ORIGINAL ARTICLE

Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients

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ABSTRACT

BACKGROUND

Bococizumab is a humanized monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9) and reduces levels of low-density lipoprotein (LDL) cholesterol. We sought to evaluate the efficacy of bococizumab in patients at high cardiovascular risk.

METHODS

In two parallel, multinational trials with different entry criteria for LDL cholesterol levels, we randomly assigned the 27,438 patients in the combined trials to receive bococizumab (at a dose of 150 mg) subcutaneously every 2 weeks or placebo. The primary end point was nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death; 93% of the patients were receiving statin therapy at baseline. The trials were stopped early after the sponsor elected to discontinue the development of bococizumab owing in part to the development of high rates of antidrug antibodies, as seen in data from other studies in the program. The median follow-up was 10 months.

RESULTS

At 14 weeks, patients in the combined trials had a mean change from baseline in LDL cholesterol levels of –56.0% in the bococizumab group and +2.9% in the placebo group, for a between-group difference of –59.0 percentage points (P<0.001) and a median reduction from baseline of 64.2% (P<0.001). In the lower-risk, shorter-duration trial (in which the patients had a baseline LDL cholesterol level of ≥70 mg per deciliter [1.8 mmol per liter] and the median follow-up was 7 months), major cardiovascular events occurred in 173 patients each in the bococizumab group and the placebo group (hazard ratio, 0.99; 95% confidence interval [CI], 0.80 to 1.22; P=0.94). In the higher-risk, longer-duration trial (in which the patients had a baseline LDL cholesterol level of ≥100 mg per deciliter [2.6 mmol per liter] and the median follow-up was 12 months), major cardiovascular events occurred in 179 and 224 patients, respectively (hazard ratio, 0.79; 95% CI, 0.65 to 0.97; P=0.02). The hazard ratio for the primary end point in the combined trials was 0.88 (95% CI, 0.76 to 1.02; P=0.08). Injection-site reactions were more common in the bococizumab group than in the placebo group (10.4% vs. 1.3%, P<0.001).

CONCLUSIONS

In two randomized trials comparing the PCSK9 inhibitor bococizumab with placebo, bococizumab had no benefit with respect to major adverse cardiovascular events in the trial involving lower-risk patients but did have a significant benefit in the trial involving higher-risk patients. (Funded by Pfizer; SPIRE-1 and SPIRE-2 ClinicalTrials.gov numbers, NCT01975376 and NCT01975389.)

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

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Monoclonal antibodies that inhibit proprotein convertase subtilisin–kexin type 9 (PCSK9) lower levels of plasma low-density lipoprotein (LDL) cholesterol and are promising agents for vascular risk reduction.[1] Patients who have received the fully human monoclonal antibodies evolocumab and alirocumab, for example, have had reductions in cardiovascular events in preliminary analyses; these drugs are under evaluation in large-scale trials involving patients with known cardiovascular disease.[2,3]

Bococizumab is a third inhibitor of PCSK9 that, unlike evolocumab and alirocumab, is a humanized monoclonal antibody in which approximately 3% of the murine sequence remains in the antigen-binding complementarity-determining region. As part of the Studies of PCSK9 Inhibition and the Reduction of Vascular Events (SPIRE) program, two large-scale trials to evaluate cardiovascular outcomes (designated SPIRE-1 and SPIRE-2) were initiated in October 2013 with the intent of evaluating the clinical efficacy and safety of bococizumab administered at a dose of 150 mg subcutaneously every 2 weeks among patients who had evidence of cardiovascular disease or who were at high risk for a first vascular event.[4] However, during the conduct of these two outcomes trials, data became available from the six SPIRE lipid-lowering trials indicating that bococizumab was commonly associated with the development of high-titer antidrug antibodies that resulted in substantive attenuation of LDL-cholesterol lowering over time. In addition, the trials showed that bococizumab was associated with a wide variation in LDL-cholesterol lowering, even among patients who were antibody negative.[5]

On the basis of the SPIRE lipid-lowering data, the sponsor elected to discontinue further development of bococizumab on November 1, 2016. As a consequence of that decision, the sponsor also elected to prematurely stop the ongoing SPIRE-1 and SPIRE-2 outcome trials. That decision was made with no knowledge by the sponsor or investigators of any unblinded data in SPIRE-1 or SPIRE-2.

Methods

Trial Design

The SPIRE bococizumab development program consisted of two parts: the six SPIRE lipid-lowering studies,[5] as reported elsewhere in the *Journal*, and the SPIRE-1 and SPIRE-2 event-driven cardiovascular outcome trials; the results of the latter two trials are reported here. The SPIRE program was sponsored by Pfizer. The protocols for SPIRE-1 and SPIRE-2 (available with the full text of this article at NEJM.org) were collaboratively designed by the academic members of the executive and steering committees and physician and statistician employees of the sponsor. Each protocol was approved at participating centers by the responsible institutional review board or ethics committee, as applicable in the 35 countries involved. In addition, 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, generated trial analyses, 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.

Patient Enrollment

Patients were eligible for enrollment if they had had either a previous cardiovascular event (secondary prevention cohort) or a history of diabetes, chronic kidney disease, or peripheral vascular disease with additional cardiovascular risk conditions or a history of familial hypercholesterolemia (high-risk primary prevention cohort). To augment the risk criteria for the primary prevention cohort, patients were also required to have one or more additional risk factors (smoking history, a high-density lipoprotein [HDL] cholesterol level of <40 mg per deciliter [<1.0 mmol per liter], a high-sensitivity C-reactive protein level of >2.0 mg per liter, a lipoprotein(a) level of >50 mg per deciliter, microalbuminuria, or evidence of asymptomatic coronary stenosis on cardiac imaging) and an age of at least 50 years for men and more than 60 years for women; the age cutoff for patients who had familial hypercholesterolemia was at least 35 years for men and 45 years for women.[4]

All the patients were required to have received treatment for at least the previous 4 weeks with a statin (atorvastatin, ≥40 mg daily; rosuvastatin, ≥20 mg daily; or simvastatin, ≥40 mg

Table 1. Characteristics of the Patients at Baseline in SPIRE-1 and SPIRE-2.*

Characteristic	SPIRE-1		SPIRE-2		Combined Trials		
	Bococizumab (N=8408)	Placebo (N=8409)	Bococizumab (N=5312)	Placebo (N=5309)	Bococizumab (N=13,720)	Placebo (N=13,718)	All Patients (N=27,438)
Mean age (yr)	63.3	63.3	62.2	62.6	62.9	63.0	62.9
Female sex (%)	26.3	26.5	34.1	35.1	29.3	29.8	29.6
Diabetes (%)	48.3	47.4	47.8	46.1	48.1	46.9	47.5
Hypertension (%)	81.2	80.9	81.3	79.6	81.3	80.4	80.8
Current smoking (%)	22.8	23.0	27.7	26.6	24.7	24.4	24.5
Mean body-mass index†	30.1	30.1	30.4	30.4	30.2	30.2	30.2
Familial hypercholesterolemia (%)	1.7	1.8	7.0	7.6	3.8	4.0	3.9
Statin use (%)							
Any	99.1	99.2	83.2	83.1	92.9	93.0	92.9
High-intensity‡	91.7	91.4	73.3	73.5	84.6	84.5	84.5
Ezetimibe use (%)	7.6	8.2	13.0	13.8	9.7	10.3	10.0
High-risk primary prevention (%)	13.0	13.8	18.9	18.5	15.3	15.6	15.5
Geographic region (%)							
Asia	3.2	3.2	1.1	1.1	2.4	2.4	2.4
Eastern Europe or Turkey	19.6	19.6	21.5	21.5	20.3	20.3	20.3
Latin America	18.0	18.0	9.8	9.8	14.8	14.8	14.8
United States or Canada	26.1	26.1	33.3	33.3	28.9	28.9	28.9
Other countries	33.1	33.1	34.4	34.4	33.6	33.6	33.6
Mean LDL cholesterol (mg/dl)	93.8	93.7	133.9	133.4	109.3	109.1	109.2
Mean apolipoprotein B (mg/dl)	80.1	79.8	105.8	105.9	90.1	89.9	90.0
Mean total cholesterol (mg/dl)	161.5	161.4	207.8	207.6	179.4	179.3	179.4
Mean non-HDL cholesterol (mg/dl)	114.3	114.0	160.5	160.2	132.2	131.9	132.1
Mean HDL cholesterol (mg/dl)	47.1	47.4	47.3	47.4	47.2	47.4	47.3
Median triglycerides (mg/dl)§	124.3	124.8	157.1	154.0	136.7	135.0	135.8
Median lipoprotein(a) (mg/dl)§	19.3	18.8	19.1	19.9	19.2	19.2	19.2
Median high-sensitivity C-reactive protein (mg/liter)§	1.8	1.7	2.3	2.3	2.0	2.0	2.0
Loss to follow-up (%)	0.6	0.7	1.3	1.1	0.9	0.8	0.9

* 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, and LDL low-density lipoprotein.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ High-intensity statin use was defined as a daily regimen of at least 40 mg of atorvastatin, at least 20 mg of rosuvastatin, or at least 40 mg of simvastatin.
§ Median values are reported because this variable had a skewed distribution.

daily) unless they could not take those doses without side effects, in which case they received a lower-intensity statin regimen. The only exception to this regimen was the use of no statin therapy among the patients in SPIRE-2 who had complete statin intolerance, which was defined as a documented inability to tolerate at least two different statin agents, including one at the lowest available daily dose, or having a documented history of statin-induced rhabdomyolysis or allergic reaction that precluded rechallenge.

Patients were required to have a directly measured LDL cholesterol level of at least 70 mg per deciliter (1.8 mmol per liter) in SPIRE-1 and of

at least 100 mg per deciliter (2.6 mmol per liter) in SPIRE-2. Patients were also eligible according to their non-HDL cholesterol level (≥100 mg per deciliter for SPIRE-1 and ≥130 mg per deciliter [3.4 mmol per liter] for SPIRE-2) at trial entry. Detailed inclusion and exclusion criteria are provided in Section B in the Supplementary Appendix, available at NEJM.org.

Table 2. Percent Changes in Lipid Levels at 14 and 52 Weeks in Combined SPIRE-1 and SPIRE-2.*

Lipid, Week, and Trial	No. of Patients	Bococizumab	Placebo	Difference (95% CI)†
		mean percent change from baseline		*percentage points*
LDL cholesterol				
14 wk				
SPIRE-1	12,916	−57.1	3.4	−60.5 (−61.3 to −59.6)
SPIRE-2	9,414	−54.6	2.2	−56.8 (−57.8 to −55.7)
Combined	22,330	−56.0	2.9	−59.0 (−59.6 to −58.3)
52 wk				
SPIRE-1	4,556	−44.9	6.5	−51.5 (−52.8 to −50.2)
SPIRE-2	5,511	−40.6	2.6	−43.2 (−44.5 to −41.9)
Combined	10,067	−41.8	5.0	−46.8 (−47.7 to −45.8)
Apolipoprotein B				
14 wk				
SPIRE-1	11,807	−55.7	2.8	−58.5 (−59.4 to −57.6)
SPIRE-2	9,251	−49.3	1.9	−51.2 (−52.2 to −50.2)
Combined	21,058	−52.8	2.5	−55.3 (−56.0 to −54.6)
52 wk				
SPIRE-1	3,600	−48.4	5.1	−53.6 (−55.1 to −52.1)
SPIRE-2	4,192	−41.0	1.4	−42.4 (−43.8 to −41.0)
Combined	7,792	−44.5	3.4	−47.9 (−49.1 to −46.7)
Total cholesterol				
14 wk				
SPIRE-1	12,901	−34.2	2.3	−36.5 (−37.0 to −35.9)
SPIRE-2	9,417	−36.5	1.3	−37.8 (−38.5 to −37.1)
Combined	22,318	−35.2	1.9	−37.0 (−37.4 to −36.6)
52 wk				
SPIRE-1	4,556	−26.8	4.0	−30.7 (−31.6 to −29.9)
SPIRE-2	5,501	−27.5	1.0	−28.5 (−29.4 to −27.6)
Combined	10,057	−26.0	2.7	−28.7 (−29.5 to −28.0)
Non-HDL cholesterol				
14 wk				
SPIRE-1	12,868	−51.7	3.2	−54.8 (−55.6 to −54.1)
SPIRE-2	9,392	−49.9	1.8	−51.7 (−52.7 to −50.8)
Combined	22,260	−50.9	2.7	−53.6 (−54.2 to −53.0)
52 wk				
SPIRE-1	4,539	−41.3	5.1	−46.4 (−47.6 to −45.2)
SPIRE-2	5,483	−38.1	1.3	−39.4 (−40.5 to −38.2)
Combined	10,022	−39.5	3.3	−42.9 (−43.7 to −42.0)

Table 2. (Continued.)

Lipid, Week, and Trial	No. of Patients	Bococizumab	Placebo	Difference (95% CI)†
		mean percent change from baseline		*percentage points*
HDL cholesterol				
14 wk				
SPIRE-1	12,872	7.3	1.2	6.1 (5.7 to 6.6)
SPIRE-2	9,393	7.9	1.1	6.9 (6.3 to 7.4)
Combined	22,265	7.6	1.2	6.4 (6.1 to 6.8)
52 wk				
SPIRE-1	4,543	7.6	2.5	5.1 (4.4 to 5.8)
SPIRE-2	5,486	8.6	2.6	6.0 (5.3 to 6.7)
Combined	10,029	8.1	2.6	5.5 (5.0 to 6.0)
Triglycerides				
14 wk				
SPIRE-1	12,905	–13.7	6.4	–20.1 (–21.7 to –18.4)
SPIRE-2	9,416	–13.4	4.8	–18.3 (–19.9 to –16.7)
Combined	22,321	–13.6	5.8	–19.4 (–20.4 to –18.4)
52 wk				
SPIRE-1	4,560	–4.6	9.0	–13.6 (–16.3 to –10.8)
SPIRE-2	5,501	–8.0	4.6	–12.6 (–14.6 to –10.6)
Combined	10,061	–5.9	7.0	–12.9 (–16.3 to –9.5)
Lipoprotein(a)				
14 wk				
SPIRE-1	11,856	–27.6	3.7	–31.4 (–33.4 to –29.4)
SPIRE-2	9,296	–25.4	4.8	–30.2 (–34.7 to –25.6)
Combined	21,152	–26.6	4.3	–30.9 (–33.3 to –28.6)
52 wk				
SPIRE-1	3,607	–23.7	5.8	–29.5 (–32.7 to –26.3)
SPIRE-2	4,207	–19.0	5.9	–24.9 (–29.9 to –19.8)
Combined	7,814	–21.3	5.6	–26.8 (–29.7 to –24.0)

* P<0.001 for all comparisons between bococizumab and placebo.
† The difference is for the bococizumab group as compared with the placebo group.

RANDOMIZATION AND FOLLOW-UP

Eligible patients entered a 6-week placebo run-in period that was designed to ensure adherence to the subcutaneous drug administration. Patients were then randomly assigned in a double-blind manner to receive either 150 mg of bococizumab subcutaneously every 2 weeks or matching placebo. Protocol-driven dose reductions of bococizumab from 150 mg to 75 mg every 2 weeks (and, if needed, a further reduction to every 4 weeks) were triggered by the observation of LDL cholesterol levels of less than 10 mg per deciliter (0.3 mmol per liter) on two consecutive visits, with sham dose modifications made in the placebo group to maintain the trial blinding.

END POINTS

All the patients were followed for incident cardiovascular events until November 1, 2016 (when the bococizumab development program was dis-

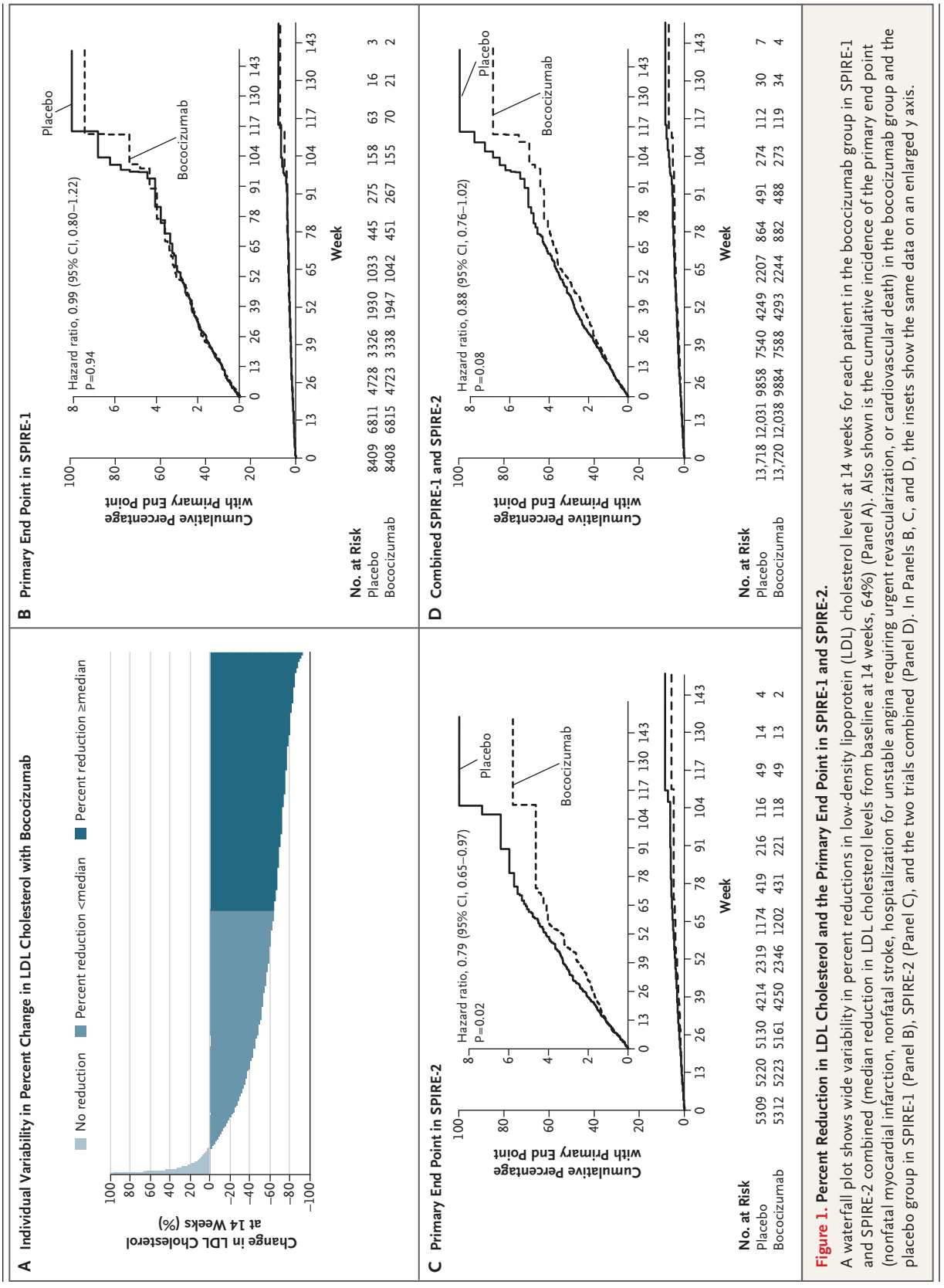

Figure 1. Percent Reduction in LDL Cholesterol and the Primary End Point in SPIRE-1 and SPIRE-2.

A waterfall plot shows wide variability in percent reductions in low-density lipoprotein (LDL) cholesterol levels at 14 weeks for each patient in the bococizumab group in SPIRE-1 and SPIRE-2 combined (median reduction in LDL cholesterol levels from baseline at 14 weeks, 64%) (Panel A). Also shown is the cumulative incidence of the primary end point (nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death) in the bococizumab group and the placebo group in SPIRE-1 (Panel B), SPIRE-2 (Panel C), and the two trials combined (Panel D). In Panels B, C, and D, the insets show the same data on an enlarged y axis.

continued by the sponsor), and were followed for adverse events through the last patient visit. This report includes all cardiovascular events that occurred by November 1, 2016, and that were adjudicated and confirmed by February 20, 2017. The prespecified primary end point of the two trials was a composite of adjudicated and confirmed nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death. The prespecified secondary composite end points are described in Section C in the Supplementary Appendix. All incident events that were components of these end points were adjudicated by a committee in which the members were unaware of study-drug assignments.

STATISTICAL ANALYSIS

As originally planned, the trial sample size for SPIRE-1 (17,000 patients for an anticipated 844 patients with an adjudicated and confirmed primary end point) would provide approximately 90% power to detect a 20% relative risk reduction in the trial primary end point, whereas the trial sample size for SPIRE-2 (11,000 patients for an anticipated 508 patients with an adjudicated and confirmed primary end point) would provide approximately 90% power to detect a 25% relative risk reduction in the trial primary end point. At the time that the sponsor discontinued the trials, enrollment was nearly complete, but neither of the two trials had continued long enough for the occurrence of the prespecified number of primary end point events. However, the virtually identical designs of the two trials permitted them to be easily combined. As such, after trial discontinuation but before unblinding, the executive committee and the sponsor prepared an integrated statistical analysis plan to allow for such a combination.

Cardiovascular outcomes were analyzed with the use of a Cox proportional-hazards model and a log-rank test within each trial and for the combined trials. After trial discontinuation but before unblinding, the decision was made to perform two subgroup analyses for the combined trials for the primary end point stratified according to the date of randomization (before the median or on or after the median) and the percent and absolute difference in LDL cholesterol levels at 14 weeks (below the median value or at or above the median value). For the combined trials, we used a Poisson regression model to analyze adverse events and a logistic-regression model to analyze laboratory measurements. We used a mixed-model repeated-measures approach to analyze the percent changes from baseline at weeks 14 and 52 for a panel of lipid biomarkers and for glucose and glycated hemoglobin. Waterfall plots were used to examine the individual biologic variability in the response of LDL cholesterol levels to bococizumab (Section D in the Supplementary Appendix).

RESULTS

PATIENTS

Before the sponsor terminated the two trials, 16,817 patients had enrolled in SPIRE-1 and 10,621 had enrolled in SPIRE-2 (Section E in the Supplementary Appendix). At baseline, the mean LDL cholesterol level was 94 mg per deciliter (2.4 mmol per liter) in SPIRE-1 and 134 mg per deciliter (3.5 mmol per liter) in SPIRE-2, with the different values reflecting design differences in the two trials (Table 1, and Table S1 in the Supplementary Appendix). The rate of familial hypercholesterolemia was higher in SPIRE-2 than in SPIRE-1 (7.3% vs. 1.8%), as was the use of ezetimibe (13.4% vs. 7.9%); the rate of statin use was lower (83% vs. 99%). In the combined trials, the mean age was 63 years, 30% of the patients were women, 48% had diabetes, 25% were current smokers, and 85% had received a diagnosis of cardiovascular disease. At the time of trial termination, the median follow-up time was 7 months in SPIRE-1 and 12 months in SPIRE-2.

EFFECTS ON LIPID LEVELS

At 14 weeks, the mean percent change from baseline in the LDL cholesterol level was −56.0% among patients in the bococizumab group and +2.9% among those in the placebo group, for a between-group difference of −59.0 percentage points ($P<0.001$) and a median reduction from baseline of 64.2% ($P<0.001$) (Table 2, and Fig. S1 in the Supplementary Appendix). At 14 weeks, 28% of the patients in the bococizumab group had LDL cholesterol levels of 25 mg per deciliter or less. Bococizumab, as compared with placebo, also had substantial early effects on levels of total cholesterol (−37.0%), apolipoprotein B (−55.3%), non-HDL cholesterol (−53.6%), lipoprotein(a)

Table 3. Hazard Ratios for Prespecified Adjudicated Clinical Outcomes in SPIRE-1 and SPIRE-2.

Adjudicated Clinical Outcome	Bococizumab	Placebo	Hazard Ratio (95% CI)	P Value
	no. of patients (rate per 100 patient-yr)			
Prespecified primary outcome*				
SPIRE-1	173 (3.01)	173 (3.02)	0.99 (0.80–1.22)	0.94
SPIRE-2	179 (3.32)	224 (4.19)	0.79 (0.65–0.97)	0.02
Combined	352 (3.16)	397 (3.59)	0.88 (0.76– 1.02)	0.08
Percent reduction in LDL cholesterol at 14 wk				
≥Median	122 (2.45)	324 (3.31)	0.75 (0.61–0.92)	0.006
<Median	152 (3.15)	324 (3.31)	0.94 (0.77–1.14)	0.50
Absolute reduction in LDL cholesterol at 14 wk				
≥Median	143 (2.78)	324 (3.31)	0.81 (0.66–0.98)	0.03
<Median	131 (2.81)	324 (3.31)	0.90 (0.73–1.11)	0.32
Randomization date				
Before median	247 (3.14)	295 (3.78)	0.83 (0.70–0.98)	0.03
On or after median	105 (3.21)	102 (3.12)	1.03 (0.78–1.35)	0.83
Prespecified secondary outcomes				
Secondary composite outcome†				
SPIRE-1‡	149 (2.59)	143 (2.49)	1.03 (0.82–1.30)	0.78
SPIRE-2	144 (2.66)	192 (3.57)	0.74 (0.60–0.92)	0.007
Combined‡	293 (2.63)	335 (3.01)	0.87 (0.74–1.02)	0.08
Secondary composite outcome plus death from any cause				
SPIRE-1‡	176 (3.06)	171 (2.98)	1.02 (0.83–1.26)	0.84
SPIRE-2	168 (3.10)	214 (3.98)	0.78 (0.64–0.95)	0.02
Combined‡	344 (3.08)	385 (3.46)	0.89 (0.77–1.03)	0.11
Secondary composite outcome, death from any cause, or unstable angina requiring urgent revascularization				
SPIRE-1‡	200 (3.48)	201 (3.51)	0.99 (0.81–1.20)	0.90
SPIRE-2	203 (3.77)	246 (4.60)	0.82 (0.68–0.99)	0.04
Combined‡	403 (3.62)	447 (4.04)	0.89 (0.78–1.02)	0.11
Components of the primary and secondary outcomes				
Cardiovascular death				
SPIRE-1	37 (0.64)	30 (0.52)	1.20 (0.74–1.95)	0.46
SPIRE-2	28 (0.51)	34 (0.62)	0.82 (0.50–1.36)	0.45
Combined	65 (0.58)	64 (0.57)	1.00 (0.71–1.41)	>0.99
Death from any cause				
SPIRE-1	66 (1.14)	58 (1.00)	1.12 (0.79–1.60)	0.53
SPIRE-2	54 (0.98)	59 (1.08)	0.91 (0.63–1.32)	0.62
Combined	120 (1.06)	117 (1.04)	1.02 (0.79–1.31)	0.91
Nonfatal myocardial infarction				
SPIRE-1	98 (1.70)	88 (1.53)	1.11 (0.83–1.48)	0.47
SPIRE-2	94 (1.73)	122 (2.26)	0.76 (0.58–1.00)	0.05

Table 3. (Continued.)

Adjudicated Clinical Outcome	Bococizumab	Placebo	Hazard Ratio (95% CI)	P Value
	no. of patients (rate per 100 patient-yr)			
Combined	192 (1.72)	210 (1.88)	0.91 (0.75–1.11)	0.35
Nonfatal stroke				
SPIRE-1	19 (0.33)	36 (0.62)	0.52 (0.30–0.91)	0.02
SPIRE-2	26 (0.48)	39 (0.72)	0.66 (0.40–1.09)	0.10
Combined	45 (0.40)	75 (0.67)	0.60 (0.41–0.86)	0.006
Unstable angina requiring urgent revascularization				
SPIRE-1	27 (0.47)	33 (0.57)	0.82 (0.49–1.36)	0.43
SPIRE-2	40 (0.73)	42 (0.77)	0.95 (0.62–1.46)	0.81
Combined	67 (0.60)	75 (0.67)	0.89 (0.64–1.24)	0.49

* The primary outcome included nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, or unstable angina requiring urgent revascularization.
† The secondary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.
‡ Although these analyses were prespecified, they should be considered exploratory, since the between-group differences in SPIRE-1 and in the combined trials were not statistically significant for the primary outcome.

(–30.9%), and triglycerides (–19.4%) (P<0.001 for all comparisons) (Table 2). There was no significant change in high-sensitivity C-reactive protein.

Consistent with findings in the SPIRE lipid-lowering trials,[5] attenuation in the reduction in LDL cholesterol levels was observed over time, so that the mean percent change among the patients in the bococizumab group was –41.8% at 52 weeks and –38.3% at 104 weeks (Table 2, and Fig. S1 in the Supplementary Appendix). As was also observed in the SPIRE lipid-lowering trials, there was wide individual variation in the patients' response with respect to LDL-cholesterol lowering (Fig. 1A, and Figs. S2 and S3 in the Supplementary Appendix). During follow-up, 46% of the patients in the bococizumab group had at least one LDL cholesterol measurement of 25 mg per deciliter or less.

EFFECTS ON CLINICAL OUTCOMES

In SPIRE-1, among the patients who had LDL cholesterol levels of 70 mg per deciliter or more at baseline, the primary end point of nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death occurred in 173 patients each in the bococizumab group and the placebo group (hazard ratio, 0.99; 95% confidence interval [CI], 0.80 to 1.22; P=0.94) (Table 3 and Fig. 1B). By contrast, in SPIRE-2, among the patients with LDL cholesterol levels of 100 mg deciliter or more at baseline, the primary end point occurred in 179 patients in the bococizumab group and in 224 patients in the placebo group (hazard ratio, 0.79; 95% CI, 0.65 to 0.97; P=0.02) (Table 3 and Fig. 1C). In the combined analysis, the primary end point occurred in 352 patients in the bococizumab group and in 397 in the placebo group (hazard ratio, 0.88; 95% CI, 0.76 to 1.02; P=0.08) (Table 3 and Fig. 1D). Similar effects were observed for the prespecified secondary composite end points. No significant between-group differences were observed in the rates of death from cardiovascular causes or from any cause.

We observed no significant difference in the primary end point in analyses that were stratified according to age, sex, smoking status, or the presence or absence of diabetes or clinical evidence of cardiovascular disease. However, effects were significant across both trials among the patients who had percent reductions in LDL cholesterol levels that were greater than or equal to the median value at 14 weeks or absolute reductions in LDL cholesterol levels that were greater than or equal to the median value at 14 weeks; there were no significant differences among the patients who had lesser degrees of reduction in LDL cholesterol levels. Effects were also significant for the patients who were randomly assigned to a study group before the median date of randomization (mean exposure period, 13.8 months) but not for those who were assigned on or after

Table 4. Adverse Events and Laboratory Measurements in Combined SPIRE-1 and SPIRE-2.*

Adverse Events and Laboratory Measurements	Bococizumab			Placebo	Incidence Rate Ratio (95% CI)†	P Value
	All LDL Cholesterol Values	≥1 LDL Cholesterol Value ≤25 mg/dl	No LDL Cholesterol Value ≤25 mg/dl			
	number of patients (rate per 100 patient-yr)					
Adverse events						
Number of patients evaluated	13,707	6285	7259	13,697		
Any adverse event	8,727 (169.3)	4049 (166.1)	4637 (173.1)	8,289 (149.1)	1.14 (1.11 to 1.18)	<0.001
Serious adverse event	1,995 (19.5)	876 (18.2)	1097 (20.5)	1,999 (19.7)	0.99 (0.93 to 1.06)	0.84
Adverse event resulting in drug discontinuation	684 (6.3)	246 (4.8)	421 (7.5)	466 (4.2)	1.49 (1.33 to 1.68)	<0.001
Injection-site irritation	1,663 (16.8)	785 (16.9)	875 (16.7)	398 (3.6)	4.71 (4.22 to 5.25)	<0.001
Injection-site reaction	1,084 (10.4)	524 (10.8)	558 (10.2)	142 (1.3)	8.33 (6.99 to 9.92)	<0.001
Myalgia	405 (3.7)	160 (3.1)	245 (4.3)	371 (3.4)	1.09 (0.95 to 1.26)	0.22
Arthralgia	425 (3.9)	185 (3.6)	240 (4.2)	392 (3.6)	1.08 (0.94 to 1.24)	0.26
Newly diagnosed diabetes	242 (4.2)	139 (4.9)	103 (3.5)	250 (4.2)	0.98 (0.82 to 1.17)	0.83
Cataract	125 (1.1)	46 (0.9)	79 (1.3)	124 (1.1)	1.00 (0.78 to 1.29)	0.97
Fatigue	293 (2.6)	110 (2.1)	183 (3.2)	253 (2.3)	1.15 (0.98 to 1.37)	0.10
Headache	356 (3.2)	134 (2.6)	220 (3.8)	308 (2.8)	1.16 (0.99 to 1.35)	0.06
Hypersensitivity	22 (0.2)	9 (0.2)	13 (0.2)	19 (0.2)	1.15 (0.62 to 2.13)	0.65
					Difference (95% CI)	
		number (percent)			*percentage points*	
Plasma enzyme measures						
AST ≥3× ULN after randomization	82 (0.6)	32 (0.5)	50 (0.7)	89 (0.6)	−0.08 (−0.38 to 0.22)	0.59
ALT ≥3× ULN after randomization	114 (0.8)	48 (0.8)	66 (0.9)	130 (0.9)	−0.13 (−0.39 to 0.12)	0.30
Creatine kinase ≥3× ULN after randomization	142 (1.0)	63 (1.0)	79 (1.1)	122 (0.9)	0.15 (−0.09 to 0.40)	0.22
			mean			
Other laboratory measures						
Glucose level (mg/dl)						
At 52 wk	124.2± 50.1	123.0±47.3	125.3±52.6	122.8±46.9		
Change from baseline to 52 wk	4.8±0.43	4.0±0.60	5.5±0.61	3.0±0.43	1.74 (0.56 to 2.92)	0.004
Glycated hemoglobin (%)						
At 52 wk	6.5±1.42	6.5±1.33	6.6±1.50	6.5±1.37		
Change from baseline to 52 wk	0.09±0.01	0.07±0.02	0.10±0.01	0.06±0.01	0.02 (−0.01 to 0.05)	0.11

* Plus–minus values are means ±SD or ±SE. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.
† The incidence rate ratio or the between-group difference is for the combined bococizumab group as compared with the placebo group.

the median date of randomization (mean exposure period, 5.7 months) (Table 3, and Figs. S4 and S5 in the Supplementary Appendix).

ADVERSE EVENTS

The rates of serious adverse events were similar in the two groups. Adverse events leading to drug discontinuation were more frequent in the bococizumab group than in the placebo group, and there was a higher rate of injection-site reactions (10.4% vs. 1.3%, P<0.001) (Table 4). Reports of newly diagnosed diabetes and of cataracts were similar in the two groups and did not vary according to the magnitude of the reduction in LDL cholesterol levels. In the bococizumab group, there was a small increase in blood glucose levels but no change in glycated hemoglobin levels at 52 weeks.

DISCUSSION

In SPIRE-1 and SPIRE-2, patients at high cardiovascular risk with two different baseline levels of LDL cholesterol were randomly assigned to receive either the PCSK9 inhibitor bococizumab or placebo. The two trials were stopped prematurely owing to the decision of the sponsor to discontinue further development of the study drug. In SPIRE-1, no significant benefit of bococizumab was observed on the primary end point. In contrast, in SPIRE-2, there was a significant benefit associated with bococizumab.

In the combined analysis of data from the two trials, no significant benefit was seen with respect to the primary end point. However, the pooled effect estimate and associated confidence intervals in the combined analysis, in which the reduction in the LDL cholesterol level at 52 weeks was 1.4 mmol per liter (hazard ratio, 0.88; 95% CI, 0.76 to 1.02; P=0.08), overlap with the values in a meta-analysis of previous lipid-lowering trials, in which the hazard ratio for patients with 1 year of follow-up or less was 0.91 (95% CI, 0.85 to 0.97) for each reduction of 1.0 mmol per liter in LDL cholesterol levels.[6]

There were several differences between the two trials. The baseline LDL cholesterol level was 70 mg per deciliter or more in SPIRE-1, as compared with 100 mg per deciliter in SPIRE-2. The absolute risk of a primary end point event was lower in SPIRE-1 than in SPIRE-2 (3.02 vs. 4.19 events per 100 person-years). The median follow-up time at the time of trial termination was 7 months in SPIRE-1 and 12 months in SPIRE-2. Therefore, the patients in SPIRE-2 were at higher risk and were treated for a longer period on average than were the patients in SPIRE-1.

The idea that the magnitude of risk and the duration of treatment may explain the differences between the two trials is supported by three additional analyses that were planned after the trial was stopped but before unblinding. In analyses of the pooled data from both trials, there was a significant reduction in the rate of the primary end point among patients who had a percent reduction in LDL cholesterol levels that was greater than or equal to the median value at 14 weeks and among those who had an absolute reduction in LDL cholesterol levels that was greater than or equal to the median value at 14 weeks, whereas those with lesser reductions in LDL cholesterol values did not have such reduced rates. In addition, patients with a randomization date before the median date had a significant event-rate reduction, whereas those with a randomization date after the median did not have such a reduction, which indicates a benefit for a longer duration of therapy.

In the SPIRE lipid-lowering program, antidrug antibodies developed in nearly half the patients who received bococizumab and neutralizing antibodies developed in 29%, which in some affected patients substantially attenuated LDL-cholesterol lowering over time. These effects would be anticipated to reduce clinical efficacy. Although an attenuation in LDL-cholesterol lowering was also seen in SPIRE-1 and SPIRE-2, the status with respect to antidrug antibodies is not yet known in these trials, and therefore further work in analyzing these effects is needed. However, our findings suggest that the formation of antidrug antibodies is limited to bococizumab and is not an issue with the fully human monoclonal antibodies evolocumab and alirocumab. This immunologic difference among PCSK9 inhibitors also provides an explanation of the high rate of injection-site reactions observed only with bococizumab.

Other than such reactions, we observed few

adverse effects and no significant increase in cataracts or new-onset diabetes. This latter issue is of particular interest, since statin therapy is associated with a modest increase in diabetes,[7,8] and genetic variations in *HMGCR* (the primary target for statin therapy) and in *PCSK9* (the target of PCSK9 inhibitors) have been associated with protective effects with respect to atherosclerosis but adverse effects with respect to diabetes.[9-11] However, our trials had a short duration and thus a limited ability to address adverse effects on glucose metabolism.

In the two trials, we also confirmed that there is wide individual variability in the response to bococizumab with respect to LDL cholesterol levels, a variation that was similar to that observed with statin therapy.[12,13] In the SPIRE lipid-lowering trials, this effect was present even among patients in whom antidrug or neutralizing antibodies did not develop.[5] As shown here, variability in LDL-cholesterol response influenced clinical outcomes. If similar variability is found to exist for other PCSK9 inhibitors, the individual LDL-cholesterol response may be a useful measure to monitor as physicians seek to find the most appropriate selection criteria for the use of these agents.

In conclusion, the SPIRE-1 and SPIRE-2 trials of PCSK9 inhibition with bococizumab were terminated early by the sponsor owing to the development of antidrug antibodies in other studies in the program. In SPIRE-1, in which there was a shorter observation period of lower-risk patients than in SPIRE-2, no benefit of bococizumab was seen with respect to the primary end point of major adverse cardiovascular events. In contrast, in SPIRE-2, after a longer duration of observation of higher-risk patients, a significant benefit of bococizumab was shown.

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

APPENDIX

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