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SCORE STUDY REPORT 12:

Development of Venous Collaterals in the Score Study

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Abstract

Purpose—To investigate the prevalence of venous collaterals after branch and central retinal vein occlusion, assess the association of venous collaterals with other clinical features (including visual acuity), and determine if treatment with intravitreal corticosteroids influences the development of new venous collaterals.

Methods—Review of data from two multicenter randomized clinical trials in the Standard of Care versus COrticosteroid for REtinal Vein Occlusion (SCORE) Study.

Results—Statistically significant associations of venous collaterals and visual acuity at baseline or at follow-up were not found. Treatment with intravitreal triamcinolone acetonide did not appear to influence the development of venous collaterals.

Conclusion—In contrast to some previous reports, development of venous collaterals did not demonstrate an independent association with visual acuity in eyes with branch retinal vein occlusion or central retinal vein occlusion in the SCORE Study. Intravitreal steroid effects do not appear to influence the development of venous collaterals.

Keywords

branch retinal vein occlusion; central retinal vein occlusion; venous collateral; corticosteroid; intravitreal pharmacotherapy; visual acuity

In the context of retinal vein occlusion, venous collaterals are pathways that facilitate the flow of blood from an obstructed vein to a neighboring unobstructed vein. Venous collaterals arise as a secondary phenomenon, resulting from alterations of the pressure and flow characteristics within the retinal vessels after an obstruction. Little is known about the features of vein occlusions that favor the development of collateral channels.

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There are conflicting data in the literature regarding the prognostic significance of venous collaterals after retinal vein occlusion. Some authors have reported better visual acuity outcomes in eyes with central retinal vein occlusion (CRVO) and collaterals.^{1–3} A more recent article suggested an association of collaterals with poorer outcomes in CRVO.⁴ There has been little analysis of the prognostic significance of collaterals in branch retinal vein occlusion (BRVO). Intravitreal corticosteroids are known to influence retinal vascular physiology in a variety of retinal vascular diseases,⁵ but it is not known if these changes favor or discourage the development of collateral vessels.

The purpose of the current study was to investigate the prevalence of venous collaterals on the optic disk and within the retina at baseline and over the course of the Standard of Care vs. Corticosteroid for RETinal Vein Occlusion (SCORE) Study, and to investigate associations of venous collateral vessels with baseline characteristics, treatment assignment, and visual acuity outcomes.

Methods

The SCORE Study design and methods, described in detail in previous SCORE Study reports,^{6–8} are summarized here in brief. The protocol and consent forms for this randomized multicenter clinical study were approved by either a clinical site's institutional review board or a centralized institutional review board (Jaeb Center for Health Research, Tampa, FL), whichever was applicable. An independent data and safety monitoring committee appointed by the National Eye Institute provided data and safety monitoring oversight. The study adhered to the tenets of the Declaration of Helsinki. Written Health Insurance Portability and Accountability Act-compliant informed consents were obtained from all participants before screening for eligibility.

The SCORE Study includes 2 multicenter phase 3 randomized clinical trials that compared contemporaneous standard of care treatment with intravitreal triamcinolone acetonide for the treatment of macular edema due to retinal vein occlusion. One trial was conducted among patients with nonischemic CRVO and the other among patients with BRVO. Eyes were randomized to treatment with intravitreal triamcinolone acetonide (4 mg), intravitreal triamcinolone acetonide (1 mg), or standard of care. For BRVO, standard of care was grid laser treatment for eyes without dense macular hemorrhage and deferral of laser until hemorrhage cleared sufficiently for laser to be administered in eyes with dense macular hemorrhage. For CRVO, standard of care was observation. The primary outcomes of the SCORE Study have been reported previously.^{9,10}

Fundus photography, fluorescein angiography, and optical coherence tomography were obtained by certified photographers at baseline and repeated at specified intervals as outlined in previously published reports.^{6–8} Collateral vessels were identified by masked graders using stereoscopic color fundus photographs sent by the clinical sites to the Fundus Photograph Reading Center, University of Wisconsin, Madison (Reading Center) when study participants reported for their baseline visit, and at regular 4-month visits through Month 36. Fluorescein angiograms were not used in the grading of collateral vessels. The

grading protocol used for the SCORE Study is available from the National Technical Information Service.¹¹

Collateral vessels in the retina (Figure 1) were defined by the Reading Center as vessels within the area of an occluded vein that have arisen to bypass the occlusion. These vessels are typically, but not always, smaller than the veins they bypass and exhibit themselves as a patch of tortuous venules often crossing the horizontal raphe. Collateral vessels lie within the retina and not anterior to it like new vessels. Collateral vessels on the optic disk (Figure 2) were defined by the Reading Center as wider and more easily visible than collateral vessels in the retina, but optic disk collaterals originate and remain within the disk margin. Optic disk collaterals are generally loopy and thick in appearance. Once developed, both types of collateral vessels typically remain even after the occlusion is resolved.

The grading scale for collateral vessels within the retina and the disk was as follows: “Absent”, “Questionable”, “Definite”, and “Cannot grade.” For the purposes of analysis, questionable and absent ratings were grouped together under absent. “Cannot grade” ratings were dropped from the analysis. Approximately 5% of Reading Center image data for the retina and 3% of Reading Center image data for the disk were given a rating of “Cannot grade” because the graders could not assess the image. Based on the common closeout, study participants had a follow-up of at least 12 months and at most 36 months.

At the Reading Center, temporal reproducibility in grading venous collaterals was assessed using an established set of baseline SCORE Study images; these images were regraded annually through the course of the SCORE Study. Fundus photographs of 74 subjects were selected randomly and were distributed on a yearly basis among the same 5 to 7 graders. The graders did not have access to the original grade of record and performed the temporal reproducibility exercise in the SCORE Study over three successive years. In addition, contemporaneous reproducibility of venous collateral gradings was performed monthly during the second and third years of the SCORE Study. A random selection of approximately 5% of the SCORE Study follow-up fundus photographs was regraded by a second grader. Contemporaneous reproducibility was analyzed in the same manner as temporal reproducibility by comparing the quality control regrade with the original grade of record.

In the SCORE Study protocols, eyes with hemi-retinal vein occlusion (HRVO) were randomized, treated, and analyzed as BRVO. For some of the analyses presented in this report, HRVO eyes are analyzed as a separate category.

Statistical Analyses

Data from the Reading Center regarding the assessment of collateral vessel status on the disk and within the retina, documented at baseline and during the 4-month examinations at the clinical sites, were analyzed by *t*-tests and Pearson chi-square tests for simple univariate analyses of continuous and categorical data, respectively. Temporal and contemporaneous reproducibility in grading venous collaterals were assessed via percent agreement and through Kappa statistics. Cumulative incidence of developing collateral vessels and the effect of treatment assignment on the development of new collateral vessels were analyzed

using the life table method, with the log-rank test used to compare groups. Logistic regression analyses were used to estimate the relationship between baseline characteristics and collateral vessel status at baseline. Analyses investigating the effect of baseline predictors on hazard rates of presence of collateral vessels were performed by multivariate (considering all the factors) Cox regression analyses, which estimate the increase in hazard associated with a predictor. We used the hazard as a measure of risk in these analyses. The following baseline factors were evaluated for potential predictive values in the development of collateral vessels in the SCORE-CRVO trial and the SCORE-BRVO trial, respectively: observation/grid photocoagulation versus 1 mg of triamcinolone, observation/grid photocoagulation versus 4 mg of triamcinolone, 1 mg of triamcinolone versus 4 mg of triamcinolone, age, gender, diabetes, coronary heart disease, systemic hypertension, duration of macular edema, disk area of retinal capillary nonperfusion, visual acuity, intraocular pressure, pseudophakia, and disk area of retinal hemorrhage. Because of the multitude of statistical tests performed predisposing for Type 1 errors, only P values ≤ 0.01 are considered to be significant for all analyses of this study. All analyses were performed in SAS 9.2 (2008; SAS Institute, Inc., Cary, NC).

Results

The SCORE Study enrolled 271 patients with CRVO and 411 patients with BRVO, with $>90\%$ of patients having data on collateral vessel status. At baseline, the prevalence of collaterals on the disk was higher in CRVO eyes (37.8%) than in BRVO eyes (including HRVO) (14.6%; $P < 0.001$, chi-square test). In contrast, the prevalence of collaterals within the retina at baseline was higher in BRVO eyes (including HRVO) (17.1%) than in CRVO eyes (6.8%; $P < 0.001$, chi-square test). The relationship between baseline venous collateral status and baseline visual acuity letter score is also presented in Table 1. In general, there were no significant differences in visual acuity letter score at baseline comparing eyes entering the study with venous collaterals either within the retina or on the disk and their counterparts without collaterals. There was a trend of BRVO eyes with collaterals on the disk at baseline having slightly poorer visual acuity (53.2 letters vs. 57.8 letters, $P = 0.011$) at baseline than those without, but this difference was eliminated when HRVO eyes were excluded from the analysis ($P = 0.224$).

Table 2 depicts status of collaterals at baseline, baseline visual acuity, and change from baseline in visual acuity letter score at 1 year for each type of vein occlusion. The CRVO eyes without collateral vessels on the disk at baseline lost more letters at 1 year than eyes with collateral vessels on the disk at baseline (-7.2 and -0.8 letters, respectively, $P = 0.048$), a difference that did not meet statistical significance as specified in this report. There were no statistically significant differences in change in visual acuity letter score from baseline to Month 12 based on the presence or absence of collateral vessels at baseline.

Results of multivariate logistic regression analyses exploring covariates associated with presence of collaterals at baseline are presented in Table 3. No characteristic was significantly associated with the presence of baseline disk collaterals in eyes with BRVO or CRVO. For eyes with BRVO, three baseline variables were associated with retinal collaterals at baseline: younger age, longer duration of macular edema, and smaller area of retinal

hemorrhage. No baseline characteristics were associated with collateral vessels within the retina for CRVO eyes.

The 12-month cumulative incidence of developing collateral vessels on the disk was 13.5% for BRVO eyes and 46.2% for CRVO eyes. The 12-month cumulative incidence of developing collateral vessels within the retina was 48.5% for BRVO eyes and 27.9% for CRVO eyes. Considering eyes without collaterals at baseline, life table analyses found no differences in the rate of development of new disk or retina collaterals among participants randomized to triamcinolone acetonide (4 mg), triamcinolone acetonide (1 mg), or standard of care for either CRVO or BRVO eyes (data not presented in tables).

Cox regression analyses, using multivariate models, examined associations between baseline characteristics and the development of new collateral vessels (Table 4). Poorer baseline vision and presence of larger areas of retinal hemorrhage at baseline were associated with a greater likelihood of future new collaterals at the disk for eyes with BRVO. No baseline feature was predictive of new disk collaterals in eyes with CRVO.

Larger area of capillary nonperfusion at baseline was associated with a greater likelihood of future new retinal collaterals for eyes with BRVO and eyes with CRVO. Absence of diabetes was associated with a greater likelihood of future retinal collaterals in eyes with BRVO. Shorter duration of macular edema was associated with a greater likelihood of future retinal collaterals in eyes with CRVO.

Reproducibility statistics for the Reading Center grading of both retinal and disk collaterals are presented in Table 5. The reproducibility data show intergrader agreement >75%. The kappa values are moderate because of skewed distribution of data, as a large percentage of eyes did not have venous collateral vessels.

Discussion

The pressure gradient between an obstructed vessel and neighboring unobstructed vessel is sufficient to explain the flow of blood through collateral channels in retinal vein occlusions.¹² In experimental BRVO, collaterals were observed to exploit existing deep capillaries within the retina and divert blood from the occluded vein to a nearby, unobstructed vein.¹³ In the setting of CRVO, the collaterals typically form on or adjacent to the optic nerve and connect the retinal veins to the choroidal venous system.¹⁴ This has been confirmed histologically in an eye with disk collaterals due to an optic sheath meningioma.¹⁵ These proposed mechanisms of collateral formation are consistent with the higher prevalence of optic disk collaterals in CRVO eyes and the higher prevalence of retinal collaterals in BRVO eyes in the current study.

It is plausible that venous collateral formation might improve the visual outcome in eyes with retinal vein occlusion by reducing the hydraulic stress on vessels upstream from the occlusion. Previous authors have suggested that collaterals portend a better prognosis in eyes with CRVO.¹⁻³ Other authors have found no such association.¹⁶⁻¹⁹

However, collaterals may be a marker for a more severe variant of CRVO. A recent natural history study by Hayreh et al⁴ found that eyes with nonischemic CRVO that developed collaterals presented with poorer visual acuity than eyes that did not develop collaterals (52% vs. 35% of eyes with visual acuity of 20/70 or worse, respectively). The time to resolution of edema was almost twice as long in eyes that developed collaterals (median time to resolution was 40 months in eyes with collaterals vs. 21 months in eyes without collaterals). Among eyes with resolution of edema, eyes with collaterals were less likely to experience improvement in vision than those without collaterals.⁴ In contrast, data from the SCORE Study did not show a statistically significant association of baseline collaterals with baseline visual acuity or with change in visual acuity during follow-up.

Three baseline features were associated with baseline intraretinal collaterals in eyes with BRVO: longer duration of macular edema, smaller area of retinal hemorrhage, and younger age. Longer duration of macular edema likely correlates with longer duration of the vein occlusion and therefore longer opportunity for development of a collateral circulation. Smaller area of retinal hemorrhage may also indicate a longer time since onset of the vein occlusion. It is also likely that smaller areas of hemorrhage allow more detailed evaluation of the retina, making it possible for graders to more readily identify collateral vessels. The reason for an association with younger age is unclear. Perhaps younger patients have a greater capacity for vascular remodeling and collateral formation. Younger patients are also likely to have clearer media, giving graders better sensitivity in detecting collaterals.

In the SCORE Study, the strongest and most consistent baseline predictor in both nonischemic CRVO and BRVO for the development of subsequent intraretinal collaterals was the area of capillary non-perfusion (Table 4). The larger area of capillary non-perfusion may be a marker for greater hemodynamic stress and a larger pressure gradient within the retinal venous system, facilitating intraretinal collateral formation. Shorter duration of macular edema was associated with development of intraretinal collaterals in eyes with CRVO. This may be explained by the likelihood that eyes with a shorter duration of macular edema were enrolled earlier in the course of their vein occlusion. For BRVO, patients with diabetes were less likely to develop intraretinal collaterals during followup than those without diabetes. The combined retinal vasculopathy of diabetes and vein occlusion may be unfavorable for formation of new collaterals.

In eyes with BRVO, poorer baseline vision and larger area of hemorrhage were associated with a greater likelihood of developing new collaterals at the disk. These associations remain statistically significant even if HRVO eyes are excluded from the analysis (data not shown). Perhaps occlusions that originate very proximal to the optic nerve result in collaterals more likely to be graded as disk collaterals. Further scrutiny of these photographs may advance our understanding of this phenomenon.

In the SCORE Study population, associations of venous collaterals with visual acuity were small or undetectable. No statistically significant association with visual acuity was found in BRVO (non-HRVO) eyes with intraretinal collaterals at baseline or for nonischemic CRVO with disk collaterals at baseline. On first analysis, disk collaterals trended with poorer baseline visual acuity letter score in eyes with BRVO, but this is explained by the inclusion

of HRVO eyes in this analysis. HRVO eyes entered with poorer visual acuity than non-HRVO BRVO eyes, and eyes with HRVO were disproportionately represented in the group of BRVO eyes with disk collaterals. The lack of any other association between visual acuity and either the presence of collaterals at baseline or the development of collaterals during the study suggests that, in the SCORE Study population, the development of a compensatory venous outflow does not have a measurable effect on vision. The length of time required to develop such a pathway may preclude any effect on visual function.

As expected, the relative frequency of the location of collateral vessels differed among the types of retinal vein occlusion. Disk collaterals were found with higher frequency in eyes with CRVO and HRVO and infrequently in eyes with BRVO (excluding HRVO eyes). Intraretinal collaterals were found with greatest frequency in eyes with BRVO. In BRVO, the occluded vein is surrounded by neighboring venous channels with unobstructed flow to the central retinal vein, allowing the potential for intraretinal collateral formation. In CRVO, the site of occlusion is at or near the lamina cribrosa. All branches of the central retinal vein are affected, so there is no pressure gradient within the retinal circulation to drive the formation of intraretinal collaterals. At the margin of the optic nerve, there is potential for collateral drainage from the retinal to the choroidal circulation.

Despite the above discussion, disk collaterals in eyes with BRVO and intraretinal collaterals in eyes with CRVO were found at baseline and did develop in some eyes throughout the course of the study. These findings contrast with reports from previous investigators and are contrary to leading hypotheses concerning the formation of collaterals after retinal vein occlusion. Approximately half of the disk collaterals observed in BRVO can be attributed to the fact that HRVO was classified as BRVO in SCORE. In HRVO, it is believed that the central retinal vein branches posterior to the lamina cribrosa, allowing one hemisphere of the retina to be spared when the other is occluded.²⁰ The anatomical variation explains the previous observation that HRVO eyes can develop intraretinal collaterals and retinochoroidal collaterals at the optic nerve.²¹

The reasons for the development of intraretinal collateral channels in eyes with CRVO are less clear. It is possible that greater surveillance by the graders at the Reading Center discovered a new finding in eyes with CRVO. It is also possible that some CRVO eyes graded with intraretinal collaterals had other vascular abnormalities that simulated venous collaterals, such as dilated venules or retinal neovascularization. Discrimination of collaterals from other vascular abnormalities can be difficult even for experienced clinicians. The clinical investigators who examined the patients were not asked to comment on the presence of collaterals, so comparison of the findings of the Reading Center with clinician assessment is not possible. Further investigation will be necessary to clarify the significance of this finding.

It is clear from laboratory and clinical data that intravitreal steroids influence the retinal vasculature in a variety of conditions with retinal vascular injury and permeability. These effects are multifactorial and include regulation of mediators of vascular permeability, including vascular endothelial growth factor, and direct effects of corticosteroids on vascular endothelium.⁵ It is not clear if these effects would be likely to influence collateral formation.

In a small case series of eyes with CRVO treated with intravitreal injections of the vascular endothelial growth factor-binding drug bevacizumab, Ferrara et al²² commented that patients experienced improvements in vision despite the observation that none of the six treated eyes developed venous collaterals. Similar observations were made in eyes with CRVO treated with intravitreal ranibizumab.^{23,24}

Among eyes entering the SCORE Study without collaterals, treatment with intravitreal triamcinolone did not influence the probability of new collateral formation, regardless of vein occlusion type (CRVO or BRVO) or the location of the collaterals (within the retina or at the optic nerve). Thus, it appears that intravitreal corticosteroids neither enhance nor inhibit the development of collaterals in eyes with retinal vein occlusions and that the observed clinical effects of steroids (i.e., visual acuity improvement and resolution of macular edema) are due to other steroid-mediated effects, such as downregulation of vascular endothelial growth factor, direct effects on retinal vessels, neuroprotective effects, or via some other mechanism. Collateral channels are neither necessary nor sufficient for improved vision after retinal vein occlusion.

In the SCORE Study, a large sample of patients was well characterized and followed prospectively. Grading for collaterals was performed at fixed intervals by trained examiners at a central reading center using standardized protocols. There are, however, limitations to the conclusions that can be drawn from these analyses. Standard photographic fields used in the SCORE Study concentrated on areas of the fundus where collaterals are most likely to occur, but it is possible that some intraretinal collaterals occurred outside the standard fields and were not counted in this study. If SCORE Study graders had used fluorescein angiograms in addition to fundus photographs, the sensitivity and specificity of collateral identification might have been enhanced.

SCORE Study inclusion/exclusion criteria were designed to exclude ischemic vein occlusions, and patients were required to have a minimum central subfield macular thickness of 250 μ m on optical coherence tomography testing.⁸ Results of the current study may not be applicable to eyes that do not meet SCORE Study eligibility criteria.

SCORE Study participants were enrolled with retinal vein occlusion of variable duration. Duration of the presence of macular edema due to vein occlusion was estimated at baseline. Mean duration was 4.3 months for CRVO and 4.4 months for BRVO.²⁵ Many patients entered the SCORE Study with collaterals already present. This study is unable to explore factors present at onset of vein occlusion associated with formation of venous collaterals and has limited ability to study the early time course of collateral formation.

In conclusion, SCORE Study data confirm that BRVO and nonischemic CRVO eyes exhibit different patterns of collateral formation. There was not a significant association between presence of collaterals, at either baseline or follow-up, and visual acuity. The lack of an association between intraretinal or disk collaterals and visual function may be a result of the time it takes to develop these compensatory pathways. In the SCORE Study, there was no evidence of an effect of intravitreal steroids on the development of new collaterals,

suggesting that the beneficial effect of steroids on visual function is via a mechanism independent from that of collateral formation.

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Fig. 1. Color fundus photograph focusing on the collateral vessels in the retina due to retinal vein occlusion. Lying within the retina, the collateral vessels are thin and very tortuous. Many of the retinal collateral vessels shown in the figure cross the horizontal raphe. Typically, collateral vessels in the retina do not leak on fluorescein angiography.

Fig. 2.

Color fundus photograph showing many collateral vessels on the optic disk. These collateral vessels are due to retinal vein occlusion and are tortuous and thick in appearance. The collateral vessels may form loops and may pass across the optic disk. Disk collateral vessels are not elevated into the vitreous and do not leak on fluorescein angiography.

Table 1

Baseline Collateral Vessels' Status on the Disk and Within the Retina

Disease/Status	Collateral Vessel Status on the Disk			Collateral Vessel Status Within the Retina		
	N (%)	Baseline Visual Acuity Letter Score	<i>P</i> [*]	N (%)	Baseline Visual Acuity Letter Score	<i>P</i> [*]
BRVO (including HRVO)	396 (100)	57.08	0.011	381 (100)	57.44	0.118
Absent	338 (85.4)	57.75		316 (82.9)	56.99	
Present	58 (14.6)	53.19		65 (17.1)	59.64	
BRVO (non-HRVO)	340 (100)	57.74	0.224	327 (100)	58.09	0.044
Absent	310 (91.2)	58.00		269 (82.3)	57.46	
Present	30 (8.8)	55.13		58 (17.7)	60.97	
HRVO	56 (100)	53.04	0.320	54 (100)	53.56	0.341
Absent	28 (50.0)	54.96		47 (87.0)	54.28	
Present	28 (50.0)	51.11		7 (13.0)	48.71	
CRVO	251 (100)	51.79	0.296	264 (100)	51.47	0.461
Absent	156 (62.2)	52.52		246 (93.2)	51.64	
Present	95 (37.8)	50.60		18 (6.8)	49.11	

* *P*-value from *t* test to test whether the baseline visual acuity letter scores differ between those with and without collateral vessels at baseline.

Table 2

Changes in Visual Acuity Letter Score Among Those With and Without Collateral Vessels on the Disk and Within the Retina Based on Baseline Status

Disease/Status	Collateral Vessel Status on the Disk				Collateral Vessel Status within the Retina			
	N (%)	Baseline Visual Acuity Letter Score	Mean Change From Baseline to Month 12 in Visual Acuity Letter Score	P*	N (%)	Baseline Visual Acuity Letter Score	Mean Change From Baseline to Month 12 in Visual Acuity Letter Score	P*
BRVO	355 (100)	57.01	4.81	0.094	340 (100)	57.37	4.43	0.908
(including HRVO)								
Absent	303 (85.4)	57.44	4.18		286 (84.1)	56.99	4.48	
Present	52 (14.6)	54.48	8.46		54 (15.9)	59.39	4.19	
BRVO	307 (100)	57.74	4.28	0.544	293 (100)	58.15	11.59	0.633
(non-HRVO)								
Absent	280 (91.2)	57.86	4.10		246 (84.0)	57.61	4.09	
Present	27 (8.8)	56.48	6.15		47 (16.0)	60.98	2.81	
HRVO	48 (100)	52.41	8.17	0.291	47 (100)	52.56	7.85	0.406
Absent	23 (47.9)	52.50	5.13		40 (85.1)	53.22	6.88	
Present	25 (52.1)	53.32	10.96		7 (14.9)	48.71	13.43	
CRVO	221 (100)	52.20	-4.70	0.048	231 (100)	51.80	-5.13	0.121
Absent	136 (61.5)	52.91	-7.15		215 (93.1)	52.02	-5.78	
Present	85 (38.5)	51.07	-0.76		16 (6.9)	48.88	3.63	

* P-value from *t*-test to test whether the changes from baseline in visual acuity letter score differ between those with and without collateral vessels at baseline.

Table 3

Multivariate Regression: Predictors of Collateral Vessels on the Disk and Within the Retina at Baseline

Baseline Characteristic	Disk			Retina		
	BRVO (Including HRVO)		CRVO	BRVO (Including HRVO)		CRVO
	Odds Ratio	P*	Odds Ratio	Odds Ratio	P*	Odds Ratio
Treatment group (1 mg)	1.52	0.479	0.68	1.03	0.458	0.83
Treatment group (4 mg)	1.33	0.838	1.01	0.62	0.179	0.45
Age	1.02	0.284	1.00	0.95	0.002	1.01
Female	0.87	0.710	1.07	0.853	0.083	0.37
Diabetes	1.05	0.915	0.57	0.64	0.335	0.71
Coronary heart disease	0.72	0.499	0.98	0.38	0.065	0.73
Systemic hypertension	1.58	0.305	1.15	2.68	0.020	2.13
Duration of macular edema	1.06	0.216	1.10	1.11	0.010	0.94
Baseline capillary nonperfusion	1.04	0.124	0.98	1.02	0.426	1.10
Baseline visual acuity letter score	0.97	0.015	0.98	0.98	0.257	0.98
Baseline IOP	1.09	0.141	1.03	1.02	0.761	1.00
Baseline lens status (pseudophakic)	1.53	0.365	0.84	1.19	0.741	0.61
Area of retinal hemorrhage	1.24	0.012	0.89	0.76	0.006	0.75

* P-value is from a multivariate logistic regression modeling the relationship between all baseline characteristics jointly and collateral vessel status on the disk at baseline or within the retina at baseline. IOP, intraocular pressure.

Table 4
Multivariate Regression: Development of Collateral Vessels on the Disk and Within the Retina Over 36 Months

Baseline Characteristic	Disk			Retina		
	BRVO (Including HRVO)			BRVO (Including HRVO)		
	Hazard Ratio	P*	Hazard Ratio	Hazard Ratio	P*	Hazard Ratio
Treatment group (1 mg)	1.35	0.419	0.80	0.472	0.86	0.457
Treatment group (4 mg)	1.33	0.443	1.16	0.627	1.10	0.612
Age	1.02	0.325	0.98	0.117	0.98	0.014
Female	0.75	0.346	1.16	0.574	0.96	0.668
Diabetes	0.84	0.669	0.90	0.727	0.48	0.002
Coronary heart disease	1.04	0.926	0.83	0.578	0.83	0.369
Systemic hypertension	0.58	0.076	1.40	0.243	1.10	0.584
Duration of macular edema	0.91	0.068	0.89	0.014	0.97	0.145
Baseline capillary nonperfusion	1.01	0.659	1.07	0.267	1.04	<0.001
Baseline visual acuity letter score	0.96	<0.001	0.99	0.159	1.00	0.596
Baseline IOP	0.95	0.252	1.01	0.798	0.98	0.344
Baseline lens status (pseudophakic)	0.89	0.784	1.21	0.599	1.57	0.047
Area of retinal hemorrhage	1.19	0.010	1.04	0.269	0.93	0.070
						1.05
						0.172

* P is from a multivariate Cox regression which estimates the increase in hazard of the presence of collateral vessels on the disk or within the retina associated with the baseline predictor, considered jointly with the other predictors over 36 months.
IOP, intraocular pressure.

Table 5

Temporal and Contemporaneous Reproducibility of Collateral Vessels in SCORE Study Color Photographs

Variables Evaluated	Temporal Reproducibility (N = 74)			Contemporaneous Reproducibility (N = 71)
	First Regrade 2007	Second Regrade 2008	Third Regrade 2009	2008–2009
Agreement on presence of collateral vessels on the disk (%)	78	77	77	87
Kappa statistic for presence of collateral vessels on the disk	0.57	0.53	0.54	0.71
Agreement on presence of collateral vessels in the retina (%)	89	89	86	79
Kappa statistic for presence of collateral vessels in the retina	0.63	0.64	0.55	0.49