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## Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

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### ABSTRACT

#### BACKGROUND

Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9) and lowers low-density lipoprotein (LDL) cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain.

#### METHODS

We conducted a randomized, double-blind, placebo-controlled trial involving 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 years.

#### RESULTS

At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter) ( $P < 0.001$ ). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92;  $P < 0.001$ ) and the key secondary end point (816 [5.9%] vs. 1013 [7.4%]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88;  $P < 0.001$ ). The results were consistent across key subgroups, including the subgroup of patients in the lowest quartile for baseline LDL cholesterol levels (median, 74 mg per deciliter [1.9 mmol per liter]). There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab (2.1% vs. 1.6%).

#### CONCLUSIONS

In our trial, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets. (Funded by Amgen; FOURIER ClinicalTrials.gov number, NCT01764633.)

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\*A complete list of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) steering committee and investigators is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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**L**OW-DENSITY LIPOPROTEIN (LDL) CHOLESTEROL is a well-established and modifiable risk factor for cardiovascular disease. Monoclonal antibodies that inhibit proprotein convertase subtilisin-kexin type 9 (PCSK9) have emerged as a new class of drugs that effectively lower LDL cholesterol levels.<sup>1</sup> Evolocumab, a member of this class, is a fully human monoclonal antibody that reduces LDL cholesterol levels by approximately 60%.<sup>2-6</sup>

Genetic studies have shown that carriage of PCSK9 loss-of-function alleles is associated with lower LDL cholesterol levels and a reduced risk of myocardial infarction.<sup>7,8</sup> Moreover, exploratory data from longer-term follow-up in phase 2 and phase 3 trials of PCSK9 inhibitors showed significant reductions in cardiovascular outcomes.<sup>9,10</sup> However, there were little more than 100 events in these studies combined. Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) was a dedicated cardiovascular outcomes trial that tested the clinical efficacy and safety of evolocumab when added to high-intensity or moderate-intensity statin therapy in patients with clinically evident atherosclerotic cardiovascular disease.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

The FOURIER trial was a randomized, double-blind, placebo-controlled, multinational clinical trial in which patients at 1242 sites in 49 countries underwent randomization (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The executive committee and Amgen, the trial sponsor, collaborated in designing the trial.<sup>11</sup> The protocol and amendments were approved by the relevant ethics committees at all participating sites. The sponsor was responsible for data collection. The raw database was provided to the Thrombolysis in Myocardial Infarction (TIMI) Study Group, which conducted data analyses independently of the sponsor. The first draft of the manuscript was written by the first author. All the coauthors participated in subsequent revisions of the manuscript. The executive committee decided to submit the manuscript for publication and assumes responsibility for the accuracy and completeness of the data and analyses and the fidelity of the trial to the protocol, available at NEJM.org.

### TRIAL POPULATION

Patients were eligible for participation in the trial if they were between 40 and 85 years of age and had clinically evident atherosclerotic cardiovascular disease, defined as a history of myocardial infarction, nonhemorrhagic stroke, or symptomatic peripheral artery disease, as well as additional characteristics that placed them at higher cardiovascular risk. (Full eligibility criteria are provided in the Supplementary Appendix.) Patients had to have a fasting LDL cholesterol level of 70 mg per deciliter (1.8 mmol per liter) or higher or a non-high-density lipoprotein (HDL) cholesterol level of 100 mg per deciliter (2.6 mmol per liter) or higher while they were taking an optimized regimen of lipid-lowering therapy, which was defined as preferably a high-intensity statin but must have been at least atorvastatin at a dose of 20 mg daily or its equivalent, with or without ezetimibe. Written informed consent was obtained from all the patients.

### RANDOMIZATION AND STUDY AGENTS

Eligible patients were randomly assigned in a 1:1 ratio to receive subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg every month, according to patient preference) or matching placebo. Randomization was performed in a double-blinded manner with the use of a central computerized system, with stratification according to the final screening LDL cholesterol level (<85 or ≥85 mg per deciliter [ $<2.2$  or  $\geq 2.2$  mmol per liter]) and region.

### END POINTS

The primary efficacy end point was major cardiovascular events, defined as the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. Other efficacy end points are listed in the Methods section in the Supplementary Appendix. Safety was assessed through collection of data on adverse events and central laboratory testing (see the Supplementary Appendix). A central clinical-events committee led by the TIMI Study Group, whose members were unaware of study-group assignments and lipid levels, adjudicated all potential efficacy end-point events and cases of new-onset diabetes. Definitions of the end

points are provided in the Supplementary Appendix.

# STATISTICAL ANALYSIS

The primary efficacy analysis was based on the time from randomized study-group assignment to the first occurrence of any element of the primary composite end point. If the rate of the primary end point was significantly lower in the evolocumab group ( $P<0.05$ ), then, in a hierarchical fashion, the key secondary end point and then cardiovascular death were to be tested at a significance level of 0.05. Additional details are provided in the Supplementary Appendix. All efficacy analyses were conducted on an intention-to-treat basis. No imputation was performed for missing data on clinical outcomes. Safety evaluations included all the patients who underwent randomization and received at least one dose of a study agent and for whom post-dose data were available. The size of the patient population in the trial was based on the key secondary end point, and we estimated that 1630 such end-point events were required to provide 90% power to detect a 15% relative risk reduction with evolocumab as compared with placebo.<sup>11</sup> Hazard ratios and 95% confidence intervals were generated with the use of a Cox proportional-hazards model with stratification factors as covariates, and P values for time-to-event analyses were calculated with the use of log-rank tests.

## RESULTS

### PATIENTS

From February 2013 through June 2015, a total of 27,564 patients underwent randomization to either the evolocumab group (13,784 patients) or the placebo group (13,780 patients) (Fig. S1 in the Supplementary Appendix). The baseline characteristics of the patients in the two groups were well matched and are shown in Table 1. The mean age of the patients was 63 years, and 24.6% of the patients were women; 81.1% of the patients had a history of myocardial infarction, 19.4% a history of previous nonhemorrhagic stroke, and 13.2% symptomatic peripheral artery disease. At baseline, 69.3% of the patients were taking high-intensity statin therapy (defined in accordance with American College of Cardiology and American Heart Association joint guidelines<sup>12</sup>; see the Methods section in the Supplementary Appen-

dix), and 30.4% were taking moderate-intensity statin therapy; 5.2% of the patients were also taking ezetimibe. During the trial, only 9.8% of patients had alterations in their background lipid-lowering therapy (see the Results section in the Supplementary Appendix for details). The rate of use of secondary preventive therapies was high, with 92.3% of patients taking antiplatelet therapy, 75.6% taking beta-blockers, and 78.2% taking an angiotensin-converting-enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB), an aldosterone antagonist, or both at trial entry.

A total of 27,525 patients (99.9%) received at least one dose of a study agent. Premature permanent discontinuation of the study regimen occurred in 12.5% of patients (5.7% per year), withdrawal of consent in 0.7% (0.3% per year), and loss to follow-up in less than 0.1% (0.03% per year), with similar rates in the two study groups (Fig. S1 in the Supplementary Appendix). The median duration of follow-up was 26 months (interquartile range, 22 to 30), which resulted in 59,865 patient-years of follow-up. Ascertainment of the primary end point was complete for 99.5% of potential patient-years of follow-up.

### LIPID DATA

The median LDL cholesterol level at baseline was 92 mg per deciliter (interquartile range, 80 to 109) (2.4 mmol per liter [interquartile range, 2.1 to 2.8]). At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59% (95% confidence interval [CI], 58 to 60;  $P<0.001$ ), for a mean absolute reduction of 56 mg per deciliter (95% CI, 55 to 57) (1.45 mmol per liter [95% CI, 1.43 to 1.47]), to a median of 30 mg per deciliter (interquartile range, 19 to 46) (0.78 mmol per liter [interquartile range, 0.49 to 1.2]). The reduction in LDL cholesterol levels was maintained over time (Fig. 1, and Fig. S2 in the Supplementary Appendix). At 48 weeks in the evolocumab group, the LDL cholesterol level was reduced to 70 mg per deciliter (1.8 mmol per liter) or lower in 87% of the patients, to 40 mg per deciliter (1.0 mmol per liter) or lower in 67% of the patients, and to 25 mg per deciliter (0.65 mmol per liter) or lower in 42% of the patients, as compared with 18%, 0.5%, and less than 0.1%, respectively, of the patients in the placebo group ( $P<0.001$  for all comparisons of evolocumab vs. placebo). Evolocumab similarly lowered related

**Table 1. Characteristics of the Patients at Baseline.\***

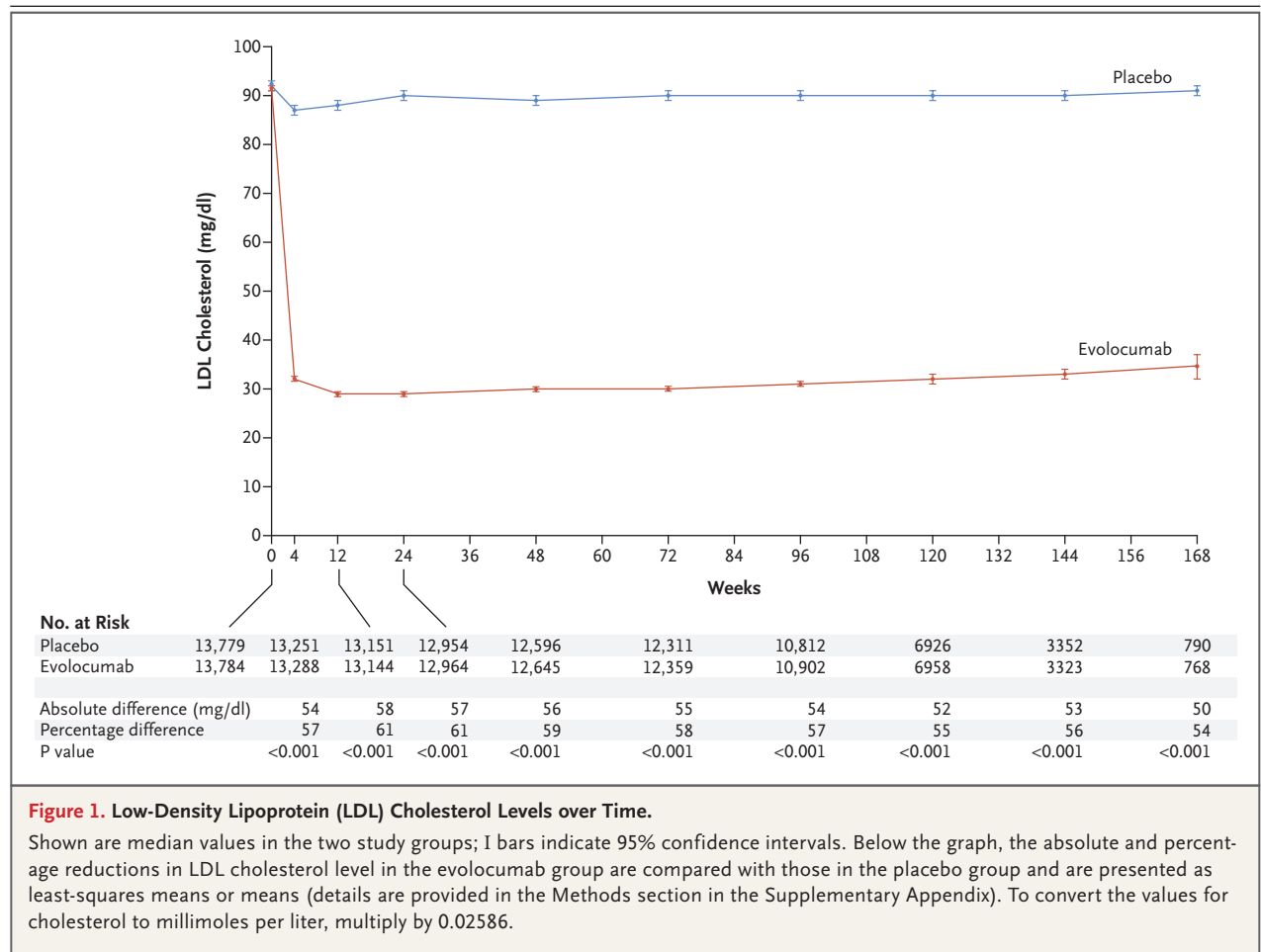
Characteristics	Evolocumab (N=13,784)	Placebo (N=13,780)
Age — yr	62.5±9.1	62.5±8.9
Male sex — no. (%)	10,397 (75.4)	10,398 (75.5)
White race — no. (%)†	11,748 (85.2)	11,710 (85.0)
Weight — kg	85.0±17.3	85.5±17.4
Region		
North America	2,287 (16.6)	2,284 (16.6)
Europe	8,666 (62.9)	8,669 (62.9)
Latin America	913 (6.6)	910 (6.6)
Asia Pacific and South Africa	1,918 (13.9)	1,917 (13.9)
Type of atherosclerosis‡		
Myocardial infarction — no. (%)	11,145 (80.9)	11,206 (81.3)
Median time from most recent previous myocardial infarction (IQR) — yr	3.4 (1.0–7.4)	3.3 (0.9–7.7)
Nonhemorrhagic stroke	2686 (19.5)	2651 (19.2)
Median time from most recent previous stroke (IQR) — yr	3.2 (1.1–7.1)	3.3 (1.1–7.3)
Peripheral artery disease — no. (%)	1,858 (13.5)	1,784 (12.9)
Cardiovascular risk factors		
Hypertension — no./total no. (%)	11,045/13,784 (80.1)	11,039/13,779 (80.1)
Diabetes mellitus — no. (%)	5,054 (36.7)	5,027 (36.5)
Current cigarette use — no./total no. (%)	3854/13,783 (28.0)	3923/13,779 (28.5)
Statin use — no. (%)§		
High intensity	9,585 (69.5)	9,518 (69.1)
Moderate intensity	4,161 (30.2)	4,231 (30.7)
Low intensity, unknown intensity, or no data	38 (0.3)	31 (0.2)
Ezetimibe — no. (%)	726 (5.3)	714 (5.2)
Other cardiovascular medications — no./total no. (%)		
Aspirin, P2Y <sub>12</sub> inhibitor, or both	12,766/13,772 (92.7)	12,666/13,767 (92.0)
Beta-blocker	10,441/13,772 (75.8)	10,374/13,767 (75.4)
ACE inhibitor or ARB, aldosterone antagonist, or both	10,803/13,772 (78.4)	10,730/13,767 (77.9)
Median lipid measures (IQR)		
LDL cholesterol — mg/dl	92 (80–109)	92 (80–109)
Total cholesterol — mg/dl	168 (151–188)	168 (151–189)
HDL cholesterol — mg/dl	44 (37–53)	44 (37–53)
Triglycerides — mg/dl	134 (101–183)	133 (99–181)
Lipoprotein(a) — nmol/liter	37 (13–166)	37 (13–164)

\* There were no nominally significant differences between the two groups in baseline characteristics with the exception of weight ( $P=0.01$ ) and the use of aspirin, a P2Y<sub>12</sub> inhibitor, or both ( $P=0.03$ ). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, HDL high-density lipoprotein, IQR interquartile range, and LDL low-density lipoprotein.

† Race was reported by the patients.

‡ Patients could have more than one type of atherosclerosis.

§ Statin intensity was categorized in accordance with the guidelines of the American College of Cardiology and American Heart Association.<sup>12</sup>



**Figure 1. Low-Density Lipoprotein (LDL) Cholesterol Levels over Time.**

Shown are median values in the two study groups; I bars indicate 95% confidence intervals. Below the graph, the absolute and percentage reductions in LDL cholesterol level in the evolocumab group are compared with those in the placebo group and are presented as least-squares means or means (details are provided in the Methods section in the Supplementary Appendix). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

atherogenic lipid measures; as compared with placebo, at 48 weeks, evolocumab had reduced non-HDL cholesterol levels by 52% and apolipoprotein B levels by 49% ( $P<0.001$  for both). Additional details are provided in the Results section and Fig. S3 in the Supplementary Appendix.

#### EFFICACY END POINTS

Evolocumab significantly reduced the risk of the primary composite end point of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The primary end point occurred in 1344 patients (9.8%) in the evolocumab group and in 1563 patients (11.3%) in the placebo group (hazard ratio, 0.85; 95% CI, 0.79 to 0.92;  $P<0.001$ ) (Table 2 and Fig. 2A). Likewise, evolocumab significantly reduced the risk of the key secondary composite end point of cardiovascular death, myocardial infarction, or stroke. The key second-

ary end point occurred in 816 patients (5.9%) in the evolocumab group and in 1013 patients (7.4%) in the placebo group (hazard ratio, 0.80; 95% CI, 0.73 to 0.88;  $P<0.001$ ) (Table 2 and Fig. 2B). The magnitude of the risk reduction with regard to the primary end point tended to increase over time, from 12% (95% CI, 3 to 20) in the first year to 19% (95% CI, 11 to 27) beyond the first year. Likewise, for the key secondary end point, the risk reduction increased from 16% (95% CI, 4 to 26) in the first year to 25% (95% CI, 15 to 34) beyond the first year (Table S1 and Fig. S4 in the Supplementary Appendix).

In terms of individual outcomes, evolocumab had no observed effect on cardiovascular mortality, and hence  $P$  values for other outcomes should be considered exploratory. There were reductions of 21 to 27% in the risk of myocardial infarction, stroke, and coronary revascularization but no observed effect on the rates of hospitalization



**Table 2. Primary and Secondary End Points.**

Outcome	Evolocumab (N=13,784)	Placebo (N=13,780)	Hazard Ratio (95% CI)	P Value*
<i>no. of patients (%)</i>				
Primary end point: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization	1344 (9.8)	1563 (11.3)	0.85 (0.79–0.92)	<0.001
Key secondary end point: cardiovascular death, myocardial infarction, or stroke	816 (5.9)	1013 (7.4)	0.80 (0.73–0.88)	<0.001
Other end points				
Cardiovascular death	251 (1.8)	240 (1.7)	1.05 (0.88–1.25)	0.62
Due to acute myocardial infarction	25 (0.18)	30 (0.22)	0.84 (0.49–1.42)	
Due to stroke	31 (0.22)	33 (0.24)	0.94 (0.58–1.54)	
Other cardiovascular death	195 (1.4)	177 (1.3)	1.10 (0.90–1.35)	
Death from any cause	444 (3.2)	426 (3.1)	1.04 (0.91–1.19)	0.54
Myocardial infarction	468 (3.4)	639 (4.6)	0.73 (0.65–0.82)	<0.001
Hospitalization for unstable angina	236 (1.7)	239 (1.7)	0.99 (0.82–1.18)	0.89
Stroke	207 (1.5)	262 (1.9)	0.79 (0.66–0.95)	0.01
Ischemic	171 (1.2)	226 (1.6)	0.75 (0.62–0.92)	
Hemorrhagic	29 (0.21)	25 (0.18)	1.16 (0.68–1.98)	
Unknown	13 (0.09)	14 (0.10)	0.93 (0.44–1.97)	
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 (0.71–0.86)	<0.001
Urgent	403 (2.9)	547 (4.0)	0.73 (0.64–0.83)	
Elective	420 (3.0)	504 (3.7)	0.83 (0.73–0.95)	
Cardiovascular death or hospitalization for worsening heart failure	402 (2.9)	408 (3.0)	0.98 (0.86–1.13)	0.82
Ischemic stroke or transient ischemic attack	229 (1.7)	295 (2.1)	0.77 (0.65–0.92)	0.003
CTTC composite end point†	1271 (9.2)	1512 (11.0)	0.83 (0.77–0.90)	<0.001

\* Given the hierarchical nature of the statistical testing, the P values for the primary and key secondary end points should be considered significant, whereas all other P values should be considered exploratory.

† The Cholesterol Treatment Trialists Collaboration (CTTC) composite end point consists of coronary heart death, nonfatal myocardial infarction, stroke, or coronary revascularization.

for unstable angina, cardiovascular death or hospitalization for worsening heart failure, or death from any cause (Table 2). The benefits of evolocumab with regard to the risk of the primary and key secondary composite end points were largely consistent across major subgroups, including those based on age, sex, and type of atherosclerotic vascular disease (Fig. S5 in the Supplementary Appendix). The benefits were also consistent across quartiles of baseline LDL cholesterol levels, from patients in the top quartile, who had a median LDL cholesterol level of 126 mg per deciliter (interquartile range, 116 to 143) (3.3 mmol per liter [interquartile range, 3.0 to 3.7]) at baseline, down to those in the lowest quartile, who had a median LDL choles-

terol level of 74 mg per deciliter (interquartile range, 69 to 77) (1.9 mmol per liter [interquartile range, 1.8 to 2.0]) at baseline. The benefit of evolocumab was also consistent across levels of intensity of statin therapy, regardless of ezetimibe use, and with both the dosing regimen of 140 mg every 2 weeks and that of 420 mg monthly.

#### SAFETY

No significant between-group differences were seen in the overall rates of adverse events, serious adverse events, or adverse events thought to be related to the study agent and leading to discontinuation of the study regimen (Table 3). Likewise, the rates of muscle-related events, cataract, neurocognitive adverse events, and hemorrhagic

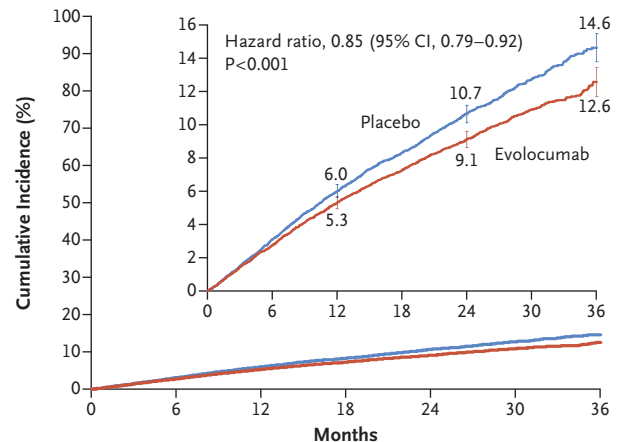
stroke did not differ significantly between the two groups. Injection-site reactions were rare, but they were more frequent with evolucumab (2.1% vs. 1.6%). The large majority of reactions (approximately 90% in each group) were classified as mild, and only 0.1% of the patients in each group stopped receiving the study agent because of an injection-site reaction. The rates of adjudicated cases of new-onset diabetes did not differ significantly between the two groups (hazard ratio, 1.05; 95% CI, 0.94 to 1.17). The rates of allergic reactions also did not differ significantly between the groups (3.1% vs. 2.9%). In the evolucumab group, new binding antibodies developed in 43 patients (0.3%), and development of neutralizing antibodies did not occur in any patient.

## DISCUSSION

When added to statin therapy, the PCSK9 inhibitor evolucumab lowered LDL cholesterol levels by 59% from baseline levels as compared with placebo, from a median of 92 mg per deciliter (2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter). This effect was sustained without evidence of attenuation. In this dedicated cardiovascular outcomes trial, we found that the addition of evolucumab to statin therapy significantly reduced the risk of cardiovascular events, with a 15% reduction in the risk of the primary composite end point of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization and a 20% reduction in the risk of the more clinically serious key secondary end point of cardiovascular death, myocardial infarction, or stroke. During a median of 26 months of follow-up, the only adverse events that were noted to be nominally significantly more common in association with evolucumab were injection-site reactions, but these were rare, and the rate of discontinuation of the study regimen was no higher with evolucumab than with placebo.

The data from our trial provide insight into the benefit of decreasing LDL cholesterol levels to median levels lower than those in previous trials. Previously, significant reductions in major cardiovascular events were found in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) and Treating to New Targets (TNT) trials, in which the more intensive

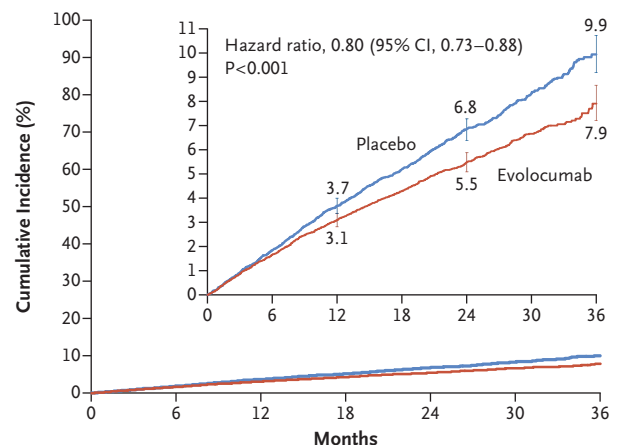
### A Primary Efficacy End Point



#### No. at Risk

Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolucumab	13,784	13,351	12,939	12,070	7771	3746	689

### B Key Secondary Efficacy End Point



#### No. at Risk

Placebo	13,780	13,449	13,142	12,288	7944	3893	731
Evolucumab	13,784	13,501	13,241	12,456	8094	3935	724

### Figure 2. Cumulative Incidence of Cardiovascular Events.

Panel A shows the cumulative event rates for the primary efficacy end point (the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization), and Panel B shows the rates for the key secondary efficacy end point (the composite of cardiovascular death, myocardial infarction, or stroke). I bars indicate 95% confidence intervals. The Kaplan–Meier rates for the primary end point in the evolucumab group versus the placebo group were as follows: at 1 year, 5.3% (95% confidence interval [CI], 4.9 to 5.7) versus 6.0% (95% CI, 5.6 to 6.4); at 2 years, 9.1% (95% CI, 8.6 to 9.6) versus 10.7% (95% CI, 10.1 to 11.2); and at 3 years, 12.6% (95% CI, 11.7 to 13.5) versus 14.6% (95% CI, 13.8 to 15.5). The Kaplan–Meier rates for the key secondary end point in the evolucumab group versus the placebo group were as follows: at 1 year, 3.1% (95% CI, 2.8 to 3.4) versus 3.7% (95% CI, 3.4 to 4.0); at 2 years, 5.5% (95% CI, 5.1 to 5.9) versus 6.8% (95% CI, 6.4 to 7.3); and at 3 years, 7.9% (95% CI, 7.2 to 8.7) versus 9.9% (95% CI, 9.2 to 10.7). P values were calculated with the use of log-rank tests. The insets show the same data on an enlarged y axis.



**Table 3. Adverse Events and Laboratory Test Results.**

Outcome	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Adverse events — no. of patients (%)		
Any	10,664 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)
Injection-site reaction*	296 (2.1)	219 (1.6)
Allergic reaction	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results — no. of patients/total no. (%)		
Aminotransferase level >3 times the upper limit of the normal range	240/13,543 (1.8)	242/13,523 (1.8)
Creatine kinase level >5 times the upper limit of the normal range	95/13,543 (0.7)	99/13,523 (0.7)

\* The between-group difference was nominally significant ( $P < 0.001$ ).

† The total numbers of patients were 8337 in the evolocumab group and 8339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.

statin regimen lowered LDL cholesterol levels from approximately 100 mg per deciliter (2.6 mmol per liter) to 70 mg per deciliter (1.8 mmol per liter).<sup>13,14</sup> More recently, the addition of ezetimibe to statin therapy in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) lowered LDL cholesterol levels from 70 mg per deciliter (1.8 mmol per liter) to 54 mg per deciliter (1.4 mmol per liter) and significantly reduced major cardiovascular events.<sup>15</sup> In extending this concept further in FOURIER, we found consistent reductions in rates of cardiovascular events across the range of baseline LDL cholesterol levels. Specifically, there was a 17% reduction in the risk of the key secondary end point among patients in the top quartile for baseline LDL cholesterol level, in whom evolocumab lowered the median LDL cholesterol level from 126 mg per deciliter (3.3 mmol per liter) to 43 mg per deciliter (1.1 mmol per liter) (with the achieved level similar to that achieved with ezetimibe in patients in the lowest quartile for admission LDL cholesterol levels in IMPROVE-IT<sup>16</sup>), and there was a 22% reduction in the risk of the key secondary end point among

the patients in the lowest quartile for baseline LDL cholesterol level, in whom evolocumab lowered the median LDL cholesterol level from 73 mg per deciliter (1.9 mmol per liter) to 22 mg per deciliter (0.57 mmol per liter). These observations align well with the effects of evolocumab on coronary atherosclerotic plaque volume in the Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial<sup>17</sup> and show that continued cardiovascular benefit can be accrued even when LDL cholesterol levels are reduced to 20 to 25 mg per deciliter (0.52 to 0.65 mmol per liter), a range that is well below current targets.<sup>18-20</sup>

A delay between the onset of LDL cholesterol lowering and the emergence of the full clinical benefit of the intervention in terms of clinical risk reduction has been well documented in trials of statins, ezetimibe, and other LDL cholesterol-lowering therapies.<sup>15,21-24</sup> Likewise, in FOURIER, the magnitude of the risk reduction with regard to the key secondary end point appeared to grow over time, from 16% during the first year to 25% beyond 12 months, which suggests that the

translation of reductions in LDL cholesterol levels into cardiovascular clinical benefit requires time. Overall, 74 patients would need to be treated over a period of 2 years to prevent a cardiovascular death, myocardial infarction, or stroke.

In an observation consistent with previous trials of more intensive LDL cholesterol-lowering therapy as compared with moderate-intensity statin therapy,<sup>15,25</sup> we found no effect of additional lowering of LDL cholesterol levels on cardiovascular mortality. The rate of use of evidence-based cardiovascular pharmacotherapies that lower cardiovascular mortality was very high in FOURIER, in which the rates of cardiovascular mortality were one third of the rates in the Scandinavian Simvastatin Survival Study (4S).<sup>26</sup> Similar to the findings in the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) and IMPROVE-IT, in our trial we found no effect on hospitalization for unstable angina. The advent of increasingly sensitive cardiac troponin assays probably makes cardiac ischemia increasingly questionable as the true cause of a hospitalization for chest-pain symptoms without biochemical evidence of myocyte injury.<sup>27</sup> Finally, the rate of urgent coronary revascularization appeared to be more modifiable than that of elective revascularization.

Given these caveats, the magnitude of benefit of evolocumab in reducing the risk of major coronary events, stroke, and urgent coronary revascularization is largely consistent with the benefit seen with statins on a per-millimole-per-liter basis of LDL cholesterol lowering (Fig. S6 in the Supplementary Appendix). These observations are in accord with meta-analyses of data from clinical trials of different lipid-lowering interventions, which show consistent clinical benefits per unit reduction in LDL cholesterol.<sup>28</sup> Likewise, these observations are supported by data from a recent mendelian randomization study in which variants in PCSK9 and variants in HMGCR were associated with nearly identical lower risks of cardiovascular events per unit reduction in LDL cholesterol.<sup>29</sup>

Achievement of these very low LDL cholesterol levels with evolocumab did not lead to any significant differences between the two study groups in the overall rates of adverse events or

in rates of study-regimen discontinuation. The rate of discontinuation of evolocumab injections because of adverse events that were ascribed to the drug was similar to the rate with placebo (0.76% vs. 0.67% per year) and compares favorably to the rates that have been found with atorvastatin at a dose of 80 mg daily (1.5% per year) and with ezetimibe (1.1% per year) in other trials.<sup>14,15</sup> The risk of new-onset diabetes in our trial appeared to be similar in the two groups, although the 95% confidence intervals did not exclude the point estimates observed with statins.<sup>30,31</sup> Potential concerns about an increased risk of neurocognitive adverse events were not borne out in this trial. In contrast to recent data for bococizumab (a humanized but not fully human monoclonal antibody against PCSK9),<sup>32</sup> evolocumab-binding antibodies were rarely detected in our trial, no neutralizing antibodies developed, and the overall LDL cholesterol-lowering effect continued without attenuation. Furthermore, similarly reassuring findings with evolocumab were observed over a period of 4 years in the Open Label Study of Long-Term Evaluation against LDL-C Trial (OSLER-1).<sup>33</sup>

The major limitation of this trial was a relatively short duration of follow-up as compared with that in other lipid-lowering trials, in which follow-up periods have averaged approximately 5 years.<sup>28</sup> Although the median follow-up period in FOURIER was originally planned to be approximately 4 years, an event rate that was approximately 50% higher than had been postulated led to a shorter required duration of follow-up to accrue the prespecified number of events. Most but not all of the patients in the trial received high-intensity statin therapy, and ezetimibe use was infrequent. However, the benefit of evolocumab was consistent regardless of the intensity of statin therapy or ezetimibe use.

In conclusion, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from the lowering of LDL cholesterol levels below current targets.

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