ORIGINAL ARTICLE

Cognitive Function in a Randomized Trial of Evolocumab

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ABSTRACT

BACKGROUND

Findings from clinical trials of proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors have led to concern that these drugs or the low levels of low-density lipoprotein (LDL) cholesterol that result from their use are associated with cognitive deficits.

METHODS

In a subgroup of patients from a randomized, placebo-controlled trial of evolocumab added to statin therapy, we prospectively assessed cognitive function using the Cambridge Neuropsychological Test Automated Battery. The primary end point was the score on the spatial working memory strategy index of executive function (scores range from 4 to 28, with lower scores indicating a more efficient use of strategy and planning). Secondary end points were the scores for working memory (scores range from 0 to 279, with lower scores indicating fewer errors), episodic memory (scores range from 0 to 70, with lower scores indicating fewer errors), and psychomotor speed (scores range from 100 to 5100 msec, with faster times representing better performance). Assessments of cognitive function were performed at baseline, week 24, yearly, and at the end of the trial. The primary analysis was a noninferiority comparison of the mean change from baseline in the score on the spatial working memory strategy index of executive function between the patients who received evolocumab and those who received placebo; the noninferiority margin was set at 20% of the standard deviation of the score in the placebo group.

RESULTS

A total of 1204 patients were followed for a median of 19 months; the mean (±SD) change from baseline over time in the raw score for the spatial working memory strategy index of executive function (primary end point) was −0.21±2.62 in the evolocumab group and −0.29±2.81 in the placebo group ($P<0.001$ for noninferiority; $P=0.85$ for superiority). There were no significant between-group differences in the secondary end points of scores for working memory (change in raw score, −0.52 in the evolocumab group and −0.93 in the placebo group), episodic memory (change in raw score, −1.53 and −1.53, respectively), or psychomotor speed (change in raw score, 5.2 msec and 0.9 msec, respectively). In an exploratory analysis, there were no associations between LDL cholesterol levels and cognitive changes.

CONCLUSIONS

In a randomized trial involving patients who received either evolocumab or placebo in addition to statin therapy, no significant between-group difference in cognitive function was observed over a median of 19 months. (Funded by Amgen; EBBINGHAUS ClinicalTrials.gov number, NCT02207634.)

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Statin therapy,[1] ezetimibe,[2] and the proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor evolocumab[3] have been shown to reduce the rate of cardiovascular events among patients with established cardiovascular disease. These therapies may result in very low levels of low-density lipoprotein (LDL) cholesterol. Postmarketing surveillance reports, observational studies, and some small randomized trials of statin therapy[4,5] have suggested that statins — or the low levels of LDL cholesterol that result from their use — may be associated with impaired cognitive function, which led the Food and Drug Administration to issue a warning in 2012.[6] However, it remains unclear whether the putative adverse effects of statins on cognitive function can be attributed to their effect of lowering LDL cholesterol level or to other effects unique to this class of drugs. For example, systematic reviews and meta-analyses have not shown consistent evidence of adverse effects of statins on cognition, and the Statin Cognitive Safety Task Force in 2014 concluded that statins are not associated with these adverse effects.[7] Furthermore, a recent study that used eight neuropsychological measures and functional magnetic resonance imaging showed no convincing evidence of memory dysfunction as a result of atorvastatin therapy.[8]

Two moderately sized trials of PCSK9 inhibitors for lowering LDL cholesterol level[9,10] and a meta-analysis that included smaller trials[11] showed an association between these drugs and cognitive adverse events reported by the patients. However, the incidence of these symptoms was less than 1%, with broad confidence intervals around the observed hazard ratio. Published data from prospective assessments of the effect of PCSK9 inhibitors on cognitive function that used validated instruments are lacking. In the Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS) study,[12] we prospectively evaluated cognition using the Cambridge Neuropsychological Test Automated Battery (CANTAB, www.cambridgecognition.com) among patients who had been randomly assigned to receive either the PCSK9 inhibitor evolocumab or placebo in addition to statin therapy. These tests have been used in more than 160 clinical trials, in all phases of drug development, and with a broad range of medications; they are sensitive to both positive and negative effects of drugs on cognition.[13-17]

Methods

Trial Design and Oversight

The EBBINGHAUS study involved a subgroup of patients from the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, which evaluated the efficacy and safety of evolocumab for the reduction of LDL cholesterol level.[3,18] An executive committee (for a list of committee members, see the Supplementary Appendix, available with the full text of this article at NEJM.org), Cambridge Cognition (the neuroscience digital health company that developed CANTAB), and Amgen (the trial sponsor) collaborated in designing the trial.[12] The protocol, available at NEJM.org, was approved by the ethics committee at each participating site. The sponsor was responsible for collection of the data and supplied the study drug and placebo. Members of the Thrombolysis in Myocardial Infarction (TIMI) Study Group conducted all analyses of the data independently of the sponsor. The first author wrote the first draft of the manuscript, and all the coauthors participated in subsequent revisions. All the authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the protocol.

Trial Population

The participants in the FOURIER trial[3,18] were between 40 and 85 years of age, had clinically evident atherosclerosis and an LDL cholesterol level of 70 mg per deciliter (1.8 mmol per liter) or higher or a non–high-density lipoprotein level of 100 mg per deciliter (2.6 mmol per liter) or higher, and were receiving moderate-intensity or high-intensity statin therapy. The participating centers in 29 countries were encouraged to enroll patients in the EBBINGHAUS study before the administration of the first dose of the study drug or placebo in the FOURIER trial, although enrollment was permitted until the 12-week visit in the FOURIER trial. Exclusion criteria were current or past diagnosis of dementia or mild cognitive impairment or any condition or situation, including other mental or neurologic disorders, that, in the investigator's opinion, could confound the study results or considerably interfere with the patient's participation in the trial. All the patients provided written informed consent.

RANDOMIZATION AND STUDY GROUPS

Patients in the FOURIER trial were randomly assigned, in a 1:1 ratio, to receive subcutaneous evolocumab (140 mg every 2 weeks or 420 mg every month, according to patient preference) or to receive matching placebo. Double-blind randomization was performed with the use of a central, 24-hour, interactive, computerized response system, with stratification according to region and final screening LDL cholesterol level (<85 mg per deciliter [2.2 mmol per liter] or ≥85 mg per deciliter).

END POINTS

The primary end point was the score on the spatial working memory strategy index of executive function, a principal component of CANTAB; CANTAB was performed at screening (training session), at baseline, at 24 weeks, yearly, and at the end of the trial. CANTAB is a language-independent and culture-independent computerized cognitive assessment tool that uses touchscreen neuropsychological tests of cognition that are specifically designed to assess central nervous system disorders and cognitive function across a range of domains, including episodic and working memory, executive function, psychomotor speed, and attention (further details of CANTAB are provided in the Supplementary Appendix). The score on the spatial working memory strategy index of executive function indicates the number of times a patient begins a search with a different box than the one used to begin the search in the previous search sequence, across a total of four rounds of testing that have six or eight boxes (scores range from 4 to 28, with lower scores representing a more efficient use of strategy and planning).

The three secondary end points were measures of other components of CANTAB. Working memory was determined on the basis of the spatial working memory between-errors score, which indicates the number of times a person revisits a box in which a token has previously been found (scores range from 0 to 279, with lower scores indicating fewer errors); episodic memory was determined on the basis of the total number of errors a patient makes in a paired associates learning test, plus an adjustment for the estimated number of errors the patients would have made on any stages that were not reached (scores range from 0 to 70, with lower scores indicating fewer errors); and psychomotor speed was determined on the basis of the median 5-choice reaction time (i.e., the median duration between the onset of a stimulus and the release of a button, with faster times representing better performance).

Between-group differences with respect to the primary and secondary end points were assessed by a comparison of z scores, with the z score for an individual patient representing the difference between the score for that patient and the mean of the baseline score for all patients, divided by the standard deviation of the baseline score for all patients. The global composite score of CANTAB end points was a prespecified exploratory end point and was calculated by averaging the combined z scores of each of the four aforementioned CANTAB end points; higher scores indicate better performance.

In a prespecified exploratory analysis of everyday cognitive function at the final visit, patients performed self-assessments using a 23-item questionnaire that represented the executive and memory domain subscales of a shortened version of the Everyday Cognition (ECog) tool (see the Supplementary Appendix).[19] For each item, patients compared the current level of everyday functioning with their retrospective assessment of their level at the beginning of the trial (scores ranged from 1 to 5, with lower scores representing better functioning). Mean overall ECog scores and mean scores for each individual domain of the ECog questionnaire were compared between study groups. Clinical cognitive adverse events were categorized according to Medical Dictionary for Regulatory Activities (MedDRA) lowest-level terms and were compared between the study groups.

STATISTICAL ANALYSIS

The primary-analysis population included patients who had a baseline CANTAB assessment before or on the day of the first dose of the study drug or placebo (which was administered in a blinded manner) and had at least one follow-up CANTAB assessment. The full-analysis population included, in addition, patients whose first CANTAB assessment occurred after the day on which the first dose of the study drug or placebo was administered. Data obtained from patients who had a stroke were censored from the analysis after the date of stroke onset.

The primary analysis was a noninferiority comparison of the mean change in score on the spatial working memory strategy index of execu-

tive function from baseline over time (i.e., the difference between the score at baseline and the mean score of all assessments after baseline) between the patients in the evolocumab group and the patients in the placebo group. A mixed-effects linear model for repeated measures was used to estimate treatment differences (the difference in change in z scores) between study groups, with associated 95% confidence intervals. The model included the stratification factors, age, educational level, score on the baseline spatial working memory strategy index, study group, visit, and interaction between study group and visit. The noninferiority boundary was set at 20% of the standard deviation (i.e., Cohen's d statistic[20] <0.20), which we estimated from observations in the placebo group. A two-sided alpha level of 5% was used to test for superiority with respect to the primary end point. We estimated that a sample size of 1500 patients would provide approximately 97% power to detect noninferiority and 83% power to detect superiority. A nominal alpha level of 0.05 was used to indicate statistical significance. Additional exploratory analyses included all secondary end-point analyses; subgroup analyses; analyses of data according to visit; analyses stratified according to lowest-attained LDL cholesterol level of 25 mg per deciliter (0.6 mmol per liter) and 40 mg per deciliter (1.0 mmol per liter), which were prespecified cutoff points; and analyses in the full-analysis population. All statistical computations were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From September 10, 2014, through August 6, 2015, a total of 2442 patients in the FOURIER trial were screened for eligibility for the EBBINGHAUS study, and 1974 were enrolled (full-analysis population). The baseline characteristics of the 1204 patients in the primary-analysis population were similar in the two study groups (Table 1), and the baseline characteristics of the patients in the full-analysis population were similar to those of the patients in the primary-analysis population (Table S1 in the Supplementary Appendix). The mean age of the patients was 63 years, 72% were men, and participants had a mean of 12.7 years of education; more than three quarters of the patients had previously had a myocardial infarction, and one fifth had previously had an ischemic stroke. The median LDL cholesterol level at the time of randomization was 92 mg per deciliter (2.40 mmol per liter); 71% of the patients were receiving high-intensity statin therapy and 29% were receiving moderate-intensity statin therapy. The median duration of follow-up was 19.4 months (interquartile range, 19.0 to 21.8) in the primary-analysis population. Figure S1 in the Supplementary Appendix shows the randomization and follow-up of the full-analysis and primary-analysis populations. One patient in the full-analysis population did not receive the study drug and did not undergo CANTAB testing after baseline.

Baseline scores for all domains of the CANTAB tests were similar in the two study groups in both the primary-analysis population (Fig. 1) and the full-analysis population (Tables S1 and S2 in the Supplementary Appendix). These baseline scores were similar to those reported in a population-based cross-sectional cohort of healthy adults 56 to 86 years of age.[21,22]

OUTCOMES

The mean change from baseline over time in the raw score on the spatial working memory strategy index of executive function (primary end point) did not differ significantly between the two study groups; the raw score at baseline was 17.8 in both study groups, and the mean (±SD) change from baseline in the score was −0.21±2.62 in the evolocumab group and −0.29±2.81 in the placebo group (P<0.001 for noninferiority [based on the z scores] and P=0.85 for superiority) (Figs. 1 and 2). The mean changes in raw scores from baseline with respect to the secondary end points did not differ significantly between the evolocumab group and the placebo group. The raw between-errors score on the spatial working memory test at baseline was 20.9 in the evolocumab group and 21.0 in the placebo group; the mean changes in score from baseline were −0.52±8.15 and −0.93±7.82, respectively (P=0.36 based on the z scores). The raw score on the paired associates learning test at baseline was 26.5 in the evolocumab group and 25.2 in the placebo group; the mean changes in score from baseline were −1.53±12.9 and −1.53±13.5, respectively (P=0.49 based on the z scores). The raw score on the median 5-choice reaction time test at baseline was 356.7 msec in

Table 1. Baseline Characteristics of the Patients in the EBBINGHAUS Study with Baseline Cognitive Assessment (Primary-Analysis Population).*

Characteristics	Placebo (N=618)	Evolocumab (N=586)
Age — yr	62.8±8.7	62.6±8.6
Male sex — no. (%)	445 (72.0)	420 (71.7)
White race — no. (%)†	572 (92.6)	541 (92.3)
Years of education	12.8±3.4	12.6±3.1
Region — no. (%)		
North America	162 (26.2)	153 (26.1)
Europe	411 (66.5)	398 (67.9)
Asia–Pacific and South Africa	45 (7.3)	35 (6.0)
Type of cardiovascular disease — no. (%)‡		
Myocardial infarction	468 (75.7)	444 (75.8)
Nonhemorrhagic stroke§	129 (20.9)	111 (18.9)
Symptomatic peripheral artery disease	101 (16.3)	112 (19.1)
CHA_2DS_2-VASc score ≥4 — no. (%)¶	309 (50.0)	324 (55.3)
Neurologic disease that was not stroke — no. (%)	86 (13.9)	86 (14.7)
Hypertension — no. (%)	530 (85.8)	506 (86.3)
Diabetes mellitus — no. (%)	212 (34.3)	218 (37.2)
Current cigarette use — no. (%)‖	231 (37.4)	185 (31.6)
Atrial fibrillation at any time — no. (%)	62 (10.0)	53 (9.0)
Congestive heart failure — no. (%)	157 (25.4)	176 (30.0)
Statin use — no. (%)		
High intensity	454 (73.5)	399 (68.1)
Moderate intensity	164 (26.5)	187 (31.9)
Ezetimibe use — no. (%)	30 (4.9)	32 (5.5)
Use of other cardiovascular medications — no. (%)		
Aspirin, $P2Y_{12}$ inhibitor, or both	556 (90.0)	525 (89.6)
Beta-blocker	459 (74.3)	435 (74.2)
ACE inhibitor or ARB, aldosterone antagonist, or both	472 (76.4)	461 (78.7)
Median LDL cholesterol level (interquartile range) — mg/dl‖**	93 (80–110)	91 (79–108)

* Plus–minus values are means ±SD. There were no nominally significant differences between the two study groups in baseline characteristics except for current cigarette use (P=0.03) and statin intensity (P=0.04). ACE denotes angiotensin-converting enzyme, ARB angiotensin receptor blocker, and LDL low-density lipoprotein. To convert the values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

† Race was reported by the patient.

‡ Patients could have more than one type of cardiovascular disease.

§ Among the patients who had nonhemorrhagic stroke, the median (interquartile range) number of years from the most recent prior stroke was 4.6 (1.4 to 8.8) in the placebo group and 3.6 (1.1 to 8.1) in the evolocumab group.

¶ CHA_2DS_2-VASc scores, which assess the risk of stroke, range from 0 to 9, with higher scores indicating greater risk; points are 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).

‖ One patient in the placebo group had missing data.

** LDL cholesterol level was calculated with the use of the Friedewald equation, unless the calculated value was lower than 40 mg per deciliter or the measured triglyceride level was higher than 400 mg per deciliter (4.52 mmol per liter), in which case ultracentrifugation was performed.

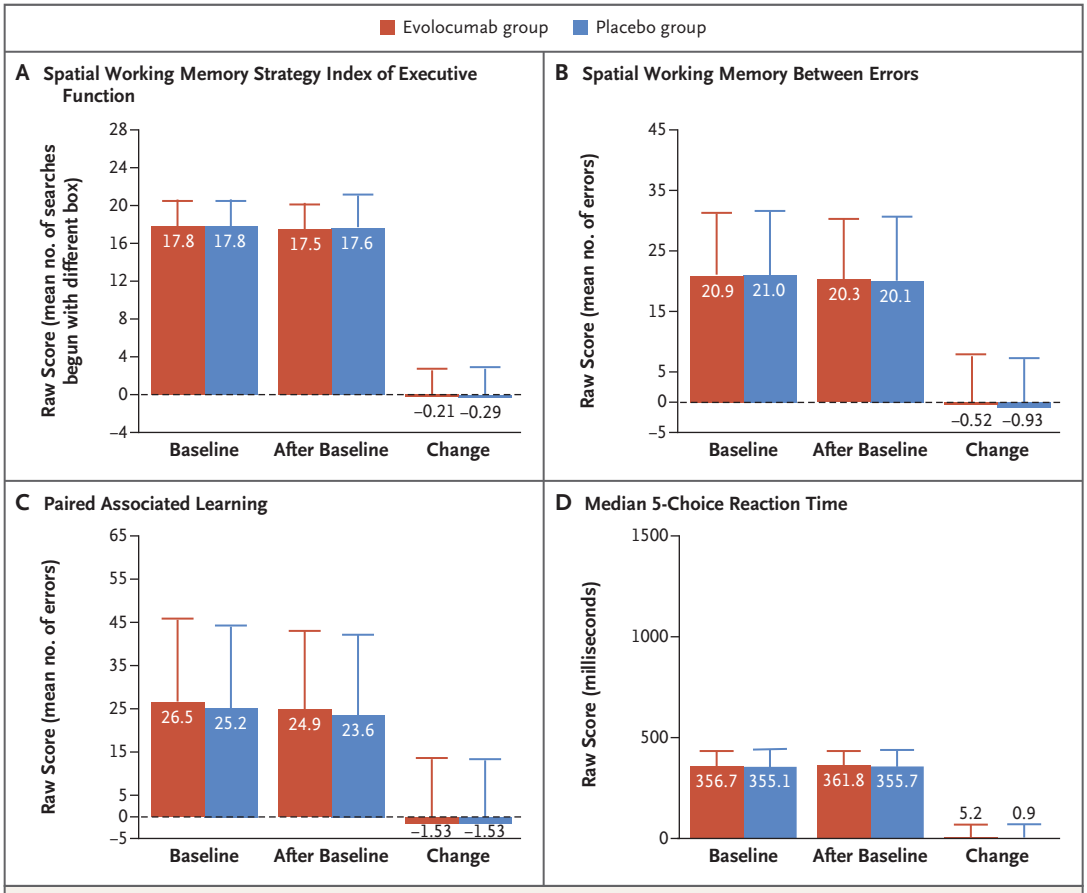

Figure 1. Primary and Secondary Cambridge Neuropsychological Test Automated Battery (CANTAB) End Points.

Panel A shows the unadjusted raw scores on the spatial working memory strategy index of executive function (the primary end point). The score indicates the number of times a patient begins a search with a different box than the one used to begin the search in the previous search sequence, across a total of four rounds of testing that have 6 or 8 boxes; scores range from 4 to 28, with lower scores representing a more efficient use of strategy and planning. Apparent discrepancies in change values are due to rounding of raw scores. Panels B through D show the raw scores for three secondary end-point assessments. Panel B shows the raw scores for working memory as assessed by the spatial working memory between-errors test, which indicates the number of times a person revisits a box in which a token has previously been found; scores range from 0 to 279, with lower scores indicating fewer errors. Panel C shows the raw scores for episodic memory, which is determined of the basis of the total number of errors a patient makes in a paired associates learning test, plus an adjustment for the estimated number of errors the patient would have made on any stages that were not reached; scores range from 0 to 70, with lower scores indicating fewer errors. Panel D shows the raw scores for psychomotor speed, which is determined on the basis of the median 5-choice reaction time (i.e., the median duration between the onset of a stimulus and the release of a button); faster times represent better performance. All scores are shown for the primary-analysis population (all patients who had a baseline CANTAB assessment before or on the same day as the first dose of study drug or placebo). The first pair of bars represents the mean scores obtained at baseline; the second pair of bars, the means of all scores obtained at the postbaseline assessments; and the third pair of bars, the change in scores over time (i.e., the difference between the score at baseline and the mean score of all assessments after baseline). Negative numbers of change represent improvement in performance as compared with the baseline score. T bars represent one standard deviation from the mean. There were no significant differences between evolocumab and placebo in any of the pairwise comparisons.

the evolocumab group and 355.1 msec in the placebo group; the mean changes in psychomotor speeds from baseline were 5.2±52.7 msec and 0.9±63.9 msec, respectively (P=0.06 based on the z scores). The global composite z score at baseline was −0.015 in the evolocumab group and −0.002 in the placebo group; changes in global composite z scores were 0.031±0.411 and 0.061±0.454, respectively (P=0.12). An analysis of outliers (poorest scores) did not show signifi-

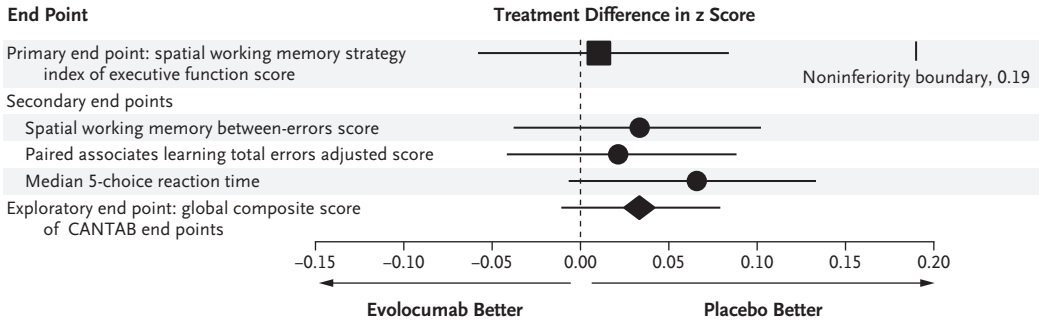

Figure 2. Change in z Scores with 95% Confidence Intervals for the Primary and Secondary CANTAB End Points and the Global Composite Score of CANTAB End Points.

Shown is the difference in change in z scores between the placebo group and the evolocumab group, based on the linear mixed model, of the spatial working memory strategy index of executive function (primary end point), in the primary-analysis population. Also shown are the between-group differences in the changes over time for three secondary CANTAB end points (spatial working memory between-errors score, paired associates learning total errors adjusted score, and median 5-choice reaction time) and for the global composite score of CANTAB end points. The noninferiority margin for the primary end point was 0.19 (20% of the standard deviation of change from baseline in z score in the placebo group). The P value for the noninferiority of the primary end point (based on the z scores) was <0.001, and the P value for superiority was 0.85. The P values for the three secondary CANTAB end points and the global composite score of CANTAB end points, as calculated by means of a two-sided superiority test for adjusted treatment difference using the linear mixed model, were 0.36, 0.49, 0.06, and 0.12, respectively.

cant differences between the study groups (Table S3 in the Supplementary Appendix).

The scores for the individual CANTAB end points and the global composite score of CANTAB end points at each visit were similar in the study groups throughout the trial. Results in the full-analysis population showed no significant differences between the study groups in the four individual CANTAB end points or in the global composite score of CANTAB end points. (See Figs. S2 and S3 and Table S2 in the Supplementary Appendix.)

The mean changes in scores from baseline were similar within study groups, when patients were stratified according to the lowest-attained LDL cholesterol level across the prespecified LDL cholesterol cutoff points (including 661 patients in the evolocumab group who had an LDL cholesterol level <25 mg per deciliter). The mean changes from baseline were also similar between the study groups, when patients were stratified according to the lowest-attained LDL cholesterol level (Table 2).

SUBGROUP ANALYSIS

The cognitive test results in prespecified subgroups were consistent with the results in the overall population. An exploratory analysis of the primary end point, with stratification according to the final screening LDL cholesterol level (≥85 vs. <85 mg per deciliter), suggested that the primary end point favored placebo among the patients with a baseline LDL cholesterol level lower than 85 mg per deciliter, whereas it favored evolocumab among patients with a baseline LDL cholesterol level of 85 mg per deciliter or higher (P=0.01 for interaction, without adjustment for multiple comparisons). However, an analysis of the secondary end points did not provide further supportive evidence for treatment modification according to baseline LDL cholesterol level. Furthermore, a post hoc analysis of the changes with respect to the primary and secondary end points, stratified according to quartiles of LDL cholesterol levels at baseline, suggested that the spatial working memory scores in the placebo group in the quartile with the lowest LDL cholesterol level (<80 mg per deciliter [2.1 mmol per liter]) may have been an outlier, because there was no consistent directional relationship between LDL cholesterol level and the primary end point. (Additional details on the results of the subgroup analyses are provided in Figs. S4 through S6 in the Supplementary Appendix.)

SELF-ASSESSMENT OF EVERYDAY COGNITION

A total of 1581 patients in the EBBINGHAUS study, which included 946 patients in the primary-

Table 2. Changes in CANTAB End Points and Global Composite Score of CANTAB End Points, Stratified According to Lowest-Attained LDL Cholesterol Level (Full-Analysis Population).*

End Point	Lowest-Attained LDL Cholesterol Level				
	Evolocumab Group			Placebo Group	
	<25 mg/dl (N=661)	*25–39 mg/dl (N=206)*	*≥40 mg/dl (N=115)*	*25–39 mg/dl (N=13)*	*≥40 mg/dl (N=969)*
Primary end point: executive function (spatial working memory strategy index of executive function raw score)†					
No. of patients with data	639	199	103	12	924
Change in score over time	–0.2±2.7	–0.3±2.9	–0.4±2.6	0.7±2.2	–0.4±3.0
Secondary end points					
Working memory (spatial working memory between-errors raw score)‡					
No. of patients	639	199	103	12	924
Change in score over time	–0.5±8.7	0.2±9.6	–0.8±8.1	0.4±9.1	–0.6±8.3
Episodic memory (paired associates learning raw score adjusted)§					
No. of patients	638	199	103	12	919
Change in score over time	–0.3±14.5	–0.6±12.3	–1.0±12.9	–3.4±18.0	–0.2±14.6
Psychomotor speed (median 5-choice reaction time raw score)¶					
No. of patients	632	199	102	12	914
Change in score (in milliseconds) over time	5.5±55.7	1.4±66.2	7.8±54.6	0.3±65.1	1.8±60.3
Exploratory end point: global composite score of CANTAB end points‖					
No. of patients	638	199	103	12	922
Change in z score over time	0.02±0.44	0.02±0.42	0.03±0.40	–0.02±0.44	0.04±0.47

* Plus–minus values are means ±SD changes from baseline over time (i.e., the difference between the mean score at baseline and the mean score of all assessments after baseline). With respect to the change values for the primary and secondary end points, negative numbers indicate an improvement in score over time. With respect to change values in the global composite score, positive numbers indicate an improvement over time. For patients who had a stroke after randomization, the final assessment was the last assessment before the stroke. Negative changes in raw score (i.e., a lower value) indicate improvement over time. Positive changes in z score indicate improvement over time. None of the comparisons between study groups or across strata of lowest-attained LDL cholesterol level were significant ($P>0.05$ for each comparison). CANTAB denotes Cambridge Neuropsychological Test Automated Battery. Six patients in the placebo group who had a lowest-attained LDL cholesterol level lower than 25 mg per deciliter were not included in the table because this was too small of a group to analyze. An additional four patients in the placebo group had no data for either CANTAB end points or LDL cholesterol level after randomization.

† The score indicates the number of times a patient begins a search with a different box than the one used to begin the search in the previous search sequence, across a total of four rounds of testing that have 6 or 8 boxes; scores range from 4 to 28, with lower scores representing a more efficient use of strategy and planning.

‡ The score indicates the number of times a person revisits a box in which a token has previously been found; scores range from 0 to 279, with lower scores indicating fewer errors.

§ The score indicates the total number of errors a patient makes in a paired associates learning test, plus an adjustment for the estimated number of errors the patients would have made on any stages that were not reached; scores range from 0 to 70, with lower scores indicating fewer errors.

¶ The score indicates the median duration (in milliseconds) between the onset of a stimulus and the release of a button; faster times represent better performance.

‖ The global composite score was a prespecified exploratory end point and was calculated by averaging the combined z scores of each of the four CANTAB end points.

analysis population, completed the ECog questionnaire at the end of the study. No significant between-group differences were observed in the scores on the individual domains or in the total score (the mean total score was 1.13 in the placebo group and 1.14 in the evolocumab group; P=0.42). A comparison of the percentage of patients who reported various levels of decline in cognition showed no significant differences between study groups. (See Tables S4 and S5 in the Supplementary Appendix.)

COGNITIVE ADVERSE EVENTS

Cognitive adverse events, which included memory or concentration difficulty occurred in 11 of 586 patients (1.9%) in the evolocumab group and in 8 of 618 patients (1.3%) in the placebo group in the primary-analysis population. In the full-analysis population, cognitive adverse events occurred in 19 of 983 patients (1.9%) in the evolocumab group and in 16 of 990 patients (1.6%) in the placebo group (Table S6 in the Supplementary Appendix).

DISCUSSION

This study evaluated cognition in 1974 patients from the FOURIER trial, a double-blind, placebo-controlled trial of the PCSK9 inhibitor evolocumab in patients with stable atherosclerotic cardiovascular disease. No significant differences in cognitive function test scores or in subjective self-assessments of everyday cognition were observed between the patients in the evolocumab group and those in the placebo group. Evolocumab, as compared with placebo, neither improved nor worsened executive function, working memory, episodic memory, or psychomotor speed, as assessed with the use of CANTAB, an established tablet-based tool, over a median follow-up of 19 months. To give perspective to the measures of cognitive testing with CANTAB in this study, we note that the changes seen over time in each study group were an order of magnitude less than the changes found in patients with mild cognitive impairment preceding dementia,[23] in patients who have received a therapeutic dose of a benzodiazepine,[24] and in persons with blood alcohol concentrations of 50 mg per deciliter.[24] Furthermore, no significant between-group differences were observed at the end of the study in the patients' self-assessment of memory, planning, organization, or attention.

The findings from the 60 prespecified subgroup analyses (12 subgroups across the five end points) were consistent with the main findings, with two exceptions — the analysis of the primary end point that was dichotomized according to screening LDL cholesterol level and the analysis of reaction time that was stratified according to the presence or absence of a neurologic disorder that was not a stroke; both showed evidence of significant subgroup–treatment effect heterogeneity. Given the large number of subgroups analyses that were performed, the absence of a monotonic relationship in an analysis of primary and secondary end points stratified according to quartile of LDL cholesterol level at the final screening visit, and the lack of similar findings across the other subgroups, the two exceptions may have been due to chance. Exploratory analyses of the CANTAB assessments that were stratified according to the lowest-attained LDL cholesterol level after randomization did not show associations between LDL cholesterol level and adverse cognitive outcomes, including among the 661 patients whose lowest-attained LDL cholesterol levels were below 25 mg per deciliter.

A meta-analysis of phase 2 and phase 3 trials of evolocumab and a drug in the same class, alirocumab, showed an association between the use of PCSK9 inhibitors and a higher risk of cognitive adverse events than with the control.[11] An analysis of prespecified cognitive adverse events among 27,564 patients enrolled in the parent FOURIER trial of the efficacy and safety of evolocumab showed no significant difference between evolocumab and placebo.[3]

Our study has several limitations. The follow-up period was short, and patients with known dementia or mild cognitive impairment were excluded. However, two other studies that showed a putative association between statins and adverse cognitive effects were only 6 months in duration.[4,5] An ongoing 5-year extension of the FOURIER trial includes CANTAB assessments in approximately 500 patients who had also participated in EBBINGHAUS and will provide longer-term data regarding cognition (ClinicalTrials.gov number, NCT02867813). Nevertheless, even longer studies

on the use of PCSK9 inhibitors[25] as well as other lipid-lowering therapies are desirable, because patients with elevated cholesterol levels are typically treated for decades. Another possible limitation is that the use of the tablet-based CANTAB tool is not standard in clinical practice or lipid research; however, it has been validated as a research tool,[26-29] is sensitive to change over time,[23,30,31] and was cleared by the Food and Drug Administration as a tool to detect memory impairment.[32] Although there is no accepted threshold for changes in cognitive function in the scores used in the tool, the magnitude of the noninferiority boundary that we selected is similar to that expected over a 6-year period of normal aging in a cohort[21] of patients with ages similar to those of the patients in the EBBINGHAUS population. Furthermore, the observed upper bound of the 95% confidence interval extended to less than half the distance to the noninferiority boundary. Finally, self-assessments of everyday cognition with the use of the ECog questionnaire were not obtained at the start of the trial, and subjective assessment of change may be subject to recall bias. The absence of a difference in self-reported clinical changes in cognition at the end of the trial supports the results of cognitive function testing and suggests that a large decline in cognition was not missed.

In conclusion, among patients who received either the PCSK9 inhibitor evolocumab or placebo in addition to statin therapy, we did not find an association between adverse cognitive effects and evolocumab, as compared with placebo, over a median of 19 months, even among patients who attained very low levels of LDL cholesterol.

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