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Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

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ABSTRACT

BACKGROUND

Patients who have had an acute coronary syndrome are at high risk for recurrent ischemic cardiovascular events. We sought to determine whether alirocumab, a human monoclonal antibody to proprotein convertase subtilisin–kexin type 9 (PCSK9), would improve cardiovascular outcomes after an acute coronary syndrome in patients receiving high-intensity statin therapy.

METHODS

We conducted a multicenter, randomized, double-blind, placebo-controlled trial involving 18,924 patients who had an acute coronary syndrome 1 to 12 months earlier, had a low-density lipoprotein (LDL) cholesterol level of at least 70 mg per deciliter (1.8 mmol per liter), a non–high-density lipoprotein cholesterol level of at least 100 mg per deciliter (2.6 mmol per liter), or an apolipoprotein B level of at least 80 mg per deciliter, and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose. Patients were randomly assigned to receive alirocumab subcutaneously at a dose of 75 mg (9462 patients) or matching placebo (9462 patients) every 2 weeks. The dose of alirocumab was adjusted under blinded conditions to target an LDL cholesterol level of 25 to 50 mg per deciliter (0.6 to 1.3 mmol per liter). The primary end point was a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.

RESULTS

The median duration of follow-up was 2.8 years. A composite primary end-point event occurred in 903 patients (9.5%) in the alirocumab group and in 1052 patients (11.1%) in the placebo group (hazard ratio, 0.85; 95% confidence interval [CI], 0.78 to 0.93; P<0.001). A total of 334 patients (3.5%) in the alirocumab group and 392 patients (4.1%) in the placebo group died (hazard ratio, 0.85; 95% CI, 0.73 to 0.98). The absolute benefit of alirocumab with respect to the composite primary end point was greater among patients who had a baseline LDL cholesterol level of 100 mg or more per deciliter than among patients who had a lower baseline level. The incidence of adverse events was similar in the two groups, with the exception of local injection-site reactions (3.8% in the alirocumab group vs. 2.1% in the placebo group).

CONCLUSIONS

Among patients who had a previous acute coronary syndrome and who were receiving high-intensity statin therapy, the risk of recurrent ischemic cardiovascular events was lower among those who received alirocumab than among those who received placebo. (Funded by Sanofi and Regeneron Pharmaceuticals; ODYSSEY OUTCOMES ClinicalTrials.gov number, NCT01663402.)

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Despite the availability of current evidence-based treatments, patients who have had an acute coronary syndrome remain at high risk for recurrent ischemic cardiovascular events.[1,2] This residual risk is attributable in part to elevated levels of low-density lipoprotein (LDL) cholesterol and other atherogenic lipoproteins. Previous clinical trials have shown that the risk is lower among patients who receive statin therapy to lower the LDL cholesterol level than among those who receive placebo,[3] among patients who receive high-intensity statins than among those who receive moderate-intensity statins,[4] and among patients who receive ezetimibe added to statin therapy than among those who receive a statin alone.[5]

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Proprotein convertase subtilisin–kexin type 9 (PCSK9) promotes degradation of LDL receptors, thereby diminishing the clearance of LDL from the circulation.[6] Studies have shown that mutations conveying gain or loss of function of PCSK9 result in a higher or lower level of LDL cholesterol, respectively, which in turn is associated with a corresponding higher[7] or lower[6] risk of incident coronary heart disease. These findings have led to the development of monoclonal antibodies to PCSK9 that produce substantial reductions in LDL cholesterol when administered alone or with a statin.[8-12] Two of these agents were reported to reduce the risk of ischemic cardiovascular events in patients who had stable atherosclerotic disease or high cardiovascular risk and an elevated level of atherogenic lipoproteins despite statin treatment,[11,13] with one agent showing benefit only among patients who had a baseline LDL cholesterol level of at least 100 mg per deciliter (2.6 mmol per liter).[12]

To date, the potential for a PCSK9 antibody to reduce cardiovascular risk after an acute coronary syndrome remains undetermined. In the ODYSSEY OUTCOMES trial, we tested the hypothesis that treatment with alirocumab, a fully human monoclonal antibody to PCSK9,[13-15] would result in a lower risk of recurrent ischemic cardiovascular events than placebo among patients who had an acute coronary syndrome within the preceding 1 to 12 months and who have levels of atherogenic lipoproteins that exceed specified thresholds despite statin therapy at a high-intensity dose or at the maximum tolerated dose.

Methods

Trial Organization and Oversight

Details of the trial design have been reported previously.[14] ODYSSEY OUTCOMES was a multicenter, randomized, double-blind, placebo-controlled trial that was sponsored by Sanofi and Regeneron Pharmaceuticals. The protocol and statistical analysis plan (available with the full text of this article at NEJM.org) were conceived by the first three authors, developed in conjunction with the other members of the executive steering committee and sponsors, and approved by the responsible regulatory authorities and ethics committees. The sponsors participated in the selection of the trial sites, the monitoring of the trial, and the supervision of data collection. Duke Clinical Research Institute led the blinded adjudication of the end points. An independent data and safety monitoring committee monitored the safety and efficacy data. Analyses were performed independently by the academic statistician (the third author) in parallel with the sponsors. The manuscript was prepared by the first author with input from all the authors. The members of the executive steering committee made the decision to submit the manuscript for publication and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Trial Population

Patients were eligible for enrollment in the trial if they were 40 years of age or older, had been hospitalized with an acute coronary syndrome (myocardial infarction or unstable angina) 1 to 12 months before randomization, and had an LDL cholesterol level of at least 70 mg per deciliter (1.8 mmol per liter), a non–high-density lipoprotein (HDL) cholesterol level of at least 100 mg per deciliter, or an apolipoprotein B level of at least 80 mg per deciliter. All qualifying lipid levels were measured after a minimum of 2 weeks of stable treatment with atorvastatin at a dose of 40 to 80 mg once daily, rosuvastatin at a dose of 20 to 40 mg once daily, or the maximum tolerated dose of one of these statins (including no statin in the case of documented unacceptable side effects). Full trial enrollment criteria are provided in the Supplementary Appendix, available at NEJM.org. All the patients provided written informed consent.

TRIAL PROCEDURES

During a prerandomization run-in phase (described in the Supplementary Appendix), patients received instruction in injecting themselves (with placebo), and lipid levels were verified for patient eligibility. Patients who met trial entry criteria were randomly assigned, in a 1:1 ratio, to receive alirocumab at a dose of 75 mg or matching placebo; randomization was stratified according to country (Table S1 in the Supplementary Appendix). All doses of alirocumab or placebo were administered by subcutaneous injection every 2 weeks.

The trial-group assignments and lipid levels during the trial were concealed from the patients and investigators. LDL cholesterol levels were calculated with the use of the Friedewald formula unless the triglyceride level exceeded 400 mg per deciliter (4.52 mmol per liter) or the calculated LDL cholesterol level was found to be less than 15 mg per deciliter (0.39 mmol per liter), in which case values were determined by beta quantification. Among patients assigned to the alirocumab group, protocol-specified dose-adjustment algorithms[14] were used to target an LDL cholesterol level of 25 to 50 mg per deciliter (0.6 to 1.3 mmol per liter) and to avoid sustained levels below 15 mg per deciliter (details can be found in the Additional Information on the Methods and Results section and in Figs. S1 and S2 in the Supplementary Appendix). Dose adjustments were performed under blinded conditions, without either the patient or the investigator being aware of the adjustment, including substitution of placebo for alirocumab in the case of sustained levels of LDL cholesterol below 15 mg per deciliter.

TRIAL END POINTS

The primary end point was a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. Prespecified main secondary end points were any coronary heart disease event (death from coronary heart disease, nonfatal myocardial infarction, unstable angina requiring hospitalization, or an ischemia-driven coronary revascularization procedure); major coronary heart disease event (death from coronary heart disease or nonfatal myocardial infarction); any cardiovascular event (death from cardiovascular causes, nonfatal ischemic stroke, nonfatal myocardial infarction, unstable angina requiring hospitalization, or an ischemia-driven coronary revascularization procedure); a composite of death from any cause, nonfatal myocardial infarction, or nonfatal ischemic stroke; death from coronary heart disease; death from cardiovascular causes; and death from any cause. Individual components of the primary end point, an ischemia-driven coronary revascularization procedure, and hospitalization for congestive heart failure were additional secondary end points. All primary and secondary end points were adjudicated by physicians who were unaware of the trial-group assignments.

STATISTICAL ANALYSIS

Efficacy was determined by the time to the first occurrence of any component of the composite primary end point; analyses were performed according to the intention-to-treat principle and included data from all patients and for all events that occurred from the time of randomization to the common trial end date. Design assumptions included an incidence of the composite primary end point of 11.4% at 4 years in the placebo group and a median baseline LDL cholesterol level of 90 mg per deciliter (2.3 mmol per liter), with an anticipated 50% lower LDL cholesterol level in the alirocumab group than in the placebo group, which would result in an expected 15% lower risk of the primary end point with alirocumab than with placebo. It was estimated that 1613 composite primary end-point events occurring in 18,000 patients over a median follow-up of approximately 3 years would provide the trial with 90% power to detect the expected difference in risk at a significance level of 0.05. In China, 614 patients underwent randomization after random assignment of the main trial cohort had been completed (as described in the Supplementary Appendix). The protocol specified that the trial was to continue until at least 1613 primary end-point events had occurred and all patients who could be evaluated were followed for at least 2 years (except the patients from

China), which would ensure a sufficient observation time in which to assess safety and efficacy. Patients from China were not followed for 2 years because a lengthy regulatory approval process delayed their random assignment to a trial group until after completion of the randomization process for the rest of the trial cohort.

LDL cholesterol was evaluated in an intention-to-treat analysis that included levels measured after premature discontinuation of the trial regimen, levels measured after dose adjustments were made under blinded conditions, and levels measured after blinded substitution of placebo for alirocumab. LDL cholesterol was also evaluated in the alirocumab group in an on-treatment analysis that excluded levels measured after premature discontinuation of alirocumab and levels measured after blinded substitution of placebo for alirocumab but included levels measured after dose adjustments of alirocumab between the 75-mg dose and the 150-mg dose were made under blinded conditions.

Hazard ratios and 95% confidence intervals were estimated with the use of a Cox proportional-hazards model, stratified according to geographic region; P values were determined with the use of stratified log-rank tests. To adjust for multiplicity, the results of the main secondary end points were to be tested in hierarchical fashion in the sequence listed above if the risk of the composite primary end point was found to be significantly lower in the alirocumab group than in the placebo group. Two prespecified interim analyses were performed when approximately 50% and 75% of the planned primary end-point events for the final analysis had occurred; neither led to early termination of the trial. To account for the two interim analyses, a two-sided P value of less than 0.0498 was required to declare statistical significance for the primary end point at the final analysis. Absolute treatment effects in prespecified subgroups were compared with the use of the Gail–Simon test.[15] The statistical analysis plan and the Supplementary Appendix provide details of the descriptive safety analyses and analytical methods.

RESULTS

PATIENTS, TRIAL REGIMEN, AND FOLLOW-UP

A total of 18,924 patients underwent randomization at 1315 sites in 57 countries; 9462 were assigned to the alirocumab group and 9462 to the placebo group (Fig. S3 in the Supplementary Appendix). Except in China, patients underwent randomization from November 2012 through November 2015. In China, 613 patients underwent randomization from May 2016 through February 2017. At the time of randomization, the characteristics of the two trial groups were well balanced (Table 1, and Table S2 in the Supplementary Appendix). The qualifying acute coronary syndrome was myocardial infarction in 83.0% of the patients and unstable angina in 16.8%. Most of the patients (92.1%) qualified with an LDL cholesterol level of 70 mg or more per deciliter; a majority of the remaining patients (7.2%) met only the non–HDL cholesterol criterion. The median time from the qualifying acute coronary syndrome to randomization was 2.6 months (interquartile range, 1.7 to 4.3).

Most of the patients received guideline-recommended medications and had undergone coronary revascularization for the index event. At the time of randomization, 88.8% of the patients were receiving atorvastatin at a dose of 40 mg to 80 mg daily or were receiving rosuvastatin at a dose of 20 mg to 40 mg daily. After 1 year of follow-up, 84.7% of the patients in the alirocumab group and 86.2% in the placebo group were receiving such treatment; after 3 years of follow-up, the percentages were 82.8% in the alirocumab group and 86.6% in the placebo group. Information on the adjustment of alirocumab doses under blinded conditions can be found in the Supplementary Appendix.

Patients were followed for a median of 2.8 years (interquartile range, 2.3 to 3.4); the common trial end date was November 11, 2017. Premature discontinuation of the assigned alirocumab or placebo for reasons other than death occurred in 1343 patients (14.2%) in the alirocumab group and in 1496 patients (15.8%) in the placebo group (Fig. S3 in the Supplementary Appendix). Exposure to the intended trial regimen as a percentage of the total follow-up time

Table 1. Demographic and Baseline Characteristics of the Patients.*

Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Age — yr	58.5±9.3	58.6±9.4
Female sex — no. (%)	2390 (25.3)	2372 (25.1)
Race — no. (%)†		
White	7500 (79.3)	7524 (79.5)
Asian	1251 (13.2)	1247 (13.2)
Black	235 (2.5)	238 (2.5)
Other	475 (5.0)	451 (4.8)
Region of enrollment — no. (%)		
Central and Eastern Europe	2719 (28.7)	2718 (28.7)
Western Europe	2084 (22.0)	2091 (22.1)
Canada or United States	1435 (15.2)	1436 (15.2)
Latin America	1293 (13.7)	1295 (13.7)
Asia	1150 (12.2)	1143 (12.1)
Rest of world	781 (8.3)	779 (8.2)
Medical history before index acute coronary syndrome — no. (%)		
Hypertension	6205 (65.6)	6044 (63.9)
Diabetes mellitus	2693 (28.5)	2751 (29.1)
Current tobacco smoker	2282 (24.1)	2278 (24.1)
Family history of premature coronary heart disease	3408 (36.0)	3365 (35.6)
Myocardial infarction	1790 (18.9)	1843 (19.5)
Percutaneous coronary intervention	1626 (17.2)	1615 (17.1)
Coronary-artery bypass grafting	521 (5.5)	526 (5.6)
Stroke	306 (3.2)	305 (3.2)
Peripheral artery disease	373 (3.9)	386 (4.1)
Congestive heart failure	1365 (14.4)	1449 (15.3)
Index acute coronary syndrome — no. (%)		
ST-segment elevation myocardial infarction	3301 (34.9)	3235 (34.2)
Non–ST-segment elevation myocardial infarction	4574 (48.3)	4601 (48.6)
Unstable angina	1568 (16.6)	1614 (17.1)
Missing data	19 (<0.1)	12 (<0.1)
Percutaneous coronary intervention or coronary-artery bypass grafting for index acute coronary syndrome — no. (%)	6798 (71.8)	6878 (72.7)
Median time from index acute coronary syndrome to randomization (IQR) — mo	2.6 (1.7–4.4)	2.6 (1.7–4.3)
Body-mass index‡	28.5±4.9	28.5±4.8

* Plus–minus values are means ±SD. There were no significant differences between the two groups in demographic or baseline characteristics. Additional baseline characteristics are listed in Table S2 in the Supplementary Appendix. Percentages may not sum to 100 because of rounding. IQR denotes interquartile range.
† Race was reported by the patient.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

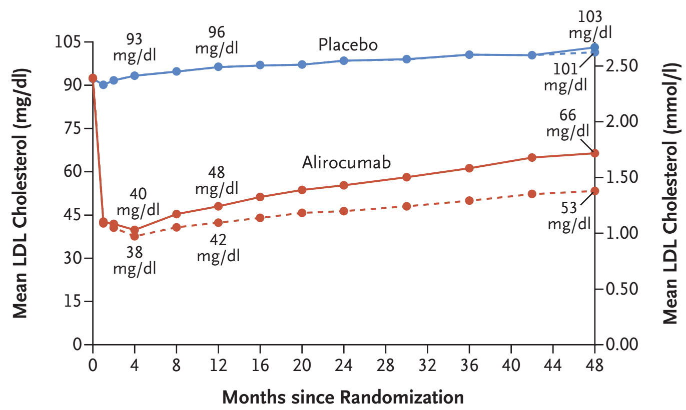

Figure 1. LDL Cholesterol Levels during the Trial.

The intention-to-treat analysis (results shown with solid lines) included all low-density lipoprotein (LDL) cholesterol values, including levels measured after premature discontinuation of the trial regimen, levels measured after dose adjustments were made under blinded conditions, and levels measured after blinded substitution of placebo for alirocumab. The on-treatment analysis (results shown with dashed lines) excluded LDL cholesterol levels measured after premature discontinuation of the trial regimen and levels measured after blinded substitution of placebo for alirocumab (but included LDL cholesterol levels measured after dose adjustments of alirocumab were made under blinded conditions between the 75-mg dose and the 150-mg dose). To convert the values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

was 90.7% in the alirocumab group (including time after blinded substitution of placebo for alirocumab) and 90.0% in the placebo group. Ascertainment of the composite primary end point was complete for 99.1% of potential patient-years of follow-up, and ascertainment of death was complete for 99.8% of potential patient-years of follow-up.

EFFECT OF TRIAL REGIMEN ON LIPID LEVELS

At baseline, the mean (±SD) LDL cholesterol level was 92±31 mg per deciliter (2.38±0.80 mmol per liter). In the alirocumab group, the mean LDL cholesterol level (intention-to-treat analysis) at 4 months, 12 months, and 48 months after randomization was 40 mg per deciliter (1.0 mmol per liter), 48 mg per deciliter (1.2 mmol per liter), and 66 mg per deciliter (1.7 mmol per liter), respectively; in the placebo group, the mean LDL cholesterol level at 4 months, 12 months, and 48 months after randomization was 93 mg per deciliter (2.4 mmol per liter), 96 mg per deciliter (2.5 mmol per liter), and 103 mg per deciliter (2.7 mmol per liter), respectively (Fig. 1). In the on-treatment analysis in the alirocumab group (which excluded values measured after discontinuation of alirocumab and after blinded substitution of placebo for alirocumab), the mean LDL cholesterol level at 4 months, 12 months, and 48 months was 38 mg per deciliter (0.98 mmol per liter), 42 mg per deciliter (1.1 mmol per liter), and 53 mg per deciliter (1.4 mmol per liter), respectively; these levels were an average of 62.7%, 61.0%, and 54.7% lower than the respective levels in the placebo group. Other lipid measurements are provided in Figure S4 in the Supplementary Appendix.

END POINTS

A composite primary end-point event occurred in 903 patients (9.5%) in the alirocumab group and in 1052 patients (11.1%) in the placebo group (Table 2); The Kaplan–Meier probability estimate at 4 years was 12.5% in the alirocumab group and 14.5% in the placebo group (hazard ratio, 0.85; 95% confidence interval [CI], 0.78 to 0.93; P<0.001) (Fig. 2). To prevent the occurrence of one primary end-point event, 49 patients (95% CI, 28 to 164) would need to be treated for 4 years. The effect of alirocumab on the relative risk of the composite primary end point did not differ significantly according to any of the prespecified subgroup variables (Fig. S5 in the Supplementary Appendix).

As would be expected, the incidence of the composite primary end point in the placebo group differed across three categories of baseline LDL cholesterol levels (<80, 80 to <100, and ≥100 mg per deciliter), with the greatest incidence among patients in the highest category. Correspondingly, in a nonprespecified analysis, the greatest absolute reduction in risk of the composite primary end point with alirocumab was also shown among the patients who had a baseline LDL cholesterol level of 100 mg or more per deciliter (P<0.001 for the interaction between treatment and baseline LDL cholesterol level) (Table S3 and Fig. S6 in the Supplementary Appendix). To prevent the occurrence of one primary end-point event among patients with a baseline LDL cholesterol level of 100 mg or more per deciliter, 16 patients (95% CI, 11 to 34) would need to be treated for 4 years. Additional analyses related to categories of baseline LDL cholesterol are

Table 2. Composite Primary End Point and Secondary End Points (Intention-to-Treat Population).

End Point	Alirocumab (N=9462)	Placebo (N=9462)	Hazard Ratio (95% CI)	P Value
	number of patients (percent)			
Primary end point: composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization	903 (9.5)	1052 (11.1)	0.85 (0.78–0.93)	<0.001
Major secondary end points, in order of hierarchical testing				
Any coronary heart disease event*	1199 (12.7)	1349 (14.3)	0.88 (0.81–0.95)	0.001
Major coronary heart disease event†	793 (8.4)	899 (9.5)	0.88 (0.80–0.96)	0.006
Any cardiovascular event‡	1301 (13.7)	1474 (15.6)	0.87 (0.81–0.94)	<0.001
Composite of death from any cause, nonfatal myocardial infarction, or nonfatal ischemic stroke§	973 (10.3)	1126 (11.9)	0.86 (0.79–0.93)	<0.001
Death from coronary heart disease	205 (2.2)	222 (2.3)	0.92 (0.76–1.11)	0.38¶
Death from cardiovascular causes	240 (2.5)	271 (2.9)	0.88 (0.74–1.05)	
Death from any cause	334 (3.5)	392 (4.1)	0.85 (0.73–0.98)	
Other end points‖				
Nonfatal myocardial infarction	626 (6.6)	722 (7.6)	0.86 (0.77–0.96)	
Fatal or nonfatal ischemic stroke	111 (1.2)	152 (1.6)	0.73 (0.57–0.93)	
Unstable angina requiring hospitalization	37 (0.4)	60 (0.6)	0.61 (0.41–0.92)	
Ischemia-driven coronary revascularization procedure	731 (7.7)	828 (8.8)	0.88 (0.79–0.97)	
Hospitalization for congestive heart failure	176 (1.9)	179 (1.9)	0.98 (0.79–1.20)	

* This end point includes death from coronary heart disease, nonfatal myocardial infarction, unstable angina requiring hospitalization, and an ischemia-driven coronary revascularization procedure (definitions can be found in the Supplementary Appendix).
† This end point includes death from coronary heart disease and nonfatal myocardial infarction.
‡ This end point includes any death from cardiovascular causes, nonfatal myocardial infarction, unstable angina requiring hospitalization, an ischemia-driven coronary revascularization procedure, or nonfatal ischemic stroke.
§ The widths of the confidence intervals for the secondary end points were not adjusted for multiplicity, so the intervals for the outcomes listed below this outcome should not be used to infer definitive treatment effects.
¶ The hierarchical analysis was stopped after the first nonsignificant P value was observed, in accordance with the hierarchical testing plan.
‖ The analysis for other end points was not adjusted for multiplicity; therefore, no P values are reported.

provided in Table S3 in the Supplementary Appendix.

Among the main secondary end points, the risks of any coronary heart disease event, major coronary heart disease events, any cardiovascular event, and a composite of death from any cause, nonfatal myocardial infarction, or nonfatal ischemic stroke were lower among patients treated with alirocumab than among those who received placebo (Table 2, and Fig. S7 in the Supplementary Appendix). A total of 334 patients (3.5%) in the alirocumab group and 392 patients (4.1%) in the placebo group died (hazard ratio, 0.85; 95% CI, 0.73 to 0.98).

Safety

The incidence of adverse events and of laboratory abnormalities was similar in the alirocumab group and the placebo group (Table 3), with the exception of local injection-site reaction (3.8% in the alirocumab group vs. 2.1% in the placebo group, P<0.001). Injection-site reactions (itching, redness, or swelling) were usually mild and self-limited and led to discontinuation of the trial regimen in 26 patients in the alirocumab group, at a median of 8.3 months after randomization, and in 3 patients in the placebo group. Neurocognitive events were reported in 1.5% of the patients in the alirocumab group and in 1.8% of

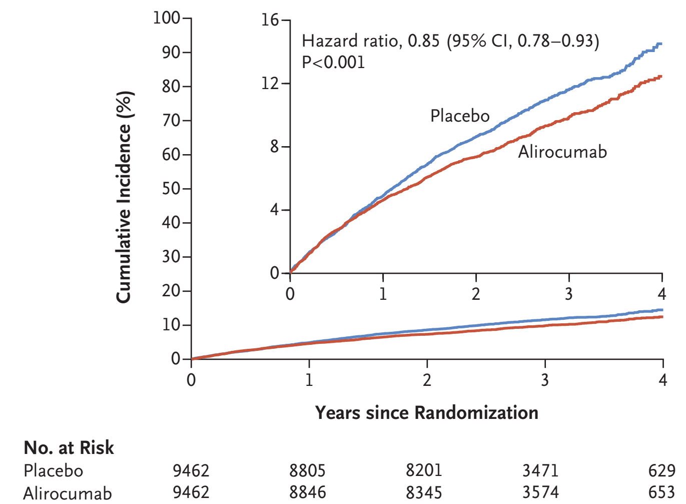

Figure 2. Cumulative Incidence of the Composite Primary End Point.
Shown is the cumulative incidence of the primary efficacy end point (a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization). The Kaplan–Meier rates for the primary end point at 4 years were 12.5% (95% CI, 11.5 to 13.5) in the alirocumab group and 14.5% (95% CI, 13.5 to 15.6) in the placebo group. The inset shows the same data on an enlarged y axis. The P value was calculated with the use of log-rank tests, stratified according to geographic region.

the patients in the placebo group, new-onset diabetes (as defined in the Supplementary Appendix) in 9.6% and 10.1%, respectively, and hemorrhagic stroke (confirmed by adjudication) in less than 0.1% and 0.2%. Neutralizing antidrug antibodies were detected in 0.5% of the patients in the alirocumab group and in less than 0.1% in the placebo group.

Discussion

Among patients who had a previous acute coronary syndrome and in whom lipid levels exceeded specified thresholds despite atorvastatin or rosuvastatin therapy at a high-intensity dose or at the maximum tolerated dose, the risk of a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization was lower among those who were treated with alirocumab than among those who received placebo. These benefits were observed in the context of background care that included extensive use of evidence-based treatments[16-19] as well as the use of a dose-adjustment strategy for alirocumab that targeted an LDL cholesterol level of 25 to 50 mg per deciliter and allowed a level of 15 to 25 mg per deciliter, but that avoided sustained levels below 15 mg per deciliter.

The absolute benefit of alirocumab with respect to the composite primary end point was more pronounced among patients who had a baseline LDL cholesterol level of 100 mg or more per deciliter than among patients with a lower baseline LDL cholesterol level. Similarly, a recent meta-analysis showed that intensive lowering of LDL cholesterol (primarily with the use of statins) resulted in a mortality benefit that was observed only among patients with a baseline LDL cholesterol level of 100 mg or more per deciliter.[20]

Over a median follow-up period of 2.8 years, with more than 8000 patients who were eligible to be followed for 3 to 5 years and 6444 patients who received the assigned alirocumab or placebo for at least 3 years, the incidence of adverse events did not differ significantly between the two groups, with the exception of local injection-site reactions. Whether the safety and efficacy of alirocumab were influenced by the blinded dose-adjustment strategy, which was designed to mitigate the occurrence of very low levels of LDL cholesterol, is unknown. Serious safety concerns were also not observed with evolocumab in the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial,[11] which had no lower limit for allowable LDL cholesterol levels; however, that trial had a shorter median follow-up, and very few patients were followed for 3 or more years. Neither trial can fully predict longer-term safety of treatment with a PCSK9 monoclonal antibody.

Lowering of LDL cholesterol levels with alirocumab was sustained but to a lesser extent than that reported in previous trials that had a shorter duration.[9] The increase in LDL cholesterol over time in the intention-to-treat analysis reflects premature discontinuation of treatment, dose reduction or substitution of placebo for alirocumab under blinded conditions, and attenuation of the intensity of statin treatment. The last factor probably also contributed to the rise in LDL cholesterol observed in the placebo group, in the

Table 3. Adverse Events and Laboratory Abnormalities.

Variable	Alirocumab (N=9451)	Placebo (N=9443)
Adverse events — no. (%)		
Any adverse event	7165 (75.8)	7282 (77.1)
Serious adverse event	2202 (23.3)	2350 (24.9)
Adverse event that led to death	181 (1.9)	222 (2.4)
Adverse event that led to discontinuation of the trial regimen	343 (3.6)	324 (3.4)
Local injection-site reaction	360 (3.8)	203 (2.1)
General allergic reaction	748 (7.9)	736 (7.8)
Diabetes worsening or diabetic complication among patients with diabetes at baseline — no./total no. (%)	506/2688 (18.8)	583/2747 (21.2)
New-onset diabetes among patients without diabetes at baseline — no./total no. (%)*	648/6763 (9.6)	676/6696 (10.1)
Neurocognitive disorder	143 (1.5)	167 (1.8)
Hepatic disorder	500 (5.3)	534 (5.7)
Cataracts	120 (1.3)	134 (1.4)
Hemorrhagic stroke, adjudicated	9 (<0.1)	16 (0.2)
Laboratory abnormalities at any time — no./total no. (%)		
Alanine aminotransferase >3 times upper limit of normal range	212/9369 (2.3)	228/9341 (2.4)
Aspartate aminotransferase >3 times upper limit of normal range	160/9367 (1.7)	166/9338 (1.8)
Total bilirubin >2 times upper limit of normal range	61/9368 (0.7)	78/9341 (0.8)
Creatine kinase >10 times upper limit of normal range	46/9369 (0.5)	48/9338 (0.5)
Antidrug antibodies†	67/9091 (0.7)	32/9097 (0.4)
Neutralizing antidrug antibodies	43/9091 (0.5)	6/9097 (<0.1)

* New-onset diabetes was defined according to the presence of one or more of the following, with confirmation of the diagnosis by blinded external review by experts in the field of diabetes: an adverse-event report, a new prescription for diabetes medication, a glycated hemoglobin level of at least 6.5% on two occasions (and a baseline level of <6.5%), or a fasting serum glucose level of at least 126 mg per deciliter (7.0 mmol per liter) on two occasions (and a baseline level of <126 mg per deciliter).

† Antidrug antibodies were defined by the presence of positive responses detected after the start of administration of the trial regimen in at least two consecutive postbaseline serum samples, separated by at least a 16-week period.

on-treatment analysis in the alirocumab group, and in previous trials involving patients who had an acute coronary syndrome.[5,21] Antidrug antibodies were detected in few patients and have been shown not to influence the lipid-lowering efficacy of alirocumab.[22]

There are noteworthy similarities and differences between our trial and the previous FOURIER and SPIRE (Studies of PCSK9 Inhibition and the Reduction of Vascular Events) trials, which evaluated the PCSK9 antibodies evolocumab and bococizumab, respectively.[11,13] The current trial and the FOURIER trial showed similar improvements in composite cardiovascular outcomes with PCSK9 inhibition among patients who had a baseline LDL cholesterol level of 70 mg or more per deciliter and whose average baseline LDL cholesterol level was approximately 90 mg per deciliter.[10] Both our trial and the SPIRE trial showed a more prominent absolute reduction in the risk of cardiovascular outcomes with PCSK9 inhibition among patients who had a baseline LDL cholesterol level of 100 mg or more per deciliter.[12] The current trial showed the efficacy of PCSK9 inhibition in high-risk patients who had a previous acute coronary syndrome, 89% of whom received high-intensity statin therapy, and used a blinded dose-adjustment strategy to achieve a target range of LDL cholesterol with PCSK9 inhibition. The longer duration of follow-up in the current trial than in previous trials, owing to the mandatory minimum 2-year follow-up, facilitated the assessment of efficacy and safety. A limitation of all three trials is the infrequent use of ezetimibe, for which cardiovascular efficacy was established[5] after most of the patients had already been enrolled and the trials were well under way.

In conclusion, among patients who had a previous acute coronary syndrome and whose levels of atherogenic lipoproteins remained elevated despite statin therapy at a high-intensity dose or at the maximum tolerated dose, the risk of major adverse cardiovascular events was lower among those who were treated with alirocumab than among those who received placebo.

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APPENDIX

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