



ebbinghaus

# EBBINGHAUS:

## ***- A Cognitive Study of Patients Enrolled in the FOURIER Trial***

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on behalf of the EBBINGHAUS Investigators

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Late-Breaking Clinical Trial  
March 18, 2017*



An Academic Research Organization of  
Brigham and Women's Hospital and Harvard Medical School



# Cognition and Statins

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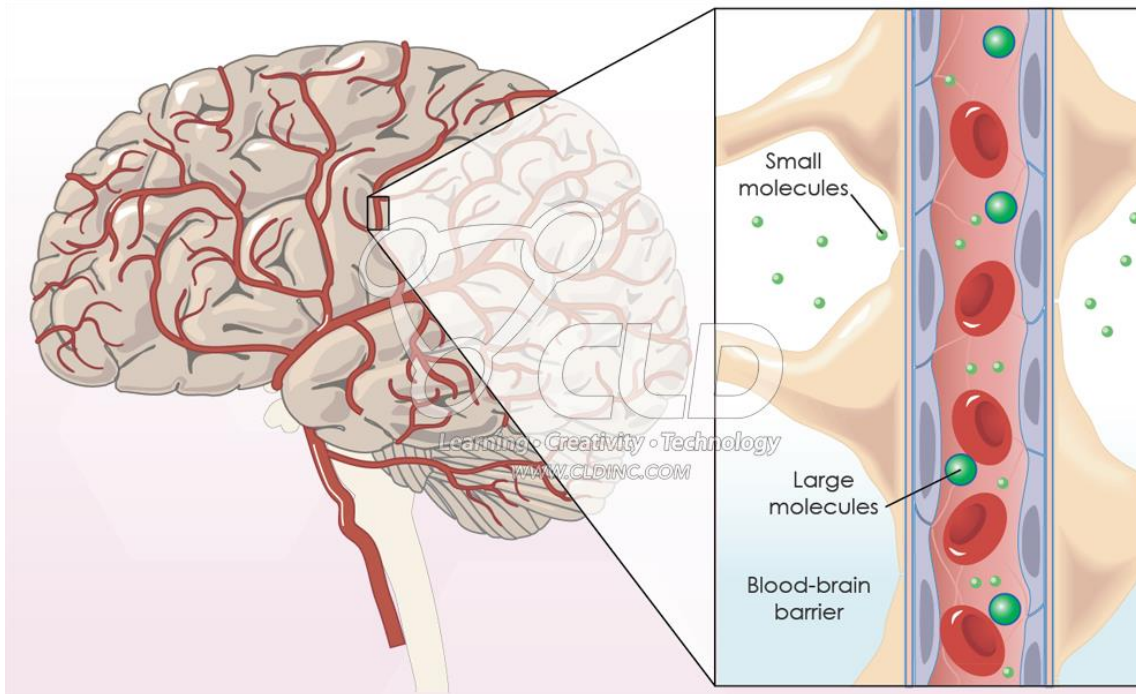
- Case series and 2 small, 6-month RCTs with statins raised concern regarding cognitive deficits
- In 2012 FDA added risk of adverse cognitive effects to label of all statins
- However analyses from large scale RCTs do not support these findings and 2014 Statin Cognitive Safety Task Force\* concluded that statins are not associated with cognitive side effects.





# Cognition and PCSK9 Inhibitors

Brain synthesizes cholesterol locally



mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier

Nevertheless meta-analysis\* of adverse events from 6 trials in 9581 pts suggested an increased risk with PCSK9 inhibitors: HR 2.3 [1.1, 4.9]

- Event rates low (<1%)
- Unadjudicated, diverse AE terms reported
- Not correlated with LDL-C achieved

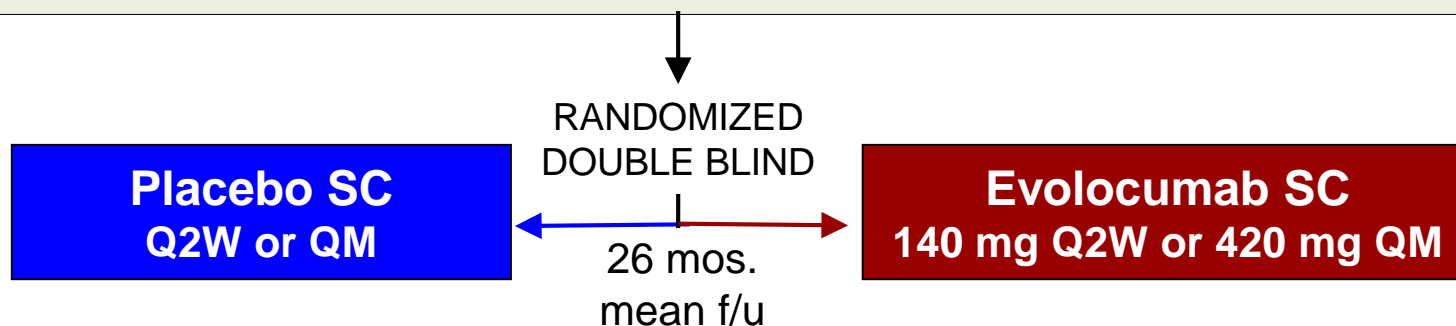




# FOURIER: Summary Results



**FOURIER Study Population:** 27,564 stable patients with CV disease, age 40-85 years; additional CV risk factor(s), LDL  $\geq$  70 mg/dL (or non-HDL  $\geq$  100)



## Evolocumab on background of statin c/w placebo:

- ↓ LDL-C by 59%
- ↓ CV outcomes on background of statin therapy
- Safe and well-tolerated





# EBBINGHAUS: Hypothesis



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**The addition of evolocumab to statin therapy in patients with clinically evident cardiovascular disease does not adversely affect cognitive function**





# Trial Organization



## *Executive Committee*

Robert P. Giugliano (Chair)

François Mach

Brian R. Ott

## *TIMI Study Group*

Marc S. Sabatine (Chairman)

Marc P. Bonaca (Safety Desk)

Sabina Murphy (Director of Stats)

Kelly Im (Assoc Dir Stats)

Estella Kanevsky

*Cambridge Cognition:* Kenton Zavitz (non-voting member of EC)

## *Sponsor: Amgen*

Christopher Kurtz

Scott M. Wasserman

Narimon Honarpour

Kelly Hanlon

Beat Knusel

Thomas Liu

Jingjing Schneider

Huei Wang

## *Participating Countries (N=30)*

Australia

Belgium

Canada

Czech Republic

Denmark

Estonia

Finland

France

Germany

Greece

Hong Kong

Hungary

Italy

Japan

Latvia

Lithuania

Malaysia

Netherlands

New Zealand

Norway

Poland

Portugal

Russia

Slovakia

South Africa

Spain

Sweden

Turkey

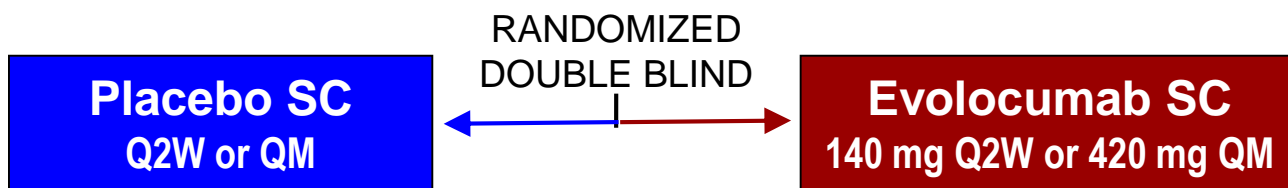
United Kingdom

USA





# Trial Design



**2442 patients screened for EBBINGHAUS**

**1974 Enrolled (Full Analysis Pop)**  
Median F/U 19.8 months

**MAJOR EXCLUSIONS**

1. Not enrolled in FOURIER
2. >12 wk FOURIER visit
3. H/O dementia, cognitive impairment or other conditions interfering with participation

**Primary Analysis Cohort (N=1204)**  
Baseline cognitive testing on/before 1<sup>st</sup> dose of study drug and had f/u cognitive testing post dosing\*  
Additional 770 pts w/ baseline assessment before week 12 visit

\*Cognitive tests performed at baseline; at 6, 12, 24 months; and end of study





# Baseline Characteristics (Full Population)



Characteristics	Value
Age, years, mean (SD)	63 (9)
Male sex	72
Education, years, mean (SD)	13 (3)
Prior stroke	20
Non-stroke neurologic disease	14
Atrial fibrillation at any time	9
Congestive heart failure	24
Hypertension	84
Current cigarette use	34
High intensity statin use	71
LDL-C, mg/dL, median [25 <sup>th</sup> , 75 <sup>th</sup> ]	92 [80-108]

→ Median time from most recent event ~3.5 yrs;







# 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





# Statistical Considerations



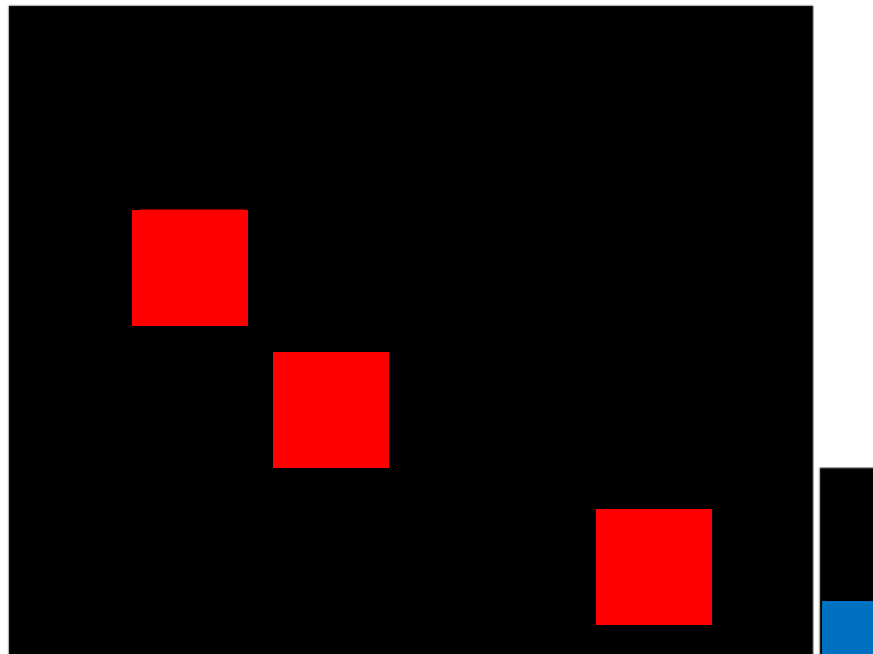
- **Primary Endpoint Analysis – Non-inferiority**
  - NI margin = 20% of placebo SD (Cohen's  $d=0.2$ )
  - Upper 95%CI of change from baseline in primary endpoint (SWM strategy index Z-score) is compared to non-inferiority (NI) margin
  
- **Other Analyses:**
  - Other 3 CANTAB tests
  - Global score = average of 4 Z-scores of CANTAB tests
  - CANTAB tests post nadir LDL-C achieved



# CANTAB - Spatial Working Memory (SWM)

- Search for the blue token hidden within a red box
- Number of red boxes increases each round (3, 4, 6, 8).
- Critical instruction: *Do not return to a box where a blue token was found.*

SWM strategy index: = # inefficient searches started. Range 4-28.

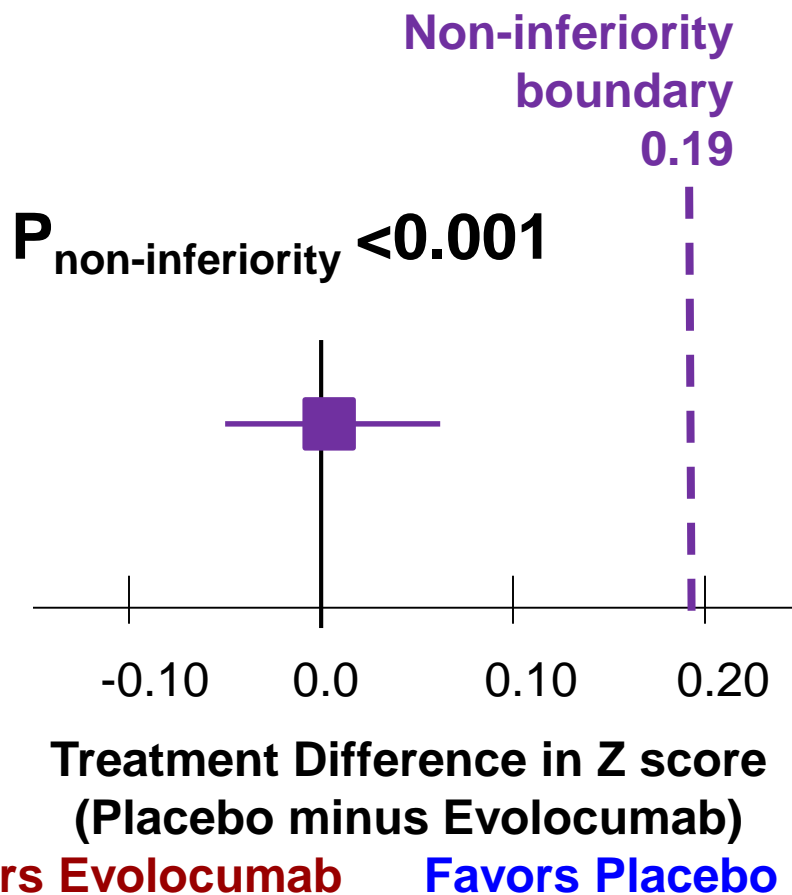
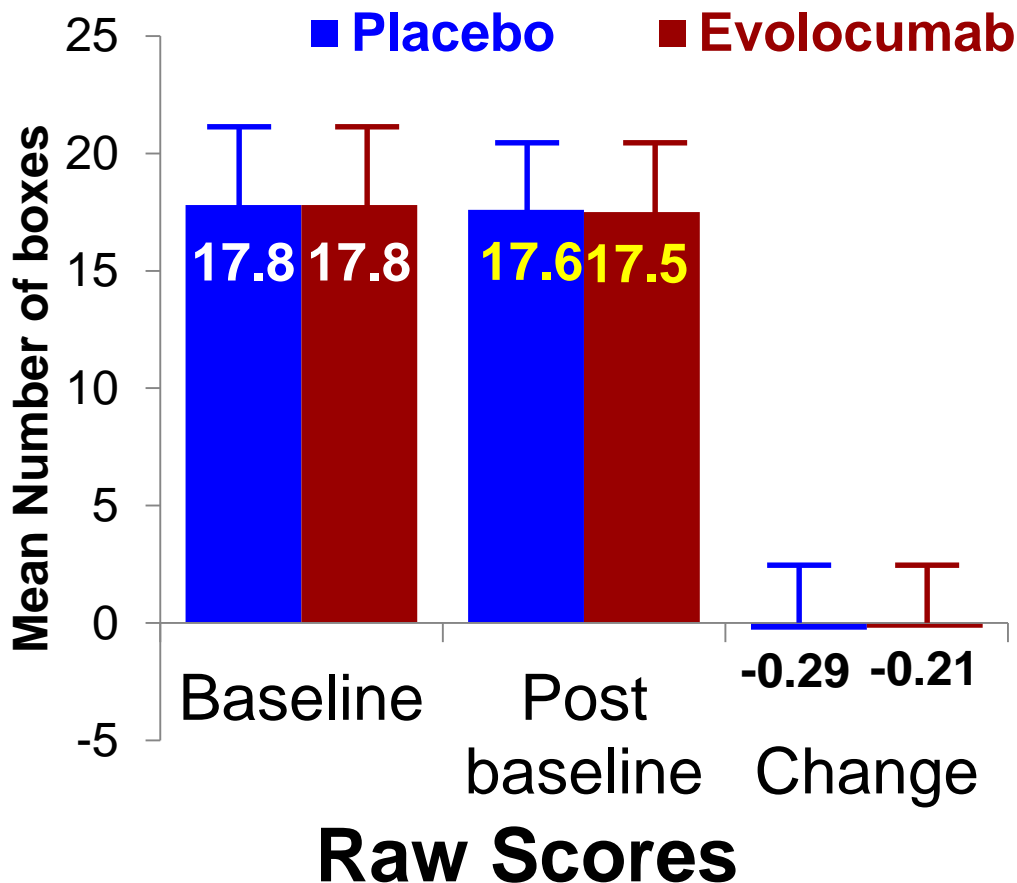


**Lower scores  
represent  
better  
performance**



# Primary Endpoint

## Spatial Working Memory Strategy Index



# Secondary Endpoints

Test Name	Task description	Scoring
Spatial Working Memory Between Errors Score	Find the hidden blue token	# times a box is re-visited in which a blue token had already been found
Paired Associates Learning	Memory matching game (Concentration)	# times errors made in finding a match
Reaction Time	Touch yellow dot quickly after it appears on screen	Time in milliseconds until dot touched

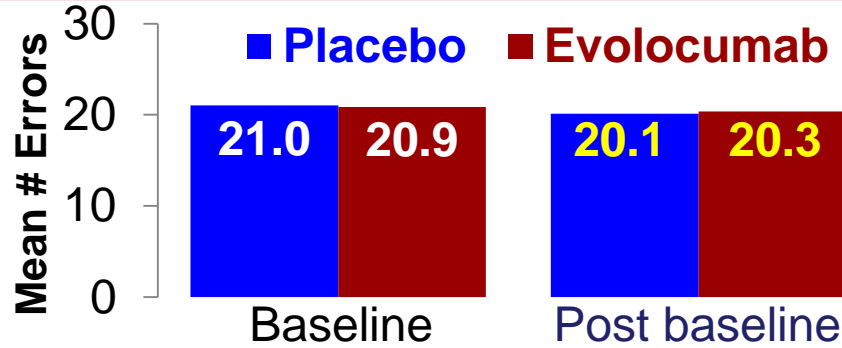
Lower scores (fewer errors, faster time) are better



# Secondary Endpoint Results

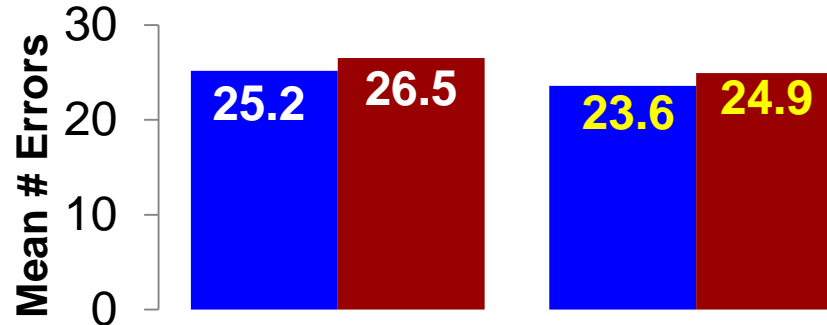


Spatial Working Memory Between Errors Score



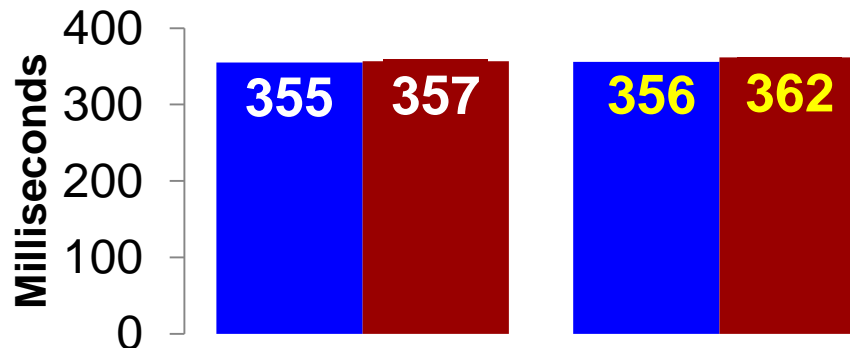
Trt diff of $\Delta$ in Z-scores	$P_{\text{superiority}}$
0.033	<b>0.36</b>

Paired Associates Learning



0.023	<b>0.49</b>
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Median 5-Choice Reaction Time

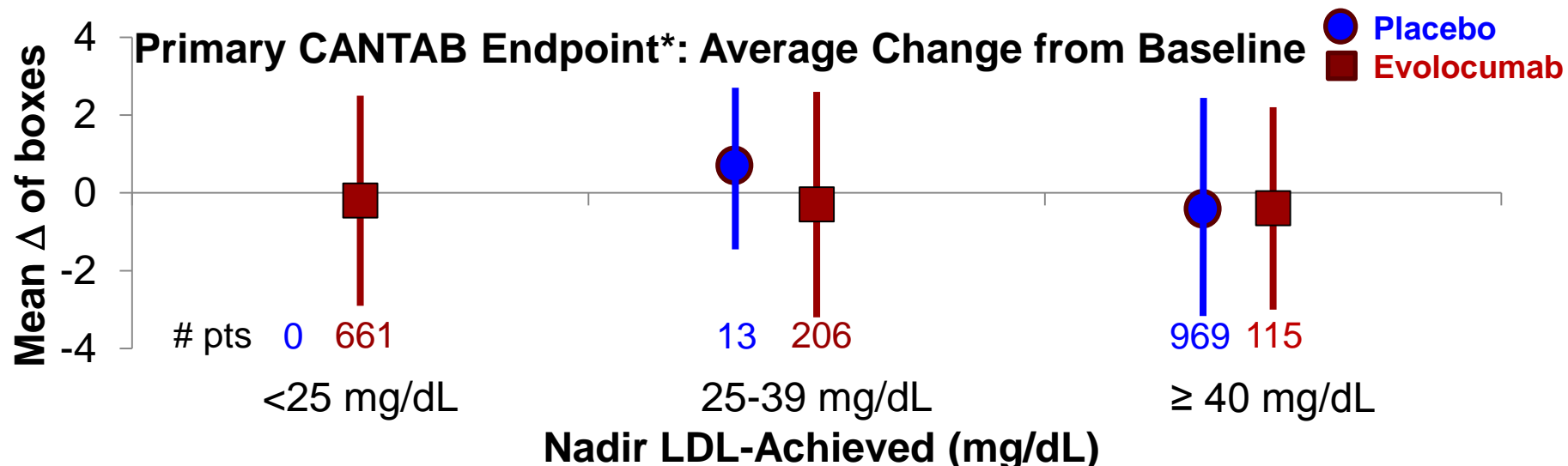


0.073	<b>0.06</b>
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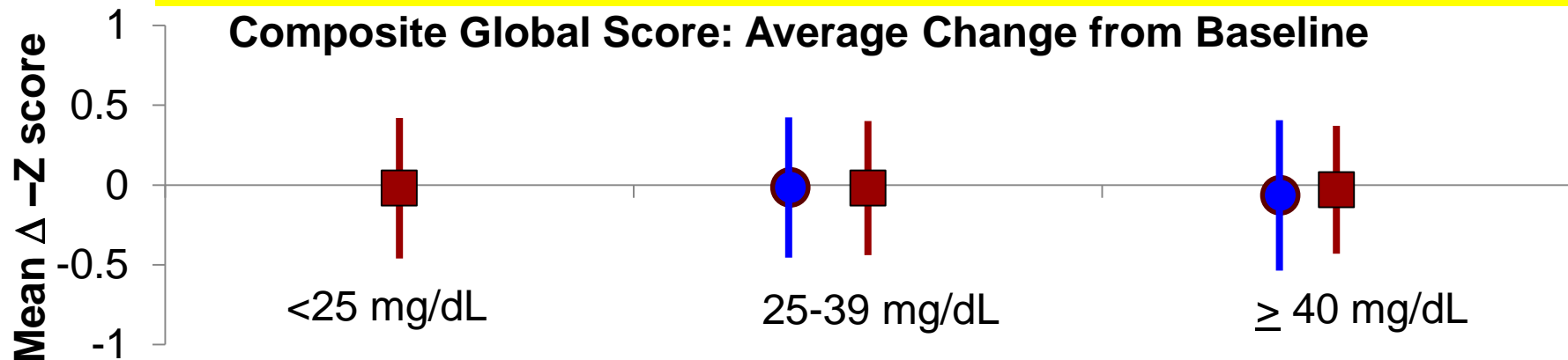




# Cognitive Assessments by Nadir Achieved LDL-C and Treatment (Full Pop)



**P=NS across LDL values achieved and also between treatments**



Negative score -> improvement  
Lower scores are better

\*Spatial working memory strategy index of executive function, raw score





# Patient Self-Report: 23 Questions Regarding Everyday Cognition



All Patients	Placebo	Evolocumab	P-Value
	(N=781)	(N=800)	
	Mean (SD)	Mean (SD)	
Memory	1.16 (0.39)	1.17 (0.39)	0.81
Executive functioning total score	1.11 (0.32)	1.12 (0.32)	0.28
Planning	1.08 (0.31)	1.10 (0.32)	0.20
Organization	1.09 (0.32)	1.10 (0.33)	0.57
Divided attention	1.15 (0.42)	1.16 (0.41)	0.54
<b>Total Score</b>	<b>1.13 (0.33)</b>	<b>1.14 (0.33)</b>	<b>0.42</b>

Patient self-report at end of study as compared to randomization, graded as

- |                                       |   |
|---------------------------------------|---|
| 1. <i>Better or no change</i>         | 2. <i>Questionable / occasionally worse</i> |
| 3. <i>Consistently a little worse</i> | 4. <i>Consistently much worse</i>           |

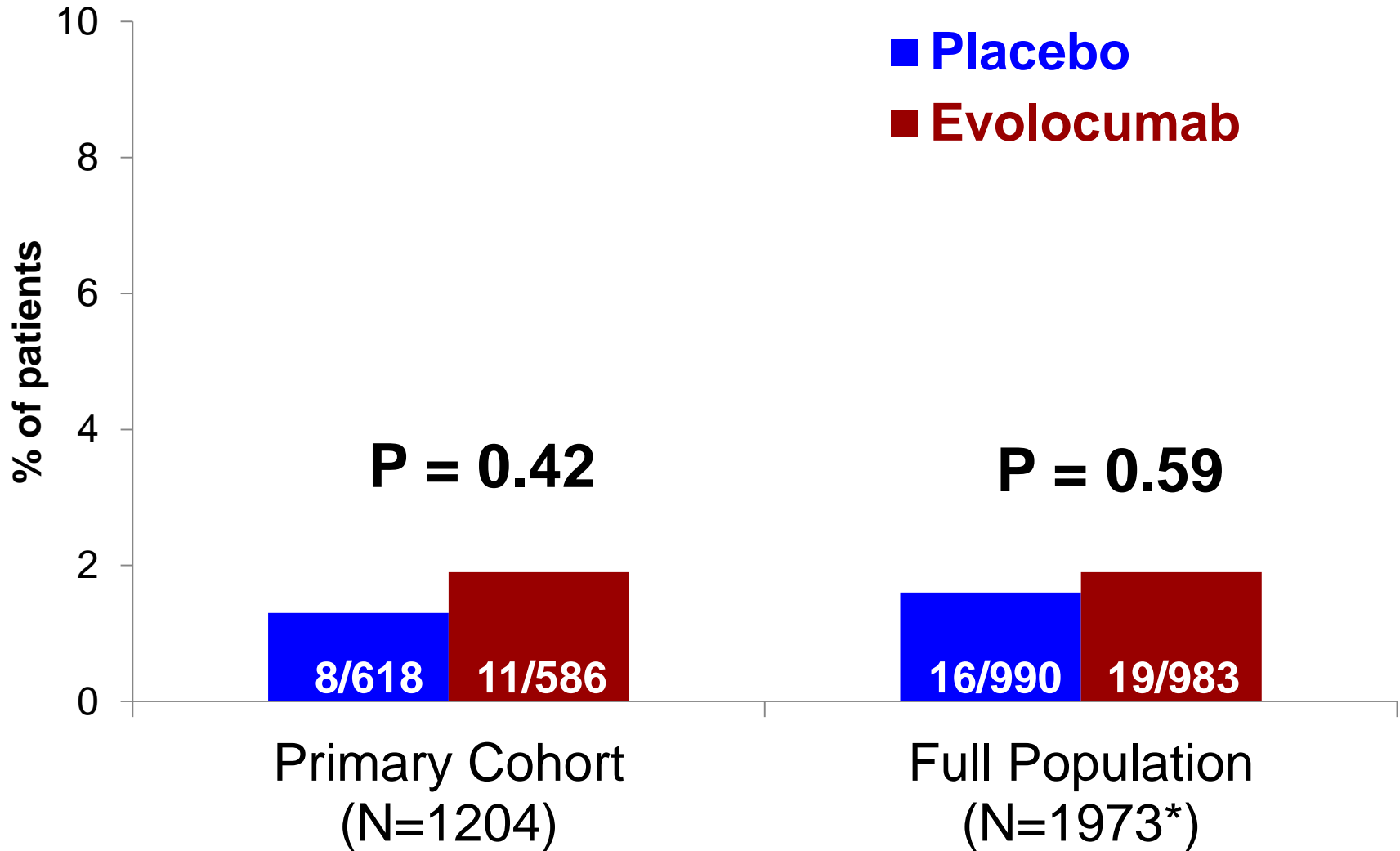
Lower scores represent better cognition







# Investigator Reported Cognitive Adverse Events





# Conclusions



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**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**

