ORIGINAL ARTICLE

A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlipidemia

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ABSTRACT

BACKGROUND

Evolocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), significantly reduced low-density lipoprotein (LDL) cholesterol levels in phase 2 studies. We conducted a phase 3 trial to evaluate the safety and efficacy of 52 weeks of treatment with evolocumab.

METHODS

We stratified patients with hyperlipidemia according to the risk categories outlined by the Adult Treatment Panel III of the National Cholesterol Education Program. On the basis of this classification, patients were started on background lipid-lowering therapy with diet alone or diet plus atorvastatin at a dose of 10 mg daily, atorvastatin at a dose of 80 mg daily, or atorvastatin at a dose of 80 mg daily plus ezetimibe at a dose of 10 mg daily, for a run-in period of 4 to 12 weeks. Patients with an LDL cholesterol level of 75 mg per deciliter (1.9 mmol per liter) or higher were then randomly assigned in a 2:1 ratio to receive either evolocumab (420 mg) or placebo every 4 weeks. The primary end point was the percent change from baseline in LDL cholesterol, as measured by means of ultracentrifugation, at week 52.

RESULTS

Among the 901 patients included in the primary analysis, the overall least-squares mean (±SE) reduction in LDL cholesterol from baseline in the evolocumab group, taking into account the change in the placebo group, was 57.0±2.1% (P<0.001). The mean reduction was 55.7±4.2% among patients who underwent background therapy with diet alone, 61.6±2.6% among those who received 10 mg of atorvastatin, 56.8±5.3% among those who received 80 mg of atorvastatin, and 48.5±5.2% among those who received a combination of 80 mg of atorvastatin and 10 mg of ezetimibe (P<0.001 for all comparisons). Evolocumab treatment also significantly reduced levels of apolipoprotein B, non–high-density lipoprotein cholesterol, lipoprotein(a), and triglycerides. The most common adverse events were nasopharyngitis, upper respiratory tract infection, influenza, and back pain.

CONCLUSIONS

At 52 weeks, evolocumab added to diet alone, to low-dose atorvastatin, or to high-dose atorvastatin with or without ezetimibe significantly reduced LDL cholesterol levels in patients with a range of cardiovascular risks. (Funded by Amgen; DESCARTES ClinicalTrials.gov number, NCT01516879.)

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This article was published on March 29, 2014, at NEJM.org.

DOI: 10.1056/NEJMoa1316222

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a serine protease that is produced predominantly in the liver, is secreted into the plasma and plays a major role in regulating levels of low-density lipoprotein (LDL) cholesterol by binding to hepatic LDL receptors and promoting their degradation.[1,2] In short-term (8-to-12-week), placebo-controlled, phase 2 trials, PCSK9 inhibitors have been shown to significantly reduce LDL cholesterol levels.[3-9] Four of these trials involved the use of evolocumab (AMG 145), a fully human monoclonal PCSK9 antibody, and assessed different doses and regimens in diverse patient populations with varying lipid phenotypes, cardiovascular disease risks, and baseline use of lipid-lowering therapy.[3-6] A longer-term, open-label extension study involving 1104 patients from the phase 2 trials compared evolocumab administered monthly (at a dose of 420 mg) plus standard medical care with standard medical care alone.[10] In the Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES), a randomized, double-blind, placebo-controlled, phase 3 trial, we compared evolocumab with placebo in patients with hyperlipidemia who received the study drug for 52 weeks after a run-in period of 4 to 12 weeks of background lipid-lowering therapy.

Methods

Study Design and Oversight

This study was conducted at 88 centers in nine countries (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org). Amgen sponsored and designed the trial (the latter in collaboration with the last author) and was responsible for data collection and analysis. Local institutional review boards approved the study protocol, which is available at NEJM.org. The first draft of the manuscript was written by the first and last authors, and Amgen provided editorial assistance. All the coauthors participated in subsequent revisions of the manuscript. The academic authors had full access to the data and vouch for their accuracy and completeness, for the analyses as presented, and for the fidelity of the study to the trial protocol.

Patients

Patients were eligible for enrollment in the trial if they were adults 18 to 75 years of age with an LDL cholesterol level of 75 mg per deciliter (1.94 mmol per liter) or higher and a fasting triglyceride level of 400 mg per deciliter (4.52 mmol per liter) or lower. Exclusion criteria were heart failure, recent myocardial infarction, recent or planned revascularization procedure, uncontrolled hypertension, hyperthyroidism or hypothyroidism, moderate-to-severe renal dysfunction, and active liver disease or hepatic dysfunction. Full details of the trial inclusion and exclusion criteria are provided in the Supplementary Appendix. All patients provided written informed consent before entering the trial.

Study Procedures

Patients who met eligibility criteria and, after receiving a 6-ml test placebo injection, agreed to undergo a regimen of monthly subcutaneous injections for a year entered a run-in period of 4 to 12 weeks, during which open-label background lipid-lowering therapy was administered (Fig. S1 and S2 in the Supplementary Appendix). All patients were counseled on the components of the Therapeutic Lifestyle Changes diet, as outlined by the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program.[11] On the basis of the screening LDL cholesterol level, previous use of statin therapy, and cardiovascular risk (as determined by the ATP-III guidelines), we assigned all patients to one of four lipid-lowering regimens: diet alone, diet with 10 mg of atorvastatin daily, diet with 80 mg of atorvastatin daily, or diet with 80 mg of atorvastatin plus 10 mg of ezetimibe daily.

At the conclusion of the first 4 weeks of the run-in period, eligibility for randomization was based on a fasting LDL cholesterol level of 75 mg per deciliter or higher, as determined by the central laboratory (for details, see the Supplementary Appendix). Among patients who met that criterion, those with coronary heart disease (or a coronary heart disease risk equivalent) who had an LDL cholesterol level of less than 100 mg per deciliter (2.59 mmol per liter) and those without coronary heart disease (or a coronary heart disease risk equivalent) who had an LDL cholesterol level of less than 130 mg per deciliter (3.36 mmol per liter) were eligible for randomization. Among patients in whom the lipid-lowering goal had not been reached, therapy was increased to the next level for an additional 4 weeks; the process was repeated a month later if the goal had still not

been reached. Patients who were receiving 80 mg of atorvastatin plus 10 mg of ezetimibe daily but whose LDL cholesterol level was still above the target value were eligible for randomization. Patients with an LDL cholesterol level of less than 75 mg per deciliter were excluded, except for those who were receiving 80 mg of atorvastatin plus 10 mg of ezetimibe daily. These patients were allowed to discontinue ezetimibe and to participate in the study if the ATP-III goal was maintained after 4 weeks on the regimen of 80 mg of atorvastatin daily.

After randomization, no changes to the assigned background lipid-lowering therapy were permitted. Randomization to the blinded phase of the trial, which was stratified according to background therapy, was performed centrally with the use of an interactive voice-response system. Patients were assigned in a 2:1 ratio to receive either 6 ml (420 mg) of evolocumab or placebo, administered subcutaneously every 4 weeks for 48 weeks. The monthly injections could be split (e.g., two 3-ml doses or three 2-ml doses).

Study visits were scheduled every 4 weeks, with additional visits at weeks 13 and 37. Final administration of a study drug occurred at week 48. Patients who discontinued a study drug for any reason were asked to continue all other study activities through week 52.

EFFICACY AND SAFETY END POINTS

The primary efficacy end point was the percent change from baseline in the LDL cholesterol level at week 52 in patients receiving evolocumab, as compared with the change in those receiving placebo. The primary efficacy end point was also assessed separately for each of the background-therapy groups. Secondary efficacy end points included the absolute change from baseline in the LDL cholesterol level at week 52, the percent change from baseline in the LDL cholesterol at week 12, and the percentage of patients with an LDL cholesterol level of less than 70 mg per deciliter (1.81 mmol per liter) at week 52. Additional secondary end points included the percent change from baseline at week 52 in levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, very-low-density lipoprotein (VLDL) cholesterol, and apolipoprotein B, the ratio of total cholesterol to HDL cholesterol, the ratio of apolipoprotein B to apolipoprotein A1, and the levels of lipoprotein(a) and triglycerides.

We assessed the long-term consistency of the effect of evolocumab, as compared with placebo, by comparing the percent change in the LDL cholesterol level at week 12 with that at week 52. All lipid analyses were performed as described previously.[5] All LDL cholesterol levels that were used as primary or secondary trial end points were measured by means of ultracentrifugation unless otherwise specified.[12,13]

Tertiary and exploratory end points are listed in the Supplementary Appendix. Long-term safety and side-effect profiles were assessed by means of adverse-event reporting, clinical examination, and laboratory testing. Anti-evolocumab antibodies were assayed at baseline and at weeks 12, 24, 36, and 52, as described previously.[14]

STATISTICAL ANALYSIS

We determined that with enrollment of 900 patients (600 in the evolocumab group and 300 in the placebo group) the study would have sufficient power (>99%) to detect at least a 20% reduction in the LDL cholesterol level in the evolocumab group, as compared with the placebo group, with a common standard deviation of 20%, after accounting for treatment attenuation and assuming that 2% of the patients would not receive a study drug. All analyses included data from patients who received at least one dose of a study drug. We analyzed all primary and secondary efficacy end points on the basis of the randomized study-group assignments.

We used a repeated-measures linear-effects model to assess the primary end point. Included in this model were terms for the study group, background-therapy group, scheduled visit, and the interaction between the treatment and the scheduled visit (with the use of an unstructured covariance matrix). Missing values were not imputed. We used residual maximum likelihood as the method of estimation and the Kenward–Roger method to estimate denominator degrees of freedom for the tests of fixed effects. Sensitivity and nonparametric analyses as well as the analysis of covariance are described in the Supplementary Appendix.

All other hypothesis testing was two-sided with a significance level of 0.05, with Hochberg adjustment used to control for multiple testing. All P values have been adjusted for multiple testing unless otherwise specified. Key safety end points included adverse events occurring during

treatment, laboratory values, and the presence of anti-evolocumab antibodies. Safety analyses were conducted with the use of descriptive statistics that were based on observed data with no imputation. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 16.1.

Figure 1 (facing page). Enrollment and Outcomes.
Patients were included in the safety and efficacy analyses if they had the required data available for the result of interest. For example, for the primary end point, patients needed to have data for low-density lipoprotein cholesterol levels at baseline and at 52 weeks. Reasons for screening exclusions before the run-in period are not available.

RESULTS

PATIENTS

The study was conducted from January 2012 through November 2013. Of the 2120 patients who were screened, 905 underwent randomization, 901 received at least one dose of a study drug, and 800 (88.4%) completed 52 weeks of treatment (Fig. 1). Of the 901 patients who received a study drug, 111 received background lipid-lowering therapy with diet alone, 383 received 10 mg of atorvastatin daily, 218 received 80 mg of atorvastatin daily, and 189 received 80 mg of atorvastatin plus 10 mg of ezetimibe daily.

Baseline demographic and clinical variables are shown in Table 1, and baseline lipid values in Table 2; baseline apolipoprotein and PCSK9 measures are shown in Tables S1 and S2 in the Supplementary Appendix. As would be anticipated, the prevalence of cardiovascular disease and of cardiovascular risk factors was higher in the groups receiving more intensive background lipid-lowering therapy (Table 1). The mean baseline levels of unbound (free) PCSK9 were lowest in the diet-alone group and increased progressively with the intensity of lipid-lowering therapy, as would be expected with statin treatment (Table S2 in the Supplementary Appendix).

EFFICACY END POINTS

At 52 weeks, the least-squares mean (±SE) reduction in LDL cholesterol from baseline in the evolocumab group, taking into account the change in the placebo group, was 57.0±2.1% at week 52 (Table 2) and 57.5±1.6% at week 12 (Fig. 2, and Fig. S3A in the Supplementary Appendix). In the analysis according to background-therapy group, the least-squares mean reduction in LDL cholesterol in the evolocumab group, taking into account the change in the placebo group, was 55.7±4.2% in the diet-alone group, 61.6±2.6% in the group receiving 10 mg of atorvastatin, 56.8±5.3% in the group receiving 80 mg of atorvastatin, and 48.5±5.2% in the group receiving 80 mg of atorvastatin plus 10 mg of ezetimibe ($P<0.001$ for all comparisons). The LDL cholesterol level at baseline and the percent reductions from baseline that were calculated with the use of the Friedewald formula (Table S1 in the Supplementary Appendix) were similar to those that were measured by means of ultracentrifugation. The level of LDL cholesterol was reduced below 70 mg per deciliter in 82.3% of patients in the evolocumab group, as compared with 6.4% of those in the placebo group (Table 2).

Evolocumab treatment, as compared with placebo, also resulted in significant least-squares mean percent reductions from baseline in levels of apolipoprotein B, non-HDL cholesterol, lipoprotein(a), and triglycerides (Table S1 in the Supplementary Appendix). After taking into account the change in the placebo group, evolocumab treatment resulted in a least-squares mean increase of 5.4±1.1% in the HDL cholesterol level ($P<0.001$) and of 3.0±0.8% in the apolipoprotein A1 level (unadjusted $P<0.001$). No meaningful changes were seen in levels of high-sensitivity C-reactive protein (Table S1 in the Supplementary Appendix).

In the evolocumab group, mean reductions from baseline in unbound PCSK9 levels that were measured at weeks 13 and 37 at an interval of 1 week after administration were 91.1±1.8% and 86.9±1.3%, respectively; in measurements performed at weeks 12, 24, 36, and 52 at an interval of 4 weeks after administration, there were mean reductions of 41.2±1.2%, 38.3±2.2%, 38.3±2.2%, and 42.4±1.8%, respectively (Table S2 in the Supplementary Appendix). Reductions after 1 week were consistently around 90% regardless of background therapy, but those at 4 weeks after drug administration were greater in the diet-alone group and the group receiving 10 mg of atorvastatin than in the two groups receiving 80 mg of atorvastatin (Table S2 and Fig. S4 and S5 in the Supplementary Appendix).

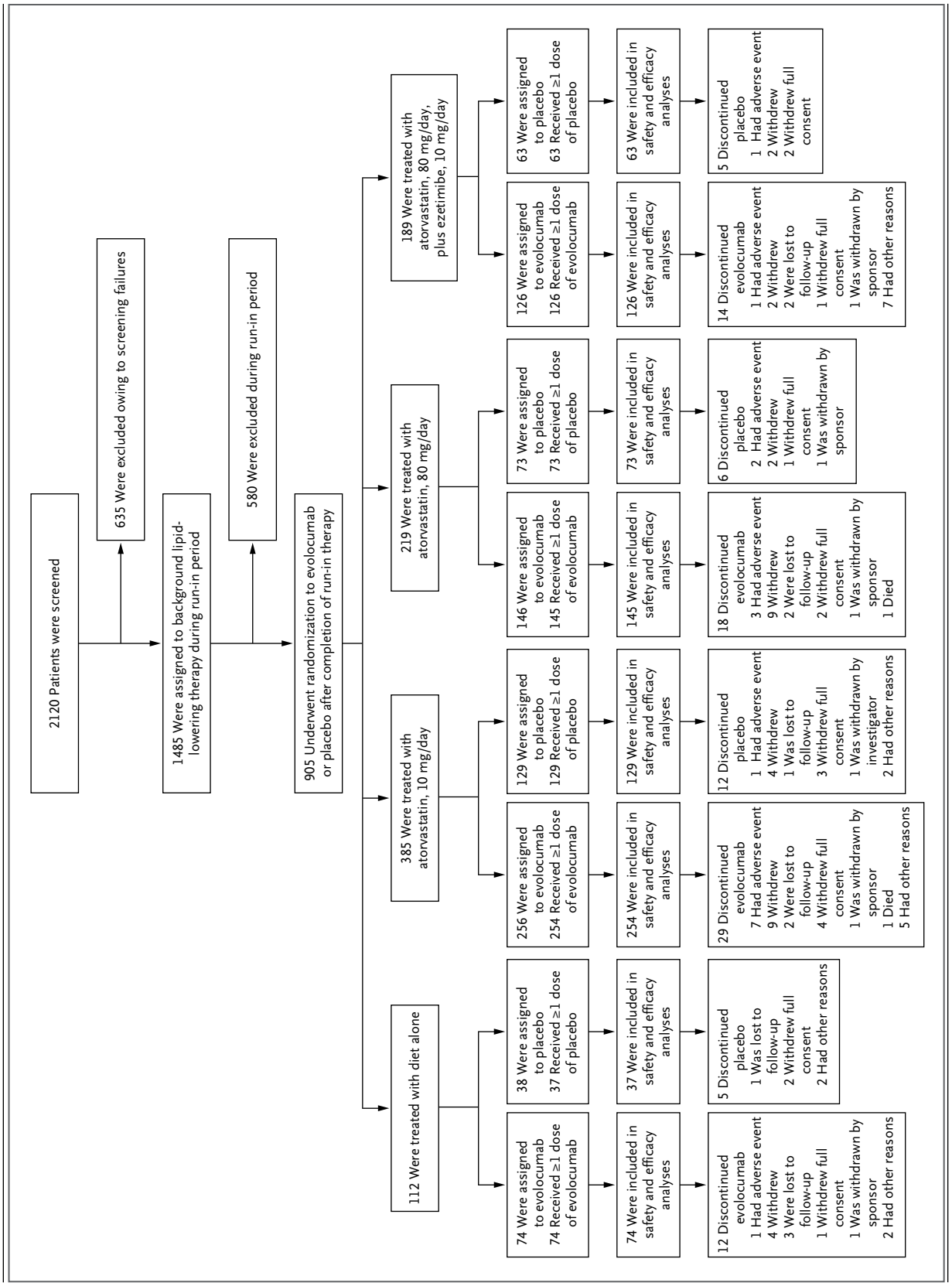

Table 1. Characteristics of the Patients at Baseline, According to Background Lipid-Lowering Therapy before Randomization.*

Characteristic	Diet Alone		Diet plus 10 mg of Atorvastatin		Diet plus 80 mg of Atorvastatin		Diet plus 80 mg of Atorvastatin plus 10 mg of Ezetimibe		All Patients	
	Placebo (N=37)	Evolocumab (N=74)	Placebo (N=129)	Evolocumab (N=254)	Placebo (N=73)	Evolocumab (N=145)	Placebo (N=63)	Evolocumab (N=126)	Placebo (N=302)	Evolocumab (N=599)
Age — yr	53.5±12.4	50.7±10.6	57.0±10.6	57.2±10.3	58.4±8.7	57.8±9.4	55.9±9.0	54.2±11.5	56.7±10.1	55.9±10.8
Male sex — no. (%)	15 (40.5)	35 (47.3)	59 (45.7)	109 (42.9)	33 (45.2)	76 (52.4)	33 (52.4)	70 (55.6)	140 (46.4)	290 (48.4)
Body-mass index†	29.4±6.3	31.1±8.1	30.2±6.4	29.6±6.0	31.6±5.9	30.3±5.7	30.2± 4.5	29.6±5.0	30.5±5.9	29.9±6.1
Race — no. (%)‡										
White	25 (67.6)	50 (67.6)	112 (86.8)	217 (85.4)	65 (89.0)	123 (84.8)	46 (73.0)	86 (68.3)	248 (82.1)	476 (79.5)
Asian	5 (13.5)	11 (14.9)	6 (4.7)	15 (5.9)	1 (1.4)	5 (3.4)	4 (6.3)	10 (7.9)	16 (5.3)	41 (6.8)
Black	7 (18.9)	11 (14.9)	8 (6.2)	18 (7.1)	5 (6.8)	12 (8.3)	3 (4.8)	12 (9.5)	23 (7.6)	53 (8.8)
Other	0	2 (2.7)	3 (2.3)	4 (1.6)	2 (2.7)	5 (3.4)	10 (15.9)	18 (14.3)	15 (5.0)	29 (4.8)
ATP-III risk category — no. (%)										
High	2 (5.4)	4 (5.4)	13 (10.1)	28 (11.0)	23 (31.5)	44 (30.3)	41 (65.1)	80 (63.5)	79 (26.2)	156 (26.0)
Moderately high	4 (10.8)	10 (13.5)	15 (11.6)	27 (10.6)	7 (9.6)	12 (8.3)	3 (4.8)	7 (5.6)	29 (9.6)	56 (9.3)
Moderate	16 (43.2)	25 (33.8)	46 (35.7)	92 (36.2)	24 (32.9)	62 (42.8)	11 (17.5)	24 (19.0)	97 (32.1)	203 (33.9)
Low	15 (40.5)	35 (47.3)	55 (42.6)	107 (42.1)	19 (26.0)	27 (18.6)	8 (12.7)	15 (11.9)	97 (32.1)	184 (30.7)
Coronary artery disease — no. (%)	0	2 (2.7)	2 (1.6)	8 (3.1)	11 (15.1)	23 (15.9)	29 (46.0)	61 (48.4)	42 (13.9)	94 (15.7)
Type 2 diabetes — no. (%)	2 (5.4)	1 (1.4)	10 (7.8)	17 (6.7)	14 (19.2)	19 (13.1)	16 (25.4)	25 (19.8)	42 (13.9)	62 (10.4)
Cardiovascular risk factors — no. (%)										
Current smoker	4 (10.8)	15 (20.3)	16 (12.4)	29 (11.4)	11 (15.1)	20 (13.8)	17 (27.0)	23 (18.3)	48 (15.9)	87 (14.5)
Hypertension	19 (51.4)	28 (37.8)	51 (39.5)	109 (42.9)	41 (56.2)	84 (57.9)	38 (60.3)	68 (54.0)	149 (49.3)	289 (48.2)
Family history of premature coronary artery disease	4 (10.8)	11 (14.9)	21 (16.3)	35 (13.8)	15 (20.5)	33 (22.8)	26 (41.3)	63 (50.0)	66 (21.9)	142 (23.7)
≥2 risk factors	10 (27.0)	23 (31.1)	40 (31.0)	62 (24.4)	35 (47.9)	66 (45.5)	43 (68.3)	73 (57.9)	128 (42.4)	224 (37.4)

* Plus–minus values are means ±SD. There was no significant between-group difference, within each background therapy or overall, in any of the baseline characteristics. ATP-III denotes Adult Treatment Panel III of the National Cholesterol Education Program.

† Body-mass index is the weight in kilograms divided by the square of the height in meters. Data on body-mass index were missing for one patient each in the diet-alone group and the group receiving 10 mg of atorvastatin and for two patients in the group receiving atorvastatin plus ezetimibe.

‡ Race was self-reported.

ADVERSE EVENTS AND IMMUNOGENICITY

The overall incidence of adverse events occurring during treatment was similar in the evolocumab group and the placebo group, with 448 of 599 patients (74.8%) and 224 of 302 patients (74.2%), respectively, having an adverse event. The most common adverse events in the evolocumab group were nasopharyngitis, upper respiratory tract infection, influenza, and back pain (Table 3, and Table S3 in the Supplementary Appendix). Serious adverse events occurred in 33 patients (5.5%) in the evolocumab group and 13 patients (4.3%) in the placebo group (Table S4 in the Supplementary Appendix). Adverse events leading to the discontinuation of a study drug occurred in 13 patients (2.2%) in the evolocumab group and 3 patients (1.0%) in the placebo group (Table S5 in the Supplementary Appendix). Injection-site reactions were reported in 34 patients (5.7%) in the evolocumab group and 15 patients (5.0%) in the placebo group, resulting in discontinuation of evolocumab in 1 patient (Table S6 in the Supplementary Appendix).

Elevations of creatine kinase levels to more than five times the upper limit of the normal range occurred in 7 patients (1.2%) in the evolocumab group and 1 patient (0.3%) in the placebo group, with myalgia reported by 24 patients (4.0%) and 9 patients (3.0%), respectively; elevations of aminotransferase levels to more than three times the upper limit of the normal range occurred in 5 patients (0.8%) and 3 patients (1.0%), respectively (Table 3). Evolocumab treatment did not have an adverse effect on glycemic measures (Table 3). Two patients in the evolocumab group had detectable binding antibodies before or at the time of randomization. One patient in the evolocumab group had newly detected transient anti-evolocumab binding antibodies during treatment. No anti-evolocumab neutralizing antibodies were detected in any patient (Table S7 in the Supplementary Appendix).

DISCUSSION

We found that treatment with 420 mg of evolocumab every 4 weeks for 52 weeks resulted in a relative reduction in LDL cholesterol levels of 57%, taking into account the change in the placebo group. This result was consistent with the effects that were observed with the same evolocumab regimen in the 12-week phase 2 trials.[3-6] In addition, we found no decrement in the effi-

Table 2. Low-Density Lipoprotein (LDL) Cholesterol Levels at Baseline and at Week 52, According to Background Lipid-Lowering Therapy before Randomization.*

Variable	Diet Alone		Diet plus 10 mg of Atorvastatin		Diet plus 80 mg of Atorvastatin		Diet plus 80 mg of Atorvastatin plus 10 mg of Ezetimibe		All Patients	
	Placebo (N=37)	Evolocumab (N=74)	Placebo (N=129)	Evolocumab (N=254)	Placebo (N=73)	Evolocumab (N=145)	Placebo (N=63)	Evolocumab (N=126)	Placebo (N=302)	Evolocumab (N=599)
Mean (±SD) LDL cholesterol at baseline — mg/dl	112.3±15.9	111.6±15.2	98.4±14.5	101.3±15.1	96.2±13.3	94.6±12.9	119.8±32.4	116.8±35.3	104.0±21.6	104.2±22.1
No. of patients evaluated at week 52†	31	67	113	233	66	130	54	112	264	542
Least-squares mean (±SE) percent change from baseline in LDL cholesterol at week 52	4.2±3.5	−51.5±2.4	6.9±2.2	−54.7±1.5	10.1±4.3	−46.7±3.1	1.7±4.3	−46.8±3.0	6.8±1.8	−50.1±1.2
Least-squares mean (±SE) percent change from baseline in LDL cholesterol vs. placebo at week 52		−55.7±4.2		−61.6±2.6		−56.8±5.3		−48.5±5.2		−57.0±2.1
Mean (±SE) LDL cholesterol at week 52 — mg/dl	117.3±4.3	53.5±2.7	103.9±2.3	44.7±1.5	104.6±3.7	49.6±3.1	115.0±5.6	63.9±4.1	107.9±1.9	50.9±1.4
Patients with LDL cholesterol <70 mg/dl at week 52 — no. (%)	1 (3.2)	56 (83.6)	6 (5.3)	210 (90.1)	4 (6.1)	105 (80.8)	6 (11.1)	75 (67.0)	17 (6.4)	446 (82.3)

* Cholesterol was measured by means of ultracentrifugation. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.
† Included are patients within each background therapy in whom LDL cholesterol was measured at baseline and at week 52.

Table 3. Adverse Events Occurring during Treatment and Laboratory Results.

Event	Placebo (N=302)	Evolocumab (N=599)
	no. of patients (%)	
Patients with adverse event		
Any	224 (74.2)	448 (74.8)
Serious	13 (4.3)	33 (5.5)
Leading to discontinuation of a study drug	3 (1.0)	13 (2.2)
Adjudicated atherosclerotic event	2 (0.7)	6 (1.0)
Death*	0	2 (0.3)
Common adverse events†		
Nasopharyngitis	29 (9.6)	63 (10.5)
Upper respiratory tract infection	19 (6.3)	56 (9.3)
Influenza	19 (6.3)	45 (7.5)
Back pain	17 (5.6)	37 (6.2)
Bronchitis	14 (4.6)	27 (4.5)
Urinary tract infection	11 (3.6)	27 (4.5)
Cough	11 (3.6)	27 (4.5)
Arthralgia	14 (4.6)	25 (4.2)
Sinusitis	9 (3.0)	25 (4.2)
Headache	11 (3.6)	24 (4.0)
Myalgia	9 (3.0)	24 (4.0)
Dizziness	8 (2.6)	22 (3.7)
Nausea	10 (3.3)	20 (3.3)
Musculoskeletal pain	9 (3.0)	20 (3.3)
Hypertension	7 (2.3)	19 (3.2)
Diarrhea	8 (2.6)	18 (3.0)
Gastroenteritis	6 (2.0)	18 (3.0)
Injection-site erythema	6 (2.0)	16 (2.7)
Oropharyngeal pain	4 (1.3)	15 (2.5)
Muscle strain	10 (3.3)	14 (2.3)
Muscle spasm	8 (2.6)	14 (2.3)
Pain in extremity	13 (4.3)	13 (2.2)
Fatigue	9 (3.0)	13 (2.2)
Upper abdominal pain	2 (0.7)	13 (2.2)
Osteoarthritis	5 (1.7)	12 (2.0)
Vomiting	5 (1.7)	11 (1.8)
Viral upper respiratory tract infection	3 (1.0)	11 (1.8)
Dyspepsia	2 (0.7)	11 (1.8)
Rash	1 (0.3)	11 (1.8)
Nasal congestion	7 (2.3)	10 (1.7)
Cystitis	4 (1.3)	10 (1.7)
Tendonitis	3 (1.0)	10 (1.7)
Anxiety	2 (0.7)	10 (1.7)
Seasonal allergy	4 (1.3)	9 (1.5)
Neck pain	3 (1.0)	9 (1.5)
Insomnia	3 (1.0)	9 (1.5)
Pharyngitis	2 (0.7)	9 (1.5)
Arthropod bite	1 (0.3)	9 (1.5)
Gastroesophageal reflux disease	8 (2.6)	8 (1.3)

Table 3. (Continued.)

Event	Placebo (N = 302)	Evolocumab (N = 599)
	no. of patients (%)	
Contusion	5 (1.7)	8 (1.3)
Injection-site pain	4 (1.3)	8 (1.3)
Noncardiac chest pain	0	8 (1.3)
Injection-site bruising	6 (2.0)	7 (1.2)
Musculoskeletal chest pain	3 (1.0)	7 (1.2)
Abdominal pain	2 (0.7)	7 (1.2)
Palpitations	1 (0.3)	7 (1.2)
Anemia	0	7 (1.2)
Nephrolithiasis	0	7 (1.2)
Laceration	5 (1.7)	6 (1.0)
Gastritis	4 (1.3)	6 (1.0)
Migraine	3 (1.0)	6 (1.0)
Eczema	3 (1.0)	6 (1.0)
Angina pectoris	2 (0.7)	6 (1.0)
Ventricular extrasystoles	2 (0.7)	6 (1.0)
Constipation	2 (0.7)	6 (1.0)
Injection-site swelling	2 (0.7)	6 (1.0)
Pyrexia	1 (0.3)	6 (1.0)
Procedural pain	1 (0.3)	6 (1.0)
Vertigo	5 (1.7)	5 (0.8)
Asthma	4 (1.3)	5 (0.8)
Ligament pain	3 (1.0)	5 (0.8)
Arthritis	3 (1.0)	5 (0.8)
Fall	5 (1.7)	3 (0.5)
Pruritus	5 (1.7)	2 (0.3)
Foot fracture	5 (1.7)	1 (0.2)
Elevated alanine aminotransferase or aspartate aminotransferase‡		
>3× ULN	3 (1.0)	5 (0.8)
>5× ULN	1 (0.3)	3 (0.5)
Elevated creatine kinase‡		
>5× ULN	1 (0.3)	7 (1.2)
>10× ULN	1 (0.3)	3 (0.5)
Potential injection-site reaction§	15 (5.0)	34 (5.7)

* The two deaths were from cardiac failure and myocardial infarction and are included as adjudicated atherosclerotic events.
† Listed are the preferred terms reported for at least 1% patients in either study group. For measures of glycemia, the mean (±SE) change from baseline for fasting glucose at week 52 was 1.3±0.7 mg per deciliter (0.07±0.04 mmol per liter) for evolocumab and 0.4±0.9 mg per deciliter (0.02±0.05 mmol per liter) for placebo. The mean change from baseline for glycated hemoglobin at week 52 was 0.02±0.02 percentage points for evolocumab and 0.00±0.03 percentage points for placebo.
‡ The elevated values relative to the upper limit of the normal range (ULN) were those that were recorded at any visit after baseline.
§ Potential events were identified by means of a broad-search strategy, in which event categories were defined with the use of preferred terms from the *Medical Dictionary for Regulatory Activities* (MedDRA) and either standard MedDRA queries or internal groupings.

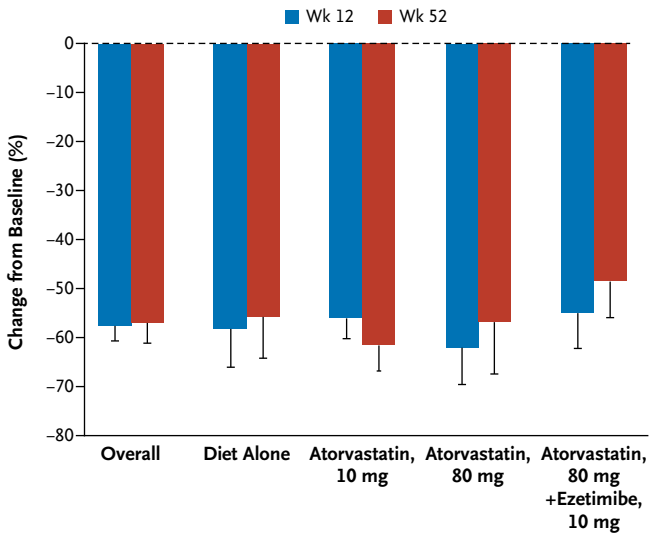

Figure 2. Percent Reduction from Baseline in Low-Density Lipoprotein (LDL) Cholesterol Levels in the Evolocumab Group, as Compared with the Placebo Group, at Weeks 12 and 52, According to Background Lipid-Lowering Therapy.

Values are means with lower 95% confidence limits (as indicated by T bars) in the active-treatment groups after taking into account the values in the placebo group. LDL cholesterol was measured by means of ultracentrifugation separation.

cacy of evolocumab from week 12 to week 52. Our findings were also similar to the finding of a relative reduction of 52% in LDL cholesterol levels reported in the first year of the Open-Label Study of Long-Term Evaluation against LDL-C (OSLER) study.[10]

Our study design called for a run-in period in which background lipid-lowering therapy was adjusted on the basis of LDL cholesterol goals, according to the patient's ATP-III–defined cardiovascular risk. These risk-based lipid-lowering therapies ranged from diet alone to a combination of 80 mg of atorvastatin plus 10 mg of the cholesterol-absorption inhibitor ezetimibe daily. Percent reductions in LDL cholesterol in the evolocumab group, taking into account the change in the placebo group, differed slightly according to background therapy, ranging from 48.5% in the group receiving atorvastatin plus ezetimibe to 61.6% in the group receiving 10 mg of atorvastatin.

Our findings provide some insights into the magnitude and duration of PCSK9 inhibition with antibodies as a function of background lipid-lowering therapy. In our study, unbound PCSK9 was measured at 1 week and at 4 weeks after the administration of evolocumab. The differences in unbound PCSK9 among background-therapy groups at 1 week were minimal, despite substantial differences in baseline levels, indicating that virtually all PCSK9 is antibody-bound initially. However, not only were baseline levels of PCSK9 higher among patients receiving high-dose atorvastatin than among patients in the other groups, but there also was a more rapid increase in PCSK9 levels 4 weeks after the administration of each dose of evolocumab in these patients, suggesting that the rate of PCSK9 production is increased in patients receiving intensive statin therapy.

The effect on PCSK9 levels that we observed and the consequent reductions in LDL cholesterol levels at 4 weeks after the administration of evolocumab were similar to those reported in patients receiving either 10 mg or 80 mg of atorvastatin plus another PCSK9 monoclonal antibody, alirocumab (at a dose of 150 mg), even though patients received alirocumab every 2 weeks rather than every 4 weeks.[7] Thus, it may be that patients who have already been treated with high-dose statins or combination lipid-lowering therapy may have slightly less capacity to further up-regulate LDL-receptor activity with PCSK9 inhibition or may require higher doses of antibody. Our findings are also in keeping with those of a number of other trials in which no synergism between statins and PCSK9 inhibition was observed. Although statins up-regulate PCSK9, this does not explain why the reduction in LDL cholesterol levels that is associated with an initial dose of a statin is relatively large in comparison to the additional 6% reduction observed when the statin dose is doubled.

The recently published cholesterol guidelines of the American College of Cardiology and the American Heart Association (ACC–AHA)[15] include several changes from the ATP-III guidelines published in 2002. Among these changes is the recommendation that the intensity of therapy be guided by cardiovascular risk rather than by LDL cholesterol goals. However, despite this recommendation, an LDL cholesterol level of less than 70 mg per deciliter remains a treatment target for patients at very high risk for cardiovascular disease in many countries. In our study, this target was achieved in more than 80% of patients with the use of 420 mg of evolocumab every 4 weeks. In addition, there were signifi-

cant reductions in the levels of other atherogenic, apolipoprotein B–containing lipoproteins, including lipoprotein(a), and modest but significant increases in levels of HDL cholesterol and apolipoprotein A1, similar to those reported with evolocumab previously.[3-6,16]

More patients in the evolocumab group than in the placebo group were reported to have serious adverse events during treatment and to have adverse events leading to drug discontinuation. However, a review of the individual adverse events in these categories does not offer any clear indication of specific risks associated with evolocumab. The most common adverse events were nasopharyngitis, upper respiratory tract infection, influenza, and back pain, all of which occurred more frequently in the evolocumab group. There were more reports of myalgia and elevated creatine kinase levels among patients receiving evolocumab.

In conclusion, among patients at risk for a wide range of coronary diseases who were receiving guideline-recommended background lipid-lowering therapy, the monoclonal PCSK9 antibody evolocumab reduced LDL cholesterol levels by 57%, as compared with placebo, at 52 weeks.

Supported by Amgen.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Meera Kodukulla, Ph.D., of Amgen, and Rick Davis, M.S., of Complete Healthcare Communications, on behalf of Amgen, for editorial support; Barbara Sgotto and Colin Weller of Amgen for assistance with clinical-trial management; and Wei Cui, M.S., and Stephen Gormley, B.Sc., for statistical programming support.

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