SCORE2 Report 13: Intraretinal Hemorrhage Changes in Eyes With Central or Hemiretinal Vein Occlusion Managed With Aflibercept, Bevacizumab or Observation. Secondary Analysis of the SCORE and SCORE2 Clinical Trials

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• PURPOSE: To investigate the relationship between intraretinal macular hemorrhage and visual acuity outcomes in eyes with central retinal vein occlusion or hemiretinal vein occlusion managed with aflibercept, bevacizumab, or observation.

• DESIGN: Retrospective analysis of data from 2 randomized clinical trials.

• METHODS: A total of 362 participants were randomized in the Study of Comparative Treatments for Retinal Vein Occlusion 2, and 88 participants randomized to observation in the Standard Care vs Corticosteroid in Retinal Vein Occlusion Study. Participants received monthly intravitreal aflibercept or bevacizumab through month 6 or observation through month 8. The main outcome was visual acuity letter score (VALS).

• RESULTS: Reduced area of hemorrhage by month 6 was observed in 70.7% (116 of 164) of aflibercept-treated eyes, 63.8% (104 of 163) of bevacizumab-treated eyes, and 42.2% (27 of 64) of observation eyes by month 8 ($P < .01$). Relative to eyes with hemorrhage during follow-up, aflibercept-treated eyes without hemorrhage at month 6 had a mean VALS improvement of 8.0 (99% confidence interval [CI]: 1.9, 14.2); bevacizumab-treated eyes without hemorrhage at month 6 had a mean VALS improvement of 3.2 (99% CI: −4.6, 11.0); and observation eyes without hemorrhage at month 8 had a mean VALS improvement of 13.5 (99% CI: 0.4, 26.5). At month 6, the presence of hemorrhage and the change in central subfield thickness (CST) were significantly associated with the change in VALS; however, CST was a more important predictor.

• CONCLUSION: Improvement in hemorrhage during follow-up was associated with visual acuity improvements and predicted visual acuity changes beyond what was explained by CST. These findings suggest that intraretinal macular hemorrhage is an important indicator of disease severity in retinal vein occlusion. (Am J Ophthalmol 2021;222:185–193. © 2020 Elsevier Inc. All rights reserved.)

ONE OF THE TYPICAL FEATURES OF RETINAL VEIN occlusion (RVO) is the presence of intraretinal hemorrhages. These hemorrhages are easily visualized during routine examination and traditionally regarded as a feature of the disease process because of vascular congestion and extravasation but are not known to directly impact visual acuity outcomes. In contrast, macular edema is the leading cause of vision loss in patients with RVO and is monitored with optical coherence tomography (OCT). There is substantial evidence that treatment with anti-vascular endothelial growth factor (anti-VEGF) agents can markedly decrease RVO-associated macular edema;[1–5] however, little is known about the effect of anti-VEGF treatment on intraretinal hemorrhage associated with central RVO (CRVO) or hemiretinal vein occlusion (HRVO).

The **S**tudy of **CO**mparative Treatments for **RE**tinal Vein Occlusion 2 (SCORE2), a multicenter randomized trial, demonstrated that after 6 monthly intravitreal injections, bevacizumab was noninferior to aflibercept in terms of mean change from baseline in visual acuity letter score (VALS) in eyes with macular edema associated with nonischemic CRVO or HRVO.[5] At month 6, a significantly higher proportion of eyes in the aflibercept-treated group compared with the bevacizumab-treated group demonstrated complete resolution of macular edema on spectral

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domain OCT (SD-OCT). The predecessor **S**tandard Care vs **CO**rticosteroid for **RE**tinal Vein Occlusion (SCORE) Study demonstrated that a gain in VALS of 15 or more at 12 months is 5 times greater with intravitreal triamcinolone than observation for eyes with vision loss associated with macular edema secondary to CRVO.[6]

This investigation is a retrospective analysis of both the SCORE and SCORE2 clinical trials and had a different goal from the previously published primary outcome reports of the 2 studies.[5,6] In this secondary analysis using both SCORE and SCORE2 datasets, we compare the area of intraretinal macular hemorrhage within the Early Treatment Diabetic Retinopathy Study (ETDRS) grid at month 6 (SCORE2 eyes) or month 8 (SCORE eyes) among aflibercept- and bevacizumab-treated eyes (SCORE2) and observation eyes (SCORE). Further, we examine the relationship between hemorrhage and VALS and central subfield thickness (CST) based on SD-OCT.

METHODS

THE SCORE STUDY AND SCORE2 WERE BOTH RANDOMIZED clinical trials that adhered to the tenets of the Declaration of Helsinki[7] and are registered on http://www.clinicaltrials.gov (identifiers: NCT01969708 and NCT00105027). The SCORE Study and SCORE2 protocols received approval from a site-specific or centralized institutional review board (Advarra, Columbia, Maryland, for SCORE2 and Jaeb Center for Health Research, Tampa, Florida, for the SCORE Study), and written informed consent was obtained from all participants. The SCORE Study and SCORE2 methods have been described in detail.[8,9]

The current report focuses on the 180 SCORE2 participants initially randomized to aflibercept (2.0 mg), the 182 participants initially randomized to bevacizumab (1.25 mg), and the 88 SCORE participants randomized to observation. In SCORE2 at months 0, 6, 12, and 24, data were collected on best-corrected electronic ETDRS (E-ETDRS) VALS, CST assessed by SD-OCT, and eye examinations. Color fundus photographs were also collected at these time points for assessment of intraretinal macular hemorrhage. Certified photographers obtained stereoscopic digital color fundus photographs of the disc and macula in the Study eye. These 30-degree fundus photographs were taken at baseline and at month 6. All images were de-identified in compliance with Health Insurance Portability and Accountability Act regulations before being sent to the Fundus Photograph Reading Center at the University of Wisconsin. Color fundus photograph grading was based on the RVO grading protocol developed during the SCORE Study.[10] Grading of stereoscopic fundus photographs was performed as a single read by a pool of 4 graders; all visits were graded independently with graders masked to treatment assignment. Graders identified retinal hemorrhage if there was an intraretinal or subretinal red lesion ≥150 μm in its longest diameter that was punctate, blot, or linear in appearance. Graders evaluated fundus photographs for the presence and area of intraretinal macular hemorrhage within the ETDRS grid and specified if the presence of the blood involved the central subfield. The grader assessed area of hemorrhage within the grid into one of 4 categories: 0%, 1%-25%, 26%-50%, and >50%. As defined in the SCORE Study protocol, the grade of intraretinal macular hemorrhage included both intraretinal and subretinal hemorrhage. Hemorrhage that was observed to be below the retinal pigment epithelium or anterior to the retina (ie, preretinal or vitreous hemorrhage) was not considered to be intraretinal macular hemorrhage. Poor quality images were graded as "cannot grade." Quality control was evaluated by regrading 5% of the color fundus photographs. Analysis of the regrading exercise showed that there was 100% agreement among graders with regard to the area and location of the blood.

From the SCORE Study, 88 Study participants randomized to observation were integrated into this secondary analysis as a control arm to compare with the SCORE2 aflibercept and bevacizumab arms. In the SCORE-CRVO trial, conducted from 2004 to 2009, participants were randomized to either 1 mg of triamcinolone acetonide, 4 mg of triamcinolone acetonide, or observation.[8] The visit schedule showing when E-ETDRS, OCT scans, and color fundus photographs were performed for the SCORE Study differed from SCORE2, so the month 8 visit from SCORE was used in this analysis to compare with the month 6 visit in SCORE2.

The eligibility criteria matched closely between the SCORE Study and SCORE2, with both having the E-ETDRS VALS inclusion criterion between 19 (approximate Snellen of 20/400) and 73 (approximate Snellen of 20/40) and defining a CRVO as an eye with retinal hemorrhage or other biomicroscopic evidence of RVO (eg, telangiectatic capillary bed) and a dilated venous system (or a previously dilated venous system) in all 4 quadrants. The SCORE Study required a retinal thickness over 250 μm in the central subfield of the OCT topographic map formed by 6 radial scans based on OCT2 or Stratus OCT, whereas SCORE2 eligibility required a CST of at least 300 μm if measured with a Carl Zeiss Meditec Cirrus SD-OCT machine and at least 320 μm if measured with a Heidelberg Spectralis OCT machine. Both studies allowed eyes to be enrolled as early as the time of diagnosis of the macular edema, but eyes were excluded from enrolling in the SCORE Study more than 24 months after diagnosis.

The primary outcomes were changes over time in VALS and CST. Comparisons were exploratory and descriptive, all calculated using SAS version 9.4 (SAS Inc, Cary, North Carolina, USA). Because no hypothesis testing is being done, we limit the number of *P* values presented from statistical tests comparing treatment outcomes and show 99% CI rather than the traditional 95% CI to give an idea of variability and help account for multiple testing.

TABLE 1. Presence at Intraretinal Macular Hemorrhage at Month 0 vs Month 6/8 by Treatment Arm

Area of Intraretinal Macular Hemorrhage at Month 0	SCORE2 Aflibercept					SCORE2 Bevacizumab					SCORE Observation				
	Month 6					Month 6					Month 8				
	0%	1% to <25%	25% to 50%	>50%	Total	0%	1% to <25%	25% to 50%	>50%	Total	0%	1% to <25%	25% to 50%	>50%	Total
0%	7 (4.3%)	1 (0.6%)	0 (0%)	0 (0%)	8 (4.9%)	4 (2.5%)	1 (0.6%)	0 (0%)	0 (0%)	5 (3.1%)	4 (6.3%)	0 (0%)	0 (0%)	0 (0%)	4 (6.3%)
1% to <25%	**46 (28.0%)**	40 (24.4%)	0 (0%)	0 (0%)	86 (52.4%)	**21 (12.9%)**	54 (33.1%)	0 (0%)	0 (0%)	75 (46.0%)	**8 (12.5%)**	27 (42.2%)	1 (1.6%)	1 (1.6%)	37 (57.8%)
25% to 50%	**18 (11.0%)**	**30 (18.3%)**	0 (0%)	0 (0%)	48 (29.3%)	**10 (6.1%)**	**32 (19.6%)**	0 (0%)	0 (0%)	42 (25.8%)	**5 (7.8%)**	**8 (12.5%)**	2 (3.1%)	2 (3.1%)	17 (26.6%)
>50%	**7 (4.3%)**	**13 (7.9%)**	**2 (1.2%)**	0 (0%)	22 (13.4%)	**6 (3.7%)**	**33 (20.2%)**	**2 (1.2%)**	0 (0%)	41 (25.2%)	**0 (0%)**	**4 (6.3%)**	**2 (3.1%)**	0 (0%)	6 (9.4%)
Total	78 (47.6%)	84 (51.2%)	2 (1.2%)	0 (0%)	164 (100%)	41 (25.2%)	120 (73.6%)	2 (1.2%)	0 (0%)	163 (100%)	17 (26.6%)	39 (73.4%)	5 (7.8%)	3 (4.7%)	64 (100%)

SCORE = **S**tudy of **CO**mparative Treatments for **RE**tinal Vein Occlusion.
Cells in bold show an improvement in follow-up over baseline.

RESULTS

OF 362 RANDOMIZED SCORE2 PARTICIPANTS (MEAN [STANdard deviation—SD] age, 69 [12] years; 157 [43.4%] women; mean [SD] VALS at baseline, 50.3 [15.2] [approximate Snellen VA mean of 20/100]; mean CST based on SD-OCT of 666 [224] μm), 360 (99.4%) had a fundus photograph that was graded for hemorrhage by the Reading Center and 340 (93.9%) had a fundus photograph graded at month 6. Of the 88 SCORE-CRVO trial participants randomized to observation (mean [SD] age, 69 [13] years; 40 [45.4%] women; mean [SD] VALS at baseline, 52.1 [13.1] [approximate Snellen VA mean of 20/100]; mean CST based on OCT of 605 [153] μm time-domain OCT), 83 (94.3%) had fundus images graded for hemorrhage by the Reading Center and 67 (76.1%) had fundus images graded at month 8.

• **ASSOCIATION OF TREATMENT WITH THE PRESENCE OF INTRARETINAL MACULAR HEMORRHAGE:** At baseline, 95.0% (171 of 180 gradable images) of aflibercept participants, 97.2% (174 of 179) of bevacizumab participants, and 95.1% (78 of 82) of observation participants had hemorrhage within the macula. Fewer eyes in the aflibercept group (67.2%; 121 of 180) had baseline hemorrhage that involved the central subfield compared with the bevacizumab group (79.3%; 142 of 179) and the observation group (87.8%; 72 of 82), whereas the remainder of participants had hemorrhage outside the central subfield. By month 6, the presence of hemorrhage decreased to 52.4% (86 of 164) of Study eyes having hemorrhage present either outside or involving the central subfield in the aflibercept group compared with 74.4% (122 of 164) of bevacizumab eyes. For observation eyes, 70.8% (46 of 65) at month 8 had hemorrhage present either outside or involving the central subfield (Supplemental Table 1).

Relative to baseline, 70.7% (116 of 164) of aflibercept eyes had improvement in the area of hemorrhage at month 6 (Table 1) compared with 63.8% (104 of 163) of bevacizumab eyes and 42.2% (27 of 64) of the SCORE observation eyes ($P < .01$). Figure 1 shows the number of steps changed from baseline to month 6 (eg, 1-step improvement would be from an area 25%-50% within the grid at baseline to 1% to <25% at month 6). Those with monthly treatment of aflibercept or bevacizumab have more eyes with improvement at month 6 than observation eyes at month 8 with 48%, 19%, and 4% having a 1-, 2-, or 3-step improvement over baseline in hemorrhage in the aflibercept-treated group, respectively, compared with 34%, 27%, and 4% in the bevacizumab-treated group and 28%, 14%, and 0% in the observation group.

• **ASSOCIATION OF INTRARETINAL MACULAR HEMORRHAGE WITH VISUAL ACUITY OUTCOMES:** Aflibercept-treated eyes without intraretinal macular hemorrhage at month 6 had a mean improvement from baseline in

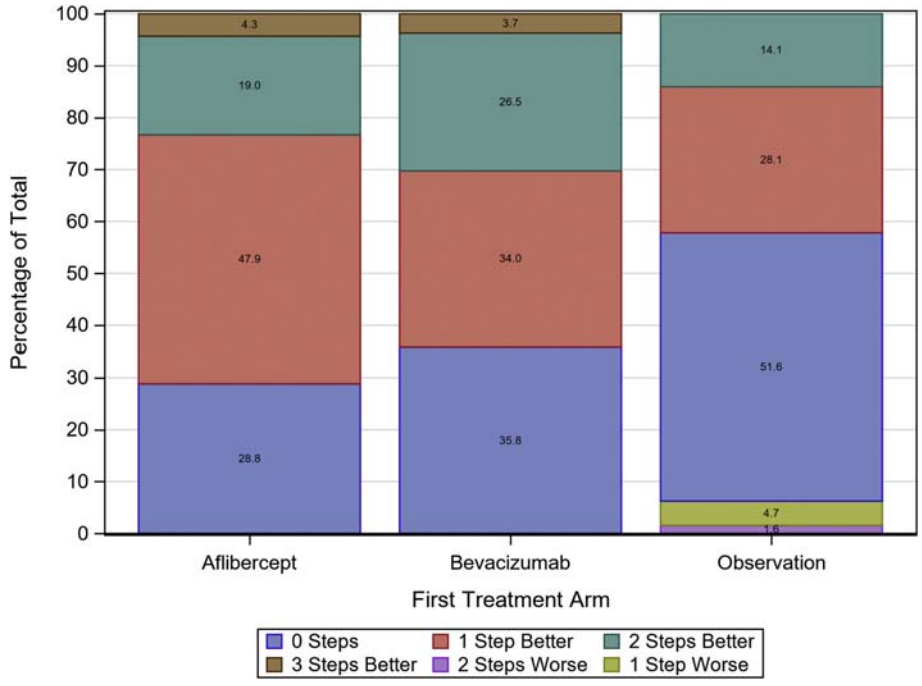

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FIGURE 1. Shift in number of steps between baseline and month 6 in the area of intraretinal macular hemorrhage.

VALS of 23.1 compared with 15.1 in those with hemorrhage, showing a mean VALS benefit of 8.0 (99% CI: 1.9, 14.2) relative to eyes without hemorrhage (Table 2). A smaller VALS difference of 3.2 (99% CI: −4.6, 11.0) was noted in the bevacizumab-treated group, with those without hemorrhage at month 6 having a mean improvement in VALS of 21.1 compared with 17.9. In the SCORE observation arm, despite an overall worsening of visual acuity from baseline to month 8, the trend of better visual acuity was also noted in eyes without hemorrhage at month 8 (mean change from baseline in VALS of −2.8) compared with those with hemorrhage (mean = −16.3), with a mean difference in VALS of 13.5 (99% CI: 0.4, 26.5) favoring observation eyes without hemorrhage at month 8. This same relationship between hemorrhage within the grid and visual acuity outcomes was also observed when examining the outcome of change in area of hemorrhage between baseline and month 6 (SCORE2) or month 8 (SCORE) (Table 2).

• **ASSOCIATION OF INTRARETINAL MACULAR HEMORRHAGE WITH SD-OCT CST:** No association was noted between the presence of intraretinal macular hemorrhage at month 6 and the change from baseline in CST when comparing mean differences from baseline in CST between the aflibercept and bevacizumab groups (Supplemental Table 2). However, aflibercept-treated eyes had a mean improvement in CST of −465.9 μm from baseline in those eyes with lesser area of hemorrhage at month 6 over baseline compared with −329.2 μm for those with the same or greater area of hemorrhage, showing a benefit of −136.7 μm (99% CI: −241.3, −32.1) to eyes with an improvement in hemorrhage. Similar findings were noted in bevacizumab-treated eyes, where there was a benefit of −111.5 μm (99% CI: −218.5, −4.5) based on a mean improvement in CST of −428.8 μm over baseline in those that had hemorrhage improvement at month 6 compared with −317.3 μm for those with no improvement in hemorrhage at month 6. For eyes in the SCORE observation arm, no trends are apparent when examining the change from baseline to month 8 in whether there was improvement or no improvement in area of hemorrhage (Supplemental Table 2).

• **ANALYSIS EXAMINING ASSOCIATION OF VISUAL ACUITY WITH SD-OCT AND INTRARETINAL MACULAR HEMORRHAGE TOGETHER:** To further investigate the relative importance of SD-OCT CST and intraretinal macular hemorrhage status on visual acuity, 3 statistical models were fit to the outcome of change in VALS from baseline to month 6 (Table 3). Model 1 included both CST and hemorrhage, whereas models 2 and 3 each included only one of these factors. Model 1 shows that both change from baseline to month 6 in CST and hemorrhage presence at month 6 are associated with the change in VALS from baseline to month 6. Table 3 also shows R^2, which gives the proportion of variance of VALS that is explained by the regression model. Although none of the regression models is extremely successful at predicting VALS, model 1 ($R^2 = 0.16$) is considerably better than model 3 ($R^2 = 0.03$), but only slightly better than model 2 ($R^2 = 0.13$). As all the betas in Table 3 are significant, this suggests

TABLE 2. Visual Acuity Outcomes by Month 6/8 Presence of and Change in Intraretinal Macular Hemorrhage and Treatment Arm

	Intraretinal Macular Hemorrhage Status Within the Grid at Month 6 (SCORE2) or Month 8 (SCORE)						Change in Area of Intraretinal Macular Hemorrhage Within the Grid from Baseline to Month 6 (SCORE2) or Month 8 (SCORE)						
							Mean Change From Baseline in Visual Acuity Letter Score						
	Intraretinal Macular Hemorrhage not Present in Grid			Intraretinal Macular Hemorrhage Present in Grid				Intraretinal Macular Hemorrhage Area Improved in Grid			Intraretinal Macular Hemorrhage Area not Improved in Grid			
Treatment Arm	N	Mean	SD	N	Mean	SD	Difference[a] in Mean Visual Acuity Letter Score (With 99% Confidence Interval)	N	Mean	SD	N	Mean	SD	Difference[b] in Mean Visual Acuity Letter Score (With 99% Confidence Interval)
SCORE2 Aflibercept	78	23.1	14.6	85	15.1	15.3	8.0 (1.9, 14.2)	115	21.1	16.7	48	13.7	10.3	7.4 (0.6, 14.2)
SCORE2 Bevacizumab	41	21.1	18.6	122	17.9	15.8	3.2 (−4.6, 11.0)	104	20.5	17.8	59	15.4	13.6	5.1 (−1.9, 12.0)
SCORE Observation	17	−2.8	16.7	46	−16.3	17.5	13.5 (0.4, 26.5)	27	−9.4	15.8	36	−15.0	19.7	5.6 (−6.7, 17.8)

SCORE = **S**tudy of **CO**mparative Treatments for **RE**tinal Vein Occlusion.

[a]Intraretinal macular hemorrhage not present in the grid minus intraretinal macular hemorrhage present in the grid.

[b]Intraretinal macular hemorrhage area improved in the grid minus intraretinal macular hemorrhage area not improved in the grid. Improved was defined as less area of hemorrhage in the grid at the outcome visit and not improved was either the same area or greater area in hemorrhage in the grid at the outcome visit.

that the change from baseline to month 6 in CST is more important than hemorrhage presence at month 6 when predicting the change from baseline in VALS at month 6. To interpret the beta coefficients in model 1 including both factors, after controlling for hemorrhage, there is an estimated mean decrease of 2.3 in VALS between baseline and month 6 for every increase in 100 μm in CST between baseline and month 6 ($P < .0001$). Those with hemorrhage at month 6 have, on average, a VALS change from baseline to month 6 of 5.6 lower than those with no hemorrhage at month 6, after adjusting for CST changes ($P = .0012$).

• **RAPIDITY OF CLEARANCE OF INTRARETINAL MACULAR HEMORRHAGE:** To determine if early clearance or improvement of intraretinal macular hemorrhage affects visual outcomes at later follow-up visits, SCORE2 eyes were categorized from the 6-month visit as hemorrhage absent, present at month 6 but improved over baseline, or present at month 6 with no improvement over baseline. Eyes with absent or improved hemorrhage had better mean VALS at month 6 of 23.4 and 18.3 letters, respectively, compared with 14.8 for eyes with unchanged or worsening hemorrhage at month 6. Figure 2 examines mean changes in VALS at months 12 and 24, and eyes with absent hemorrhage continue to have high mean visual acuity at month 12, with VALS improvement of 24.6 in both the aflibercept and bevacizumab groups. This finding was markedly better than in eyes with no month 6 improvement of hemorrhage over baseline, with month 12 mean improvement over baseline in VALS of 12.6 and 16.5 in the aflibercept and bevacizumab groups, respectively.

DISCUSSION

RELATIVELY LITTLE IS UNDERSTOOD REGARDING THE impact of intraretinal macular hemorrhage on visual acuity outcomes in patients with CRVO or HRVO treated with anti-VEGF. Natural history data have been reported previously,[11–13] but more recent work has examined this topic in the anti-VEGF era.[14] In this Study by Mir,[14] retrospective analysis of 289 eyes with CRVO were split into eyes with fovea involving and fovea sparing retinal hemorrhages. Eyes with foveal involvement were associated with increased rates of cystoid macular edema, including greater CST and increased anti-VEGF injection burden, but similar final visual acuity outcomes to the fovea sparing counterparts. That Study does differ from the current analysis in several important ways. In particular, all eyes in the SCORE and SCORE2 datasets have macular edema at baseline, whereas 207 of 289 (71.6%) have macular edema at baseline in the Study from Mir and associates.[14] Although the studies defined different anatomic boundaries, it is likely that foveal and macular hemorrhages reflect a somewhat overlapping phenomenon of importance.

TABLE 3. Relationship of Central Subfield Thickness and Intraretinal Macular Hemorrhage Outcomes and Visual Acuity Outcome at Month 6

	Outcome: Change From Baseline to Month 6 in Visual Acuity Letter Score						
	Change From Baseline to Month 6 in CST (Unit = 100 μm)			Intraretinal Macular Hemorrhage Present (Relative to no Presence) at Month 6			
Model	Beta Coefficient	99% CI	*P* Value	Beta Coefficient	99% CI	*P* Value	R^2
1. Both CST and intraretinal macular hemorrhage in model	−2.35	−3.25, −1.45	<.0001	−5.87	−10.52, −1.21	.0012	0.16
2. CST only in model	−2.36	−3.28, −1.45	<.0001	—	—		0.13
3. Intraretinal macular hemorrhage only in model	—	—		−5.97	−10.81, −1.13	.0015	0.03

CST = central subfield thickness.
[a]Models also adjusted for the treatment arm (bevacizumab or aflibercept).

Extensive intraretinal macular hemorrhage has been reported to reflect a more severe phenotype and biomarker of ischemia in CRVO eyes.[15,16] Intraretinal hemorrhage has also been reported to be a marker of disease severity in the staging of diabetic retinopathy.[17] The current analysis demonstrates that anti-VEGF therapy was effective in decreasing the area of hemorrhage in eyes with CRVO or HRVO (SCORE2 cohorts) compared with the natural history of this condition (SCORE cohort). This analysis also confirms prior analyses of the ranibizumab registration trials (CRUISE and BRAVO), in which the analysis of hemorrhage at 12 months revealed that compared with sham injections, monthly ranibizumab was associated with a greater proportion of patients without hemorrhage and fewer patients with >10 hemorrhages within the entire retina.[1,2]

The present analysis also importantly demonstrates an association between visual acuity outcomes and both presence of and improvement of intraretinal macular hemorrhage. In eyes treated with monthly intravitreal anti-VEGF injections for CRVO- or HRVO-associated macular edema, the persistence of hemorrhage at 6 months for SCORE2 or 8 months for the SCORE Study was associated with, on average, 8-letter worse visual outcomes in eyes treated with aflibercept and 3 letters worse in bevacizumab-treated eyes, compared with those without residual hemorrhage. Eyes without hemorrhage at 6 months in SCORE2 or 8 months in the SCORE Study have the most favorable visual outcomes, followed by eyes with improvement but not clearance of hemorrhage, and lastly by eyes without improvement in hemorrhage. Visual outcomes were similar when assessed by mean VALS improvements from baseline to month 6. The resolution of macular hemorrhage at 6 months is associated with a more favorable visual acuity at 12 and 24 months compared with eyes with persistent hemorrhage at 6 months. These analyses directly link visual acuity and phenotypic appearance of eyes with CRVO or HRVO. In one retrospective analysis, individuals with fovea-involving hemorrhage from branch RVO demonstrated lower baseline and final visual acuities, and increased risk of cystoid macular edema, compared with branch RVO eyes without fovea-involving hemorrhage.[18]

The relationship between macular edema, retinal hemorrhage, and visual acuity is complicated as these factors vary along with disease severity. Eyes with more hemorrhage would be expected to have an increased likelihood of ischemia, more edema, and worse visual acuity.[12] Anti-VEGF injections disrupt the negative feedback cycle in eyes with RVO and have been associated with less macular edema, modest improvement in capillary nonperfusion,[19,20] and reduction in the presence of retinal hemorrhages.[1] The present Study newly demonstrates that changes in SD-OCT CST and the presence of hemorrhage are both independent predictors of visual acuity for eyes with CRVO- or HRVO-associated macular edema, and, therefore, retinal hemorrhage may account for why there is only a modest correlation between OCT and visual acuity in eyes with macular edema and RVO in the SCORE Study. In that Study, we found only a modest correlation between OCT-measured center point thickness and VALS.[11] The modest correlation between OCT and visual acuity has been more robustly established in the diabetic retinopathy literature where similar ischemia-driven VEGF upregulation is present.[21–24]

Along with OCT characteristics, the persistence of intraretinal hemorrhages is simple to visualize and may be an important indicator of other disease activity. For example, in eyes in which visual acuity does not improve despite the resolution of macular edema and intraretinal hemorrhage, other factors are likely driving the vision loss such as macular ischemia. Treatment other than continued anti-VEGF therapy might be considered in such cases.

It is unknown exactly how anti-VEGF therapy affects intraretinal macular hemorrhage and its distribution in patients with CRVO, but it has been proposed to relieve

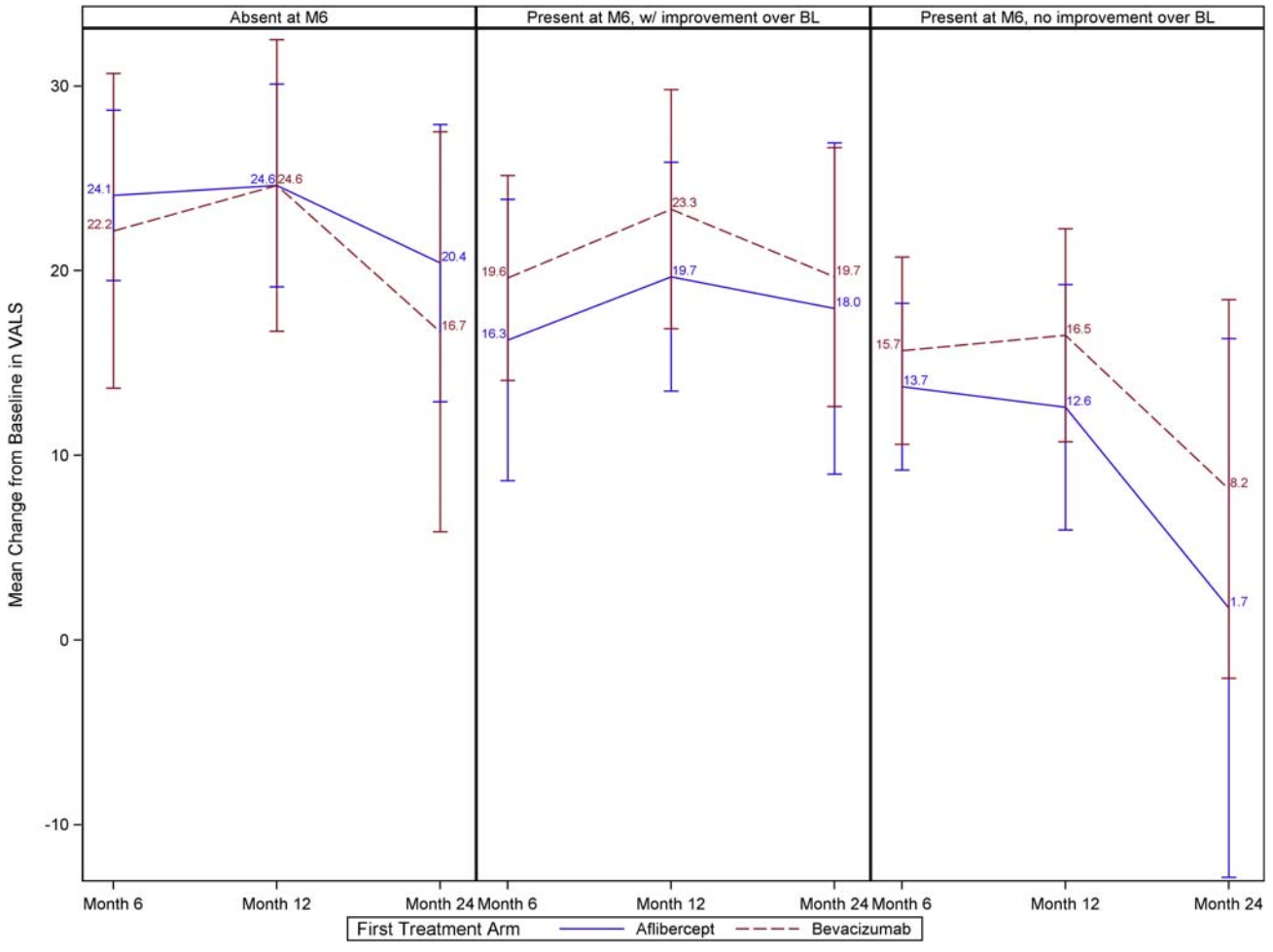

FIGURE 2. Mean change from baseline in visual acuity letter score (VALS) by change in retinal hemorrhage, among those with retinal hemorrhage at baseline.

leukostasis and reduce capillary nonperfusion in animal models.[25] Anti-VEGF injections have been associated with a reduction in capillary nonperfusion compared with the natural history,[19] and the area of retinal hemorrhage is correlated with the area of capillary nonperfusion.[20] The mechanisms of intraretinal hemorrhage development and effects on physiology are not completely understood. It is possible that (1) hemorrhages result from the breakdown of damaged capillary beds and are indirectly associated with areas of nonperfusion, (2) hemorrhages themselves are directly toxic to cellular processes and therefore detrimental to visual function, or (3) hemorrhages are simply a visible feature of RVO. Further Study to understand the mechanisms of hemorrhage pathophysiology are necessary and have broad implications for many common diseases. It is possible that anti-VEGF injections may have disease-modifying capacity in RVO beyond just reducing macular edema and improving hemorrhage such as in diabetic retinopathy. In diabetic retinopathy, the disease-modifying effects of anti-VEGF therapy are well established and include improvement in other pathologic features such as diabetic retinopathy severity score and/or neovascularization.[26]

These secondary analyses are limited in that they mostly involve associations, and definitive conclusions regarding causation between the impact of intraretinal macular hemorrhage area changes and VALS cannot be made. Further, area measurements of intraretinal hemorrhage were made only within the macula as ultra-widefield color photographs were not available in this Study. In addition, the area of blood was graded using 4 categories (eg, 0%, 1%-25%) rather than using a continuous variable, and this limited the ability to show more detailed changes over time. Lastly, this investigation included comparison data from the original SCORE Study that used time-domain OCT at 8 months instead of 6 months, with a mean baseline CST of 605 μm, compared with a mean baseline CST of 666 μm from SCORE2 based on SD-OCT. There were many similarities in the design and participant populations of the SCORE Study and SCORE2, including the

definition of a CRVO, the visual acuity eligibility criterion, the baseline characteristics of age, gender, and VALS, the methods by which visual acuity measurements were performed by certified staff, and the use of the same Reading Center, which graded images using similar methodologies. For these reasons, we believe that data from the SCORE Study provide a useful reference.

In summary, this SCORE2 secondary analysis provides information on the intraretinal macular hemorrhage changes in eyes with CRVO- or HRVO-associated macular edema treated with anti-VEGF injections or observation, and the association of changes in the area of hemorrhage with changes in VALS. The resolution of hemorrhage occurred in eyes treated with anti-VEGF therapy and was associated with visual acuity improvement at month 6. Hemorrhage status at month 6 also independently predicted visual acuity changes at month 6 beyond what was explained by changes in CST. These findings suggest that intraretinal macular hemorrhage is an important indicator of disease severity in RVO.

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