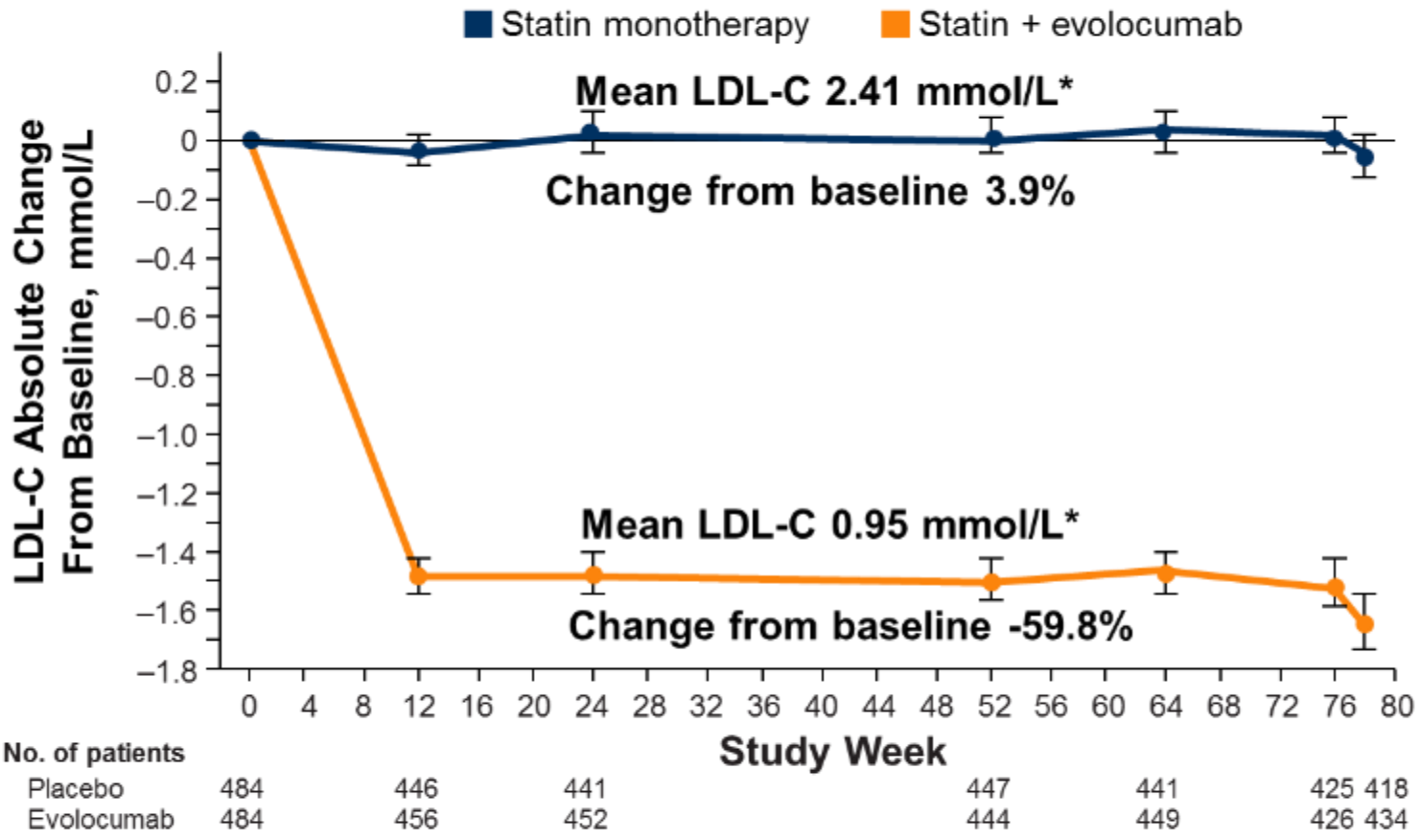
Mean Absolute Change in LDL-C



Absolute change for evolocumab-statin group: -1.46 (-1.54 to -1.38); *P* < 0.001

Data shown are Mean (95% CI) *Time-weighted LDL-C; LDL-C = low-density lipoprotein cholesterol

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Nissen SE, et al. *American Heart Association Scientific Sessions*, Nov 12 - 16, 2016, New Orleans, Louisiana. Oral Presentation.

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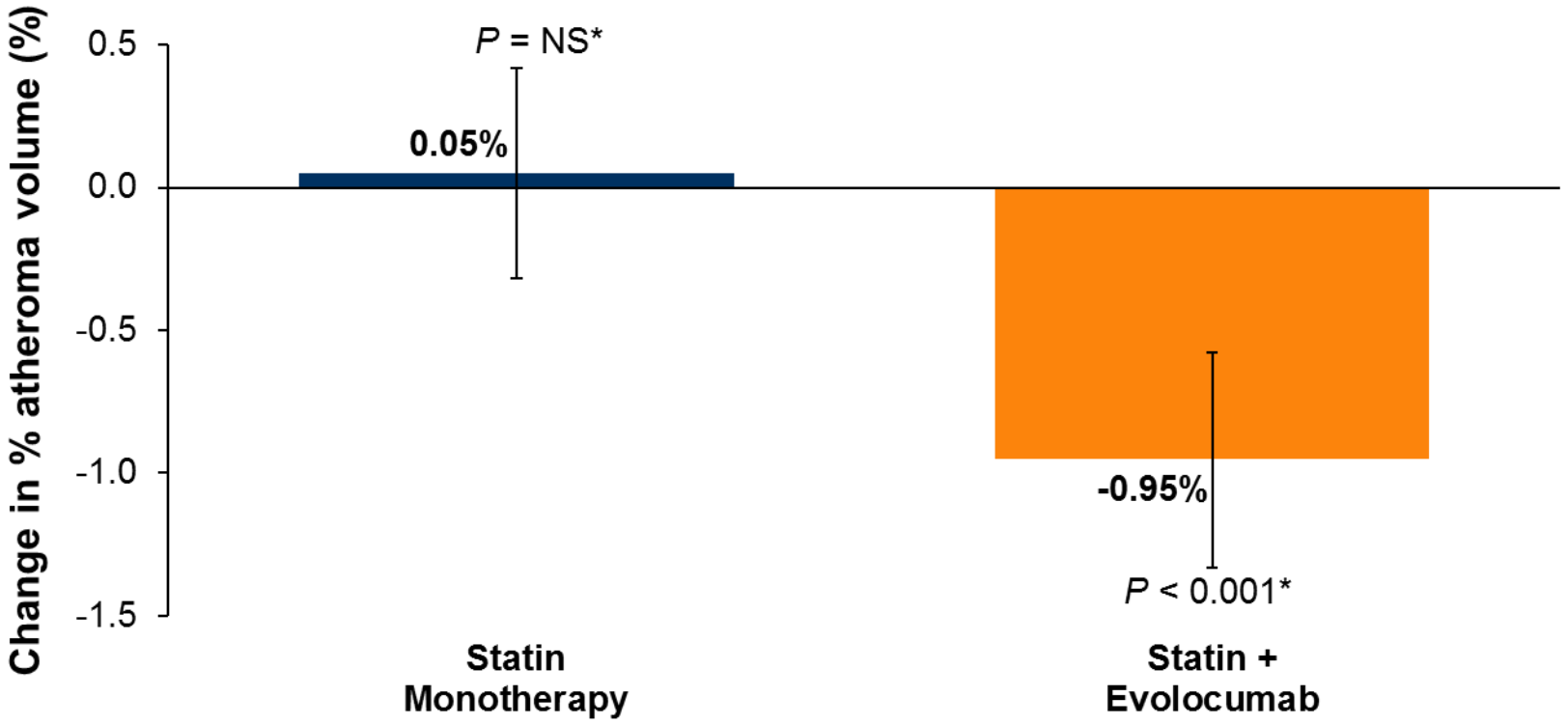
Primary Endpoint: Nominal Change in PAV From Baseline to Week 78



Difference between groups: -1.0% (-1.8 to -0.64); *P* < 0.001

Data shown are least-squares mean (95% CI). PAV = Percent Atheroma Volume
*Comparison versus baseline
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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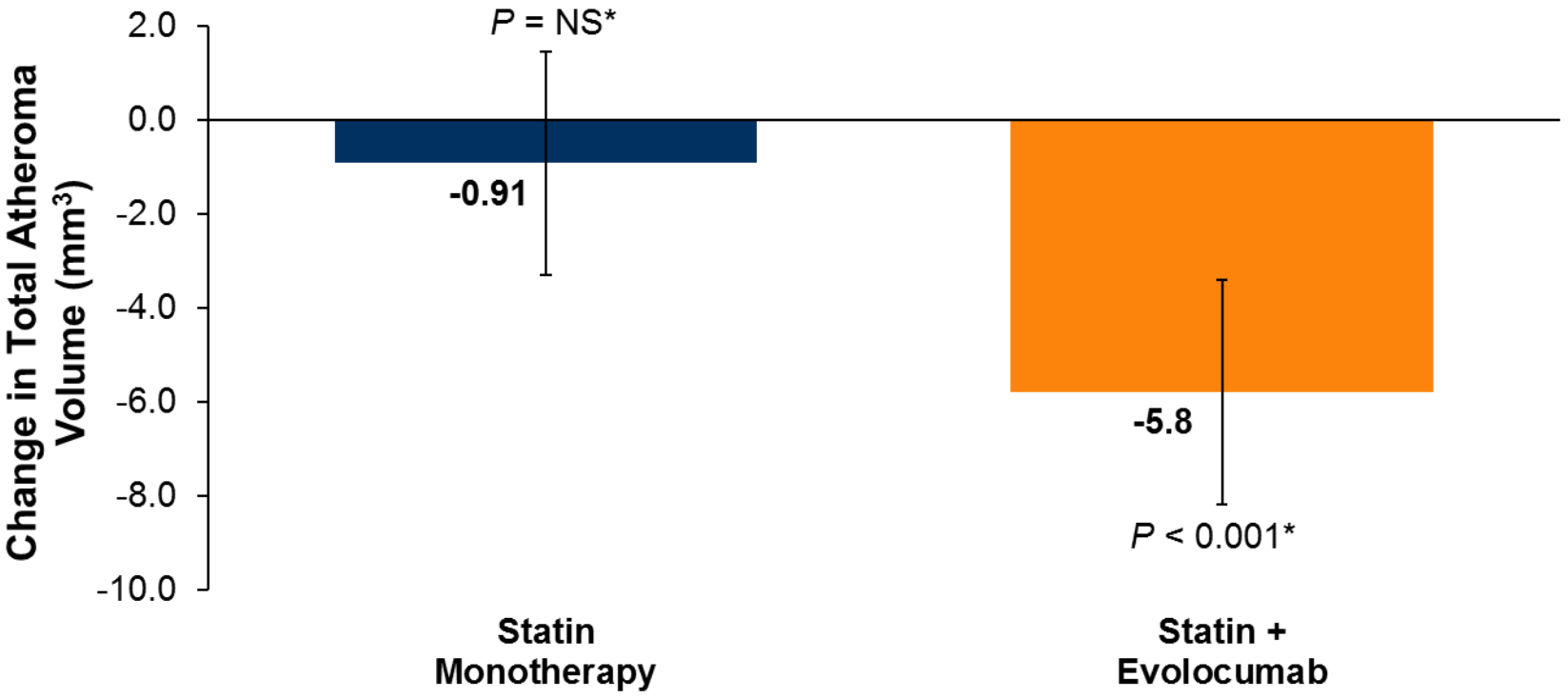
Secondary Endpoint: Nominal Change in TAV From Baseline to Week 78



Difference between groups: -4.9mm^3 (-7.3 to -2.5); *P* < 0.001

Data shown are least-squares mean (95% CI). TAV = Total Atheroma Volume
*Comparison versus baseline
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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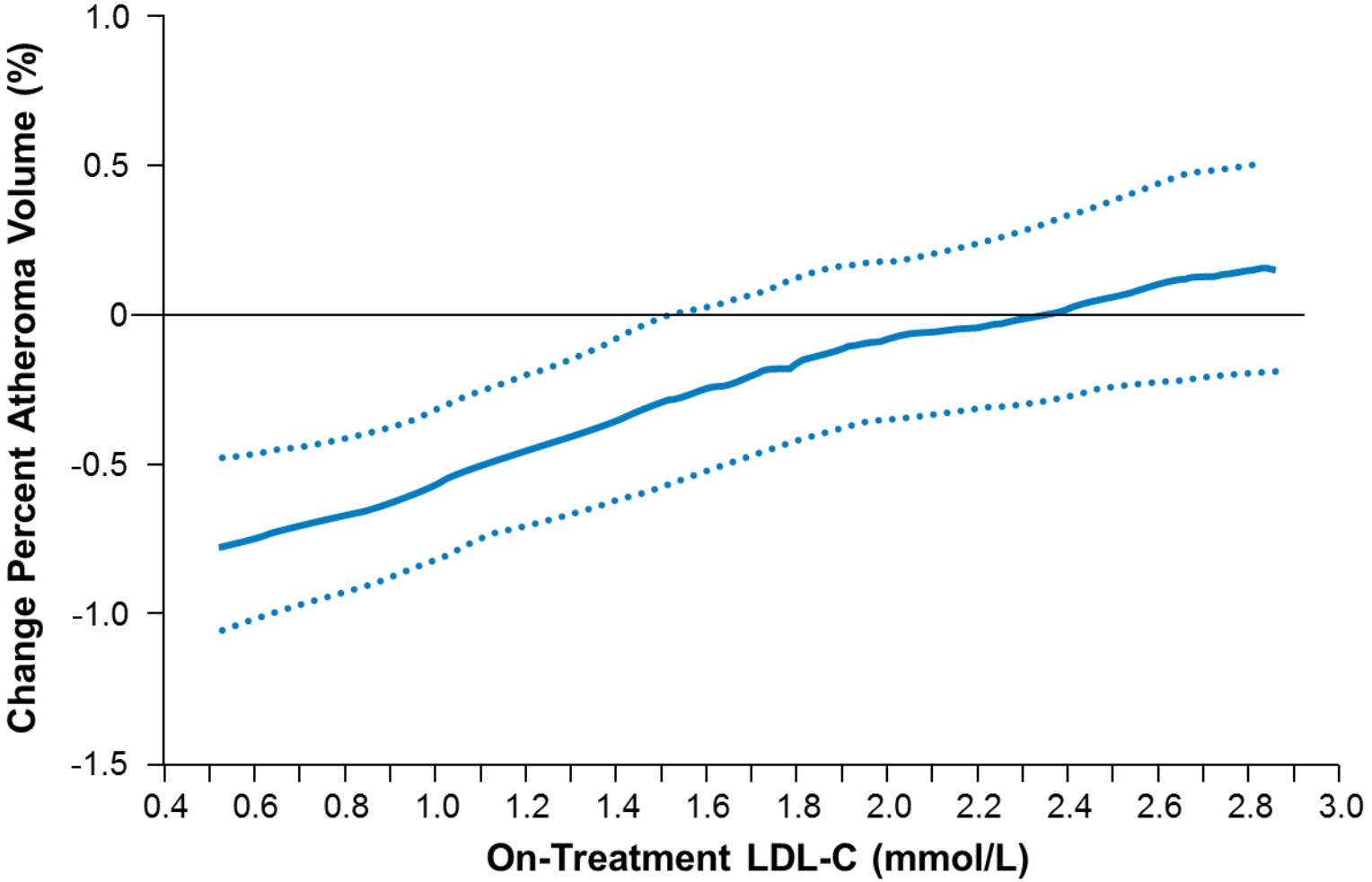
Exploratory Analysis: Achieved LDL-C and Change in PAV in All Patients



Local regression (LOESS) curve illustrating the association (with 95% CI) between achieved LDL-C levels and change in PAV in all patients undergoing serial IVUS evaluation. PAV = percentage atheroma volume; LDL-C = low-density lipoprotein cholesterol

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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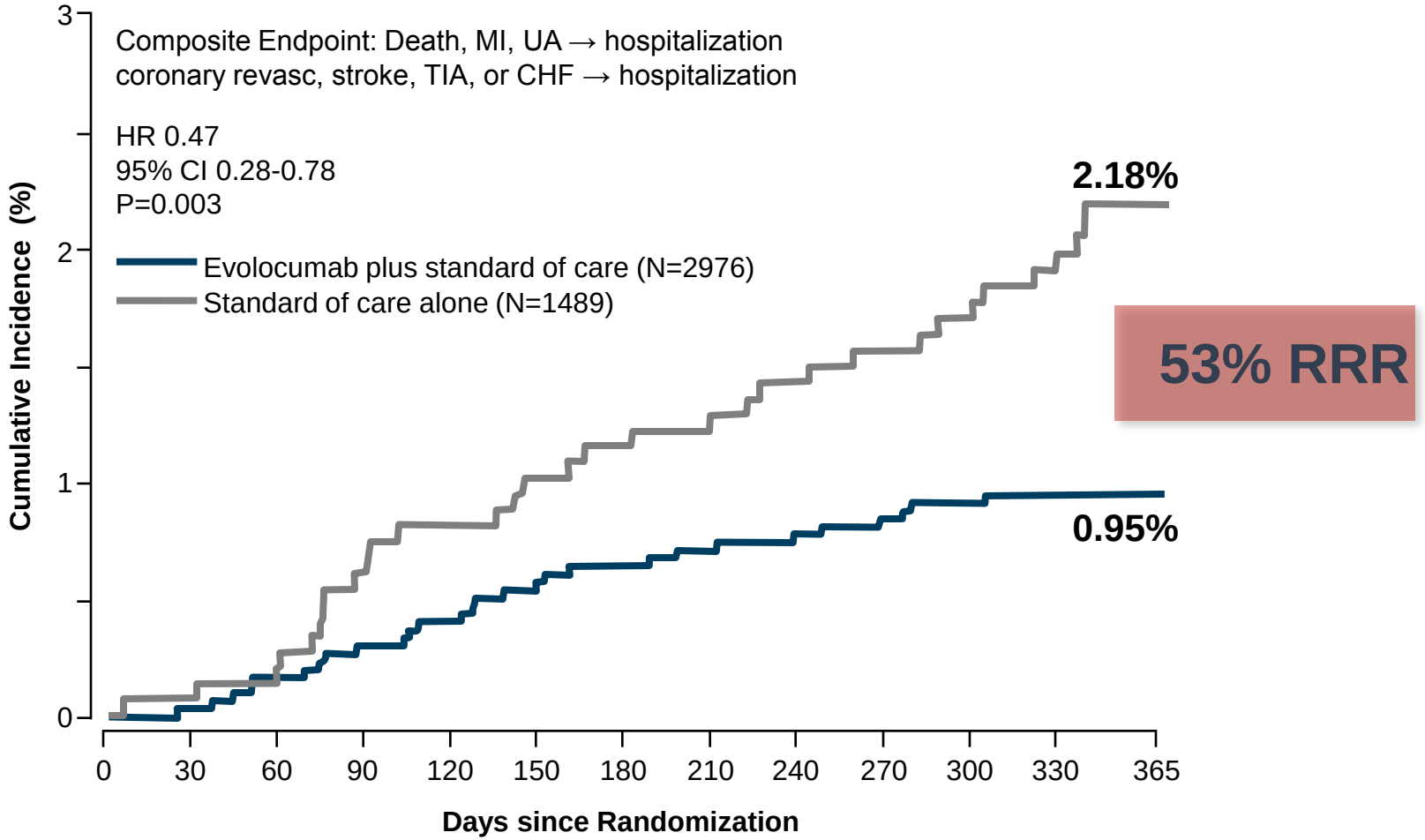
Does atherosclerosis regression as documented by IVUS translate into a reduction in major cardiovascular events?

OSLER: Reduction in the Rate of Cardiovascular Events Among Patients Receiving Evolocumab -Pre-Specified Analysis*



*Pre-specified exploratory analysis from open-label extension studies OSLER 1 and 2 of adjudicated cardiovascular events.

Sabatine MS, et al. N Engl J Med. 2015;372(16):1500-9.

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FOURIER

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

MS Sabatine, RP Giugliano, AC Keech, N Honarpour,
SM Wasserman, PS Sever, and TR Pedersen,
for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 17, 2017

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**

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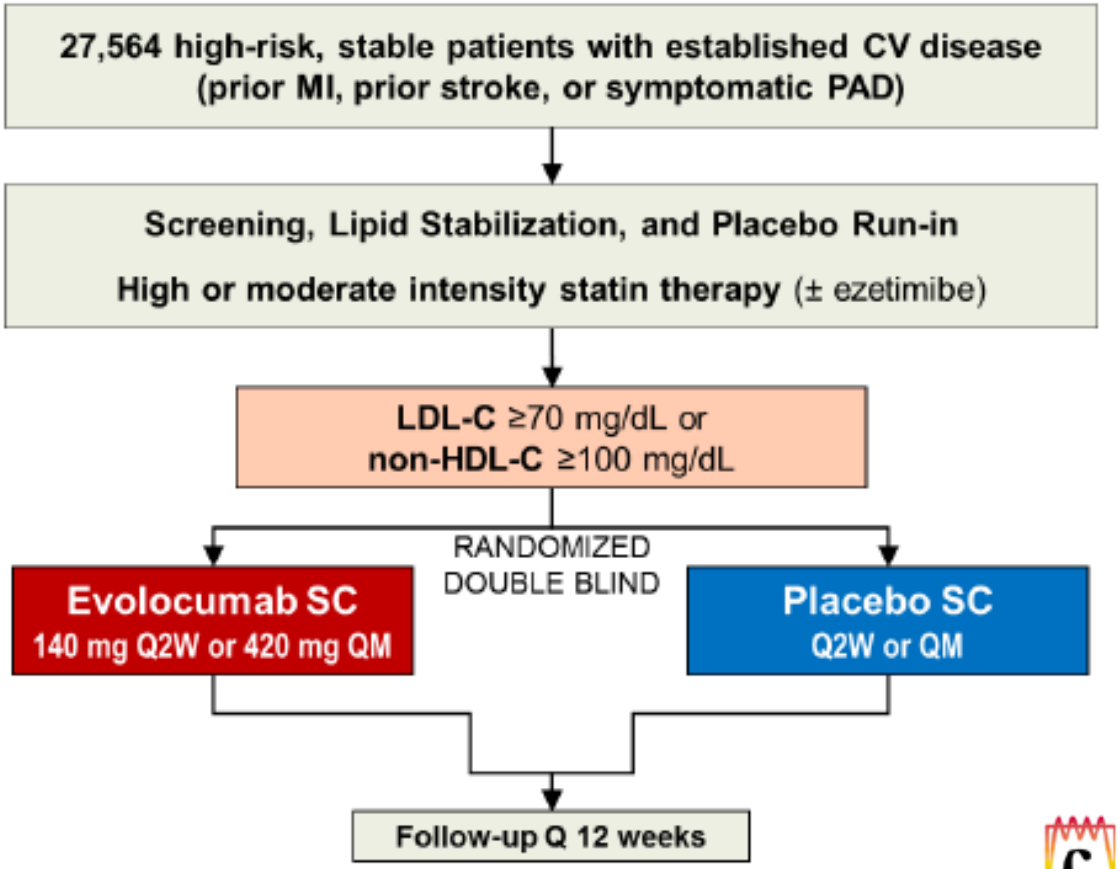
Trial Design



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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

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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

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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.

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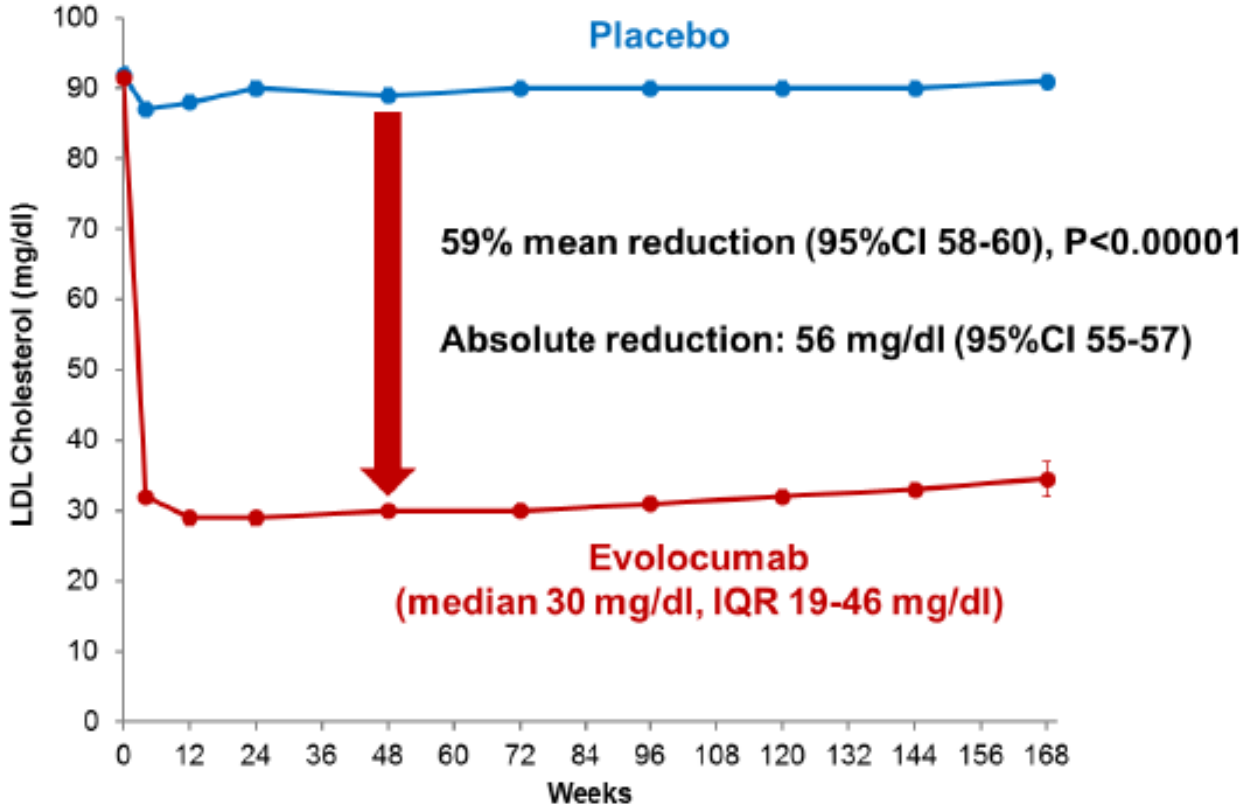
LDL-C Reduction



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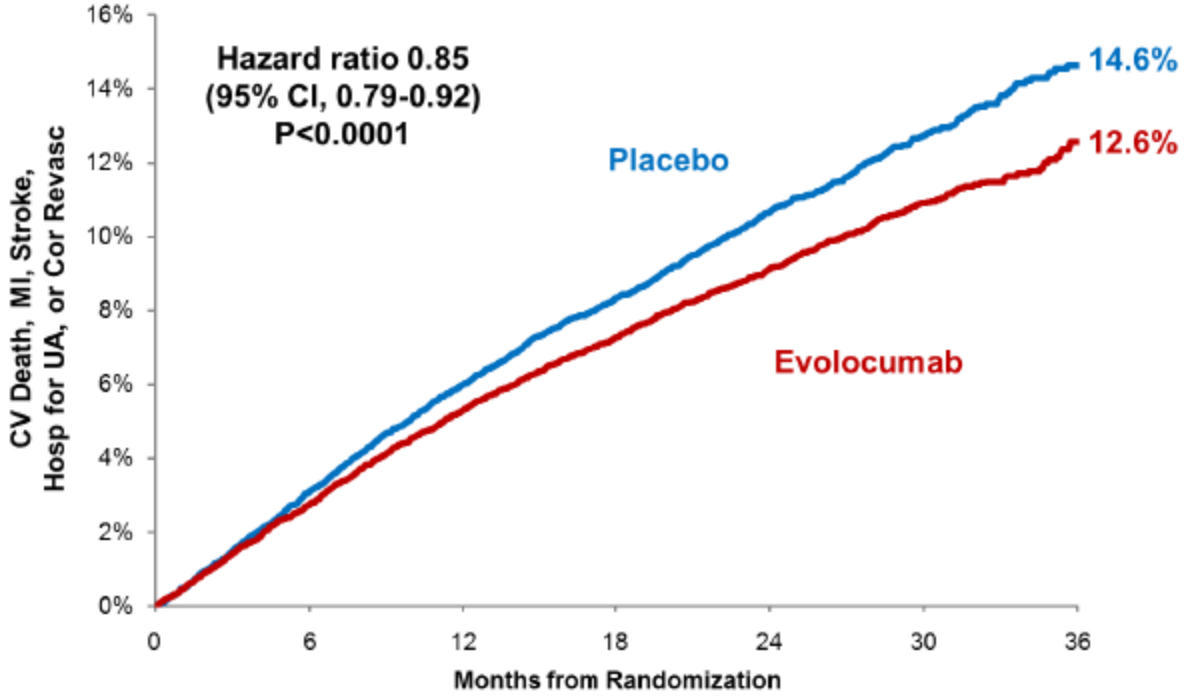
Primary Endpoint



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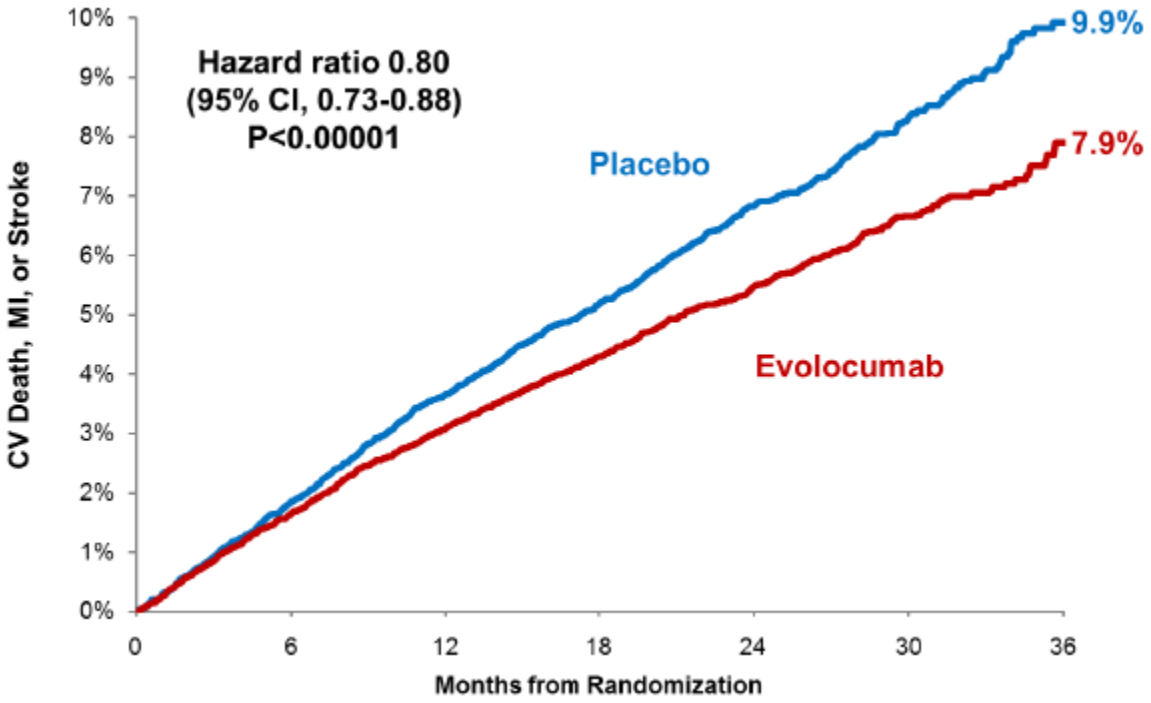
Key Secondary Endpoint



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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)**

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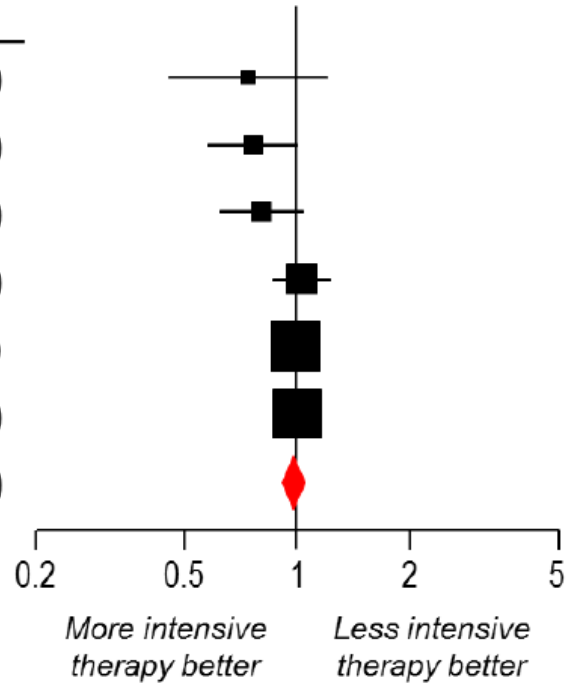
Secondary Prevention Statin Trials of Intensive LDL-C Lowering

No clear benefit on CV mortality

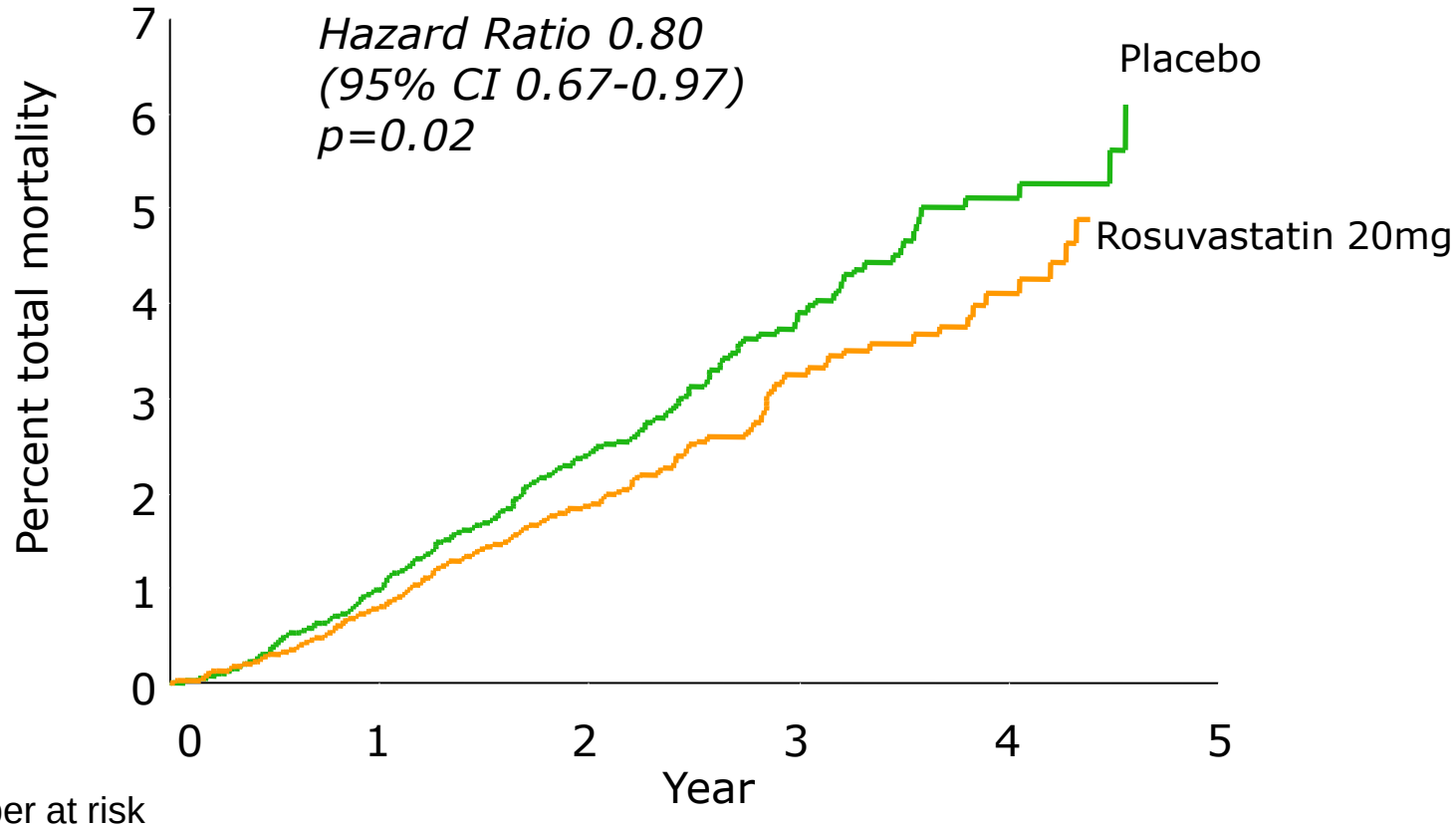
Trial	Year	# of CV Deaths: More Intensive Rx Arm	# of CV Deaths: Less Intensive Rx Arm	HR (95% CI)
PROVE-IT TIMI 22	2004	27	36	0.74 (0.45-1.22)
A2Z	2004	86	111	0.76 (0.57-1.01)
TNT	2005	101	127	0.80 (0.61-1.03)
IDEAL	2005	223	218	1.03 (0.85-1.24)
SEARCH	2010	565	572	0.99 (0.88-1.11)
IMPROVE-IT	2015	538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



Primary Prevention – JUPITER

Death from any cause

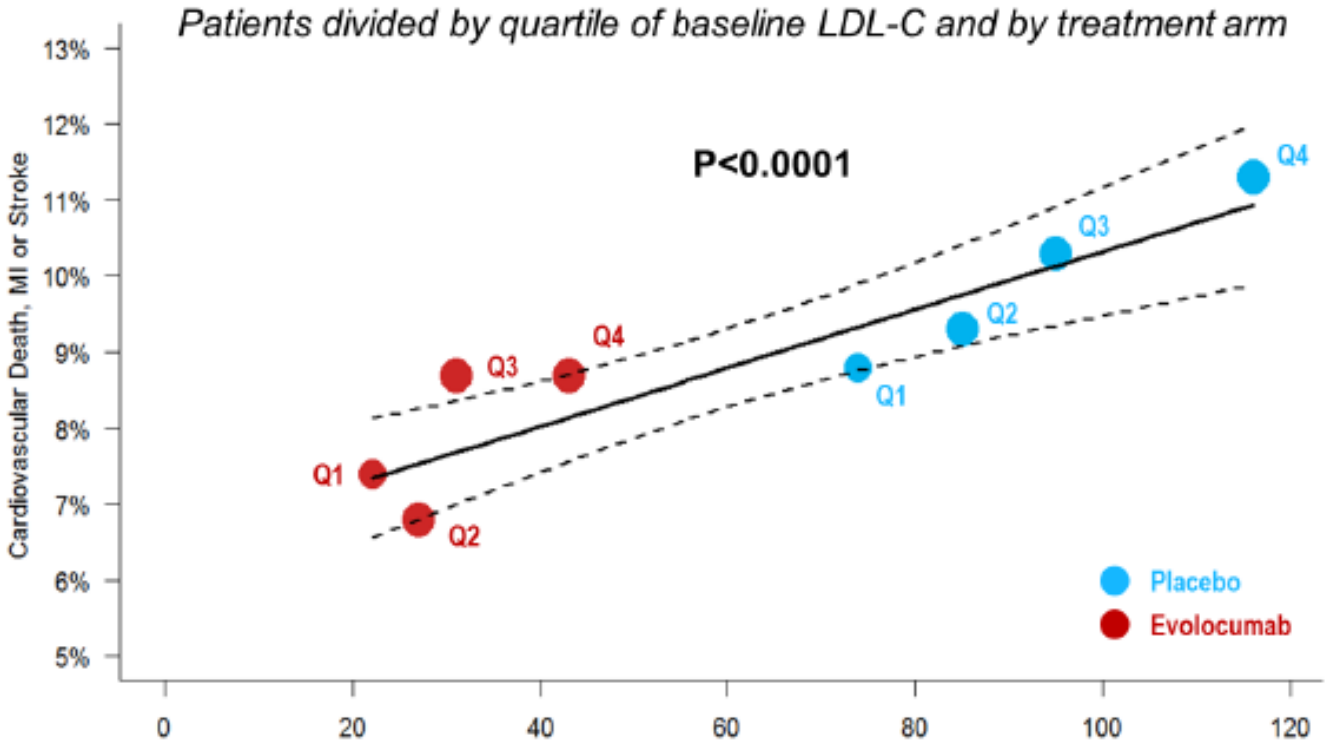


Number at risk

RSV	8901	8787	4312	1602	676	227
Placebo	8901	8775	4319	1614	681	246

Ridker P *et al*. *N Eng J Med* 2008;359: 2195-2207

Lower is Better



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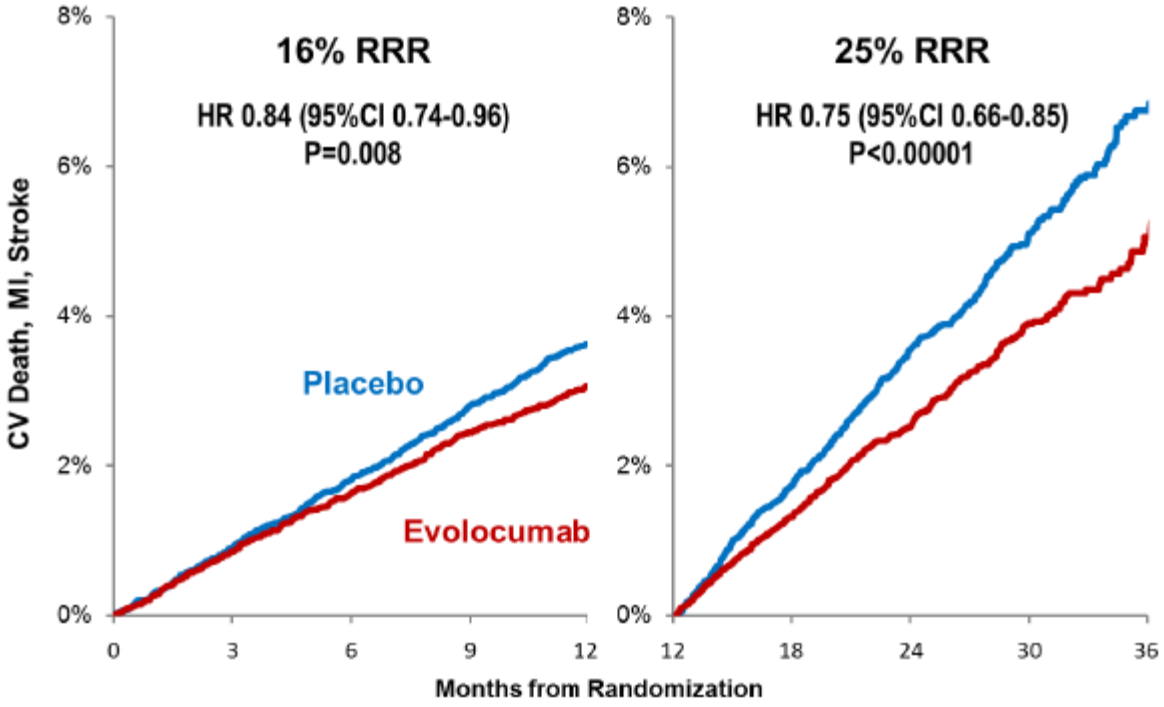
Benefit Increased Over Time



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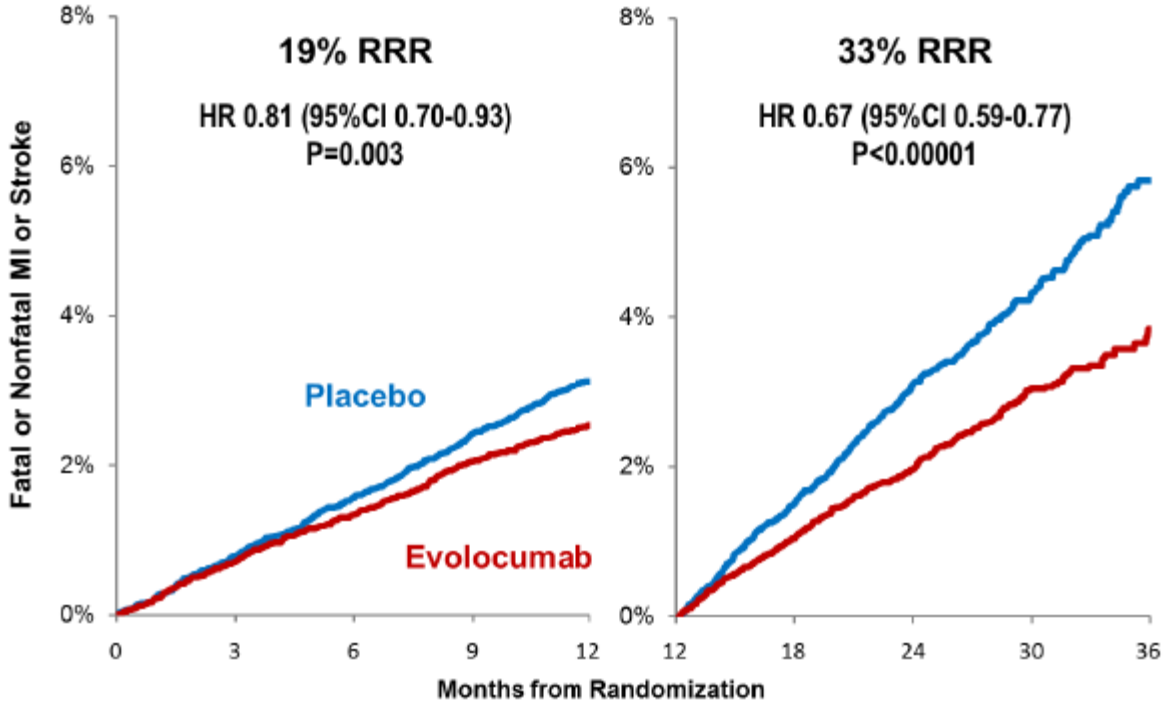
Fatal or Nonfatal MI or Stroke



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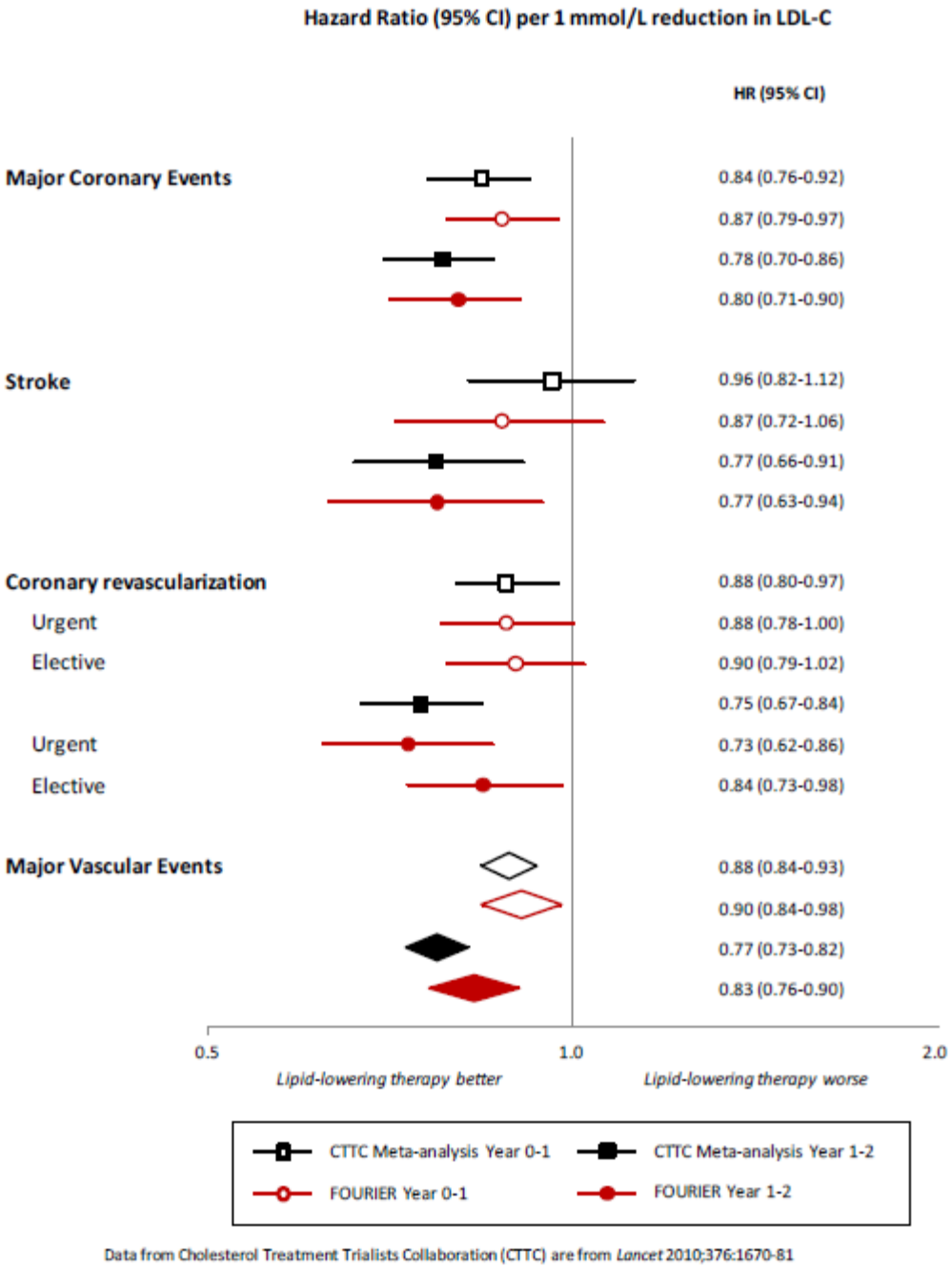

Data from Cholesterol Treatment Trialists Collaboration (CTTC) are from *Lancet* 2010;376:1670-81

Comparison with CTTC meta-analysis of benefit of LDL-C reduction by statin therapy

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Adverse Events

	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

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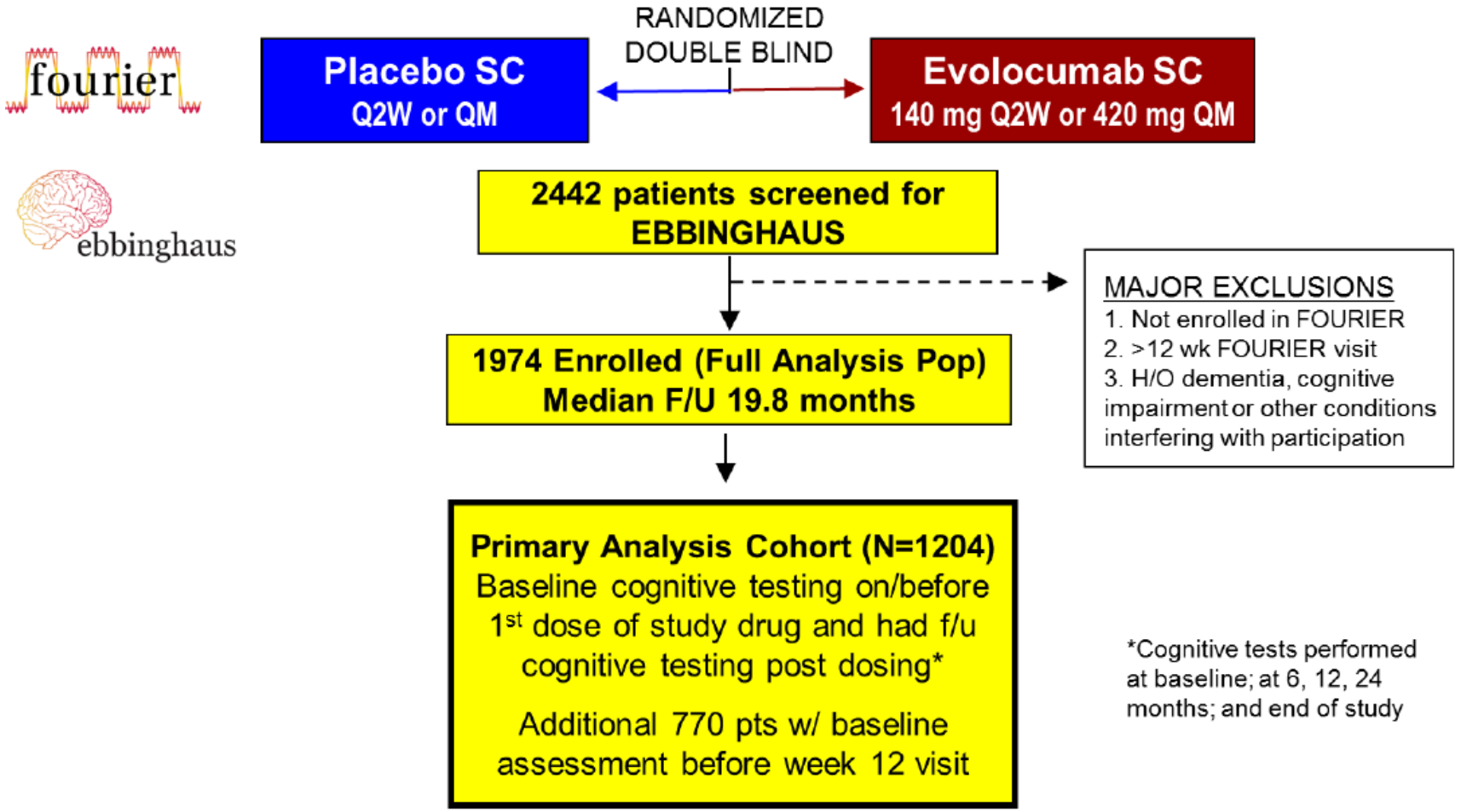
EBBINGHAUS Study Design



Endpoints

1. **Cambridge Neuropsychological Test Automated Battery (CANTAB) Assessments, a standardized, well-validated computer tablet-based testing platform.**
   Assessed at baseline, 6, 12, 24, 48 mos and study end.
   - **Primary:** **Spatial working memory strategy index of executive function**
   - Secondary: Spatial working memory between errors
     Paired associates learning
     Reaction time
   - Exploratory: Global score (combines above 4 tests)
2. **Patient survey of everyday cognition* at study end**
3. **Investigator report of cognitive AEs**

*Memory and executive function domains

ebbinghaus

Conclusions

In patients with known cardiovascular disease on background statin followed for 20 months

1. **No differences btw evolocumab vs placebo**
   A. A battery of cognitive tests
   B. Patient-reported everyday cognition
   C. Adverse cognitive events reported by MD

2. **No evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL (0.65 mmol/L)**

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FOURIER: Key findings

- **↓ 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

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Conclusions

In further confirmation of the 'cholesterol hypothesis' lowering LDL-C well below current targets by addition of a PCSK9 inhibitor to statin therapy:

- **elicits regression of atherosclerosis**
- **significantly reduces major cardiovascular events**
- **benefit is related to LDL-C level achieved**
- **risk reduction improves with duration of therapy**
- **no signal for adverse effects of very low levels of LDL-C**

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N ENGL J MED 376;1 NEJM.ORG JANUARY 5, 2017

A Highly Durable RNAi Therapeutic Inhibitor of PCSK9

Kevin Fitzgerald, Ph.D., Suellen White, B.S.N., Anna Borodovsky, Ph.D., Brian R. Bettencourt, Ph.D., Andrew Strahs, Ph.D., Valerie Clausen, Ph.D., Peter Wijngaard, Ph.D., Jay D. Horton, M.D., Jorg Taubel, M.D., Ashley Brooks, M.B., Ch.B., Chamikara Fernando, M.B., B.S., Robert S. Kauffman, M.D., Ph.D., David Kallend, M.D., Akshay Vaishnaw, M.D., and Amy Simon, M.D.

A Change in LDL Cholesterol Level in Single-Dose Cohorts