ORIGINAL ARTICLE

Lipid-Reduction Variability and Antidrug-Antibody Formation with Bococizumab

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ABSTRACT

BACKGROUND

Bococizumab, a humanized monoclonal antibody targeting proprotein convertase subtilisin–kexin type 9 (PCSK9), reduces levels of low-density lipoprotein (LDL) cholesterol. However, the variability and durability of this effect are uncertain.

METHODS

We conducted six parallel, multinational lipid-lowering trials enrolling 4300 patients with hyperlipidemia who were randomly assigned to receive 150 mg of bococizumab or placebo subcutaneously every 2 weeks and who were followed for up to 12 months; 96% were receiving statin therapy at the time of enrollment. The patients were assessed for lipid changes over time, stratified according to the presence or absence of antidrug antibodies detected during the treatment period.

RESULTS

At 12 weeks, patients who received bococizumab had a reduction of 54.2% in the LDL cholesterol level from baseline, as compared with an increase of 1.0% among those who received placebo (absolute between-group difference, −55.2 percentage points). Significant between-group differences were also observed in total cholesterol, non–high-density lipoprotein cholesterol, apolipoprotein B, and lipoprotein(a) ($P<0.001$ for all comparisons). However, high-titer antidrug antibodies developed in a substantial proportion of the patients who received bococizumab, which markedly diminished the magnitude and durability of the reduction in LDL cholesterol levels. In addition, among patients with no antidrug antibodies, there was wide variability in the reduction in LDL cholesterol levels at both 12 weeks and 52 weeks. Major cardiovascular events occurred in 57 patients (2.5%) who received bococizumab and in 55 (2.7%) who received placebo (hazard ratio, 0.96; 95% confidence interval, 0.66 to 1.39; $P=0.83$). The most common adverse event among patients who received bococizumab was injection-site reaction (12.7 per 100 person-years).

CONCLUSIONS

In six multinational trials evaluating bococizumab, antidrug antibodies developed in a large proportion of the patients and significantly attenuated the lowering of LDL cholesterol levels. Wide variation in the relative reduction in cholesterol levels was also observed among patients in whom antidrug antibodies did not develop. (Funded by Pfizer; SPIRE ClinicalTrials.gov numbers, NCT01968954, NCT01968967, NCT01968980, NCT02100514, NCT02135029, and NCT02458287.)

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*A complete list of the Studies of PCSK9 Inhibition and the Reduction of Vascular Events (SPIRE) investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Reducing levels of low-density lipoprotein (LDL) cholesterol with statin therapy is a highly effective method for reducing cardiovascular risk.[1] Trial data, observational studies, and genetic analyses indicate that further reductions in LDL cholesterol levels are likely to confer greater cardiovascular benefits.[2-4] Yet, recent studies have shown wide variability in the individual response of patients to statin therapy in terms of the percent reduction in LDL cholesterol levels.[5,6]

Inhibitors of proprotein convertase subtilisin–kexin type 9 (PCSK9) reduce plasma LDL cholesterol levels by slowing PCSK9-mediated degradation of the LDL receptor.[7] Fully human monoclonal antibodies such as alirocumab and evolocumab that interfere with the LDL receptor–binding domain of PCSK9 reduce circulating LDL cholesterol levels by approximately 60% and are promising agents for further reductions in cardiovascular events.[8,9]

Bococizumab is a third monoclonal antibody targeting PCSK9 that, in a dose-finding study among statin-treated patients, lowered LDL cholesterol levels by approximately 55 mg per deciliter (1.4 mmol per liter) from baseline when administered in a regimen of 150 mg subcutaneously every 2 weeks.[10] Unlike alirocumab and evolocumab, however, bococizumab is a humanized, rather than a fully human, therapeutic monoclonal antibody with approximately 3% murine sequence remaining in the antigen-binding complementarity-determining regions and as such may be more likely to induce the development of antidrug antibodies.[11] As part of the bococizumab development program, we conducted six parallel trials comparing 150 mg of bococizumab subcutaneously every 2 weeks with placebo in patients with hyperlipidemia, including one trial in which some patients received atorvastatin instead of placebo and another in which some patients received 75 mg of bococizumab instead of 150 mg. All the patients were assessed for group and individual changes in lipid levels, durability of effect, safety, and incidence of cardiovascular events.

METHODS

TRIAL DESIGN AND OVERSIGHT

The Studies of PCSK9 Inhibition and the Reduction of Vascular Events (SPIRE) program for the development of bococizumab consists of six parallel, multinational lipid-lowering studies and the SPIRE-1 and SPIRE-2 event-driven cardiovascular outcome trials.[12] The findings of the SPIRE lipid-lowering studies are reported here. The results of the SPIRE-1 and SPIRE-2 outcome trials are also reported elsewhere in the *Journal*.[13]

The protocols for each SPIRE study (available with the full text of this article at NEJM.org) were collaboratively designed by academic members of the SPIRE executive and steering committees and physician and statistician employees of the sponsor (Pfizer). Each protocol was approved at participating centers by the responsible institutional review board or ethics committee, as applicable in the 35 countries involved in the SPIRE program. The sponsor supervised data collection. A single independent data and safety monitoring committee oversaw the trials. The first author and an independent academic statistician at Brigham and Women's Hospital had full access to the trial databases and independent responsibility for generating trial analyses for publication, prepared the first draft of the manuscript, and made the decision to submit the manuscript for publication. All the authors critically reviewed the manuscript and vouch for the completeness and accuracy of the data and all analyses, and for the fidelity of the trials to the protocols.

ENROLLMENT, RANDOMIZATION, AND FOLLOW-UP

The six studies in the lipid-lowering program included SPIRE-HR (which enrolled 711 patients with hyperlipidemia who were at high risk for cardiovascular events and who were receiving the maximum tolerated statin therapy), SPIRE-LDL (which enrolled 2139 patients with hyperlipidemia who had multiple cardiovascular risk factors and a directly measured LDL cholesterol level of ≥70 mg per deciliter [1.8 mmol per liter]), SPIRE-FH (which enrolled 370 patients with heterozygous familial hypercholesterolemia), SPIRE-LL (which enrolled 746 patients who had a directly measured LDL cholesterol level of ≥100 mg per deciliter [2.6 mmol per liter] while receiving statin therapy and for whom additional lipid lowering was under consideration), SPIRE-SI (which enrolled 184 patients with hyperlipidemia who were statin intolerant), and SPIRE-AI (which enrolled 299 patients who had a directly measured LDL cholesterol level of ≥70 mg per deciliter and who received bococizumab with an autoinjector device). Detailed inclusion and exclusion criteria for the six SPIRE trials are provided in the Supplementary Appendix, available at NEJM.org. All the

patients in the SPIRE trials provided written informed consent.

In SPIRE-HR, SPIRE-LDL, and SPIRE-FH, eligible patients underwent identical baseline lipid evaluations, were randomly assigned (in a 1:1 ratio) to receive either 150 mg of bococizumab subcutaneously every 2 weeks or placebo, and were then followed for 52 weeks; patients in SPIRE-LL were assigned to the same regimen but in a 2:1 ratio with placebo. In SPIRE-SI, eligible patients were randomly assigned in a 2:1:2 fashion to receive 150 mg of bococizumab subcutaneously every 2 weeks, 40 mg of atorvastatin orally daily, or matching doses of placebo and were followed for 6 months. In all these studies, the patients administered bococizumab or placebo themselves through subcutaneous injections. By contrast, in SPIRE-AI, eligible patients were randomly assigned to receive bococizumab or placebo that they administered themselves with an autoinjector device and were followed for 12 weeks; in this study, patients were randomly assigned in a 2:2:1:1 ratio to receive 150 mg of bococizumab subcutaneously every 2 weeks, 75 mg of bococizumab subcutaneously every 2 weeks, or matching doses of placebo. In total, 4449 patients were enrolled in the SPIRE lipid-lowering program, of whom 4263 were assigned to receive either 150 mg of bococizumab or placebo. For the analyses of clinical outcomes, the 37 patients in the SPIRE-SI study who were assigned to receive 40 mg of atorvastatin were included in the placebo group. Results for the remaining 149 patients in the SPIRE-AI study, who were assigned to receive 75 mg of bococizumab or placebo, are also reported here for completeness.

We performed the 12-month trials using an identical protocol that included a 4-week prerandomization screening period to verify eligibility and ensure that patients were receiving the maximum tolerated statin dose. The SPIRE-SI protocol included a statin rechallenge group. In the 12-month trials, protocol-driven dose reductions in bococizumab were triggered by the observation of directly measured LDL cholesterol levels of 10 mg per deciliter (0.3 mmol per liter) or less on two consecutive visits, with sham dose modifications made in the placebo group to maintain the study blinding.[12]

Levels of antidrug antibodies, neutralizing antibodies, total PCSK9 levels, and bococizumab were measured with the use of validated assays (see the Methods section in the Supplementary Appendix).

TRIAL END POINTS

In all six SPIRE lipid-lowering trials, the primary end point was the percent change from baseline in fasting LDL cholesterol levels, as measured with a direct assay at week 12; in addition, the long-term persistence of any effects on the LDL cholesterol level was evaluated throughout the 12-month follow-up period for the longer-term studies. Secondary end points were the percent changes in other lipid levels, lipoprotein(a), and high-sensitivity C-reactive protein at weeks 12 and 52. All plasma samples were obtained after a minimum 10-hour fast, and all assays were performed at a core laboratory.

STATISTICAL ANALYSIS

We analyzed lipid-lowering data separately for each of the six SPIRE trials at 12 weeks and 52 weeks and used a random-effects method in meta-analyses of the combined data. In the combined analyses, we excluded the patients who had been assigned to receive atorvastatin in SPIRE-SI and those who were assigned to receive 75 mg of bococizumab or matching placebo in SPIRE-AI. In addition, we used waterfall plots to examine the individual biologic variability in LDL cholesterol response to bococizumab at 12 weeks and 52 weeks. Waterfall plots were limited to the patients who had reported taking either bococizumab or placebo within 21 days before the lipid measurement. Analyses were stratified according to the presence or absence of detectable antidrug antibodies or neutralizing antibodies, with patients classified as positive if antibodies were detected at any time during the trial. Analyses of the effects of neutralizing antibodies were limited to the two trials in which they were measured (SPIRE-HR and SPIRE-FH).

Per protocol, we examined safety events and the incidence of adjudicated cardiovascular events occurring after the time of randomization. The prespecified events that contributed to the latter analysis were the first occurrence of nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or cardiovascular death.[12] For adverse events, weighted rate ratios are provided in which the weight for each study was calculated according to the inverse of the exposure time, similar to a Mantel–Haenszel method. We used a Cox proportional-hazards model to analyze cardiovascular outcomes on pooled data stratified according to trial. Further details with respect to the statistical analyses are provided in

Table 1. Clinical Characteristics of the Patients at Baseline and Loss to Follow-up in the Six Lipid-Lowering SPIRE Trials.*

Characteristic	SPIRE-HR (N=711)	SPIRE-LDL (N=2139)	SPIRE-FH (N=370)	SPIRE-LL (N=746)	SPIRE-SI (N=184)	SPIRE-AI N=299)	All Trials (N=4449)
Age (yr)	61.3	62.0	56.1	61.6	63.9	60.0	61.3
Female sex (%)	37.4	40.6	41.9	44.2	53.8	45.8	41.7
Diabetes (%)	49.4	62.9	20.3	56.4	24.5	44.1	53.3
Hypertension (%)	84.0	82.6	51.9	77.5	70.1	74.2	78.3
Current smoking (%)	16.2	19.1	18.6	22.1	7.6	15.7	18.4
Familial hypercholesterolemia (%)	7.2	1.9	100.0	7.0	10.9	1.3	12.1
Statin use (%)							
Any	100.0	99.7	99.5	99.9	0.0	100.0	99.8†
High-intensity‡	91.6	93.5	94.9	64.7	0.0	62.2	86.0†
LDL cholesterol (mg/dl)	114.9	112.2	147.1	135.5	174.3	111.9	122.0
Total cholesterol (mg/dl)	187.5	184.7	224.0	210.0	256.2	179.0	195.2
Apolipoprotein B (mg/dl)	94.5	93.2	114.4	106.7	128.6	90.2	98.7
Non-HDL cholesterol (mg/dl)	138.6	136.6	174.5	161.4	204.1	129.7	146.5
Triglycerides (mg/dl)§	138.0	147.4	123.5	168.3	165.5	119.5	145.0
Lipoprotein(a) (mg/dl)§	22.9	21.0	28.8	23.3	13.9	NA	21.7
High-sensitivity C-reactive protein (mg/liter)§	1.6	2.0	0.9	2.2	NA	NA	1.8
Loss to follow-up by study end (%)¶	1.4	2.7	0.0	2.9	0.5	0.7	2.1

* All the listed values are means unless otherwise indicated. Complete data with respect to individual study groups in each trial are provided in Table S1 in the Supplementary Appendix. 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. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and NA not available.
† Total values for statin use do not include SPIRE-SI.
‡ High-intensity statin use was defined as a daily dose of at least 40 mg of atorvastatin, at least 20 mg of rosuvastatin, or at least 40 mg of simvastatin.
§ Values for normally distributed variables are means, and values for triglycerides, lipoprotein(a), and high-sensitivity C-reactive protein are medians.
¶ All the trials had 12 months of follow-up except SPIRE-SI (6 months) and SPIRE-AI (12 weeks).

the Methods section in the Supplementary Appendix.

RESULTS

TRIAL PATIENTS AND FOLLOW-UP

The baseline clinical characteristics of the patients who were enrolled in each of the six trials are summarized in Table 1 and in Table S1 in the Supplementary Appendix. The mean age of the patients was 61 years, 42% were women, 53% had diabetes, 18% were current smokers, and 12% had a diagnosis of familial hypercholesterolemia. With the exception of those in the SPIRE-SI (statin-intolerant) trial, 99% of the patients were receiving statin therapy; of these patients, 86% were receiving high-intensity regimens, as defined by recent clinical guidelines. Across the program, a total of 92 patients (2%) were lost to follow-up.

TREATMENT RESPONSES AT 12 WEEKS AND 52 WEEKS

In each trial, directly measured LDL cholesterol levels at 12 weeks were significantly lower among the patients who received 150 mg of bococizumab subcutaneously every 2 weeks than among those who received placebo (Table 2). At week 12, the mean percent change in LDL cholesterol was −54.2% among the patients who received bococizumab and an increase of 1.0% among those who received placebo (between-group difference, −55.2 percentage points; 95% confidence interval [CI], −57.9 to −52.6; P<0.001); the median between-group difference was −59.2 percentage points (95% CI, −60.5 to −57.8; P<0.001). The numbers of patients with missing data for LDL cholesterol levels in each SPIRE trial at 12 weeks and 52 weeks are provided in Table S2 and the results for each individual trial in Figure S1 and Tables S3 and S4 in the Supplementary Appendix.

Across the six trials, 150 mg of bococizumab

Table 2. Percent Change from Baseline in Lipid Levels at 12 Weeks and 52 Weeks.*

Lipid Fraction and Study Period	No. of Patients	Percent Change from Baseline		Between-Group Difference (95% CI)†	P Value
		Bococizumab	Placebo		
		%		*percentage points*	
LDL cholesterol					
12 wk	3969	−54.2	1.0	−55.2 (−57.9 to −52.6)	<0.001
52 wk	3460	−40.4	2.1	−42.5 (−47.3 to −37.8)	<0.001
Total cholesterol					
12 wk	3981	−35.5	0.1	−36.0 (−37.6 to −34.4)	<0.001
52 wk	3466	−27.4	−0.2	−27.1 (−30.4 to −23.7)	<0.001
Apolipoprotein B					
12 wk	3972	−49.6	0.3	−49.5 (−52.1 to −47.0)	<0.001
52 wk	3456	−36.8	0.1	−37.3 (−40.8 to −33.8)	<0.001
Non-HDL cholesterol					
12 wk	3977	−49.7	0.3	−50.2 (−52.5 to −47.9)	<0.001
52 wk	3463	−37.9	−0.2	−37.7 (−41.7 to −33.8)	<0.001
HDL cholesterol					
12 wk	3979	6.4	0.6	6.2 (4.7 to 7.6)	<0.001
52 wk	3463	6.0	1.3	4.6 (3.3 to 5.9)	<0.001
Triglycerides					
12 wk	3982	−12.1	1.9	−14.2 (−16.8 to −11.6)	<0.001
52 wk	3466	−11.0	−0.6	−10.9 (−13.7 to −8.2)	<0.001
Lipoprotein(a)					
12 wk	3821	−25.9	3.0	−28.9 (−32.0 to −25.8)	<0.001
52 wk	3451	−16.4	3.7	−20.6 (−29.5 to −11.8)	<0.001

* All the listed analyses do not include data for the patients who were assigned to receive 40 mg of atorvastatin in SPIRE-SI and those who were assigned to receive 75 mg of bococizumab or placebo in SPIRE-AI.

† The between-group difference is the difference between the patients who received bococizumab and those who received placebo. The percent difference and the corresponding 95% confidence intervals (CIs) and P values were modeled from a meta-analysis of all pertinent SPIRE trials with the use of the DerSimonian–Laird approach.

also had favorable effects at 12 weeks on other lipid levels, including between-group differences from placebo of −36.0 percentage points in total cholesterol, −49.5 percentage points in apolipoprotein B, −50.2 percentage points in non–high-density lipoprotein (HDL) cholesterol, −14.2 percentage points in triglycerides, −28.9 percentage points in lipoprotein(a), and 6.2 percentage points in HDL cholesterol (P<0.001 for all comparisons) (Table 2, and Figs. S2 through S7 in the Supplementary Appendix). No significant effect was observed with respect to high-sensitivity C-reactive protein (data not shown).

At 52 weeks, the magnitude of percent reduction in LDL cholesterol that could be attributed to bococizumab was attenuated in all 1-year SPIRE trials, so that the modeled average between-group difference from placebo in LDL cholesterol lowering at 52 weeks was −42.5 percentage points (95% CI, −47.3 to −37.8). Similar attenuation was observed at 52 weeks for total cholesterol, apolipoprotein B, non-HDL cholesterol, lipoprotein(a), HDL cholesterol, and triglycerides (Table 2, and Figs. S8 through S16 in the Supplementary Appendix).

ANTIDRUG ANTIBODIES AND TREATMENT RESPONSE

At 1 year, 48% of the patients who received bococizumab had detectable antidrug antibodies; most of the antibodies developed after week 12. For the patients who received bococizumab and who were in the lowest third and middle third of maximum titers of antidrug antibodies (<1:1176), the observed mean change in the LDL cholesterol level at 52 weeks (−43.1%) was virtually identical to that observed among those who did not have detectable antidrug antibodies (−42.5%). However, at 52 weeks, among the 16% of the patients who received bococizumab and who had antidrug-antibody titers in the top third of maximum titers (≥1:1176), the mean change in the LDL choles-

terol level was –30.7%. In the subgroup of patients with antidrug-antibody titers in the top 10% (≥1:5674), the mean change in LDL cholesterol level was –12.3% (Fig. 1A).

The patients with antidrug antibodies had titer-dependent attenuation in both total PCSK9 response and plasma bococizumab levels (Fig. 1B and 1C). Further characterization of the antidrug-antibody response showed that neutralizing antibodies developed in 29% of the patients who received bococizumab. The reduction in the LDL cholesterol level at 52 weeks was substantially attenuated in the subgroups of patients who had increasing neutralizing-antibody titers, an effect that was seen as early as 4 weeks (Fig. 1D, and Figs. S17 and S18 in the Supplementary Appendix).

VARIATION IN RESPONSE AT 12 WEEKS AND 52 WEEKS

Although the average group effect of bococizumab on LDL cholesterol levels at 12 weeks was large, waterfall plots showed wide variation among the patients, such that 4% had no reduction in LDL cholesterol levels, 28% had a reduction in LDL cholesterol levels of less than 50%, and 68% had a reduction of 50% or more (Fig. 2A). By 52 weeks, among the patients with antidrug antibodies, only 52% maintained a reduction of 50% or more in LDL cholesterol levels (Fig. 2B). However, among the patients with no antidrug antibodies, there was also a wide variation in the individual response to bococizumab at 52 weeks (Fig. 2C). Wide variation in the reduction in LDL cholesterol levels among the patients was further observed in similar analyses stratified according to the antibody response at 12 weeks and at 52 weeks, including among patients who did not have neutralizing antibodies at 52 weeks (Figs. S19 through S22 in the Supplementary Appendix).

ADVERSE OUTCOMES AND CLINICAL EVENTS

The rates of adverse events that were categorized as serious were 11.3 per 100 person-years of exposure among the patients who received bococizumab and 13.3 per 100 person-years among the patients who received placebo (Table 3). The rate of injection-site reactions was 12.7 per 100 person-years among the patients who received bococizumab (of whom 68% had antidrug antibodies); these rates did not progress over time and led to the discontinuation of bococizumab in less than 1% of the patients. Although arthralgia was more common in the bococizumab group than in the placebo group, rates for other monitored events and for laboratory abnormalities were similar in the two groups.

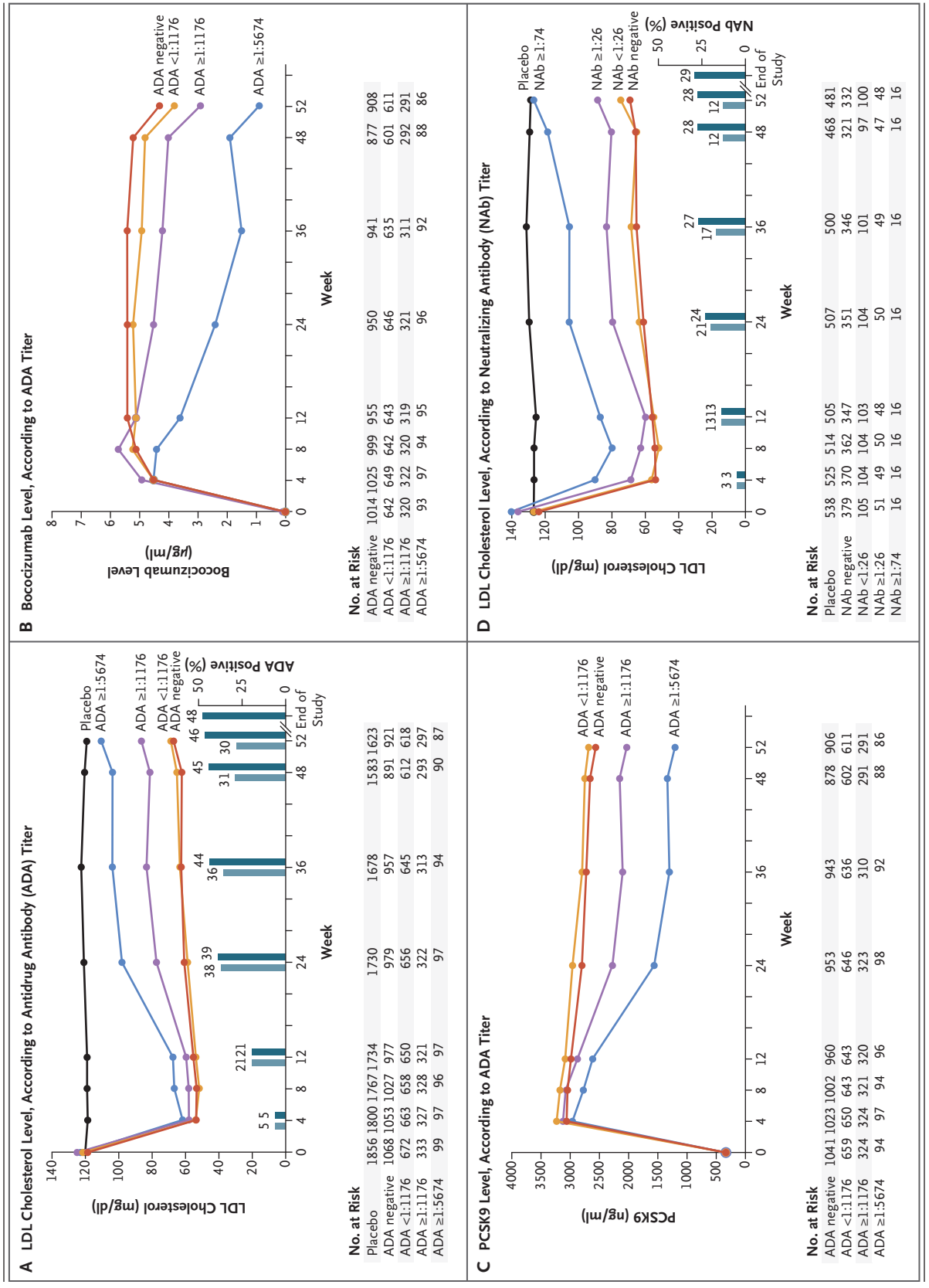
Figure 1 (facing page). Effect of Antidrug Antibodies on the Durability of Low-Density Lipoprotein (LDL) Cholesterol Lowering and on Plasma Bococizumab and PCSK9 Levels.

Panel A shows the effect of generalized antidrug antibodies (ADAs) on LDL cholesterol levels among the patients who received placebo and among those who received bococizumab, according to whether the patients were ADA-negative throughout the trial, had ADA titers in the lowest two thirds of maximum titers (<1:1176) during follow-up, had ADA titers in the highest third of titers (≥1:1176) during follow-up, or were in the subgroup with ADA titers in the top 10% (≥1:5674). The light blue bars indicate prevalent rates of antibodies at each time point, and the dark blue bars the cumulative incidence of antibody positivity during follow-up. Panel B shows plasma bococizumab levels and Panel C total plasma proprotein convertase subtilisin–kexin type 9 (PCSK9) levels over time, according to the ADA titer. Panel D shows the effect of the neutralizing antibody (NAb) titer on LDL cholesterol levels. Data are shown for the patients who received placebo and those who received bococizumab, according to whether the patients were NAb-negative throughout the trial, had NAb titers in the lowest two thirds of maximum titers (<1:26) during follow-up, had NAb titers in the highest third of titers (≥1:26) during follow-up, or had NAb titers in the top 10% (≥1:74). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

Major adverse cardiovascular events including coronary revascularization occurred in 57 patients (2.5%) who received bococizumab and in 55 (2.7%) who received placebo (hazard ratio, 0.96; 95% CI, 0.66 to 1.39; P=0.83) (Table 3, and Fig. S23 in the Supplementary Appendix). The more restricted clinical end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death was reported in 34 patients (1.5%) who received bococizumab and in 27 (1.3%) who received placebo (hazard ratio, 1.16; 95% CI, 0.70 to 1.94; P=0.56) (Table 3, and Fig. S24 in the Supplementary Appendix).

DISCUSSION

Therapeutic monoclonal antibodies targeting PCSK9 include those that are fully human (e.g., alirocumab and evolocumab) and those that are humanized (e.g., bococizumab). Although antidrug antibodies can develop in response to either



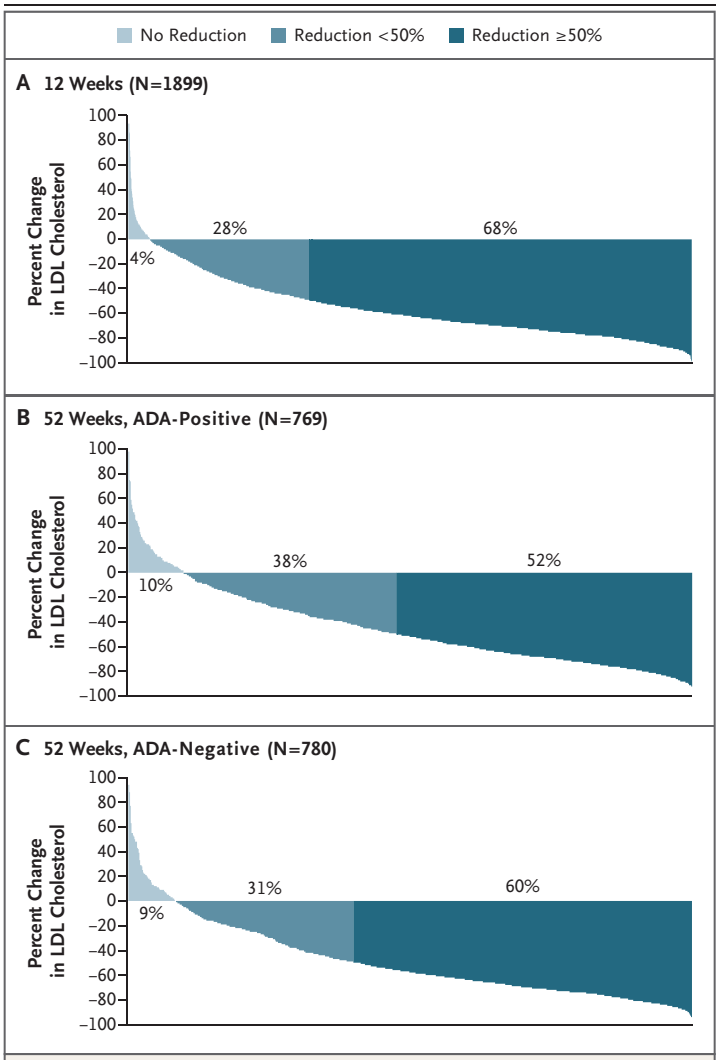


Figure 2. Variability in the Reduction in LDL Cholesterol Levels, According to the Presence or Absence of Antidrug Antibodies (ADAs).

Waterfall plots for individual patients who received bococizumab show the percent change from baseline in LDL cholesterol levels at 12 weeks (Panel A) and at 52 weeks among the patients in whom antidrug antibodies developed (Panel B) and among those in whom antidrug antibodies did not develop (Panel C). Data are limited to the patients who reported having received bococizumab in the 21 days before the measurement of LDL cholesterol.

fully human or humanized monoclonal antibodies, neither alirocumab nor evolocumab has been associated with clinically significant antibody production (see the letter by Roth et al., now published in the *Journal*[14]). In addition, each of these agents has shown durable reductions in LDL cholesterol levels with prolonged treatment.[8,9]

As shown in this report of six parallel trials, bococizumab at a dose of 150 mg subcutaneously every 2 weeks reduced LDL cholesterol levels at 12 weeks by 55.2 percentage points as compared with placebo, with significant reductions in other atherogenic lipid fractions as well. However, this early benefit was substantially attenuated over time among the 16% of patients in whom high-titer anti–bococizumab antibodies developed during the study. In such patients, the reduction from baseline in LDL cholesterol levels with bococizumab was only 31% at 52 weeks (and only 12% among those with the very highest antibody titers). By contrast, for the patients in whom antidrug antibodies did not develop, the observed reduction in LDL cholesterol levels at 52 weeks was 43%. Similar results were observed when only neutralizing antibodies to bococizumab were examined.

Given the observation in our data that the attenuation of LDL cholesterol lowering was similar among patients with antidrug antibodies and those with neutralizing antibodies, it is reasonable to assume (in the absence of experimental data) that most antidrug antibodies to bococizumab are formed against the murine sequence located in or near the complementarity-determining regions responsible for PCSK9 binding. No clinical data are available regarding cross-reactivity to other PCSK9 inhibitors among the patients who received bococizumab in whom antidrug antibodies developed and who were subsequently treated with either evolocumab or alirocumab. However, given the specificity of binding domains, such effects are unlikely to occur.

Bococizumab immunogenicity influenced the rate of adverse event rates and perhaps clinical outcomes. Specifically, bococizumab was associated with a substantially higher rate of injection-site reactions (12.7 per 100 person-years) than rates that were previously reported with either evolocumab or alirocumab. With regard to clinical efficacy, we believe that the report of no significant reduction in major cardiovascular outcomes with bococizumab should be interpreted with caution, given the small number of events accrued and the brief exposure period. Nonetheless, despite similar caveats, preliminary reports of post hoc analyses of evolocumab and alirocumab have shown substantial and statistically significant reductions in vascular events with even smaller sample sizes.[8,9]

Beyond issues of reduced durability, our data also show that there was wide variation among the patients in the magnitude of LDL cholesterol response to bococizumab and that this variation was present as early as 12 weeks (largely before

Table 3. Adverse Events, Laboratory Measurements, and Prespecified Adjudicated Clinical Outcomes.*

Variable	Bococizumab (N=2377)	Placebo (N=2058)	Incidence Rate Ratio (95% CI)	P Value
	number (rate per 100 patient-yr)			
Adverse event				
Any adverse event	1586 (147.4)	1325 (125.4)	1.17 (1.09 to 1.26)	<0.001
Serious adverse event	241 (11.3)	255 (13.3)	0.85 (0.71 to 1.01)	0.08
Adverse event resulting in drug discontinuation	115 (5.4)	98 (4.6)	1.17 (0.89 to 1.54)	0.26
Injection-site reaction	263 (12.7)	34 (1.6)	7.80 (5.42 to 11.22)	<0.001
Myalgia	63 (2.9)	65 (3.0)	0.96 (0.68 to 1.37)	0.82
Arthralgia	97 (4.4)	65 (3.1)	1.41 (1.03 to 1.94)	0.03
Fatigue	43 (2.0)	53 (2.6)	0.76 (0.51 to 1.14)	0.18
Headache	68 (3.0)	62 (3.0)	0.99 (0.70 to 1.41)	0.95
Type 2 diabetes mellitus	56 (2.4)	46 (2.3)	1.08 (0.72 to 1.60)	0.71
Hypersensitivity reaction	3 (0.1)	4 (0.2)	0.72 (0.12 to 4.42)	0.72
Cataract	15 (0.6)	11 (0.6)	1.11 (0.49 to 2.55)	0.80
	(N=2377)	**(N=2058)**	**Between-Group Difference (95% CI)†**	
	number (percent)			
Laboratory measurement				
Aspartate aminotransferase ≥3×ULN after randomization	18 (0.8)	15 (0.7)	0.03 (–0.49 to 0.55)	0.91
Alanine aminotransferase ≥3×ULN after randomization	21 (0.9)	14 (0.7)	0.17 (–0.36 to 0.71)	0.53
Creatine kinase ≥3×ULN after randomization	37 (1.6)	32 (1.6)	–0.02 (–0.79 to 0.75)	0.96
	(N=2283)	**(N=2017)**	**Hazard Ratio (95% CI)‡**	
	number (percent)			
Adjudicated clinical outcome				
Nonfatal myocardial infarction	24 (1.1)	16 (0.8)	1.39 (0.74 to 2.64)	0.31
Nonfatal stroke	6 (0.3)	9 (0.4)	0.58 (0.20 to 1.65)	0.30
Unstable angina requiring urgent revascularization	9 (0.4)	7 (0.3)	1.01 (0.37 to 2.73)	0.99
Any coronary revascularization	40 (1.8)	38 (1.9)	0.99 (0.63 to 1.54)	0.95
Cardiovascular death	4 (0.2)	2 (0.1)	1.99 (0.36 to 10.86)	0.42
MACE	34 (1.5)	27 (1.3)	1.16 (0.70 to 1.94)	0.56
MACE plus unstable angina requiring revascularization	42 (1.8)	34 (1.7)	1.11 (0.70 to 1.75)	0.66
MACE plus any revascularization	57 (2.5)	55 (2.7)	0.96 (0.66 to 1.39)	0.83

* Included in the analyses of adverse events and laboratory measurements are the 4435 patients who received at least one dose of bococizumab or placebo. For the adjudicated clinical outcomes, included are the 4300 patients who underwent randomization to receive 150 mg of bococizumab or placebo or 40 mg of atorvastatin, regardless of whether they received the study drug. No adjudicated clinical outcomes occurred in the 75-mg dose group in the short-term SPIRE-AI study. MACE denotes major adverse cardiovascular event (defined as the first event of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death), and ULN upper limit of the normal range.
† The between-group difference is the difference between the patients who received bococizumab and those who received placebo.
‡ Hazard ratios were calculated with the use of a Cox proportional-hazards model stratified according to study.

the detection of antidrug antibodies). Furthermore, wide individual variation in LDL cholesterol response was observed at 52 weeks among patients who did not have an antidrug-antibody response. The clinical and genetic determinants of this variation are currently uncertain. However, these data show that the biologic response to bococizumab was not uniform and was difficult to predict for individual patients. Whether wide individual-level variation in LDL cholesterol reduction exists for other monoclonal antibodies targeting PCSK9 requires formal evaluation.[15]

Wide individual variation has previously been shown with statins, agents that share a common metabolic pathway.[5,6]

On November 1, 2016, the sponsor elected to discontinue further development of bococizumab. This decision was based in part on the high rate of immunogenicity of the drug, as well as on the wide variation in the LDL cholesterol response among the patients.

In conclusion, in six parallel, randomized trials, bococizumab, a humanized monoclonal antibody that targets PCSK9, significantly reduced LDL cholesterol levels in most patients with hyperlipidemia at 12 weeks. However, bococizumab was commonly associated with the development of high-titer antidrug antibodies, an effect that resulted in substantive attenuation of LDL cholesterol lowering at 52 weeks. Bococizumab was also associated with wide individual variation in LDL cholesterol lowering among the patients who were antibody-negative.

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

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