

ORIGINAL INVESTIGATIONS

Cognition After Lowering LDL-Cholesterol With Evolocumab



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ABSTRACT

BACKGROUND The EBBINGHAUS (Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects) trial demonstrated that evolocumab added to a background statin did not affect cognitive performance in a subset of 1,204 patients enrolled in FOURIER (Further Cardiovascular Outcomes Research With PCSK9 inhibitors in Subjects With Elevated Risk).

OBJECTIVES The authors describe patient-reported cognition in the entire FOURIER trial using a self-survey.

METHODS FOURIER was a randomized, double-blind, placebo-controlled trial involving patients with atherosclerotic cardiovascular disease and low-density lipoprotein cholesterol (LDL-C) levels ≥ 70 mg/dl or non-high-density cholesterol ≥ 100 mg/dl despite statin therapy. At the final visit, patients completed a 23-item survey on memory and executive domains from the Everyday Cognition (ECog) scale. Patients compared their levels of everyday function at the end of the trial with their levels at the beginning and scored as 1 (no change or improvement), 2 (occasionally worse), 3 (consistently little worse), or 4 (consistently much worse). ECog scores were compared by the 2 randomized treatment arms and by achieved LDL-C at 4 weeks.

RESULTS A total of 22,655 patients completed ECog after a median duration of 2.2 years. The proportions of patients reporting cognitive decline (ECog score ≥ 2) at the end of the study were similar for placebo versus evolocumab, both for total score 3.6% versus 3.7% ($p = 0.62$) and for subdomains (memory, 5.8% vs. 6.0%; total executive, 3.6% vs. 3.7%). The proportion of patients reporting a decline in total cognitive score was similar among the 2,338 patients who achieved very low LDL-C levels (< 20 mg/dl) compared to the 3,613 patients with LDL-C ≥ 100 mg/dl (3.8% vs. 4.5%, $p = 0.57$).

CONCLUSIONS The addition of evolocumab to maximally tolerated statin therapy had no impact on patient-reported cognition after an average of 2.2 years of treatment, even among patients who achieved LDL-C < 20 mg/dl. (J Am Coll Cardiol 2020;75:2283–93) © 2020 by the American College of Cardiology Foundation.



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ABBREVIATIONS AND ACRONYMS

CANTAB = Cambridge
Neuropsychological Test
Automated Battery
CI = confidence interval
CV = cardiovascular
ECog = Everyday Cognition
LDL-C = low-density
lipoprotein cholesterol
PCSK9 = proprotein
convertase subtilisin kexin 9

Low-density lipoprotein cholesterol (LDL-C) is a well-established causal risk factor for atherosclerotic cardiovascular (CV) disease (1). Previous clinical trials of lipid-lowering drugs have shown that the relative reduction in CV events is proportional to the absolute decrease in LDL-C (2). The 2018 U.S. cholesterol guidelines recommend starting with high-intensity statin therapy to reach an LDL-C reduction of $\geq 50\%$ in patients with established atherosclerotic CV disease and to consider the addition of ezetimibe or a proprotein convertase subtilisin kexin 9 (PCSK9) inhibitor in patients who remain above the LDL-C treatment threshold of 70 mg/dl (1.8 mmol/l) (1). The 2019 European guidelines for the management of dyslipidemia categorize patients with histories of myocardial infarction as very high risk and recommend both a reduction of LDL-C of $\geq 50\%$ and an LDL-C target of < 55 mg/dl (< 1.4 mmol/l) (3). The recommendations for PCSK9 inhibitors were based on the findings from the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trials, which demonstrated significant reductions in CV events with evolocumab and alirocumab, respectively, when added to a statin, with no major safety concerns (4-6). The FOURIER trial showed that the addition of evolocumab to a statin reduced stroke (1.5% vs. 1.9%; $p = 0.01$) without affecting clinical neurocognitive adverse events (1.6% vs. 1.5%) and was safe even in patients with very low achieved LDL-C levels (< 20 mg/dl) (4,7). Similar findings were reported with alirocumab versus placebo with respect to stroke (1.2% vs. 1.6%; hazard ratio: 0.73; 95% confidence interval [CI]: 0.57 to 0.93) and neurocognitive

disorder (1.8% vs. 1.5%) in the ODYSSEY Outcomes trial among 18,924 patients (5). The EBBINGHAUS (Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects) trial investigated neurocognitive function of 1,204 patients from the FOURIER trial who underwent formal serial objective cognitive testing in the domains of executive and memory functions using the objective and computer-based Cambridge Neuropsychological Test Automated Battery (CANTAB) (8). The EBBINGHAUS trial did not show changes in cognitive performance between evolocumab and placebo over an average treatment period duration of 19 months (8).

To date, no large-scale trial has investigated the impact of evolocumab and low LDL-C levels on patient-reported cognition. The integration of patient-reported outcomes in CV trials to explore patients' experience with a therapeutic intervention has been recommended (9), particularly in the setting of chronic diseases requiring long-term therapies (9). We now report the patient-reported outcomes for cognitive function in the FOURIER cohort using a patient self-survey extending previously reported findings in 1,581 patients from the EBBINGHAUS trial to the entire FOURIER population.

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METHODS

STUDY POPULATION. FOURIER was a randomized, double-blind, placebo-controlled trial that enrolled 27,564 patients 40 to 85 years of age with atherosclerotic CV disease (previous myocardial infarction, previous nonhemorrhagic stroke, or symptomatic peripheral arterial disease) and additional risk factors placing them at increased CV risk (4). Eligible patients had LDL-C ≥ 70 mg/dl or non-high-density lipoprotein cholesterol ≥ 100 mg/dl while treated with

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC author instructions page.

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optimized lipid-lowering therapy consisting of a high- or moderate-intensity statin, with or without ezetimibe. Key exclusion criteria included any clinical disorder, condition, or disease that in the investigator's opinion could considerably interfere with the patient's participation in the trial or ability to comply with study procedures, previous hemorrhagic stroke, estimated glomerular filtration rate <20 ml/min/1.73 m², New York Heart Association functional class III or IV heart failure, or malignancy in the previous 10 years (10). All patients provided written informed consent. The protocol was approved by the ethics committee at each center.

RANDOMIZATION AND STUDY GROUPS. Patients in the FOURIER trial were randomly assigned, in a 1:1 ratio, to receive either subcutaneous evolocumab (140 mg every 2 weeks or 420 mg every month, according to patient preference) or matching placebo. Double-blind randomization was performed with stratification according to region and final screening levels of LDL-C (<85 mg/dl or ≥85 mg/dl [<2.2 or ≥2.2 mmol/l]).

ENDPOINTS. The primary endpoint of patient-reported cognition was measured only at the final visit and directly reported by patients using an abbreviated 23-item questionnaire including the executive and memory domain subscales of the Everyday Cognition (ECog) scale (Supplemental Table 1). The ECog questionnaire was designed as a multidimensional and psychometrically sound measure of everyday function in older adults (11). The ECog-23 shortened version has been developed and validated against the complete version, including 39 items with an excellent discrimination of clinical diagnosis groups (12). For each item, patients rated their current ability to perform certain tasks in comparison with the beginning of the study. Change over time was rated on a 4-point scale for each item, with lower scores representing better function: 1) better or no change; 2) questionable or occasionally worse; 3) consistently a little worse; and 4) consistently much worse.

The memory domain consisted of 8 questions evaluating whether patients had changes in remembering or recalling different aspects of life (e.g., contents of previous conversations, location of objects, current date, future appointments). Executive function was divided into the evaluation of planning, organization, and divided attention. The planning subdomain of executive function evaluated abilities such as planning, anticipation, and thinking ahead. The organization subdomain of executive function evaluated abilities with workspaces, checkbooks,

TABLE 1 Baseline Characteristics of Patients in the FOURIER Study With a Completed Everyday Cognition Questionnaire

	Placebo (n = 11,292)	Evolocumab (n = 11,363)
Age, yrs	62.5 ± 8.9	62.5 ± 9.0
Male	8,577 (76.0)	8,619 (75.9)
White race	9,602 (85.0)	9,680 (85.2)
Region		
North America	1,771 (15.7)	1,795 (15.8)
Europe	7,144 (63.3)	7,187 (63.2)
Latin America	704 (6.2)	696 (6.1)
Asia-Pacific and South Africa	1,673 (14.8)	1,685 (14.8)
Type of cardiovascular disease		
Myocardial infarction	9,215 (81.6)	9,181 (80.8)
Nonhemorrhagic stroke	2,111 (18.7)	2,123 (18.7)
Symptomatic peripheral artery disease	1,458 (12.9)	1,508 (13.3)
CHA ₂ DS ₂ -VASc score* ≥4	5,120 (45.3)	5,270 (46.4)
Nonstroke-related neurological disorder	967 (8.6)	1,026 (9.0)
Atrial fibrillation at any time	944 (8.4)	884 (7.8)
Congestive heart failure	2,269 (20.1)	2,277 (20.0)
Hypertension	8,916 (79.0)	8,948 (78.7)
Diabetes	4,049 (35.9)	4,079 (35.9)
Current cigarette use	3,127 (27.7)	3,106 (27.3)
Statin use		
High intensity	7,712 (68.3)	7,795 (68.6)
Moderate intensity	3,556 (31.5)	3,537 (31.1)
Ezetimibe use	601 (5.3)	616 (5.4)
Use of other cardiovascular medications		
Aspirin or P2Y ₁₂ inhibitor	10,412 (92.2)	10,535 (92.8)
Beta-blocker	8,496 (75.3)	8,571 (75.5)
ACE inhibitor or ARB, aldosterone antagonist, or both	8,759 (77.6)	8,852 (77.9)
Lipid measures		
LDL-C, mg/dl	92 (80-108)	91 (80-108)
Total cholesterol, mg/dl	167 (151-188)	167 (151-188)
HDL-C, mg/dl	44 (37-53)	44 (37-53)
Triglycerides, mg/dl	133 (99-182)	134 (101-183)
Lipoprotein(a), nmol/l	37 (13-165)	37 (12-166)

Values are mean ± SD, n (%), or median (interquartile range). p > 0.05 for all comparisons. *CHA₂DS₂-VASc score is assigned as follows: congestive heart failure (1 point), hypertension (1 point), 75 years of age or older (2 points), diabetes mellitus (1 point), prior stroke or transient ischemic attack (2 points), vascular disease (1 point), 65 to 74 years of age (1 point), and female sex (1 point).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; FOURIER = Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

financial records, task prioritization, and medication schedules. The divided attention subdomain of the executive function evaluated the ability to perform multitasking activities (Supplemental Table 1).

STATISTICAL ANALYSIS. The study population included patients who completed the ECog questionnaire at the final visit of the FOURIER trial (Supplemental Figure 1). ECog measurements were analyzed in the main analysis as binary and ordinal

TABLE 2 Frequency of Responses on the Everyday Cognition Questionnaire at the End of the Study With Evolocumab Versus Placebo

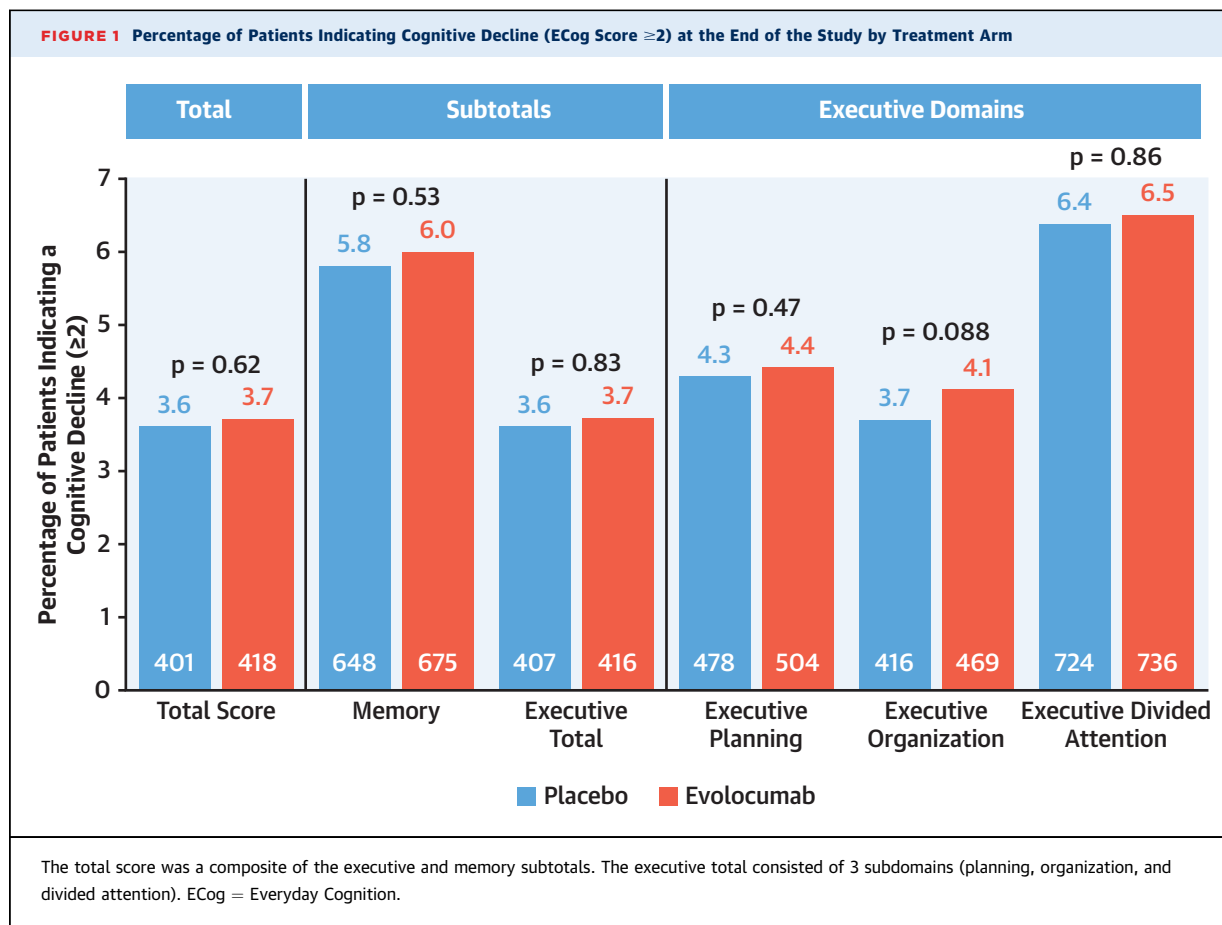
	Placebo	Evolocumab	Between-Group Difference, % (95% CI)	p Value
Memory	11,263	11,348		0.87
1.00	7,795 (69.2)	7,892 (69.6)	−0.3 (−1.5 to 0.9)	
1.00-1.99	2,820 (25.0)	2,781 (24.5)	0.5 (−0.6 to 1.7)	
2.00-2.99	528 (4.7)	555 (4.9)	−0.2 (−0.8 to 0.4)	
3.00-3.99	106 (0.94)	105 (0.93)	0.02 (−0.24 to 0.27)	
4.00	14 (0.12)	15 (0.13)	−0.01 (−0.11 to 0.09)	
Executive: planning	11,255	11,339		0.35
1.00	9,585 (85.2)	9,597 (84.6)	0.5 (−0.4 to 1.5)	
1.00-1.99	1,192 (10.6)	1,238 (10.9)	−0.3 (−1.1 to 0.5)	
2.00-2.99	379 (3.4)	408 (3.6)	−0.2 (−0.7 to 0.3)	
3.00-3.99	85 (0.76)	84 (0.74)	0.01 (−0.21 to 0.24)	
4.00	14 (0.12)	12 (0.11)	0.02 (−0.07 to 0.11)	
Executive: organization	11,254	11,338		0.19
1.00	9,459 (84.1)	9,483 (83.6)	0.4 (−0.6 to 1.4)	
1.00-1.99	1,379 (12.3)	1,386 (12.2)	0.0 (−0.8 to 0.9)	
2.00-2.99	316 (2.8)	355 (3.1)	−0.3 (−0.8 to 0.1)	
3.00-3.99	82 (0.73)	100 (0.88)	−0.15 (−0.39 to 0.08)	
4.00	18 (0.16)	14 (0.12)	0.04 (−0.07 to 0.14)	
Executive: divided attention	11,238	11,321		0.29
1.00	9,037 (80.4)	9,000 (79.5)	0.9 (−0.1 to 2.0)	
1.00-1.99	1,477 (13.1)	1,585 (14.0)	−0.9 (−1.8 to 0.0)	
2.00-2.99	567 (5.1)	583 (5.2)	−0.1 (−0.7 to 0.5)	
3.00-3.99	127 (1.1)	128 (1.1)	0.0 (−0.3 to 0.3)	
4.00	30 (0.27)	25 (0.22)	0.05 (−0.09 to 0.18)	
Executive: total score	11,260	11,345		0.60
1.00	8,332 (74.0)	8,348 (73.6)	0.4 (−0.7 to 1.6)	
1.00-1.99	2,521 (22.4)	2,581 (22.8)	−0.4 (−1.5 to 0.7)	
2.00-2.99	320 (2.8)	333 (2.9)	−0.1 (−0.5 to 0.3)	
3.00-3.99	77 (0.68)	76 (0.67)	0.01 (−0.20 to 0.23)	
4.00	10 (0.09)	7 (0.06)	0.03 (−0.05 to 0.11)	
Total score (memory or executive)	11,263	11,349		0.75
1.00	7,254 (64.4)	7,289 (64.2)	0.2 (−1.1 to 1.4)	
1.00-1.99	3,608 (32.0)	3,642 (32.1)	−0.1 (−1.3 to 1.2)	
2.00-2.99	326 (2.9)	348 (3.1)	−0.2 (−0.6 to 0.3)	
3.00-3.99	67 (0.59)	63 (0.56)	0.04 (−0.16 to 0.24)	
4.00	8 (0.07)	7 (0.06)	0.01 (−0.06 to 0.09)	

Values are n (%) unless otherwise indicated. Lower scores indicate better function, and higher scores indicate worse performance. The p value for association between Everyday Cognition score and treatment group is based on the Mantel-Haenszel chi-square test.
CI = confidence interval.

scales. Categorical response was defined either as a 5-level category or as a binary outcome using the cutoff of ≥ 2 versus < 2 , as in the EBBINGHAUS trial (8). The Mantel-Haenszel chi-square test and log-linear regression were used to analyze these categorical outcomes. The ordinal outcome was defined in line with the response scale for each ECog domain using cutoffs of 1.00, 1.00 to 1.99, 2.00 to 2.99, 3.00 to 3.99, and 4.00. For the ordinal ECog scale, the partial proportional odds model was fitted separately for the ECog total score and each of the subdomains. As shown in the [Supplemental Appendix](#), we used the Tobit regression to model continuous ECog scores. The Tobit regression is a type of linear regression model

that can account for the distribution of a continuous outcome that has a number of its values clustered at a limiting value (i.e., left and/or right censoring in outcome variable), as previously reported in studies evaluating ECog scores (13).

In addition, patients were also categorized into 5 pre-specified subgroups on the basis of their achieved LDL-C values at 4 weeks and irrespective of treatment assignment: < 20 , 20 to < 50 , 50 to < 70 , 70 to < 100 , and 100 mg/dl or higher (7). We tested trends in ECog scores across increasing levels of achieved LDL-C using the partial proportional odds model for ordinal scale as well as Tobit regression for censored continuous outcome ([Supplemental Appendix](#)). The



trend tests were adjusted for previously described baseline predictors of achieving a low LDL-C level: age, sex, race, body mass index, geographic region, baseline LDL-C, diabetes, chronic kidney disease, and use of a P2Y₁₂ inhibitor (7). The differences in mean total score by treatment group were further examined by pre-specified subgroups of interest for assessment of interaction. Because of the exploratory nature of analyses and the use of ECog score as a safety endpoint, no adjustments for multiple testing were made. Thus, statistical significance was assessed at a nominal alpha level of 0.05. All reported p values are 2-sided. All statistical computations were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 22,655 patients (11,292 randomized to placebo and 11,363 randomized to evolocumab, 82.2% of the overall trial) underwent assessments of patient-

reported cognition and constituted the study sample for these analyses. The baseline characteristics are provided in [Table 1](#), as well as in [Supplemental Tables 2 and 3](#) (for comparisons with the ECog nonresponder population).

The reported scores in everyday cognitive function with evolocumab versus placebo had a similar trend in both groups for all cognitive domains ([Table 2](#)). As seen in [Figure 1](#), the percentages of patients reporting declines in cognition (average ECog score ≥ 2) were similar between placebo and evolocumab for the total score (3.6% vs. 3.7%; $p = 0.62$), memory function (5.8% vs. 6.0%; $p = 0.53$), executive total score (3.6% vs. 3.7%; $p = 0.83$), executive planning (4.3% vs. 4.4%; $p = 0.47$), executive organization (3.7% vs. 4.1%; $p = 0.088$), and executive divided attention (6.4% vs. 6.5%; $p = 0.86$). The mean patient-reported changes in memory, executive function, and total scores were comparable across the treatment arms and for each of the explored subdomains ([Supplemental Table 4](#)).

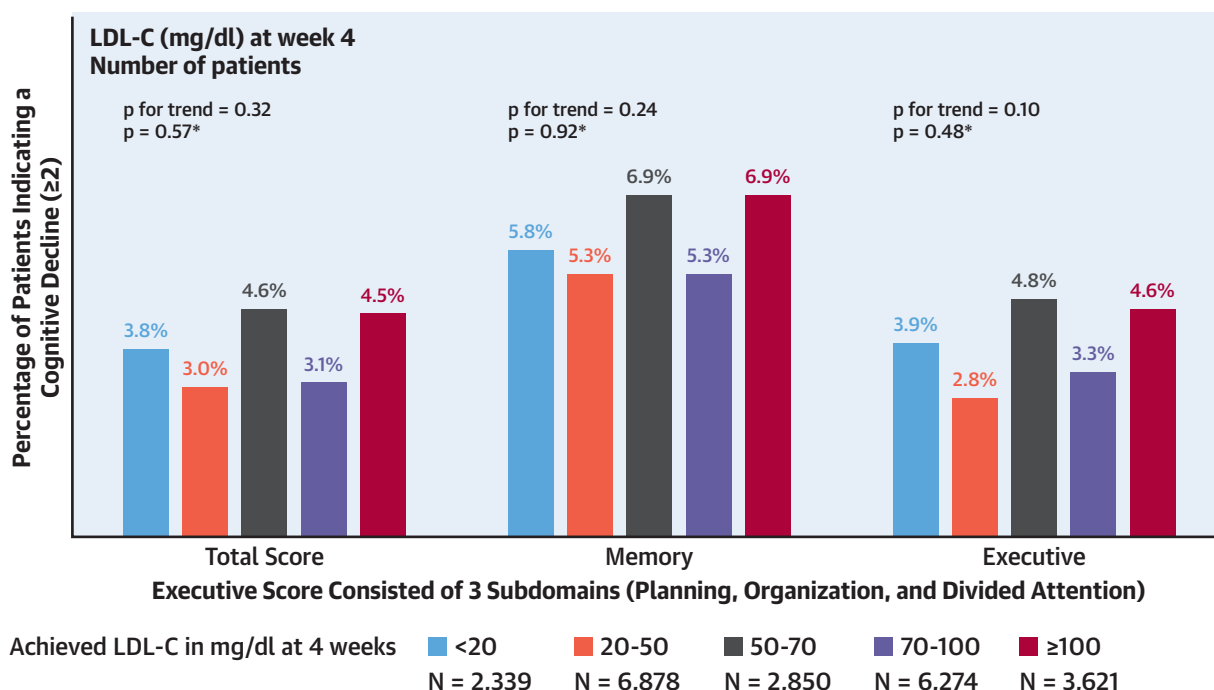
TABLE 3 Changes in Everyday Cognition at the End of the Study by LDL-C Level Achievement at 4 Weeks

	Pre-Specified LDL-C at 4 Weeks (mg/dl) (N = 21,962)					p Value for Trend
	<20 (n = 2,339)	20-50 (n = 6,878)	50-70 (n = 2,850)	70-100 (n = 6,274)	≥100 (n = 3,621)	
Memory function	2,338	6,869	2,843	6,258	3,613	0.12
1.00	1,636 (70.0)	4,857 (70.7)	1,894 (66.6)	4,370 (69.8)	2,474 (68.5)	
1.00 to 1.99	566 (24.2)	1,650 (24.0)	752 (26.5)	1,554 (24.8)	891 (24.7)	
2.00 to 2.99	114 (4.9)	302 (4.0)	163 (5.7)	266 (4.3)	201 (5.6)	
3.00 to 3.99	19 (0.8)	51 (0.7)	31 (1.0)	60 (1.0)	43 (1.2)	
4.00	3 (0.1)	9 (0.1)	3 (0.1)	8 (0.1)	4 (0.1)	
Executive function	2,338	6,868	2,841	6,256	3,613	0.38
1.00	1,717 (73.4)	5,188 (75.5)	2,032 (71.5)	4,655 (74.4)	2,600 (72.0)	
1.00 to 1.99	531 (22.7)	1,488 (21.7)	674 (23.7)	1,397 (22.3)	846 (23.4)	
2.00 to 2.99	72 (3.1)	153 (2.2)	113 (4.0)	156 (2.5)	135 (3.7)	
3.00 to 3.99	16 (0.7)	36 (0.5)	22 (0.8)	43 (0.7)	27 (0.8)	
4.00	2 (0.1)	3 (0.04)	0 (0)	5 (0.1)	5 (0.1)	
Total function	2,338	6,870	2,843	6,258	3,613	0.33
1.00	1,501 (64.2)	4,521 (65.8)	1,757 (61.8)	4,037 (64.5)	2,293 (63.5)	
1.00 to 1.99	749 (32.0)	2,144 (31.2)	955 (33.6)	2,026 (32.4)	1,158 (32.1)	
2.00 to 2.99	72 (3.1)	176 (2.6)	114 (4.0)	150 (2.4)	133 (3.7)	
3.00 to 3.99	14 (0.6)	27 (0.4)	16 (0.6)	40 (0.6)	26 (0.7)	
4.00	2 (0.1)	2 (0.03)	1 (0.04)	5 (0.1)	3 (0.1)	

Values are n or n (%). The analysis population includes those who have both LDL-C and ECog measurements. The LDL-C groups were pre-specified on the basis of a previous publication from FOURIER (7). Lower scores indicate better function, and higher scores indicate worse performance. The p value for trend is based on partial proportional odds models. The models apply to patients who had both LDL-C values at 4 weeks and ECog surveys completed and were adjusted for age, sex, race, body mass index, geographic region, use of a P2Y₁₂ inhibitor, LDL-C at baseline, diabetes, and chronic kidney disease.

Abbreviations as in Table 1.

FIGURE 2 Percentage of Patients Indicating Cognitive Decline (ECog Score ≥2) at the End of the Study by Achieved LDL-C Target at 4 Weeks



The analysis population includes those who have both LDL-C and ECog measurements. The total score was a composite of the executive and memory domains. The executive total score was the composite of executive function in planning, organization, and divided attention. The models apply to patients who had both LDL-C values at 4 weeks and ECog surveys completed and were adjusted for age, sex, race, body mass index, geographic region, use of a P2Y₁₂ inhibitor, low-density lipoprotein cholesterol (LDL-C) at baseline, diabetes, and chronic kidney disease. *Comparing proportion of patients indicating cognitive decline (ECog ≥2) between achieved LDL-C <20 mg/dl and LDL-C ≥100 mg/dl. ECog = everyday cognition.

TABLE 4 Frequency of Patients Indicating a Decline on the Everyday Cognition Questionnaire (Score ≥ 2) at the End of the Study With Evolocumab Versus Placebo in Pre-Specified Subgroups

Subgroup	Number	Placebo	Evolocumab	Odds Ratio (95% CI)	p Value for Interaction
Age					0.63
<65 yrs	12,518	188 (3.0)	200 (3.2)	1.07 (0.87-1.31)	
≥ 65 yrs	10,094	213 (4.3)	218 (4.3)	1.00 (0.83-1.21)	
Age					0.14
<75 yrs	20,613	328 (3.2)	356 (3.5)	1.08 (0.93-1.26)	
≥ 75 yrs	1,999	73 (7.4)	62 (6.1)	0.81 (0.57-1.15)	
Sex					0.41
Male	17,165	273 (3.2)	273 (3.2)	0.99 (0.84-1.18)	
Female	5,447	128 (4.7)	145 (5.3)	1.13 (0.88-1.44)	
Region of enrollment					0.40
Europe	14,306	320 (4.5)	313 (4.4)	0.97 (0.83-1.14)	
North America	3,549	29 (1.7)	40 (2.2)	1.36 (0.84-2.21)	
Asia Pacific	3,357	26 (1.6)	33 (2.0)	1.26 (0.75-2.12)	
Latin America	1,400	26 (3.7)	32 (4.6)	1.26 (0.74-2.13)	
Final LDL-C at screening					0.91
≥ 85 mg/dl	14,656	271 (3.7)	282 (3.8)	1.03 (0.87-1.22)	
<85 mg/dl	7,953	130 (3.3)	136 (3.4)	1.05 (0.82-1.34)	
Prior cerebrovascular disease					0.99
Yes	5,129	136 (5.3)	142 (5.5)	1.03 (0.81-1.32)	
No	17,483	265 (3.0)	276 (3.2)	1.04 (0.87-1.23)	
High-intensity statin					0.96
Yes	15,471	289 (3.8)	303 (3.9)	1.04 (0.88-1.22)	
No	7,141	112 (3.1)	115 (3.2)	1.03 (0.79-1.34)	
CHA ₂ DS ₂ -VASC score*					0.29
>4	10,370	254 (5.0)	283 (5.4)	1.09 (0.91-1.29)	
≤ 3	12,241	147 (2.4)	135 (2.2)	0.93 (0.73-1.17)	
Current smoker					0.78
Yes	6,221	113 (3.6)	120 (3.9)	1.07 (0.82-1.39)	
No	16,389	288 (3.5)	298 (3.6)	1.02 (0.87-1.21)	
Atrial fibrillation					0.61
Yes	1,817	43 (4.6)	46 (5.2)	1.15 (0.75-1.76)	
No	20,795	358 (3.5)	372 (3.6)	1.03 (0.88-1.19)	
Nonstroke neurological disease					0.56
Yes	1,990	46 (4.8)	56 (5.5)	1.15 (0.77-1.72)	
No	20,622	355 (3.5)	362 (3.5)	1.02 (0.88-1.18)	
Diabetes					0.40
Yes	8,109	163 (4.0)	182 (4.5)	1.11 (0.90-1.38)	
No	14,503	238 (3.3)	236 (3.2)	0.98 (0.82-1.18)	

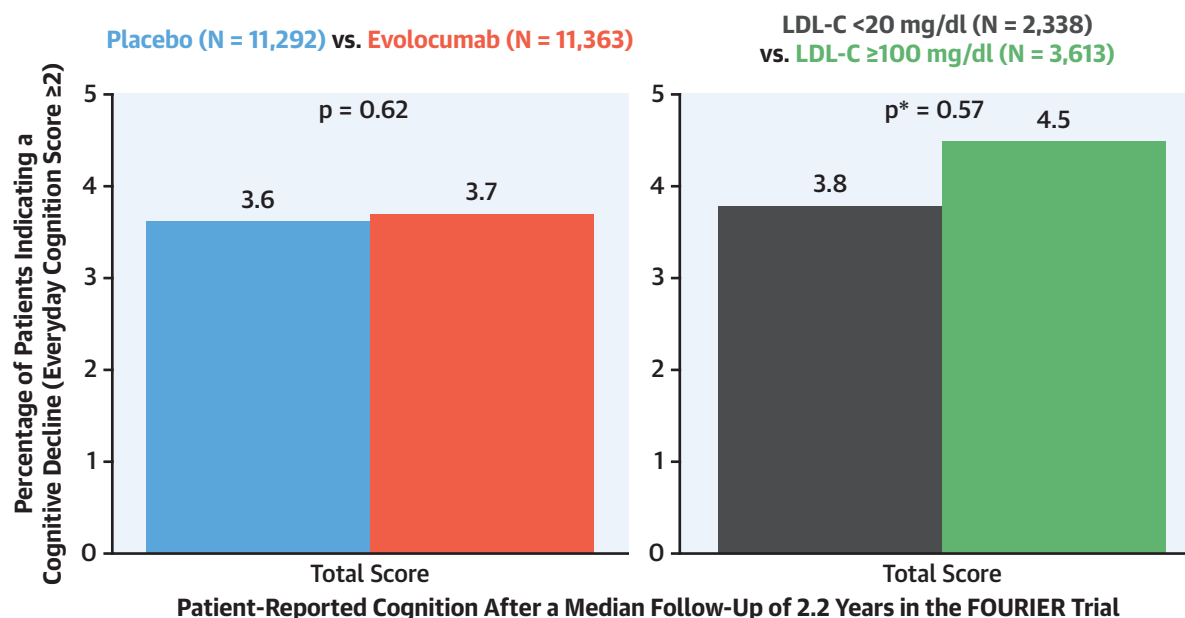
Values are n (%) unless otherwise indicated. The p values for interaction are from chi-square tests. *CHA₂DS₂-VASC score is assigned as follows: congestive heart failure (1 point), hypertension (1 point), 75 years of age or older (2 points), diabetes mellitus (1 point), prior stroke or transient ischemic attack (2 points), vascular disease (1 point), 65 to 74 years of age (1 point), and female sex (1 point).

CI = confidence interval; LDL-C = low-density lipoprotein cholesterol.

The trend in patient-reported cognition at the end of the study did not significantly differ by achieved LDL-C at week 4 (Table 3). There was no significant trend across the groups of achieved LDL-C after multivariate adjustment for total score, memory or executive score ($p_{\text{trend}} = 0.33$, $p_{\text{trend}} = 0.12$, and $p_{\text{trend}} = 0.38$, respectively). In Figure 2, the frequency of participants reporting declines in cognition (average ECog score ≥ 2) was similar between those

with very low LDL-C (<20 mg/dl; $n = 2,338$) and those with LDL-C (≥ 100 mg/dl; $n = 3,613$) for total score (3.8% vs. 4.5%; $p = 0.57$), memory function (5.8% vs. 6.9%; $p = 0.92$), and executive function (3.9% vs. 4.6%; $p = 0.48$). The mean patient-reported changes at the end of the study were comparable across achieved LDL-C levels at week 4 (Supplemental Table 5).

Patient-reported decline in cognition with placebo versus evolocumab was consistent across of all pre-

CENTRAL ILLUSTRATION Percentage of Patients Indicating Cognitive Decline (Everyday Cognition Score ≥ 2) at the End of the Study by Treatment Arm and Achieved Low-Density Lipoprotein-Cholesterol Target at 4 WeeksGencer, B. *et al.* J Am Coll Cardiol. 2020;75(18):2283-93.

The total score consisted of the 2 subdomains (executive and memory function). *The comparison of scores based on achieved low-density lipoprotein cholesterol (LDL-C) applies to patients who had both LDL-C values at 4 weeks and ECog surveys completed and were adjusted for age, sex, race, body mass index, geographic region, use of a P2Y₁₂ inhibitor, LDL-C at baseline, diabetes, and chronic kidney disease. FOURIER = Further Cardiovascular Outcomes Research With PCSK9 inhibitors in Subjects With Elevated Risk.

specified baseline subgroups with no significant interactions, including in patients stratified at 75 years of age (Table 4, Supplemental Table 6).

DISCUSSION

In an analysis of 22,655 patients with stable atherosclerotic CV disease, we found no significant impact of evolocumab on patient-reported cognition after a median follow-up period of 2.2 years. Furthermore, no association was found between on-treatment LDL-C concentration at 4 weeks and subsequent cognitive function, even among the 2,339 patients who achieved LDL-C concentrations <20 mg/dl (Central Illustration). These findings are unique in that they represent the first analysis of a large randomized clinical trial reporting patient-reported cognition with a PCSK9 inhibitor in whom the median LDL-C was 30 mg/dl.

Our current data concur with similar observations from the EBBINGHAUS trial of 1,204 patients, which

revealed no significant differences between evolocumab and placebo in objective cognitive function assessed using the CANTAB over a median of 19 months (8). In addition, no association was found between achieved LDL-C and changes in cognitive function as measured using the CANTAB (8). Of note, CANTAB assessments consisted of a battery of objective, tablet-based tests, differing from the subjective patient-reported ECog survey of everyday cognitive function.

Some observational data indicate that naturally low serum cholesterol levels are associated with poorer cognitive performance (14). In 2012, the U.S. Food and Drug Administration issued a warning regarding potential adverse effects of statin therapy on cognition, on the basis of the Adverse Events Reporting System and a review of published medical research (15), although rigorous reviews of the available evidence concluded that no strong evidence supported this conjecture (16,17). In the Heart Protection Study in 20,536 patients with CV disease or

other high-risk conditions, simvastatin reduced the risk for vascular events by 20% (95% CI: 8% to 29%), including ischemic events (18). No significant differences were observed between simvastatin and placebo in the percentage of patients with impaired cognition (23.7% simvastatin vs. 24.2% placebo), and similar numbers were reported for the incidence of dementia during follow-up (0.3% vs. 0.3%) (18). In the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) study, no differences were found in cognitive testing among 5,804 participants with pre-existing vascular disease or at increased risk because of smoking, hypertension, or diabetes between the pravastatin and placebo arms over a median follow-up period of 3 years (19). The 2014 National Lipid Association Task Force on Statin Safety concluded that statin therapy was not associated with adverse effects on cognition and did not recommend assessing cognitive function before initiating treatment with a statin (20). Finally, a meta-analysis of 25 RCTs including 46,836 subjects concluded that adverse cognitive outcomes attributable to statins were rarely reported in trials involving cognitively normal or impaired subjects, and cognitive test data in 27,643 participants receiving either statin or placebo supported these findings (21).

Interventions to further lower LDL-C, especially in high-risk patients, have been shown to consistently reduce stroke with statin, as well as ezetimibe and PCSK9 inhibitors in addition to standard care (4,5,22,23). An individual participant data analysis of 134,537 participants in 22 statin trials reported a relative risk reduction of 15% (95% CI: 11% to 20%) per 1 mmol/l reduction in LDL-C of any stroke events with statin or more intensive therapy regardless of age (24).

Vascular dementia is a common finding at autopsy in population-based cohorts in subjects with and those without clinical manifestation of stroke (25), so the reduction of stroke events with lipid-lowering therapies could potentially diminish the risk for vascular dementia (26). Recently, pretreatment with a PCSK9 inhibitor has been shown to protect the brain against cardiac ischemia/reperfusion injury by reducing neuronal inflammation and amyloid beta aggregation (27). A previous meta-analysis including 7 observational studies reported a risk reduction of cognitive impairment with the use of statin compared with nonusers (relative risk: 0.43; 95% CI: 0.31 to 0.62) (28). While further studies should consider the long-term impact of

PCSK9 inhibition on the reduction of dementia, both evolocumab and alirocumab have shown reductions in stroke without any increase in neurocognitive side effects (4,5).

The major strength of this study is the use of patient-reported everyday cognition over the study period. Given the very large size of FOURIER, we had >95% power to detect a 1 percentage point absolute treatment difference. Likewise, we had 90% power to detect an approximately 2 percentage point absolute difference between the lowest and highest LDL-C groups and a minimum detectable difference of 1.2 percentage points. Lipid-lowering therapies, especially statins, can be negatively perceived by patients (29,30). The public perception of the adverse effects of statins is often exaggerated, in part as a consequence of media reports (31). In this context, the use of patient-reported outcomes has a particular significance to reassure patients and doctors.

STUDY LIMITATIONS. Patient-reported cognition with ECog was measured only at 1 time point, at the end of the study, after a follow-up period of only 2.2 years. Not all patients from FOURIER completed the survey (82% of the randomized participants), but by and large there were not clinically important differences between the ECog responders and nonresponders. The dropout rates were 18% in both arms, but we acknowledge that the participants who reported ECog had lower rates of incident major adverse CV events compared with their nonresponder counterparts. ECog is considered a validated and appropriate instrument for the measurement of everyday function in older adults, but it does not include an exhaustive list of all aspects of cognitive function (11). The instrument is sensitive, however, to detect differences in levels of functional impairment across a range of clinical diagnostics (normal vs. mild cognitive impairment vs. dementia) (32). Finally, achieved LDL-C concentration at 4 weeks is a post-randomization variable, but we used multivariate adjustment to limit confounding due to differences in baseline characteristics across the groups of achieved LDL-C, as had been performed previously (7).

CONCLUSIONS

We observed that patients treated with evolocumab, as well as those who achieved progressively very low LDL-C at 4 weeks in the FOURIER trial, had similar self-reported cognition in comparison with those receiving placebo and those with higher achieved

LDL-C levels, extending previous findings reported in the EBBINGHAUS trial. These data confirm the neurocognitive safety of intensive LDL-C reduction with evolocumab while reducing recurrent CV events in high-risk patients, and suggest that very low achieved LDL-C levels may be safely targeted for high-risk patients.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: Addition of a PCSK9 inhibitor to a maximally tolerated dose of statin medication has no adverse impact on patient-reported neurocognitive function, even when LDL-C falls below 20 mg/dL.

TRANSLATIONAL OUTLOOK: More data are needed to characterize patient-reported experiences with long-term CV therapies.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.