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Month 24 Outcomes After Treatment Initiation With Anti–Vascular Endothelial Growth Factor Therapy for Macular Edema Due to Central Retinal or Hemiretinal Vein Occlusion

SCORE2 Report 10: A Secondary Analysis of the SCORE2 Randomized Clinical Trial

Ingrid U. Scott, MD, MPH; Neal L. Oden, PhD; Paul C. VanVeldhuisen, PhD; Michael S. Ip, MD; Barbara A. Blodi, MD; Clement K. Chan, MD; for the SCORE2 Investigator Group

IMPORTANCE Two-year outcomes are reported comparing eyes originally assigned to aflibercept or bevacizumab to assess the need for continued anti–vascular endothelial growth factor (VEGF) therapy for macular edema due to central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO) from participants in the Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2) trial.

OBJECTIVE To investigate outcomes 1 year after cessation of the SCORE2 treatment schedule.

DESIGN, SETTING, AND PARTICIPANTS In this secondary analysis of the SCORE2 randomized clinical trial, follow-up included 117 participants originally randomized to aflibercept and 119 participants originally randomized to bevacizumab between September 17, 2014, and November 18, 2015. Data for the analyses were frozen on September 13, 2018.

INTERVENTIONS SCORE2 participants completed the treatment protocol at month 12, were subsequently treated at investigator discretion, and underwent assessment at month 24.

MAIN OUTCOMES AND MEASURES Visual acuity letter score (VALS) and central subfield thickness (CST) on spectral-domain optical coherence tomography.

RESULTS Among 362 participants randomized to aflibercept or bevacizumab, 65.2% (236 of 362) completed a protocol visit at month 24 (mean [SD] age, 68.5 (12.0) years; 53.8% male). The mean (SD) VALS improved from baseline to 12 months by 21.6 (14.5) in the aflibercept group compared with 21.9 (16.6) in the bevacizumab group (difference, −0.3; 99% CI, −5.6 to 4.9), then worsened from those values by a mean (SD) VALS of 7.6 (17.5) in the aflibercept group and 7.5 (14.5) in the bevacizumab group (difference, −0.1; 99% CI, −5.6 to 5.3) at month 24. The mean (SD) CST improved from baseline to 12 months by 394 (231) µm in the aflibercept group compared with 420 (274) µm in the bevacizumab group (difference, 26 µm; 99% CI, −62 to 114 µm), then worsened from those values by a mean (SD) of 58 (192) µm in the aflibercept group compared with 48 (186) µm in the bevacizumab group (difference, 10 µm; 99% CI, −58 to 78 µm) at month 24.

CONCLUSIONS AND RELEVANCE No differences in VALS or CST outcomes at month 24 were identified when participants originally assigned to aflibercept were compared with those assigned to bevacizumab. Caution in interpretation is needed because of loss to follow-up. In both groups, VALS and CST improved through month 12 and then worsened somewhat during the second year, when treatment was at investigator discretion. This analysis suggests that CRVO and HRVO warrant close monitoring and treatment as needed over at least 2 years to optimize outcomes in eyes treated with anti-VEGF therapy.

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Supplemental content

Author Affiliations: Department of Ophthalmology, Penn State College of Medicine, Hershey, Pennsylvania (Scott); Department of Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania (Scott); The Emmes Company, LLC, Rockville, Maryland (Oden, VanVeldhuisen); Doheny Eye Institute, UCLA (University of California, Los Angeles) (Ip); Fundus Photograph Reading Center, University of Wisconsin–Madison (Blodi); Southern California Desert Retina, Palm Desert (Chan).

Group Information: The members of the SCORE2 Investigator Group appear at the end of the article.

Corresponding Author: Paul C. VanVeldhuisen, PhD, The Emmes Company, LLC, 401 N Washington St, Ste 700, Rockville, MD 20850 (score2@emmes.com).

Macular edema (central retinal swelling) is the leading cause of visual impairment in patients with retinal vein occlusion.[1-3] The Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2) randomized clinical trial showed that bevacizumab, an anti-vascular endothelial growth factor (anti-VEGF) treatment commonly used off-label, is noninferior to aflibercept, a more expensive anti-VEGF treatment approved by the US Food and Drug Administration, with respect to visual acuity (VA) at 6 months in eyes with macular edema associated with central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO).[4] The present investigation evaluated longer-term outcomes among the SCORE2 participants 24 months after initiation of treatment, which is 12 months after cessation of the SCORE2 protocol-defined treatment schedule.

Key Points

Question From month 12 to 24 in the Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2) trial, when treatment was at investigator discretion, what were outcomes among participants initially randomized to aflibercept or bevacizumab for treatment of macular edema due to central retinal or hemiretinal vein occlusion?

Findings Among 236 participants in this secondary analysis of the SCORE2 randomized clinical trial, visual acuity letter score and optical coherence tomography–measured central subfield thickness improvement from baseline to month 12 subsequently worsened from month 12 to 24 in both groups, with no differences between treatment groups.

Meaning Management of macular edema due to retinal vein occlusion likely warrants close monitoring for at least 2 years, although follow-up of only two-thirds of participants at month 24 limits confidence in these results.

Methods

The study adhered to the tenets of the Declaration of Helsinki[5] and is registered at ClinicalTrials.gov (NCT01969708). Institutional review board (IRB) approval of the protocol was obtained from a site-specific or centralized IRB (Advarra, Columbia, Maryland), and written informed consent was obtained from all participants.

Study Design

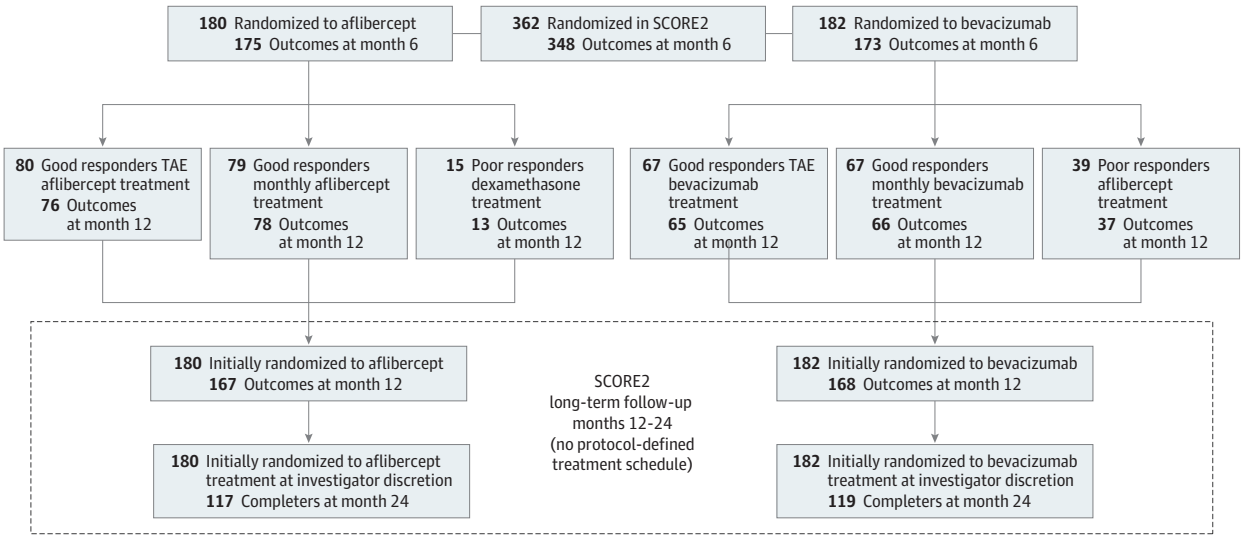
The SCORE2 methods have been described in detail.[6] Between September 17, 2014, and November 18, 2015, a total of 362 patients (305 patients with CRVO and 57 patients with HRVO) were randomly assigned to receive intravitreous injection of aflibercept (2.0 mg) or bevacizumab (1.25 mg) at randomization and every 4 weeks through month 5. The primary outcome was change from baseline in best-corrected, electronic Early Treatment Diabetic Retinopathy Study visual acuity letter score (VALS) at month 6 (with a noninferiority margin of 5).[4,6] After assessment of the primary outcome at month 6, participants originally assigned to treatment with aflibercept who met the protocol-defined criteria for a good response were rerandomized to either continuing aflibercept therapy every 4 weeks (n = 79) vs changing to a treat-and-extend regimen (n = 80); 15 participants with a protocol-defined poor or marginal response at 6 months were to receive a dexamethasone implant. Participants originally assigned to treatment with bevacizumab who met the protocol-defined criteria for a good response were rerandomized to either continuing bevacizumab therapy every 4 weeks (n = 67) vs changing to a treat-and-extend regimen (n = 67); 39 participants with a protocol-defined poor or marginal response at 6 months were to receive treatment with aflibercept. The SCORE2 participants' last visit as part of the SCORE2 protocol-defined treatment schedule was at month 12. This secondary analysis of the SCORE2 randomized clinical trial at 64 centers in the United States focuses on the follow-up of 117 participants initially randomized to treatment with aflibercept at month 0 and 119 participants initially randomized to bevacizumab at month 0 who completed the month 24 visit (defined as month 24 completers). A graphical description of the SCORE2 participant flow through month 24 is shown in **Figure 1**.

After month 12, there was no protocol-defined treatment schedule. Rather, physicians could treat as they deemed necessary using any commercially available drug (including nonstudy drug or no drug) based on their typical practice and on any schedule. Only intravitreous injections given in the study eye for treatment of macular edema secondary to CRVO or HRVO during this period were documented. Study data included injections given at nonstudy offices provided they were documented in the medical record. At month 0, 6, 12, and 24, data were collected on best-corrected, electronic Early Treatment Diabetic Retinopathy Study VALS and central subfield thickness (CST) assessed by spectral-domain optical coherence tomography (SD-OCT) and eye examinations. The SD-OCT images were sent to the Fundus Photograph Reading Center at the University of Wisconsin–Madison for grading. At month 24, there was a medical record review of new ocular conditions, procedures, and other new conditions occurring since month 12. Data for these analyses were frozen on September 13, 2018.

Statistical Analysis

The primary outcomes were VALS and CST. Comparisons were exploratory and descriptive, all calculated using statistical software (SAS, version 9.4; SAS Institute Inc). Because no hypothesis testing was being done, no *P* values from statistical tests comparing treatment outcomes are provided, and 99% CIs are presented rather than the traditional 95% CIs to give an idea of variability and help account for multiple testing. Confidence intervals for injection rates were calculated by bootstrapping the SCORE2 participants' injection histories separately within treatment groups. Because not all participants completed a visit at month 24, we performed propensity score matching[7] (PSM) with statistical tests and *P* values to investigate whether the results we report for VALS and CST are representative of the entire SCORE2 population. A brief exegesis of PSM as applied to the SCORE2 data is provided in the eAppendix in the Supplement.

Figure 1. SCORE2 Participant Flow Through Month 24



SCORE2 indicates Study of Comparative Treatments for Retinal Vein Occlusion 2; TAE, treat and extend.

Results

Cohort Description

Among 236 participants randomized to treatment with aflibercept or bevacizumab (mean [SD] age, 68.5 [12.0] years; 53.8% [127 of 236] male), the original randomly assigned groups exhibited similar retention, with 117 of 180 participants (65.0%) randomized to aflibercept at month 0 and 119 of 182 participants (65.4%) randomized to bevacizumab at month 0 having a visit at month 24. Reasons for the 126 participants who did not complete a month 24 visit were as follows: were not willing to return or were not interested in returning (n = 35), were unable to contact (n = 25), were deceased (n = 19), had health issues (n = 14), withdrew consent (n = 11), had transportation or mobility issues (n = 10), were at 2 sites that did not participate in long-term follow-up (n = 5), moved out of the area (n = 4), and gave no reason (n = 3). Month 24 completers were similar to month 24 noncompleters with respect to month 0 VALS, CST, and treatment assignment, but they received on average 1 more anti-VEGF treatment between month 0 and up to month 12 (mean [SD], 10.8 [1.4] vs 9.7 [2.9] treatments), had an average of 3 more months between diagnosis of macular edema and randomization (mean [SD], 7.7 [15.5] vs 4.4 [10.1] months), and had 8.7% fewer black participants (28 of 236 [11.9%] vs 26 of 126 [20.6%]) than the month 24 noncompleters (**Table 1**).

Table 1. Characteristics at Month 0 and Between Months 0 and 12 by Month 24 Completers vs Month 24 Noncompleters in the SCORE2 Long-term Follow-up

Variable	Month 24, No. (%)	
	Completers (n = 236)	Noncompleters (n = 126)
Treatment group		
Aflibercept	117 (49.6)	63 (50.0)
Bevacizumab	119 (50.4)	63 (50.0)
Age, mean (SD), y	68.5 (12.0)	69.7 (12.0)
Received prior anti-VEGF treatment at randomization	84 (35.6)	37 (29.4)
Time between diagnosis of macular edema and randomization, mean (SD), mo	7.7 (15.5)	4.4 (10.1)
Female sex	109 (46.2)	48 (38.1)
Hispanic or Latino ethnicity	24 (10.2)	14 (11.1)
Black race	28 (11.9)	26 (20.6)
Hemiretinal vein occlusion	41 (17.4)	16 (12.7)
Type 2 diabetes	74 (31.4)	39 (31.0)
Hypertension	174 (73.7)	104 (82.5)
Coronary artery disease	34 (14.4)	22 (17.5)
VALS, mean (SD)	50.4 (15.1)	50.3 (15.6)
SD-OCT central subfield thickness, mean (SD), μm	665 (227)	667 (220)
No. of anti-VEGF treatments between month 0 and up to month 12, mean (SD)	10.8 (1.4)	9.7 (2.9)

Abbreviations: SCORE2, Study of Comparative Treatments for Retinal Vein Occlusion 2; SD-OCT, spectral-domain optical coherence tomography; VALS, visual acuity letter score; VEGF, vascular endothelial growth factor.

Treatment Between Month 12 and 24

Between months 12 and 24, the bevacizumab group received 1 more treatment per participant than the aflibercept group (mean [SD], 4.5 [3.5] vs 3.6 [3.2] treatments) (**Table 2**). The annualized rates of injection were substantially lower during months 12 to 24 than in earlier periods. To illustrate, injections during months 12 to 24 decreased by 817 injections, or 7.7 injections per participant-year, from months 0 to 12 in aflibercept completers and by 813 injections, or 7.6 injections per participant per year, from months 0 to 12 in bevacizumab completers (rate difference, 0.1; 99% CI, −1.1 to 1.3). From

Table 2. Treatment for Macular Edema in Month 24 Completers Between Months 12 and 24, When Participants Were No Longer Required to Receive the Originally Assigned Treatment Protocol

Variable	Original Randomization Assignment, No. (%)	
	Aflibercept (n = 117)	Bevacizumab (n = 119)
No. of treatments between months 12 and 24		
Mean (SD)	3.6 (3.2)	4.5 (3.5)
Median	3.0	4.0
Treated with anti-VEGF only	77 (65.8)	78 (65.5)
Annualized treatment rates in completers, injections per participant per year		
Months 0-5	12.72	12.72
Months 6-11	9.96	11.52
Months 12-24	2.40	4.56
All participants	117 (100)	119 (100)
No treatment	33 (28.2)	29 (24.4)
Aflibercept only	42 (35.9)	22 (18.5)
Bevacizumab only	24 (20.5)	33 (27.7)
Ranibizumab only	3 (2.6)	6 (5.0)
Dexamethasone only	2 (1.7)	0
Aflibercept plus bevacizumab	5 (4.3)	12 (10.1)
Aflibercept plus dexamethasone	3 (2.6)	4 (3.4)
Aflibercept plus ranibizumab	0	1 (0.8)
Aflibercept plus ranibizumab plus dexamethasone	0	1 (0.8)
Aflibercept plus bevacizumab plus ranibizumab	1 (0.9)	1 (0.8)
Bevacizumab plus dexamethasone	1 (0.9)	3 (2.5)
Bevacizumab plus kenalog	0	2 (1.7)
Bevacizumab plus ranibizumab	2 (1.7)	3 (2.5)
Bevacizumab plus kenalog plus dexamethasone	0	1 (0.8)
Dexamethasone plus ranibizumab	1 (0.9)	1 (0.8)

Abbreviation: VEGF, vascular endothelial growth factor.

months 0 to month 24, there were 1657 injections (7.4 per participant per year) in aflibercept completers and 1877 injections (8.2 per participant per year) in bevacizumab completers (rate difference, 0.8; 99% CI, 0.2-1.5).

Most participants received either no treatment for their macular edema (24.4% [29 of 119] of originally assigned bevacizumab participants and 28.2% [33 of 117] of originally assigned aflibercept participants) or only 1 type of drug (51.3% [61 of 119] of bevacizumab participants and 60.7% [71 of 117] of aflibercept participants). **Figure 2** shows the percentage of treatment types at the 3 main follow-up periods (months 0-5, months 6-11, and months 12-24) for each of the 2 originally randomized groups. In both groups, the percentage receiving the originally randomized treatments declined with time, and a substantial percentage of participants received no treatment during months 12 to 24. Among the 155 of 236 completers (65.7%) treated only with anti-VEGF therapy between months 12 and 24, the mean (SD) number of injections was 5.1 (2.7) for those originally assigned to aflibercept and 5.9 (2.8) for those originally assigned to bevacizumab. Among the 121 of 236 completers (51.3%) treated only with aflibercept or only with bevacizumab during months 12 to 24, the mean (SD) number of injections was 4.7 (2.5) for those originally assigned to aflibercept and 5.5 (2.8) for those originally assigned to bevacizumab. Of the month 24 completers, 65 of the 117 participants (55.6%) originally assigned to aflibercept were treated exclusively with aflibercept between months 0 and 24, and 48 of the 119 participants (40.3%) originally assigned to bevacizumab were treated exclusively with bevacizumab between months 0 and 24. Continuing the original treatment assignment was slightly more common than switching to the other drug or discontinuing drug therapy (Table 2). In the aflibercept group, 42 continued, 24 switched, and 33 discontinued. In the bevacizumab group, 33 continued, 22 switched, and 29 discontinued.

Outcome Analysis

Among the SCORE2 participants randomized to the aflibercept or bevacizumab groups, 65.2% (236 of 362) completed a month 24 visit in both groups. Among month 24 completers, the mean (SD) VALS improved from baseline to 12 months by 21.6 (14.5) (99% CI, 18.1-25.1) in the aflibercept group compared with 21.9 (16.6) (99% CI, 17.9-25.9) in the bevacizumab group (difference, −0.3; 99% CI, −5.6 to 4.9), then worsened from those values with a mean (SD) VALS of −7.6 (17.5) (99% CI, −11.8 to −3.3) in the aflibercept group compared with −7.5 (14.5) (99% CI, −10.9 to −4.0) in the bevacizumab group (difference, −0.1; 99% CI, −5.6 to 5.3) at month 24 (**Table 3**).

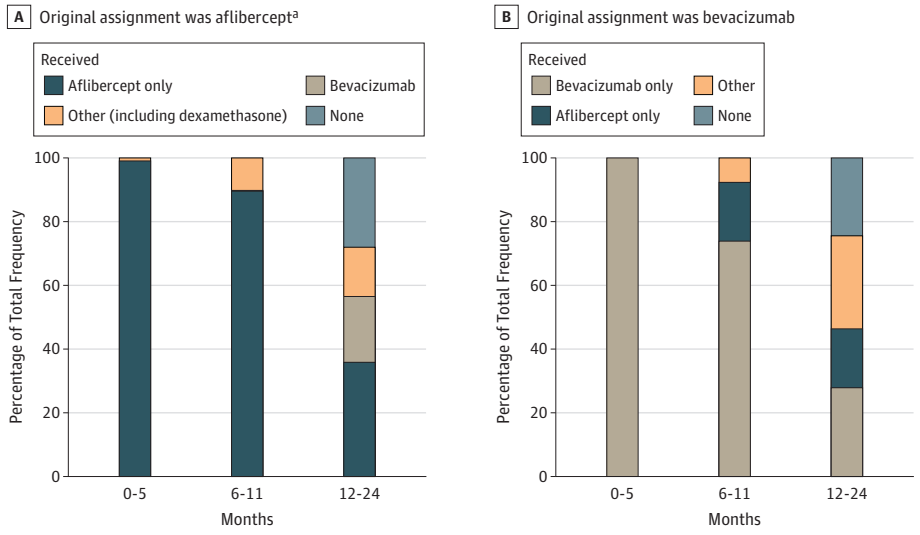
The mean CST improved from baseline to 12 months, with values (SDs) of −394 (231) µm (99% CI, −452 to −337 µm) in the aflibercept completers compared with −420 (274) µm (99% CI, −487 to −352 µm) in the bevacizumab completers (difference, 26 µm; 99% CI, −62 to 114 µm). Mean CST then worsened from those values by a mean (SD) of 58 (192) µm (99% CI, 8-108 µm) in the aflibercept completers compared with 48 (186) µm (99% CI, 1-95 µm) in the bevacizumab completers (difference, 10 µm; 99% CI, −58 to 78 µm) at month 24 (Table 3).

Fifty-five percent (130 of 236) of the SCORE2 month 24 completers achieved a VALS of 70 letters (approximate Snellen VA equivalent 20/40) or better at 24 months, with little difference between the 2 original treatment groups (56.4% [66 of 117] of the aflibercept group and 53.8% [64 of 119] of the bevacizumab group). Apart from a lower CST in the aflibercept group than in the bevacizumab group at month 6 (227 vs 290), the 2 original treatment groups were similar. The SCORE2 participants who completed the month 24 visit had a longer duration between diagnosis of macular edema and randomization (7.7 vs 4.4 months, $P = .02$) and a smaller proportion with black race (11.9% vs 20.6%, $P = .05$) than those who did not complete the visit.

Propensity Score Analysis

About 35% (126 of 362) of participants did not complete a month 24 visit. This outcome raises the question of whether the missing participants differ from, and thus are not representative of, the entire SCORE2 cohort. To investigate this possibility, we applied PSM to this SCORE2 cohort by regressing a month 24 completer/month 24 noncompleter indicator on 18 covariates measured at month 0 in all 362 SCORE2 partici-

Figure 2. Percentage of Types of Treatments Received During the 3 Follow-up Periods in Month 24 Completers



In both groups, the percentages receiving the originally randomized treatments declined with time, and a substantial percentage of participants received no treatment during months 12 to 24.

[a] One participant randomized to aflibercept mistakenly received bevacizumab in month 2.

pants (236 for month 24 completers and 126 for month 24 noncompleters). Month 12 was the last completed visit for 78.6% (99 of 126) of the noncompleters, with the remainder having a last completed visit before month 12. The matched month 24 completers and month 24 noncompleters were compared with respect to VALS and CST using the paired *t* test. The mean (SD) noncompleter VALS at the last visit was 65.4 (21.6) (approximate Snellen VA equivalent of the mean, 20/50), an increase of 14.7 from baseline, compared with 72.3 (16.3) (approximate Snellen VA equivalent of the mean, 20/40) for the corresponding visit of the completers, an increase of 22.1 from baseline (eTable 1 in the Supplement). Matched month 24 completers have a VALS approximately 6 higher than month 24 noncompleters, but they do not differ significantly with respect to CST. Eighteen of the 126 month 24 noncompleters died before 24 months. Repeating the PSM after removing these 18 participants did not alter the results appreciably. When propensity score analysis was carried out separately within the 2 treatment groups, month 24 noncompleter VALS was lower than the matched month 24 completer VALS in both treatment groups, but the month 24 completer minus month 24 noncompleter difference was significant only in the aflibercept group (difference for the aflibercept group, 8.53; $P = .009$; difference for the bevacizumab group, 2.66; $P = .47$).

Safety

Rates of ocular safety events did not differ appreciably in month 24 completers between months 0 and 12 and between months 12 and 24 (eTable 2 in the Supplement) except that, within the aflibercept group, there were more cases of open-angle glaucoma and more cataract extractions between months 12 and 24. For cataract extractions, in the aflibercept group, there were 12 events between months 12 and 24 compared with 3 events between months 0 and 12. In the bevacizumab group, there were 7 events between months 12 and 24 and 0 events between months 0 and 12. Five completers experienced Antiplatelet Trialists Collaboration (APTC) events during months 0 to 12, and 6 completers experienced APTC events during months 12 to 24. No participants with APTC events died. Because month 24 completers cannot have died before month 24, death statistics are presented for the entire SCORE2 cohort, with more deaths between months 12 and 24 than between months 0 and 12 (14 vs 5). There were no differences between the aflibercept and bevacizumab groups in deaths between months 0 and 24 (11 of 180 deaths [6.1%] in the aflibercept group and 8 of 182 deaths [4.4%] in the bevacizumab group).

Discussion

Among participants with macular edema associated with CRVO or HRVO, the SCORE2 trial demonstrated that intravitreous bevacizumab is noninferior to intravitreous aflibercept with respect to VA after 6 months of monthly injections.[4] Although treatment with bevacizumab was associated with a significantly lower proportion of eyes that achieved complete resolution of macular edema at 6 months, this finding did not translate into poorer VA outcomes at 6 months.[4] The original treatment assignment was not associated with significant differences in VALS or CST at month 24, which is 12 months after participants exited the SCORE2 treatment protocol, although eyes originally treated with bevacizumab received a mean of 1 more injection between months 12 and 24 compared with eyes originally treated with aflibercept. Therefore, the poorer anatomic outcomes associated with bevacizumab compared with aflibercept during the first 6 months of the study did not translate into poorer VA or anatomic outcomes at month 24.

Most of the improvement in VALS and CST observed in the SCORE2 trial occurred during the first 6 months of the study, when treatment was administered monthly. This initial improvement decreased during months 12 to 24, when participants went off the treatment protocol. This finding is consis-

Table 3. VALS and SD-OCT Central Subfield Thickness Outcomes in Month 24 Completers

Variable	VALS			SD-OCT Central Subfield Thickness		
	Total (N = 236)	Aflibercept (n = 117)	Bevacizumab (n = 119)	Total (N = 236)	Aflibercept (n = 117)	Bevacizumab (n = 119)
Mean (99% CI)						
Baseline	50.4 (47.8 to 52.9)	50.0 (46.5 to 53.5)	50.7 (47.0 to 54.4)	663 (625 to 702)	648 (596 to 700)	678 (621 to 735)
Month 12	72.1 (69.3 to 74.9)	71.6 (67.5 to 75.6)	72.6 (68.8 to 76.4)	256 (236 to 276)	251 (223 to 280)	261 (232 to 289)
Month 24	64.6 (60.7 to 68.4)	64.0 (58.1 to 69.9)	65.1 (60.0 to 70.3)	311 (282 to 339)	310 (271 to 349)	312 (270 to 353)
Mean change from baseline (99% CI)						
Month 12	21.7 (19.1 to 24.4)	21.6 (18.1 to 25.1)	21.9 (17.9 to 25.9)	−407 (−451 to −363)	−394 (−452 to −337)	−420 (−487 to −352)
Month 24	14.2 (10.5 to 17.9)	14.0 (8.6 to 19.3)	14.5 (9.3 to 19.6)	−345 (−395 to −294)	−329 (−392 to −267)	−359 (−439 to −280)
Mean change from month 12 (99% CI)						
Month 24	−7.5 (−10.2 to −4.8)	−7.6 (−11.8 to −3.3)	−7.5 (−10.9 to −4.0)	53 (19 to 86)	58 (8 to 108)	48 (1 to 95)
VALS ≥15 improvement from baseline (99% CI)						
Month 12	73.3 (65.8 to 80.8)	76.9 (66.7 to 87.2)	69.8 (58.7 to 80.8)	NA	NA	NA
Month 24	52.1 (43.7 to 60.6)	53.0 (40.9 to 65.1)	51.3 (39.2 to 63.3)	NA	NA	NA
VALS ≥15 worsening from baseline						
Month 12	2.1 (0.0 to 4.6)	1.7 (0.0 to 4.9)	2.5 (0.0 to 6.3)	NA	NA	NA
Month 24	8.9 (4.1 to 13.7)	6.8 (0.7 to 13.0)	10.9 (5.2 to 18.4)	NA	NA	NA
Percentage VALS ≥70 (Snellen VA equivalent 20/40) (99% CI)						
Baseline	9.3 (4.4 to 14.2)	6.8 (0.7 to 13.0)	11.8 (4.0 to 19.5)	NA	NA	NA
Month 12	69.5 (61.7 to 77.3)	67.5 (56.1 to 78.9)	71.4 (60.5 to 82.3)	NA	NA	NA
Month 24	55.1 (46.7 to 63.5)	56.4 (44.4 to 68.5)	53.8 (41.8 to 65.8)	NA	NA	NA
VALS ≥15 Improvement from month 12 (99% CI)						
Month 24	1.3 (0.0 to 3.2)	1.7 (0.0 to 4.9)	0.8 (0.0 to 3.0)	NA	NA	NA
VALS ≥15 of worsening from month 12 (99% CI)						
Month 24	18.6 (12.0 to 25.2)	18.0 (8.6 to 27.3)	19.3 (9.8 to 28.8)	NA	NA	NA

Abbreviations: NA, not applicable ; SD-OCT, spectral-domain optical coherence tomography; VALS, visual acuity letter score.

tent with the results from the GALILEO study,[8] in which patients with macular edema associated with CRVO were treated with monthly aflibercept until week 24 and then switched to as-needed dosing; after week 52, the monitoring interval was changed from monthly to every 8 weeks. At week 76, there was a decrease in the visual and anatomic improvements initially observed at week 24. Similarly, in the COPERNICUS study,[9] with the same dosing schedule as in the GALILEO study, the visual and anatomic improvements observed at week 24 were diminished at 2 years. Furthermore, in the HORIZON trial,[10] an open-label extension trial of the 12-month BRAVO and CRUISE trials that investigated ranibizumab treatment for treatment of macular edema secondary to branch retinal vein occlusion and CRVO, respectively, reduced follow-up and fewer ranibizumab injections in the second year of treatment were associated with a decline in the visual and anatomic improvements achieved during the first year of treatment in participants with CRVO. Moreover, in the RETAIN study[11] (an open-label, single-arm extension study of the HORIZON trial that included the 7 highest-enrolling HORIZON study sites), among the 32 participants with CRVO and a mean follow-up of 51.4 months from the CRUISE trial baseline, only 14 (43.8%) had resolution of macular edema; the remaining 18 of 32 participants (56.3%) still required 6 injections of ranibizumab on average during their last year of follow-up. Finally, authors of a prospective case series[12] of 40 eyes with CRVO-associated macular edema treated with anti-VEGF agents with a mean of 78 months' follow-up also noted

the need for continued treatment, with a reported annual treatment rate of 4.4 injections (the mean number of injections per year decreased from 8.6 in year 1 to 3.1 in year 6). In their cohort, the mean VALS improved by 12 letters by month 6 and was maintained at this level through month 36, after which time the mean VALS decreased with less treatment. These clinical trial and case series results, taken together with the 2-year outcomes of the SCORE2 trial, suggest that close monitoring and treatment as indicated are needed to optimize the long-term visual and anatomic outcomes of patients treated initially with anti-VEGF therapy for macular edema due to CRVO or HRVO.

The propensity scores herein suggest that the month 24 VALS outcomes among the entire SCORE2 cohort would, if we knew them, have been lower than the outcomes we report for month 24 completers. This upward bias caused by the missing data is supported by the significantly lower VALS in month 24 noncompleters than in matched month 24 completers as of the last month 24 noncompleter visit (eTable 1 in the Supplement). The fact that, when propensity score analysis was carried out within treatment groups, noncompleter VALS differed significantly from completer VALS only in the aflibercept group suggests that missing data were upwardly biasing month 24 completer VALS outcomes in the aflibercept group but not the bevacizumab group. If so, the missing data, if we knew them, would even more strongly support long-term bevacizumab noninferiority to aflibercept with respect to VALS. In contrast to VALS, propensity score analysis of the CST outcomes does not suggest a bias because of missing data.

Limitations

Our study has some limitations. Because participants went off the treatment protocol after month 12, month 24 results did not compare aflibercept monotherapy with bevacizumab monotherapy. Furthermore, only 65.0% (117 of 180) of the original SCORE2 participants were retained at month 24. Propensity score analysis suggests that, among the entire SCORE2 cohort, the month 24 VALS outcomes may have been lower than the month 24 completer outcomes we report herein. In addition, definitive conclusions regarding causation during months 12 and 24 between less treatment and lessening improvement of outcome measures compared with baseline values cannot be made because treatment decisions between months 12 and 24 were not based on a structured treatment protocol with protocol-defined treatment criteria. Finally, we do not present outcomes separately for eyes with CRVO and eyes with HRVO because the low number of recruited patients with HRVO did not permit meaningful analyses in this group. However, outcomes after the initial 6 months of anti-VEGF therapy were similar in eyes with HRVO and eyes with CRVO in the SCORE2 trial.[4]

Conclusions

In summary, this SCORE2 secondary analysis provides longer-term (2-year) information on the outcomes of anti-VEGF therapy for macular edema due to CRVO or HRVO at 12 months after cessation of the SCORE2 treatment protocol. Although participants improved substantially in VALS and CST through month 12, this improvement over baseline was lessened during the second year when fewer treatments were received. Nevertheless, month 24 outcomes were significantly better than at randomization into the SCORE2 trial. Poorer anatomic outcomes associated with bevacizumab compared with aflibercept during the first 6 months of the study did not translate into poorer VA or anatomic outcomes at month 24. No significant VALS or CST differences were observed at month 24 between the originally randomized groups, although caution is warranted in interpreting these results because of the considerable level of participant loss and investigator-chosen treatment plan and treatment frequency between months 12 and 24. It is not known whether the VA outcomes would have been better at month 24 had a structured treatment protocol been instituted between months 12 and 24. This analysis suggests that CRVO and HRVO warrant close monitoring and treatment as indicated over at least a 2-year period as needed to optimize outcomes in eyes treated with anti-VEGF therapy. Long-term outcomes out to 5 years after randomization are being investigated by the SCORE2 Investigator Group.

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Concept and design: Scott, VanVeldhuisen, Blodi.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Scott, VanVeldhuisen.
Critical revision of the manuscript for important intellectual content: Oden, VanVeldhuisen, Ip, Blodi, Chan.
Statistical analysis: Oden, VanVeldhuisen.
Obtained funding: Scott, VanVeldhuisen, Blodi.
Administrative, technical, or material support: VanVeldhuisen, Ip, Blodi, Chan.
Supervision: VanVeldhuisen.

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Group Information: The SCORE2 Investigator Group members include the following: *SCORE2 Executive Committee:* Ingrid U. Scott (Study Chair), Penn State College of Medicine; Michael S. Ip (Study Co-Chair), Doheny Eye Institute UCLA; Barbara A. Blodi (Principal Investigator), Fundus Photograph Reading Center; Sangeeta Bhargava (Director, Clinical Trials), NEI, NIH; Paul C. VanVeldhuisen (Data Coordinating Center [DCC] Principal Investigator), The Emmes Company, LLC; Neal L. Oden (DCC Statistician), The Emmes Company, LLC; Maria J. Figueroa (DCC Project Director), The Emmes Company, LLC. *SCORE2 Data and Safety Monitoring Committee:* David C. Musch (Chair), University of Michigan; Sangeeta Bhargava, NEI, NIH; Dennis P. Han, Medical College of Wisconsin; Srinivas R. Sadda, Doheny Eye Institute UCLA; George A. Williams, Beaumont Eye Institute; Stephen Wisniewski, University of Pittsburgh. *Penn State University:* Ingrid U. 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Personnel are listed by their primary role as principal investigator (PI), subinvestigator (SI), clinic coordinator (CC), visual acuity technician (V), photographer (P), pharmacist (PH), and other (O). *Black Hills Regional Eye Institute:* Prema Abraham (PI), Beth Bement-Stump (V), Leah Callahan (CC), Mindi Dockter (V), Kristi Livermont (CC), Robert Nixon (SI), Dan Parks (P), Nathan Steinle (SI), Alison Thompson (CC), Dylan Yu (SI). *Casey Eye Institute–Oregon Health & Science University:* Steven Bailey (SI), Jordan Barth (P), J. 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Andrew Pearson (PI), Susan Phillips (O), Lyudmila Pigulko (V), Michele Reg (CC), Stephen Sitzlar (PH), Lakisha Smith (V). *University of Rochester Flaum Eye Institute:* Rachel Aleese (V), Mina Chung (PI), Arielle Conrad (V), Andrea Czubinski (V), David DiLoreto (SI), Tanya Forbes (CC), Gary Gagarinas (V), Rachel Hollar (P), Lisa Latchney (CC), Katherine Nedrow (CC), Taylor Pannell (P), Brittany Richardson (P). *University of Wisconsin:* Angie Adler (CC), Michael Altaweel (PI), Barbara Blodi (SI), Shirley Craanen (P), Kristine Dietzman (V), Justin Gottlieb (SI), Michael S. Ip (SI), Denise Krolnik (P), Jennie Perry-Raymond (CC), Sandie Reed (P), Christopher Smith (V), John Peterson (P). *University of Nebraska Medical Center Truhlsen Eye Institute:* Bryan Angle (PI), Lola Berg (P), Maria Blaiotta (V), Christopher Blodi (PI), Kunal Dansingani (PI), Diana Do (SI), Lisa Greer (CC), Fayez Jawed (V), Kristi Miller (CC), Donna Neely (P), Quan Nguyen (PI), Julie Sigmund (CC). *University of Washington Medicine Eye Institute:* Brad Clifton (P), Patricia Ernst (V), Ron Jones (P), James Kinyoun (PI), Soojin Kyle (P), Jim Leslie (P), Juli Pettingill (V), Jeffrey Purcell (PH), Sue Rath (CC), Kasra Rezaei (SI), Gurunadh Vemulakonda (SI), Bao-Chau Vo (O). *Valley Retina Institute:* Rohit Adyanthaya (SI), Lazaro Aguero (P), Samuel Alonso (P), Deyla Anaya (CC), Isaac Cabrera (V), Monica Cantu (V), Tabatha Deluna (V), Roberto Diaz-Rohena (SI), Santos Garza (P), Victor Gonzalez (PI), Hector Jasso (P), Karina Miranda (V), Jessica Muniz (P), Nehal Patel (SI), Jessica Rodriguez (CC), Rachel Rodriguez (V), Kethsaly Salinas (CC), Nancy Salinas (CC), Yesenia Salinas (CC), Juan Santiago (SI), Lissete Villanueva (CC). *Vanderbilt Eye Institute:* Tony Adkins (P), Anita Agarwal (SI), Milam Brantley (PI), Joshua Carlson (SI), Edward Cherney (SI), Anthony Daniels (SI), Gowtham Jonna (SI), Stephen Kim (SI), Janice Law (SI), Rocky Munn (P), Sandy Owings (CC), Shriji Patel (SI), Scott Ruark (CC), Richard Skellie (P), Paul Sternberg (SI), Maryann Taylor-Ward (V). *Virginia Eye Institute:* Lea Anderlini (V), Mark Bartlett (P), James Combs (SI), Eleanore Ebert (SI), Michael Hughes (P), Byron Ladd (PI), Kristin McKeever (V), Lynn Roderick (P), George Sanborn (SI), Karen Sullivan (CC), Melissa Vaughan (CC). *Vitreoretinal Associates of Washington:* A. Samuel Barloon (SI), Charles Birnbach (SI), Andrea Blustein (V), Robert Francis (SI), Renee Gagnon (CC), Pamela Goldman (P), Ray Hunt (V), Frances Kipp (V), Todd Klesert (SI), DeShawn Minnis (P), Robert Nash (SI), Tetyana Nazarchuk (CC), David Saperstein (PI), Craig Wells (SI). *Vitreoretinal Surgery:* Steven Bennett (SI), Tamra Bogolin (V), Carmen Chan-Tram (CC), Holly Cheshier (P), John Davies (SI), Sundeep Dev (PI), Julianne Enloe (CC), Peggy Gilbert (V), Timothy Gromov (V), Jill Johnson (SI), Tori Jones (P), Robert Mittra (SI), Neal Oestreich (CC), D. Wilkin Parke (SI), Polly Quiram (SI), Robert Ramsay (SI), Carol Rogers (V), Joy Royle (V), Trenise Steele (P), Jessica Tonsfeldt (P), David Williams (SI).

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