JAMA Ophthalmology | Original Investigation | CLINICAL TRIAL

Baseline Factors Associated With 6-Month Visual Acuity and Retinal Thickness Outcomes in Patients With Macular Edema Secondary to Central Retinal Vein Occlusion or Hemiretinal Vein Occlusion

SCORE2 Study Report 4

Ingrid U. Scott, MD, MPH; Paul C. VanVeldhuisen, PhD; Michael S. Ip, MD; Barbara A. Blodi, MD; Neal L. Oden, PhD; Jacqueline King, MS; Andrew N. Antoszyk, MD; Mark A. Peters, MD; Michael Tolentino, MD; for the SCORE2 Investigator Group

IMPORTANCE Macular edema (ME) is the leading cause of decreased visual acuity (VA) associated with retinal vein occlusion (RVO). Identifying factors associated with better outcomes in RVO eyes treated with anti–vascular endothelial growth factor (VEGF) therapy may provide information useful in counseling patients.

OBJECTIVE To investigate baseline characteristics associated with 6-month VA and central subfield thickness (CST) outcomes in participants in the Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2).

DESIGN, SETTING, AND PARTICIPANTS A total of 362 patients with central RVO or hemi-RVO were enrolled between September 17, 2014, and November 18, 2015, and randomized 1:1 in a masked fashion to receive bevacizumab or aflibercept. At month 6, 348 participants (96%) had VA outcomes measured and 335 participants (93%) had spectral domain optical coherence tomography outcomes measured. The current data analysis was conducted from February 27, 2017, to April 7, 2017.

INTERVENTIONS Eyes were randomly assigned to receive an intravitreal injection of bevacizumab, 1.25 mg, or aflibercept, 2.0 mg, at baseline and every 4 weeks, with the primary outcome measured at 6 months.

MAIN OUTCOMES AND MEASURES Change from baseline in VA letter score (VALS), VALS gain of 15 or more, change from baseline in CST, CST less than 300 µm, and resolution of ME. Baseline factors associated with 6-month outcome at the 0.05 level in univariate regressions were included in multivariate regressions, with those significant after multiplicity control by the Hochberg method reported.

RESULTS The mean (SD) age of patients was 69 (12) years, and 43% were women. Younger patient age (odds ratio [OR], 0.95 per year of age; 95% CI, 0.93-0.98; $P = .007$) and lower baseline VALS (OR, 0.96 per letter; 95% CI, 0.94-0.98; $P < .001$) were associated with a 6-month VALS gain of 15 or greater. Compared with bevacizumab, aflibercept treatment was associated with a higher odds of ME resolution (OR, 3.59; 95% CI, 2.22-5.80; $P < .001$) and CST less than 300 µm (OR, 5.30; 95% CI, 2.40-11.67; $P = .001$), but not with a better VA outcome. Macular edema was less likely to resolve in eyes that received anti-VEGF treatment prior to study participation (OR, 0.33; 95% CI, 0.17-0.64; $P = .03$).

CONCLUSIONS AND RELEVANCE In eyes treated with bevacizumab or aflibercept, younger age and worse baseline VALS were associated with better 6-month VA outcomes. Aflibercept treatment was associated with more favorable spectral domain optical coherence tomography outcomes but not VA outcomes. These findings may be useful in assessing expected response at month 6 after monthly injection of anti-VEGF agents for treating ME due to CRVO and HRVO.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01969708

JAMA Ophthalmol. 2017;135(6):639-649. doi:10.1001/jamaophthalmol.2017.1141
Published online May 9, 2017.

Invited Commentary page 649

Related article at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The SCORE2 Investigator Group members are listed at the end of this article.

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

The Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2), a phase 3 randomized clinical trial, was conducted to investigate whether bevacizumab, a treatment commonly used off-label, is noninferior to aflibercept, a treatment approved by the US Food and Drug Administration, with respect to visual acuity (VA) in eyes with macular edema (ME) associated with central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO).[1] Between September 2014 and November 2015, 304 patients with CRVO and 58 patients with HRVO were enrolled at 66 private practice or academic centers in the United States and randomly assigned to receive intravitreal injection of bevacizumab, 1.25 mg, or aflibercept, 2.0 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 (e-ETDRS) VA letter score (VALS) at month 6, with a noninferiority margin of 5. At month 6, bevacizumab was noninferior to aflibercept (mean VALS improvement from baseline, 18.6 vs 18.9; noninferiority $P = .001$, lower 1-tailed 97.5% CI = −3.1 to infinity). Central subfield thickness (CST) measured with spectral domain optical coherence tomography (SD-OCT) decreased significantly through month 6 in both arms, with a higher proportion of aflibercept-treated eyes achieving resolution of ME than bevacizumab-treated eyes (54% vs 29%, $P < .001$).[1] There were no differences in the adverse event profile between the 2 arms. The purpose of the current report is to investigate baseline factors associated with month 6 VA and SD-OCT outcomes in patients with ME secondary to CRVO or HRVO in SCORE2.

Key Points

Question What baseline factors are associated with 6-month visual acuity (VA) and central subfield thickness outcomes in eyes with vision loss from macular edema due to central retinal vein occlusion or hemiretinal vein occlusion treated with bevacizumab or aflibercept?

Findings In this secondary analysis of a randomized clinical trial with 362 participants, younger age and worse baseline VA were associated with better 6-month VA. Aflibercept treatment was associated with better central subfield thickness but not VA outcomes than bevacizumab.

Meaning These factors may be useful in assessing expected response to monthly injections of anti–vascular endothelial growth factor for eyes with macular edema due to central retinal vein occlusion or hemiretinal vein occlusion.

Methods

The SCORE2 design and methods have been described in detail[2] and are summarized here. The study adhered to the tenets of the Declaration of Helsinki.[3] Institutional review board approval of the protocol was obtained from either a site-specific or centralized institutional review board, and written informed consent was obtained from all participants before eligibility screening and again before randomization into the study. Institutional review board approval is not required for each subsequent analysis. Stratification at randomization occurred within 1 of 3 VA groups: VALS of 73 to 59 (approximate Snellen VA 20/40 to 20/63), VALS of 58 to 49 (approximate Snellen VA 20/80 to 20/100), and VALS of 48 to 19 (approximate Snellen VA 20/125 to 20/400).

Study Population

The analyses included 348 participants (96%) with a 6-month VALS measurement and 335 participants (93%) with gradable 6-month SD-OCT images of the 362 SCORE2 participants. The mean (SD) age of SCORE2 participants was 69 (12) years, with 43% women, 76% white, and 15% black. The mean VALS was 50 (approximate Snellen 20/100; VALS range, 19-73) and participants had ME for an average of 7 months (range, 0-104 months) before randomization. The mean CST was 666 µm (range, 219 µm-1420 µm), 33% had received anti–vascular endothelial growth factor (VEGF) treatment prior to study participation, 8% had prior intravitreal steroid treatment, and 16% were diagnosed as having HRVO.[1]

Testing and Treatment Protocol

Study visits were scheduled every 4 weeks for 6 months. At each study follow-up visit, both eyes had VA assessed by the e-ETDRS method,[4] intraocular pressure measurement, and slit-lamp and dilated funduscopic examinations. Spectral domain OCT images were obtained monthly. At the reading center, OCT scans were converted to DICOM format, allowing graders to view and analyze scans in a custom software program. This grading method is independent of the OCT device, minimizing the measurement incongruity between different OCT manufacturers. Central subfield thickness values presented in this article are based on grading from the reading center. Resolution of ME was defined as CST less than 300 µm, no subretinal or intraretinal fluid, and no cystoid spaces within the ETDRS grid based on reading center evaluation. Stereoscopic fundus photographs taken at baseline and month 6 were analyzed for area of retinal hemorrhage and the presence or absence of other CRVO features such as retinal neovascularization, macular atrophy, and macular pigment. At selected sites, ultra-widefield fluorescein angiograms were obtained at baseline and month 6 to evaluate for retinal nonperfusion and vascular leakage. Study participants were masked to treatment assignment through month 6. At month 6, VA examiners and SD-OCT technicians were masked to treatment assignments.

Statistical Analysis

The primary goal of this article is to identify baseline characteristics of the SCORE2 population associated with VA and SD-OCT outcomes at month 6. For VA, 2 outcomes were investigated: mean change from baseline in best-corrected VALS (ie, the baseline score subtracted from the month 6 score) and a VALS gain from baseline of 15 or greater. Baseline factors associated with a VALS loss of 15 or greater from baseline were not analyzed because less than 2% of SCORE2 participants experienced this visual loss outcome at month 6. Three SD-OCT outcomes were evaluated based on reading center grading:

Table 1. Univariate Regression Models for Examining Baseline Factors Associated With 6-Month Visual Acuity[a]

Baseline Factor[b]	No.	VALS Gain of ≥15		Change From Baseline	
		No. (%)	Unadjusted *P* Value	Mean (SD)	Unadjusted *P* Value
Total	348	220 (63.2)	NA	18.8 (15.8)	NA
Treatment arm					
Bevacizumab	173	106 (61.3)	NA	18.6 (16.4)	NA
Aflibercept	175	114 (65.1)	.45	18.9 (15.2)	.88
Age, y					
<65	131	97 (74.0)	NA	22.1 (14.6)	NA
≥65	217	123 (56.7)	NA	16.7 (16.1)	NA
Continuous (per 1-y increase)	NA	NA	<.001	NA	<.001
e-ETDRS visual acuity letter score					
59-73 (20/40 to 20/63)	130	69 (53.1)	NA	13.5 (10.1)	NA
49-58 (20/80 to 20/100)	82	51 (62.2)	NA	18.4 (14.2)	NA
19-48 (20/125 to 20/400)	136	100 (73.5)	NA	24.0 (19.2)	NA
Continuous (per 1-letter increase in score)	NA	NA	<.001	NA	<.001
Time between diagnosis of macular edema and randomization, mo					
<2	217	147 (67.7)	NA	21.1 (16.1)	NA
≥2	131	73 (55.7)	NA	14.9 (14.5)	NA
Continuous (per 1-mo increase)	NA	NA	.008	NA	.001
Lens status					
Natural lens	259	174 (67.2)	NA	20.1 (15.3)	NA
Prior lens extraction	89	46 (51.7)	.009	14.9 (16.6)	.008
Prior anti-VEGF treatment					
No	232	158 (68.1)	NA	20.8 (16.3)	NA
Yes	116	62 (53.4)	.008	14.6 (14.0)	<.001
Prior steroid treatment					
No	323	209 (64.7)	NA	19.5 (15.7)	NA
Yes	25	11 (44.0)	.04	9.7 (14.6)	.003
SD-OCT central subfield thickness, μm					
<500	97	53 (54.6)	NA	15.9 (12.6)	NA
≥500	251	167 (66.5)	NA	19.9 (16.7)	NA
Continuous (per 100 increase)	NA	NA	.003	NA	<.001

Abbreviations: e-ETDRS, electronic Early Treatment Diabetic Retinopathy Study; NA, not applicable; SD-OCT, spectral domain optical coherence tomography; VALS, visual acuity letter score; VEGF, vascular endothelial growth factor.

[a] Effects with unadjusted $P < .05$ are noted in bold. Baseline factors for which an unadjusted $P \geq .05$ in either of the 2 visual acuity outcomes are not displayed in this table, with the exception of treatment group, which was retained. The following factors were tested and were not associated with outcomes: sex, race, ethnicity, diabetes, hypertension, coronary heart disease, smoking status, National Eye Institute Visual Functioning Questionnaire 25 composite score, type of retinal vein occlusion, history of open-angle glaucoma, posterior vitreous detachment (clinical assessment), SD-OCT outcomes of retinal thickness, macular volume, subretinal fluid, posterior vitreous detachment, epiretinal membrane, and retinal traction and distortion; and color fundus photograph assessment of area of intraretinal or subretinal hemorrhage within the Early Treatment Diabetic Retinopathy Study grid.

[b] For continuous variables, the variable was divided into a categorical variable to assess the relationship between factor and outcome, but the statistical test considered the variable as continuous.

mean change from baseline in CST (ie, the baseline CST subtracted from the CST at month 6), a 6-month CST measurement of less than 300 μm, and resolution of ME at month 6.

For the binary outcomes in the analyses (eg, a VALS gain from baseline of ≥15), the log odds of the outcome were modeled as a linear function of the baseline variable using logistic regression to determine whether the baseline factors in question were important. For continuous outcomes (eg, change from baseline in VALS), a standard linear regression was performed, again investigating whether the baseline factors were important.

The statistical tests of the univariate relationships between these baseline factors and the 5 outcome variables at the 6-month follow-up visit resulted in 140 *P* values. Nominal *P* values were used as a "filter" with which to control the number of baseline variables later included in multivariate analyses. To control for type 1 error, the familywide error of the multivariate tests was set at 5% using the Hochberg[5] sequentially rejective method. A baseline factor was considered significant if its Hochberg-adjusted multivariate *P* value was less than .05 (2-sided).

Results

Table 1 displays univariate analyses uncorrected for multiple testing of baseline factors associated with VALS at month 6, which are consistent across the 2 VA outcomes. Younger age, lower baseline VALS, shorter duration between diagnosis of ME and randomization, a natural lens, no prior anti-VEGF treatment, no prior steroid treatment, and larger baseline CST were all associated with better VA outcomes at month 6 based on higher odds of a VALS gain of 15 or more and greater positive mean changes from baseline in VALS at month 6. A larger baseline CST was associated with positive (beneficial) changes for odds of a VALS gain of 15 or greater and mean change from baseline in VALS at month 6. However, compared with bevacizumab, aflibercept treatment was not associated with a better VA

outcome. Further, no other demographic, clinical, or study eye variables were identified as associated with VA at month 6.

Table 2 summarizes the univariate analyses for baseline associations with SD-OCT outcomes in study participants. There were many nominally significant factors associated with SD-OCT outcomes from these unadjusted analyses, and described here are only those variables that are statistically significant on 2 or more SD-OCT outcomes. Randomization assignment of aflibercept, relative to bevacizumab, was associated with positive (beneficial) SD-OCT changes at month 6, with higher odds of ME resolution and CST of less than 300 µm. Eyes with a natural lens, relative to a prior lens extraction at baseline, had better SD-OCT outcomes, with higher odds of ME resolution and a larger CST reduction from baseline. Shorter duration between diagnosis of ME and randomization also had a positive impact on SD-OCT outcomes, with higher odds of ME resolution and a larger reduction from baseline in CST than those with a longer duration of ME. Last, the presence of subretinal fluid as identified on the SD-OCT by the reading center was associated with positive outcomes based on higher odds of CST less than 300 µm and greater mean reduction from baseline in CST.

The multivariate analyses showing the results only for baseline factors that were statistically significant with an adjusted *P* value less than .05 based on the Hochberg[5] method were consistent across the 2 VA outcomes (**Table 3**). Both younger age and lower (worse) baseline VALS were associated with greater odds of a VALS gain of 15 or more and a greater mean increase from baseline in VALS. More specifically, the estimated odds ratio for VALS gain of 15 or greater is multiplied by 1/0.95 = 1.05 for every 1-year decrease in age ($P = .007$) and by 1/0.96 = 1.04 for every 1-unit decrease in baseline VALS ($P < .001$). Also, estimated mean VALS change from baseline increases by 0.27 for every year of decrease in age ($P = .006$) and by 0.38 for every unit of decrease in baseline VALS ($P < .001$).

For the CST outcomes, many of the nominally significant univariate variables were no longer significant in the multivariate model after adjusting for multiple comparisons (**Table 4**). Randomization to aflibercept treatment, compared with bevacizumab, remained significant, with aflibercept treatment having higher odds of ME resolution (odds ratio, 3.59; 95% CI, 2.22-5.80; $P < .001$) and higher odds of CST less than 300 µm (odds ratio, 5.30; 95% CI, 2.40-11.67; $P = .001$). Study eyes that were anti-VEGF naive at baseline had odds for resolution of ME that were 1/0.33 = 3 times greater than eyes with prior anti-VEGF treatment ($P = .03$). Further, higher baseline CST was associated with a greater decrease in CST from baseline to month 6 (ie, a mean decrease of 79 µm in CST for every 100 µm in CST at baseline; $P = .002$) and higher baseline VALS was associated with less of a decrease in CST from baseline to month 6 (ie, the decrease was approximately 4 µm less in CST for every 1-letter increase in VALS at baseline; $P = .04$).

Discussion

This analysis was conducted to identify baseline factors associated with VA and SD-OCT outcomes in patients treated with intravitreal anti-VEGF therapy for ME due to CRVO or HRVO in SCORE2.

In the multivariate analyses, younger age and lower baseline VALS were associated with better VA outcomes as assessed by VALS gain of 15 or greater and an increase from baseline in VALS. Age was also identified in the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE)-CRVO Trial (which compared intravitreal triamcinolone with observation for ME secondary to CRVO) as a significant baseline factor of 6-month VA outcomes, with younger age associated with a gain of 15 or greater in VALS.[6] As hypothesized when discussing the SCORE Study findings,[6] this may be the result of an enhanced resilience of younger patients' photoreceptors that may permit the retina to recover after an acute insult such as RVO compared with photoreceptors of older patients. Among patients treated with grid photocoagulation for ME in the Central Vein Occlusion Study, VA outcome tended to be better for younger patients, although this interaction between treatment effect and age was not statistically significant, perhaps due to the limited sample size.[7] As is the case in SCORE2, the COPERNICUS Study[8] (a randomized trial that compared intravitreal aflibercept with sham injections for CRVO-associated ME) also found that a lower baseline VALS was associated with greater improvement from baseline in VALS; this is most likely due to a ceiling effect (ie, starting from a higher baseline VALS leaves less room for VA improvement with anti-VEGF therapy than starting from a lower baseline VALS). With anti-VEGF treatment of diabetic ME, younger age and worse baseline VA have also been shown to be associated with greater VA improvement, and greater baseline retinal thickening has been shown to be associated with greater reduction in retinal thickening.[9-12] This suggests similarities between treatment response of eyes with ME from diabetes and CRVO and HRVO.

Multivariate analyses identified the following baseline factors associated with favorable SD-OCT outcomes: aflibercept treatment, no prior anti-VEGF treatment, and higher baseline CST. In SCORE2, randomization to aflibercept (compared with bevacizumab) was associated with higher odds of ME resolution and higher odds of CST less than 300 µm. These month 6 findings are consistent with results of Diabetic Retinopathy Clinical Research Network Protocol T, in which aflibercept was more effective at reducing retinal thickness than bevacizumab at 1 year and at 2 years in eyes with diabetic ME.[9,10] The greater effectiveness of aflibercept relative to bevacizumab in reducing retinal thickness may be due to aflibercept's broader mechanism of action and/or tighter binding affinity. While aflibercept and bevacizumab inhibit all isoforms of VEGF-A, aflibercept also inhibits VEGF-B and placental growth factor.[11] In addition to its broader mechanism of action, aflibercept has been reported to have a higher binding affinity to VEGF-A than bevacizumab.[13,14] In SCORE2, eyes with prior anti-VEGF treatment at baseline, compared with anti-VEGF–naive study eyes, had lower odds of ME resolution. This finding may be explained by anti-VEGF treatment prior to randomization signifying worse disease, which has already been refractory to anti-VEGF therapy and which, therefore, may be more likely to be refractory to additional anti-VEGF treatment. Higher baseline CST was predictive of a larger reduction from baseline in

Table 2. Univariate Regression Models for Examining Baseline Factors Associated With 6-Month SD-OCT CST Outcomes[a]

Baseline Factor[b]	Resolution of Macular Edema			CST < 300 µm			Change From Baseline		
	No. of Eyes With Nonmissing Data	No. (%) Resolved	Unadjusted *P* Value	No. of Eyes With Nonmissing Data	No. (%) With CST < 300 µm	Unadjusted *P* Value	No.	Mean (SD)	Unadjusted *P* Value
Total	341	141 (41.3)	NA	335	281 (83.9)	NA	328	−405.5 (245.2)	NA
Treatment arm									
Aflibercept	169	92 (54.4)	NA	164	154 (93.9)	NA	160	−425.1 (230.5)	NA
Bevacizumab	172	49 (28.5)	<.001	171	127 (74.3)	<.001	168	−386.8 (257.7)	.16
Ethnicity									
Non-Hispanic	308	127 (41.2)	NA	302	254 (84.1)	NA	297	−396.9 (246.5)	NA
Hispanic	33	14 (42.4)	.89	33	27 (81.8)	.73	31	−487.7 (219.3)	.05
Smoking status									
Never smoker	187	83 (44.4)	NA	182	156 (85.7)	NA	180	−445.0 (264.4)	NA
Prior smoker	120	48 (40.0)	.45	120	96 (80.0)	.19	116	−350.1 (213.3)	.001
Current smoker	34	10 (29.4)	.11	33	29 (87.9)	.74	32	−384.0 (201.6)	.19
e-ETDRS visual acuity letter score									
59-73 (20/40 to 20/63)	128	51 (39.8)	NA	127	111 (87.4)	NA	123	−302.1 (196.5)	NA
49-58 (20/80 to 20/100)	78	43 (55.1)	NA	78	64 (82.1)	NA	78	−387.1 (182.5)	NA
19-48 (20/125 to 20/400)	135	47 (34.8)	NA	130	106 (81.5)	NA	127	−516.9 (274.0)	NA
Continuous (per 1-letter increase in score)	NA	NA	.43	NA		.89	NA	NA	<.001
Time between diagnosis of macular edema and randomization, mo									
<2	213	103 (48.4)	NA	213	178 (83.6)	NA	210	−432.4 (251.4)	NA
≥2	128	38 (26.7)	NA	122	103 (84.4)	NA	118	−357.6 (226.9)	NA
Continuous (per 1-mo increase)	NA	NA	.003	NA		.48	NA	NA	.03
Lens status									
Natural lens	256	114 (44.5)	NA	251	212 (84.5)	NA	247	−421.8 (241.8)	NA
Prior lens extraction	85	27 (31.8)	.04	84	69 (82.1)	.62	81	−355.7 (250.0)	.04
Prior anti-VEGF treatment									
No	228	114 (50.0)	NA	227	192 (84.6)	NA	222	−421.2 (245.8)	NA
Yes	113	27 (23.9)	<.001	108	89 (82.4)	.61	106	−372.7 (241.8)	.09
Prior steroid treatment									
No	317	135 (42.6)	NA	312	261 (83.7)	NA	305	−414.0 (248.0)	NA
Yes	24	6 (25.0)	.10	23	20 (87.0)	.68	23	−293.1 (170.5)	.02
Type of occlusion									
CRVO	285	124 (43.5)	NA	279	235 (84.2)	NA	274	−418.4 (245.1)	NA
HRVO	56	17 (30.4)	.07	56	46 (82.1)	.70	54	−339.8 (237.1)	.03
SD-OCT									
Posterior vitreous detachment									
Absent/questionable	190	80 (42.1)	NA	185	160 (86.5)	NA	184	−376.0 (234.0)	NA
Present	146	58 (39.7)	.66	145	116 (80.0)	.12	141	−446.3 (255.9)	.01
CST, µm									
<500	90	41 (45.6)	NA	88	74 (84.1)	NA	81	−150.9 (102.9)	NA
≥500	251	100 (39.8)	NA	247	207 (83.8)	NA	247	−489.0 (219.3)	NA
Continuous (per 100 increase)	NA	NA	.30	NA		.72		NA	<.001
Subretinal fluid									
Absent/questionable	94	35 (37.2)	NA	90	68 (75.6)	NA	89	−270.2 (228.0)	NA
Present	183	80 (43.7)	.30	181	159 (87.8)	.01	179	−418.8 (205.8)	<.001

(continued)

Table 2. Univariate Regression Models for Examining Baseline Factors Associated With 6-Month SD-OCT CST Outcomes[a] (continued)

Baseline Factor[b]	Resolution of Macular Edema			CST < 300 µm			Change From Baseline		
	No. of Eyes With Nonmissing Data	No. (%) Resolved	Unadjusted *P* Value	No. of Eyes With Nonmissing Data	No. (%) With CST < 300 µm	Unadjusted *P* Value	No.	Mean (SD)	Unadjusted *P* Value
Retinal thickness: total volume									
<10	303	130 (42.9)	NA	299	255 (85.3)	NA	292	−409.4 (253.8)	NA
≥10	38	11 (29.0)	NA	36	26 (72.2)	NA	36	−373.8 (157.6)	NA
Continuous (per 1-unit increase)	NA	NA	.84	NA	NA	.98	NA	NA	<.001
Color fundus photograph: area of intraretinal and/or subretinal hemorrhage within ETDRS grid, %									
Blood 1 to <25 of grid	167	64 (38.3)	NA	162	136 (84.0)	NA	161	−352.1 (233.7)	NA
Blood 25 to <50 of grid	90	45 (50.0)	.07	89	75 (84.3)	.95	86	−422.4 (234.4)	.03
Blood 50 or more of grid	64	24 (37.5)	.91	64	51 (79.7)	.45	62	−559.5 (240.2)	<.001

Abbreviations: CRVO, central retinal vein occlusion; CST, central subfield thickness; e-ETDRS, electronic Early Treatment Diabetic Retinopathy Study; ETDRS, Early Treatment Diabetic Retinopathy Study; HRVO, hemiretinal vein occlusion; NA, not applicable; SD-OCT, spectral domain optical coherence tomography; VEGF, vascular endothelial growth factor.

[a] Effects with unadjusted $P < .05$ are noted in bold. Baseline factors for which an unadjusted $P \geq .05$ in any of the 3 SD-OCT outcomes are not displayed in this table. The following factors were tested and were not associated with outcomes: sex, race, diabetes, hypertension, coronary heart disease, National Eye Institute Visual Functioning Questionnaire 25 composite score, history of open-angle glaucoma, posterior vitreous detachment (clinical assessment), and SD-OCT outcomes of epiretinal membrane, retinal traction, and distortion.

[b] For continuous variables, the variable was divided into a categorical variable to assess the relationship between factor and outcome, but the statistical test considered the variable as continuous.

Table 3. Multivariate Regression Models for 6-Month Visual Acuity Outcomes[a]

Variable	VALS Gain of ≥15		Change From Baseline	
	OR (95% CI)[b]	Adjusted *P* Value[c]	Difference (95% CI)[b]	Adjusted *P* Value[c]
Age				
Continuous (per 1-y increase)	0.95 (0.93 to 0.98)[d]	.007	−0.27 (−0.42 to −0.13)[d]	.006
e-ETDRS visual acuity letter score				
Continuous (per 1-letter increase in score)	0.96 (0.94 to 0.98)[d]	<.001	−0.38 (−0.50 to −0.26)[d]	<.001

Abbreviations: e-ETDRS, electronic Early Treatment Diabetic Retinopathy Study; OR, odds ratio; VALS, visual acuity letter score.

[a] All variables significant in the univariate models are considered for the multivariate model. Only effects with adjusted $P < .05$ based on the Hochberg[5] method are included in the table.

[b] For change from baseline in VALS, an effect on visual acuity is considered beneficial if it increases the odds of 15 or greater gain or increases the positive change from baseline. For example, considering the baseline predictor of age and an OR of 0.95, a 50-year-old person has a 5% decrease in odds of 15 or greater gain compared with a 49-year-old person. Confidence intervals are not adjusted for multiple testing.

[c] *P* value adjusted for multiplicity control by the Hochberg[5] method.

[d] Detrimental effect on vision.

CST compared with a lower baseline CST. This may be because anti-VEGF therapy is, in general, quite effective in reducing ME and eyes with a higher baseline CST have a greater potential CST reduction than eyes with a lower baseline CST. Similar to SCORE2, in the SCORE Study, a higher baseline central retinal thickness was also associated with a greater reduction in central retinal thickness.[6] There needs to be caution when interpreting a variable whose baseline value is part of the calculation of the outcome because this relationship is affected by "part-whole correlation."[15] For example, the negative correlation between baseline CST and change in CST from baseline to month 6 may be because, to calculate the 6-month change, the baseline value is subtracted from the month 6 thickness. Finally, note that a few of the outcomes in Table 4 could be at least partially the result of regression to the mean. For example, one inclusion criterion for SCORE2 is a baseline CST of 300 µm or greater. Because of measurement error, some participants with true CST less than 300 µm may have been accidentally included. Even if the participants' true CST did not change, these participants will appear improved at 6 months. A similar argument applies to the effect of baseline VALS on VA outcomes.

In univariate analyses of SCORE2 data, shorter duration between diagnosis of ME and randomization was associated with higher odds of a VALS gain of 15 or greater, a larger improvement from baseline in VALS at month 6, higher odds of ME resolution, and a greater reduction in CST from baseline. This is consistent with findings in both of the previously reported randomized trials, which compared intravitreal aflibercept with sham injections for CRVO-associated ME (the COPERNICUS[8] and GALILEO[16] studies), in which time since diagnosis of CRVO of 2 months or less was associated with better VA outcomes than time since CRVO diagnosis of greater than 2 months. Similarly, in the SCORE Study, shorter duration of ME was associated with a greater reduction from baseline in OCT-measured center point thickness.[6] One may hypothesize that retinal anatomic changes

Table 4. Multivariate Regression Models for 6-Month SD-OCT Central Subfield Thickness Outcomes[a]

Variable	Resolution of Macular Edema		Central Subfield Thickness <300 µm		Change From Baseline	
	OR (95% CI)[b]	Adjusted *P* Value	OR (95% CI)[b]	Adjusted *P* Value[c]	Difference (95% CI)[b]	Adjusted *P* Value[c]
Treatment arm						
Bevacizumab	1 [Reference]	NA	1 [Reference]	NA	NA	NA
Aflibercept	3.59 (2.22 to 5.80)[d]	<.001	5.30 (2.40 to 11.67)[d]	.001	NA	NA
Prior anti-VEGF treatment						
No	1 [Reference]	NA	NA	NA	NA	NA
Yes	0.33 (0.17 to 0.64)[e]	.03	NA	NA	NA	NA
SD-OCT central subfield thickness						
Continuous (per 100-µm increase)	NA	NA	NA	NA	−79.72 (−117.25 to −42.18)[d]	.002
e-ETDRS visual acuity letter score						
Continuous (per 1-letter increase in score)	NA	NA	NA	NA	3.94 (1.54 to 6.33)[e]	.04

Abbreviations: e-ETDRS, electronic Early Treatment Diabetic Retinopathy Study; NA, not applicable; OR, odds ratio; SD-OCT, spectral domain optical coherence tomography; VEGF, vascular endothelial growth factor.

[a] All variables significant in the univariate models are considered for the multivariate model. Only effects with adjusted $P < .05$ based on the Hochberg[5] method are included in the table.

[b] For SD-OCT central subfield thickness, an effect on vision is considered beneficial if it increases odds of resolution of macular edema or a thin macula (<300) or decreases the positive change from baseline (ie, negative change). Confidence intervals are not adjusted for multiple testing.

[c] *P* value adjusted for multiplicity control by the Hochberg[5] method.

[d] Beneficial effect on vision.

[e] Detrimental effect on vision.

of shorter duration are more likely to be reversible compared with more chronic changes in retinal architecture. However, in multivariate models analyzing SCORE2 data after adjustment for multiple testing, duration between diagnosis of ME and randomization was not identified as significantly associated with VALS or SD-OCT outcomes.

In SCORE2, systemic factors investigated were not associated with either VALS or SD-OCT outcomes. While history of coronary artery disease may be a marker for more underlying systemic ischemia, which may be hypothesized to portend a graver VA and anatomic prognosis after CRVO, history of coronary artery disease was not found to be an important baseline factor in the SCORE-CRVO trial[6] or SCORE2, perhaps because patients judged by the investigator to have an ischemic CRVO were excluded from these trials. Although hypertension is a well-reported risk factor for the development of an RVO,[17-25] a history of hypertension was not significantly associated with outcome in either SCORE2 or the SCORE Study.[6] As hypothesized previously,[6] this may be due, at least in part, to the fact that patients with a history of hypertension (which was assessed in SCORE2 and in the SCORE Study based on patient self-report) were aware of their diagnosis and, thus, were likely being treated for hypertension. The association between undiagnosed, untreated, or poorly controlled hypertension and outcome in patients with RVO is unknown.

Limitations

Extrapolating results from clinical trials to clinical practice should be made with caution. For example, the findings reported in this article need to be interpreted in light of excellent adherence, with approximately 90% of participants receiving 6 monthly anti-VEGF injections. There are also caveats that should be considered with cross-trial comparisons. For example, this analysis focuses on 6-month outcomes (which is consistent with the primary outcome time point in the previously reported phase 3 studies of aflibercept for CRVO-associated ME [the Copernicus[8] and Galileo[16] studies]) while the primary outcome time point in the SCORE Study was at 1 year.[26] Timing of measuring outcome may influence the identification of baseline factors based on short-term vs longer-term impact of treatment.

Conclusions

The SCORE2 Study identified a number of baseline factors associated with 6-month outcomes. Consistent with other studies, younger age and worse baseline VA are consistently associated with greater improvement in VA at month 6. Compared with bevacizumab, aflibercept treatment was associated with better SD-OCT outcomes of CST less than 300 µm and resolution of ME but not VA outcomes. These findings may assist clinicians in assessing response to treatment over a 6-month period for patients with ME secondary to CRVO or HRVO who receive monthly anti-VEGF treatment, but they do not change the conclusions of the primary outcome results that bevacizumab was noninferior to aflibercept for mean VA improvement at 6 months.

ARTICLE INFORMATION

Accepted for Publication: March 15, 2017.

Published Online: May 9, 2017. doi:10.1001/jamaophthalmol.2017.1141

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 Corporation, Rockville, Maryland (VanVeldhuisen, Oden, King); Doheny Eye Institute, University of California–Los Angeles (Ip); Fundus Photograph Reading Center, University of Wisconsin, Madison (Blodi); Charlotte Eye Ear Nose & Throat Associated PA, Charlotte, North Carolina (Antoszyk); Retina Northwest PC, Portland, Oregon (Peters); Center for Retina and Macular Disease, Winter Haven, Florida (Tolentino).

Author Contributions: Drs VanVeldhuisen and Oden had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Scott, VanVeldhuisen, Ip, Blodi, Oden, Tolentino.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Scott, VanVeldhuisen, Ip, Oden.
Critical revision of the manuscript for important intellectual content: VanVeldhuisen, Ip, Blodi, Oden, King, Antoszyk, Peters, Tolentino.
Statistical analysis: VanVeldhuisen, Oden, King.
Obtained funding: VanVeldhuisen, Blodi.
Administrative, technical, or material support: Scott, VanVeldhuisen, Ip, Blodi.
Supervision: VanVeldhuisen, Ip, Blodi.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Scott has received grants from the National Eye Institute and other funding from Thrombogenics. Dr VanVeldhuisen has received grants from the National Eye Institute. Dr Ip has received personal fees from Thrombogenics, Omeros, Genentech (consultant), Quark, and Boehringer Ingelheim. Dr Peters has received grants from the National Eye Institute and support from Genentech and Regeneron Pharmaceuticals. Dr Tolentino has received grants from the National Eye Institute, grants and other support from Regeneron (speaker) , grants from Allergan, and grants and other support from Alcon/Novartis (consultant). No other disclosures were reported.

Funding/Support: This study was supported by grants U10EY023529, U10EY023533, and U10EY023521 from the National Eye Institute, National Institutes of Health, Department of Health and Human Services. Support was also provided in part by Regeneron Inc and Allergan Inc through donation of investigational drug. This work was supported in part by an unrestricted grant from Research to Prevent Blindness Inc to the University of Wisconsin, Madison Department of Ophthalmology and Visual Sciences.

Role of the Funder/Sponsor: The National Institutes of Health participated in oversight of the conduct of the study and review of the manuscript but not directly in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or in the preparation of the manuscript. Regeneron Inc and Allergan reviewed the protocol and Regeneron provided comments on the manuscript.

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 Center UCLA; Barbara A. Blodi (principal investigator), Fundus Photograph Reading Center; Sangeeta Bhargava (program director, CCR), National Eye Institute, National Institutes of Health; Paul VanVeldhuisen (DCC principal investigator), The Emmes Corporation; Neal L. Oden (DCC statistician), The Emmes Corporation; and Maria J. Figueroa (DCC project director), The Emmes Corporation. *SCORE2 Data and Safety Monitoring Committee:* David C. Musch (chair), University of Michigan; Sangeeta Bhargava, National Eye Institute, National Institutes of Health; Dennis P. Han, Medical College of Wisconsin; Srinivas R. Sadda, Doheny Eye Institute; George A. Williams, Beaumont Eye Institute; and Stephen Wisniewski, University of Pittsburgh. *Penn State University Study Chair's Office:* Ingrid U. Scott (study chair) and Janelle Gaston (research project manager). *SCORE2 Data Coordinating Center:* Paul VanVeldhuisen (principal investigator), Maria Figueroa (project director), Lena Bradley, Jodi De Stefano, Eileen Guan, Anne Hoehn, Alexa Irazabal, Sue Isman, Jacquie King, Radhika Kondapaka, Hamsa Kumar, Matt Lahut, Robert Lindblad, Neal Oden, Michael Patschak, Ro Shauna Rothwell, Rosemary Smith, Janet Van Dyke, Valerie Watson, and Lauren Yesko. *SCORE2 Fundus Photograph Reading Center:* Barbara A. Blodi (principal investigator), Amitha Domalpally (research director), Susan Reed (research program manager), and Pam Vargo (lead imaging specialist). *Institute for Personalized Medicine:* Cynthia Reed (patient enrollment specialist). *SCORE2 clinical sites that participated in this study:* Sites are listed in alphabetical order. 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), and Stephen Khachikian (SI); *Casey Eye Institute-OHSU:* Steven Bailey (SI), Jordan Barth (P), J. Peter Campbell (SI), Christina Flaxel (SI), Christopher Howell (P), Jocelyn Hui (P), Thomas Hwang (SI), Shirley Ira (V), Andreas Lauer (PI), Phoebe Lin (SI), Ann Lundquist (CC), Susan Nolte (V), Scott Pickell (P), Dawn Ryan (P), Mitchell Schain (CC), Peter Steinkamp (P), Chiedozie Ukachukwu (P), Sara Blefgen (PH), Brad Fujisaki (PH), Jeanne Liming (PH), Frank Mistretta (PH), and Jennifer Petrolati (PH); *Center for Retina and Macular Disease:* Adam Berger (SI), Erika Darby (P), Vera Dilts (V), Richard Hamilton (SI), Tammy McCarty (CC), Esmeralda Medina (CC), David Misch (SI), Suk Jin Moon (SI), Kari Owen (P), John Randolph (SI), Jason Strickland (P), Michael Tolentino (PI), Laura Holm (V), and Dawn Sutherland (CC); *Charlotte Eye Ear Nose & Throat:* Andrew Antoszyk (PI), David Browning (SI), Loraine Clark (P), Sarah Ennis (V), Christina Fleming (CC), Sherry Fredenberg (V), Lisa Jackson (P), Angie Karow (CC), Donna McClain (P), Michael McOwen (P), Angela Price (CC), Omar Punjabi (SI), Lynn Watson (P), Uma Balasubramaniam (P), Swann Bojaj (P), Autumn Finch (P), and Beverly Rowland (P); *Cumberland Valley Retina Consultants:* Allen Hu (SI), Donna King (V), Christa McChancy (P), Wendy McCullough (V), George Sanborn (SI), Becca Varner (P), Leslee Wallech (V), Shayla Ward (CC), David Warrow (SI), Cherie Wenger (P), Alison Wentz (CC), John Wroblewski (PI), Nicole Hollimon (P), Ejiatu Sesay (P), Veronica Shetler (V), and Kimberly Wood (P); *Dean McGee Eye Institute:* Shannon Almeida (CC), Joann Booth (P), Reagan Bradford (SI), Russ Burris (P), Mandi Butt (P), Stephen Fransen (SI), Sonny Icks (V), Ronald Kingsley (PI), Robert Leonard (SI), Alisha Parrett (CC), Vinay Shah (SI), and Vicki Wolzen (P); *Delaware Valley Retina Associates:* Krista Bayer (P), Morgan Harper (V), Darmakusuma Ie (PI), Lauren Knezek (P), Jeffrey Lipkowitz (SI), Beverly Sannazzaro (CC), Kekul Shah (SI), Lorraine Eggert (V), and Susan Geraghty (P); *East Bay Retina Consultants Inc:* Renjini Balakrishnan (CC), Fazilla Bano (V), Daniel Brinton (SI), Elyssa Casugay (CC), Roby Casupanan (V), Patty Chung (V), Caroline Frambach (V), Afsoon Jamali (P), Scott Lee (SI), Eugene Lit (PI), Scotty Renslow (CC), Soraya Rofagha (SI), Heidi Winje (CC), Heather Enyart (P), and Khaliah Jackson (V); *Elman Retina Group PA:* Jennifer Belz (CC), Theresa Cain (P), Teresa Coffey (V), Michael Elman (PI), Henry Leder (SI), Ashley Metzger (P), Dallas Sandler (V), Jennifer Simmons (V), Perel Simpson (V), Pamela Singletary (V), Peter Sotirakos (P), JoAnn Starr (CC), Amy Thompson (V), Ashley Davis (V), and Peggy Orr (V); *Emory University Eye Center:* Judy Brower (V), Linda Curtis (CC), Jannah Dobbs (P), Deborah Gibbs (CC), Andrew Hendrick (PI), G. Baker Hubbard (SI), Jiong Yan (SI), Debbie Jordan (P), Darien Middleton (O), and Susan Rogers (PH); *Florida Retina Consultants:* Steve Carlton (P), Damanda Fagan (CC), Scott Friedman (PI), Allen McKinney (V), Nader Moinfar (SI), Paige Walters (V), Katrina Dawson (CC), and Kimberly Williamson (CC); *Georgia Retina:* Jini Jones (P), Leslie Jones (V), Scott Lampert (SI), Leslie Marcus (CC), Krishna Mukkamala (SI), Maria Rogers (V), Atul Sharma (SI), Robert Stoltz (PI), Morgan West (P), Lindsey Neal (P), Lauren Nunn (CC); *Henry Ford Health System:* Nitin Kumar (SI), Megan Allis (P), Paul Edwards (PI), John Grybas (P), Julianne Hall (CC), Nicole Massu (P), Mary Monk (CC), Jessica Nelson (P), Brian Rusinek (P), Jenny Shaheen (P), Bradley Stern (P), Tracey Troszak (P), David Burley (P), Uday Desai (SI), Hua Gao (SI), Thomas Hessburg (SI), Melina Mazurek (V), Janet Murphy (V), and Katie Ventimiglia (V); *Illinois Eye and Ear Infirmary UIC:* Catherine Carroll (P), Felix Chau (SI), Mark Janowicz (P), Tametha Johnson (V), Jennifer Lim (PI), Yesenia Ovando (V), Natasa Stankovic (V), Jie (Jessica) Sun (CC), Lauren Talasnik (CC), Yannek Leiderman (SI), Marcia Niec (CC), and Lawrence Ulanski (SI); *Loma Linda University:* Raquel Hernandez (CC), Armand Assissini (P), Marvyn Cerdenio (CC), Joseph Fan (SI), Lynn Huang (SI), William Kiernan (V), Jesse Knabb (P), Michael Rauser (PI), Gisela Santiago (CC), Mukesh Suthar (SI), and Brandon Williams (P); *Long Island Vitreoretinal Consultants:* Michael Chitjian (P), Kristen DAmore (CC), Vincent Deramo (SI), David Fastenberg (SI), Philip Ferrone (PI), Barry Golub (SI), Kenneth Graham (SI), Sandra Jaya (V), Jonathan Jonisch (SI), David Rhee (SI), Juan Romero (SI), Brett Rosenblatt (SI), Marianne Schlameuss (CC), Jeffrey Shakin (SI), Eric Shakin (SI), Vasanti Sookhai (V), and Jamie Szczepanski (V); *Mayo Clinic:* Sophie Bakri (PI), Andrew Barkmeier (SI), Jean Burrington (V), Shannon Goddard (P), Denise Lewison (P), Jessica Morgan (V), Joan Overend (V), Heidi Rubin (CC), Wendy Smith (SI), Jamie Tesmer (P), Stephanie Thatcher (P), Betsy Baker (CC), Gillian Currie (CC), Melissa Franzen (CC), Rebecca Nielsen (CC), and Diane Vogen (CC); *Medical Center Ophthalmology Associates:* Darren Bell (SI), Carrisa Bolado (CC), Jason Burns (SI), Melissa Dominguez (V), Rosa Escobar (P), Richard Evans (SI), Shelli Goel (P),

Roxanne Gomez (V), Felicia Huron (V), Judy Rittimann (CC), Vincent Segovia (P), Michael Singer (PI), Catherine Ellis (CC), Guillermo Montoya (CC), and Cynthia Myrick (CC); *Medical College of Wisconsin:* Vicki Barwick (V), Joe Beringer (P), Joseph Carroll (SI), Thomas Connor (SI), Eleanor Dorsey (CC), Kristy Keller (P), Judy Kim (PI), Katie McKenney (CC), Stephanie Moebius (P), Krissa Packard (CC), David Weinberg (SI), Vesper Williams (CC), Pat Winter (V), William Wirostko (SI), Mara Goldberg (P), and Kimberly Stepien (SI); *Mid Atlantic Retina:* Hannah Benfield (CC), Christina Centinaro (V), Allen Chiang (SI), Lauren Devine (V), Mitchell Fineman (SI), Michele Formoso (CC), Sunir Garg (SI), Cedric George (O), Elaine Gonzales (P), Lisa Grande (V), Omesh Gupta (SI), Allen Ho (SI), Samuel Houston (SI), Jason Hsu (SI), Maryann Jay (P), Richard Kaiser (SI), Brianna Kenney (CC), Lisa Lavetsky (P), Theresa Listner (CC), Joseph Maguire (SI), Sonia Mehta (SI), Jill Noble (O), Carl Park (SI), Ehsan Rahimy (SI), David Reed (SI), Carl Regillo (PI), Noga Senderowitsch (CC), Arunan Sivalingam (SI), Marc Spirn (SI), and Jamilla Sudler (V); *Midwest Eye Institute:* Neil Finnen (PI), Charlotte Harris (P), Ingrid Kerr (CC), Raj Maturi (SI), Bethany Sink (CC), Thomas Ciulla (SI), Tammy Dale (V), Cindi Hood (P), Kristin Phillips (V), Ashley Radtke (V), Shyla Robson (P), and Tom Steele (P); *National Ophthalmic Research Institute:* A. Thomas Ghuman (PI), Cheryl Kiesel (CC), Ray Kiesel (P), Eileen Knips (P), Anita Leslie (V), Kristi Maro (CC), Crystal Peters (CC), Paul Raskauskas (SI), Cheryl Ryan (CC), Ashish Sharma (SI), Danielle Turnbo (V), Joseph Walker (SI), Laura Greenhoe (CC), Jessica Lynn Saez (CC), Natalie Torres (Crawford) (CC), and Glenn Wing (SI); *New Jersey Medical School:* Tamara Berezina (P), Neelakshi Bhagat (PI), Kathryn Boschert (CC), Eileen Buroff (V), Janie Ellenberger (CC), Catherine Fay (CC), Marian Konop (P), Michael Lazar (P), Tatiana Mikheyeva (P), Monique Roy (SI), and Marco Zarbin (SI); *New York Eye and Ear Infirmary:* Wanda Carrasquillo-Boyd (P), Yuen Ping Chui (SI), Ronald Gentile (SI), Melissa Rivas (CC), Richard Rosen (PI), Katy Tai (CC), Meliza Unson (V), Paul Whitten (P), Priya Mehta (V), and Alex Yang (V); *NJ Retina:* Howard Fine (SI), Laura Fox Gadless (CC), Eric Friedman (SI), Stuart Green (SI), Bruce Keyser (SI), Amy Leviton (V), Celeste Nelson (CC), Jennifer Pilato (CC), Jonathan Prenner (SI), Daniel Roth (SI), Alex Schlosser (P), Sumit Shah (PI), H. Matthew Wheatley (SI), David Yarian (SI), and Robyn Green (CC); *Northern California Retina Vitreous Assoc:* Alok Bansal (SI), Edwin Boldrey (SI), Jesus Borrillo (SI), Louis Chang (SI), Sharon Depaz (CC), Andrea Gadda (V), Rahul Khurana (PI), Diana Lam (CC), James Palmer (SI), Olga Sessions (P), Mark Wieland (SI), Amy Dennis (V), Amy Goldstein (P), and Celeste Obando (P); *Orange County Retina Medical Group:* Trisha Ambrocio (CC), Marinel Casiano (CC), Eugene Chang (SI), Sanford Chen (PI), Millie Liu (V), Jessica Lowery (P), John Maggiano (SI), Rajiv Rathod (SI), and Timothy You (SI); *Paducah Retinal Center:* Carl Baker (PI), Tracey Caldwell (CC), Alecia Camp (P), Samantha Kettler (P), Margaret Orr (V), Mary Jill Palmer (V), Ron Tilford (SI), Lynnette Lambert (CC), Tracey Martin (V), and Tana Williams (P); *Palmetto Retina Center:* Lloyd Clark (PI), Rene Griggs (O), David Johnson (SI), Stephanie Karuza (CC), Peggy Miller (CC), Tiffany Ogbuewu (V), John Payne (SI), Robin Spivey (P), Ashley Studebaker (P), Deborah Watts (O), John Wells (SI), Ruth Bearden (O), Pamela Darlington (O), Tiffany Swinford (V), Mallie Taylor (CC), and Amanda Wilson (O); *Palmetto Retina Center, LLC Florence:* W. Lloyd Clark (SI), Ashley Floyd (V), Cassandra Garrison (CC), David Johnson (SI), Crystal Parker (V), John Payne (PI), Erin Poston (P), Kristin Welch (CC), John Wells (SI), Tyler Huggins (P), and Ashley Williams (P); *Retina & Vitreous of Texas:* Diana Abdelgani (CC), Colin Blank (P), Emmanuel Chang (SI), Deborah Fredrickson (V), Joseph Khawly (PI), Desiree Lopez (P), Donald Lowd (P), Jason Muniz (P), Erica Pineda (V), Hassan Rahman (SI), Lorena Martinez (V), Pam Miller (CC), and Arthur Willis (SI); *Retina Associates:* Ivan Batlle (PI), Karla Batlle (CC), Kiersten Bruce (V), Lexie Manning (CC), Samantha Perkins (P), Katherine Pippin (P), Frank Yeager (P), Ryan Christensen (SI), Blake Cooper (SI), David Dyer (SI), Gregory Fox (SI), Ravi Singh (SI), and Beatty Suiter (SI); *Retina Associates of Cleveland Inc:* Brett Amonett (CC), Cindy Boehm (P), Joseph Coney (SI), Jim Coyne (P), Tia Drugan (V), John DuBois (P), Gregg Greanoff (P), Mary Ilc (V), Aimee Kenska (P), Elizabeth McNamara (P), David Miller (SI), Michael Novak (SI), Llewelyn Rao (SI), Susan Rath (CC), Cecelia Rykena (V), Jerome Schartman (SI), Lawrence Singerman (PI), Vivian Tanner (CC), and Veronica Smith (CC); *Retina Associates of Kentucky:* Michelle Buck (P), Vernie Daniels (CC), Diana Holcomb (CC), Ricky Isernhagen (SI), John Kitchens (SI), Thomas Stone (SI), Jeanne Van Arsdall (V), Brenda VanHoose (V), William Wood (PI), Andrew Moshfeghi (PI), and Ed Slade (P); *Retina Associates of Western New York:* Mindy Burgess (V), Brian Connolly (SI), Mary Jo Doran (CC), Ernest Guillet (SI), Edward Hall (PI), Anne Reynard (V), Steven Rose (SI), Joseph Territo (P), Margaret Whelehan (P), Meg Yagoda (CC); *Retina Centers:* Dyonne Bachmann (V), Sally Brandon (CC), Crystal Duncan (P), Stacey Halper (P), Amy Kan (CC), Shree Kurup (SI), George Novalis (SI), Ryan Wong (SI), Martin Worrall (PI), Kassandra Burdick (V), Jennifer Carreon (CC), Susana Flores (V), Henry Hudson (SI), Claudia Mendoza (P), Brianna Morris (V), and Patricia Wilkins (CC); *Retina Consultants of Houston PA:* Belinda Almanza (V), Matthew Benz (SI), David Brown (PI), JoLene Carranza (CC), Eric Chen (SI), Richard Fish (SI), Amy Hernandez (CC), Eric Kegley (P), Rosa Kim (SI), Nubia Landaverde (CC), James Major (SI), Beau Richter (P), Amy Schefler (SI), Robert Smith (O), Veronica Sneed (V), Tien Wong (SI), Charles Wykoff (SI), Meredith Berry (CC), Brenda Dives (V), Lauren Epp (CC), Nikki Franks (CC), Debbie Gillaspia (CC), Elizabeth Quellar (V), Tressa Royse (V), Cary Stoever (P), and Sushma Vance (SI); *Retina Consultants of Nevada:* Kelly Anderson (CC), Jennie Fabro (V), Joe Galura (P), Nikki Garcia (V), Leide Gomes (V), Rodney Hollifield (SI), Roy Loo (SI), Janet Marchese (CC), Ifeyinwa Okeke (V), Matthew Pezda (SI), Treseelyn Spencer (P), Allen Thach (PI), Jason Wickens (SI), Meher Yepremyan (SI), Thomas Arambula (P), Marcy Henry (P), Javier Rendorio (P), and Irene Voo (SI); *Retina Group of Florida:* Scott Anagnoste (SI), Lawrence Halperin (SI), Monica Hamlin (CC), Ann Marie Lamb (V), Angelia Mannarelli (P), Jamie Mariano (V), Krista Rosenberg (SI), Barry Taney (SI), W. Scott Thompson (SI), Eduardo Uchiyama (SI), Rita Veksler (P), Mario del Cid (PI), Jaclyn Brady-Pyka (CC), Mandeep Dhalla (SI), and Linda O'Koren (V); *Retina Group of New England:* Heather Casey (V), Nauman Chaudhry (PI), Justin Cocilo (P), Alison Fontecchio (V), and Emma German (CC); *Retina Northwest:* Peggy Charpentier (V), Michele Connaughton (P), Richard Dreyer (SI), Stephanie Ho (V), Christine Hoerner (P), Marcia Kopfer (CC), Michael Lee (SI), Joseph Logan (P), Colin Ma (SI), Apurva Patel (SI), Mark Peters (PI), Paul Tlucek (SI), Stephen Hobbs (CC), and Amanda Milliron (V); *Retina Research Institute of Texas:* Leah Adams (V), Cecilia Escamilla (O), Geneva Espinoza (P), Kristen Garcia (CC), Grant Janzen (SI), Seong Lee (SI), Priscilla Moreno (V), Sunil Patel (PI), Cindy Petty (CC), Gary Rickert (P), Deisy Villarreal (CC), and Eric Zavaleta (SI); *Retina Vitreous Consultants:* Robert Bergren (PI), Paul Conrad (SI), Dawn DiPerna (P), Amanda Fec (P), Keith McBroom (P), Lori Merlotti (CC), Karl Olsen (SI), David Steinberg (P), Lois Stepansky (V), Avni Vyas (SI), Julie Walter (V), Jennifer Chamberlin (CC), Bernard Doft (SI), James Eadie (SI), Moryssa Grossman (P), Pamela Rath (SI), andChristina Schultz (V); *Retina Vitreous Surgeons of CNY PC:* Jamin Brown (SI), Stefanie DeSantis (P), Teresa Deforge (P), Christine Dorr (CC), G. Robert Hampton (PI), Lynn Kwasniewski (V), Michelle Manley (V), Nicole Robarge (P), Kevin Rosenberg (SI), Rajeev Seth (SI), Laurie Sienkiewycz (CC), Brandi Bellows (V), Viki Gabris (CC), Cindy Grinnell (CC), Christy Hall (CC), and Peter Hay (P); *Retinal and Ophthalmic Consultants PC:* Kim Clark (P), Brett Foxman (SI), Scott Foxman (SI), Natalie Mahan (CC), Thomas Margolis (PI), Chastity Mendez (V), Felisha Morales (P), Suzie Post (P), Julie Rosenthal (SI), and Qahdirah Torres (V); *Retinal Consultants Medical Group:* Margaret Chang (SI), Robert Equi (SI), Danny Lopez (P), Erin Nickerman (CC), Arun Patel (SI), Joel Pearlman (PI), Nanette Podesta (CC), J. Brian Reed (SI), David Telander (SI), Tony Tsai (SI), Brooke Waller (V), Robert Wendel (SI), and Kimberlee Wong (V); *Retinal Consultants of AZ:* Mark Barakat (SI), Dayna Bartoli (P), Pravin Dugel (SI), David Goldenberg (SI), L. Milad Haak (SI), Valerie Hoback (CC), Sujit Itty (SI), Karim Jamal (SI), Norma Jimenez (P), Derek Kunimoto (PI), Ashleigh Levison (SI), Georgina Lopez-Wood (CC), John Martin (P), Sachin Mehta (SI), Neal Palejwala (SI), Edward Quinlan (SI), Nohemi Ramirez (V), Ignacio Torres (P), Diania Joy Wilson (CC), Sandra Arenas (V), and Elena Marcos (V); *Retinal Consultants of San Antonio:* Jaynee Baker (CC), Moises Chica (SI), Sarah Holy (SI), Lita Kirschbaum (CC), Richard Gary Lane (SI), Calvin Mein (PI), Brenda Nakoski (P), C. Sean Wienecke (P), Elaine Castillo (V), and Tori Moore (V); *Sabates Eye Centers:* Michael Cassell (PI), Yin Chen (CC), Gary Gallimore (P), Abraham Poulose (SI), Nelson Sabates (SI), Kelli Burge (V), Heather Elliott (P), Kristen Kietzman (CC), Nancy Kunjukunju (SI), Jeanne Niblock (V), Felix Sabates (PI), and April Snider (V); *Sarasota Retina Institute:* Melvin Chen (PI), Evelyn Inlow (CC), Peggy Jelemensky (CC), Marc Levy (SI), Rosa Miller (V), Tara Raphael (V), and Mark Sneath (P); *Scheie Eye Institute:* Jim Berger (P), Alexander Brucker (PI), Dominique Caggiano (CC), Judy Chen (CC), Sheri Drossner (V), Joan DuPont (CC), Benjamin Kim (SI), Sara Morales (P), Jessica Morgan (SI), Beth Serpentine (P), Brian VanderBeek (SI), and Armin Farazdaghi (V); *Southeast Retina Center:* Thomas Bailey (V), Ken Ivey (P), Dennis Marcus (PI), Siobhan Ortiz (CC), Harinderjit Singh (SI), Kim Tuey (CC), Michele Woodward (CC), Amina Farooq (CC), and Allison Foster (CC); *Southeastern Retina Associates PC:* Joseph Googe (SI), Raul Lince (P), Lisa Lovelady (CC), Tod McMillan (SI), Steve Morris (CC), Sarah Oelrich (P), Kristina Oliver (CC), Julie Rauen (V), R. Keith Shuler (PI), Justin Walsh (V), Patricia Coppola (V), and Jerry Whetstone (P); *Southern California Desert Retina:* Clement Chan (PI), Tiana Gonzales (CC), Kenneth Huff (P), Maziar Lalezary

(SI), Steven Lin (SI), Lenise Myers (V), and Kim Walther (CC); *Tennessee Retina:* Everton Arrindell (SI), Carl Awh (PI), Amanda Briley (V), Brandon Busbee (SI), Talisha Campbell (V), Narey Cooper (CC), Tara Farmer (P), Sarah Hines (CC), Kenneth Moffat (SI), Stephanie Morrow (P), Franco Recchia (SI), David Reichstein (SI), Eric Schneider (SI), Natalie Schwebel (V), Shari Scott (V), Peter Sonkin (SI), Caleb Walker (P), R. Trent Wallace (SI), Julia Wray (P), Michelle Bowers (P), Amanda Ferrell (CC), Casi Fleischman (P), Paul (Dustin) Freeman (P), Kris Rose (V), Gina Smith (CC), Cora Sonnier (CC), Kyra Stepney (V), Katlyne Thompson (V), and Susan Wiser (CC); *Texas Retina Associates-Arlington:* Melissa Alva (CC), Michelle Curry (CC), Bob Boleman (P), David Callanan (SI), Jodi Creighton (V), Chris Dock (P), Sandy Lash (V), Wayne Solley (SI), and Patrick Williams (PI); *Texas Retina Associates-Dallas:* Rajiv Anand (SI), Sally Arceneaux (V), Daniel Carpintero (P), Deborah Chong (SI), Lori Coors (SI), Karl Csaky (SI), Karen Duignan (CC), Gary Fish (PI), Dwain Fuller (SI), Nick Hesse (P), Diana Jaramillo (CC), Michael Mackens (P), Samantha Marin (P), Brenda Sanchez (V), Tina Stanley (P), Robert Wang (SI); *The Ohio State University:* William Bloom (CC), PJ Fish (P), Alan Letson (PI), Barbara Mihalik (V), Matthew Ohr (SI), Jerilyn Perry (V), Jill Salerno (CC); *The Retina Group of Washington:* Daniel Berinstein (PI), Justin Davis (P), Irene Fanous (CC), Richard Garfinkel (SI), Jessica Iglesias (O), Thomas Johnson (SI), Molly Kalisch (V), Michael Lai (SI), Myradis Marin-Quinones (O), Alexander Melamud (SI), Bryan Murphy (P), Steve Rauch (P), Gayatri Reilly (SI), Maya Talatory (CC), Danielle Walker (V), Tanya Alexander-Snowden (CC), Sekou Alou (P), Thomas Blondo (V), Jennifer Camia (V), Ashley Chancey (CC), Clete Clark (O), William Deegan (SI), Vanessa Denny (V), Bryan Gallerson (V), Smitha Gopakumar (CC), Sarah Hanselman (V), Yury Iraheta (V), Andrew King (V), Robert Murphy (SI), Stacie Orencia (P), Michael Osman (SI), Jennifer Phosaksee (V), Pamela Renteria (V), Michael Rivers (SI), Reginald Sanders (SI), Nicole Schorer (V), Mona Shah (V), Manali Shah (CC), Tiffany Tam (V), and Manfred von Fricken (SI); *The Retina Institute:* Kevin Blinder (PI), Lynda Boyd (V), Erika Hoehn (CC), Ginny Nobel (CC), Kelly Pepple (V), Brooke Pulliam (V), Diana Reardon (V), Gaurav Shah (SI), Bradley Smith (SI), Maria Stuart (V), Rhonda Weeks (CC), Jarrod Wehmeier (P), Tim Wright (P), and Stephanie Guevara (V); *The Retina Research Center:* Brian Berger (PI), Saradha Chexal (SI), Boris Corak (V), Ivana Gunderson (V), Kimberly Hosein (CC), Chirag Jhaveri (SI), Ginger Manhart (CC), Yong Ren (P), Tina Seidu (CC), Chandler Stovall (P), Chelsey Bravenec (V), Brandon Nguyen (V), and Ryan Reid (V); *TLC Eyecare & Laser Centers:* Kristi Ballard (P), Ashley Blaisdell (P), Carmelina Gordon (PI), Heather Hill (V), Susan Partridge (V), Jennifer Wireman (CC), April Clay (CC), Shellie Fuentes (CC), Stephanie Gillispie (CC), Hailey Litzer (P), Elaine Lok (P), Bonnie Minier (CC), Tiffany Westgate (P), and Celia Wohlscheid (CC); *University of California-Davis:* Ashley Bryant (PH), Dominique Cargill (PH), Karishma Chandra (P), Sashi Deo (P), Lawrence Morse (SI), Ala Moshiri (SI), Susanna Park (PI), Ellen Redenbo (P), Marisa Salvador (V), Nadir Sarwary (PH), Igor Slabosnitskiy (P), Peter Trovitch (PH), Jessica Turner (PH), Cindy Wallace (CC), Marie Andrada (PH), and Katrina Imson (CC); *University of California-San Francisco:* Jacque Duncan (PI), Don Eubank (CC), Scott Fields (PH), Betty Hom (P), Mary Lew (V), Andrew Light (P), Arshia Mian (CC), and Jay Stewart (SI); *University of Florida:* Kakarla Chalam (PI), Ashley Cowart (V), Sandeep Grover (SI), Shailesh Gupta (SI), Shamim Haji (V), Ghulam Hamdani (CC), Sherri Hart (P), and Kumar Sambhav (CC); *University of Kentucky:* Miroslava Aprelkov (V), Claire Fraser (SI), Mike Hanson (P), Eric Higgins (SI), Mark Kleinman (SI), Deborah McDonald (P), P. Andrew Pearson (PI), Susan Phillips (O), Michele Reg (CC), Stephen Sitzlar (PH), Lakisha Smith (V), Peter Blackburn (SI), and Lyudmila Pigulko (V); *University of Rochester Flaum Eye Institute:* Mina Chung (PI), Gary Gagarinas (V), Rachel Hollar (P), Lisa Latchney (CC), Brittany Richardson (P), Andrea Czubinski (V), David DiLoreto (SI), Tanya Forbes (CC), and Taylor Pannell (P); *University of Wisconsin:* Angie Adler (CC), Michael Altaweel (PI), Barbara Blodi (SI), Kristine Dietzman (V), Justin Gottlieb (SI), Michael Ip (SI), Denise Krolnik (P), Jennie Perry-Raymond (CC), Sandie Reed (P), Christopher Smith (V), and John Peterson (P); *UNMC Truhlsen Eye Institute:* Lola Berg (P), Kristi Miller (CC), Maria Blaiotta (V), Diana Do (SI), Lisa Greer (CC), Fayez Jawed (V), Donna Neely (P), and Quan Nguyen (SI); *UW 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), and Bao-Chau Vo (O); *Valley Retina Institute:* Rohit Adyanthaya (SI), Monica Cantu (V), Santos Garza (P), Victor Gonzalez (PI), Jessica Muniz (P), Nehal Patel (SI), Yesenia Salinas (CC), Nancy Salinas (CC), Juan Santiago (SI), Lazaro Aguero (P), Deyla Anaya (CC), Roberto Diaz-Rohena (SI), Hector Jasso (P), Karina Miranda (V), Rachel Rodriguez (V), Jessica Rodriguez (CC), Kethsaly Salinas (CC), and Lissete Villanueva (CC); *Vanderbilt Eye Institute:* Tony Adkins (P), Milam Brantley (PI), Rocky Munn (P), Scott Ruark (CC), Richard Skellie (P), Anita Agarwal (SI), Joshua Carlson (SI), Edward Cherney (SI), Anthony Daniels (SI), Gowtham Jonna (SI), Stephen Kim (SI), Janice Law (SI), Sandy Owings (CC), Shriji Patel (SI), Paul Sternberg (SI), and Maryann Taylor-Ward (V); *Virginia Eye Institute:* Lea Anderlini (V), Mark Bartlett (P), James Combs (SI), Eleanore Ebert (SI), George Sanborn (SI), Michael Hughes (P), Byron Ladd (PI), Lynn Roderick (P), Karen Sullivan (CC), Melissa Vaughan (CC), and Kristin McKeever (V); *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), and Craig Wells (SI); and *Vitreoretinal Surgery:* Steven Bennett (SI), Tamra Bogolin (V), Holly Cheshier (P), John Davies (SI), Sundeep Dev (PI), 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), Joy Royle (V), Trenise Steele (P), Jessica Tonsfeldt (P), David Williams (SI), Carmen Chan-Tram (CC), Julianne Enloe (CC), Peggy Gilbert (V), and Carol Rogers (V).

Meeting Presentation: This study was presented at the Association for Research in Vision and Ophthalmology Annual Meeting; May 9, 2017; Baltimore, Maryland.

REFERENCES

1. Scott IU, VanVeldhuisen PC, Ip MS, et al; SCORE2 Investigator Group. Effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion: the SCORE2 randomized clinical trial [published online May 9, 2017]. *JAMA*. doi:10.1001/JAMA.2017.4568

2. Scott IU, VanVeldhuisen PC, Ip MS, et al; SCORE2 Investigator Group. SCORE2 report 2: study design and baseline characteristics. *Ophthalmology*. 2017;124(2):245-256.

3. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.

4. Beck RW, Moke PS, Turpin AH, et al. A computerized method of visual acuity testing: adaptation of the early treatment of diabetic retinopathy study testing protocol. *Am J Ophthalmol*. 2003;135(2):194-205.

5. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 1988;75:800-802.

6. Scott IU, VanVeldhuisen PC, Oden NL, et al; Standard Care versus Corticosteroid for Retinal Vein Occlusion Study Investigator Group. Baseline predictors of visual acuity and retinal thickness outcomes in patients with retinal vein occlusion: Standard Care Versus Corticosteroid for Retinal Vein Occlusion Study report 10. *Ophthalmology*. 2011;118:345-352.

7. Central Vein Occlusion Study Group. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion: the Central Vein Occlusion Study Group M report. *Ophthalmology*. 1995;102(10):1425-1433.

8. Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor trap-eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS Study. *Ophthalmology*. 2012;119(5):1024-1032.

9. Wells JA, Glassman AR, Ayala AR, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372(13):1193-1203.

10. Wells JA, Glassman AR, Ayala AR, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology*. 2016;123(6):1351-1359.

11. Wells JA, Glassman AR, Jampol LM, et al; Diabetic Retinopathy Clinical Research Network. Association of baseline visual acuity and retinal thickness with 1-year efficacy of aflibercept, bevacizumab, and ranibizumab for diabetic macular edema. *JAMA Ophthalmol*. 2016;134(2):127-134.

12. Bressler SB, Qin H, Beck RW, et al; Diabetic Retinopathy Clinical Research Network. Factors associated with changes in visual acuity and central subfield thickness at 1 year after treatment for diabetic macular edema with ranibizumab. *Arch Ophthalmol*. 2012;130(9):1153-1161.

13. Stewart MW. Aflibercept (VEGF trap-eye): the newest anti-VEGF drug. *Br J Ophthalmol*. 2012;96(9):1157-1158.

14. Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ; CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364(20):1897-1908.

15. Sokal RR, Rohlf FJ. *Biometry: The Principles and Practice of Statistics in Biological Research*. 3rd ed. New York, NY: WH Freeman; 1995:570-571.

16. Holz FG, Roider J, Ogura Y, et al. VEGF trap-eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO Study. *Br J Ophthalmol*. 2013;97(3):278-284.

17. The Eye Disease Case-Control Study Group. Risk factors for central retinal vein occlusion. *Arch Ophthalmol*. 1996;114(5):545-554.

18. The Eye Disease Case-control Study Group. Risk factors for branch retinal vein occlusion. *Am J Ophthalmol*. 1993;116(3):286-296.

19. Sperduto RD, Hiller R, Chew E, et al; The Eye Disease Case-Control Study Group. Risk factors for hemiretinal vein occlusion: comparison with risk factors for central and branch retinal vein occlusion: the eye disease case-control study. *Ophthalmology*. 1998;105(5):765-771.

20. Elman MJ, Bhatt AK, Quinlan PM, Enger C. The risk for systemic vascular diseases and mortality in patients with central retinal vein occlusion. *Ophthalmology*. 1990;97(11):1543-1548.

21. Appiah AP, Trempe CL. Risk factors associated with branch vs central retinal vein occlusion. *Ann Ophthalmol*. 1989;21(4):153-155, 157.

22. Appiah AP, Greenidge KC. Factors associated with retinal-vein occlusion in Hispanics. *Ann Ophthalmol*. 1987;19(8):307-309, 312.

23. Rath EZ, Frank RN, Shin DH, Kim C. Risk factors for retinal vein occlusions: a case-control study. *Ophthalmology*. 1992;99(4):509-514.

24. Johnston RL, Brucker AJ, Steinmann W, Hoffman ME, Holmes JH. Risk factors of branch retinal vein occlusion. *Arch Ophthalmol*. 1985;103(12):1831-1832.

25. McGrath MA, Wechsler F, Hunyor AB, Penny R. Systemic factors contributory to retinal vein occlusion. *Arch Intern Med*. 1978;138(2):216-220.

26. Ip MS, Oden NL, Scott IU, et al; SCORE Study Investigator Group. SCORE Study report 3: study design and baseline characteristics. *Ophthalmology*. 2009;116(9):1770-1777.e1.

Invited Commentary

Comparing Anti–Vascular Endothelial Growth Factor Therapies for Central Retinal Vein Occlusion

Jennifer K. Sun, MD, MPH

Central retinal vein occlusion (CRVO) is a common problem encountered in general ophthalmology and retina clinics worldwide. Macular edema can result from abnormal vascular permeability due to CRVO and lead to substantial vision loss in some patients if left untreated. Over the last decade, multiple clinical trials have established the efficacy of intravitreous anti–vascular endothelial growth factor (VEGF) therapy for improving visual acuity with CRVO. However, it has been largely unclear which, if any, of the available anti-VEGF agents provides the best functional or anatomic outcomes. Given substantial differences in cost and availability between anti-VEGF drugs, a rigorous comparison of efficacy and safety among the most widely used agents has major implications for both individual patient treatment decisions and public health policy.

Related article page 639

Related article at jama.com

To address this issue, the Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2) trial, through funding from the National Eye Institute, randomly assigned patients with macular edema from CRVO or hemi-RVO to monthly treatment with either aflibercept or bevacizumab. The primary results from this study are reported in *JAMA*.[1] At 6 months, the primary outcome of mean visual acuity letter score improvement from baseline was similar in the 2 groups among 362 study participants: 18.9 in the aflibercept group and 18.6 in the bevacizumab group (equivalent to a mean improvement of slightly less than 4 Snellen lines in each group). The lower bound of the confidence interval for the treatment group difference was less than the prespecified noninferiority margin of 5 letters. Thus, one can conclude from these results that average visual acuity outcomes at 6 months are not worse in eyes treated with bevacizumab compared with aflibercept for macular edema from CRVO. The proportions of eyes with 15 or more letter visual acuity gain were similar between the treatment groups (aflibercept, 65% vs bevacizumab, 61%), as were the percentages of eyes that achieved visual acuity of approximately 20/40 or better (aflibercept, 58% vs bevacizumab, 57%). Interestingly, although the visual outcomes were equivalent between aflibercept- and bevacizumab-treated eyes, retinal thickness outcomes were better with aflibercept, with more eyes attaining resolution of macular edema after treatment with aflibercept as compared with bevacizumab (54% vs 29%). No major differences were found in ocular or systemic adverse events between the treatment groups.

The SCORE2 report is encouraging in that it suggests that the lower cost and presumably most globally used anti-VEGF agent, bevacizumab, can be used to provide similar visual acuity gains to those obtained with aflibercept through at least 6 months in eyes with macular edema from CRVO. It should be noted that bevacizumab is not approved for this indication by the US Food and Drug Administration. Furthermore, there are clinical questions that remain after the SCORE2 primary results. These include whether alternate dosing regimens or use of commercially available repackaged or compounded bevacizumab will impact patient outcomes and whether these findings will generalize to eyes with branch RVO. Also critical is the question of whether equivalent visual acuity results in the bevacizumab vs aflibercept groups at 6 months will be maintained as patients continue in their randomized treatment assignments over longer-term follow-up. The fact that eyes in the SCORE2 bevacizumab group were more likely to have persistent macular edema at 6 months suggests the possibility that there could be worse visual outcomes in the bevacizumab vs the aflibercept group as these eyes are followed up for a longer period.